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КРАТКИЕ СООБЩЕНИЯ

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CRYSTAL STRUCTURE OF OLANZAPINIUM BENZOATE (1:1)

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Olanzapinium benzoate, 1-methyl-4-(2-methyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)-piperazin-1-ium benzoate, $(C_{17}H_{21}N_4S)^+(C_7H_5O_2)^-$ (**I**), crystallizes in triclinic space group *P*-1 with unit cell dimensions $a = 9.2957(6)$, $b = 11.2416(7)$, $c = 12.0003(8)$ Å; $\alpha = 64.585(1)$, $\beta = 87.568(1)$, $\gamma = 83.248(1)°$; $V = 1124.8(1)$ Å^3. The asymmetric part of the structure comprises a singly charged olanzapinium cation and a singly charged benzoate anion. The central 1,5-diazepine ring adopts the expected boat conformation, while the piperazine ring favors the chair conformation. The olanzapinium and benzoate ions are linked by intermolecular N—H…O hydrogen bonds forming infinite chains running along the c-axis of the crystal.

K e y w o r d s: ZYPREXA, atypical agents, piperazine, protonation, intermolecular hydrogen bond.

ZYPREXA is the brand name for a medication approved for the treatment of schizophrenia, for maintenance of treatment response in schizophrenia, for treatment of acute mania associated with bipolar disorder in patients displaying a manic or mixed episode as monotherapy and in combination therapy with divalproex and lithium, as well as maintenance treatment in bipolar disorder. The scientific name for ZYPREXA is olanzapine. Along with clozapine, quetiapine, risperidone and ziprasidone, olanzapine belongs to the newer generation of atypical agents [1—4].

Our particular interest lies in the crystalline complex of olanzapine with aromatic acids, providing a means both for a structural study of important drug and for examining the interactions between the components. In this context, recently we reported the crystal structure of olanzapinium nicotinate [5]. In the present study, the crystal structure determination of olanzapinium benzoate was undertaken and the results are presented here.

In order to prepare olanzapinium benzoate, $(C_{17}H_{21}N_4S)^+(C_7H_5O_2)^-$ (**I**), olanzapine and benzoic acid were mixed in 1:1 stoichiometric ratio and dissolved in aqueous methanol solution (90 %, 10 mL) for slow evaporation and crystallization. A colorless block of the title compound with dimensions 0.23×0.12×0.09 mm was selected and studied.

Diffracted intensities were collected at room temperature on Bruker SMART Apex CCD diffractometer with graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) up to $2\theta = 25°$ using ω-scan mode [6]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames; final unit cell dimensions were determined from 6244 reflections. Integration and scaling of intensity data were accomplished using SAINT program [6]. Out of 10884 measured reflections, 3947 reflections were unique.

The structure of **I** was solved by direct methods using SHELXS-97 [7] and refined by the full-matrix least-squares method (on F^2) using SHELXL-97 [7]. Anisotropic thermal parameters were included for all non-hydrogen atoms. Hydrogen atoms attached to N3 and N4 were located from a difference density map and were refined isotropically. All other H-atoms were positioned geometrically

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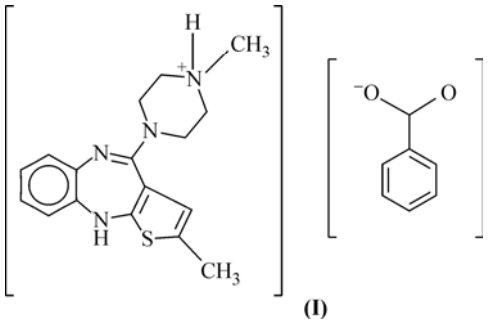

(I)

and treated as riding atoms, with C—H distances in the range 0.93—0.98 Å and with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H and $1.2U_{eq}(C)$ for other H.

A summary of crystal data is presented in Table 1. The final coordinates and equivalent isotropic displacement parameters of non-hydrogen atoms are listed in Table 2. Selected bond distances and angles are listed in Table 3, the parameters of hydrogen bonding, in Table 4. Molecular graphics was computed using SHELXTL [8] program. ORTEP diagram with atom-numbering scheme is shown in Fig. 1.

The asymmetry unit of I consists of one singly charged olanzapine cation and one singly charged benzoate anion. In terms of interatomic distances and angles, the geometry of the present structure, is in good agreement with olanzapine freebase [9], olanzapine methanol solvate [10], olanzapine methanol solvate monohydrate [11] and olanzapinium nicotinate [5]. The expected proton transfer from benzoic acid to olanzapine is established at atom N3 of the piperazine ring. The mean value of N3—C (1.486(2) Å) is greater than the mean value of N2—C (1.455(2)] Å), as expected for a protonated system. In olanzapine nicotinate structure, similar lengthening was observed for the protonated N atom of the piperazine ring; the mean values for N3—C and N2—C bonds are 1.491(4) Å and 1.456(3) Å, respectively. The corresponding mean values for olanzapine freebase (1.456 and 1.463 Å), olanzapine methanol (1.454 and 1.445 Å) and olanzapine methanol hydrate (1.467 and 1.464 Å) are almost equal. The sum of three C—N—C angles around N3 is 333.3° indicating the tetrahedral configuration, quaternary character and positive charge. The corresponding value for olanzapine nicotinate is 337.6°. The relationship of the protonated piperazine ring system to the aromatic ring system may be important for neuroleptic activity [12].

As observed in all olanzapine structures, the central 1,5-diazepine ring adopts a boat conformation and can be described by three planes: a bow (C3, N4, C5), a central plane (C2, C3, C5, C6) and a stern plane (C2, N1, C7, C6). The puckering parameters [13] are $q_2 = 0.743(1)$, $q_3 = 0.140(2)$, $Q_T = 0.756(2)$, $\varphi_2 = 47.7(1)°$, $\varphi_3 = -101.9(6)°$ and $\theta_2 = 79.3(1)°$. The bow angle is

Table 1

Crystal data and experimental parameters

Crystal data	
Empirical formula	$(C_{17}H_{21}N_4S)^+(C_7H_5O_2)^-$
Formula weight	434.55
Crystal system, space group	Triclinic, P-1
a, *b*, *c*, Å	9.2957(6), 11.2416(7), 12.0003(8)
α, β, γ, deg.	64.585(1), 87.568(1), 83.248(1)
V, Å^3	1124.8(1)
Z	2
D_{calc}, g/cm^3	1.283
Collected reflections	
Total / unique / observed	10884 / 3947 / 3540
Refinement	
Data / restraints / parameters	3947/ 0 / 290
GOOF	1.037
R indices [$I > 2\sigma(I)$]	$R1 = 0.0375$, $wR2 = 0.1015$
R indices (all data)	$R1 = 0.0413$, $wR2 = 0.1048$
Peak/hole, e/Å^3	0.27 / –0.17
Deposition	
CCDC deposition number	601897

Table 2

Atomic coordinates ($\times 10^4$) *and equivalent isotropic displacement parameters* (Å $\times 10^2$) *for* **I**

Atom	*x*	*y*	*z*	U_{iso}	Atom	*x*	*y*	*z*	U_{iso}
S(1)	5968(1)	2525(1)	4062(1)	49(1)	C(14)	1028(2)	5818(2)	1326(2)	48(1)
N(1)	2368(1)	4060(1)	997(1)	40(1)	C(15)	4925(2)	1857(2)	321(1)	43(1)
N(2)	4053(1)	3106(1)	93(1)	41(1)	C(16)	5845(2)	2020(2)	–787(2)	47(1)
N(3)	4938(2)	2500(1)	–1919(1)	44(1)	C(17)	3990(2)	3727(2)	–2092(1)	46(1)
N(4)	3029(1)	2771(1)	3654(1)	44(1)	C(18)	3094(2)	3522(2)	–963(1)	42(1)
C(2)	1910(2)	4616(2)	1821(1)	39(1)	C(19)	5837(2)	2706(2)	–3020(2)	69(1)
C(3)	2167(2)	4013(2)	3100(1)	41(1)	O(1)	2874(2)	1932(2)	6327(1)	71(1)
C(5)	4432(2)	2802(2)	3183(1)	39(1)	O(2)	3042(1)	871(1)	8355(1)	52(1)
C(6)	4767(2)	3159(1)	1979(1)	37(1)	C(20)	1050(2)	568(2)	7382(1)	42(1)
C(7)	3638(2)	3453(1)	1044(1)	36(1)	C(21)	307(2)	833(2)	6315(2)	52(1)
C(8)	6286(2)	3219(2)	1762(1)	39(1)	C(22)	–974(2)	309(2)	6362(2)	60(1)
C(9)	7080(2)	2903(2)	2783(2)	44(1)	C(23)	–1530(2)	–486(2)	7469(2)	68(1)
C(10)	8680(2)	2892(2)	2899(2)	60(1)	C(24)	–807(3)	–745(2)	8534(2)	81(1)
C(11)	1556(2)	4623(2)	3825(2)	51(1)	C(25)	479(2)	–231(2)	8497(2)	62(1)
C(12)	697(2)	5821(2)	3306(2)	58(1)	C(26)	2431(2)	1165(2)	7333(1)	43(1)
C(13)	445(2)	6427(2)	2055(2)	55(1)	H(3N)	4380(20)	1840(20)	–1803(19)	68(6)
					H(4N)	2982(18)	2453(17)	4442(17)	46(5)

The coordinates and U_{iso} are listed only for the located hydrogen atoms.

133.0(1)° and the stern angle is 146.2(1)°. As a result, the tricyclic thienobenzodiazepine ring skeleton forms an extended *V*-shaped conformation. The benzene and thiophene rings adjoining the diazepine ring are planar. The dihedral angle between these two aromatic rings is 119.6(2)°. The corresponding angles are 119.9(1)° for olanzapine nicotinate, 127.2(1)° for olanzapine freebase, 124.3(2)° for olanzapine methanol and 117.67(5)° for olanzapine methanol hydrate. The molecular modeling of olanzapine using HYPERCHEM [14] calculates this angle as 135° [15].

Table 3

Selected bond distances d, Å *and angles* φ, deg.

Bond	*d*	Bond	*d*	Bond	*d*	Bond	*d*
S1—C5	1.730(2)	N2—C7	1.383(2)	N3—C19	1.479(2)	N4—C5	1.398(2)
S1—C9	1.736(2)	N2—C18	1.452(2)	N3—C16	1.486(2)	N4—C3	1.421(2)
N1—C7	1.282(2)	N2—C15	1.458(2)	N3—C17	1.486(2)	O1—C26	1.232(2)
N1—C2	1.408(2)					O2—C26	1.266(2)

Angle	φ	Angle	φ	Angle	φ
C7—N1—C2	122.9(1)	C14—C2—N1	116.3(1)	O1—C26—O2	124.0(1)
C7—N2—C18	119.4(1)	C3—C2—N1	125.5(1)	O1—C26—C20	119.2(1)
C7—N2—C15	121.6(1)	C11—C3—N4	120.0(1)	O2—C26—C20	116.7(1)
C18—N2—C15	111.3(1)	C2—C3—N4	120.2(1)	N2—C15—C16	109.6(1)
C19—N3—C16	111.5(1)	C6—C5—N4	125.2(1)	N3—C16—C15	111.1(1)
C19—N3—C17	111.1(1)	N1—C7—N2	118.4(1)	N3—C17—C18	111.0(1)
C16—N3—C17	110.7(1)	N1—C7—C6	126.3(1)	N2—C18—C17	109.1(1)
C5—N4—C3	113.0(1)	N2—C7—C6	115.2(1)		

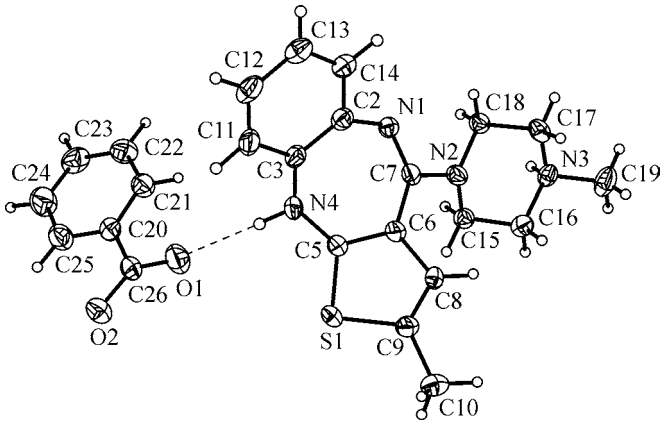

Fig. 1. Asymmetric unit of **I**. Thermal ellipsoids are shown at 30 % probability; H atoms are shown as small spheres of arbitrary radii. The hydrogen bond is shown as a dashed line

The piperazine ring adopts the expected chair conformation (puckering parameters: $q_2 = 0.038(2)$, $q_3 = -0.573(2)$, $Q_T = 0.574(2)$, $\varphi_2 = 166.5(23)°$ and $\theta_2 = 176.2(2)°$) which is similar to those observed in the related olanzapine structures. The piperazine ring is in syn-periplanar (+sp) orientation with respect to the diazepine ring as evidenced from the torsion angle N1—C7—N2—C18 of 4.5(2)°. The corresponding angles are 2.3(4)° for olanzapine nicotinate, –11.8(2)° for olanzapine free-base, –5.9(8)° for olanzapine methanol solvate and 5.6(2)° for olanzapine methanol hydrate. As observed in the other olanzapine structures, the methyl group attached to the piperazine ring is oriented equatorially with respect to the ring. The dihedral angles between the plane of the four C-atoms of the piperazine ring and the planes of the benzene and thiophene rings are 31.6(1)° and 36.4(1)°, respectively. An r.m.s overlay using central 1,5-diazepine ring (r.m.s deviation = 0.006 Å) of the present structure with that of the olanzapinium nicotinate shows significant similarities (Fig. 2).

Table 4

Hydrogen bonding parameters (Å, deg.)

D—H…A	D—H	H…A	D…A	DHA
N3—H3N…O2#1	0.91(2)	1.70(2)	2.600(2)	168(2)
N4—H4N…O1	0.86(2)	2.08(2)	2.932(2)	173(2)

#1 $x, y, z-1$.

The deprotonated carboxylate group of benzoate anion is essentially coplanar (O1—C26—C20—C21 angle equals –176.2(2)°) with its parent benzene ring. This coplanarity might facilitate the intermolecular N—H…O hydrogen bond.

Hydrogen bonds are used extensively as a tool to design the structure of molecular crystals, because of their strength, as well as their directional nature, compared to other intermolecular non-

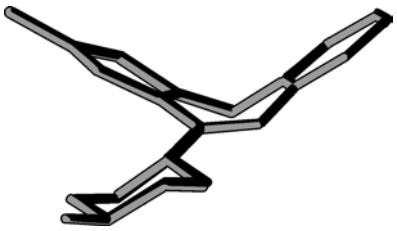

Fig. 2. An r.m.s overlay of present structure (black) and olanzapinium nicotinate (grey)

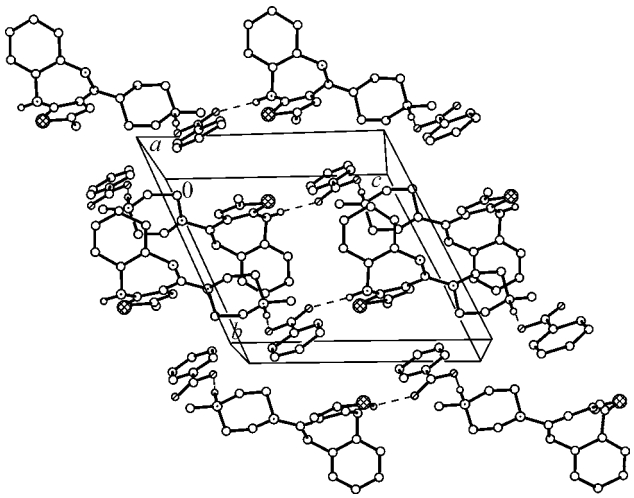

Fig. 3. Crystal packing viewed down a-axis. Dashed lines indicate N—H…O hydrogen bonds. H-atoms attached to C-atoms have been omitted for clarity

covalent interactions [16]. The crystal structure of **I** has hydrogen bonds whose geometrical parameters are listed in Table 4. The positive charge of the olanzapine cation is balanced by the negative charge of the benzoate anion, which is connected to cation through an intermolecular N—H…O hydrogen bond.

The hydrogen bonding patterns in previously studied olanzapinium nicotinate and in the title structure are very similar. The atom N3 of the piperazine ring is connected to the deprotonated carboxylate atom O2 of the benzoate anion via N—H…O hydrogen bond. The hydrogen bonding assembly forms infinite chains of alternating cations and anions. The chains propagate along crystallographic c-axis (Fig. 3).

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