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КРАТКИЕ СООБЩЕНИЯ

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CRYSTAL STRUCTURES OF DUAL DOPAMINE D_2 AND SEROTONIN 5-HT_{1A} ACTIVE ARYLPIPERIDINYL-2(1*H*)-3,4-DIHYDROQUINOLINONES

N. Ullah, M. Altaf, M. Mansha, A.O. Ba-Salem

Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran, Saudi Arabia
E-mail: nullah@kfupm.edu.sa

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8-(1-((5-Cyclopentenylpyridin-3-yl)methyl)piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one (**1**) and 8-(1-(3-cyclopentenylbenzyl)piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one (**2**) are synthesized and obtained in the crystalline state for X-ray diffraction studies. In the asymmetric unit of compound **1**, there are two independent molecules (A and B) having similar conformations. In the crystals of compounds **1** and **2**, individual molecules are linked by pairs of N—H···O hydrogen bonds forming A—A and B—B inversion dimers with $R_2^2(8)$ ring motifs. The dimers are stabilized by N—H···O hydrogen bonds and are linked via C—H···O short contact interactions, forming a three-dimensional and two-dimensional networks in **1** and **2** respectively. The network in **2** is further stabilized by a number of C—H···π interactions. Compounds **1** and **2** have a dual dopamine D_2 and serotonin 5-HT_{1A} receptor profile.

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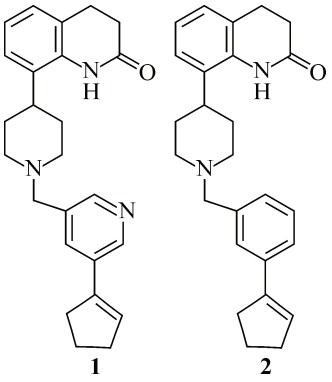
K e y w o r d s: arylpiperidinyl-2(1*H*)-3,4-dihydroquinolinones, 5-HT_{1A} receptor, D_2 receptor, schizophrenia, adoprazine.

Schizophrenia is a severe psychiatric illness afflicting 1 % of the population worldwide. The symptoms of the disease are divided into two classes: positive and negative. The positive symptoms constitute thought disorder, delusions, and auditory hallucinations whereas the negative symptoms are emotional flattening, poverty of speech, and motivational deficits [1]. Typical antipsychotics suffer from liabilities such as extrapyramidal symptoms (EPS) and hyperprolactinemia [2] whereas typical antipsychotics possess several limitations such as diabetes, weight gain and an increased risk of seizures and agranulocytosis [3]. The achievement of improved overall therapeutic benefit, combining D_2 receptor blockade with 5-HT_{1A} receptor activation rather than antagonism has been a subject of recent research attention [4, 5]. Several mechanistic considerations [6—8] and preclinical evidences [9—11] have demonstrated the potential of such an approach. In our continuing effort, we have synthesized and reported dual D_2 and 5-HT_{1A} receptor binding affinities of a series of compounds which are structural analogs of adoprazine and bifeprunox [12, 13].

Herein we disclose the crystal structure of **1** and **2** (Fig. 1) by X-ray diffraction studies. Compounds **1** and **2** have dual dopamine D_2 and serotonin 5-HT_{1A} receptor profiles [14]. The D_2 receptor binding assay of these compounds revealed that **1** (K_i = 8.56 nM) exhibited higher affinity than **2** (K_i = 102.0 nM). However, in the 5-HT_{1A} receptor binding assay, **2** (K_i = 3.75 nM) showed higher affinity than **1** (K_i = 4.15 nM). The synthesis of **1** and **2** was accomplished based on our previously reported procedures [15].

Fig. 1. Chemical structures of compounds **1** and **2**



Experimental. The suitable crystals for the X-ray analysis of compounds **1** and **2** were obtained from recrystallization of the final products using a mixture of dichloromethane and methanol in 1.5:8.5 and 8:2 ratios respectively.

X-ray diffraction study. Single crystal data collection for complexes **1** and **2** was performed at 173 K (–100 °C) on a Stoe Mark II-IPD system [16] equipped with a two-circle goniometer and using MoK_α graphite monochromated radiation. Diffraction data for **1** and **2** were collected using ω rotation scans of 0—180° at $\phi = 0°$ and of 0—180° at $\phi = 90°$ with a step $\Delta\omega = 1.0°$, exposures of 1 min per image, 2θ range = 2.29—59.53° and d_{min}—d_{max} = = 17.779—0.716 Å. The distance between the imaging plate and the sample was 100 mm. The structures were solved by direct methods using the SHELXS program; the refinement and further calculations were carried out using SHELXL [17]. For compound **1**, the H atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. A numerical absorption correction was applied using the X-SHAPE program [16]. For compound **2**, the bound H atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. A semi-empirical absorption correction was applied using the MULSCAN routine in PLATON [18]. For both **1** and **2** the non-H atoms were refined anisotropically, using weighted full-matrix least squares on F^2. The molecular structures of (**1**) and (**2**), along with the crystallographic numbering schemes are illustrated in the ORTEP [19] drawings, (Figs. 2, *b* and 3, *b* respectively). The crystal packing for **1** and **2** is illustrated in the PLATON [18] drawings (Fig. 2, *a* and *b* respectively). Selected bond distances and bond angles are given in Table 1. Crystal data and refinement details of compounds **1** and **2** are summarized below.

Compound **1**: $T = 173(2)$ K, $C_{25}H_{29}N_3O$, $FW = 387.51$, monoclinic, $P2_1/n$, $a = 17.739(2)$, $b = 9.0745(7)$, $c = 26.440(3)$ Å, $\beta = 106.507(9)°$, $V = 4080.7(8)$ Å^3, $Z = 8$, $D_{cal} = 1.262$ g/cm^{-3}, $\mu = 0.08$ mm^{-1}, $1.2 \le \theta \le 24.4°$, 26238 collected, 7708 unique, $R_{int} = 0.117$, 524 parameters, GOOF = = 0.58, *R* indices for $I > 2\sigma(I)$ $R1 = 0.038$, $wR2 = 0.088$, *R* indices(all data) $R1 = 0.145$.

Compound **2**: $T = 173(2)$ K, $C_{26}H_{30}N_2O$, $FW = 386.52$, triclinic, $P\bar{1}$, $a = 7.4101(15)$, $b = 12.372(3)$, $c = 13.441(4)$ Å, $\alpha = 63.950(18)$, $\beta = 85.56(2)$, $\gamma = 77.680(17)°$, $V = 1081.4(5)$ Å^3, $Z = 2$,

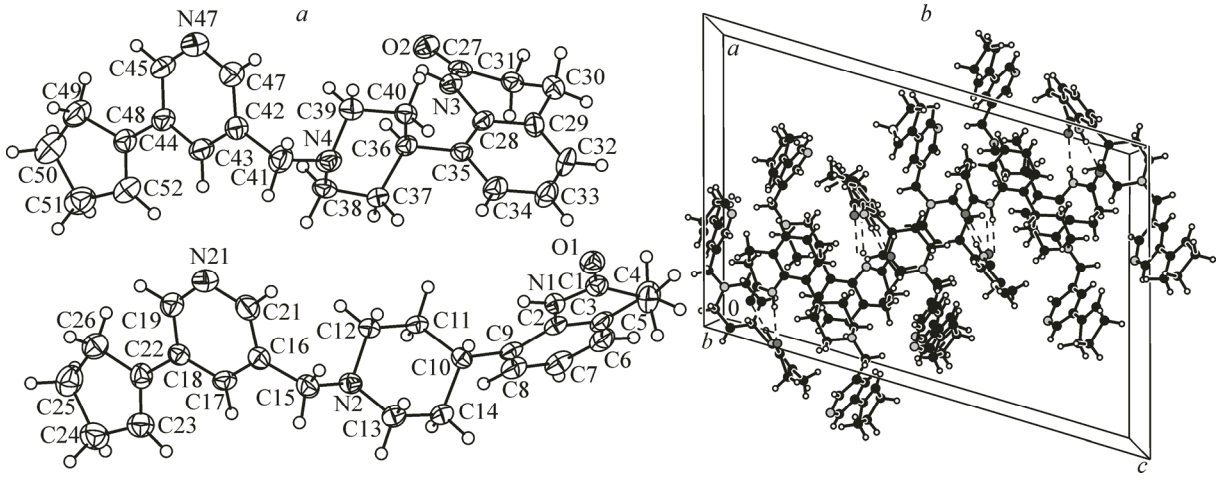


Fig. 2. An ORTEP view of the molecular structure of compound **1** with the atom labeling scheme and without the disordered phenyl ring (*a*). Displacement ellipsoids are drawn at the 50 % probability level and H atoms are shown as small spheres of arbitrary radii. A crystal packing drawing of compound **1** with the dotted line showing hydrogen bonding interactions (*b*)

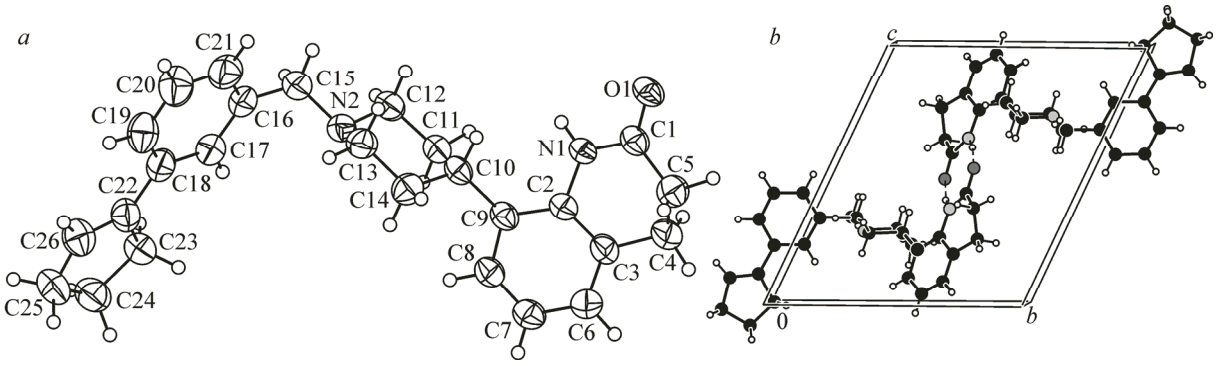


Fig. 3. An ORTEP structure with the atom labeling scheme of compound **2** (*a*). Displacement ellipsoids are drawn at the 50 % probability level and H atoms are shown as small spheres of arbitrary radii. A view of the crystal packing of compound **2**, showing N—H…O hydrogen bonding and C—H…O short contact interaction resulting in the formation of a two-dimensional network (*b*)

D_{cal} = 1.187 g/cm^{-3}, μ = 0.07 mm^{-1}, 1.7 ≤ θ ≤ 24.8°, 11913 collected, 3648 unique, R_{int} = 0.131, 267 parameters, GOOF = 0.80, *R* indices for $I > 2\sigma$ *R*1 = 0.069, *wR*2 = 0.178, *R* indices (all data) *R*1 = 0.127.

Results and discussion. The molecular structure of compound **1** with the molecular formula $C_{25}H_{29}N_3O$ is illustrated in Fig. 2. The suitable crystal for the X-ray analysis was obtained by recrystallization of the final product using a mixture of dichloromethane and methanol (2:8). In the asymmetric unit of compound **1** there are two independent molecules (A and B). The conformations of the two molecules are very similar. Each of the bridging piperidine rings has a *chair* conformation while the piperidinone rings of the dihydroquinolinone moieties have *screw boat* conformations. The C—O bond length of the carbonyl moiety of piperidinone rings are very similar in both molecules (Table 1). Likewise, other bond lengths are also similar in these molecules. The cyclopentenyl and pyridine rings of the cyclopean tenylpyridine moiety are inclined to one another by 8.54(16)° and 11.11(17)° in molecules A and B, respectively. The mean plane of the central piperidine ring is inclined to the benzene ring of the dihydroquinolinone moiety by 84.13(15)° in A and 75.50(14)° in B. However, central piperidine is inclined to the adjacent pyridine ring of the cyclopentenylpyridine moiety by 62.18(15)° in A and 75.04(14)° in B, respectively. In the crystal, individual molecules are linked by pairs of N—H···O hydrogen bonds forming A—A and B—B inversion dimers with $R_2^2(8)$ ring motifs [18, 19]. The dimers are stabilized by N—H···O hydrogen bonds and are linked via C—H···O short contact interactions,

T a b l e 1

Selected bond lengths (Å) *and bond angles* (deg.) *in compounds* **1** *and* **2**

Bond length		Bond angles		Bond length		Bond angles	
Compound **1**				Compound **2**			
O1—C1	1.241(3)	C1—N1—C2	124.7(2)	O1—C1	1.256 (4)	C1—N1—C2	126.08(3)
N1—C1	1.353(3)	C15—N2—C12	110.2(2)	N1—C1	1.336 (4)	C15—N2—C12	109.5(3)
N1—C2	1.426(4)	C15—N2—C13	107.8(2)	N1—C2	1.428 (4)	C15—N2—C13	112.6(3)
N2—C15	1.457(3)	C12—N2—C13	109.1(2)	N2—C15	1.448 (4)	C12—N2—C13	109.8(3)
N2—C12	1.481(3)	O1—C1—N1	120.8(3)	N2—C12	1.464 (4)	O1—C1—N1	121.3(3)
N2—C13	1.485(3)	O1—C1—C5	123.5(3)	N2—C13	1.465 (4)	O1—C1—C5	122.3(3)
C1—C5	1.485(4)	N1—C1—C5	115.7(3)	C1—C5	1.478 (5)	N1—C1—C5	116.3(3)
C2—C3	1.390(4)	C3—C2—C9	121.1(3)	C2—C3	1.393 (4)	C3—C2—C9	121.7(3)
C2—C9	1.417(4)	C3—C2—N1	118.4(3)	C2—C9	1.397 (4)	C3—C2—N1	117.5(3)
C4—C38	1.447(4)	C9—C2—N1	120.5(3)	C3—C6	1.392 (5)	C9—C2—N1	120.7(3)
N4—C41	1.453(3)	C6—C3—C2	119.2(3)	C3—C4	1.504 (5)	C6—C3—C2	118.8(3)
N4—C39	1.468(3)	C6—C3—C4	121.7(3)	C4—C5	1.482 (5)	C6—C3—C4	123.2(3)
O2—C27	1.242(3)			C6—C7	1.372 (6)		

forming a three-dimensional network as shown in Fig. 2, *b*. The hydrogen bond angles and bond lengths of compound **1** are given in Table 2.

The molecular structure of compound **2** with the molecular formula $C_{26}H_{30}N_2O$ is shown in Fig. 3. The suitable crystal of the compound for the X-ray analysis was obtained by recrystallization from a mixture of CH_2Cl_2 and CH_3OH in the 8:2 ratio. The bridging piperidine ring has a *chair* conformation while the piperidin-2-one ring of the dihydroquinolinone moiety has a *screw boat* conformation. The cyclopentenyl and benzene rings of the cyclopentenylbenzene moiety are inclined to one another by 4.2(2)°. The plane angle of the central piperidine ring inclined to the benzene ring of the dihydroquinolinone moiety is 81.33(18)°, whereas it is inclined to the adjacent benzene ring of the cyclopentenylbenzene moiety by 89.99(18)°. In the crystal, individual molecules are linked by pairs of N—H···O hydrogen bonds forming A—A and B—B inversion dimers, with $R_2^2(8)$ ring motifs [20, 21]. The dimer is stabilized by N—H···O hydrogen bonds, and linked via C—H···O short contact interactions forming a two-dimensional network. The network is further stabilized by a number of C—H···π interactions as shown in Fig. 3, *b*. The hydrogen bond angles and bond lengths of compound **2** are given in Table 2.

Table 2

Hydrogen-bond geometry (Å, deg.) *in compounds* **1** *and* **2**

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
Compound **1**				
N1—H1*N*···O2^{i}	0.88	2.06	2.922(3)	167
N3—H3*N*···O1^{ii}	0.88	2.18	3.030(3)	161
C31—H31*B*···N4^{ii}	0.99	2.55	3.487(3)	157
Compound **2**				
N1—H1*N*···O1^{i}	0.85(3)	2.04(4)	2.881(4)	169(3)
C5—H5*A*···O1^{ii}	0.99	2.53	3.450(6)	155

Symmetry codes compound **1**: ^{i} –*x*+1/2, *y*+1/2, –*z*+1/2; ^{ii} –*x*+1/2, *y*–1/2, –*z*+1/2; compound **2**: ^{i} –*x*+1, –*y*+1, –*z*+1; ^{ii} –*x*+2, –*y*+1, –*z*+1.

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Supplementary crystallographic data with CCDC deposit numbers are 992407and 992408 for complexes **1** and **2**, respectively and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(0)1223-336033.

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