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Crystal Structures of Aripiprazole, a New Anti-psychotic Drug, and of Its Inclusion Compounds with Methanol, Ethanol and Water

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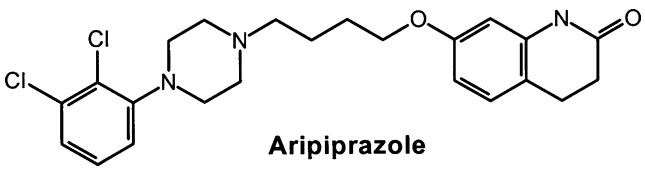
Abstract

Aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, is an important new neuroleptic drug used in the treatment of schizophrenia and related psychoses. This study elucidates its detailed molecular structure and two preferred conformational forms, and relates to the solvates of this compound when crystallized from different environments. The latter is associated with the hydrogen-bonding capacity of aripiprazole through the piperazinyl and dihydrocarbostyril functions. Four unique crystal forms of this compound have been characterized using X-ray single crystal determinations, including an anhydrous structure (**1**), methanol (**2**) and hemi-ethanol (**3**) solvates and a hydrate (**4**). They were found to consist of hydrogen bonded dimers of the aripiprazole moieties that involve the cyclic $(–NH–CO–)_2$ di-amide interaction synthon in **1**–**3** (with the solvent molecules attached to them in **2** and **3**), or of hydrogen bonded polymeric aggregates sustained by extended multiple bonding through water bridges in **4**. These modes of supramolecular association involve two different conformers with similar energy of the drug moiety.

Introduction

Aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydrocarbostyril, is an important anti-psychotic drug for treating psychoses (e.g., schizophrenia), and is available for oral administration (FDA approval, Nov. 2002). Although the actual mechanism of action of aripiprazole is unknown, it is believed that its beneficial effect is due to its high affinity for dopamine (e.g., D_2 and D_3) and serotonin (5-HT_{1A} and 5-HT_{2A}) receptors. Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as antagonists at serotonin 5-HT_{2A} receptor. Thus, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors [1]. As for many other drug compounds containing aliphatic chains and saturated rings in their molecular framework, aripiprazole, exhibits high propensity for conformational isomerism (and potential polymorphism) [2], as e.g., its therapeutic competitor Olanzapine [3]. Bearing proton-donating and proton-accepting sites of hydrogen-bonding capacity, it is also readily exposed to interaction with polar and protic species to yield various inclusion compounds (solvates and hydrates) [3]. In view of the importance of solid crystalline aripiprazole in pharmaceutical formulations [1], we describe here precise structural characterizations of the anhydrous compound (**1**), its methanol (**2**) and hemi-ethanol (**3**) solvates, as well as of its hydrate (**4**). The structural results throw light on the conformational flexibility and the molecular recognition features of the aripiprazole framework (Scheme 1), and demonstrate its potential to yield diverse solvated structures.



Scheme 1.

Experimental

Single crystals of pure aripiprazole (**1**) suitable for X-ray diffraction analysis (m.p. 136–138 °C) were obtained by dissolving its solid powder (supplied by Teva, Pharmaceutical Industries, Ltd.) in 1,4-dioxane at 80 °C, followed by slow cooling and evaporation of the solvent. Similar crystallizations from polar protic solvents as methanol, ethanol and a mixture of acetone and water afforded single crystals of the corresponding solvates **2** (**1**·MeOH) and **3** (**1**·½EtOH), and a hydrate **4** (**1**·H_2O), respectively. All additional attempts to crystallize other

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polymorphs of aripiprazole or to obtain different solvates yielded either **4** (when other solvent mixtures containing water were used), or **1** (when dry aprotic solvents as THF or benzene were applied).

The X-ray measurements (Nonius Kappa CCD diffractometer, MoKα radiation) were carried out at ca. 110 K to $2\theta_{max} = 55°$, on crystals coated with a thin layer of amorphous hydrocarbon oil in order to minimize deterioration, possible structural disorder and related thermal motion effects, and to optimize the precision of the crystallographic results. The crystal and experimental data are summarized in Table 1. These structures were solved by direct methods (SIR-97), and refined by full-matrix least-squares on F^2 (SHELXL-97) [4]. All non-hydrogen atoms were refined anisotropically. Most of the hydrogen atoms were located in idealized positions, and were refined using a riding model, with $U_{iso} = 1.2\ U_{eq}$ or $1.5\ U_{eq}$ of the parent atom. Those attached to N and O atoms were positioned from difference-Fourier maps. Crystals of **1** contain two molecules, approximately mirror images of one another, of the drug in the asymmetric unit. In **3**, the ethanol species are located on, and disordered about, centers of inversion. In **4**, the dihydrocarbostyril ring has a disordered conformation with the carbonyl group deviating either up or down from the plane of the ring (the disorder of the adjacent ring atoms is apparent from their elongated ellipsoids, but it could not be resolved reliably). The water molecule hydrogen-bonded to this carbonyl appears to be disordered between two positions. In spite of the latter, the crystallographic refinements of all structural models converged smoothly to relatively low *R*-values, thus resulting in reliable characterizations of the molecular structures and supramolecular organization in the corresponding solids. Ortep plots of the molecular structures in the four crystalline phases are shown in Figure 1. The composition of **1**–**4** was confirmed by thermal analysis. The lowest onset temperature of solvent desolvation was observed to be 76.3 °C in **2**.

CCDC reference numbers 285533–285536.

Results and discussion

Aripiprazole consists of four linked residues: a rigid 2,3-dichlorophenyl ring, a piperazinyl entity in the stable chair conformation that is linked equatorially to neighboring moieties through the two N-atoms, an *n*-butoxyl fragment, and a dihydrocarbostyril group. It also bears sites of hydrogen bonding capacity, of particular significance in directing the intermolecular organization in the crystal. The –NH–CO– amide fragment provides one strong proton donor and one strong proton acceptor sites, and self-complementary hydrogen-bonding features. It can be used in the formation of intermolecular dimeric assemblies, similar to the well-known synthons of carboxylic acid dimers [5]. The ether O-site (O1) has a very weak affinity for hydrogen bonding. Tertiary amines, as the piperazinyl N-atoms,

Table 1. Crystal data and experimental parameters of the structural analysis

Compound*	**1**	**2**	**3**	**4**
Formula weight	448.38	480.42	471.41	466.39
Crystal system	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	P $\bar{1}$	P $\bar{1}$	P $\bar{1}$	P $2_1/n$
T, °C	−163(2)	−163(2)	−163(2)	−163(2)
A, Å	10.1499(3)	8.3928(3)	7.6582(2)	7.9880(1)
B, Å	12.0800(4)	10.1051(3)	10.6525(2)	27.9025(5)
C, Å	18.6028(7)	15.2474(7)	15.2924(5)	10.6159(2)
α, deg.	82.759(2)	84.083(1)	84.627(1)	90.0
β, deg.	81.447(2)	82.484(1)	78.899(1)	105.921(1)
γ, deg.	83.246(2)	66.731(2)	73.140(1)	90.0
V, Å^3	2226.2(1)	1175.9(1)	1170.63(5)	2275.37(7)
Z	4	2	2	4
μ(MoKα), mm^{-1}	0.32	0.31	0.31	0.32
ρ_{calcd}, g cm^{-3}	1.338	1.357	1.337	1.361
Data collected	18,255	9027	8409	10,203
Unique reflections	9469	4920	4843	4896
R_{int}	0.041	0.044	0.026	0.022
Data with $I > 2\sigma$	7095	2960	3607	3801
Refined parameters	543	294	291	301
R ($I > 2\sigma$)	0.052	0.053	0.046	0.045
R (all data)	0.079	0.105	0.068	0.063
R_w ($I > 2\sigma$)	0.100	0.114	0.112	0.110
R_w (all data)	0.111	0.135	0.126	0.121
$\lvert\Delta\rho\rvert_{max}$ e·Å^{-3}	0.37	0.32	0.37	0.48

*Chemical formulae: **1** – $C_{23}H_{27}Cl_2N_3O_2$; **2** – $C_{23}H_{27}Cl_2N_3O_2 \cdot CH_4O$; **3** – $C_{23}H_{27}Cl_2N_3O_2 \cdot \frac{1}{2}(C_2H_6O)$; **4** – $C_{23}H_{27}Cl_2N_3O_2 \cdot H_2O$.

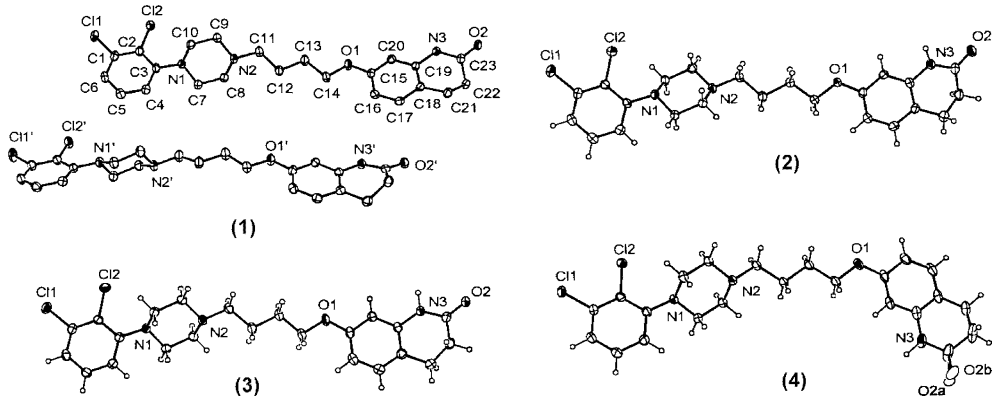

Figure 1. Ortep plots of the aripiprazole molecular structures in **1–4** (showing 50%-probability thermal displacement ellipsoids and the atom labeling scheme which is the same in the four structures). The crystallization solvent is omitted. Note the two nearly mirror-related molecules in the asymmetric unit of **1**, with atoms denoted by unprimed and primed labels, respectively. The hydrogen atoms were excluded for clarity in this part of the Figure, to allow assignment of the atomic labels. Note also the ~180° different orientation of the dihydrocarbostyril moiety around the O1–C15 bond in **4** than in **1–3**. The N, O, and Cl atoms are represented by darkened ellipsoids (except for the disordered O2 in **4**).

are generally somewhat stronger proton acceptors. In the present case, however, this applies only to the N2 rather than the N1 atom, as the nonbonding electron pair of the latter is partly de-localized into the adjacent dichlorophenyl ring.

The observed molecular structures of the anhydrous compound and its three solvates (Figure 1), are characterized by essentially the same conformational features of the dichlorophenyl-piperazinyl-butoxyl fragment, as shown in Table 2 and in the supplementary detailed torsion angle data (in the corresponding CIF files). The conformationally flexible *n*-butoxyl moiety remains in its least sterically hindered fully extended form, the relative orientation of the dichlorophenyl and the piperazinyl groups is within a narrow range in either one of the enantiomeric entities (the dihedral angles between the mean planes of the phenyl ring C1–C6 and of the four C-atoms of the piperazinyl ring are 47.2 and 48.4, 43.5, 47.5 and 45.9 in **1**, **2**, **3**, and **4**, respectively), the latter preserving in all cases its stable chair shape. The four structures differ more, however, in the conformational aspects about the O1–C15 bond. Thus, in **1–3** slight, though significant, variations (within the range of up to 10°) are observed in the orientation of the peripheral dihydrocarbostyril ring with respect to the *n*-butoxyl chain (Table 2). Structure **4** consists, however, of an entirely different conformer. It involves rotation of the dihydrocarbostyril moiety by 170–180° about the O1–C15 bond in relation to the molecular conformations observed in **1–3**, yielding a folded (as opposed to extended) molecular conformation of the aripiprazole, in which the Cl-substituents and the amide residue are located on opposite sides of the principal molecular axis. Minor variations of ring puckering (Table 2) occur also in the saturated dihydroquinolinone group that adopts an 'envelope' conformation, wherein the C22, C23 and

Table 2. Selected conformational data for structures **1–4**

Compound	**1**[a]	**2**	**3**	**4**
Torsion angles (°)				
C7–N1–C3–C2	158.6(2), −157.7(2)	162.7(2)	−159.3(2)	−159.9(2)
C10–N1–C3–C2	−71.4(3), 73.8(3)	−70.2(3)	73.2(3)	70.9(2)
C8–N2–C11–C12	70.3(2), −75.2(3)	74.9(3)	−71.9(2)	−67.9(2)
C14–O1–C15–C16	−4.5(3), −1.5(3)	2.2(4)	5.1(3)	176.6(2)
C14–O1–C15–C20	175.3(2), 178.1(2)	−179.5(2)	−173.8(2)	−3.3(3)
C19–C18–C21–C22	33.6(3), −31.6(3)	−32.8(4)	33.8(3)	−30.8(3)
C18–C21–C22–C23	−49.4(3), 49.1(3)	44.6(4)	−51.2(2)	47.4(3)
C21–C22–C23–N3	34.4(3), −38.7(3)	−29.3(4)	35.2(3)	−35.5(4)
C19–N3–C23–C22	−0.7(3), 7.7(3)	−1.1(4)	1.5(3)	4.4(4)
Deviation of atoms C22, C23 and O2 from the plane of the C15–C20 phenyl ring (Å)				
C22	0.659(4), −0.680(4)	−0.642(5)	0.871(4)	0.585(4)
C23	0.272(4), −0.235(4)	−0.360(5)	0.442(4)	0.1733(4)
O2	0.245(5), −0.112(5)	−0.481(6)	0.508(4)	0.416(5)[b]
				−0.223(6)

[a]In **1** there are two molecules in the asymmetric unit. The left and right columns relate to molecules designated by unprimed and primed atomic labels, respectively.

[b]In **4** the conformation of the dihydroquinolinone ring is disordered. While in the C atoms the disorder could not be resolved, two possible positions were assigned to O2 in the final structural model.

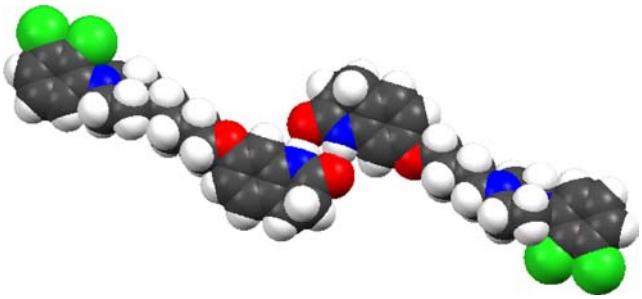

Figure 2. Space-filling illustration of the N3–H···O2=C hydrogen-bonded dimers of the aripiprazole species formed in structures **1**–**3** (Table 3). Color code in the Web version of this paper: C – black, N – blue, O – red, Cl – green and H – white.

O2 atoms show slightly different deviations from the plane of the adjacent phenyl residue (C15 through C20).

Semi-empirical force-field calculations were carried out with several different force-field potentials, in order to assess the relative energies of the two conformers in an isolated form, using the observed structures as input models [6]. The outcome of these calculations (which involved minor geometric optimization, e.g., of the C–H bond lengths, of the two models by energy minimization) indicated clearly that the observed conformations represent two equally stable (within 1 kcal/mol) structures of the aripiprazole.

The intermolecular organization of aripiprazole is strongly affected by the molecular recognition features of its molecular framework. In structures **1**–**3** it is dominated by the self-complementary hydrogen-bonding capacity of the amido group. This leads to the formation of di-amido dimers sustained by cyclic four-point hydrogen bonding, as depicted in Figure 2 [5]. In **1,** the elongated dimeric entities align parallel to one another in the crystal, their packing being stabilized by common dispersive/van der Waals interactions (Figure 3). Noteworthy are only the relatively short nonbonding contacts between neighboring molecules Cl2···N2′ (at x, $y+1$, z) of 3.675 Å and Cl2′···N2 (at $x-1$, y, z) of 3.187 Å.

Presence of additional (though weak) proton acceptors in the molecule, and absence of complementary proton donors, provides the driving force for possible co-crystallization of the aripiprazole with protic solvents and occurrence of pseudo-polymorphism in this compound. The methanol solvate of aripiprazole, **2**, serves as a simple example to this end. Thus in **2**, in addition to the cyclic di-amido dimerization involving the strongest proton donors and acceptors of this compound, a methanol species is included in the lattice by hydrogen bonding to one of the piperazinyl N-atoms. The solvated dimers can still crystal-pack efficiently parallel to one another in an offset manner, to allow the methanol entities bound to one dimer to protrude between adjacent dimeric species (Figure 4).

Another example is provided by the ethanol solvate **3**, which reveals rather similar molecular recognition features. Aripiprazole associates again into elongated dimeric units, and the ethanol molecule is attracted by hydrogen bonding to the N2 atom of the piperazinyl ring (Table 3). Consistent with the 2:1 aripiprazole:ethanol stoichiometry in this structure, the solvent molecule is disordered between two anti-parallel orientations thus interacting only with 50% of the N2 atoms. At any given site of the crystal its OH function hydrogen bonds to one drug molecule, while its terminal methyl group points at the piperazinyl ring of another species (Figure 5).

The four-point cyclic dimeric hydrogen bonding, which is preserved in structures **1**–**3**, represents a robust intermolecular interaction, characteristic of amides [5]. Yet it can be disrupted in the presence of other polar components with strong proton-donating and proton-accepting capacity, which can successfully compete with the amide group for preferred hydrogen bonding. In the present context it has been realized by crystallizations of the aripiprazole from a number of aqueous mixtures of various polar solvents. These experiments yielded in all cases the same crystal structure **4** of a monohydrated aripiprazole compound in which the dihydrocarbostyril residue adopts an alternative orientation with respect to the remaining fragment of the molecule (in relation to the molecular conformation observed in **1**–**3**) and imparts a bent shape to it (Figure 1). Inspection of the intermolecular organization in **4** provides a possible explanation of this conformational flip. Thus, the polar water molecule incorporated into the lattice can make much stronger, and less sterically hindered, hydrogen bonds than the methanol or ethanol species in the other structures. In the correspondingly self-assembled structure **4** the water species were found to induce the formation of polymeric chains sustained by multiple hydrogen bonds with optimal involvement of all hydrogen-bonding functions, as shown in Figure 6. They cluster in pairs across centers of inversion, and every pair interlinks with six surrounding molecules of aripiprazole by hydrogen bonding to their NH3, N2 and

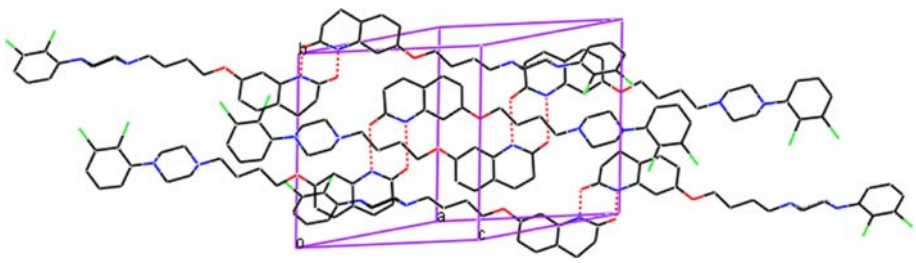

Figure 3. Crystal structure of **1**, showing the intermolecular organization of the di-amido dimers. The N–H···O=C hydrogen bonds are indicated by red dotted lines. Color code in the Web version of this paper: C – black, N – blue, O – red and Cl – green (H-atoms are omitted for clarity).

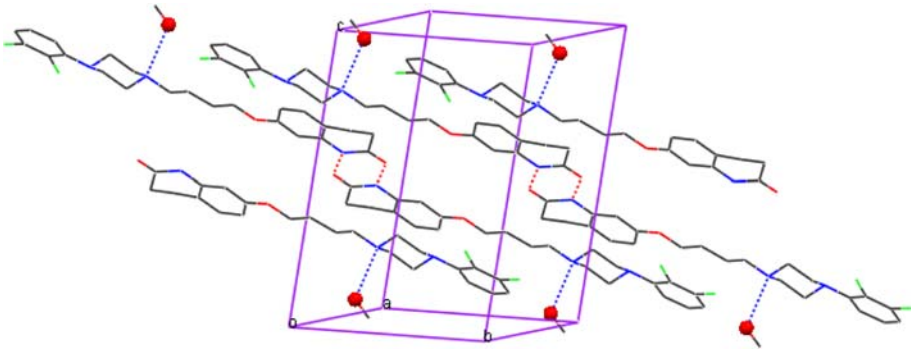

Figure 4. Crystal structure of **2**, showing the intermolecular organization of the methanol solvated di-amido dimers. The N–H···O = C hydrogen bonds within these dimers are indicated by red dotted lines. The O-atom of the methanol solvent is marked by a small sphere, and the O–H(methanol)···N(aripiprazole) hydrogen bonds are indicated by blue dotted lines. Color code in the Web version of this paper: C – black, N – blue, O – red, and Cl – green (H-atoms are omitted for clarity).

Table 3. Hydrogen-bonding parameters

O–H	A(O/N)	O–H (Å)	H···A (Å)	O···A (Å)	O–H···A (°)
Compound **1**					
NH(3)	O2 (2−*x*, 1−*y*, 1−*z*)	0.85	2.00	2.843(2)	178
NH(3′)	O2′ (1−*x*, −*y*, 1−*z*)	0.84	2.02	2.855(2)	173
Compound **2**					
NH(3)	O2 (1−*x*, *y*−2, 1−*z*)	0.88	2.03	2.903(3)	170
OH(3)[a]	N2 (2−*x*, 1−*y*, 1−*z*)	1.04	1.87	2.855(3)	158
Compound **3**					
NH(3)	O2 (2−*x*, 3−*y*, −*z*)	0.99	1.87	2.858(2)	178
OH(3)[b]	N2 (1−*x*, 1−*y*, 1−*z*)	0.92	1.95	2.854(3)	166
Compound **4**[c]					
NH(3)	O3a (*x*−1, *y*, *z*)	0.98	1.93	2.858(3)	159
NH(3)	O3b (*x*−1, *y*, *z*)[b]	0.98	2.08	3.038(3)	179
OH(3a)	N2 (*x*, *y*, *z*)	–	–	2.962(3)	–
OH(3b)	N2 (*x*, *y*, *z*)	–	–	2.619(3)	–
OH(3b)	O2a (−1−*x*, −*y*, 2−*z*)	–	–	2.912(3)	–
OH(3a)	O3b (1−*x*, −*y*, 2−*z*)	–	–	2.825(3)	–

[a]Methanol OH.
[b]Ethanol OH.
[c]O3a and O3b are two disordered sites of water.

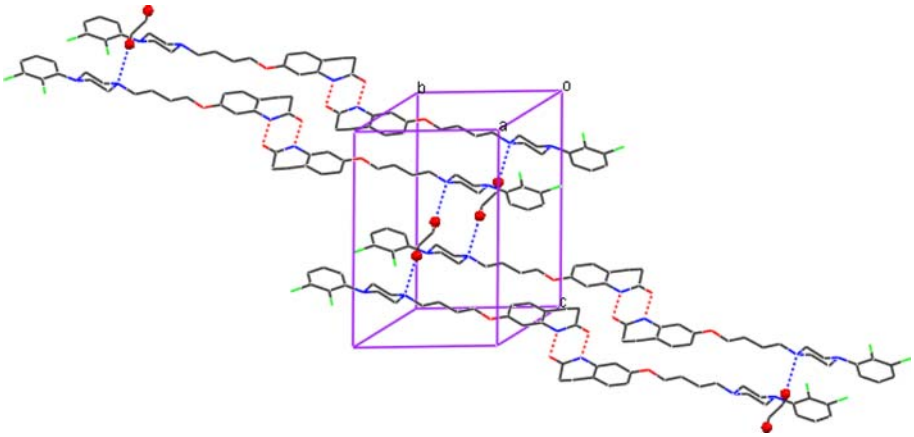

Figure 5. Crystal structure of **3**. Note the conserved expanded conformation of the molecules. The N–H···O = C hydrogen bonds within the H-bonded dimers are indicated by red dotted lines. The alternating O-atom positions (each with 50% occupancy) of the orientationally disordered ethanol solvent are shown as small spheres, and the possible O–H(ethanol)···N(aripiprazole) hydrogen bonds are indicated by blue dotted lines. Color code in the Web version of this paper: C – black, N – blue, O – red and Cl – green (H-atoms are omitted for clarity).

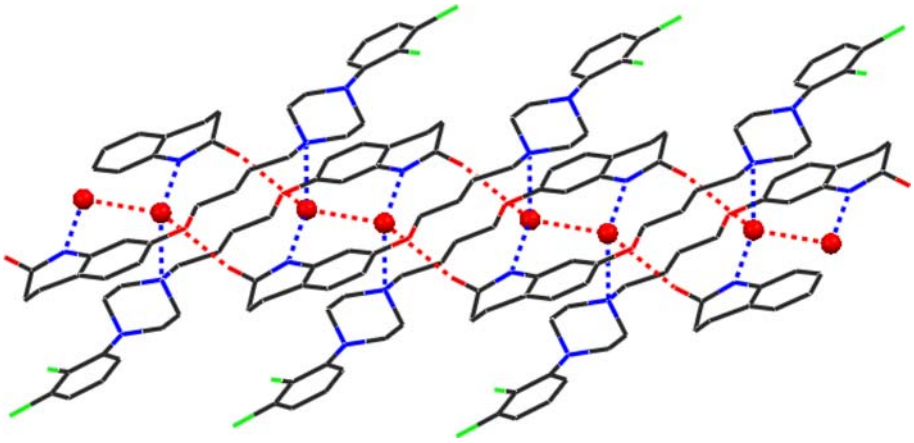

Figure 6. The extended polymeric hydrogen-bonding scheme in **4**. Small red spheres indicate the bridging water molecules (each representing an average position between the two disordered sites O3a and O3b). Every water site lies in hydrogen-bonding proximity to three different drug moieties and another water (Table 3), creating hydrogen-bonded chains that propagate throughout the crystal. The O···O and N···O hydrogen-bonding interactions are denoted by red and blue dotted lines, respectively. Color code in the Web version of this paper: C – black, N – blue, O – red and Cl – green (H-atoms are omitted for clarity).

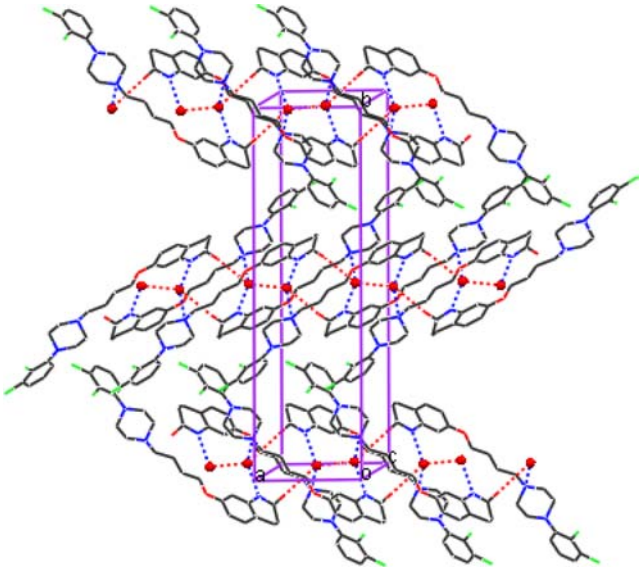

Figure 7. Crystal structure of **4**, showing three hydrogen-bonded chains centered at $y = 0$, ½ and 1. Note the outline of the dichlorophenyl residues at the interface between the chains. Small red spheres indicate the average position of the water molecules. The O···O and N···O hydrogen-bonding interactions are denoted by red and blue dotted lines, respectively. Color code in the Web version of this paper: C – black, N – blue, O – red and Cl – green (H-atoms are omitted for clarity).

(partly, due to the positional disorder of the water) C = O2 sites (Table 3). In fact only one of the twofold disordered water sites lies in hydrogen bonding proximity to O2.

The polymeric arrays, lined on both sides with the C–Cl bonds, propagate parallel to the **a**-axis of the crystal (Figure 7). Their tight packing along the **b** (in a herringbone manner) and **c** directions is stabilized by common van der Waals forces. Noteworthy also are specific Cl1···Cl2 interactions at 3.613 Å [7], between molecules related by the *n*-glide plane, at the inter-array interfaces at $y = \frac{1}{4}$ and $y = \frac{3}{4}$.

The above results provide yet another example of an organic compound of pharmaceutical significance which readily forms various solvate structures, due to its conformational flexibility (with at least two conformers of similar stability) and strong affinity for hydrogen bonding bearing proton-donating as well as proton-accepting sites distributed along its framework [2, 3]. In fact, the observed intermolecular organization is directed by optimization of the hydrogen bonding interactions (and thus of their stabilizing enthalpic contribution), in accordance with well-established hierarchy of hydrogen bond formation in organic crystals [8, 9]. The above crystal-engineering-related features (variable conformation and diverse hydrogen-bonding potential) of the aripiprazole moiety, along with the nature of the interacting solvent, results in the occurrence of polymeric as

well as dimeric supramolecular assemblies in these materials sustained by hydrogen bonding synthons little affected by steric hindrance. The elongated shape of the former facilitates tight crystal packing between the uncoordinated surfaces of the molecular units by favorable dispersion, whether in the anhydrous or the solvated forms, all structures being characterized by nearly the same density and lack of any additional void space in the corresponding crystals. Any drug design process of pharmaceutically active organic species of similar type should thus take into account the high potential of their appearance in diverse solvated forms. While such phenomena can be often a nuisance in a large-scale manufacturing process, they also affect the physical properties of the pharmaceutical solids in question and can be advantageously explored in directing production of the preferred form of the drug. To the best of the authors' knowledge, this study provides the first detailed crystallographic characterization report of this important pharmaceutical agent. Further evaluations are needed to explore in full all possible crystal forms of this compound.

Acknowledgement

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