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An Investigation Into Vortioxetine Salts: Crystal Structure, Thermal Stability, and Solubilization

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ABSTRACT

Three 1:1 salts containing vortioxetine (VOT), an orally antidepressant drug, and 3 aryl monoacids have been designed and successfully prepared by liquid-assisted grinding based on the ΔpK_a rule. The C-O bond lengths (~1.25 Å) in the COOH groups show that the proton transfer has occurred from aryl monoacid to piperazine N1 atom of vortioxetine in the crystal structures. Three salts feature cyclic [2 + 2] structural units through $R^4_4(12)$ N—H···O hydrogen bonding interactions which result in the remarkable thermal stabilities, and VOT—*p*-aminobenzoic acid shows 2-dimensional framework by linking cyclic [2 + 2] units through additional hydrogen bonding interactions. The equilibrium solubility of VOT in VOT—*p*-aminobenzoic acid salt can be largely improved up to 0.50 mg/mL (about 450% above the free base) at 25°C in water, which also accelerates the intrinsic dissolution rate.

Introduction

The cocrystal and salt form are the most common and important modification to improve the physicochemical properties of drugs, for example, thermal stability, solubility, dissolution rate, and bioavailability.[1-3] Sometimes, the cocrystal and salt are simultaneous occurrence in some drug. Recently, the design rule and synthesis of cocrystal/salt have made great progress based on the ΔpK_a rule [$\Delta pKa = pKa(base) - pKa(acid)$]: salt formation requires at least 3 units pK_a difference.[4-6]

Vortioxetine, 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (abbreviated as VOT), is a new chemical class of bis-arylsulfanyl amine psychotropics for the treatment of major depressive disorder as the serotonin reuptake inhibitor with an activity on serotonin receptor 1A (5-HT_{1A}) and the serotonin receptor 3 (5-HT_3) in adults.[7-9] Vortioxetine features low solubility and basic nature because of the presence of secondary amine group (pK_a of N1 8.85). Therefore, vortioxetine is marketed under the brand name Brintellix in the form of VOT·HBr salt approved by Federal Food and Drug Administration on September 30, 2013, which is an immediate-release tablet for oral administration.[10] VOT is very easy to form a pharmaceutically acceptable salt with different acid, such as HCl, fumarate, maleate and lactic acid, and so forth.[11-13] However, these salts are found to form easily polymorphs or the salt solvates.[11] To search for pharmaceutically applicable salt forms based the ΔpK_a rule, 3 aryl monocarboxylic acids, *p*-toluic acid (PTA), *p*-nitrobenzoic acid (PNA), and *p*-aminobenzoic acid (PAA), are selected to investigate the salt formation and formation process in solution and solid forms. The solubilities and intrinsic dissolution rates are also investigated in details.

Experimental

Materials

Vortioxetine (>99%) was purchased from Shanghai Neosun Pharmaceutical Technology Co. Ltd., China. The acids (purity: ≥99.0%) were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. All solvents (analytical grade) were obtained commercially without further purification.

Nuclear Magnetic Resonance

Nuclear magnetic resonance spectra were recorded on the Bruker 400 MHz instrument using d_6-DMSO as solvent and TMS as an internal standard.

Thermogravimetric and Differential Scanning Calorimetry

Thermogravimetric and differential scanning calorimetry (TG-DSC) experiments were carried out in Netzsch TG STA449C

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Table 1
Crystallographic Parameters of 3 VOT Salts

Variable	VOT-PTA	VOT-PNA	VOT-PAA
Chemical formula	$C_{18}H_{23}N_2S\cdot C_8H_6O_2$	$C_{18}H_{23}N_2S\cdot C_7H_4NO_4$	$C_{18}H_{23}N_2S\cdot C_7H_6NO_2$
Formula weight	434.58	465.56	434.56
Space group	Monoclinic	Monoclinic	Monoclinic
T (K)	298	298	298
a (Å)	7.2773(4)	11.7591(16)	19.463(5)
b (Å)	26.6653(13)	6.6784(9)	8.424(2)
c (Å)	12.4565(6)	30.147(4)	14.870(4)
β (deg)	103.869(3)	93.664(3)	102.078(4)
V ($Å^3$)	2346.7(2)	2362.7(6)	2384.0(10)
Z	4	4	4
D_{calc} (g/cm^3)	1.230	1.217	1.211
μ (mm^{-1})	0.163	0.174	0.161
R_1	0.0446	0.0524	0.0483
ωR_2	0.1120	0.1344	0.1353
Goodness-of-fit	1.043	1.041	1.033
Continuous Change Detection and Classification algorithm	1454623	1454624	1454625

equipment with the heating rate of 10°C/min under a nitrogen gas purge with a flow of 20 mL/min. The samples are about 5-10 mg.

Infrared Spectroscopy

Fourier infrared spectra were performed on a Bruker Vector 33 in the 4000-400 cm^{-1} range. The ground solid-state samples (about 15-20 mg) were tableted with KBr.

Powder X-Ray Diffraction

Powder X-ray diffraction (PXRD) patterns were obtained with a German Bruker corporation D8 ADVANCE powder diffractometer coupled with a Cu Kα radiation tube (λ = 1.5418 Å, V = 40 kV, and I = 40 mA) and 2θ scan in the 3°-60° range.

Single-Crystal X-Ray Crystallography

All the single-crystal data were determined using a Bruker Apex II CCD diffractometer operating at 50 kV and 30 mA using Mo Kα radiation (λ = 0.71073 Å), and the structures were solved by direct methods using SHELXS program and refined with SHELXL program.[14] The final refinements were performed by full-matrix least-squares methods with anisotropic thermal parameters for all nonhydrogen atoms on F^2.[15] The hydrogen atoms on noncarbon atoms were located from difference Fourier maps and the hydrogen atoms riding on the carbon atoms were determined with theoretical calculation and refined isotropically. Crystallographic parameters are listed in Table 1.

Crystallization

The samples were prepared by the quick and green method: liquid-assisted grinding.[16] All the crystals suitable for X-ray diffraction were obtained through the slow evaporation of the corresponding solution. The salts were confirmed by ^{1}HNMR, IR, PXRD, and TG-DSC.

VOT-PTA Salt (1:1)

A total of 500 mg VOT (1.68 mmol) and 225 mg PTA (1.68 mmol) were ground in an agate mortar for 30 min using CH_3CN as solvent. Then, 30 mg of the ground material was dissolved in 6 mL of hot CH_3CN and left for slow evaporation at room temperature after filtrating. The colorless needle crystals were obtained after 8 days that were suitable for X-ray diffraction. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.82 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.7 Hz, 3H), 7.15-7.05 (overlap, 3H), 6.92 (m, 1H), 6.39 (d, J = 7.6 Hz, 1H), 3.00 (s, 8H), 2.35 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H).

VOT-PNA Salt (1:1)

The VOT-PNA solid was obtained by similar method of VOT-PTA with ethyl acetate as solvent. The colorless needle crystals were obtained in ethyl acetate after 5 days for slow evaporation at room temperature. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.21 (d, J = 7.9 Hz, 2H), 8.11 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.24 (s, 1H), 7.18-7.04 (overlap, 3H), 6.95 (m, 1H), 6.48-6.35 (m, 1H), 3.18 (dd, J = 13.6, 4.6 Hz, 8H), 2.33 (s, 3H), 2.25 (s, 3H).

VOT-PAA Salt (1:1)

The VOT-PAA solid was obtained by similar method of VOT-PTA with ethyl acetate as solvent. ^{1}H-NMR(400 MHz, d_6-DMSO): δ 7.61 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.23 (s, 1H), 7.11-7.08 (overlap, 3H), 6.89 (m, 1H), 6.54 (d, J = 7.7 Hz, 2H), 6.38 (d, J = 7.7 Hz, 1H), 5.84 (s, 2H), 2.89 (dd, J = 8.5, 3.2 Hz, 8H), 2.32 (s, 3H), 2.23 (s, 3H).

Equilibrium Solubility and Dissolution Rate Measurements

Equilibrium solubility was measured in water using the shake-flask method.[17] An excess amount of the salt was added in double-distilled water, and the resulting suspension was shaken for 24 h at 25°C. After equilibration, the suspension was filtered through 0.25-μm syringe filter, and the concentration of the salt was quantified by high-performance liquid chromatography

Table 2
Basic Properties and Solubilization of VOT and 3 Salts in the Water

Compound	pKa	△pKa	Stoichiometric Ratio	Equilibrium Solubility (mg/mL)	IDR in Water ($\times 10^{-2}$ mg/min/cm)
VOT	8.85(N1)			0.09	0.37
VOT-PTA	4.26	4.59	1:1	0.10	2.13
VOT-PNA	3.46	5.39	1:1	0.13	2.18
VOT-PAA	4.77(COOH)	4.08	1:1	0.50	5.63