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Two Voriconazole salts: Syntheses, crystal structures, solubility and bioactivities

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ABSTRACT

Two Voriconazole salts, namely, $(H_2\mathbf{FZ})^{2+}\cdot 2(Cl^-)$ (**1**) and $(H\mathbf{FZ})^{+}\cdot NO_3^-$ (**2**) (**FZ** = (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidiny)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol) have been obtained through the reaction of Voriconazole, hydrochloric acid and nitrate acid, respectively. They were structurally characterized by FT-IR, elemental analyses (EA), single crystal X-ray diffraction, and thermogravimetric analysis (TGA). A variety of hydrogen bonds (O—H···N, N—H···Cl/O, C—H···N/OF/Cl) were observed in the compounds **1** and **2**, through which a 3D supramolecular architecture is generated. Both two salts **1** and **2** show the promising bioactivities against *Aspergillus* species (*Aspergillus niger, Aspergillus terreus, Aspergillus fumigatus and Aspergillus flavus*) and *Candida* ones (*Candida albicans, Candida krusei, Candida glabrata and Cryptococcus neoformans*), which is obviously more excellent than that of **FZ**. Additionally, the solubility of two salts is considerably higher than that of the drug Voriconazole.

1. Introduction

Voriconazole, (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidiny)-1- (1*H*-1,2,4-triazol-1- yl)-2-butanol, contains two kinds of *N*-heterocyclic groups such as triazole group and fluoropyrimidine one (Scheme 1). Importantly, Voriconazole is a new broad-spectrum triazole antifungal drug which is suitable for both oral and parenteral administration [1]. Compared with other triazole antifungals, Voriconazole has been proven to extend antifungal activity and to improve bioavailability, which have excellent *in vitro* and *in vivo* activities against some species such as *Aspergillus*, *Candida*, *Scedosporium* as well as *Fusarium* [2]. Additionally, one Zn-based complex containing Voriconazole has been proven to be powerful efficiency against the species of *Candida* and *Aspergillus* [3]. Thus, the investigation and development of potent bioactive compounds containing Voriconazole still remains great challenge.

On the other hand, salts with drug-based moieties exhibit more powerful bioactivities compared with the drugs themselves, which can be attributed of the fact that salt formation is usually easy to generate, and can be used to modify the solubility, to enhance stability or toxicity and to lessen hygroscopicity of a drug product [4]. For example, pamoic acid is a pharmaceutically dicarboxylic acid that is not easily soluble in some common solvents. Its salt-former can improve the solubility of the pharmaceutical compounds containing *N*-heterocyclic derivatives [5]. Sertaconazole nitrate has been proven to be a broad spectrum of drug, which displays fungistatic, anti-inflammatory, and anti-itch bioactivities [6]. Additionally, serval organic compounds with Voriconazole have been reported by Nangia, Desiraju and Dickinson, which show interesting structural motifs [7]. Therefore, it is extremely indispensable to investigate and develop the specified salts with the potent biological activities.

Under stimulation of these elegant works, we would envision to design and develop novel drug-based compounds in order to improve its bioactivities and solubility. Herein, we would like to report two salts containing Voriconazole, namely, $(H_2\mathbf{FZ})^{2+}\cdot 2(Cl^-)$ (**1**) and $(H\mathbf{FZ})^{+}\cdot NO_3^-$ (**2**) (**FZ** = (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidiny)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol), which have been easily obtained through the reaction of Voriconazole, hydrochloric acid and nitrate acid, respectively. They have been structurally characterized by FT-IR, elemental analyses (EA) and single crystal X-ray diffraction. The bioactivities of two salts were screened in details. Interestingly, both compounds **1** and **2**

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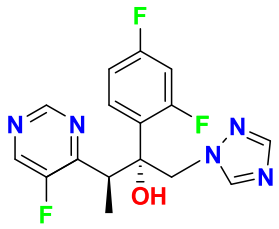

Scheme 1. The structure of Voriconazole.

crystallize in the formation of chiral space group, which show the promising biological activities against the species of *Aspergillus* and *Candida.* To our knowledge, there does not exist any report on Voriconazole-based salts with biological activities. In an addition, the thermal properties of **1** and **2** have been evaluated in details and their soluble behaviors were studied.

2. Experimental

2.1. Materials and measurements

Reagents and solvents employed were commercially available and not purified further. C, H, and N microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer. IR spectra were recorded on KBr discs on a Bruker Tensor 27 spectrophotometer in the 4000–400 cm^{-1} region. The powder X-ray diffraction (PXRD) data were collected on a Bruker D8 diffractometer using Cu-Ka radiation. UV–Vis absorption spectra was tested on a SHIMADZU UV-2600 spectrometer.

2.2. Synthesis of $(H_2FZ)^{2+}\cdot 2(Cl^-)$ (*1*)

A mixture of **FZ** (0.035 g, 0.1 mmol) and hydrochloric acid (0.2 mmol) in mixed solvents containing CH_3OH (6 ml) and H_2O (1 ml) was added to a 10 ml test tube. The colorless crystals suitable to single crystals X-ray diffraction were obtained by slow evaporation of the solution at ambient temperature for seven days (Fig. 1a). Yield 78.62%. Elemental analysis calcd (%) for $C_{16}H_{16}Cl_2F_3N_5O$ (422.23): C, 45.51; H, 3.82; N, 16.59; found (%): C, 45.39; H, 3.83; N, 16.54. IR (KBr, cm^{-1}): 3344(br), 3063(m), 3003(w), 2360(m), 1997(m), 1848(w), 1634(m), 1502(s), 1430(s), 1320(m), 1262(m), 1095(m), 1050(m), 958(m), 866(s), 762(w), 653(m).

2.3. Synthesis of $(HFZ)^+\cdot NO_3^-$ (*2*)

A mixture of **FZ** (0.035 g, 0.1 mmol) and HNO_3 (0.2 mmol) in mixed solvents containing CH_3OH (6 ml) and H_2O (1 ml) was added to a 10 ml test tube. The colorless crystals suitable to single crystals X-ray diffraction were obtained by slow evaporation of the solution at ambient temperature for seven days (Fig. 1b). Yield 86.62%. Elemental analysis calcd (%) for $C_{16}H_{15}F_3N_6O_4$ (412.33): C, 46.61; H, 3.67; N, 20.38; found (%): C, 46.76; H, 3.66; N, 20.44. IR (KBr, cm^{-1}): 3404(br), 3109(w), 2760(w), 2666(w), 2571(w), 2353(w), 1910(w), 1829(w), 1752(w), 1618(m), 1552(w), 1498(m), 1459(m), 1405(m), 1385(m), 1321(m), 1267(w), 1241(w), 1196(w), 1125(w), 1101(w), 1063(w),1005(w), 965(m), 920(m), 858(w), 823(w), 783(w), 719(w), 689(w), 625(m), 592(m), 521(w), 485(w), 418(w).

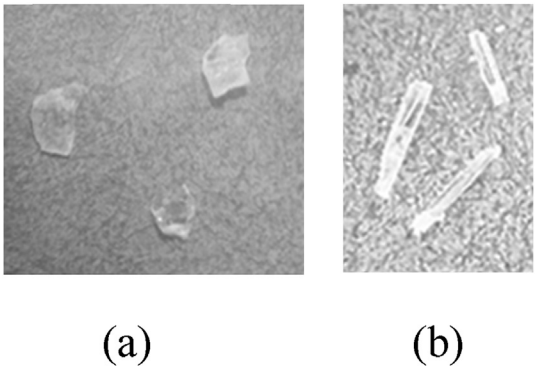

Fig. 1. The photographs of compounds **1** ($(H_2FZ)^{2+}\cdot 2(Cl^-)$, a) and **2** ($(HFZ)^+\cdot NO_3^-$, b).

2.4. Single-crystal structure determination

The suitable single crystals of compounds **1** and **2** were selected and mounted in air onto the thin glass fiber. X-ray intensity data were measured at 296 K on a Bruker SMART APEX CCD-based diffractometer with graphite-monochromatic Mo *Ka* radiation ($\lambda = 0.71073$ Å). Data reductions and absorption corrections were performed with the SAINT and SADABS software packages [8], respectively. The structures were solved by direct methods using the SHELXS program of the SHELXTL package and refined with SHELXL [9]. All structures were solved by a combination of direct methods and difference Fourier syntheses and against F^2 by the full matrix least-squares technique. Anisotropic displacement parameters were refined for all no hydrogen atoms. All hydrogen atoms were added theoretically and were constrained to ride on their parent atoms. Crystallographic data and other pertinent information for compounds **1** and **2** are summarized in Table 1. Corresponding hydrogen bonding data are listed in Table 2.

2.5. Solubility measurement

Equilibrium solubility experiments were performed on a round bottomed flask at 37 °C in the 0.1 N HCl solution medium. In a typical experiment, 5 ml of 0.1 N HCl medium was added to a round flask containing 20 mg of each solid material at 500 rpm. After 24 h the resulting solution was filtered, and the absorbance was

Table 1
Crystal parameters and refinement of compounds **1** and **2**.

Compound reference	1	2
Chemical formula	$C_{16}H_{16}F_3N_5O$, 2(Cl)	$C_{16}H_{15}F_3N_6O_4$
Formula Mass	422.24	412.34
Crystal system	Orthorhombic	Orthorhombic
a/Å	9.0652(3)	6.8355(12)
b/Å	12.5400(5)	9.8086(18)
c/Å	15.8517(6)	27.812(5)
α/°	90.00	90.00
β/°	90.00	90.00
γ/°	90.00	90.00
Unit cell volume/Å^3	1801.98(12)	1864.7(6)
Temperature/K	296	296
Space group	$P2_12_12_1$	$P2_12_12_1$
No. of formula units per unit cell, *Z*	4	4
Radiation type	Mo Kα	Mo Kα
Absorption coefficient, μ/mm^{-1}	0.407	0.128
No. of reflections measured	28050	25567
No. of independent reflections	4152	4600
R_{int}	0.074	0.0725
Final R_1 values ($I > 2\sigma(I)$)[a]	0.0471	0.0427
Final w$R(F^2)$ values ($I > 2\sigma(I)$)[b]	0.0981	0.0918
Final R_1 values (all data)[a]	0.0679	0.1029
Final w$R(F^2)$ values (all data)[b]	0.1060	0.1151
Goodness of fit on F^2	1.02	0.949
CCDC number	15551522	15551523

[a] $R_1 = \sum||F_o|-F_c||/\sum|F_o|$.
[b] $wR_2 = [\sum[w(F_o^2-F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.