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Synthesis and Crystal Structure of [α-(2,4-Difluorophenyl)-α-(1*H*-1,2,4-triazole-1-ylmethyl)-1*H*-1,2,4-triazole-1-ethanol]Cu(II) Complex

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A novel complex of copper(II) was prepared by reaction of $CuCl_2$ and fluconazole at reflux in water and tetrahydrofuran. Its structure was determined by single crystal X-ray diffraction analysis. The crystals are monoclinic space group C2/c with a = 23.490(2), b = 9.4719(9), c = 19.8459(18) Å, α = 90.00, β = 123.639(2), γ = 90.00°, V = 3676.2(6) Å^3, Z = 4, $F_{(000)}$ = 1676, Dc = 1.480 g/cm^3, μ = 0.815 mm^{-1}, the final R = 0.0526 and wR = 0.1688. A total of 8828 reflections were collected, of which 3244 were independent (R_{int} = 0.0344).

Keywords: Fluconazole, Copper complex, Synthesis, Crystal structure.

INTRODUCTION

Fluconazole [α-(2,4-difluorophenyl)-α-(1*H*-1,2,4-triazole-1-ylmethyl)-1*H*-1,2,4- triazole-1-ethanol] is a triazole antifungal agent which is used in the treatment and prevention of superficial and systemic fungal infections[1-5] such as or *Opharyngeal candidiasis* and *Cryptococcal meningitis* in AIDS. Fluconazole can inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeasts to mycelial forms. In addition, it may also inhibit purine uptake and impair triglyceride and/or phospholipid biosynthesis. This compound belongs to the phenylpropylamines containing a phenylpropylamine moiety, which consists of a phenyl group substituted at the third carbon by an propan-1-amine. In order to improve the bioavailability or treatment effect and develop new applications for fluconazole, metal complex of it has been extensively investigated in our group. In this paper, as a contribution in this filed, we report here the crystal structure of the complex of fluconazole with copper.

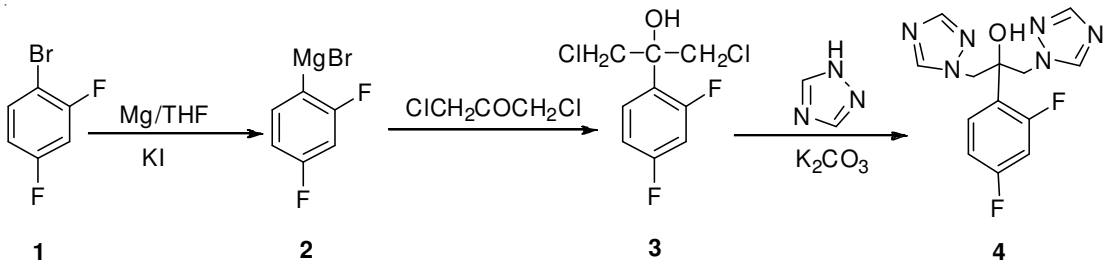
EXPERIMENTAL

Determination of crystal structure: The crystal of title compound with dimensions of 0.48 mm × 0.42 mm × 0.40 mm was mounted on a Rigaku Saturn CCD area-detector diffractometer with a graphite-monochromated MoK_α radiation (λ = 0.71073 Å) by using a phi and scan modes at 298 K in the range of 2.1° ≦ θ ≦ 25°. The crystal belongs to monoclinic system with space group C2/c and crystal parameters of a = 23.490(2), b = 9.4719(9), c = 19.8459(18) Å, α = 90.00, β = 123.639(2), γ = 90.00°, V = 3676.2(6) Å^3, Z = 14, F(000) = 1676, Dc = 1.480 g/cm^3. The absorption coefficient μ = 0.815 mm^{-1}. The final R_1 = 0.0526 (> 2σ(I)) and wR_2 = 0.1688. A total of 8828 reflections were collected, of which 3244 were independent (R_{int} = 0.0344). The structure was solved by direct methods with SHELXS-97[6] and refined by the full-matrix least squares method on F^2 data using SHELXL-97[7]. The empirical absorption corrections were applied to all intensity data. H atom of N-H was initially located in a difference fourier map and were refined with the restraint Uiso (H) = 1.2 Ueq (N). Other H atoms were positioned geometrically and refined using a riding model, with d (C-H) = 0.93-0.98 Å and Uiso (H) = 1.2 Ueq (C) or 1.5 Ueq (C-methyl). The final full-matrix least squares refinement gave 0.0392 and wR = 0.0928.

Synthesis: To a solution of 2,4-difluoro-bromobenzene (0.10 mol) in THF, metal Mg (0.11 mol) and KI (catalyst dosage) were added. The mixture was stirred at 50 °C for 2 h and then 1,3-dichloropropan-2-one (0.10 mol) was added to the mixture for another 3 h at room temperature. The solvent was removed. The residue was dispersed in toluene and K_2CO_3 was added with stirring for 3 h at 90 °C. Then the mixture was filtered and the toluene was removed in vacuum. The residue was recrystallized to afford compound **4** (white powder).

RESULTS AND DISCUSSION

The complex was prepared by reaction of $CuCl_2$ and fluconazole at reflux in water and tetrahydrofuran. Then the mixture was evaporated slowly affording colourless crystals suitable for X-ray analysis.



Scheme-I: Route for the synthesis of title compound

Structure of the title compound: The title compound has been confirmed by single crystal X-ray diffraction analysis. Crystallographic and refinement parameters are given in Table-1. The selected bond lengths and bond angles are listed in Tables 2-4, respectively. The weak hydrogen bonds of the O-H...O, O-H...N and O-H...Cl (dotted lines) in the crystal structure of the title compound are listed in Table-5. The structure was solved by direct methods. Anisotropic displacement parameters were applied to all nonhydrogen atoms in full-matrix least-square refinements based on F^2. The hydrogen atoms were set in calculated positions with a common fixed isotropic thermal parameter.

The molecular structure and the dimentional network of the title complex are shown in Figs. 1 and 2, respectively. The water chloride clusters (supramolecular interaction) of the title complex is shown in Fig. 3.

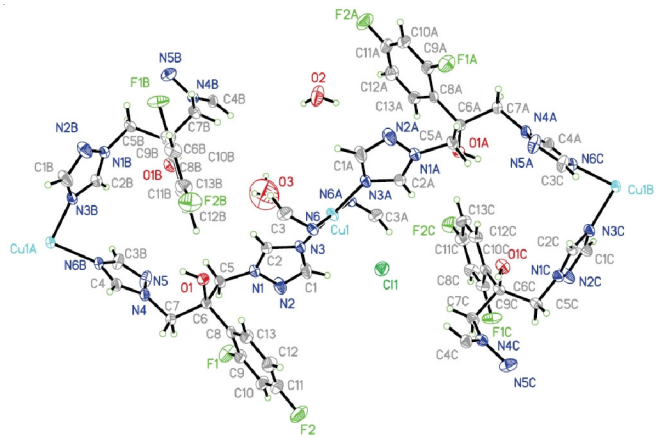


Fig. 1. Molecular structure of the title compound

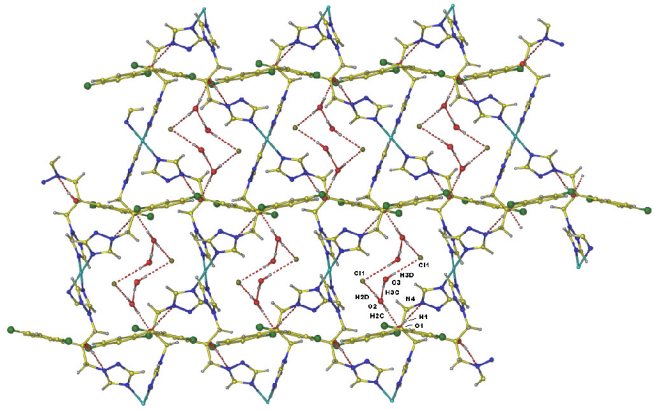


Fig. 2. Two-dimensional network of hydrogen bonds (dashed lines)

TABLE-1
CRYSTAL DATA AND STRUCTRE REFINEMENT OF TITLE COMPOUND

	Data
Empirical formula	$C_{26}H_{24}N_{12}O_2Cl_2F_4Cu(4H_2O)$
Formula weight	819.09
Crystal system	Monoclinic
a (Å)	23.490(2)
b (Å)	9.4719(9)
c (Å)	19.8459(18)
α (°)	90.00
β (°)	123.639(2)
γ (°)	90.00
Volume (Å^3)	3676.2(6)
Z	4
Temperature (K)	298
Space group	C2/c
Calculated density (g/cm^3)	1.480
μ (mm^{-1})	0.815
F (000)	1676
Crystal size (mm^3)	0.48 × 0.42 × 0.40
θ Range for data collection (°)	2.1 to 25.0
Reflections collected	8828
Independent reflections	3244 R_{int} = 0.0344
Final R indexes [I ≥ 2σ(I)]	R_1 = 0.0526, wR_2 = 0.1688

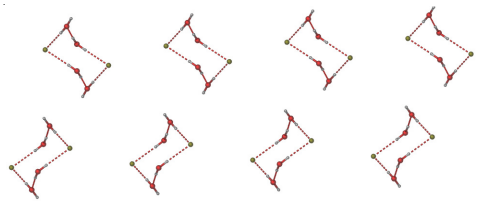


Fig. 3. Water chloride clusters for the crystal

TABLE-2
SELECTED BOND LENGTHS OF TITLE COMPOUND

Bonds	Dist. (Å)	Bonds	Dist. (Å)
Cu(1)-N(3)	2.009(3)	Cu(1)-N(6)	2.042(3)
N(4)-C(4)	1.327(5)	N(4)-N(5)	1.359(5)
N(4)-C(7)	1.451(5)	N(6)-C(3)	1.352(6)
O(1)-C(6)	1.411(5)	C(5)-C(6)	1.535(6)
C(6)-C(8)	1.532(6)	C(6)-C(7)	1.547(5)
C(10)-C(11)	1.359(7)	C(8)-C(9)	1.382(6)

The title complex crystallizes in the monoclinic space group C2/c. The unit cell contains four molecule of title complex. As can be seen in Fig. 1, the complex molecular structure consists of two phenyl rings and four triazole rings. The tree rings possess independent plane (7.3764 x + 8.6944y – 7.4598 z = 4.6593, 3.4890 x – 0.6283 y + 14.6696 z = 0.9252, 12.5477 x

TABLE-3
SELECTED BOND ANGLES [º] OF TITLE COMPOUND

Angles	Data. (º)	Angles	Data. (º)
N(3)#1-Cu(1)-N(6)	89.65(13)	N(3)-Cu(1)-N(6)#1	89.65(13)
N(3)#1-Cu(1)-Cl(1)	91.27(11)	N(3)-Cu(1)-Cl(1)	88.73(11)
N(6)#1-Cu(1)-Cl(1)	89.56(10)	C(2)-N(1)-N(2)	109.7(3)
C(2)-N(1)-C(5)	129.2(4)	N(2)-N(1)-C(5)	121.0(3)
C(2)-N(3)-Cu(1)	126.4(3)	C(1)-N(3)-Cu(1)	130.8(3)
N(5)-N(4)-C(7)	119.6(3)	C(3)#2-N(5)-N(4)	102.7(4)
C(4)#3-N(6)-C(3)	103.2(4)	C(4)#3-N(6)-Cu(1)	129.2(3)
C(3)-N(6)-Cu(1)	127.1(3)	C(4)-N(4)-C(7)	130.6(4)
N(6)#2-C(4)-N(4)	110.1(4)	N(1)-C(5)-C(6)	110.6(3)
O(1)-C(6)-C(8)	111.1(3)	O(1)-C(6)-C(5)	104.6(3)
C(8)-C(6)-C(5)	111.3(3)	O(1)-C(6)-C(7)	110.1(3)
N(4)-C(7)-C(6)	114.0(3)	N(5)#3-C(3)-N(6)	114.2(4)

#1 –x + 1/2, -y + 3/2, -z + 1; #2 –x + 1/2, y-1/2, -z + 1/2; #3 –x + 1/2, y + 1/2, -z + 1/2

TABLE-4
SELECTED BOND TORSIONAL ANGLES [º] OF TITLE COMPOUND

Angles	Data (º)	Angles	Data (º)
C(4)-N(4)-C(7)-C(6)	-107.2(5)	N(5)-N(4)-C(7)-C(6)	77.1(5)
N(6)-Cu(1)-N(3)-C(2)	53.3(4)	C(8)-C(6)-C(7)-N(4)	177.4(3)
C(7)-C(6)-C(8)-C(9)	64.4(5)	C(5)-C(6)-C(7)-N(4)	-59.8(5)
Cl(1)-Cu(1)-N(3)-C(2)	143.8(4)	O(1)-C(6)-C(8)-C(13)	5.0(5)
N(6)-Cu(1)-N(3)-C(1)	-127.5(5)	C(7)-C(6)-C(8)-C(13)	-115.8(4)
Cl(1)-Cu(1)-N(3)-C(1)	-37.0(5)	C(5)-C(6)-C(8)-C(9)	-58.7(5)
Cl(1)-Cu(1)-N(6)-C(3)	-179.6(4)	C(11)-C(12)-C(13)-C(8)	1.5(8)
N(1)-N(2)-C(1)-N(3)	0.3(7)	C(2)-N(3)-C(1)-N(2)	0.1(6)
Cu(1)-N(3)-C(1)-N(2)	-179.3(4)	C(2)-N(1)-C(5)-C(6)	-71.3(6)
C(1)-N(3)-C(2)-N(1)	-0.4(5)	N(2)-N(1)-C(5)-C(6)	105.3(5)
Cu(1)-N(3)-C(2)-N(1)	178.9(3)	N(1)-C(5)-C(6)-O(1)	68.9(4)
N(2)-N(1)-C(2)-N(3)	0.6(5)	N(1)-C(5)-C(6)-C(8)	-51.1(5)

TABLE-5
HYDROGEN BONDS OF TITLE COMPOUND

D-H-A	d(D-H) (Å)	d(H-A) (Å)	d(D-A) (Å)	D-H-A (°)
O(1)-H(1)...N(4)	0.82	2.45	2.903(5)	115.8
O(2)-H(2C)...O(1)#4	0.85	1.81	2.662(5)	179.4
O(2)-H(2D)...Cl(1)#5	0.85	2.22	3.074(4)	179.4
O(3)-H(3C)...O(2)#6	0.85	1.83	2.677(13)	174.1
O(3)-H(3D)...Cl(1)#5	0.85	2.42	3.264(11)	174.8

#3 –x + 1/2, y + 1/2, -z + 1/2; #4 x,-y + 1, z + 1/2 ; #5 x, y-1, z ; #6 –x + 1/2, -y + 1/2, -z + 1

+ 1.9980 y – 19.3986 z = 0.3436), respectively. The dihedral angle between the triazole ring (N1, N2, C1, C11, N3, C2) and the triazole rings (N4, N5, C3B, N6B, C4) is 75.2º. Similarly, the dihedral angle between the phenyl ring (C8, C9, C10, C11, C12, C13) and the triazole ring (N1, N2, C1, C11, N3, C2 and N4, N5, C3B, N6B, C4) is 55.9º and 42.1º, respectively. The centre distance of the two five-members triazole rings is 4.424(3) Å. The phenyl rings are fairly planar with distance of 10.820 Å. The vertical distance of Cu atom to the phenyl ring plane (C8, C9, C10, C11, C12, C13) and triazole ring plane (N4, N5, C3B, N6B, C4) are 5.410 and 6.799 Å, respectively.

As shown in Figs. 2 and 3, van der Waals' interactions stabilize the solid state of the crystal structure in the crystal packing.

Supplementary material

CCDC 1010418 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

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