

Akhmatkhodja N. Yunuskhodjayev, Shokhista F. Iskandarova and Vahobjon Kh. Sabirov*

Molecular and crystal structure of a copper(II) complex of sildenafil

<https://doi.org/10.1515/znb-2021-0145>

Received August 5, 2021; accepted November 15, 2021;

published online December 10, 2021

Abstract: The crystal structure of a copper(II) complex of protonated sildenafil, $\text{CuCl}_3\text{C}_{22}\text{H}_{31}\text{N}_6\text{O}_4\text{S}\cdot 2\text{H}_2\text{O}$ was studied by single crystal X-ray diffraction. The compound crystallizes in the monoclinic space group $P2_1/n$ with the unit cell parameters $a = 15.4292(2)$, $b = 9.06735(12)$, $c = 21.1752(2)$ Å, $V = 2945.48(7)$ Å³, $Z = 4$. The Cu atom is coordinated by the sildenafil ligand via the N2 atom of the pyrazolopyrimidine ring and by three chloride anions. Sildenafil is protonated at the methylated N6 atom of the piperazine ring and it is cation ligand with a 1+ charge.

Keywords: cation of sildenafil; conformation; copper (II) complex; sildenafil viagra; the coordination mode.

1 Introduction

Sildenafil, 5-[2-ethoxy-5-(4-methylpiperazin-1-yl) sulfonyl-phenyl]-1-methyl-3-propyl-6H-pyrazolo[4,3-d]pyrimidin-7-one, is used in medicine to improve penile erections in men with erectile dysfunction by selectively inhibiting the cGMP-specific phosphodiesterase type 5 [1]. Sildenafil is a bioavailable pyrazolopyrimidine derivative structurally related to zaprinast, with vasodilating and potential anti-inflammatory activities [2] (Figure 1).

The crystal structures of the base sildenafil [3], sildenafil citrate monohydrate [4], sildenafil saccharinate [5, 6] and a number of co-crystals of sildenafil [7] have been reported. Complexes of sildenafil citrate with some bivalent metals, for example, Mg^{2+} , Ca^{2+} , Zn^{2+} and Cd^{2+} were synthesized and their chemical composition and lattice

parameters were reported [8]. Complexes of sildenafil with divalent metals are also of interest for coordination and bioinorganic chemistry.

The aim of the present study was to determine the crystal and molecular structure of a novel copper(II) complex of sildenafil by single-crystal X-ray diffraction analysis. For convenience we denote the pyrimidine, pyrazole, phenyl, and piperazine rings in the sildenafil molecule by capital letters A, B, C, and D, respectively (Figure 1).

2 Results and discussion

The complex crystallizes in the monoclinic space group $P2_1/n$ with the Cu atom surrounded in tetrahedral mode

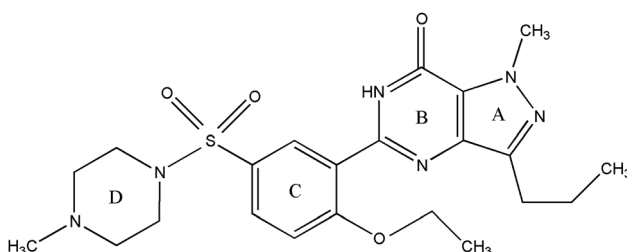


Figure 1: Molecular structure of the base sildenafil.

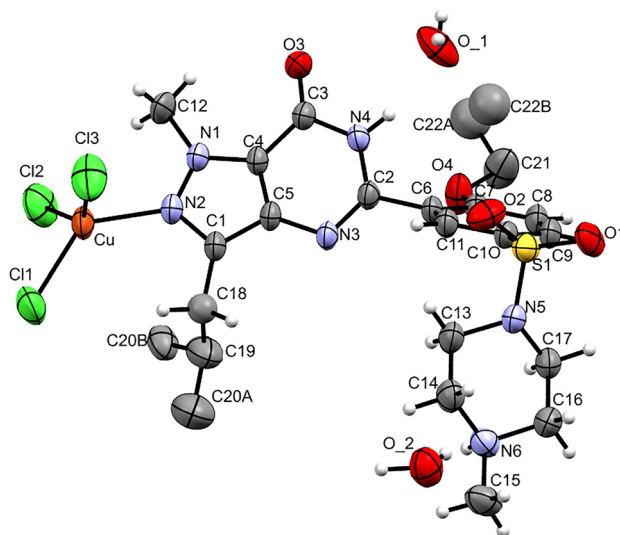


Figure 2: ORTEP drawing of the molecular structure of the title compound.

*Corresponding author: Vahobjon Kh. Sabirov, Innovation Center of Pharmacy, 46 Building, 19 Quarter, Yunusabad District, 100114, Tashkent, Uzbekistan; and Tashkent State Technical University, Almalyk Branch, Ulug'bek Str., 45, 110100, Almalyk, Uzbekistan, E-mail: v_sabirov@mail.ru

Akhmatkhodja N. Yunuskhodjayev, Innovation Center of Pharmacy, 46 Building, 19 Quarter, Yunusabad District, 100114, Tashkent, Uzbekistan

Shokhista F. Iskandarova, Tashkent Pharmaceutical Institute, Aybek Str., 45, 100015, Tashkent, Uzbekistan

Table 1: Selected torsion angles ($^{\circ}$) in the structure of the title compound with estimated standard deviations in parentheses.

Torsion angle	$\tau, ^{\circ}$	Torsion angle	$\tau, ^{\circ}$
C1-C18-C19-C20A	179.8(7)	C7-O4-C21-C22B	-102(1)
C1-C18-C19-C20B	-62.9(6)	C8-C7-O4-C21	-24.7(5)
C5-C1-C18-C19	-89.6(4)	C10-S1-N5-C13	-75.7(3)
C7-O4-C21-C22A	-135.3(5)		

with the monodentate sildenafil cation and three Cl^- ions. The Cu atom is coordinated by the cationic sildenafil ligand via the N2 atom of the pyrazolopyrimidine ring (Figure 2).

In the given structure, sildenafil is protonated at the methylated N6 atom of the piperazine ring and it is a cation with a 1+ charge. That cationic form of sildenafil occurs in the crystal structure of sildenafil citrate monohydrate [4], i.e. sildenafil retains its cationic form in a complexation process with the Cu atom.

The coordination tetrahedron of the Cu atom is distorted: the Cu–N2 bond length is 2.051(2) and Cu–Cl bond lengths lie

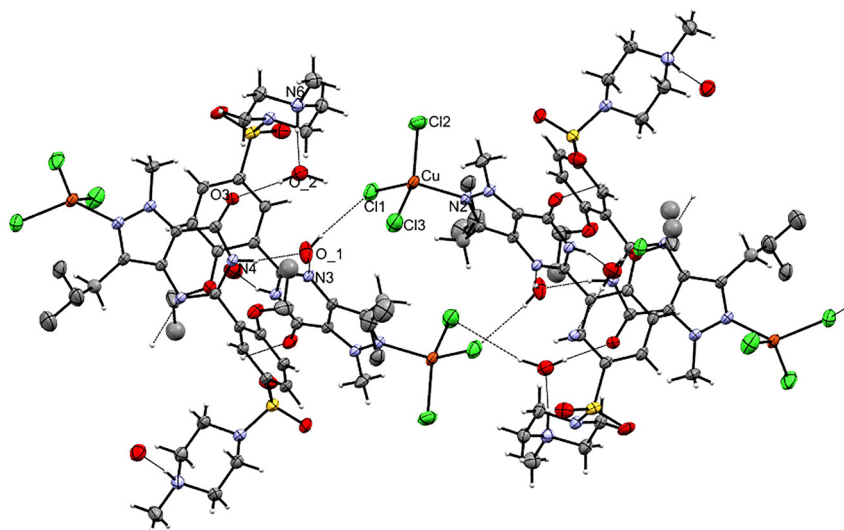
in the range 2.200(1)–2.2505 Å. The bond angles Cl–Cu–Cl are far from those in an ideal tetrahedron and equal to 99.19(5), 99.85(5) and 136.91(6) $^{\circ}$. The bond angles N–Cu–Cl are 92.7(2), 102.3(1), 132.2(8) and 136.93(6) $^{\circ}$. The endocyclic angle C1–N2–N1 (108.3(2) $^{\circ}$) is more narrow in comparison with angle in the molecular structure of sildenafil citrate (111.25(19) $^{\circ}$) due to the inclusion of the lone electron pair at the N2 atom in coordination bond with the metal. This effect is attributed to the VSEPR theory by Gillespie [9].

The pyrazolopyrimidine bicyclic system (A + B) and the phenyl ring (C) in the sildenafil base, citrate and sildenafil saccharinate are almost coplanar. In the structure of the title compound, the intramolecular hydrogen bond N4–H...O4 is broken and the pyrazolopyrimidine ring and the benzene ring are noncoplanar: the dihedral angle between these planes is 61.2(4) $^{\circ}$.

The ethoxy groups of the above mentioned compounds lie also almost within the A + B + C plane. In the present complex, the ethoxy group is disordered in two positions and goes out of the above-mentioned plane. The propyl

Table 2: Hydrogen bonds and selected short contacts in title compound.

D–H...A	D–H	H...A	D...A	D–H...A	Symmetry
N4–H4...O_1	0.86	1.95	2.754(5)	155	
N6–H6...O_2	0.98	1.77	2.747(4)	173	
O_1–Ha_1...N3	1.08(6)	1.82(6)	2.867(5)	163(5)	$-x, 1/2 + y, 1/2 - z$
O_1–Hb_1...Cl1	0.59(6)	2.74(6)	3.280(5)	155(7)	$-1 + x, -3/2 - y, -1/2 + z$
O_2–Hb2O3	0.71(6)	2.20(6)	2.871(4)	161(7)	$-x, -1/2 + y, 1/2 + z$
C9–H9O1	0.93	2.51	2.881(4)	104	
C12–H12bO3	0.96	2.50	3.175(4)	127	
C13–H13b...O2	0.97	2.43	2.865(5)	107	
C17–H17a...O1	0.97	2.54	2.959(4)	106	
C17–H17B...O3	0.97	2.35	3.308(4)	169	

**Figure 3:** Intermolecular hydrogen bonds in the title compound.

group is also situated out of the A + B + C plane. As in other sildenafil compounds [3–6], the propyl group is on the same side as the methylpiperazine fragment. The torsion angles defining the conformation of sildenafil are presented in Table 1.

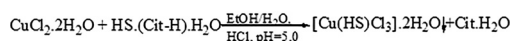
Two water molecules of crystallization and three chlorine ions increase the number of hydrogen bonds in the crystal structure (Table 2). The Cu(II) complex of sildenafil takes part in two hydrogen bonds as *p*-donor and in three hydrogen bonds as *p*-acceptor. Besides these, it forms five non-bonded short contacts with adjacent molecules. These bonds and short contacts link the structural units into a three-dimensional framework (Figure 3).

3 Conclusions

The molecular and crystal structure of a copper(II) complex of sildenafil have been determined by single-crystal X-ray diffraction. Coordination of the Cu atom by the sildenafil ligand occurs *via* the N2 atom of the pyrazolopyrimidine ring. Three chloride anions complete the tetrahedral environment of the Cu atom. The sildenafil molecule is protonated at the N6 atom of the pyrazolopyrimidine ring and thus, a ligand has a cationic form with a 1+ charge. The ethoxy and propyl groups are disordered over two positions. The presence of chloride anions and water molecules in the crystal structure increases the number of weak hydrogen bonds.

4 Experimental section

Crystals of title compound were prepared by slowly evaporation at room temperature of a hydroalcohol solution containing sildenafil citrate monohydrate (“Pharmaceuticals Ltd”, India) and CuCl₂·2H₂O (Sigma-Aldrich) in a molar ratio of 1:1. For synthesis of the Cu complex, 672 mg (1.0 mM) of sildenafil citrate monohydrate was dissolved in 10 mL of the water-alcohol solute (in a volume ratio of 1:1) and was added to 85.24 mg (0.5 mM) of a powder of CuCl₂·2H₂O with stirring on magnetic stirrer at 50 °C (Scheme 1). Green color crystals of thin and long prism form dissipated after two days.



Scheme 1: Synthesis of the copper(II) complex of sildenafil.

Analysis of C, H and O were performed on a German Elemental Vario EL instrument. Yield: 88%. Elemental analysis for CuCl₃C₂₂H₃₁N₆O₄S·2H₂O (681.51): calcd. C 38.74; H 5.13; N 12.32%; found: C 38.65; H 5.38; N 12.72%.

Table 3: Crystal data and structure refinement for the title complex.

Identification code	exp_64_Sabirov
Empirical formula	C ₂₂ H ₃₅ N ₆ O ₆ Cl ₃ CuS
Formula weight	681.529
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> /Å	15.4292(2)
<i>b</i> /Å	9.06735(12)
<i>c</i> /Å	21.1752(2)
β /°	96.1357(11)
Volume/Å ³	2945.48(7)
<i>Z</i>	4
ρ_{calc} /g cm ⁻³	1.54
μ /mm ⁻¹	4.6
<i>F</i> (000)	1413.6
Crystal size/mm ³	0.35 × 0.30 × 0.30
Crystal shape	Prism
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/°	6.76–135.38
Index ranges	–18 ≤ <i>h</i> ≤ 18, –10 ≤ <i>k</i> ≤ 8, –25 ≤ <i>l</i> ≤ 25
Reflections collected	15,831
Independent reflections	5301 [<i>R</i> _{int} = 0.0296, <i>R</i> _{sigma} = 0.0305]
Data/parameters	5301/374
Goodness-of-fit on <i>F</i> ²	1.035
Final <i>R</i> indexes [<i>I</i> ≥ 2 σ (<i>I</i>)]	<i>R</i> ₁ = 0.0486, <i>wR</i> ₂ = 0.1467
Final <i>R</i> indexes [all data]	<i>R</i> ₁ = 0.0555, <i>wR</i> ₂ = 0.1538
Largest diff. peak/hole/e Å ⁻³	0.76/–0.52
Deposit number	2100787

Experimental and refinement details of the X-ray diffraction study are summarized in Table 3.

4.1 X-ray structure determination

The X-ray data for the title compound was collected on an ‘XtaLAB Synergy, HyPix3000’ (CuK α -radiation, λ = 1.54184 Å), ω -scan mode, mirror monochromator (at 293 K) single crystal diffractometer [10]. The crystal structure of the title compound was solved with OLEX2 [11] using the SHELXT program [12], and refined (full-matrix least-squares refinement on *F*²) using the SHELXL program refinement package using least squares minimization [13]. All non-hydrogen atoms, with the exception of disordered atoms, were refined anisotropically. Hydrogen atoms were inserted at calculated positions and constrained with isotropic displacement parameters. The molecular drawings were plotted with the MERCURY program package [14]. Using the software Platon [15, 16], additional water molecules, the hydrogen bonds and short non-bonded contacts were analyzed. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre (Deposit Number 2100787). The data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: E-mail: deposit@ccdc.cam.ac.uk.

Acknowledgments: The authors are grateful to the co-workers in the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan for assistance in the X-ray experiment.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

1. Laties A., Zrenner E. *Prog. Retin. Eye Res.* 2002, 21, 485–506.
2. Badwan A. A., Nabulsi L., Al Omari M. M., Daraghme N., Ashour M. In Brittain H. G., Ed. *Sildenafil Citrate Monograph* 27. Academic Press: New York, 2001; pp. 339–376.
3. Stepanovs D., Mishnev A. Z. *Naturforsch.* 2012, 67b, 491–494.
4. Yathirajan H. S., Nagaraj B., Nagaraja P., Bolte M. *Acta Crystallogr.* 2005, E61, o489–o491.
5. Banerjee R., Bhat P. M., Desiraju G. R. *Cryst. Growth Des.* 2006, 6, 1468–1478.
6. Sanphui P., Tothadi S., Ganguly S., Desiraju G. R. *Pharmaceutics* 2013, 10, 4687–4697.
7. Sawatdee S., Pakawatchai C., Nitichai K., Srichana T., Phetmung H. *Saudi Pharm. J.* 2015, 23, 504–514.
8. Melnikow P., Cuin A. C., Secco M. A. J. *Pharm. Sci.* 2006, 95, 225–227.
9. Gillespie R. J. *J. Chem. Educ.* 1963, 40, 283.
10. Xcalibur. CrysAlisPro (version 1.171.33.44); Oxford Diffraction Ltd, 2009.
11. Dolomanov O. V., Bourhis L. J., Gildea R. J., Howard J. A. K., Puschmann H. J. *Appl. Crystallogr.* 2009, 42, e339–e341.
12. Sheldrick G. M. *Acta Crystallogr.* 2015, A71, 3–8.
13. Sheldrick G. M. *Acta Crystallogr.* 2015, C71, 3–8.
14. Macrae C. F., Bruno I. J., Chisholm J. A., Edington P. R., McCabe P., Pidcock E., Rodriguez-Monge L., Taylor R., van de Streek J., Wood P. A. J. *Appl. Crystallogr.* 2008, 41, 466–470.
15. Spek A. L. *Acta Crystallogr.* 2015, C71, 9–18.
16. Spek A. L. *Acta Crystallogr.* 2009, D65, 148–155.