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Biological activity of two new imidazole-based Cu(II) Frameworks resulting from a one-pot reaction

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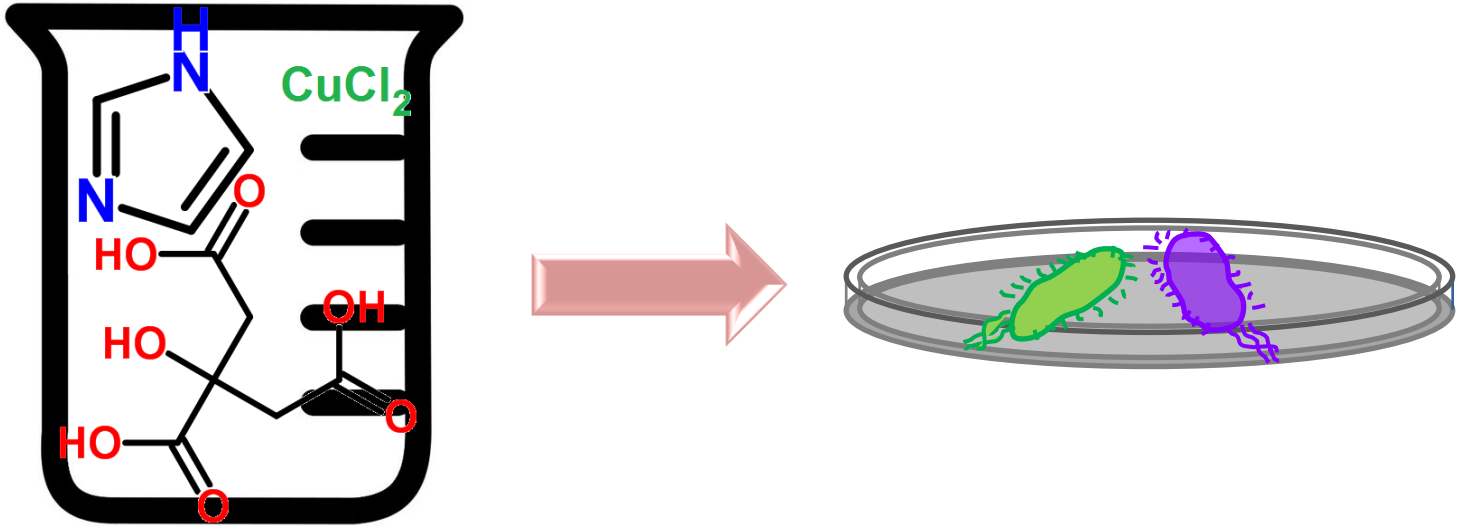
Graphical Abstract



Abstract:

Two new penta-coordinated copper(II) complexes with mixed-ligands, namely: imidazole and citric acid have been synthesized and obtained from a one-pot reaction. The biological screening of the resulting compounds has shown that they could be considered as promising materials with interesting antimicrobial and antifungal inhibition activities. Moreover, the obtained biological results have been confirmed by undertaking chemical reactivity calculations.

Keywords: Imidazole-based complexes, Cu(II) frameworks, one-pot synthesis, ab-initio calculations, biological properties

Introduction

Imidazole occurs in most proteins as part of the side chain of histidine and constitutes a binding site for various transition metal ions in a large number of metalloproteins [1]. Consequently, the bonding between imidazole and transition metal ions is widely known [2] and of considerable interest especially in biological systems [3,4]. Consequently, copper(II)–imidazole systems with different ratios of imidazole to copper have been prepared and investigated by several researchers [5].

Moreover, being studied as models for copper proteins that contain both functionalities in the side chain [6], some mononuclear copper(II)–imidazole complexes with carboxylate ligands have been found to display a variety of pharmacological effects, including antitumor [7], superoxide dismutase and catecholase activities [8].

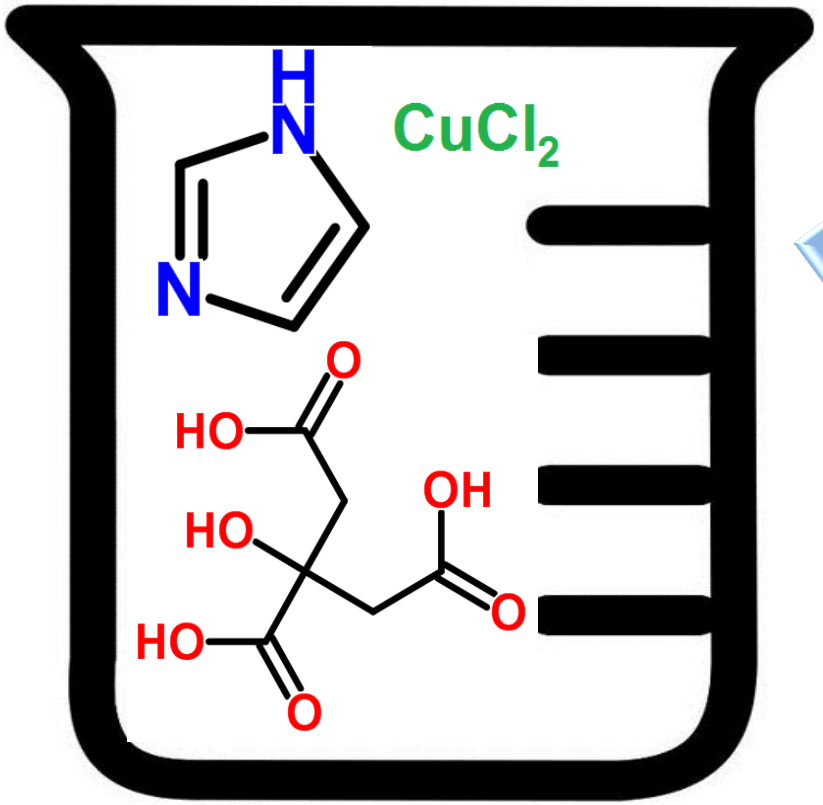
Introduction

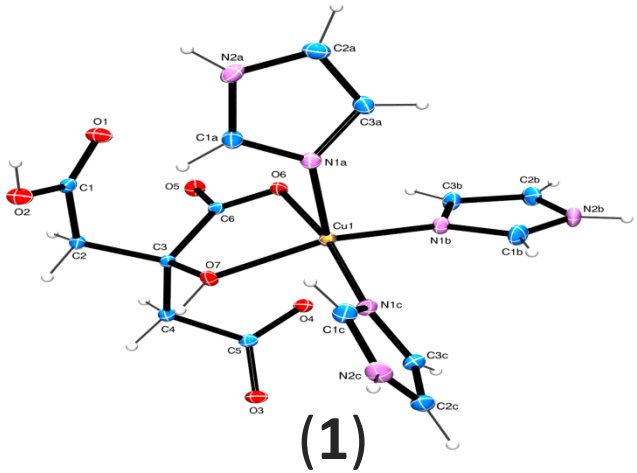
In order to contribute to the study of these systems, we have synthesized two new penta-coordinated copper(II) complexes with mixed-ligands, namely: imidazole and citric acid. The resulting compounds have shown remarkable antimicrobial and antifungal inhibition activities, which have been predicted by exploring the computational chemical reactivity of the two complexes [9].

[1] J. Reedijk & E. Bouwman, Bioinorganic Catalysis, Marcel Dekker Inc., New York & Basel, 1999. [2] K. D. Karlin & Z. Tyeklar, Bioinorganic Chemistry of Copper, Chapman & Hall, New York, 1993. [3] E. Colacio, M. Ghazi, R. Kivekäs, M. Klinga, F. Lloret & J. M. Moreno, Inorg. Chem, 2000, 39(13), 2770–2776. [4] M. T. Caudle, J. W. Kampf, M. L. Kirk, P. G. Rasmussen & V. L. Pecoraro, J. Am. Chem. Soc, 1997, 119(39), 9297–9298. [5] (a) S. M. Morehouse, A. Polychronopoulou & G. J. B. Williams, Inorg. Chem, 1980, 19(12), 3558–3561. (b) G. Fransson & B. K. S. Lundberg, Acta Chem. Scand. A, 1974, 28(5), 578–588. (c) D. L. McFadden, A. T. McPhail, C. D. Garner & F. E. Mabbs, J. Chem. Soc., Dalton Trans, 1976, 47–52. [6] H. Beinert, Coord. Chem. Rev, 1980, 33, 55. [7] J. R. J. Sorrenson, Prog. Med. Chem, 1989, 26, 437. (and references therein). [8] A. L. Abuhijleh & C. Woods, Inorg. Chim. Acta, 1993, 209, 187. [9] Direm, A. Abdelbaky, M. S. M. Sayın, K. Cornia, A. Abosede, O. & García-Granda, S. (2018). Inorg. Chim. Acta. 478. 59–70. and references therein.

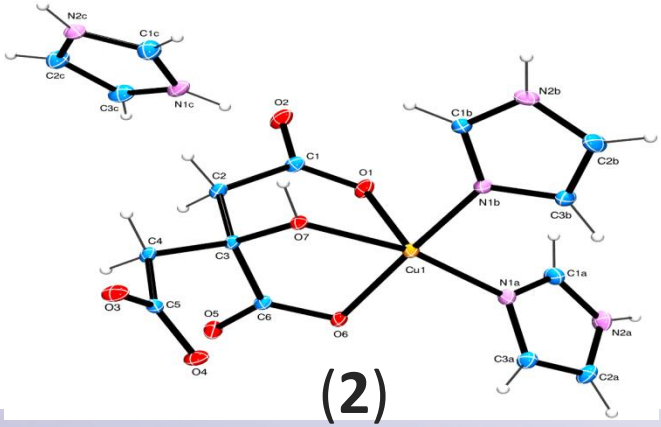
Results and discussion

One-pot reaction





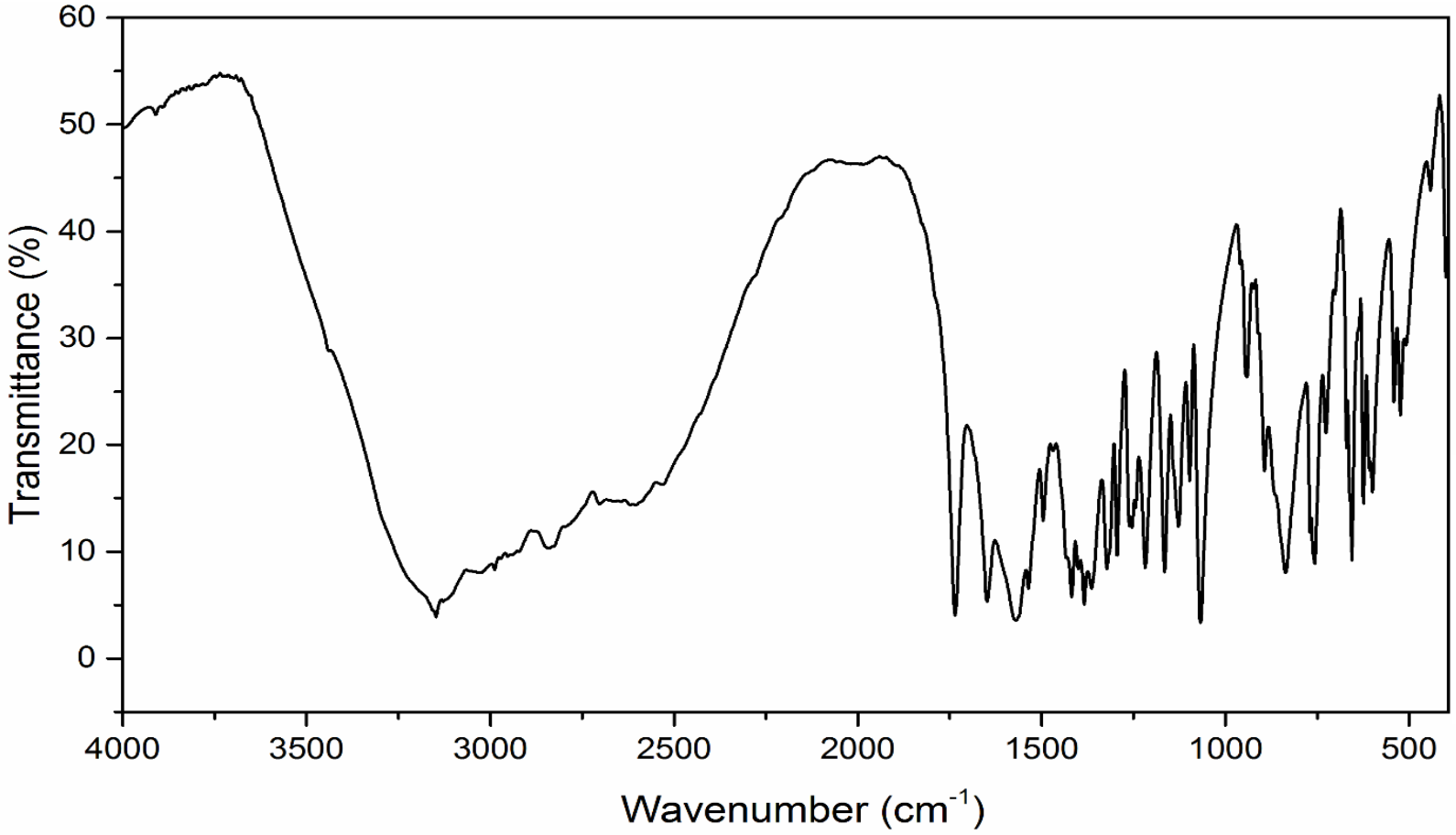
(1)



(2)

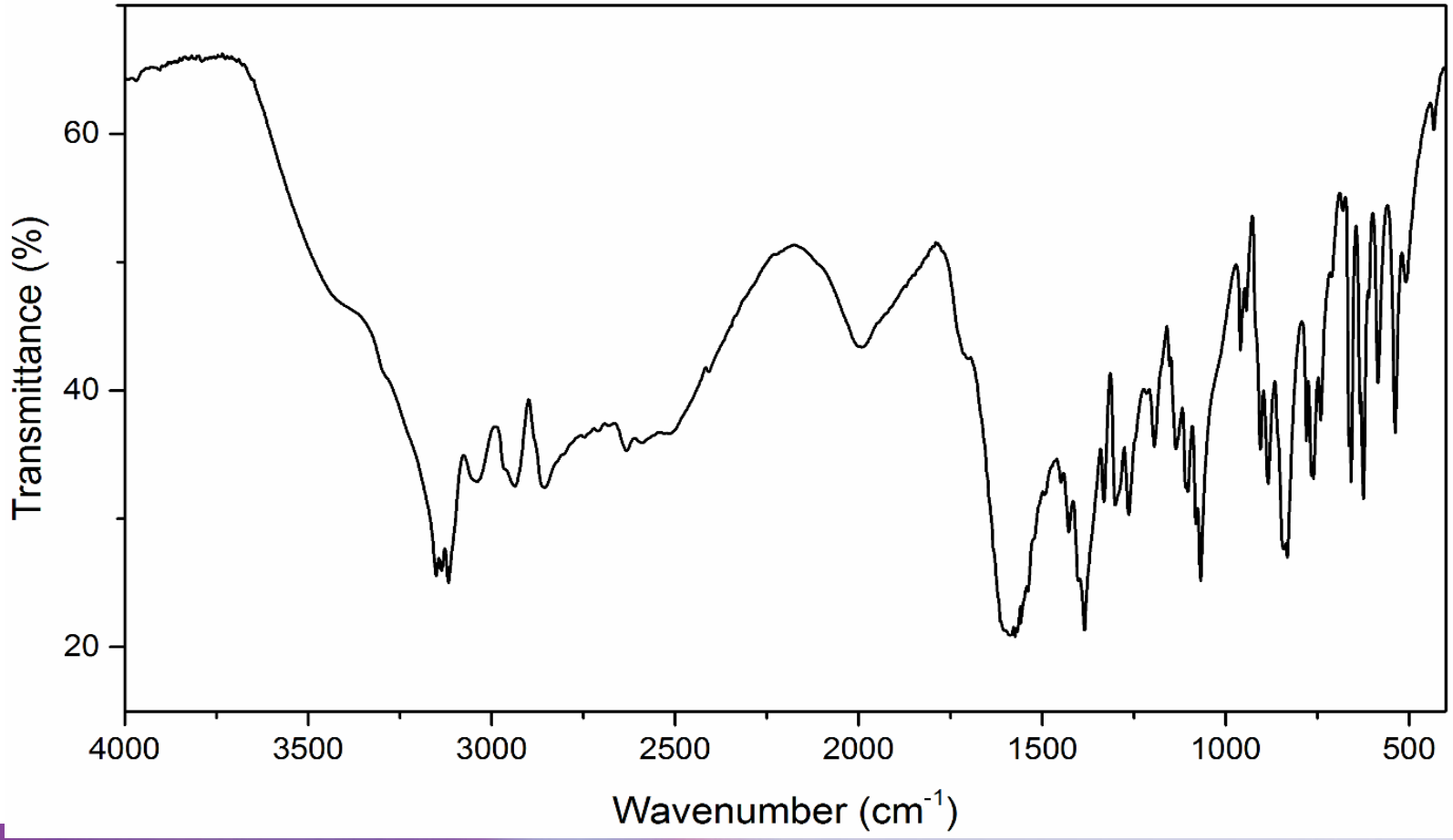
Results and discussion

FTIR spectroscopy



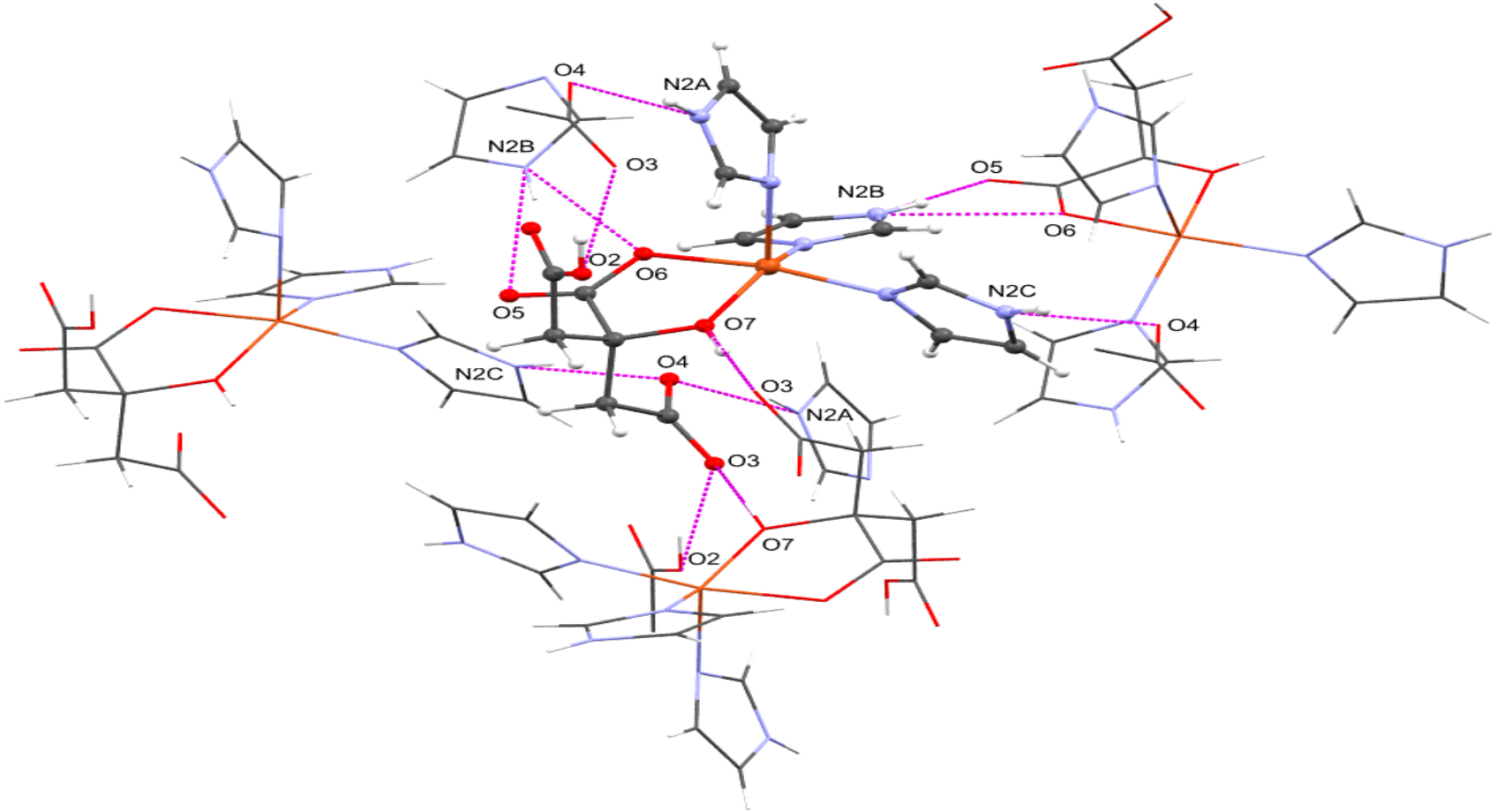
Results and discussion

FTIR spectroscopy



Results and discussion

Crystal structures and Hydrogen bonds



Results and discussion

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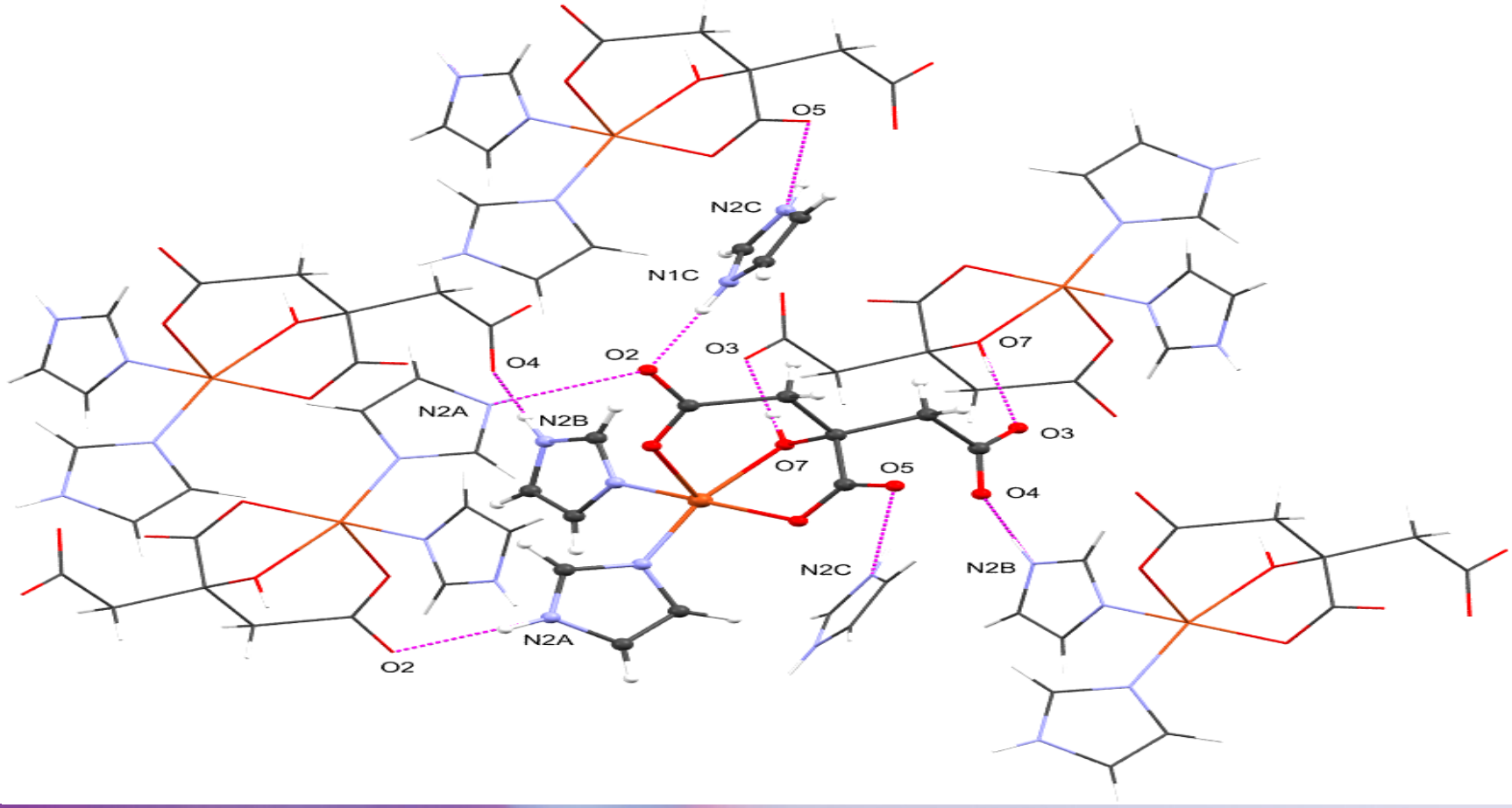

Results and discussion

Biological activity

Each complex was tested for its in-vitro antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* as examples of Gram-positive bacteria and Gram-negative bacteria, respectively.
Furthermore, both complexes were screened against two fungi, namely *Candida specie* and *Aspergillus niger*.

Results and discussion

Biological activity

	Complex (1)		Complex (2)	
	C_1 = 10 mg·mL^{-1}	C_2 = 20 mg·mL^{-1}	C_1 = 10 mg·mL^{-1}	C_2 = 20 mg·mL^{-1}
Staphylococcus aureus	15	18	18	21
Escherichia coli	NE	10	NE	NE
Candida specie	10	13	16	21
Aspergillus niger	15	18	20	23

Results and discussion

Biological activity

On the basis of the minimum inhibitory concentration (M.I.C) and the diameter of the inhibition zone, complex (**1**) showed higher fungicidal activity against *Aspergillus niger* (15 mm at 10 mg·mL-1) compared to its inhibition of *Candida specie* (10 mm at 10 mg·mL-1).

The same behavior was observed for complex (**2**) but with higher response (20 mm at 10 mg·mL-1 for *Aspergillus niger* vs. 16 mm at 10 mg·mL-1 for *Candida specie*).

Results and discussion

Biological activity

Moreover, both complexes were found to have high activity against *Staphylococcus aureus* (15 mm for complex (**1**) and 18 mm for complex (**2**), at 10 mg·mL-1).
Significantly, antibacterial activity of complex (**1**) against *Escherichia coli* was observed to be significant (10 mm at 20 mg·mL-1) compared to complex (**2**), which showed no effect on the same bacteria.

Results and discussion

Biological activity

Complex (**2**) has the additional advantage of combining the free ligand and the coordinated-ligand molecule in its structure, resulting in a more potent antifungal and antibacterial activity compared to complex (**1**).

Results and discussion

Biological activity

Significantly, the calculated electronic structure descriptors indeed predict a greater chemical reactivity for (**2**) than for (**1**).

	E_{SOMO} (eV)	σ (eV^{-1})	μ (Debye)	α (a.u)	β (a.u)
Complex (1)	-8.857	0.167	12.955	189.785	106.681
Complex (2)	-4.611	0.224	30.660	152.778	353.385

Results and discussion

Biological activity

Chemical reactivity increases with the increase of E_{SOMO}, σ, μ, α and β. As a result, chemical reactivity ranking should be as follow:

Complex (**2**) > Complex (**1**) (in E_{SOMO}, σ, μ and β)
Complex (**1**) > Complex (**2**) (in α)

Results and discussion

Biological activity

On the other hand, the chemical reactivity increases with decreasing E_{LUMO}, E_{GAP} and η. According to these parameters, the chemical reactivity ranking should be as follow:
Complex (**2**) > Complex (**1**) (in E_{GAP} and η)
Complex (**1**) > Complex (**2**) (in E_{LUMO})

	E_{LUMO} (eV)	E_{GAP} (eV)	η (eV)
Complex (1)	3.088	11.945	5.972
Complex (2)	4.311	8.922	4.461

And thus, complex (**2**) is more reactive than complex (**1**).

Conclusions

Two newly synthesized copper (II) complexes based on imidazole and citrate ligands were prepared from a one-pot synthesis and characterized by FTIR spectroscopy and single-crystal X-ray diffraction, which showed the presence of an extensive 3D propagating frameworks as a result of strong and moderate O−H…O and N−H…O hydrogen-bonds.

The antimicrobial screening suggested that the obtained complexes are promising against *Staphylococcus aureus*, though only complex (**1**) was found to be effective against *Escherichia coli*. Furthermore, (**1**) and (**2**) showed significant fungicidal activity against *Aspergillus niger* and *Candida specie*. However, (**2**) displayed higher activity compared to (**1**), this behavior was predicted by exploring the computational chemical reactivity of the two complexes.

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