

## SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SALICYLALDEHYDE SCHIFF BASE-CU(II) COMPLEX AND ITS CATALYTIC ACTIVITY IN *N*-ARYLATION REACTIONS

Afrooz Majdi–Nasab<sup>1</sup>, Fariba Heidarizadeh<sup>1</sup>, ✉, Hossein Motamedi<sup>1</sup>

<https://doi.org/10.23939/chcht17.03.557>

**Abstract.** Salicylaldehyde Schiff base-Cu complex (1:1 [M:L] chelate) was synthesized using salicylaldehyde, urea, and CuCl<sub>2</sub>. Its catalytic activity was then assessed in *N*-arylation of aromatic amines (1*H*-indole, 1*H*-pyrazole, 1*H*-imidazole, 1*H*-benzo[d][1,2,3]triazole, and aniline) with aryl halides. This reaction does not need aryl boronic acids as the active aryl source or palladium-based catalyst. Cu is cheaper than many other catalysts, and required ligands usually having quite simple structure and being inexpensive. On the other hand, with a proper ligand selection we can have a modified solubility, reactivity, and reaction efficiency. The structure and composition of this novel complex were approved by FT-IR, UV-Vis, atomic absorption spectroscopy, elemental analysis, and TGA/DTA. Investigating the antibacterial activity of the Cu complex suggests a significant antibacterial activity against standard species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis*.

**Keywords:** salicylaldehyde Schiff base-Cu complex, antimicrobial study, catalytic activity, *N*-arylation, aryl halide.

### 1. Introduction

Schiff bases are among the main groups of materials with great application in medicinal fields.<sup>1</sup> They have<sup>2</sup> the capability of coordinating metal centers as ligands.<sup>3,4</sup> In addition, Schiff bases and their complexes have been applied as biological models for realizing the bimolecular structures and biological procedures.<sup>5</sup> Several complexes comprising N, O, and S atoms in the chelating ligands, connected to the metal ion with different methods, revealed biological activities, including antibacterial,<sup>6</sup> herbicidal,<sup>7</sup> anticancer,<sup>8</sup> anti-inflammatory,<sup>9</sup> analgesic,<sup>10</sup> antifungal<sup>11</sup>, and anti-tumor<sup>12</sup> ones. It has been reported that metal chelation improves the biological activity of several

bioactive organic materials.<sup>13-14</sup>

The simple synthesis process, flexibility, and wide-range applications of Schiff base complexes have created an interesting research field. Recently, the applications of transition metal complexes with tetradentate Schiff base ligands have been extended in different areas, including catalytic reactions.<sup>15-19</sup>

*N*-Aryl heterocycles constitute the core of several natural and biologically active products.<sup>20</sup> Several important common techniques have been proposed for synthesizing or modifying such materials. One of these reactions is the cross-coupling of *N*-heterocycles with aryl halides to form related *N*-arylated heterocycle (Ullmann coupling). *N*-Arylation of azole was performed using metal-mediated reactions,<sup>21-23</sup> aromatic nucleophilic substitution,<sup>24,25</sup> and Pd- or Cu-catalyzed arylation. The copper catalysts presented a cheaper and more effective procedure for *N*-arylation of *N*-H including heterocycles with aryl halides compared to palladium.<sup>26</sup>

There have been many Cu-catalyzed approaches up to now developed for this type of transformation.<sup>27-28</sup> Following these studies, numerous groups of mono, bidentate, and polydentate chelating ligands have been improved for accelerating the reaction rates and a considerably lower reaction temperature of Cu-based C–N coupling reaction.<sup>29-33</sup> Despite the important development made in this area, more advantageous, air-stable, and cheaper ligands or metal-complexes are still required for accelerating these coupling reactions under milder conditions. Although a low catalytic activity is observed for salicylaldehyde Schiff base-Pd complexes in the C–N coupling reaction, Salicylaldehyde Schiff base-Cu complexes are assumed to be a group of efficient catalysts for the C–N coupling reaction.<sup>34</sup>

Considerable investigations have been conducted so far on salicylaldimine-derived Schiff base complexes. A wide range of physicochemical studies conducted on these complexes presented a clear perception of their stereochemical and electronic features. The flexible synthetic process is the main benefit of the salicylaldimine ligand system resulting in the preparation of a wide range

<sup>1</sup> Shahid Chamran University of Ahvaz, Ahvaz, 6135743169, Iran  
✉ heidarizadeh@yahoo.com

© Majdi-Nasab A., Heidarizadeh F., Motamedi H., 2023

of complexes with a specified metal, the features of which regularly depend on the ligand structure.<sup>35</sup>

As it is traditionally believed and according to recent studies, copper and its alloys have antimicrobial activities. These mechanisms are very complicated and occur inside and in the interstitial space between cells. However, the polarity of Cu will decrease after chelation, which subsequently improves its penetration through the lipophilic layers of the cellular membrane, resulting in hindering the bacterial growth.<sup>36</sup>

In the current research, the synthesis, characterization, and antibacterial<sup>37</sup> observation of a new salicylaldehyde Schiff base-Cu complex is reported. The catalytic activity of this complex is then investigated in the *N*-arylation of a range of *N*-heterocyclic aromatic amines with aryl halides.

## 2. Experimental

**Reagents and solvents.** The solvents and reagents were purchased from Sigma-Aldrich and they were used as received. The metal(II) chloride [CuCl<sub>2</sub>·2H<sub>2</sub>O] was used as a metal salt.

**Synthesis of bis-urea salicylaldehyde.** 10 mL of salicylaldehyde ethanolic solution (2 mmol, 0.244 g) were added to the same volume of urea ethanolic solution (1 mmol, 0.06 g). Few drops of 10% NaOH were added to adjust pH=8 and the obtained mixture then reflux under stirring for 2 h. After the reaction was completed, the precipitate was obtained by filtration, recrystallized from ethanol, and dried at room temperature with 80 % yield.<sup>36</sup>

**Synthesis of Cu complex of bis-urea salicylaldehyde.** 10 mL ethanolic solution of CuCl<sub>2</sub>·2H<sub>2</sub>O (1 mmol, 0.17 g) was mixed with the same volume of the Schiff base (1 mmol, 0.268 g) and pH was adjusted to 8-10 with some drops of ammonia solution. The mixture was stirred for 2 h to ensure the accomplishment of the reaction. The obtained complex was filtered off, washed with ethanol, and dried (yield is 0.2080 g, 98.97 %).

**General procedure for the synthesis of *N*-arylimidazole in Ullman-type coupling.** Imidazole (0.117 g, 1 mmol) or 4-nitroaniline (0.163 g, 1 mmol) and iodobenzene (0.203 g, 1 mmol), K<sub>3</sub>PO<sub>4</sub> (0.4222 g, 2 mmol), CuLCl<sub>2</sub> (0.04 g, 0.1 mmol) and 10 mL of DMF solvent were added to a 25 mL round bottom flask; the mixture was stirred at 373 K for 8 h. The reaction progress was monitored by TLC (EtOAc/*n*-hexane; 1:3 v/v) and after completion, 10 mL of distilled water were added to the reaction medium. The residual was extracted from the solution. The solid was filtered and recrystallized with ethanol. The catalyst was utilized directly for the next run. The isolated product was dried under vacuum overnight to obtain a 93 % yield for imidazole and 90 % yield for 4-bromoaniline. All products are available in the literature

and were recognized by comparison of their FT-IR, <sup>1</sup>H, and <sup>13</sup>C NMR spectra with the literature data. Selected characterization data are given below.

***N*-Phenylimidazole:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.22 (br s, 1H), 7.30 (br s, 1H), 7.35-7.41 (m, 3H), 7.46-7.51 (m, 2H), 7.87 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 118.2, 121.5, 127.4, 129.9, 130.4, 135.7, 137.4; IR (film, cm<sup>-1</sup>): 3407, 3117, 1718, 1600, 1507, 1303, 1056, 963, 757, 685.

***N*-(4-Nitrophenyl) aniline:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): d=8.12 (d, 2H), 7.39 (t, J = 2H), 7.16-7.22 (m, 3H), 6.94 (d, 2H), 6.37 ppm (br s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): d=150.3, 139.8, 139.6, 129.8, 126.3, 124.8, 122.0, 113.8 ppm.

***N*-Phenylindole:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.68 (d, 1H), 7.55 (d, 1H), 7.50-7.47 (m, 4H), 7.35-7.31 (m, 2H), 7.21 (t, 1H), 7.16 (t, 1H), 6.67 (d, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 139.8, 135.8, 129.8, 129.5, 128.0, 126.4, 124.4, 122.4, 121.1, 120.4, 110.5, 103.7, IR (film, cm<sup>-1</sup>): 2924, 1596, 1502, 1138, 745, 688.

**The antibacterial activity.** The *in vitro* antibacterial screening effects of the prepared salicylaldehyde Schiff base-Cu complex was tested against standard species *E.coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis*.

The standard Kirby-Bauer disc diffusion method was used for this purpose. The ligand and its Cu complex were dissolved in THF and four different concentrations including 80, 40, 20, and 10 mg/mL were prepared from them. A sterile blank disc was also saturated with the solvent. The target bacteria, *i.e.*, *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 9027), *Staphylococcus aureus* (ATCC 6538), and *Bacillus subtilis* (ATCC 6633) were cultured in Mueller-Hinton broth and incubated overnight at 310 K. Following bacterial growth until 0.5 McFarland turbidity, a lawn culture was prepared on Mueller-Hinton agar (Merck, Germany) and the mentioned discs were placed on each culture. The plates were incubated for 24 h at 310 K and the inhibition zone diameter (mm) was measured and recorded.

## 3. Results and Discussion

### 3.1. Chemistry

Schiff base was prepared by condensing 2 mmol salicylaldehyde and 1 mmol urea. Then, the reaction between the Schiff base and CuCl<sub>2</sub>·2H<sub>2</sub>O resulted in the CuLCl<sub>2</sub> complex. According to the analytical data respective to the complex, the stoichiometry of the prepared complex is 1:1. The large variation between the melting point of the ligand and its corresponding Cu complex demonstrated the successful synthesis of the complex. The synthesized complex was stable in an air atmosphere and

non-hygroscopic condition. The complex is insoluble in EtOH, MeOH, H<sub>2</sub>O, and CH<sub>3</sub>CN, while it is soluble in THF, DMF, and DMSO.

The complex molar conductivity in THF solvent was obtained as 10 ohm<sup>-1</sup>·cm<sup>2</sup>·mol<sup>-1</sup>. Based on these values it is approved that the prepared complex has an electrolytic nature.

The Cu concentration in the catalyst was measured with atomic absorption spectroscopy (AAS) and the outcomes showed the existence of 0.21 mmol/g of this catalyst. Analytical data and general behavior of the ligand and complex are given in Table 1.

The IR spectrum of the free ligand (Fig. 1) and a metal complex (Fig. 2) were compared for investigating the mode of binding Schiff base to metal in the complex. The absence of OH-related band at 3334 cm<sup>-1</sup> in complexes indicates OH group deprotonating and complex formation. However, metal-oxygen bond creation is confirmed by a new band at 550 and 443 cm<sup>-1</sup>, which is not observed in the free ligand spectrum and can be related to  $\nu(\text{Cu-O})$  and  $\nu(\text{Cu-N})$ , respectively. In addition, the absorption band at 1260 cm<sup>-1</sup> relating to  $\nu(\text{C-O})$  vibration of the ligand is shifted to a larger frequency showing its participation in coordinating with the metal ions via the oxygen atoms. The band at 1543 cm<sup>-1</sup> shows the participation of  $-\text{C}=\text{N}$ , which is due to the coordination of the metal ions. This area is shifted to a shorter frequency compared with its location in the original ligand (1570 cm<sup>-1</sup>). However, the disappearance of the  $\nu(\text{N-H})$  group in the ligand and complex spectrum approve its contribution to the formation of the imine group. The  $\nu(\text{C}=\text{O})$  group shows no change in both ligand and complex, suggesting that this group is not involved in

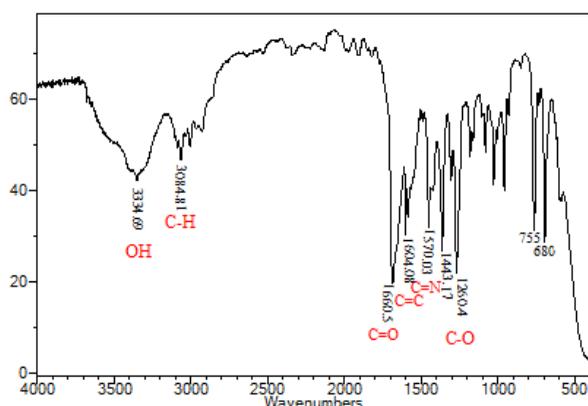
chelation.

The UV-Vis spectra provide very useful data for confirming the geometry of the metal ions in the complex considering the places and number of  $d-d$  transition bands. The Schiff base spectral data display a band at 288 nm (34662 cm<sup>-1</sup>) corresponding to transitions of  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$ . Both bands present a red shift upon coordination of a metal ion in the complex. These observations signify a further indication for the coordination of the ligand to the metal ions. Spectra of copper(II) complex has two bands appeared at 314 and 373 nm, corresponding to  ${}^4\text{B}_1\text{g} \rightarrow {}^4\text{E}_1\text{g}$  and  ${}^4\text{B}_1\text{g} \rightarrow {}^4\text{B}_2\text{g}$ , respectively, presenting charge transfer transition and octahedral geometry.<sup>38-40</sup>

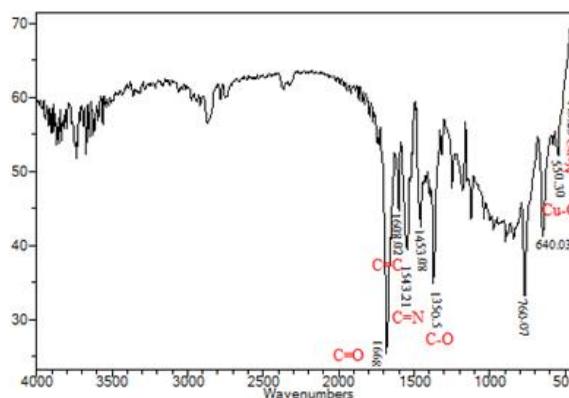
Thermal gravimetric analysis (TGA) and differential thermal analysis (DTA) of the complex were also conducted. The mass losses of various stages were computed from TGA curves and theoretically compared with those calculated for the recommended formulae according to the outcomes of elemental analysis along with the measurements of molar conductance. Thermal analysis plays a key role in investigating the metal complexes regarding the stability, melting point, structure, and decomposition features. The observed and computed mass losses, relative residues, and temperature in all steps of TGA/DTA curves are shown in Figs. 3 and 4. The TGA corresponding to the Cu(II) complex was investigated from ambient temperature to 1073 K. The TGA/DTA curves of the complex display three decomposition steps at 433, 503, and 623 K with the measurement of mass losses of the complex. These stages are the elimination of coordinated Cl<sub>2</sub> molecule and two Schiff base molecules and formation of CuO as a final product.

**Table 1.** Elemental analysis and metal estimation

Ligand/complex	MW	Color	m.p., K	C, %	H, %	N, %	$\Delta m$	AA, mmol/g
C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> (L)	268	Light yellow	373–375	67.50	4.40	10.18	–	–
CuLCl <sub>2</sub>	329	Dark green	> 623	50.12	4.24	8.81	10	0.2



**Fig. 1.** IR spectrum of ligand



**Fig. 2.** IR spectrum of the complex

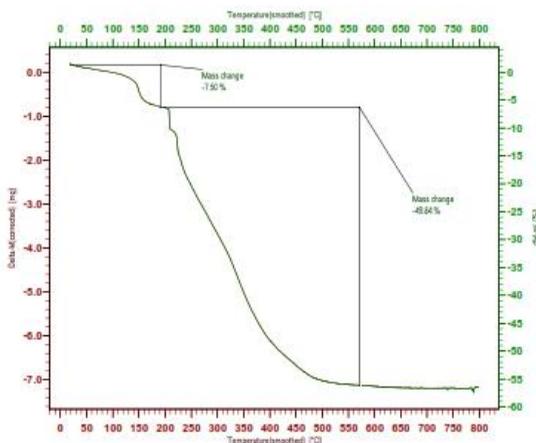


Fig. 3. TGA curve of the complex

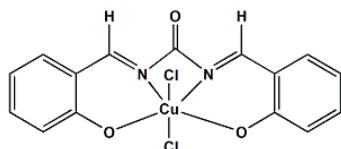


Fig. 5. Structure of  $\text{CuLCl}_2$

The complex catalytic activity was estimated through the *N*-arylation reaction of several *N*-heterocycles and aryl halide. Iodobenzene (1 mmol) and imidazole (1 mmol) were chosen as the substrate model of the reaction for the reaction optimization. Since no *N*-arylation reaction occurred in the absence of a base, numerous bases were studied among which  $\text{K}_3\text{PO}_4$  provided the maximum recovery. The solvent type was optimized using some solvents, including water, ethanol, methanol, acetonitrile, dimethylformamide, dimethylsulfoxide, and THF. The best result was achieved using DMF. The reaction was examined at different temperatures; it was seen that no reaction occurs after 24 h stirring at ambient temperature. With the enhancement of the temperature, the maximum reaction speed was observed at 373 K. and further increase in temperature did not change the reaction time. Moreover, opti-

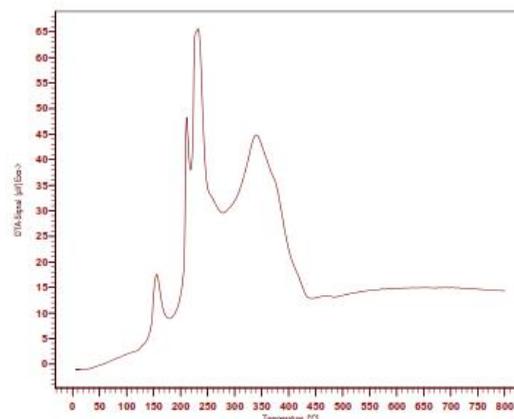


Fig. 4. DTA curve of the complex

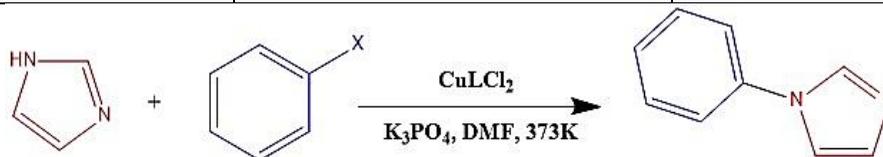
mizing the catalyst indicated that no coupling reaction occurred without using a catalyst. Different levels of the catalyst were investigated and 0.1 mmol of the catalyst was selected for the coupling reaction (Table 2).

After choosing the best conditions for the reaction, the scope of the substrates was examined by applying this novel catalytic system (Schemes 1 and 2).

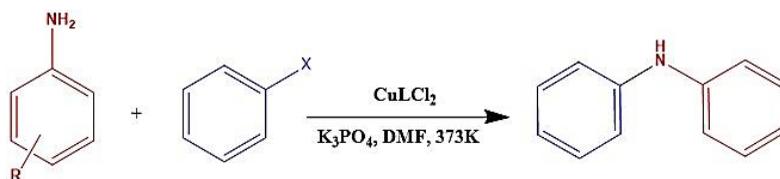
A variety of functionalized aryl halides was reacted with several *N*-heterocycles, such as imidazole, pyrazole, indole, and benzotriazole. In addition, several aromatic amines were tested as a nucleophile with aryl halides in *N*-arylation. Generally, all of the *N*-heterocycles and several aniline derivatives reacted with aryl halide and proceeded smoothly for giving the related *N*-arylated products with good improvement. It was observed that the higher reactivity was observed for aryl iodides containing electron-withdrawing group compared to aryl iodides containing groups of electron-donating. Sterically hindered aryl iodides, such as *N*-(2-methoxyphenyl)imidazole, proceeded slower compared with *N*-(4-methoxyphenyl)imidazole (Table 3). A suggested mechanistic pathway for the  $\text{CuLCl}_2$  catalyzed *N*-arylation of imidazole and aniline is shown in Scheme 3.

Table 2. Effect of increasing amount of  $\text{CuLCl}_2$  on the *N*-arylation reaction of 4-nitroiodobenzene and imidazole

$\text{CuLCl}_2$ , mmol	Time, h	Yield, %
None	48	0
0.02	8	65
0.05	8	75
0.1	8	93
0.15	8	93

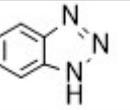
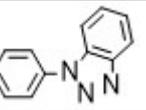
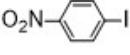
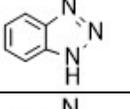
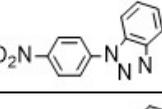
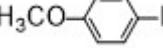
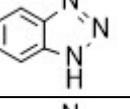
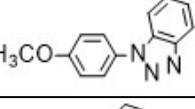
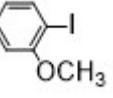
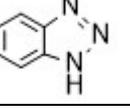
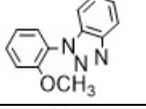
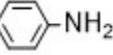
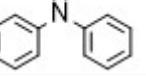
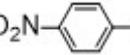
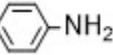
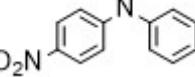
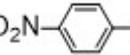
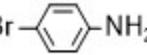
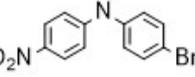
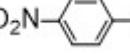
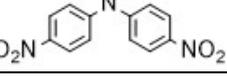


Scheme 1.  $\text{CuLCl}_2$  catalyzed *N*-arylation of imidazole

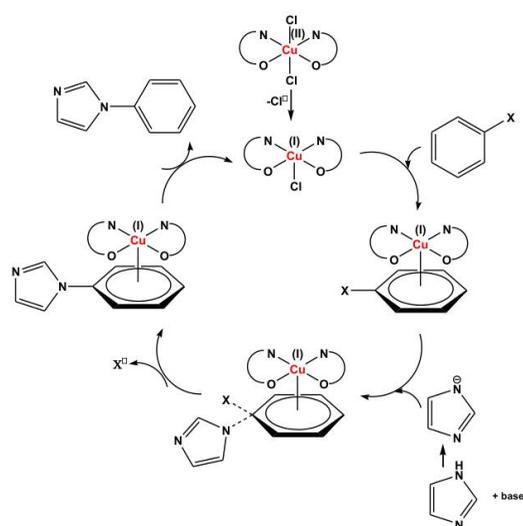
Scheme 2.  $\text{CuCl}_2$  catalyzed *N*-arylation of aniline**Table 3.** Reactions of arylhalides with indole, pyrazole, imidazole, tetrazole, aniline to form corresponding *N*-arylindoles, *N*-arylpyrazoles and *N*-arylimidazoles, *N*-aryltetrazole, *N*-arylaniline

Substrate 1	Substrate 2	Product <sup>a</sup> 3	Time, h 4	Yield, <sup>b</sup> % 5	Ref. 6
			8	92	[41]
			4	98	[42]
			12	85	[42]
			14	75	[42]
			12	75	[41]
			24	30	[40]
			8	85	[43]
			5	95	[43]
			10	75	[43]
			12	68	[43]
			12	62	[43]
			12	93	[43]
			5	93	[43]
			12	67	[44]
			15	60	[44]

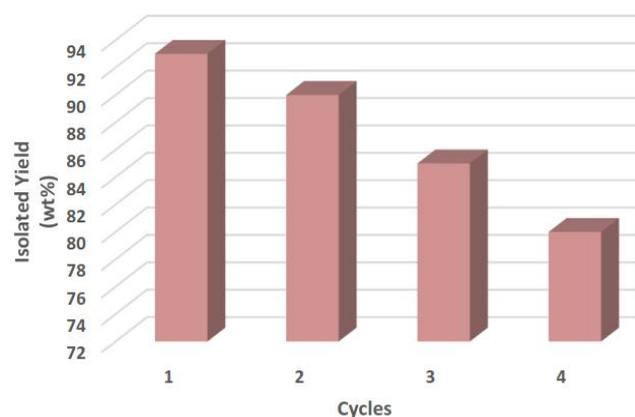
Continuation of Table 3

1	2	3	4	5	6
			12	65	[44]
			6	85	[45]
			4	93	[46]
			6	75	[47]
			10	70	[47]
			8	90	[41]
			8	93	[48]
			12	90	[49]
			10	90	[50]

Notes: <sup>a</sup> Reaction conditions: arylhalide (1 mmol), *N*-heterocycle or *N*-aryl (1 mmol), Cu complex (0.1 mmol),  $K_3PO_4$  (2 mmol) in DMF solvent at 373 K; <sup>b</sup> Isolated yield



**Scheme 3.** The proposed mechanistic pathway for the  $CuCl_2$  catalyzed *N*-arylation of imidazole ( $\pi$ -complexation mechanism)



**Fig. 6.** The recyclability diagram of the catalyst for *N*-arylation of imidazole with 4-nitroiodobenzene and imidazole

The catalyst reusability for the reaction of imidazole with iodobenzene was studied. After completing the

reaction, the extraction of product from solvent was performed by the addition of distilled water, and the complex was recovered after the solvent evaporation. Then, the recovered complex was applied in four runs, the results of which are presented in Fig. 6.

A comparison was made between this technique and the lately reported approaches for the imidazole arylation (Table 4). The reported process has great advantages, such as the application of a recyclable catalyst, elimination of the use of organic solvents, moderate reaction condition, great improvement, and shorter reaction time.

**Table 4.** Comparison of this method with recent reported protocols for *N*-arylation of imidazole with iodobenzene

System	Temperature, K	Time, h	Yield, %	Ref.
CuLCl <sub>2</sub> /K <sub>3</sub> PO <sub>4</sub> /DMF	373	8	93	[this work]
[Cu(Im <sup>12</sup> ) <sub>2</sub> ]/CuCl <sub>2</sub> /K <sub>2</sub> CO <sub>3</sub> /TBAB <sup>a</sup> /H <sub>2</sub> O	353	12	85	[28]
CuI/tripod-ligand <sup>b</sup> /Cs <sub>2</sub> CO <sub>3</sub> /DMF	383	24	95	[41]
CuI/TEPA <sup>c</sup> /TBAB/H <sub>2</sub> O	398	24	86	[43]
CuO/AB <sup>d</sup> /toluene/KO <sup>t</sup> Bu	453	18	100	[51]
CuI/diamine ligands/DMF or dioxane/Cs <sub>2</sub> CO <sub>3</sub> /reflux	383	24	74	[52]

Notes: <sup>a</sup> tetrabutylammonium bromide; <sup>b</sup> tripod-ligand: 1,1,1-tris(hydroxymethyl)ethane; <sup>c</sup> TEPA: teraethylenepentaamine; <sup>d</sup> AB: acetylene black

**Table 5.** Antibacterial activity of ligand and complex against standard species\*

Compound	Bacteria															
	<i>S. aureus</i> , mg				<i>E. coli</i> , mg				<i>B. subtilis</i> , mg				<i>P. aeruginosa</i> , mg			
	80	40	20	10	80	40	20	10	80	40	20	10	80	40	20	10
C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> L	13	12	11	9	11	10	9	10	11	11	10	9	11	10	9	8
CuLCl <sub>2</sub>	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C

Note: \* Zone of inhibition in mm in DMF solvent; C means completely sensitive

### 3.2. Microbiology

In this study, the antibacterial potential of copper-based metallodrug was investigated. To this end, the standard Kirby-Bauer disc diffusion method was used.<sup>49</sup> As a result, it was found that both ligand and complex have broad antibacterial activity against tested bacteria, *i.e.*, Gram-positive and Gram-negative bacteria (Table 5). There was a significant difference between the antibacterial activity of ligand and complex. This shows that the complex of ligand with Cu significantly enhanced its antibacterial activity. These results revealed that the target site of this complex is beyond the bacterial cell wall, and hence, both Gram-positive and Gram-negative species are completely inhibited, and no bacterial growth was found around the discs saturated with the complex. The complex can affect metabolic pathways and/or replication of bacterial cells. Furthermore, the active enzymes of the bacterial cells could be inhibited by Cu since the complex showed high bactericidal activity. Such complex gives hope for finding new antimicrobial agents for controlling these infectious agents, especially in hospital environment.<sup>53-55</sup>

### 4. Conclusions

This paper presents the synthesis of a new salicylaldehyde Schiff base-Cu(II) complex. The complex was simply prepared using inexpensive starting substances that are stable in both air atmosphere and moisture. The complex was characterized using analytical, spectral, and thermal investigations. All of the analyses suggested a reasonable octahedral structure of the metal complex. In the second section of the current study, the Cu-salicylaldehyde Schiff base complex was investigated in terms of its catalyst activity for *N*-arylation reaction with ArX (X = I, Br) in good to excellent yield. Simple synthesis procedure, catalyst stability in air and moisture, mild conditions of the reaction, the use of aryl halide in place of aryl boronic acid, and no need for protection using an inert atmosphere are the main advantages of the catalytic technique proposed in the present study.

Furthermore, the action of ligand and copper-based metallodrug as sensitive microbial were examined using *in vitro* antimicrobial activity. The results show its high effectiveness against standard species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and

*Bacillus subtilis*. It is approved that the complex has a higher antibacterial activity than the parent ligand and chelating increases the antibacterial activity of the ligand.

## Acknowledgments

The authors gratefully acknowledge financial support of this research by Shahid Chamran University of Ahvaz.

## References

- [1] Salve, P.; Alegaon, S.; Sriram, D. Three-Component, One-Pot Synthesis of Anthranilamide Schiff Bases Bearing 4-Aminoquinoline Moiety as Mycobacterium Tuberculosis Gyrase Inhibitors. *Bioorg. Med. Chem. Lett.* **2017**, *27* (8), 1859-1866. <https://doi.org/10.1016/j.bmcl.2017.02.031>
- [2] Zhou, X.-X.; Fang, H.-C.; Ge, Y.-Y.; Zhou, Z.-Y.; Gu, Z.-G.; Gong, X.; Zhao, G.; Zhan, Q.-G.; Zeng, R.-H.; Cai, Y.-P. Assembly of a Series of Trinuclear Zinc(II) Compounds with N2O2 Donor Tetradentate Symmetrical Schiff Base Ligand. *Cryst. Growth Des.* **2010**, *10* (9), 4014-4022. <https://doi.org/10.1021/CG100612B>
- [3] Arslan, H.; Duran, N.; Borekci, G.; Ozer, C. K.; Akbay, C. Antimicrobial Activity of Some Thiourea Derivatives and Their Nickel and Copper Complexes. *Molecules* **2009**, *14*, 519-527. <https://doi.org/10.3390/molecules14010519>
- [4] Mohammed Hello, K.; Mohammad, A. K. T.; Jumaah Ali, H. Solid Melamine Sulfate for Schiff Base Synthesis. *Chem. Chem. Technol.* **2019**, *13* (2), 198-204. <https://doi.org/10.23939/chcht13.02.198>
- [5] Singh, W.M.; Dash, B. C. Synthesis of Some New Schiff Bases Containing Thiazole and Oxazole Nuclei and Their Fungicidal Activity. *Pesticides* **1988**, *22*, 33-37.
- [6] More, P.G.; Bhalvankar, R.B.; Pattar, S.C. Synthesis and Biological Activity of Schiff Bases of Amino-thiazoles. *J. Indian Chem. Soc.* **2001**, *78* (9), 474-475.
- [7] Wang, Y.-E.; Yang, D.; Huo, J.; Chen, L.; Kang, Z.; Mao, J.; Zhang, J. Design, Synthesis, and Herbicidal Activity of Thioether Containing 1,2,4-Triazole Schiff Bases as Transketolase Inhibitors. *J. Agric. Food Chem.* **2021**, *69*, 11773-11780. <https://doi.org/10.1021/acs.jafc.1c01804>
- [8] Shkawat, D.; Sabnis, S.; Deliwala, C. Potential Anticancer Agents, Schiff Bases from *p*-(3-Azaspiro [5, 5]undec-3-yl) Benzaldehydes. *Bull. Haffkine Ins.* **1973**, 35-39.
- [9] Sathe, B.; Jaychandran, E.; Jagtap, V.; Sreenivasa, G. Synthesis Characterization and Anti-Inflammatory Evaluation of New Fluorobenzothiazole Schiff's Bases. *Int. J. Pharm. Res. Dev.* **2011**, *3*, 164-169. <https://doi.org/10.1155/2013/893512>
- [10] Chinnasamy, Sundararajan, R.; Govindaraj, S. Synthesis, Characterization, and Analgesic Activity of Novel Schiff Base of Isatin Derivatives. *J. Adv. Pharm. Technol. Res.* **2010**, *1*, 342-347. <https://doi.org/10.4103/0110-5558.72428>
- [11] Chaitanya, M.S.; Nagendrappa, G.; Vaidya, V.P. Synthesis, Biological and Pharmacological Activities of 2-Methyl-4H-Pyrimido[2,1-b][1,3]Benzothiazoles. *J. Chem. Pharm. Res.* **2010**, *2* (3), 206-213. <https://www.jocpr.com/abstract/synthesis-biological-and-pharmacological-activities-of-2methyl4hpyrimido21b13benzothiazoles-376.html>
- [12] Hodnett, E.M.; Dunn, W.J. Structure-Antitumor Activity Correlation of Some Schiff Bases. *J. Med. Chem.* **2002**, *13*, 768-770. <https://doi.org/10.1021/jm00298a054>
- [13] Goel, S.; Gupta, A.; Singh, K.P. Structural and Optical Studies of Polypyrrole Nanostructures. *Int. J. Appl. Chem.* **2006**, *2* (3), 157-168.
- [14] Mohindru, A.; Fisher, J.M.; Rabinovitz, M. Bathocuproine Sulphonate: A Tissue Culture-Compatible Indicator of Copper-Mediated Toxicity. *Nature* **1983**, *303*, 64-65. <https://doi.org/10.1038/303064A0>
- [15] Thurman, R.B.; Gerba, C.P. The Molecular Mechanisms of Copper and Silver Ion Disinfection of Bacteria and Viruses. *Crit. Rev. Environ. Control* **1989**, *18*, 295-315. <https://doi.org/10.1080/10643388909388351>
- [16] Thakurta, S.; Rizzoli, C.; Butcher, R.J.; Gómez-García, C.J.; Garribba, E.; Mitra, S. Sterically-Controlled Nuclearity in New Copper(II) Complexes with Di-Compartmental Ligands: Formation of Antiferromagnetically Coupled Angular Trimer and Mononuclear Inclusion Complex. *Inorg. Chim. Acta* **2010**, *363*, 1395-1403. <https://doi.org/10.1016/j.ica.2009.12.053>
- [17] Mandal, S.; Rout, A.K.; Fleck, M.; Pilet, G.; Ribas, J.; Bandyopadhyay, D. Synthesis, Crystal Structure and Magnetic Characterization of a Series of Four Phenoxo-Bridged Binuclear Manganese(III) Schiff Base Complexes. *Inorg. Chim. Acta* **2010**, *363*, 2250-2258. <https://doi.org/10.1016/j.ica.2010.03.039>
- [18] Ge, Y.-Y.; Li, G.-B.; Fang, H.-C.; Zhan, X.-L.; Gu, Z.-G.; Chen, J.-H.; Sun, F.; Cai, Y.-P.; Thallapally, P.K. Auxiliary Ligand-Dependent Assembly of Several Ni/Ni-Cd Compounds with N2O2 Donor Tetradentate Symmetrical Schiff Base Ligand. *Cryst. Growth Des.* **2010**, *10*, 4987-4994. <https://doi.org/10.1021/cg101082t>
- [19] Li, X.-G.; Huang, M.-R.; Duan, W.; Yang, Y.-L. Novel Multifunctional Polymers from Aromatic Diamines by Oxidative Polymerizations. *Chem. Rev.* **2002**, *102*, 2925-3030. <https://doi.org/10.1021/cr010423z>
- [20] Chen, D.; Martell, A.E. Dioxygen Affinities of Synthetic Cobalt Schiff Base Complexes. *Inorg. Chem.* **2002**, *26*, 1026-1030. <https://doi.org/10.1021/ic00254a013>
- [21] Corbert, J.-P.; Mignani, G. Selected Patented Cross-Coupling Reaction Technologies. *Chem. Rev.* **2006**, *106* (7), 2651-2710. <https://doi.org/10.1021/cr0505268>
- [22] Kuwabara, Y.; Ogawa, H.; Inada, H.; Noma, N.; Shirota, Y. Thermally Stable Multilayered Organic Electroluminescent Devices Using Novel Starburst Molecules, 4,4',4"-Tri(N-Carbazolyl)Triphenylamine (TCTA) and 4,4',4"-Tris(3-Methylphenylphenylamino)Triphenylamine (m-MTDATA), as Hole-Transport Materials. *Adv. Mater.* **1994**, *6* (9), 677-679. <https://doi.org/10.1002/adma.19940060913>
- [23] Maiorana, S.; Baldoli, C.; Del Buttero, P.; Di Ciolo, M.; Pagnani, A. Aromatic Nucleophilic Substitution on Haloarene Chromium Tricarbonyl Complexes: Mild N-Arylation on Indoles. *Synthesis* **1998**, *5*, 735-738. <https://doi.org/10.1055/S-1998-2058>
- [24] Hu, N.-X.; Xie, S.; Popovic, Z.; Ong, B.; Hor, A.-M.; Wang, S. 5,11-Dihydro-5,11-Di-1-Naphthylindolo[3,2-b]Carbazole: Atropisomerism in a Novel Hole-Transport Molecule for Organic Light-Emitting Diodes. *J. Am. Chem. Soc.* **1999**, *121*, 5097-5098. <https://doi.org/10.1021/ja9906554>
- [25] Kiyomori, A.; Marcoux, J.F.; Buchwald, S.L. An Efficient Copper-Catalyzed Coupling of Aryl Halides with Imidazoles. *Tetrahedron Lett.* **1999**, *40* (14), 2657-2660. [https://doi.org/10.1016/S0040-4039\(99\)00291-9](https://doi.org/10.1016/S0040-4039(99)00291-9)

- [26] Smith, W.J.; Sawyer, J.S. A Novel and Selective Method for the N-Arylation of Indoles Mediated by  $\text{KAlF}_2\text{O}_3$ . *Tetrahedron Lett.* **1996**, *37* (3), 299-302. [https://doi.org/10.1016/0040-4039\(95\)02157-4](https://doi.org/10.1016/0040-4039(95)02157-4)
- [27] Heidarizadeh, F.; Majdi-Nasab, A. A Green, Homogeneous and Reusable Surfactant/Copper Based Ionic Liquid for the N-Arylation of Indoles, Pyrazoles and Imidazoles. *Tetrahedron Lett.* **2015**, *56* (46), 6360-6363. <https://doi.org/10.1016/j.tetlet.2015.09.128>
- [28] Anbu, N.; Dhakshinamoorthy, A.  $\text{Cu}_3(\text{BTC})_2$  Metal-Organic Framework Catalyzed N-Arylation of Benzimidazoles and Imidazoles with Phenylboronic Acid. *J. Ind. Eng. Chem.* **2018**, *65*, 120-126. <https://doi.org/10.1016/j.jiec.2018.04.020>
- [29] Guo, X.X.; Gu, D.W.; Wu, Z.; Zhang, W. Copper-Catalyzed C-H Functionalization Reactions: Efficient Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115* (3), 1622-1651. <https://doi.org/10.1021/cr500410y>
- [30] Klapars, A.; Huang, X.; Buchwald, S.L. A General and Efficient Copper Catalyst for the Amidation of Aryl Halides. *J. Am. Chem. Soc.* **2002**, *124* (25), 7421-7428. <https://doi.org/10.1021/ja0260465>
- [31] Lu, Z.; Twieg, R. J. Copper-Catalyzed Aryl Amination in Aqueous Media with 2-Dimethylaminoethanol Ligand. *Tetrahedron Lett.* **2005**, *46* (17), 2997-3001. <https://doi.org/10.1016/j.tetlet.2005.03.027>
- [32] Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. Copper-Catalyzed Arylation of Amines Using Diphenyl Pyrrolidine-2-Phosphonate as the New Ligand. *J. Org. Chem.* **2005**, *70* (20), 8107-8109. <https://doi.org/10.1021/jo051221w>
- [33] Zhang, H.; Cai, Q.; Ma, D. Amino Acid Promoted CuI-Catalyzed C-N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles. *J. Org. Chem.* **2005**, *70* (13), 5164-5173. <https://doi.org/10.1021/jo0504464>
- [34] Chen, Y.J.; Chen, H.H. 1,1,1-Tris(Hydroxymethyl)Ethane as a New, Efficient, and Versatile Tripod Ligand for Copper-Catalyzed Cross-Coupling Reactions of Aryl Iodides with Amides, Thiols, and Phenols. *Org. Lett.* **2006**, *8* (24), 5609-5612. <https://doi.org/10.1021/ol062339h>
- [35] Liu, P.; Feng, X.-J.; He, R. Salen and Half-Salen Palladium (II) Complexes: Synthesis, Characterization and Catalytic Activity toward Suzuki-Miyaura Reaction. *Tetrahedron*, **2010**, *66*, 631-636. <https://doi.org/10.1016/j.tet.2009.11.072>
- [36] Lubenets, V.; Karpenko, O.; Ponomarenko, M.; Zahoriy, G.; Krychkovska, A.; Novikov, V. Development of New Antimicrobial Compositions of Thiosulfonate Structure. *Chem. Chem. Technol.* **2013**, *7* (2), 119-124. <https://doi.org/10.23939/chcht07.02.119>
- [37] Fraser, C.; Bosnich, B. Bimetallic Reactivity. Investigation of Metal-Metal Interaction in Complexes of a Chiral Macrocyclic Binucleating Ligand Bearing 6- and 4-Coordinate Sites. *Inorg. Chem.* **1994**, *33* (2), 338-346. <https://doi.org/10.1021/ic00080a024>
- [38] Lever, A.B.P. *Inorganic Electronic Spectroscopy*; Elsevier: Amsterdam, 1984.
- [39] Tas, E.; Kilic, A.; Konak, N.; Yilmaz, I. The Sterically Hindered Salicylaldehyde Ligands with Their Copper (II) Metal Complexes: Synthesis, Spectroscopy, Electrochemical and Thin-Layer Spectroelectrochemical. *Polyhedron* **2008**, *27*, 1024-1032. <https://doi.org/10.1016/j.poly.2007.11.038>
- [40] Abdseed, F.A.; El-ajaily, M.M. Preparation and Spectroscopic Investigation of a Schiff Base Metal Complexes. *Int. J. Pharm. Tech. Res.* **2009**, *1* (4), 1097-1103. [https://sphinxsai.com/PTVOL4/pdf\\_vol4/PT=21%20\(1097-1103\).pdf](https://sphinxsai.com/PTVOL4/pdf_vol4/PT=21%20(1097-1103).pdf)
- [41] Chen, H.-H.; Huang, H.-M.; Chen, S.-C.; Chen, Y.-J. Highly Efficient CuI-Catalyzed N-Arylation of Azaheterocycles with Aryl Iodides Using 1,1,1-Tris(Hydroxymethyl)Ethane as a Tridentate O-Donor Ligand: A Shorter Route to Toloxatone and Formal Synthesis of Linezolid. *J. Chin. Chem. Soc.* **2010**, *57*, 14-18. <https://doi.org/10.1002/jccs.201000002>
- [42] Swapna, K.; Murthy, S.N.; Nageswar, Y.V.D. Copper Iodide as a Recyclable Catalyst for Buchwald N-Arylation. *Eur. J. Org. Chem.* **2010**, *2010* (34), 6678-6684. <https://doi.org/10.1002/ejoc.201000964>
- [43] Yang, Q.; Wang, Y.; Yang, L.; Zhang, M. N-Arylation of Heterocycles Promoted by Tetraethylenepentamine in Water. *Tetrahedron*, **2013**, *69*, 6230-6233. <https://doi.org/10.1016/j.tet.2013.05.027>
- [44] Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.; Wang, X. 1,2,3,4-Tetrahydro-8-Hydroxyquinoline-Promoted Copper-Catalyzed Coupling of Nitrogen Nucleophiles and Aryl Bromides. *J. Org. Chem.* **2008**, *73*, 8639-8642. <https://doi.org/10.1021/jo8015488>
- [45] Begtrup, M.; Elguero, J.; Faure, R.; Camps, P.; Estopá, C.; Ilavský, D.; Fruchier, A.; Marzin, C.; de Mendoza, J. Effect of N-Substituents on the  $^{13}\text{C}$  NMR Parameters of Azoles. *Magn. Reson. Chem.* **1988**, *26*, 134-151. <https://doi.org/10.1002/mrc.1260260210>
- [46] Meshram, H.; Reddy, B.; Palakuri, R.; Rao, N.N. An Efficient and Improved Protocol for the N-Arylation of N-Heteroaryls Using Ionic Liquid as a Reaction Media. *Der Pharma Chemica* **2012**, *4* (4), 1544-1551. <https://www.derpharmachemica.com/pharmachemica/an-efficient-and-improved-protocol-for-the-narylation-of-nheteroaryls-using-ionic-liquid-as-a-reaction-media.pdf>
- [47] Hu, K.; Niyazymbetov, M. E.; Evans, D. H. Nucleophilic Aromatic Substitution by Paired Electrosynthesis: Reactions of Methoxy Arenes with 1H-Tetrazoles. *Tetrahedron Lett.* **1995**, *36*, 7027-7030. [https://doi.org/10.1016/0040-4039\(95\)01455-Q](https://doi.org/10.1016/0040-4039(95)01455-Q)
- [48] Wadia, M.S.; Patil, D.V. A Convenient Preparation of N-Alkyl and N-Arylamines by Smiles Rearrangement - Synthesis of Analogues of Diclofenac. *Synth. Commun.* **2003**, *33*, 2725-2736. <https://doi.org/10.1081/SCC-120021996>
- [49] Chauhan, S.M.S.; Singh, R.; Geetanjali. An Improved Synthesis of N-Substituted-2-Nitroanilines. *Synth. Commun.* **2003**, *33*, 2899-2906. <https://doi.org/10.1081/SCC-120022180>
- [50] Kim, J.; Kim, S.; Kwag, H.J.; Park, S.H. Method for Preparation of 4,4'-Dinitrodiphenylamine and 4,4'-Bis(Alkylamino)Diphenylamine by Using 4-Nitroaniline. U.S. Patent US8759587B2, June 24, 2014.
- [51] Kim, A.Y.; Lee, H.J.; Chan Park, J.; Kang, H.; Yang, H.; Song, H.; Park, K.H. Highly Efficient and Reusable Copper-Catalyzed N-Arylation of Nitrogen-Containing Heterocycles with Aryl Halides. *Molecules* **2009**, *14*, 5169-5178. <https://doi.org/10.3390/molecules14125169>
- [52] Antilla, J.C.; Baskin, J.M.; Barder, T.E.; Buchwald, S.L. Copper-Diamine-Catalyzed N-Arylation of Pyrroles, Pyrazoles, Indazoles, Imidazoles, and Triazoles. *J. Org. Chem.* **2004**, *69*, 5578-5587. <https://doi.org/10.1021/jo049658b>
- [53] Sobhani, S.; Pordel, M.; Beyramabadi, S.A. Design, Synthesis, Spectral, Antibacterial Activities and Quantum Chemical Calculations of New Cu(II) Complexes of Heterocyclic Ligands. *J. Mol. Struct.* **2019**, *1175*, 677-685. <https://doi.org/10.1016/j.molstruc.2018.08.034>
- [54] Xu, Y.; Shi, Y.; Lei, F.; Dai, L. A Novel and Green Cellulose-Based Schiff Base-Cu (II) Complex and Its Excellent Antibacterial Activity. *Carbohydr. Polym.* **2020**, *230*, 115671. <https://doi.org/10.1016/j.carbpol.2019.115671>

[55] Pan, Y.-Q.; Zhang, Y. Y.; Yu, M.; Zhang, Y.Y.; Wang, L. Newly Synthesized Homomultinuclear Co (II) and Cu (II) Bissalicylamide-like Complexes: Structural Characterizations, Hirshfeld Analyses, Fluorescence and Antibacterial Properties. *Appl. Organomet. Chem.* **2020**, *34*, e5441. <https://doi.org/10.1002/aoc.5441>

Received: February 26, 2021 / Revised: March 16, 2021 /

Accepted: September 02, 2021

**СИНТЕЗ ТА АНТИМІКРОБНА АКТИВНІСТЬ  
КОМПЛЕКСУ САЛІЦИЛАЛЬДЕГІДНА ОСНОВА  
ШИФФА-Cu(II) ТА ЙОГО КАТАЛІТИЧНА  
АКТИВНІСТЬ У РЕАКЦІЯХ N-АРИЛЮВАННЯ**

**Анотація.** Синтезовано комплекс саліцилальдегідна основа Шиффа-Си (1:1 [M:L] хелат) з використанням саліцилальдегіду, сечовини та  $\text{CuCl}_2$ . Проведено оцінювання його каталітичної активності для реакції N-арилювання ароматичних

амінів (1H-індол, 1H-піразол, 1H-імідазол, 1H-бензо[d][1,2,3]тріазол та анілін) арилгалогенідами. Реакція не потребує арилборних кислот як активного джерела арилу або каталізатора на основі паладію. Мідь є дешевою, ніж багато інших каталізаторів, а необхідні ліганди зазвичай мають досить просту структуру і коштують недорого. Показано, що при правильному виборі ліганду є можливість змінювати розчинність, реакційну здатність та ефективність реакції. Структура та склад нового комплексу підтверджені методами FT-IR, UV-Vis, атомно-абсорбційної спектроскопії, елементарного аналізу та TGA/DTA. Встановлено, що комплекс Си має значну антибактеріальну активність щодо стандартних видів *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* і *Bacillus subtilis*.

**Ключові слова:** комплекс саліцилальдегідна основа Шиффа-Си, антимікробне дослідження, каталітична активність, N-арилювання, арилгалогенід.