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Design Synthesis and Preliminary Antibacterial Evaluation of Schiff Base Metal Complexes of Ampicillin and Cephalexin

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Abstract

In the present study, new Schiff bases derived from two beta lactam antibiotics, ampicillin and cephalexin were synthesized from condensation of the aforementioned drugs with Terephthalaldehyde and their metal complexes counterparts with copper (II) have been synthesized. In both drugs the free amino group of the acylamino side chain allowed to react with Terephthalaldehyde to obtain Schiff bases which were, subsequently, allowed to react with copper chloride separately to form Schiff base copper complexes. All the derivatives and metal complexes are analyzed by FT-IR, elemental analysis and ^{1}H NMR analysis. The antibacterial activity of the prepared compounds was screened against several bacterial strains namely S. aureus, E. coli and P. aeruginosa. The antibacterial screening tests elicit that both copper complexes besides Schiff bases exhibited promising antibacterial activity against these microorganisms so that they are of improved antibacterial activity than the parent drugs.

***Keywords**: Schiff base; Ampicillin; Cephalexin; Metal complexes; Terephthalaldehyde.*

Introduction

Schiff bases are compounds that are synthesized by condensation reaction of primary amines with carbonyl groups [1,2]. In the past many Schiff base derivatives have been prepared and employed for applications like catalysis and enzymatic reactions, luminescent material, magnetism and molecular architectures [3]. However recently Schiff bases metal complexes gain massive attention in the domain of biological chemistry and coordination chemistry [4].

The incidence of infection has increased significantly as a result of multidrug resistance which gain a great clinical significant that motivate additional urgency for finding out a novel antibacterial agent which preferably act by a different mechanism of action or by broadening the antibacterial spectrum of the current antibiotics for example by forming a mutual prodrug [5,6].

The terrifying development of outbreaks by multidrug-resistant organisms constitute a great challenge when treating these infections, as these isolates often respond to a limited number of antibiotics and are in most cases life threatening [1,7,8]. Schiff bases are among the most efficient strategies tried to enhance the antimicrobial activity of many compounds including antibiotics and/or extend the spectrum of that individual antibiotic to include a resistant bacterial strain or a common bacterial pathogen [9-14].

Schiff's bases represent an important class of pharmacologically active molecules so that have engaged a great concern by medicinal chemist as they possess a variety of pharmacological properties. *A number of Schiff's base derivatives have been reported to exert notably antibacterial, antifungal, antitubercular, antitumor, antileishmanial, DNA-binding activities, etc*

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[6,15-18]. It is believed that different biological activity of Schiff bases like antitumor, antibacterial, antifungal and herbicidal activities are attributed to the azomethine linkage [19,20].

Many Schiff base derivatives of β- lactam antibiotics have been synthesized and screened for their antimicrobial activity in order to enhance their potency and/ or extend their spectrum of antibacterial activity; Schiff base ligands and their metal complexes derived from different aldehydes with cefadroxil [21], cephradine [2,22], ceftriaxone [2,23] and cephalothin [24], amoxicillin [25-29] have been synthesized and generally found that there is an enhancement in the activity of the prepared ligands and their metal complexes counterparts over the parent drug.

Ampicillin and cephalexin have been synthesized as metal complexes and as Schiff base derivatives by combining the drug molecule with different aldehydes, metal complexes for the prepared Schiff bases also synthesized. The prepared compounds were tested for their prospective antibacterial properties [30-50]. Pharmacological research interest in the design of metal–drug complexes since it was found that metal – drug combination help boost its activity and lower the incidence of toxic effects [19].

Experimental

Materials

All chemicals and solvents used were of analytical grade (Merk, Fluka and Sigma- Aldrich) and were used without further purification.

Measurement

Melting points were measured by open capillary method and are reported uncorrected (**TABLE 1**). IR spectra were obtained on Perkin Elmer IR spectrophotometer (KBr disc) in faculty of pharmacy/ university of kufa **(TABLE 2).** Elemental microanalysis was accomplished at the Jordanian University using CHN Elemental Analyzer (Euro-vector EA3000A, Italy) (**TABLE 1**). Nuclear magnetic resonance spectrum ^{1}H NMR for Schiff base and copper complexes was recorded in DMSO-d6 using a Bruker 500 MHz instrument using a tetra methyl silane (TMS) as an internal standard in Terbia Modares University.

Preparation of schiff base ligands

Two Schiff base ligands were produced by reacting the drug substances with Terephthalaldehyde separately. The method of preparation was as follows. The solution of Terephthalaldehyde in absolute methanol was appended drop wise into 25 mL of either cephalexin or ampicillin in the same solvent with persistent stirring in 1:2 molar ratios. To this, KOH (0.1% in methanol) was appended to adjust the PH of the medium between pH 7 and 8 and the mixture was kept under reflux for 5 hours. After that the crude mixture has condensed to about one-third of its volume by vacuum evaporation. A bright yellow colored Schiff base was extracted by the addition of diethyl ether which was then filtered, followed by the addition of methanol and then drying under vacuum. Recrystallization was done in methanol.

TABLE 1. **Physical properties and micro analytical data of ligand and its metal complexes.**

Compound	**Color**	**Melting point**	**Percent of yield**	**Elemental analysis found (calculated)**			
				C	**H**	**N**	**M**
terephthalaldehydeneampicillin	yellow	229	79	60.83 **(60.29)**	4.97 **(5.06)**	10.19 **(10.55)**	-
terephthalaldehydenecephalexin	yellow	195	74	60.15 **(60.59)**	4.22 **(4.58)**	10.78 **(10.60)**	-
Terephthalaldehydeneampicillin- Cu (II)	green	318	68	51.94 (51.58)	4.54 (4.33)	9.37 (9.02)	6.38 (6.82)
Terephthalaldehydenecephalexin- Cu(II)	Light green	274	66	52.07 (51.81)	3.59 (3.91)	9.33 (9.06)	6.48 (6.85)

FIG.1. **Synthesis of terephthalaldehydenecephalexin.**

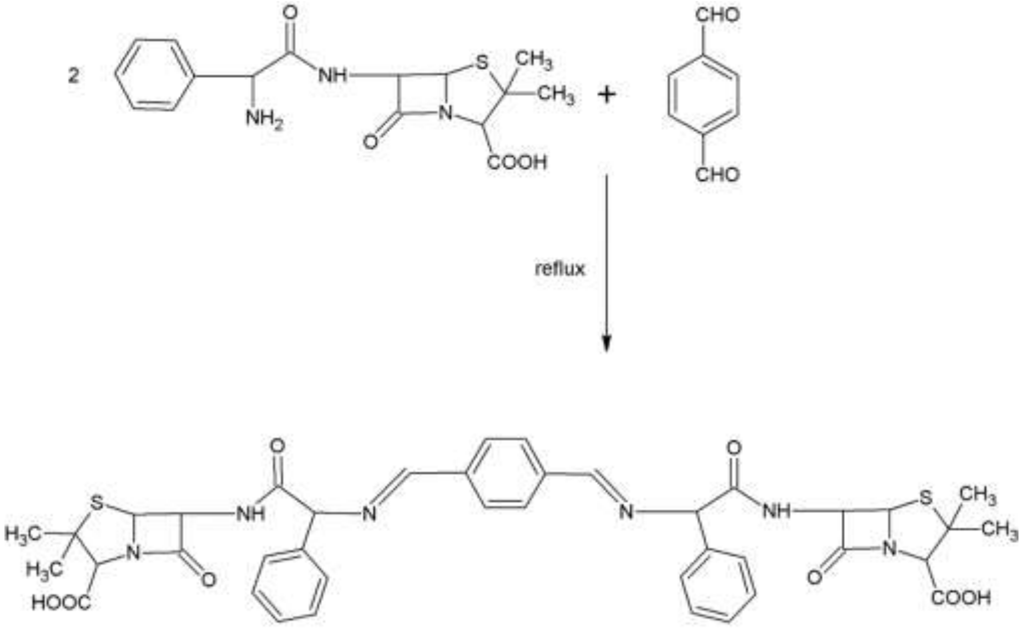
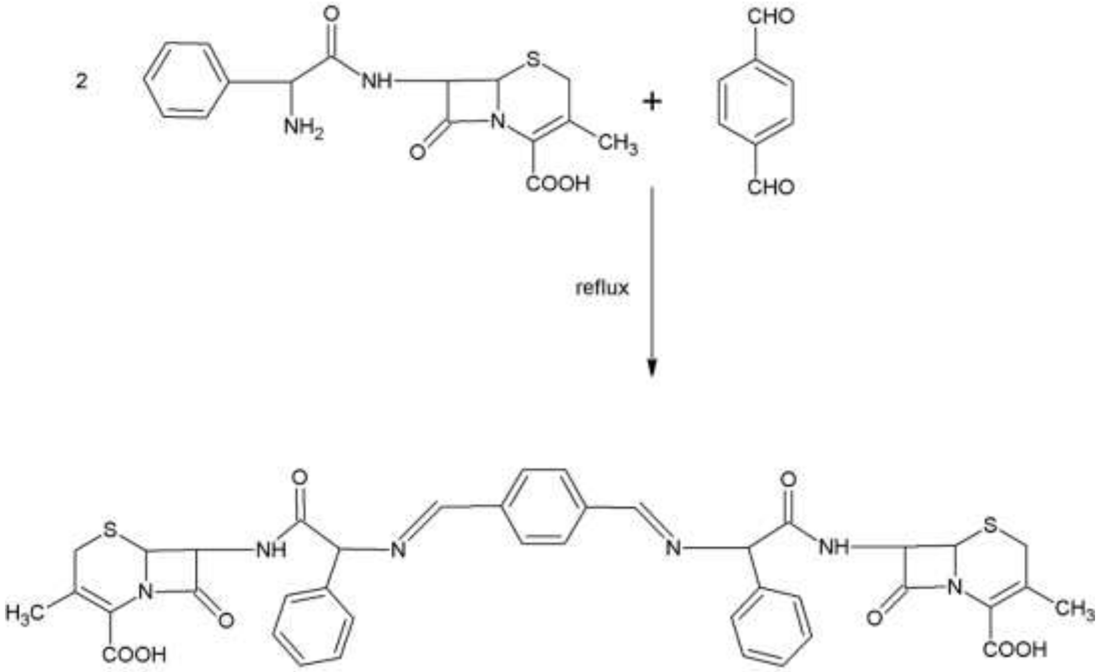


FIG.2. **Synthesis of terephthalaldehydeneampicillin**.



Preparation of Schiff base copper complexes

2 mmol of the previously prepared Schiff base ligand dissolved in methanol (25 ml) then added to 25 ml of methanol containing 2 mmol of copper chloride Cu (II). The mixture was then kept under reflux for 4 h. Then reducing the mixture volume under vacuum, filtering it off, washing with methanol and finally drying under vacuum.

Antimicrobial activity

The prepared Schiff bases along their metal complexes were screened for their potential activity against some selected microorganisms, especially against Escherichia coli, staphylococcus aureus, and Pseudomonas aeruginosa by measuring the zone of inhibition in culture medium in mm. The antibacterial activity was performed according to filter paper disc plate method at concentration 100 μg/mL and the results reported in **TABLE 3**. The culture medium was Muller Hinton agar & Sabouroud Dextrose agar while the solvent control was DMSO.

Results and Discussion

The Schiff base metal complexes were obtained by reacting with copper chloride with Schiff base ligands in methanol under reflux separately. The solubility of the intermediates and final products was assayed in water and certain organic solvents. The ligands were soluble in water, methanol, DMF (Dimethylformamide) and DMSO (Dimethyl sulfoxide), while metal complexes were soluble in DMF and DMSO but not dissolve in more nonpolar organic solvents. The Schiff bases and the copper complexes were sufficiently hygroscopic.

It is possible to explore the bonding pattern of ligands to the metal elements from the comparison of FT-IR spectral data of the Schiff bases to those of copper complexes counterparts. These data indicate the formation of Schiff base ligands through the –C=N- bond and ligands coordinate with copper ion through nitrogen and oxygen.

TABLE 2. **IR spectral data of the synthesized compounds.**

Compound	**C=O**	**C=N**	**M-N**	**M-O**
Terephthalaldehydeneampicillin	1672	1638	-	-
Terephthalaldehydenecephalexin	1668	1632	-	-
Terephthalaldehydeneampicillin-Cu (II)	1655	1618	483	436
Terephthalaldehydenecephalexin-Cu(II)	1643	1615	507	439

TABLE 3. **The antibacterial activity of ligands and complexes.**

Compound	***E. coli***	***S. aureus***	***P. aeruginosa***
Terephthalaldehydeneampicillin	25	29	18
Terephthalaldehydenecephalexin	27	27	16
Terephthalaldehydeneampicillin-Cu (II)	28	32	20
Terephthalaldehydenecephalexin-Cu(II)	29	30	15

The absorption bands for azomethine group of the Schiff base ligands appears in the range of 1620-1650 while those for metal complexes are slightly revolved to slightly higher values denoting the coordination of Schiff bases with metal ion through –N=C which contrary to bands related to the carboxylic acid group which remain in its range as this group does not participate with the metal ion. A new absorption bands exist in the range of 480- 510 for (M–N) and 415- 450 for (M-O) indicating the coordination of the ligands with the metal ion through N and O atoms.

The 1H NMR spectrum of terephthalaldehydeneampicillin show a signal that is related to the chemical shift of the two methyl protons on the Thiazolidine ring existed at δ 1.2 and 1.39 ppm. The protons of N-CH and CO-CH on the beta-lactam ring and NH proton of amide have chemical shifts of δ 4.75, 4.55 and 8.23 ppm respectively. The azomethine proton appeared at δ 8.45 ppm while aromatic protons found at 6.85- 7.97 (m). No signal in the chart attributed to the chemical shift of the free amino group of ampicillin as it takes part in azomethine group formation. The 1H NMR spectrum of terephthalaldehydeneampicillin Cu (II) complex in DMSO exhibited signals belong to chemical shifts of the protons of aromatic moiety, protons of CO-CH and N-CH on the beta-lactam ring observed at δ (6.68-7.76), 4.71, 4.95 ppm respectively. While signals occurred at δ 8.72 and 8.71 are related to the NH proton of the amide and azomethine proton respectively [32,33,51-53].

The 1HNMR spectrum of terephthalaldehydenecephalexin exhibited signals that are related to amide proton, azomethine proton and aromatic protons occurred at δ 9.07, 8.65 and (6.71-7.85) respectively. The chemical shifts occurred at δ2.25, 4.52 and 5.03 were attributed to protons of methyl group, protons of CO-CH and N-CH on the beta-lactam ring respectively. There is no signal to appear for the free amino group of cephalexin as it is utilized in formation of Schiff base. The 1H NMR spectrum of terephthalaldehydenecephalexin Cu (II) complex in DMSO showed signals occurred at δ 2.33, 5.27 and 4.85 and were attributed to chemical shifts of methyl protons, protons of N-CH and CO-CH on the beta-lactam ring respectively. The chemical shift values at δ9.38, 8.97 and (6.65-7.72) are attributed to the protons of amide, azomethine and aromatic group respectively [32,33,51-53].

Conclusion

Two new Schiff base derivatives of ampicillin or cephalexin with Terephthalaldehyde were synthesized at first then these Schiff bases are complexed with copper to form metal complex, the structures of the metal complexes as well as Schiff bases were proved by elemental analysis, NMR and FTIR spectra. The elemental analysis suggest that the 1:1 (M_2L_2) composition of the metal complexes where "M" depicts metal ion and "L" depicts the free ligand, indicating that the four azomethine groups of the two Schiff base ligands are coordinated with two central metal ions via "N" and "O" atoms, which is advocated by the FT-IR spectra.

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