***Synthesis , characterization and solubility study of new substituted Via Schiff Bases for ampicillintrihydrate drug with various aldehydes***

***Maha K. Mahmmod***

University of Kerbala, College of Education of pure science, Unit of Chemistry

**Abstract**: **Abstract**: Some of aldehydeamino-N-ampicillin (Schiff bases) were prepared by condensation of ampicillin trihydrate drug with many substitute aromatic aldehydes, the synthesized compounds were tested using U.U , FT-IR and 1H-NMR spectroscopy . The solubility study show increasing solubility of these compounds compeer with ampicillin . The biological activity expected to be more than ampicillin and they still to be doun.

***تحضير وتشخيص ودراسة الذوبانية لمعوضات جديدة عن طريق قواعد شف لدواء الامبسلين بأستخدام الديهايدات مختلفة***

مها قاسم محمود

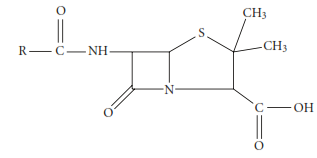
كلية التربية للعلوم الصرفة / قسم الكيمياء/ جامعة كربلاء

***الخلاصة***

تم في هذا البحث تحضير عدد من معوضات الديهايد امينو امبسلين عن طريق تكثيف دواء الامبسلين مع عدد من معوضات البنزلديهايد . تم تشخيص المركبات المحضرة باستخدام مطيافية الاشعة فوق البنفسجية والاشعة تحت الحمراء ومطيافية الرنين النووي المغناطيسي وكانت جميع النتائج مطابقة لما هو متوقع , دراسة الذوبانية للمشتقات المحضرة تمت بأستخدام مذيبات مختلفة وبينت زيادة في الذوبانية لها مقارنة بالانبسلين نفسة . الفعالية البايلوجية للمركبات المحضرة يتوقع ان تكون عالية وهي قيد الانجاز.

**INTRODUCTION**

Semisynthetic beta-lactam antibiotics are the most important class of antibacterial agents. Their use in veterinary and human medicine is in continuous expansion. Some examples of semisynthetic penicillins and cephalosporins are amoxicillin, ampicillin, cephalexin, cefadroxil, and cefazolin, among many others. They have in common the presence of the beta-lactam ring, responsible for their antimicrobial activity. They irreversibly inhibit the last step of the bacterial cell wall biosynthesis. The beta-lactam antibiotics can be described in terms of a beta-lactam nucleus with a side-chain (Figure 1).



**Figure 1: General structure of beta-lactam antibiotics.**

Many deferent side-chains are found in the antibiotics that are in use today,

for example, replacing the phenylacetic acid side-chain with D-phenylglycine results in the beta-lactam antibiotic ampicillin (I). Ampicillin (6-[2-amino-2-phenylacetamide] penicillanic acid) that is orally stable1-4, was the ﬁrst antibiotic to be used in therapy 5,6. It is one of most widely used semisynthetic beta-lactam antibiotics which was utilized for Gram-negative and Gram-positive bacteria 7,8. Multiple-antibiotic-resistant organisms are a problem for healthcare facilities and cause an increase in fatalities. 9 Alternative structures of ampicillin have specific advantages in clinical applications. 10 Compound containing imines bases (Schiff bases)have not only found extensive application in organicsynthesis,11,12 but several of these molecules display significant biological activity such as antimalarial,13 anticancer,14,15 antibacterial,16-18 antifungal,13 antiinflammetery,19 antimicrobial,20,21 and antiviral22. The formation of carbon–nitrogen double bond can be achieved by the reaction of aromatic aldehydes and amines Schiff’s bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. The Schiff bases are also used as versatile components in nucleophilic addition with organ metallic reagents,23 and in cycloaddition reactions. 25 When a drug is orally administered, solubilization in the drug is essential for bioavailability because only the dissolved drug can be absorbed. 26 Therefore, the solubility of a drug directly affects its clinical application27. Ampicillin solubility increases with the pH. This behavior can be explained by its determined values of the acid group pK (2.66) and amine group pK (7.24) and calculated of its isoelectric point (4.95). Hence, above the pH correspondent to its isoelectric point the number of ampicillin molecules with a neutral charge (which is the most insoluble form) decreases, leading to higher solubility values. This eﬀect becomes more important for pH above 7.0.

The present work is oriented towards synthesis of some Schiff bases of ampicillin by condensing with different aromatic aldehydes in ethanol at 50-600C(scheme 2.). Also study the solubility of the new ampicillin derivatives and compeer them with ampicillin. All synthesized compounds have been characterized on the basis of their m.p, U.V , FTIR and 1H-NMR .

**Experimental Section**

Melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using percolated TLC plates (MERCK, 60F) using chloroform: methanol (8:2) solvent system, compounds were visualized by using I2 vapor. The developed chromatographic plates were visualized under iodine. IR spectra were recorded using KBr on Shimadzu FTIR model 8400 spectrophotometer

**General procedure for the synthesis of Schiff bases of ampicillin (II-IV).**

The benzaldehyde (0.003 mol, 0.08 ml), 1,4-dichlorobenzaldehyde (0.003mol,0.24 gm.) and 1,4-dihydroxybenzaldehyde ( 0.003mol, 0.2gm) were dissolved in methanol (10 ml) and added to the amoxicillin trihydrate (0.003mol,0.25gm) dissolved in methanol (10 ml). To this KOH (0.1 % in methanol) was added to adjust the pH of the solution between 7-8 and then the mixture respectively was refluxed for 3-4hrs. After complete refluxation Schiff base was separated out on removal of the solvent at room temp. A light yellowish and brown colored crystalline solid obtained.

**N-(benzylidine)-ampicillin (II):**

IR (KBr cm-1): 1597.40 (HC=N), 2964.96 (C-H str), 1670.54 (C=Ostr), H-NMR : ( ppm ) 1.35 (H aliphatic), 7-7.6 (H aromatic), 8.10 ( H Schiff bases) . UV: ( max ) 234 and 321. This and ethers absorption are seen in table ( 1) fig. (1) and ( 4 ).

**N-(2,4-dichloro benzylidine)-ampicillin (III):**

IR (KBr cm-1): 1593.82 (HC=N), 2966.38 (C-H str), 1670.40 (C=Ostr), 1089(C-Cl str). UV: ( max ) 234 and 321. This and ethers absorption are seen in table ( 1) fig. (2).

**N-(2,4-dihydroxy benzylidine)-ampicillin (IV):**

IR (KBr cm-1): 1585.82 (HC=N), 2966.38 (C-H str), 1670.40 (C=Ostr), 3338(C-OHArstr). UV: ( max ) 234 and 321. This and ethers absorption are seen in table ( 1) fig. (3).

**Table(1):The Physical property and spectroscopic data of [II-IV].**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **1H-NMR spectral data ppm** | | | | | **FTIR spectral data cm-1** | | | **Comp.**  **No.** |
| ****  **Schiff bases** | ****  **Aliphatic** | | **H)**  **Aromatic** | | **(C-H)**  **Aromatic** | **(C=O)**  **Amide** | **(C=N)**  **Schiff bases** |
| 8.45 | 1.35 | | 7.1-7.8 | | 3034 | 1670.54 | 1597.40 | **II** |
| **max (nm)** | **RfValuo** | | **Yield**  **%** | | **Melting**  **Points****C** | **Color** | **Molecular formula** |
| 234, 321 | 0.72 | | 60 | | 118 | Yellow | C23H23O4N3S |
| ****  **Schiff bases** | ****  **Amide** | | **H)**  **Aromatic** | | **(C-Cl)** | **(C=O)**  **Amide** | **(C=N)**  **Schiff bases** | **III** |
| - | - | | **-** | | 1089 | 1670.40 | 1593.82 |
| **max (nm)** | **RfValuo** | | **Yield**  **%** | | **Melting**  **points****C** | **Color** | **Molecular formula** |
| 256,333 | 0.41 | | 70 | | 150 | Yellow | C23H21O4N3SCl |
| ****  **Schiff bases** | | **** | | **H)**  **Aromatic** | **(C=O)**  **Amide** | **(OH)** | **(C=N)**  **Schiff bases** | **IV** |
| - | - | | - | | 1670.40 | 3338 | 1585.82 |
| **max (nm)** | **RfValuo** | | **Yield**  **%** | | **Melting**  **points****C** | **Color** | **Molecular formula** |
| 256,333 | 0.52 | | 75 | | 72 | Brown | C23H23O6N3S |
| **Table( 2 ):The solubility study of compounds [II and III]**   |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | | **Comp.**  **No.** | **Water** | **Acetone** | **Methanol** | **10%HCl** | **10%NaOH** | **DMF** | **DMSO** | | **Ampic.** | **\_** | **\_** | **\_** | **+** | **++** | **+** | **+** | | **I** | **+** | + | **+** | **+** | **+** | **+** | **+** | | **II** | **+** | \_ | **+** | **+** | **+** | **+** | **+** | | **III** |  |  |  |  |  |  |  | | | | | | | | | | |



**Scheme: 2 Synthesis of Schiff Bases (II to IV)**

**RESULTS AND DISCUSSION**

The Schiff base compounds [II-IV] were synthesized from the reaction of ampicillin with different substituted aldehydes and purified by successive recrystallization using ethanol. If we focus on the mechanism of transformation of aldehydes and amines in to Schiff bases, two synthetic methods are possible which are mechanized in Scheme-2. In method I, there is nucleophiles attack of primary amine on carbonyl carbon affords hydroxyl compound which on dehydration gives Schiff bases. The formation of Schiff bases in the second step largely depends upon the rate of removal of water from reaction mixture. Originally, the classical synthetic route for synthesis of Schiff bases was reported by Schiff 24 which involves condensation of primary amines with carbonyl compounds under isotropic distillation28 with the simultaneous removal of water. The removal of water during this condensation also conventionally facilitated by using molecular sieves or a Dean-Stark Apparatus.29 To overcome the difficulties in the removal of water, alternative method II has been employed in which Lewis acids used as catalyst which accelerates nucleophilic attack of amines on carbonyl carbon as well as serving as dehydrating agent for removal of the water in the second step. Alumina30, P2O531 and also by using materials like Hydrotalcite32.

**Method -I**



**Method –II**



**Scheme I: Mechanism for acid catalyzed Schiff base synthesis**

The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their FTIR and U.V The synthesis of these compounds was carried out a according to the steps outlined in scheme (2), and the physical properties are given in Table (1).

*FTIR studies*.- In the FTIR spectra of ampicillin derivatives (II-IV) showed disappearance of  (N-H) absorption bands and showed strong absorption bands

at 1585-1597 cm-1 for C=N group of Schiff base and this is good indicated for complete the reaction as seen in fig. (3-5) .

*UV*–*Vis studies*.- UV–Vis spectra of the compounds were measured in DMF using 10−2 as well as 10−4 M solutions, for ampicillin derivatives (I-III) showed two very strong bands at ( 234 nm , 321 nm) , (256 nm , 333 nm) and ( 256 nm, 333 nm) all these absorption due to π→π\* and n→π\* transition as seen in table (1) .

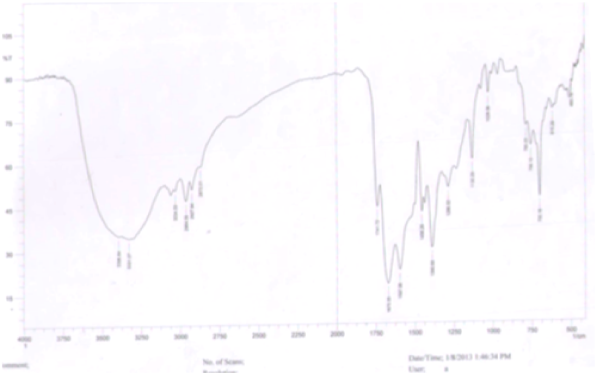
*H-NMR studies*.- 1H-NMR spectra of compound (II) showed signals at =(7.1-7.8) ppm belong to aromatic and protons at =( 8.45) ppm for Schiff base proton, this and ether signals are seen in fig.(2).

*solubility studies*.- the solubility study of the ampicillin derivatives was determined following Gude et al. 33 using deferent types of solvent improve increase solubility of these derivatives than free ampicillin and it was still to be doun.

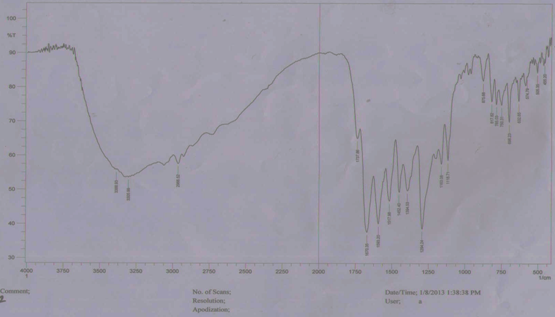
*biological activity studies*.- biological activity of the compounds expected to be more than ampicillin and it was still to be doun .

**Acknowledgements**

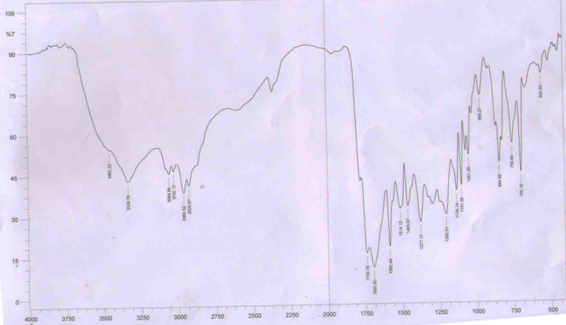
For the financial support, thanks give to chemistry department college of Education of pure science/ University of Karbala for offering requirement to facilities this work, also compound thanks for Samarra drug industries for supplying me the ampicillin drug.

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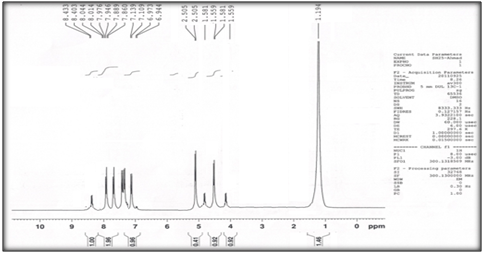
**Fig.(1): the FTIR spectrum of compound (I)**

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**Fig.(2): the FTIR spectrum of compound (II)**

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**Fig.(3): the FTIR spectrum of compound (III)**

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**Fig.(4): the FTIR spectrum of compound (III)**

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