Open Access
Baghdad Science Journal Vol.14(4)2017

DOI: http://dx.doi.org/10.21123/bsj.2017.14.4.0756

New Synthesis of Cyclic Imide Compounds for Ampicillin Drug and Studying Their Biological Activity

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Received 23/6/2016
Accepted 24/9/2017

Abstract

Some new cyclic imides are prepared by the reaction of ampicillin drug with different cyclic anhydrides as a first step to form amic acids for ampicillin drug. The second step includes the reaction of prepared amic acids with acetic anhydride and anhydrous sodium acetate with heating in THF as a solvent to give cyclic imide compounds. These compounds are identified by melting points, FT-IR, ^{1}H-NMR, and biological activity

Keywords: Ampicillin, Amic acids, Cyclic Imides.

Introduction:

Ampicillin is D -α - aminobenzyl penicillin, which is a semi synthetic product. The α - amino group plays a significant role in its broader activity, like other penicillins; it is quite effective against the gram. Positive organisms also have a bactericidal action against a variety of gram- negative organisms [1, 2]. Ampicillin is acid stable; therefore, it can be administered orally and absorbed from the intestinal tract to produce adequatz blood concentrations in about two hours. As it is rapidly excreted through the kidneys, oral doses must be repeated every six hours. At present, it is mainly used in the treatment of urinary tract infections, bronchitis and influenza [3, 4].

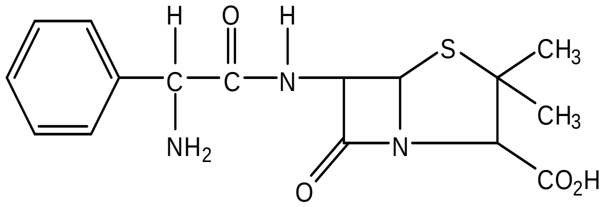

Figure 1. The Structure of Ampicillin

Amic acids are organic compounds containing a carboxyl group and amide group. They can be prepared by the reaction of primary aliphatic or aromatic amines with different cyclic anhydrides such as maleic, phthalic, and succinic anhydride[5, 6, 7, 8].

Dehyration of amic acids usually produces cyclic imides.A good review on the use of dehydrating agents for amic acid to imide is written by Roderick and Bhatia [9]. It seems that dehydration with acetic anhydride plus sodium acetate anhydrous at elevated temperatures has general a utility for the synthesis of N- substituted imide[10-14].

Ampicillin is a beta- lactam antibiotic that is part of the aminopenicillin family and is roughly equivalent to its successor, amoxicillin in terms of spectrum and level of activity [15]. It is effective for ear infections and respiratory infections such as sinusitis caused by bacteria, and epiglottis [16]. Ampicillin is on the World Health Organizations WHO list of essential medicines, a list of the most important medication needed in a basic health system [17].

Materials and Methods:

Instrumentals

Melting points are determined on a Gallenkamp melting point apparatus and are uncorrected.

FT-IR spectra are recorded on shimadzu. FT-IR 8400 spectrophotometer as KBr disc. The ^{1}H-NMR is recorded on a make Bruker model Ultrashild 300MHZ at Al- Albyt University of

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Jordon- DMSO- d_6 and used as solvent and TMS as internal reference.

Materials:

All chemical compounds are obtained from Fluka or Aldrich. The ampicillin is obtained from Samara, Iraq.

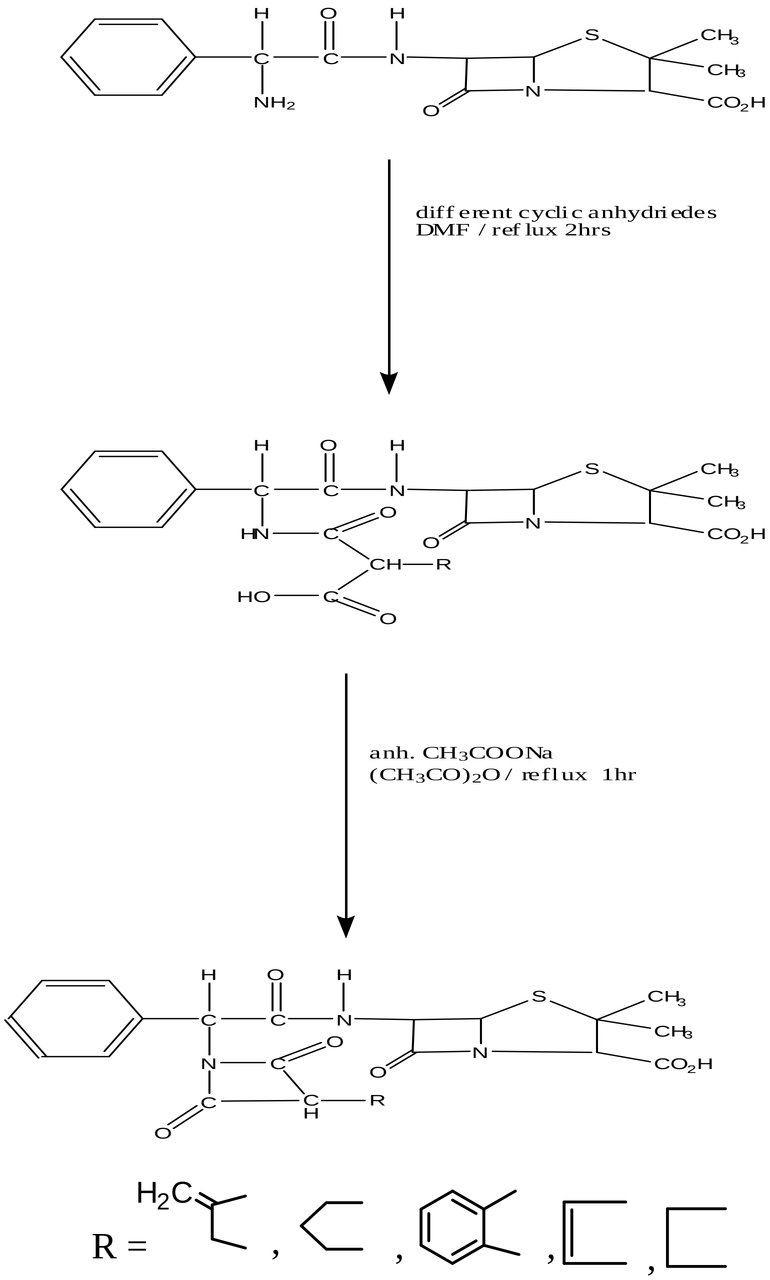
The reaction sequence leading to the formation of new compounds is outlined in Scheme1.

General Preparation of Amic Acids Compounds (1-5) [5-8].

On round bottom flask (250ml), Ampicillin (0.01mol), (3.49gm) was dissolved on (20ml) THF and added (0.01mol) of different cyclic anhydrides. The mixture was refluxed for 2hrs. The solution of all prepared compounds were precipitated from acetone. The product was dried and recrystallized from THF, physical properties are listed in Table(1).

Preparation of Cyclic Imide Compounds (6 -10) [9, 10].

In an around bottom flask (250ml) were dissolved (1-5) compounds (0.17gm) on (7ml) of hot THF, and then (0.1gm) of anhydrous sodium acetate with (15ml) of acetic anhydride. The reaction mixture is refluxed at 40 °C for 1hr; the solid product is formed, filtered, dried and recrystallized from THF. The Physical properties are listed on Table(2).



Scheme 1
Steps of Synthesis Cyclic Imide Compounds of Ampicillin

Table 1. The Physical Properties of Amic Acids Compounds (1-5)

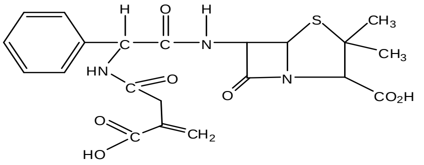
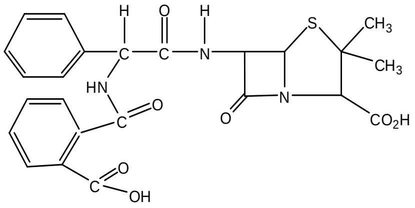
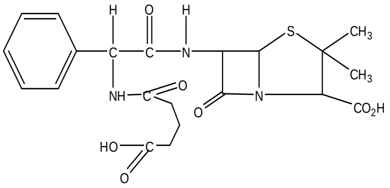
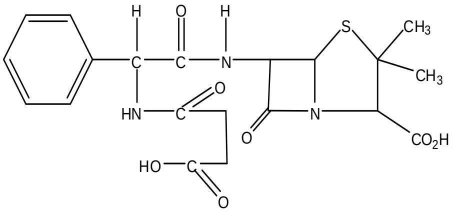
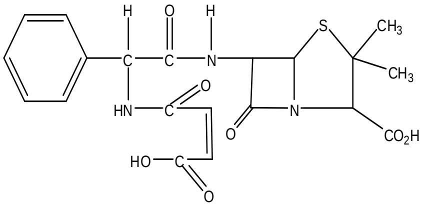
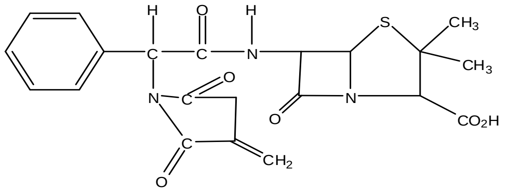
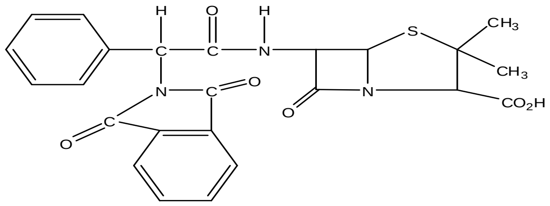
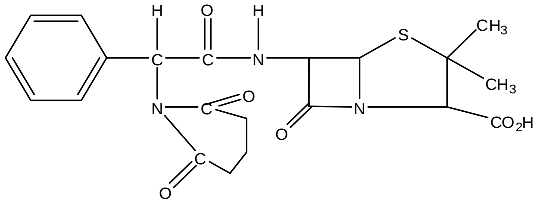
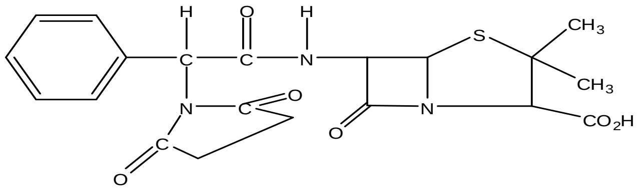
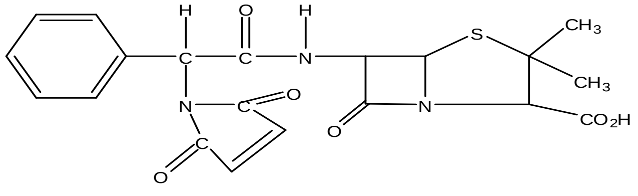
Comp. No.	Compound Structure	Molecular Formula	Melting point ^{o}C	Color	Yield %
1	 6-(2-(3-carboxybut-3-enamido)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{21}H_{22}N_3O_7S$	130-132	Yellow	51
2	 6-(2-acetamido-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with benzoic acid (1:1)	$C_{24}H_{22}N_3O_7S$	178-180	Yellow	44
3	 6-(2-(4-carboxybutanamido)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{21}H_{24}N_3O_7S$	140-142	White	55
4	 6-(2-(3-carboxypropanamido)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{20}H_{22}N_3O_7S$	134-136	White	59
5	 (*Z*)-6-(2-(3-carboxyacrylamido)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{20}H_{20}N_3O_7S$	162-164	Dark-Brown	54

Table 2. The Physical Properties of Imide Cyclic Compounds (6-10]

Comp. No.	Compound Structure	Molecular Formula	Melting point °C	Color	Yield %
6	 3,3-dimethyl-6-(2-(3-methylene-2,5-dioxopyrrolidin-1-yl)-2-phenylacetamido)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{21}H_{20}N_3O_6S$	124-126	Pal Yellow	73
7	 6-(2-(1,3-dioxoisoindolin-2-yl)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{24}H_{20}N_3O_6S$	154-156	Pal-Yellow	55
8	 6-(2-(2,6-dioxopiperidin-1-yl)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{21}H_{22}N_3O_6S$	132-134	Brown	61
9	 6-(2-(2,5-dioxopyrrolidin-1-yl)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{20}H_{20}N_3O_6S$	128-130	Yellow	62
10	 6-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	$C_{20}H_{18}N_3O_6S$	146-148	orang	67

Results and Discussion:

The amic acid compounds (1-5) are synthesized from the reaction of ampicillin with different cyclic anhydrides. Synthesis of these compounds are carried out according to the steps outlines in Scheme (1).

The structures of (1-5) compounds are confirmed by physical properties listed on Table (1), and by spectral methods, such as FT-IR and some them by ^{1}H- NMR. FT.TR spectra of the compounds (1-5) show characteristic absorption bands at (1651-1658) cm^{-1},(1710-1720) cm^{-1}, (3200- 3294) cm^{-1}, (1369-1388) cm^{-1}, (3035-3062) cm^{-1},(2970) cm^{-1}, and (1519-1600) cm^{-1}due to $v(C = O)$ amide, $v(C = O)$ acidic, $v(N - H)$ amide, v(C-N), v(C-H) aromatic, v(C-H) aliphatic, and v (C=C) aromatic. These bands and others are shown on Table (3).

FT-IR spectra of cyclic imide compounds (6-10) show characteristic absorption bands at (1770-1795) cm^{-1}, (1654-1660) cm^{-1}, (1710-1717) cm^{-1} (1388-1408) cm^{-1},(3035-3062)cm^{-1}, (2966-2978)cm^{-1}, and (1550-1610)cm^{-1} due to v (C=O) imide, v(C=O) amide, v(C=O) acidic, $v\,(C - N)$, v (C-H) aromatic, v (C-H) aliphatic and v(C=C) aromatic. These bands and others are listed in Table (4) as shown in Figures (2-4) .

The 1H-NMR spectra of compounds (1, 2, 4, and 5) show the signal at (10.7, 10.8, 10.5 and 10.6) ppm due to (O-H) proton and signal at (8.0, 7.9, 7.9 and 8.0) ppm due to (N-H) proton of amide, while the other signals are listed in Table (5) as shown in Figures (5-8) .

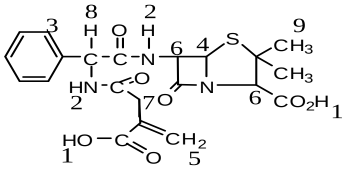
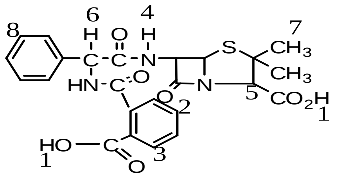
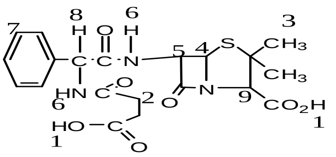
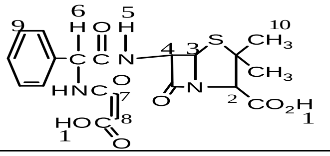
Table 3. FT –IR Spectra of the Prepared Amic Acid Compounds (1-5) .

Comp. No	v(C = O) Amide	v(C = O) acidic	v (N − H)	v(C − O)	v(C-N)	v(*C* − *H*) aromatic	v(*C* − *H*) aliphatic	V(C=C) aromatic
1	1658	1710	3260	1219	1369	3055	2877-2970	1531 1590
2	1654	1715	3210	1273	1373	3062	2870-2970	1539 1600
3	1651	1730	3255	1215	1388	3059	2880-2970	1519 1595
4	1651	1720	3294	1215	1388	3035	2880-2970	1523 1594
5	1658	1720	3200	1230	1373	3055	2880-2970	1519 1597

Table 4. FT- IR Spectra of the Prepared Compounds (6-10) .

Comp. No.	v(C = O) Imide	v(C = O) Amide	v(C = O) acidic	v(C − O)	v(C-N)	v(*C* − *H*) aromatic	v(*C* − *H*) aliphatic	V(C=C) aromatic
6	1774	1654	1717	1276	1388	3035	2927-2970	1550 1604
7	1770	1666	1716	1276	1388	3035	2931-2978	1577 1600
8	1770	1654	1716	1257	1408	3062	2931-2970	1562 1604
9	1774	1654	1710	1261	1388	3062	2927-2966	1543 1605
10	1795	1662	1716	1253	1408	3062	2974	1570 1610

Table 5. The^{1}H-NMR Chemical Shifts for Selected Compounds (ppm).

Comp. No.	Structure	Chemical shifts
1		δ 10.7(S,H,OH^1) ; δ8.0(S,H,NH^2); δ7.2(*S, H*3 *Ar*); δ5.9(S,CH-S);δ 5(S,H,CH^5); δ4.5-5.1(m,H,CH^6); δ3.1(S,H,CH^7); δ2.8(S,H,CH^8); δ2.4(S,H,CH^9) .
2		δ10.8(S,H,OH^1); δ7.9-8.1(S,H,NH^4); δ4.55.3(m,H,H^5); δ2.8(S,H,CH^6);δ2.5(S,3H^7); δ7.4 (S,H^{8}Ar).
4		δ10.5(S,H,OH^1);δ3.1-4.1(m,4H^2); δ2.5(S,3H^3); δ5.2-5.5(S,H,CH^4);δ4.4-5(m,H,CH^5);δ7.9(S,H,NH^6);); δ2.8(S,H,CH^8);δ2.7(S,H,CH^9); δ7.2(S,H^{7}Ar).
5		δ10.6(S,H,OH^1);δ2.7(S,1H^2);δ4.4- 4.9(m,H,CH^4);δ8(S,H,NH^5); δ2.8(S,H,CH^6);δ3.1-3.9(m,2H^{7,8}); δ2.5(S,3H^3); δ7.3(S,H^{9}Ar).

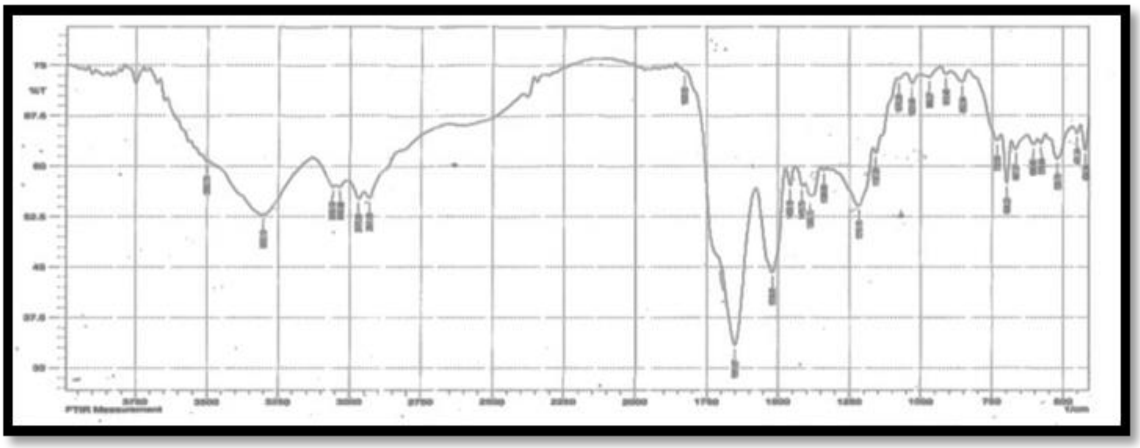


Figure 2. FT-IR Spectrum of Compound 2

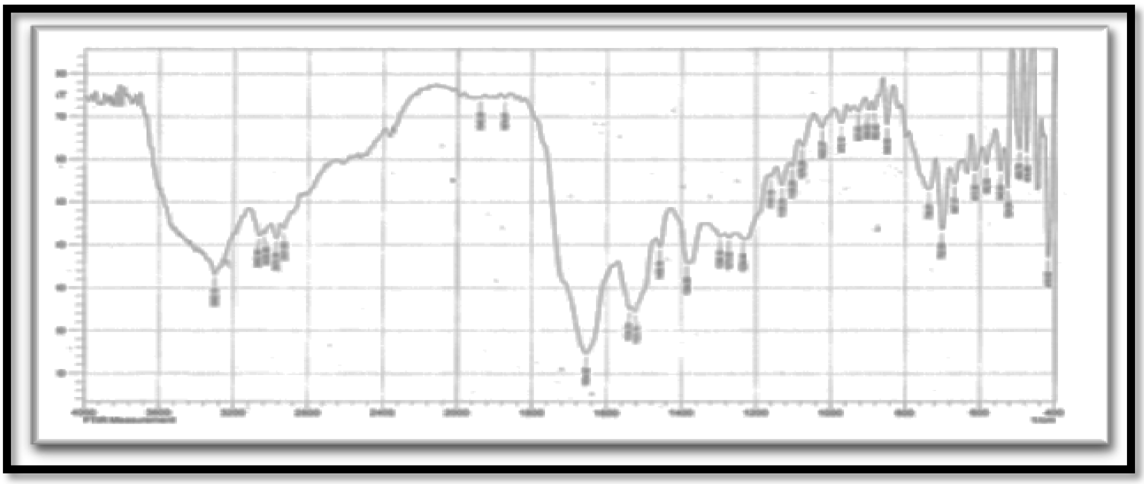


Figure 3. FT-IR Spectrum of Compound 3

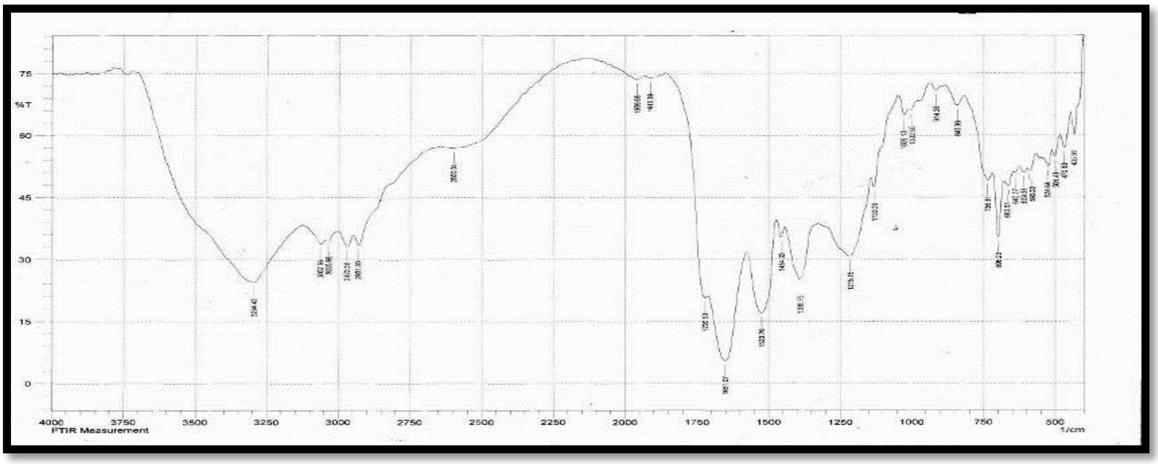


Figure 4. FT-IR Spectrum of Compound 4

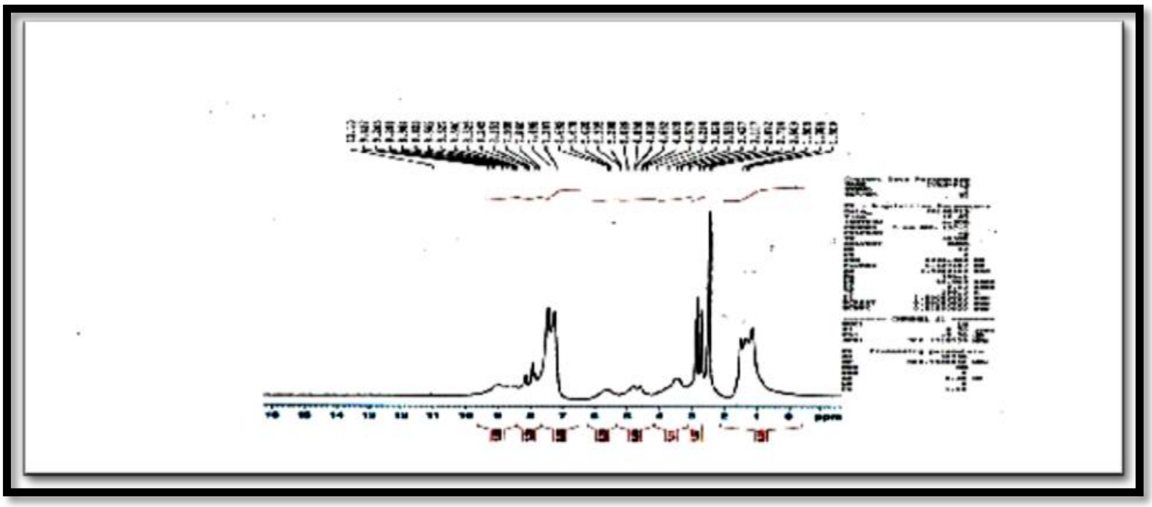


Figure 5. ^{1}H-NMR Spectrum of Compound 1

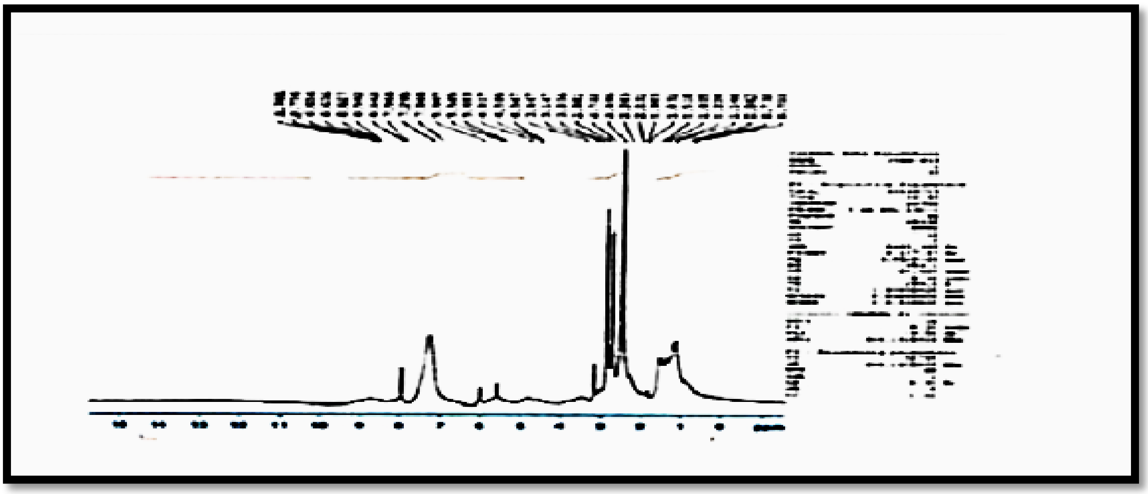


Figure 6. ^{1}H-NMR Spectrum of Compound 2

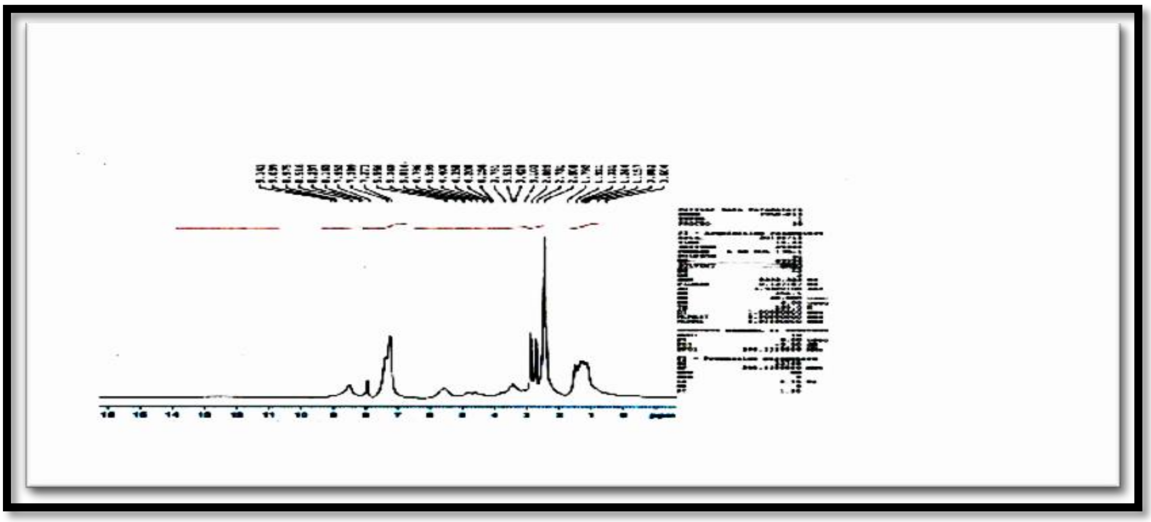


Figure 7. ^{1}H-NMR Spectrum of Compound 4

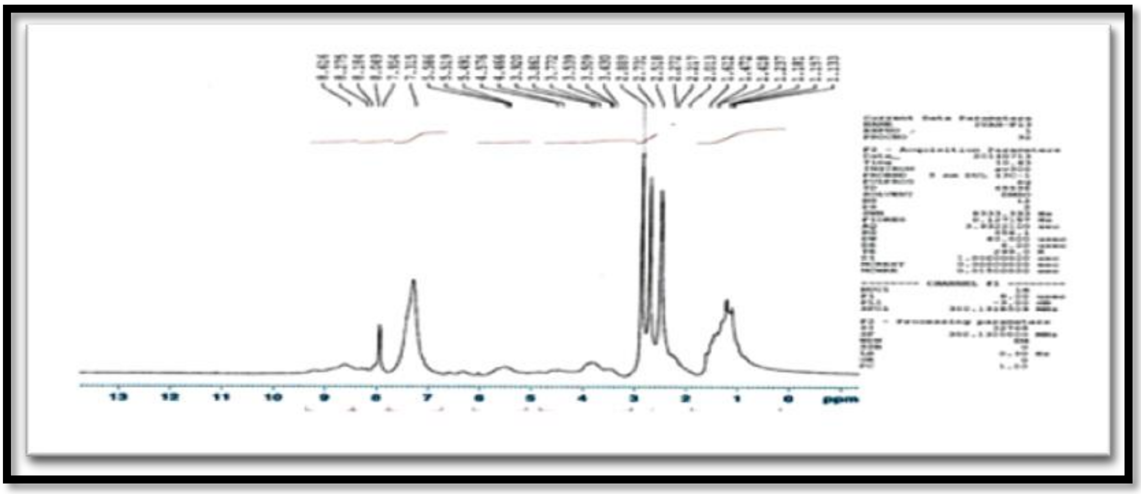


Figure 8. ^{1}H-NMR Spectrum of Compound 5

Biological Activity:

The antimicrobial activity of the synthesized compound (6, 8 and 10) is examined by the agar diffusion method using two different bacterial species, staphylococcus Aurous and E.col. Mueller Hinton agar suitable spaced apart holes are made (6mm in diameter). Suitable spaced apart holes are filled with (0.1ml) of preparing compounds concentration that dissolve in DMSO beffer spread the bacteria on agar. These plates are incubated at 37^{o}C for 24hrs, the zone of inhibition of bacteria growth around the hole is observed and measured in mm of diameter and clarity, The results are given in Table (6).

Conclusion:

The results indicate that the synthesized compounds (6, 8 and 10) have a microbial activity against the tested organisms up to 3.2mg / disk.

The organisms *staph. aureus* and *E. coli* show higher sensitivity toward the compound 6 than the 8 and 10 compounds.

Table 6. The Antimicrobial Activity of the Tasted Compounds after 24 hrs.

Comp. No.	*Staph Aureus*	*E.coli*
6	+++	+++
8	+	+
10	++	++

Keys to asymbols (+) = 9-11 mm , (++) = 18- 24mm , (+++) = 28- 33mm

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تحضير مركبات حلقية ايميدية جديدة لدواء الامبيسلين ودراسة فعاليتها البايولوجية

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الخلاصة:

حضرت عدد جديد من الايمايدات الحلقية المرتبطة بجزيئة الامبيسلين وذلك عن طريق تفاعل الامبيسلين مع انهيدريدات حلقية مختلفة.الخطوة الاولى هي تكوين حوامض الاميك لدواء الامبيسيلين اما الخطوة الثانية فتضمنت تفاعل حوامض الاميك المحضرة مع انهيدريد الخليك بوجود خلات الصوديوم اللامائية في مذيب THF مع التسخين لتعطي مركبات ايميدية حلقية. شخصت هذه المركبات بقياس درجات الانصهار واطياف الاشعة تحت الحمراء وتقنية الرنين النووي المغناطيسي للبروتون ، ثم قياس الفعالية البايولوجية لها.

الكلمات المفتاحية : الامبيسلين، حوامض الاميك، ايميدات حلقية.