RESEARCH ARTICLE

Synthesis and Characterization of New Compounds Derived from Amoxicillin and Evaluation of its Biological Activity

Nawar J. Abdulrada,[1*] Saja A. Almsjmaie,[2] Faqad T. Ahmed,[2]
Tareq K. Ibraheem,[2] Ziad T. I. Alkayar[2]

[1]*Department of Chemistry, Collage of Education for Pure Science Ibn Al-Hathim, University of Baghdad, Baghdad, Iraq*
[2]*Department of Chemistry, Collage of Education for Pure Science, University of Diyala, Baqubah, Iraq*

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ABSTRACT

Amoxicillin 1 was treated with thiosemicarbazide and Phosphoryl chloride to obtain a new derivatives that contains 1,3,4-thiadiazole moiety 2. Schiff bases compounds were synthesized by the reaction of compound 2 with different aldehydes such as benzaldehyde and some substituted Benzaldehyde; p-hydroy, p-Chloro, p-Nitro, p-Dimethylamino, p-Methyl, p-Methoxy, p-Ethoxy to give compounds 3a-h. The obtained compounds have tested towards gram -ve and gram +ve bacteria. The compound shows good to moderate result towards the bacteria.

Keywords: Amoxicillin, Biological activity, Schiff bases, Thiosemicarbazide.

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INTRODUCTION

Heterocyclic compounds such as thiazole,[1] 1,2,3,4-terazine,[2] benzotriazole,[3] pyrazole,[4] 1,3,4-thiadiazole possess biological effect. Amoxicillin is a β-lactam derivative and is one of the most important antibiotics which are utilized for a long time to treat many bacterial infections.[5] Amoxicillin was discovered in 1958 and used as in medicine in 1972.[6,7] It is one of the widely used as an antibiotic for children.[8] It is possess a similar antibacterial effect to ampicillin against many organisms.[9] It is a twice active than ampicillin towards enterococci and Salmonella.[10,11] Nowadays, the reduction of effectiveness of such drug due to the resistance is a very big issue. However, to overcome such problem would be necessary to find a new derivative that related to the drugs with better biological effect. Therefore, tethering the heterocyclic ring to the β–lactam drugs can lead to enhance the activity towards wide range of bacteria.

EXPERIMENTAL

The reactions for the synthesis and purification of the compounds were carried out in the efficient fume cupboard. The amoxicillin was obtained from SDI Company. The other material have brought from Fulka, Across Organic and Sigma-Aldrich chemical companies. Solvents and reagents have purchased from markets and were of analytical grade. Spectra of FT-IR were obtained in KBr pellets from (FT-IR 8300) Shimadzu spectrophotometer in the range 4000–400 (cm^{-1}) region. All the reactions were followed by the thin layer chromatography (TLC) using silica plates and visualizing by Ultraviolet at 254 (nm), potassium permanganate chamber was used for staining.

Synthesis of Compound 2

To a mixture of amoxicillin 1 (1.0 gm, 2.3 mmol) and thiosemicarbazide (2.0 gm, 2.3 mmol) in ethanol (10 mL), was added phosphoryl chloride (8.0 mL) and then refluxed. After 4 h, cold water was added 20 mL and stirred for 5 hours, the solution was neutralised with KOH 10%. Filtration and washed with water to obtain compound 2 in % yield; IR υ_{max}(film)/cm^{-1} 3485, 3316, 2974, 1680, 1531, 1307, 1102, 832. ^{1}H NMR (400 MHz, DMSO-d_6) δ= 9.8 (4H, s, NH_2), 8.96 (1H, s, NH), 7.64 (4H, m, ArH), 4.01 (6H, s, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ= 169.9, 148.4, 137.6, 128.5, 122.7, 46.3.

Synthesis of Compounds 3_{a-g}

Compound 2 (0.8 gm, 1.6 mmol) and aldehyde (1.6 mmol) in ethanol (10 mL) was heated under reflux for 5 h. Then, the mixture was cold to room temperature and filtered to give compounds 3_{a-g}.

Compound 3_a; IR υ_{max}(film)/cm^{-1} 3488, 3320, 3117, 2982, 1678, 1587, 1437. ^{1}H NMR (400 MHz, DMSOd_6) δ= 8.75 (H, s, NH), 7.56 (4H, m, ArH), 7.43 (1H, s, HC=N); ^{13}C NMR (101 MHz, DMSOd_6) δ= 170.1, 147.2, 139.5, 127.1, 121.7, 47.3.

**Author for Correspondence: tariq.phd744@gmail.com*

Compound 3_b; IR υ_{max}(film)/cm^{-1} 3476, 3317, 3095, 2973, 1667, 1624, 1582, 1429. ^{1}H NMR (400 MHz, $DMSOd_6$) δ= 8.73 (H, s, NH), 7.49 (4H, m, ArH), 7.22 (1H, s, HC=N); ^{13}C NMR (101 MHz, $DMSOd_6$) δ= 173.5, 150.4, 141.2, 132.1, 122.4, 47.9.

Compound 3_c; IR υ_{max}(film)/cm^{-1} 3482, 3320, 3106, 2980, 1669, 1630, 1585, 1431. ^{1}H NMR (400 MHz, $DMSOd_6$) δ= 8.81 (H, s, NH), 7.52 (4H, m, ArH), 7.26 (1H, s, HC=N); ^{13}C NMR (101 MHz, $DMSOd_6$) δ= 176.9, 154.1, 147.2, 133.9, 125.5, 49.8.

Compound 3_d; IR υ_{max}(film)/cm^{-1} 3477, 3315, 3112, 2969, 1675, 1622, 1570, 1433. ^{1}H NMR (400 MHz, $DMSOd_6$) δ= 8.60 (H, s, NH), 7.51 (4H, m, ArH), 7.31 (1H, s, HC=N); ^{13}C NMR (101 MHz, $DMSOd_6$) δ= 168.9, 144.1, 125.9, 123.8, 119.3, 45.7.

Compound 3_e; IR υ_{max}(film)/cm^{-1} 3460, 3312, 3109, 2954, 1671, 1620, 1568, 1429. ^{1}H NMR (400 MHz, $DMSOd_6$) δ= 8.55 (H, s, NH), 7.49 (4H, m, ArH), 7.27 (1H, s, HC=N); ^{13}C NMR (101 MHz, $DMSOd_6$) δ= 165.3, 142.9, 123.1, 120.1, 117.8, 42.9.

Compound 3_f; IR υ_{max}(film)/cm^{-1} 3462, 3320, 3111, 2960, 1669, 1630, 1563, 1433. ^{1}H NMR (400 MHz, $DMSOd_6$) δ= 8.57 (H, s, NH), 7.52 (4H, m, ArH), 7.30 (1H, s, HC=N); ^{13}C NMR (101 MHz, $DMSOd_6$) δ= 167.9, 144.6, 125.5, 122.6, 42.9.

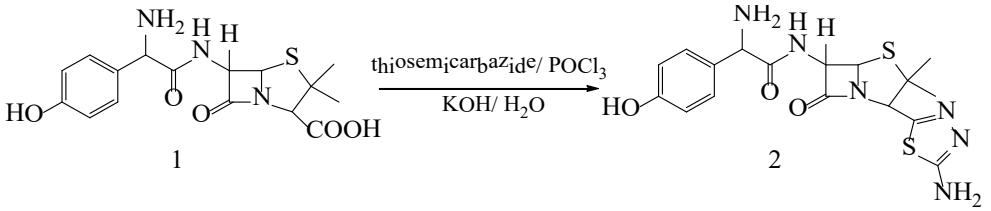
Compound 3_g; IR υ_{max}(film)/cm^{-1} 3420, 3309, 3102, 1650, 1619, 1551, 1427. ^{1}H NMR (400 MHz, $DMSOd_6$) δ= 8.40 (H, s, NH), 7.42 (4H, m, ArH), 7.10 (1H, s, HC=N); ^{13}C NMR (101 MHz, $DMSOd_6$) δ= 164.8, 140.7, 123.1, 119.6, 43.2.

RESULT AND DISCUSSION

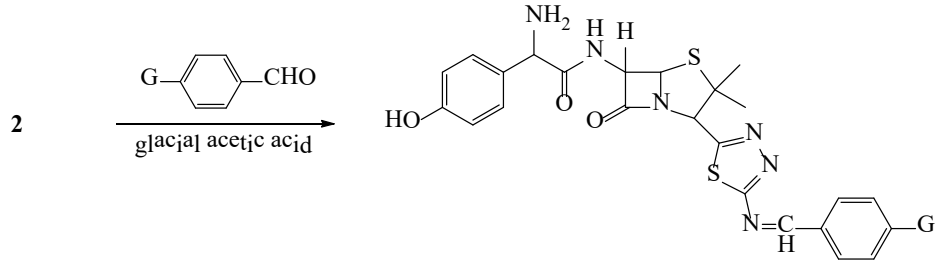
New derivatives of Amoxicillin 1 were prepared containing 1,3,4-thiadiazole ring, the first step was treating of compound 1 with thiosemicarbazide and phosphoryl chloride in alcohol to give compound 2 see schedule 1. Having compound 2 will allow us to examine the condensation reaction with various aldehydes.

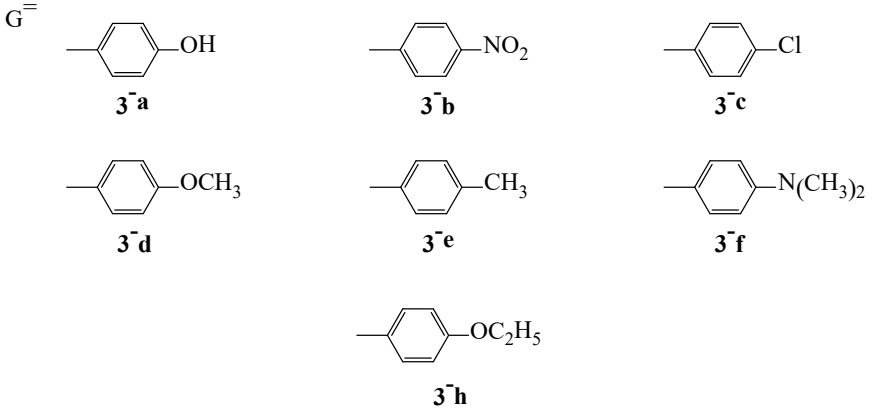
To do so, aldehydes were treated with compound 2 in alcohol in the presence of glacial acetic acid to give compounds 3_{a-g}, see Scheme 1 and 2.

The FT-IR spectrums of the synthesized compounds show no aldehydic C–H and NH_2 peaks, and peak of HC=N was appeared instead. ^{13}C-NMR spectra of the all obtained



Scheme 1





3¯a **3¯b** **3¯c** **3¯d** **3¯e** **3¯f** **3¯h**

Scheme 2

Table 1: Biological test for Amoxicillin 1 and synthesized compounds 3_{a-g}

	Zone of inhibition in (mm)		
Comp No.	*E. Coli*	*M. tuberculosis*	*P. mirabilis*
2	19	17	16
3_a	24	18	19
3_b	18	12	17
3_c	22	16	15
3_d	17	15	18
3_e	12	10	11
3_f	16	14	12
3_g	21	19	14
Amoxicillin	20	17	18
DMSO Solvent	0	0	0

compounds indicate that all the peaks matches the expected values see section method. Table 1 illustrate all the data for the synthesized compounds.

Antibacterial activity

The big challenging problem is the treatment of infectious diseases, and this because of important factor including the resistance to the bacteria. The biological effect of the synthesized compound have screened against gram –ve and gram +ve. Table 1 shows the result of the biological test for Amoxicillin 1 and synthesized compounds 3_{a-g}, some compounds showed good antibacterial activity.

The antibacterial tests of the obtained compounds were tested against the *Proteus mirabilis* and *Escherichia Coli* (gram -ve) and *Mycobacterium tuberculosis* (gram +ve) organisms. Here, Amoxicillin are tested as reference drugs to compare the activity towards the bacteria. The test was carried out using the paper disc diffusion method.[7]

Clearly, Table 1 shows that the activities of the chosen strains of prepared compounds have enhanced the antibacterial activity against the selected bacteria. Data exhibit that the effects of the some substance under investigation towards Proteus mirabilis, *Escherichia Coli* and *M. tuberculosis* better than the reference.

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