ISSN 0975-2366
DOI:https://doi.org/10.31838/ijpr/2021.13.01.026

Research Article

Synthesis and Antibacterial Activity of New Cefotaxime Derivatives

WASFI A. AL-MASOUDI[1], RITA S. ADAM[2], SAMAR S. GHAZI
[1]Department of Physiology, Pharmacology and Chemistry, College of Veterinary Medicine, University of Basrah, Basrah,, Iraq
[2]Department of Engineering of Environmental and Pollution Technology, Southern Technical University, Basrah, Iraq.
[2]Department of veterinary hygiene College of veterinary medicine, University of Basra-Iraq
Author for corresponding.
E-mail: almasoudi59@yahoo.com,
Received: 19.08.20, Revised: 03.09.20, Accepted: 07.10.20

ABSTRACT
Condensation of cefotaxime drug with aromatic aldehydes (Piperonal, 2-hydroxy-1-naphthaldehyd, 4-hydroxy-3-methoxy benzaldehyde, 3,4-dihydroxy benzaldehyde and p-phthaldehyde yielded Schiff bases in good yield. Spectroscopic characterization such as, IR and NMR of new compounds have been obtained by using nuclear magnetic resonance 600 MHz.
The synthesized compounds were tested against, Escherichia coli, Staphylococcus aureus
Bacillus cereus and klebsella pneumonia for antibacterial activity.
and fungicidal activity against Candida trobicalis Candida albicans, Candida krusi, Aspergillus fumigatus and Aspergillus niger. A new compounds exhibited potent antibacterial and antifungal activity.

Keywords: Cefotaxime, Schiff base, Antibacterial activity, Piperonal, p-phthaldehyde

INTRODUCTION

The rapid development of resistance to various antimicrobial drugs has made infectious diseases caused by bacteria and fungi a major health problem worldwide.
By inhibiting peptidoglycan layer synthesis from the cell wall, β-lactam is a synthetic antibiotic active against Gram-positive and Gram-negative bacteria [1].
The mechanism which makes β-lactam resistant to bacteria is due to the synthesis of β-lactamase enzymes which break the β-lactam ring and the antibiotic can not bind to the peptidoglycan layer [2].
Aurora etal have prepared some transition metal(II) complexes with Schiff base derived from cefotaxime and study their antimicrobial activity [3].
Cefotaxime (Hcefotax) interacts with transition metal ions to provide
[M(cefotax)Cl]complexes (M = Mn(II), Fe(III), Co(II), Ni(II), Cu(II), and Cd(II)).
The complexes had been tested against many bacteria for antibacterial activity.
The [Cu(cefotax)Cl] complex has been found to have higher activity than that of cefotaxime against the strains of bacteria tested under the test conditions , suggesting that its [4].

EXPERIMANTAL

Instrumental

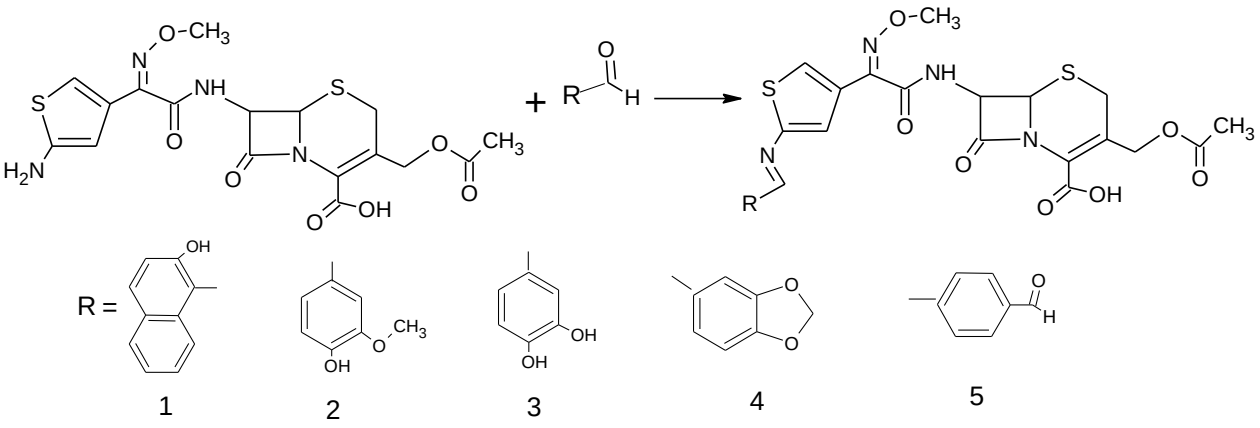
The IR spectrum was recorded
at the Polymer Research Center, University of Basra h, on the Pye Unicam SP3-300 spectrometer, in the range 4000-200 cm-1 using KBr discs.^{1}H,^{13}C-NMR spectra were measured at 600 MHz on a Brucker, with TMS as internal reference at the University of Konstanz, Germany. The melting point was determined by a melting point system from Philip Harris at the Veterinary college of Basrah University.

Synthesis

Synthesis of Schiff base

1 mmol (0.45 gm) of cefotaxime in 20 ml methanol was added to 1 mmol of hot methanolic solution of aldehyde, two drops of glacial acetic acid were added and the resulting solution was refluxed for 3 hours and then raised in the refrigerator during the

night, the solid product collected was filtered and acetone cleaned, and the product was recrystallized using methanol to produce cefotaxime derivatives.



Scheme 1: Preparation of cefotaxime derivatives 1-5

Schiff base of cefotaxime and 2-Hydydroxy naphthaldehyde 1

From 2-hydroxynaphthaldehyde (172 mg). Yield: 74 %; Mp: 242 °C (dec.) for $C_{28}H_{24}N_4O_8S_2$ (Mr 608.6): ^{1}H NMR (400 MHz, DMSO-d_6, □, ppm): 13.21(1H, s, O**H**), 10.79(1H, s, COO**H**), 9.96 (1H, d, N**H**$_{amide}$, J = 8.6 Hz), 9.87 (1H, s, **H**C=N), 8.09-7.25 (6H, m, C**H**$_{arom.}$), 7.18 (2H, s, C**H**$_{thiazole}$), 5.28(1H, s, C**H**-N$_{lactam}$), 4.84(1H, s, C**H**-S$_{lactam}$), 4.14-3.81(H, m, C**H**$_{2aliphatic}$), 3.45(2H, m,C**H**$_2$-S), 1.2-1.23 (6H, s, 2C**H**$_3$). ^{13}C NMR □□400 MHz, □□□DMSO-d_6, ppm□□□22.0 (C**H**$_3$**C**=O), 28.0 (S**C**H$_2$), 57.1 (**C**H$_2$-O), 61.2 (**C**H$_2$-N), 63.1 (**C**H$_2$-NH), 64.0 (**C**H$_3$-O), 106.4-135.2(**C**H(arom.), 159.9 (**C**H=N), 163.5 (**C**OOH), 165.0 (**C**=O(lactam)), 163.2 (**C**=O(amid.)), 170.2 (**C**=O(ester.)),171.0 (**C**-OH).

Schiff base of cefotaxime and 4-hydydroxy-3-methoxy benzaldehyde 2

From 4-hydroxy-3-methoxy benzaldehyde (152 mg). Yield: 68 %; Mp: 230 °C (dec.) for $C_{25}H_{24}N_4O_9S_2$ (Mr 588.6): ^{1}H NMR (400 MHz, DMSO-d_6, □, ppm): 12.74(1H, s, O**H**), 10.33(1H, s, COO**H**), 9.24 (1H, d, N**H**$_{amide}$), 9.06 (1H, s, **H**C=N), 7.45-7.17 (3H, m, C**H**$_{arom.}$), 7.14 (2H, s, C**H**$_{thiazole}$), 5.17(1H, s, CH-N$_{lactam}$), 4.60(1H, s, C**H**-S$_{lactam}$), 4.63-3.82(H, m, C**H**$_{2aliphatic}$), 3.01(2H, m,C**H**$_2$-S), 1.34-1.27 (9H, s, 3C**H**$_3$). ^{13}C NMR □□400 MHz, □□□DMSO-d_6, ppm□□□24.4 (C**H**$_3$**C**=O), 28.2 (S**C**H$_2$), 57.6 (**C**H$_2$-O), 62.6 (**C**H$_2$-N), 63.7 (**C**H$_2$-NH), 63.8 (**C**H$_3$-O), 107.3-132.5(**C**H(arom.), 160.1 (**C**H=N), 163.2 (**C**OOH), 164.9 (**C**=O(lactam)), 163.1 (**C**=O(amid.)), 170.1 (**C**=O(ester.)),171.4 (**C**-OH).

Schiff base of cefotaxime and 3,4-dihydydroxy benzaldehyde 3

From 3,4-dihydroxy benzaldehyde (138 mg). Yield: 69 %; Mp: 255 °C (dec.) for $C_{24}H_{22}N_4O_9S_2$ (Mr 574.5): ^{1}H NMR (400 MHz, DMSO-d_6, □, ppm): 12.88(1H, s, O**H**), 10.76(1H, s, COO**H**), 9.93 (1H, d, NH$_{amide}$, J = 8.6 Hz), 8.98 (1H, s, **H**C=N), 7.51-7.07 (3H, m, C**H**$_{arom.}$), 7.13 (2H, s, C**H**$_{thiazole}$), 5.22(1H, s, CH-N$_{lactam}$), 4.74(1H, s, C**H**-S$_{lactam}$), 4.21-3.78(H, m, C**H**$_{2aliphatic}$), 3.20(2H, m,C**H**$_2$-S), 1.20,1.25 (6H, s, 2C**H**$_3$). ^{13}C NMR □□400 MHz, □□□DMSO-d_6, ppm□□□23.8 (C**H**$_3$**C**=O), 28.5 (S**C**H$_2$), 57.8 (**C**H$_2$-O), 62.4 (**C**H$_2$-N), 63.6 (**C**H$_2$-NH), 63.9 (**C**H$_3$-O), 105.4-130.5(**C**H(arom.), 160.2 (**C**H=N), 163.2 (**C**OOH), 164.9 (**C**=O(lactam)), 163.1 (**C**=O(amid.)), 170.2 (**C**=O(ester.)),171.6 (**C**-OH).

Schiff base of cefotaxime and piperonal 4

From 1,3-benzodioxole-5-carbaldehyde(piperonal) (150 mg). Yield: 71 %; Mp: 226 °C (dec.) for $C_{25}H_{22}N_4O_9S_2$ (Mr 586.5): ^{1}H NMR (400 MHz, DMSO-d_6, □, ppm): 9.81(1H, s, COO**H**), 9.97 (1H, d, NH$_{amide}$, J = 8.5 Hz), 8.90 (1H, s, **H**C=N), 7.55-7.18 (3H, m, C**H**$_{arom.}$), 7.13 (2H, s, C**H**$_{thiazole}$), 6.17(2H, s,OC**H**$_2$-O), 4.82(1H, s, C**H**-N$_{lactam}$),

4.59(1H, s, C**H**-S_{lactam}), 3.82-3.41(H, m, C$\mathbf{H}_{2aliphatic}$), 3.43(2H, m,C$\mathbf{H}_2$-S), 1.23 (6H, s, 2C**H** $_3$). ^{13}C NMR 400 MHz, DMSO-d_6, ppm 22.0 (C$\mathbf{H}_3$**C**=O), 28.9 (S**C**H_2), 53.2 (**C**H_2-O), 60.5 (**C**H-NH), 62.2 (**C**H-N), 63.9 (**C**H_3-O),100.3(O**C**H_2-O), 116.8-150.5(**C**H(arom.), 160.0 (**C**H=N), 163.5 (**C**OOH), 167.3 (**C**=O(lactam)), 169.1 (**C**=O(amid.)), 171.5 (**C**=O(ester)).

Schiff base of cefotaxime and p-phathaldehyde 5

From 1,3-benzodioxole-5-carbaldehyde(piperonal) (134 mg). Yield: 79 %; Mp: 262 °C (dec.) for $C_{25}H_{24}N_4O_8S_2$ (Mr 570.5): ^{1}H NMR (400 MHz, DMSO-d_6, , ppm): 10.01(1H, s, COO**H**), 9.95 (1H, d, NH_{amide}, J = 8.6 Hz), 9.32(1H, s, C**H**O), 9.06 (1H, s, **H**C=N), 7.76-7.17 (4H, m, C$\mathbf{H}_{arom.}$), 7.18 (2H, s, C$\mathbf{H}_{thiazole}$), 6.18(2H, s,O**C**H_2-O), 4.86(1H, s, C**H**-N_{lactam}), 4.71(1H, s, C**H**-S_{lactam}), 3.82-3.43(H, m, C$\mathbf{H}_{2aliphatic}$), 3.41(2H, m,C$\mathbf{H}_2$-S), 1.23-1.21 (6H, s, 2C**H** $_3$). ^{13}C NMR 400 MHz, DMSO-d_6, ppm 19.3 (C$\mathbf{H}_3$**C**=O), 23.6 (S**C**H_2), 52.8 (**C**H_2-O), 60.8 (**C**H-NH), 62.7 (**C**H-N), 64.1 (**C**H_3-O),100.0(O**C**H_2-O), 119.8-146.4(**C**H(arom.), 160.2 (**C**H=N), 162.8 (**C**OOH), 167.5 (**C**=O(lactam)), 168.4 (**C**=O(amid.)), 172.5 (**C**=O(ester)), 185.7(CHO).

Antibacterial activity

The synthesized compounds were tested in vitro for their antibacterial action against: Escherichia coli Staphylococcus aureus, Pseudomonas aregenosa and Klebsiella pneumoni using the diffusion technique of the paper disc-agar [5].

The test compounds were dissolved in DMSO solvent and the suggested concentrations were (50, 100 and 200µg / mL), each concentration was used in the technique of diffusion from the disc-agar. Cefotaxime has been used as a standard bacterial guide.

For antibacterial activity petri plates containing 20 mL of Mueller Hinton agar were used as a culture medium for antibacterial action. Filter of Sterile Whatman No. 1 p.

RESULTS AND DISCUSSION

In present work, we have selected cefotaxime as Starting material for synthesizing new series of derivatives of cefotaxime by convenient method.

Thus, subsequent treatment of cefotaxime with the desired aryl aldehydes such as: 2-Hydroxy naphthaldehyde, 4-Hydroxy-3-methoxy benzaldehyde, 3,4-Dihydroxy benzaldehyde, Piperonal and p-phthaldehyde in ETOH in the presence of two drops of glacial acetic acid at 80 ^{0}C temperature for 4 h, to give the Schiff base of cefotaxime derivatives **1-5** in 68 to 79% yield (scheme 1). The structures of synthesized compounds were characterized on their NMR spectra (1H and 13C), which showed very similar patterns of Pregnen scaffold proton and carbon atoms. 1H NMR spectra of synthesized compounds 1-5 reveal signals at 9.87-8.87 ppm due to azomethine protons (CH = N) [6].

^{1}H NMR spectra of Schiff bases show a singlet at the range 9.97-9.23 ppm due to NH amide groups. The aromatic protons of all synthesized compounds appeared as multiplets at the regions 7.07-8.09. ^{1}H NMR spectra show a singlet at the range 9.81-10.23 ppm due to carboxyl groups COOH. ^{1}H NMR spectra of synthesize compounds **1-3** show singlet at 12.47- 13.21 ppm due to phenolic OH.

In the ^{13}C-NMR spectra of **1-5**, the chemical shift in the regions δ 162.8-159.9 ppm were assigned to CH=N [7], whereas the carbonyl in lactam group appeared at δ 167.5-164-6 ppm. The ^{13}C-NMR spectra of compounds **1-3** show signals at δ 171.6-170.0 ppm for phenolic group C-OH. The signals around δ 150.5-105.4 ppm due to C-aromatic groups (C-Ar). The ^{13}C-NMR spectrum of compound **5** show signal at 185.7 ppm due to CHO group.

Biological activity

Although many antibiotics have been discovered in recent years, the need to alter the structural modification or development of those antibiotics is essential because of the resistance of microorganisms to those antibiotics. Consequently, drug-resistant bacteria has become a major global problem in public health today and requires constant research to develop anti-bacterial drugs. Antibacterial resistance to antibodies depends on the interaction between the type of bacteria and their location in the body, distribution of antibiotics in the body, and their concentration at the site of the infection, as well as on the patient's immune status factor [8]. The results of biological tests for synthesized compounds **1-5** showed good efficacy against a number of bacteria, Table 1.

However, the antibacterial activity of cefotaxime derivatives (Schiff-bases) was lower than cefotaxime drug, while some derivatives showed higher efficacy than some known antibiotics, Table 1.

Table 1: The antimicrobial activity of the synthesized compounds

S= cefotaxime/standard

Bacteria types	S 100 mm	Zone inhibition of antimicrobial sensitivity test of compounds (mm)														
		Comp.1 µg/ml			Comp.2 µg/ml				Comp.3 µg/ml			Comp.4 µg/ml		Comp.5 µg/ml		
		50	100	200	50	100	200	50	100	200	50	100	200	50	100	200
Staphylococcus aureus	15	-	-	-	20	22	25	17	20	30	-	-	-	17	20	22
Escherichia coli	10	8	10	12	-	-	-	-	-	10	-	6	10	7	10	12
Klebsiella pneumonia	13	12	12	15	-	-	-	9	13	20	-	-	-	10	13	15
Pseudomons aregenosa	20	-	-	-	10	11	13	-	-	-	-	-	-	-	-	-

ACKNOWLEDGMENT

We thank prof. Dr. Najim A. Al-Masoudi (Konstanz University, German) for equipping NMR analysis, and the grateful continued to physiology, Pharmacology and Chemistry department in our college for facilities.

REFERENCES

1. Wadher, S., Puranik, M., Karande, N. & Yeole P.(2009). Synthesis and Biological Evaluation of Schiff base of Dapsone and their derivative as Antimicrobial age International Journal of PharmTech Research, 1(1), 22-33.
2. Fu, K., Foleno, B., Lafredo, S., LoCoco, J. & Isaacson, D. (1993). In vitro and invivo antibacterial activities of FK037, a novel parenteral broad-spectrum cephalosporin, Antimicrobial Agents and Chemotherapy, 37(2), 301-307.
3. Reiss, A., Chifiriuc, M., Amzoiu, E., & Spînu, C. (2014). Transition Metal(II) Complex with Cefotaxime-Derived Schiff Base: Synthesis, Characterization, and Antimicrobial Studies, Bioinorganic Chemistry and Applications, 2014, 1-17. https://doi.org/10.1155/2014/926287.
4. Anacona, J. & Gladys, D. (2005), Synthesis and antibacterial activity of cefotaxime metal complexes, Journal of the Chilean Chemical Society, 50(2), 447-450.
5. Wayne, A. (1997), (National Committee for Clinical Laboratory Standards, NCCLS Approved standard M27- PA), USA.
6. Al-Masoudi W., Al-Diwan M. & Orass S.(2016), Synthesis, characterization and acute toxicity of new Schiff base derived from L-arginine and vanillin, European Journal of Chemistry, 7(3), 280-282.
7. Al-Masoudi, W., Al-Masoudi, N., Bernhard, W. & Rainer, W, (2017), Synthesis, X-ray structure, in vitro HIV and kinesin Eg5 inhibition activities of new arene Ruthenium complexes of pyrimidine analogs, Journal of Coordination Chemistry, 17(12), 2061-2067
8. Hawkey, P (1998). The origins and molecular basis of antibiotic resistance, British
9. Medical Journal, 317, 657–660.