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Baghdad Science Journal **Vol.12(3)2015**

Synthesis, Characterization and Antibacterial Activity of Cefalexin Dervatives

Entesar O. AL-Tamimi* ***Raad M. Muslih*****
Khalida A.Thejeel****

*Department of Chemistry, College of Science, University of Baghdad
**Department of Chemistry, College of Science for Women, University of Baghdad
***Department of Pharmaceutical Chemistry, College of Pharmacy, University of AL-Mustansria

Received 11, June, 2014
Accepted 6, August, 2014

Abstract:

New series of Schiff bases 2(a-j) and corresponding beta-lactam derivatives 3(a-j) were synthesized from cefalexin (1) as starting material. The compound (1) was reacted with different aldehydes and ketones to give Schiff bases derivatives 2(a-j). The synthesized Schiff bases were cyclized by chloroacetyl chloride in the presence of triethylamine to form beta-lactam derivatives 3(a-j). The compounds were characterized by deremination melting point, FT-IR and ^{1}H NMR. The beta-lactam derivatives were screened in vitro antibacterial against some bacterial species.

Key words: cefalexin, Schiff base, Beta-lactam, Antibacterial activity.

Introduction:

Azetidinones, are very well known compound for the organic and medicinal chemist [1]. Since it forms a part of the antibiotic molecules. Compounds containing 2-azetidinone ring system shown to pssess marked biological activity[2]. The earliest usage was in the form of antibacterials known as beta-lactam drugs.The most widely used antibiotic such as Penicillins, Nocardicins and Cephalosprins contains the beta-lactam ring[3]. Azetidinones are known to exhibit antibacterial activity[4]. The development of several synthetic and semi-synthetic beta-lactam antibiotics by the pharmaceutical industry was due to the growing resistance of bacteria towards the beta-lactam a more specific antibacterial activity [5]. First synthesized in 1907 by Staudinger[6,7]. Azetidinones prepared by cyclization reaction of Schiff bases with chloroacetyl chloride in presence of triethylamine[8]. Schiff bases are importantant intermediates for the synthesis bioactive compounds. Schiff bases are typically formed by the condensation of primary amine and aldehyde or ketone [9].

Materials and Methods:

All chemicals used were of A.R.grade. Melting points were determined in an open capillary tube and are uncorrected. Infrared spectra were recorded in KBr on Shimadzu spectrophotometer. The ^{1}HNMR were measured in DMSO-d6 solutions on a Bruker-400 MHz spectrometer using TMS as internal reference(chemical shift in ppm).

Synthesis Schiff bases 2(a-j)[10]

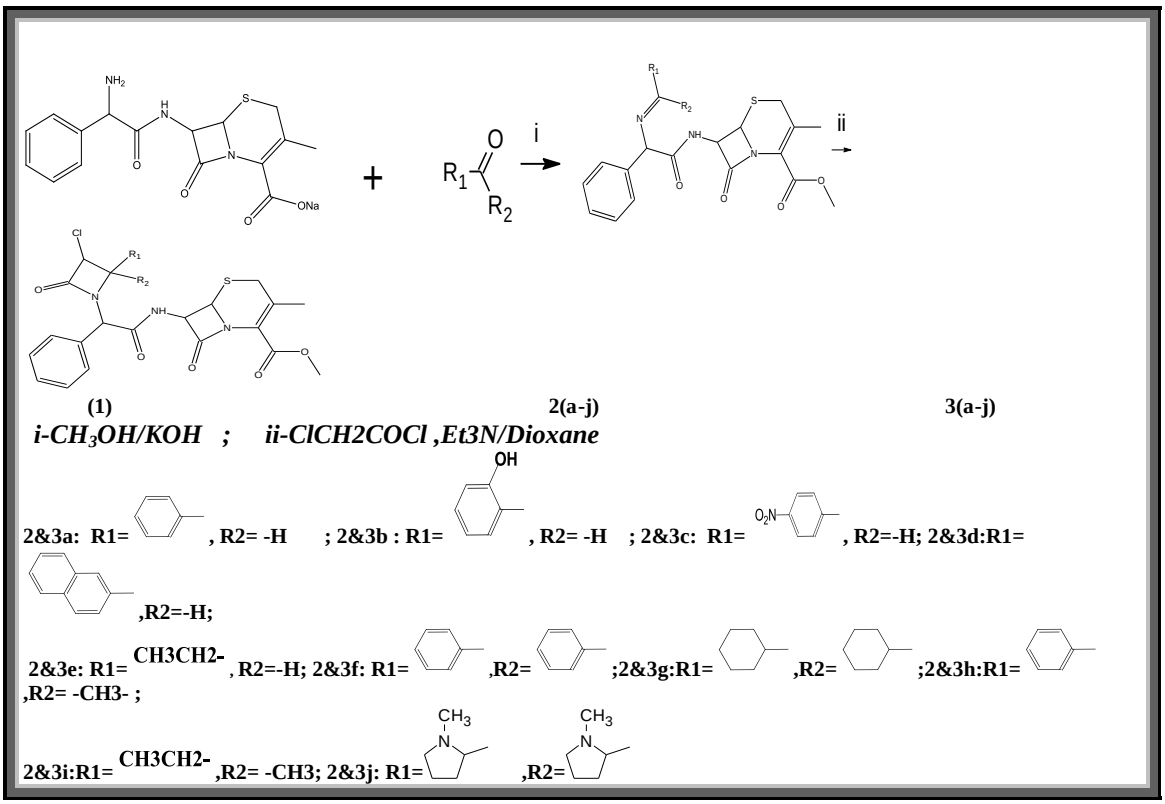
Sodium cefalexin (2 m mol ,0.7748g) dissolved in methanol (25ml) was mixed with carbonyl compound (2mmol) dissolved in methanol (25ml). To this KOH (0.1% methanol) was added to adjust the pH of the solution between 7-8 and the mixture was refluxed for 4-6 hr (approx.). A clear colored solution was obtained. The Schiff base was isolated by crystallization by suitable solvent after volume reduction by evaporation. The crystalline product was dried under vacuum and kept in desicator till further use.

Synthesis beta-lactam derivatives 3(a-j) [11]

Chloroacetyl chloride(2m mol) was added to Schiff base (1m mol) and triethyl amine dissolved in 1,2-dioxane (25ml) at 10^{o} C. The mixture was stirred for 24 hr. The triethyl amine hydrochloride precipitate formd was filtered and washed several times with dry 1,4-dioxane. The filterate and washing were mixed and concentrated under reduced pressure the residue was poured into crushed ice and the crude product obtained was recrystallized from ethanol.

Results and Discussion:

The reaction sequenced for different compounds is outlined in scheme-**1**



Scheme -1:preparation of synthesized compounds.

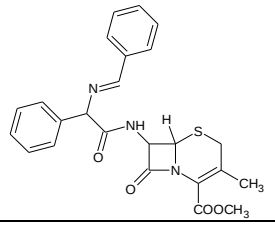
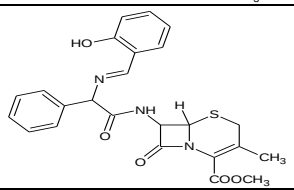
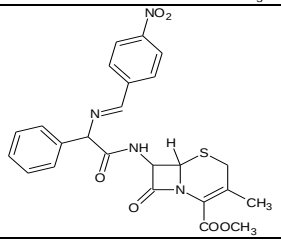
The physical properties of synthesized compounds in table-1.

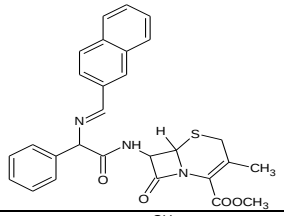
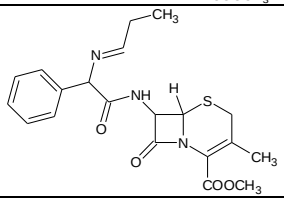
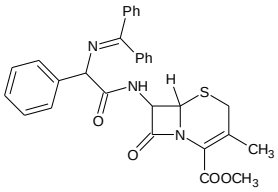
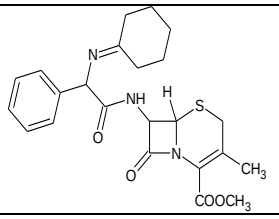
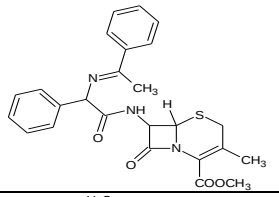
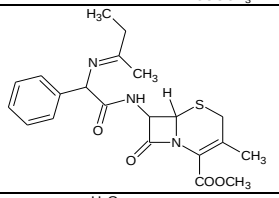
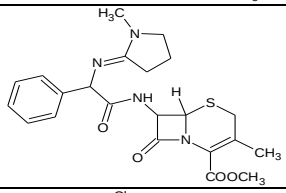
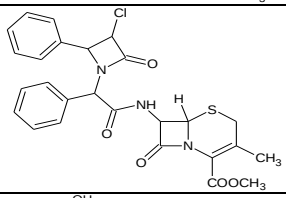
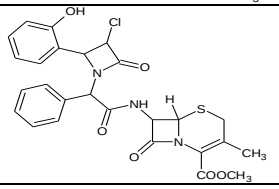
Table -1:The physical properties of compounds 2&3(a-j)

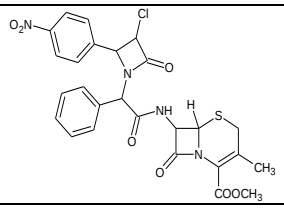
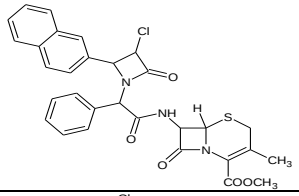
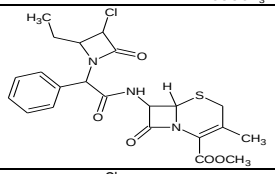
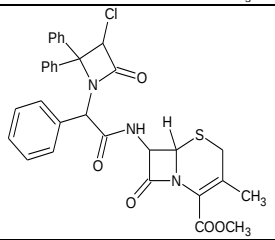
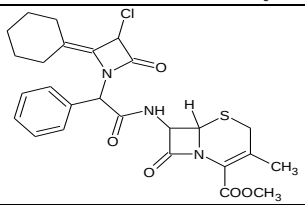
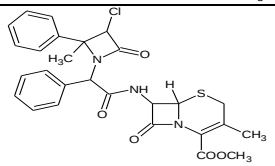
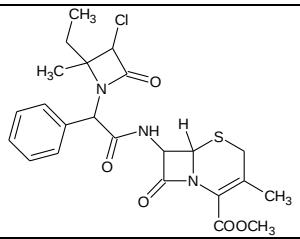
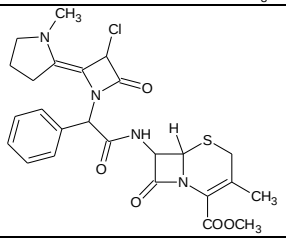
Comp. Code	Molecular Formula	Molecular Weight	Dec.p	%	Color
2a	$C_{24}H_{23}N_3O_4S$	449.52	125	94	Yellow
2b	$C_{24}H_{23}N_3O_5S$	465.52	115	96	yellow
2c	$C_{24}H_{22}N_4O_6S$	494.519	140	96	orange
2d	$C_{28}H_{25}N_3O_4S$	499.58	122	91	yellow
2e	$C_{20}H_{23}N_3O_4S$	401.479	144	81	yellow
2f	$C_{30}H_{27}N_3O_4S$	525.618	130	98	orange
2g	$C_{23}H_{27}N_3O_4S$	441.54	190	77	orange
2h	$C_{25}H_{25}N_3O_4S$	463.55	166	87	yellow
2i	$C_{21}H_{25}N_3O_4S$	415.5	172	82	yellow
2j	$C_{22}H_{26}N_4O_4S$	442.53	128	90	yellow
3a	$C_{26}H_{24}ClN_3O_5S$	526	oily	25	brown
3b	$C_{26}H_{24}ClN_3O_6S$	542	-	36	brown
3c	$C_{26}H_{23}ClN_4O_7S$	571	-	51	brown
3d	$C_{30}H_{26}ClN_3O_5S$	576.06	-	28	brown
3e	$C_{22}H_{24}ClN_3O_5S$	477.96	-	41	brown
3f	$C_{32}H_{28}ClN_3O_5S$	602.09	-	37	brown
3g	$C_{26}H_{28}ClN_3O_5S$	530.035	-	31	brown
3h	$C_{27}H_{26}ClN_3O_5S$	540.03	-	34	brown
3i	$C_{23}H_{26}ClN_3O_5S$	491.98	-	29	brown
3j	$C_{25}H_{27}ClN_4O_5S$	531.023	-	30	brown

The structural evaluation of performed FT-IR,[1] HNMR techniques which are in agreement with proposed structures table- 2 and 3.The FT-IR spectral of 2(a-j) compounds showing the absorption at ν (~ 1590 cm^{-1}) for –C=N- , while the 3(a-j) compounds the absorption at ν (~720 cm^{-1}) for C-Cl and disappearance the absorption of –C=N- group. ^{1}HNMR spectral of compounds 2a 2b singlate signal at δ = 8.21ppm and at δ = 8.11ppm due to (–CH=N-) proton and signals for 3a and 3b at δ = 5.23 ppm due to (CH-Cl azetidinone) proton.

Table-2-FT-IR Spectral data of 2&3(a-j) compounds

Comp. Code	Comp. Structure	IR (ν) cm^{-1}
2a		3061(C-H aromatic), 2975(C-H aliphatic), 3355(N-H),1565(N=CH-), 1740(C=O azetidinone), 1595,1510(C=C aromatic), 1673(C=O amide), 1362(C-N), 645(C-S-C),
2b		3063C-H aromatic), 2967(C-H aliphatic), 3342(N-H), 1568(N=CH-), 1738(C=O azetidinone), 1599,1505(C=C aromatic), 1666(C=O amide), 1355(C-N), 644(C-S-C) ,3450(O-H).
2c		3030(C-H aromatic), 2969(C-H aliphatic), 3353(N-H), 1564(N=CH-), 1738(C=O azetidinone), 1592,1502(C=C aromatic), 1670(C=O amide), 1360(C-N), 637(C-S-C) 142O(NO_2)

2d		**3048(C-H aromatic), 2972(C-H aliphatic), 3324(N-H), 1571(N=CH-), 1733(C=O azetidinone), 1605,1512(C=C aromatic), 1674(C=O amide), 1381(C-N), 642(C-S-C)**
2e		**3060(C-H aromatic), 2986(C-H aliphatic), 3389(N-H), 1566(N=CH-), 1739(C=O azetidinone), 1596,1508(C=C aromatic), 1670(C=O amide), 1361(C-N), 646(C-S-C)**
2f		**3045(C-H aromatic), 2972(C-H aliphatic), 3364(N-H), 1560(N=CH-), 1744(C=O azetidinone), 1602,1500(C=C aromatic), 1682(C=O amide), 1359(C-N), 637(C-S-C)**
2g		**3038(C-H aromatic), 2975(C-H aliphatic), 3364(N-H), 1565(N=CH-), 1740(C=O azetidinone), 1594,1511(C=C aromatic), 1678(C=O amide), 1371(C-N), 639(C-S-C)**
2h		**3035(C-H aromatic), 2973(C-H aliphatic), 3360(N-H), 1560(N=CH-), 1740(C=O azetidinone), 1600,1513(C=C aromatic), 1675(C=O amide), 1362(C-N), 649(C-S-C)**
2i		**3064(C-H aromatic), 2977(C-H aliphatic), 3357(N-H), 1566(N=CH-), 1741(C=O azetidinone), 1596,1511(C=C aromatic), 1671(C=O amide), 1359(C-N), 647(C-S-C)**
2j		**3062(C-H aromatic), 2976(C-H aliphatic), 3355(N-H), 1570(N=CH-), 1740(C=O azetidinone), 1598,1507(C=C aromatic), 1668(C=O amide), 1364(C-N), 652(C-S-C)**
3a		**3062(C-H aromatic), 2976(C-H aliphatic), 3345(N-H), 1744(C=O azetidinone), 1598,1508(C=C aromatic), 1669(C=O amide), 1360(C-N), 652(C-S-C), 722(C-Cl)**
3b		**3059(C-H aromatic), 2975(C-H aliphatic), 3353(N-H), 1747(C=O azetidinone), 1593,1511(C=C aromatic), 1668(C=O amide), 1364(C-N), 643(C-S-C), 720(C-Cl), 3443(OH)**

3c		**3063(C-H aromatic), 2977(C-H aliphatic), 3356(N-H), 1741(C=O azetidinone), 1599,1508(C=C aromatic), 1668(C=O amide), 1365(C-N), 653(C-S-C), 709 (C-Cl), 1474(NO2).**
3d		**3062(C-H aromatic), 2976(C-H aliphatic), 3355(N-H), 1742(C=O azetidinone), 1598,1507(C=C aromatic), 1668(C=O amide), 1364(C-N), 652(C-S-C), 698(C-Cl).**
3e		**3062(C-H aromatic), 2976(C-H aliphatic), 3355(N-H), 1737(C=O azetidinone), 1601,1503(C=C aromatic), 1665(C=O amide), 1364(C-N), 652(C-S-C), 715(C-Cl).**
3f		**3067(C-H aromatic), 2976(C-H aliphatic), 3355(N-H), 1741(C=O azetidinone), 1598,1507(C=C aromatic), 1668(C=O amide), 1364(C-N), 652(C-S-C) ,725(C-Cl)**
3g		**3030(C-H aromatic), 2974(C-H aliphatic), 3353(N-H), 1740(C=O azetidinone), 1598,1507(C=C aromatic), 1668(C=O amide), 1364(C-N), 652(C-S-C), 716(C-Cl)**
3h		**3061(C-H aromatic), 2976(C-H aliphatic), 1739(C=O azetidinone), 1597,1506(C=C aromatic), 1666(C=O amide), 1361(C-N), 651(C-S-C), 719(C-Cl).**
3i		**3062(C-H aromatic), 2976(C-H aliphatic), 3355(N-H), 1740(C=O azetidinone), 1598,1507(C=C aromatic), 1668(C=O amide), 1364(C-N), 652(C-S-C), 724 (C-Cl).**
3j		**3062(C-H aromatic), 2976(C-H aliphatic), 3355(N-H), 1740(C=O azetidinone), 1598,1507(C=C aromatic), 1668(C=O amide), 1364(C-N), 652(C-S-C),729 (C-Cl)**

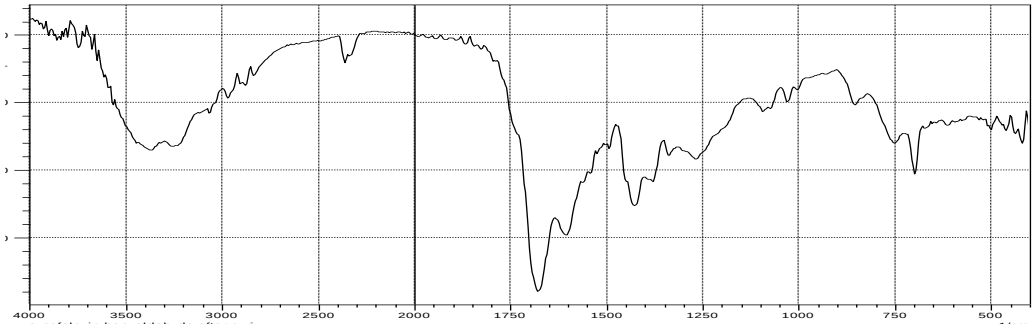


Fig.1:FT-IR 2a compound.

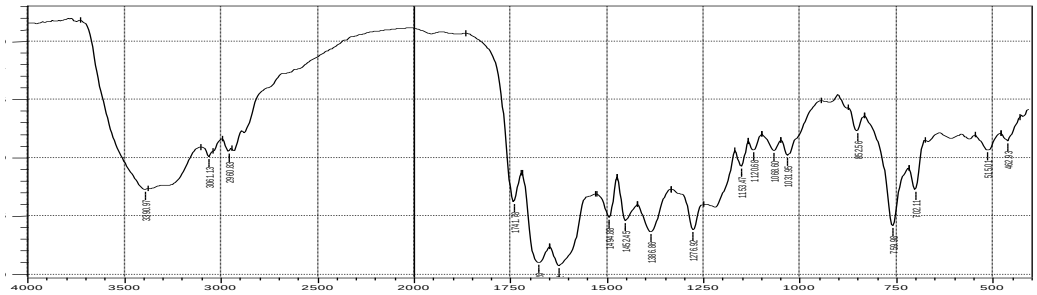


Fig.2: FT-IR 2b compound.

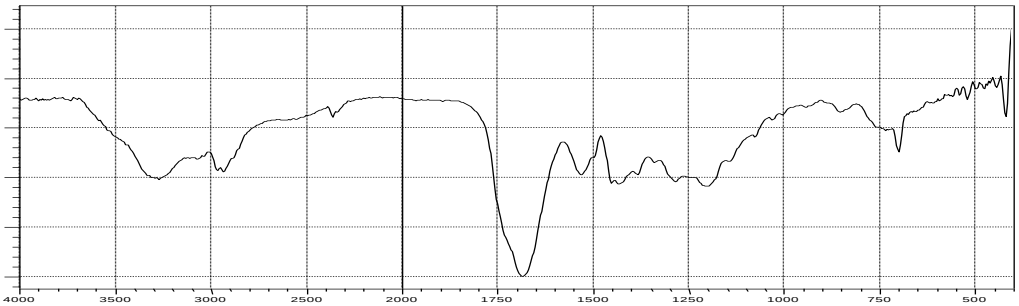


Fig.3: FT-IR 2e compound.

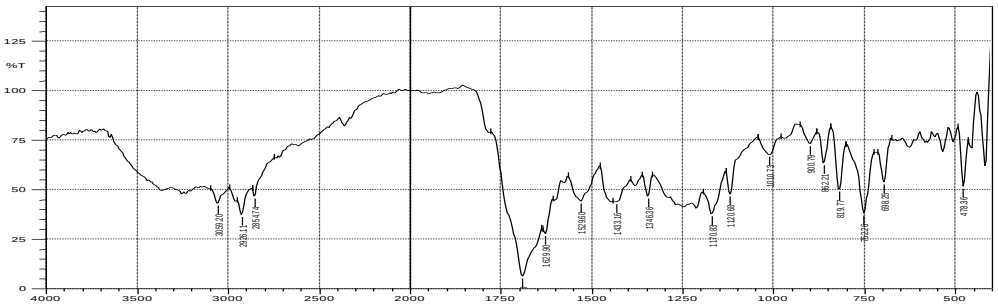
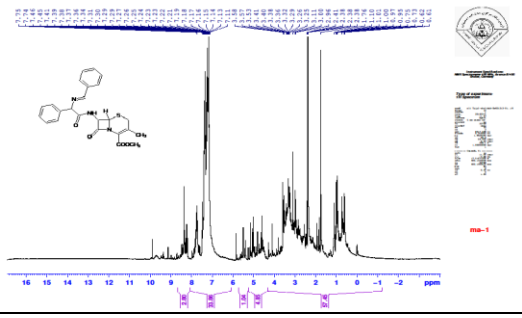
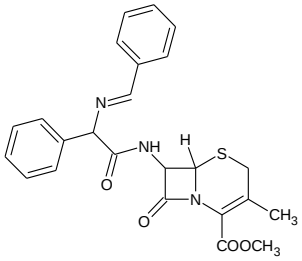
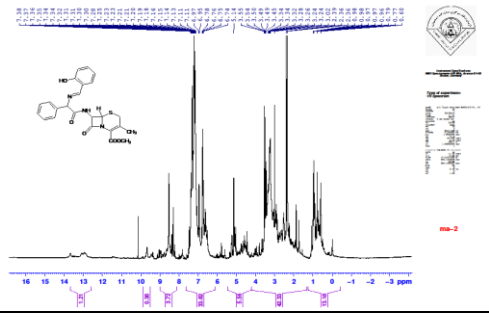
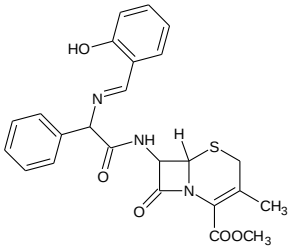
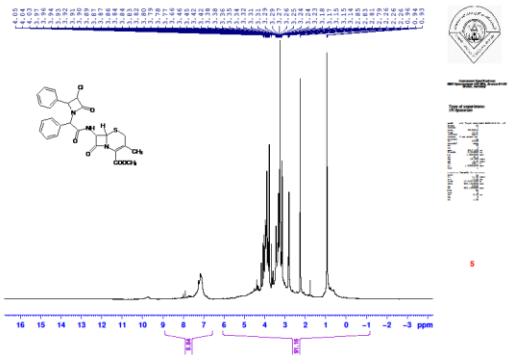
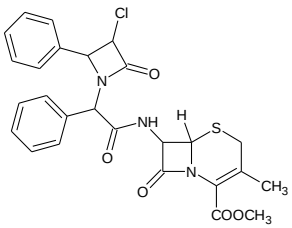
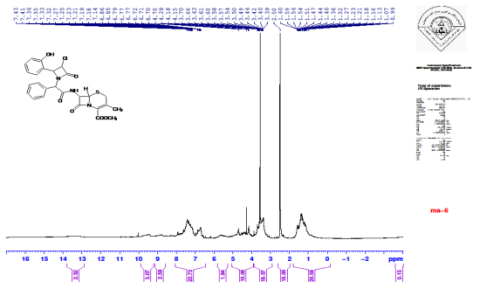
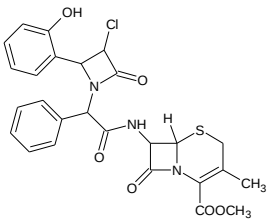


Fig.4: FT-IR 3d compound.

Table-3-^{1}HNMR figures and data of 2a,2b,3a&3b compounds.

Comp. Code	Comp. Structure	^{1}HNMR δppm
2a 		**7.02-7.66(m, 10H, Ar-H), 8.11(s, 1H, CH=N), 3.77(s, 3H, CH_3-O), 1.82(s, 3H, Ar-CH3) 3.16 (s, 2H, S-CH2), 8.03(s, 1H, CONH).**
2b 		**7.23-7.83(m, 10H, Ar-H), 8.21(s, 1H, CH=N), 3.66(s, 3H, CH_3-O),1.82(s, 3H, Ar-CH3) 3.18 (s, 2H, S-CH2), 8.06(s, 1H, CONH), 5.35(s, 1H, Ar-OH).**
3a 		**7.23-7.4(m, 10H, Ar-H), 5.23(s, 1H, CH-Cl azetidinone), 4.44(d, 1H, azetidinone proton), 3.67(s, 3H, CH_3-O) ,1.83(s, 3H, Ar-CH3) 3.16 (s, 2H, S-CH2), 8.05(s, 1H, CONH),**
3b 		**6.9-7.33(m, 9H, Ar-H), 5.23(s, 1H, CH-Cl azetidinone), 4.64(d, 1H, azetidinone proton), 3.76(s, 3H, CH_3-O),1.84(s, 3H, Ar-CH3) 3.2 (s, 2H, S-CH2), 8.03(s, 1H, CONH), 5.35(s, 1H, -OH).**

Anti-bacterial activity

Synthesized compounds 3(a-j) were screened for antibacterial activity against different bacterial strains gram positive bacteria: Bacillus and S.aureus and gram negative bacteria: E.coli and Pseudomonas, at concentration 400µg/ml by agar-well diffusion method[12]. DMSO served as control and due this there was no visible

change in bacterial growth and cefalexin was used as a standard drug. The plates were incubated at 37ºC for 24 h and diameter of zone of inhibition were measured and recorded in table 4. The results revealed that the majority of the synthesized compounds showed varying degree of inhibition against the tested against the gram-positive bacteria was higher than of the gram-negative bacteria. The compound 3d, 3g and 3i showed better activity in their respective groups against different gram positive and gram negative bacterial strains.

Table-4- Antibactrial activity of compounds 3(a-j) , standard and DMSO

Comp. Code	Zone of inhibition (in mm) Gram negative Gram positive			
	E.coli	Pseudomonas	Bacillus	S.aureus
3a	11	-	21	30
3b	11	-	21	36
3c	11	-	20	35
3d	12	12	24	34
3e	11	-	25	35
3f	11	-	24	34
3g	12	-	30	33
3h	11	-	24	32
3i	13	11	23	37
3j	11	-	20	33
Cefalexen	11	-	21	32
Control	-	-	-	-

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تحضير وتشخيص وايجاد الفعالية البايولوجية لمشتقات السيفالكسين

انتصار عبيد التميمي * رعد محجوب مصلح خالدة علي ثجيل*****

*قسم الكيمياء/كلية العلوم/ جامعة بغداد
**قسم الكيمياء/كلية العلوم للبنات/جامعة بغداد
***قسم الكيمياء الصيدلانية /كلية الصيدلة/ الجامعة المستنصرية.

الخلاصة:
سلسلة جديدة من مشتقات قواعد شف2(أ-ي) والبيتالاكتام المقابلة 3(أ-ي)تم تحضيرها من السيفالكسين (1) كمادة اولية بتفاعل المركب (1) مع الديهايدات وكيتونات مختلفة لتعطي قواعد شف2(أ-ي) والمركبات المحضرة تم غلقها بوساطة كلورو اسيتايل كلورايد بوجود ثلاثي اثيل امين لتكوين مشتقات البيتالاكتام 3(أ-ي) . شخصت المركبات الجديدة بوسطة نقطة الانصهار واطياف تحت الحمراء والرنين النووي المغناطيسي للبروتون كما تم دراسة الفعالية البايولوجية لمركبات البيتا لاكتام ضد بعض الانواع البكتيرية .

الكلمات المفتاحية: السيفالكسين، قواعد شف، بيتا-لاكتام، الفعالية المضادة للبكتيريا.