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Designing and Synthesising Novel Benzophenone Biscyclic Imides Comprising Drug Moity with Investigating their Antimicrobial Activity

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Abstract:

The present work involved designing and synthesizing of a series of new. compounds which their molecules are composed from two biologically active components namely sulfamethoxazole or β-lactam containing drugs and cyclic imides. The target new compounds were synthesized by two steps in the first one a series of six bis (*N*-drug phthalamic acid_4-yl) ketone (1-6) were prepared from the reaction of sulfamethoxazole or β-lactam containing drugs with benzophenone 3, 3′, 4, 4′ -tetracarboxylic dianhydride. In the second step, compounds (1-6) were introduced in dehydration reaction via fusion process producing the target compounds bis (*N*-drug phthalimidyl-4-yl) ketone (7-12). The antibacterial and antifungal high activities of the prepared compounds (7-12) were tested against (*Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas auroginosa and Staphylococcus aurus*) and all compounds showed good to high antibacterial activity. However, the maximum inhibition zone was 38 mm against *Staphyloccus aurus*, 36 mm against *Bacillus subtilis*, 35 mm against *Pseudomonas auroginosa*, 28mm against *Klebsiella pneumoniae* and 19 mm against *Rhizosporium fungi*.

Keywords: Bis (*N*-drug phthalamic acid-4-yl) ketone, Bis (N-drug phthalimidyl-4-yl) ketone, Cyclic imide.

Introduction:

Cyclic imides are valuable and important groups in creation of novel pharmaceuticals and bioactive compounds that showed many activities like anti-inflammatory, antitumor, antimicrobial, anticancer and anti-hyperlipidemic activities. In the pharmaceutical industry, cyclic imides are becoming increasingly popular. Cyclic imide structures are seen in several medicinal compounds. Antineoplastic medications include lenalidomide, carmofur, fluorouracil, and aminoglutethimide; antiflu medications include flutamide; and antiepileptic, antiarrhythmic, and sedative-hypnotic medications include phensuximide, phenytoin, and glutethimide[1-7]. β-Lactam-containing antibiotics are still one of the most important antibiotics[8] that used in treatment of a wide range of different infections. Cefotaxime, ampicillin and amoxicillin are examples for pharmacologically active β-lactam antibiotics used for treatment and prevention of gastrointestinal, skin bacterial and urinary infections[9-12].

In the light of all these facts beside increasing the problem of multidrug resistant micro-organisms and the urgent need for new antibiotics used in treatment of different bacterial and fungal infections, we thought it is very valuable to design and synthesize new developed β-lactams via incorporation of imide cycles in cefotaxime, ampicillin, amoxicillin, cifixime and cephalexin molecules followed by their antimicrobial activity screening. The work involved also incorporation of the well known sulfa drug (sulfamethoxazole) which contain sulfonamide skeleton[13-16] with cyclic imide in the same molecule and the resulted compound and the other new target β-lactam compounds are anticipated have quite big antimicrobial since they′ve been involved composed from two biologically energetic segments. In this study, a number of drugs were developed by incorporating imide rings into its composition, which resulted in new compounds with high anti-bacterial and anti-fungal efficacy.

Materials and Methodologies:

Melting points of the synthesized compounds were determined by Gallen kamp melting point apparatus and were uncorrected. FTIR spectra were recorded as KBr disc on Shimadzu FTIR-8400 Fourier Transform Infrared Spectrophotometer while ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Bio Spin apparatus, GmbH.

Method:

Synthesis of bis (*N*-drug phthalamic acid-4-yl) ketone (1-6)

The titled compounds were synthesized according to literature procedures[17,18] with minor modifications.

The solution of β-lactam containing drug (amoxicillin, ampicillin, cefotaxime, cifixime, cephalexin) 0.02 mole or sulfamethoxazole in dry acetone 30mL was added dropwise to the solution of benzophenone 3, 3′, 4, 4′-tetracarboxylic dianhydride 0.01mol, 3.229 g in dry acetone (25mL) with stirring and cooling at 0-5 ℃. After completion of addition the mixture was stirred for 3 hours at room temperature then the formed precipitate was filtered, washed with ether, dried and finally purified by recrystallization from a suitable solvent.

Synthesis of bis (N-drug phthalimide -4-yl) ketone (7-12)

The titled compounds were synthesized via dehydration of compounds (1-6) by fusion method[18]. Compounds (1-6), 1.0 g of was heated in oil bath until complete fusion then oil bath temperature was raised to ten degrees above melting point value of the used compound for additional 3 hours. Finally the product was left at room temperature and the resulted solid was purified by recrystallization from a suitable solvent.

Biological activity

The antimicrobial activity of several of the newly synthesized cyclic imides was tested using the agar diffusion technique using cap plates and incubation at 37 ℃ for 24 hours[19], with the inhibition zone quantified in micrometers.

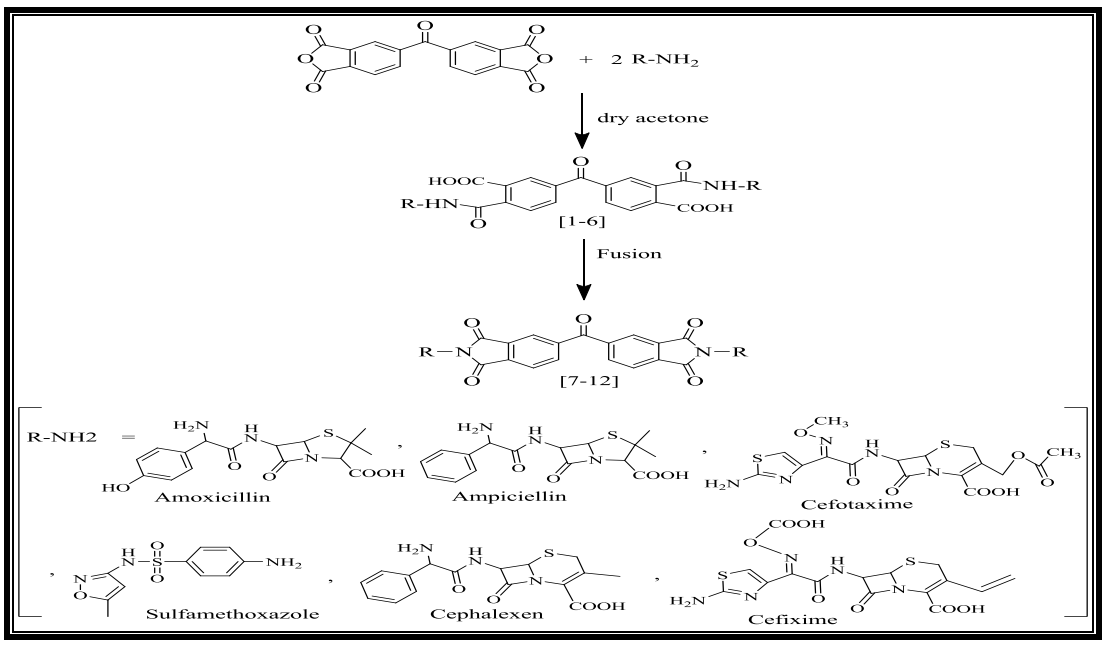
Results and Discussion:

Research has been directed towards preparing new biologically active compounds. Thus, by combining two imide cycles with sulfamethoxazole or β-lactam containing medicinal molecules, novel pharmacological combinations can be produced that, by their antibacterial action, can help to solve the problem of multidrug resistant microorganisms.

In order to perform this target in the begining was choose many drugs including (sulfamethaxole, amoxycillin, ampicillin, cefotaxime, cefixim and cephalexin) which contain amino group ready for introducing in reaction with cyclic anhydride producing bis(*N*-drug phthalamic acid 4-4′) ketone (1-6). In the second step compounds amic acid (1-6) were introduced in dehydration reaction by using fusion method[18].

During fusion process bis amic molecules (1-6) lose two water molecules followed by ring closure leading to bis cyclic imides formation (7-12)[18].

These steps are indicated in Scheme .1.



Scheme 1. Synthesis of compounds (1-12)

Physical properties of compounds (1-6) and (7-12) are shown in Tab.1 and 2 respectively.

FT-IR spectra of compounds (1-6) showed new band absorption at 3222-3461 cm^{-1} for to $\nu_{(O-H)}$ and $\nu_{(N-H)}$ and new absorption bands for $\nu_{(C=O)}$ carboxyl and amide appeared at 1766-1793 cm^{-1} and 1699-1718 cm^{-1} although absorption bands are formed for to $\nu_{(C=O)}$ ketone and $\nu_{(C=C)}$ showed up at 1652-1672 cm^{-1} and 1515-1639 cm^{-1} respectively[20]. All specifics about compounds (1-6) of FT-IR spectral data are shown in Tab.3.

The newly synthesized material's FT-IR spectra of compounds (7-12) exhibited clear bands of absorption at 3130-3483 cm^{-1} for to $\nu_{(O-H)}$ and $\nu_{(N-H)}$ while absorption bands as a result of $\nu_{(C-H)}$ aromatic, asym. $\nu_{(C-H)}$ aliphatic and sym. $\nu_{(C-H)}$ aliphatic showed up at 3062-3080 cm^{-1}, 2910-2993 cm^{-1} and 2812-2880 cm^{-1} respectively[21]. At the same time, other absorption bands emerged 1772-1784 cm^{-1}, 1720-1735 cm^{-1}, 1668-1670 cm^{-1} and 1650–1679 cm^{-1} that are due to $\nu_{(C=O)}$ lactam, $\nu_{(C=O)}$ imide and carboxyl, $\nu_{(C=O)}$ amide and $\nu_{(C=O)}$ ketone respectively[21].

Finally absorption bands as a result of $\nu_{(C=C)}$ and $\nu_{(C-N)}$ imide[19] showed up at 1514-1593 cm^{-1} and 1342-1379 cm^{-1}. FT-IR spectral data in its entirety for compounds (7-12) are shown in Tab.4 and Fig. 1.

Chemical structures of the prepared compounds in this work are proved also by ^{1}H-NMR and ^{13}C-NMR spectra.

^{1}H-NMR spectrum of amic acids (1,3,6) showed indication at (δ=2.04-2.74) ppm, (δ=6.66-8.39) ppm and at (δ=9.05-13.16) ppm which are belong to methyl group protons, aromatic protons and (O-H) carboxyl protons respectively[18]. ^{1}H-NMR spectrum of compounds (1and 3) showed indication at (δ=4.21-4.64) ppm belong to protons in lactam ring while spectra of compounds (3and 6) showed indication at (δ=5.86-6.24) ppm belong to vinylic protons.

^{13}C-NMR spectral analysis of compounds (1,3,6) showed indication at (δ=30.49-31.26) ppm, 113.26-163.72 ppm, 169.01-173.16 ppm and 193.81-194.54 ppm, which belong to methyl groups carbons, aromatic carbons, (C=O) amid carbons, (C=O) carboxyl carbons and (C=O) ketone carbons respectively[20]. All details of ^{1}H-NMR and ^{13}C-NMR spectral data for amic acids (1,3,6) are shown in Tab.5, 6 and Fig. 2.

On the other hand, ^{1}H-NMR spectrum of imide compounds (7,9,12) showed indication at (δ=2.1-2.75) ppm, (δ=6.72-8.52) ppm and (δ=8.1-9.77) ppm which belong to methyl group protons, aromatic protons and (N-H) protons respectively. The spectra of compounds (7) and (9) showed indication at (δ=4.21-4.85) ppm which belong to the protons in lactam ring while the spectra of compounds (9) and (12) showed indication at (δ=6.1-6.24) ppm belong to vinylic protons.

All details of ^{1}H-NMR spectrum data for imides (7,9,12) are shown in Tab.7 and Fig. 3.

Table 1. Chemical structures and compounds physical properties (1-6):

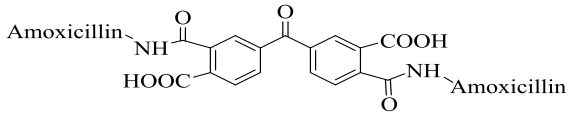
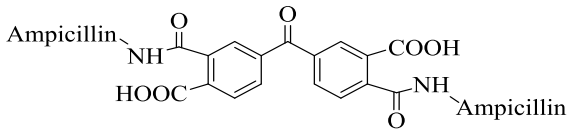
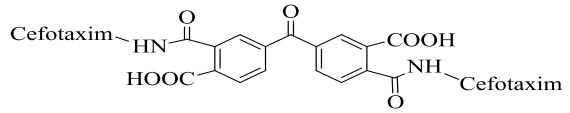
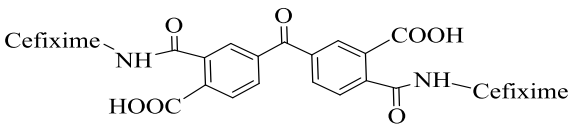
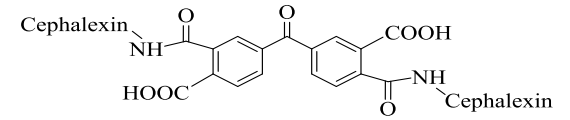
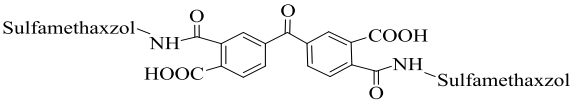
Comp. No.	Structure	Color	Yield%	M.p ℃	Recrystallization dissolvent
1		Orange	93%	144-146	Ethanol
2		Pale yellow	91%	135-137	Ethanol
3		Yellow	90%	180-182	Acetone
4		Light yellow	85%	143-145	Ethanol
5		Yellow	84%	139-141	Acetone
6		Pale yellow	88%	126-128	Acetone

Table 2. Chemical structures and compounds physical properties (7-12):

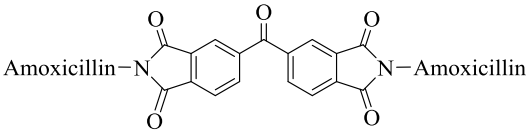
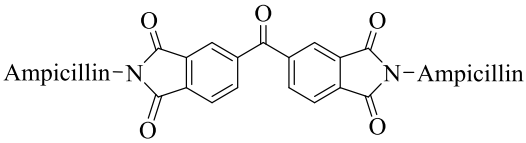
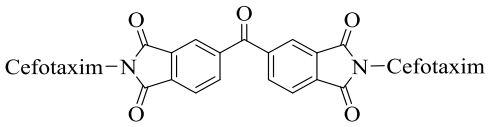
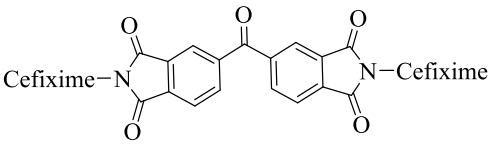
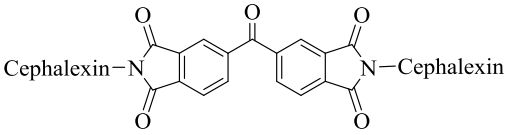
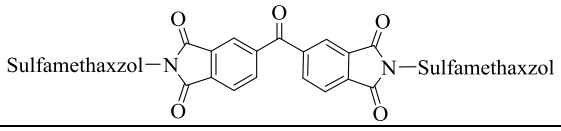
Comp. No.	Structure	Color	Yield%	M.p ℃	Recrystallization dissolvent
7		Dark yellow	83%	228-230	Ethanol
8		Bright brown	87%	177-179	Acetone
9		Brown	82%	215-217	Acetone
10		Brown	85%	211-213	Ethanol
11		Light brown	84%	202-204	Acetone
12		Dark brown	85%	281-282	Dioxane

Table 3. FT-IR spectral data (cm^{-1}) of compounds (1-6):

Comp. No.	$\nu_{(O-H)}$ $\nu_{(N-H)}$	$\nu_{(C-H)}$ Aromatic	$\nu_{(C-H)}$ Aliphatic	$\nu_{(C=O)}$ Lactam	$\nu_{(C=O)}$ Acid Amide	$\nu_{(C=O)}$ Ketone	$\nu_{(C=C)}$	Other
1	3461 3392 3350	3047	2974 2813	1766	1714 1699	1652	1515	-
2	3444 3355 3261	3062	2974 2813	1793	1714 1699	1654	1539	-
3	3409 3390	3040	2937 2889	1776	1718	1654	1542	$\nu_{(C=O)}$ Ester 1718(overlap)
4	3460 3350 3270	3068	2935 2866	1770	1699	1658	1541	-
5	3436 3386 3290	3049	2960 2880	1768	1718	1672	1639 1548	-
6	3454 3386 3344 3222	3070	2987 2887	-	1714	1670	1595	$\nu_{(C=N)}$ 1618 Asym. $\nu_{(SO2)}$ 1375 sym. $\nu_{(SO2)}$ 1159

Table 4. FT-IR spectral data (cm^{-1}) of compounds (7-12):

Comp. No.	$\nu_{(O-H)}$ $\nu_{(N-H)}$	$\nu_{(C-H)}$ Ar	$\nu_{(C-H)}$ Aliph	$\nu_{(C=O)}$ Lactam asym.Imide	$\nu_{(C=O)}$	$\nu_{(C=O)}$ Ketone	$\nu_{(C=C)}$	$\nu_{(C-N)}$ Imide	Other
7	3375 3334 3263	3068	2968 2880	1778	1720	1666	1514	1375	-
8	3380 3332 3282	3062	2966 2812	1776	1722	1662	1514	1379	-
9	3448 3388 3483	3066	2910 2839	1772	1722 1668	1650	1541	1342	$\nu_{(C=O)}$ Ester 1730 $\nu_{(C=N)}$ 1622
10	3377	3062	2966 2842	1778	1722	1679	1514	1373	-
11	3444 3384	3080	2945 2820	1780	1735 1670	1652	1539	1344	-
12	3307 3130 3222	3066	2993 2860	1784	1720	1668	1593	1375	$\nu_{(C=N)}$ 1614 Asym. $\nu_{(SO2)}$ 1375 sym. $\nu_{(SO2)}$1170

Table 5. ^{1}H-NMR spectral data (ppm) of Amic acids (1,3,6)

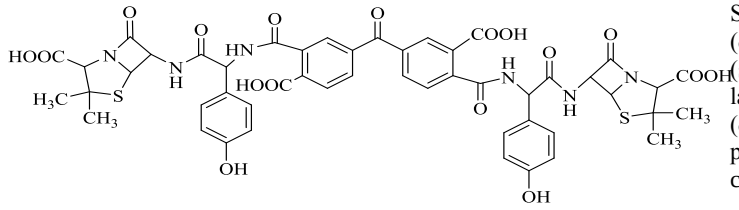
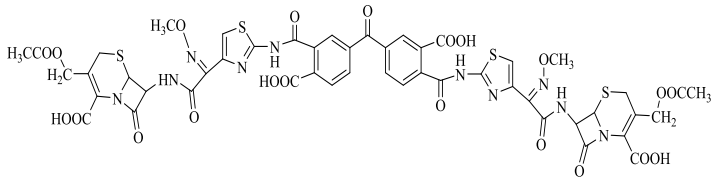
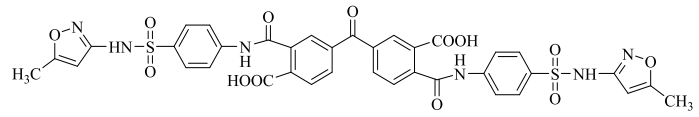
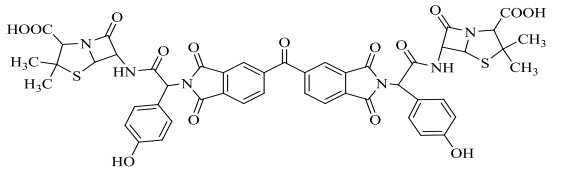
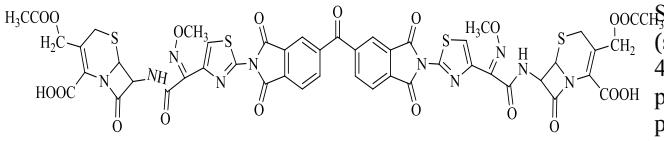
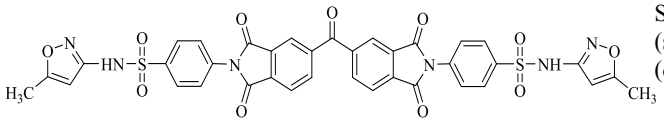
Compound structure	Signals in ^{1}H-NMR spectra (ppm)
 Compound (1)	Signals at (δ=2.04-2.74) ppm (s, 4CH_3) protons, (δ=2.84) ppm (s, proton in hetero ring), (δ=3.58) ppm (s, benzylic protons), (δ=4.21-4.64) ppm (d, protons in lactam ring), (δ=5.08) ppm (s, O-H phenolic protons), (δ=5.43-5.57) ppm (N-H amide protons), (δ=6.81-8.39) ppm (d, aromatic protons), (δ=9.05-9.23) ppm (s, O-H carboxyl protons).
 Compound (3)	Signals at (δ=2.09-2.74) ppm (s, 2CH3 protons), (δ=2.90) ppm (s, -CH_2S) protons), (δ=3.57-3.63) ppm (s, OCH_2 protons), (δ=3.83-3.89) ppm (s, OCH_3 protons), (δ=4.59-4,63) ppm (d, protons in lactam ring), (δ=5.23-5.64) ppm (s N-H protons), (δ=5.86) ppm (s, vinylic proton in thiazole ring), (δ=6.84-8.24) ppm (d, aromatic protons, (δ=9.61-9.75) ppm (d, N-H protons), (δ=13.16) ppm (s, O-H carboxyl protons).
 Compound (6)	Signals at (δ=2.27) ppm (s, 2CH3 protons), (δ=6.14-6.24) ppm (s, vinylic protons), (δ=6.66-7.96) ppm (d, aromatic protons), (δ=8.13-8.33) ppm (s, N-H protons), (δ=10.99) ppm (s, O-H carboxyl protons).

Table.6 ^{13}C-NMR spectral data (ppm) of Amic acids (1,3,6)

Comp. No.	Signals in ^{13}C-NMR spectra (ppm)
1	Signals at (δ=30.49-31.25) ppm (4CH_3 carbons), (δ=34.83) ppm (C- $(CH_3)_2$) carbons, (δ=36.3) ppm benzylic carbons, (δ=58.67) ppm (CH- COOH) in hetero ring, (δ=59.08-59.31) and (64.24) ppm (carbons in lactam ring, (δ=115.50-163.72) ppm aromatic carbons, (δ=168.20-169.62) ppm (C=O) amide carbons, (δ=170.56-170.93) ppm (C=O) lactam carbons, (δ=173.16) ppm (C=O) carboxyl carbons, (δ=194.54) ppm (C=O) ketone carbon.
3	Signals at (δ=31.26) ppm (2CH_3 carbons), (δ=36.28) ppm (-CH_2S) carbons, (δ=56.54-58.14) ppm (carbons in lactam ring), (δ=59.36) ppm (-OCH_2-) carbons, (δ=71.02) ppm ($NOCH_3$) carbons, (δ=110.88-117.89) ppm vinylic carbons, (δ=124.99-142.52) ppm aromatic carbons, (δ=150.34) ppm (C=N) thiazole carbons, (δ=162.83-162.94) ppm (C=N) carbons, (δ=163.69-164.09) ppm (C=O) amide carbons, (δ=167.9-168.75) ppm (C=O) lactam carbons, (δ=169.01-171.61) ppm (C=O) carboxyl carbons, (δ=193.97) ppm (C=O) ketone carbon.
6	Signals at (δ=30.96) ppm (2CH_3 carbons), (δ=95.78-95.88) ppm (vinylic carbons), (δ=113.26-158.43) ppm aromatic carbons, (δ=166.85-167.87) ppm (C=N) carbons, (δ=168.10-169.03) ppm (C=O) amide carbons, (δ=170.47-170.89)

ppm (C=O) carboxyl carbons, (δ=193.81-193.98) ppm (C=O) ketone carbons.

Table.7 ^{1}H-NMR spectral data (ppm) of Imides (7,9,12)

Compound structure	Signals in ^{1}H-NMR spectra (ppm)
 Compound (7)	Signals at (δ=2.10-2.75) ppm (s, $\underline{4CH_3}$ protons), (δ=2.90) ppm (s, proton in hetero ring), (δ=3.19) ppm (s, benzylic protons), (δ=4.21-4.75) ppm (d, protons in lactam ring), (δ=4.98-5.77) ppm (s, O-H phenolic protons), (δ=6.73-8.51) ppm (d, aromatic protons), (δ=9.05-9.77) ppm (d, N-H amide protons), (δ=11.67) ppm (s, O-H carboxyl protons).
 Compound (9)	Signals at (δ=2.1) ppm (s, $\underline{2CH_3}$ protons), (δ=2.79-2.91) ppm (s, $-CH_2S$ protons), (δ=3.81) ppm (s, OCH_3 protons), (δ=4.56-4.85) ppm (d, protons in lactam ring), (δ=6.1) ppm (s, vinylic protons), (δ=6.89-8.52) ppm (d, aromatic protons), (δ=8.85-9.6) ppm (d, N-H amide protons), (δ=10.4-11.7) ppm (s, O-H carboxyl protons).
 Compound (12)	Signals at (δ=2.32) ppm (s, $\underline{2CH_3}$ protons), (δ=6.13-6.24) ppm (s, vinylic protons), (δ=6.72-7.84) ppm (d, aromatic protons), (δ=8.10-8.27) ppm (s, N-H protons).

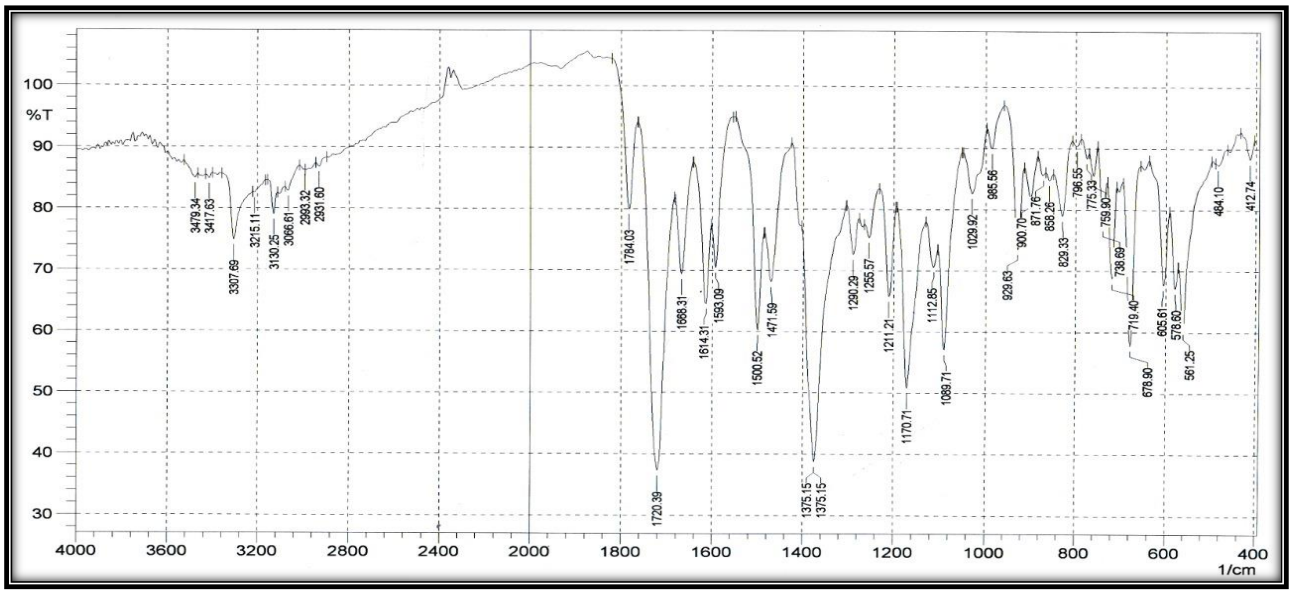


Figure 1. FT-IR spectrum of compound (12)

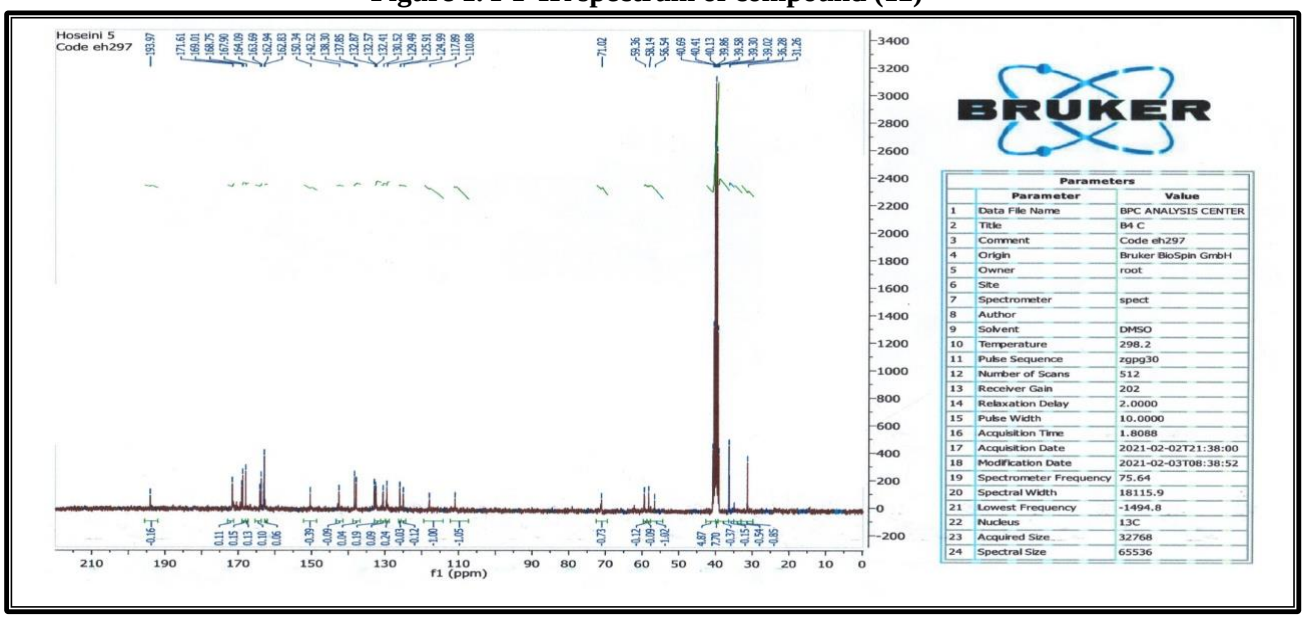


Figure 2. ^{13}C-NMR spectrum (75MHz, DMSO-d_6) of compound (3)

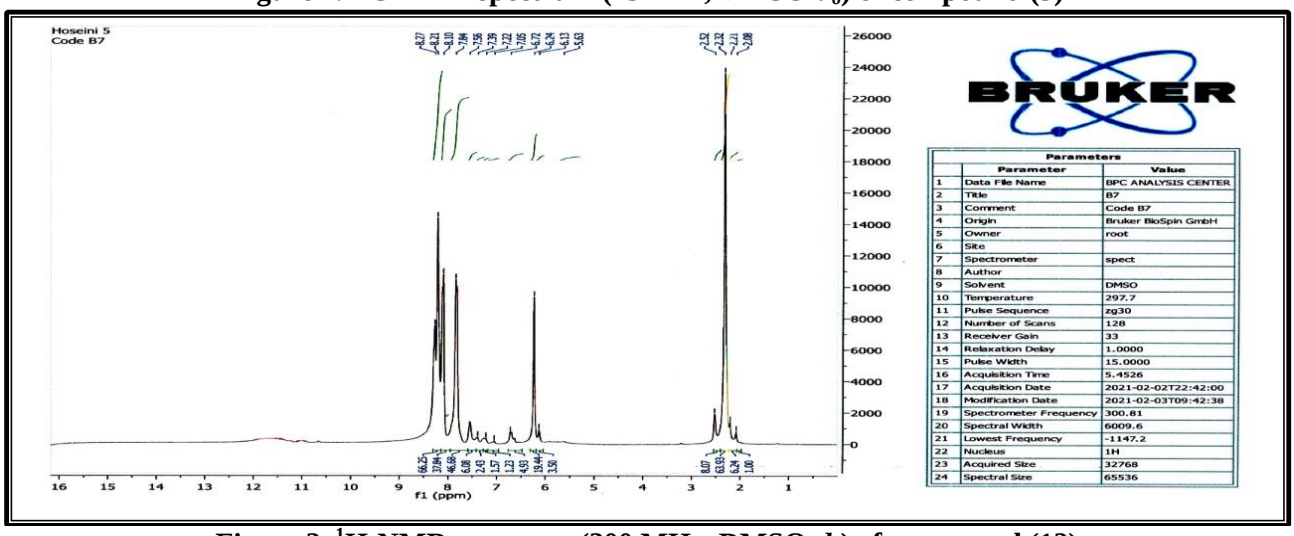


Figure 3. ^{1}H-NMR spectrum (300 MHz, DMSO-d_6) of compound (12)

Table 8. Inhibition zones (mm) of antibacterial and antifungal activities of compounds (7-12):

Comp. No.	*pseudomonas auroginosa*	*Staphylococcus aurus*	*Klebsiella pneumoniae*	*Bacillus subtilis*	*Rhizosporium fungi*
7	28	15	23	27	20
8	16	16	15	27	11
9	18	37	26	28	18
10	20	35	27	26	20
11	28	17	22	27	18
12	35	38	28	36	19
control	13	15	20	18	11

Biological Activity study

Biological activity study in this work involved evaluation of antibacterial activity of compounds (7-12) against several types of bacteria including *Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas auroginosa and Staphylococcus aurus* bacteria and evaluation of antifungal activity of the same compounds against *Rhizosporium fungi*. Inhibition zones in (mm) caused by the new compounds (7-12) against the tested organisms (bacteria and fungi) are shown in Tab. 8 and these results compounds (7, 10 and 11) have been identified showed a high level of activity against *Pseudomonas auroginosa* while compound (12) showed very high activity and compounds (8 and 9) showed moderate regulation against this bacterium. The compounds (9, 10 and 12) exhibited very high regulation against *Staphylococcus aurus* because the ability of some of these compounds to dissolve the fatty layer of this wall bacteria, which causes cell fluids to drain out and destroy them. The possibility of forming hydrogen bonds between hydroxyl groups, N and S in compounds and water molecules in the cell, which is 80-90% of the cell weight, and this leads to disruption of vital activities cell and destroy it, because the compound kills microorganisms or inhibits their growth by damaging or preventing their formation cell walls or through a defect in the permeability of the cytoplasmic membranes and the physical and chemical structure of protein and nucleic acids in the cell by imbalance in cellular enzymatic activity as well as by preventing protein synthesis and nucleic acids the resistance to any type of bacteria varies its genera of chemical compounds results from the presence of a thick envelope surrounding the cell because it contains a high percentage of fat, which prevents these substances from entering the cell.

Compound (12) showed very high activity against *Bacillus subtilis* and high activity against *Klebsiella pneumoniae* while compounds (7, 9, 10 and 11) exhibited high activity against these two types bacteria. Finally Compound (8) showed high activity against *Bacillus subtilis* bacteria.

On the other hand, the results in Tab .8 indicated that the new compounds (7, 9, 10, 11 and 12) showed high antifungal activity while compound (8) showed moderate activity against the tested fungi.

Conclusion:

In this work were study the changes in various physical properties for Prepared compounds. The properties studied by FTIR, ^{1}H-NMR and ^{13}C-NMR spectroscopies. Development was made in some drug molecules through introducing biscyclic imides moieties in original drug molecule. Introducing of these moieties increased antibacterial and antifungal activity of the resulted molecules, thus most of them showed very high antibacterial antifungal activity. These promising results can lead to find new drugs which may fight different bacterial infections.

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.
- Authors sign on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Author's Contribution:

The idea was proposed by the supervisor, Prof. Dr. Ahlam Marouf Al-Azzawi, and the work and application was made by the doctoral student Zaynab Hussein Fadel. As for the interpretation of the spectral identification, it was done in cooperation with both of us.

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تصميم وتحضير بنزوفينون ثنائي ايمايدات حلقية جديد تحتوي على مكونة دوائية مع التحري عن فعاليتها المضادة للميكروبات

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الخلاصة :

يتضمن هذا البحث تصميم وتحضير سلسلة من مركبات جديدة تتكون جزيئاتها من مكونين فعالة بايولوجيا هما السلفاميث اوكسازول أوالادوية الحاوية على بيتا-لاكتام والايمايدات الحلقية .تم تحضير المركبات الجديدة بخطوتين تضمنت الخطوة الاولى تحضير سلسلة من ستة مركبات (1-6) جديدة هي ثنائي(N- دواء حامض الفثال اميك-4-يل) كيتون وذلك من تفاعل سلفاميث اوكسازول أوالادوية الحاوية على بيتا-لاكتام مع بنزوفينون 4′, 4, 3′, 3- رباعي كاربوكسيل ثنائي أنهدريد. في الخطوة الثانية ، تم سحب ماء من المركبات المحضرة (1-6) بأستخدام عملية الصهر مما أسفر عن تكوين المركبات المحضرة (7-12) وهي ثنائي (N- دواء فثال ايمايديل-4-يل) كيتون. تم دراسة الفعالية المضادة للبكتيريا والفطريات للمركبات المحضرة (7-12) ضد (*Bacillus subtilis*، *Klebsiella pneumoniae*، *pseudomonas auroginosa and Staphylococcus aurus*) وأظهرت جميع المركبات فعالية مضادة للبكتريا جيدة إلى عالية. ومع ذلك ، كانت منطقة التثبيط الاعلى 38 ملم ضد *Staphyloccuss aurus* و 36 ملم ضد *Bacillus subtilis* و 35 ملم *Pseudomonas auroginosa* ، و 28 ملم ضد *Klebsiella pneumoniae* و 19 ملم ضد فطريات *Rhizosporium fungi* .

الكلمات المفتاحية: ثنائي (N- دواء حامض الفثال اميك-4-yl) كيتون ، ثنائي(N- دواء فثال ايميديل 4-yl) كيتون ، إيمايد حلقي.