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Synthesis of Benzylpenicillin esters and evaluate the change in the anti-bacterial effects by Docking and bacteriological study

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Abstract

Background: Benzylpenicillin is an antibiotic that possesses effectiveness mainly against gram-positive and some gram-negative bacteria. The carboxylic acid of beta-lactam is essential for its antibacterial activity. However, many prodrugs have been produced through the esterification of this carboxylic acid group, like Pivampicillin.

Objective: To evaluate the antibacterial effects of Benzylpenicillin when the free carboxylic acid mask with different chemical groups of different polarity.

Patients and Methods: Four Benzylpenicillin derivatives (compounds p1-p4) were chemically synthesized through the esterification of the carboxylic acid group with different groups of different polarity, and the antibacterial activities were examined by docking and bacteriological studies.

Results: All the compounds showed different antibacterial results. The docking results showed that; the compound of the highest polarity (compound p1) has the best Binding energy. Also; The results of in vitro antibacterial activity showed that; compound p1 had the largest zones of inhibition and the highest antibacterial activity among all the other compounds.

Conclusion: Masking the free carboxylic acid of benzylpenicillin with polar group will enhance the antibacterial activity.

Keywords: Beta lactam antibiotics, Benzylpenicillin, anti-bacterial activities, docking, esterification.

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Introduction

Since the 1940 practical implementation of Benzylpenicillin, which was discovered in 1929, antibiotics have become the main method for treating bacterial infection [1]. The success of these compounds has encouraged research into the production of additional derivatives. β-lactam antibiotics, such as penicillin, monobactam, carbapenem, narrow- and extended-spectrum cephalosporins, were discovered as a result of

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the investigation [2, 3]. The existence of a highly reactive β-lactam ring, which is made up of three carbon atoms and one nitrogen, is what makes β-lactam antibiotics unique [4, 5]. In order to prevent bacteria from synthesizing cell walls, beta-lactam antibiotics bind and acylate the active site of penicillin-binding proteins (PBP). This procedure sets off series of events that gradually weaken the cell wall, activate hydrolases and autolysases, and prevent the regulation of intracellular osmotic pressure, leading to cell lysis at the end [4, 6]. In recent years, bacterial infections have expanded to pose a serious treatment challenge on a global scale [7]. Despite the availability of effective medications, the growth of multidrug-resistant bacterial infections and the advent of novel infectious diseases pose a danger to the efficacy of antibiotics [8]. The challenge posed by both Gram-positive and Gram-negative bacteria calls for the urgent development of new chemicals [9, 10]. Antibiotics are available over-the-counter in some nations, which has led to an increase in drug-resistant bacterial infections and pose a significant challenge for healthcare providers [11]. Drug-resistant microorganisms are a serious issue, and there is a critical need for innovative compounds that can entirely eradicate these diseases. The bulk of bacterial resistance mechanisms, such as enzymatic degradation, target modification, increased efflux pump expression, and decreased uptake, have been found and described [12]. Multidrug-resistant bacteria, which show resistance to three or more antibiotic classes, are a significant cause of mortality, according to the World Health Organization (WHO) [10]. Multidrug-resistant bacteria are becoming more widespread, there is an increased demand for the development of novel antimicrobials as a treatment for diseases that can cause severe or even fatal complications [13, 14]. Most developed drug candidates fail the clinical stages due to their substandard pharmacokinetic properties, and the introduction of a new treatment to the market normally takes 10 to 15 years and a substantial expenditure. Therefore, it is imperative to construct fresh, cutting-edge methods for creating new medications, especially antibiotics [15]. Antimicrobial actions and selectivity with target sites have been enhanced through the use of technology like computational methods like in silico and Fragment-based drug design FBDD [16]. The majority of the methods used today are based on prodrugs and the synthesis of novel compounds, but the latter process has disadvantages in that it is expensive and time-consuming. Prodrugs make up 10% of commercially available drugs, making them a more practical and cost-effective choice [17]. Research from the past has shown that a basic benzylpenicillin derivative, specifically [N-(3-dimethylamino-propyl)benzylpenicillin amide], which is obtained by swapping its free carboxyl group, has a propensity to accumulate in macrophages. The hypothesized distributions of weak organic acids and bases across biological membranes can account for the observed behavior. On the basis of general considerations, it is specifically predicted that weak organic bases will accumulate in acidic membrane-bound compartments, such as cells and lysosomes [18]. However, weak organic acids will not be allowed to enter the same compartments. In this context, it is clear that the presence of

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a free carboxyl group or a comparable proton donor, which is essential for their functional efficiency, causes β-lactams to exhibit properties of weak organic acids [19]. In order for basic derivatives of β-lactams created by substituting this acid to boost their intracellular accumulation to be useful for chemotherapy, they must replenish the free antibiotic intracellularly.

Phthalimidomethylampicillin (PIMA) is an example of a novel simple ester of ampicillin designed for this use [20].

The aim of this study is to evaluate the changing in the antibacterial effects of Benzylpenicillin when the free carboxylic acid group mask with different chemical groups of different polarity.

Patients and Methods

Chemical synthesis and identification

All the chemical materials, reagents, and solvents were used in chemical synthesis and the formulation were purchased from reliable resources. FTIR Spectrometer (JASCOFT/IR-4600 spectrometer (Japan)), NMReady-60PRO (60 MHZ) (Canada) spectrometer, and EuroEA 3000 (United Kingdom) Elemental analyzer were used for identification of the new products.

General procedure for esterification of Benzyl penicillin

Synthesis of Benzylpenicillin esters was carried out by esterification reactions with inositol, methanol, ethanol, and propanol to synthesize compounds p1-p4 respectively. The obtained esters were purified using column chromatography. Esters were then characterized by FTIR, 1H-NMR, and elemental analysis.

In a flask with a round bottom and 30 ml of either methanol, ethanol, or propanol. 5 g of benzoylpenicillin was added. The esterification reaction was catalyzed by adding 0.5 ml of concentrated sulfuric acid to the aforementioned solutions. The resulting solutions were kept under reflux for one night while being stirred with a magnetic stirrer. TLC was used to evaluate the reaction's completion with a 1:1 ethyl acetate and hexane mobile phase. The solution was neutralized using sodium bicarbonate solution once it had cooled to room temperature. After that, the final dry powder of compounds P2-P4 was obtained using a Rotary Evaporator [21,22].The same method described above was used to create compound p1, with the exception of the solvent being anhydrous dichloromethane. Benzylpenicillin (5 gm) and inositol (2.7 gm) were combined in an esterification process to create compound p1. Following that, the pure products were isolated using column chromatography with a mobile phase made up of n-Hexane, and ethyl acetate in a 7:1 ratio.

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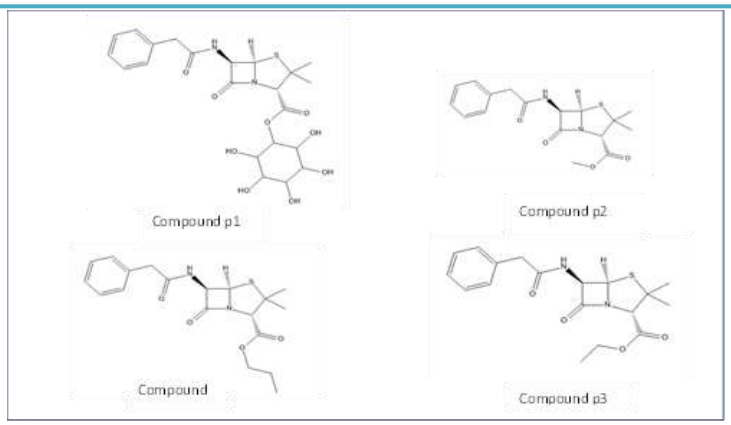

Figure (1): The chemical structures of the Benzylpenicillin derivatives by Chem Office program

Docking study

Penicillin binding proteins (PBP) used to be thought to be essential for the synthesis of bacterial cell walls. PBP1b was chosen as the study's primary target. The Protein Data Bank (PDB) was used to gather the PBP1b (2y2q) 3-Dimensional (3D) structures, which were then shown using Py-MOL viewer. After identifying and removing co-crystallized ligands from the target protein, water molecules were taken out, Hydrogen atoms were added, and minimizations were performed using the Swiss pdb viewer. The 3D coordinates of the Benzylpenicillin derivatives were drawn using ChemSketch and the energy were minimized by Avogadro program. All the structures had hydrogen atoms added, and during docking, the shape of each molecule was optimized using chimera to account for the flexible conformations of the compounds.

With the help of Auto-Dock version 4.0, the automatic docking investigations were completed. Utilizing the graphical user interface AUTODOCKTOOLS (ADT 1.4.6), the PBP1b 3D structure was created. Non-polar hydrogens were added, Kollman United Atoms charges were loaded, and all hydrogens were united with carbon atoms. The generated PDBQT file was saved together with the starting conditions. The 3D ligand molecule structures were created, enhanced, and converted into Mol2 file format using Avogadro program. The charges of the non-polar hydrogen atoms are taken up by the atom to which they are bound. PDBQT files were used to store the created files. The grid box was created to contain all the amino acids in the drug binding site for the ligands on PBP1b which was mentioned in previous study (Asp337, Phe341, Thr342, Ala345, Glu346, Glu349, Tyr443, Gln447, Asn448, Asn449, Phe452, Asp453, Glu540) [22]. AUTODOCK 4.0 was used to perform all docking calculations. The AUTODOCKTOOLS were used to generate the grid parameter files and docking parameter files. The docking parameters were also used to calculate docking scores for benzylpenicillin derivatives and Pymol and ligplus were used for visualization [23].

Bacteriological study

The effectiveness of the synthesized compounds (p1-p4) as antibacterial agents were screened by evaluating their activity and comparing it to Benzylpenicillin result.

The antibacterial assay was tested on four different strains of bacteria: two Gram-

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positive strains, *Staphylococcus aureus* ATCC 25923 and *Staphylococcus epidermidis* ATCC 12228, and Escherichia coli ATCC 25922 and *Salmonella abony* ATCC 6017 as the two Gram-negative strains.

Disk diffusion method

The antibacterial activity was screened against 4 species of bacteria. Prepared and sterilized filter paper disks measuring 6 mm in diameter were added to each prepared solution of the compounds and left to soak for 4 hours. Bacteria for the experiment were streaked onto Muller-Hinton agar. The disks were then placed on the Petri dishes at uniform intervals and incubated for 24 hours at 37^{0}C. Clear inhibition zones on the agar surface were recorded after the dishes were incubated [24,25].

Statistical Analysis

The statistical differences among the antibacterial effects of all compounds on the two Gram-negative strains *Escherichia coli* ATCC 25922 and *Salmonella abony* ATCC 6017 was calculated using analysis of Tukey's post-hoc test. The data were analyzed by using SPSS program version 28.

Results

The synthesized compounds (p1-p4) were chemically identified by elemental analysis, FT-IR, and 1H-NMR Spectrometers as shown in Tables (1) and (2). The 1H-NMR and IR spectrums of compound p1 are shown in Figure (2).

Table (1): The chemical names, percentage of yield, and Elemental analysis values of compounds p1-p4

Compounds	Chemical names	Percentage of yield	Elemental analysis values
P1	2,3,4,5,6-pentahydroxycyclohexyl 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate	72%	C, 52.87 H, 6.14 N, 5.21
P2	methyl 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate	82%	C, 58.23 H, 5.93 N, 7.96
P3	ethyl 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate	84%	C, 59.27 H, 6.38 N, 7.54
P4	propyl 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate	87%	C, 60.12 H, 6.76 N, 7.13

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Table (2): The FT-IR bands and 1H-NMR signals of compounds p1-p4

Compounds	FT-IR bands (cm^{-1})	^{1}H NMR signals (DMSO) (ppm)
P1	2973 (C-H) of methyl group, 1751 C=O stretching vibration of ester group, 3567 (NH) stretching vibration of amid group, 3239 stretching vibration of alcohol (OH).	1.18-1.75 H of methyl groups (CH_3), 3.29-3.70 H of methylene groups(CH_2), 4.40 H of alcohol (OH),5.85 propiolactam(CH) 7.32–7.61 H of benzene ring, 8.08 H of secondary amide (NH).
P2	2966 (C-H) of methyl group, 1748 C=O stretching vibration of ester group, 3534 (NH) stretching vibration of amid group	1.51 and 3.59 H of methyl groups (CH_3), 3.32-4.81 H of methylene groups(CH_2),5.18 propiolactam(CH) 7.11 – 7.32 H of benzene ring, 8.03 H of secondary amide (NH).
P3	2964 (C-H) of methyl group , 1744 C=O stretching vibration of ester group, 3571 (NH) stretching vibration of amid group	1.29-1.56 H of methyl groups (CH_3), 3.31-4.64 H of methylene groups (CH_2),5.23 propiolactam(CH) 7.18 – 7.33 H of benzene ring, 8.02 H of secondary amide (NH).
P4	2968 (C-H) of methyl group , 1743 C=O stretchingvibration of ester group, 3569 (NH) stretching vibration of amid group	0.95-1.52 H of methyl groups (CH_3), 2.11-4.35 H of methylene groups (CH_2),5.19 propiolactam(CH) 7.11 – 7.36 H of benzene ring ,8.03 H of secondary amide (NH).

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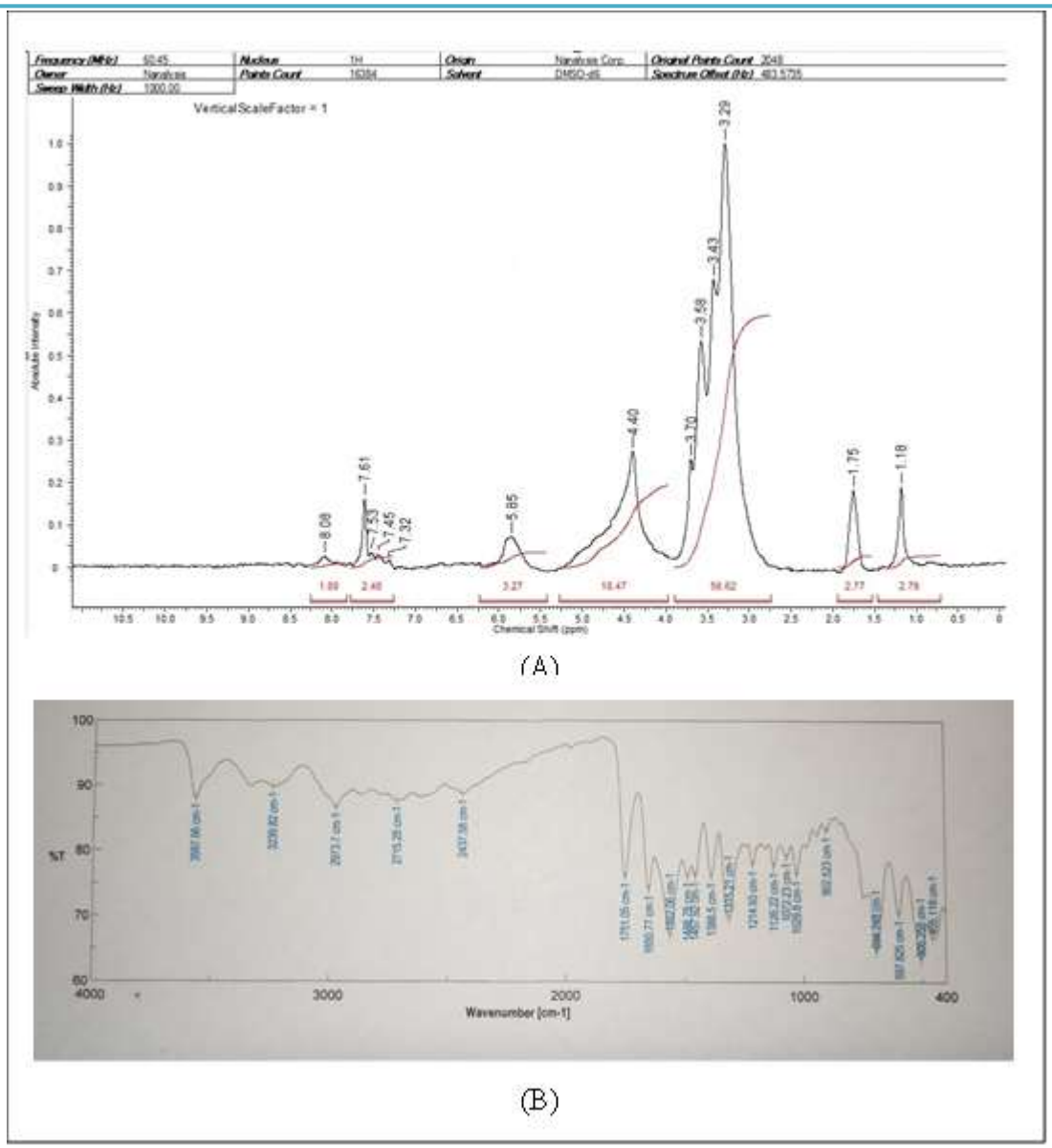

Figure (2): (A) 1H-NMR spectrum of compound p1 in DMSO. (B) FT-IR spectrum of compound p1

The results of the Insilco study of all the newly synthesized compounds (p1-p4) and benzylpenicillin are shown in Table (3) .

Furthermore, the2D and 3D interaction between compound p1 and PBP1b are shown in Figure (3).

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Table (3): Binding affinities and Inhibition constant of benzylpenicillin and compounds p1-p4

Compounds	Binding energy (kcal/mol)	Inhibition constant, µM
Benzylpenicillin	-6.16	30.43
Compound P1	-8.76	379.47
Compound P2	-7.38	3.89
Compound P3	-6.86	9.39
Compound P4	-5.45	101.72

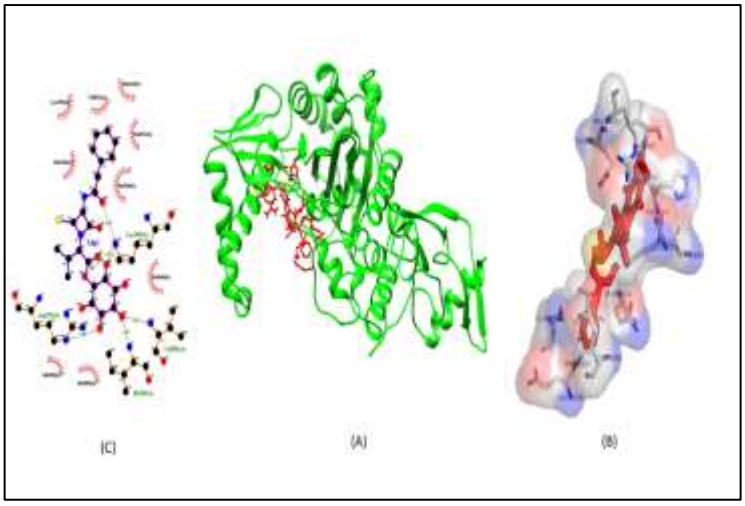

Figure (3): Molecular docking simulation, hydrogen bonds and hydrophobic interaction between compound p1 and PBP1b using the auto dock (A), Pymol (B) and LIGPLOT (C)

The in-vitro antibacterial activates of the synthesized compounds (p1-p4) and benzylpenicillin were assessed against two Gram-positive strains, *Staphylococcus aureus* ATCC 25923 and *Staphylococcus epidermidis* ATCC 12228, and *Escherichia coli* ATCC 25922 and *Salmonella abony* ATCC 6017 as the two Gram-negative strains. And the results are shown in table 4 and Figure (4).

Table (4): The approximate zone of inhibition of compounds (p1-p4) against bacteria determined by the Kirby- Bauer method

Compounds	*Staphylococcus aureus* ATCC 25923	*Staphylococcus epidermidis* ATCC 12228	*Escherichia coli* ATCC 25922	*Salmonella abony* ATCC 6017
Compound P1	>36 mm	30 mm	18 mm	20 mm
Compound P2	>36 mm	24 mm	12 mm	14 mm
Compound P3	>36 mm	24 mm	14 mm	16 mm
Compound P4	>36 mm	26 mm	14 mm	18 mm
Benzylpenicillin	>36 mm	26 mm	10 mm	14 mm

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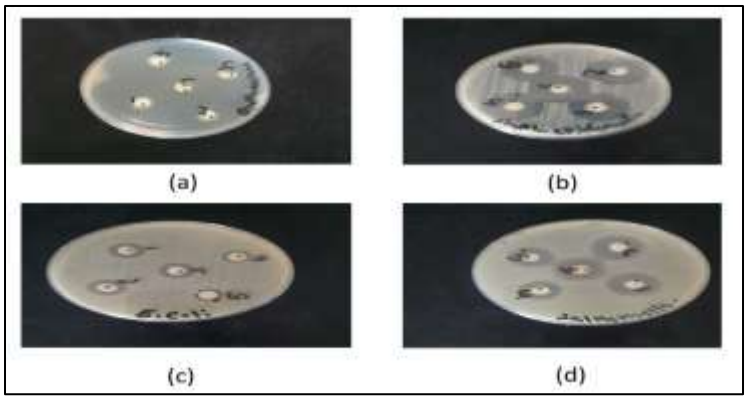

Figure (4): Zone of inhibition of compound p1 (2), compound p2 (4), compound p3 (3), compound p4 (1) and benzylpenicillin (5) against *Staphylococcus aureus* (a), *Staphylococcus epidermidis* (b), *Escherichia coli* (c), and *Salmonella abony* (d)

Table (5): The statistical results of the antibacterial effects of all compounds on the Gram-negative strain *Escherichia coli* ATCC 25922 by Tukey's post-hoc test

Compounds	Mean ± sd.	Compare to Compounds	P. value
compound p1	18.1 ± 0.264	compound p2	<.001
		compound p3	<.001
		compound p4	<.001
		benzylpenicillin	<.001
compound p2	12 ± 0.264	compound p1	<.001
		compound p3	<.001
		compound p4	<.001
		benzylpenicillin	<.001
compound p3	14.06 ± 0.152	compound p1	<.001
		compound p2	<.001
		compound p4	.962
		benzylpenicillin	<.001
compound p4	13.93 ± 0.208	compound p1	<.001
		compound p2	<.001
		compound p3	.962
		benzylpenicillin	<.001
benzylpenicillin	9.96 ± 0.321	compound p1	<.001
		compound p2	<.001
		compound p3	<.001
		compound p4	<.001

*The P value is significant at the 0.05 level

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Table (6): The statistical results of the antibacterial effects of all compounds on the Gram-negative Strain *Salmonella abony* ATCC 6017 by Tukey's post-hoc test

Compounds	Mean ± sd.	Compare to Compounds	P. value
compound p1	20 ± 0.450	compound p2	<.001
		compound p3	<.001
		compound p4	<.001
		benzylpenicillin	<.001
compound p2	14.1 ± 0.264	compound p1	<.001
		compound p3	<.001
		compound p4	<.001
		benzylpenicillin	.977
compound p3	15.96 ± 0.321	compound p1	<.001
		compound p2	<.001
		compound p4	<.001
		benzylpenicillin	<.001
compound p4	18.2 ± 0.1	compound p1	<.001
		compound p2	<.001
		compound p3	<.001
		benzylpenicillin	<.001
Benzylpenicillin	14.23 ± 0.152	compound p1	<.001
		compound p2	.977
		compound p3	<.001
		compound p4	<.001

*The P value is significant at the 0.05 level

Discussion

All the results of elemental analysis, FT-IR, and ^{1}H-NMR have confirmed the synthesis of the new compounds (p1-p4). The results of the elemental analysis were almost identical to the calculated results, the 1H-NMR spectrum of compounds (p1-p4) showed the disappearance of H signals of carboxylic acid at 10-12 ppm, and the FT-IR spectrum showed the appearance of the ester bands (C=O stretching) at the range between 1743-1751 cm^{-1}, these results are agreed with the previous studies [26,27]. as shown in Table (1), Table (2), and Figure (2). The docking results showed that; compound p1 has the best antibacterial activity compared to all the other synthesized compounds and benzylpenicillin; the Binding energy was (-8.76 kcal/mol), and the Inhibition constant was (379.47 μM), as shown in Table (3). This is because Compound p1 made different hydrogen bonds and hydrophobic interactions inside the active site of PBP1b and this is highly agreed with previous study regarding the importance of hydrogen bonding in protein-ligand interactions [28]. as shown in Figure (3). On the other hand, the docking results of the remaining synthesized compounds (p2-p4) were less than of compound p1 and their inhibitory effects reduced with increasing the number of carbons of substituted hydrocarbons.

The results of in vitro antibacterial activity showed that; compound p1 had the largest zones of inhibition and the highest antibacterial activity among all the other compounds. Moreover, all the synthesized compounds (p1-p4) showed larger inhibition

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zones (≥ 12mm) and higher antibacterial activities than benzylpenicillin against the Gram-negative Bacteria *Escherichia coli* ATCC 25922 and **Salmonella abony** ATCC 6017, which mean both of these Gram-negative strains are highly sensitive to the synthesized compounds (p1-p4) and these results agreed with the previous studies [29,30], as shown in Table (4) and Figure (4). The statistical results showed that; the antibacterial effects of compounds p1, p3 and p4 were significantly better than the antibacterial effect of benzylpenicillin on the Gram-negative strains *Escherichia coli* ATCC 25922 and *Salmonella bony* ATCC 6017. On the other hand, the antibacterial effects of compound p1 on the Gram-negative strains were significantly better than the results of all the other compounds, as shown in Table (5) and Table (6). The reason behind these results was the reduction of benzylpenicillin's acidity through masking the carboxylic acid moiety and this increase the penetration and accumulation of these compounds inside the bacterial cells. which is totally agreed with previous studies [7,18].

Conclusions

Masking the free carboxylic acid of benzylpenicillin with polar or nonpolar groups may enhance the antibacterial activity. On the other hand, masking the free carboxylic acid with polar groups will give higher antibacterial activity than using nonpolar groups to mask the free carboxylic acid because polar groups can make more hydrogen bonds inside the active sites of penicillin-binding proteins (PBPs) to make the complex of drug and PBP more stable.

Recommendations

Many benzylpenicillin derivatives can be synthesized through esterification of the beta lactam carboxylic acids with different polar groups, and the antibacterial activities can be evaluated by docking and bacteriological studies to reach to the best derivative which can give a great value in treating the cases of Multidrug-resistant bacteria.

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Ethical clearance: This study was conducted according to the approval of college of pharmacy/ Hawler Medical University.

Conflict of interest: Nil

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تحضير استرات البنزيل بنسيلين وتقييم التغير في التأثير المضاد للبكتيريا عن طريق الالتحام الجزيئي والدراسة البكتريولوجية

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الملخص

خلفية الدراسة: البنزيل بنسيلين هو مضاد حيوي يمتلك فعالية بشكل رئيسي ضد البكتيريا إيجابية الجرام وبعض البكتيريا سالبة الجرام. يعد حمض الكربوكسيل الموجود في المضادات الحيوية من نوع البيتا لاكتام ضروريًا لنشاطها المضاد للبكتيريا. ومع ذلك، فقد تم إنتاج العديد من العقاقير الأولية من خلال أستره مجموعة الحمض الكربوكسيلي هذه، مثل بيفامبيسيلين.

اهداف الدراسة: لتقييم التأثيرات المضادة للبكتيريا للبنزيل بنسيلين عند اخفاء حمض الكربوكسيل الحر بمجموعات كيميائية مختلفة ذات قطبية مختلفة.

المرضى والطرائق: تم تصنيع أربعة مشتقات للبنزيل بنسيلين كيميائيا من خلال استرة مجموعة حمض الكربوكسيل مع مجموعة مركبات مختلفة قطبية، وتم فحص الأنشطة المضادة للبكتيريا عن طريق دراسة الالتحام الجزيئي والدراسات البكتريولوجي.

النتائج: أظهرت جميع المركبات نتائج مختلفة ضد البكتيريا. وأظهرت نتائج دراسة الالتحام الجزيئي أن؛ المركب ذو القطبية الأعلى لديه أفضل طاقة ربط. وكذلك أظهرت نتائج النشاط المضاد للبكتيريا مختبريا أن لهذا المركب أكبر مناطق تثبيط وأعلى نشاط مضاد للبكتيريا بين جميع المركبات الأخرى.

الاستنتاجات: إن إخفاء الحمض الكربوكسيلي الحر للبنزيل بنسيلين كيميائيا مع مجموعة قطبية سيعزز النشاط المضاد للبكتيريا لهذا المركب.

الكلمات المفتاحية: المضادات الحيوية من نوع بيتا لاكتام، البنزيل بنسيلين، الأنشطة المضادة للبكتيريا، الالتحام الجزيئي، تفاعلات الأسترة.

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