In Silico Molecular Docking Study for Prediction of Binding Affinities to Penicillin Binding Proteins and β-Lactamases of Amino Acids-Cephalexin conjugates

Shakir Mahmood Alwan[*1] and Jaafar S. Shia[1]

[1]*Department of Pharmacy, Al-Farabi University College, Baghdad, Iraq*

[*] Corresponding author e-mail: shakir.alwan@alfarabiuc.edu.iq

Received: September28, 2022; Revised: October 12, 2022; Accepted: November 5, 2022

Abstract

Cephalexin is a first generation cephalosporin with high antibacterial activity against a number of microbes. Cephalexin is highly sensitive and could be hydrolyzed by almost all of β-lactamases. An in silico prediction and evaluation study is performed to find a possibility of bringing new life to cephalexin, and other cephalosporins that are susceptible to hydrolysis by lactamases. This approach includes an introduction of an amino acid moiety into cephalexin through an amide bond with its primary amine group. This amino acid moiety is expected to provide steric hindrance and protecting the β-lactam ring from being hydrolyzed. In silico study included measurement of binding affinity to penicillin binding proteins (PBPs) and D-alanyl-D-alanine carboxypeptidases and to β-lactamases. Drug likeness and Molinspiration calculations were recorded to find a reliable correlation with better activity and stability against β-lactamases. The newly suggested conjugates that recorded the best score of binding affinity on PBPs are L-Phe-Cephalexin, L-Arg-Cephalexin, L-Tyr-Cephalexin and L-Thr-Cephalexin. Two of these conjugates, namely, L-Arg-Cephalexin and L-Tyr-Cephalexin recorded high binding affinity scores on D-alanyl-D-alanine carboxypeptidases. Moreover, the predicted stability of L-Arg-Cephalexin and L-Tyr-Cephalexin conjugates against β-lactamases was recorded. Drug-Likeness parameters have shown that L-Cys-Cephalexin, L-Lys-Cephalexin and L-Arg-Cephalexin conjugates were the best compounds recording the highest binding affinity. In conclusion, the amino acid-linked cephalexin conjugates were found to possess high binding affinity to PBPs, D-alanyl-D-alanine carboxypeptidases and β-lactamases, which may encourage the synthesis and intensive evaluation.

Keywords: Cephalexin, Amino acids, Molecular docking, PBPs, β-lactamases, Molinspiration calculations, drug-likeness.

1. Introduction

Cephalexin is a first generation cephalosporin that has a D-phenylglycyl amino group as a substituent at the C_7-amino and a methyl group at C_3 positions of the cephem ring. It is a bactericidal agent and acts by inhibiting synthesis of the bacterial cell wall and is highly active against G (+) cocci > G (+) bacilli > G (-) bacilli > G (-) cocci > anaerobes (Dunn, 1982). Cephalexin is effective against bacterial infections of the respiratory tract, bones, skin, ears, genital and urinary tracts (Lieberthal *et al*., 2013; Kamar *et al*., 1988.). Compared to second and third generation cephalosporins, cephalexin is more active against G (+) and less active against G (-) organisms. In 2012, cephalexin was recorded as one of the top100 highly prescribed pharmaceuticals in the United States (Fisher *et al.*, 2005) and in Australia; it was one of the 15 most

prescribed drugs (Australia, 2012). Cephalexin is not effective against infections caused by *Methicillin-Resistant Staphylococcus aureus* (MRSA), most *Enterococcus*, or *Pseudomonas aeruginosa*. Affinity of cephalexin to penicillin binding proteins (PBP 3) of *S. aureus* and also to PBP 4 of sporulation cells of *B. cereus* is strongly bound (Spratt and Cromie, 1998). Cephalexin is highly susceptible to hydrolysis by almost all bacterial β-lactamases and inactive against most strains of *Acinetobacter calcoaceticus*, Enterobacter species, *Morganella morganii*, *Proteus vulgaris*, *Pseudomonas* species, and *MRSA* (Drawz and Bonomo, 2010). Resistance of certain cephalosporins against β-lactamases may be due to one of the following causes; failure of the antibiotic to reach the site of action and/or alterations in the penicillin-binding proteins (PBPs). The most predominant mechanism of resistance is the destruction of β-lactam ring by β-lactamases. This is an important factor, which decides the future of cephalexin and others of similar chemical structures, as useful therapeutic agents. Accordingly, there is always a great need to synthesize new derivatives of cephalosporins that may retain or show improvements in the spectrum of activity and may have resistance against certain β-lactamases. Various derivatives of cephalexin were synthesized in order to improve its antibacterial spectrum, resistance against β-lactamases and physicochemical properties (Baig *et .al., 2014*; Dale and Smith, 1974).) Dithiocarbamic acid and imines of cephalexin were prepared and showed improved activities (Oliveira *et.al.*, 2019; Abdel *et al.*, 1997.). Schiff bases of cephalexin were also prepared and showed slightly better activities and stability against few β-lactamases (Joshi *et. al*., 2011; Aruna and Gowrama, 2014). Certain ureido derivatives of cephalexin showed improved activity and resistance against few β-lactamases (Valcavi, *et.al., 1980.*). Amino acids linked to cephalosporins are previously synthesized by linking with the aminothiazole at C7 side chain with improved water solubility, oral absorption and excellent antimicrobial activities (Kakeya *et al.*, 1985 ; Muro *et al.*, 1995) .

In view of bringing a new life for cephalexin and a rational design of preparing amino acid-linked cephalexin that may have improved antibacterial spectrum and stability against β-lactamases, this approach was considered. This new approach includes reaction of the α-carboxyl group of the amino acid with the primary amino group of cephalexin forming an amide linkage close to the β-lactam ring of the cephem nucleus, which may provide protection against β-lactamases. Molecular properties, drug-likeness and docking study on PBPs, D-alanyl-D-alanine carboxypeptidases and specific β-lactamases of the amino acid-linked cephalexin are to be calculated to predict the bioactivity scores for comparison. Based on the molecular docking, the most potent derivatives are to be synthesized and evaluated for their antimicrobial activities in comparison with cephalexin and certain reference cephalosporins on PBPs and β-lactamases.

2. Experimental work

2.1. The design of the investigated amino Acid Cephalexin conjugates

The new conjugates of cephalexin are designed as amides by linking the α-carboxyl group of several amino acids with the primary amino group of cephalexin. The chemical structures of the new conjugates and their SMILES (Simplified Molecular-Input Line-Entry Systems) notations were constructed using one of chemoffice software (Chemdraw ultra 10.0). Reference cephalosporins were selected from the approved five generations, which are of various degree of activity and stability against β-lactamases, such as, Ceftriaxone, Cefixime, and Ceftobiprole and were used for the relative comparison. The successful candidates were selected as those that have high binding affinities based on the lowest

docking scores on PBPs and D-Alanyl-D-alanine-carboxypeptidases. The prediction of the bioactivity scores, as enzyme inhibitors (EI) was calculated by using Molinspiration website-based software (www.molinspiration.com).

2.2. Calculation of molecular properties and bioactivity scores

The designed conjugates and reference cephalosporins were subjected to evaluation for their molecular modeling and Molinspiration calculations. Drug likeness, bioactivity scores and molecular modeling calculations were evaluated using Molinspiration web-based software. Drug likeness scores were calculated as a sum of fragments based contributions and correction factors (Masayasu *et al.*, 1999). Prediction of the bioactivity scores of the new conjugates and reference cephalosporins were recorded by calculating the activity scores of G-protein coupled receptors (GPCR ligand), ion channel modulator (ICM), nuclear receptor ligand (NRL), kinase inhibitor (KI), protease inhibitor (PI) and enzyme inhibitor (EI). The molecular properties are important parameters for a drug pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion (ADME). The values of Molinspiration Log partition coefficient (miLogP, octanol/water) and the topological polar surface area (TPSA) of the new conjugates and the reference cephalosporins were calculated using the methodology developed by Molinspiration (Masayasu *et.al.*, 1999).

2.3. Molecular Docking study on penicillin binding proteins (PBPs)

Molecular docking of the investigated conjugates and reference cephalosporins was conducted on specific PBPs (PDP ID, 1pyy, *Streptococcus pneumonia*), PBP2x (PDP ID, 1qmf, *Streptococcus pneumonia*) and CyPBP37 (PDP ID, 3jsk, *Neurospora crassa*) for the prediction of their antimicrobial activities in comparison with reference cephalosporins. Molecular docking on two types of carboxypeptidases (D-Alanyl-D-Alanine carboxypeptidase produced by *Streptomyces sp*. (1pw1) and that produced by *E. coli* (3ita) has also been conducted, since the cephalosporins are proved to be inhibitors of the above enzymes. These docking studies were conducted in order to determine the docking scores of the binding energies (kcal/mol) and, hence, predict their antimicrobial activities, in comparison with cephalexin and certain reference cephalosporins. The chemical structures of PBPs were retrieved from protein data bank (PDB) and the molecular docking was conducted using 1-click-docking software (mcule.com).

2.4. Molecular Docking on specific β-lactamases

The suggested new conjugates and the reference cephalosporins were subjected to molecular docking on different β-lactamases produced by *E. coli* (1xgj), *K. Pneumonia* (3q6x), *S. aureus* (1ome) and *P. aeruginosa* (2wzz) to calculate the docking scores of the binding energies and consequently, predict the possibility of stability against the above β-lactamases. The chemical structures of the bacterial β-lactamases were retrieved from PDB.

3. Results and Discussion

3.1. Molinspiration Calculations

Molinspiration calculations of certain parameters of those suggested amino acid-cephalexin conjugates were recorded using Molinspiration cheminformatics, which are available from http://www.molinspiration.com.

Molecular properties of reference cephalosporins and amino acid-cephalexin conjugates were calculated on the bases of Lipinski's rule and its components. These conjugates have higher TPSA than cephalexin. Moreover, L-Arg-Cephalexin has high TPSA, which make it similar to ceftobiprole (5th. generation) and higher than that of cefixime. While, L-Glu-Cephalexin, or L-Tyr-Cephalexin have higher TPSA values than cephalexin Table-1. Noteworthy,

the TPSA values of the reference cephalosporins are higher than cephalexin, as those represent the advanced generations, particularly, Ceftriaxone (221.61) and Ceftobiprole (203.18) and do not comply with Lipinski's rule Table-1. TPSA is a very useful descriptor used to evaluate drug absorption and oral bioavailability, transport across blood brain barriers and permeability through Caco-2 cells and (Ertl *et.al.,* 2001). The values of OH/NH polar fragments representing the proton donor/acceptor of the suggested conjugates of cephalexin linked to arginine, glutamine, or tyrosine were higher and recording 6 to 9 with n-violation of 2, compared to that of cephalexin with n-violation of zero and higher to comparable to those of the reference cephalosporins Table-1. Based on Lipinski's rule, the OH-NH values centered polar fragments should be <5 and ≤ 10 respectively. Accordingly, certain amino acid-cephalexin conjugates do not fulfill the basic requirements of Lipinski's rule. The higher values of TPSA and OH-NH interactions may indicate that these compounds have smooth and efficient binding to receptor, as compared with the reference cephalosporins Table-1. However, drug molecules having TPSA values of 140 Å or higher are expected to have very low absorption (Lipinski *et.al.,* 2001.). Lipophilicity (miLogP) and TPSA values are essential parameters that may refer or predict the degree of oral bioavailability of drugs (Davies *et.al., 2007*).

3.2. Prediction of drug-likeness and bioactivity scores

The prediction of bioactivity scores of the investigated amino acid-cephalexin conjugates and the reference cephalosporins were determined for GPCR ligand, ICM, NRL, KI, PI and EI. A number of the new conjugates showed that the predicted drug-likeness scores were much more than those of cephalexin and comparable to those of the reference cephalosporins, particularly, L-Cys-Cephalexin, L-Lysine-Cephalexin and L-Arginine-Cephalexin Table-2. Likewise, all conjugates recorded consistent negative values in most of the categories, while, reference cephalosporins recorded numerical values. Accordingly, all conjugates are predicted to have better activity than cephalexin, particularly, in relation to PI values Table-2. Those results comply with the previously reported bioactivity scores and drug-likeness evaluation of previously reported newer cephalosporins (Alwan, 2012).

3.3. Molecular Docking on PBPs and carboxypeptidases

The predicted binding affinity of these conjugates on specific PBPs and carboxypeptidases showed lower docking scores than cephalexin, and hence, are considered as more potent Table-3. A number of conjugates showed interesting high binding affinity on PBPs, such as, L-Leu-Cephalexin, L-Arg-Cephalexin and L-Glu-Cephalexin in comparison with cephalexin and reference cephalosporins Table-3. This may refer to better antimicrobial activities. Moreover, L-Arg-Cephalexin, L-Phe-Cephalexin and L-Tyr-Cephalexin conjugates recorded reasonably high docking scores in comparison with cephalexin and comparable results with the reference cephalosporins on PBPs type 1QMF Table-3. L-Phe-Cephalexin recorded the highest binding affinity score on PBP type 1QMF Table-3. The interaction of L-Arg-Cephalexin on this target is represented on Figure 1. The amino acids that are involved in this interaction are as follows: Glu334 (A), Trp374 (A), Asn397 (A) and Gln552 (A). While, L-Leu-Cephalexin, L-Arg-Cephalexin and L-Glu-Cephalexin recorded the highest scores on PBPs type 1pyy It is noteworthy that PBPs of sporulation of Bacillus cereus is sensitive to cephalexin. This may indicate that a wide range of PBPs are sensitive to cephalexin (Miyamoto *et.al.,* 1997).

Table 1. Molinspiration calculations of the amino acid-cephalexin conjugates.

Compound	Molinspiration Calculations					
	MW	miLogP	TPSA	OH-NH interaction	n Violation	Volume
L-Leucine-Cephalexin	460.55	0.604	141.83	5	0	408.16
L-Isoleucine-Cephalexin	460.50	0.576	141.83	5	0	408.16
L-Methionine-Cephalexin	478.60	-0.253	141.83	5	0	409.7
L-Serine-Cephalexin	434.47	-1.680	162.05	6	1	366.2
L-Cysteine-Cephalexin	450.54	-0.728	141.83	5	0	375.87
L-Threonine-Cephalexin	462.50	-1.047	162.05	6	1	399.61
L-Lysine-Cephalexin	475.57	-1.198	167.85	7	1	419.904
L-Arginine-Cephalexin	475.53	-2.187	203.73	9	2	404.12
L-Glutamine-Cephalexin	475.53	-1.776	184.92	7	2	405.28
L-Phenylalanine-Cephalexin	494.57	0.755	141.83	5	0	424.62
L-Tyrosine-Cephalexin	510.57	0.276	162.05	6	2	437.64
L-Glutamic Acid Cephalexin	347.4	-1.486	112.73	4	0	293.2
Cephalexin	347.4	-1.486	112.74	4	0	293.2
Cefixime	453.46	-1.053	184.52	5	1	350.14
Ceftriaxone	540.60	-2.110	221.61	5	2	405.45
Ceftobiprole	534.58	-1.504	203.18	6	3	424.33

Key notes: MW= molecular weight, TPSA = topological polar surface area, miLogP = Molinspiration Log partition coefficient.

Table 2. Molinspiration drug-likeness of the amino acid-cephalexin conjugates.

Compound	Drug-Likeness					
	GPCR	ICM	KI	NRL	PI	EI
L-Leucine-Cephalexin	-0.16	-0.46	-0.81	-0.72	0.73	0.22
L-Isoleucine-Cephalexin	-0.23	-0.58	-0.86	-0.87	0.69	0.21
L-Methionine-Cephalexin	-0.22	0.54	-0.96	0.80	0.67	0.29
L-Serine-Cephalexin	-0.17	-0.59	-0.73	-0.85	0.66	0.27
L-Cysteine-Cephalexin	-0.18	-0.59	-0.76	-0.8	0.86	0.45
L-Threonine-Cephalexin	-0.15	-0.42	-0.83	-0.77	0.69	0.27
L-Lysine-Cephalexin	-0.06	-0.38	-0.67	-0.71	0.74	0.30
L-Arginine-Cephalexin	0.00	-0.33	-0.76	-0.98	0.89	0.20
L-Glutamine-Cephalexin	-0.16	-0.50	-0.73	-0.71	0.67	0.22
L-Phenylalanine-Cephalexin	-0.10	-0.45	-0.69	-0.67	0.62	0.21
L-Tyrosine-Cephalexin	-0.08	-0.44	-0.65	-0.57	0.59	0.23
L-Glutamic acid-Cephalexin	-0.13	-0.47	-0.76	-0.70	0.65	0.26
Cephalexin	-0.35	-0.73	-1.03	-0.98	0.50	0.13
Cefixime	-0.27	-0.81	-0.80	-0.88	0.19	0.35
Ceftriaxone	-0.18	-0.73	-0.80	-1.07	0.03	0.33
Ceftobiprole	-0.21	-0.499	-0.62	-1.02	0.29	0.41

Key notes: GPCR = G-protein coupled receptor, ICM = Ion channel modulator, KI = Kinase inhibitor, NRL = Nuclear receptor ligand, PI = Protease inhibitor, EI= Enzyme inhibitor.

3.4. Molecular docking on Lactamases

The proposed conjugates were also docked on specific β-lactamases, in order to select the best with excellent resistant to β-lactamases, as shown on Table 4. Docking scores of the investigated conjugates recorded comparable results with the reference cephalosporins and much higher binding affinity than cephalexin on β-lactamases, particularly, L-Arg-Cephalexin, L-Phe-cephalexin and L-Tyr-Cephalexin Table-4. L-Arg-Cephalexin has a guanidine group that may contribute to binding affinity to target site. L-Phe-Cephalexin has a phenyl ring, which is a hydrophobic moiety that recorded additional binding affinity to β-lactamase. The new conjugates have recorded lower docking scores on β-lactamases compared to Cefixime and comparable results to those of Ceftriaxone.

Table (3) Docking scores (kcal/mol) of the amino acid-cephalexin conjugates on PBPs and D-alanyl-D-alanine carboxypeptidases.

Compound	Docking scores (kcal/mol) *				
	PBPs			D-alanyl-D-alanine carboxypeptidases	
	1pyy	*1qmf*	*3jsk*	*3ita*	*1pw1*
L-Leucine-Cephalexin	-7.22	-8.35	-8.32	-5.52	-7.42
L-Isoleucine-Cephalexin	-6.60	-7.37	-7.82	-5.45	-7.12
L-Methionine-Cephalexin	-5.92	-7.65	-7.85	-5.07	-7.35
L-Serine-Cephalexin	-6.40	-7.55	-7.75	-5.52	-7.62
L-Cysteine-Cephalexin	-6.60	-7.37	-8.27	-5.02	-7.30
L-Threonine-Cephalexin	-5.97	-8.00	-8.75	-5.6	-7.72
L-Lysine-Cephalexin	-6.30	-7.15	-8.50	-5.02	-7.75
L-Arginine-Cephalexin	-7.05	-8.48	-9.22	-5.2	-8.57
L-Glutamine-Cephalexin	-6.30	-7.65	-8.50	-5.2	-8.22
L-Phenylalanine-Cephalexin	-6.80	-8.37	-9.47	-5.32	-8.32
L-Tyrosine-Cephalexin	-6.27	-7.87	-8.47	-6.1	-8.35
L-Glutamic acid-Cephalexin	-7.17	-7.70	-8.57	-5.2	-7.57
Cephalexin	-5.75	-6.67	-8.15	-4.82	-7.37
Cefixime	-6.27	-6.65	-8.02	-4.65	-7.75
Ceftriaxone	-7.27	-8.17	-8.75	-5.47	-8.50
Ceftobiprole^{+}	-7.47	-8.50	-9.80	-5.70	-8.45

* The more negative values indicate higher binding affinity. Four docking poses appeared for each compound on each enzyme and the given scores represent the average. + Ceftobiprole showed 3 poses for 1qmf, two poses for 3ita and only one pose for the other types.

The conjugates that recorded the highest binding scores may have great potential as antibacterial agents with resistance against certain β-lactamases Table-4. These are encouraging results and may lead to the synthesis of these conjugates for further and intensive evaluation. Furthermore, L-Tyr-Cephalexin recorded high docking scores on *P. aeruginosa* (2wzz) in comparison with cephalexin and comparable result with the reference cephalosporins Table-4. The interaction of L-Arg-Cephalexin and L-Tyr-Cephalexin with the amino acids of the targets is shown on Figure-1 and 2. The interaction of L-Tyr-Cephalexin with the target *P. aeruginosa* (2wzz) involved the following amino acids; Ser90 (A), Asn179 (A) and Asn 370 (A), Figure-2. L-Glu-Cephalexin recorded the highest score on β-lactamases of *E. Coli* type 1XGJ. Moreover, L-Tyr-Cephalexin recorded the highest docking scores on β-lactamases of *S. aureus* (type 1ome) and of *P. aeruginosa* (type 2wzz). The new conjugates showed a slight improvement in binding affinity on *K. pneumonia* type 3Q6X Table-4.

Table (4) Docking scores (kcal/mol) of the amino acid-cephalexin conjugates on specific β-lactamases.

Compound	Docking scores of the investigated conjugates and reference cephalosporins on β-lactamases (Kcal/mol) *			
	***E. coli* 1xgj**	***K. Pneumonia* 3q6x**	***S. aureus* 1ome**	***P. aeruginosa* 2wzz**
L-Leucine-Cephalexin	-7.5	-6.80	-7.10	-7.67
L-Isoleucine-Cephalexin	-7.07	-6.10	-6.35	-7.95
L-Methionine-Cephalexin	-7.62	-6.22	-6.70	-7.52
L-Serine-Cephalexin	-6.8	-7.00	-6.32	-8.00
L-Cysteine-Cephalexin	-7.22	-6.60	-6.47	-7.40
L-Threonine-Cephalexin	-7.42	-6.40	-7.10	-7.90
L-Lysine-Cephalexin	-7.17	-7.00	-6.20	-7.50
L-Arginine-Cephalexin	-7.80	-5.90	-6.60	-8.17
L-Glutamine-Cephalexin	-7.67	-6.35	-6.92	-8.12
L-Phenylalanine-Cephalexin	-8.15	-6.70	-7.70	-7.80
L-Tyrosine-Cephalexin	-8.05	-6.47	-7.80	-8.45
L-Glutamic acid-Cephalexin	-8.37	-5.95	-	-7.80
Cephalexin	-6.95	-6.35	-6.35	-7.60
Cefixime	-7.22	-6.07	-6.20	-7.82
Ceftriaxone	-8.47	-7.20	-6.92	-9.32
Ceftobiprole+	-8.65	-7.90	-7.30	-9.40

*The more negative values indicate higher binding affinity. Four docking poses were taken for each compound on each enzyme and scores represent the average.

+Two docking poses appeared on β-lactamases of *P. aeruginosa* and *K. pneumonia* and only one pose appeared on *E. coli* and *S. aureus*.

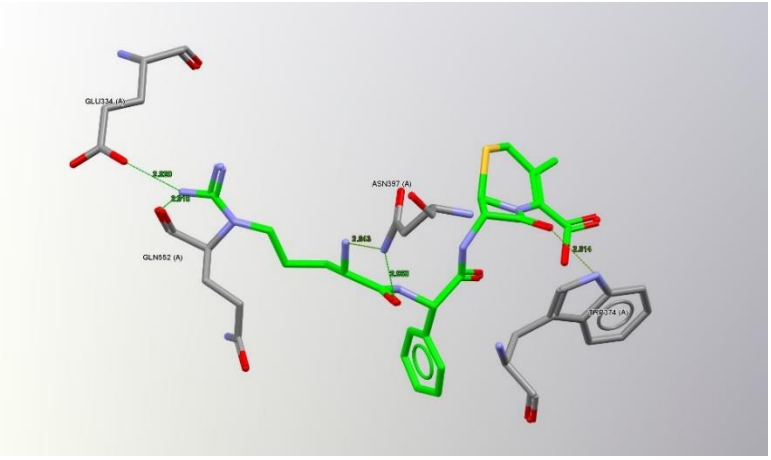


Figure 1. The interaction of L-Arg-Cephalexin with PBP type 1QMF.

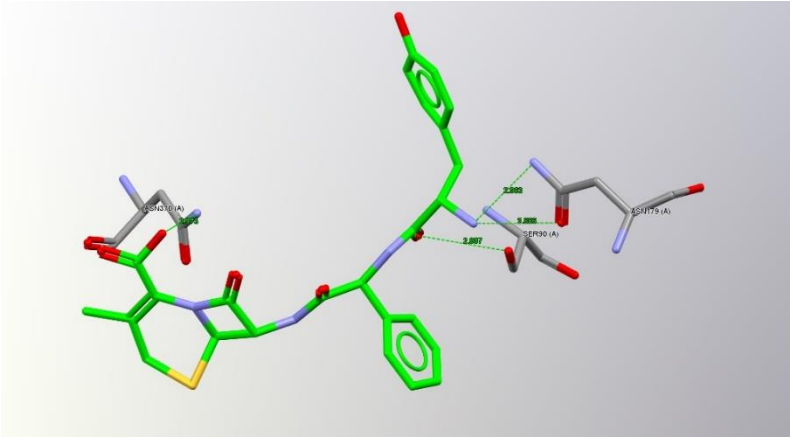


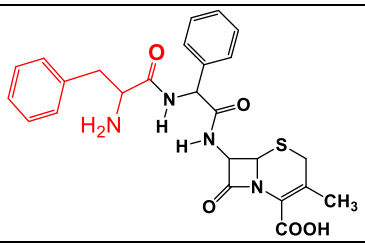
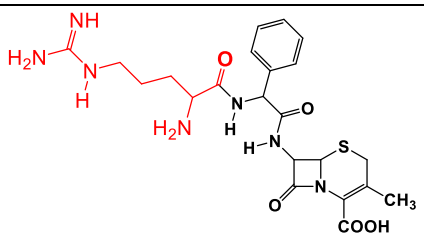
Figure 2. The interaction of L-Tyr-Cephalexin with β-lactamase of *P. aeruginosa* 2wzz.

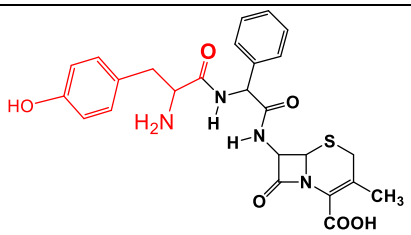
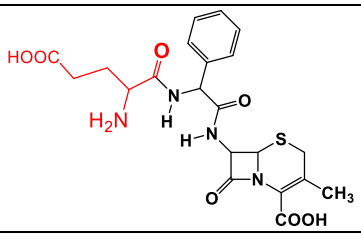
Similarly, the in silico computational methods were employed for the prediction of binding affinities of certain β-blockers as potential SARs-CoV-2 spike inhibitors (Ana *et al.,* 2022). A computational model was used for the prediction of brain distribution of drugs based on biomimetic chromatographic data (Vallianatou *et al.,* 2022).

In silico prediction of pharmacokinetic properties by molecular docking of N-Cinnamoyl tetraketide derivatives as inhibitors of cyclooxygenase-2 enzyme was attempted to evaluate their binding affinities and consequently, their activities (Nyandoro, S. N., et al., 2018).

A number of conjugates were recorded with high binding affinities and reasonable stability against specific β-lactamases and selected to be the most useful candidates. These conjugates include, L-Phe-Cephalexin, L-Arg-Cephalexin, L-Try-Cephalexin and L-Glu-Cephalexin are the most promising candidates and are highly considered. Their chemical structures and names are listed on Table 5.

Table 5. Overview of the new amino acids-cephalexin conjugates of highly predicted bioactivity and stability against β-lactamases.

Compound	Chemical structure	Chemical Name
Phenylalanine-Cephalexin		**7-(2-(2-amino-3-PhenylPropan amido)-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid.**
Arginine-Cephalexin		**7-(2-(2-amino-3-guanidino-propan amido)-2-phenyl acetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid.**

Tyrosine-Cephalexin		**7-(2-(2-amino-3-(4-hydroxy phenyl) propanamido)-2-phenyl acetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid**
Glutamic-Cephalexin		**7-(2-(2-amino-4-carboxy butanamido)-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid**

Conclusions

It is concluded that the amino acid-cephalexin conjugates were found to possess high binding affinities to PBPs, D-alanyl-D-alanine carboxypeptidases and β-lactamases. The conjugates with high results including L-Arg-Cephalexin, L-Glu-Cephalexin, L-Phe-Cephalexin and L-Tyr-Cephalexin, which showed high binding affinities and will be selected as useful candidates. The results are very interesting and encouraging and definitely will lead to high consideration.

References

- **Abdel Aziz R. *et al.*, (1997).** Synthesis and antimicrobial activity of some penicillin and cephalosporin derivatives. ***Ind. J. Chemistry*** Vol. 36B, 1997, pp. 196-198.
- **Ana C. Puhl *et al.*, (2022).** Computational and Experimental Approaches Identify Beta-Blockers as Potential SARS-CoV-2 Spike Inhibitors**;** ***ACS Omega*, 7, 27950-58.**
- **Alwan SM. (2012).** Synthesis and Preliminary Antimicrobial Activities of New Arylideneamino-1,3,4-Thiadiazole-(thio/dithio) Acetamido Cephalosporanic Acids. ***Molecules,*** 17:1025-38.
- **Aruna NT. and Gowrama BS, (2014).** biological evaluation of some novel Schiff bases of cephalexin. ***Int. J. Pharm. Sci***., Vol. 5 (3), 1008-1014.
- **Australia H, (2012)**.The thirteenth Biennial Health Report of the Australian Instit. Health and Welfare. Aust. Instit. Health and Welfare. p 408.
- **Baig MH. *et al.*, (2014)**. Insight into the Effect of Inhibitor Resistant S130G Mutant on Physico-Chemical Properties of SHV Type Beta-Lactamase: A Molecular Dynamics Study. ***PLoS ONE*** 9(12): e112456. doi:10.1371/journal. Pone. 0112456.
- **Dale JW. and Smith JT. (1974).** R-Factor-Mediated 3-Lactamases that hydrolyze Oxacillin: evidence for two distinct groups. ***J. Bacteriology***. pp. 351-35.
- **Davies TA. *et.al.*, (2007).** Binding of Ceftobiprole and comparators to the Penicillin-Binding Proteins of *E. coli, P. aeruginosa, Staph. aureus, and Str. pneumonia*, ***Antimicrob. Agents Chemother*.** 51 (7): 2621-4.
- **Drawz SM. and Bonomo RA. (January 2010).** ***Clinical Microbiology Reviews***. 23 (1): 160–201. DOI:10.1128/CMR.00037-09. PMC 2806661. PMID 20065329.
- **Dunn GL. (1982).** Ceftizoxime and other third-generation cephalosporins: structure-activity relationships. ***J.***

Antimicrobial. Chemotherapy, 10, Suppl. C, 1-10.

- **Ertl P. Rohde B. and Selzer P. (2000).** Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and its Application to the Prediction of Drug Transport Properties., ***J. Med. Chem***. 43 (20): 3714-7.
- **Fisher JF. Meroueh SO. and Mobashery S. (February 2005).** "Bacterial resistance to beta-lactam antibiotics: compelling opportunism, compelling opportunity". ***Chemical Reviews***. 105 (2): 395–424. DOI:10.1021/cr030102i. PMID 15700950.
- **Gerber MA. *et al.*, (2009).** Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. ***Circulation***. 119:1541-51. [PubMed 19246689].
- **Joshi S. *et. al*., (2011).** Antibacterial and antioxidant properties of Mn (II), Co (II), Ni (II) and Zn (II) complex of Schiff bases derived from cephalexin, ***Res. J. Pharm. Biol. and Chem. Sci***.Vol.2 (1), 61-64.
- **Kamar A. *et al*., (1988).** Comparative study of cephalexin hydrochloride and cephalexin monohydrate in the treatment of skin and soft tissue infections. ***Antimicrob. Agents Chemother***. 32:882-5. [IDIS 244249], (PubMed; 3046484).
- **Lieberthal AS. *et. al*., (2013)**. The diagnosis and management of acute otitis media. ***Pediatrics***. 131: e964-99. (PubMed 23439909).
- **Lipinski CA, *et.al*., (2001)**. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Stings., ***Adv. Drug Delivery Rev***. 46, (1-3): 3-26.
- **Masayasu K. *et.al*., (1999).** AS-924, A novel orally active bifunctional prodrugs of Ceftizoxime. Synthesis and relationship between physicochemical properties and oral absorption. ***Chem. Pharm. Bull***. 47(8) 1081-1088.
- **Miyamoto TM. *et.al*., *(Sep.*1997).** Penicillin-binding protein sensitive to cephalexin in sporulation of *Bacillus cereus*, ***Microbiol. Res***., 1997, 152(3):227-232. doi: 10.1016/s0944-5013 (97) 80032-8.
- **Nyandoro SN. *et al*., (2018).** In silico pharmacokinetic and molecular docking studies of N-Cinnamoyltetraketide derivatives as inhibitors of cyclooxygenase-2 enzyme. ***Tanzania J. Sci***. 44(2): 1-15, ISSN 0856-1761, e-ISSN 2507-7961.
- **Oliveira JW. de F. *et.al*., (2019).** Application of Dithiocarbamates as Potential New Anti-Trypanosomatids Drugs: Approach Chemistry, Functional and Biological. 24, 2806.
- **Shulman ST. *et al*., (2012)**. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: update by the Infectious Diseases Society of America. ***Clin. Infect. Dis.*** 55:1279-82. (PubMed 23091044).
- **Spratt BG. and Cromie KD. (Jul-Aug 1988)** . Penicillin-binding proteins of gram-negative bacteria. ***Rev. Infect.***

Dis.;10(4):699-711. doi: 10.1093/clinids/10.4.699.

- **Wilson W. *et. al*., (2007)**. Prevention of infective endocarditis. Guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. ***Circulation*** 2007; 116:1736-1754 (Circulation is available at **http://circ.ahajournals.org**.
- **Valcavi U. *et.al*., (1980)**. Synthesis and antibacterial activity of some ureido cephalexin and cefadroxil derivatives., ***Farmaco Sci***. 35(7), 563-572.
- **Vallianatou T, Tsopelas F, Tsantili-Kakoulidou A. (2022).** Prediction Models for Brain Distribution of Drugs Based on Biomimetic Chromatographic Data., ***Molecules***. 27(12):3668. **doi: 10.3390/molecules27123668.PMID: 35744794.**

دراسة الارساء الجزئي لتحديد درجة الارتباط مع بروتينات البنسلين الرابطة وانزيمات البيتالاكتميز لمركبات الاحماض الأمينية المرتبطة بالسيفالكسين

شاكر محمود علوان وجعفر ستار شياع

قسم الصيدلة/ كلية الفارابي الجامعة/ بغداد - العراق

الخلاصة

السيفالكسين مضاد حيوي من الجيل الأول من مجموعة السيفالوسبورينات وفعال ضد عدد كبير من البكتريا. السيفالكسين حساس جدا ويتحلل بسرعة بواسطة معظم انزيمات البيتالاكتميز. أجريت دراسة الارساء الجزيئي على بروتينات البنسلين الرابطة وبروتينات الالنين-الانلين كربوكسامايد وانزيمات البيتالاكتميز لبكتريا معينة لتحديد درجة ارتباطها وانعكاس ذلك على الفعالية وادرجة ثباتها واستقرارها امام انزيمات البيتالاكتميز لعدد من مركبات السيفالكسين المرتبطة بالأحماض الامينية. يتضمن هذا المقترح ربط احماض امينية بواسطة اصرة امايد وذلك بربط مجموعة الكربوكسيل في الاحماض الامينية مع مجموعة الأمين الموجودة في السيفالكسين. مجموعة الحامض الاميني في هذا الموقع من المتوقع ان توفر جدار صد وحماية مجموعة البيتالاكتام في السيفالكسين. كما تمت دراسة تحديد المواصفات والتشابه مع ادوية فعالة بموجب برنامج مول انس بريشين للتعرف على درجة التشابه مع ادوية معروفة من نفس مجموعة السيفالوسبورينات. أظهرت النتائج بان الاحماض الامينية الفنيل الالنين والارجنين والتايروسين والثريونين المرتبطة بالسيفالكسين كانت الاعلى من حيث درجة الارتباط مع بروتينات البنسلين الرابطة واتضح بان الاحماض الامينية الارجنين والتايروسين سجلت اعلى درجة ارتباط مع بروتينات الالنين-الالنين كربوكسامايد وانزيمات البيتالاكتميز. اما الايسين والسيستايين المرتبطة بالسيفالكسين فأظهرت نتائج إيجابية جيدة من حيث درجة التشابه مع ادوية من نفس مجموعة السيفالوسبورينات من حيث دراسة بعض المواصفات للجزيئات. يستنتج من هذه الدراسة بان بعض الاحماض الامينية المرتبطة بالسيفالكسين أظهرت نتائج ممتازة كمضادات حيوية ولها درجة ثبات واستقرار امام انزيمات البيتالاكتميز.