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Research Article:

Docking Study for New 7-Aminocephalosporinic Acid Derivatives as Potential Inhibitors for β-Lactamases

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Abstract

Background: Antibiotics with β-Lactam rings (β-Lactams), since they were discovered, have enhanced the typical treatment for bacterial infections. Though their resistance can quickly spread on a universal scale, bacterial resistance is primarily caused by the production of β-lactamases. Hence, there is a serious demand to design and create new anti-β-lactamases or inhibitors. Nowadays, the use of β-lactamase inhibitors with β-lactams reduces this resistance. **Aim and Methods:** This work aimed to help *in silico* design and dock two new series of 7-aminocephalosporinic acid derivatives (Schiff's bases and amides) against both the TEM-1 and the IMP-1 β-lactamases. **Results:** The results revolve around the possible enhanced activity of eight amides and six Schiff base compounds compared with the standard inhibitors (clavulanic acid, sulbactam, and avabactam). These compounds show promising docking interactions with an active pocket site in both enzymes. We can conclude that both the halogenated and the hydrophobic substituents, alone or when containing oxygen atoms, will potentiate the affinity and the binding ability of any compounds when they are added to their structures to act as β-lactamase inhibitors.

1. Introduction

Antibiotics with β-Lactam rings (β-Lactams) (penicillins, cephalosporins, and carbapenems) are the greatest efficient accomplishment in the last decade in the record of the medical and pharmaceutical industries. They are the most commonly utilized antibiotic class in the world. Their mechanism includes suppression of peptidoglycan synthesis (the main component of the bacterial cell wall), thus resulting in the eternal impairment and fatality of the bacteria (bactericidal) (1). Continual utilization of these antibiotics has sparked the spread of bacterial resistance (2). Microbial resistance is a normal biological pathway that is initiated by improper use of antibiotics, decreased or absence of suitable monitoring, self-prescription, or using fake drugs (3). Resistant microorganisms harm patients and the public by prolonging disease episodes, making infections difficult to treat, increasing death rates, and increasing the cost of treating such infections (3). It is now the chief health hazard challenging the world (2,3). Antibacterial resistance has now reached alarming levels with major bacterial pathogens (4,5). Hence, there is a crucial necessity to develop newly β-lactamases inhibitors in order to overcome this situation (5).

The β-lactamases produced by bacteria which gives resistance response to β-lactams (6,7). The Ambler arrangement conceder amino acid composition to classify β-lactamases into four modules: A, B, C, and D (8). The A, C, and D styles were serine β-lactamases (SBLs) whereas the class B enzymes were metallo β-lactamases (MBLs) (9), which makes use of one or double of the zinc ions to stimulate majority of solvent as nucleophile (10), while SBLs utilize the serine in the active site as nucleophile. Both procedures ended by a ring breaking and abolishing drug product (11) .

The β-Lactamase inhibitors disturb the bacterial ability to deactivate β-lactam drugs. Their administration in combination with antibacterial drugs were the extremely successful measures to defeat bacterial resistances (12,13). These inhibitors combine with the β-lactamases allowing the β-lactams to capture the transpeptidase (responsible of peptidoglycan synthesis), causing destruction of the cell wall (13). The primary β-Lactamase inhibitors are clavulanic acid

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and sulbactam and tazobactam (14). Many new β-lactamase inhibitors correlated to penicillanic and clavulanic acid, cephems, penems and monobactams, are currently developed (12,15).

Molecular docking is a design method, which mimics the interaction of molecules and calculates the combining quality and attractiveness among both ligands and the receptors. This is very important in identifying drug binding sites and explaining drug action mechanisms (15,16). This approach recently used in drug design examination field aided by the rapid progress of computer hardware, software, and algorithms, this considerably decrease the time and cost of drug enhancement (17,18).

Estimation of potential scuffled for a specific enzyme utilizing the docking technique is usually applied to find the hit or the prime structure from the scuffled databanks depending on the function of their score (18,19). Consuming the database for such purposes is not only helpful for investigators, but also considerably declines the research budget (20).

Hugo Schiff's registered the initial preparation of imines (Schiff's bases) in the previous decade. All imines will have azomethine group (-N=CH-) (21). Schiff's bases promote many important biologically actions like antibacterial, antituberculosis, antifungal, antitumor, anticonvulsant, antiviral, anti-HIV, antimalarial, anti-inflammatory, antiprotozoal, analgesic, and also anthelmintic activities (22). Schiff's bases recognized as powerfully against a wide spectrum of organisms as; Candida Albicans, the Gram(-)ve Escherichia coli and Mycobacteria, Gram(+)ve bacteria Staphylococcus aureus (21,22).

The amide compounds are believed to be important and effective functional group in natural products, pharmaceuticals, polymers, and agrochemicals, since they offer extreme polarity and stability of their bond (23). The amide bond synthesis is the most commonly used reaction in the drug preparation process (16% of synthetic procedures). The amides preparations found in 25% of drug candidates (ex: Lisinopril, Diltiazem, Valsartan and Atorvastatin) (23,24).

The aim of this work is to Insilco docking of new two series of 7 amino cephalosporinic acid (7ACA) derivatives (Schiff's bases and amides) with two classes of the β-lactamase enzymes. This is an initial work in order to choose the best compound to be synthesized in the future work.

2. Methodology

The Docking Analysis was performed by using the online platform Mcule (https://mcule. com/ apps/1-click-docking/) (15). The structure of the bacterial class A TEM-1 β- lactamase (1PZO) and the class B IMP-1 β-lactamase (2DOO) were acquired from Protein Drug Bank (PDB) (15,18). Both enzymes were selected on the bases of the more precise resolution. The docking study for the examined compounds was performed in order to investigate the affinity toward both enzymes to be contrasted with standard inhibitors (sulbactam, avabactam and clavulanic acid). The structure of the tested compound (and also all the chemical compounds illustrated in this work) are drown by ChemDraw program (PerkinElmer company), version 16.0.0.82 (15). The docking scores of the binding energies due to the interaction between the active ligands (inhibitors) and the enzymes pockets taken in unit Kcal./mol (18).

The best docking scores of the binding energies made by the interface between the ligands (the standard inhibitors and the designated compounds) and the enzymes pockets were done by two stages. In the first the visual judgment to choose the superior pose out of 4 poses (acquired by the docking practice) was made for every molecular structure of the tested compound within the both enzymes; as it best fitting in the enzyme pocket comparing with standard inhibitors, afterward the score for the best visualized one (analyzed using discovery studio visualizer v20.1.0.19295) has been taken (25). While steps 2 include choosing the best compounds that have the best score for both enzymes as compared with the other designated compounds (18,25).

3. Results and Discussion

3.1 Molecular docking study of the standard inhibitors:

1PZO is a type A β-lactamase (TEM-1) with active pocket interaction site identified by (X: 4.3193, Y: 13.6421, Z: 21.7741). While 2DOO is a type B β-lactamase (IMP-1) with active pocket interaction site centered by (X: 31.0591, Y: 44.1942, Z: 37.0118).

First the standard inhibitors (clavulanic acid, sulbactam and avabactam) were tested by docking proses with both enzymes, and the results presented in **Table1**, these results will be as a control for the tested compound in order to compare with their results. The interactions of 2D structures of the standard inhibitors within the pocket active site of both the TEM-1 (1PZO) and the IMP-1(2DOO) β-lactamases enzymes were representing in **Figure 1** and **2** respectively.

From **Figure 1** we can consider four amino acids to be the key for interaction of inhibitors within the pocket active site of the TEM-1 enzyme (1PZO) which are (SER 210, GLY 211, ARG 218 and GLY 219), these amino acid combined with the three standard inhibitors in addition to three more (ILE 220, ASN249 and ILE 252) that bound with the clavulanic acid and two other more (ALA 192 and LEU 195) that interact with the avabactam.

The picture is different in the IMP-1 β-lactamase (2DOO) **Figure 2**, each standard inhibitor bound separately to a group of amino acids differ from each other's (clavulanic acid with TYR160 and GLY 161, sulbactam with SER 77, ASP 78 and HIS 194 and avabactam with TRP 25, LYS 158 and GLU 208), here we consider all of them as the key of interaction. This variation in the rout of interaction could be due to that the IMP-1 is a class B (metalo) β-lactamase, in which the active pocket site is larger from the other classes, and it requires a complex of metal to occupy its pocket. The standard inhibitors and the tested compounds bound variably in both the active and the allosteric sites within the pocket. The most important issue here is that the inhibitor must bound strongly with high affinity with the active site and prevents the enzyme from catching the β-lactam antibiotic by occupying part or the whole of the pocket.

Table 1. Results of the standard inhibitors docked with TEM-1 (1PZO) and the IMP-1(2DOO) β-lactamases enzymes (kcal/mol).

Name	Docking Scour		Name	Docking Scour		Name	Docking Scour	
	1PZO	2DOO		1PZO	2DOO		1PZO	2DOO
Clavulanic acid	-5.8	-5.8	Sulbactam	-4.9	-5.9	Avibactam	-6.1	-6.3

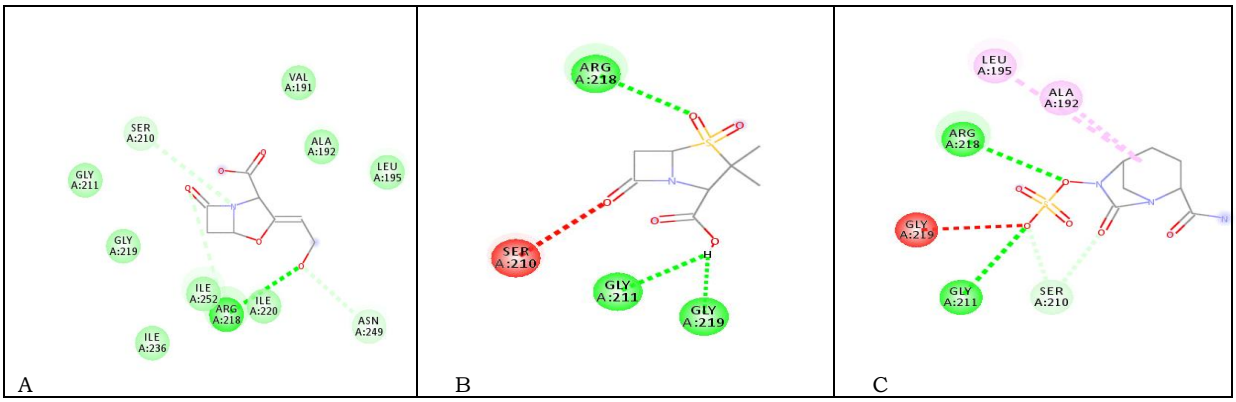


Figure 1. 2D chemical structure for clavulanic acid (A), sulbactam (B) and avabactam (C) with the TEM-1 (1PZO) enzyme.

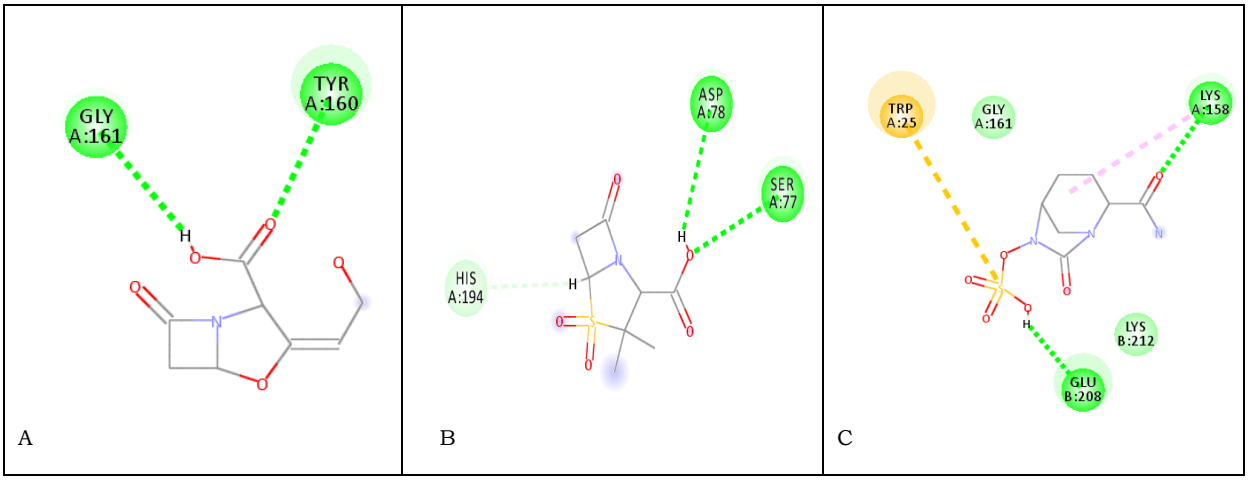


Figure 2. 2D chemical structure for clavulanic acid (A), sulbactam (B) and avabactam (C) within the active pocket site of the IMP-1 β-lactamase (2DOO) enzyme.

The picture is different in the IMP-1 β-lactamase (2DOO) **Figure 2**, each standard inhibitor bound separately to a group of amino acids differ from each other's (clavulanic acid with TYR160 and GLY 161, sulbactam with SER 77, ASP 78 and HIS 194 and avabactam with TRP 25, LYS 158 and GLU 208), here we consider all of them as the key of interaction. This variation in the rout of interaction could be due to that the IMP-1 is a class B (metalo) β-lactamase, in which the active pocket site is larger from the other classes, and it requires a complex of metal to occupy its pocket. The standard inhibitors and the tested compounds bound variably in both the active and the allosteric sites within the pocket. The most important issue here is that the inhibitor must bound strongly with high affinity with the active site and prevents the enzyme from catching the β-lactam antibiotic by occupying part or the whole of the pocket.

3.2 Molecular docking study of the amides compounds:

The structures of the studied substituents are scheduled in **Table 2**, and the docking outcomes with both enzymes are summarized in **Table 3** for best poses selected based on score value (kcal/mol) and manual inspection. The interactions of 2D structures of the amides with the amino acids residues of both the TEM-1 (1PZO) and the IMP-1 (2DOO) β-lactamases were representing in **Figure 3** and **4** respectively.

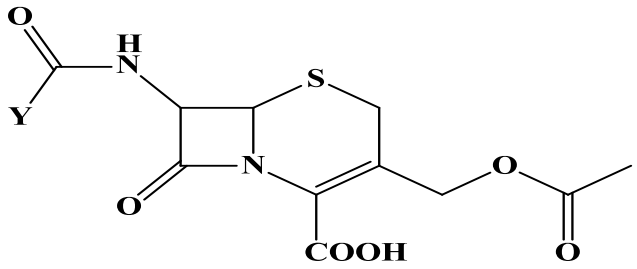


Table 2: The designed structures of the amide substituents.

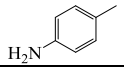
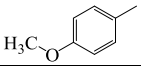
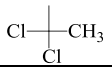
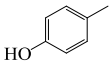
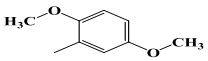
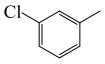
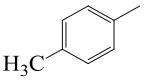
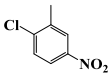
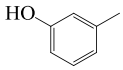
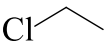
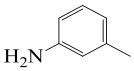
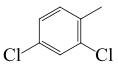
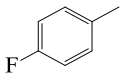
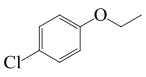
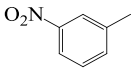
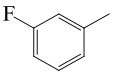
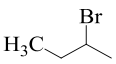
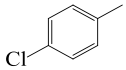
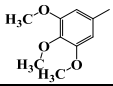
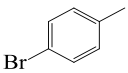
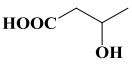
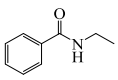
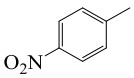
Item	Y	Item	Y	Item	Y
Y1		Y12		Y23	
Y2		Y13		Y24	
Y3		Y14		Y25	
Y4		Y15		Y26	
Y5		Y16		Y27	
Y6		Y17		Y28	
Y7		Y18		Y29	
Y8		Y19		Y30	
Y9		Y20		Y31	
Y10		Y21		Y32	
Y11		Y22			

Table 3. Docking study results for the amide compounds with TEM-1 β- lactamase (1PZO) and the IMP-1 β-lactamase (2DOO) enzymes (kcal/mol)

No.	Docking Scour		No.	Docking Scour		No.	Docking Scour	
	1PZO	2DOO		1PZO	2DOO		1PZO	2DOO
Y1	- 6.5	-6.4	Y12	-6.8	-8.3	Y23	-6.5	-6.2
Y2	-6.9	-8.6	Y13	-6.7	-7.7	Y24	-6.3	-6.7
Y3	-7.2	-8.9	Y14	-7.2	-9.0	Y25	-6.7	-6.7
Y4	-6.7	-7.8	Y15	-7.4	-8.0	Y26	-6.0	-6.7
Y5	-7.0	-8.7	Y16	-7.2	-7.6	Y27	-6.6	-7.0
Y6	-7.2	-8.7	Y17	-7.0	-9.4	Y28	-7.9	-8.5
Y7	-7.0	-8.7	Y18	-6.8	-7.5	Y29	-6.5	-7.0
Y8	-7.1	-7.5	Y19	-6.9	-7.3	Y30	-6.8	-6.8
Y9	-6.4	-8.8	Y20	-6.9	-8.5	Y31	-6.3	-7.2
Y10	-7.0	-6.5	Y21	-6.7	-7.0	Y32	-8.3	-7.9
Y11	-6.8	-8.0	Y22	-7.7	-9.1			

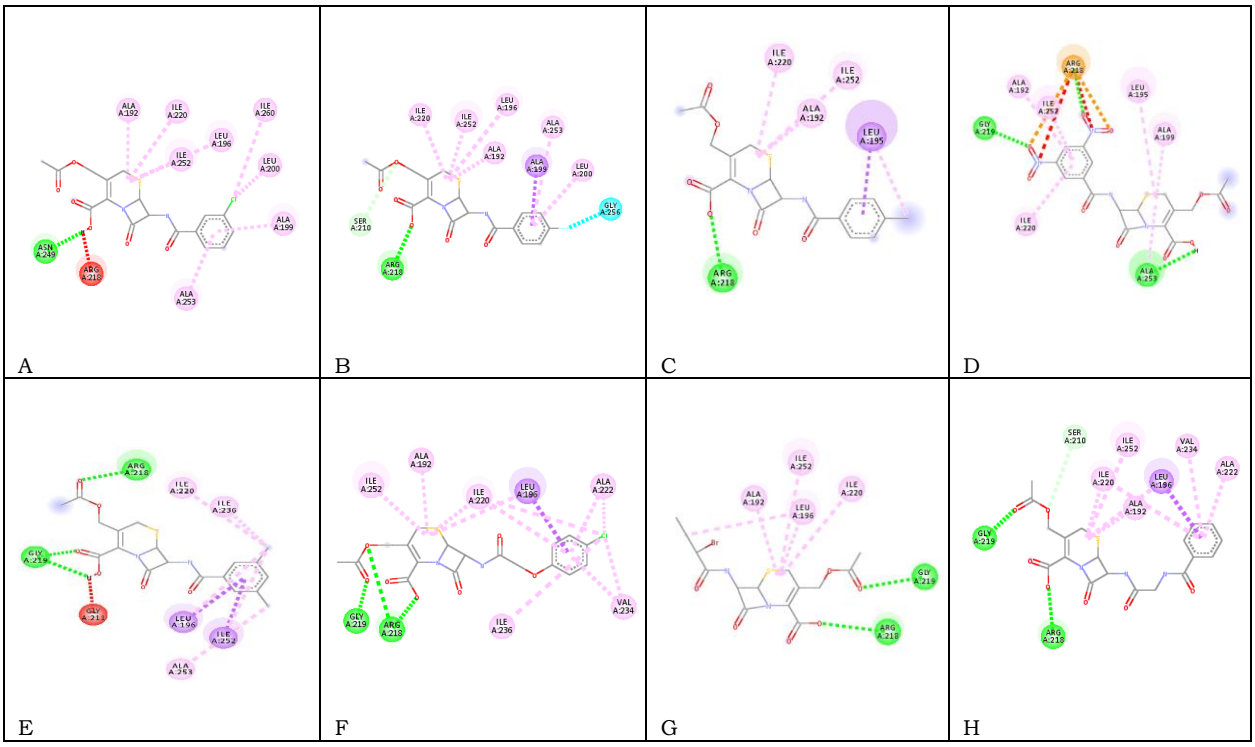


Figure 3. 2D chemical structure for the amides Y3 (A), Y6 (B), Y14 (C), Y17 (D), Y22 (E), Y28 (F), Y30 (G) and Y32 (H) within the pocket active site of the TEM-1 enzyme (1PZO).

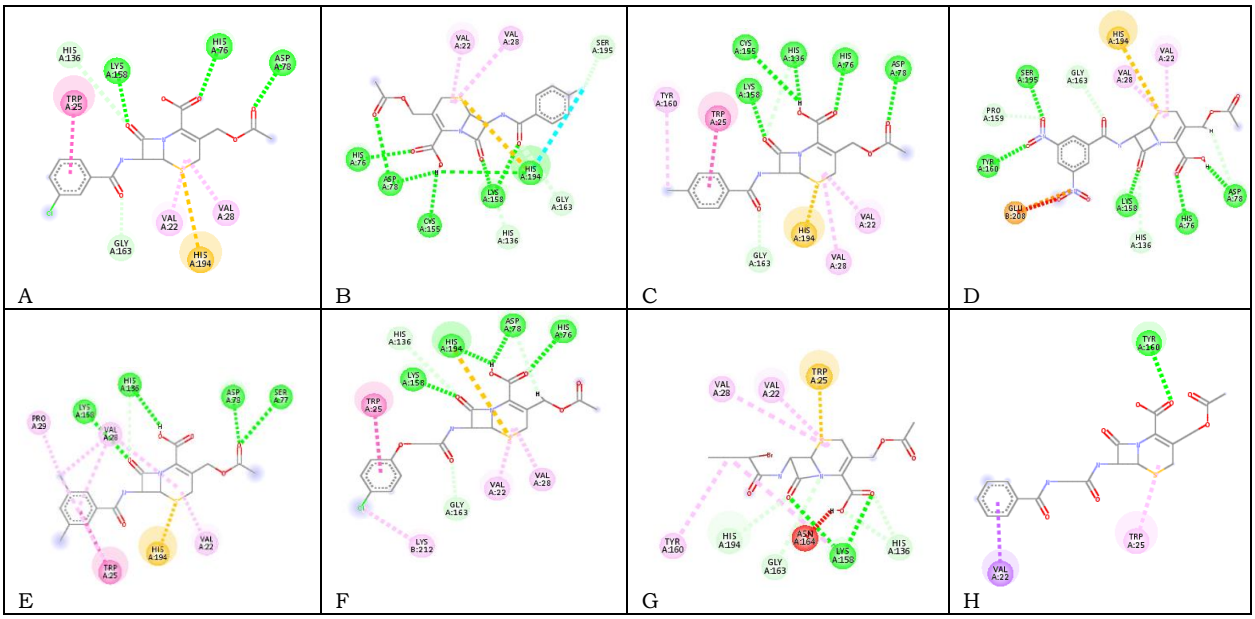


Figure 4. 2D chemical structure for the amides Y3 (A), Y6 (B), Y14 (C), Y17 (D), Y22 (E), Y28 (F), Y30 (G) and Y32 (H) within the active pocket site of the IMP-1 β-lactamase (2DOO) enzyme.

The tested amide compounds (Y groups + 7ACA) show promising results. The docking process with the both enzymes gives us comparable or even a better score than the standard inhibitors **Table 3**. Eight tested amides out of thirty two were selected on the base of the best docking results in both enzymes; these are with (Y3, Y6, Y14, Y17, Y22, Y28, Y30 and Y32), which bound to 5-6 out of 9 amino acids (those define the interacting space) of the TEM-1 β-lactamase, in addition to four amino acids that potentiate the interaction of the compounds with (Y3, Y6 and Y28), and two more for compounds with (Y17 and Y22) , and only one more in compound with (Y32) **Figure 3**. The same amides bound to 5-7 out of 8 amino acids (those define the interacting space) of the IMP-1 β-lactamase, compounds with (Y6, Y14, Y17 and Y30) bound to 5 more additional amino acids residues that potentiate their binding, the compound with (Y3, Y22 and Y28) have another 4 amino acids, and the compound with (Y32) has only one additional amino acid residue **Figure 4**.

It is worth to mention that all the eight selected amides represent docking results more than that of the standard inhibitors in both enzymes. The substituents (Y3, Y6, Y28 and Y30) all were halogenated, while (Y14, Y22, Y28 and Y32) were hydrophobic in nature, although (Y22 and Y28) have an oxygen atom that can potentiate the interaction by adding hydrogen bonding. On the other hand Y17 has a couple nitro groups only.

From the above we can conclude that the active pocket site of both enzymes classes prefer hydrophobic residues, this is in agreement with previous studies on type A β-lactamase (15,18). Another conclusion is that the halogenated substituents with Meta or Para positions or even in aliphatic chain all could potentiate the binding with the both enzymes classes. Also the addition of the oxygen atom to both the halogenated and the hydrophobic substituents will potentiate the interaction with the both enzymes by promoting additional hydrogen bonding with amino acids residue in the binding sites.

3.3 Molecular docking study of the Schiff bases compounds:

The chemical structures of the studied substituents are listed in **Table 4**, while the docking results with both enzymes are summarized in **Table 5** for best poses selected based on score value (kcal/mol)and manual inspection. The interactions of 2D configurations of the Schiff bases with both the TEM-1 (1PZO) and the IMP-1(2DOO) β-lactamases were representing in **Figure 5** and **6** respectively.

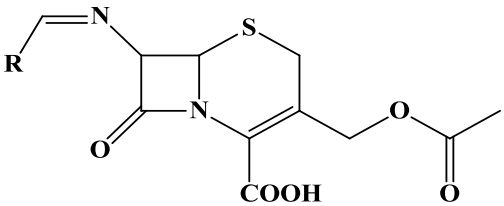


Table 4. The structures of the designed Schiff base compound.

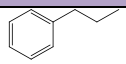
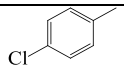
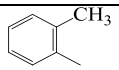
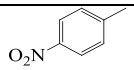
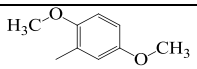
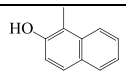
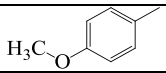
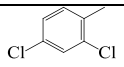
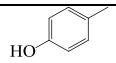
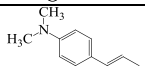
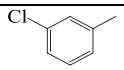
Item	R	Item	R	Item	R
R 1		R 6		R 11	
R 2		R 7		R 12	
R 3		R 8		R 13	
R 4		R 9		R 14	
R 5		R 10			

Table 5. The results for the Schiff base compounds docked with TEM-1 β- lactamase (1PZO) and the IMP-1 β-lactamase (2DOO) enzymes (kcal/mol)

No.	Docking Scour		No.	Docking Scour		No.	Docking Scour	
	1PZO	2DOO		1PZO	2DOO		1PZO	2DOO
R1	-7.0	-8.1	R6	-7.0	-9.5	R11	-7.7	-7.9
R2	-6.9	-8.4	R7	-6.5	-7.7	R12	-6.9	-8.2
R3	-6.6	-8.4	R8	-6.6	-7.8	R13	-7.4	-9.0
R4	-6.4	-7.8	R9	-6.4	-8.8	R14	-6.9	-8.0
R5	-6.9	-7.8	R10	-7.1	-8.6			

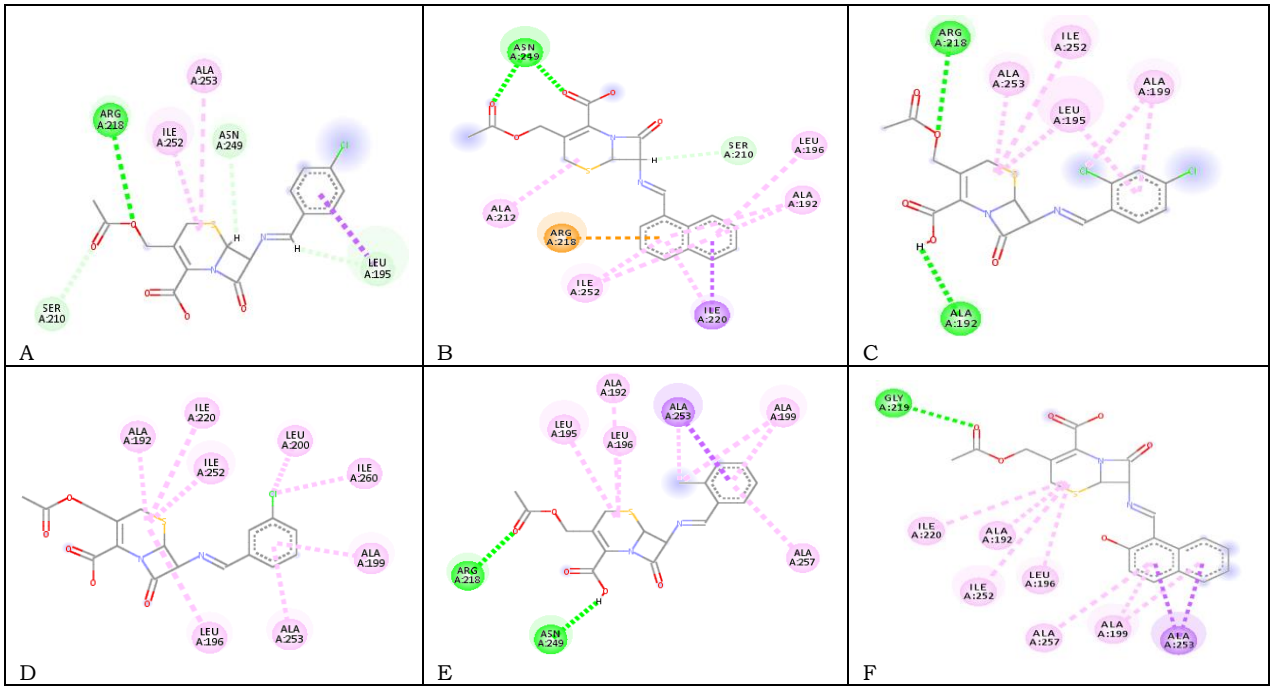


Figure 5. 2D chemical structure for the Schiff bases R2 (A), R6 (B), R9 (C), R10 (D), R12 (E) and R13 (F) with the TEM-1 (1PZO) β-lactamase enzyme.

Schiff bases compounds (R groups + 7ACA) also show very good results comparing with the standard inhibitors but still less than those of the amides. This could be due to the hydrogen bonding formed by the carbonyl group of the amide bond which can potentiate the interaction, while the (-CH=N-) group of the Schiff basses lack such interaction.

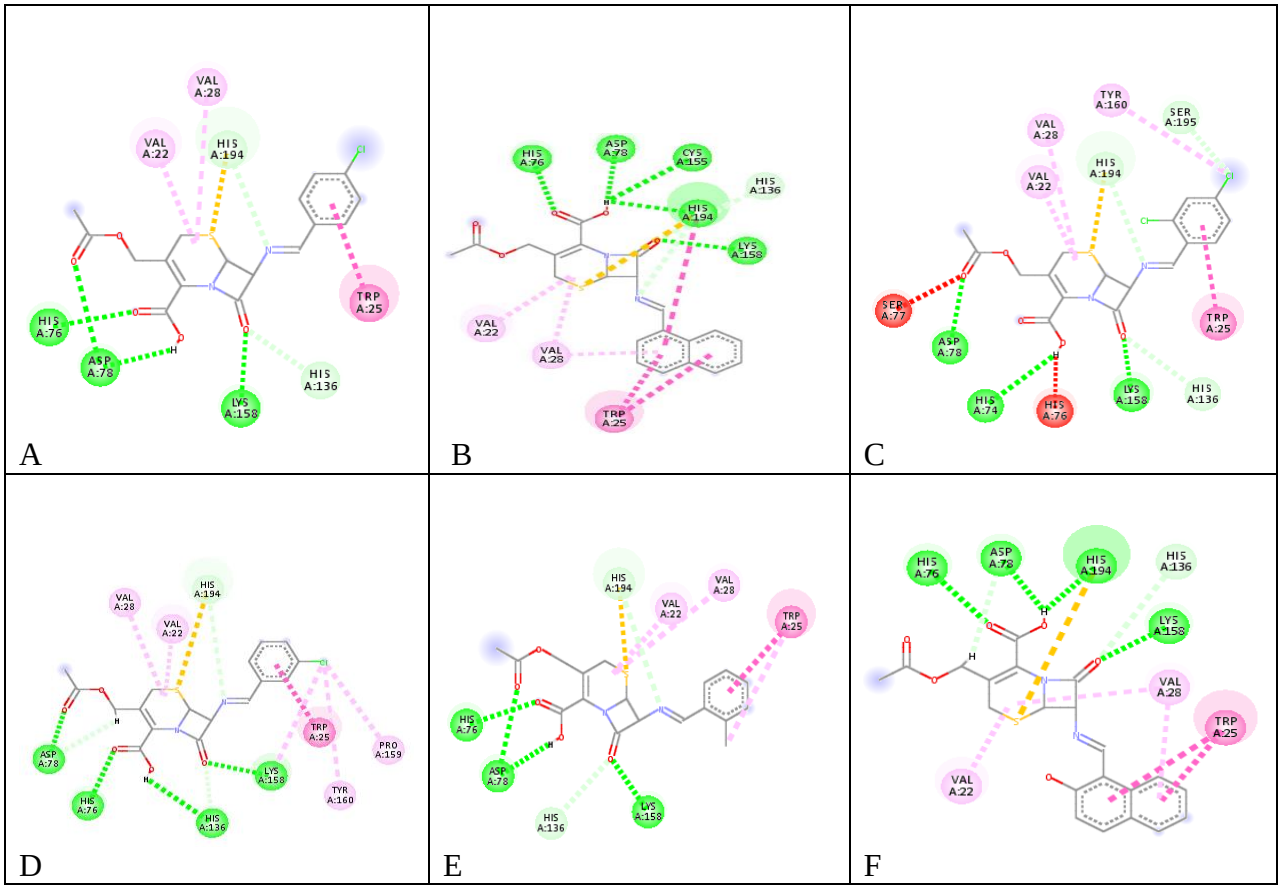


Figure 6. 2D chemical structure for the Schiff bases R2 (A), R6 (B), R9 (C), R10 (D), R12 (E) and R13 (F) within the active pocket site of the IMP-1 β-lactamase (2DOO) enzyme.

Six tested Schiff bases out of fourteen were selected on the base of the best docking results in both enzymes **Table 5**; these are with (R2, R6, R9, R10, R12 and R13), which bound to 4-6 out of 9 amino acids (those define the interacting space) of the TEM-1 β- lactamase , in addition to four amino acids for the compound with (R9 and R10), and three more for compounds with (R12 and R13), and compounds with (R2 and R6) only have 2 additional amino acids **Figure 5**. The same Schiff bases bound to 4-6 out of 8 amino acids (those define the interacting space) of the IMP-1 β-lactamase, compounds with (R9) bound to 6 additional amino acids residues that potentiate their binding, the compounds with (R6 and R10) have another 5 amino acids, and the compounds with (R2, R12 and R13) have 4, 3 and 2 additional amino acids residues **Figure 6**.

The substituents (R2, R9 and R10) all are halogenated, while (R6, R12 and R13) were hydrophobic in nature. Again as mentioned with the amides the halogenated substituents and the hydrophobic residues potentiate the affinity and the binding ability of any compounds when they added to their structures to act as β-lactamase inhibitors.

4. Conclusion

Molecular docking for 46 derivatives of 7 amino cephalosporinic acid (7ACA) against both the TEM-1 β-lactamase (1PZO) and the IMP-1 β-lactamase (2DOO) enzymes indicate possible enhanced activity of 8 amides and 6 Schiff bases compound compared with the standard inhibitors (clavulanic acid, sulbactam and avabactam). These compounds show promising docking interactions with active pocket site in both enzymes. We can conclude that the active pocket site of both enzymes classes prefer hydrophobic residues, and the halogenated substituents with Meta or Para positions or even in aliphatic chain all could potentiate the binding with the both enzymes classes. Also, both the halogenated and the hydrophobic substituents containing oxygen atom will potentiate the affinity and the binding ability of any compounds when they added to their structures to act as β-lactamase inhibitors.

5. Acknowledgements

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6. Conflict Of Interest

The authors declare that there is no conflict of interest.

7. References

1. Singh GS and Sudheesh S. β-Lactams in natural lactones and lactams: synthesis, occurrence and biological activity; Janecki, T., Ed.; *Wiley-VCH*, 2014:101–145.
2. Halat DH and Moubareck CA. The current burden of carbapenemases: review of significant properties and dissemination among gram-negative bacteria. *Antibiotics*, 2020;9:186.
3. Jubeh B, Breijyeh Z and Karaman R. Antibacterial Prodrugs to Overcome Bacterial Resistance. *Molecules*, 2020;25:1543.
4. Monaco M, Giani T, Raffone M, Arena F, Garcia FA, Pollini S, Grundmann H, Pantosti A, Rossolini GM. Colistin resistance superimposed to endemic carbapenem-resistant Klebsiella pneumoniae: a rapidly evolving problem in Italy, November 2013 to April 2014. *Euro surveillance*, 2014;19(42):20939.
5. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. *Curr. Opin. Pharmacol*, 2014;18:56-60.
6. Adesoji AT, Onuh JP and Okunye OL. Bacteria resistance to cephalosporins and its implication to public health. *Journal of Bacteriology and Mycology*, 2016;3(1):1021.
7. Elshamy AA and Aboshanab KM. A review on bacterial resistance to carbapenems: epidemiology, detection and treatment options. *Future Sci. OA,* 2020;6(3),FSO438.
8. Bush K. Past and present perspectives on betalactamases. *Antimicrob. Agents Chemother.* 2018; 62(10):18.
9. Ferri M, Ranucci E, Romagnoli P and Giaccone V. Antimicrobial resistance: A global emerging threat to public health systems. *Crit. Rev. Food Sci. Nutr.*, 2017;57:2857–2876.
10. Reddy N, Shungube M, Arvidsson PI, Baijnath S, Kruger HG, *et al.* A 2018-2019 patent review of metallo beta-lactamase inhibitors, *Expert Opinion on Therapeutic Patents*, 2020;30(7). https://doi.org/10.1080/13543776.2020.1767070
11. Bonomo RA. *b*-Lactamases: A focus on current challenges. *Cold Spring Harb. Perspect. Med.*, 2017; 7(1):a025239.
12. Drawz1 SM and Bonomo RA. Three decades of b-lactamase inhibitors. american society for microbiology, *Clinical Microbiology Reviews*, 2010;23(7):160-201.
13. Olugbenga OO. Bacterial Resistance; A Perspective on Beta-Lactamase Enzymes. *EC Microbiology,* 2020;16(3):1-12.
14. King AM. Discovery and characterization of novel beta-lactamase inhibitors. Ph.D. Thesis, McMaster University, Chemistry and Chemical Biology, 2016.
15. Mahmood AAJ, Al-Iraqi MA and Al-Abacchi FT. Design, synthesis and anti-β-lactamase activity for new monobactam compounds. *Materials Today: Proceedings*, 2021;42:1860-1866 .
16. Gawehn E, Hiss JA and Schneider G. Deep learning in drug discovery. *Mol. Inform.*, 2016;35:3-14.
17. Shah B, Modi P & Sagar SR. In Silico Studies On Therapeutic Agents For Covid-19: Drug Repurposing Approach. *Life Sciences,* 2020;252:117652.
18. Mahmood AAJ, Al-Iraqi MA and Abachi FT. Design, synthesis, and evaluation the anti-β-lactamase activity of new sulphathiazole-derived monobactam compounds. *Iraqi Journal of Pharmacy,* 2020,17(1):19-36
19. Mahmood AAJ, Al-Iraqi MA and Abachi FD. "New 4,4′-methylenedianiline monobactame compounds: Synthesis, antioxidant and antimicrobial activities evaluation", AIP Conference Proceedings, 2022;2660: 020024.
20. Gawehn E, Hiss JA and Schneider G. Deep learning in drug discovery. *Mol. Inform.*, 2016,35:1-12.
21. Abdul Hameed A, al-Rashida M, Uroos M, Ali SA and Khan KM. Schiff bases in medicinal chemistry: a patent review (2010-2015), *Expert Opin Ther Pat*, 2017, 27(1):63-79.
22. Mahmood AAJ. Green synthesis of Schiff bases: a review study. *Iraqi Journal of Pharmacy*, 2022,18(2):180-193.
23. Dunetz JR, Magano J and Weisenburger GA. Large-scale applications of amide coupling reagents for the synthesis of pharmaceuticals. Org. Process Res. Dev., 2016;20:140-177.
24. Bousfield TW, Pearce KPR and Nyamini SB. Synthesis of amides from acid chlorides and amines in the bio-based solvent Cyrene. *The Royal Society of Chemistry; Green Chem.*, 2019; 21:3675-3681
25. Lin X, Li X and Lin X. A review on applications of computational methods in drug screening and design. *Molecules*, 2020;25:1375.
26. Mahmood AAJ, Al-Iraqi MA and Abachi FT. Fluorine important element in new drugs synthesis: Review Study. *Iraqi Journal of Pharmacy*, 2018;15(1):37-45.

دراسة الرسو الجزيئي لمركبات جديدة مشتقة من حامض الـ 7-امين السيفالوسبورين كمثبطات محتملة لـ انزيم البيتالاكتميز

عملت مضادات البتالاكتام الحيوية منذ اول اكتشاف لها على تعزيز العلاج الفعال للعدوى البكتيرية. وعلى الرغم من ذلك فان مقاومتهم يمكن أن تنتشر بسرعة على نطاق عالمي وذلك بإنتاج انزيم البيتا لاكتاميز والذي يعتبر المصدر الرئيسي للمقاومة البكتيريا. ومن هنا تاتي اهمية القيام بعمل جاد لتصميم ووتصنيع مضادات أو مثبطات لهذه المقاومة . يعتبر استخدام مثبطات بيتا لاكتاماز مع مضادات البتالاكتام الحيوية الخط الوحيد المتوفر حاليا لموجهة هذه المقاومة . يهدف هذا العمل إلى تصميم والقيام بالإرساء الجزيئي لسلسلتين جديدتين (قواعد شيف وأميدات) من مشتقات حامض الـ 7-امين السيفالوسبورين ضد كل من انزيم TEM-1 و IMP-1 . اظهرت النتائج ان هناك نشاط معزز محتمل لـ 8 أميدات و 6 قواعد شيف مقارنة بالمثبطات القياسية (حمض كلافولانيك و سلباكتام وأفاباكتام) . كما أظهر هذه المركبات قابلية ارساء والتحام واعدة مع مواقع الجيب النشط في كلا الإنزيمين . من هذه الدراسة يمكننا أن نستنتج أن كلاً من المعوضات المهلجنة والكارهة للماء لوحدها أو عند احتوائها على ذرة الأكسجين ستقوي قدرة وقوة الارتباط لأي مركبات عندما تضاف إلى هياكلها لتعمل كمثبطات لانزيمات البيتا لاكتاماز.

الكلمات المفتاحية : انزيم البيتالاكتميز، الارساء الجزيئي ، مضادات البيتالاكتميز ، حامض الـ 7-امين السيفالوسبورين ، قواعد شيف ، اميدات .