RECIBIDO EL 24 DE FEBRERO DE 2021 - ACEPTADO EL 24 DE MAYO DE 2021

A PEDAGOGICAL VIEW ABOUT THE DESIGN OF ISOXAZOLYL-PENICILLINS OF THE AMPC BETALACTAMASE RECEPTOR 1FCM USING THE DOCKING MOLECULAR TECHNIQUE

UNA MIRADA PEDAGOGICA SOBRE EL DISEÑO DE ISOXAZOLIL-PENICILINAS DEL RECEPTOR 1FCM DE LA BETALACTAMASA AMPC EMPLEANDO LA TÉCNICA DE ACOPLAMIENTO MOLECULAR

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RESUMEN

El presente trabajo expone Expone principalmente el resultado de la búsqueda de moléculas, derivadas de los cambios estructurales del fármaco Cloxacilina en su radical fenilo, el cual se encuentra clorado. Así mismo, pone en evidencia la selección del grupo farmacóforo, el cual permitió concretar el objetivo anteriormente mencionado. En segundo lugar, el target seleccionado fue la betalactamasa, con nomenclatura 1FCM, registrada en la base de datos, Protein Data Bank. De igual manera se encuentran los aminoácidos involucrados en las interacciones no covalentes. En este orden de ideas, se plantearon 22 moléculas que presentaron una energía de afinidad menor a -8.0 Kcal/mol, dato que sirve de referencia para postular 6 moléculas que hayan registrado una afinidad menor, generada por el software autodock vina. Finalmente, como resultado se obtiene la optimización estructural del fármaco líder junto con sus nuevas interacciones en los aminoácidos LYS64, ASN149, THR313 y SER61.

PALABRAS CLAVE:

Cloxacilina, Isoxazolil penicilinas, Betalactamasa, Docking molecular.

ABSTRACT

The present work mainly exposes the result of the search for molecules, derived from the structural changes of the drug Cloxacillin in its phenyl radical, which is chlorinated, likewise, the selection of the pharmacophore group is evidenced, which allowed to specify the aforementioned objective. Secondly, the selected target was beta-lactamase, with 1FCM nomenclature, registered in the database, Protein Data Bank, in the same way, the amino acids involved in non-covalent interactions are found, in this order of ideas, they were raised, 22 molecules that presented an affinity energy lower than -8.0 Kcal/mol, this data stated above, will become the reference value, to postulate 6 molecules that have registered a lower affinity, generated by the Autodock Vina software. To conclude, the structural optimization of the leading drug is given as a result, together with its new interactions in the amino acids LYS64, ASN149, THR313 and SER61.

KEY WORDS:

Cloxacillin, Isoxazolyl penicillins, Betalactamase, Molecular docking.

INTRODUCTION

The history of mankind has been characterized mainly by discoveries that have an immediate or future utility. This premise is evident in the discovery of penicillin, which is attributed to Alexander Fleming (Fleming, 1929). Penicillin would give way to the new family of drugs called beta-lactams. After about 70 years, beta-lactams have become the most prescribed antimicrobials in clinical treatments against bacterial strains such as Streptococcus pneumoniae (Ruvinsky, 2001).

Despite the fact that no really new beta-lactam has been available for more than 2 decades, the incessant increase in resistance and the advances in the knowledge of its molecular mechanisms, has conditioned the existence of a large amount of information in the medical literature on each of the components of this family of antibiotics (Cantón & Horcajada, 2013).

In this order of ideas, it is possible to establish that beta-lactams are antibiotics, which are mainly characterized by inhibiting the last stage of bacterial cell wall synthesis. Their action is slow, depends only on time, and has very low toxicity (Choque, 1993).

JUSTIFICATION

The β-lactams have been characterized by their success in the treatment of bacterial infections; however, bacterial resistance has become a limiting factor to perform effective treatments in new infected patients; consequently, there is a demand to develop new beta-lactams that allow overcoming the challenge of bacterial resistance. The main objective of this scientific article is to show the results of the Isoxazolyl-penicillin design of the 1FCM receptor of the beta-lactamase ampc using the molecular docking technique. In this order of ideas, it will be necessary to make structural modifications to Cloxacillin, in other words, to add atoms or functional groups that increase/intensify the drug-target interactions.

CHARACTERIZATION OF THE BETA-LACTAM FAMILY

The structural identification of the beta-lactam family is evidenced by the presence of the beta-lactam ring, which, in turn, defines the chemical characteristics of this family as shown in Figure 1.

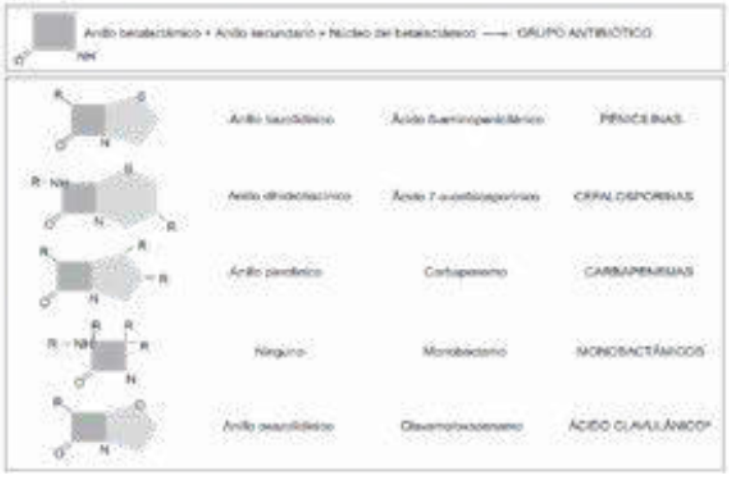


Figure 1. Chemical structure of beta-lactams. **Source:** (Suarez, 2009)

At the same time, this determines the mechanism of action (inhibition of cell wall synthesis), as well as the low direct toxicity (it acts on the cell wall of the microorganism, which is not present in the eukaryotic animal cell) and the main mechanism of resistance (beta-lactamases) of this large family of antibiotics. It should be noted that for the beta-lactam to be active, it must be bound to other radicals (usually other rings). The modifications of the properties of the resulting compound are not only mediated by the basic skeleton, which is formed by the 2 rings (called nucleus), but also by the union of different types of linear chains, to give way to the general classification of beta-lactam antibiotics: penicillins, cephalosporins, carbapenemics, monobactams and beta-lactamase inhibitors (Cué & Morejón, 1998).

In other words, it is possible to establish that, within each group, small alterations in the chemical structure are capable of modifying the characteristics of the antibiotic, such as spectrum, affinity for certain receptors or resistance to beta-lactamases (Cué & Morejón, 1998).

In summary, this first section highlights the importance of making structural modifications, preferably in silico or through computer-assisted molecular modeling, for subsequent testing,

either in antibiograms or in patients with bacterial infection.

MECHANISM OF ACTION OF BETA-LACTAMS

It is necessary to emphasize that beta-lactam antibiotics are considered as bactericidal agents, which have 2 mechanisms of action: 1) To inhibit the synthesis of the bacterial wall 2) To induce bacterial autolysis (Livermore, 1993). Because of this, it is necessary to take into account that the bacterial wall is a structure that covers bacteria of all genera, except for mycoplasmas; it is located outside the cytoplasmic membrane and is mainly composed of a protein called peptidoglycan (Curtis & Schnek, 2008).

Figure 2 shows a graphic representation of the stages of bacterial cell wall formation.

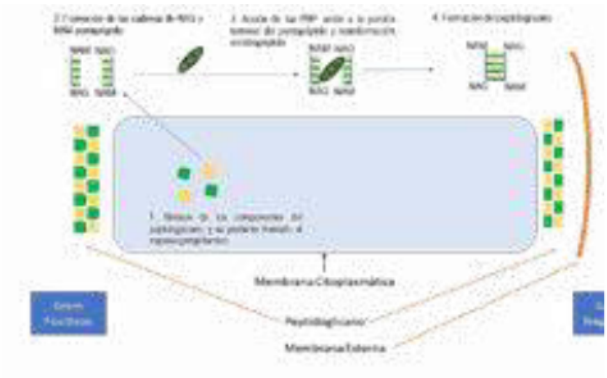


Figure 2. Stages of cell wall formation; NAM: N-acetylmuramic acid; NAG: N-acetylglucosamine acid; PBP: Penicillin Binding Protein. **Adapted from:** (Suarez, 2009)

Figure 2 shows that gram-positive bacteria have a thicker cell wall and their most characteristic component is peptidoglycan. On the other hand, gram-negative bacteria have a thinner and more complex cell wall, which is mainly composed of lipids, proteins and a slightly thinner inner layer of peptidoglycan (Curtis & Schnek, 2008).

The peptidoglycan is formed by long chains of glucids, where the repetition of N-acetylmuramic acid and N-acetylglucosamine is found. These components are synthesized in the cytoplasm and subsequently transported to the periplasmic space, giving rise to the assembly of the green and yellow structure in Figure 2 (Barcelona, Marín & Stamboulian, 2008).

The last phase in the conformation of the cell wall, has as its objective, the formation of tetrapeptides, taking as a starting point the pentapeptides, demanding the presence of enzymes in the periplasmic space, which are commonly known as transpeptidases (Garcia et al., 2014).

In summary, without the presence of the cell wall, the microorganism will be exposed to the environment, generating a death due to changes in the oncotic pressure, however, for there to be an effective pharmacological action by the beta-lactams, it is essential that the bacteria is still in the multiplication phase, since this is the time when bacteria perform the synthesis of their cell wall (García, Castillo & Salazar, 2014). In view of the absence of the cell wall, beta-lactams activate an endogenous bacterial autolysin, which disintegrates the peptidoglycan, sometimes strains of bacteria do not present autolysin, which are usually tolerant to beta-lactams, this means that they inhibit their growth with the presence of the beta-lactam group, but present a complete lysis (Agudelo et al., 2009). Figure 3 shows a graphic representation of the stages of action of beta-lactams

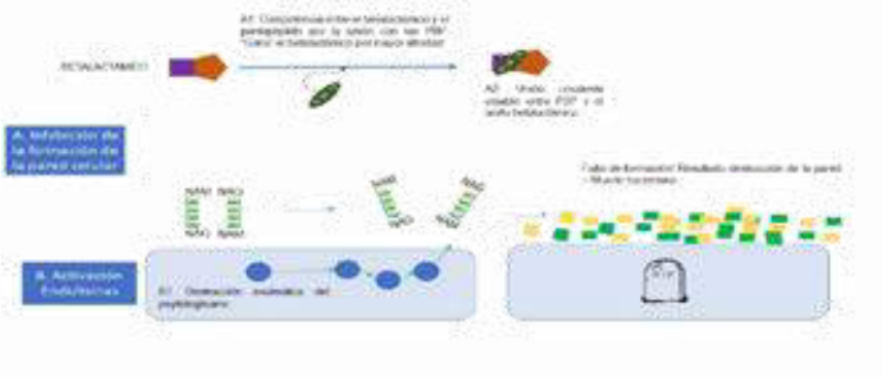


Figure 3. Mechanism of action of beta-lactams; NAM: N-acetylmuramic acid; NAG: N-acetylglucosamine acid; PBP: Penicillin Binding Protein. **Adapted from:** (Suarez, 2009)

ISOXAZOLYL PENICILLINS

Manuel Brugueras and Moisés García point out that the Isoxazolyl penicillins are mainly composed of Cloxacillin, Dicloxacillin, Flucloxacillin and Oxacillin (Figure 4), which in turn are resistant to penicillinases and gastric acids. The authors state that their structures are similar, but differ specifically in their absorption. In this order of ideas, it is considered an adequate treatment in infections caused by Streptococcus pneumoniae and Staphylococcus epidermidis (Lipman, 1993).

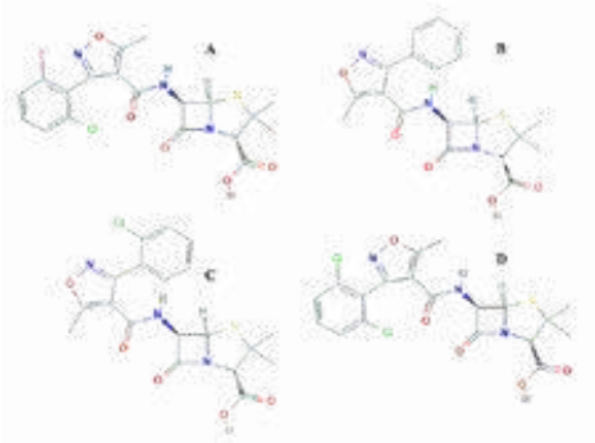


Figure 4. Chemical structure of Isoxazolyl penicillins. **Source:** Own elaboration. **(A)** Flucloxacillin. **(B)** Oxacillin. **(C)** Cloxacillin. **(D)** Dicloxacillin.

SELECTION OF A MOLECULE FROM THE ENTIRE SERIES OF BETA-LACTAMS

CHARACTERIZATION OF CLOXACILLIN

Cloxacillin is part of the beta-lactam family, which presents the characteristic beta-lactam ring, it is also formed by four members, one of these, an amine group, together with a keto group, which gives it a very important polarity in terms of the intermolecular interactions to be performed, as in this case, the interactions with the selected target (1FCM).

DESCRIPTION OF CLOXACILLIN

Cloxacillin (Figure 4C) is a molecule that is made up of 9 Heteroatoms, which can be grouped as, Chlorine, Nitrogen and Oxygen; Cloxacillin, is characterized by presenting the characteristic ring of the beta-lactam family, it is identified by forming a four-membered ring that is joined to a 5-membered ring, in which the Nitrogen heteroatom is located (Gomez et al., 2015).

It is considered as a beta-lactam antibiotic. It inhibits the synthesis of the bacterial cell wall through the non-covalent coupling or binding of one or more Penicillin-binding proteins (e.g. carboxypeptidases, endopeptidases, transpeptidases) in the periplasmic membrane. As it happens in the great majority of beta-lactams,

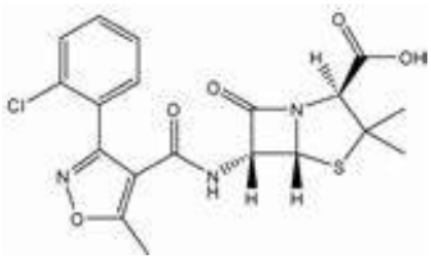
the studied drug blocks the final transpeptidation step of peptidoglycan synthesis. The cell dies by the action of autolytic enzymes (Autolysins and Murein hydrolases) after exposure to the beta-lactam antibiotic (Sharon, 2007).

WHEN AND BY WHOM WAS IT DISCOVERED?

Interestingly, the commercial molecule Cloxacillin Sodium was discovered through the Drug Discovery technique and is also part of a subfamily of beta-lactam antimicrobial drugs, Penicillins. Cloxacillin was patented in 1960 and approved for medical use in 1965. It is on the World Health Organization's List of Essential Medicines. Designed by the Beechman Group, which is named in memory of Thomas Beecham, whose commercial activity at the time was to sell herbal remedies, already in 1842 his success was quite marked when he marketed a product called Beechams Pills, a laxative of renown for that time.

Table 1 shows relevant information about the selection of the molecule and its target

Table 1: Summary of Cloxacillin characterization. **Source:** Own elaboration

Familia	Estructura química	Targets	Target de Interés
Beta-Lactámicos		Penicillin-binding protein 1A Beta-lactamase Penicillin-binding protein 2a Penicillin-binding protein 2B Penicillin-binding protein 3	Proteína Betalactamasa 1 FCM

PHARMACOPHORE GROUP

Determining a pharmacophore is the most relevant first step in understanding the interaction between a receptor and a ligand. In the early 1900s, Paul Ehrlich postulated that a pharmacophore is conceived as "A molecular fragment that presents (Phoro) the essential characteristics responsible for the biological activity of a drug" (Güner et al 2000). This premise has been valid for more than 60 years; however, the current definition presented by Peter Gund in 1977 established that: "A pharmacophore is a set of structural characteristics of a molecule that is recognized at a receptor site and is responsible for the biological activity of that molecule" (Güner et al, 2000).

At this point, mention is made of the pharmacophore group selected for Structure-Based Virtual Screening:

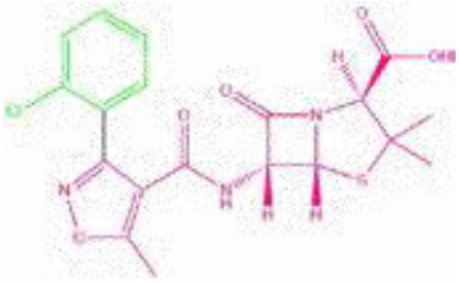


Figure 5: Leader molecule (Cloxacillin).
Source: Own elaboration in ChemDraw 20.0 software.

Figure 5 refers to the leading molecule Cloxacillin. The magenta region is the pharmacophore group selected for this screening, as evidenced in the structure, the beta-lactam ring is present, together with its acid group, amide and finally the isoxazole, these three components are considered of vital importance for the biological activity of the possible derivatives of Cloxacillin; On the other hand, it is evident in the emerald green region, an aromatic ring with a substituent of the halogen group, i.e., this will become the target of structural changes to perform the molecular optimization regarding the affinity between the ligand and target selected in this article.

TARGET SELECTION (1FCM)

Table 2: Characterization of 1FCM Protein **Source:** Own elaboration

Nomenclatura	Clasificación	Estructura	Resolución
1FCM	Betalactamasa	 **Figura 6**: Estructura Cristalina 1FCM; **Fuente:** Protein Data Bank	

MOLECULAR COUPLING

Automated molecular docking is understood as the search for the optimal conformation and position of a ligand with respect to a molecular target, which can be an enzyme, an ion channel or a receptor (Saldívar, 2017). Automated molecular docking has 2 key components: 1) Molecular docking or the process of searching for the conformation and orientation of molecules, and b) Scoring, which consists of assigning a value and/or score that measures the interaction that exists between the two (2) structures, which usually presents units of kcal/mol (Prieto, 2018).

AUTODOCK VINA

The AutoDock Vina software is the program that allows molecular docking to be performed in conjunction with virtual screening. AutoDock Vina, presented a considerable acceleration, compared to the molecular docking software previously developed by the same firm (AutoDock 4), likewise, significantly improves the accuracy of predictions in the form of interaction, the authors, Oleg Trott and Arthur Olson, claim that through optimizations made over time, they have managed to make proper use of multicore machines, allowing to generate maps and group results in a more user-friendly way (Trott, 2010).

METHODOLOGY

COMPUTATIONAL PHASE

In this phase, three fundamental points are required: the first one is the selection of the target to be studied, in this case the protein registered in the PDB (Protein Data Bank) with nomenclature 1FCM Beta-Lactamase, and the molecule to interact, the drug Cloxacillin, belonging to the beta-lactam family, were taken. Secondly, it is necessary to save the corresponding files for each part, i.e., in .pdb extension, in the case of the protein, and in. cdxml format (ChemDraw) for the selected drug.

The molecular coupling demands to perform optimizations in its 3D structure, in this order of ideas, this optimization with respect to the drug Cloxacillin, will be mediated by two main free download software, these are Avogadro and ChemDraw, the first will be based on performing energy optimization regarding its molecular spatial structure, however to optimize this criterion, the drawing was first performed in a single plane or planar structure, in ChemDraw software, which was subsequently recorded on the hard disk of each researcher with the extension. sdf or MDLSD file V3000, to be later optimized geometrically in the Avogadro program.

It should be noted that the optimizations of the selected molecule and those of the pharmacological family were performed in the Force Field MMFF94s, which is recommended for organic molecules. The selection of this force field refers mainly to the fact that it is not based on quantum mechanics, but rather on the laws of classical mechanics, among which we can mention that the MMFF94s model allows the analysis of interactions between non-bonded atoms.

In summary of these first two points mentioned, it is recommended to save the .pdb and. mol2 extension files (result of the optimization in the Avogadro software) in different folders, in order to avoid confusion and/or errors at the moment of coupling with autodock Vina in company of AutoDockTools. The aforementioned software allows defining the coupling criteria, in other words, it facilitates establishing the grid box, assigning the polar hydrogens, and the elimination of aqueous residues, especially to avoid interferences.

The criteria established for the grid box are understood as the coordinates necessary for the software to recognize where the interaction between the target and the molecule to be studied should take place, in this first scenario,

Cloxacillin, obtaining the following coordinate data, which were extracted through the position of the amino acids involved, according to PDB, in the non-covalent bonds: center_x=24. 556, center_y=5.833, center_z=18.194; Similarly, the size or dimensions of the "Grid Box", was left at its default values size_x=40, size_y=40, size_z=40.

The output data were recorded under the name 1FCM_out. pdbqt. Regarding structural modifications, it was necessary to consider two optimization criteria, structural analysis of other commercially active drugs (Isoxazolyl Penicillins), together with bio isosteres, which are chemical substituents or groups with similar physical and chemical properties that produce similar biological effects to another chemical compound and that were related to the receptor, these in order to perform a structural design closer to reality, depending on its possible synthesis and eventual dosage. After carrying out the steps of structural modification of Cloxacillin, analysis of functional groups that present an interaction with the protein of interest, the molecular docking of 55 candidate molecules was carried out, where one was chosen, fulfilling two characteristics, 1) Increase of affinity in at least one unit with respect to cloxacillin, 2) "Realistic" design, with attempt of synthesis.

Finally, a toxicity prediction was performed on the website called Lazars Toxicity Predictions, where 2 toxicity evaluation criteria were chosen, Ames Test, Carcinogenicity (Mice/Rats). These data were recorded in Table 5.

Figure 7 schematically shows the methodology proposed in this research.

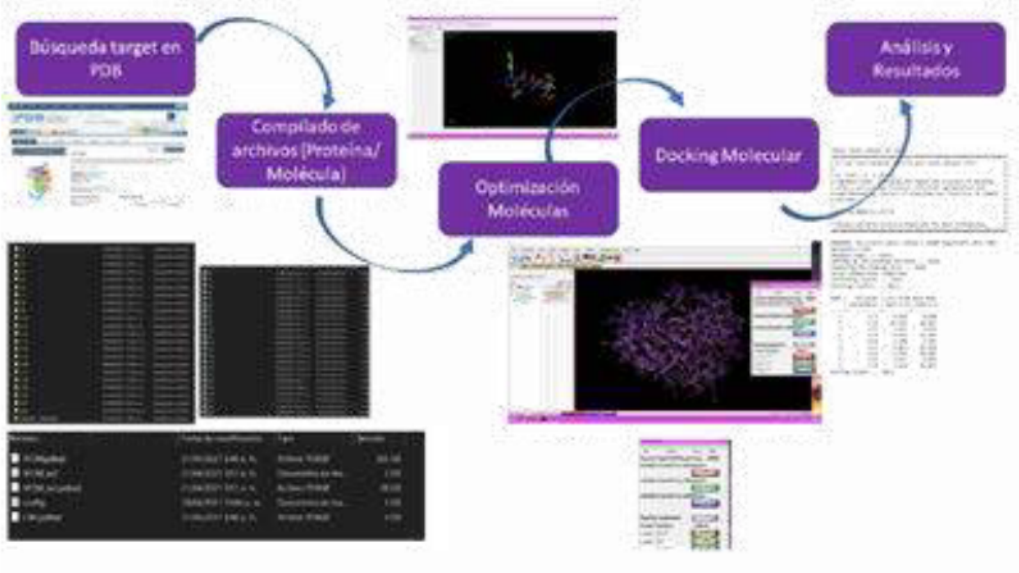


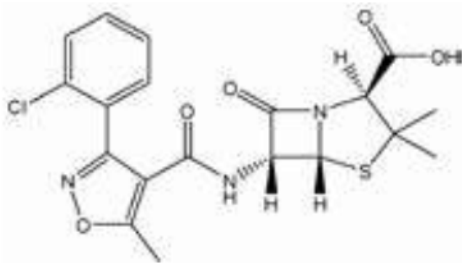
Figure 7: Graphical representation of the methodology used. **Source:** Own elaboration

RESULTS

COMPUTATIONAL PHASE

Table 3 shows the affinity energy of cloxacillin with the 1FCM receptor of the beta-lactamase ampc, product of the molecular docking performed. This energy is the result of the average of the computational calculations obtained from Autodock Vina, which were performed in triplicate.

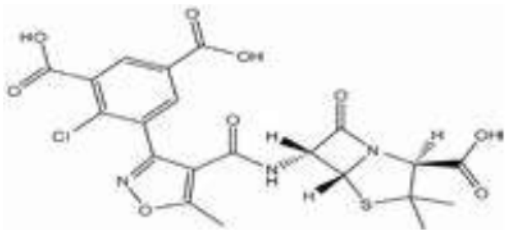
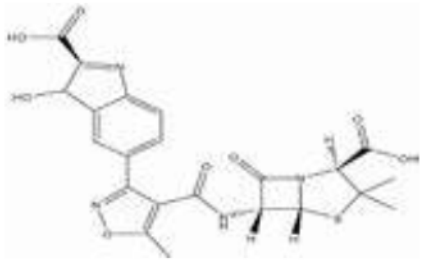
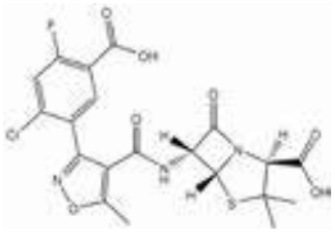
Table 3. Molecular coupling of cloxacillin with the 1FCM receptor of beta-lactamase ampc. **Source:** Own elaboration.

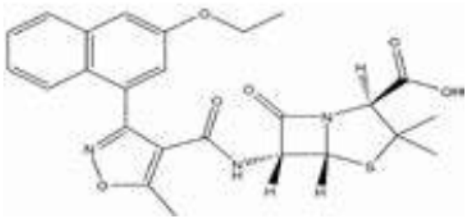
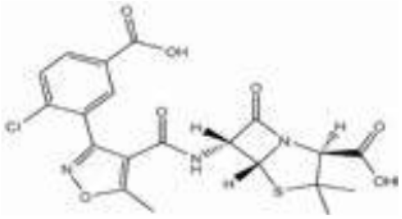
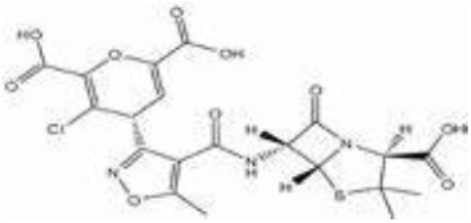
Molécula	Energía (Kcal/ mol)	Estructura química	Aminoácidos	Distancia (Å)
Cloxacilina	-8.0	 **Figura 8.** Cloxacilina. **Fuente:** Elaboración propia.	ASN343 ARG293 ALA291 MET262 GLU147 ARG145 LEU116	1.7 2.7 2.9 2.9 2.7 2.4 3.1

Using the energy obtained from Cloxacillin, 55 modifications were made on its chemical structure. Molecular docking was performed on 55 molecules, of which 6 exceeded the free energy (-8.0 Kcal/mol) of Cloxacillin against the 1FCM receptor. Table 4 shows the free energy of the 6 molecules and their corresponding structures.

Tabla 4. Molecules with higher free energy with respect to Cloxacillin (-8.0kcal/mol). **Source:** Own elaboration

The 6 molecules have been ordered according to their free energy. In addition, the amino acid residues, with which the hydrogen bonds were established, as well as the corresponding distances are shown. The structures in Table 4 were designed by ChemDraw.

Molécula	Energía (Kcal/ mol)	Estructura química	Aminoácidos	Distancia (Å)
1	-9.3		ASN343 GLU147 LEU116	2.3 2.9 1.9
2	-9.2		ASN343 LEU116	2.3 2.8
3	-8.9		ASN343 ALA291 LEU116	1.7 2.9 2.4

4	-8.9		ALA291 GLU147	2.7 2.6
5	-8.7		ASN343 ALA291 GLU147 LEU116	1.8 2.9 3.0 2.4
6	-8.7		ASN343 GLU147 LEU116	3.0 3.0 2.8

In Table 5, the molecules that were able to demonstrate an interaction with at least two amino acids of the lead molecule were evaluated. The toxicological predictions made through the Lazar Toxicity Predictions website are presented below, selecting the evaluation criteria called: Ames test (mutagenicity) and Carcinogenicity in rats and mice.

Tabla 5. Toxicological predictions made in Lazar. **Source:** Lazar Toxicity Predictions

Molécula	Prueba de Ames	Carcinogenicidad (Ratones/ratas)
Cloxacilina	No mutágeno	Negativo
1	No mutágeno	Negativo
2	No mutágeno	Negativo
3	No mutágeno	Negativo
4	No mutágeno	Negativo
5	No mutágeno	Negativo
6	No mutágeno	Negativo

SYNTHESIS PROPOSAL: MOLECULE N°1

Product of the computational phase, it is possible to propose the synthesis of the molecule((2S,5R,6R)-6-[[3-[3-(5-dicarboxy-2-chlorophenyl)-5-methyl-1,2-oxazol-4-carbonyl] amino]-3,3-dimethyl -7-oxo-acid-4-tia-1-zabicyclo [3. 2.0] heptane-2-carboxylic acid), it is noteworthy that, in future research, it may be optimized some steps, reagents with the aim to perform some kind of optimization. Where it was necessary to add two carboxyl groups to the 2-chlorobenzaldehyde, followed by the procedure of Zhonghua (2002).

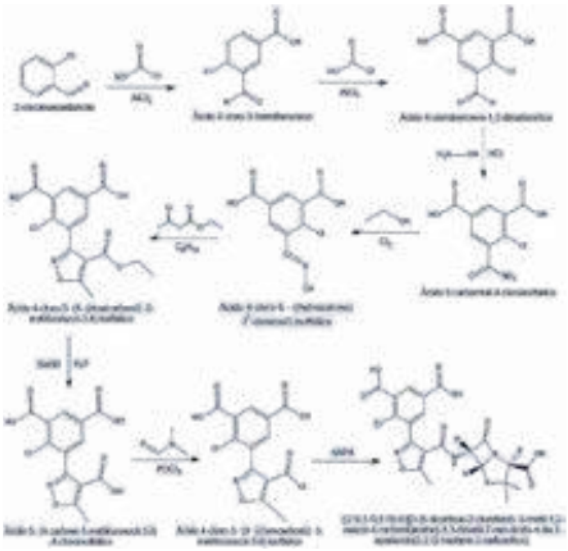


Figure 9. Synthesis of target molecule N°1. **Source:** Own elaboration

RESULTS ANALYSIS

COMPUTATIONAL PHASE

The first criterion to perform the virtual screening was the affinity energy, which is one of the results of the molecular docking and which is specific to the algorithm of the different softwares. It is established that the affinity energy is part of the scoring functions "which are force fields based on molecular mechanical physics that estimate the energy of the pose; a low (negative) energy indicates a stable system and, therefore, a probable binding interaction" (Gaba et al., 2010). (Gaba et al., 2010). From the literature it means that the lower the calculated affinity energy the higher the probability of a ligand-protein interaction. Therefore, by molecular docking the resulting affinity energy of Cloxacillin against the 1FCM receptor is (-8.0 Kcal/mol). We started from this ligand making structural changes to establish a lower free energy. Continuing with this premise, 55 molecules were designed, where only 6 of them (Table 4) achieved a higher probability of binding to the 1FCM receptor than cloxacillin.

The second criterion for molecular docking was the interactions established by the ligand with the amino acids of the protein. The research of Patera et al. (2020) reported that the amino acid GLU147 is part of the binding site or catalytic region of the 1FCM receptor, which is vital in the binding of the ligand to the protein. (Figure 10).

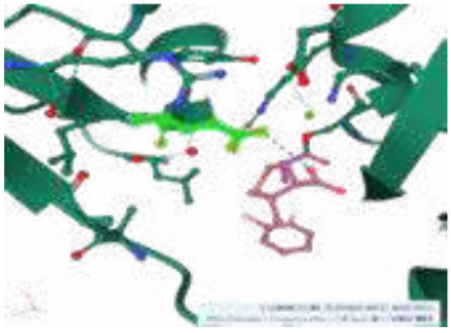


Figure 10. 1FCM receptor binding site. **Source:** Protein Data Bank

The 1FCM beta-lactamase receptor ampc (green) crystallized next to the ligand Cloxacillin CXU (purple). The amino acid (GLU147) labeled light green interacts directly with the ligand and is considered to be the binding site.

Of the 6 molecules raised in Table 4, only 4 showed interactions smaller than 3.0 Å in reference to the amino acid GLU147, this would indicate a higher probability of interaction between ligand and receptor (Fu, Zhao, & Chen, 2018). In view of the interactions found, it is possible to affirm that the amino acid GLU147, is responsible for the anchoring, as observed in Figure 11, this due to the hydrogen bonds with very short distances between the hydroxyl of the carbon of the ligand and with the atoms with available electronic pairs of the amino acid.

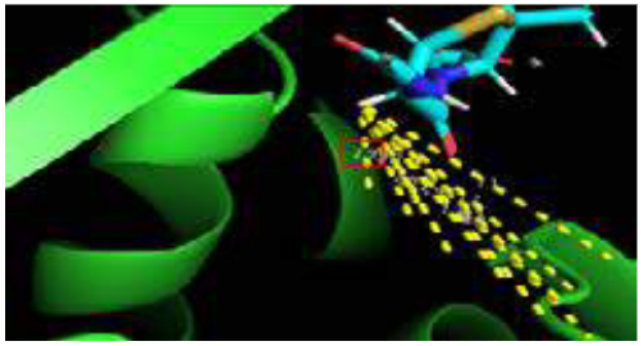


Figure 11. Binding site of the 1FCM receptor with molecule N°1. **Source:** Own elaboration

The 1FCM receptor of beta-lactamase ampc (green), ligand molecule N°1 (blue). Distance in Å of the ligand to GLU147 (red box).

The next screening criterion was the results obtained through the Lazar toxicity website (Table 5). Notably, all 6 molecules advanced in this stage of the screening because they matched or exceeded the toxicological property predictions for Cloxacillin. None of the designed molecules are gene mutagenic, they were measured by the Ames test, which is a simple method for testing the mutagenicity of a compound, suggested by Dr. Ames. Where he

uses several strains of Salmonella typhimurium bacteria that carry mutations in genes involved in histidine synthesis, thus requiring histidine for growth. The variable being tested is the ability of the mutagens to cause a reversion to growth in a medium without histidine. (Bruce et al., 1973).

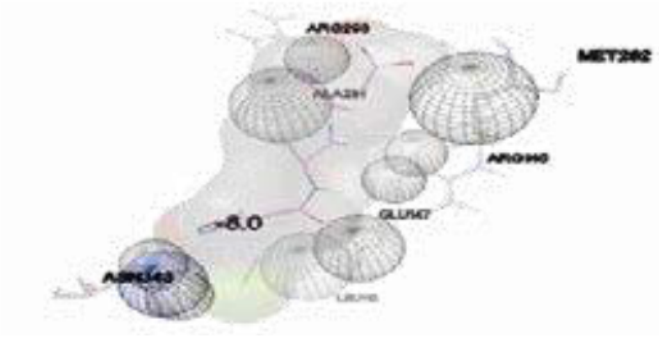


Figure 12. Interactions of the 1FCM receptor with Cloxacillin. **Source:** Own elaboration

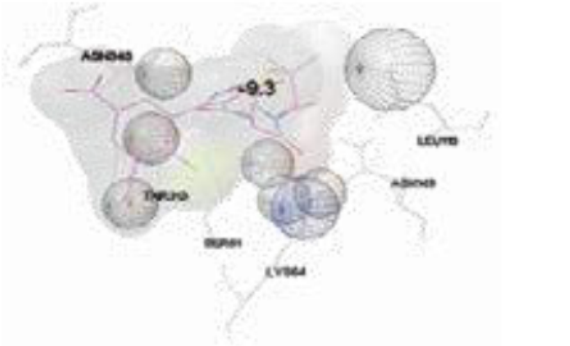


Figure 13. Interactions of the 1FCM receptor with molecule N°1. **Source:** Own elaboration

Figure 12 shows the interactions of Cloxacillin with the amino acids ASN343, ARG293, ALA291, MET262, GLU147, ARG145, LEU116 of the 1FCM receptor. By applying the molecular docking of the 1FCM receptor with molecule N°1 we show the interaction with other amino acids not reported with the Cloxacillin ligand, these are LYS64, ASN149, THR313 and SER61 is the most relevant amino acid, because β-lactamases classified as ampc are enzymes with serines in the active site, and b-lactam antibiotics inhibit transpeptidase and DD-carboxypeptidase activities by acylating the active site serine of PBPs. 13 Alterations in PBPs reduce their binding affinity for b-lactam antibiotics, leading to drug resistance. (Kumar, Anbarasu & Ramaiah,2014).

At this point we have molecule N°1 (Table 4) as a potential b-lactam for the 1FCM receptor of the betalactamase ampc, however, it is valid to clarify that the computational methods have limitations that prevent having total certainty of the metabolic action that these molecules develop in living organisms, it is for this reason that at this point the in-vivo assays would be an important complement to verify the hypotheses that have arisen from this study. Finally, it is important to propose a synthesis for molecule N°1, resulting from the molecular docking technique.

CONCLUSIONS

The design of 55 structures allowed us to propose 6 molecules with an acceptable affinity compared to the leading molecule, which, in this case, was Cloxacillin, as a result of structural modifications made in the region of the chlorinated phenyl group.

The design of Isoxazolyl-penicillins of the 1FCM receptor of the beta-lactamase ampc, which presented an increase in ligand-receptor affinity, was successfully carried out using the molecular docking technique.

As a result of the structural optimization of the lead drug, a lower free energy was evidenced in the proposal of molecule N°1 recorded in Table 4, taking as a starting point the new interactions not reported, of the amino acids LYS64, ASN149, THR313 and SER61 in comparison to cloxacillin.

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ACKNOWLEDGEMENTS

Thanks to Dr. James Guevara for providing the tools to his students and expanding the frontiers of scientific knowledge.