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Docking studies on novel analogs of quinolones against DNA gyrase of *Escherichia coli*

[Estudios de acoplamiento molecular de nuevos análogos de quinolonas a la ADN girasa de *Escherichia coli*]

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Abstract

Context: Bacterial resistance to antibiotics is the inevitable consequence of the use of antimicrobial agents. Thus, quinolones are an important class of antibacterials; these agents generally consist of a 1-subtituted-1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety combined with an aromatic or heteroaromatic ring fused at the 5- and 6-position.

Aims: To determine the binding of quinolones to DNA gyrase of *Escherichia coli*.

Methods: An analysis was performed using an *in silico* approach to determine, by docking calculations and energy descriptors, the conformer of 4-oxo-1,4-dihydroquinoline skeleton that forms the most stable complex with DNA gyrase of *E. coli*.

Results: The complex shows that the pose of the quinolones coincides with the amino acid residues Asp87, Thr88, Arg91 and Met92, which is expected to be critical in the binding of quinolones to DNA gyrase of *E. coli*. A series of quinolones were computationally designed, and the interactions between the quinolones and the amino acid residues of the DNA gyrase were calculated.

Conclusions: Among the designed compounds, compounds 105 and 115 exhibit higher binding energy values and interact with amino acids Asp87, Thr88, Arg91 and Met92.

Keywords: Arguslab; DNA gyrase; docking; *Escherichia coli;* quinolones.

Resumen

Contexto: La resistencia bacteriana a los antibióticos es la consecuencia inevitable del uso de agentes antimicrobianos. Por lo tanto, las quinolonas son una clase importante de antibacterianos; estos agentes generalmente consisten en un resto ácido 1-sustituido-1,4-dihidro-4-oxopiridina-3-carboxílico combinado con un anillo aromático o heteroaromático fusionado en las posiciones 5 y 6.

Objetivos: Determinar la unión de quinolonas a ADN girasa de *Escherichia coli*.

Métodos: Se realizó un análisis utilizando un enfoque *in silico* para determinar, mediante cálculos de unión y descriptores de energía, el confórmero del esqueleto de 4-oxo-1,4-dihidroquinolina que forma el complejo más estable con la ADN girasa de *E. coli*.

Resultados: El complejo muestra que la postura de las quinolonas coincide con los residuos de aminoácidos Asp87, Thr88, Arg91 y Met92, que se espera que sean críticos en la unión de quinolonas a ADN girasa de *E. coli*. Se diseñó computacionalmente una serie de quinolonas, y se calcularon las interacciones entre las quinolonas y los residuos de aminoácidos de la ADN girasa.

Conclusiones: Entre los compuestos diseñados, los compuestos 105 y 115 exhiben valores de energía de unión más elevados e interactúan con los aminoácidos Asp87, Thr88, Arg91 y Met92.

Palabras Clave: acoplamiento molecular; ADN girasa; Arguslab; *Escherichia coli*; quinolonas.

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INTRODUCTION

Despite modern antibiotics, transmissible diseases are responsible for nearly one third of human deaths worldwide. Bacterial resistance to antibiotics is the inevitable consequence of the use of antimicrobial agents. Thus, quinolones are an important class of antibacterial; these agents generally consist of a 1-subtituted-1,4-dihydro-4-oxo-pyridine-3-carboxylic acid moiety combined with an aromatic or heteroaromatic ring fused at the 5- and 6-positions (Wube et al., 2012).

Quinolones are highly effective antimicrobial drugs that target bacterial DNA gyrase and type II topoisomerase. Unfortunately, resistance to this class of drugs has become increasingly prevalent and is usually attributable to mutations in the DNA gyrase or a decrease in intracellular drug levels caused by changes in the membrane permeability or the overexpression of drug efflux pumps (Chen et al., 2013).

The level of drug resistance varies depending on the mutations and bacterial species. Quinolone inhibition of DNA gyrase occurs through the formation of a stable ternary complex between DNA gyrase, DNA and the quinolone molecule that blocks the progression of DNA replications (Lupala et al., 2013).

The computational strategies for structure-based drug discovery offer a valuable alternative to the costly and time-consuming process of random screening (Salgado-Moran et al., 2013). In this sense, docking calculations have been applied in pharmaceutical research for nearly two decades. Virtual screening on protein templates provides an opportunity for the identification of active compounds (Perez et al., 2014).

Considering these points, several quinolones with different substitutions were computationally designed. In this study, several quinolones as targets for antibiotics based on the molecular docking between new inhibitors and DNA gyrase using Arguslab were designed (Hafeez et al., 2013; Tangyuenyongwatana and Jongkon, 2016).

In this study, antibiotic design was conducted with the modifications of hydrophilic and lipophilic characters of the molecules. The theoretically calculated binding affinities and binding positions of nalidixic acid, oxolinic acid, pipemidic acid, ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, rufloxacin, and sitafloxacin, which are commonly used antibiotics (Fig. 1) were compared with the new quinolones (supplementary data) (Lupala et al., 2013; Perez et al., 2014).

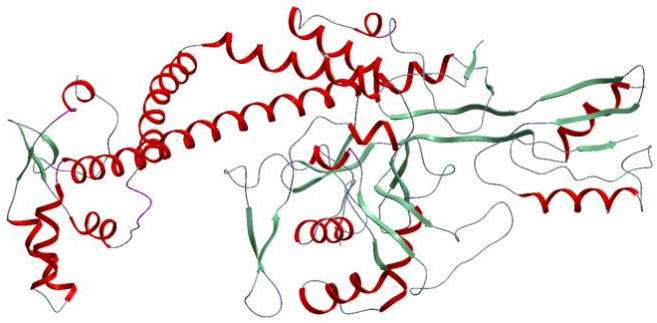

Figure 1. 3D representation of DNA gyrase.

MATERIAL AND METHODS

The docking procedure is conceivable as a complicated optimization or an exhaustive search that involves many degrees of freedom. Hence, the development of efficient docking algorithms would be of vital importance for the design of new drugs (Zarate et al., 2016). The ultimate goal is to find the optimal ligand/protein configurations as well as to consistently predict their binding free energy without relying on formal statistical mechanics approaches. To computationally accomplish the key objective within a reasonable time framework, an empirical scoring function (AScore) and a docking engine (ShapeDock) were developed in the ArgusLab program (Oda and Takahashi, 2009).

The AScore is based on the deconvolution of the total protein–ligand binding free energy into different components:

$$\Delta G_{binding} = \Delta G_{vdW} + \Delta G_{hydrophobic} + \Delta G_{H\text{-}bond} + \Delta G_{H\text{-}bond(chg)} + \Delta G_{deformation} + \Delta G^{\circ}$$

The dissected terms account for the van der Waals interaction between the ligand and the protein (ΔG_{vdW}), the hydrophobic effect ($\Delta G_{hydrophobic}$), the hydrogen bonding between the ligand and the protein ($\Delta G_{hydrophobic}$), the hydrogen bonding that involves the charged donor and/or acceptor groups ($\Delta G_{H\text{-}bond(chg)}$), the deformation effect ($\Delta G_{deformation}$), and the effects of the translational and rotational entropy loss in the bidding process ($\Delta G°$).

The ShapeDock engine approximates a complicated search problem. Flexible ligand docking is available by describing the ligand as torsion tree. In this torsion tree approach, groups of bonded atoms that do not have rotatable bonds are nodes, while torsions are connections between the nodes. The topology of a torsion tree is a determinative factor that influences efficient docking. A balanced tree with a large central node is presumably the favorite case. Two grids overlay the binding site and distinguish grid points with respect to the free volume of the binding site. A fine grid is used to examine whether the atoms at an artificial position are inside or outside the binding site, while a coarse grid is used to establish the search points inside the binding site. A set of energetically favorable rotations is generated by placing the root node of a ligand on a search point in the binding site. The torsion search of the artificial positions is defined by constructing the torsions in a breadth-first order for each rotation. Of the surviving artificial position candidates, the *N*-lowest energy poses make the final set of positions to undergo coarse minimization, re-clustering and ranking. The AScore/ShapeDock docking protocol is rapid and reproducible and formally explores all of the energy minima (Tangyuenyongwatana and Jongkon, 2016).

Candidate optimized conformations of MP3 semiempirical calculations (Hafeez et al., 2013) quinolones bound to their target structures, the DNA gyrase complex (Chen et al., 2013) . Proposed were using Arguslab. Here, docking was conducted with a set of 115 4-oxo-1,4-dihydroquinoline skeleton (see supplementary data). They were defined to contain the potential binding pocket between Ala67 and Gln106 (Fig. 2).

RESULTS AND DISCUSSION

The docking results between the DNA gyrase receptor and designed 4-oxo-1,4-dihydroquinoline skeleton are reported in Fig. 3.

The standard antimicrobial agents nalidixic acid, oxolinic acid, pipemidic acid, ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, rufloxacin, and sitafloxacin, on docking with DNA gyrase produce energy values of -7.9880, -6.9640, -7.7810, -6.4840, -7.5950, -7.2860, -7.7860, -7.2980, -7.1710 and -8.1440 Kcal/mol, respectively.

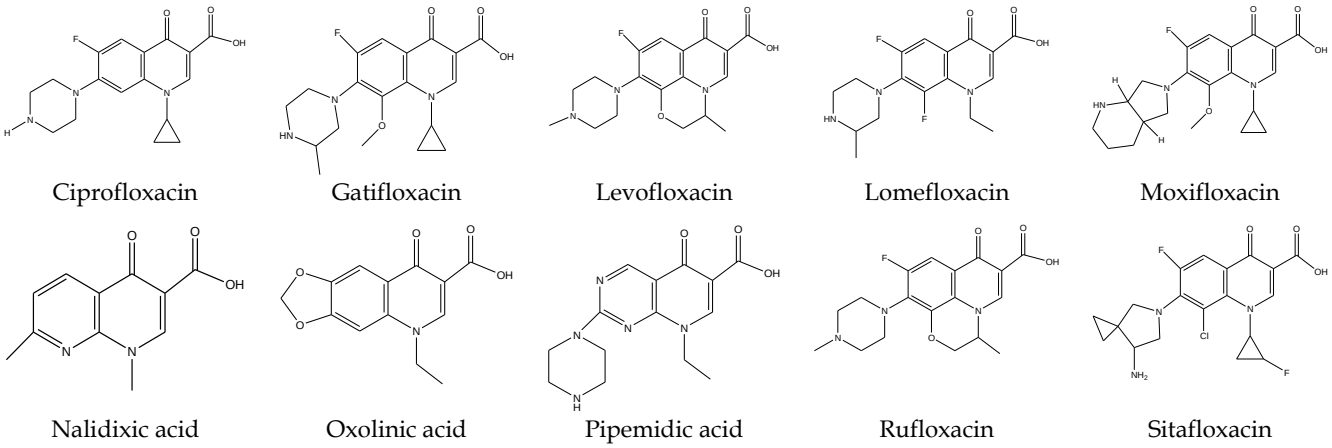

Figure 2. Structures of the quinolones used in the docking calculations.

To recognize the hypothetical binding mode and interaction of quinolones with crucial amino acid residues in the DNA gyrase complex, a molecular docking study was conducted using the crystal structure of DNA gyrase. The percentage frequency of the interaction of quinolones with different amino acids (a maximum distance is 20 Å) is as follows: 20% Ala67, 10% Lys76, 20% Tyr77, 30% His78, 10% Pro79, 30% His80, 20% Gly81, 40% Asp82, 50% Ser83, 50% Ala84, 40% Val85, 30% Tyr86, 100% Asp87, 80% Thr88, 60% Ile89, 70% Val90, 80% Arg91, 70% Met92, 50% Ser97, 50% Leu98, 20% Arg99, 20% Met101, and 60% Leu102.

For the most stable conformer of the quinolones (Fig. 4), its crucial amino acid residues (Asp87, Thr88, Arg91 and Met92) are at the following distances (from the C_α of the amino acid to the C_1 of the quinolones): 8.068 Å, 9.7170 Å, 8.5810 Å and 7.4230 Å, respectively, for nalidixic acid; 10.0358 Å, 6.9688 Å, 5.9936 Å and 4.7015 Å, respectively, for oxolinic acid; 10.6030 Å, 7.8760 Å, 6.9830 Å and 6.7880 Å, respectively, for pipemidic acid; 11.3730 Å, 8.2780 Å, 7.990 and 7.1580 Å, respectively, for ciprofloxacin; 8.2100 Å, 6.5070 Å, 10.9330 Å and 11.9860 Å, respectively, for gatifloxacin; 7.1750 Å, 5.3080 Å, 6.8080 Å and 8.4380 Å, respectively, for levofloxacin; and 11.6980 Å, 8.2490 Å, 7.9380 Å and 5.5570 Å, respectively, for rufloxacin.

DNA gyrase is a target of quinolone. However, the molecular details of the quinolone-gyrase interaction are not clear. Quinolone resistance mutations frequently occur at the residues Ser83 and Asp87 of the GyrA subunit; thus, it is possible that these residues are involved in drug binding. Moreover, Asp87 might be critical in the binding of fluoroquinolones (Wu et al., 2013).

Efforts to develop novel bacterial topoisomerase inhibitors that aim to overcome quinolone resistance have led to the identification of new binding sites, which suggests that in addition to the cleavage site-specific targeting strategy, alternative drug binding modes for promoting cell death should also be explored (Banoth et al., 2017).

These results allow us to explain the experimental results because Asp87 is the amino acid that has the highest frequency of interaction with the quinolones and has been found to be critical in the binding of these drugs (see Fig. 3).

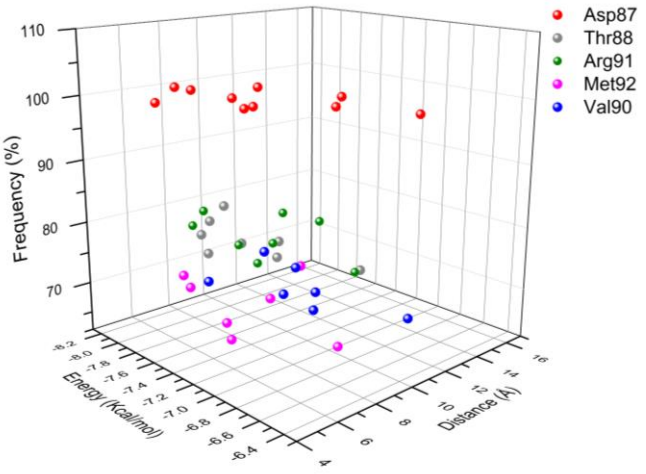

Figure 3. Graphic linking energy, distances from the C_α of the amino acid to the C_1 of the quinolones and the percentage frequency of interaction of the quinolones with different amino acids.

Interactions between the quinolones and selected amino acids were observed; this interaction is achieved by high affinity groups forming hydrogen bonds on the carboxyl group (C=O) and amine group (NH_2) of the amino acids [S_1] which, in theory, could possess an inhibitory action on the enzyme *E. coli* gyrase. Of the new 115 quinolone structures (see supplementary data) that have been evaluated, considering the energy criteria, distance and type of amino acid, there were two new structures that could present an inhibitory action on the gyrase enzyme. These structures are numbers 105 and 115, which had an energy interaction of -4.1122 and -5.4234, respectively; furthermore, they showed an interaction with the amino acids Asp87, Thr88, Arg91 and Met92 with distances of 10.7745 Å, 7.4566 Å, 7.0545 Å and 5.3309 Å, respectively, for structure 105, and 10.7618, 7.5107, 6.8671, and 5.1444, respectively, for structure 115. These new compounds could be potential antibacterial quinolones.

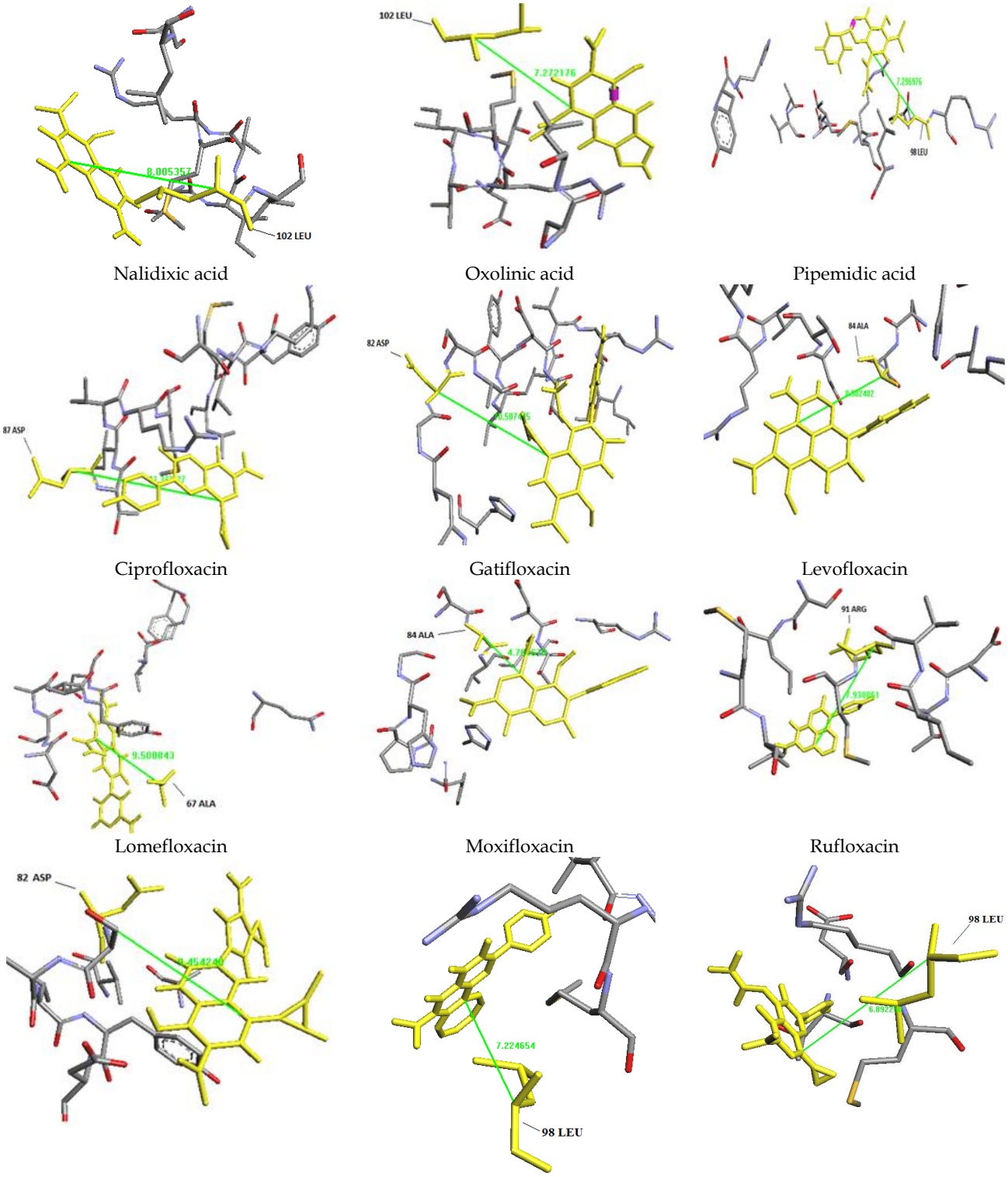

Figure 4. Structure and the distances from the C_α of the amino acid to the C_1 of the quinolones.

CONCLUSIONS

DNA gyrase, which is an essential target for novel drug design, was docked with the standard antimicrobial agents nalidixic acid, oxolinic acid, pipemidic acid, ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, rufloxacin, and sitafloxacin. When the designed quinolone analogs were docked against the DNA gyrase, the results indicate that the 105 and 115 compounds can be potent antibacterial agents. Analysis of the binding models suggests that the amino acid residues Asp87, Thr88, Arg91 and Met92 are critical in the binding of quinolones to the DNA gyrase of *E. coli*.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION:

Contribution	Davila C	Llach L	Salgado-Moran G	Ramirez-Tagle R
Concepts or ideas	x			
Design	x			
Definition of intellectual content	x			
Literature search	x			
Experimental studies	x			
Data acquisition	x			
Data analysis	x	x		
Statistical analysis		x		
Manuscript preparation			x	x
Manuscript editing				x
Manuscript review	x	x	x	x

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