Insight into DNA Gyrase Inhibition Using Quantitative Structure-Activity Relationships and Structure-Based Drug Design Approaches.

Aperçu de l'inhibition de l'ADN Gyrase à l'aide de relations quantitatives structure-activité et d'approches de conception de médicaments fondées sur la structure.

Matmour Derouicha[1,2,3,4], MeradYassine[2], Toumi Houari[3], Yasri Aziz[4]

1. Therapeutic Chemistry Laboratory, Department of Pharmacy, University of Sidi Bel-Abbes, 22000, Algeria.

2. Central Laboratory, University Hospital Center of Sidi Bel-Abbes, 22000, Algeria.

3. Research in Pharmaceutical Development Laboratory, Pharmacovigilance Department, University Hospital Center 1st November, University of Oran, 31000, Algeria.

4. General Directorate of Scientific Research and Technological Development (DGRSDT), Algiers, Algeria.

Corresponding author:
Derouicha MATMOUR
drmatmour24@hotmail.fr

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ABSTRACT

The emergence of certain bacterial strains resistant to antibiotics has become a major public health problem, hence the need to develop new antibiotic molecules. Bacterial DNA gyrase, a type II DNA topoisomerase found in all bacteria is a proven target for antibacterial chemotherapy. Our objective is designing novel DNA Gyrase inhibitors using Quantitative Structure-Activity Relationships and Structure-Based Drug Design Approaches. We used bioinformatics tools, biological databases like PDB (Protein DataBank), Binding Databases and software's like, MarvinView, MarvinSketch, PyMOL, AutoDockTools-1.5.6. The 3D crystal structure of DNA Gyrase was extracted from PDB (code: 4DHU) and we characterized the active site. Using 83 compounds with different Ki were extracted from Binding Databases, we built and validated a QSAR Model (PLS regression) and we confirmed the interesting correlation between predicted and experimental Ki (R^2=0,843). Four molecules were chosen to be docked into DNA Gyrase active site using AutoDockTools. The compound which has the low Ki (Benzimidazole urea analogue 5) shows more binding affinity with score value of ΔG= -8,6 kcal/mol than the others compounds. So, it would be very interesting to synthesis this promising compound and to test in vitro its antibacterial properties.

Keywords: DNA gyrase, Inhibitors, QSAR, SBDD, Docking.

RÉSUMÉ

L'émergence de certaines souches bactériennes résistantes aux antibiotiques est devenue un problème majeur de santé publique, d'où la nécessité de développer de nouvelles molécules antibiotiques. L'ADN gyrase bactérienne, une ADN topoisomérase de type II présente chez toutes les bactéries, est une cible avérée pour la chimiothérapie antibactérienne. Notre objectif est de concevoir de nouveaux inhibiteurs de l'ADN gyrase en utilisant des relations quantitatives structure-activité et des approches de conception de médicaments basées sur la structure. Nous avons utilisé des outils bioinformatiques, des bases de données biologiques telles que PDB (Protein DataBank), des bases de données de liaison et des logiciels tels que MarvinView, MarvinSketch, PyMOL, AutoDockTools-1.5.6. La structure cristalline 3D de l'ADN Gyrase a été extraite de la PDB (code : 4DHU) et nous avons caractérisé le site actif. En utilisant 83 composés avec différents Ki extraits des bases de données de liaison, nous avons construit et validé un modèle QSAR (régression PLS) et nous avons confirmé la corrélation intéressante entre le Ki prédit et expérimental (R2=0,843). Quatre molécules ont été choisies pour être arrimées au site actif de l'ADN Gyrase en utilisant AutoDockTools. Le composé qui a le Ki le plus faible (Benzimidazole urée analogue 5) montre plus d'affinité de liaison avec une valeur de score de ΔG= -8,6 kcal/mol que les autres composés. Il serait donc très intéressant de synthétiser ce composé prometteur et de tester in vitro ses propriétés antibactériennes.

Mots clés : ADN gyrase, Inhibiteurs, QSAR, SBDD, Docking.

INTRODUCTION

The strategy of Structure-Based Drug Design (SBDD) has accelerated many drugs discovery projects and has already yielded several promising antibacterial leads acting towards different targets, including DNA gyrase **[1].** The Quantitative Structure-Activity Relationship (QSAR) techniques have been widely used for predicting a broad spectrum of biological activities **[1]**. Nowadays, the emergence of certain bacterial strains resistant to antibiotics has become a major public health problem, hence the need to develop new antibiotic molecules. Bacterial DNA gyrase, a type II DNA topoisomerase found in all bacteria is a proven target for antibacterial chemotherapy **[2]**.

It's unique in catalyzing the negative supercoiling of DNA and is essential for efficient DNA replication, transcription, and recombination **[2]**.

Although inhibition of gyrase by fluoroquinolones is an effective therapeutic approach, growing resistance to this class of drugs has become a serious health concern and there is still need for new classes of antibacterial agents **[3]**. In addition, quinolones can cause certain adverse effects, such as CNS effects, phototoxicity, tendonitis, hypoglycemia, and serious cardiac dysrhythmias **[4]**.

In this study, we identified new antibiotic drug candidates that can inhibit the DNA Gyrase using QSAR and SBDD approaches.

MATERIALS AND METHODS

This study used two drug design approaches, 2D-QSAR and SBDD.

1. 2D-QSAR Approach

MOE software **[5]** was used for models' construction and 1121compounds candidates were extracted from Binding Database **[6]** but except 83 compounds were selected because of their 3D structure and experimental biological activities Ki value wich converted to pKi. The model's quality was evaluated using the statistical parameters (correlation coefficient 'R', determination coefficient 'R^2', and Root Mean Square Error 'RMSE') **[7]**.

2. SBDD Approach

The 3D crystal structure of DNA Gyrase was extracted from PDB (code: 4DHU) and we characterized the active site, the dimensions grid-box were set at (X=30.69A°, Y= 4.97A° and Z=6.12A°). Four molecules were selected to study their interactions with DNA Gyrase by SBDD approach using AutoDock vina software **[8]** to perform the molecular docking and PyMOL software **[9]** to interpret the different interactions.

RESULTS AND DISCUSSION

1. 2D-QSAR Approach

Figure 1 showed linear correlation plots of 2D-QSAR between the observed values versus predicted values of DNA Gyrase inhibitors. The correlation regression analysis showed a linear relationship with RMSE = 0.2369, R = 0.9178 and R^2 = 0.8425. The correlation coefficient between observed and predicted values of test set compounds was 0,67.

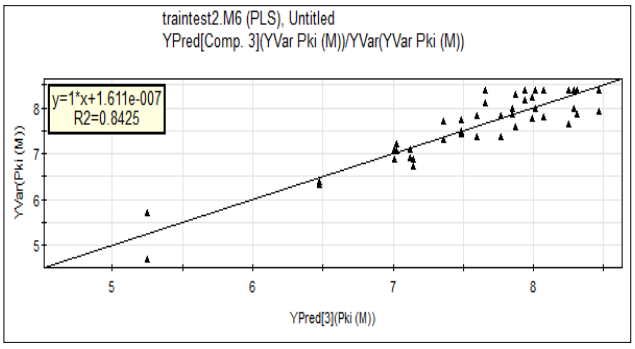

Figure 1. Linear correlation plots of 2D-QSAR (Observed values versus predicted values)

Figure 2 showed the importance of each variable (descriptor) in the model with its confidence interval and we have also verified that the model is valid with R2 = 0.14 and Q2 = - 0.35 **(Figure 3)**.

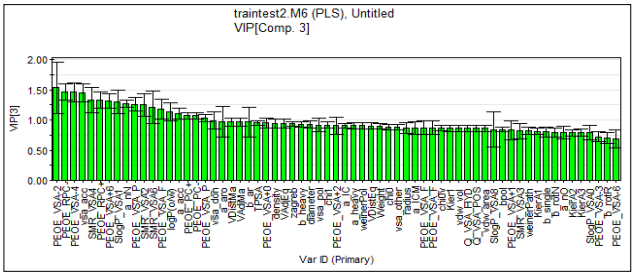

Figure 2. Variables Importance in model.

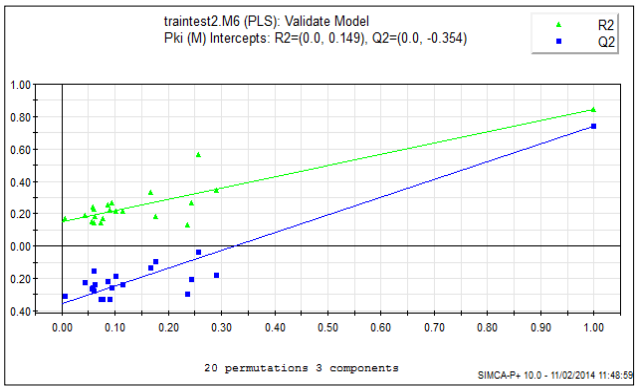

Figure 3. Model validation.

2. SBDD Approach

Four molecules with different Ki (low, medium and high) were chosen to be docked into the DNA Gyrase active site using the AutoDockTools-1.5.6.

Figure 4 shows the 3D crystal structure of DNA gyrase extracted from PDB (Code: 4DHU). **Figure 5** shows the selected target site of DNA gyrase, the white spheres represent where the molecular docking was focused.

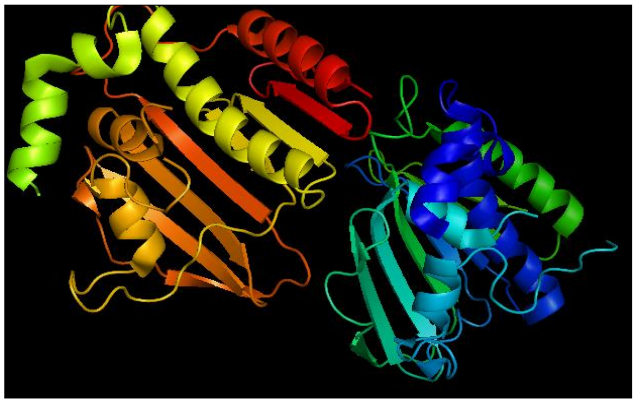

Figure 4. 3D crystal structure of DNA gyrase

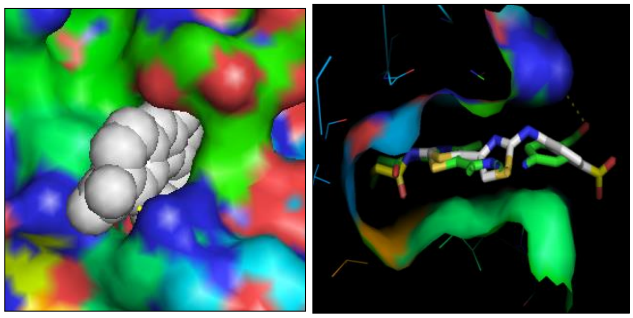

Figure 5. Selected target site of DNA gyrase

Analysis of interaction between DNA Gyrase and the different ligands

The different compounds were successfully docked into the binding site as is shown in **Figure 6**. The Four compounds occupied the common binding site of the DNA Gyrase. The binding energy of DNA Gyrase_21366124 Compound, DNA Gyrase_11624303 Compound, DNA Gyrase_18008864 Compound and DNA Gyrase_249713303 Compound was respectively: -8.9 Kcal /mol, -7.8 Kcal /mol, -8.6 Kcal /mol and -6.8 Kcal /mol.

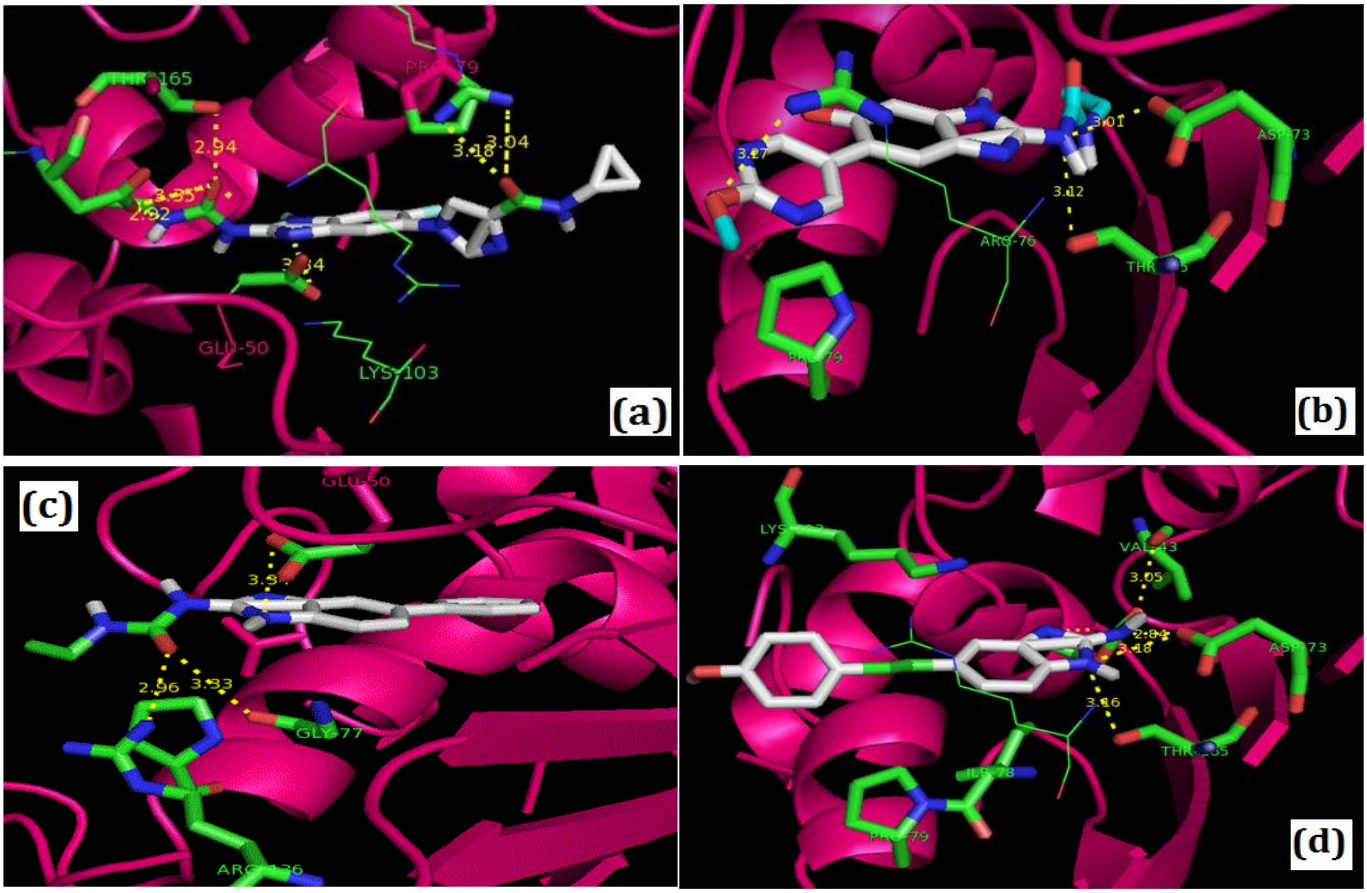

Figure 6. Panel (a): Interaction between 21366124 compound and DNA Gyrase.
Panel (b): Interaction between 11624303 compound and DNA Gyrase.
Panel (c): Interaction between 18008864 compound and DNA Gyrase.
Panel (c): Interaction between 249713303 compound and DNA Gyrase.

Table I. Characteristics of docked compounds

Docked Compound CID	Ki (nM)	N° of Chosen configuration	ΔG (kcal/mol)
21366124	4	05	-8,9
11624303	15	02	-7,8
18008864	470	01	-8,6
249713303	600	04	-6,8

Table I shows the characteristics of docked compounds and **Table II** represent the binding Energy, the hydrogen bond distances of key residues that interact with inhibitors and the Hydrophobic pockets.

Figures 6_Panel (a) shows that the 21366124 Compound formed hydrogen bonds with the residues: Arg136, Thr165 and Asp73 whose lengths: 3.04 A°, 2.94 A° and 2.92 A°. Three Hydrophobic pockets were formed and interaction pi Stacking between the imidazole nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

Figures 6_Panel (b) shows that the 11624303 Compound formed hydrogen bonds with the residues: Asp73 and Thr165 whose lengths: 3.01 A° and 3.12 A°. Three Hydrophobic pockets were formed and interaction pi Stacking between the pyrimidine nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

Figures 6_Panel (c) shows that the 18008864 Compound formed hydrogen bonds with the residues: Arg166 and Glu50 whose lengths: 2.96 A° and 3.34 A°. One Hydrophobic pockets was formed and interaction pi Stacking between the imidazole nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

Figures 6_Panel (d) shows that the 249713303 Compound formed hydrogen bonds with the residues: Asp166 and Val43 whose lengths: 2.84 A° and 3.05 A°. Three Hydrophobic pockets were formed and interaction pi Stacking between the Benzene nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

We have studied the interaction between DNA Gyrase and the four compounds using QSAR approach and molecular docking to explain the binding mechanism. The 21366124 Compound with Ki: 4 nM formed three hydrogen bonds with the residues: Arg136, Thr165 and Asp73 whose lengths: 3.04 A°, 2.94 A° and 2.92 A°, three hydrophobic pockets and interaction pi Stacking between the imidazole nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

The 11624303 Compound with Ki: 15 nM formed tow hydrogen bonds with the residues: Asp73 and Thr165 whose lengths: 3.01 A° and 3.12 A°, three hydrophobic pockets and interaction pi Stacking between the pyrimidine nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

The 18008864 Compound with Ki: 470 nM formed tow hydrogen bonds with the residues: Arg166 and Glu50 whose lengths: 2.96 A° and 3.34 A°, one hydrophobic pocket and interaction pi Stacking between the imidazole nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

The 249713303 Compound with Ki: 600 nM formed tow hydrogen bonds with the residues: Asp166 and Val43 whose lengths: 2.84 A° and 3.05 A°, three hydrophobic pockets and interaction pi Stacking between the Benzene nucleus of ligand and pyrrolidine nucleus of L-proline amino acid.

We note that the compound with the weakest Ki is more affine and it has more interactions than the others.

CONCLUSION

The 2D-QSAR and SBDD studies revealed that the 21366124 Compound (benzimidazole urea analogue 5) which has the low Ki shows more binding affinity with score value of ΔG = -8,6 kcal/mol than the other compounds with a high Ki. So, it would be very interesting to synthesis this promising compound and to test in vitro its antibacterial properties **(figure 7).**

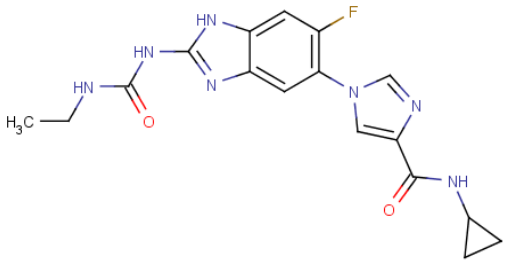

Figure 7. Promising compound

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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