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COMPUTER AIDED DISCOVERY OF CIPROFLOXACIN ANALOGUE ON DNA GYRASE AS ANTIMICROBIAL AGENTS

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ABSTRACT

A series of Fluoroquinolones containing benzimidazole compounds were computationally designed and optimized with the HEX to investigate the interactions between the target compounds and the amino acid residues of the DNA gyrase enzyme. These compounds docked into the active site of DNA gyrase (PDB code, 3G75) using Hex docking tools software which showed good affinity for the enzyme when compared with the binging energies of standard drugs ciprofloxacin (-204.93). Among all the designed compounds, the compound 3 shows more binding energy values (-292.51). Further we planned to synthesis these benzimidazole derivatives and screen for *in-vitro* anti bacterial effect on different micro organisms.

INTRODUCTION

Fluoroquinolones had become the most commonly prescribed class of antibiotics. Fluoroquinolones have been clinically successful and are used to treat bacterial infections in both community, hospital settings. Quinolones target bacterial type II topoisomerases, generally DNA gyrase in Gram-negative bacteria and DNA topoisomerase IV in Gram-positive bacteria. [1-5].

Resistance to ciprofloxacin and other fluoroquinolones may evolve rapidly, even during a course of treatment. Numerous pathogens, including *Staphylococcus aureus*, e*nterococco,* and *Streptococcus pyogenes* now exhibit resistance worldwide.

The most intensive structural variation has been carried out on amines at the 7-position, partially due to the ease of their introduction through a nucleophilic aromatic-substitution reaction on the corresponding halide. Piperazine, aminopyrrolidine and their substituted derivatives have been the most successfully employed side chains, as evidenced by the compounds currently available in the market. Originally, the newer fluoroquinolones arose with the development of 7-piperazinyl quinolones, such as ciprofloxacin and norfloxacin. Recently, as part of an ongoing program to find potent and broad-spectrum antibacterial agents that display strong Gram-positive activity [5-7], the authors have focused their present attention on modification of the C-7 basic group of the quinolone. Therefore, present strategy to achieve a better antimicrobial profile has focused on introducing new functionality on the piperazine ring.

As many number of benzimidazole derivatives are reported as potent anti microbial agents, we have planned to introduce various 2-subtituted benzimidazole at C-7 piperazine of the quinolones to produce better anti microbial agents and then docked in to the target of Fluoroquinolones using HEX software.

MATERIALS AND METHODS

For our present study we used bioinformatics tools, biological databases like PDB (Protein Data Bank) and software's like Hex, ACD ChemSketch. Hex is an Interactive Molecular Graphics Program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. Hex can also calculate Protein-Ligand Docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes [8]. It uses Spherical Polar Fourier (SPF) correlations to accelerate the calculations and its one of the few docking programs which has built in graphics to view the result [9].

The PDB (Protein Data Bank) is the single world wide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) [10]. It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc. RASMOL [Raster Display of Molecules] is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes.

METHODOLOGY

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. Computer – Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug – receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases [11]. The structure of DNA gyrase carrier protein synthase which is an essential target for novel antibacterial drug design was retrievedfrom PDB.

Using Chemsketch the structures of these drugs were sketched. The docking analysis of these compounds with 3G75 was carried by using HEX docking software.

Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme DNA gyrase receptor fit together and dock to each other well. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of drug and receptor complex was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations.

The parameters used in HEX for the docking process were

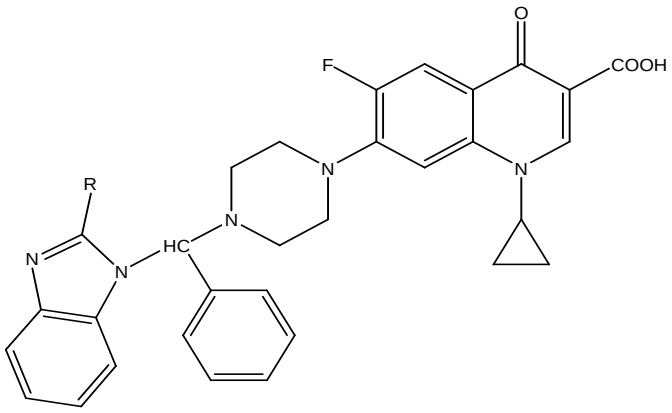
- Correlation type – Shape only
- FFT Mode – 3D fast lite
- Grid Dimension – 0.6
- Receptor range – 180
- Ligand Range – 180
- Twist range – 360
- Distance Range – 40

The drug and its analogues were docked with the receptor using the above parameters.

RESULTS AND DISCUSSION

Docking results between DNA gyrase (3G75) receptor and designed flouroquinalones derivatives containing N-substituted piperazinyl benzimidazoles are reported in Table 1.

TABLE 1: Docking Results of 3G75 enzyme with flouroquinalones derivatives containing N-substituted piperazinyl quinolones



COMPOUND DOCKED	R	E-VALUE
1	H	-252.15
2	$-CH_3$	-256.97
3	$-CH_2C_6H_5$	-272.07
4	-CH=CH- C_6H_5	-285.40
5	**$-C_6H_4(OH)$**	**-292.51**
6	-CH(OH)CH(OH)-COOH	-266.15
7	$-CH_2-CH_2-COOH$	-278.95
8	$-CH_2-CH_3$	-268.52
9	$-CH_2SH$	-256.91
10	$-C_6H_4(NH_2)$	-255.47
11	Ciprofloxacin	-204.93

Based on the literature it has been shown clearly that flouroquinolones containing N-substituted piperazinyl quinolones which can be a potent anti bacterial agent, have been used to target DNA gyrase. The standard antimicrobial agent ciprofloxacin on docking with DNA gyrase produce energy value of -204.93. The energy values were calculated using Hex. It was observed using

RasMol that among all the designed compounds, the compound 5 containing o-hydroxy phenyl group at 2nd position of benzimidazole with piperazinyl quinolones is showing better binding nature, which resulted in a decrease in the energy value.

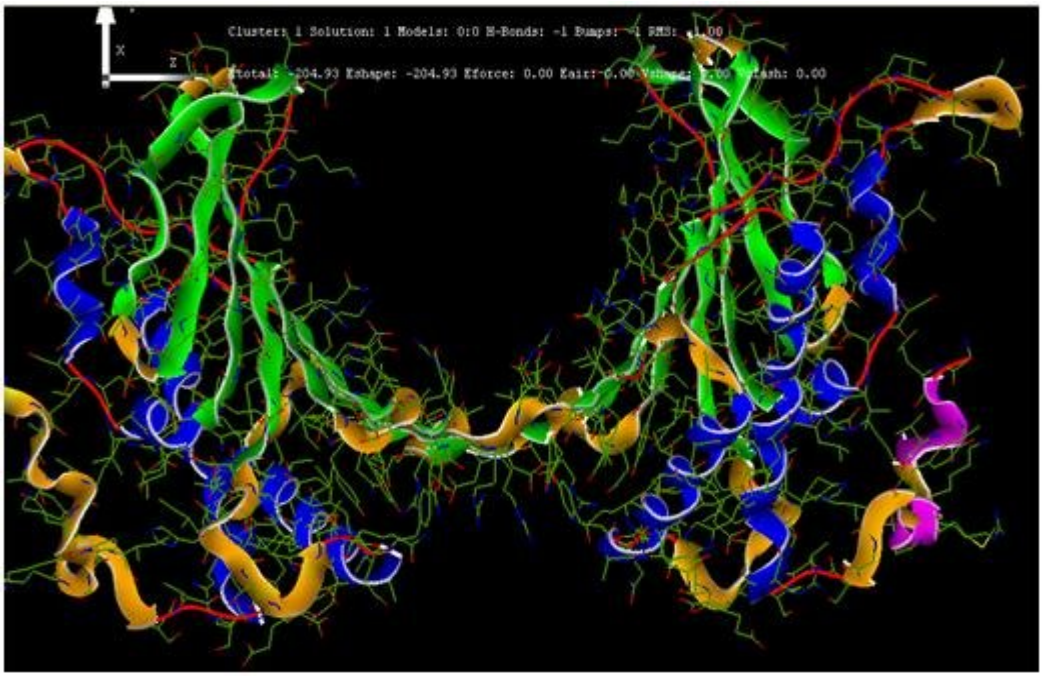


Figure 1: Interaction and binding energy of Ciprofloxacin with DNA Gyrase (3G75)

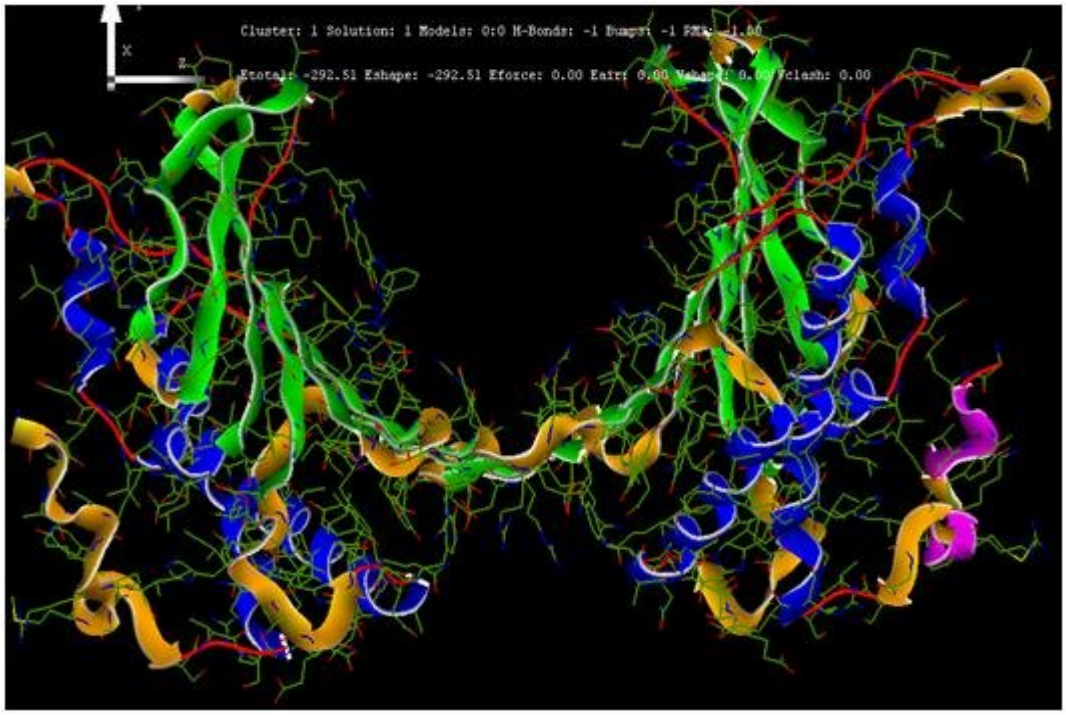


Figure 2: Interaction and binding energy of compound 5 with DNA Gyrase(3G75)

This particular compound showed a decreased in energy values (-292.51) (Figure 2) which means it was more compatible with the receptor than the standard and other designed benzimidazole containing N-substituted piperazinyl quinolones.

CONCLUSION

When the DNA gyrase receptor which is an essential target for novel antibacterial drug design was docked with ciprofloxacin and the energy values obtained is -204.93. When the designed ciprofloxacin analogues containing benzimidazole were docked against the same receptor, the energy values (-292.51) are grater than the standards. So it can be concluded that the designed compounds can be potent anti bacterial agent. In future research work we planned to synthesis these benzimidazole derivatives and screen for their *in-vitro* anti bacterial activity.

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