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In-silico approach: docking study of novel Schiff base congeners of pyrimidine nucleus

Abstract

Pyrimidine nucleus has a wide spectrum use in medicinal chemistry. Based on structure activity relationship of pyrimidine nucleus we are going to synthesize 4-amino-2-methyl-6-phenylpyrimidine-5-carbonitrile derivatives. In this structure one primary amine group is free at 4th position. Schiff base has excellent antibacterial, antifungal, antiviral activities due to presence of azomethine (CH=N) group. Schiff base compounds have extensive applications in various fields such as analytical, inorganic, organic, and biological fields. They have excellent pharmacology application prospects in the modern era and are widely used in the pharmaceutical industry. In the present work in silico docking studies of five Schiff base compounds were carried out against Staphylococcus aureus.

Keywords: schiff base, antimicrobial activity, In-silico study

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Introduction

The research in the field of therapeutics is of great importance for the improvement of the quality of human life and for reducing human diseases. A vast number of diseases is due to pathogenic organisms. Pathogens are microorganisms that are harmful to the human body. Bacteria, viruses, fungus, prion, protozoan, viroid, etc. are the different types of pathogens. Microbial infections are drastically increased in living beings due to multidrug-resistant microorganisms even though the human body can defend against potential pathogens.[1–3] *S. aureus* is one of such multi-drug-resistant microorganisms.

Because of their biological functions, pyrimidines and their oxo byproducts are six-membered heterocyclic compounds of significance for medicinal chemistry. These are similar to nucleic acids, as they are pretty much alike in structure to the pyrimidine bases. Maybe as an antitumor, antiviral, hypotensive, hypoglycemic, and anti-inflammatory agents, substances with such heterocycles in their structure have been documented because of this structural similarity.[4–8]

Multicomponent reactions (MCRs) are one-pot synthetic processes that originate with the mixing of three or more reagents, but react in series. In general, these reactions are driven by an irreversible phase which, in favour of the final product, precedes balance. Here the proposed molecules can be synthesized by microwave (green approach of synthesis) assisted method with good yield.

Brief attention on pyrimidine nucleus

Pyrimidines are one of the fascinating heterocyclic compounds due to their vast range of biological activities in recent years. These compounds are of considerable importance because they represent an important class of natural and non-natural materials, many of which exhibit biological activities and therapeutic applications that are useful.[9,10]

SAR studies (Figure 1) offer insights into the molecular properties that induce affinity and selectivity of the receptor. Replacements in the hydrophobic domain can be due to the promising existence of the compounds. Structure Activity Relationship of Pyrimidine is as following

I. The insertion of five saturated heterocycle rings at the 1st position leads to anti-cancer and anti-viral operations.

II. If Keto group replacement or Amino substitution or combined substitution will be occurred at the 2nd and 4th positions of pyrimidine nucleus, then it leads to anti-cancer, anti-viral, anti-fungal activities.

III. Halogen groups, substituted amine group or heterocycles ring if will be placed at 5th position of pyrimidine ring it will give anticancer, anti-bacterial activity.

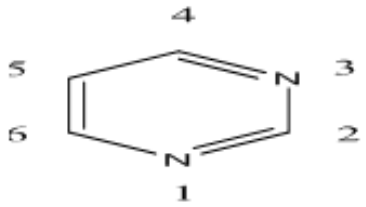

Figure 1 Pyrimidine nucleus.

Schiff base scaffolds

Double bond between Carbon-nitrogen plays a crucial role in the advancement of chemical science. Schiff bases are prepared by condensation of an amine and carbonyl compounds and these are significant types of ligands that coordinate to metal ions through azomethine nitrogen.[9] It is regarded as a nitrogen analogue of an aldehyde or ketone where the imine group substitutes the C=O group. Therefore, it is also known as imine or azomethine. The lone pair of electrons in the sp2 hybrid orbital of N atom in –C=NH- linkage present in Schiff bases enhances their biological and chemical importance.[10,11] Microwave assisted synthetic process of Schiff base is speedy and effectual with no use of solvent. The yield of products is also more and decontamination is done by modest recrystallization system.[12] Azomethine nitrogen not only affords a binding site for metallic ions, but also binds to bio-molecules such as proteins and amino acids in biological systems and to germ-causing diseases with different substrates. Azomethine group helps to prevent the synthesis of histamine, prostaglandin, 5 hydroxy tryptamines in body which leads to provide several antimicrobial activities.

Materials and methods

The process of docking, interaction, and binding the structure of ligand with protein has executed using Auto dock Vina software.

Preparation of ligands and proteins- Chem-draw software was used to determine the structure of the Schiff bases in MOL format. The protein structure was downloaded in PDB format using RCSB PDB. Using Auto dock Vina, water molecules and ligands already present in the proteins were removed, and hydrogen atoms were added and saved in PDB format. 2D and 3D representation of the compounds have represented by Figure 3–5. Prediction of active site- In structure-based drug design, the active site prophecy is critical. The program BIOVIA Discovery Studio was used to calculate the coordinates of the proteins' binding locations.

Results and discussion

Schiff bases (Figure 2) are generally prepared by the condensation of carbonyl compounds (aldehyde/ketones) with aromatic or aliphatic primary amines.[13] To identify the mechanism by which the chemicals restrict S. aureus development, a molecular docking research (in-silico study) was undertaken. The Schiff bases have a high affinity for the dihydrofolate reductase enzyme, which was the target protein (PDB ID: 2W9S) Table 1.[14–19]

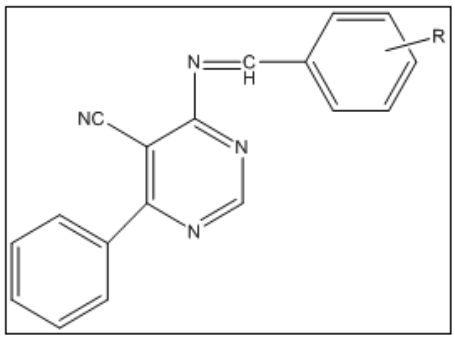

Figure 2 Schiff base scaffolds.

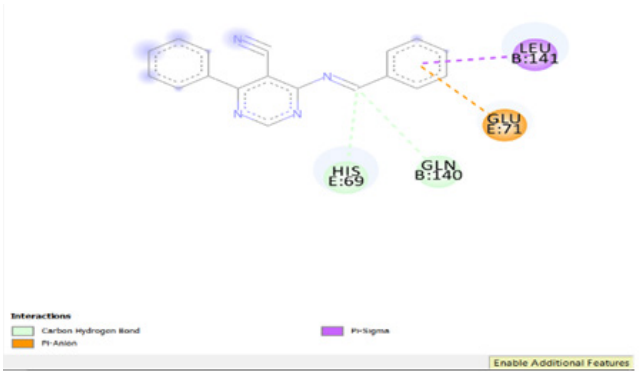

Figure 3 2D interaction.

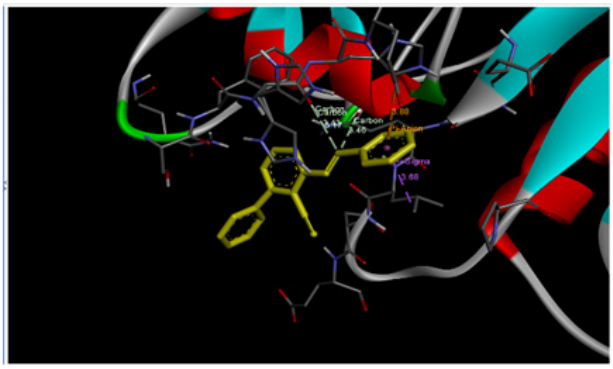

Figure 4 3D interaction.

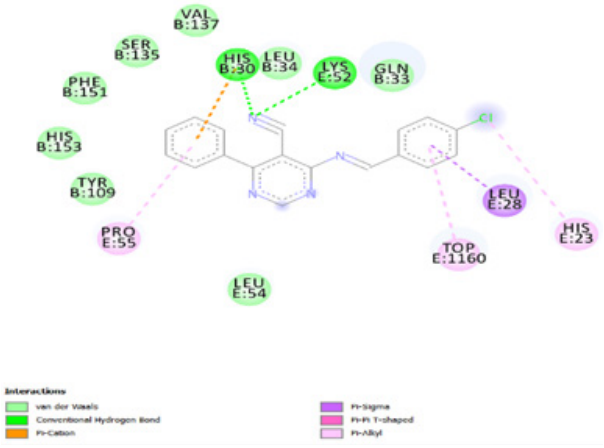

Figure 5 2D interaction.

Table 1 Binding energy

SL. N.	Drug molecule	R	Binding energy (kcal/mol)
1	Benzene derivative	H	-6.7
2	Chloro benzene	p-Cl	-8.1
3	Dinitrobenzene	m, p-NO2	-7
4	Methoxybenzene	p-OCH3	-6.4
5	Nitrobenzene	p-NO2	-8.5

Docking figure for compound 1-

Docking figure for compound 2-

Hydrogen bond interactions such as conventional and non-conventional H bonds, hydrophobic interactions such as amide-pi stacked, pi-pi stacked, pi-sigma, pi-pi T-shaped, alkyl and pi-alkyl interactions, electrostatic interactions such as pi-anion and pi-cation interactions, van der Waals interaction, and unfavourable donor-donor and acceptor-acceptor interactions are commonly seen between protein and ligand. The sum of all interactions and binding energy between the chemical and the target protein determines its binding affinity. Binding energies of the compounds have been noted in Table 1.

Conclusion

For chloro and nitro scaffolds docked with 2W9S, maximum binding energies of – 8.1 and – 8.5 kcal/mol were observed, indicating that the significant growth-inhibitory power of these Schiff bases against the pathogenic bacteria S. aureus is primarily due to deactivation of the enzyme dihydrofolate reductase.

Interactions with amino acid residues-

Vander Waals bond- VAL137, SER135, PHE151, TYR109.

Hydrogen bond- HIS30, LYS52, HIS23.

Pi-Sigma- LEU141, PRO55.

We can conclude from the result of docking study of these novel compounds that the scaffolds having Cl and NO_2 groups substitution (containing negative inductive effect) will be excellent drug congeners against DHFR enzyme for treatment of *S aureus* bacterial infection.

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Conflicts of interest

There is none among the others.

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