Indian Journal of Advances in Chemical Science

Research Article

In silico Biological Potential Assessment of Schiff Base Derived from Amino Acid and Diketone

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ABSTRACT

A Schiff base (L`) designed with glycine and 2,3-butanedione was opted and evaluated for the antibacterial, antifungal and anticancer potential against virulent factors of *S. aureus* (bacteria), *C. albicans* (fungus), *A. flavus* (fungus) and HeLa cancer cell line. The PDB file structure of (L`) was prepared and uploaded on webserver of PATCHDOCK for the molecular docking study against receptor biomolecules PDBs 2spzn (SpA; Staphylococcal Protein A) of *S. aureus*, 2ylh (ALS; Agglutinin-like sequence) of *C. albicans*, 7WGI (AflSQS; Squalene Synthase) of *A. flavus* and 1M17 (EGFR; Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib) of HeLa cell. The surface interaction score, atomic binding energy score results and H-bond/s prediction/s are in favour of studied biological efficacies of Schiff base (L`).

Key words: Antibacterial, Anticancer, Antifungal, Carbonyl compounds, Computational studies, Imine, Primary amine.

1. INTRODUCTION

Schiff bases are molecules belonging to an organic moiety decorated with a –C=N (azomethine) functional group. The reaction product of a primary amine with an aldehyde, following the reaction conditions proposed by Hugo Schiff, is a famous organic compound named a Schiff base in honor of its inventor [Scheme 1] [1,2]. The reaction mechanism of Schiff base synthesis is well known and supported by many researchers [Scheme 2] [3,4]. Several amines and carbonyl compounds have been utilized to develop Schiff base molecules of versatile applications [5-10]. Being an important constituent of biological systems, amino acids are now gaining credence to synthesize bio-efficient Schiff base molecules [11-16]. Schiff bases are a scaffold for a variety of molecular skeletons, describing the versatility of this class of compound [17,18]. Among various classes of primary amine sources, amino acids are intriguing due to applications in many emerging fields, including pharmaceuticals, environmental remediation, catalysis, smart devices, and sensors [19-22]. The rapid growth of microorganism-based diseases poses a threat to human health, and the need for antibiotics is the need of the time [23]. The need to design potent Schiff bases and corresponding metal complexes is escalating to prepare innovative, affordable, and accessible antibiotics. Amino acids, being constituents of proteins, are considered a safer class of compounds in pharmaceuticals [24]. Many recent studies accentuated the high applicability of Schiff bases as antibacterial, antifungal, and anticancer agents [25,26]. The assessment of the biological potential of several globally designed Schiff base molecules has been performed by adopting *in vitro* and *in vivo* methods. However, in this advanced era of computational developments, the bio-efficacy of Schiff base molecules may also be evaluated through *in silico* means, such as other groups of chemical compounds. For computer-based bio-efficiency studies, many tools, software, and web servers are available either on a paid basis or free of cost. Among various computerized tools, molecular docking studies provide a good platform to find out the interaction probability of the targeted biomolecule, namely, protein, enzyme, nucleic acid, etc., with the opted Schiff base (Ligand) in a very short span of time. Such a great utility of Schiff base molecules and advantages of computer-based bio-efficacy studies influenced the authors to put their efforts into evaluating antibacterial, antifungal, and anticancer activities of amino acid-based Schiff base molecules previously developed in their laboratory.

2. EXPERIMENTAL

2.1. In Silico Antimicrobial and Anticancer Potential Studies

Protein Data Bank (PDB) format of the Schiff compound ligand (L') [Scheme 3] [27] was used for *in silico* studies to evaluate its antibacterial and antifungal potency, against bacteria *S. aureus* and fungus *C. ablicans* and *A. flavus*, respectively. Anticancer potential was assessed using the human cervical cancer (Henrietta Lacks [HeLa]) cell line. The selected ligand (L') was saved in PDB format using ChemDraw Ultra 7.0 and Chimera 1.19 software and subsequently used for in silico studies to examine its antibacterial, antifungal, and anticancer activities. The virulence factor (staphylococcal protein A [SpA]; PDB ID: 2spz) of *S. aureus* [28], virulence factor (agglutinin-like sequence [ALS] PDB ID: 2ylh) of *Candida albicans* [29], virulent factor (squalene synthase [AflSQS] PDB ID: 7WGI) of *Aspergillus flavus* and epidermal growth factor receptor (EGFR) tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib ([EGFR]); PDB ID: 1M17) of HeLa [30] were procured from PDB [Figure 1].

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ISSN NO: 2320-0898 (p); 2320-0928 (e)

DOI: 10.22607/IJACS.2026.1403005

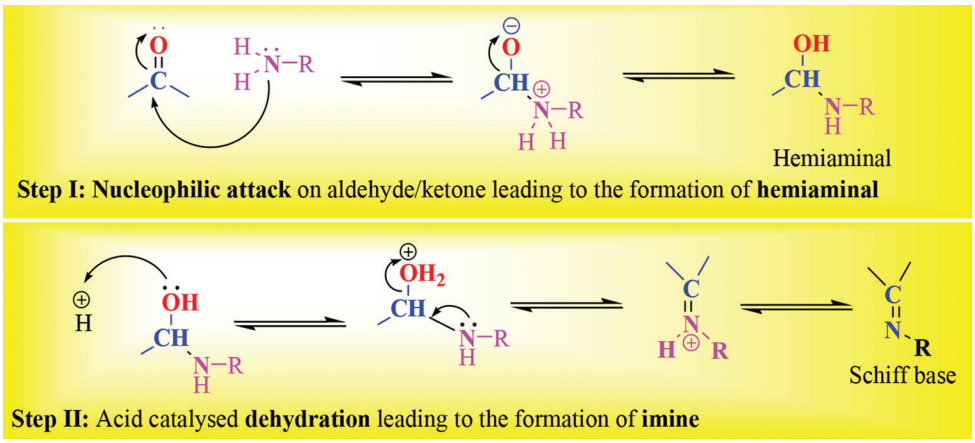
Received: 13th June 2026;

Revised: 22th June 2026;

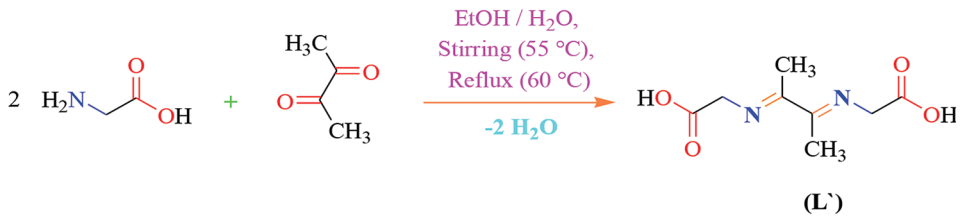
Accepted: 11th August 2026;

Published: 01st September 2026

Scheme 1: Reaction involved in the formation of the first reported Schiff base [3,4].



Scheme 2: Mechanism involved in the formation of Schiff base (imine) [4].



Scheme 3: Synthesis route of selected Schiff base (L') [27].

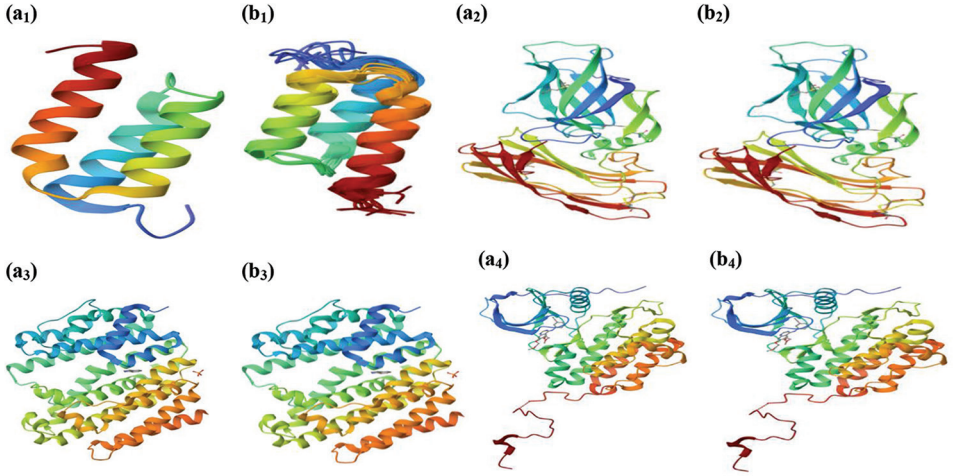


Figure 1: 3D structural representations of biological assemblies (a_1-a_4) and asymmetric units (b_1-b_4) of staphylococcal protein A (2spz; Protein Data Bank [PDB]), agglutinin-like sequence (2ylh; PDB), AflSQS (7WGI; PDB) of *Aspergillus flavus* and HeLa (1M17; PDB) [31].

2.2. Molecular Docking

For analysis of the binding affinity of compounds with virulent factors, the online tool PATCHDOCK [32] was employed. The docked molecules were visualized using Chimera 1.19 software [33]. The best results showing H-bond/s between the ligand and receptor molecules and their corresponding binding energy generated by the PATCHDOCK server results of molecular docking were selected to predict the bio-efficacy.

3. RESULTS AND DISCUSSIONS

The molecular docking results of ligand **(L')** with SpA (PDB ID:2SPZ) of *S. aureus*, ALS (PDB ID:2YLH) of *C. albicans*, AflSQS (PDB

ID:7WGI) of *A. flavus,* and EGFR tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib EGFR (PDB ID: 1M17) of HeLa were observed. The score values, atomic contact energy (AC) values (binding energy), and H-bonding among docked amino acids of receptors and ligand atom/s were observed to predict the bio-efficacy of the studied Schiff base molecule [34,35].

3.1. In Silico Antibacterial Studies

The targeted virulence factor of the bacterium *S. aureus* showed docking interactions with (L'). The carboxylic group available at the end of the Schiff base interacts with the glutamine amino acid (GLN 32) portion of SpA [Figure 2a]. The docking score was 2632, which is high enough to reveal the good fitting of the ligand (L') on the surface of the receptor SpA. The ACE value was observed as −91.43, which also favors efficient interaction during binding among the atoms of the ligand and receptor molecules [36]. Visualized interaction clearly displayed that the NH2 group available on GLN forms an H-bond of 2.528 Å with the –COOH group of the ligand (L') [Figure 2b].

3.2. In Silico Antifungal Studies

Molecular docking outputs of (L') with the ALS virulent factor of *C. albicans* and the AflSQS factor of *A. flavus* fungal strains are quite good to favor the efficient antifungal potential of the selected Schiff base moiety. From the visualization of the best docking result PDB received on the PATCHDOCK server, it was predicted that (L') interacts with the threonine (THR 168) amino acid of the ALS via formation of an H-bond (2.951 Å) between the –OH group of THR and the carboxylic group available at one end of the ligand. The carboxylic group available at another end of (L') also interacts with glutamic acid (GLU 27) of ALS with H-bond formation, having a bond distance of 3.255 Å [Figure 3a and b]. The docking score and ACE values for these interactions were noted as 3290 and −120.94, respectively. These data are quite sufficient to prove the fitment of the ligand on the receptor's surface and molecular binding, solvent removal and interaction energies of ligand and receptor atoms [31].

AflSQS factor interaction visualization displayed H-bond formation of tyrosine (TYR 180), arginine (ARG 237), and lysine (LYS 94) with (L'). The H-bond distance was measured as 3.150 Å, 3.040 Å, and 3.449 Å for (L'-TYR), (L'-ARG), and (L'-LYS) interactions, respectively. One end carboxylic group of (L') interacted with the chain-end NH_2-group of LYS, whereas the other end carboxylic group of (L') got attached with chain end NH_2- of ARG and the phenolic OH- of TYR through the same atom of the -COOH group [Figure 4a and b]. The dock score was 3404, indicating significant fitting of (L') on the AflSQS surface.

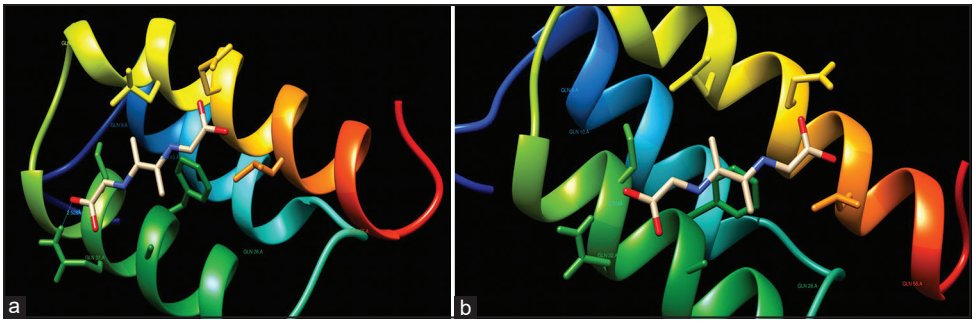


Figure 2: (a and b) Molecular docking visualization images indicating interacting amino acids of the receptor staphylococcal protein A, H-bond formation, and H-bond distance with ligand (L'),

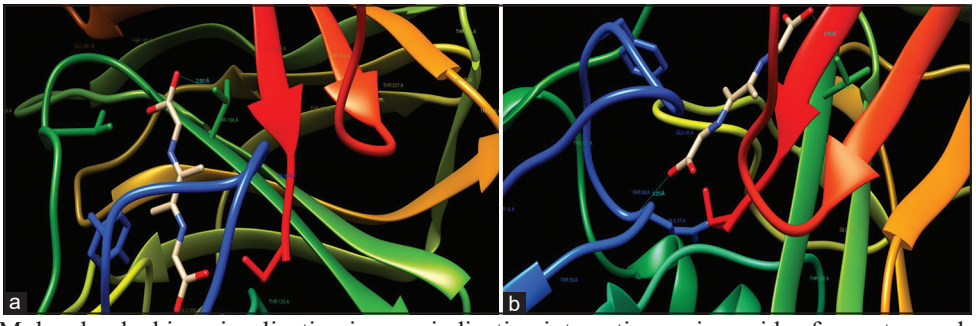


Figure 3: (a and b) Molecular docking visualization images indicating interacting amino acids of receptor agglutinin-like sequence, H-bond formation, and H-bond distance with ligand (L'),

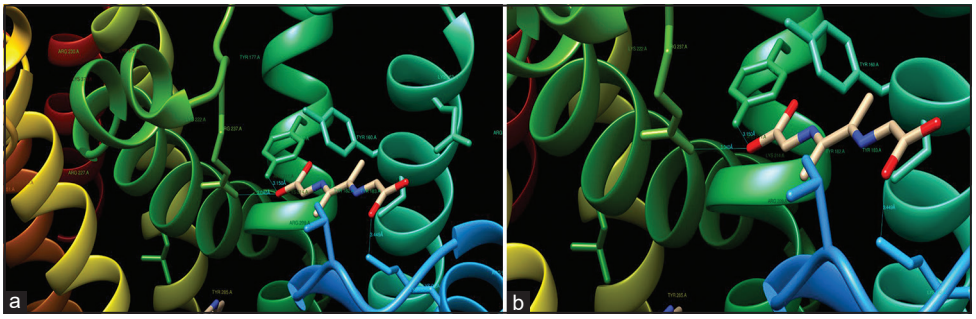


Figure 4: (a and b) Molecular docking visualization images indicating interacting amino acids of receptor squalene synthase of *Aspergillus flavus*, H-bond formation, and H-bond distance with ligand (L'),

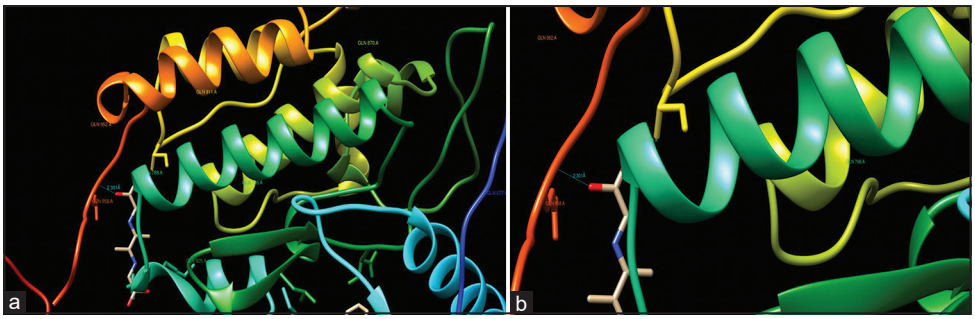


Figure 5: (a and b) Molecular docking visualization images indicating interacting amino acids of receptor epidermal growth factor receptor (1M17), H-bond formation, and H-bond distance with ligand (L'),

The ACE value of −52.94 supported the atomic interaction energy and desolvation energy at the time of atomic binding of the ligand and receptor molecules.

3.3. In Silico Anticancer Studies

The EGFR virulent factor of the HeLa cell line was docked with (L') successfully on the PATCHDOCK server, and the resultant outputs were recorded. As per the best result produced on the web server, the glutamine (GLN 958) amino acid of the receptor interacts with one carboxylic group of (L'). The visualization of the docked PDB received on Chimera software exhibited H-bond formation between the non-amide NH_2- group of GLN and the carboxylic group of (L'). The computed H-bond distance was recorded as 2.301 Å [Figure 5a and b]. The surface interaction score value was found to be 3264, and the noted ACE value was −88.14 for this interaction. These values are enough in number to justify the feasible interaction of the receptor and ligand molecule. Other than this, some other interaction results were also obtained from the web server outputs. Surface interaction scores at 3176 and 3144, along with ACE values of −98.79 and −62.33, displayed H-bond formation between GLN (2.742 Å) and LYS (1.162 Å), respectively, with one carboxylic group of (L') [31].

4. CONCLUSION

Schiff base moiety (L') derived from glycine and 2,3-butanedione was opted as ligand to test its biological efficacy as antibacterial, antifungal and anticancer agent *via in silico* means against the PDB structures of SpA (PDB ID: 2SPZ), ALS (PDB ID: 2YLH), AflSQS (PDB ID: 7WGI), and EGFR tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib of HeLa cell line (EGFR; PDB ID: 1M17) on PATCHDOCK molecular docking web server. The results were predicted on the basis of outputs received from the web server, and their visualization in Chimera software revealed that the tested ligand (L') possessed biopotency to interact with targeted receptors. Among all the tested target receptors, the binding extent of (L') was observed most with virulent factor AflSQS; PDB ID: 7WGI of *A. flavus* fungi. The molecular docking data are suggestive of further *in vitro* experiment design of the Schiff base ligand (L') to explore the biological potential as antibacterial, antifungal, and anticancer agents.

5. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest related to finance, persons, or institutions that can influence the present work.

6. ACKNOWLEDGMENTS

The authors are thankful to the authorities of their institutions for providing the necessary facilities to proceed with this research work.

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