Conventional synthesis *versus* Green Synthesis and molecular docking studies of N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine

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ABSTRACT:

N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine is a new Schiff's base developed using a tamarind water-based green synthesis and traditional synthesis techniques. Novel Schiff's base compound was developed through the condensation of *o*-phenylenediamine with indole-3-carboxaldehyde. Mass spectral and physical analysis were used to describe the produced schiff's base compound. Molecular docking studies using AutoDock software on the developed schiff's base compound exhibits significant binding interactions with the active site region of human peroxisome proliferator activated receptor gamma PPARγ (PDB ID: 2PRG), topoisomerase II (PDB ID: 3QX3), cyclooxegenase-1 (PDB ID: 3KK6), and cyclooxegenase-2 (PDB ID: 5IKR), in comparison to standard ligand.

KEYWORDS: Green synthesis, schiff's base, indole-3-aldehyde, N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine, docking studies

INTRODUCTION:

The most widely utilised organic compounds are Schiff's bases, which have a wide range of uses as catalysts, intermediates, and pigments, colours, and colours in several organic reactions[1,2]. One of the most promising classes of heterocyclic compounds is thought to be the Schiff's bases due to their use in the biological, analytical, and pharmaceutical fields as well as their function as catalysts in organic synthesis[3-6]. For a variety of biological uses, such as antifungal[7-9], antibacterial[10-12], antiproliferative[13], anticoagulant[14], anti-inflammatory[15,16], and antiviral[17] drugs, the presence of the azomethine group in Schiff base derivatives makes them extremely important. They have been extensively utilised in coordination chemistry, mostly as

a result of their simple synthesis, favourable electrical characteristics, and high solubility in common solvents[18]. Schiff bases with aryl substituents are significantly more stable and easier to synthesis than those with alkyl substituents, which are more prone to instability. Aliphatic aldehyde Schiff bases tend to be more unstable and easily polymerize, compared to aromatic aldehydes with efficient conjugation. Schiff bases are chemical compounds that have an azomethine group and were produced when an amine was condensed with an aldehyde or ketone. A wide range of applications, including biological activity, catalytic activity, and use as ligands to obtain metal complexes[19], are available for Schiff bases derived from aromatic amines and aromatic aldehydes. Because of these Schiff bases' excellent anticorrosion properties, various metals in various media are frequently used in these applications. The condensation products of primary amines and carbonyl compounds are schiff bases. Hugo Schiff, a German scientist and Nobel Prize laureate, made their discovery in 1864. Schiff base is a structural equivalent of a ketone or aldehyde in which the carbonyl group has been changed to an imine or azomethine group. It is often referred to as imine or azomethine. Imines are organic compounds that have an azomethine (-HC=N-) group as part of their structure. A Schiff base compound with a functional group that has an aryl or alkyl group as the nitrogen atom's connection to carbon[20-22].

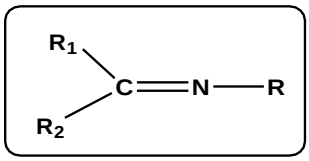


Fig 1: Schiff's base

Schiff bases are organic substances that have a wide range of applications in industries including medicine, agriculture, cosmetics, etc. Due to their distinctive characteristics, Schiff base complexes have recently received attention in biochemistry and biomedicine[23-26]. Schiff bases are useful because they can be used as synthons to create bioactive compounds like 4-thiazolidinones, 2-azetidinones, benzoxazines, formazans, etc. Schiff bases are frequently utilised as organic intermediates for the creation of medicinal or rubber additives[27]and amino protecting groups in chemical synthesis[28-32], They are also employed in analytical[33], medical[34,35], and polymer chemistry[36] processes as liquid crystals[37]. By reacting o-phenylenediamine with two moles of indole-3-carboxaldehyde, a novel schiff's base, N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine, was created in the current work. The

molecular docking studies at different target sites was investigated using the newly developed Schiff's base molecule.

MATERIALS AND METHODS:

Chemicals and reagents used for the synthesis of a novel Schiff's base were bought from Merck, a commercial supplier, and they weren't purified before use. With the use of E.Merck grade silica gel 60GF-254 pre-coated plates, thin layer chromatography was used to monitor both the reaction's progress and completion. Uncorrected electrical melting point apparatus was used to determine melting points. Using the KBr pellet method, the compounds IR spectra were captured using the Bruker FT-IR spectrophotometer. On a Bruker-AMX spectrophotometer operating at 400 MHz and 100 MHz, respectively, chemical shifts in ppm of ^{1}H-NMR and ^{13}C-NMR spectra were noted in relation to tetramethylsilane (TMS) as internal standard. The Agilent-LC-MSD-1200 mass spectrometer was used to measure and record the mass spectra (MS). Both conventional and green synthesis methods were used to develop novelschiff's base. Using the AutoDockVina, ChemDraw, and BIOVIA discovery studio softwares, molecular docking studies were performed to examine binding interactions in comparison to standard ligands.

Preparation of tamarind water: From the *Tamarindus indica* tree, unripe tamarind fruits were collected. The tamarind fruit's outer shell and interior kernel were cut away. The juice was filtered through filter paper to remove solid material after the hard material (15 g) and water (50 ml) were cooked, cooled, and then added back to the pot. Using a mini centrifuge, the filtrate was further spun down. The transparent portion of the unripe tamarind fruits aqueous extract (pH 3.1) is known as tamarind water and is employed as a catalyst for the formation of schiff bases. As a result, the aqueous extract of unripe tamarind fruit (tamarind water) contains organic acids, making it acidic and potentially acting as an acid catalyst for the condensation of indole-3-carboxaldehyde and *o*-phenylenediamine.

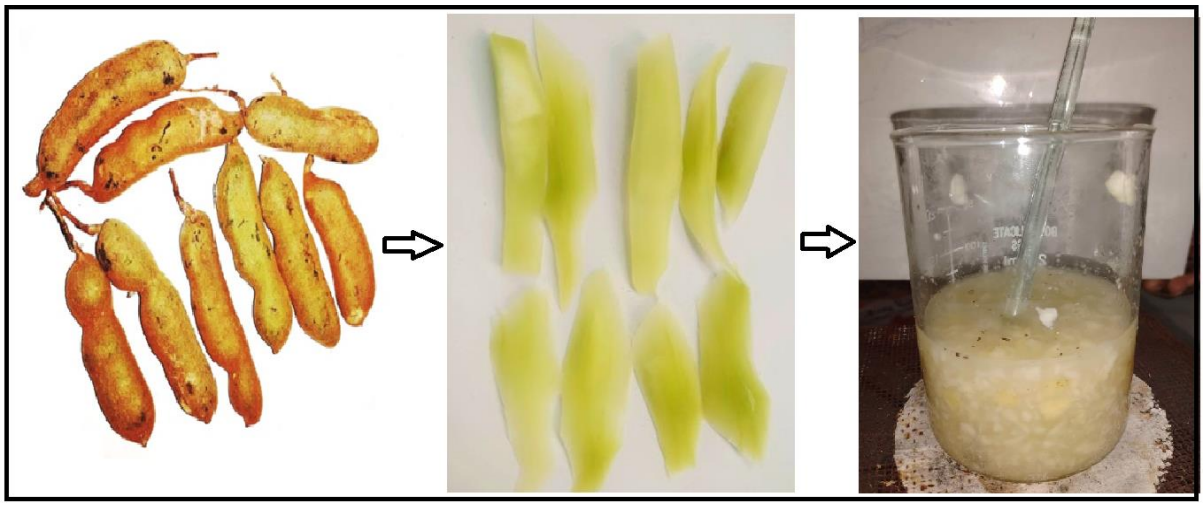


Fig 2: Tamarind water as acid catalyst

Synthesis of N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine

Conventional synthesis: To a solution of *o*-phenylenediamine(1 mmol) in 10 ml of ethanol, add a solution of indole-3-carboxaldehyde (2mmol) in 10 ml of ethanol. Resulting solution was refluxed with stirring for two hours. Completion of the reaction was monitored by TLC, the reaction mixture was allowed to cool to the room temperature. The obtained precipitate was collected by filtration through Buchnner funnel, recrystallized from ethanol, and dried at room temperature to afford desired product.

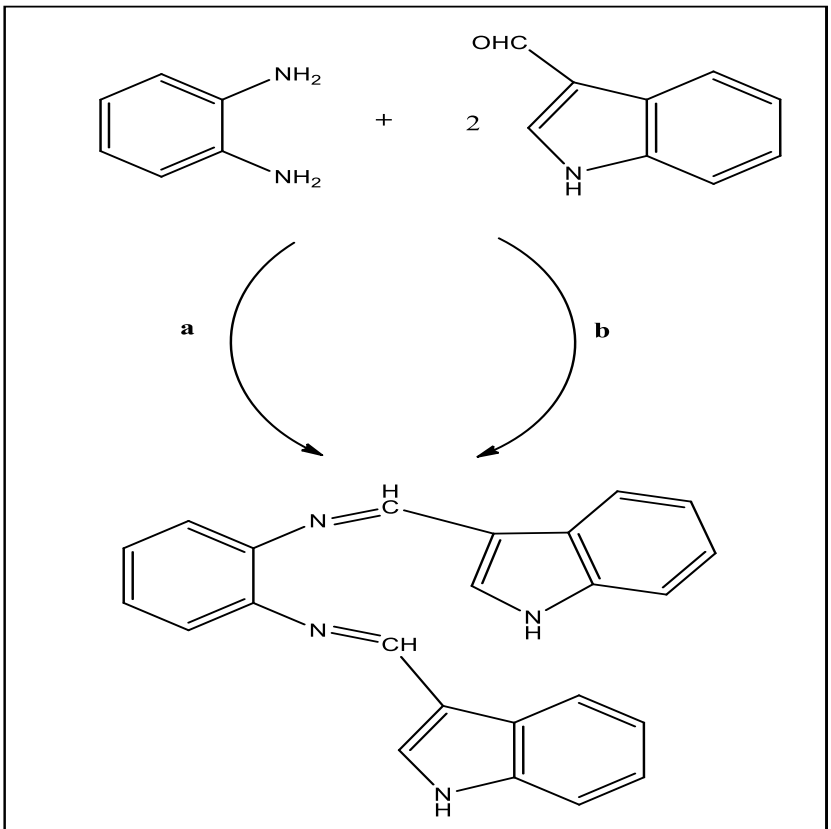
Green route synthesis: A mixture of indole-3-carboxaldehyde (2mmol), *o*-phenylenediamine (1 mmol), ethanol (10 ml) and tamarind water (10 ml) were taken in a round bottom flask and it was stirred by magnetic stirrer at room temperature for 1 hour. The progress of the reaction was monitored by TLC over silica gel (using Silica Gel - G stationary phase and ethylacetate: hexane, 3:7 v/v as mobile phase). When the reaction was found to be complete, 10 ml of water was added to it. The solid product was collected by filtration through buchnner funnel and washed with hot water. The crude product was purified by recrystallization from ethanol.

Molecular Docking Studies

Human peroxisome proliferator activated receptor gamma (PPARγ)[38], topoisomerase-II[39,40], COX-1[41-43], COX-2[44-47] target proteins were used in molecular docking experiments to predict molecular mechanisms as potential hypoglycemic, anti-cancer, analgesic, antipyretic, and anti-inflammatory agents. The PDB files for the 3D crystal structures of the PPARγ protein, topoisomerase II, cyclooxegenase-1, and cyclooxegenase-2 can be downloaded from the RCBS protein data bank at https://www.rcsb.org/. Using BIOVIA Discovery studio visualizer 2021,

the obtained proteins were made ready for docking by having water molecules and heteroatoms removed. By adding Kollman charges, Gasteiger charges, and polar hydrogens, the protein structures were reduced to the lowest energy state for further investigation.ChemDraw Ultra 12.0 was used to create the intended and produced ligand structure, and Chem 3D-Pro 12.0 was used to reduce and save the structure in SDF file format. Rosiglitazone (Pubchem Id: 77999), Doxorubicin (Pubchem Id: 31703), and Diclofenac (Pubchem Id: 3033) standard ligand structures SDF file formats were retrieved from the PubChem database. Additionally, using the Open Babel software, all SDF format files are translated to PDB format. The protein transformations and other ligand molecules were converted from PDB to PDBQT file format, grid-based docking experiments were conducted using default parameters, and docking was carried out by connecting the protein-ligand using MGL AutodockVina. Using command prompt, the docking poses of ligands that best connect to the active site areas of the proteins were observed. BIOVIA Discovery Studio was used to display the ligands' two- and three-dimensional binds to the target proteins.

RESULTS AND DISCUSSION:



***N*^{1},*N*^{2}-bis[(1*H*-indol-3-yl)methylene]benzene-1,2-diamine**

a = ethanol, reflux (conventional route synthesis)
b = tamarind water, stirring (green route synthesis)

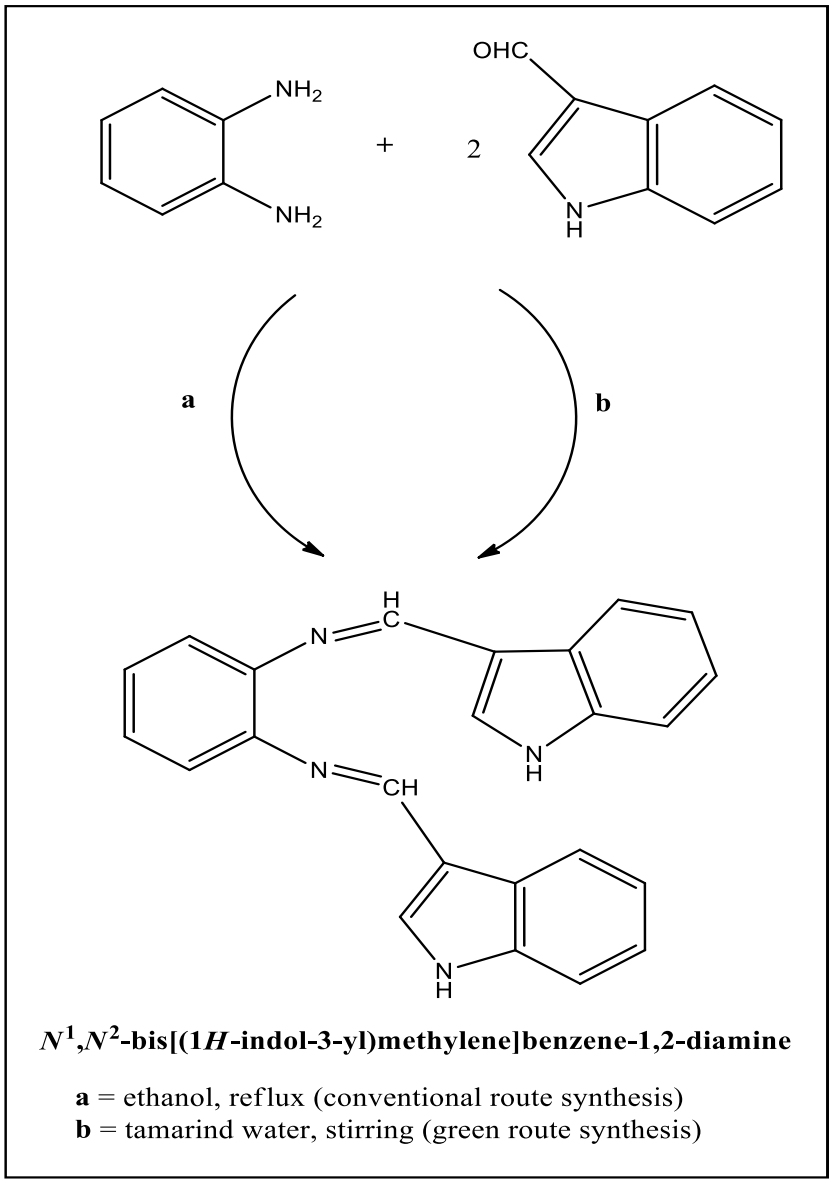


Fig3: Scheme of synthesis of N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]benzene-1,2-diamine

According to the methods described in the literature[48-50], the first novel Schiff's base, N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine, was made by combining *o*-phenylenediamine with two moles of indole-3-carboxaldehyde. Fig-3 shows the synthesis plan in detail. The following information includes physical characterization data, comparisons of conventional and green synthesis in terms of yield percentages, reaction time intervals, and spectrum data.

75.84% (yield from conventional synthesis), 92.10% (yield from green synthesis), yellow crystalline solid, melting point 184-186°C, R_f value 0.65 from using ethylacetate and hexane (3:7 v/v). IR [KBr ν cm^{-1}]: 3324.50 (-NH-), 3024.23 (=C-H), 1310.52 (C-N), 1655.30 (C=C). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 8.421 (2H, s, -N=C<u>H</u>-), 12.040 (2H, s, indole-N<u>H</u>-),

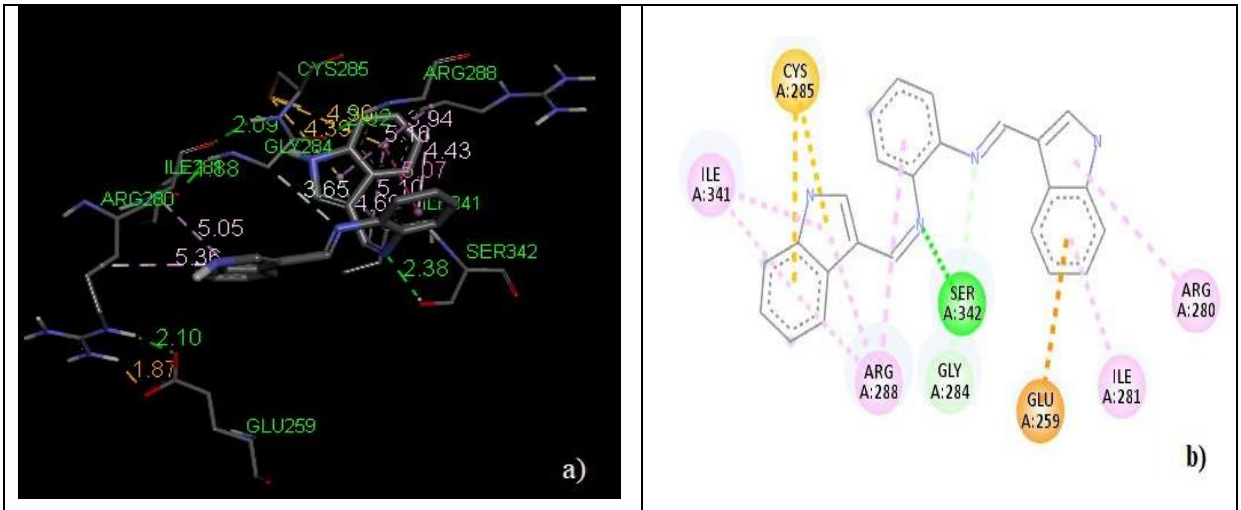
6.982-7.258 (2H, d, phenyl C_3-H & C_4-H), 6.982-7.258 (2H, t, phenyl C_2-H & C_5-H), 7.587-8.674 (10H, d & t, indole). ^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 102.45, 111.15, 118.24, 120.12, 122.33, 124.03, 126.48, 129.66, 131.86, 136.74, 141.92, 161.16. ESI-MS: (M^+) m/z 362.15.

Molecular docking results

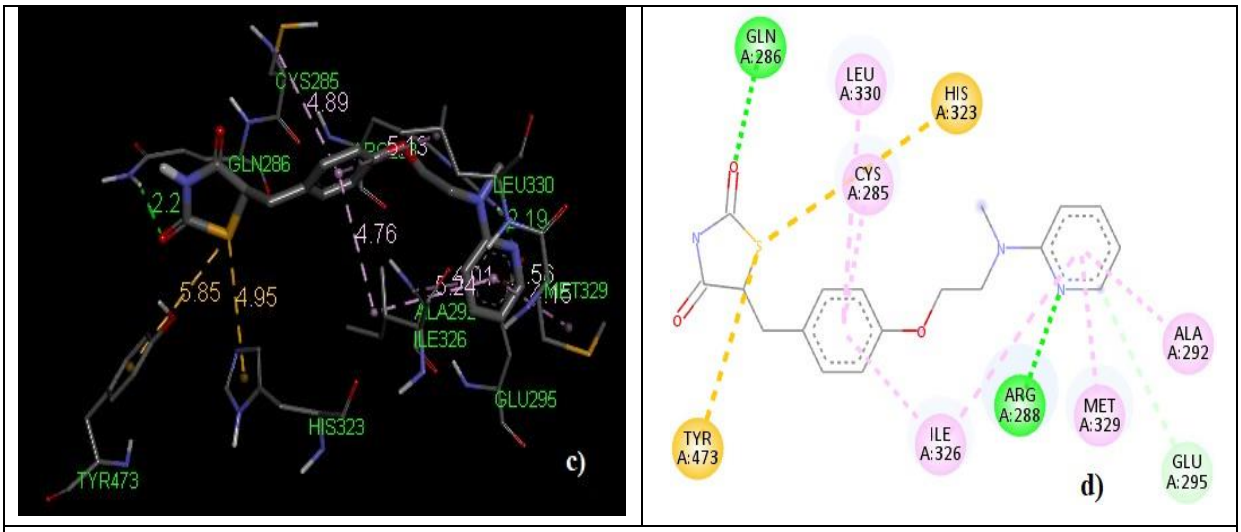
By completing molecular docking investigations in comparison with standard pharmacological ligands, hypoglycemic action, topoisomerase-II inhibitory activity, analgesic, antipyretic, and anti-inflammatory effects have been predicted computationally.

Docking at PDB structure of PPARγ protein (PDB ID: 2PRG)

The docking interaction of designed ligand was analyzed at active site region of PPARγ protein (2PRG) in comparison with standard Rosiglitazone ligand. The computational screening results for PPARγ protein 2PRG with designed ligand and Rosiglitazone were shown in *Table 1* and *Fig-4*. The hydrogen bond interactions with the key amino acid residues at the active site SER-342, GLY-284 and ARG-280 with the interaction distances 2.38, 3.65, and 5.05 respectively. Interacted amino acid residues in the pose of active site GLU-259, ARG-280, ILE-281, GLY-284, CYS-285, ARG-288, ILE-341 and SER-342. Docking energy of the designed ligand at the active site region −10.22 kcal/mol was found to be more as compared to interacted standard Rosiglitazole ligand at the active site region −9.25 kcal/mol, indicating that the designed ligand is considered to be significantly more likely ligand at PPARγ protein.



Two-dimensional (a) and three-dimensional (b) binding mode of designed ligand at active site region of PPARγ protein 2PRG

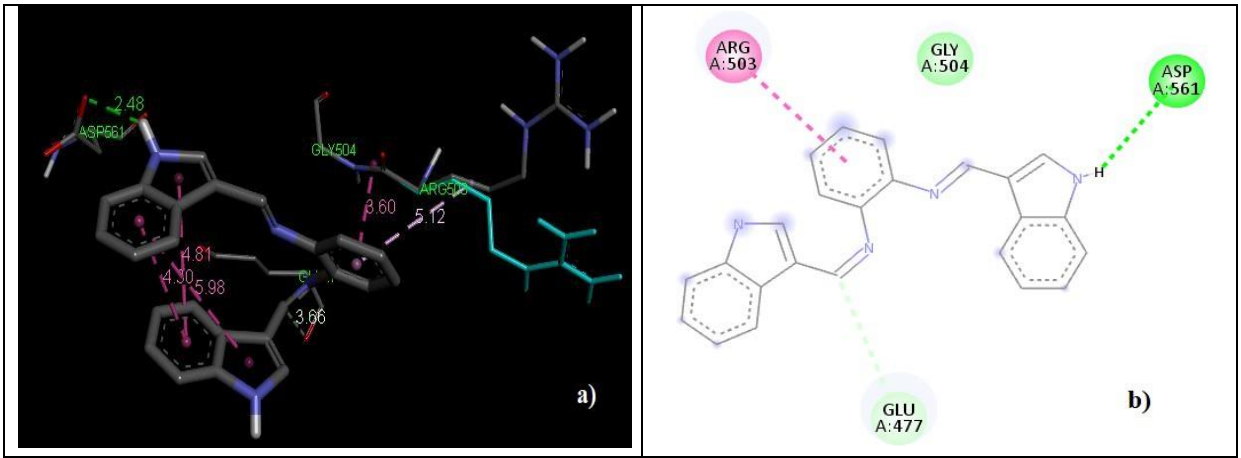


Two-dimensional (c) and three-dimensional (d) binding mode of standard ligand Rosiglitazone at active site region of PPARγ protein 2PRG

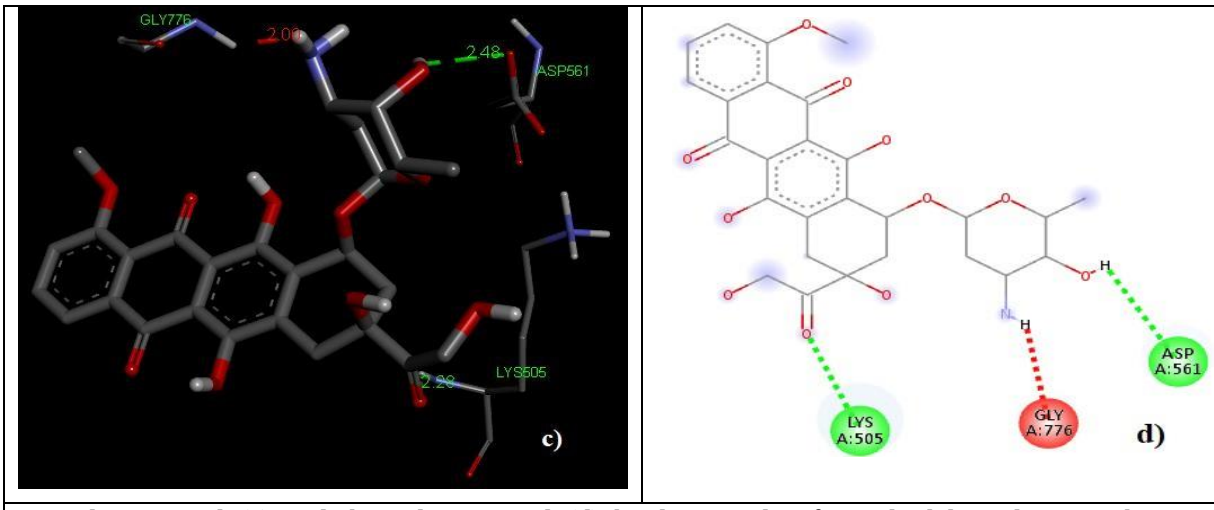
Fig4: Docking of designed ligand and standard ligand at PPARγ protein 2PRG

Docking at PDB structure of topoisomerase-II (PDB ID: 3QX3)

The docking interaction of designed ligand was analyzed at active site region of topoisomerase-II protein (3QX3) in comparison with standard Doxorubicin ligand. The computational screening results for topoisomerase-II protein 3QX3 with designed ligand and standard ligand Doxorubicin were shown in *Table 1* and *Fig-5*.Hydrogen bond interactions with the key amino acid residues at the active site ASP-561, GLU-477, ARG-503 and GLY-504 with the interaction distances 2.48, 3.66, and 3.60 respectively. Interacted amino acid residues in the pose of active site GLU-477, ARG-503, GLY-504 and ASP-561. Docking energy of the interacted standard ligand Doxorubicin at the active site region −6.80 kcal/mol was found to be more as compared to that of designed ligand docking energy −6.52 kcal/mol, indicating that designed ligand is considered to be less likely ligand attopoisomerase-II protein.



Two-dimensional (a) and three-dimensional (b) binding mode of designed ligand at active site region of topoisomerase II protein PDB ID- 3QX3

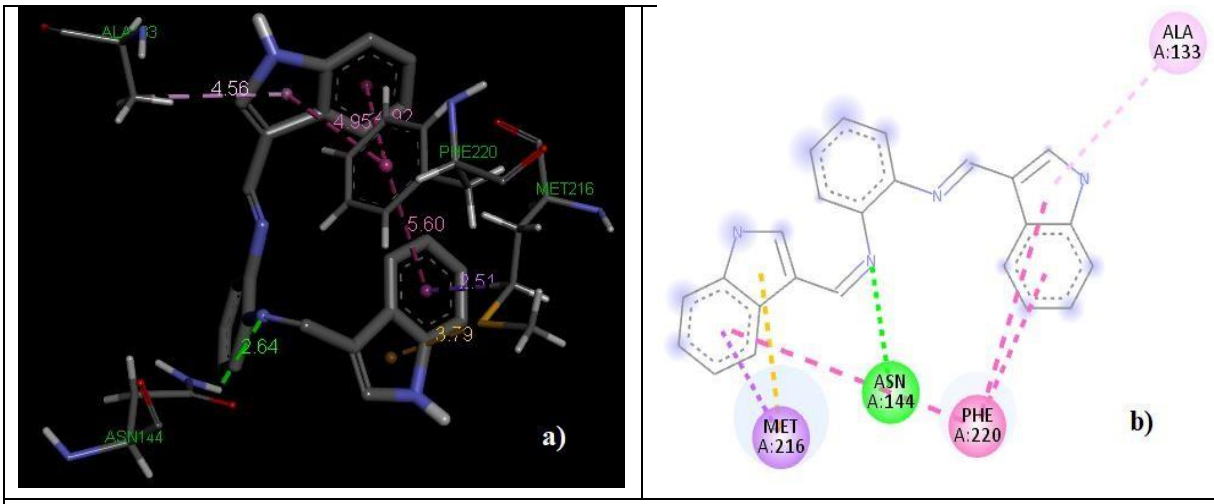


Two-dimensional (c) and three-dimensional (d) binding mode of standard ligand Doxorubicin at active site region of topoisomerase II protein PDB ID- 3QX3

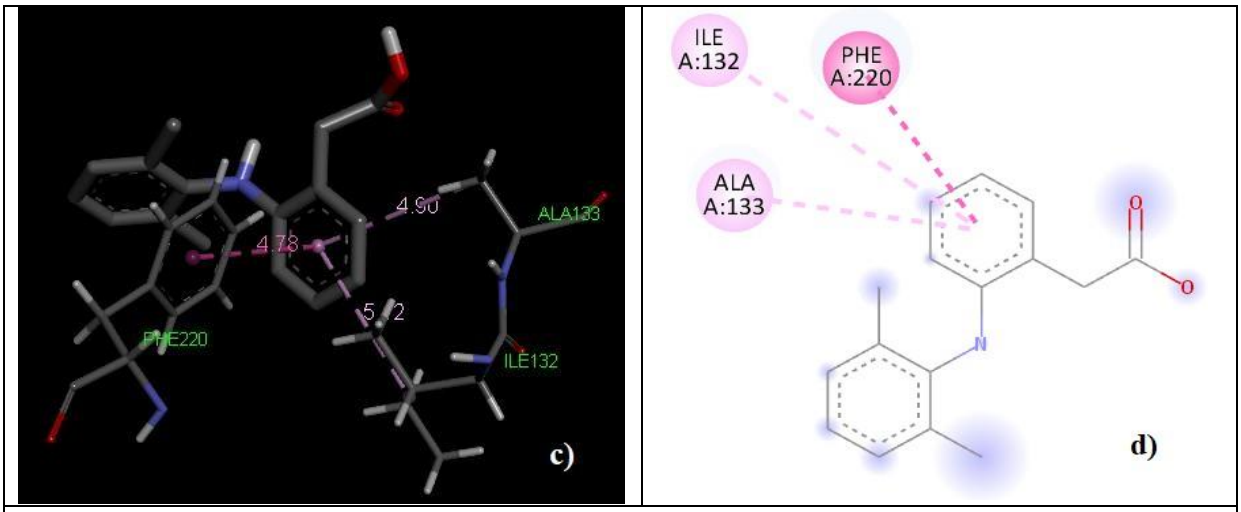
Fig 5: Docking of designed ligand and standard ligand at topoisomerase-II protein 3QX3

Docking at PDB structure of cyclooxegenase-1 (PDB ID: 3KK6)

Designed ligand was screened at active site region of cyclooxegenase-1 (3KK6) in comparison with standard ligand Diclofenac. Screening results for cyclooxegenase-1 protein 3KK6 with designed ligand and standard ligand Diclofenac were shown in *Table 1* and *Fig-6*.Interacted amino acid residues in the pose of active site by schiff's base ligandASN-144, MET-216, ALA-133 and PHE-220. Docking energy of the interacted standard ligand Diclofenac at the active site region −3.95 kcal/mol was found to be less as compared to that of designed ligand docking energy −5.63 kcal/mol, indicating that the designed ligand is considered to be significant more likely ligand at cyclooxegenase-1 protein.



Two-dimensional (a) and three-dimensional (b) binding mode of designed ligand at active site region of cyclooxegenase-1 protein PDB ID- 3KK6

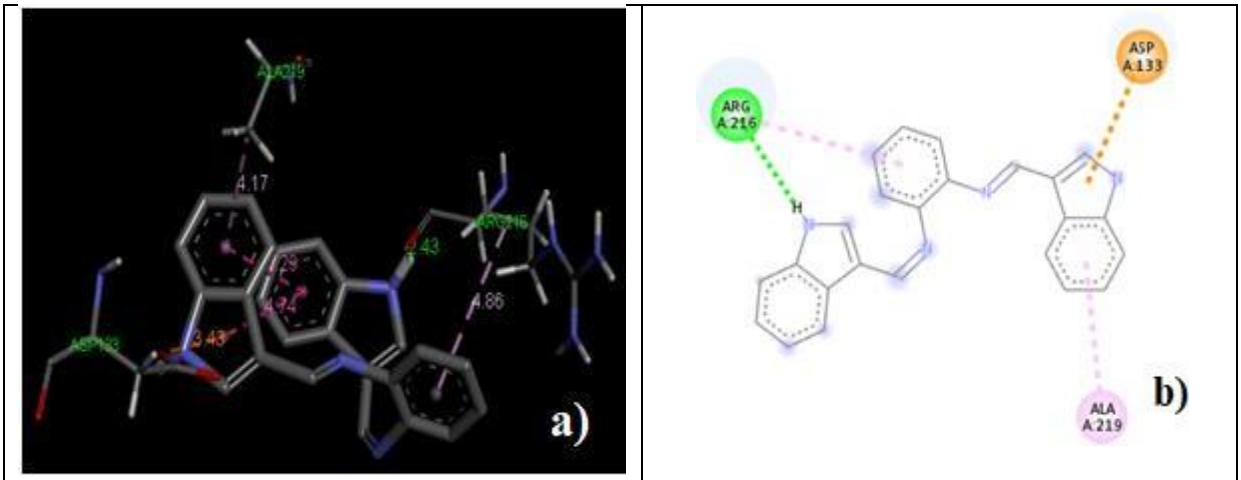


Two-dimensional (c) and three-dimensional (d) binding mode of standard ligand Diclofenac at active site region of cyclooxegenase-1 protein PDB ID- 3KK6

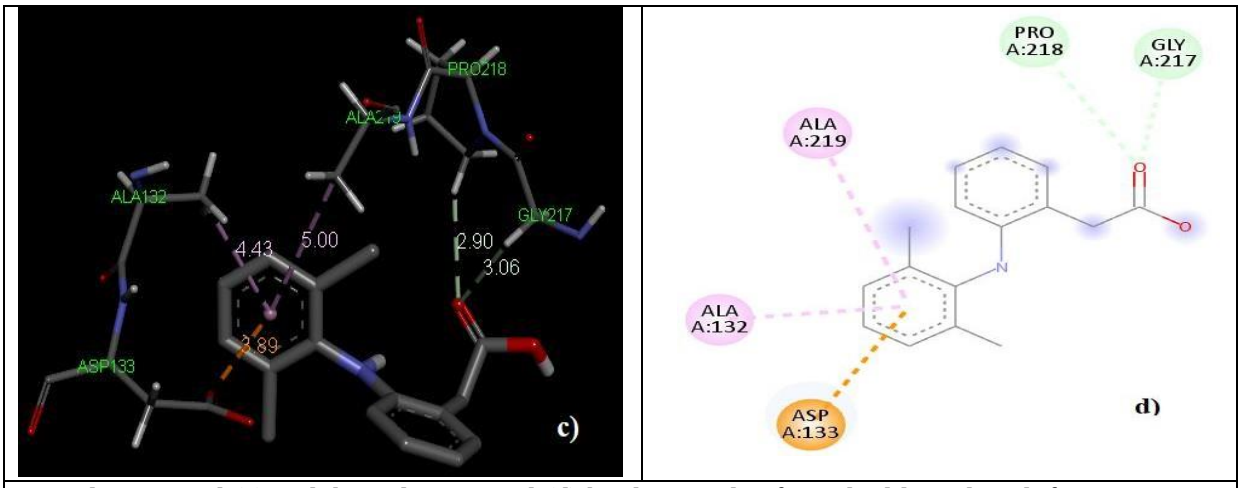
Fig 6: Docking of designed ligand and standard ligand at cyclooxegenase-1 protein 3KK6

Docking at PDB structure of cyclooxegenase-2 (PDB ID: 5IKR)

Designed ligand was screened at active site region of cyclooxegenase-2 (5IKR) in comparison with standard ligand Diclofenac. Screening results for cyclooxegenase-2 protein 5IKR with designed ligand and standard ligand Diclofenac were shown in *Table 1* and *Fig-7*.Hydrogen bond interactions with the key amino acid residues at the active site ALA-219, ARG-216 and ASP-133 with the interaction distances 4.17, 4.86 and 3.43 respectively. Interacted amino acid residues in the pose of active site ALA132, GLY217, PRO218, ASP133 and ALA219. Docking energy of the interacted standard ligand Diclofenac at the active site region −4.27 kcal/mol was found to be less as compared to that of designed ligand docking energy −5.97 kcal/mol, indicating that the designed ligand is considered to be significant more likely ligand at cyclooxegenase-2 protein.



Two-dimensional (a) and three-dimensional (b) binding mode of designed ligand at active site region of cyclooxegenase-2 protein PDB ID- 5IKR



Two-dimensional (c) and three-dimensional (d) binding mode of standard ligand Diclofenac at active site region of cyclooxegenase-2 protein PDB ID- 5IKR

Fig 7: Docking of designed ligand and standard ligand at cyclooxegenase-2 protein 5IKR

Table 1: Binding energy, Protein PDB targets, hydrogen bond lengths& amino acid residues interacted

Compound	**Binding energy (kcal/mol)**	**Target PDB ID**	**Hydrogen bond length**	**Interacted amino acid residues**
Novel Schiff base	-10.22	2PRG	2.38, 3.65, 5.25, 5.36, 2.10, 4.43, 3.94, 5.10	GLU-259, ARG-280, ILE-281, GLY-284, CYS-285, ARG-288, ILE-341, SER-342
Rosiglitazone	-9.25	2PRG	2.21, 5.85, 4.95, 5.13, 2.19, 5.24, 3.58	GLN-286, TYR-473, LEU-330, HIS-323, CYS-285, ILE-326, ARG-285, MET-329, ALA-292, GLU-295
Novel Schiff base	-6.52	3QX3	2.48, 3.66, 3.60, 5.12, 4.81	ASP-561, GLU-477, ARG-503, GLY-504
Doxorubicin	-6.80	3QX3	2.00, 2.28, 2.48	LYS-505, GLY-776, ASP-561
Novel Schiff base	-5.63	3KK6	5.60, 2.51, 3.79, 2.64, 4.56	ASN-144, MET-216, ALA-133, PHE-220
Diclofenac	-3.95	3KK6	4.78, 4.90, 5.12	ILE-132, PHE-220, ALA-133
Novel Schiff base	-5.97	5IKR	4.17, 4.86, 3.43	ALA-219, ARG-216, ASP-133
Diclofenac	-4.27	5IKR	3.06, 4.43, 3.89, 2.90, 5.00	ALA-132, GLY-217, PRO-218, ASP-133, ALA-219
Novel Schiff base: N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine				

CONCLUSION:

In this study, a novel schiff's base, N^1,N^2-bis[(1*H*-indol-3-yl)-methylene]-benzene-1,2-diamine, was established by reacting *o*-phenylenediamine with two moles of indole-3-carboxaldehyde using the conventional and green routes (using tamarind water as a catalyst), which produced a higher yield in less time than the conventional route. According to molecular docking studies,

the newly created schiff's base was thought to be a significantly more likely ligand at the PPARγ protein 2PRG, the cyclooxegenase-1 protein 3KK6, and the cyclooxegenase-2 protein 5IKR, and a significantly less likely ligand at the topoisomerase-II protein 3QX3. According to computational research, it may have considerable hypoglycemic, analgesic, antipyretic, and anti-inflammatory effects, but less so topoisomerase-II inhibitory effects.

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