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Research Article

N-[(1*h*-Indol-3-Yl)Methylene]-Substituted Aniline Derivatives As Schiff's Bases: Design, Green Synthesis Using Amla Water & *In-Silico* Molecular Docking Studies

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Abstract

N-[(1*H*-indol-3-yl)-methylene]-substituted aniline derivatives as schiff's bases were developed using a amla water-based green synthesis technique. Novel Schiff's base compound was developed through the condensation of reaction of indole-3-aldehyde and aromatic amines in presence of amla water extract as acid catalyst. Aqueous amla extract (pH 3.4) of the *E. officinalis* fruits considered as amla water, used as catalyst for the development of schiff bases. Aqueous extract of *E. officinalis* fruits (amla water) is acidic due to presence of organic acids and hence considered as an acid catalyst for the synthesis of Schiff's bases. Physical and spectral analysis were used to describe the produced schiff's base compounds. Molecular docking studies using AutoDock software on the developed schiff's base compound exhibits significant binding interactions with the active site region of cyclooxegenase-1 (PDB ID: 3KK6), and cyclooxegenase-2 (PDB ID: 3LN1), in comparison to standard ligand.

Keywords: Green synthesis, schiff's base, indole-3-aldehyde, N-[(1*H*-indol-3-yl)-methylene]-substituted aniline derivatives, molecular docking studies.

INTRODUCTION

Schiff's bases are an important class of organic compounds. Schiff's bases are condensation products of primary amines with carbonyl compounds. The common structural feature of these compounds is the azomethine group with the general formula R-HC = N-R_1, where R and R_1 are alkyl, aryl, cycloalkyl, or heterocyclic groups [1]. They were first reported by Hugo Schiff in 1864 [2]. Structurally, a Schiff's base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (>C = O) is replaced by an imine or azomethine group. Schiff's bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral and antipyretic properties [3-6]. Imine or azomethine groups are present in various natural, naturally derived and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities [7-11].

A Schiff base is a nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme:

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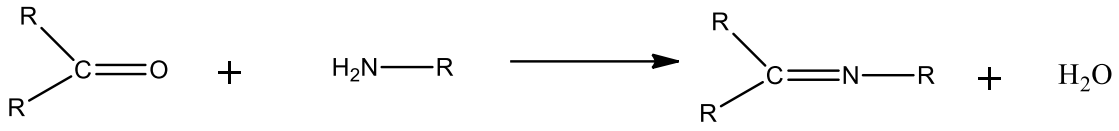

Aldehyde/ Ketone **Primary amine** **Schiff base**

Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable while those of aromatic aldehydes having effective conjugation are more stable. Nowadays, the research field dealing with Schiff base coordination chemistry has expanded enormously. Several Schiff bases have been reported for their significant biological activities like antitumor, antiviral, anti-inflammatory agents, insecticidal, antibacterial, antituberculosis, antimicrobial, anticonvulsant activity etc. Schiff bases also exhibit antimalarial, antiproliferative, and antipyretic activities [12,13]. In this study, N-[(1*H*-indol-3-yl)-methylene]-substituted aniline derivatives as schiff's bases were developed. The molecular docking studies at COX isoenzymes target sites was investigated using the newly developed Schiff's base molecule.

MATERIALS & 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, chemical shifts in ppm of ^{1}H-NMR spectra were noted in relation to tetramethylsilane (TMS) as internal standard. Using the AutoDockVina, ChemDraw, and BIOVIA discovery studio softwares, molecular docking studies were performed to examine binding interactions in comparison to standard ligands.

EXPERIMENTAL

Collection and preparation of *Phyllanthus emblica (Emblica officinalis)*extract [16,17]

Phyllanthus emblica (*Emblica officinalis*) commonly known as Indian "gooseberry" or amla, belonging to family Euphorbiaceae is an important herbal drug used in ayurvedic systems of medicine. *E. officinalis* has been reported to play a beneficial role to treat diseases such as diabetes, ulcer, and anemia and possesses cardio protective properties. *E. officinalis* fruit extracts contain chemicals including quercetin, ascorbic acid, gallic acid, tannins, flavonoids, and pectin and polyphenolic compounds. The present work reports the investigation of using *E. officinalis* fruit extract as a catalyst for the synthesis of schiff's bases. The fruits sample of *E. officinalis* was collected from the local area plant near Gudlavalleru, Krishna district, India. *E. officinalis* fruits were thoroughly washed with water and finely chopped. The *E. officinalis* fruit pieces were then crushed into the mortar and pestle. 10 g of finely chopped and crushed *E. officinalis* was weighed and boiled with 100 ml of double distilled water at 60°C-80°C for 10 minutes. After boiling, the solution was filtered through the Whatman filter paper and stored at 4°C for use. The clear portion of the aqueous extract (pH 3.4) of the *E. officinalis* fruits considered as amla water, used as catalyst for the development of schiff bases. Thus an aqueous extract of *E. officinalis* fruits (amla water) is acidic due to presence of organic acids and hence it may be work as an acid catalyst for the synthesis of Schiff's bases.

Fig-1: Preparation of Amla extract

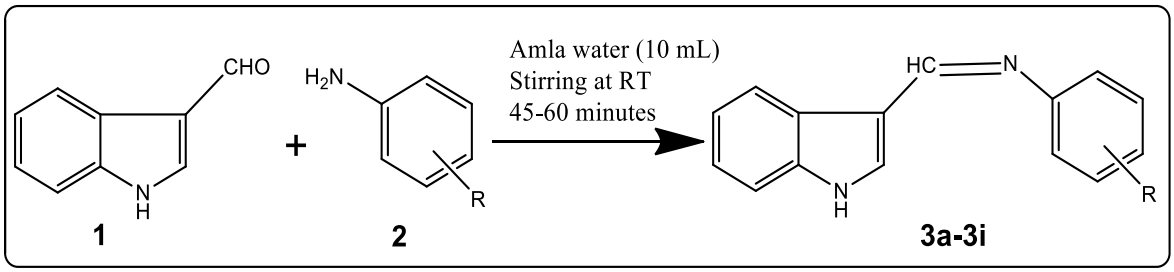

Fig-2: Scheme of synthesis of Schiff bases (3a-3i)

General procedure for synthesis of Schiff bases (3a-3i) [18]
A mixture of indole-3-aldehyde **1** (1 mmol), aromatic amine **2** (1 mmol) and amla water (10 mL) were taken in a round bottom flask and it was stirred by magnetic stirrer at room temperature. 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, 10-15 mL of ice-cold water was added to it. The solid product was collected by simple filtration and washed with hot water. The crude products were purified by recrystallization from ethanol.

Physical characterization of the synthesized compounds
Melting points were determined by open ended capillary tube and are uncorrected. Purity of the compounds was identified by the TLC by using silica gel-G as stationary phase.

Table-1: Physical characterization data

Compound	R	Mol. Formula	Mol. Wt	M.P. (˚C)	% Yield	Rf value
3a	2-Cl	$C_{15}N_2H_{11}Cl$	254.71	176-178	80.21	0.51
3b	4-Cl	$C_{15}N_2H_{11}Cl$	254.71	190-192	85.44	0.6
3c	2-NO_2	$C_{15}H_{11}N_3O_2$	265.27	184-186	87.48	0.53
3d	3-NO_2	$C_{15}H_{11}N_3O_2$	265.27	184-186	89.72	0.6
3e	2-OH	$C_{15}H_{12}N_2O$	236.27	210-212	83.26	0.56
3f	3-OH	$C_{15}H_{12}N_2O$	236.27	182-184	90.31	0.65
3g	4-CH_3	$C_{16}H_{14}N_2$	234.3	196-198	80.38	0.57
3h	2-OCH_3	$C_{16}H_{14}N_2O$	250.3	188-190	82.2	0.51
3i	4-OCH_3	$C_{16}H_{14}N_2O$	250.3	178-180	89.78	0.6

Spectral Data
N-[(1*H*-indol-3-yl)methylene]-4-methylaniline (3g):
IR (KBr) νmax, cm^{-1}**:** 3406.37 (-NH-), 3057.99 (=C-H), 2941.73 (C-H), 1583.06 (C=C), 1678.64 (C=N). **^{1}H-NMR (DMSO, 400 MHz):** 11.306 (1H, s, indole NH), 2.541 (3H, s, CH_3), 7.219- 7.478 (4H, m, Phenyl), 7.506-7.526 (1H, t, indole C_5-H& C_6-H), 7.742-7.747 (1H, d, indole C_2-H), 7.880-7.899 (1H, d, indole C_7-H), 8.069 (1H, s, –CH=N-) 6.882-7.200 (1H, d, indole C_4-H).

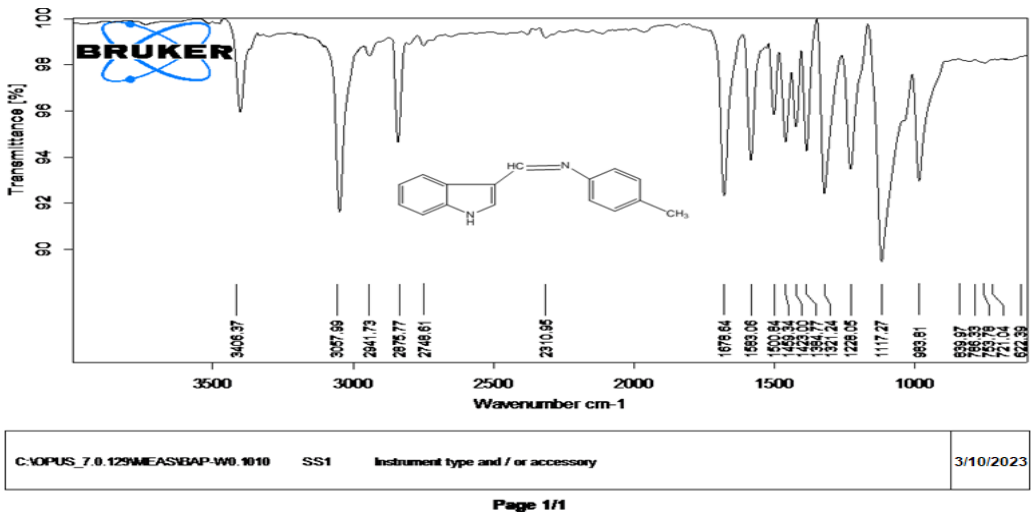

Fig-3: IR spectral data of N-[(1*H*-indol-3-yl)methylene]-4-methylaniline (3g)

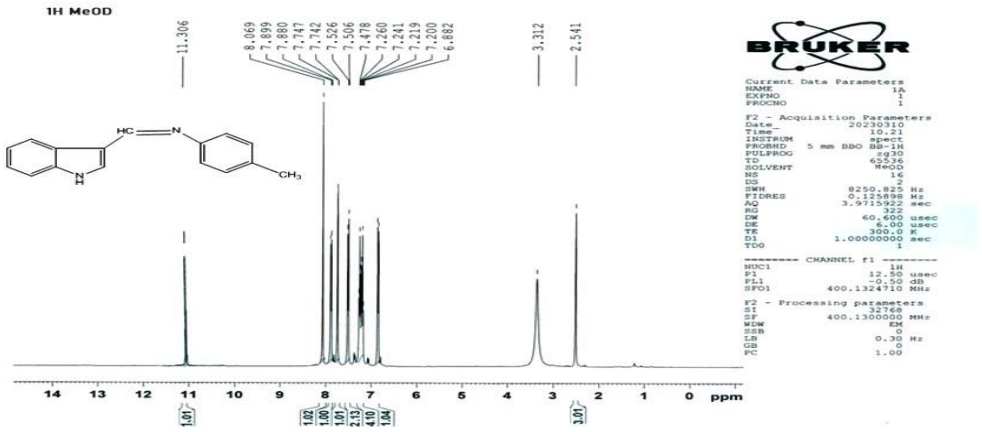

Fig-4: ^{1}H-NMR spectral data of N-[(1*H*-indol-3-yl)methylene]-4-methylaniline (3g)

N-[(1*H*-indol-3-yl)methylene]-4-methoxyaniline (3i):

IR (KBr) νmax: 3458.16 (-NH-), 3063.14 (=C-H), 2930.09 (C-H), 1627.59 (C=C), 1676.32 (C=N). **^{1}H-NMR (DMSO, 400 MHz):** 12.008 (1H, s, indole NH), 2.330 (3H, s, OCH_3), 7.236-7.369 (4H, m, Phenyl), 7.506-7.533 (2H, t, indole C_5-H & C_6-H), 7.749-7.780 (1H, d, indole C_2-H), 7.874-7.990 (1H, d, indole C_7-H), 8.143 (1H, s, –CH=N-) 6.890-7.222 (1H, d, indole C_4-H).

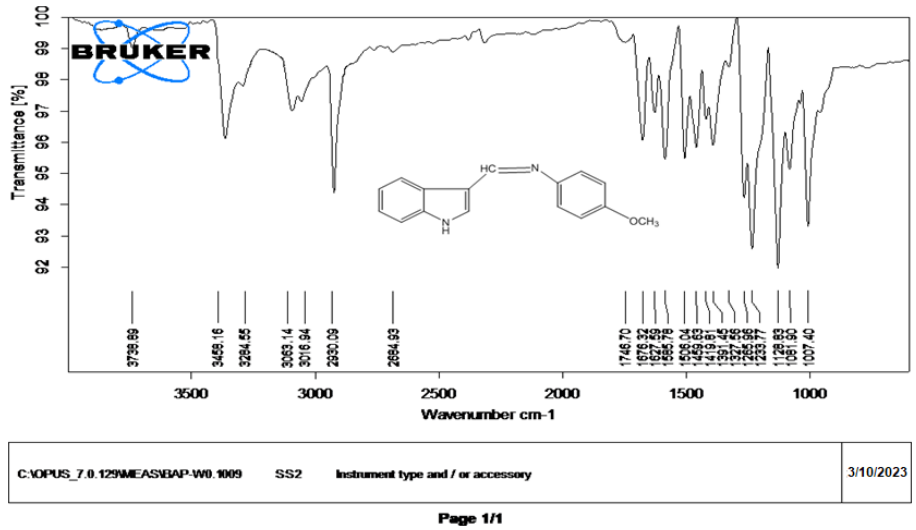

Fig-5: IR spectral data of N-[(1*H*-indol-3-yl)methylene]-4-methoxyaniline (3i)

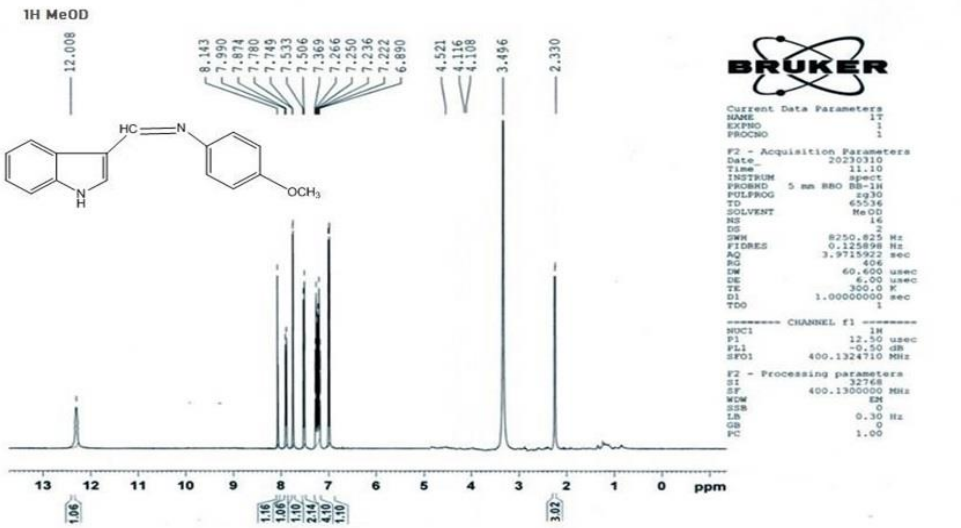

Fig-6: ^{1}H-NMR spectral data of N-[(1*H*-indol-3-yl)methylene]-4-methoxyaniline (3i)

Molecular docking studies at COX-1 and COX-2 isoenzymes

Molecular Docking is a method which anticipates the favored orientation of ligand against receptor (Protein) to make a stable complex [19,20]. Favored orientation possibly utilized to predict the strength of connection or binding affinity among ligand and protein by utilizing scoring functions. Docking is often applied to anticipate the binding orientation of drug candidates against protein targets in order to predict the affinity and activity of the drug. Non-steroidal anti-inflammatory drugs (NSAIDs) are COX inhibitors and prevent PG synthesis, thus exhibiting analgesic, antipyretic and anti-inflammatory actions. However, NSAIDs have a number of adverse effects, mainly because of their inhibition of the constitutive isoform of COX. The major adverse effects of NSAID are gastrotoxic effects (*e.g.*, damage of gastric mucosa, gastric bleeding and gastroduodenal ulcers), increased bleeding tendency and delay of the birth process [21]. The two definitely known isoforms of cyclooxygenases (COX), named COX-1 and COX-2, show distinct expressions patterns and distinct biological activities. COX isoenzymes were the targets for determining the anti-inflammatory activity and the target proteins were downloaded from a protein databank PDB ID: 3KK6 (COX-1) and PDB ID: 3LN1 (COX-2) having a resolution of 2.75 Å and 2.9 Å, respectively. AutoDock 4.2.6 software was utilized to know the type of interactions of the designed ligands with the 3KK6 and 3LN1 active site regions. ChemDraw Ultra 12.0 software was used to draw the designed structures and they were converted into suitable 3D models. By applying molecular mechanics they were subjected to energy minimizations, which are required for molecular docking and for the preparation of corresponding pdb files. Docking studies were performed to find out the possible locations for the ligand in the active site region of the receptor. Grid-based docking studies was carried out using default parameters and docking was performed by considering indomethacin and celecoxib as standard ligands at COX-1 and COX-2 active sites respectively [22,23].

RESULTS AND DISCUSSION

Indole moiety containing various schiff's bases were designed and prepared.Diverse schiff's bases **(3a-3i)** were synthesized using the appropriate below synthetic procedure i.e. reaction of indole-3-aldehyde (**1**) and aromatic amines (**2**) in presence of amla water extract as acid catalyst**.** Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr discs on an Bruker (300 FT-IR). ^{1}H-NMR spectra were recorded on a Bruker 400 spectrometer operating at 400.13 MHz for 1H in DMSO.

All the designed ligand molecules were subjected to molecular docking to investigate their binding mode at COX-1 and COX-2 isoenzymes. Biological target of COX-1 and COX-2 isoenzymes were

downloaded from the protein data bank (COX-1 PBD ID: 3KK6 & COX-2 PDB ID: 3LN1). AutoDock molecular docking technique was employed to dock the designed ligands against COX isoenzymes PDB IDs to trace the interaction between various ligand molecules and COX isoenzymes. Indomethacin and Celecoxib were taken as reference ligands. Molecular docking was performed using recently updated version AutoDock docking engine 4.2 software tool. Computed binding energy values, number of hydrogen bonds, hydrogen bond length and interacted amino acid residues of all the ligands along with the reference compounds at 3KK6 and 3LN1 were depicted in the **Table-2** and **Table-3** respectively.

The interaction of Indomethacin at the COX-1 isoenzyme active site 3KK6 has showed binding energy of -8.21 kcal/mol and the interacted amino acids are Gly495, Leu500, Ala496, Arg89, Val492, Val318, Leu321, Val85, Ser322, Tyr324, and Leu328. The interaction of compound **3c** at the COX-1 isoenzyme active site 3KK6 has showed binding energy of -8.72 kcal/mol and the interacted amino acids are Ile491, Val317, Met490, Leu320, Ala495, Val84, Leu327, Ser498, Leu499, Ser321, Arg88, and Tyr323. The interaction of compound **3g** at the COX-1 isoenzyme active site 3KK6 has showed binding energy of -8.24 kcal/mol and the interacted amino acids are Leu499, Ile491, Ala495, Met490, Tyr323, Leu327, Val84, Leu320, and Val317. Compound **3c** shown promising binding affinity at 3KK6 active site.

The interaction of Celecoxib at the COX-2 isoenzyme active site 3LN1 has showed binding energy of -10.07 kcal/mol and the interacted amino acids are Leu328, Tyr324, Arg89, Ala496, Val318, Tyr354, Val492, Leu321, Trp356, Phe487, Gln161, and Phe350. The interaction of compound **3c** at the COX-2 isoenzyme active site 3LN1 has showed binding energy of -9.09 kcal/mol and the interacted amino acids are Val492, Trp356, Ala496, Val318, Arg89, Tyr354, Phe487, Ser499, and Leu500. The interaction of compound **3g** at the COX-2 isoenzyme active site 3LN1 has showed binding energy of -9.66 kcal/mol and the interacted amino acids are Val492, Ala496, Leu500, Arg89, Val318, Gly495, Trp356, Met491, Phe350, Tyr354, and Leu353. Compound **3g** shown promising binding affinity at 3LN1 active site.

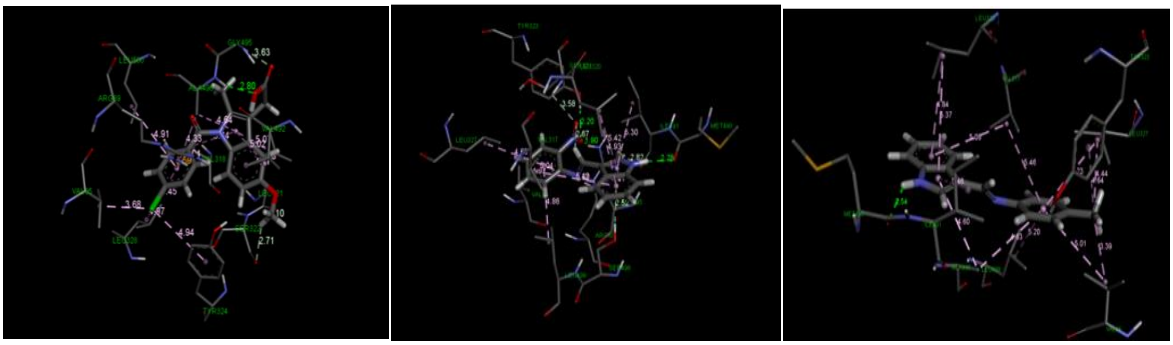

Fig-7: 3D interactions of Indomethacin, compound 3c and 3g at 3KK6.

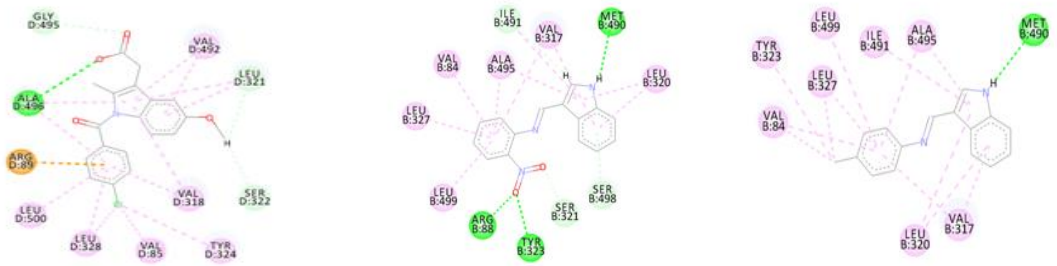

Fig-8: 2D interactions of Indomethacin, compound 3c and 3g at 3KK6.

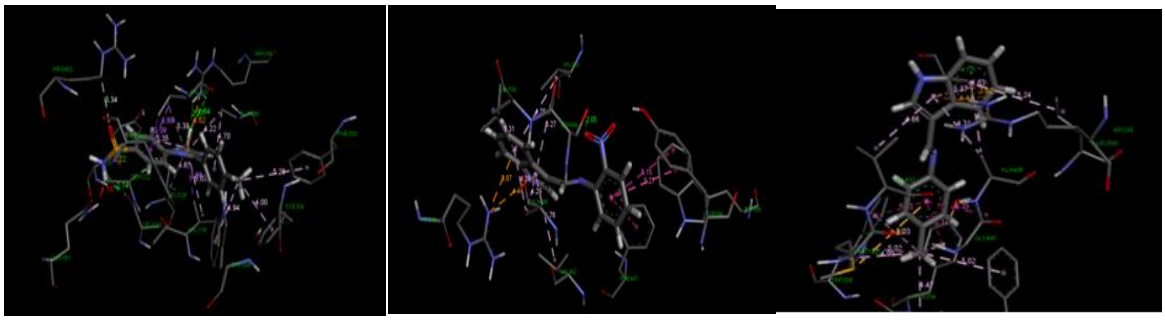

Fig-9: 3D interactions of Celecoxib, compound 3c and 3g at 3LN1

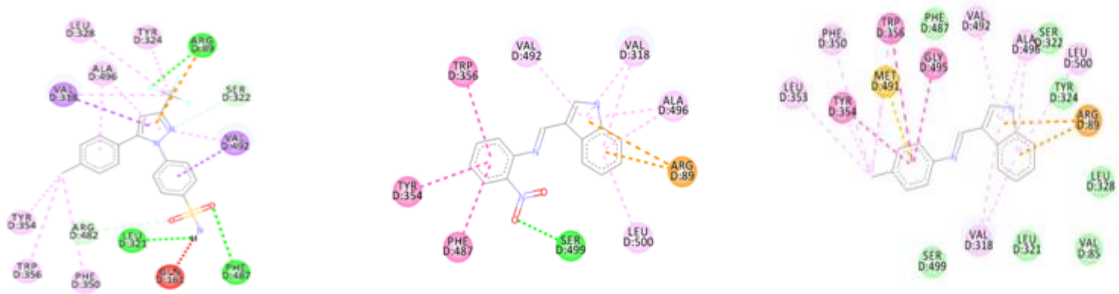

Fig-10: 2D interactions of Celecoxib, compound 3c and 3g at 3LN1

Table-2: Binding energy and amino acid residues interacted by the compounds **3a-3i** with the target COX-1 isoenzyme protein PDB ID – 3KK6.

Compound	**Binding energy** (kcal/mol)	**No. of H bonds**	**H-bond length**	**Amino acid residues interacted**
Indomethacin	-8.21	11	3.63, 2.80, 4.64, 4.91, 4.33, 5.04, 3.68, 4.94, 2.97, 3.10, 3.45	Gly495, Leu500, Ala496, Arg89, Val492, Val318, Leu321, Val85, Ser322, Tyr324, Leu328
3a	-7.78	5	3.24, 4.54, 5.10, 4.56, 3.21	Val318, Met490, Ala495, Val84, Ser498, Leu499, Ser321, Arg88, Leu320
3b	-8.10	9	5.24, 3.33, 5.23, 4.85, 5.10, 4.63, 5.43, 3.50, 4.70	Met490, Leu320, Val317, Ala495, Ile491, Leu499, Tyr323, Leu327, Val84
3c	-8.72	10	2.20, 3.57, 2.66, 2.82, 2.51, 5.42, 5.30, 4.41, 5.48, 4.92	Ile491, Val317, Met490, Leu320, Ala495, Val84, Leu327, Ser498, Leu499, Ser321, Arg88, Tyr323
3d	-8.06	7	3.48, 2.28, 4.56, 3.48, 4.61, 5.48, 3.52	Leu500, Arg89, Val492, Val318, Val85, Tyr324, Leu328, Gly495
3e	-8.04	12	4.94, 5.47, 5.26, 4.86, 5.40, 3.67, 4.20, 4.91, 4.40, 2.77, 2.35, 5.28	Ile491, Ala495, Met490, Tyr323, Leu320, Val84, Ser498, Leu327, Val317, Leu499
3f	-8.14	8	4.85, 3.26, 2.25, 3.48, 5.18, 2.16, 5.43, 2.62	Ala495, Val84, Ser321, Arg88, Tyr323, Leu327, Val317, Leu499
3g	-8.24	10	3.84, 5.37, 5.46, 4.44, 3.29, 5.01, 5.20, 4.60, 2.54, 3.46	Leu499, Ile491, Ala495, Met490, Tyr323, Leu327, Val84, Leu320, Val317
3h	-7.89	7	4.45, 5.12, 4.35, 2.18, 4.61, 5.22, 2.48	Val85, Tyr324, Leu328, Gly495, Tyr323, Leu320, Val84
3i	-7.76	7	4.91, 5.45, 5.27, 4.12, 4.63, 3.04, 4.56	Leu327, Tyr323, Leu320, Val84, Gly494, Val317, Ala495

Table-3: Binding energy and amino acid residues interacted by the compounds **3a-3i** with the target COX-2 isoenzyme protein PDB ID – 3LN1.

Compound	Binding energy (kcal/mol)	No. of H bonds	H-bond length	Amino acid residues interacted
Celecoxib	-10.07	7	2.72, 3.36, 3.22, 5.70, 4.66, 5.35, 5.34	Leu328, Tyr324, Arg89, Ala496, Val318, Tyr354, Val492, Leu321, Trp356, Phe487, Gln161, Phe350
3a	-8.48	5	2.46, 5.48, 2.54, 3.52, 5.10	Ala496, Leu500, Phe350, Tyr354, Ala496, Val318, Arg89
3b	-8.38	11	4.62, 5.36, 3.92, 4.44, 4.35, 2.68, 4.32, 5.04, 4.98, 5.21, 4.48	Phe350, Met491, Phe487, Val492, Ala496, Ser322, Trp356, Tyr354, Leu328, Val318
3c	-9.09	8	2.06, 5.15, 5.27, 3.27, 4.31, 4.29, 3.76, 2.87	Val492, Trp356, Ala496, Val318, Arg89, Tyr354, Phe487, Ser499, Leu500
3d	-8.96	7	3.46, 5.18, 2.32, 3.38, 3.79, 2.59, 5.01	Leu500, Arg89, Val318, Gly495, Leu353, Trp356
3e	-8.93	9	5.82, 5.24, 4.09, 3.85, 3.54, 5.25, 4.85, 3.78, 4.38	Val492, Leu328, Ala496, Tyr324, Val318, Leu500, Gly495, Tyr354, Met491, Arg89
3f	-8.78	6	4.64, 5.48, 2.35, 3.54, 3.39, 4.25	Val318, Tyr354, Trp356, Phe487, Gln161, Tyr354, Leu328, Val318
3g	-9.66	8	5.24, 4.66, 5.21, 4.35, 5.02, 4.42, 3.08, 4.32	Val492, Ala496, Leu500, Arg89, Val318, Gly495, Trp356, Met491, Phe350, Tyr354, Leu353
3h	-9.00	5	2.56, 4.84, 3.57, 2.82, 3.66	Gly495, Tyr354, Phe487, Met491, Leu500, Gly495, Leu353
3i	-8.67	9	5.12, 5.06, 3.87, 4.09, 4.21, 3.15, 5.30, 5.66, 3.70	Val492, Arg89, Leu500, Val318, Ala496, Leu328, Gly495, Met491, Tyr354, Phe487,

CONCLUSION

In the present work, facile method under green reaction conditions using amala water as catalyst has been developed for the synthesis of diverse aryl substituted schiff's bases in good yields. All the compounds synthesized were characterized by physically (R_f values, Melting point, Molecular weight, Molecular formula) and few compounds were characterized by spectral data (^{1}H-NMR, IR spectra). Among the synthesized compounds N-[(1*H*-indol-3-yl)methylene]-3-aminophenol (**3f**) gives high percentage yield (90.31%). Molecular docking studies at COX-1 isoenzyme protein PBD ID- 3KK6 states that the compounds **3c** and **3g** showed good binding affinity -8.72 kcal/mol, -8.24 kcal/mol respectively in comparison to the reference compound Indomethacin -8.21 kcal/mol. Molecular docking studies at COX-2 isoenzyme protein PBD ID- 3LN1 states that the compounds **3c** and **3g** showed good binding affinity -9.09 kcal/mol, -9.66 kcal/mol respectively in comparison to the reference compound Indomethacin -10.07 kcal/mol. Finally from the molecular docking studies, it was concluded that compounds **3c** and **3g** possess non-selective inhibition towards the COX isoenzymes.

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