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DOCKING, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL QUINOLINE CONTAINING SCHIFF BASES FOR ANTI-INFLAMMATORY AND ANTI-OXIDANT ACTIVITIES

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Keywords:

Quinolines, *In-silico*, Docking, Anti-inflammatory, Grind stone technique, Reflux, 2-chloro quinoline 3-carbaldehyde

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ABSTRACT: Quinolines bears a very good synthon so that a variety of novel heterocyclic with good pharmaceutical profile can be designed. There are various biological activities for quinolones such as antibacterial, antimalarial and various drugs possessing quinolone as nucleus are ciprofloxacin (Cipro), lomefloxacin (Maxaquin), norfloxacin (Noroxin), ofloxacin (Floxin), moxifloxacin (Avelox) and levofloxacin (Levaquin). So, in the present work 2-chloro quinoline 3-carbaldehyde containing quinolines were synthesized by using solvent conservation techniques like reflux technique. Various quinolines derivatives were synthesized by the condensation reaction between dimethylformamide, $PoCl_3$, and different substituted aniline to give 2-chloro 3-carbaldehyde (1a). The reaction of 2-chloro 3- carbaldehyde with metformin gives quinolines Schiff bases as final compound (2a-2d). The obtained product was purified and structures were confirmed by TLC, MP & IR spectroscopy. All the compounds were screened for *in-vitro* anti-inflammatory activity using diclofenac sodium as standard by using protein denaturation method. Further, the selected compounds also studied for anti-inflammatory activity by *in-vitro* methods and anti-oxidant activity by hydrogen peroxide methods. Some of the compounds have shown significant activities compared to standard.

INTRODUCTION: Quinolines was discovered in coal tar distillate by Runge in 1832 & named Leukol. It is a heterocyclic scaffold of paramount importance to the human race. Quinoline (or) 1-azo-napthlene or benzo (b) pyridine is nitrogen-containing aromatic compound, it has molecular formula of C_9H_7N & its molecular weight is 129.16.

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The logP value is 2.09 & has an acidic Pkb of 4.85 & basic Pka of 9.5. It is a weak tertiary base. It shows both electophilic and nucleophilic substitution reactions. It is non-toxic to humans on oral absorption and inhalation. Quinoline nucleus is occurred from several natural compounds (cinchona alkaloids) and pharmacologically active substance displaying abroad range of biological activity [1-5].

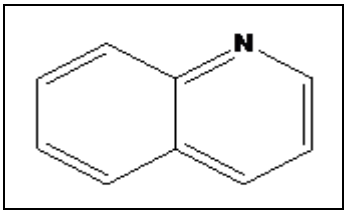


FIG. 1: QUINOLINE

The rootstock of quinoline alkaloids is specific to the plant family Rutaceae embodying about hundred and fifty genera with sixteen species. Though alkaloids are natural products. They are also used as synthetic intermediates for the preparation of other quinoline alkaloids and polyheterocycles. Variety methods are such, as Doebner-von miller, skraup and combes. Friedlander and knorr synthesis can be used for the preparation of quinolines and their derivatives. Molecular docking is used to predict the structure of the intermolecular complex formed between two molecules [6-10]. The small molecule called ligand usually interacts with protein's binding sites. Binding sites are areas of protein known to be active in forming of compounds.

Therefore, the synthesis of quinolines derivatives attracted many researchers and various methods have been developed using a variety of catalysts and conditions. In the last few years, considerable attention has been focused on quinoline derivatives due to their interesting biological activities like anti-diabetes, anti-bacterial, anti-cancer, anti-inflammatory, anti-oxidant, *etc.* Quinolines also play a significant role in synthetic chemistry. So, in the present work we aimed to synthesize Schiff bases containing quinoline nucleus, characterize the derivatives using physical and spectral methods, evaluate the *in-silico* anti-inflammatory activity by docking studies, screen the *in-vitro* antioxidant activity and anti-inflammatory activities.

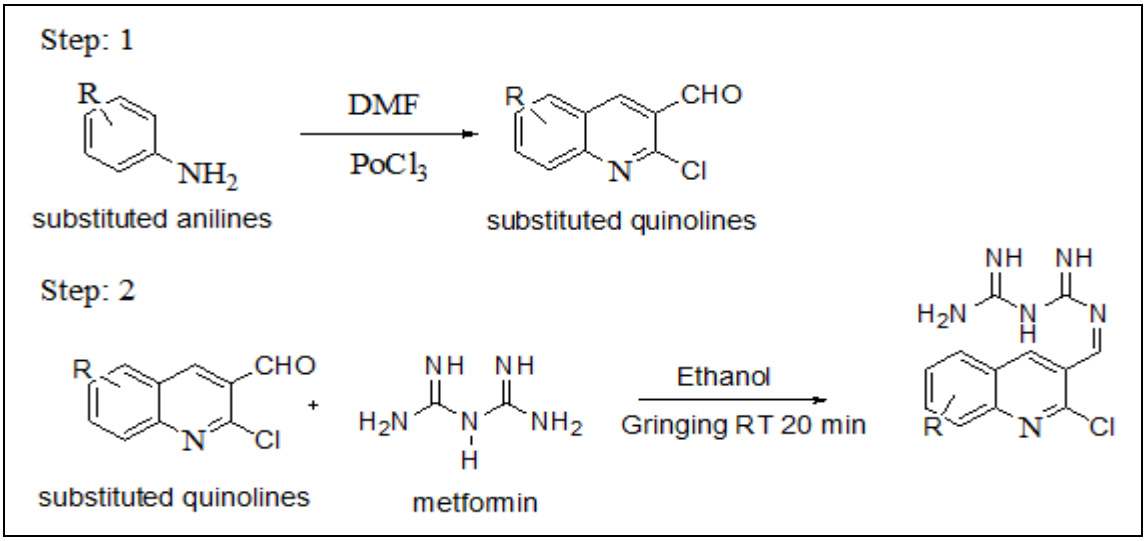
MATERIALS AND METHODS: All the chemicals and solvents used were of synthetic grade from finer chemicals Ltd., (Mumbai, India), E. Merck, SD Fine-Chemicals. Melting points were determined in open capillary tubes using melting point apparatus and are uncorrected. The purity of the compound was verified by a single spot in TLC using F254, 0.25 mm aluminum plates with mobile phase n-hexane and ethyl acetate (8:2, 7:3). The IR spectra were recorded on SHIMADZU FT-IR Spectrophotometer by using 1% potassium bromide discs.

Experimental:

Methodology:

Step: 1 Synthesis of Quinolines: [11-16] Take accurately weighed amount of substituted aniline (0.1 Mol) into a round-bottomed flask and add 0.1 mol of dimethylformamide (7.7 ml) and phosphorous oxytrichloride 0.01 mol (0.2 ml). Then the contents are refluxed for 4 to 5 h. After completion of reaction time, take out the RBF from the water bath. The product was poured into crushed ice and precipitate was obtained. After the formation of precipitate the product was filtered off. Finally, collect the product and then air-dried. After the formation of the dried product, it was recrystallized by using ethanol.

Step 2: Synthesis of Quinoline Contains Metformin (Grind Stone Technique): Accurately weighed equimolar concentration of metformin and first step product (substituted quinoline) were taken in a mortar and 20 ml methanol or ethanol was added. The compounds are ground for 20 min continuously in one direction.



SCHEME 1

The product was added to ice. Then the product was filtered and air-dried. After the formation of dried product, it was recrystallized by using ethanol. Finally, the reaction completed is identified by monitoring melting point and TLC.

RESULTS AND DISCUSSION: Identification and characterization of the synthesized Schiff bases containing quinoline derivatives were performed by the following procedure to establish that all the derivatives had different chemical nature compared to that of the parent compounds.

- Melting point
- Solubility
- Thin-layer chromatography
- Infrared spectroscopy

Determination of Melting Point: Melting points of the synthesized organic compounds were determined using the open capillary tube method. Melting point is one of the physical parameters that indicate the purity of the organic compounds in the form of pure crystals having sharp and definite melting points. The melting point of the recrystallized derivatives was performed using heco melting point apparatus.

TABLE 1: PHYSICAL DATA OF QUINOLINE SCHIFF BASES

S. no.	Compound	R	Molecular formula	Molecular weight	M.P(ºC)	Yield (%)
1	Cpd1	OH	$C_{12}H_{11}ON_6Cl$	290.74	191 ºC - 193 ºC	92%
2	Cpd2	COOH	$C_{13}H_{11}O_2N_6Cl$	318.71	201 ºC - 203 ºC	85%
3	Cpd3	OCH_3	$C_{13}H_{13}ON_6Cl$	304	165 ºC - 168 ºC	75%
4	Cpd4	Cl	$C_{12}H_{10}Cl2N_6$	309.154	179 ºC - 180 ºC	80%

TABLE 2: IUPAC NAME OF THE SYNTHESISED COMPOUNDS

Compounds	R	IUPAC name
Cpd1	OH	*N*-[(*E*)-(2-chloro-6-hydroxyquinolin-3-yl)methylidene]imidodicarbonimidic diamide
Cpd2	OCH3	*N*-[(*E*)-(2-chloro-6-methoxyquinolin-3-yl)methylidene]imidodicarbonimidic diamide
Cpd3	COOH	3-{(*E*)-[(*N*-carbamimidoylcarbamimidoyl)imino]methyl}-2-chloroquinoline-6-carboxylic acid
Cpd4	Cl	*N*-[(*E*)-(2,6-dichloroquinolin-3-yl)methylidene]imidodicarbonimidic diamide

Solubility: Solubility of synthesized derivatives was tested using different solvents. The solubility characters were listed.

Thin Layer Chromatography: In the process of identification of the formation of new compounds and determination of their purity, an important analytical technique is a chromatography. For each of the compounds, R_f value is the unique characteristic parameter. Commercial aluminum chromatographic plates were purchased from SD fine chemicals, Mumbai.

TABLE 3: R_f VALUES OF SYNTHESIZED COMPOUNDS

S. no.	Compound code	R_f Value
1	CPD1	0.51
2	CPD-2	0.43
3	CPD-3	0.61
4	CPD-4	0.36

Solvent System Preparation: The solvent system is mobile phase to carry out TLC analysis was prepared by mixing n-hexane: ethyl acetate. The mobile phase is placed in the development chamber.

Application Sample: The derivatives and their compounds were dissolved in the appropriate solvent system and were spotted on the TLC plates using capillary tube on the baseline, 2 cm above from the bottom of the plates.

Then the plates were allowed to dry at room temperature and placed in the development chamber.

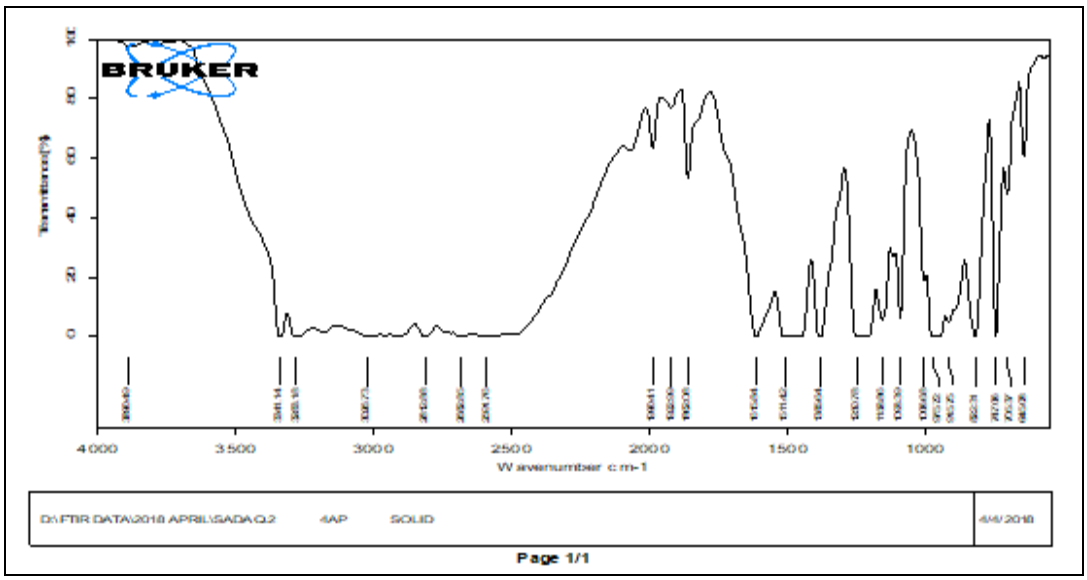
Chromatogram Development: Ascending technique was used for the development of chromatogram. Plates were taken out of the chamber when the solvent front hat reached $3/4^{th}$ of the plate and dry at room temperature

Detection of Spots: Under UV chamber the developed TLC plates were placed and spots were observed.

R_f Value: Using the following formula, the R_f values were calculated:

R_f value = Distance traveled by sample / Distance traveled by solvent front

IR Spectroscopy:



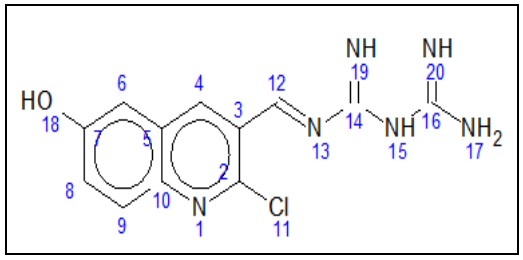
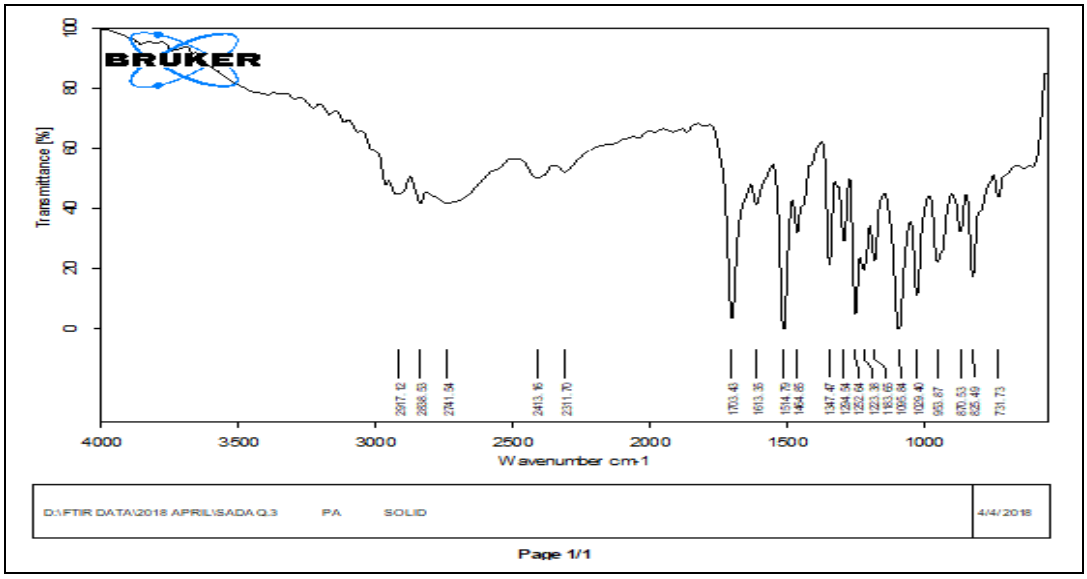


FIG. 2: IR SPECTRUM OF COMPOUND 1



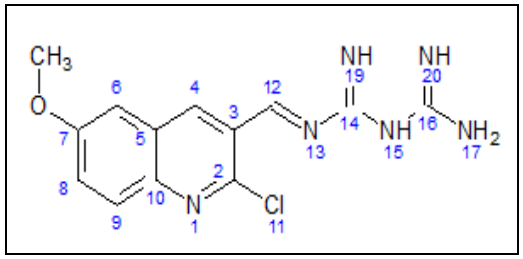
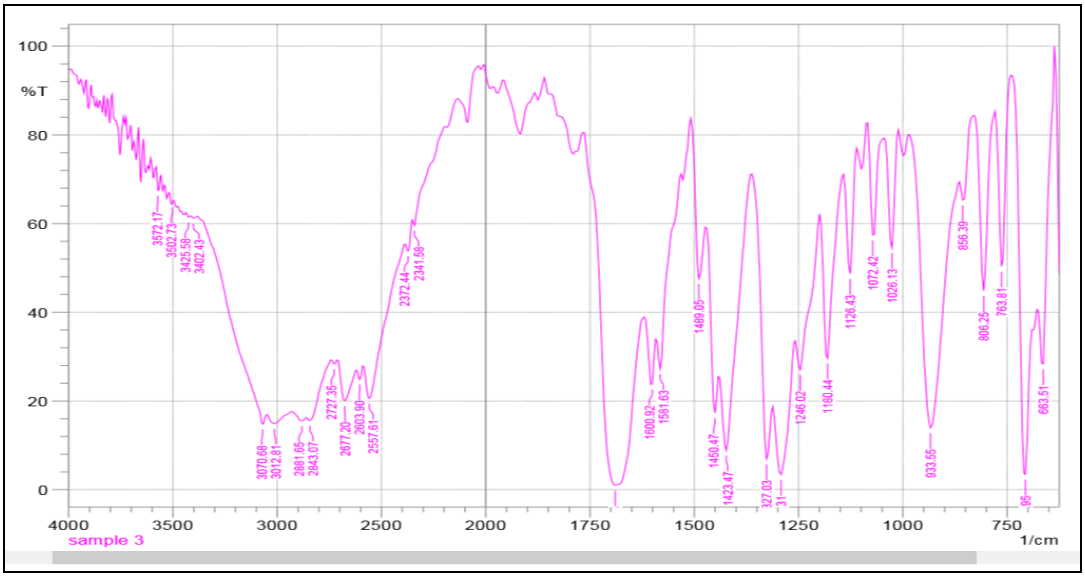


FIG. 3: IR SPECTRUM OF COMPOUND 2



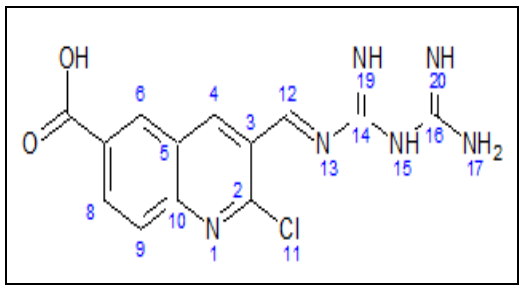
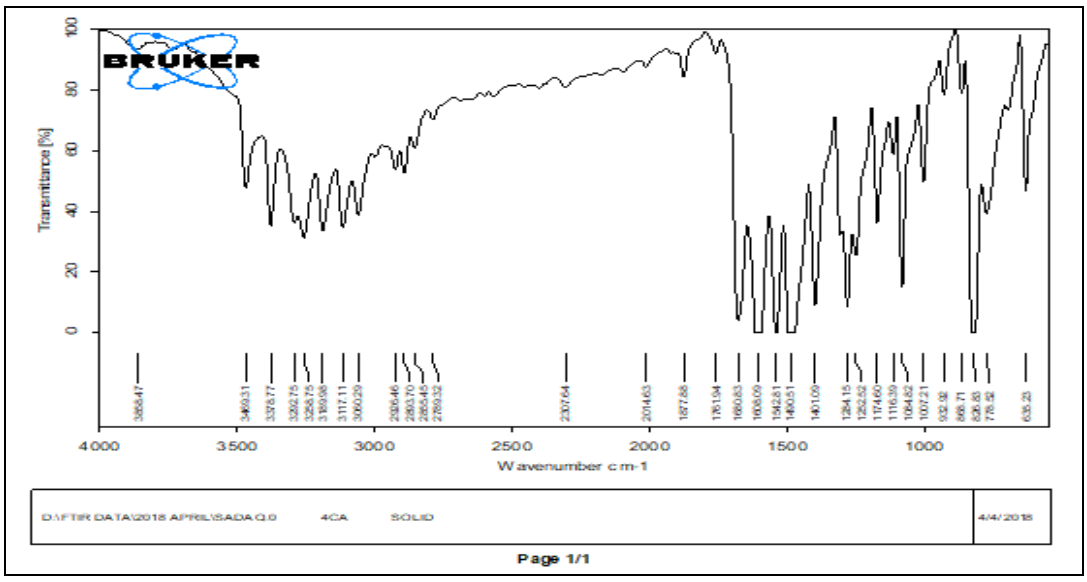


FIG. 4: IR SPECTRUM OF COMPOUND 3



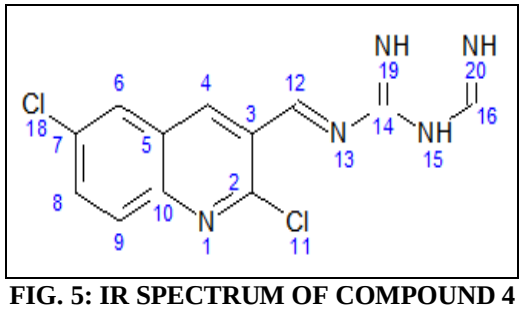


FIG. 5: IR SPECTRUM OF COMPOUND 4

TABLE 4: SPECTRAL DATA OF THE COMPOUNDS

Compound	R	IR stretching frequency of the compounds
Cpd1	OH	Aromatic(N-H) 3341.55 Aromatic (C-H) 2812.95 C=C 1511.77 C=N 1466.33
Cpd2	OCH_3	Aromatic(N-H) 2917.12 Aromatic (C-H) 2838.81 C=C 1514.79 C=N 1454.65
Cpd3	COOH	Aromatic(N-H) 3402.43 Aromatic (C-H) 3070.66 C=C 1561.63 C=N 1450.47
Cpd4	Cl	Aromatic(N-H) 3433.31 Aromatic (C-H) 3117.11 C=C 1542.81 C=N 1430.51

TABLE 5: IR SPECTRAL DATA OF COMPOUND 1

Functional group	Vibrations	Absorption frequency (cm^{-1})
Aromatic (N-H)	Stretch	3341.55
Aromatic (C-H)	Stretch	2812.95
C=C	Stretch	1511.77
C=N	Stretch	1466.33

TABLE 6: IR SPECTRAL DATA OF COMPOUND 2

Functional group	Vibrations	Absorption frequency (cm^{-1})
Aromatic (N-H)	Stretch	2917.12
Aromatic (C-H)	Stretch	2838.81
C=C	Stretch	1514.79
C=N	Stretch	1454.65

TABLE 7: IR SPECTRAL DATA OF COMPOUND 3

Functional group	Vibrations	Absorption frequency (cm^{-1})
Aromatic (N-H)	Stretch	3402.43
Aromatic (C-H)	Stretch	3070.66
C=C	Stretch	1561.63
C=N	Stretch	1450.47

TABLE 8: IR SPECTRAL DATA OF COMPOUND 4

Functional group	Vibrations	Absorption frequency (cm^{-1})
Aromatic (N-H)	Stretch	3433.31
Aromatic (C-H)	Stretch	3117.11
C=C	Stretch	1542.81
C=N	Stretch	1430.51

In-vitro Anti-Inflammatory Activity: [17-22]

Albumin Denaturation Assay: The test compounds were prepared in different concentrations. From the test solution, 1 ml was taken and 1 ml of 1% aqueous solution of Egg albumin fraction was added and pH was adjusted to 6.8 by using glacial acetic acid. The sample was incubated at 72 ºC for 5 min and then cooling for 10 min. After the turbidity was obtained, the absorbance of the sample was measured spectro-photometrically at 660 nm. The experiment was performed in triplicate.

***In-vitro* Anti-oxidant Assay:** The test sample of different concentrations were prepared by taking required amount of sample dissolved in 10 ml phosphate buffer solution. These are labeled as the standard solution. From these solutions 0.1 ml of sample was taken and 0.6 ml H_2O_2 was added and this is labeled as standard dilution B. From the B Standard solution different serial dilutions were carried out to obtain different concentrations *i.e.* 200 µg/ml, 400 µg/ml, 600 µg/ml, 800 µg/ml and 1000 µg/ml. These samples were incubated at 70 ºC for 5 min and then cooled for 10 min. The absorbance was measured spectrophotometrically at 230 nm. The experiment was performed in triplicate.

TABLE 9: ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS BY PROTEIN DENATURATION METHOD

S. no.	Concentration % inhibition	Compound 1 % inhibition	Compound 2 % inhibition	Compound 3 % inhibition	Compound 4 % inhibition
1	200 µg	70.46	12.21	19.59	28.81
2	400 µg	72.28	38.46	49.40	56.87
3	600 µg	76.84	44.94	66.63	65.78
4	800 µg	81.40	47.67	79.67	72.22
5	1000 µg	88.69	54.96	93.89	87.56

TABLE 10: ANTI-INFLAMMATORY ACTIVITY OF STANDARD C: (STANDARD)

S. no.	Concentration (µg/ml)	% Inhibition
1	200	68.64
2	400	75.02
3	600	80.47
4	800	86.87
5	1000	94.16

RESULTS AND DISCUSSION: In this present research work, based on the wide literature survey, novel derivatives of quinoline Schiff bases were synthesized in two-step facile procedures and the four in number.

All the reaction**s** were monitored by TLC and purification was done by recrystallization process. All the derivatives were characterized using special studies like FT-IR spectroscopy.

The newly synthesized compounds have been subjected to the following screening tests by appropriate standard methods.

1. *In-silico* anti-inflammatory activity (docking studies).
2. *In-vitro* anti-inflammatory activity (Protein denaturation method).
3. *In-vitro* anti-oxidant activity (Hydrogen peroxide method).

All the four derivatives were screened for their *in-vitro* anti-inflammatory activity using protein denaturation method and these were also subjected to *in-silico* anti-inflammatory activity study using docking methodology against protein arginine demainase as a target.

***In-vitro* Antioxidant Activity:** The antioxidant activity of the synthesized derivatives, II-a to II-d was carried out using Hydrogen peroxide scavenging method employing Ascorbic acid as standard at various concentrations from 200 to 1000 µg/ml. Out of all the four synthesized compounds, except III-a, remaining three derivatives have shown good to excellent activities similar minimum inhibitory concentrations compared to that of the standard ascorbic acid.

TABLE 11: ANTIOXIDANT ACTIVITY OF SYNTHESIZED COMPOUNDS BY HYDROGEN PEROXIDE METHOD

S. no.	Concentration % inhibition	Compound 1 % inhibition	Compound 2 % inhibition	Compound 3 % inhibition	Compound 4 % inhibition
1	200 µg	89.16	86.15	89.98	85.89
2	400 µg	90.18	91.12	93.14	90.96
3	600 µg	91.12	93.18	96.93	93.99
4	800 µg	93.28	97.12	99.23	95.13
5	1000 µg	99.78	93.98	99.11	99.99

TABLE 12: ANTIOXIDANT ACTIVITY OF ASCORBIC ACID: (STANDARD)

S. no.	Concentration (µg/ml)	% Inhibition
1	200	90.15
2	400	92.18
3	600	93.87
4	800	97.99
5	1000	99.55

***In-silico* Anti-Inflammatory Activity:** For all the derivatives, docking study was performed by AUTODOCK 4.2 version for theoretical prediction of anti-inflammatory activity using "Protein arginine deaminase" as the target site. Results revealed that the synthesized derivatives possess more binding affinity towards the target.Based on the results the derivates with hetero atoms like "O" and "N" in the ring or in substituted groups showed high binding affinity to the target.

III d> IIIC>IIIB>IIIA

QSAR Parameters: All the derivatives were subjected to QSAR study to obtain the QSAR of parameters data like molecular weight. Log P, number hydrogen bond donors, no. of hydrogen bond acceptors, no. of rotatable bonds, total polar surface area, and ADME test. Based on the results obtained, all the derivatives were found to follow Lipinski's rule of 5 and passes ADME test.

The experimental details of each of the methods employed to evaluate the compounds in the present studies were presented along with the observations that were recorded in the form of tables. The experimental findings were discussed in comparison with standards employed for each of the activity.

Compound 01 docking interactions with Protein Arginine Deiminase (PDB ID: 5N0M):

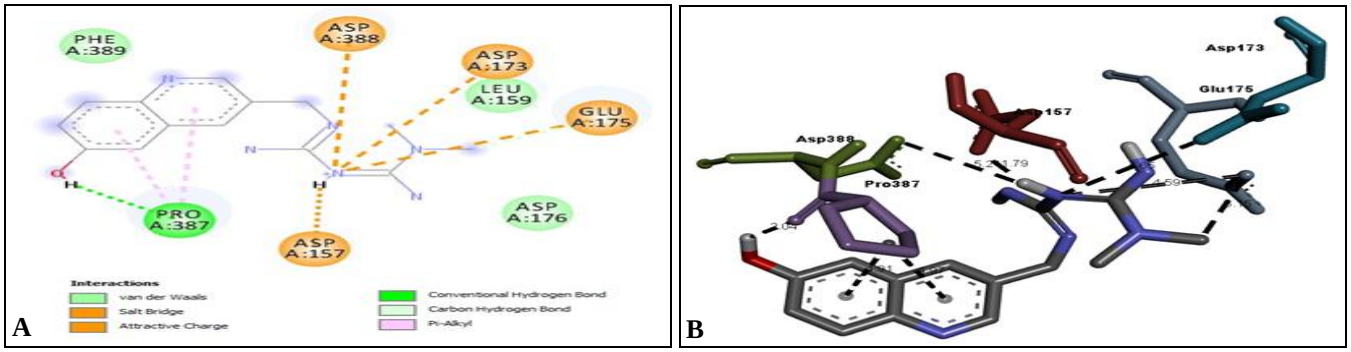


FIG. 6: A) REPRESENTS 2D INTERACTIONS OF COMPOUND 01, B) REPRESENTS 3D INTERACTION FORMED BY THE COMPOUND 01WITH PROTEIN ARGININE DEIMINASE DRUG TARGET

Compound 02 docking interactions with Protein Arginine Deiminase (PDB ID: 5N0M):

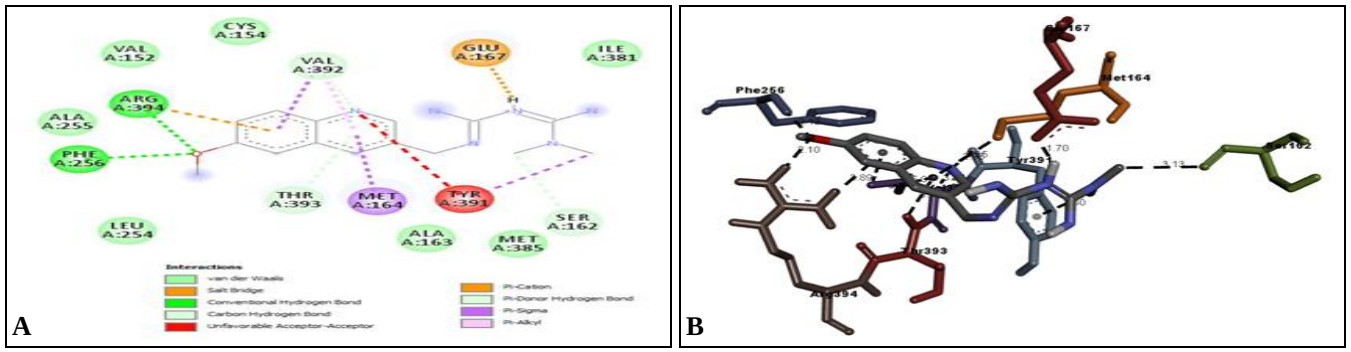


FIG. 7: A) REPRESENTS 2D INTERACTIONS OF COMPOUND 02, B) REPRESENTS 3D INTERACTION FORMED BY THE COMPOUND 02 WITH PROTEIN ARGININE DEIMINASE DRUG TARGET

Compound 03 docking interactions with Protein Arginine Deiminase (PDB ID: 5N0M):

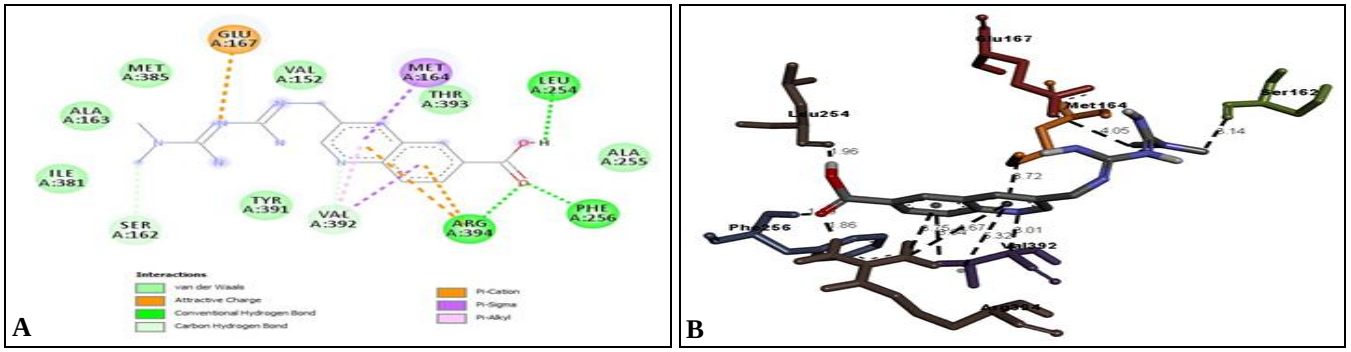


FIG. 8: A) REPRESENTS 2D INTERACTIONS OF COMPOUND 03, B) REPRESENTS 3D INTERACTION FORMED BY THE COMPOUND 03 WITH PROTEIN ARGININE DEIMINASE DRUG TARGET

Compound 04 docking interactions with Protein Arginine Deiminase (PDB ID: 5N0M):

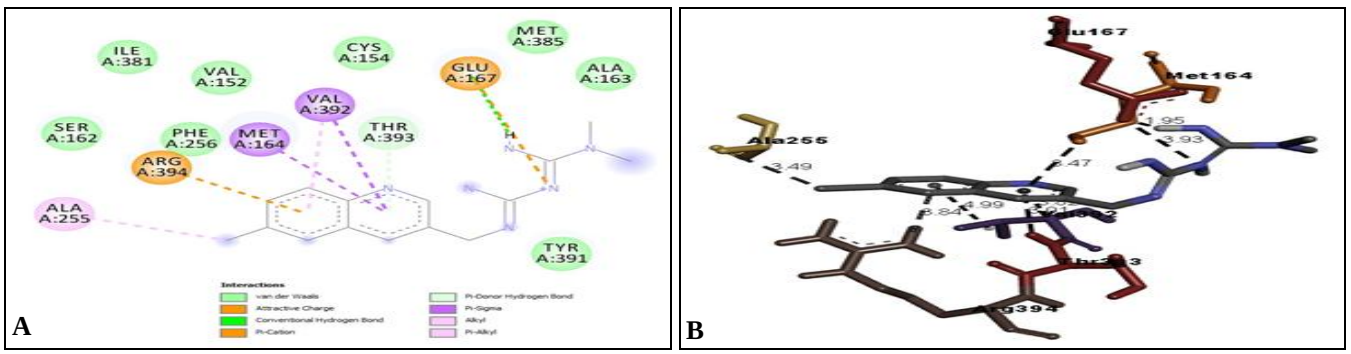


FIG. 9: A) REPRESENTS 2D INTERACTIONS OF COMPOUND 05, B) REPRESENTS 3D INTERACTION FORMED BY THE COMPOUND 05 WITH PROTEIN ARGININE DEIMINASE DRUG TARGET

TABLE 13: MOLECULAR DOCKING STUDIES OF COMPOUNDS WITH PROTEIN ARGININE DEAMINASE

S. no.	Compound Code	R	Binding interactions	
			Type of interaction	Amino acid residue
1	Compound 1	OH	Vander wall conventional hydrogen bond carbon-hydrogen bond Pi-Alkyl	PHE A:389, ASPA:388, ASP A:173 GLU A: 175, ASPA; 157. PRO A : 387 PRO A : 387 PHE A : 389 PRO A : 387
2	Compound 2	OCH_3	Vander walls, Conventional hydrogen bond carbon-hydrogen bond Pi-carbon, R- hydrogen bond Pi-alkyl	ALA A: 255, VAL A: 152 ILE A: 381 MET A: 385, ALA A:163 LEU A: 284. GLU A: 167 ARG A: 394, PHE A: 394. TYR A : 391 LEU A: 254, THR A: 393, SER A : 162 GLU:167, ARG A :394 THR A : 393 MET A : 164 VAL A : 392
3	Compound 3	COOH	Vander wall, Attractive charge conventional hydrogen bond, Carbon Hydrogen bond Pi-Carbon R-sigma Pi-Alkyl	ILE A : 381, ALA A :163, MET A : 385 VAL A:152, THR A : 393 ALA A : 225 TYR A : 391 GLU A : 167 LEU A : 254, PHE A : 256, ARG A : 394 ARG A : 394 GLU A : 167 MET A : 164 VAL A : 392
4	Compound 4	Cl	Vander wall, Attractive charge conventional hydrogen bond R-carbon P-Carbon hydrogen bond pi-sigma, pi-alkyl	SER A: 162, ILE A: 381, PHE A : 256, VAL A : 152, CYS A : 154, MET A : 385, ALA A : 163. ARG A : 394, GLU A :167, TYR A : 391 ARG A : 394, GLU A : 167 THE A : 393 MET A : 164, VAL A : 392 ALA A: 255 VAL A : 392

TABLE 14: DOCKING RESULTS OF COMPOUND-01 TO COMPOUND-05 TARGETING PROTEIN ARGININE DEIMINASE (PDB ID: 5N0M)

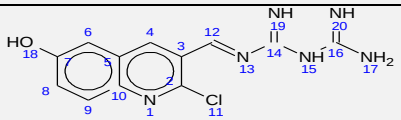
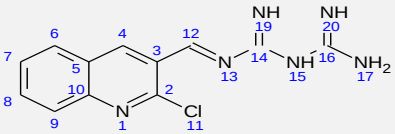
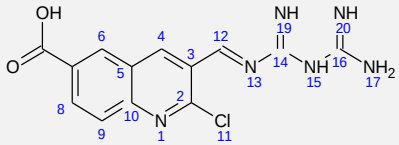
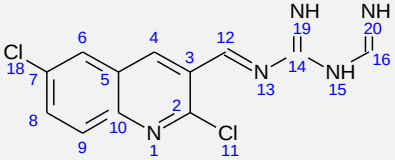
S. no.	Drug target	Compound name	Compound Structure	Binding Energy in Kcal/mol	Predicted IC_{50} value (nano molar)
1	Protein Arginine Deiminase (PDB ID: 5N0M)	Compound 01		-9.36	137.41 nM
2		Compound 02		-9.69	79.37 nM
3		Compound 03		-9.55	99.42 nM
4		Compound 04		-9.64	86.12 nM

TABLE 15: QSAR MOLECULAR DESCRIPTOR VALUES OF THE COMPOUNDS 01 TO 04 FOR ADME PREDICTIONS ACCORDING TO LIPINSKI'S RULE OF FIVE

S. no.	Compound name	Molecular formula	Mol. wt.	Log P	No. of H-bond donors	No. of H-bond acceptors	No. of rotatable bonds	TPSA	ADME pass/fail
1	Compound 01	$C_{12}H_{11}ON_6Cl$	290.74	0.6795	4	7	1	112.56	PASS
2	Compound 02	$C_{13}H_{11}O_2N_6Cl$	318.71	0.9552	3	7	2	101.56	PASS
3	Compound 03	$C_{13}H_{13}ON_6Cl$	304	0.8688	4	8	2	129.63	PASS
4	Compound 04	$C_{12}H_{10}Cl2N_6$	309.154	0.3479	4	7	1	118.35	PASS

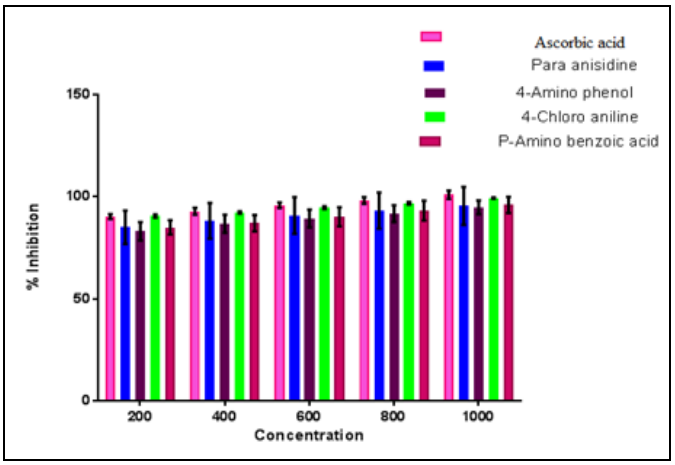


FIG. 10: ANTI-OXIDANT ACTIVITY OF SYNTHESIZED COMPOUNDS

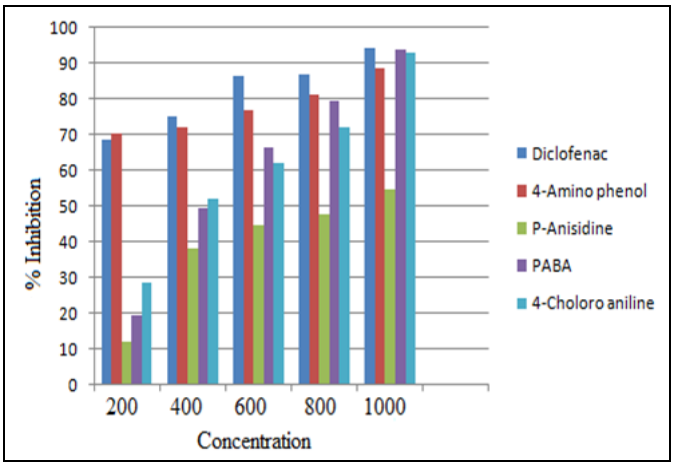


FIG. 11: ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS BY PROTEIN DENATURATION METHOD

CONCLUSION: Four derivatives have been synthesized by using ecofriendly techniques like grind stone technique with the use of minimal solvent and in good yields. The chemical structures of synthesized compound were confirmed on the basis of physical and spectral data. The anti inflammatory activity of synthesized compounds were evaluated by carrying out docking studies to understand the interactions of synthesized molecules with Protein arginine deaminase.

III a> IIIC>IIId>IIIb

All the derivatives were found to follow Lipinski's rule of 5 and pass ADME test. The antioxidant activity by H_2O_2 method showed few compounds have shown significant activity. Further suitable modifications of the compounds may show profound biological activities.

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CONFLICTS OF INTEREST: Declared none

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