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RESEARCH ARTICLE
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# INSILICO, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL QUINOLINE DERIVATIVES

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**Abstract**
The purpose of this research is to functionalize to synthesise 4,7-disubstituted quinoline.Intially quinoline derivatives was docked using**3U2D** DNA Gyrase as a target for anti-bacterial activity by using schrodinger software, from the results obtained from docking only those compounds which shown potent activity were subjected for synthesis using facile method.The synthesized compounds wascharacterized by IR, NMR and Mass spectrometry,

The synthesized compounds **(TM1-TM8)** were screened for antibacterial activity studies at various concentrations of 5, 10, 25, 50 and 75µg/ml using DMF as a control against ***Staphylococcus aureus, Enterococcus faecalis, Escherichia coli*** **and** ***Klebsiella pneumonia,*** by agar-well diffusion method. **Ciprofloxacin** was used as standard drug.

Among the synthesized compounds **TM4**shown moderate activity when compared with the standard, rest of the derivatives possesses weak antibacterial activity.

**Keywords:** Quinolines, DNA Gyrase, *p*-Hydroxy benzaldehyde, Sodium acetate, Potassium hydroxide, Choroacetyl chloride, Choropropionyl chloride, Antimicrobial activity.

## INTRODUCTION

Quinoline[1] nucleus is exist in many naturally compounds and having diverse biological activities. Quinoline moiety is of great importance to chemists as well as biologists as it is chemically useful molecules having diverse biological activities such as anti-inflammatory, anti HIV, antibiotic,

antimalarial, anticancer, antihypertensive. A large variety of quinoline derivatives have been used as antimalarial agents. The antimalarial agents are quinine, quinidine, mefloquine, chloroquine, amodiaquinine and primaquine. Quinolines displayed potent antibacterial activities.There is a growing interest in the synthesis of quinolines bearing various substituents such as alkenyl, akynyl, aryl or primary amino groups on the 3- and 4-positions of quinoline moiety. The quinoline derivatives bearing alkynyl or amine group at position 4 of the quinoline ring were synthesized and tested for selectivity in binding to the estrogen receptor β (ER β), which plays an important role in the development, maintenance, and function of the mammalian reproductive system, as well as non-sexual tissues [2].

The Antibacterial agent [3]continuous development of pharmaceutical, it is becoming increasingly difficult to find new structures to make antibacterial drugs from natural sources. Moreover, because these drugs play important roles in clinics, their widespread use and even abuse have led to the evolution of drug-resistant bacteria that pose a threat to human health and survival. This has prompted the development of chemical synthetic drugs. Synthetic chemical drugs still occupy a large proportion compared to biopharmaceuticals and traditional Chinese medicines, and chemical synthetic drugs play a major role in bacterial infections.

Drug discovery and developing a new medicine is a long, complex, costly and highly risky process that has few peers in the commercial world. This is why computer aided drug design (CADD) approaches are being widely used in the pharmaceutical industry to accelerate the process. Use of computational ability to streamline drug discovery and development process. Advantage of chemical and biological information about Ligands and/or targets to discover and optimize novel drugs[4].

The molecular manipulation of a promising lead compound is still a major line of approach for the discovery of new drugs. Molecular manipulation involves the efforts to combine the separate groups having similar activity in one compound by eliminating, substituting or adding new moiety to a parent lead compound thus by making gradual changes in the structure of the compounds resulting in gradual change in the physicochemical properties of the drug and the biological activity of the compound.

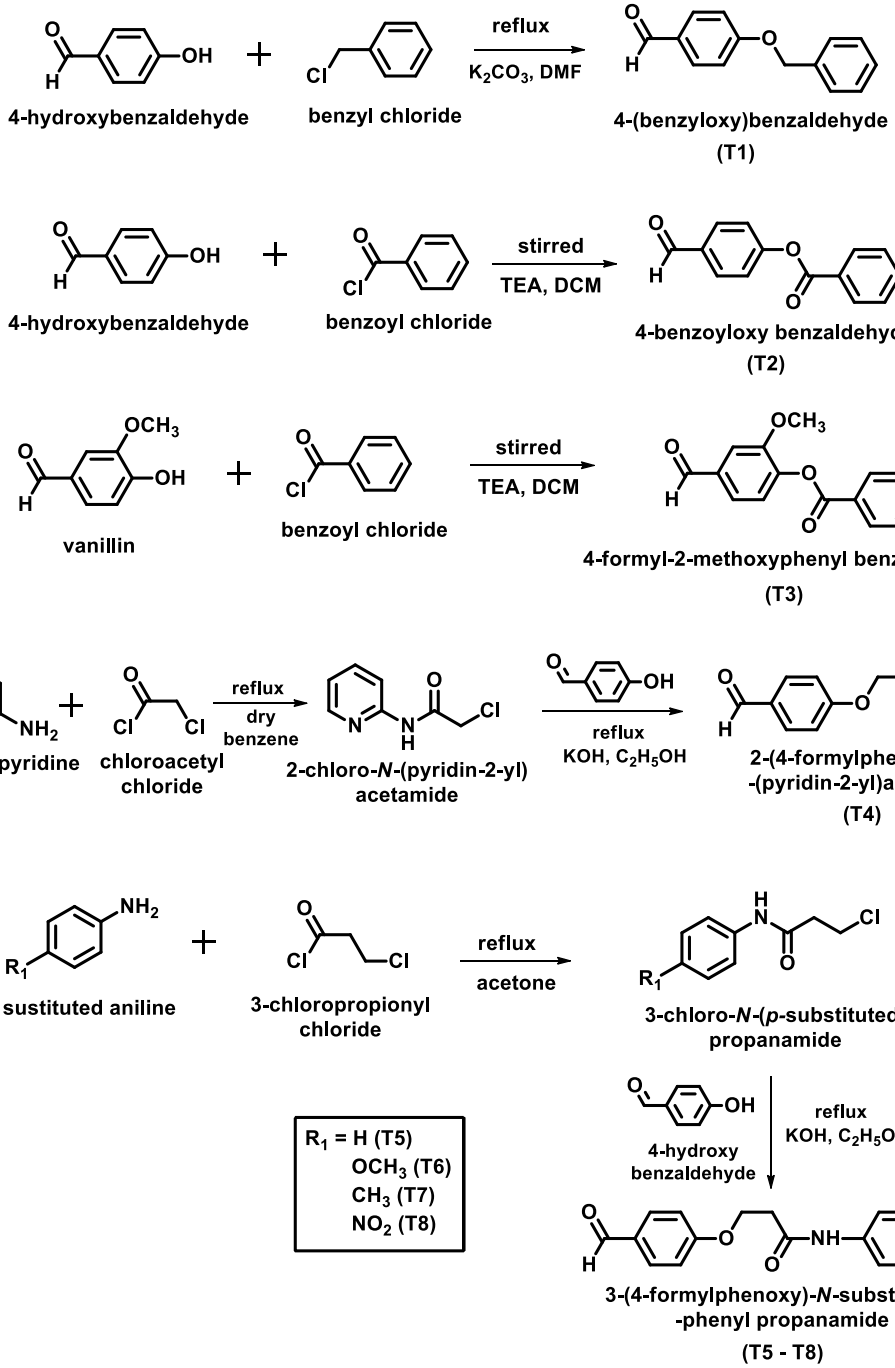
Due to wide range of pharmacological activities of quinoline derivatives Hence the present attempt was made to lead optimize using docking studies. By the results of docking attempt was made to synthesize, characterized, and biologiacal evaluation of optimized lead compounds or quinoline derivatives.

## MATERIALS AND METHOD

All the chemicals are purchased sigma Aldrich the melting point was determined by using open capillary tubrmethod.Characterization of synthesized compound were done by FTIR, NMR by Brooker and Mass analysis by ESMS.

## METHODOLOGY

### SCHEME-1

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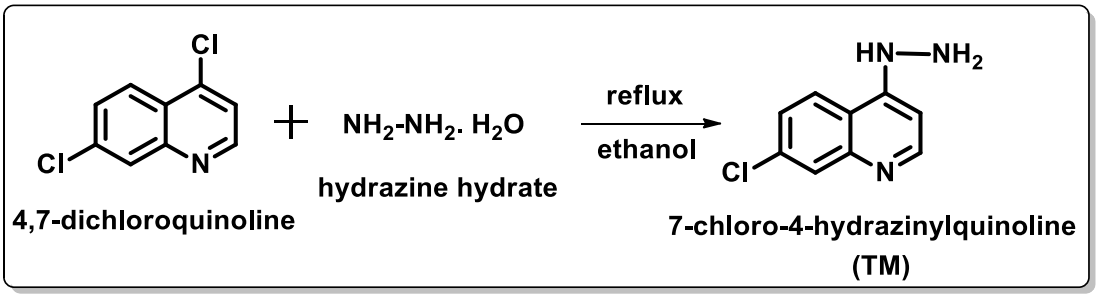
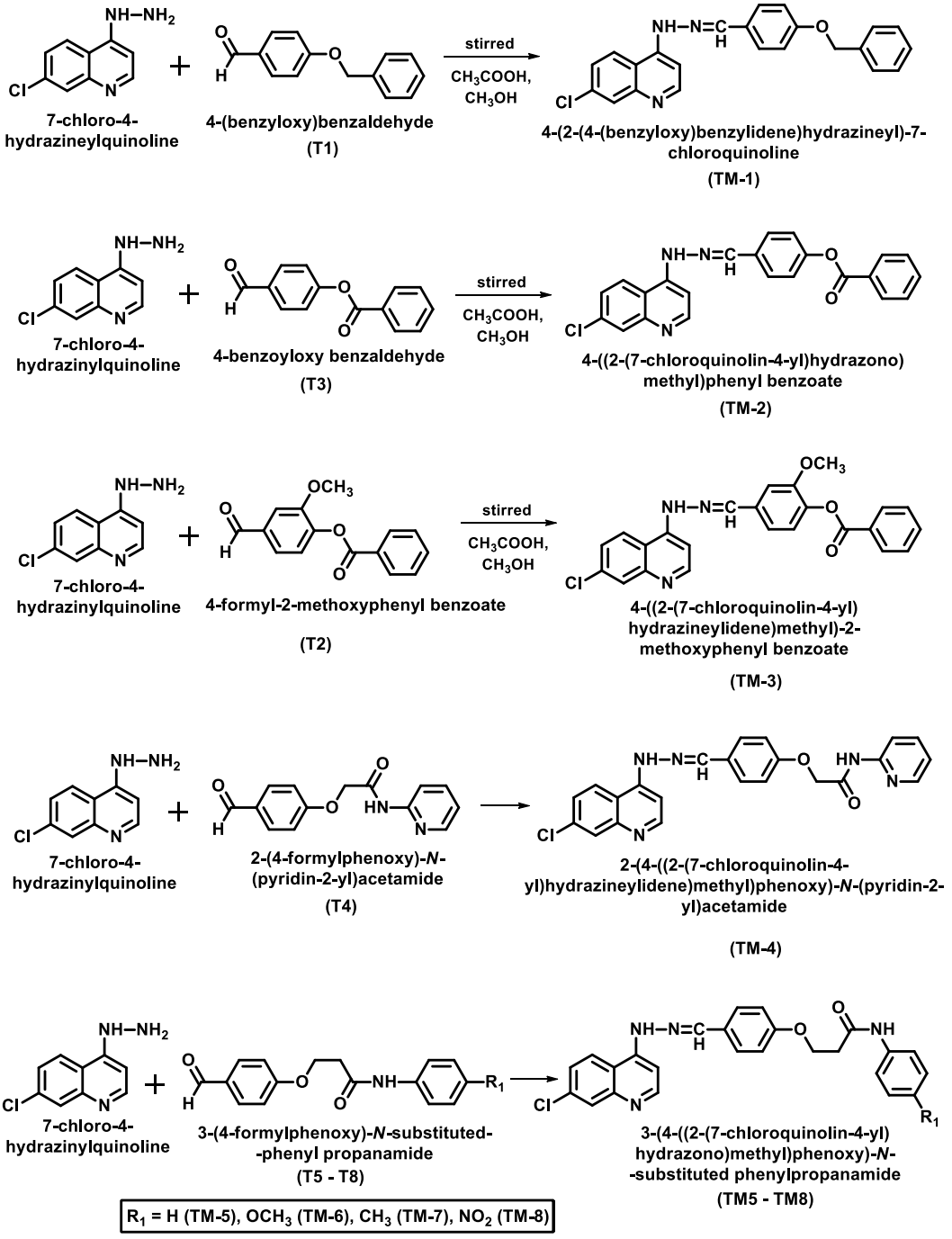





**Procedure for the preparation of 4-(benzyloxy) benzaldehyde (T1):**

In a round bottom flask dissolve *p*-hydroxybenzaldehyde (10 G, 8 mmol), pottassium carbonate (11 G, 7 mmol) in dimethylformamide (10 ml, 12 mmol). The mixture was refluxed for 60-90 minutes. Then add benzylchloride (1.4 ml, 1 mmol). Then this mixture was kept reflux for overnight. Then mixture is added to water and cooled in ice bath, the obtained solid is filtered and dried. (70% yield, m.p. 71-75 $^{o}$C).

**Procedure for the preparation of 4-benzoyloxy benzaldehyde/4-benzoyloxy-3-methoxy benzaldehyde (T2 and T3):**

In a round bottom flask *p*-hydroxybenzaldehyde (1.080 g, 8.85 mmol) and triethylamine (1.5 ml, 10.78 mmol) were dissolved in 25-30 ml of dichloromethane. The mixture was stirred for 30-45 minutes at room temperature. To this reaction mixture benzoyl chloride (1 ml, 8.85 mmol) was added drop by drop and the resulting solution was stirred at room temperature for 1-3 hours.To the above mixture a saturated aqueous solution of sodium carbonate (20 ml) was added three times. The

organic phase was dried over magnesium sulphate and the solvent was removed under reduced pressure, thus affording 75 % yield, m.p. 90-92 $^{o}$C and 72 % yield, m.p. 70-72 $^{o}$C respectively.

**Procedure for the preparation of 2-(4-formylphenoxy)-N-(pyridine-2-yl) acetamide(T4):**
Chloroacetyl chloride (0.02 mol, 1.6 ml) was slowly added to a solution of 2-aminopyridine (0.01 mol, 0.94 g) in dry benzene, maintaining the temperature 0-5 $^{o}$C. The reaction mixture was refluxed for 4-5 h(TLC monitored), and the excess of solvent was removed under vacuum. The residue was washed with 5% aqueous solution of sodium bicarbonate (20 ml) and then with water (20 ml). The crude product was recrystallized from ethanol to give pink crystals of 2-chloro-*N*-(pyridin-2-yl) acetamide. Yield 60 %, m.p. 128-130 $^{o}$C.

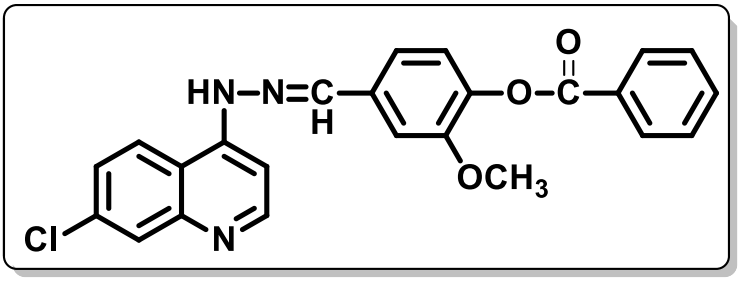
To a suspension of 2-chloro-N-(pyridin-2-yl)acetamide (1.70 g, 0.01 mol), *p*-hydroxybenzaldehyde (1.22 g, 0.01 mol) in sufficient alcohol and anhydrous potassium hydroxide (1.38 g, 0.01 mol) was added. The reaction mixture was refluxed overnight (TLC monitored). The precipitate was collected on evaporation of solvent, dried and recrystallized from ethyl alcohol. Crystals of 2-(4-formylphenoxy)-*N*-(pyridine-2-yl) acetamide were collected. Yield 60 %, m.p. 250-254 $^{o}$C

**Procedure for the preparation of 3-(4-formylphenoxy)-*N*-substituted-phenylpropanamide (T5-T8):**
A mixture of 3-chloropropionyl chloride (3.0 ml) and acetone (6 ml) is added drop wise to a refluxing mixture of substituted aniline (5.75 ml) and acetone (10 ml). The reaction mixture is refluxed for 1-2 h. The progress of reaction was monitored by TLC ethyl acetate and n-hexane (1:1). The reaction mixture was cooled in an ice bath, and poured into a mixture of 6N HCl (5.0 ml) and water (35 ml). The resulting solid is filtered, washed with water, dried. The physical characterization data of synthesized compounds 3-chloro-*N*-(*p*-substituted phenyl) propanamide was given in the **Table No-1**

To a suspension of 3-chloro-*N*-(*p*-substituted phenyl) propanamide (0.01 mol), *p*-hydroxybenzaldehyde (0.01 mol) in sufficient alcohol and anhydrous potassium hydroxide (0.01 mol) was added. The reaction mixture was refluxed overnight (TLC monitored). The precipitate was collected on evaporation of solvent, dried and recrystallized from ethyl alcohol. Crystals of 3-(4-formylphenoxy)-*N*-substituted-phenylpropanamide**(T5-T8)** were collected. The physical characterization data of synthesized compounds **(T5-T8)**

**Procedure for the preparation of 7-chloro-4-hydrazinylquinoline (TM):**
In to a clean dry round bottomed flask containing 4,7-dichloroquinoline (10 g, 5 mmol) absolute ethanol (30 ml), hydrazine hydrate (100%, 25 ml, 50 mmol) was added drop wise with stirring. The mixture was refluxed for 2-3 h (TLC monitored). After 30 minutes a golden yellow color begins to precipitate. The mixture was allowed to cool, and the golden yellow precipitate was collected by filtration, washed with absolute ethanol and recrystallized from ethanol to give 7-chloro-4-hydrazinoquinoline. Yield 80 %, m.p. 223-225 $^{o}$C.

**Characterization**
**4-(2-(4-(Benzoyloxy)-3-methoxybenzylidene)hydrazinyl)-7-chloroquinoline (TM3)**



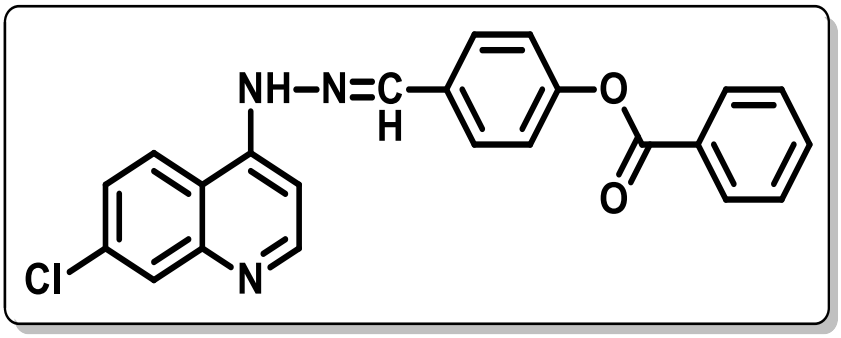
**FTIR : 3250cm$^{-1}$ NH, 3050cm$^{-1}$ Ar-CH, 2800cm$^{-1}$ $OCH_3$ 1580cm$^{-1}$ C=O, 1420 cm$^{-1}$ C=N, 1150cm$^{-1}$ C-O-C, 800cm$^{-1}$ C-Cl.**

**TABLE NO-1: $^1$HNMR Spectra (DMSO-$d_6$, δ ppm):**

| Value (δ ppm) | Nature of segment | No of protons | Types of protons |
|---|---|---|---|
| 12.8-13.2 | Broad singlet | 1H | 1H of NH of **NH**-N |
| 7.4-8.4 | Multiplet | 14H | 13H of Ar-H and 1H of CH of N=**CH** |
| 3.8-3.9 | Singlet | 3H | 3H of $CH_3$ of O**$CH_3$** |

Mass spectrometry M/Z Molecular ion peak 431, Base peak 280.

**4-(2-(4-(Benzoyloxy)benzylidene)hydrazinyl)-7-chloroquinoline (TM2)**




**FTIR : 3400cm$^{-1}$ NH, 3100cm$^{-1}$ , Ar-CH, 1620cm$^{-1}$C=O, 1430 cm$^{-1}$ C=N, 1180cm$^{-1}$ C-O-C, 760cm$^{-1}$ C-Cl.**

**TABLE NO-2: $^1$HNMR Spectra (DMSO-$d_6$, δ ppm):**

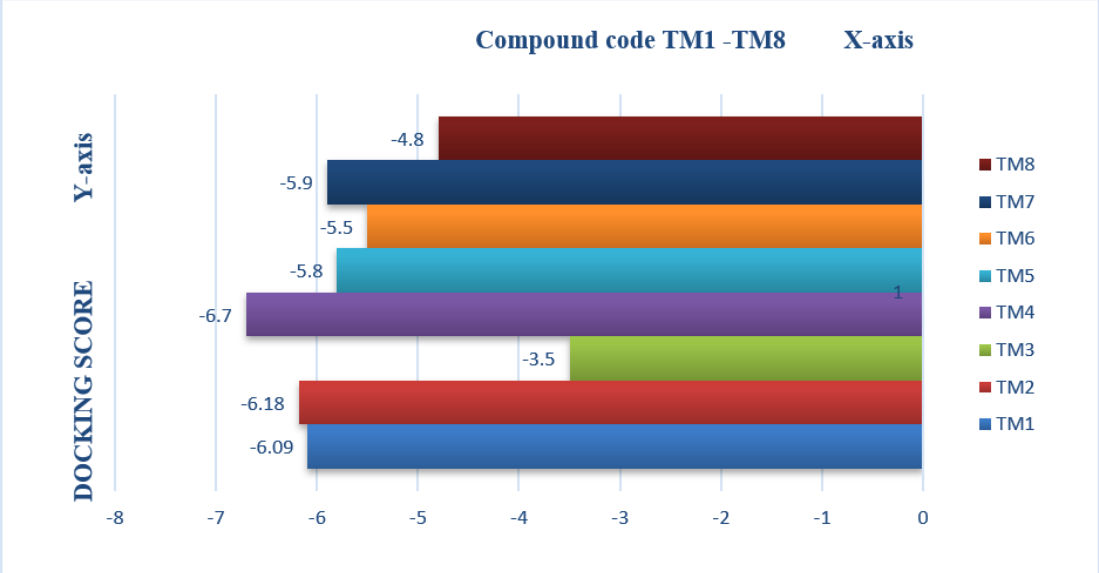
| Value (δ ppm) | Nature of segment | No of protons | Types of protons |
|---|---|---|---|
| 11.2-11.4 | Broad singlet | 1H | 1H of NH of **NH**-N |
| 7.3-8.5 | Multiplet | 15H | 14H of Ar-H and 1H of CH of N=**CH** |

Mass spectrometry M/Z Molecular ion peak 404, Base peak 370

## RESULTS AND DISCUSSION

**TABLE NO-3: MOLECULAR DOCKING:**

| S.No | Compound Code | Docking Score | Glide Energy (kcal/mole) | Aminoacid Interaction | Type of Interaction |
|---|---|---|---|---|---|
| 1 | **TM1** | -6.091 | -42.33 | Arg-144 Val-79 | Pi-cation Halogen-Bond |
| 2 | **TM2** | -6.188 | -45.96 | R-84 T-173 D-81 | Pi-cation H-Bond |
| 3 | **TM3** | -3.588 | -32.01 | Arg-144 | Pi-cation |
| 4 | **TM4** | -6.735 | -49.29 | Arg-144 Lys-93 | Pi-cation Halogen-Bond |
| 5 | **TM5** | -5.806 | -49.31 | R-144 T-173 | Pi-cation H-Bond |
| 6 | **TM6** | -5.526 | -43.71 | Thr-173 | H-Bond |
| 7 | **TM7** | -5.955 | -48.26 | Arg-84 | Pi-cation Halogen-Bond H-Bond |
| 8 | **TM8** | -4.877 | -40.93 | Arg-144 Val-79 | H-Bond Halogen-Bond |

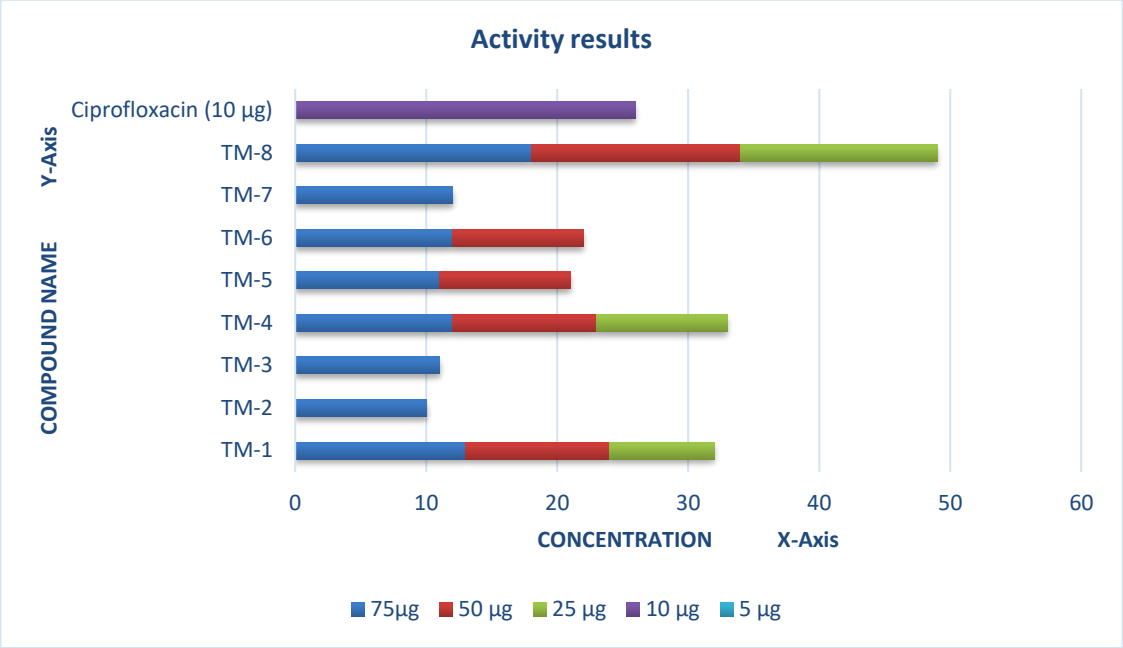



All the synthesized 8 compounds (**TM1-TM8**) were subjected for docking studies with gyrase B ATP-binding domain of DNA gyrase (PDBID **3U2D**). Total 8 synthesized compounds were docked into the newly generated grid of DNA gyrase enzyme (**3U2D**). The 3D structures of the synthesized compounds were docked into three dimensional structure of target DNA gyrase enzyme. The dock score of the docked compounds was in the range of **-6.73 to -3.58.** Molecular docking study of compounds **TM1-TM8** suggested that the docked compounds found to interact with enzyme by several Van der Waals, covalent, H-bond, π-π and π-cation interactions, among these the π-cation bond interactions are the key force for binding of compounds **TM1-TM8** with **3U2D** protein which was clearly observed from the **Table No 5** the interaction map of enzyme and docked compounds. However the affinity towards the enzyme was not strong as expected which was also reflected in the biological activity screening data of synthesised compounds.

**Antibacterial activity data of newly synthesized compounds(TM1-TM8) against *Staphylococcus aureus***

**TABLE NO-4**

| **Compound / Conc** | ***Inhibition zone diameter in mm** | | | | |
|---|---|---|---|---|---|
| | **75µg** | **50 µg** | **25 µg** | **10 µg** | **5 µg** |
| **TM-1** | 13 | 11 | **8** | R | R |
| **TM-2** | 10 | R | R | R | R |
| **TM-3** | 11 | R | R | R | R |
| **TM-4** | 12 | 11 | **10** | R | R |
| **TM-5** | 11 | 10 | R | R | R |
| **TM-6** | 12 | 10 | R | R | R |
| **TM-7** | 12 | R | R | R | R |
| **TM-8** | 18 | 16 | **15** | R | R |
| **Ciprofloxacin (10 µg)** | -- | -- | -- | 26 | R |




The synthesized compounds **(TM1-TM8)** were screened for antibacterial activity studies at a concentration of 5, 10, 25, 50 and 75µg/ml using DMF as a control against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli* and *Klebsiella pneumonia*, by agar-well diffusion method. Ciprofloxacin was used as standard drug for the comparison at the concentration 10 µg/ml and 5 µg/ml against Gram positive and Gram negative organism

The results obtained from Table no-4indicates that the compounds were found to possess moderate and weak activity. The synthesized compounds **TM1-TM8** showed moderate activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia* coli, and *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli* and *Klebsiella pneumonia*.

## CONCLUSION

The present work, which has undertaken is bonafide, for the synthesis of new 4-(2-benzylidene hydrazinyl)-7-chloroquinolines as possible potent inhibitors of the DNA gyrase of antibacterial.In this view we have made an attempt in reviewing the literature on substituted quinoline and its derivatives for their medicinal significance with the help of chemical abstract, journals and internet sites.The literature review and survey was carried out from 1960 to 2022 related to quinoline derivatives as antibacterial agents and as as potent inhibitors of the DNA gyrase.In the light of above, for the synthesis of 4-(2-benzylidene hydrazinyl)-7-chloroquinolines were established on literature survey.All the structures of the synthesized compounds were subjected for molecular docking studies.Around 8 new compounds were synthesized, with the standard chemicals and procedures.The synthesized compounds were tested for their preliminary tests, physical constants and TLC.The structure of the final compounds was confirmed by $^{1}$H NMR, IR analysis.The selected 8 synthesized compounds were screened for their anti-bacterial activity against different bacterial strains.

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