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Synthesis, structural investigation and molecular docking studies of pyridinyl tetrahydroisoquinoline, morpholine and piperidine containing schiff's bases

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***Abstract*---**The present work was conducted to synthesize some Schiff's bases derived from pyridinyl tetrahydroisoquinoline, morpholine and piperidine moieties by the condensation reaction of aminobenzaldehyde with various aromatic amines in good to excellent yield. The structures of synthesized compounds were confirmed by ^{1}H NMR, 13C NMR and mass spectra (ESI-MS) data. These compounds also evaluated for their *in silico* anti-microbial properties by molecular docking studies. Docking studies were carried out by using Argus Lab 4.0.1 software.

***Keywords*---**Schiff's bases, pyridinyl tetrahydroisoquinoline, morpholine, piperidine, aromatic amines, aminobenzaldehyde.

Introduction

Schiff bases contain the imine functional group (–RC=N–) and are prepared by the condensation of primary amine (R–NH_2) and active carbonyl (RCOR′) compounds, where R, R′ is alkyl or aryl group (figure 1). Gupta RR *et al.,* 1998. The essential part in these kinds of compounds is azo-methine group. These compounds have numerous applications in different fields and also used in inorganic synthesis (Sadia M et *al.,* 2021). Schiff's bases shows a broad range of biological actions, including anti-microbial, antimalarial, antiviral, anticancer, anti-inflammatory, and antipyretic actions (Santos FL *et al.,* 2013). 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 (Dhar DN *et al.*, 1982, Guo Z *et al.*, 2007).

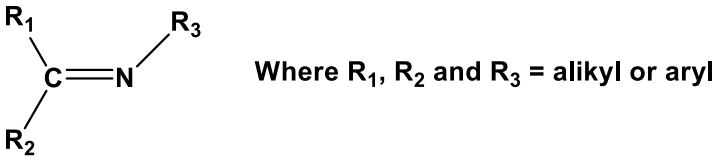


Figure 1: General structure of Schiff base

Morpholine containing Schiff bases are found to be used as antitumor agents. Morpholine as a substitution in many heterocyclic moieties has been reported to possess potential analgesic, anti-inflammatory, antimicrobial, antimalarial and anticancer activities because of their specific structures (Cai HY *et al.*, 2018). Piperidine: Piperidine has been a rich source of numerous pharmacologically active drug substances since several decades. Due to their often biological activities, optically active piperidine alkaloids containing a stereogenic carbon atom at the 2-position are an important group of natural products, and they have been the target of a number of synthetic strategies (Sakthikumar K *et al* 2018).

The tetrahydroisoqunioline ring system provide a primary scaffold of different alkaloids isolated from natural sources and in large quantities found in various plants, soils, and marine microorganisms (Karthik CS et al 2016, Zaman K *et al.*, 2019). Molecules set with these scaffolds are important in pharmaceutical intermediates in medicinal chemistry because of their broad spectrum of pharmacological properties. Many tetrahydroisoquinoline compounds are considered as antitumor (Bentley KW *et al.*, 2005, Castillo JC *et al.*, 2018), anticonvulsant, antithrombotic (Pingaew R *et al.*, 2014 painreliever Ko YS *et al.*, 2017), anti-inflammatory (Fodale V *et al.*, 2002), antifungal, and antibacterial agents (Siegfried L *et al.*, 1988). Moreover, tetrahydroisoquinolines are useful compounds as antagonist to NMDA and D_1 receptors (Scott JD *et al.*, 2002 Parkinson's, Gao M *et al.*, 2006), enzyme inhibitory actions for glucosidases (Sano T *et al.*, 1997), and monoamine oxidases (Takada K *et al.*, 2004).

Molecular docking technique is usually used in modern drug discovery for understanding the drug-receptor interaction. This technique has been used to predict the binding affinity and orientation of small drug molecules at the target site. Aims of docking studies are accurate structural modelling and correct calculation of activity. Macromolecular docking studies give the most detailed possible view of drug receptor interaction and have created a new rational approach to drug design, where the structure of drug is designed based on its fit to 3D structures of a receptor site (Kenchappa R *et al.*, 2017). The main objective behind this study is to development to design and synthesize different Schiff bases and evaluate their *in silico* activities for development of novel antimicrobial compound.

Materials and Method

All chemicals used were commercially available with analytical grade of purity and were purchased from Sigma-Aldrich, Alfa Aesar, Acros and other commercial

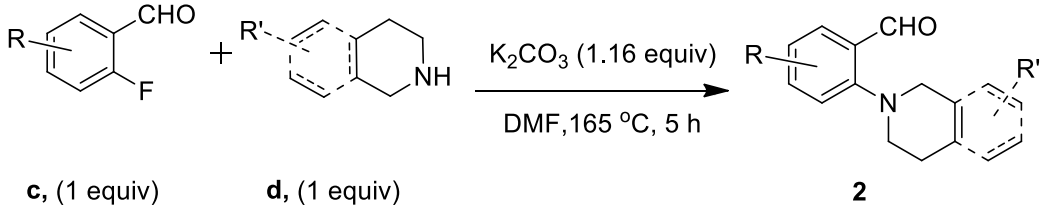
suppliers and used as received without further purification. TLC analysis was performed on Merck 60 F_{254} silica gel TLC plates. ^{1}H and $^{13}CNMR$ spectra were recorded on Bruker 300 and 600 MHz spectrometer. The chemical shift values are reported in δ (ppm) relative to TMS (Tetra methyl silane) as internal standard. HRMS (m/z) was recorded in Q-T of Micro mass spectrometer (LC-MS, ESI mode). Melting points were determined in a capillary melting point apparatus and are uncorrected.

Molecular docking is carried out in order to provide a binding site with a population of probable ligand orientations and conformations (Dewangan *et al.*, 2018; Ahirwar *et al.*, 2018a; Ahirwar *et al.*, 2018b). DNA gyrase (1KZN) crystal structure was obtained from the protein data bank (RCSB). The 2D structure of the ligands (i.e., synthesized molecules and standard drug (Clorobiocin) was designed with the help of chem draw professional 16.0 software. Molecular mechanics optimization of the 2D structures of ligands was done by converting them into 3D structures with the help of chem 3D 16.0 application of the same software (Chem draw professional 16.0). Argus Lab 4.0.1 was used for the docking. The grid with dimension X=46.034, Y= 46.575, and Z= 41.034 Å are assigned to cover entire 3-dimensional active site of DNA gyrase. Upon testing the docking technique, dynamic molecular docking was done on the active site of proteins. Finally, the software retrieved the result of binding energy. The protein-ligand interaction was visualized by using Discovery studio 2016 software (Kamdi *et al.*, 2021; Dewangan *et al.*, 2021).

Result and Discussion

Starting Material Preparation: Derivatives of Aminobenzaldehyde

To make the starting material i.e. amino-benzaldehyde **2a-2c**, various 2-fluoro benzaldehydes **c** were reacted with different amines **d.** THIQs were taken as aminoaldehyde to prepare **2a**; whereas morpholine and piperidine were taken to prepare **2b** and **2c** respectively. Pastine SJ *et al* 2005.



Scheme 1: General scheme for amino-benzaldehyde Preparation

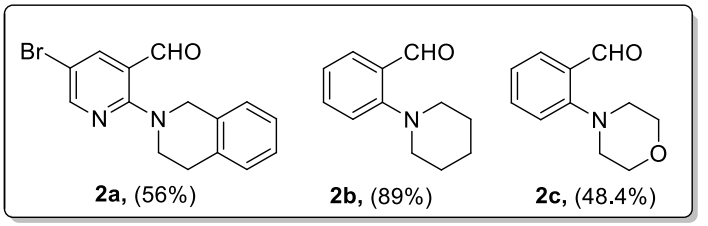
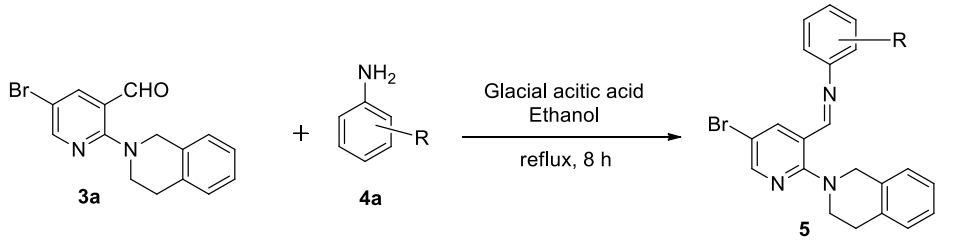
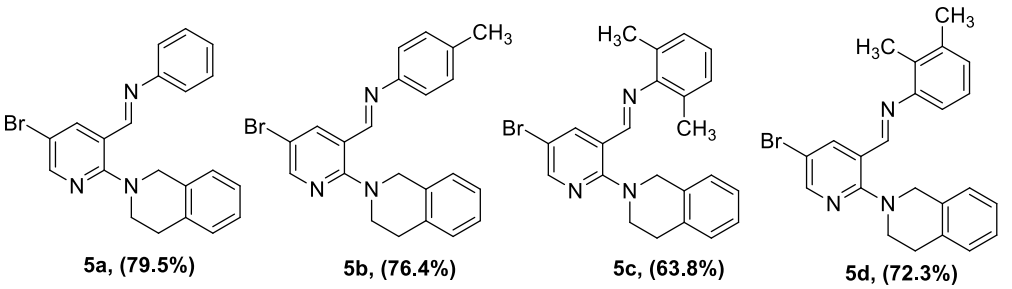


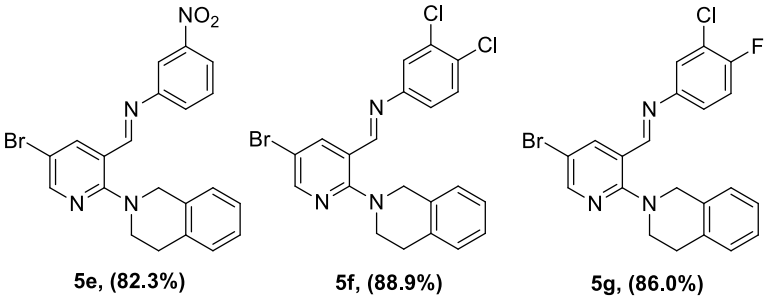
Figure 2: Different aminobenzaldehyde derivatives

Synthesis of Pyridinyl tetrahydroisoquinoline containing Schiff Bases

A mixture of pyridinyl tetrahydroisoquinoline based aminobenzaldehyde (0.5 mmol) and various aromatic amines (0.5 mmol) were refluxed with a catalytic amount of acetic acid for 8 hours with monitoring by TLC. Then the reaction mixture was filtered and the pure crystalline product recovered by recrystallization with absolute ethanol.





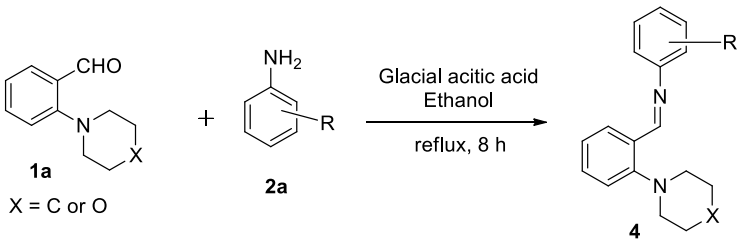


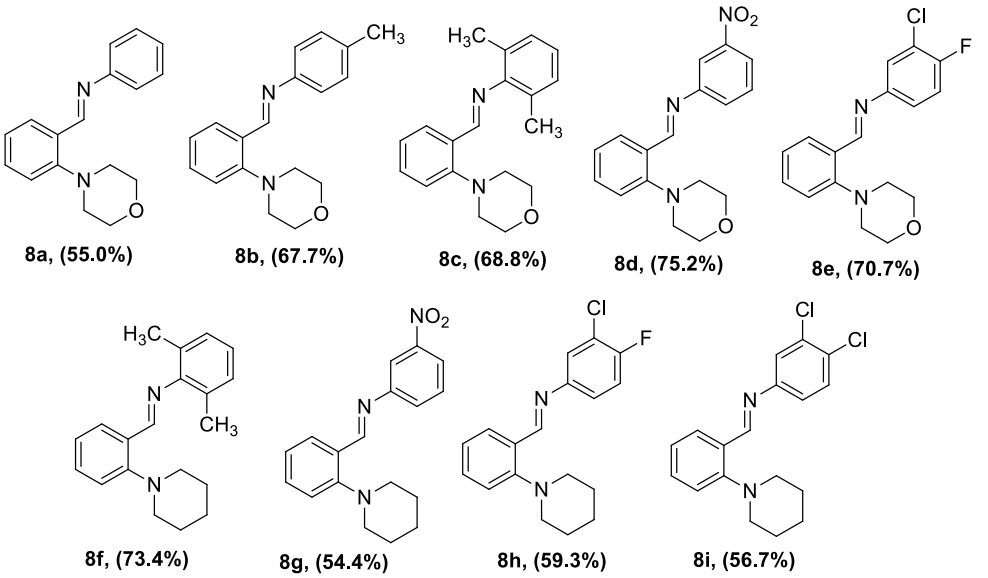
Reaction condition: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (6 ml), Isolated yield.

Scheme 2: Synthesis of Pyridinyl Tetrahydroisoquinoline containing Schiff bases and its Substrate Scope

Synthesis of Morpholine and/or piperidine based Schiff Bases

A mixture of Morpholine/piperidine containing aminobenzaldehyde (0.5 mmol) and various aromatic amines (0.5 mmol) were refluxed with a catalytic amount of acetic acid for 8 hours with monitoring by TLC. Then the reaction mixture was filtered and the pure crystalline product recovered by recrystallization with absolute ethanol.





Reaction condition: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (6 ml), Isolated yield.

Scheme 3: Synthesis of Morpholine or piperidine containing Schiff bases and its Substrate Scope

Characterization Data

(E)-N-((5-bromo-2-(3,4-dihydroisoquinolin-2(1H)-yl)pyridin-3-yl)methylene)-3,4-dichloroaniline [5f]

Yield 88.9%; Yellow solid; mp 140-141°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.07 (t, *J* = 5.9 Hz, 2H), 3.63 (t, *J* = 5.8 Hz, 2H), 4.59 (s, 2H), 7.08 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.17 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.20-7.25 (comp, 3H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 8.5, 1.7 Hz, 1H), 8.42 (s, 2H), 8.50 (s, 1H) .**^{13}C NMR** (150 MHz, $CDCl_3$) δ 29.30, 50.79, 52.08, 112.53, 120.54, 121.84, 122.91, 126.30, 126.57, 126.64, 128.94, 130.20, 130.99, 133.16, 133.95, 134.03, 139.42, 150.86, 150.95, 157.25, 160.56; **HRMS** (ESI, m/z) calcd for $C_{21}H_{16}BrCl_2N_3$ $[M+Na]^+$ 484.1818, observed 484.0024.

(E)-N-((5-bromo-2-(3,4-dihydroisoquinolin-2(1H)-yl)pyridin-3-yl)methylene)aniline [5a]

Yield 79.5%; Yellow solid; mp 108-110°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.08 (t, *J* = 5.8 Hz, 2H), 3.63 (t, *J* = 5.8 Hz, 2H), 4.60 (s, 2H), 7.1-7.28 (comp, 1H), 7.20-7.23 (comp, 3H), 7.24-7.27 (comp, 2H), 7.28-7.32 (comp, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 8.41 (d, *J* = 2.5 Hz, 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 8.56 (s, 1H). **^{13}C NMR** (150 MHz,

$CDCl_3$) δ 29.38, 50.79, 51.91, 112.63, 121.02 (2C), 122.63, 126.22, 126.53, 126.59, 126.63, 128.90, 129.36 (2C), 134.14 (2C), 139.27, 150.28, 151.46, 155.89, 160.43; **HRMS** (ESI, m/z) calcd for $C_{21}H_{18}BrN_3$ $[M+Na]^+$ 415.2917, observed 415.0681.

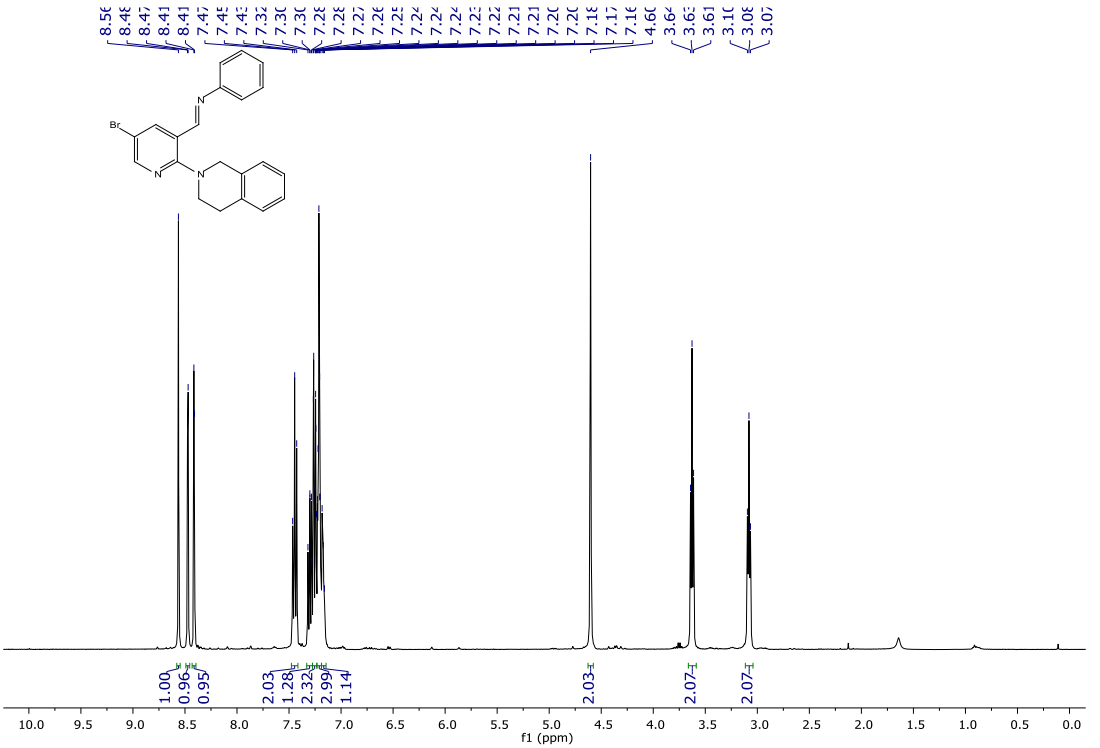


Figure 3: ^{1}H NMR of 5a

(E)-N-((5-bromo-2-(3,4-dihydroisoquinolin-2(1H)-yl)pyridin-3-yl)methylene)-2,3-dimethylaniline [5d]

Yield 72.3%; Yellow crystalline solid; mp 95-97°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.37 (s, 3H), 3.09 (t, *J* = 5.8 Hz, 2H), 3.63 (t, *J* = 5.8 Hz, 2H), 4.60 (s, 2H), 6.79 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.12 (dd, *J* = 17.2, 7.2 Hz, 2H), 7.18 (d, *J* = 4.7 Hz, 1H), 7.19-7.24 (comp, 3H), 8.41 (d, *J* = 2.5 Hz, 1H), 8.45 (s, 1H), 8.49 (d, *J* = 2.6 Hz, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 13.96, 20.18, 29.36, 50.70, 51.96, 112.68, 115.26, 123.02, 126.18 (2C), 126.50, 126.61, 127.80, 128.91, 130.85, 134.17, 137.75, 139.17 (2C), 150.06, 150.60, 154.96, 160.37; **HRMS** (ESI, m/z) calcd for $C_{23}H_{22}BrN_3$ $[M+Na]^+$ 443.3449, observed 443.0998.

(E)-2,6-dimethyl-N-(2-morpholinobenzylidene)aniline [8c]

Yield 68.8%; Light Yellow crystalline solid; mp 136-138°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.18 (s, 6H), 3.05-3.07 (comp, 4H), 3.84-3.86 (comp, 4H), 7.00 (dd, *J* = 8.1, 6.9 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.20 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.24-7.28 (comp, 1H), 7.52 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 8.24 (dd, *J* = 7.7, 1.7 Hz, 1H), 8.65 (s, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 18.40 (2C), 53.96 (2C), 67.04 (2C), 119.22, 123.56, 123.91, 127.01, 128.09 (2C), 128.33, 129.99, 132.11 (2C), 151.65, 153.52, 160.77; **HRMS** (ESI, m/z) calcd for $C_{19}H_{22}N_2O$ $[M+Na]^+$ 317.3980, observed 317.1730.

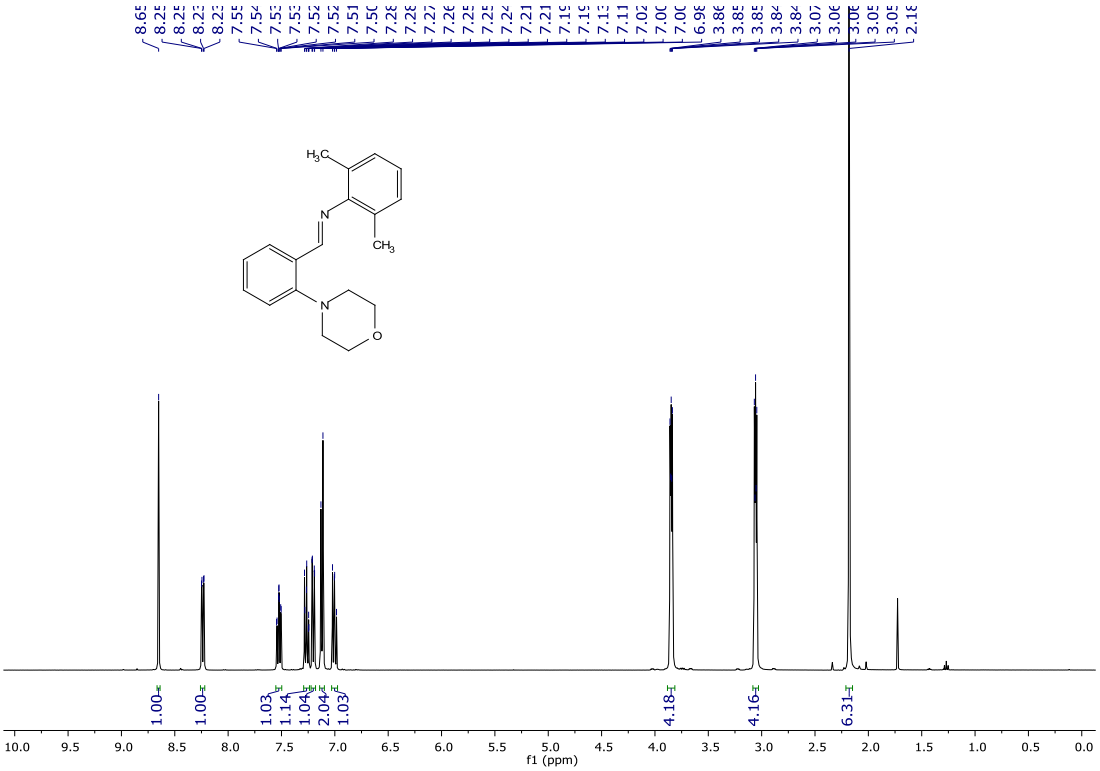


Figure 4: ^{1}H NMR of **8c**

(E)-3-chloro-4-fluoro-N-(2-morpholinobenzylidene)aniline [8e]
Yield 70.7%; Grayish Yellow crystalline solid; mp 124-125°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.03-3.06 (comp, 4H), 3.89-3.91 (comp, 4H), 7.11 (ddd, *J* = 8.7, 4.3, 2.6 Hz, 1H), 7.15-7.23 (comp, 3H), 7.27-7.29 (comp, 1H), 7.50 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 8.09 (dd, *J* = 7.7, 1.7 Hz, 1H), 8.83 (s, 1H); **HRMS** (ESI, m/z) calcd for $C_{17}H_{16}ClFN_2O$ $[M+Na]^+$ 341.7731, observed 341.0924.

(E)-2, 6-dimethyl-N-(2-(piperidin-1-yl)benzylidene)aniline [8f]
Yield 73.4%; Yellow crystalline solid; mp 131-132°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.57-1.61 (comp, 2H), 1.68-1.73 (comp, 4H), 2.19 (s, 6H), 2.37 (s, 4H), 6.99 (dd, *J* = 8.0, 17.0 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 7.14-7.21 (comp, 2H), 7.48 (td, *J* = 7.7, 1.8 Hz, 1H), 8.20 (dd, *J* = 7.7, 1.7 Hz, 1H), 8.58 (s, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 18.28 (2C), 24.10, 26.29 (2C), 55.15 (2C), 119.10, 122.88, 123.34, 127.11, 127.98 (2C), 128.00, 129.82, 131.84 (2C), 151.89, 155.08, 161.42; **HRMS** (ESI, m/z) calcd for $C_{20}H_{24}N_2$ $[M+Na]^+$ 315.4180, observed 315.1938.

(E)-N-(2-morpholinobenzylidene)aniline [8a]
Yield 55.0%; Light Yellow crystalline solid; mp 136-138°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.05-3.07 (comp, 4H), 3.84-3.86 (comp, 4H), 6.81 (dd, *J* = 8.0, 6.9 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 2H), 7.12 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.16-7.21 (comp, 1H), 7.25-7.33 (comp, 2H), 7.48 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1H), 8.20 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.65 (s, 1H).; **HRMS** (ESI, m/z) calcd for $C_{17}H_{18}N_2O$ $[M+Na]^+$ 289.3376, observed 289.0731.

(E)-4-methyl-N-(2-morpholinobenzylidene)aniline [8b]

Yield 67.7%; Yellow crystalline solid; mp 126-127°C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.02-3.07 (comp, 4H), 3.65-3.72 (comp, 4H), 7.08 (d, *J* = 7.2 Hz, 2H), 7.19-7.24 (comp, 4H), 7.41 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 8.21 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.65 (s, 1H).; **HRMS** (ESI, m/z) calcd for $C_{18}H_{20}N_2O$ $[M+Na]^+$ 303.3642, observed 303.1242.

Docking studies: In this research, the synthesized molecule produced improved effects, which led us to consider its mechanism of action. We have, therefore, chosen the docking studies as an instrument to support our results. DNA gyrase inhibition has been the most powerful method for treatment of bacterial infection. In this analysis, we contrasted the findings with Clorobiocin for the docking of our synthesized compounds.

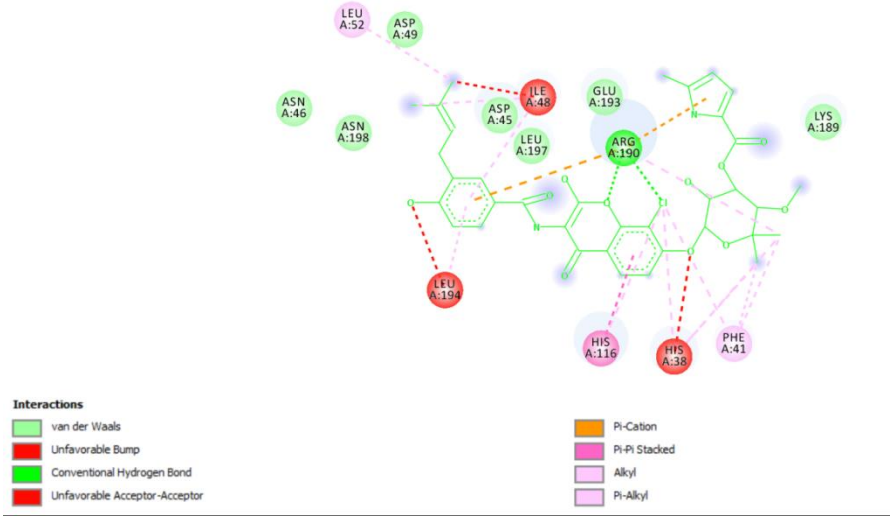


Figure 5: 2D interaction of clorobiocin with DNA gyrase enzyme (**1KZN)**

The binding data obtained from Argus Lab revealed, synthesized compounds have a good affinity towards DNA gyrase enzymes with binding energy ranges in between -8.2845 to -10.6466 kcal/mol. Analysis of residual interaction between the inhibitor and target enzyme at the active binding site revealed that the Clorobiocin bind with DNA gyrase enzymes by Van der Waals interaction, conventional hydrogen bond, Pi-cation interaction, Pi-Pi Stacked interaction, alkyl, and Pi-alkyl interaction (**fig. 5**). Out of 14 amino acid residue which interacts with Clorobiocin, 8 were found common with synthesized compounds **8a** and **8b**. The compound **8b** showed even better binding affinity values compared with **8a** (**Table I**). Both the compounds bind with DNA gyrase enzymes by Van der Waals interaction, conventional hydrogen bond, Pi-cation interaction, Pi-Pi Stacked interaction, alkyl, and Pi-alkyl interaction (**fig. 6 & 7**) in similar fashion as that of standard drug Clorobiocin.

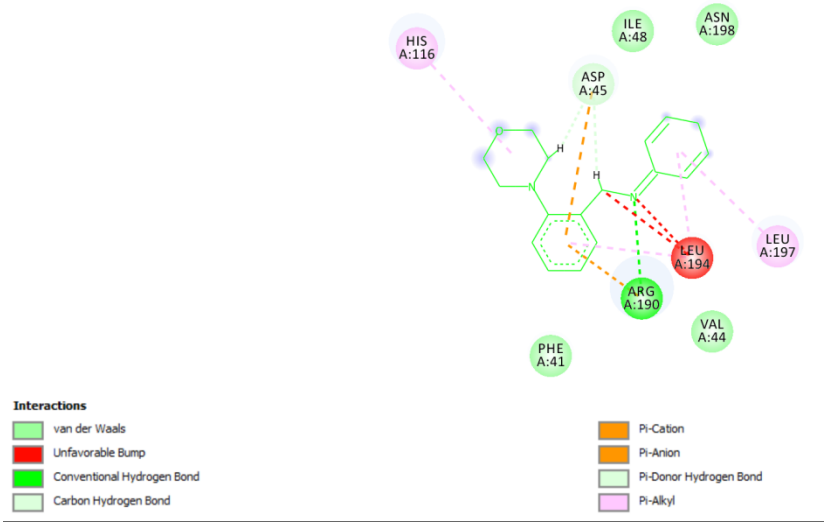


Figure 6: 2D interaction of compound **8a** with DNA gyrase enzyme (**1KZN)**

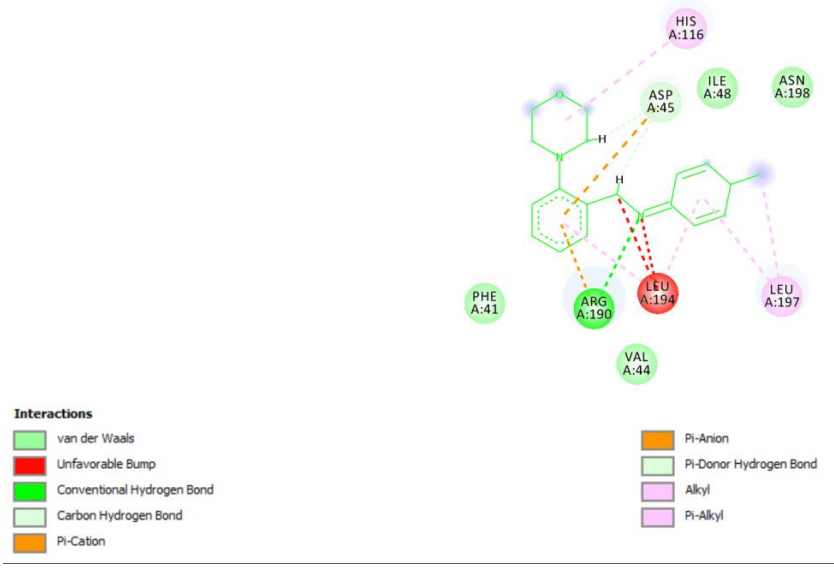


Figure 7: 2D interaction of compound **8b** with DNA gyrase enzyme (**1KZN)**

These interaction patterns give a strong impression that synthesized compounds possess good inhibitory potential against DNA gyrase enzyme.

Table I- Docking results of ligands and standard drug against DNA GYRASE (1KZN)

Compound ID (s)	Binding Energy (kcal/mol)	Enzyme's Binding Site residue
5a	-10.0335	43 VAL, 46 ASN, 50 GLU, 76 ARG, 77GLY, 78 ILE, 90N ILE, 91 MET, 96 ALA, 120 VAL, 132 LEU, 165 THR, 167 VAL,
5b	-10.4197	43 VAL, 46 ASN, 47 ALA, 50 GLU, 71 VAL, 76 ARG, 77 GLY, 78 ILE, 79 PRO, 90 ILE, 91 MET, 96 ALA, 120 VAL, 165 THR, 166 MET, 167 VAL,
5c	-10.3014	46 ASN, 47 ALA, 49 ASP, 50 GLU, 76 ARG, 78 ILE, 79 PRO, 86 ALA, 87 ALA, 90 ILE, 91 MET, 136 ARG, 120 VAL, 165 THR,
5d	-10.5482	43 VAL, 46 ASN, 47 ALA, 50 GLU, 71 VAL, 73 ASP, 78 ILE, 79 PRO, 90 ILE, 91 MET, 119 GLY, 120 VAL, 121SER, 165 THR, 167 VAL
5e	-9.95408	43 VAL, 46 ASN, 47 ALA, 50 GLU, 71 VAL, 72 GLN, 73 ASP, 76 ARG, 77 GLY, 78 ILE, 79 PRO, 90 ILE, 91 MET, 120 VAL, 121 SER, 136 ARG, 165 THR, 167 VAL,
5f	-978378	43 VAL, 46 ASN, 50 GLU, 71 VAL, 73 ASP, 76 ARG, 78 ILE, 79 PRO, 90 ILE, 91 MET, 119 GLY, 120 VAL121 SER, 165 THR, 167 VAL
5g	-9.67269	43 VAL, 46 ASN, 50 GLU, 71 VAL, 73 ASP, 77 GLY, 78 ILE, 79 PRO, 90 ILE, 91 MET, 119 GLY, 120 VAL, 121 SER, 165 THR, 167 VAL,
8a	-8.26437	41 PHE, 44 VAL, 45 ASP, 48 ILE, 116 HIS, 190 ARG, 194 LEU, 197 LEU, 198 ASN,
8b	-8.4511	41 PHE, 44 VAL, 45 ASP, 48 ILE, 116 HIS, 190 ARG, 194 LEU, 197 LEU, 198 ASN,
8c	-8.45968	32 ASP, 33 GLY, 34 THR, 37 HIS, 38 HIS, 41 PHE, 186 ILE, 189 LYS, 190 ARG, 193 GLU,
8d	-8.65042	43 VAL, 46 ASN, 47 ALA, 50 GLU, 71 VAL, 72 GLN, 73 ASP, 78 ILE, 90 ILE, 91 MET, 120 VAL, 165 THR, 167 VAL
8f	-9.08493	46 ASN, 50 GLU, 77 GLY, 78 ILE, 79 PRO, 86 ALA, 87 ALA, 90 ILE, 93 MET, 96 ALA, 120 VAL, 165 THR, 167 VAL
8g	-9.19368	43 VAL, 46 ASN, 47 ALA, 49 ASP, 50 GLU, 71 VAL, 72 GLN, 73 ASP, 78 ILE, 90 ILE, 91 MET, 120 VAL, 165 THR, 167 VAL
8e	-9.26575	43 VAL,46 ASN, 47 ALA, 50 GLU, 73 ASP, 78 ILE, 79 PRO, 86 ALA, 87 ALA, 90 ILE, 91 MET, 120 VAL, 165 THR, 167 VAL
8h	-9.11335	33 GLY, 34 THR, 37 HIS, 38 HIS, 41 PHE, 183 GLU, 185 GLU, 186 ILE, 189 LYS, 190 ARG, 193 GLU,
Clorobiocin	-10.0199	38 HIS, 41 PHE, 45 ASP, 46 ASN, 48 ILE, 49 ASP, 52 LEU, 116 HIS, 189 LYS, 190 ARG, 193 GLU, 194 LEU, 197 LEU, 198 ASN,

Grid Parameters (Argus Lab.): Spacing 0.4 Å and Grid size 46.034X Å, 46.575Y Å and 41.034Z Å

Conclusion

We have designed and synthesized various Pyridinyl tetrahydroisoquinoline (5a-5g), morpholine and piperidine (8a-8i) containing Schiff bases in a moderate to excellent yield. The docking studies revealed that the synthesized compounds

have a good affinity towards DNA gyrase enzymes with binding energy ranges in between -8.2845 to -10.6466 kcal/mol. The interaction pattern showed a strong impression that synthesized compounds possess good inhibitory potential against DNA gyrase enzyme in similar fashion as that of standard drug Clorobiocin.

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