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Synthesis, antimicrobial, and molecular docking studies of furan-based Schiff bases derived from 4 -nitrobenzene - 1, 2 - diamine

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Abstract: Schiff base compounds contain the azomethine group. They have diverse biological activities such as antibacterial, antifungal, antiviral, antimicrobial, and anticancer. They are frequently used as catalyst, corrosion inhibition agents and dyes in industrial process. This structure group can also be called as a main structural part of natural products and synthetic drugs. Schiff bases **3a, 3b**, **3c**, **3d**, and **3e** were synthesized by reacting 4-nitrobenzene-1,2-diamine with furfural derivatives without acid, base, or Lewis catalytic agents. Reaction progress was monitored by thin-layer chromatography. Each synthesized Schiff base was characterized by UV-visible, FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS techniques. Nitro-substituted Schiff base **3b** shows remarkable antimicrobial activities against bacterial strains *E. Coli*, *S. aureus*, and *E. faecalis* as compared to **3a, 3c, 3d**, and **3e** which was confirmed by molecular docking studies with protein of *E. Coli* DNA gyrase (1KZN), *S. aureus* cell division protein FtsZ (3VOB), and *E. faecalis* nucleoside diphosphate kinase(3Q8U).

Keywords: Schiff bases; synthesis; characterization; antimicrobial activities; molecular docking.

1. Introduction

Schiff bases are synthetically important compounds due to the presence of an azomethine group (>C=N-), which was discovered in 1864 by Hugo Schiff.[1] Different products are obtained from the reaction of primary, secondary, and tertiary amines with aldehydes, and ketones.[2] Imines are obtained from primary amines,[3] while secondary amines give enamines. When aryl group substituent is a structural part, such compound is stable, and called as Schiff base.[4] Schiff-bases are ~~an~~ important type of ligand with diverse donor atoms having remarkable coordination sites towards transition metals.[5-7] Due to the presence of an azomethine group, Schiff bases and their metal complexes shows enhanced biological activities[8-21] such as antimicrobial, antifungal, antiviral, analgesic, antimalarial, growth-inhibiting, anti-inflammatory, antifebrile, bioscreening,[22-24] antioxidant, [25-26] cancer diagnosis, and therapy,[27] anticancer,[28] materials chemistry, and industry.[29-30] They are also used in dye-sensitized solar cells,[31] polymers, paint, dye-manufacturing, organic semiconductors, catalysis, and corrosion inhibitors.[32-33] Schiff bases have been synthesized from amines and aldehydes or ketones by various methods.[34-35] Furan and other related molecules are better ligands due to the presence of one or more ring oxygen atoms with a lone pair of electrons.[36-38]

Healthcare-associated infections can be caused by common gram-positive bacteria such as *S. aureus*, and gram-negative bacteria such as *E. coli and K. pneumoniae. E. coli* is found in the intestines of both animals and humans. Most strains of *E. coli* are beneficial and play a vital role in maintaining the gut microbiome.[39-41] However, *E. coli* and *S. aureus* spread diseases such as pneumonia, meningitis, and

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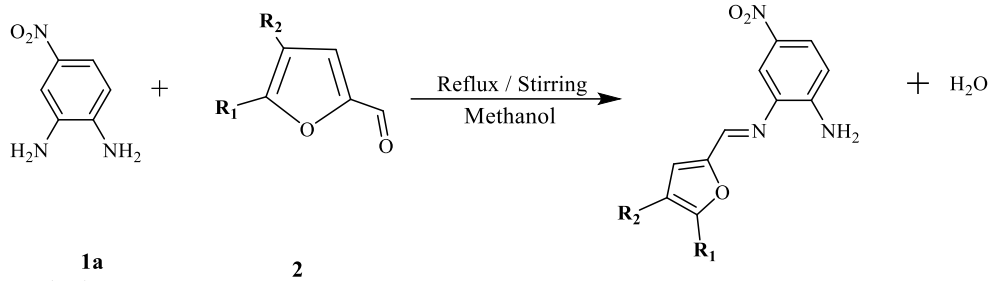
osteomyelitis.[42-43] The use of antibiotics increases resistance against drugs, therefore, to cure bacterial infections some novel drug is required.[44-45] There are various synthetic methods, and developing catalyst-free, high-yield approach is still a desirable goal. In acidic conditions, the nucleophile ($-NH_2$) may get protonated ($-NH_3^+$), and thus its lone pair of electrons is not available, it is not in a position to attack positive carbonyl carbon therefore the reactivity decreases; to get a better yield, simplify product separation, eliminates the use of equipment such as the Dean-Stark apparatus, and avoid use of acid, base or Lewis catalyst our catalyst-free synthesis approach of Schiff base derivatives is the optimum way of synthesizing with high yield.

Molecular docking is an important tool for predicting the potential drug activities against bacterial strains of *E. coli, and S. aureus*.[46-49]

Here in, we reported the design, and synthesis of catalyst-free synthesis of novel Schiff bases having both O, and N donors in the framework by condensing 4-nitrobenzene-1,2-diamine, ~~and~~ substituted furanaldehyde [Scheme1], ~~and~~ their antimicrobial activities, and molecular docking studies against gram-negative bacterial strain *E. Coli*, *K. pneumoniae*, and gram-positive bacterial strain *S. aureus*, and *E. faecalis*.



1a
4-nitrobenzene-1,2-diamine

2
4 or 5 substituted 2-furanaldehyde

3
(**3a**,**3b**,**3c**,**3d**,**3e**)
Schiff bases

R1 = H, NO_2, CH_3, Br, I

R2 = H, Br

2a: 5-methylfuran-2-carbaldhyde

2b: 5-nitrofuran-2-carbaldehyde

2c: 5-Bromofuran-2-carbaldehyde

2d: 4-Bromofuran-2-carbaldehyde

2e: 5-iodo 2-furanaldehyde

Scheme 1. General synthesis of Schiff bases

2. Experimental

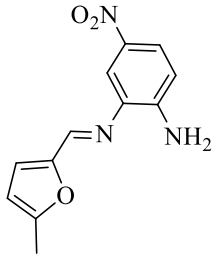
2.1. Generals

Chemicals used in this study were reagents of Sigma Aldrich, TCI chemicals, and Qualigene including 4-nitrobenzene-1,2-diamine, 5-methylfuran-2-carbaldehyde, 5-nitrofuran-2-carbaldehyde, 5-bromofuran-2-carbaldehyde, 4-bromofuran-2-carbaldehyde, 5-iodofuran-2-carbaldehyde, methanol, diethyl ether, Hexane, and dimethyl sulphoxide (DMSO). Melting points of Schiff bases were measured on a Digital melting point apparatus EQ 730. The electronic absorption spectra were recorded using the Agilent Technologies model carry 100 UV-visible spectrophotometers. Infrared spectra were recorded on a Brucker Germany, model 3000 Hyperion Microscope with Vertex 80 FTIR system in the region 4000–450 cm^{-1} using KBr pellets. The ^1H NMR, and ^{13} C NMR spectra were recorded with a JEOL, Japan model ECZR Series 500, 600 MHz NMR spectrometer in DMSO-*d6* as a solvent against tetramethyl silane as an internal standard. LC-HRMS spectra were recorded on an Agilent Technologies USA mass spectrometer, model 1290 infinity UHPLC system,1260 infinity Nano HPLC with Chipcube, and 6550 i Funnel Q-TOFs. The progress of the reaction was monitored by thin-layer chromatography (TLC) using TLC sheets coated with UV fluorescent silica gel Merck 60 F254 plates. It was visualized using a UV-visible cabinet, and ethyl acetate mixed in petroleum ether solvents as a mobile phase. All reagents and solvents were purified and dried using standard techniques.

2.2. Chemistry

*2.2.1.N^1-((5-methylfuran–2-yl) methylene)-5- nitrobenzene -1,2–diamine (**3a**)*:

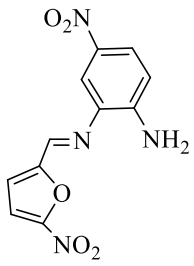
The Schiff base N^1-((5-methyl furan–2-yl) methylene)-5-nitrobenzene-1,2–diamine was synthesized by refluxing reaction mixture of 4-nitrobenzene-1,2-diamine, and 5-methylfuran-2-carbaldehyde in 1:1 ratio in 10 mL methanol about 2 hours at 50^0C, yellowish shiny crystals of Schiff base **(3a)** appeared, precipitate obtained was filtered wash with methanol, diethyl ether, and hexane. The volatile solvent present in product was removed by using a rotary vacuum evaporator (Scheme 1) (Supporting information, S1- S5).



*Spectral Data of **3a***: Yellow solid, Yield: 90%, R_f: 0.25(20% ethyl acetate: Petroleum ether), M.P :124 ^{0}C. UV – Visible absorption band at 308 nm corresponds to π – π*and 397nm corresponds to n – π*transition. FTIR: 3466 cm^{-1} (Asy stretching -NH_2) 3350 cm^{-1} (Sym stretching -NH_2), 1631 cm^{-1} -C=N stretching, 1528cm^{-1} (Asy stretching -NO_2) 1368 cm^{-1} (Sym stretching -NO_2), 1176 cm^{-1} -C-N stretching, 3046 cm^{-1} -C-H stretching. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.51 (s, 1H), 7.90 (d, J = 1.2 Hz, 1H), 7.90 – 7.88 (m, 1H), 7.15 (d, J = 3.3 Hz, 1H), 6.76 (d, J = 9.4 Hz, 1H), 6.55 (s, 2H), 6.39 (dd, J = 3.3, 0.9 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 155.9, 150.1, 150, 146.8, 135.5, 134, 123.2, 119.3, 112.1, 111.9, 108.7, 13.1. HRMS (ESI): *m/z* calculated for $[(C_{12}H_{11}N_3O_3)+H]^+$: 246.0834, found: 246.0859.

*2.2.2. 5–nitro-N^1-((5–nitrofuran–2-yl) methylene) benzene–1,2–diamine(**3b**)*:

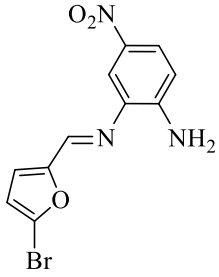
The Schiff base 5–nitro-N^1-((5–nitrofuran–2-yl) methylene) benzene–1,2–diamine was prepared by stirring the reaction mixture at room temperature of 4-nitrobenzene-1,2-diamine, and 5-nitrofuran-2-carbaldehyde in 1:1 ratio in 10 mL methanol about 10 hours pinkish crystals of Schiff base**(3b)** was precipitated, filtered crude product washed with methanol, diethyl ether, and hexane. The volatile solvent present in product was removed by using a rotary vacuum evaporator (Scheme 1) (Supporting information, S6-S10).



*Spectral Data of **3b***: Pink solid, Yield: 95 %, Rf: 0.15(20% ethyl acetate: Petroleum ether), M. P: 1350C.UV – Visible absorption band at 269 nm corresponds to π – π*and 387 nm corresponds to n – π*transition. FTIR: 3458 cm^{-1} (Asy stretching -NH_2) 3333 cm^{-1} (Sym stretching -NH_2), 1622 cm^{-1} -C=N stretching, 1504 cm^{-1} (Asy stretching -NO_2) 1320 cm^{-1} (Sym stretching -NO_2), 1150 cm^{-1} -C-N stretching. ^{1}H NMR (600 MHz, DMSO-d6): δ 8.79 (s, 1H), 8.11 (d, J = 2.5 Hz, 1H), 7.92 (dd, J = 9.1, 2.5 Hz, 1H), 7.82 (d, J = 3.9 Hz, 1H), 7.54 (d, J = 3.9 Hz, 1H), 6.85 (s, 2H), 6.77 (d, J = 9.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6): δ 153.9, 152.7, 151.8, 147.1, 136.5, 132.7, 125.8, 117.9, 114.9, 113.9, 113.9. HRMS (ESI): *m/z* calculated for [(C11H8N4O5)+H]+: 277.0528, found: 277.0536.

*2.2.3. N^1-((5–bromofuran–2-yl) methylene)–5-nitrobenzene1,2-diamine(**3c**)*:

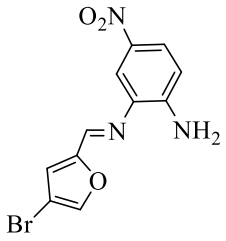
The Schiff base N^1-((5–bromofuran–2-yl) methylene)–5 -nitrobenzene1,2-diamine was prepared by refluxing reaction mixture of 4-nitrobenzene-1,2-diamine, and 5-bromofuran-2-carbaldehyde in 1:1 ratio in 10 mL methanol about 5 hours yellowish crystals of Schiff base **(3c)** was obtained, filtered the product washed with methanol, diethyl ether, and hexane. The volatile solvent present in product was removed by using a rotary vacuum evaporator (Scheme 1) (Supporting information, S11-S15).



*Spectral Data of **3c***: Yellow solid, Yield: 95 %, Rf: 0.25(20% ethyl acetate: Petroleum ether), M.P: 1300C. UV – Visible absorption band at 309nm corresponds to π – π*and 398 nm corresponds to n – π*transition. FTIR: 3450 cm^{-1} (Asy) 3346 cm^{-1} (Sym) -NH_2,1638 cm^{-1}-C=N, 1493 cm^{-1} (Aym) 1339 cm^{-1} (Sym) -NO_2,1149 cm^{-1} -C-N,599 cm^{-1} -C-Br. ^{1}H NMR (500 MHz, DMSO-d6): δ 8.56 (s, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.92 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.27 (d, *J* = 3.5 Hz, 1H), 6.88 (d, *J* = 3.5 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 6.63 (s, 2H).^{13}C NMR (126 MHz, DMSO): δ 154.4, 151.2, 147.2, 136.4, 134.2, 127.2, 124.8, 120.4, 115.3, 113.5, 113.2. HRMS (ESI): *m/z* calculated for [(C11H8N4O5)+H]+: 309.9783, found: 309.9807.

*2.2.4. N^1-((4–bromofuran–2-yl) methylene)–5–nitrobenzene-1,2–diamine(**3d**)*:

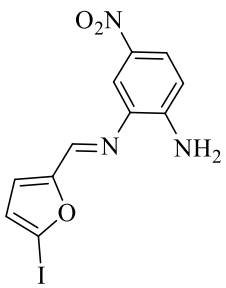
The Schiff base N^1-((4–bromofuran–2-yl) methylene)–5–nitrobenzene-1,2–diamine was prepared by refluxing reaction mixture of 4-nitrobenzene-1,2-diamine, and 4-bromofuran-2-carbaldehyde in 1:1 ratio in 10 mL methanol about 5 hours yellowish crystals of Schiff base was obtained, filtered the product washed with methanol, diethyl ether, and hexane. The volatile solvent present in product was removed by using a rotary vacuum evaporator (Scheme 1) (Supporting information, S16-S20).



*Spectral Data of **3d***: Yellow solid, Yield: 96 %, Rf: 0.210 (20% ethyl acetate: Petroleum ether), M.P.: 131^{0}C. UV – Visible absorption band at 306 nm corresponds to π – π*and 399 nm corresponds to n – π*transition. FTIR: 3495 cm^{-1} (Asy)3389 cm^{-1} (Sym) -NH_2,1630 cm^{-1} -C=N-, 1491 cm^{-1} (Asy) 1339 cm^{-1} (Sym) -NO_2, 1157cm^{-1} -C-N, 587cm^{-1} -C-Br. ^{1}H NMR (500 MHz, DMSO): *δ* 8.63 (s, 1H), 8.23 (s, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.92 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.44 (s, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 6.67 (s, 2H). ^{13}C NMR (126 MHz, DMSO): *δ* 153.3, 151.4, 147.4, 145.1, 136.4, 133.7, 125, 118.9, 113.4, 113.4, 101.8. HRMS (ESI): *m/z* calculated for [($C_{11}H_8N_4O_5$)+H]+: 309.9783, found:309.9818.

*2.2.5. N^1-((5–iodofuran–2-yl) methylene)–5-nitrobenzene-1,2–diamine(**3e**)*:

The Schiff base N^1-((5–iodofuran–2-yl) methylene)–5-nitrobenzene-1,2–diamine was synthesized by stirring a reaction mixture of 4-nitrobenzene-1,2-diamine, and 5-iodofuran-2-carbaldehyde in 1:1 ratio in 10 mL methanol about 5 hours at room temperature, yellowish crystals of Schiff base were obtained, filtered the product washed with methanol, diethyl ether, and hexane. The volatile solvent present in product was removed by using a rotary vacuum evaporator (Scheme 1) (Supporting information, S21-25).



*Spectral Data of **3e***: Yellow solid, Yield: 93 %, Rf: 0.238 (20% ethyl acetate: Petroleum ether) M.P: 1260C. UV – Visible absorption band at 315 nm corresponds to π – π*and 403 nm corresponds to n – π*transition. FTIR: 3470cm^{-1} (Asy) 3346 cm^{-1} (Sym) -NH_2,1626 cm^{-1} -C=N, 1485 cm^{-1} (Asy) 1308 cm^{-1} (Sym) -NO_2, 1175 cm^{-1} -C-N, 492 cm^{-1} -C-I. 1H NMR (500 MHz, DMSO): δ 8.53 (s, 1H), 7.95 (d, *J* = 2.3 Hz, 1H), 7.91 (dd, J = 9.0, 2.3 Hz, 1H), 7.16 (d, J = 3.4 Hz, 1H), 6.98 (d, J = 3.4 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 6.61 (s, 2H).13C NMR (126 MHz, DMSO): δ 157.4, 151.2, 147.1, 136.4, 134.4, 124.7, 123.3, 120.5, 113.5, 113.2, 99.5. HRMS (ESI): *m/z* calculated for [(C11H8N4O5)+H]+: 357.9644, found:357.9672.

2.3. *Antimicrobial Activity*

The antimicrobial activity of Schiff bases was examined by disc diffusion method against two Gram-negative bacterias (*Escherichia coli*, and *Klebsiella pneumoniae*) and two Gram-positive bacterias (*Staphylococcus aureus* and *Enterococcus faecalis*) on Muller Hinton agar medium, by incubation in standard medium for 24 hours at 37°C using ceftriaxone as a control. Each Schiff base was dissolved in DMSO solvent to prepare a solution at a concentration of 10 mg/mL. Paper discs made of Whatman filter paper, each of a standard size of 5 cm, were cut and sterilized in an autoclave.[50] The paper discs soaked in the desired solution were placed aseptically on Petri dishes containing Muller Hinton agar medium inoculated with *Escherichia Coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Klebsiella pneumoniae*. The minimum inhibitory concentration (MIC) and IC50 values of Schiff bases were determined using a tool called AAT Bioquest.

2.4. Molecular Docking

The proteins used for interaction with Schiff bases were *E. Coli* DNA gyrase (PDB ID: 1KZN), *S. aureus* cell division protein FtsZ (PDB ID: 3VOB), and *E. faecalis* nucleoside diphosphate kinase(3Q8U) was downloaded from www.rcsb.org, software NRG Suite was used for molecular docking analysis.[51-53] This free software was available as a plugin for PyMOL (www.pymol.org). It can detect the surface cavities in a protein and use them as target binding sites for docking simulations with the help of FlexAID. It uses the genetic algorithm for conformational search, simulates ligand and side-chain flexibility, and allows for the simulation of covalent docking. In the present work, flexible–rigid docking protocol was employed with the following default settings to get optimum performance from NRGsuite: binding sites input method—spherical shape (diameter: 18Å); spacing of three-dimensional grid—0.375Å; side chain flexibility—no; ligand flexibility—yes; ligand pose as a reference—no; constraints—no; Hetero groups—included water molecules; van der Walls permeability—0.1; solvent types—no type; the number of chromosomes—1000; the number of generations—1000; fitness model—share; reproduction model—population boom; and number of top Schiff base complexes—5 (**3a, 3b, 3c, 3d,** and **3e**).

3. Results and Discussion

3.1. Chemistry

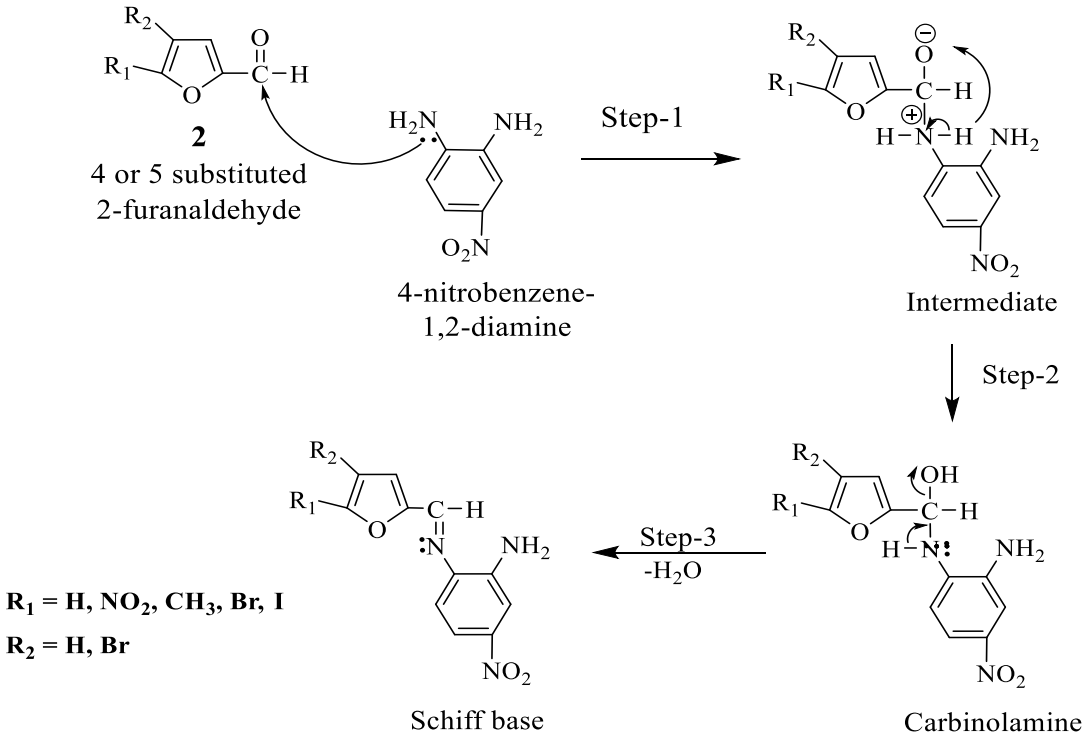
Variable controlled experiments were carried out within the scope of parameter optimization studies for the synthesis of furan-based Schiff bases derived from 4-nitrobenzene-1, 2-diamine. Spectral data of the compounds obtained are given section 2.2.

Schiff bases were synthesized by reacting 4-nitrobenzene1,2-diamine with substituted furanaldehyde derivatives. Synthesis of Schiff bases was carried out without using acid/ ,base or catalyst in a single step using methanol as solvent, all Schiff bases were obtained in good yield (Scheme 1). UV-visible absorption spectra of Schiff bases **3a** to **3e** were observed at 308, 269, 309, 306, and 315 nm corresponding to π – π* transition, and the absorption band at 397, 387, 398, 399, and 403 nm corresponds to n-π* transition shows the presence of azomethine (-C=NH) group. FTIR data of Schiff bases were evaluated as, the stretching frequencies of -NH_2 groups of Schiff bases **3a** – **3e** were reported in the experimental part. ^{1}H NMR data were evaluated as the characteristic downfield chemical shift for identification of Schiff base derivatives >C=NH (Azomethine) proton was observed as a singlet at δ 8.51, 8.79, 8.56, 8.9, and 8.53 ppm for Schiff bases **3a- 3e** respectively. -NH_2 protons were observed as a broad singlet at δ 6.55, 6.85, 6.63, 6.67, and 6.61 ppm for Schiff bases **3a** – **3e** respectively. The benzenoid proton of Schiff base derivatives **3a – 3e** were observed between δ 8.23 – 6.77 ppm as a doublet with meta coupling due to 1H, double doublet or multiplet with ortho, and meta coupling due to 1H, doublet with ortho coupling due to 1H in up field region because proton was present near -NH_2 group. Furanoid proton in Schiff base derivatives **3a**, **3b**, **3c**, and **3e** were observed between 7.82 – 6.39 ppm as doublet having ortho coupling, while two singlet peaks were observed at 8.23 due to 1H and 7.44 due to 1H

proton for Schiff base **3d**. Singlet peak at 2.41 ppm due to 3H was observed for Schiff base **3a** corresponding to -CH_3 group ^{13}C NMR data has evaluated as downfield shift due to >C = NH were observed at 155.9, 153.9, 154.4, 153.3, and 157.4 ppm for Schiff base derivatives **3a** – **3e** respectively. Aromatic carbons were observed between 152.7 – 99.5 ppm for Schiff base derivatives **3a** – **3e**. -CH_3 carbon was observed at 13.1 for Schiff base **3a**. Observed [M+1] *m/z* 246.0859, 277.0536, 309.9807, 309.9818, and 357.9672 were in good agreement with calculated *m/z* 246.0834, 277.0528, 309.9783, 309.9783, and 357.9644 for Schiff base derivatives **3a** -**3e** respectively.

Schiff base formation reaction of 4-nitrobenzene1,2-diamine and substituted furan aldehyde in the absence of a catalyst involves the following steps:

(1) Nucleophilic addition of -NH_2 group across >C=O bond (Step 1, Scheme 2),
(2) Formation of intermediate (Step- 1, Scheme 2),
(3) Formation of carbinolamine (Step- 2, Scheme 2) and
(4) Formation of Schiff base product (Step- 3, Scheme 2).



Scheme 2. Proposed mechanistic steps for Schiff base formation

3.4. Antimicrobial Activity

Among all five Schiff bases, **3b** shows, remarkable activities against bacterial strains *E. coli, K. pneumoniae, S. aureus,* and *E. faecalis*. The observed MIC and IC_{50} values for Schiff base **3b** were found to be 0.313, 0.313, 0.625, 0.0395, 0.0727, and 0.5618 (See Table S1 in Supporting Information) for bacterial strains, *S. aureus, E. faecalis, K. pneumoniae, and E. coli* respectively. All other Schiff bases **3a**, **3c, 3d,** and **3e** were found to be inactive against the tested bacterial strains *S. aureus, E. faecalis, K. pneumoniae, and E. coli.*

3.5. Molecular Docking Studies

The binding energy serves as an indicator of the strength of the interaction between the compound and the protein. There is an inverse relationship, where a lower binding energy indicates a stronger interaction between the Schiff base compound and protein. Schiff bases **3a**, **3b**, **3c**, **3d,** and **3e** show well and different binding scores -7.0509 kcal/mol, -7.1768 kcal/mol, -7.0092 kcal/mol, 7.2215 kcal/mol, -7.2215 kcal/mole, and -7.0849 kcal/mol (Table 1) sequentially against the target protein DNA gyrase 7.1304 kcal/mol (1KZN), -7.7640 kcal/mol, -7.3139 kcal/mol, -7.4632 kcal/mol, and -7.7039 kcal/mol (Table 1) sequentially against the target cell division protein FtsZ (3VOB), and -5.4678 kcal/mol, -5.6779 kcal/mol, -5.5258 kcal/mol, -5.4012, and -5.5510 kcal/mol (Table 1) sequentially against the target protein nucleoside diphosphate kinase(3Q8U). A literature survey shows that a greater negative value of binding energy favours the binding affinity between a target protein and a Schiff base ligand.[52]

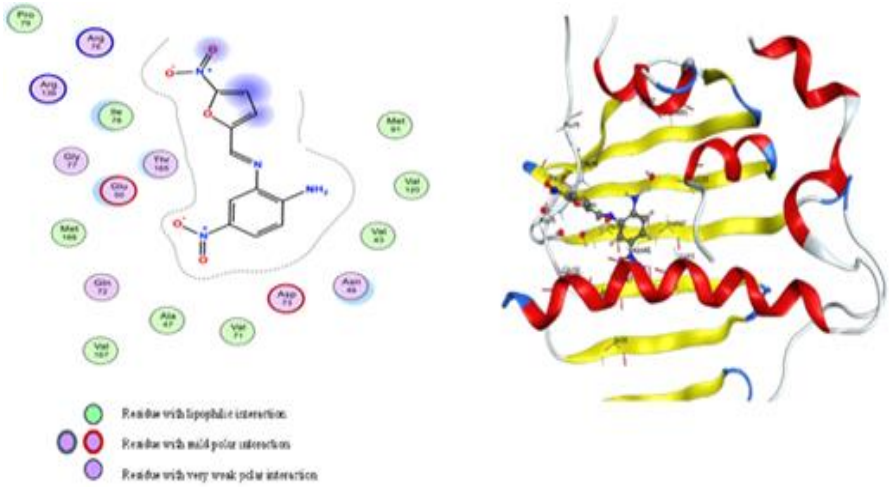


Figure 1. 2D, 3D Interaction of Schiff base **3b** with protein DNA gyrase (1 KZN)

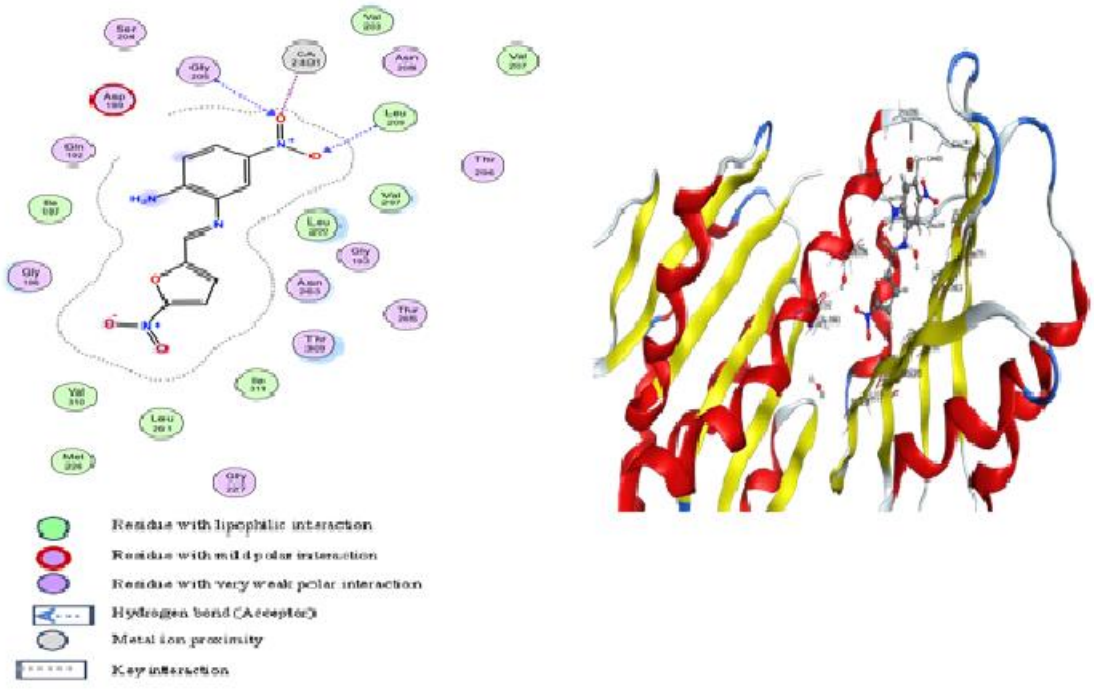


Figure 2. 2D, and 3D interaction of Schiff base **3b** with Cell division protein FtsZ (3VOB)

Table 1. Summary of Schiff base compounds against target proteins with the binding energies, hydrogen bond interaction, and Interacting residues

Enzyme	Schiff base	Free binding energy kcal/mole	Hydrogen bond interaction	Interacting residues
DNA Gyrase	3a	-7.0509	-	Pro79, Met 166, Val71, Ala47, Val167, Val43, Val120, Met91, Glu50, Asp73, Arg136, Arg76, Gly77, Thr165, Gln72, Asr146, Ile78.
	3b	-7.1768	-	Pro79, Met166, Val167, Ala47, Val71, Val43, Val120, Met91, Arg76, Arg136, Glu50, Asp73, Thr165, Gly77, Gin72, Asn46.
	3c	-7.0092	-	Pro79, Ile78, Val71, Met166, Val167, Ala47, Val120, Val43, Met91, Glu50, Arg76, Arg136, Asp73, Thr165, Gly77, Gin72, Asn46.
	3d	-7.2215	-	Pro79, Ile78, Met166, Val167, Val71, Ala47, Val43, Val120, Met91, Arg136, Arg76, Glu50, Asp73, Gly77, Thr165, Gln72, Asn46.
	3e	-7.0849	-	Pro79, Val71, Val43, Val167, Ala47, Val120, Met91, Glu50, Arg76, Asp73, Gly77, Thr165, Gin72, Asn46, Ile78.
Cell division protein FtsZ	3a	-7.1304	Asp199(ligand is donor)	Val203, Leu200, Ile197, Val310, Ile228, Ile311, Leu209, Val297, The265, Gin192, Thr309, Gly227, Gly193, Gly196, Asn263, CA2:401.
	3b	-7.7640	Gly205, Leu209(ligand is acceptor)	Ile197, Val310, Met226, Leu261, Ile311, Leu200, Val297, Val207, Val203, Asp199, Ser204, Gin192, Gly196, Gly227, Thr309, Asn263, Gly193, Thr265, Thr296, Asn208, CA2:401.
	3c	-7.3139	Asp199(ligand donor)	Val203, Leu200, Ile311, Ile197, Ile228, Val310, Val297, Leu203, Thr309, Gin192, Gly193, Gly227, Gly196, Asn263, CA2:401, Thr265.
	3d	-7.4632	Gly205, Leu209	Val297, Ile197, Val310, Ile311, Leu200, Leu261, Val207, Val203, Asp199, Ser204, Thr265, Gly196, Gly227, Thr309, Asn263, Thr296, Asn208, CA2:401.
	3e	-7.7039	Leu209(ligand acceptor)	Val297, Ile197, Val310, Ile311, Leu261, Leu200, Val203, Val207, Asp199, Thr296, Ser204, GIn192, Thr265, Gly193, Gly196, Gly227, Thr309, Asn263, Asp208, Gly205, Thr296, CA2:401.
Nucleoside diphosphate kinase	3a	-5.4678	NO_2 and H_2O	Val109, Phe57, Leu61, Lys9, Asp60, Gly110, Tyr49, His52, Thr91
	3b	-5.6779	-	Val109, Phe57, Leu61, MG2:159, Asp60, Lys9, Gly110, Thr91, Tyr49, Asn112, His52.
	3c	-5.5258	NH_2 andH_2O	Val109, Phe57, Leu61, MG2:159, Lys9, Asp60, Gly110, Asn112, Tyr49, Thr91, His52.
	3d	-5.4012	NH_2 and H_2O	Val109, Phe57, Leu61, MG2:159, Lys9, Gly110, Yhr91, Tyr49, Asr112, His52.
	3e	-5.5510	NH_2 and H_2O	Phe57, Val109, Leu61, Lys9, Asp60, Gly110, Thr91, Tyr49, Asn112, His52.

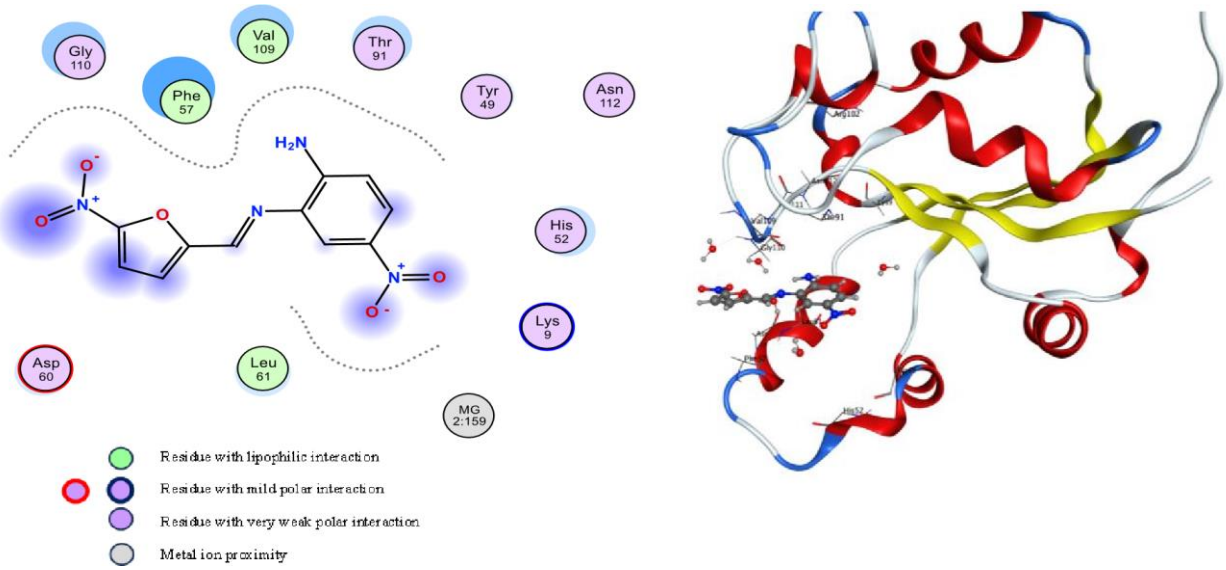


Figure 3. 2D, and 3D interaction of Schiff base **3b** with nucleoside diphosphate kinase (3Q8U)

From Figures 1, 2, and 3, it is clear that the molecules have established a variety of interactions with the receptors. The interaction pattern mostly involves polar, and lipophilic interactions, which have been tabulated in Table 1. The molecules have adopted different conformations inside the active site of receptors, which highlights the flexible nature of the ligands (Schiff bases), and the presence of appropriate pharmacophoric features, thus contributing to the understanding of the mechanism of action of these molecules.

4. Conclusion

In this study, a new Schiff base derivatives **3a -3e** having azomethine (>C=N-) group with N, and O donor sites were prepared from the condensation reaction of 4-nitrobenzene1,2-diamine, and substituted furanaldehyde in good yield, this synthetic method is quite eco-friendly. Structure, and bonding in newly synthesized Schiff base derivatives **3a-3e** were confirmed by UV-visible spectroscopy, FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic techniques. Schiff base **3b** found the lowest MIC and IC50 values against *S. aureus* compared to other bacterial strains **3a**,**3c**,**3d**, and **3e**. It has significant antimicrobial activities against gram-positive bacterial strains *S. aureus*, *E. faecalis*, and gram-negative bacteria *E. coli*. The binding energies -7.1768 kcal/mol, -7.7640 kcal/mol, and -5.6779 kcal/mol indicate strong binding affinities of **3b** with the target proteins DNA gyrase, cell division protein FtsZ, and nucleoside diphosphate kinase, respectively. The presence of a strong electron-withdrawing nitro group (–NO_2), on the furan moiety, and also on the aromatic ring, creates an electron-deficient site that can promote a viable condition for interaction between the compound, and the receptor, and hence Schiff base **3b** shows the highest antimicrobial activity amongst all other prepared Schiff bases **3a**, **3c**, **3d,** and **3e**. Therefore, Schiff base **3b** has the potential to be used as an antibacterial drug.

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