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Synthesis, spectral, antibacterial and docking analyses of (3,4-bis((*E*)-(arylidene)amino)phenyl)(phenyl)methanones

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Biologically active Schiff bases namely (3,4-bis((*E*)-(arylidene)amino) phenyl)(phenyl)methanones have been synthesized through ultrasonicated condensation of (3,4-diaminophenyl)(phenyl)methanone and various benzaldehydes in ethanol medium. Synthesised Schiff bases have been examined by different techniques like molecular formula calculation, molecular weight determination, melting point determination, micro analysis and spectroscopic data. The *in vitro* antibacterial actions of these *E*-imines have been assessed against bacterial strains by zone inhibition and serial dilution methods. Further, molecular docking analysis of all *E*-imines have been accomplished to comprehend the order of binding of Schiff bases with protein.

Keywords: Schiff bases, IR spectra, NMR spectra, Antibacterial activity, Docking study

An imine is an organic substrate comprising a >C=N- functional moiety attached between alkyl or aryl clusters. If an alkyl or aryl cluster is attached to the nitrogen, it can be stated to as Schiff base[1]. The characteristic >C=N- bond with the nitrogen atom dative to the central element is responsible for the biotic actions of Schiff base complexes[2]. Therefore, it is possible to become a potential analog of cisplatin, which favours them to exhibit biological properties[3,4]. Hugo Schiff, a great scientist from Germany discovered Schiff base ligands also known as *E*-imines or azomethine concluded by the condensation of amines with aldehyde or ketones[5]. Schiff base derivatives were utilized as ligands for the production of inorganic complexes and as a bioactive agent in medicinal fields. Schiff bases derived from aliphatic aldehydes are usually unstable. Whereas, Schiff bases from aryl aldehydes are more stable due to presence of conjugative effect[6]. Variety of bioinformatics techniques are available to study the ligand-receptor interactions. To name a few are molecular docking, screening and molecular kinetic simulations. Molecular docking is a regularly used technique in computer- aided structural oriented coherent drug design. It analyzes how the ligands bind together with the macromolecule. Depending upon the binding character of ligand and target substrate, it assigned the three-dimensional structure of co-ordination compound. Molecular docking makes dissimilar probable substrate assemblies that are graded and clustered together by means of scoring function of the software[7]. Al Rasheed *et al*. have synthesized some 1,3,5-triazine Schiff base derivatives, examined by spectral data, antiproliferative action and molecular docking studies with promising results[8]. Effective antimicrobial and anticancer activities of fused thiazoloquinazolinone compounds were reported by Deshineni and coworkers[9]. Effective synthesis and molecular docking studies of hydrazine-carbothioamides has been examined by Krishna *et al*.[10], and revealed that the ligands are potent as drugs for target enzyme. Numerous catalyst and solvents have been employed for Schiff bases synthesis through conventional and greener solvent-free synthetic techniques[11-15]. Recently, Dinesh Kumar *et al*., have studied the synthesis crystal, spectral and DFT analysis of pyridine and naphthalene based imines[16]. Thus, the reports of the previous research works inspired us towards the synthesis, assessment of their antibacterial and molecular docking activities. Their structural characteristics were confirmed by various

systematic methodological techniques. Hence, in the present work the authors aim the synthesis and evaluation of antimicrobial activities and determine the molecular docking character of (3,4-bis((*E*)-(arylidene)amino) phenyl)(phenyl)methanones.

Experimental Details

Chemicals utilized in this study were acquired from commercial companies such as Sigma-Aldrich, E-Merck and BDH. The melting point of all Schiff bases were determined in a Mettler electric melting point apparatus (230 V AC, 5 Amp) and are uncorrected. The VARIOMICRO V2.2.0 CHN analyzer was used to carry out the elemental analysis. FT-IR spectra of all Schiff bases were recorded in AVATAR-330 FT-IR spectrometer using KBr discs. ^{1}H and ^{13}C NMR spectra of all the synthesized compounds were recorded using BRUKER AVANCE III 400 MHz NMR spectrometer operating at 400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR employing in $CDCl_3$/DMSO solvent and TMS as an internal standard. Mass spectra (EI) (70 eV) of all imines were recorded in a Finnegan MAT 95S spectrometer.

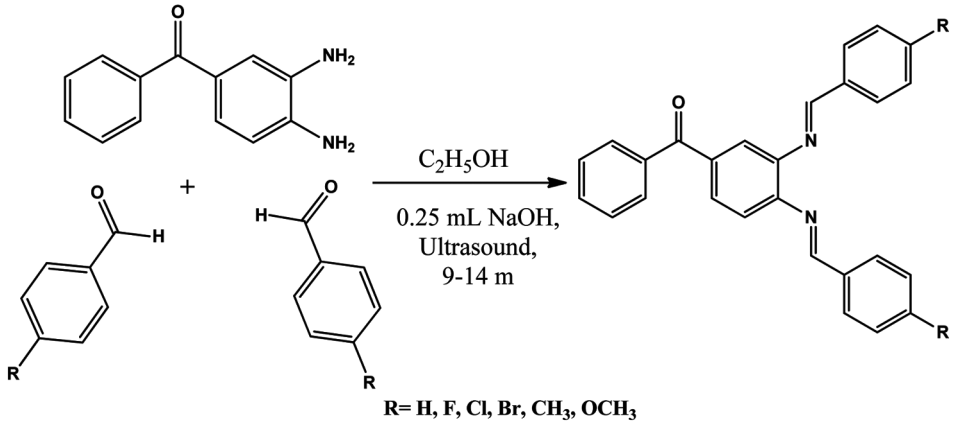
Synthesis of *E*-imines

The new (3,4-bis((*E*)-(arylidene) amino)phenyl) (phenyl)methanones **1-6** were prepared through the ultrasonicated condensation of one mole of (3,4-diaminophenyl) (phenyl)methanone with two moles 4-substituted benzaldehydes in presence of 0.25 mL of sodium hydroxide in ethanol (20 mL) for 9-14 min (Scheme 1). The feasibility of the reaction was examined by thin layer chromatogram. The crude product was separated by filtration, washed with water, dried and recrystallized using ethanol. In this reaction, the yield obtained was in the range 80-90%. The synthesized Schiff bases were characterized by their elemental analysis, FT-IR, ^{1}H and ^{13}C NMR and mass spectral data. Complete characterization data of synthesized *E*-imines are given here.

(3,4-bis((*E*)-Benzylideneamino)phenyl) (phenyl) methanone, 1: Yield 86%. Colourless solid. m.p.204-206°C. IR (KBr): 3008.98, 2941.05, 1657.63, 1565.28, 1500.58, 1447.80, 1416.88, 1337.39, 1311.37, 1229.28, 1146.41, 699.70 cm^{-1}; ^{1}H NMR: δ 8.78 (s, 1H, NH), 7.03-7.67 (m, 18H, Ar-H); ^{13}C NMR: δ 190.72 (CO), 168.26 (CN), 119.73-145.02 (Ar-C). Anal. for $C_{27}H_{20}N_2O$, Found (Calcd) C, 83.40(83.44); H, 5.11(5.19); N, 7.18 (7.21)%. M.Wt. 388. MS: *m/z* 388[M^+], 311, 298, 284, 207, 180, 179, 105, 104, 98, 90, 77.

(3,4-bis((*E*)-(4-Fluorobenzylideneamino)phenyl)(phenyl)-methanone, 2: Yield 83%. White solid. m.p.226-228°C. IR (KBr): 3046.31, 2979.31, 1635.59, 1516.82, 1491.54, 1445.31, 1392.90, 1321.27, 1304.82, 1248.41, 1129.06, 643.05 cm^{-1}; ^{1}H NMR: δ 8.63 (s, 1H, NH), 6.95-7.93 (m, 16H, Ar-H); ^{13}C NMR: δ 189.93 (CO), 160.95 (CN), 115.21-144.13(Ar-C). Anal. for $C_{27}H_{18}F_2N_2O$, Found (Calcd) C, 76.38 (76.40); H, 4.20 (4.27); N, 6.59 (6.52)%. M.Wt. 424. MS: *m/z* 424[M^+], 426[M^{2+}], 428[M^{+4}], 405, 329, 316, 302, 2225, 207, 197, 180, 122, 108, 105, 95, 77, 19.

(3,4-bis((*E*)-(4-Chlorobenzylideneamino)phenyl)(phenyl)-methanone, 3: Yield 83%. White solid. m.p.242-244°C. IR (KBr): 3047.60, 2930.19, 1636.06, 1512.30, 1444.44, 1392.06, 1335.33, 1295.80, 1245.33, 1177.52, 642.36 cm^{-1}; ^{1}H NMR: δ 8.72 (s, 1H, NH), 7.22-7.68 (m, 16H, Ar-H); ^{13}C NMR: δ 189.38 (CO), 161.26 (CN), 120.29-144.39(Ar-C). Anal. for $C_{27}H_{18}Cl_2N_2O$, Found (Calcd) C, 70.86 (70.91); H, 3.89 (3.97); N, 6.06 (6.13)%. M.Wt. 457. MS: *m/z* 456[M^+], 458[M^{2+}], 460[M^{+4}], 421, 345, 332, 318, 283, 241, 213, 207, 180, 138, 124, 111, 105, 77, 35.



Scheme 1 — Synthesis of (3,4-bis((*E*)-(arylidene)amino)phenyl)(phenyl)methanones

(3,4-bis((*E*)-(4-Bromobenzylideneamino)phenyl)(phenyl)-methanone, 4: Yield 82%. Pale yellow solid. m.p.266-268°C. IR (KBr): 3044.76, 2976.39, 1633.99, 1519.63, 1444.97, 1390.64, 1390.64, 1325.86, 1299.38, 1242.96, 1167.96, 638.24 cm^{-1}; ^1H NMR: δ 8.67 (s, 1H, NH), 7.21-7.66 (m, 16H, Ar-H); ^{13}C NMR: δ 201.71 (CO), 160.69 (CN), 116.34-141.02(Ar-C). Anal. for $C_{27}H_{18}Br_2N_2O$, Found (Calcd) C, 59.39 (59.37); H, 3.29 (3.32); N, 5.08(5.13)%. M.Wt. 546. MS: *m/z* 546[M^+], 548[M^{2+}], 550[M^{4+}], 465, 389, 362, 326, 285, 283, 257, 207, 182, 181, 180, 168, 155, 105, 79.

(3,4-bis((*E*)-(4-Methylbenzylideneamino)phenyl)(phenyl)-methanone, 5: Yield 87%. White solid. m.p.190-192°C. IR (KBr): 3064.88, 2932.08, 2857.05, 1642.46, 1574.38, 1493.60, 1449.65, 1422.65, 1320.73, 1279.371231.15, 1160.60, 639.48 cm^{-1}; ^1H NMR: δ 8.78 (s, 1H, NH), 2.25 (s, 3H, CH_3), 7.22-7.96 (m, 16H, Ar-H); ^{13}C NMR: δ 187.06 (CO), 141.21 (CN), 117.61-139.42 (Ar-C), 22.72 (CH_3). Anal. for$C_{29}H_{24}N_2O$, Found (Calcd) C, 83.65 (83.63); H, 5.78 (5.81); N, 6.68 (6.73)%. M.Wt. 416. MS: *m/z* 416[M^+], 410, 325, 312, 298, 283, 221, 207, 194, 180, 118, 105, 104, 91, 31, 15.

(3,4-bis((*E*)-(4-Methoxybenzylideneamino)phenyl)(phenyl)-methanone, 6: Yield 90%. White solid. m.p.176-178°C. IR (KBr): 3071.38, 2918.26, 2849.44, 1642.76, 1567.91, 1490.37, 1445.34, 1324.19, 1284.17, 1119.91, 692.11 cm^{-1}; ^1H NMR: δ 8.70 (s, 1H, NH), 4.01 (s, 3H, OCH_3), 6.96-7.95 (m, 16H, Ar-H); ^{13}C NMR: δ 196.65 (CO), 160.74 (CN), 115.21-144.13(Ar-C), 51.59 (OCH_3). Anal. for $C_{29}H_{24}N_2O_3$, Found (Calcd) C, 77.69 (77.66); H, 5.32 (5.39); N, 6.18 (6.25)%. M.Wt. 448. MS: *m/z* 448[M^+], 433, 417, 341, 328, 314, 299, 237, 209, 207, 194, 180, 134, 122, 120, 107, 17, 31, 15.

Measurement of antibacterial activity assay

The antimicrobial action of synthesized *E*-imines was measured by well-known Bauer-Kirby disc diffusion[20] and serial dilution techniques[21-23]. In this experiment, each of three gram +ve and –ve stains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes*, *Klebsiella pneumonia*, *E.coli* and *Pseudomonas aeruginosa* were used for measuring the antibacterial actions of synthesized compounds. Commercial *Ciprofloxacin* 40 µg /disc drug was used as standard. Antibacterial actions of all *E*-imines were assessed by calculating the mm of zone of inhibition.

Serial dilution method

Two-fold serial dilution technique[21] was utilized for finding minimum inhibitory concentration (MIC) of all synthesized Schiff bases with the strengths of 10^{-6} to 10^{-7} cfu/mL of seeded broth. Different concentration of *E*-imines was prepared within the series of 200, 100, 50, 25, 12.5, 3.13, 1.56, 0.78 and 0.39 µg/mL for determination of MIC's using diluent of seeded broth. Likewise, the ciprofloxacin drug standard solution was also prepared within the above range of concentrations *i.e.* 200-0.39 µg/mL employing germ-free distilled water and DMSO as control throughout the experiment using a series of 10 assay tubes of prepared Schiff bases against their strain. First assay consists of 1.6 mL of broth and 0.4 mL of compound and made up to 200 µg/mL of strength. Residual nine analysis tubes were filled with 1 mL of seeded broth and per mL of the solution was pipetted out into a second assay tube and mixed thoroughly. This dilution was repeated for all 10 assay tubes serially. Also, this serial dilution was continued for standard drug taken, duplicate was maintained in germ-free environment. These serially diluted analysis tubes were kept in the incubator and maintained in the temperature range of 37 ± 1°C for 24 h. After incubation, the strengths of the analysis tubes were streaked into the nutrient agar plate due to turbidity of the drug mixture. The least strength of prepared Schiff bases which completely inhibits the growth-development of bacterium was taken as the MIC.

Results and Discussion

Six new Schiff bases have been synthesized from (3,4-diaminophenyl)(phenyl)methanone with 4-substituted benzaldehydes in ethanol using ultrasonication process. The observed yields were more than 80%. The electron contributing substituents gave highest yield as compared to the electron withdrawing groups. Here the authors studied the influence of solvent-media on the synthesis by resources of obtained yields. This condensation was done with solvents such as methanol, ethanol, dichloromethane, chloroform, dioxane and tetrahydrofuran. The obtained yields are given in Table 1. From the table, methoxy substituent gave high yields in all solvents. Comparatively, electron withdrawing substituents gave lower yields. In general, the observed yields are more than 80% in all the solvents investigated.

FT-IR spectral investigation

Aromatic compounds commonly exhibit multiple weak bands in the region 3150-2930 cm^{-1} (Ref. 17) which is proven in this case by the bands acquired in the range of 3071.38-2918.26 cm^{-1}. The C-H stretching in alkanes absorbs at lesser wavelengths than aromatic rings. The band at 2850 cm^{-1} is ascribed to methyl group of compounds **5** and **6**. A band observed in the regions of 1657.63-1633.59 and 1567.91-1512.30 cm^{-1} is ascribed to C=O/C=N stretching, which is the important elementary confirmation for the development of Schiff bases. The ring C=C vibrations as arc stretches usually occur in the interval 1400-1625 cm^{-1} (Ref. 18) which is proven in this case by the band notorious in the region 1500.58-1390.64 cm^{-1}. The peak appeared at 1337.39-1231.15 cm^{-1} has been designated to C-H in- plane bending modes of vibrations. Vibrational bands appearing in 1177.52-638.24 cm^{-1} are owing to the aromatic C-H out-of-plane bending mode of vibrations. These data are supported for the development of Schiff bases.

NMR spectral study

The measured chemical shifts of all the synthesized Schiff base compounds are summarized in the Experimental Section. The signal obtained in the range δ 7.22-6.95 is attributed to the aromatic proton of all the synthesized Schiff base. The -CH=N- proton signal of all the synthesized *E*-imines appeared in the interval δ 8.78-8.63 (Ref. 19). For compound **6**, the methoxy proton signal appeared at δ 4.01. The up-field peak appeared at δ 2.25 which corresponds to methyl proton in compound **5**. Azomethine carbon signal for the compounds **1-6** appear in the range of δ 160.69-186.95 (Ref. 14). The signal between δ 115.21 and 148.67 is attributed to aromatic carbon. The *ipso* carbons should absorb at a higher frequency compared to other aromatic carbons which are revealed in this case by the signal appearing in the range δ 161.17-141.21. Signals at δ 22.72 and 51.59 are corresponding to methyl and methoxy carbon present in compounds **5** and **6**, respectively.

Table 1 — Effect of solvents on the yield

Entry	X	Yield (%) in solvents					
		EtOH	MeOH	DCM	CM	DO	THF
1	H	86	85	83	83	84	81
2	F	83	80	80	81	80	82
3	Cl	83	82	80	82	83	80
4	Br	82	82	80	80	81	80
5	CH_3	87	86	83	84	80	82
6	OCH_3	90	88	84	86	85	84

EtOH: Ethanol; MeOH: Methanol; DCM: Dichloromethane; CM: Chloroform; DO: Dioxane; THF: Tetrahydrofuran

Mass spectral study

All Schiff bases gave the expected molecular ion peaks and the isotopic peaks appeared for the halogen substitutions. Each compound shows the -C=N-Ph-R peaks at corresponding *m/z* values. All compounds show the characteristic Ph-$COPh^{+\cdot}$ And $PhCO^{+}$ peaks at *m/z* 180 and 105. Further, the usual fragments were observed for all compounds. These data are supported for the synthesized Schiff bases.

Antibacterial studies of compounds 1-6

The zone of inhibition[20-26] values of compounds **1-6** along with the standard drug for comparison is furnished in Table 2 and the statistical bacterial activity column chart for the antibacterial activity by the measurement of zone of inhibitions against bacterial strains are shown in Fig. 1.

The antibacterial study showed that, all prepared compounds show good antibacterial activity against *S. aureus*, *S. pyogenes*, *K. pneumonia* and *E.coli* strains. Moderate activity is observed against *B. subtilis* strain. Satisfactory and good anti-bacterial activities are observed against *P. aeruginosa* strain when compared to ciprofloxacin standard.

The antibacterial activities of all synthesized Schiff bases by means of MIC values from the serial dilution method are presented in Table 3. From Table 3, all synthesized Schiff bases showed good antibacterial

Table 2 — Study of anti-bacterial activities of compounds **1-6** by disc diffusion method

Entry	X	Zone of Inhibition (mm)					
		S. aureus	*B. subtilis*	*S. pyogenes*	*K. pneumoniae*	*E.coli*	*P.aeruginosa*
1	H	9	8	10	11	10	12
2	F	10	8	11	9	9	10
3	Cl	9	9	10	10	10	11
2	Br	12	11	13	13	10	11
5	CH_3	13	9	14	11	9	8
6	OCH_3	11	10	12	10	8	9
	Standard	19	20	17	14	13	17

activities against their strain. The chloro substituted Schiff base compound **3** shows maximum MIC values against Ciprofloxacin standard.

Docking analysis of Schiff base compounds 1-6

To explain the Topoisomerase selectivity of some newly synthesized *E-imine* analogs, docking analysis were accomplished using the Schrodinger program[27,28], examining analogue docking in Topoisomerase enzyme pockets. The crystallographic enzyme-ligand complex was obtained from the RCSB Protein Data Bank (PDB entry 3TTZ) and the picture was presented in Fig. 2.

To understand the detailed binding characteristics of Schiff base derivatives, by modifying their aromatic group in ligand **1** the deeper docking study into Topoisomerase protein were performed. Since docking analysis may well be in agreement with more insight into accepted protein–ligand interactions and the structural characteristics of the active location of protein to the binding interactions. Fig. 3a-f represent the probable adhering modes of compounds **1-6** in the Topoisomerase protein.

Molecular basis of interactions between target enzyme and synthesized ligands can be understood with the assistance of docking analysis and docking scores were summarized in Table 4. As shown in Fig. 4a-f compounds **1-6** bind to the active location of Topoisomerase and have several interactions with nearby residues. Compound **1** has binding energy –5.438 with hydrophobic interaction *viz*. ILE102, LEU103, ILE175, VAL79, ILE51, ILE86 and PRO87, when introducing substitution (F, Cl, Br, CH_3 and OCH_3) in phenyl group. It is pertinent to note that the more active ligand **4** exhibits nice binding energy of –5.579. Fig. 4d clearly presents the H-interactions with ASP81. In addition, ligand 4 has hydrophobic interaction with ILE102, LEU103, ILE51, ILE175, ILE86, PRO 87 and VAL79 residues.

The ligand **5** has a binding energy (–5.278) among the selected ligands. It forms a hydrophobic interaction with ILE102, LEU103, ILE51, ILE175, ILE86 and PRO87. As seen in Fig. 4e, the ligand **5** locates in a large polar pocket in contact with SER129, ASN54, SER55 and THR173. However, it indicates the hydrogen bond interaction at the amine with ASP81. Finally, the methoxyphenyl group in compound **6** formed a hydrophobic interaction with ILE102, LEU103, ILE175, VAL79, ILE51, ILE86 and PRO87. On the other hand, the amino acids such as SER55, ASN54 and THR173 formed polar

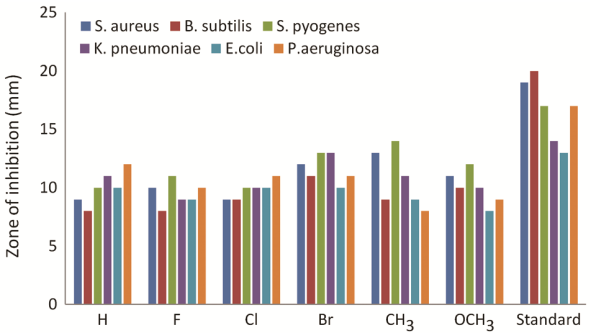


Fig. 1 — The chart representation of the antibacterial activity of compounds **1-6**.

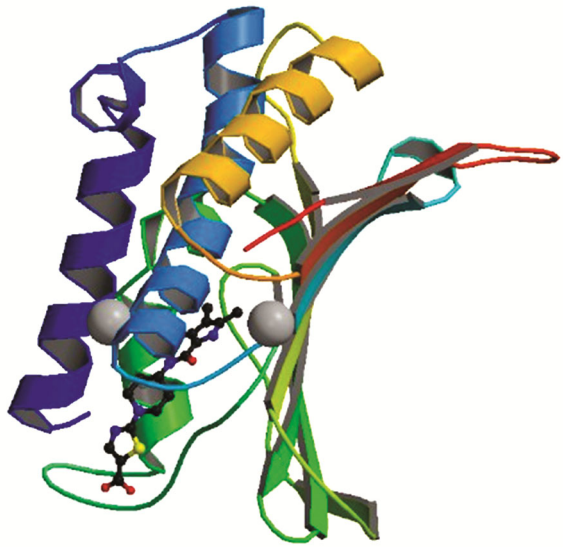


Fig. 2 — X-ray crystal structure of protein Topoisomerase

Table 3 — Study of anti-bacterial activities of compounds **1-6** by two fold serial dilution method

Entry	X	MIC (µg/mL)					
		S. aureus	*B. subtilis*	*S. pyogenes*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*
1	H	20	12	14	22	28	36
2	F	40	42	36	38	48	28
3	Cl	80	60	80	80	80	88
4	Br	40	32	28	44	54	48
5	CH_3	48	32	36	38	36	40
6	OCH_3	18	26	30	40	40	34
Standard		8.5	6.5	10.5	6.8	10	7.5

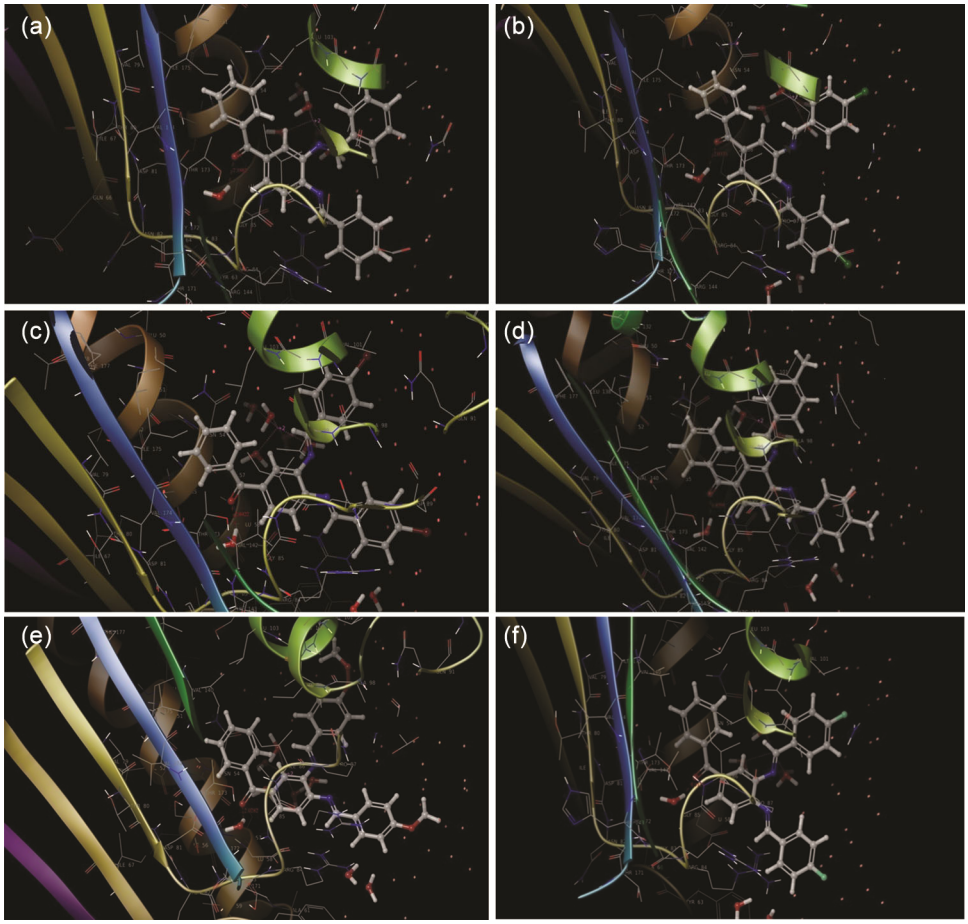


Fig. 3a-f — Docking conformation of compounds **1-6**

Table 4 — Docking score, glide energy, hydrophilic and hydrophobic interaction of Schiff base compounds **1-6**

Ligand	Docking score	Glide energy (kcal/mol)	Glide g score (kcal/mol)	Hydrophobic interaction	Hydrogen bond Interaction	Polar interaction
1	–5.438	–34.23	–5.439	ILE102, LEU103, ILE175, VAL79, ILE51, ILE86, PRO87	–	THR173, ASN54, SER55
2	–5.519	–38.33	–5.816	ILE102, LEU103, ILE175, ILE51, VAL79, ILE86, PRO87	–	THR173, ASN54, SER55
3	–5.503	–36.58	–5.802	VAL130, VAL131, ILE102, ILE51, LEU103, ILE175, PRO87, ILE86	–	SER128, SER129, ASN54, SER55, THR173
4	–5.579	–39.44	–5.783	ILE102, LEU103, ILE51, ILE175, ILE86, PRO87, VAL79	ASP81	SER129, ASN54, SER55, THR173
5	–5.278	–33.12	–5.279	ILE102, LEU103, ILE51, ILE175, ILE86, PRO87	ASP81	SER129, ASN54, SER55, THR173
6	–5.066	–37.66	–5.792	ILE102, LEU103, ILE175, VAL79, ILE51, ILE86, PRO87	–	SER55, ASN54, THR173
Standard	–7.682	–28.747	–5.962	ILE175, ILE51, LEU103, ILE102, ILE86, PRO86	–	ASN54, SER55, THR173

interaction with the same ligand. In the designed compound, **6** has the lowest binding energy. With a target to detect the maximum dynamically favoured binding pose, the results have been compared with standard Ciprofloxacin. The consequences of molecular docking analysis enlightened the better inhibitory activity which is close to docking scores of **4**. These dry lab findings are very well agreeable with the results of *in vitro* antibacterial activity.

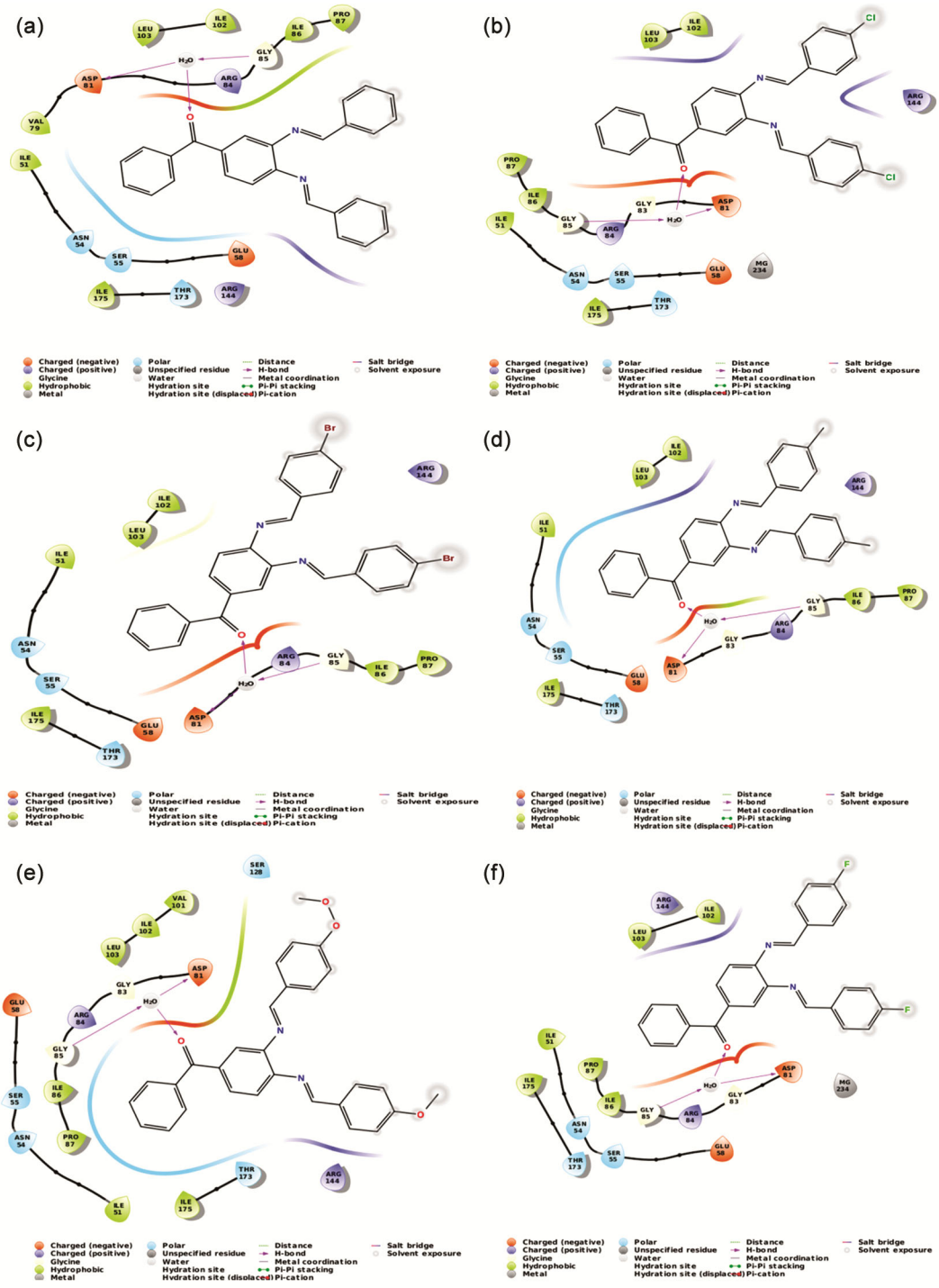


Fig. 4a-f — The 2-D interaction of compounds **1-6**

Conclusion

Schiff bases (3,4-bis((*E*)-(arylidene)amino)phenyl) (phenyl)methanones were prepared through the condensation of (3,4-diaminophenyl)(phenyl) methanone and 4-substituted benzaldehydes. They were characterized using elemental analysis, IR, NMR, mass spectra and analytical techniques. Infrared spectral studies reveal that the C=N stretching appeared in the region 1567.91-1512.30 cm^{-1}. The appearance of the C=N band is the preliminary evidence for the formation of Schiff bases. From NMR spectral studies, the methine proton (N=C*H*) signal appeared in the interval δ 8.78-

8.63. From ^{13}C NMR chemical shift values, C=N signals around δ 155 confirms the development of synthesized Schiff bases **1-6**. All synthesized Schiff bases show moderate, satisfactory and good antibacterial activities against their strain comparatively ciprofloxacin standard in disc diffusion method. The chloro substituted Schiff base compound **3** shows maximum MIC values in serial dilution method. The synthesized ligands **1-6** were docked against Topoisomerase protein. The outcome of the docking analysis clearly proves that Schiff base **4** has the value which is closer to the standard Ciprofloxacin.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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