



Synthesis, antimicrobial and docking studies of some novel (N^1E , N^2E)- N^1 , N^2 -bis(2-amino-3,5-dibromobenzylidene)-aryl-1,2-diamines

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The diamino derivative is utilized to synthesize various substituted derivatives, which are characterized by IR and NMR. The antibacterial properties of synthesized compounds have been explored. Novel (E)-4,6-dibromo-N1-(4-substitutedbenzylidene)benzene-1,2-diamine derivatives (**1-6**) have been obtained in good yields from 2-amino-3,5-dibromobenzaldehyde and 4-substituted benzene-1,2 diamines in a single pot synthesis. The antimicrobial activity of the synthesized compounds have been screened against different strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Escherichia coli* and compared with Ciprofloxacin as a standard and compound **6** shows significant activity against *Staphylococcus aureus*. The docking study results also support the antimicrobial activity data.

Keywords: Schiff base, IR, NMR, antibacterial activities, docking study

Biologically active compounds contain heterocyclic moieties which act as pharmaceutical ingredients intermediates. Hence the heterocycles plays a very vital role in our day to day life and society as well¹⁻³. Most of the molecules such as Fluconazole with Imidazole, Raltegravir with oxadiazole, Ranolazine with pyrazine and Ceftazidime with pyridine ring are known for their potential outstanding used as drugs in various therapeutic applications⁴⁻⁸. Pyridine is a basic heterocyclic organic compound which occurs in many important compounds, including azines, pyridoxine, etc. Heterocyclic compounds can be usefully classified based on their structure. The saturated heterocycles act like the acyclic derivatives. Thus, piperidine and tetrahydrofuran are predictable amines and ethers, with improved steric shapes. Therefore, the study of heterocyclic chemistry efforts exclusively on unsaturated byproducts, and the preponderance of work and claims involve unstrained 5- and 6-membered rings such as pyridine, thiophene, pyrrole, and furan. Another large class of heterocycles are bonded to benzene rings, which for pyridine, thiophene, pyrrole, and furan are quinoline, benzothiophene, indole and benzofuran respectively. Fusion of two benzene rings gives rise to a third large domestic of compounds, respectively the acridine, dibenzothiophene, carbazole, and dibenzofuran. The unsaturated rings can be

classified according to the participation of the heteroatom in the conjugated system.

Heterocyclic ring systems that are formally derived by fusion with other rings, either carbocyclic or heterocyclic, have a variety of common and systematic names. For example, with the benzo-fused unsaturated nitrogen heterocycle, pyrrole provides indole or isoindole depending on the orientation. The pyridine analogue is quinoline or isoquinoline. For azepine, benzazepine is the preferred name. Likewise, the compounds with two benzene rings fused to the central heterocycle are carbazole, acridine, and dibenzoazepine.

The aminopyridine moiety is of remarkable interest for the synthesis of heterocyclic compounds and for its biological, docking and pharmaceutical properties. A wide spectrum of biological activities can be found in a large number of natural resources of biologically active compounds⁹⁻¹¹. Quinoline derivatives are discovered in several natural products as active candidates due to their therapeutical activities such as anti-oxidant¹², anti-plasmodial¹³, antihypertensive¹⁴, anti-fungal¹⁵ and anti-inflammatory¹⁶. In this work, there are six Schiff base derivatives have been synthesized and characterized by Elemental analysis, IR and NMR spectra, Antibacterial activity and Docking study.

Results and Discussion

The title compound **1** was prepared by refluxing 4-substituted benzene-1,2-diamine and 2-amino-3,5-dibromobenzaldehyde in ethanol. They were characterized by FT-IR, ^1H and ^{13}C NMR and elemental analysis^{19,20}. The physical constants, analytical and elemental analysis data of title compounds are shown in Table I.

FT-IR spectral analysis of compounds 1-6

The IR stretching frequencies of all the synthesized Schiff base compounds were shown in Table II.

For the title compound **1**, the band at 1627.42cm^{-1} is assigned for the C=N formation. The C=N stretching appeared in the region 1627.42cm^{-1} and becomes the preliminary evidence for the formation of Schiff base. Thirunarayanan *et al.*¹⁶ synthesized oxazine amine derivatives and reported N-H stretching in the region $3532\text{-}3559\text{cm}^{-1}$. The strong bands in the region 3419cm^{-1} is assigned to N-H stretching. The multiple weak bands in the region $2971.81\text{-}3055.63\text{cm}^{-1}$ corresponds to the aromatic region²¹. For Schiff base **2** the band at 1611.39cm^{-1} is assigned for the C=N formation. The strong bands in the region 3415cm^{-1} correspond to the N-H stretching. The multiple weak bands at $2969.21\text{-}2929.21\text{cm}^{-1}$ support the presence of aromatic ring. For Schiff base **3** the band at 1582.08cm^{-1} assigned for the C=N bond. The strong band at 3422.60cm^{-1} is due to the hydrogen bonding of N-H.

For Schiff base **4** the band at 1606.25cm^{-1} refers to the formation of C=N bond. The N-H stretching at 3428.09cm^{-1} implies the presence of the NH_2 group. The various weak signals at $2986.17\text{-}2934.57\text{cm}^{-1}$ refers to the aromatic region. For Schiff base **5** the band at 1608.71cm^{-1} corresponds to the C=N formation. The strong band at 3413.13cm^{-1} refers to N-H stretching. The characteristic weak band at 3054.69cm^{-1} assures the aromatic ring. The low frequency band at 2922.34cm^{-1} compared to the aromatic band supports the presence of alkyl group. Further, the weak bands at $2980\text{-}2870\text{cm}^{-1}$ correspond to CH_3 stretching frequencies. The band at 1607.75cm^{-1} , 3413.13cm^{-1} and 3399.44cm^{-1} assigned for the C=N, N-H and aromatic groups respectively in compound **6**. The band at 2876.87cm^{-1} implies the C-H stretching frequency of alkyl group.

NMR spectral analysis of compounds 1-6

^1H and ^{13}C NMR spectral data of all the synthesized Schiff base compounds are given in Table III. C=N bond formation is confirmed by the appearance of a signal (Singlet) for H- C=N at 8.63 ppm in compound **1**. N-H bond formation confirmed by the signal (Broad or narrow) at 4.73ppm and multiplets from 6.96 ppm to 7.98 ppm is the characteristic signals for aromatic protons. For compound **2** the proton attached to C=N bond appeared at 8.95 ppm. N-H bond formation confirmed by the signal at 4.49 ppm and Ar-H appears in the region 6.96ppm and 7.82ppm. The signal at 8.64 ppm confirms the formation of C=N bond in

Table I — Physical constants, yields and analytical data of compounds 1-6

Entry	X	Mol. Formula	Mol. Wt.	Yield (%)	m.p. (°C)	Found (Calcd) (%)		
						C	H	N
1	H	$\text{C}_{20}\text{H}_{14}\text{Br}_4\text{N}_4$	629.97	84	210-212	38.07 (38.13)	2.20 (2.24)	8.81 (8.89)
2	Cl	$\text{C}_{20}\text{H}_{13}\text{Br}_4\text{FN}_4$	647.96	89	226-228	37.04 (37.07)	2.00 (2.02)	8.55 (8.65)
3	Br	$\text{C}_{20}\text{H}_{13}\text{Br}_4\text{ClN}_4$	664.41	90	244-246	35.96 (36.15)	1.87 (1.97)	8.40 (8.43)
4	NO_2	$\text{C}_{20}\text{H}_{13}\text{Br}_5\text{N}_4$	708.86	91	196-198	33.72 (33.89)	1.80 (1.85)	7.85 (7.90)
5	CH_3	$\text{C}_{21}\text{H}_{16}\text{Br}_4\text{N}_4$	643.99	86	170-172	39.09 (39.17)	2.45 (2.50)	8.65 (8.70)
6	OCH_3	$\text{C}_{21}\text{H}_{16}\text{Br}_4\text{N}_4\text{O}$	659.99	82	170-172	38.12 (38.22)	2.12 (2.24)	8.40 (8.49)

Table II — The FT-IR spectral data (ν , cm^{-1}) of compounds 1-6

Compd	1	2	3	4	5	6
	H	Cl	Br	NO_2	CH_3	OCH_3
$\nu_{\text{N-H}}$	3419.21	3415.44	3422.60	3428.09	3413.13	3399.44
$\nu_{\text{Ar-C-H}}$	3055.63	2969.21	3040.50	2986.17	3054.69	3060.67
$\nu_{\text{Alk-C-H}}$	3015.34	2997.43	3046.25	3002.34	2922.34	2876.87
$\nu_{\text{C=N}}$	1627.42	1611.39	1582.08	1606.25	1608.71	1607.75
$\nu_{\text{C=C}}$	1598.00	1565.58	1496.42	1512.36	1576.26	1586.33
$\beta_{\text{C-H}}$	1267.68	1249.34	1263.92	1229.50	1232.98	1385.69
$\Gamma_{\text{C-H}}$	1171.95-714.40	1131.83-671.21	1132.34-695.35	1130.60-669.41	1146.26-662.08	1235.00-662.11

Table III — The chemical shifts of NMR (δ , ppm) spectral values of compounds **1-6**

Compd	X	$^1\text{H NMR}$					$^{13}\text{C NMR}$			
		CH_3/OCH_3	N-H	Ar-H	N=CH	C=N	<i>Cipso</i>	Ar-C	CH_3/OCH_3	
1	H	—	4.73	6.96-7.98	8.63	163.63	149.08	113.89-142.24	—	
2	Cl	—	4.49	6.96-7.82	8.95	159.62	146.99	122.94-146.31	—	
3	Br	—	4.07	7.19-7.93	8.64	164.73	147.77	123.44-142.33	—	
4	NO_2	—	4.66	7.09-7.98	8.75	164.29	152.62	118.50-148.96	—	
5	CH_3	2.19	4.56	6.92-7.98	8.45	164.22	148.24	121.80-137.96	30.66	
6	OCH_3	3.74	4.56	7.19-7.99	8.68	163.11	145.69	111.32-137.08	57.43	

compound **3**. N-H bond formation confirmed by the signal at 4.07 ppm and Ar-H appears in 7.19 ppm and 7.93 ppm. For Schiff base **4** the signal at 8.75 ppm and the signal at 4.66 ppm assure the formation of C=N and N-H bond respectively. The signals in the region 7.09 ppm and 7.98 ppm corresponds to the aromatic protons. The signal at 8.45 ppm, 4.56 ppm and signals in the region 6.92 ppm to 7.98 ppm are the characteristic signals of C=N, N-H and aromatic protons in compound **5**. The peak at 2.19 ppm corresponds to the methyl group. For Schiff base **6** the signal at 8.68 ppm, 4.56 ppm and between 7.19 ppm to 7.99 ppm are due the C=N, N-H and the aromatic protons respectively.

For Schiff base **1** the weak signal in the region 163.63 corresponds to C=N bond. The signals from 113.89 to 142.24 ppm are the characteristic peaks of aromatic carbons. The *ipso* carbon signal appeared at 149.08 ppm which is in higher frequency than the aromatic carbons as expected. For compound **2** the weak signal in the region 159.62 ppm belongs to C=N bond. Schiff base **3** has the weak signal at 164.73 ppm is due to the presence of C=N bond. For Schiff base **4** the weak signal in the region 164.29 ppm belongs to C=N bond. Compound **5** has the weak signal in the region 164.22 ppm and 121.80-137.96 ppm refers to C=N bond and the aromatic protons. The signal at 30.66 ppm refers to the methyl group. The signal at 148.24 ppm corresponds to the *ipso* carbon, which is higher compared to the aromatic carbons. Schiff base **6** has the signal at 163.11 ppm and 111.32-137.08 ppm belongs to C=N bond and aromatic carbons respectively. The signal appeared at 145.69-148.53 ppm corresponds to *ipso* carbons which are higher compared to the aromatic carbons²² and methoxy carbon appeared at 57.43 ppm confirms the structure of compound **6**.

Antibacterial studies of compounds **1-6**

The bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes*,

Table IV — Antibacterial activities of compounds **1-6** by disc diffusion method

Pathogens	Diameter of zone of Inhibition (mm)							Ciprofloxacin
	Concentration of compound (40 μg)							
	1	2	3	4	5	6		
<i>Staphylococcus aureus</i>	9	9	8	8	7	15	28	
<i>Bacillus subtilis</i>	12	10	10	10	9	12	22	
<i>Streptococcus pyogenes</i>	10	13	9	11	8	10	31	
<i>Klebsiella pneumoniae</i>	9	13	11	9	10	8	24	
<i>E. coli</i>	9	7	9	9	9	9	23	
<i>Pseudomonas aeruginosa</i>	9	7	9	8	7	7	16	

Klebsiella pneumoniae, *E. coli* and *Pseudomonas aeruginosa* were used for antibacterial study^{13, 25-28}. Ciprofloxacin is used as the standard for the bacterial strain. The Zone of inhibition values of compounds **1-6** along with the standard drug for comparison is furnished in Table IV. The antibacterial screening effect of substituted compounds **1-6** are shown in Figure 1 (plates 1-6).

The antibacterial activity of compounds by a zone of inhibition values are given in Table I, which indicate that all the tested compounds exhibited good range 7-15 mm. Compound **6** showed moderate antibacterial activity against *S. aureus* strain, whereas the remaining compounds showed activity in the region 7-9 mm¹⁷. The designed compounds **1-4** and **6** showed moderate antibacterial activity against *Bacillus subtilis*. The Schiff base **5** showed poor antibacterial activity against the same strain. The compounds **1, 2, 4** and **6** show moderate activity within 10-13 mm of a zone of inhibition and the compounds **3** and **5** show satisfactory activity against *Streptococcus* strain^{15,16,23,24}. The methyl group substituted Schiff base **2** shows good antibacterial activity against *Klebsiella pneumoniae* strain.

All the compound gave activity in the inhibition region 8-11 mm. Compound **3** show satisfactory antibacterial activity against *K. pneumoniae* strain. The compounds **1-6** shown poor activity within 7-9 mm of a zone of inhibition, whereas standard drug

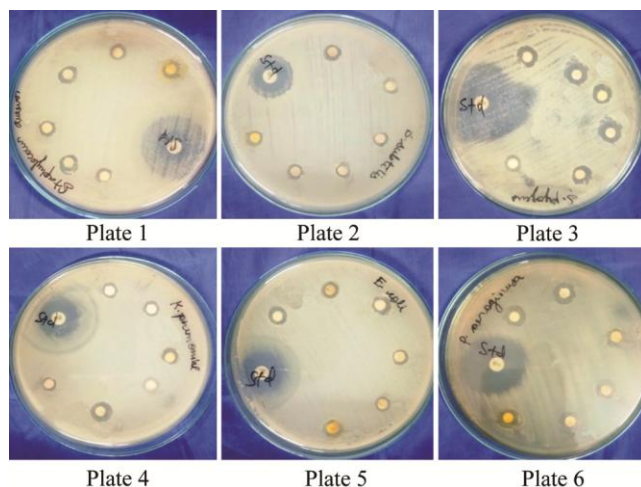


Figure 1 — Zone of inhibition of compounds 1-6 –Petri plates

shows satisfactory activity against *E. coli* strain. The compound 1 and 3 show satisfactory activity against *Pseudomonas aeruginosa*, whereas the remaining compounds show poor activity against *Pseudomonas aeruginosa*.

Docking analysis of compounds 1-6

To explain the Topoisomerase selectivity of some newly synthesized imine analogs, docking studies were performed using the Schrodinger program, 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 is shown in Figure 2.

In order to explore the detailed binding characteristics of Schiff base derivatives, we modify the aromatic group in ligand 1 to perform the deeper docking study into Topoisomerase protein. Since docking analysis has been done to understand the protein-ligand interactions, the active sites present in the structures and to know the binding interactions. Figure 3a-f shows the possible binding modes of compounds 1-6 in the Topoisomerase protein. Molecular basis of interactions between target enzyme and synthesized ligands could be understood with the help of docking analysis and docking scores were summarized in Table V. As shown in Figure 3a-f compounds 1-6 bind to the active site of Topoisomerase and makes several interactions with nearby residues.

Compound 1 has binding energy -5.149 with H-bonding with ASP81, GLY85 amino acids. In addition, the ligand formed hydrophobic interaction

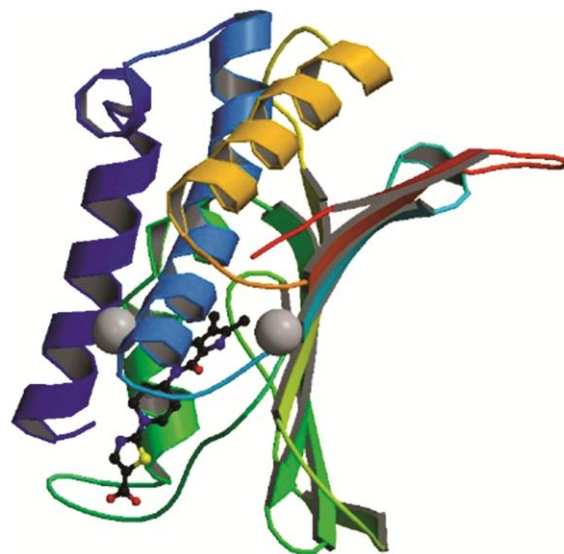


Figure 2 — X-ray crystal structure of protein Topoisomerase
viz. ILE102, LEU103, ILE86, PRO87, VAL79, ILE51, ILE86 and PRO87, when introducing substitution (F, Cl, Br, CH₃ and OCH₃) in phenyl group. It is pertinent to note that the more active ligand 4 exhibit nice binding energy -5.711 . Figure 3d clearly presented that the H-interactions with ASP81 and GLY85. In addition, ligand 4, has hydrophobic interaction with ILE102, LEU103, ILE51, ILE175, ILE86, and PRO87 residues. The ligand 5 has binding energy -4.707 among selected ligands. It forms a hydrophobic interaction with VAL101, ILE102, LEU103, ILE86, PRO87, ILE51 and ILE175. As seen in Figure 3d, the ligand 5 locates in a large polar pocket in contact with SER128, SER55, ASN54, and THR173. However, it showed hydrogen bond interaction with ASP81, GLY85. Finally, the methoxyphenyl group in compound 6 formed a hydrophobic interaction with ILE102, LEU103, ILE51, ILE175, PRO87 and ILE86. On the other, the amino acids such as ASN54, SER55, THR173 formed polar interaction with the same ligand. With an aim to identify the most energetically favoured binding pose, we compared the results with standard Ciprofloxacin, which is close to docking scores of 4. These dry lab findings are well supported by the results of *in vitro* antibacterial activity.

Experimental Section

Materials and methods

All the chemicals required for synthesis were obtained from Sigma Aldrich. Elemental analysis was carried out on the VARIOMICRO2.2.0 CHN

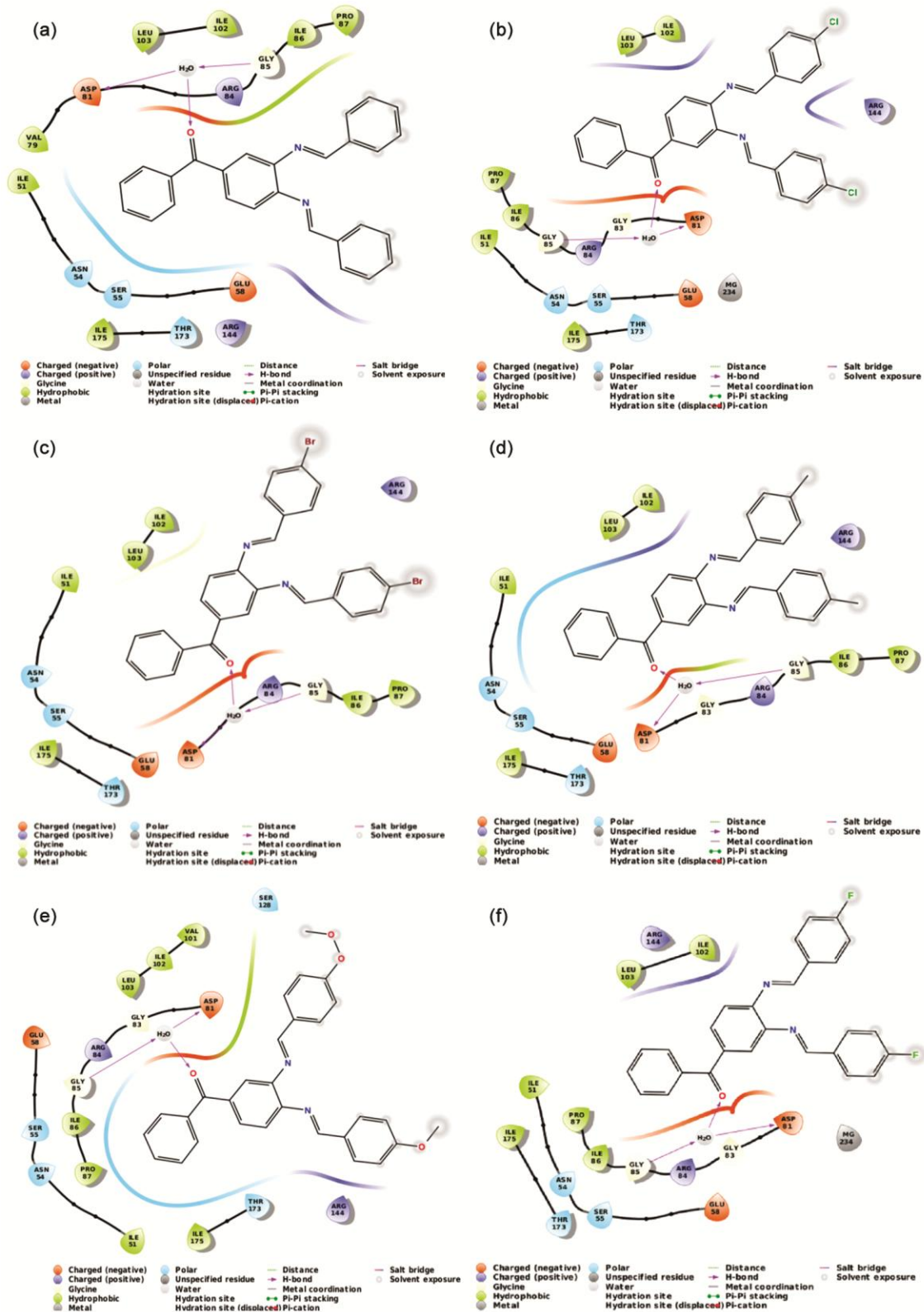
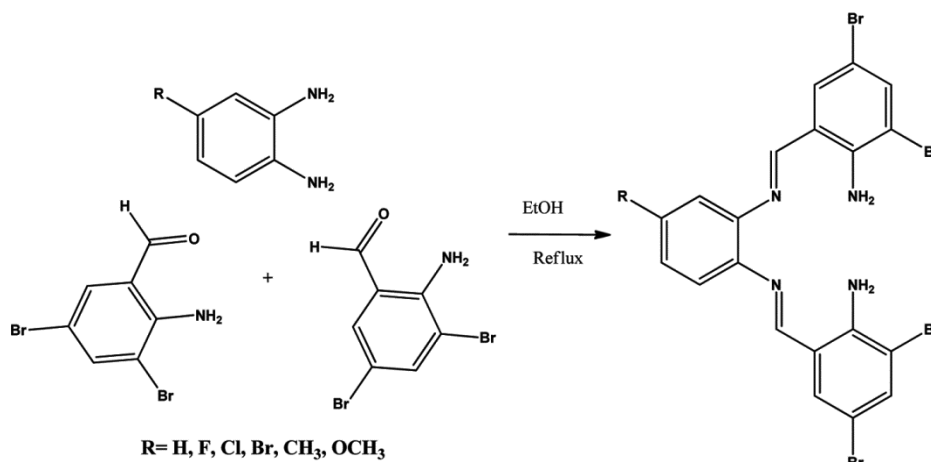


Figure 3 — (a) 2-D Interaction of compound 1; (b) 2-D Interaction of compound 2; (c) 2-D Interaction of compound 3; (d) 2-D Interaction of compound 4; (e) 2-D Interaction of compound 5 and (f) 2-D Interaction of compound 6

Ligand	Docking score	Table V — Docking score, glide energy, hydrophilic and hydrophobic interaction				Hydrogen bond Interaction	Polar interaction
		Glide energy (kcal/mol)	Glide g score (kcal/mol)	Hydrophobic interaction			
1	-5.149	-36.52	-5.614	ILE102, LEU103, ILE86, PRO87, VAL79, ILE51, ILE86, PRO87		ASP81, GLY85	ASN54, SER55, THR173
2	-4.94	-37.4	-5.656	ILE102, LEU103, PRO87, ILE86, ILE51, ILE175		ASP81, GLY85 V	ASN54, SER55, THR173
3	-4.881	-36.03	-4.882	ILE102, LEU103, ILE86, PRO87, ILE51, ILE175		GLY85	ASN54, SER55, THR173
4	-5.711	-38.36	-4.713	ILE102, LEU103, ILE51, ILE175, ILE86, PRO87		ASP81, GLY85	ASN54, SER55, THR173
5	-4.707	-37.89	-4.709	VAL101, ILE102, LEU103, ILE86, PRO87, ILE51, ILE175		ASP81, GLY85	SER128, SER55, ASN54, THR173
6	-4.584	-45.36	-5.192	ILE102, LEU103, ILE51, ILE175, PRO87, ILE86		—	ASN54, SER55, THR173
Ciprofloxacin	-7.682	-28.747	-5.962	ILE175, ILE51, LEU103, ILE102, ILE86, PRO86		—	ASN54, SER55, THR173



Scheme I — Synthesis of (*N*¹*E*, *N*²*E*)-*N*¹, *N*²-bis(2-amino-3,5-dibromobenzylidene)-aryl-1,2-diamines **1-6**

analyzer. FT-IR of all the synthesized compounds was taken in the range of 4000-400 cm^{-1} in AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr. NMR spectra were recorded on a BRUKER AVANCE III NMR spectrometer operating at 400.13 MHz for ^1H NMR and 100.61 MHz for ^{13}C NMR in $\text{CDCl}_3/\text{DMSO}$ employing TMS as an internal standard. The antimicrobial activities of these synthesized title compounds were measured by disc diffusion method¹⁷. The docking studies were conducted by Glide module implemented in Maestro version 9.3.5 of Schrodinger software suite 2010 (Ref. 18).

Systematic procedure for the synthesis of (*N*¹*E*, *N*²*E*)-*N*¹, *N*²-bis(2-amino-3,5-dibromobenzylidene)-aryl-1,2-diamines

A mixture of 4-substituted benzene-1,2-diamine and 2-amino-3,5-dibromobenzaldehyde (0.2 mol) was

refluxed in the presence of ethanol. At water bath temperature, reflux was continued for 8 hrs. The crystalline solid was formed by vacuum filtration and washing with absolute ethanol. Scheme I shows a schematic picture representing the synthesis of a molecule.

Conclusion

Single pot synthesis of (*N*¹*E*, *N*²*E*)-*N*¹, *N*²-bis(2-amino-3,5-dibromobenzylidene)-aryl-1,2-diamine have been developed with good yields. The structure of the prepared compounds characterized by FT-IR, NMR and Elemental analysis. The antibacterial properties of the compounds were explored. The docking studies of the compounds revealed the role of active sites in the compounds with proteins. To explore the detailed binding characteristic of Schiff base derivatives, we compared binding energy, docking score, Glide energy and Hydrophobic

interaction of compounds prepared. With an aim to identify the most favoured binding, we compared the results with standard Ciprofloxacin, which is close to docking scores of 6. This finding was well supported by results *in vitro* antibacterial activity.

References

- 1 Bellina F, Cauteruccio S, Montib S & Rossi R, *Bioorg Med Chem*, 16 (2006) 5757.
- 2 Vlahakis J Z, Humb M & Rahman M N, *Bioorg Med Chem*, 17 (2009) 2461.
- 3 Bhandari K, Srinivas N & Marrapu V K, *Bioorg Med Chem Lett*, 20 (2010) 291.
- 4 Fang Z, Wang S & Zhao L, *Mater Lett*, 61 (2007) 4803.
- 5 Ge Z, Hayakawa T & Ando S, *Chem Mater*, 20 (2008) 2532.
- 6 Lai M Y, Chen C H & Huang W S, *Angew Chem Int Ed*, 47 (2008) 591.
- 7 Fang Z, Wang S & Zhao L, *Mater Chem Phys*, 107 (2008) 305.
- 8 Chen C H, Huang W S & Lai M Y, *Adv Funct Mater*, 19 (2009) 2661.
- 9 Chang Y T, Hsu S L & Su M H, *Adv Funct Mater*, 21 (2009) 2093.
- 10 Caruso F, Rossi M & Benson A, *J Med Chem*, 55 (2012) 1072.
- 11 Kataoka M, Tatsuta M & Yasoshima K, *Bioorg Med Chem Lett*, 15 (2005) 805.
- 12 Revanasiddappa H D, Prasad K S, Kumar L S, Jayalakshmi B, *Int J Chemtech Res*, 2 (2010) 1344.
- 13 Thirunarayanan G, Muthuvel I & Sathiyendiran V, *Int Lett Chem Phys Astron*, 48 (2015) 114.
- 14 Vein D L, Colthup N B, Fateley W G & Grasselli J G, *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules* (Academic Press, New York) (1991).
- 15 Mohan, *Organic Spectroscopy* (Narosa Publishing House, New Delhi) (2004).
- 16 Thirunarayanan G, *Int Lett Chem Phys Astron*, 4 (2014) 109.
- 17 Bauer A W, Kirby W M M, Sherris J C & Truck M, *Amer J Clin Path*, 45 (1966) 493.
- 18 Phase, Version 3.2, Schrodinger, LLC, New York (2010).
- 19 Tsai M S, Hsu Y C & Lin J T, *J Phys Chem C*, 111 (2007) 18785.
- 20 Chang Y T, Hsu S L & Chen G Y, *Adv Funct Mater*, 18 (2008) 2356.
- 21 Shin R Y C, Kietzke T & Sudhakar S, *Chem Mater*, 19 (2007) 1892.
- 22 Cohen M L, *Science*, 257 (1992) 1050.
- 23 Silverstein R M & Webster F X, *Spectroscopic Identification of Organic Compounds*, 7th Edn (Wiley, New York) (2005).
- 24 Roeges N P G, *A Guide to the Complete Interpretation of Infrared Spectra of Organic Structure* (Wiley, New York) (1994).
- 25 Usha V, Thangaraj V & Thirunarayanan G, *Org Prep Proced Int*, 50 (2018) 459.
- 26 Sakthnathan S P, Suresh R, Kamalakkannan D, Mala V, Sathiyamoorthi K, Vanangamudi G & Thirunarayanan G, *J Chilean Chem Soc*, 63 (2018) 3918.
- 27 Usha V, Thangaraj V & Thirunarayanan G, *Indian J Chem*, 56B (2017) 1094.
- 28 Vanangamudi G, Subramanian M & Thirunarayanan G, *Arabian J Chem*, 10 (2017) S1254.