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Synthesis, spectral, crystal, computational studies and antimicrobial activities of (*E*)-N-(substituted arylidene)-3-(trifluoromethyl)anilines

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A series of (*E*)-N-(substituted arylidene)-3-(trifluoromethyl) anilines have been synthesised by $ZnFe_2O_4$ catalyzed microwave promoted condensation of 3-trifluoromethyl aniline and various aryl aldehydes. This condensation gives more than 90% yield of products. The synthesised imines have been characterized by their analytical, micro analysis and spectroscopic data. From single crystal X-ray analysis, the structure of [(*E*)-*N*-(naphthalene-1-ylmethylene)-3-(trifluoromethyl) aniline has been established. The optimized geometrical structures, molecular electrostatic potential and FMO studies of these amines have been investigated by DFT theoretical-computational method. The Mulliken charge analysis of these amines have been predicted. *In vitro* antimicrobial activities of prepared imines have been assessed using Bauer-Kirby disc diffusion method.

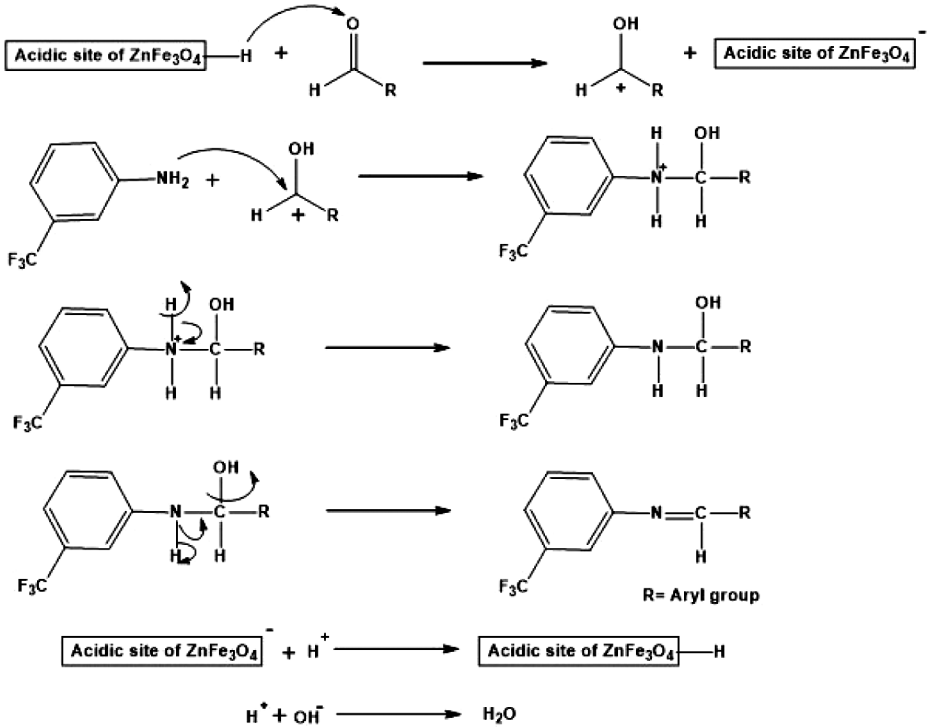
Keywords: (*E*)-N-(Substituted arylidene)-3-(trifluoromethyl)anilines, Greener synthesis, IR and NMR spectra, SC-XRD analysis, Computational study, Antimicrobial activities

Schiff bases of imines or azomethines are important class of carbon nitrogen unsaturated compounds. They possess the general molecular formula $R_1R_2C{=}NR_3$; R_3 is alkyl or aryl and not hydrogen). First, the German chemist Hugo Schiff derived these compounds were derived in 1864 by the condensation of carbonyl compounds with anilines[1]. Then these compounds were named as aldimines and ketoimines, if aldehydes and ketones were employed in the condensation. Numerous Schiff bases were synthesised by conventional and solvent-free greener methods[2-10]. In these methods many catalysts were employed for increasing the yield of the reaction[11]. They possess the ligand character for complexation with metal cations. Schiff bases exhibit delightful biological activities such as antimicrobial[5,6,10], anti-oxidant[12], anti-HIV[13], anti-depressants[14], anti-inflammatory[15], anti-histamine[15], antinociceptive[15], anti-analgesic[16], cardiovascular[17] and anxiolytic[18] activities. Yang and his co-workers[19] used the microwave for the synthesis of imines through condensation of aldehyde (or ketone) with amine and they obtained higher percentage of yield. Khan *et al.*[20] reported the synthesis of pyrazole containing Schiff bases, by the reaction of 3,5-dimethyl-1-phenylpyrazoe-4-carbaldehyde and the corresponding active amines under microwave irradiation. Thalla *et al.*[21] developed an efficient greener synthesis of ten Schiff bases of nicotinohydrazide such as *N*-(substituted-benzylidene) nicotinohydrazide. The optimum yields of these compounds were synthesized by ultrasonication assisted condensation of nicotinohydrazide and various benzaldehydes in ethanol-water media in the absence of catalyst. They concluded that the microwave method is a more superior green alternative method than the conventional method. Suresh and his co-workers[22] derived some *E*-imines by condensation of 4-chloroaniline and substituted benzaldehydes using microwave irradiation in the presence of fly-ash PTS catalyst under solvent-free green method. Mayavel and Thirunarayanan reported perchloric acid catalysed solvent-free synthesis and antibacterial activities of some aryl imines[7]. The synthesis and spectral correlation studies of some symmetrical diimines were reported by Thirunarayanan[8]. The infrared and nuclear magnetic spectral correlation and SC-XRD structure analysis of some (*E*)-*N*-(substituted benzylidene)-1-benzylpiperidin-4-amines were reported by Mayavel *et al.*[4] The solvent-free microwave assisted synthesis, spectral correlation and biological activities of some 2-chloro-4-methyl aniline-based

Schiff bases were investigated by Sakthinathan *et al*.[5] Thiazole aryl imines were synthesised by tungsten oxide modified AlTUD-1 mesoporous acid catalyst assisted solvent-free microwave promoted method of condensation was reported by Rajarajan *et al*.[6] Density functional theory (DFT) establishes a group of atoms or molecules of approached quantum mechanical (QM) electronic structure calculations with expensive applications to organic as well as complicated molecule systems[23]. Density Function Theory (DFT) calculations have been carried out to give systematic theoretical studies and to compare the experimental and calculated results. There is a few DFT investigations made on the Schiff base compounds and are reported in literature[24-26]. Dineshkumar *et al*. have synthesised and investigated the crystal structure and DFT studies on (*E*)-1-benzyl-*N*-(4-chlorobenzylidene) piperidin-4-amine[2]. The solvent-free greener synthesis, spectral, crystal study and DFT calculations of (*E*)-1-benzyl-N-(4-fluorobenzylidene) piperidin-4-amine and (*E*)-1-benzyl-N-(naphthalen-2-ylmethylene) piperidin-4-amines were reported by Dineshkumar and his co-workers[3]. In the literature review, there is no report available on the synthesis, spectral, SC-XRD structural analysis, theoretical-computational and biological activities of some (*E*)-N-(substituted arylidene)-3-(trifluoromethyl)anilines. Hence, the authors have taken-up the study of the solvent-free synthesis, structural elucidation and biological activities of above said (*E*)-N-(substituted arylidene)-3-(trifluoromethyl)anilines.

Results and Discussion

In our research laboratory, the authors attempt to synthesis high yields of some (*E*)-N-(substituted arylidene)-3-(trifluoromethyl)anilines by solvent-free microwave irradiated $ZnFe_2O_4$ catalyzed condensation of 3-trifluyoromethyl aniline and various higher aryl aldehydes. In this condensation the obtained yield was more than 90%. Imine **1** (*E*)-*N*-(naphthalen-1-ylmethylene)-3-(trifluoromethyl)aniline, crystals existed as orthorhombic systems. This condensation acid undergoes catalyzed nucleophilic addition of amine to carbonyl system followed by elimination of water gave the desired Schiff bases. First step is the protonation of aldehydic carbonyl oxygen leads to form aldehydic carbon cation by supply of hydrogen from the zinc ferrite catalyst. Second step is the attack of aldehydic carbon cation by amino group of 4-trifluoromethyl aniline and the N atom gets positive charge. This positive charge was neutralized by the loss of proton. The third step is the elimination of water which afforded an imine. The plausible mechanistic steps of this condensation are illustrated in Scheme 1.



Scheme 1 — The plausible mechanistic steps of condensation of 3-trimethylfluoromethylaniline and aryl aldehydes

IR and NMR spectral study

The infrared and NMR spectral data of these imines are presented in Table 1. An absorption band obtained in the range of the 3017 and 3051 cm^{-1} were represent the aromatic C-H stretches. The absorption band appeared at 1509 cm^{-1} is denotes the aromatic ring C=C stretching frequency. A strong absorption band appeared at 1625 cm^{-1}, caused by imine C=N vibration. Schiff base **1-7** shows medium or strong vibrational bands at the range of 1611–1626 cm^{-1} is assigned to C=N stretches. The C-F vibrational bands of all compounds obtained at the range of 1287-1330 cm^{-1}.

The ^{1}H NMR spectral chemical shifts (δ, ppm) of the synthesized Schiff bases **1-7** were was displayed in Table 1. The azomethine (CH=N) proton chemical shifts (ppm) of all compounds of this series was observed in the range of 8.596 – 9.127 ppm. The peaks that appeared as multiplet at 7.452 – 8.098 ppm range was assigned to aromatic protons. The chemical shifts of the methoxy protons of the compounds **2** and **5** were observed as singlet at 4.031 and 4.092 ppm.

The ^{13}C NMR chemical shifts (δ, ppm) of compounds **1-7** are given in Table 1. The ^{13}C NMR chemical shifts of imine carbon (H**C**=N-) signal appeared in the range of 155.83 and 161.75 ppm and the aromatic carbon signals were observed at 117.87 to 133.95 ppm. The up-field signal at 55.68 and 55.65 ppm were attributed to the ^{13}C NMR chemical shift of the methoxy carbons of compounds **2** and **5**. The CF_3 carbon chemical shifts of all compounds obtained in the range of 121.36 to 124.51 ppm.

Single-crystal structure description

Single-crystal structure description of (*E*)-N-(naphthalene-1-ylmethylene)-3-(trifluoromethyl) aniline, 1

Single crystal X-ray analysis affirmed that the compound **1** crystallizes in the orthorhombic system with space group P-b_c along with a cell parameter a = 12.049(6) Å, b = 7.905(8) Å, c = 30.896(13) Å, and α = β = γ = 90°. It has eight molecules in the unit cell and adopts an *E* conformation (CCDC No. 2026697). The crystal data and structure refinement parameters are recorded in Table 2. The ORTEP structure and optimized molecular structure with the numeration of atoms have displayed in Fig. 1. The experimental structure of the packing diagram for compound **1** has appeared in Fig. 2. The optimized structural parameters like bond length and bond angles of compound **1** was determined by the B3LYP method with 6-31G(d,p) as a basis set. These data are compared with experimental parameters acquired from the X-ray diffraction studies and are listed in Table 3.

Table 2 — Crystal data and structure refinement parameters for Schiff base **1**

Empirical formula	$C_{18}H_{12}F_3N$	
Formula weight	299.29 g/mol	
Temperature	301(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P-b_c	
Unit cell dimensions	a = 12.049(6)Å	α = 90°
	b = 7.905(8)Å	β = 90°
	c = 30.896(13)Å	γ = 90°
Volume	2943.(3)Å^3	
Z	8	
Density (calculated)	1.351 g/cm^3	
Absorption coefficient	0.106mm^{-1}	
F(000)	1248	
Crystal size	0.250×0.310×0.350 mm^3	
Theta range for data collection	2.14 to 29.92°	
Index ranges	-15<=h<=15, -11<=k<=11, -43<=l<=43	
Reflections collected	25820	
Independent reflections	4165 [R(int) = 0.0932]	
Coverage of independent reflections	97.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7460 and 0.6497	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4165 / 0 / 199	
Goodness-of-fit on F^2	1.183	
Final R indices [I>2sigma(I)]	R1 = 0.0947, wR2 = 0.2791	
R indices (all data)	R1 = 0.1958, wR2 = 0.4010	
Largest diff. peak and hole	0.795 and -0.569 e.Å^{-3}	
CCDC: 2026697		

Table 1 — The IR stretching frequencies (ν, cm^{-1}) and NMR chemical shifts (δ, ppm) of synthesized Schiff bases **1-7**

Compd	IR (ν, cm^{-1})					^{1}H NMR (δ, ppm)			^{13}C NMR (δ, ppm)			
	C=N	Ar-CH	Ali-CH	C=C	CF	$\delta_{CH=N}$	δ_{Ar-H}	δ_{O-CH3}	$\delta_{C=N}$	δ_{Ar-C}	δ_{O-CH3}	δ_{CF3}
1	1625	3017	-	1509	1328	9.065	7.452-8.098	-	161.68	117.87-133.95	-	124.21
2	1620	3055	2945	1502	1287	9.127	7.467-7.699	4.031	156.56	109.59-138.69	55.68	122.71
3	1619	3059	-	1485	1314	8.596	7.225-8.204	-	161.74	111.34-136.49	-	122.46
4	1620	3069	-	1515	1317	8.984	7.262-8.303	-	157.55	111.97-134.09	-	124.05
5	1626	3073	2938	1510	1324	9.011	7.261-8.284	4.092	158.71	103.26-139.66	55.65	124.51
6	1611	3040	-	1511	1320	8.739	7.257-8.280	-	161.75	110.91-138.74	-	122.09
7	1626	3099	-	1516	1330	8.655	7.257-8.518	-	155.83	111.43-136.91	-	121.36

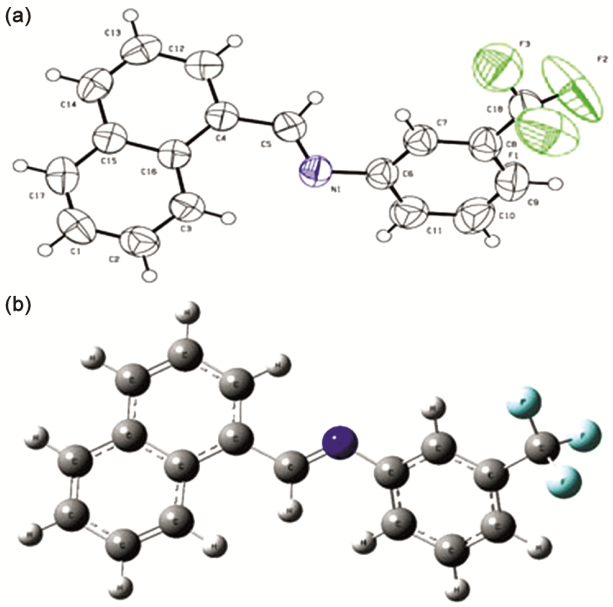


Fig. 1 — The ORTEP (a) and optimized molecular (b) structure of Schiff base **1**

Theoretical studies of Schiff bases 1-7

Geometry optimization of Schiff bases 2 and 5-7

The optimized molecular structure of the Schiff bases **2-7** are afforded from the B3LYP method with 6-31G(d,p) as a basis set, and are displayed in Fig. 3.

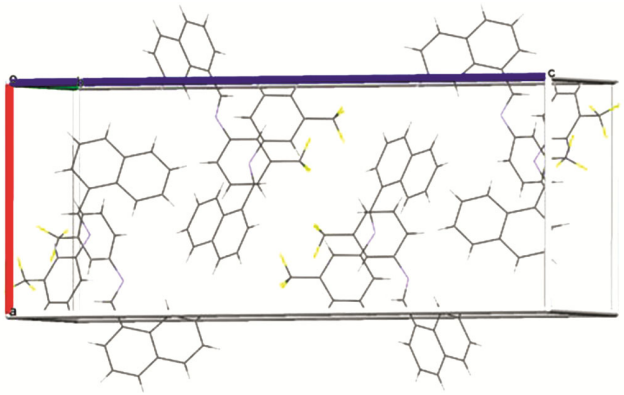


Fig. 2 — Packing diagram of Schiff base **1**

Table 3 — Bond lengths [Å] and angles [°] for Schiff base **1**

Bond lengths [Å]

Atom	XRD	DFT	Atom	XRD	DFT
F(1)-C(18)	1.313(6)	1.351	C(6)-C(11)	1.390(5)	1.404
F(2)-C(18)	1.260(5)	1.355	C(6)-C(7)	1.397(5)	1.4
F(3)-C(18)	1.324(6)	1.352	C(7)-C(8)	1.386(5)	1.419
N(1)-C(5)	1.270(4)	1.284	C(8)-C(9)	1.385(6)	1.425
N(1)-C(6)	1.421(4)	1.409	C(8)-C(18)	1.496(6)	1.545
C(1)-C(17)	1.368(6)	1.374	C(9)-C(10)	1.384(7)	1.388
C(1)-C(2)	1.399(6)	1.413	C(10)-C(11)	1.397(6)	1.391
C(2)-C(3)	1.372(5)	1.413	C(12)-C(13)	1.401(5)	1.405
C(3)-C(16)	1.420(5)	1.422	C(13)-C(14)	1.375(6)	1.378
C(4)-C(12)	1.388(5)	1.39	C(14)-C(15)	1.416(5)	1.418
C(4)-C(16)	1.445(5)	1.44	C(15)-C(17)	1.426(5)	1.421
C(4)-C(5)	1.465(5)	1.467	C(15)-C(16)	1.437(5)	1.437

Bond angles [°]

Atom	XRD	DFT	Atom	XRD	DFT
C(5)-N(1)-C(6)	118.5(3)	122.44	C(6)-C(11)-C(10)	119.6(4)	120.19
C(17)-C(1)-C(2)	119.6(4)	119.63	C(4)-C(12)-C(13)	122.3(4)	121.6
C(3)-C(2)-C(1)	121.1(4)	120.76	C(14)-C(13)-C(12)	119.6(4)	120
C(2)-C(3)-C(16)	121.5(4)	121.37	C(13)-C(14)-C(15)	121.2(4)	120.88
C(12)-C(4)-C(16)	118.8(3)	119.54	C(14)-C(15)-C(17)	121.6(3)	120.76
C(12)-C(4)-C(5)	115.4(3)	118.92	C(14)-C(15)-C(16)	119.5(3)	119.64
C(16)-C(4)-C(5)	125.8(3)	121.53	C(17)-C(15)-C(16)	119.0(3)	119.58
N(1)-C(5)-C(4)	126.3(3)	121.7	C(3)-C(16)-C(15)	117.4(3)	117.56
C(11)-C(6)-C(7)	119.3(3)	118.81	C(3)-C(16)-C(4)	124.1(3)	124.11
C(11)-C(6)-N(1)	118.1(3)	115.46	C(15)-C(16)-C(4)	118.5(3)	118.31
C(7)-C(6)-N(1)	122.6(3)	125.71	C(1)-C(17)-C(15)	121.4(4)	121.07
C(8)-C(7)-C(6)	120.8(4)	122.36	F(2)-C(18)-F(1)	108.5(5)	106.75
C(9)-C(8)-C(7)	119.8(4)	116.71	F(2)-C(18)-F(3)	103.1(5)	106.67
C(9)-C(8)-C(18)	119.7(4)	121.4	F(1)-C(18)-F(3)	100.7(5)	107.46
C(7)-C(8)-C(18)	120.6(4)	121.85	F(2)-C(18)-C(8)	115.6(4)	111.58
C(10)-C(9)-C(8)	119.9(4)	120.93	F(1)-C(18)-C(8)	112.7(4)	112.01
C(9)-C(10)-C(11)	120.7(4)	120.94	F(3)-C(18)-C(8)	114.9(4)	112.02

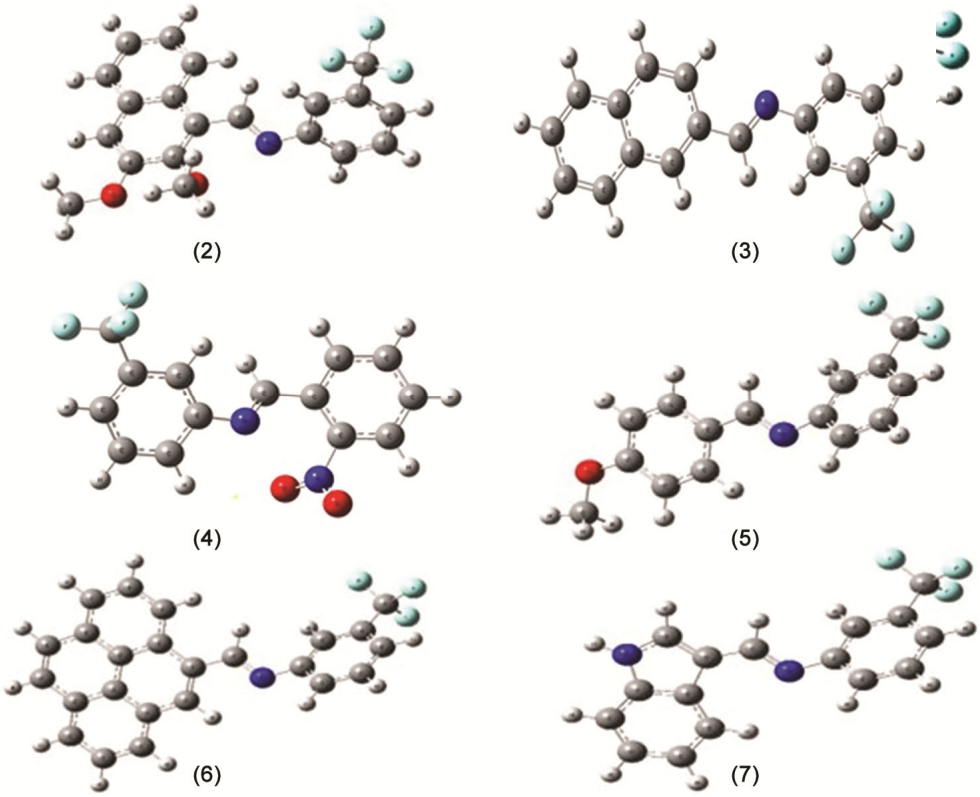


Fig. 3 — Optimized molecular structure of Schiff bases **2** and **5-7**

Molecular electrostatic potential analysis of Schiff bases 1-7

Based on the molecular electrostatic potential (MEP) concepts, the author have studied the MEP analysis of synthesized Schiff bases **1-7**. The plot of MEP for all compounds of this series is displayed in Fig. 4.

In most MEPs, the imine group and oxygen of the methoxy moieties act as an electrophilic region, and is illustrated as red color. Also, the nucleophilic region has graphically showed as a blue color[27,28]. As displayed in Fig. 4, the charge dispersal differed by changing the number and the position of the methoxy groups in compounds **2** and **5**. Molecular surfaces of this series of compounds obtained by B3LYP level 6-31G(d,p) as the basis set.

Frontier molecular orbital analysis of Schiff bases 1-7

Based on the FMO concepts, the author studied the FMOs analysis for this series of compounds **1-7**. The FMOs examinations were performed for prediction of the electronic properties of compounds **1-7** at B3LYP level and 6-31G(d,p) along with the basis set combination. The FMOs pictures are displayed in Fig. 5. FMOs investigation results consists of gap energies (ΔE), lies between 4.29 to 3.37 eV and the assessed band gap was found to be maximum for compound **6** and minimum for compound **7**. The HOMOs are spread over between –6.58 to –5.52 eV and the LUMOs lie in the range of –2.44 to –1.33 eV. From the results, the ascending order of gap energy (ΔE) of inspected compounds becomes **6** < **1** < **2**< **3** < **4** < **5** < **7**. The gap energies and other global parameters of all compounds are calculated theoretically and presented in Table 4. Regarding chemical hardness of these compounds related with the gap energy, the higher value of ΔE denotes more hardness or low softness of a molecule. Thus, the compound **7** mentioned to as a hard molecule referred with other compounds. Another global reactivity descriptor is the electrophilicity index of a system. It describes the electron-accepting tendency of the systems with quite analogous to hardness and chemical potential.

Authors has studied the Mulliken charge analysis of this series of compounds **1-7**. The atom labelling with numeral scheme was adopted in this study is given in Fig. 6. The distribution of Mulliken atomic charges of compounds **1-7** was shown in Fig. 7 and the data are tabulated in Table 5.

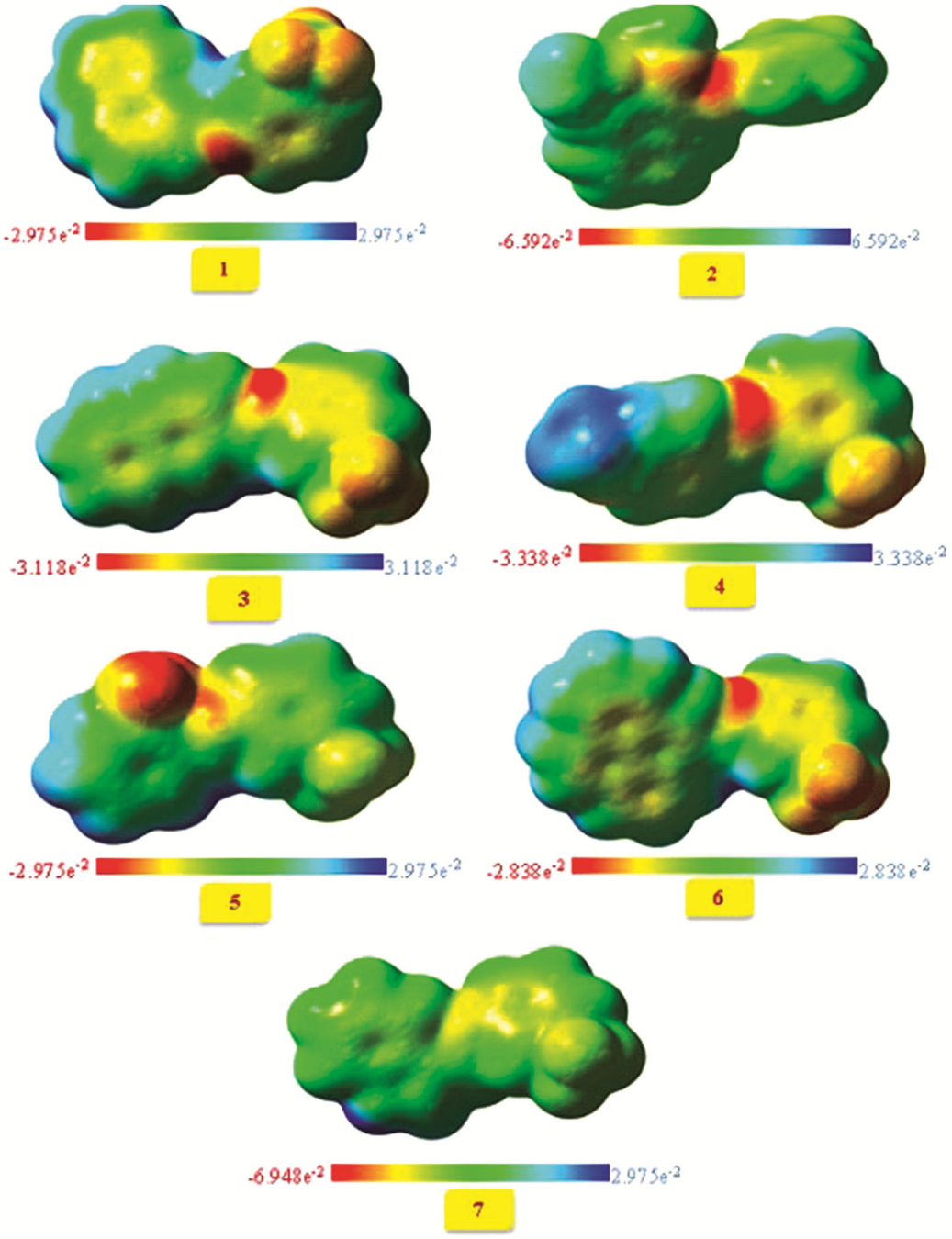


Fig. 4 — The MEP plots of Schiff bases **1-7**

As indicated by this table, N8, F4', F4" and F4"' atoms of (**1-7**) and methoxy group oxygen atoms of (**2** and **5**) have the most negative charges and act as donor atoms. The carbon of trifluoromethyl group atom (C4), the carbon atom (C9) attached to nitrogen of compounds **1-7**, and methoxy group linked phenyl carbon atoms like (C11, C19) and (C12) of compound (**2** and **5**) have positive energies and acts as acceptor atoms. All the hydrogen atoms of Schiff base (**1-7**) were shown a net positive charge.

Antimicrobial studies

Antibacterial activities of Schiff bases 1-7

In this investigation, the synthesized (*E*)-imines were examined for their ability to inhibit the *in vitro* growth of strains *viz*., *Staphylococcus aureus*,

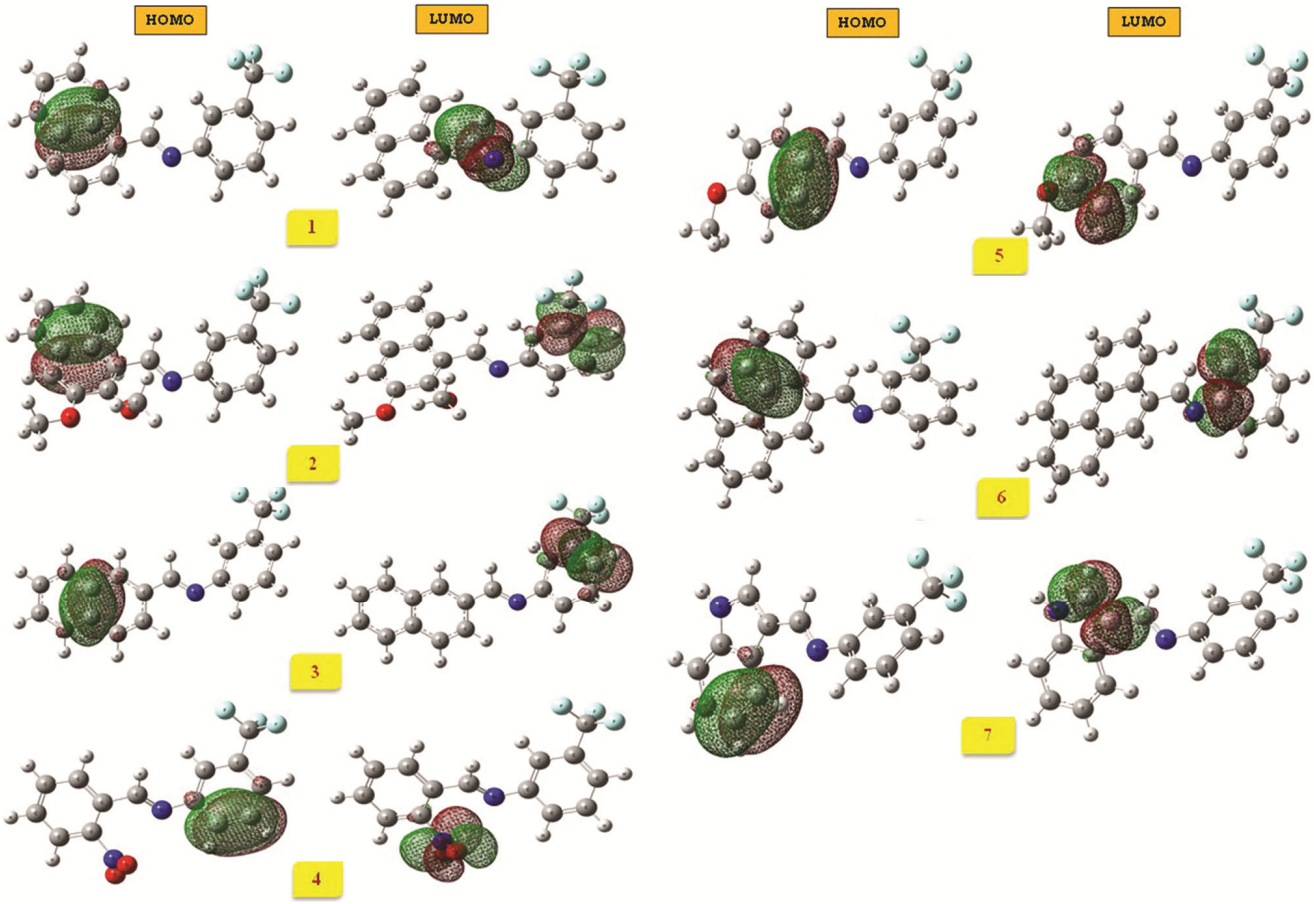


Fig. 5 — The HOMO and LUMO of the Schiff bases **1-7**

Table 4 — Calculated global parameters of Schiff bases **1-7**

Schiff base No.	Total Energy (a.u)	FMO Orbital's (eV)	Energy Gap(Δ) (eV)	Chemical potential (μ)	Electronegativity (χ)	Hardness (η)	Softness (S)	Electrophilicity (ω)
1	-1047.4482	HOMO = -5.8967 LUMO = -2.0362	3.8605	3.9664	-3.9664	1.9302	0.2590	4.0753
2	-1276.7900	HOMO = -6.0156 LUMO = -1.9720	4.0436	3.9938	-3.9938	2.0218	0.2473	3.9446
3	-1047.4539	HOMO = -6.0172 LUMO = -1.9279	4.0893	3.9725	-3.9725	2.0446	0.2445	3.8591
4	-1098.2895	HOMO = -6.5859 LUMO = -2.4427	4.1432	4.5143	-4.5143	2.0716	0.2413	4.9186
5	-1008.3327	HOMO = -5.8858 LUMO = -1.6024	4.2834	3.7441	-3.7441	2.1417	0.2334	3.2727
6	-1277.3311	HOMO = -5.5236 LUMO = -2.1526	3.3710	3.8381	-3.8381	1.6855	0.2966	4.3699
7	-1025.3826	HOMO = -5.6305 LUMO = -1.3336	4.2969	3.4820	-3.4820	2.1484	02327	2.8217

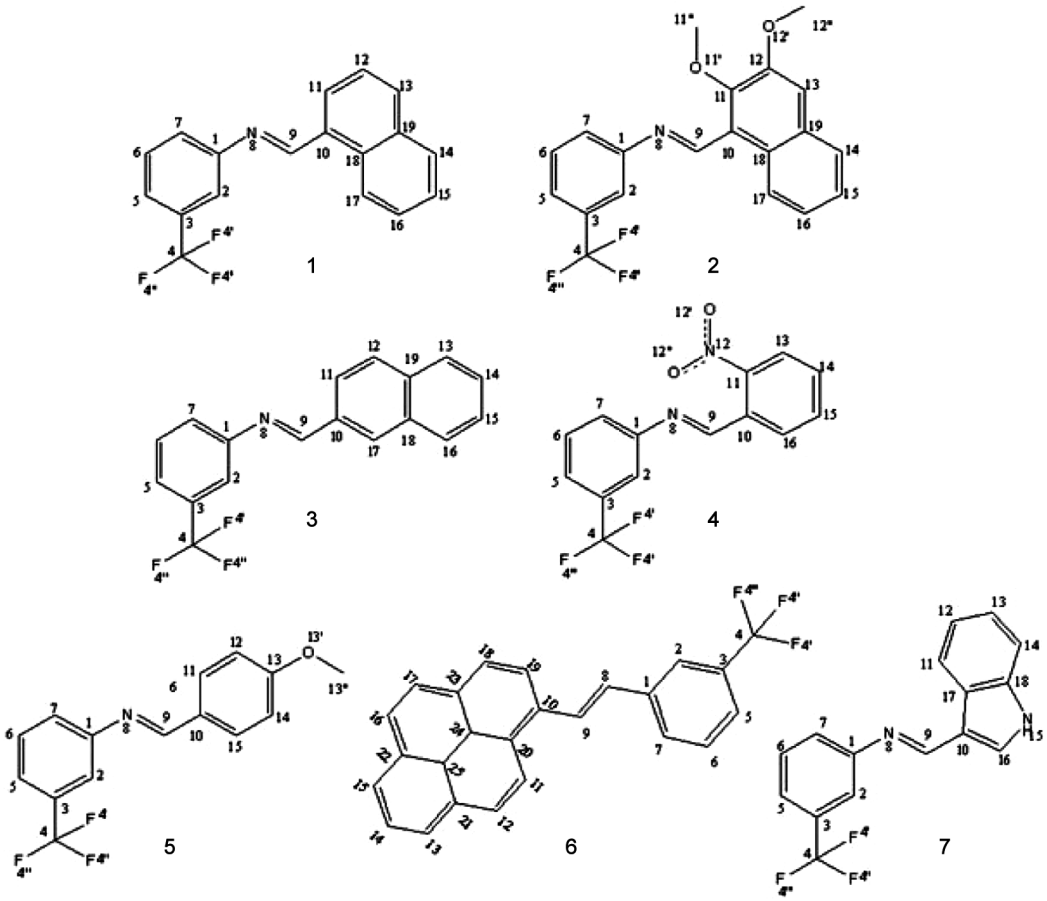


Fig. 6 — Mulliken numbering pattern of Schiff bases **1-7**

Bacillus subtilis, *Salmonella paratyphi A*, *Proteus mirabilis* and *Pseudomonas aeruginosa.* The disc diffusion method was employed through the Bauer-Kirby[29] technique at the concentration of 30 μg mL^{-1} with Amoxicillin was utilized as the standard drug.

The antibacterial activities by means of petri-plates of all synthesized (*E*)-*N*-(substituted arylidene)-3-(trifluoromethyl)anilines (**1-7**) were shown in Fig. 8. and the zone of inhibition values are given in Table 6. The corresponding clustered column chart is shown in Fig. 9.

The (*E*)-imines **2**, **4** and **7** (compounds possess 2, 3-dimethoxy-1-naphthyl, 2-nitrophenyl and 3-indole moieties) have shown good antibacterial activity. The remaining Schiff bases **1**, **3**, **5** and **6** (compounds possess 1-naphthyl, 2-naphthyl, 4-methoxyphenyl and 1-pyrene moieties) have shown satisfactory antibacterial activity against *S. aureus.* Here the +I and resonance conjugative effects of methoxy groups, -I effect of CF_3, NO_2 and NH groups involves the improvement of antibacterial activity.

The (*E*)-imine compound **1** (have 1-naphthyl moiety) has shown better antibacterial activity against *B. subtilis*. Here the -I effect of CF_3 and naphthyl group increases the antibacterial activity. Remaining compounds **4**-**6** (compounds possess 2,3-dimethoxy-1-naphthyl, 2-naphthyl, 4-methoxyphenyl, 2-nitrophenyl, 1-pyrene moieties and 3-indole moieties) have shown moderate antibacterial activity. Surprisingly, here the +I and +R effect of $-OCH_3$, -I effect of CF_3, NO_2 substituents and NH groups reduced the antibacterial activity against their strain

The (*E*)-imine **7** (compound have indole moiety) has shown better antibacterial activity against *S. paratyphi A.* The remaining compounds show good antibacterial activity. Here the inductive both +I, -I and +R effects of substituents enhanced the antibacterial activity.

The Schiff bases **5** and **7** (compounds have 4-methoxyphenyl and 3-indole moieties) have shown good antibacterial activity. Here the +I effect of methoxy group, –NH- group of indole moiety and -I

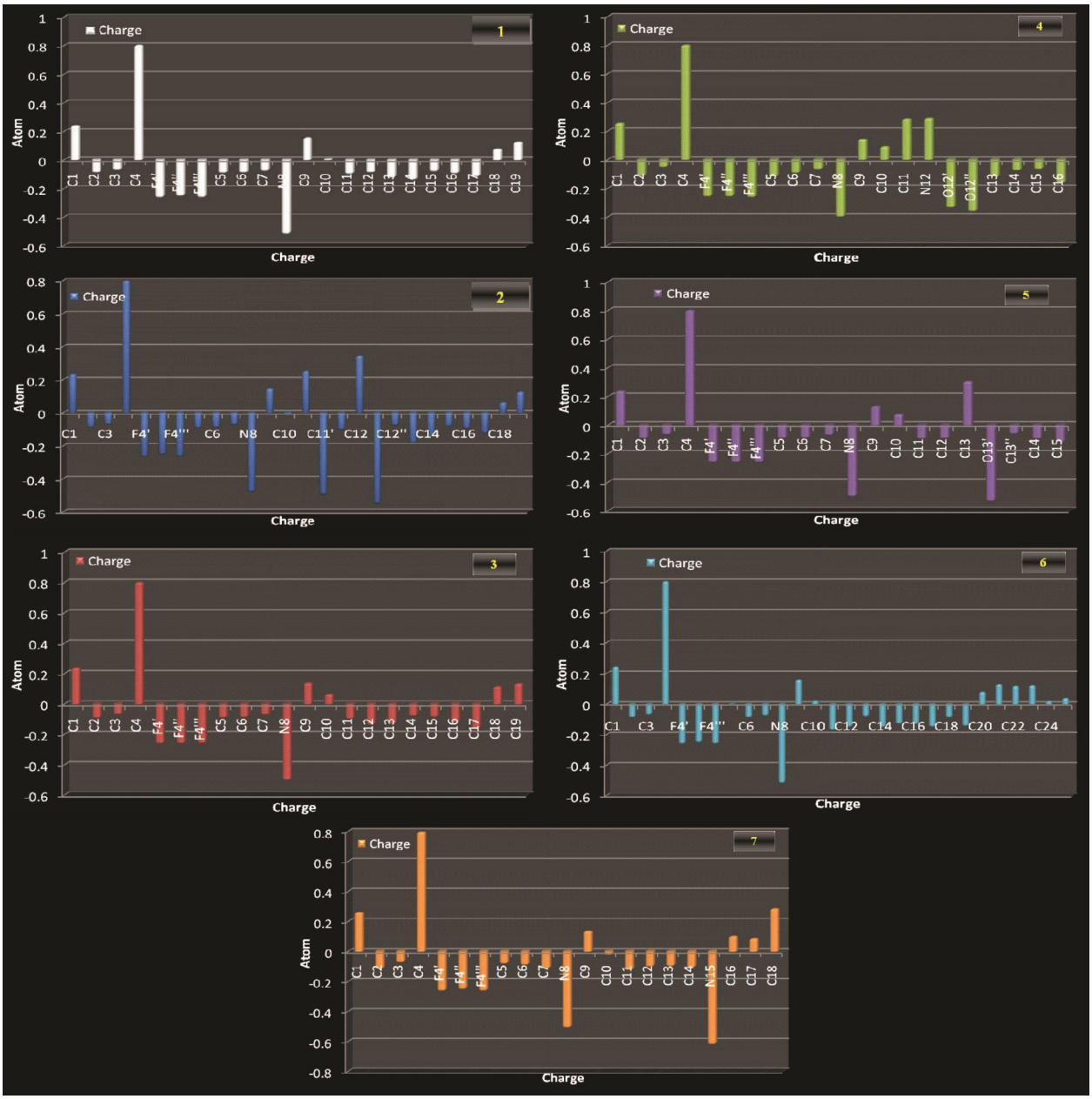


Fig. 7 — Mulliken atomic charge distribution of Schiff bases**1-7**

effect of CF_3 substituent enhances the antibacterial activity. The remaining compounds **1-4** and **6** (imine possess 1-naphthyl, 2,3-dimethoxy-1-naphthyl, 2-naphthyl, 2-nitrophenyl and 1-pyrenyl moieties) shows a moderate antibacterial activity against *P. mirabilis.* This is due to the less effectiveness of inductive both +I, -I and +R effects of substituents.

All (*E*)-imines have shown excellent antibacterial activity against *P. aeruginosa* strain except compound **4** (imine have 2-nitrophenyl group). Here, the +I, –I and +R effects all substituents well enhanced the antibacterial activity against their strain except –I and steric effect effects of NO_2 group.

Antifungal activities of Schiff base 1-7

The antifungal activities of all the synthesized compounds **1-7** have been studied against the fungal species *viz.*, *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, and *Candida albicans* species. The antifungal activity of the synthesized (*E*)-*N*-(substituted arylidene)-3-(trifluoromethyl)aniline (**1-7**) was presented in Fig. 10 and the zone of inhibition

Table 5 — Calculated Mulliken atomic charge of Schiff base **1-7**

Compd 1 Atom	Charge	Compd 2 Atom	Charge	Compd 3 Atom	Charge	Compd 4 Atom	Charge
C1	0.240	C1	0.234	C1	0.238	C1	0.255
C2	-0.094	C2	-0.094	C2	-0.099	C2	-0.119
C3	-0.075	C3	-0.075	C3	-0.074	C3	-0.059
C4	0.802	C4	0.800	C4	0.801	C4	0.801
F4'	-0.266	F4'	-0.267	F4'	-0.266	F4'	-0.263
F4"	-0.256	F4"	-0.257	F4"	-0.266	F4"	-0.263
F4"'	-0.265	F4"'	-0.266	F4"'	-0.265	F4"'	-0.268
C5	-0.097	C5	-0.098	C5	-0.097	C5	-0.124
C6	-0.094	C6	-0.095	C6	-0.095	C6	-0.100
C7	-0.081	C7	-0.078	C7	-0.078	C7	-0.073
N8	-0.521	N8	-0.481	N8	-0.508	N8	-0.405
C9	0.155	C9	0.146	C9	0.137	C9	0.142
C10	0.006	C10	-0.012	C10	0.064	C10	0.090
C11	-0.104	C11	0.253	C11	-0.104	C11	0.285
C12	-0.093	C11'	-0.498	C12	-0.143	N12	0.290
C13	-0.128	C11"	-0.107	C13	-0.139	O12'	-0.340
C14	-0.143	C12	0.346	C14	-0.087	O12"	-0.365
C15	-0.084	C12'	-0.553	C15	-0.093	C13	-0.125
C16	-0.101	C12"	-0.082	C16	-0.131	C14	-0.082
C17	-0.121	C13	-0.187	C17	-0.174	C15	-0.072
C18	0.077	C14	-0.149	C18	0.115	C16	-0.169
C19	0.125	C15	-0.086	C19	0.133	-	-
-	-	C16	-0.101	-	-	-	-
-	-	C17	-0.126	-	-	-	-
-	-	C18	0.062	-	-	-	-
		C19	0.126				

Compd 5 Atom	Charge	Compd 6 Atom	Charge	Compd 7Atom	Charge
C1	0.237	C1	0.241	C1	0.260
C2	-0.099	C2	-0.093	C2	-0.120
C3	-0.074	C3	-0.075	C3	-0.076
C4	0.801	C4	0.802	C4	0.796
F4'	-0.265	F4'	-0.266	F4'	-0.266
F4"	-0.266	F4"	-0.253	F4"	-0.256
F4"'	-0.265	F4"'	-0.265	F4"'	-0.266
C5	-0.097	C5	-0/097	C5	-0.087
C6	-0.095	C6	-0.094	C6	-0.095
C7	-0.078	C7	-0.081	C7	-0.117
N8	-0.504	N8	-0.522	N8	-0.512
C9	0.131	C9	0.156	C9	0.136
C10	0.074	C10	0.020	C10	-0.025
C11	-0.103	C11	-0.175	C11	-0.130
C12	-0.099	C12	-0.154	C12	-0.106
C13	0.305	C13	-0.086	C13	-0.103
O13'	-0.538	C14	-0.156	C14	-0.112
C13"	-0.069	C15	-0.135	N15	-0.624
C14	-0.102	C16	-0.138	C16	0.103
C15	-0.127	C17	-0.154	C17	0.086
-	-	C18	-0.094	C18	0.285
-	-	C19	-0.149	-	-
-	-	C20	0.076	-	-
-	-	C21	0.129	-	-
-	-	C22	0.116	-	-
-	-	C23	0.120	-	-
-	-	C24	0.018	-	-
-	-	C25	0.036	-	-

values are given in Table 7. The corresponding clustered column chart is shown in Fig. 11.

The (*E*)-imines **1**, **7** and **4** (compounds have 1-naphthyl, 2-naphthyl and 3-nitrophenyl moieties) shown excellent antifungal activity against *A. niger* and the remaining compounds **2**, **5** and **6** (compounds have 2,3-dimethoxy-1-naphthyl, 4-methoxyphenyl and 1-pyrenyl) shown good activity. Here the inductive, resonance and steric effects of all substituents are well enhancing the antifungal activity against their strains.

All the Schiff bases **1-7** showed excellent antifungal activity against *P. chyrsogenum* fungal

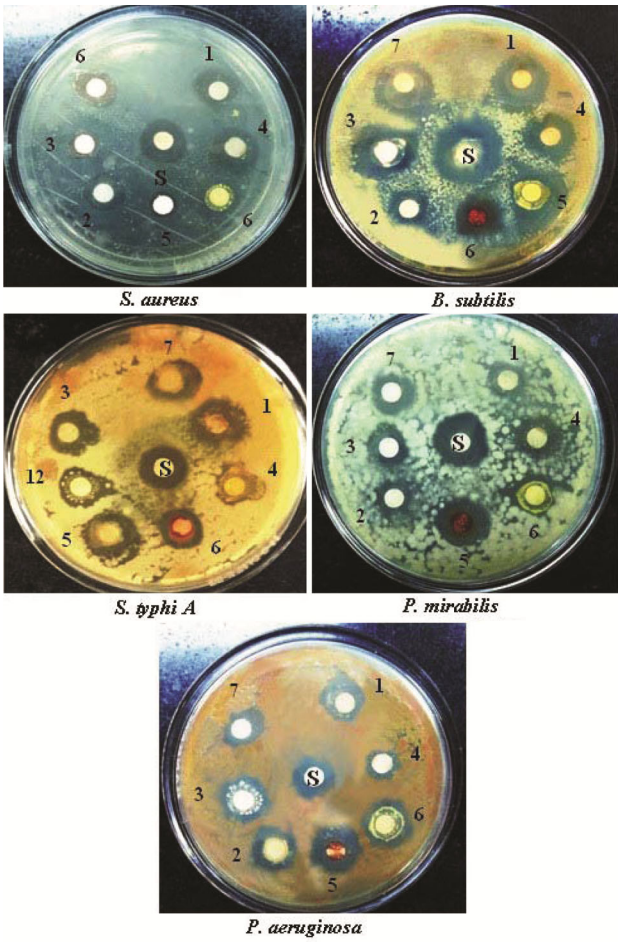


Fig. 8 — Antibacterial activities (petri dishes) of Schiff bases **1-7**

Table 6 — Antibacterial activities of Schiff bases **1-7**

Schiff base No.	Zone of inhibition (mm)				
	Gram-positive		Gram-negative		
	S. aureus	*B. subtilis*	*S. typhi A*	*P. mirabilis*	*P. aeruginosa*
1	16	19	15	15	24
2	17	20	17	13	25
3	14	25	14	14	20
4	18	17	18	15	15
5	10	15	17	19	26
6	12	20	15	12	20
7	17	15	20	17	22
Amoxicillin	22	26	20	22	18

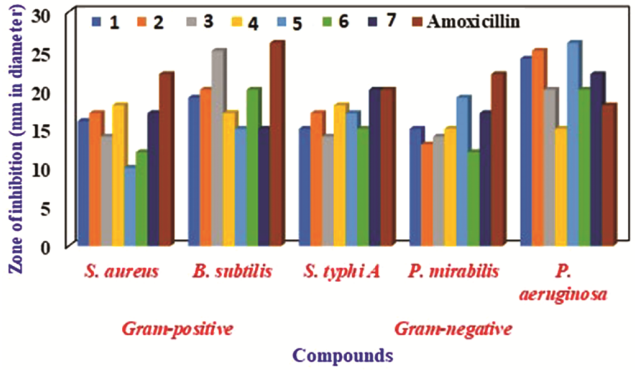


Fig. 9 — The chart representation of the antibacterial activity of Schiff base **1-7**

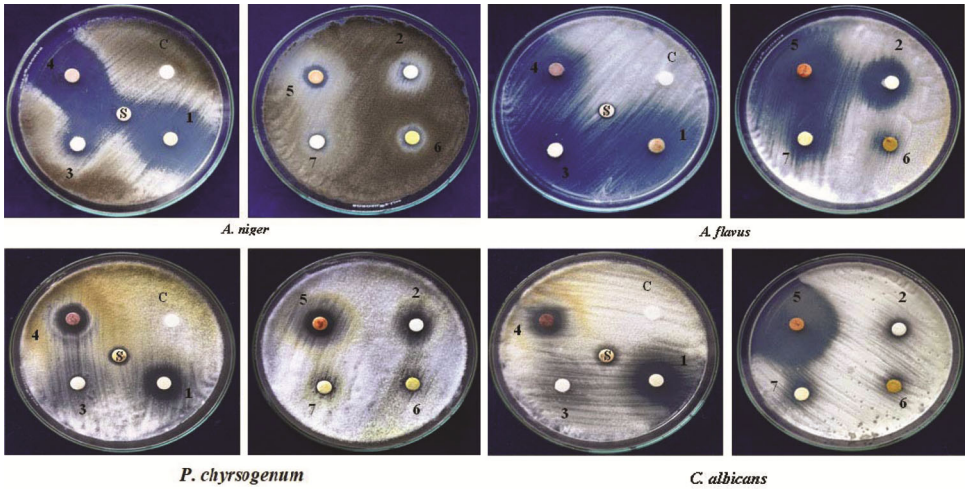


Fig. 10 — Antifungal activities (petri dishes) of Schiff bases **1-7**

Table 7 — Antifungal activities of Schiff bases **1-7**

Schiff base No.	Zone of Inhibition (mm in diameter) Pathogens			
	A. niger	*A. flavus*	*P. chyrsogenum*	*C. albicans*
1	33	31	19	25
2	12	25	14	12
3	15	29	11	9
4	30	28	15	16
5	14	34	16	37
6	13	12	12	11
7	9	19	12	14
Amphotericin-B	16	11	10	25

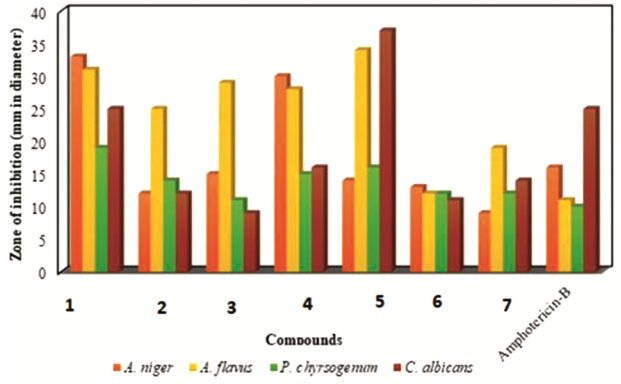


Fig. 11 — The chart representation of the antifungal activity of Schiff bases **1-7**

strain. In this case, the electronic effect such as (inductive, resonance and steric effects) of all substituents were enhances the antifungal activity.

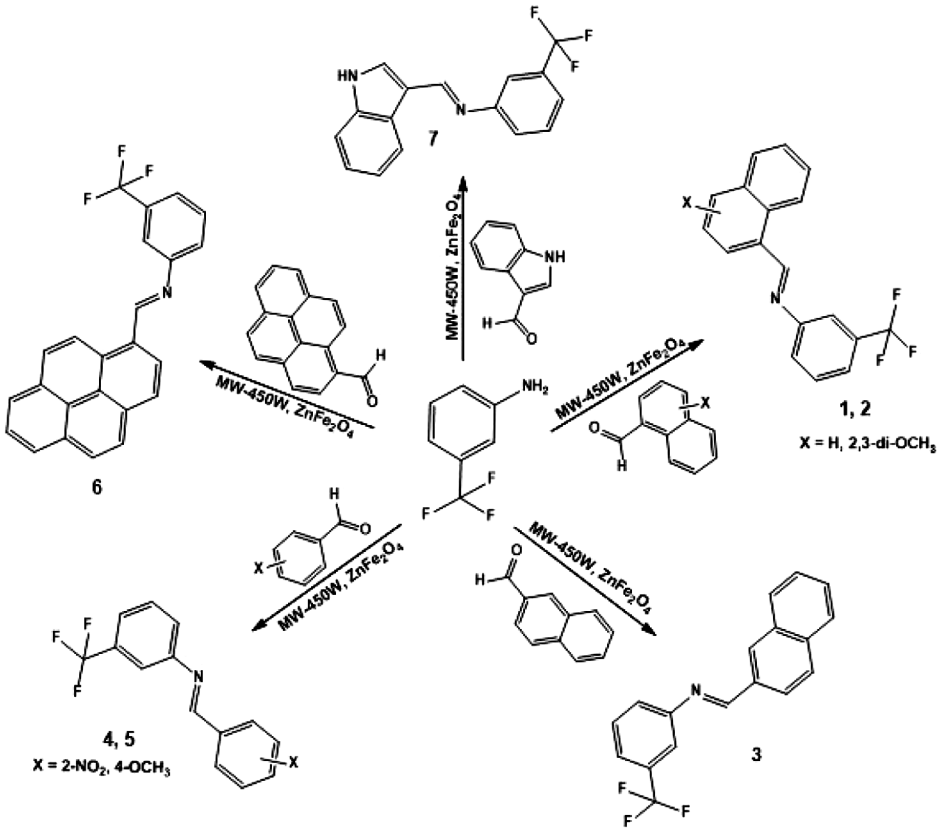
The (*E*)-imines **1** and **5** (compounds have 1-naphthyl and 4-methoxyphenyl moieties) shown better antifungal activity against *C. albicans*. Here the +I and +R effects of methoxy and -I effect of CF_3 substituents are well actively enhances the antifungal activity. Schiff base **4** (compound have 2-nitrophenyl moiety) shown moderate antifungal activity and all the remaining compounds **2**, **3**, **6** and **7** (imine possess 2,3-dimethoxy-1-naphthyl, 2-naphthyl, 1-pyrenyl, and 3-indole moieties) have shown poor antifungal activity against *C. albicans*. Here, the –I and steric effects of NO_2 substituent show a just activeness for showing moderate antifungal activity. The poor antifungal activity was attributed to the absence +I and +R effect of OCH_3 and -I effect of CF_3 substituents.

Experimental Section

In these investigations, the chemical used were purchased from Sigma-Aldrich Chemical Company, Bengaluru, India. The melting points (uncorrected) of all imines were recorded in open glass capillary tubes in SUNTEX melting point apparatus. Elemental investigations of all imines were done on Perkin-Elmer-240 CHN analyzer. The IR spectra of all prepared Schiff bases were recorded on AVATAR–330 FT–IR spectrometer (Thermo Nicolet) and only noteworthy absorption levels (reciprocal centimeters) are listed. FT-IR spectra of all imines were measured between the wavenumber of 4000 and 400 cm^{-1} by using KBr to make pellets. The ^1H NMR spectra of all imines were recorded on a Bruker AVANCE III 400 MHz NMR spectrometer working at 400.13 MHz for ^1H and 100.61 MHz for ^{13}C spectra. Samples were prepared by dissolving about 50 mg of the compound in 0.5 mL of $CDCl_3$ containing 1% TMS as standard. Mass spectra of all synthesized Schiff bases were recorded in Varian-Saturn 2200 GC-MS spectrometer using Electron Impact (70e V) and chemical ionization mode FAB technique. The Schiff base crystal was grown by slow evaporation technique. Accurate unit cell parameters and orientation matrix were acquired by a least-squares fitness of numerous high angle reflections in the range $1.7° \leq \theta \leq 25.0°$ using Mo Kα radiation ($\lambda = 0.71073$) on BRUCKER AXS (Kappa Apex II) area detector using ω scan mode. Cell refinement and data reduction were carried out by utilizing the APEX2 program. The molecular assembly was assigned by the direct method procedure and the non-hydrogen atoms were subjected to anisotropic enhanced refinement by adopting full-matrix least-squares on F2 using SHELXL –2016. The geometries of the synthesized imine were optimized employing DFT-B3LYP 6-31G level with respective Gaussian 09W package program[30] and the compound assembly was visualized with GUASSION 5.0 program[31]. Initial molecular geometry of imines was assessed from typical structural parameter data and was minimized without any constraint in the potential energy surface at *ab initio* adopting the typical standard 6-31G basis set.

Typical procedure for the synthesis of (*E*)-N-(substituted arylidene)-3-(trifluoromethyl)anilines

A homogeneous mixture of 3-trifluoromethylaniline (1 mmol), aryl aldehydes (1 mmol) and $ZnFe_2O_4$ catalyst[32] (5 mg) were irradiated using microwave at 450W for 6 minutes in a microwave oven (Scheme 2) [Samsung microwave oven GW73BD model, 230V A/c, 50 Hz, 100-750 W (ICE-705)]. The reaction progress was monitored by thin-layer chromatography for every 60 sec. After



Scheme 2 — Synthesis (*E*)-N-(substituted arylidene)-3-(trifluoromethyl)anilines

cooling to RT, the reaction product mixture was extracted with dichloromethane (10 mL). The solid crude product was obtained by evaporation of organic layer. The crude was recrystallized using ethanol to afforded the pure compound as yellow crystals.

The imines **(1)** (*E*)-*N*-(naphthalen-1-ylmethylene)-3-(trifluoromethyl)aniline crystal exist in an orthorhombic system. The remaining azomethines exist as powder form. The yield, analytical microanalysis and mass spectral data of these (*E*)-N-(substituted arylidene)-3-(trifluoromethyl) anilines were tabulated in Table 8.

Measurement of antimicrobial activities

The antimicrobial activities of the compounds were analyzed through assessment of biological assay measurement with microorganisms like bacteria and fungi. This involves the measurement of the relative efficiency and inhibition activity of Schiff bases by deciding the quantity needed to produce a stipulated effect on a suitable organism under typical conditions. The chemicals namely nutrient broth, Mueller-Hinton Agar, potato dextrose agar, tween-80 solution and other materials required have been procured from Himedia, Chemical company, Mumbai-400086, India.

The following Gram-positive strains *Staphylococcus aureus and Bacillus subtilis* and Gram-negative stains *Salmonella paratyphi A*, *Proteus mirabilis and Pseudomonas aeruginosa* that have been utilized for this study and they obtained from the Rajah Muthaiah Medical College, Annamalai University, Annamalainagar 608 002, India. The standard Bauer-Kirby[29,30] method procedure was followed for the preparation of Inoculum, agar slants, Mueller-Hinton agar slants, potato dextrose agar medium, fungal inoculum and test compounds. The following fungal species *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chyrsogenum* and *Candida albicans* have been utilized for this study were obtained from microbial type culture collection center (MTCC), Chandigarh 160 036, India.

Antibacterial sensitivity assay measurement

Antibacterial sensitivity assay was performed utilizing the Kirby-Bauer[29] disc diffusion technique. In each Petri-plate about 0.5 mL of the test bacterial

Table 8 — The yield, analytical, micro analysis and MS (m/z) data of (*E*)-N-(substituted arylidene)-3-(trifluoromethyl)anilines

Compd	Aldehyde	Nature	MF	Mol. Wt.	Yield (%)	m.p. (°C)	Micro analysis (%) (Calcd)			MS (*m/z*)
							C	H	N	
1	1-Naphthaldehyde	Yellow orthorhombic	$C_{18}H_{12}F_3N$	299	93	66-65	72.28 (72.24)	3.99 (4.04)	4.64 (4.68)	299[M^+], 300[M^{+1}], 301[M^{+2}], 303[M^{+4}], 305[M^{+6}]
2	2,3-Dimethoxy-1-naphthaldehyde	Yellow powder	$C_{20}H_{16}F_3NO_2$	359	95	66-67	66.91 (66.85)	4.46 (4.49)	3.86 (3.90)	359[M^+], 360[M^{+1}], 361[M^{+2}], 363[M^{+4}], 365[M^{+6}].
3	2-Naphthaldehyde	Pale yellow powder	$C_{18}H_{12}F_3N$	299	92	68-69	72. 19 (72.24)	4.12 (4.04)	4.63 (4.68)	299[M^+], 300[M^{+1}], 301[M^{+2}], 303[M^{+4}], 305[M^{+6}].
4	2-Nitro benzaldehyde	Orange powder	$C_{14}H_9F_3N_2O_2$	294	93	60-61	57.21 (57.15)	3.03 (3.08)	9.48 (9.52)	294[M^+], 295[M^{+1}], 296[M^{+2}], 298[M^{+4}], 300[M^{+6}].
5	4-Methoxy benzaldehyde	Glittering yellow solid	$C_{15}H_{12}F_3NO$	279	95	108-109	64.56 (64.51)	4.29 (4.33)	4.98 (5.02)	279[M^+], 280[M^{+1}], 281[M^{+2}], 283[M^{+4}], 285[M^{+6}].
6	1- Pyredinaldehyde	Pale yellow solid	$C_{15}H_{12}F_3NO$	373	92	128-129	77.15 (77.20)	3.82 (3.78)	3.70 (3.75)	373[M^+], 374[M^{+1}], 375[M^{+2}], 377[M^{+4}], 379[M^{+6}].
7	3-Indolaldehyde	Pale yellow solid	$C_{16}H_{11}F_3N_2$	288	92	178-179	66.70 (66.66)	3.82 (3.85)	9.67 (9.72)	288[M^+], 289[M^{+1}], 300[M^{+2}], 302[M^{+4}], 304[M^{+6}].

sample was spread consistently over the solidified Mueller-Hinton agar utilizing a sterile glass spreader. Then the disc with 5 mm diameter made up of Whatman No. 1 filter paper, impregnated with the solution of the compound were set on the medium utilizing sterile forceps. The plates were incubated for 24 h at 37°C by keeping the plates upside down to avoided the collection of water droplets over the medium. After 24 h the plates were visually inspected and the diameter values of the zone of inhibition were scaled. Triplicate results were recorded by repeating the same procedure. Amoxicillin was used as standard reference.

Antifungal sensitivity assay measurement

Antifungal sensitivity assay was performed using the Kirby-Bauer[29] disc diffusion technique. PDA medium was prepared and sterilized as above. It was poured (ear bearing heating condition) in the Petri-plate, which was filled with 1 mL of the fungal species. The plate was turned clockwise and counter-clockwise for consistent spreading of the species. The disc was impregnated with the test solution. The test solution was prepared by dissolving 20 mg of the imine in 1 mL of $CHCl_3$ solvent. The solution was permitted to solidify and kept for 24 h. Then the plates were visually analyzed and the diameter values of a zone of inhibition were measured. Triplicate results were recorded by repeating the same procedure[33-39].

Conclusions

More than 92% yields of seven (*E*)-N-(substituted arylidene)-3-(trifluoromethyl) anilines were synthesized by $ZnFe_2O_4$ catalyzed microwave irradiation induced condensation of 3-trifluoromethylaniline and various aryl aldehydes. These are characterized by their physical constants and spectroscopic data. The Schiff base **1** exists as monoclinic system. The monoclinic system was confirmed by XRD spectroscopy. The optimized geometrical structures, molecular electrostatic potential and FMO studies of these amines have been investigated by DFT theoretical-computational method. The Mulliken charge of all Schiff bases were predicted from the electron densities of these compounds. All imines showed good and satisfactory antibacterial activities against their bacterial stain. This is due to the +I and resonance conjugative effects of methoxy groups, –I effect of CF_3, NO_2, NH groups and steric effects involves the enhances the antibacterial activity. All the Schiff bases **1-7** Showed excellent antifungal activity against *P. chyrsogenum* fungal strain. Here, the electronic effect such as (inductive, resonance and steric effects) of all substituents were enhances the antifungal activity. The (*E*)-imines **1** and **5** (compounds have 1-naphthyl and 4-methoxyphenyl moieties) shown better antifungal activity against *C. albicans.* This is due to the +I and +R effects of methoxy and -I effect of CF_3 substituents are well actively enhances the antifungal activity.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776. The XRD crystal study analysis files available in CCDC: 2026697 number.

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References

1 Choudhury L H & Parvin T, *Tetrahedron*, 67 (2011) 8213.
2 Dineshkumar N, Suppuraj P, Mayavel P, Muthuvel I & Thirunarayanan G, *Mater Today Proc*, 29 (2020) 1059.
3 Dineshkumar N, Mayavel P, Muthuvel I & Thirunarayanan G, *Chem Data Coll*, 30 (2020) 100547.
4 Mayavel P, Thirumurthy K, Dineshkumar S & Thirunarayanan G, *Indian J Chem*, 54B (2015) 779.
5 Sakthinathan S P, Suresh R, Kamalakkannan D, Mala V, Sathiyamoorthi K, Vanangamudi G & Thirunarayanan G, *J Chile Chem Soc*, 63 (2018) 3918.
6 Rajarajan M, Pachamuthu M P, Thirunarayanan G, Vanangamudi G & Hamdy M S, *SN Appl Sci*, 1 (2019), Article No.940. DOI: https://doi.org/10.1007/s42452-019-0928-z.
7 Mayavel P & Thirunarayanan G, *Annales-UMCS*, 69 (2014) 160.
8 Thirunarayanan G, *Bull Chem Soc Ethiopia*, 28 (2014) 73.
9 Thirunarayanan G, Mayavel P, Thirumurthy K, Vanangamudi G, Lakshmanan K & Sekar K G, *Int J Chem*, 1 (2012) 166.
10 Suresh R, Kamalakkannan D, Ranganathan K, Arulkumaran R, Sundararajan R, Sakthinathan S P, Vijayakumar S, Sathiyamoorthi K, Mala V, Vanangamudi G, Thirumurthy K, Mayavel P & Thirunarayanan G, *Spectrochim Acta*, 101A (2013) 239.
11 Thirunarayanan G, Mayavel P, Thirumurthy K, Vanangamudi G, Sekar K G & Lakshmanan K, *J Chile Chem Soc*, 58 (2013) 2231.
12 Lu J, Li C, Chai Y F, Yang D Y & Sun C R, *Bioorg Med Chem Lett*, 22 (2012) 5744.
13 Mizuhara T, Oishi S, Ohno H, Shimura K, Matsuoka M & Fujii N, *Org Biomol Chem*, 10 (2012) 6792.
14 Michaluk L A, Romańska I, Wąsik A & Michaluk J, *Neurotox Res*, 32 (2017) 94.
15 Rouleau A, Stark H, Schunack W & Schwartz J C, *J Pharmacol Exp Ther*, 295 (2000) 219.
16 Hunashal R D, Ronad P M, Maddi V S, Satyanarayana D & Kamado M A, *Arabian J Chem*, 7 (2014) 1070.
17 Hu Q, Guo F, Zhao F, Tang G & Fu Z, *J Biomater Sci Polym Ed*, 28 (2017) 768.
18 Li G, Golani L K, Jahan R, Rashid F & Cook J M, *Synthesis*, 50 (2018) 4124.
19 Yang H, Sun W H, Li Z & Wang L, *Synthetic Commun*, 32 (2006) 2395.
20 Khan S A, Asiri A M, Bashwike A A & Sharma K, *Eur J Chem*, 4 (2013) 454.
21 Thalla N, Devineni S R, Parimi B N & Naga Raju C, *Der Chemica Sinica*, 34 (2012) 808.
22 Suresh R, Sakthinathan S P, Kamalakkannan K, Ranganathan K, Sathiyamoorthi K, Mala V, Arulkumaran R, Vijayakumar S, Sundararajan R, Vanangamudi G, Subramanian M, Thirunarayanan G, Vanaja & Kanagambal P, *Bull Ethiopian Chem Soc*, 29 (2015) 275.
23 Gutiérrez M R, Chafaa F, Nacereddine A K, Djerourou L & Domingo R, *J Mol Graph Model*, 70 (2016) 296.
24 Song C, Qu S, Tao Y, Dang Y & Wang Z X, *ACS Catal*, 4 (2014) 2854.
25 Nasir F I, Lee W F M, Chong Y Y, Kassim M B, Hasbullah S A, Philp D & Hassan N I, *Malaysian J Anal Sci*, 24 (2020) 422.
26 Özkinali S, Çavuş M S & Sakin B U, *J Turkish Chem Soc*, 5A (2018) 159. (https://doi.org/10.18596/jotcsa.346278).
27 Ghiasuddin M, Akram M, Adeel M, Khalid M N, Tahir M U, Khan M A, Asghar M, Aman U & Iqbal M, *J Mol Struct*, 1160 (2018) 129.
28 Luque F J, Lopez J M & Orozco M, *Theor Chem Acc*, 103 (2000) 343.
29 Bauer A W, Kirby W M M, Sherris J C & Truck M, *Am J Clin Pathol*, 45 (1966) 493.
30 Frisch M J, Trucks G W, Schlegel H B, Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Mennucci B & Petersson G A, *GAUSSIAN 09*, *Revision A 02*, (Gaussian, Inc., Wallingford, CT) (2009).
31 Dennington R, Keith T, Millam J & Gauss View, Version 5, (Semichem Inc., Shawnee Mission KS) (2009).
32 Suppuraj S, Muthuvel I & Thirunarayanan G, *Mat Sci Appl Chem*, 34 (2017) 5.
33 Usha V, Thirunarayanan G & Manikandan S, *Indian J Chem*, 61B (2022) 521.
34 Dineshkumar S, Muthuvel I, Mayavel P, Markanadan R, Usha V & Thirunarayanan G, *Indian J Chem*, 60B (2021) 1373.
35 Manikandan V, Vanangamudi G, Arulkumarn R, Christhuraj P & Thirunarayanan G, *Indian J Chem*, 59B (2020) 399.
36 Mala V, Muthuvel I, Thirunarayanan G, Sakthinathan S P, Arulkumaran R, Manikandan V, Sundararajan R, Kamalakkannan D, Suresh R & Usha V, *Ovidius Univ Annal Chem*, 31 (2020) 152.
37 Boobal Arasu V, Thirunarayanan G & Kulanthaivel S, *Biointer Res Appl Chem*, 13 (2023) 533. https://doi.org/10.33263/ BRIAC136.533
38 Anam K R & Thirunarayanan G, *Indian J Chem*, 62 (2023) 91.
39 Muthuvel I, Manikandan S, Thirunarayanan G, Usha V & Sathiyendiran V, *Indian J Chem*, 62 (2023) 131.