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Green synthesis of novel pyrazole containing Schiff base derivatives as antibacterial agents on the bases of *in-vitro* and DFT

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ABSTRACT

A series of pyrazole containing Schiff bases were synthesized, by the reaction of 3,5-dimethyl-1-phenylpyrazole-4-carboxaldehyde and the corresponding active amines under microwave irradiation. The structures of the synthesized compounds were established by spectroscopic data (FT-IR, ^{1}H NMR, ^{13}C NMR and ESI-MS) and elemental analyses. The anti-bacterial activity of these compounds were tested *in vitro* by the disc diffusion assay against two Gram-positive and two Gram-negative bacteria, and then the minimum inhibitory concentration using chloramphenicol as reference drug. All the molecules were modeled and optimized by using density functional theory, DFT/B3LYP method. Calculated descriptors, the lower unoccupied molecular orbital and the density were used to interpret the antibacterial activity of the compounds. The results showed that compound **3** is better inhibitor of both types of test bacteria as compared to chloramphenicol.

1. Introduction

Development of antibiotics for gram-positive and gram-negative bacteria such as *S. aureus, S. pyogenes, S. typhimurium* and *E. coli* are among the most powerful and successful achievements of modern science for the control of infectious diseases. These bacteria's have and are causing serious health problem such as food poisoning, rheumatic, salmonellosis and diarrhea [1,2]. More than 50 million people worldwide are infected and up to 150,000 die yearly due to these bacterial infections [3]. Amoxicillin, norfloxacin, chloramphenicol, ciprofloxacin are the most common drugs used for these bacterial infections but are associated with severe side effects [4]. However, critical lateral effects have been described, i.e. neurological alterations produced by interaction of the drug with the central nervous system [5]. Therefore, it is necessary to search for new antibiotic agents. Five member heterocyclic compounds such as pyrazole are important are important nitrogen containing compounds and numerous pyrazole derivatives have been found to possess considerable biological activities [6], such as antimicrobial [7-9], antiamoebic [10,11], antinociceptive [12], anticancer [13], antidepressant [14] and anti-inflammatory [15]. On the other hand, pyrazoline derivatives are also widely used in materials science fields such as non-linear optics (NLO) [16], optical limiting [17], electro-chemical sensing [18], Langmuir films and photoinitiated polymerization [19]. On the other hand a pyrazole ring linked to five or six member heterocyclic systems with an azomethine group also showed a variety of biological activity such as anti-bacterial [20], anti-fungal [21], anti-inflammatory [22], antihypertensive [23], anti-HIV [24], antitumor [25], and anticonvulsant activities. Thus, the pyrazole containing bi-cyclic heterocyclic Schiff base seems to be a possible pharmacophore in various pharmacologically active agents.

Aforementioned facts prompted us to synthesize new pyrazole containing heterocyclic Schiff bases from reaction of 3,5-dimethyl-1-phenylpyrazole-4-carboxaldehyde with the corresponding heterocyclic active amines under microwave irradiation as antibacterial agent.

2. Experimental

3,5-Dimethyl-1-phenylpyrazole-4-carboxaldehyde, amino-phenazone, 5-amino-3,4-dimethylisoxazole, 2-amino pyridine, 3-amino 1,2,4 triazole were purchased from Acros Organic and 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, 5,6-diphenyl-1,2,4-triazin-3-amine were synthesized by published methods [26,27]. The other reagents and solvents (A.R.) were obtained commercially and used without further purification except dimethylformamide (DMF), ethanol and methanol. Melting points were recorded on a Thomas Hoover capillary melting apparatus without correction. IR spectra were recorded on a Nicolet Magna 520 FTIR spectrometer. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker DPX 600 MHz spectrometer using TMS as internal standard. The mass spectra have been scanned on the Waters Micromass Q-T of Micro (ESI) spectrometer. Elemental analyses were performed using a Carlo Erba EA1180 microanalyser. We have been used the Microwave Dual Hertz 220 V, 50Hz and 60Hz for the reaction.

2.1. General procedure for the synthesis of Schiff bases

The Schiff base derivatives were synthesized by using the literature procedure.

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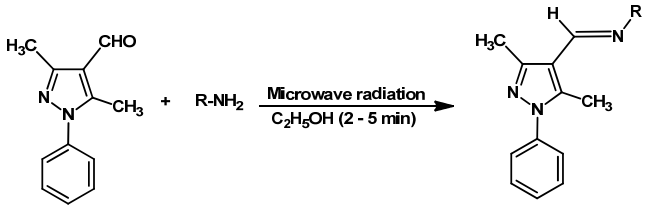
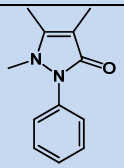
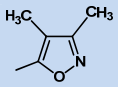
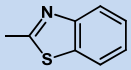
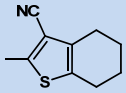
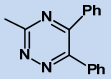
Table 1. Physicochemical data of the synthesized compounds (**1-7**).



Compound	R	Molecular formula	M.p. (°C)/ Crystallization solvent	Yield (%)	Reaction Time (min)
1		$C_{23}H_{23}N_5O$	206/$CHCl_3$	88.5	3.0
2		$C_{17}H_{18}N_4O$	105/CH_3OH	86.4	2.5
3		$C_{19}H_{16}N_4S$	145/CH_2Cl_2	82.4	2.0
4		$C_{14}H_{14}N_6$	136/$CHCl_3$	90.2	3.0
5		$C_{21}H_{20}N_4S$	138/CH_3OH	89.5	3.5
6		$C_{17}H_{16}N_4$	132/$CHCl_3$	86.2	5.0
7		$C_{27}H_{22}N_6$	175/$CHCl_3$	82.2	4.0

A mixture of 3,5-dimethyl-1-phenyl pyrazole-4-carboxaldehyde (5.8 mmol) and heterocyclic amines (5.8 mmol) in anhydrous methanol (15 mL), in a beaker (100 mL), in the presence of few drop of acetic acid, and the reaction mixture was heated inside a microwave oven for 2-5 min. (at 210 Watts, i.e. 30% microwave power). Progress of reaction was monitored by TLC. After completion of the reaction and cooling, the product was obtained and recrystallized from the proper solvent. The melting points, recrystallization solvent and reaction time of the compounds are recorded in Table 1.

4-{[(E)-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)methylidene]amino}-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (**1**): Color: Brown. FT-IR (KBr, *v*, cm^{-1}): 2924 (C-H), 1641 (C=C), 1589 (C=N), 1130 (C-N). ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 9.82 (s, 1H, $CH_{olefinic}$), 7.49-7.29 (m, 10H, Ar-H), 3.13 (s, 3H, N-CH_3), 2.55 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 161.20, 151.81, 151.15, 149.83, 140.53, 139.18, 134.89, 129.15, 129.09, 127.82, 126.72, 125.19, 124.18, 119.67, 117.59, 36.07, 13.55, 11.69, 10.13. MS (ESI, *m/z*, (%)): 387 (M+1, 62). Anal. calcd. for $C_{23}H_{23}N_5O$: C, 71.67; H, 6.01; N, 18.17. Found: C, 71.65; H, 5.97; N, 18.12%.

N-[(E)-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-3,4-dimethylisoxazol-5-amine (**2**): Color: Brown. FT-IR (KBr, *v*, cm^{-1}): 3063(C-H), 1665 (C=C), 1597 (C=N), 1142 (C-N). ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 8.84 (s, 1H, $CH_{olefinic}$), 7.62-7.48 (m, 5H, Ar-H), 2.24 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.75 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 185.26, 153.76, 151.81, 144.77, 138.17, 129.35, 129.27, 128.77, 128.41, 125.38, 125.38, 114.82, 13.34, 12.60, 11.94, 10.48, 6.63. MS (ESI, *m/z*, (%)): 296 (M+1, 54). Anal. calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.32; H, 6.12; N, 18.98%.

N-[(E)-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-1,3-benzothiazol-2-amine (**3**): Color: Light orange. FT-IR (KBr, *v*, cm^{-1}): 3062 (C-H), 1667 (C=C), 1598 (HC=N), 1118 (C-N). ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 10.20 ((s, 1H, $CH_{olefinic}$), 7.52-7.40 (m, 9H, Ar-H), 2.55 (s, 3H, CH_3), 2.52 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 185.26, 151.82, 144.71, 138.17, 129.35, 129.20, 128.77, 125.39, 118.96, 12.59, 11.41. MS (ESI, *m/z*, (%)): 334 (M+1, 58). Anal. calcd. for $C_{19}H_{16}N_4S$: C, 68.65, H; 4.85; N, 16.85. Found: C, 68.61; H, 4.82; N, 16.82%.

N-[(E)-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-4H-1,2,4- triazol-3-amine (**4**): Color: Light brown. FT-IR (KBr, *v*, cm^{-1}): 3065 (C-H), 2928 (C-H), 1667 (C=C), 1544 (C=N), 1177 (C-N). ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 10.16 (s, 1H, $CH_{olefinic}$), 7.52-7.46 (m, 5H, Ar-H), 7.50 (s, 1H, CH), 2.55 (s, 1H, N-H), 2.53 (s, 3H, CH_3), 2.51 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 185.26, 151.82, 144.77, 138.17, 129.35, 128.77, 125.39, 115.96, 12.59, 11.41. MS (ESI, *m/z*, (%)): 268 (M+1, 72). Anal. calcd. for $C_{14}H_{14}N_6$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.12; H, 5.28; N, 31.52%.

Table 2. Antibacterial activity of pyrazole Schiff base derivative (**1**-**7**), positive control chloramphenicol and negative control (DMSO) measured by the Halo Zone Test (Unit, mm).

Compounds	Corresponding effect on microorganisms			
	S. aureus	*S. Pyogenes*	*S. typhimurium*	*E. coli*
1	11.2±0.2	10.5±0.2	9.6±0.3	9.6±0.4
2	11.4±0.2	12.4±0.4	10.5±0.3	14.6±0.2
3	18.2±0.3	18.6±0.4	17.8±0.4	21.4±0.4
4	11.5±0.3	15.2±0.5	10.5±0.4	11.5±0.1
5	17.2±0.2	17.8±0.3	17.5±0.4	20.2±0.4
6	12.5±0.4	14.2±0.4	11.6±0.5	10.2±0.5
7	12.4±0.3	12.6±0.5	12.8±0.2	11.6±0.5
Chloramphenicol	17.0±0.5	18.2±0.4	17.2±0.8	20.0±0.2
DMSO	-	-	-	-

Table 3. Minimum inhibition concentration (MIC) of pyrazole Schiff base derivative (**1**-**7**) products, positive control: chloramphenicol.

Bacterial Strain	MIC (µg/mL) compound							Positive control
	1	**2**	**3**	**4**	**5**	**6**	**7**	
S. aureus	512	256	16	256	32	256	128	32
S. pyogenes	256	64	16	512	54	512	512	32
S. typhimurium	256	128	32	256	32	256	128	32
E. coli	512	256	16	128	32	64	256	32

(E)-2-(((3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)methylene) amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**5**): Color: Dark Yellow. FT-IR (KBr, *ν*, cm^{-1}): 3032 (C-H), 2937 (C-H), 1635 (C=C), 1595 (C=N), 1140 (C-N). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 8.84 (s, 1H, $CH_{olefinic}$), 7.57-7.48 (m, 5H, Ar-H), 2.70-1.82 (m, 8H, -CH_2), 2.62 (s, 3H, CH_3), 2.54 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 161.90, 152.21, 151.27, 142.87, 138.60, 134.60, 130.51, 129.28, 128.45, 125.26, 115.86, 114.88, 104.93, 25.18, 24.35, 23.17, 22.08, 13.0. MS (ESI, *m/z*, (%)): 362 (M+1, 76). Anal. calcd. for $C_{21}H_{20}N_4S$: C, 69.97; H, 5.59; N, 15.54. Found: C, 69.95; H, 5.54; N, 15.52%.

N-[(E)-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)methylidene] pyridine-2-amine (**6**): Color: Light Brown. FT-IR (KBr, *ν*, cm^{-1}): 3064 (C-H), 2929 (C-H), 1666 (C=C), 1554 (C=N), 1176 (C-N). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 10.08 (s, 1H, $CH_{olefinic}$), 7.54-7.39 (m, 9H, Ar-H), 2.55 (s, 3H, CH_3), 2.53 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 185.26, 151.81, 144.77, 138.17, 129.35, 128.76, 125.38, 117.96, 12.60, 11.41. MS (ESI, *m/z*, (%)): 278 (M+1, 62). Anal. calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.84; H, 5.72; N, 20.22%.

(E)-N-((3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)methylene)-5,6-diphenyl-1,2,4-triazin-3-amine (**7**): Color: Orange. FT-IR (KBr, *ν*, cm^{-1}): 2937 (C-H), 2988 (C-H), 1659 (C=C), 1554 (C=N), 1140 (C-N). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 9.92 (s, 1H, $CH_{olefinic}$), 7.51-7.30 (m, 15H, Ar-H), 2.55 (s, 3H, CH_3), 2.53 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 185.22, 161.16, 157.26, 150.75, 136.01, 135.37, 129.50, 129.35, 129.35, 128.77, 128.53, 128.37, 125.38, 116.62, 12.59, 11.41. MS (ESI, *m/z*, (%)): 430 (M+1, 72). Anal. calcd. for $C_{27}H_{22}N_6$: C, 75.33; H, 5.15; N, 19.52. Found: C, 75.28; H, 5.06; N, 19.48%.

2.2. Organism culture and in vitro screening

The antibacterial activity was assessed by the disc-diffusion method with minor modifications. *S. aureus, S. pyogenes, S. typhimurium* and *E. coli* were sub-cultured in BHI medium and incubated for 18 h at 37 °C, and then the bacterial cells were suspended, according to the McFarland protocol in saline solution to produce a suspension of about 10^{-5} CFU/mL: 10 µL of this suspension was mixed with 10 mL of sterile antibiotic agar at 40 °C and poured onto an agar plate in a laminar flow cabinet. Five paper disks (6.0 mm diameter) were fixed onto nutrient agar plate. 1 mg of each test compound was dissolved in 100 µL DMSO to prepare stock solution from stock solution different concentration 10, 20, 25, 50, and 100 µg/µL of each test compound were prepared. These compounds of different concentration were poured over disk plate on to it. Chloramphenicol (30 µg/disk) was used as standard drug (positive control) and DMSO poured disc was used as negative control. The susceptibility of the bacteria to the test compounds was determined by the formation of an inhibitory zone after 18 h of incubation at 36 °C. Table 2 reports the inhibition zones (mm) of each compound and the controls. The minimum inhibitory concentration (MIC) was evaluated by the macro dilution test using standard inoculums of 10^{-5} CFL/mL. Serial dilutions of the test compounds, previously dissolved in dimethyl sulfoxide (DMSO) were prepared to final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 µg/mL to each tube was added 100 µL of a 24 h old inoculum. The MIC, defined as the lowest concentration of the test compound, which inhibits the visible growth after 18 h, was determined visually after incubation for 18h, at 37 °C, and the results are presented in Table 3. DMSO and chloramphenicol used as negative and positive controls, respectively.

2.3. Calculation method

The theoretical structures **1** to **7** were generated using Spartan'04 (Version 1.0.3) Windows with the aim to predict their antibacterial activities. The optimized geometries of all the molecules were calculated by using quantum chemical calculations including Semi-empirical and Ab initio method. These methods have been previously used successfully for the small molecule calculations [28,29]. All the molecules were modelled and sent to energy minimization, and then all their possible conformers were obtained using Semi-empirical PM3 calculations. However, only the most lowest energy conformer of each molecule was submitted for the higher level of calculations that is Hartree-Fock (HF) with 3-21G* basis set, and then to HF/6-31G* basis set. The resulting wave function, Hessian matrix, and geometry of the molecules obtained were used and submitted for final calculation that is Density Functional Theory (DFT) with 6-31G* (Figure 1). Analytical vibrational frequency calculations were performed for all the molecules. Exact zero imaginary vibrations characterize stationary points. The asterisk means that "d" polarized functions were added for C, O, N and S atoms.

3. Result and discussion

3.1. Chemistry

Schiff base derivatives were synthesized by the reaction of 3,5-dimethyl-1-phenylpyrazole-4-carboxaldehyde and the chosen active amines, by using microwave irradiation in good yield [30].

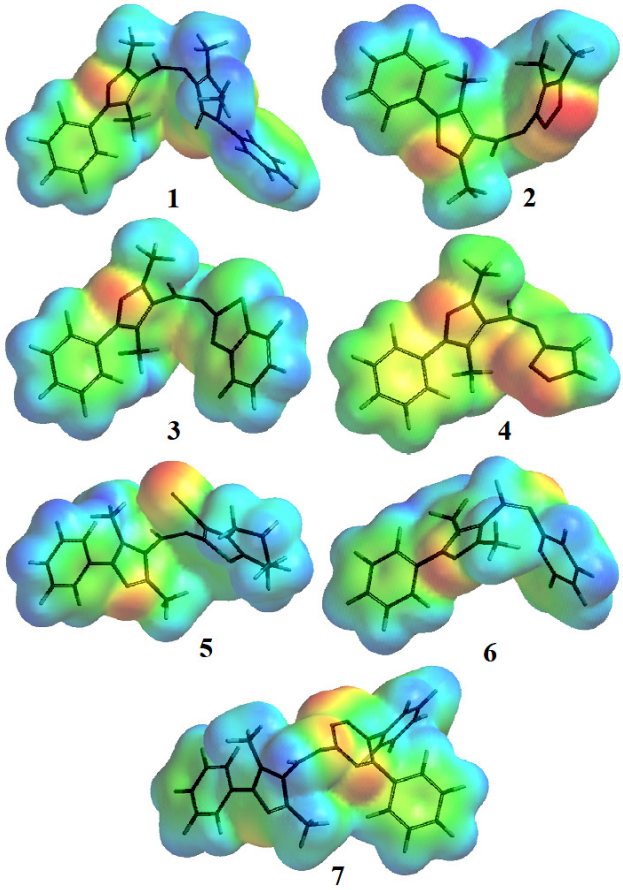


Figure 1. Density and potential map of all Schiff bases **1** to **7** calculated with DFT/ RB3LYP method is shown.

Conventional methods present several hurdles, such as toxic reagents, waste disposal problem, strong acidic conditions and low selectivity makes these methods environmentally hazardous. In this respect solvent phase synthesis under microwave irradiations is considered as eco-friendly alternative. The obtained compounds are stable in the solid state as well as in the solution state. The structure of all the compounds was established by spectral data (IR, ^{1}H NMR, ^{13}C NMR and GC-MS). Assignments of selects characteristic IR band positions provide significant indication for the formation of the Schiff base derivative. The FT-IR spectra of pyrazole schiff bases **1**-**7** showed absorption bands at 2912-2974 cm^{-1} for aromatic C-H and at 1544-1598 cm^{-1} for azomethine group (-CH=N-). The absence of absorption band at 1700-1750 cm^{-1} also confirms the conversion of -CHO group to -CH=N- group. Further evidence for the formation of Schiff base derivative was obtained from the ^{1}H NMR spectra, which provide diagnostic tools for the positional elucidation of the protons. The structural assignments of the NMR spectra are given in the experimental section. Assignments of the signals are based on the chemical shifts and intensity patterns. The ^{1}H NMR spectra of Schiff bases showed peaks of aromatic, methyl, and olefinic (-N=CH-) proton. These were all singlets and each one indicating intensity of one proton in 600 MHz ^{1}H NMR. The ^{1}H NMR spectrum of Schiff bases (**1**-**7**) showed sharp singlets at 8.84-10.20 ppm indicating the presence of azomethine (-CH=N-) proton. The two sharp singlets at 2.03-2.62 ppm indicated the -CH_3 group attached to the carbon. The appearance of multiplets at 7.29-7.62 ppm was due to aromatic protons. Moreover, ^{13}C NMR spectra showed signals in the range of 114.82-118.96 ppm and at 125.39-130.15 ppm due to aryl carbon and azomethine carbon, respectively. In the mass spectrum, compound **1** showed a peak at *m/z* 387, which matches its molecular formula $C_{23}H_{23}N_5O$. A peak at *m/z* 296 was observed for compound **2** which is in conformity with the molecular formula $C_{17}H_{18}N_4O$. Mass spectra of other compound are given in experimental section.

3.2. Antimicrobial activity

The compounds (**1**-**7**) were tested for their antibacterial activities by disc-diffusion method using nutrient broth medium [contained (g/L): beef extract 3 g; peptone 5 g; pH = 7.0] [31]. The Gram-positive bacteria and Gram-negative bacteria utilized in this study consisted of *S. aureus, S. pyogenes, S. typhimurium* and *E. coli*. In the disc-diffusion method, sterile paper discs (0.5 mm) impregnated with compound dissolved in dimethylsulfoxide (DMSO) at concentration 100 µg/mL were used. Then, the paper discs impregnated with the solution of the compound tested were placed on the surface of the media inoculated with the microorganism. The plates were incubated at 35 ^{o}C for 24 h. After incubation, the growth inhibition zones are shown in Table 2. The Schiff base derivative was further checked by MIC method. The results are presented in Table 3.

3.3. Computation

Some selected descriptors such as total energy, molecular weight, LUMO, volume and density, calculated with DFT/B3LYP method are presented in Table 4 [32].

Table 4. Table of all selected descriptors used in this study, calculated by DFT/RB3LYP method.

Compound	Total energy (au)	Molecular weight	LUMO (eV)	Volume (Å^3)	Density
1	-1239.19998	385.471	-0.84	392.93	0.981
2	-952.78993	294.358	-1.25	313.48	0.939
3	-1350.82148	332.431	-1.67	360.55	0.922
4	-870.36216	266.308	-1.47	280.62	0.949
5	-1429.42854	360.485	-1.66	387.62	0.930
6	-876.40910	276.343	-0.93	283.14	0.976
7	-1370.55273	430.515	-1.55	443.37	0.971

The antibacterial activity of the pyrazole Schiff bases is a function of LUMO (Lowest Unoccupied Molecular Orbital) energy and the density. Descriptor LUMO is an electronic parameter, which measures the electrophilicity of the molecules. When a molecule acts as a Lewis acid, incoming electrons are received in its LUMO. Molecules with low-lying LUMO are more able to accept electrons than those with high energy LUMO, and thus will show higher activity. Density is a 3-D-spatial descriptor that is defined as the ratio of molecular weight to molecular volume. Density reflects the types of atoms and how tightly they are packed in a molecule. Density is negatively correlated with activity. This means that if molecule is compact, it will reduce the density and thereby increase the activity.

Molecule **3** has the lowest LUMO energy and the lowest density as compared to all the other molecules studied in this study (see Table 4). Thus one can conclude the highest antibacterial activity of compound **3**. In addition, molecule **5** has also lower LUMO energy and the lower density as compare to molecule **2**, **4**, **6** and **7**. Thus, compound **5** will show higher antibacterial activity than **2**, **4**, **6** and **7**. However, Molecule **1** has the higher LUMO energy and the higher density. Thus, one can conclude its lowest antibacterial activity.

4. Conclusions

Heterocyclic Schiff bases were synthesis and screened for antibacterial activity based on *in-vitro* and DFT/B3LYP model. These pyrazole containing Schiff bases were synthesized by the reaction of 3,5-dimethyl-1-phenylpyrazole-4-carboxaldehyde with the corresponding active heterocyclic amines under microwave irradiation. The antibacterial activity of these compounds was examined using cultures of bacteria and the results showed that the sulphur containing pyrazole Schiff base increased the antibacterial activity. Among the seven compounds, thiazole containing pyrazole Schiff base (**3**) showed better antibacterial activity for both types of the bacterias (Gram-positive and Gram-negative) as compared to reference drug chloramphenicol. Our experimental results were found in good collaboration with the theoretical results. Structure activity relationship studies revealed that pyrazole substituted derivatives play important role in antimicrobial activity. A little structure variation can cause immense difference in the activity of the drug. This approach can open new vistas in the chemotherapy of the infective disease. The field is further open for pharmacokinetics and clinic studies to establish these molecules as drugs in the market.

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