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ORIGINAL ARTICLE

Synthesis, characterization and antibacterial activity of some new pyrazole based Schiff bases

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Abstract In the present study a series of new Schiff bases were synthesized. All the synthesized compounds were characterized by IR, ^{1}H NMR, mass spectral and elemental analyses. Newly synthesized compounds were screened for their antibacterial (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa*) activity. The results revealed that, compounds **3f** and **3c** have exhibited significant biological activity against the tested microorganisms.

1. Introduction

Increasing resistance of microorganisms to currently available antimicrobial drugs is the major cause of morbidity and mortality throughout the world. Thus development of novel antimicrobial drugs is still in demand. The compounds carrying azomethine functional group –C═N– which are known as Schiff bases have gained importance in medicinal and pharmaceutical fields due to the most versatile organic synthetic intermediates and also showing a broad range of biological activities, such as antituberculosis (Patole et al., 2006; Hearn and Cynamon, 2004), anticancer (Ren et al., 2002), analgesic and anti-inflammatory (Bhandari et al., 2008), anticonvulsant (Sridhar et al., 2002; Kaplan et al., 1980) antibacterial and antifungal activities (Shi et al., 2007). These Schiff bases are good intermediates for the synthesis of many heterocyclic ring systems like thiazolidinones (Kucukguzel et al., 2006), azetidinones (Kalsi et al., 1990) etc. The chemistry of 1,2,4-triazole and its fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. 1,2,4-Triazole moieties have been incorporated into a variety of therapeutically interesting drug candidates including antiviral (ribavarin), anti migraine (rizatriptan), antifungal (flucanazole), antianxiety compounds (alprazolam). Moreover sulfur containing heterocyclic compounds represent an important group of compounds that are promising on practical application (Holla

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et al., 2003; Wu et al., 2007). The pharmacological importance of heterocycles derived from 1,2,4-triazole paved the way towards active research in a triazole chemistry. Pyrazoles represent a key motif in heterocyclic chemistry and occupy a prime place in medicinal and pesticide chemistry due to their capability to exhibit a wide range of bioactivities, such as antimicrobial (Sultivan et al., 2007; Gilbert et al., 2006; Prakash et al., 2009; Isloor et al., 2009), anticancer (Magedov et al., 2007), anti-inflammatory (Szabo et al., 2008; Benaamane et al., 2008), antidepressant (Prasad et al., 2005), anticonvulsant (Ozdemir et al., 2007), antipyretic (Sener et al., 2002), selective enzyme inhibitory activities (Wachter et al., 1996) etc. Amongst a large array of medicinally important pyrazole derivatives, 4-functionalized pyrazoles occupy a unique position and their evaluation as antimicrobial agents has attracted much attention in the past (Prakash et al., 2009; Sridhar et al., 2004; Bekhit et al., 2003; Bekhit et al., 2008; Vijesh et al., 2010). Pyrazoles with various functional groups at position-4, such as cyano or oxime (Prakash et al., 2009), aldehyde or carboxylate (Sridhar et al., 2004) have been known to show good antimicrobial properties. In view of these and in continuation of our research on biologically active molecules, we hereby report the synthesis of some new Schiff bases bearing triazole and pyrazole moieties and their antibacterial studies.

2. Experimental

2.1. Measurements

Melting points were determined by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Thermo Nicolet avatar 330-FT-IR spectrophotometer. ^{1}H NMR spectra were recorded (DMSO-d_6) on a Bruker (400 MHz) spectrometer using TMS as internal standard. Chemical shift values are given in δ scales. The mass spectra were recorded on LC–MS-Agilent 1100 series and API 2000 LC/MS system. Elemental analyses were performed on a Flash EA 1112 series CHNS-O analyser. The completion of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminium sheets (silica gel 60 F254). Commercial grade solvents and reagents were used without further purification. The reaction pathway has been summarized in Scheme 1.

2.2. Synthesis

2.2.1. Synthesis of 4-amino-5-substituted-4H-1,2,4-triazole-3-thiol **1a–c**

The compounds were synthesized according to previously reported procedure (Isloor et al., 2009).

2.2.2. Synthesis of 3-(4-substitutedphenyl)-1H-pyrazole-4-carbaldehyde **2a–e**

The compounds were synthesized according to previously reported procedure (Lebedev et al., 2005).

2.2.3. General procedure for the synthesis of 4-[(3-substituted-1H-pyrazol-3-yl)methyleneamino]-5-substituted-4H-1,2,4-triazole-3-thiols **3a–j**

An equimolar mixture of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol **1a–c** (0.001 mol) and *3*-(4-substitutedphenyl)-1*H*-pyrazole-4-carbaldehyde **2a–e** (0.001 mol) was refluxed in ethanol-dioxane mixture for 7 h in the presence of a catalytic amount of concentrated sulfuric acid. The resulting solution was cooled to room temperature and the precipitated solid was filtered under suction, washed with ethanol and recrystallised from ethanol-dioxane mixture.

2.3. Characterization of synthesized compounds

2.3.1. 5-Ethyl-4-{[(E)-(3-phenyl-1H-pyrazol-4-yl)methylidene]amino}-4H-1,2,4-triazole-3-thiol **3a**

Yield 79%, m.p. 217–219 °C. IR (cm^{-1}): 3094 (N–H), 3035 (Ar–H), 2916 (C–H), 1584 (C═N). ^{1}H NMR (DMSO-d_6) δ = 13.67 (br s, 2H, SH&NH), 9.76 (s, 1H, N═CH), 8.23 (s, 1H, pyrazole-5H), 7.5–7.75 (m, 5H, Ar–H), 2.69 (q, 2H, –CH_2), 1.21 (t, 3H, –CH_3). MS [EI] *m*/*z* 299 [M + 1]. Elemental analysis ($C_{14}H_{14}N_6S$); calcd. C, 56.36; H, 4.73; N, 28.17; found C, 56.29; H, 4.68; N, 28.11%.

2.3.2. 5-Ethyl-4-({(E)-[3-(4-methoxyphenyl)-1H-pyrazol-4-yl]methylidene}amino)-4H-1,2,4-triazole-3-thiol **3b**

Yield 65%, m.p. 227–229 °C. IR (cm^{-1}): 3103 (N–H), 3013 (Ar–H), 2929 (C–H), 1603 (C═N), 1169 (C–O). ^{1}H NMR (DMSO-d_6) δ = 13.66 (br s, 2H, SH&NH), 9.68 (s, 1H, N═CH), 8.26 (s, 1H, pyrazole-5H), 7.67 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.0 (d, 2H, *J* = 8.4 Hz, Ar–H), 3.82 (s, 3H, –OCH_3), 2.67 (q, 2H, –CH_2), 1.21 (t, 3H, –CH_3). MS [EI] *m*/*z* 329 [M + 1]. Elemental analysis ($C_{15}H_{16}N_6OS$); calcd. C, 54.86; H, 4.91; N, 25.59; found C, 54.81; H, 4.88; N, 25.53%.

2.3.3. 5-Ethyl-4-({(E)-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]methylidene}amino)-4H-1,2,4-triazole-3-thiol **3c**

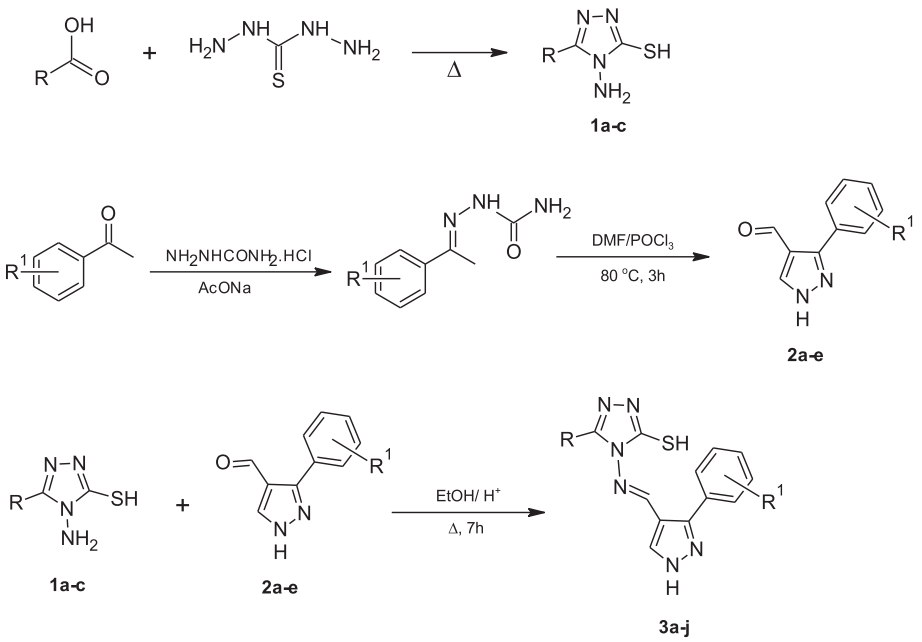
Yield 63%, m.p. 242–244 °C. IR (cm^{-1}): 3109 (N–H), 3054 (Ar–H), 2877 (C–H), 1599 (C═N), 1157 (C–F). ^{1}H NMR (DMSO-d_6) δ = 13.68 (br s, 2H, SH&NH), 9.72 (s, 1H, N═CH), 8.4 (s, 1H, pyrazole-5H), 7.35–7.80 (m, 4H, Ar–H), 2.65 (q, 2H, –CH_2), 1.19 (t, 3H, –CH_3). MS [EI] *m*/*z* 317 [M + 1]. Elemental analysis ($C_{14}H_{13}FN_6S$); calcd. C, 53.15; H, 4.14; N, 26.57; found C, 53.11; H, 4.09; N, 26.52%.

2.3.4. 4-({(E)-[3-(4-Chlorophenyl)-1H-pyrazol-4-yl]methylidene}amino)-5-ethyl-4H-1,2,4-triazole-3-thiol **3d**

Yield 67%, m.p. 248–250 °C. IR (cm^{-1}): 3129 (N–H), 3078 (Ar–H), 2911 (C–H), 1597 (C═N), 831 (C–Cl). ^{1}H NMR (DMSO-d_6) δ = 13.69 (br s, 2H, SH&NH), 9.76 (s, 1H, N═CH), 8.57 (s, 1H, pyrazole-5H), 7.75 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.57 (d, 2H, *J* = 8.4 Hz, Ar–H), 2.65 (q, 2H, –CH_2), 1.19 (t, 3H, –CH_3). MS [EI] *m*/*z* 333 [M + 1]. Elemental analysis ($C_{14}H_{13}ClN_6S$); calcd. C, 50.52; H, 3.94; N, 25.25; found C, 50.47; H, 3.88; N, 25.19%.

2.3.5. 4-({(E)-[3-(2,4-Dichlorophenyl)-1H-pyrazol-4-yl]methylidene}amino)-5-ethyl-4H-1,2,4-triazole-3-thiol **3e**

Yield 64%, m.p. 238–240 °C. IR (cm^{-1}): 3125(N–H), 3051 (Ar–H), 2974 (C–H), 1596 (C═N), 853 (C–Cl). ^{1}H NMR (DMSO-d_6) δ = 13.67 (br s, 2H, SH&NH), 9.74 (s, 1H, N═CH), 8.54 (s, 1H, pyrazole-5H), 8.0 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.56 (d, 1H, *J* = 2.8 Hz, Ar–H), 7.45 (m, 1H, Ar–H). MS [EI] *m*/*z* 366 [M$^+$]. Elemental analysis ($C_{14}H_{12}Cl_2N_6S$); calcd. C, 45.79; H, 3.29; N, 22.88; found C, 45.73; H, 3.22; N, 22.83%.



3a: R=C_2H_5, R^1=H; **3b**: R=C_2H_5, R^1=4-OCH_3; **3c**: R=C_2H_5, R^1=4-F; **3d**: R=C_2H_5, R^1=4-Cl; **3e**: R=C_2H_5, R^1=2,4-Cl_2; **3f**: R=H, R^1=H; **3g**: R=H, R^1=4-OCH_3; **3h**: R=H, R^1=4-F; **3i**: R=H, R^1=4-Cl; 3j: R= C_3H_7, R^1=4-F.

Scheme 1 Synthetic route for the new Schiff bases.

*2.3.6. 4-{[(E)-(3-Phenyl-1H-pyrazol-4-yl)methylidene]-amino}-4H-1,2,4-triazole-3-thiol **3f***

Yield 69%, m.p. 253–255 °C. IR (cm^{-1}): 3138 (N–H), 3014 (Ar–H), 2971 (C–H), 1569 (C=N). ^{1}H NMR (DMSO-d_6) δ = 13.8 (s, 1H, SH), 13.75 (br s, 1H, NH), 9.54 (s, 1H, N=CH), 8.77 (s, 1H, triazole-5H), 8.13 (s, 1H, pyrazole-5H), 7.52–7.75 (m, 5H, Ar–H), 3.82 (s, 3H, –OCH_3). MS [EI] *m*/*z* 271 [M + 1]. Elemental analysis ($C_{12}H_{10}N_6S$); calcd. C, 53.32; H, 3.73; N, 31.09; found C, 53.27; H, 3.68; N, 31.14%.

*2.3.7. 4-({(E)-[3-(4-Methoxyphenyl)-1H-pyrazol-4-yl]methylidene}amino)-4H-1,2,4-triazole-3-thiol **3g***

Yield 66%, m.p. 244–246 °C. IR (cm^{-1}): 3137 (N–H), 3067 (Ar–H), 2935(C–H), 1598 (C=N), 1167 (C–O). ^{1}H NMR (DMSO-d_6) δ = 13.89 (s, 1H, SH), 13.68 (br s, 1H, NH), 9.47 (s, 1H, N=CH), 8.78 (s, 1H, triazole-5H), 8.13 (s, 1H, pyrazole-5H), 7.66 (d, 2H, *J* = 6.8 Hz, Ar–H), 7.09 (d, 2H, *J* = 8.4 Hz, Ar–H), 3.82 (s, 3H, –OCH_3). MS [EI] *m*/*z* 301 [M + 1]. Elemental analysis ($C_{13}H_{12}N_6OS$); calcd. C, 51.99; H, 4.03; N, 27.98; found 51.93; H, 4.06; N, 27.91%.

*2.3.8. 4-({(E)-[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]methylidene}amino)-4H-1,2,4-triazole-3-thiol **3h***

Yield 63%, m.p. 276–278 °C. IR (cm^{-1}): 3139 (N–H), 3072 (Ar–H), 2969 (C–H), 1600 (C=N), 1148 (C–F). ^{1}H NMR (DMSO-d_6) δ = 13.90 (s, 1H, SH), 13.76 (br s, 1H, NH), 9.48 (s, 1H, N=CH), 8.79 (s, 1H, triazole-5H), 8.20 (s, 1H, pyrazole-5H), 7.35–7.83 (m, 4H, Ar–H). MS [EI] *m*/*z* 289 [M + 1]. Elemental analysis ($C_{12}H_9FN_6S$); calcd. C, 49.99; H, 3.15; N, 29.15; found C, 49.94; H, 3.11; N, 29.12%.

*2.3.9. 4-({(E)-[3-(4-Chlorophenyl)-1H-pyrazol-4-yl]methylidene}amino)-4H-1,2,4-triazole-3-thiol **3i***

Yield 76%, m.p. 283–285 °C. IR (cm^{-1}): 3131 (N–H), 3021 (Ar–H), 2964 (C–H), 1599 (C=N), 822 (C–Cl). ^{1}H NMR (DMSO-d_6) δ = 13.91 (s, 1H, SH), 13.76 (br s, 1H, NH), 9.48 (s, 1H, N=CH), 8.52 (s, 1H, triazole-5H), 8.12 (s, 1H, pyrazole-5H), 7.53–-7.81 (m, 4H, Ar–H). MS [EI] *m*/*z* 305 [M + 1]. Elemental analysis ($C_{12}H_9ClN_6S$); calcd. C, 47.29; H, 2.98; N, 27.58; found C, 47.23; H, 2.94; N, 27.52%.

*2.3.10. 4-({(E)-[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]methylidene}amino)-5-propyl-4H-1,2,4-triazole-3-thiol **3j***

Yield 66%, m.p. 225–227 °C. IR (cm^{-1}): 3154 (N–H), 3048 (Ar–H), 2963 (C–H), 1610 (C=N), 1244 (C=S), 1154 (C–F). ^{1}H NMR (DMSO-d_6) δ = 13.71 (br s, 1H, SH&NH), 9.72 (s, 1H, N=CH), 8.37 (s, 1H, pyrazole-5H), 7.33–7.79 (m, 4H, Ar–H), 2.64 (t, 2H, –CH_2), 1.64 (m, 2H, –CH_2), 0.92 (t, 3H, –CH_3). MS [EI] *m*/*z* 331 [M + 1]. Elemental analysis ($C_{15}H_{15}FN_6S$); calcd. C, 54.53; H, 4.58; N, 25.44; found C, 54.48; H, 4.51; N, 25.41%.

2.4. Antimicrobial studies

All the newly synthesized compounds were screened for their antibacterial activity. For this, *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* microorganisms were employed. Anti-microbial study was assessed by Minimum Inhibitory concentration (MIC) by a serial dilution method (Mackie and Cartney, 1989). Several colonies of *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* were picked off

a fresh isolation plate and inoculated in corresponding tubes containing 5 mL of trypticase soya broth. The broth was incubated for 6 h at 37 °C until there was visible growth. Mc Farland No. 5 standard was prepared by adding 0.05 mL of 1% w/v $BaCl_2{\cdot}2H_2O$ in phosphate buffered saline (PBS) to 9.95 mL of 1% v/v H_2SO_4 in PBS. The growth of all the four cultures was adjusted to Mc Farland No. 5 turbidity standard using sterile PBS. This gives a 108 cfu/mL suspension. The working inoculums of the aforementioned four different microorganisms containing 105 cfu/mL suspension was prepared by diluting the 108 cfu/mL suspension, 103 times in trypticase soya broth.

2.4.1. Preparation of anti-microbial suspension (1 mg/mL)
Dissolved 10 mg of each compound in 10 mL of dimethyl formamide to get 1 mg/mL concentration.

2.4.2. Preparation of dilutions
In all, for each of the 10 anti-microbial compounds and standard anti-microbial i.e. Ceftriaxone, 24 tubes of 5 mL capacity were arranged in 4 rows with each row containing 6 tubes. Then 1.9 mL of trypticase soya broth was added in the first tube in each row and then 1 mL in the remaining tubes. Now, 100 mL of anti-microbial suspension dissolved in dimethyl formamide was added to the first tube in each row and then after mixing the content, 1 mL was serially transferred from these tubes to the second tube in each of the rows. Then the contents in the second tube of each of the rows were mixed and transferred to the third tube in each of the rows.

This serial dilution was repeated till the sixth tube in each of the rows. This provided anti-microbial concentrations of 50, 25, 12.5, 6.25, 3.125, 1.6125 mg/mL in the first to sixth tube, respectively, in each row. Finally, 1 mL of 105 cfu/mL *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* suspension was added to the first, second, third and fourth rows of tubes, respectively. Along with the test samples and Ceftriaxone (standard), the inoculums control (without antimicrobial compound) and broth control (without anti-microbial compound and inoculum) were maintained. All the test sample and control tubes were then incubated for 16 h at 37 °C.

2.4.3. Interpretation
After incubation, the tubes showing no visible growth were considered to be representing the MIC. The details of results are furnished in Table 1. Inoculums control showed visible growth, where as broth control showed no growth.

3. Result and discussion

3.1. Chemistry

The route for the synthesis of Schiff bases **3a–j** starting from **1a–c** and **2a–e** is illustrated in Scheme 1. The Schiff bases were synthesized by the condensation of 4-amino-5-substituted-4H-1,2,4-triazole-3-thiol (**1a–c**) with various 3-substituted-pyrazoles-4-carboxaldehydes (**2a–c**) in the presence of concentrated sulfuric acid in ethanol-dioxane mixture. Structures of all synthesized compounds in Scheme 1 were confirmed on the basis of IR, ^{1}H NMR, mass and elemental analyses. The IR spectrum of compound **3a** showed absorption bands at 3094, 3035, 2916, 1584 which were due to N–H, Ar–H, C–H and C═N groups, respectively. The ^{1}H NMR spectrum of **3a** showed broad singlet at δ 13.67 which was due to the presence of S–H and N–H protons. The Schiff base proton i.e. N═CH and pyrazole-5H proton resonated as singlet at δ 9.76 and 8.23, respectively. A quartet at δ 2.69 and a triplet at δ 1.21 confirm the presence of alkyl side chain protons. The mass spectrum of **3a** showed molecular ion peak at m/z = 299 (M + 1), which is in agreement with the molecular formula $C_{14}H_{14}N_6S$. Similarly the spectral values for all the compounds and C, H, N analyses are given in the experimental part. Figs. 1 and 2 represents the IR spectrum and NMR spectrum of compound **3d,** respectively.

3.2. Antibacterial activity

All the newly synthesized compounds were screened for their antibacterial activity. For this, *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* microorganisms were employed. Antimicrobial study was assessed by Minimum Inhibitory concentration (MIC) by serial dilution method. Antimicrobial results

Table 1 Antibacterial data of Schiff bases in MIC.

Comp. No.	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*
3a	3.125	3.125	6.25	1.6125
3b	3.125	3.125	1.6125	3.125
3c	3.125	1.6125	1.6125	1.6125
3d	3.125	3.125	6.25	6.25
3e	12.5	3.125	3.125	6.25
3f	1.6125	1.6125	1.6125	1.6125
3g	12.5	12.5	12.5	Growth in all concentrations
3h	3.125	3.125	12.5	6.25
3i	6.25	12.5	12.5	6.25
3j	12.5	Growth in all concentrations	Growth in all concentrations	6.25
Ceftriaxone (Standard)	3.125	1.6125	1.6125	1.6125
Inoculum control	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
Broth control	No growth	No growth	No growth	No growth

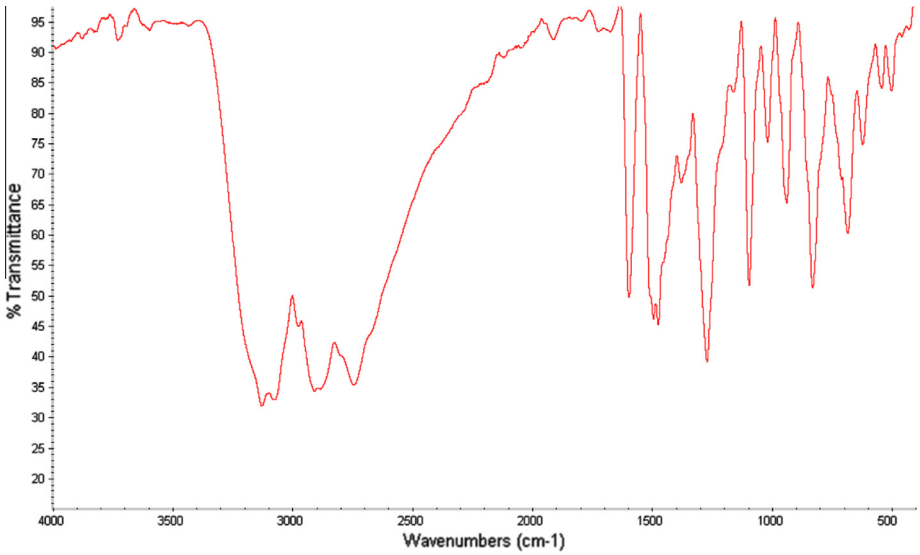


Figure 1 IR spectrum of compound **3d**.

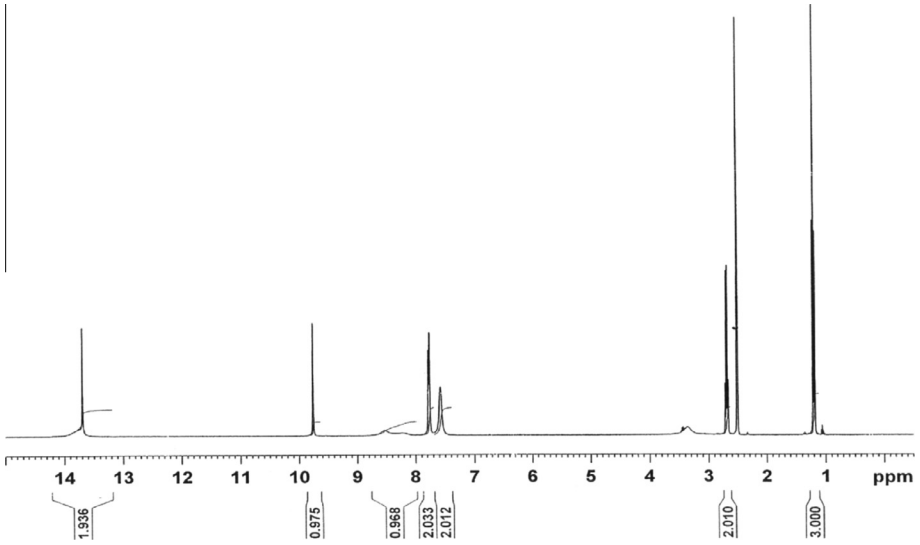


Figure 2 NMR spectrum of compound **3d**.

indicate that, most of the synthesized compounds have shown good to moderate activity against *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* microorganisms. In particular, compound **3f** has exhibited excellent activity against *S. aureus* whereas it has shown activity equal to that of standard drug Ceftriaxone against *B. subtilis, E. coli* and *P. aeruginosa* microorganisms. In the case of compound **3c** the activity was found to be equal to that of standard drug Ceftriaxone for all four microorganisms. Remaining compounds exhibited similar or moderate antibacterial activity than compared to standard.

4. Conclusions

In the present work, a series of new pyrazole based Schiff bases were synthesized and characterized by spectral studies. All the synthesized compounds were evaluated for their antibacterial activities against *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* microorganisms by serial dilution method. Compound **3f** has exhibited excellent activity against *S. aureus* as compared to standard drug Ceftriaxone, whereas similar activity as that of standard against remaining three microorganisms. Also compound **3c** was active at same concentration as that of the standard in case of all four microorganisms.

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