

Synthesis and Antimicrobial Screening of Some Novel Chloroquinolines in DMF and DMSO

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Abstract: A series of novel chloroquinolines; pyrazolines and sulphonamide derivatives were synthesized which have medical interest and high biological activity. For these synthesized compounds, antimicrobial screening was done against some Gram positive and Gram negative bacterial and fungal strains in N, N, dimethylformamide (DMF) and dimethyl sulfoxide (DMSO).

Keywords: Chloro Quinolines, Antibacterial Activity, Antifungal Activity, DMF, DMSO

1. Introduction

Infection diseases such as bacterial and fungal infections have been increasing continuously worldwide [1]. So, the effectiveness of drugs available in the market is somewhat in doubt in future because microorganisms are becoming resistant to more and more antimicrobial agents [2]. It leads to the discovery of new antimicrobial agents.

Various nitrogen containing heterocyclic compounds have been studied extensively for the development of pharmaceutically important antimicrobial agents. These nitrogen containing compounds have played an important role in drug discovery owing to their diverse pharmacological actions.

The compounds containing chloro quinoline ring system have been of great interest to synthetic and medicinal chemists for a long time due to the unique chemical and biological properties imparted by hetero atom because of their utilization as effective biologically active agent like antimalarial, antiviral, insecticidal, analgesic, antitumor etc. [3-7]. Quinoline contains a phenyl ring fused to a pyridine ring. Thus, the important role displayed by quinoline and its derivatives for various therapeutic and biological activities prompted us to synthesize some novel pyrazoline and sulphonamide derivatives.

Pyrazolines are special due to their marked physiological and pharmacological activity. These derivatives were

reported to possess wide spectrum of biological activities such as insecticidal [8], analgesic [9], anticancer [10], antibacterial and antifungal [11], antiamebic [12], anti-TB [13], anti-inflammatory [14], antidepressant and anticonvulsant [15] etc.

The discovery of sulphonamides marked the beginning of chemotherapeutic era by making possible a direct attack on microbial infections [16]. Sulfonamides were intensively investigated as the first effective antibacterial agents. Sulphonamides are continued to be used antibacterial because they are effective, inexpensive and free of infection problems of the broad spectrum antibiotics [17]. Literature survey shows that various substituted sulphonamides possess anti convulsant [18], anticancer [19], cytotoxic [20], antimicrobial [21, 22], antitumor [23], antimalarial [24] activities. Further, various other biological properties have also been studied [25-30].

Thus, due to wide spectrum of biological activities of various compounds having chloro quinoline moiety, in continuation of our previous work [31], some new derivatives such as pyrazolines and sulphonamides are designed as potential compounds.

2. Experimental

Synthesis of pyrazoline derivatives

Synthesis of 2-chloro-3-[3-(4-methoxyphenyl)-4, 5-dihydro-1H-pyrazol-5-yl] benzo[h] quinoline

Synthesis of N-(naphthalen-1-yl) acetamide- A mixture of 1-naphthyl amine (0.01M) and acetic anhydride (0.01M) in methanol (LR) (20 ml) was refluxed in water bath for 2-3 hrs using CH_3COOH as catalyst. The crude product was isolated and crystallized from methanol.

Synthesis of 2-chloro benzo[h]quinoline-3-carbaldehyde- N-(naphthalen-1-yl) acetamide (0.01M) was added in a mixture of Vilsmeier-Haack reagent (prepared by drop wise addition of 6.5 ml POCl_3 in ice cooled 2 ml DMF) and refluxed for 27 hrs. The reaction mixture was poured into ice and kept for overnight followed by neutralization using sodium bicarbonate. The crude product was isolated and crystallized from methanol.

Synthesis of 3-(2-chlorobenzo[h]quinolin-3-yl)-1-(4-methoxy-Phenyl) prop-2-en-1-one- To a well stirred solution of 2-chloro benzo[h]quinoline-3-carbaldehyde (0.01M) and p-methoxy-acetophenone (0.01M) in the binary mixture of ethanol (25 ml): DMF (5 ml), 40% NaOH was added till the solution became basic. The reaction mixture was stirred for 48 hrs. The contents were poured into ice, acidified, filtered and crystallized from methanol.

Synthesis of 2-chloro-3-[3-(4-methoxyphenyl)-4, 5-dihydro-1H-pyrazol-5-yl] benzo[h] quinoline (SP-1)-A mixture of 3-(2-chlorobenzo[h]quinolin-3-yl)-1-(4-methoxy-phenyl) prop -2-en-1-one (0.01 M) and hydrazine hydrate (0.012 M) in ethanol (20 ml) was refluxed on a water bath for 6 hrs. The product was isolated and recrystallized from DMF.

Similarly, other derivatives have been prepared.

Synthesis of sulphonamide derivatives

Synthesis of N'-[(2-chlorobenzo[h]quinolin-3-yl)methylidene] -4-methyl benzenesulfonyl hydrazide- Synthesis of N-(naphthalen-1-yl) acetamide and 2-chloro benzo[h]quinoline-3-carbaldehyde are same as above.

Synthesis of 2-chloro-3-[hydrazinylidenemethyl] benzo[h] quinoline- A mixture of 2-chloro benzo[h]quinoline-3-carbaldehyde (0.012 M) in ethanol and hydrazine hydrate (0.01M) was refluxed for 2 hrs. The contents were poured in crushed ice and neutralized excess hydrazine hydrate with hydrochloric acid. The product was crystallized from DMF.

Preparation of 4-methyl benzene sulfonyl chloride- It was prepared by the condensation of p- methyl benzoic acid (0.01M) with chloro sulphonic acid (0.01M) by refluxing it in water bath for 6 hours. The content was isolated and crystallized using ethanol.

Similarly, other aryl sulphonyl chlorides were prepared.

Synthesis of N'-[(2-chlorobenzo[h]quinolin-3-yl)methylidene] -4-methyl benzene sulfonyl hydrazide (SS-1)- A mixture of 4-methyl benzene sulfonyl chloride (0.01M) and 2-chloro- 3-[hydrazinylidenemethyl] benzo[h]quinoline (0.01M) in dry pyridine (10 ml) was refluxed on a water bath for 5-6 hrs. The contents were poured into crushed ice and neutralized. The product was crystallized from DMF.

Similarly, other sulphonamide derivatives have been prepared.

The reaction scheme for both pyrazoline and sulphonamide compounds are given in Fig. 1 [A] and 1 [B] respectively. The physical data of all the compounds are given in Table 1.

Table 1. Physical constants of [A] pyrazolines and [B] Sulphonamide derivatives.

[A]

Sr. No	Code	R	M.F.	M.Wt (g/mol)	R _f Value	M.P.°C	Yield %
1	SP-1	4-OCH ₃ -C ₆ H ₄ -	C ₂₃ H ₁₈ ClN ₃ O	387.8	0.51	185	51
2	SP-2	4-CH ₃ -C ₆ H ₄ -	C ₂₃ H ₁₈ ClN ₃	371.8	0.64	189	64
3	SP-3	4-Br-C ₆ H ₄ -	C ₂₂ H ₁₅ BrClN ₃ O	436.7	0.63	208	60
4	SP-4	4-NH ₂ -C ₆ H ₄ -	C ₂₂ H ₁₇ ClN ₄	372.8	0.65	195	55
5	SP-5	4-NO ₂ -C ₆ H ₄ -	C ₂₂ H ₁₅ ClN ₄ O ₂	402.7	0.70	210	61
6	SP-6	3-OH-C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃ O	373.8	0.48	202	64
7	SP-7	4-Cl-C ₆ H ₄ -	C ₂₂ H ₁₅ Cl ₂ N ₃	392.2	0.53	198	58
8	SP-8	3-NO ₂ -C ₆ H ₄ -	C ₂₂ H ₁₅ ClN ₄ O ₂	402.2	0.60	212	55
9	SP-9	4-OH-C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃ O	373.8	0.73	202	50
10	SP-10	H-C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃	357.8	0.55	225	57

[B]

Sr. No	Code	R	M.F.	M.Wt (g/mol)	R _f Value	M.P.°C	Yield %
1	SS-1	4-OCH ₃ -C ₆ H ₄ -	C ₂₁ H ₁₆ ClN ₃ O ₂ S	410.8	0.24	208	61
2	SS-2	3-COOH,6-CH ₃ -C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃ O ₄ S	453.8	0.48	244	60
3	SS-3	3-COOH,4-CH ₃ -C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃ O ₄ S	453.6	0.50	210	49
4	SS-4	2-COOH,4-CH ₃ -C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃ O ₄ S	453.8	0.64	218	55
5	SS-5	3-COOH,6-OCH ₃ -C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃ O ₅ S	469.8	0.49	221	51
6	SS-6	3-COOH,4-OCH ₃ -C ₆ H ₄ -	C ₂₂ H ₁₆ ClN ₃ O ₅ S	469.8	0.55	215	62
7	SS-7	3-COOH,6-Cl-C ₆ H ₄ -	C ₂₁ H ₁₃ Cl ₂ N ₃ O ₄ S	474.3	0.58	211	44
8	SS-8	3-COOH,4-Cl-C ₆ H ₄ -	C ₂₁ H ₁₃ Cl ₂ N ₃ O ₄ S	474.3	0.60	219	52
9	SS-9	3-COOH,-C ₆ H ₄ -	C ₂₁ H ₁₄ ClN ₃ O ₄ S	439.8	0.58	202	59
10	SS-10	4-NHCOCH ₃ -C ₆ H ₄ -	C ₂₂ H ₁₇ ClN ₄ O ₃ S	452.9	0.49	225	58

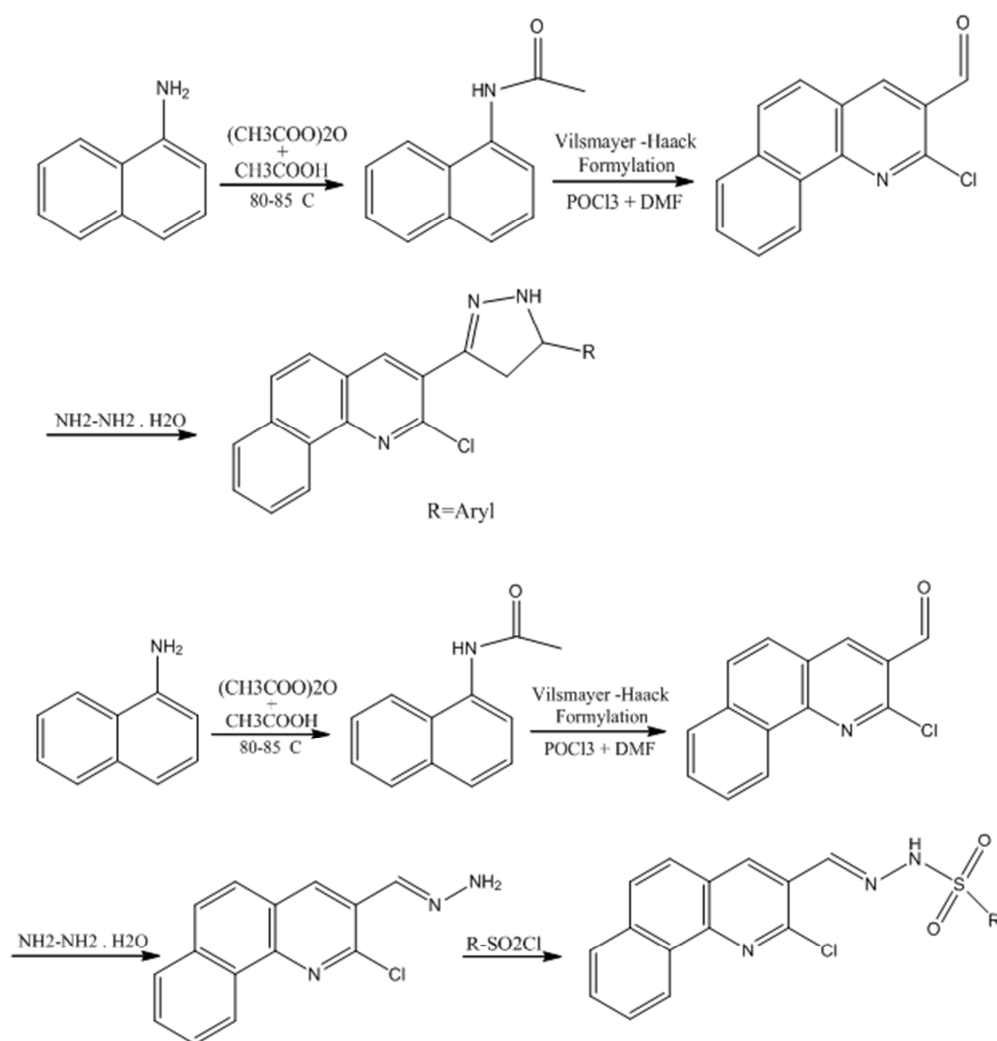


Figure 1. Reaction Scheme for the synthesis of [A] pyrazoline and [B] sulphonamide derivatives.

Characterization of synthesized compounds

The structures of all the synthesized compounds were confirmed by IR, ^1H NMR and mass spectral data. IR spectra were recorded on IR affinity 1S (fourier transform infra-red spectroscopy). ^1H NMR spectra were taken on a Bruker AVANCE II 400. In all the cases, ^1H NMR spectra were obtained in DMSO-d_6 using TMS as an internal standard. The NMR signals are reported in δ ppm.

Antimicrobial activities

The antibacterial and antifungal activities of all synthesized compounds were studied in DMSO and DMF, which were purified by standard procedure [32]. All the synthesized compounds were recrystallized prior to use. For all the compounds, agar well diffusion method was used.

Test Microorganisms

The synthesized compounds were tested against Gram positive bacteria viz. *Staphylococcus aureus* ATCC 25923, *Bacillus megaterium* ATCC9885, Gram negative bacteria viz. *Klebsiella pneumoniae* NCIM2719 and *Proteus mirabilis* NCIM2241 and for antifungal activity *Candida tropicalis* ATCC4563 was used.

All the strains were obtained from National Chemical

Laboratory (NCL), Pune, India and were maintained at 4°C on nutrient agar slants (for bacteria) and MGYD slant (For fungi).

Preparation of test compounds

The solutions were prepared at a concentration of 20 mg/ml for all the compounds.

Preparation of the plates and microbiological assay- The antibacterial evaluation was done by agar well diffusion method [33] using Mueller Hinton agar No. 2 (for bacteria) and Sabouraud dextrose agar (for fungi) as the nutrient medium. The agar well diffusion method was preferred to be used in this study because it was found to be better than the disc diffusion method as suggested by Parekh et al. [34] The bacterial strains were activated by inoculating a loop full of test strain in 25 ml of N-broth and the same was incubated for 24 h in an incubator at 37°C . 0.2 ml of the activated strain was inoculated in molten agar. Mueller Hinton Agar kept at 45°C was then poured in the Petri dishes and allowed to solidify. After solidification of the media, 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the test solution (2mg/ml). The plates were incubated for 24 h at 37°C . The mean value obtained

for the three wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain and each solvent. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of these synthesized compounds.

3. Results and Discussion

Spectral Data

SP-1

IR (KBr): 3037 (Ar, C-H str.), 2953 (C-H str.), 1564 (Ar, C=C str.), 1593 (C=N str.), 1458 (C-H ben.), 1307 (C-N), 1247 (C-O-C str.), 1003 (C-O-C str.), 843 (N-O), 736 (C-Cl) cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ ppm 3.82 (s, OCH_3), 3.41 (dd, $J = 7.2$ Hz, Pyr-H), 4.15 (dd, $J = 7.2$ Hz, Pyr-H), 6.96-6.99 (d, 1H, $J = 8.52$ Hz, Ar-H), 7.29-7.60 (m, 1H, Ar-H), 7.86 (s, 1H, -Ar-H), 9.65 (d, 1H, Ar-H). MS: $m/z = 388$.

SS-1

IR (KBr): 3474 (N-H str.), 3059 (Ar, C-H str.), 2958 (C-H str.), 1512 (Ar, C=C str.), 1599 (C=N str.), 1445 (C-H ben.), 1362 (S=O str.), 1260 (C-N str.), 831 (N- SO_3), 725 (C-Cl) cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ ppm 3.79 (s, $-\text{CH}_3$), 7.00 (s, N-H), 7.18-7.19 (d, 1H, $J = 8.52$ Hz, Ar-H), 7.29 (m, 1H, Ar-H), 7.54 -7.71 (m, $J = 7.60$ Hz, -Ar-H), 7.90 (s, N=CH). MS: $m/z = 411$.

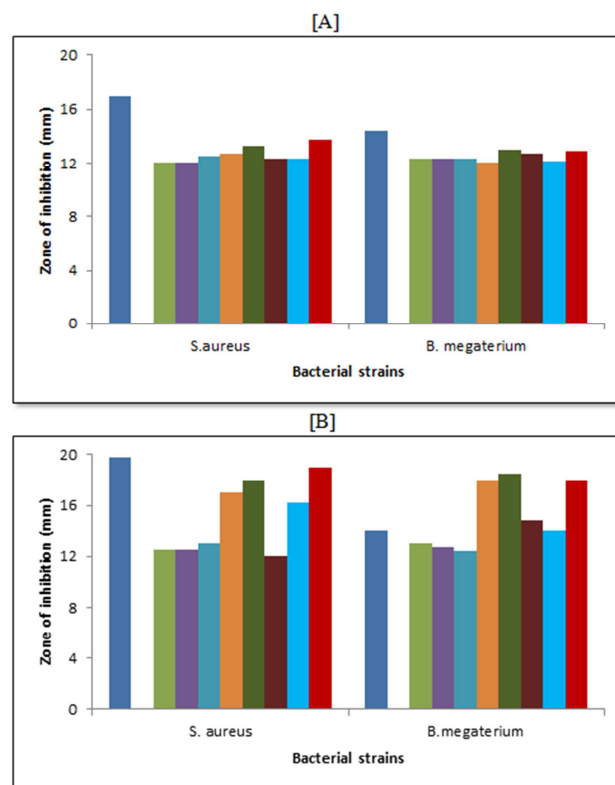
Antimicrobial activity

Pyrazolines- Figure 2 shows inhibition against Gram positive bacteria in DMSO and DMF. Against both the strains *S. aureus* and *B. megaterium*, SP-1 showed maximum inhibition in DMSO. Minimum is observed for SP-3 and SP-4 for *S. aureus* whereas *B. megaterium*, SP-9 showed minimum. SP-2 could not affect for both the strains.

The inhibition depends upon three S: strain, solvent and structure. All the compounds have the same central moiety but different side chains. So, presence of different side chain affects inhibition in the studied compounds. Thus, in DMSO, p-methoxy group is most effective for the studied bacteria.

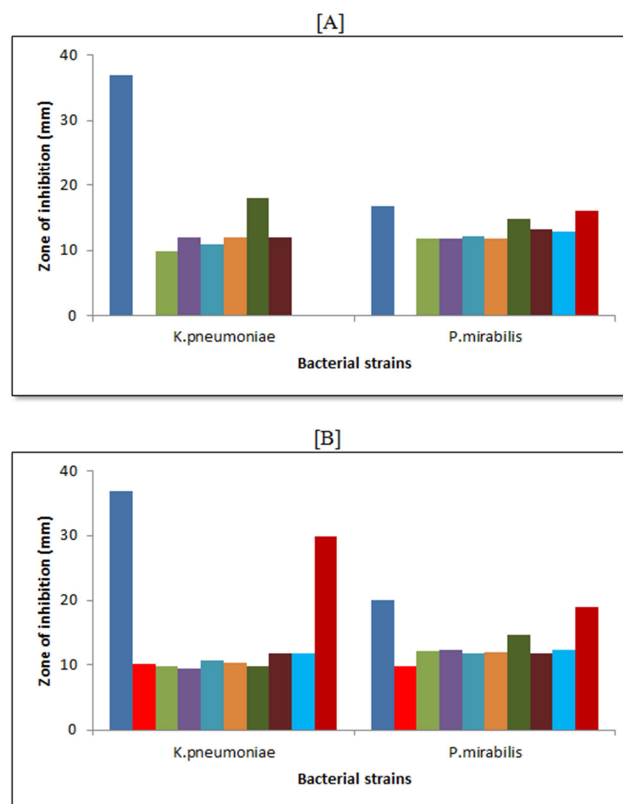
In DMF, compound SP-1 and SP-10 showed equally maximum inhibition for *S. aureus*, whereas SP-8 shows minimum inhibition. Against *B. megaterium*, SP-1 and SP-7 shows equally maximum inhibition, whereas SP-5 and SP-9 shows equally minimum inhibition. For both bacterial strains, SP-2 shows no inhibition at all. Thus, in DMF also, methoxy group is most effective for the studied bacteria. Further, DMF is better solvents for the studied compounds against these two Gram positive bacteria.

The zones of inhibition against Gram negative bacteria in DMSO and DMF are shown in Figure 3 for the studied compounds. Again, inhibition is maximum for SP-1 for both the strains in both the solvents. In DMSO, against *K. pneumoniae*, SP-2, SP-9 and SP-10 and for *P. mirabilis*, SP-2, showed no inhibition at all. In DMF, all the studied compounds showed inhibition. For both Gram negative bacteria, inhibition is maximum for SP-1 which is followed by SP-10. Thus, for Gram negative bacteria also, p-methoxy group is most effective in both the solvents.



■:SP-1, ■:SP-2, ■:SP-3, ■:SP-4, ■:SP-5, ■:SP-6, ■:SP-7, ■:SP-8, ■:SP-9, ■:SP-10.

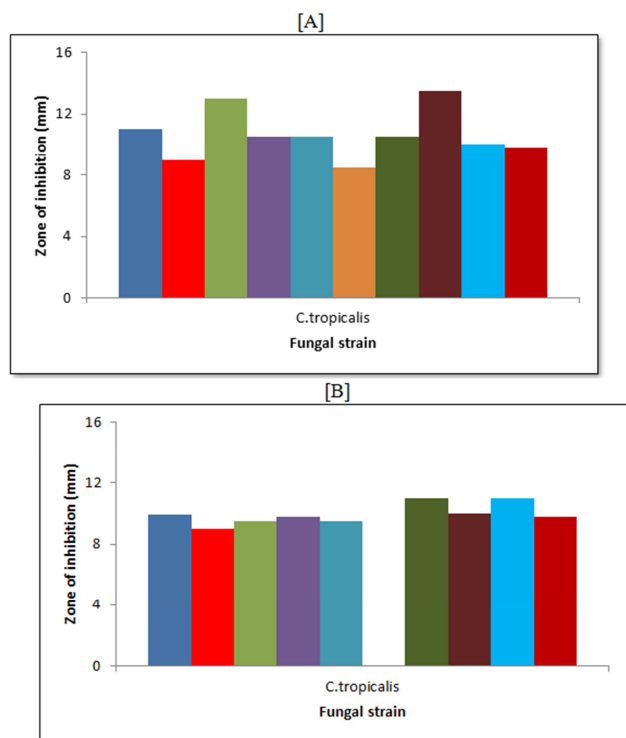
Figure 2. Antibacterial activity of pyrazolines against Gram positive bacteria in [A] DMSO and [B] DMF.



■:SP-1, ■:SP-2, ■:SP-3, ■:SP-4, ■:SP-5, ■:SP-6, ■:SP-7, ■:SP-8, ■:SP-9, ■:SP-10.

Figure 3. Antibacterial activity of pyrazolines against Gram negative bacteria in [A] DMSO and [B] DMF.

Figure 4 shows zone of inhibition against a fungal strain *C. tropicalis* in DMSO and DMF. In DMSO, all the studied compounds exhibited inhibition whereas in DMF SP -6 had no effect at all. In DMSO, SP -8 is most effective which contains m-nitro group. In DMF, SP -7 and SP -9 are equally most effective, which contain p-chloro and p-hydroxy groups respectively. The inhibition is more in DMSO than in DMF.



■:SP-1, ■:SP-2, ■:SP-3, ■:SP-4, ■:SP-5, ■:SP-6, ■:SP-7, ■:SP-8, ■:SP-9, ■:SP-10.

Figure 4. Antifungal activity of pyrazolines in [A] DMSO and [B] DMF.

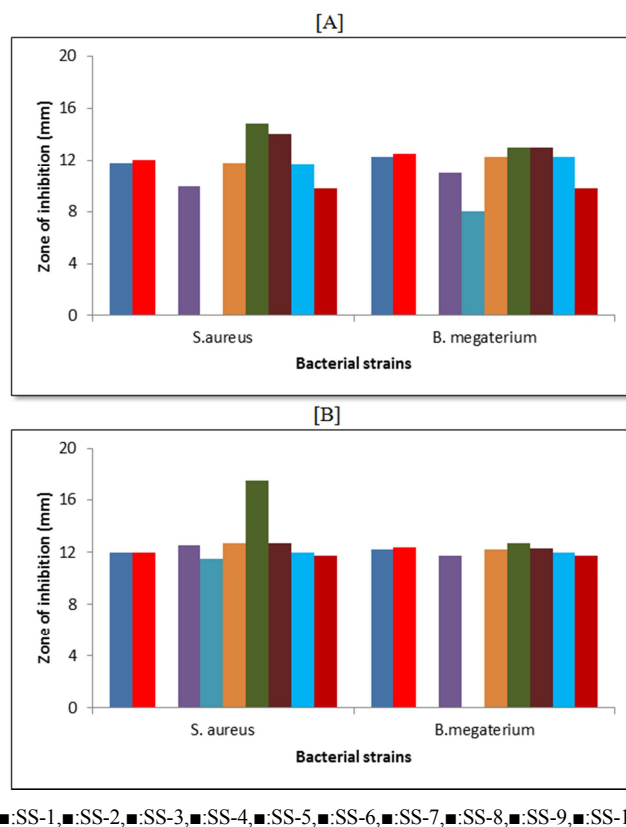
Thus, both solvent and substitution plays an important role in inhibiting any strain.

Sulphonamides-

The inhibition against Gram positive bacteria is shown in Figure 5 for both DMSO and DMF.

It is observed that against both the strains in both the solvents SS-3 exhibited no inhibition. In DMSO, for *S. aureus*, VSM-7 showed maximum inhibition and SS -10 showed minimum inhibition. SS -3 and SS -5 showed no inhibition at all. For *B. megaterium*, both SS -7 and SS -8 showed maximum inhibition whereas SS -5 exhibited minimum inhibition. Thus, in DMSO, SS -7 is the most effective compound for the studied bacteria. It contains chloro group at 6th position and carboxylic group at 3rd position.

In DMF also, SS-7 exhibited maximum inhibition for both the studied Gram positive bacteria. The inhibition depends on the solvent, substitution of compound structure and bacterial strain. SS-3, SS-5, SS-7 and SS-10 contain 3- carboxylic-4-chloro, 3-carboxylic-4-methoxy, 3-carboxylic-6-chloro and acetamide as a substituent respectively. Thus, the presence of 3-carboxylic-6-chloro increases the inhibition in the studied solvents against studied strains.



■:SS-1, ■:SS-2, ■:SS-3, ■:SS-4, ■:SS-5, ■:SS-6, ■:SS-7, ■:SS-8, ■:SS-9, ■:SS-10.

Figure 5. Antibacterial activity of sulphonamides against Gram positive bacteria in [A] DMSO and [B] DMF.

Figure 6 shows zone of inhibition against Gram negative bacteria in DMSO and DMF. Against *K. pneumoniae*, again the inhibition is maximum for SS-7 and minimum for SS-4 in DMSO. SS-3 and SS-5 showed no inhibition at all. For *P. mirabilis*, all the studied compounds are found to be effective in DMSO, among which SS-8 showed maximum inhibition. Thus, for Gram negative bacteria, 3-carboxylic-6-chloro (in SS-7) and 3-carboxylic- 4-chloro (in SS-8) are most effective in inhibiting *K. pneumoniae* and *P. mirabilis* respectively in DMSO.

In DMF, against *K. pneumoniae*, SS-5 showed maximum activity, whereas SS-1, SS-2, SS-3 and SS-4 showed no inhibition at all. For *P. mirabilis*, SS-2 showed maximum inhibition, whereas SS-3 shows no inhibition at all. Thus, in DMF, 3-carboxylic-6-methoxy (in SS-5) and 3- carboxylic-6-methyl (in SS-2) are most effective in inhibiting *K. pneumoniae* and *P. mirabilis* respectively.

Comparison of inhibition in both the solvents shows that DMF is better solvent for the studied Gram negative bacteria.

Figure 7 shows the zone of inhibition against a fungal strain in DMSO and DMF. In both the solvents, all the studied compounds exhibited inhibition against this fungal strain. However, inhibition is more in DMSO than in DMF.

In DMSO, SS-1, SS-2, SS-5 and SS-7 exhibited maximum inhibition whereas in DMF, SS-2, SS-7, SS-8 and SS-9 showed maximum inhibition.

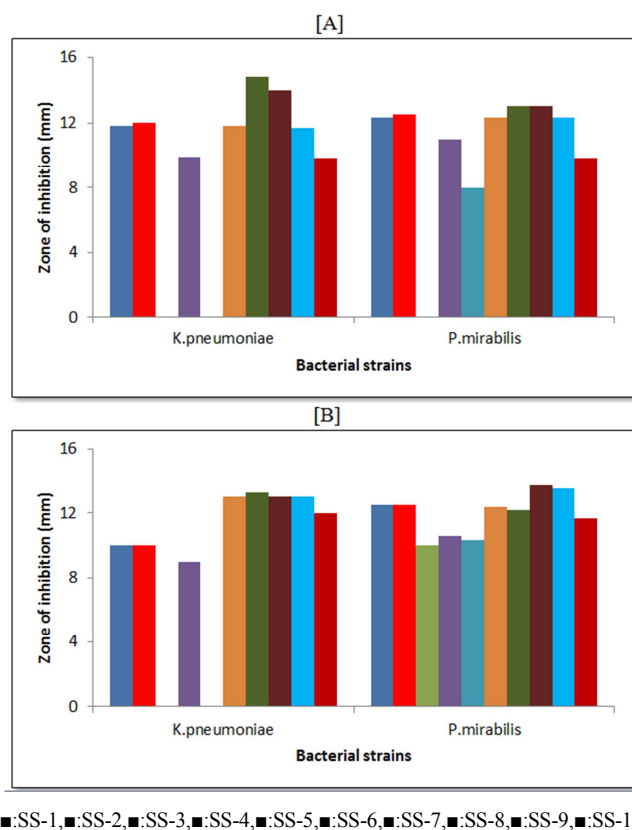


Figure 6. Antibacterial activity of sulphonamides against Gram negative bacteria in [A] DMSO and [B] DMF.

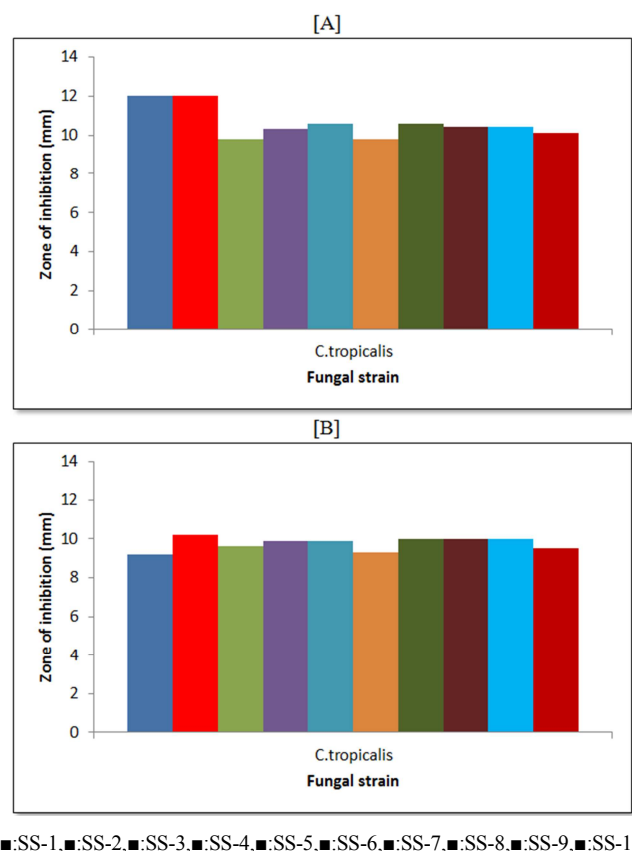


Figure 7. Anti fungal activity of sulphonamides in [A] DMSO and [B] DMF.

Thus, it is concluded that most of the studied compounds are effective for this fungal strain *C. tropicalis* and DMSO is better solvent for this strain.

4. Conclusion

The inhibition depends upon three S: strain, solvent and structure. In the studied two classes of compounds, substitution effect is different in different solvents for different strains.

In pyrazoline compounds, DMF is good solvent for Gram positive and Gram negative bacteria and methoxy group is most effective. However, against fungal strain, m-nitro group containing compound exhibited more inhibition in DMSO whereas in DMF, p-chloro and p-hydroxy groups are most effective.

In sulphonamide compounds also, DMF is good solvent for Gram positive and Gram negative bacteria but chloro group is most effective. For fungal strain, DMSO is good solvent.

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