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Review Article

BIOLOGICAL ACTIVITIES OF SOME NOVEL QUINOLINE DERIVATIVES

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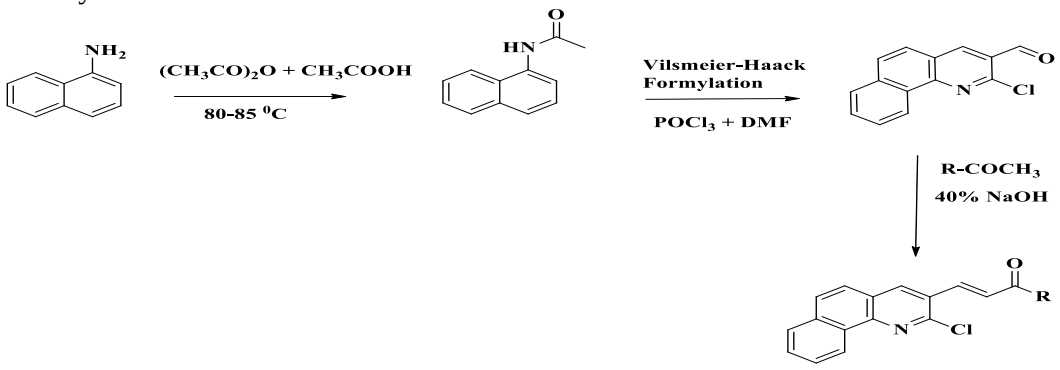
ABSTRACT
Some novel derivatives of quinoline have been synthesized and their structures were confirmed by IR ^{1}H NMR, and Mass spectral data. All these synthesized compounds were tested *in vitro* for their biological activity in N, N-dimethyl formamide and dimethylsulfoxide against Gram positive and Gram negative bacterial strains as well as fungal strains.

Keywords: *Cyanopyridines, Amino Pyrimidines, Benzodiazepines, Agar-well Diffusion Method, N, N-dimethyl Formamide, Dimethylsulfoxide*

INTRODUCTION
Quinolines are heterocyclic aromatic organic compounds containing nitrogen. These heterocycles has been of considerable interest because a large number of natural products and drugs contain this heterocyclic unit (Bouraiou *et al.*, 2006). Further, these compounds are used as building blocks of various other compounds (Datta *et al.*, 2002) such as chalcones, pyrazolines, cyanopyridines, isoxazoles, sulphonamides, arylamides, thiopyrimidines, amino pyarimidines etc. Literature survey shows that these compounds are known to possess biological activities such as anti bacterial, anti cancer, anti inflammatory, antifungal etc by (Khan *et al.*, 1998).
Owing to these interesting applications of quinoline heterocycles, in the present study, some novel quinoline derivatives such as cyanopyridines, amino pyrimidines, benzodiazepines have been synthesized. The screening of antimicrobial activity of these synthesized compounds was done *in vitro* against some Gram positive and Gram negative strains of bacteria as well as fungal strains in N, N-dimethyl formamide and dimethylsulfoxide.

MATERIALS AND METHODS
Synthesis of Chalcones
Synthesis of N-(naphthalen-1-yl) acetamide: Equimolar mixture of 1-naphthyl amine and acetic anhydride in methanol was refluxed for 2-3 hrs using acetic acid as catalyst. The crude product was isolated and crystallized from absolute ethanol.



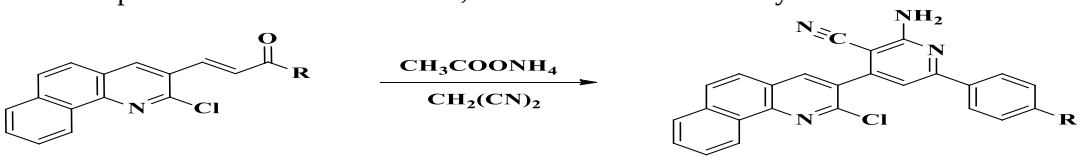
Synthesis of 2-chloro benzo(h)quinoline-3-carbaldehyde: The above synthesized N-(naphthalen-1-yl) acetamide was added in a mixture of Vilsmeier-Haack reagent (prepared by drop wise addition of $POCl_3$ in ice cooled DMF) and the mixture was refluxed for 27 hrs. The reaction mixture was poured into ice and

was kept overnight followed by neutralization using sodium bicarbonate. The crude product was isolated and crystallized from ethanol.

Synthesis of Chalcones: Equimolar 2-chloro benzo(h)quinoline-3-carbaldehyde and substituted acetophenone were dissolved in binary mixture of ethanol and DMF and stirred. To this solution, 40% sodium hydroxide was added till the solution became basic. The reaction mixture was again stirred for 48 hrs. The contents were poured into ice, acidified, filtered and crystallized from ethanol.

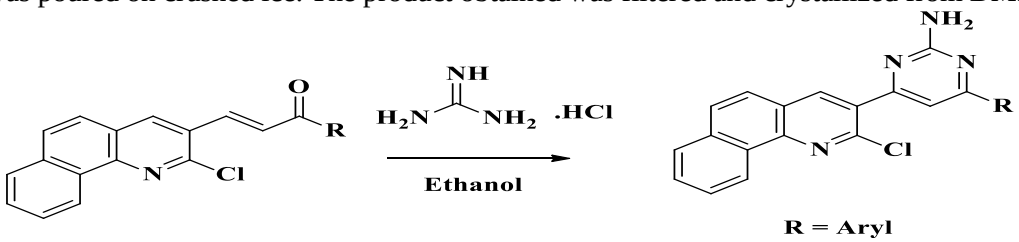
Different chalcones were synthesized using different substituted acetophenones. These chalcones are then used for the synthesis of different cyanopyridines, aminopyridines and benzodiazepines, which are given as follows:

Synthesis of Cyanopyrimidines (CP-1 to CP-10): A mixture of above synthesized chalcone, malononitrile and ammonium acetate in ethanol was refluxed for 10-12 hrs. The content was poured on crushed ice. The product obtained was filtered, washed with water and crystallized from DMF.



R = Aryl

Synthesis of aminopyrimidines (JRM-1-JRM-10): Equimolar mixture of chalcones and guanidine hydrochloride was refluxed in ethanol for 8-10 hours in presence of potassium hydroxide. The resulting mixture was poured on crushed ice. The product obtained was filtered and crystallized from DMF.



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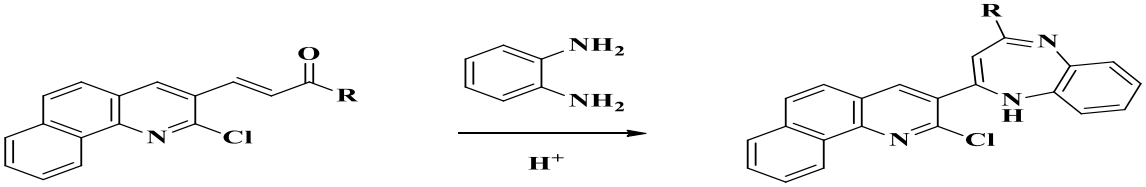
Synthesis of 1, 5-benzodiazepines (MRV-1-MRV-10): Above synthesized chalcone and o-phenylenediamine were dissolved in binary mixture of ethanol and DMF in equimolar amount. To this solution 3-4 drops of glacial acetic acid was added and the solution was refluxed for 8-10 hrs. The resulting mixture was poured on crushed ice. The product obtained was filtered and crystallized from ethanol.



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The structure of all these synthesized compounds was confirmed by IR, NMR and mass spectral data.

Microorganisms Tested: The antibacterial and antifungal activities of all synthesized compounds were studied in DMSO and DMF, which were purified by standard procedure. All the synthesized compounds were recrystallized prior to use. For all the compounds, agar well diffusion method 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 MGYP slant (For fungi). The solutions were prepared at a concentration of 20 mg/ml for all the compounds.

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.

Preparation of the plates and microbiological assay: The antibacterial evaluation was done by agar well diffusion method (Perez *et al.*, 1990) using Mueller Hinton agar No. 2 (for bacteria) and Sabroad 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.*, (2005). 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 37o C. 0.2 ml of the activated strain was inoculated in molten agar. Mueller Hinton Agar kept at 45oC 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 37oC. 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.

RESULTS AND DISCUSSION

The physical properties of synthesized compounds are given in Tables 1, 2 and 3.

Antimicrobial Activity

Cyanopyridines

Figure 1 shows zone of inhibition for synthesized cyanopyridine compounds against Gram positive bacteria in both DMSO and DMF. For both Gram positive bacteria, CP-6 exhibited maximum inhibition in both the solvents. Against S. aureus, in DMSO CP-5 and CP-7 and in DMF, CP-7 showed no inhibition at all. For B. megaterium, only CP-1, CP-2, CP-3, CP-4 and CP-6 exhibited inhibition in DMSO. Other compounds had no effect at all. In DMF, except CP-7 all compounds showed inhibition against B. megaterium.

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. CP-6 contains m-hydroxy group which is most effective in comparison to other groups.

Comparison of inhibition in both the solvents shows that inhibition is more in DMF than in DMSO. So, for Gram positive bacteria, DMF is good solvent. In DMSO B. megaterium is most resistant bacteria.

Figure 2 shows zone of inhibition against Gram negative bacteria in DMSO and DMF for the studied compounds. Again, inhibition is maximum for CP-6 in both the solvents against K. pneumoniae and P. mirabilis. In DMSO, CP-7 showed no inhibition against K. pneumoniae and P. mirabilis. However, in DMF CP-7 and CP-8 for K. pneumoniae and CP-5 against P. mirabilis exhibited no inhibition.

Thus, for Gram negative bacteria also, m-hydroxy substitution is most effective in both the solvents. Whereas, p-nitro (as in CP-5), p-chloro (as in CP-7) and m-nitro (as in CP-8) had no effect on studied Gram negative bacteria.

Further, for Gram negative bacteria, inhibition is more in DMSO than in DMF. So, DMSO is better solvent for the studied Gram negative bacteria.

Figure 3 shows zone of inhibition against fungal strain *C. tropicalis*. In DMSO, CP-2 and in DMF, CP-6 exhibited more inhibition. CP-7 had no effect in DMSO whereas in DMF both CP-5 and CP-7 showed no effect at all. Comparison of Figure 3(A) and Figure 3(B) shows that in DMF, maximum compounds exhibited inhibition as compared to DMSO. So, DMF is good solvent.

Aminopyrimidines

Figure 4 shows zone of inhibition for synthesized aminopyridine compounds against Gram positive bacteria in both DMSO and DMF. It is observed that in DMSO, against both *S. aureus* and *B. megaterium*, JRM-1, JRM-5 and JRM-6 had no effect at all whereas in DMF, except JRM-1, all the compounds showed inhibition. In both DMSO and DMF, JRM-9 showed maximum inhibition. This compound contains p-hydroxy group, which is found to be most effective in both DMSO and DMF for these Gram positive bacteria. Overall, DMF is good solvent for the studied Gram positive bacteria.

The zone of inhibition against Gram negative bacteria is shown in Figure 4 for both DMSO and DMF. In DMSO, against K. Pneumoniae, JRM-1, JRM-5 and JRM-6 showed no activity and JRM-9 exhibited maximum inhibition. For P. mirabilis, further JRM-1 failed, whereas JRM-9 shows maximum inhibition. Thus, the presence of p-hydroxy (as in JRM-9) increases the inhibition against both the Gram negative bacterial strains in DMSO. In DMF, most of the compounds exhibit inhibition. Against K. Pneumoniae, JRM-1 and JRM-4 showed no inhibition and maximum is observed for JRM-2. Whereas against P. mirabilis all compounds showed inhibition and JRM-5 showed maximum inhibition. Thus, p-methyl group is most effective against K. Pneumoniae whereas p-hydroxy causes maximum inhibition against P. mirabilis. Figure 6 shows zone of inhibition against C. tropicalis fungi in DMSO and DMF. Again, in DMSO, JRM-9 is most effective whereas JRM-6 showed minimum inhibition. JRM-1 exhibited no effect at all. In DMF, JRM-5 is most effective, whereas JRM-1 and JRM-6 showed equally minimum inhibition. Further, all the compounds showed inhibition in DMF. Thus, against the studied fungal strain, in DMSO, p-hydroxy (as in JRM-9) is most effective group whereas p-methoxy (as in JRM-1) is not effective at all. In DMF, p-nitro is highly effective.

Thus, in this series of compounds, against both Gram positive and Gram negative bacterial and fungal strain, DMF is found to be good solvent.

1, 5 benzodiazepines

Figure 7 shows the inhibition against Gram positive bacteria in DMSO and DMF. It is observed that against both *S. aureus* and *B. megaterium*, all the compounds except MRV-8 exhibited inhibition in both the solvents. In DMSO, MRV-2 showed maximum inhibition and MRV-3 showed minimum inhibition against both Gram positive bacteria. In DMF also, against S. aureus, MRV-2 shows maximum inhibition whereas MRV-3 had minimum inhibition. Against, *B. megaterium*, MRV-6 exhibited maximum inhibition whereas MRV-9 showed minimum inhibition. Thus, in DMSO p-methyl group (as in MRV-2) is most effective whereas p-bromo group (as in MRV-3) is least effective for both studied bacterial strains. In DMF, for S. aureus, p-methyl group (in MRV-2) is most effective whereas p-bromo group (in MRV-3) is least effective but against *B. megaterium*, m-hydroxy is found to be more effective because MRV-6 exhibited maximum inhibition. MRV-8 contains m-nitro group which is not effective at all for the studied Gram positive bacteria in both the solvents. For these Gram positive bacteria, DMF is good solvent. Figure 8 shows zone of inhibition against Gram negative bacteria in DMSO and DMF for the studied compounds. For K. pneumoniae, all the studied compounds showed inhibition in DMSO, among which activity is maximum for MRV-1(containing p-methoxy group) and minimum for MRV-3 (containing p-bromo group). For P. mirabilis, MRV-2 exhibited maximum inhibition whereas MRV-3 and MRV-7 showed equally lowest inhibition. MRV-7 shows no inhibition at all. Thus, in DMSO, p-methoxy and p-methyl groups are effective for K. pneumoniae and P. mirabilis respectively. In DMF, MRV-6 showed maximum activity against K. pneumoniae, where as MRV-1 and MRV-3 exhibited no inhibition. For P. mirabilis, all compounds showed inhibition. Among them, MRV-6 and MRV-2 showed maximum inhibition whereas MRV-8 exhibited minimum inhibition.

Table I: Physical properties of cyanopyridines (CP-1 to CP-10)

Compound Code	Substitution R	M.F.	M.W.	Yield (%)
CP-1	4-OCH_3-C_6H_4-	$C_{27}H_{17}ClN_4O$	436.8	70
CP-2	4-CH_3-C_6H_4-	$C_{26}H_{17}ClN_4$	420.8	68
CP-3	4- Br-C_6H_4-	$C_{25}H_{14}BrClN_4$	485.7	71
CP-4	4-NH_2-C_6H_4-	$C_{25}H_{16}ClN_5$	421.8	65
CP-5	4-NO_2-C_6H_4-	$C_{25}H_{14}ClN_5O_2$	451.8	69
CP-6	3-OH-C_6H_4-	$C_{25}H_{15}ClN_4O$	422.8	67
CP-7	4- Cl-C_6H_4-	$C_{25}H_{14}Cl_2N_4$	441.3	72
CP-8	3-NO_2-C_6H_4-	$C_{25}H_{14}ClN_5O_2$	451.8	63
CP-9	4-OH-C_6H_4-	$C_{24}H_{15}ClN_4O$	422.8	65
CP-10	H-C_6H_4-	$C_{25}H_{15}ClN_4$	406.8	73

Table II: Physical properties of Aminopyrimidines (JRM-1 to JRM-10)

Compound Code	Substitution R	M.F.	M.W.	Yield (%)
JRM-1	4-OCH_3-C_6H_4-	$C_{24}H_{17}ClN_4O$	412.8	64
JRM-2	4-CH_3-C_6H_4-	$C_{24}H_{17}ClN_4$	396.8	69
JRM-3	4- Br-C_6H_4-	$C_{23}H_{14}BrClN_4$	461.7	59
JRM-4	4-NH_2-C_6H_4-	$C_{23}H_{16}ClN_5$	397.8	55
JRM-5	4-NO_2-C_6H_4-	$C_{23}H_{14}ClN_5O_2$	427.8	62
JRM-6	3-OH-C_6H_4-	$C_{23}H_{15}ClN_4O$	398.8	57
JRM-7	4- Cl-C_6H_4-	$C_{23}H_{14}Cl_2N_4$	417.3	67
JRM-8	3-NO_2-C_6H_4-	$C_{23}H_{14}ClN_5O_2$	427.8	63
JRM-9	4-OH-C_6H_4-	$C_{23}H_{15}ClN_4O$	398.8	60
JRM-10	H-C_6H_4-	$C_{23}H_{15}ClN_4$	382.8	65

Table III: Physical properties of benzodiazepines (MRV-1 to MRV-10)

Compound Code	Substitution R	M.F.	M.W.	Yield (%)
MRV-1	4-OCH_3-C_6H_4-	$C_{29}H_{20}ClN_3O$	461.9	53
MRV-2	4-CH_3-C_6H_4-	$C_{29}H_{20}ClN3$	445.9	58
MRV-3	4- Br-C_6H_4-	$C_{28}H_{17}BrClN3$	510.8	48
MRV-4	4-NH_2-C_6H_4-	$C_{28}H_{19}ClN_4$	446.9	60
MRV-5	4-NO_2-C_6H_4-	$C_{28}H_{17}ClN_4O_2$	476.9	55
MRV-6	3-OH-C_6H_4-	$C_{28}H_{18}ClN_3O$	447.9	46
MRV-7	4- Cl-C_6H_4-	$C_{28}H_{17}Cl_2N_3$	466.3	52
MRV-8	3-NO_2-C_6H_4-	$C_{28}H_{17}ClN_4O_2$	476.9	50
MRV-9	4-OH-C_6H_4-	$C_{28}H_{18}ClN_3O$	447.9	60
MRV-10	H-C_6H_4-	$C_{28}H_{18}ClN_3$	431.9	52

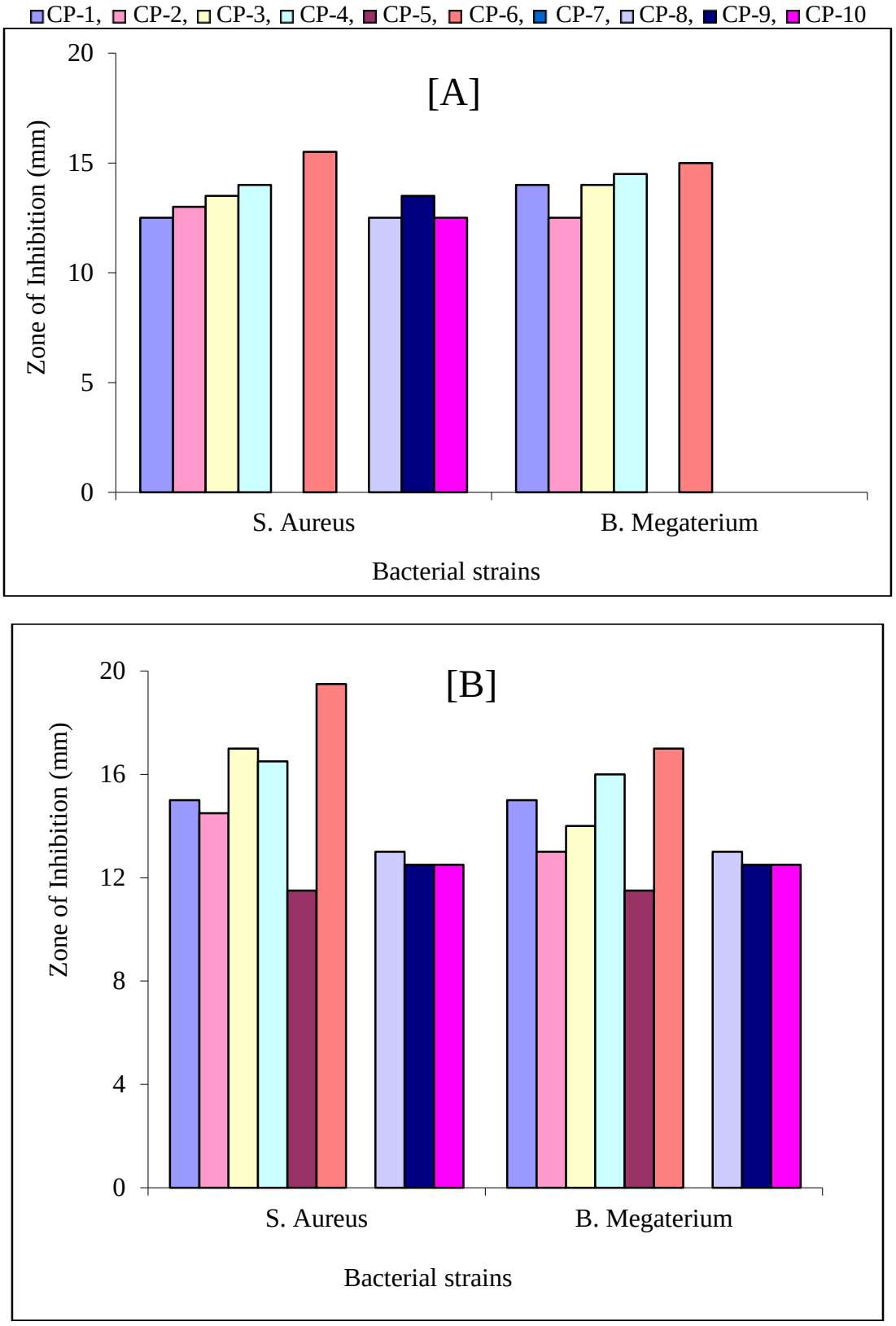

Figure 1: Antibacterial activity of cyanopyridines against Gram positive bacteria in (A) DMSO and (B) DMF

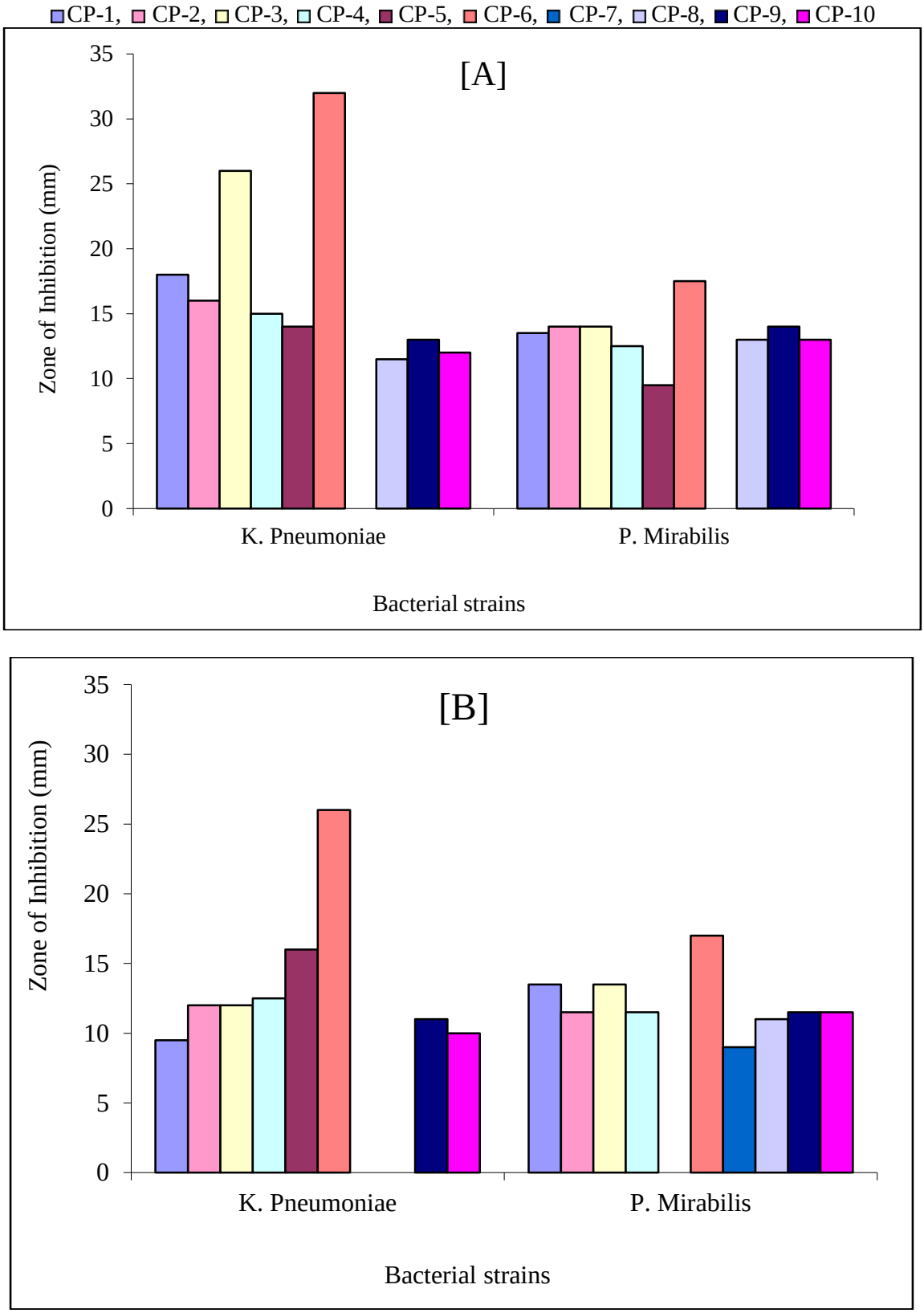

Figure 2: Antibacterial activity of cyanopyridines against Gram negative bacteria in (A) DMSO and (B) DMF

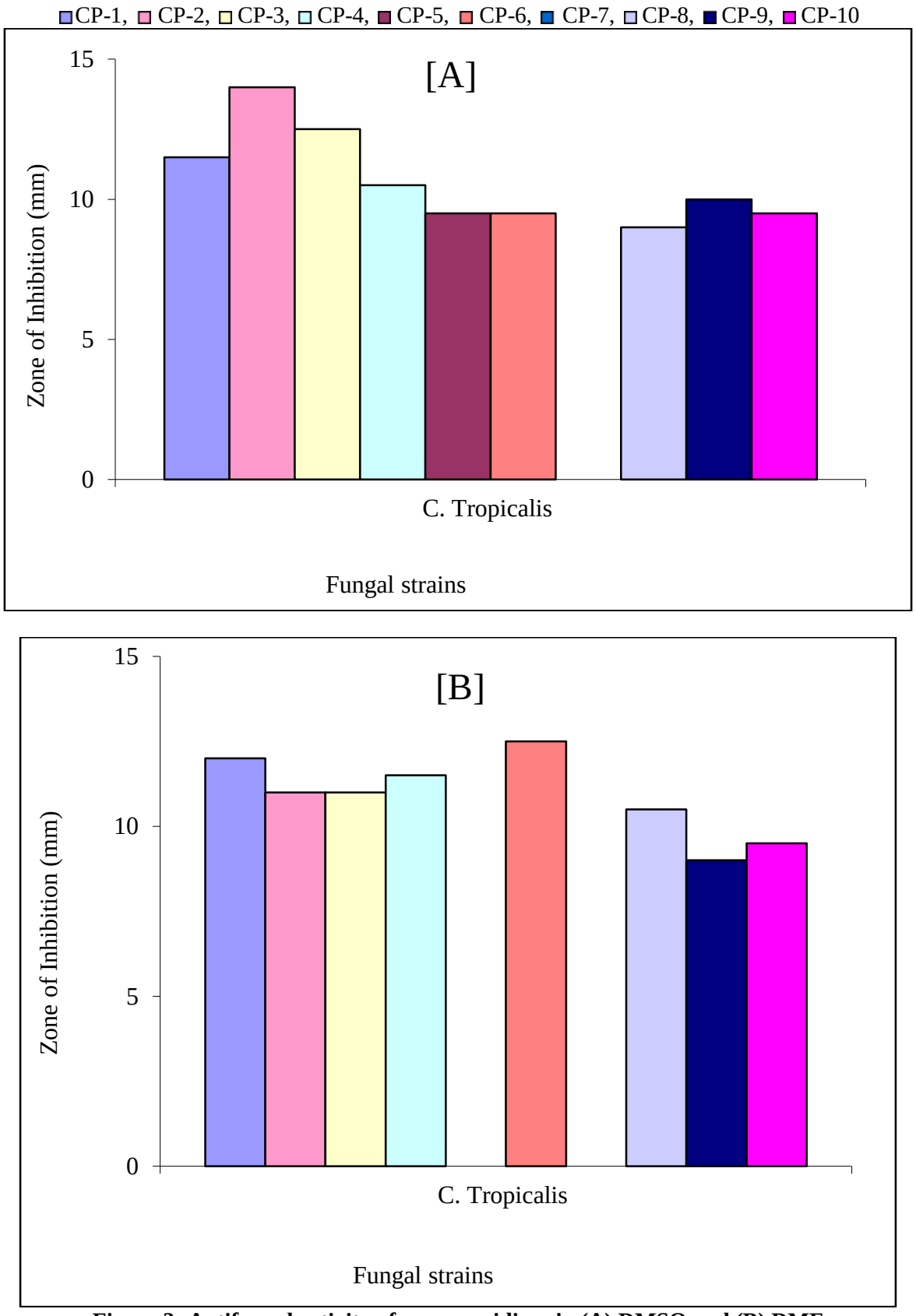

Figure 3: Antifungal activity of cyanopyridines in (A) DMSO and (B) DMF

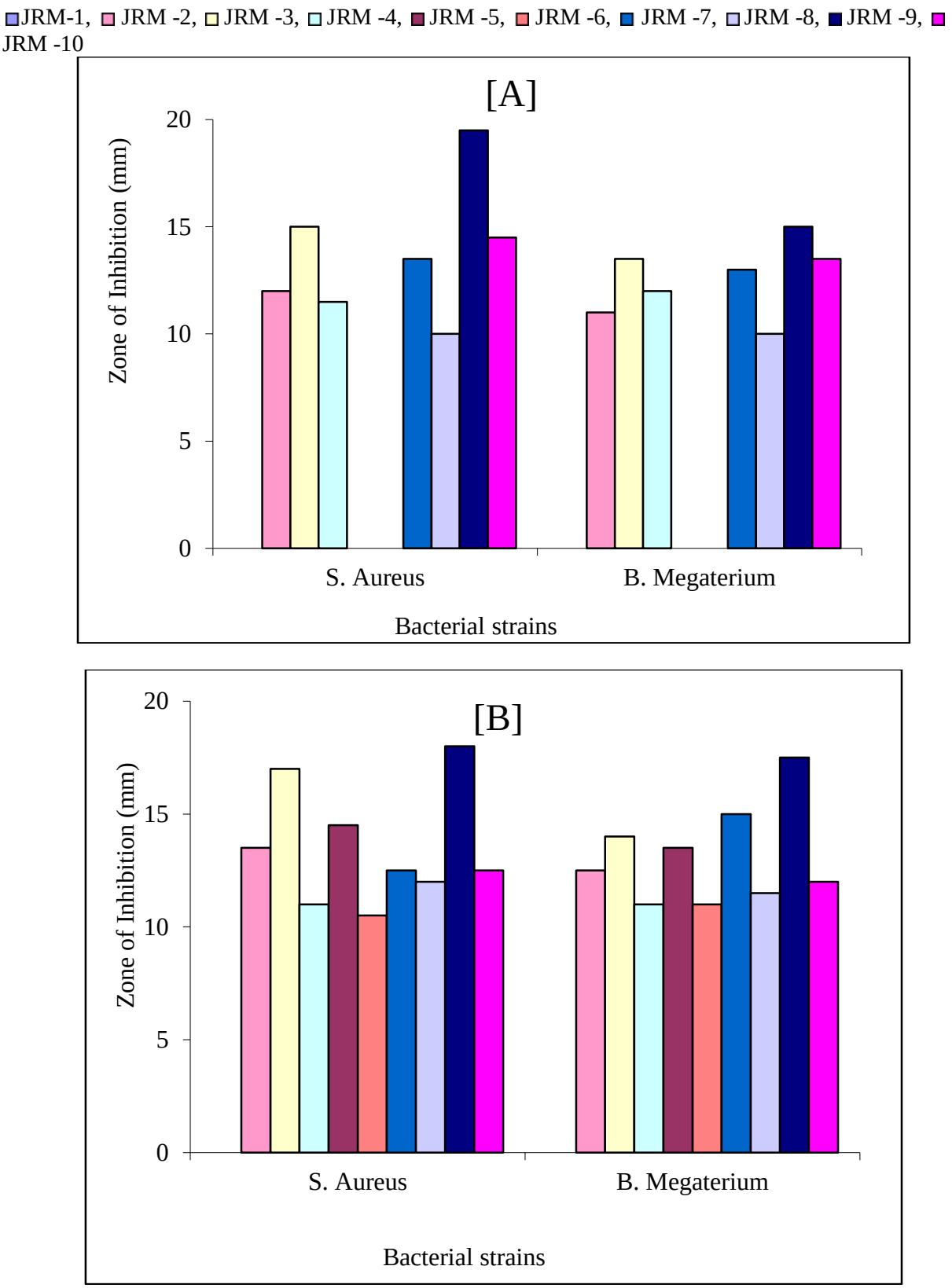

Figure 4: Antibacterial activity of aminopyrimidines against Gram positive bacteria in (A) DMSO and (B) DMF

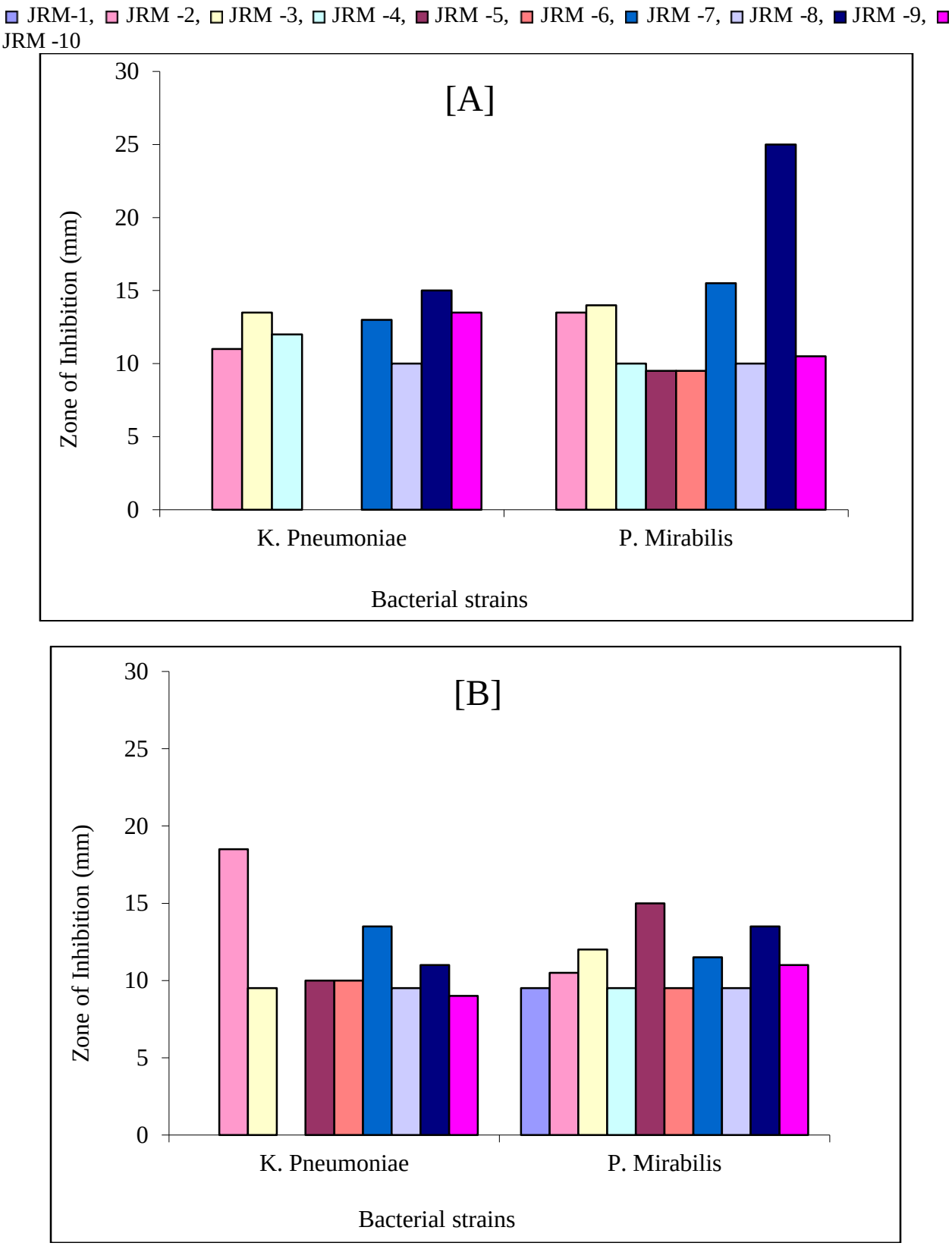

Figure 5: Antibacterial activity of aminopyrimidines against Gram negative bacteria in (A) DMSO and (B) DMF

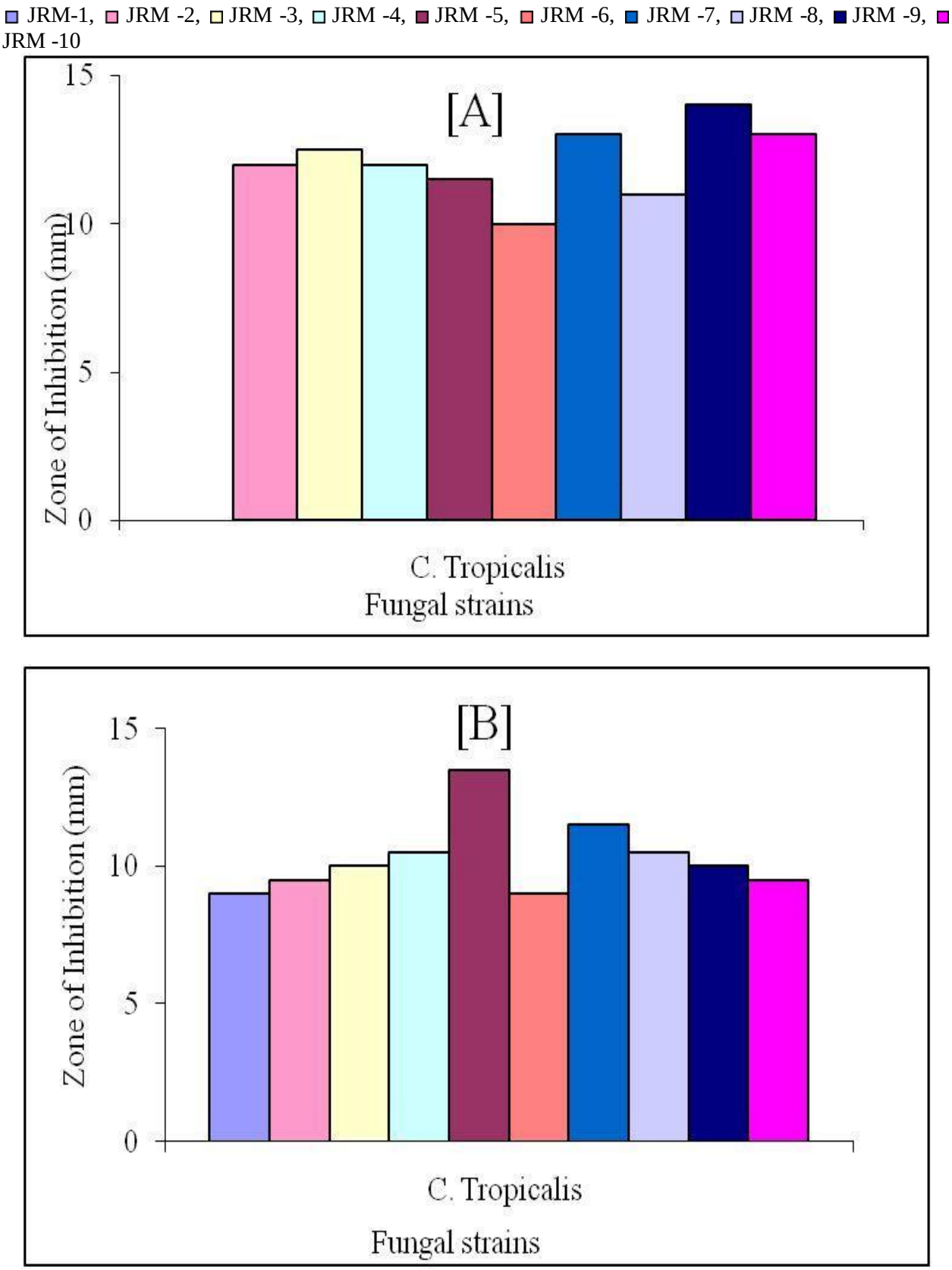

Figure 6: Antifungal activity of aminopyrimidines in (A) DMSO and (B) DMF

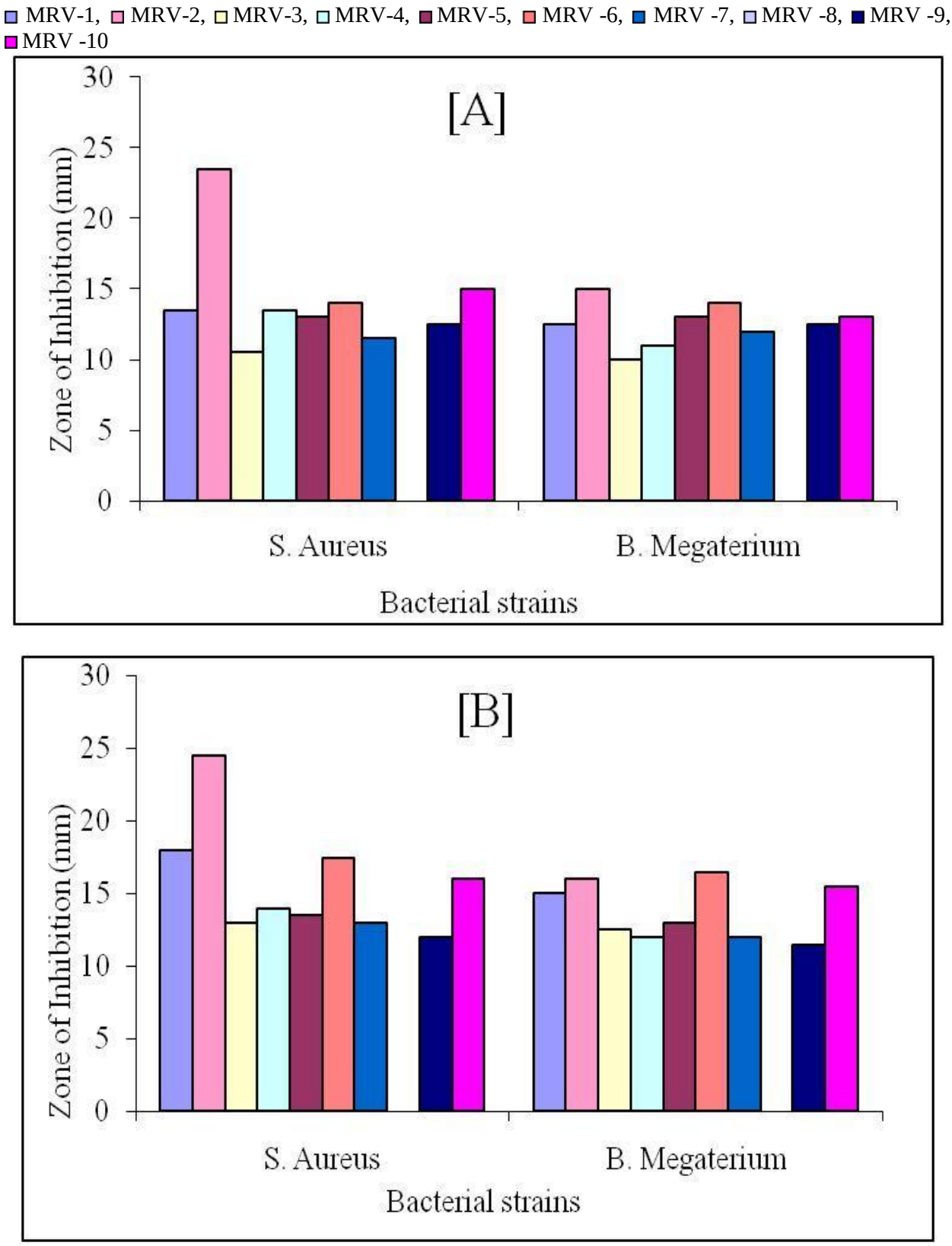

Figure 7: Antibacterial activity of 1, 5-benzodiazepines against Gram positive bacteria in (A) DMSO and (B) DMF

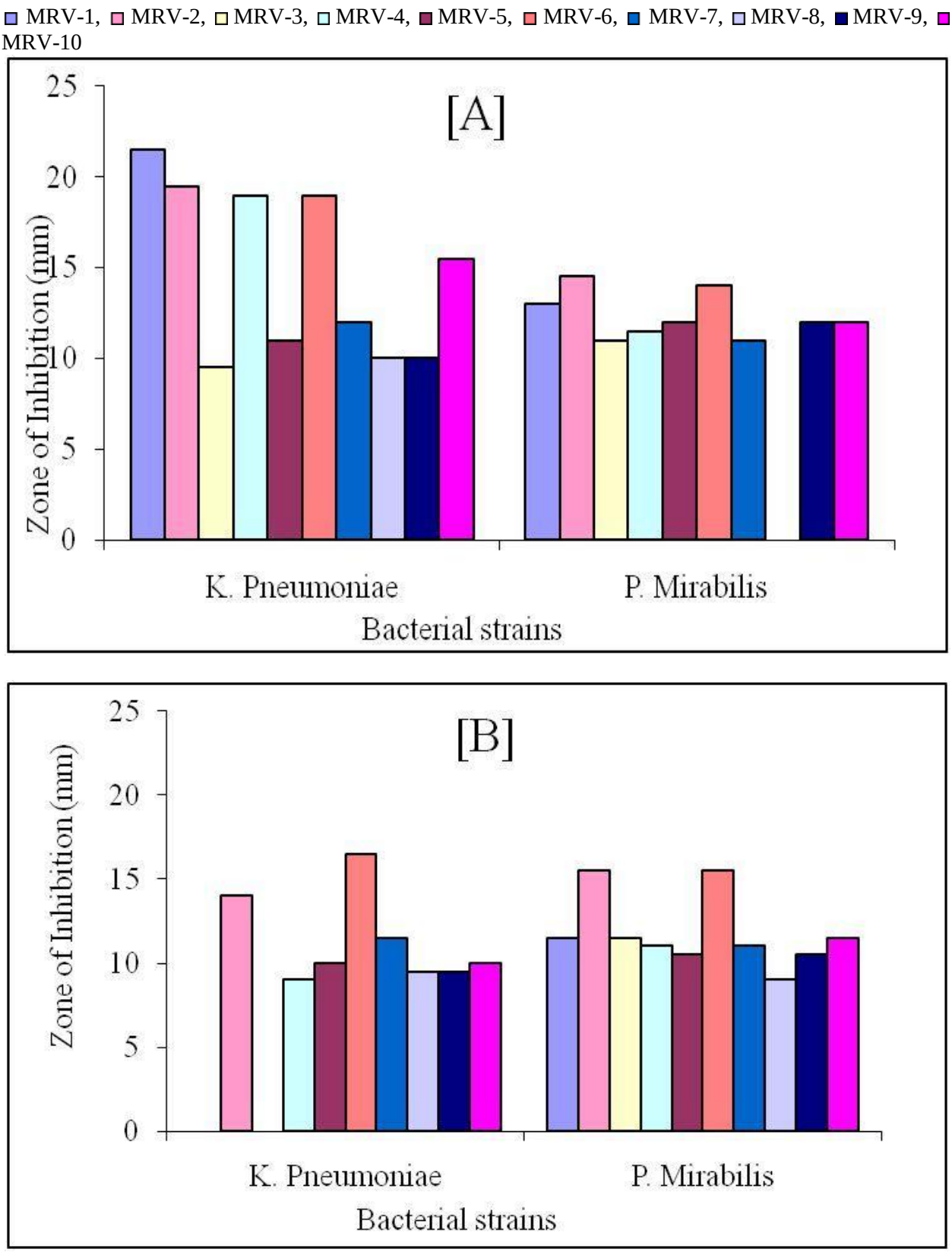

Figure 8: Antibacterial activity of 1, 5-benzodiazepines against Gram negative bacteria in (A) DMSO and (B) DMF

MRV-1, MRV-2, MRV-3, MRV-4, MRV-5, MRV-6, MRV-7, MRV-8, MRV-9, MRV-10

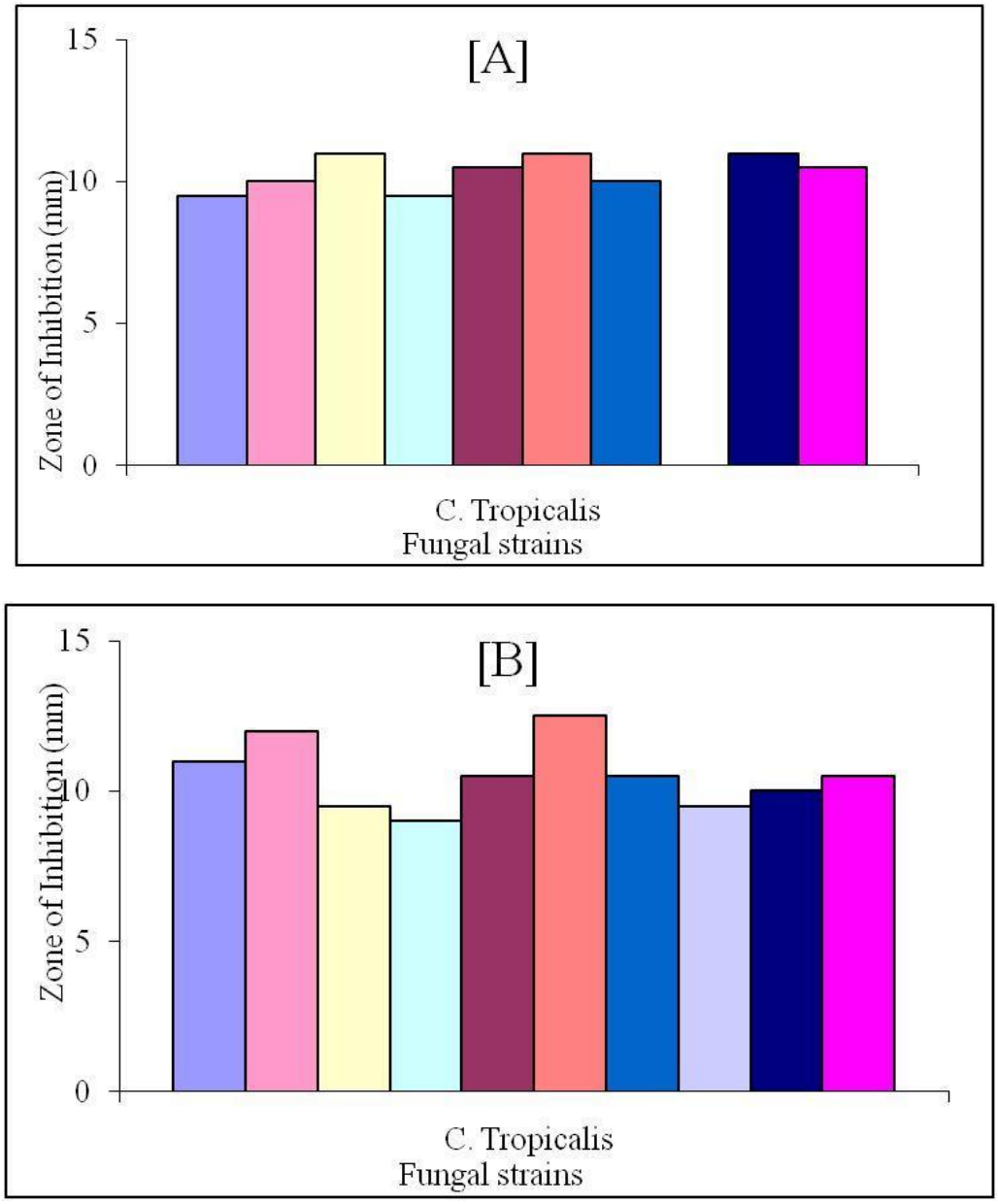

Figure 9: Antifungal activity of 1, 5-benzodiazepines in (A) DMSO and (B) DMF

Thus, in DMF compound with -OH substitution at meta position (in MRV-6) is most effective for both bacterial strains. Comparison of Figure 8(A) and Figure 8(B) shows that for Gram negative bacteria DMSO is good solvent.

Figure 9 shows zone of inhibition against a single fungal strain in DMSO and DMF. It is clear from figure that inhibition is more in DMF than in DMSO. In DMSO, MRV-8 exhibited no inhibition whereas MRV-3, MRV-6 and MRV-9 showed equally maximum inhibition. In DMF, MRV-6 showed higher inhibition whereas MRV-4 showed minimum inhibition.

Thus, again for the studied fungal strain, DMF is better solvent and -OH substitution at meta position (in MRV-6) is most effective.

CONCLUSION

It is concluded that solvent and substitution play an important role in inhibition. In case of cyanopyridine derivatives (CP series), in DMSO, p-methyl (as in CP-2) and in DMF m-hydroxy (as in CP-6) are most effective. For amino pyridine derivatives (JRM series), p-hydroxy group is most effective for both bacterial and fungal strains. Further, DMF is found to be good solvent against both bacterial and fungal strains. In MRV series, compound with m-hydroxy group (MRV-6) is most effective for both bacterial and fungal strains.

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