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# Biological evaluation of some quinoline derivatives

Shipra Baluja[1]*, Sumitra Chanda[2], Paras Ramavat[1] and Rahul Talaviya[1]

[1] *Department of Chemistry, Saurashtra University, Rajkot-360005 (Gujarat), India*
[2] *Department of Bio Science, Saurashtra University, Rajkot-360005 (Gujarat), India.*

* Corresponding author: Shipra Baluja; e-mail: shipra_baluja@rediffmail.com

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## ABSTRACT

*Some new quinoline derivatives viz., benzodiazepines and aminopyrimidine were synthesized and their characterization was done by spectral data of IR, NMR and mass. The antibacterial activities were studied against Gram positive and Gram negative bacteria in DMSO and DMF by agar well diffusion method. It was observed that activity depends upon solvent, strain as well as substitution.*

**Keywords:** 1,5-Benzdiazepines, Aminopyrimidines, Gram positive bacteria and Gram negative bacteria, DMSO, DMF.

## 1. INTRODUCTION

Biological activity is an expression describing the beneficial or adverse effects of a drug on living matter. When the drug is a complex chemical mixture, this activity is exerted by the substance's active ingredient or pharmacophore but can be modified by the other constituents. The main kind of biological activity is a substance's toxicity.

Nitrogen containing heterocyclic compounds like quinoline has received considerable attention in recent years, due to their biological and pharmaceutical activities. These derivatives are known to have wide spectrum of therapeutic activities [1-9], such as antibacterial, antifungal, antihypertensive, anti-inflammatory, antiulcer, antimalarial etc.

Thus, the important role displayed by quinoline and its derivatives for various therapeutic and biological activities prompted us to synthesize some benzodiazepines and aminopyrimidine bearing quinoline nucleus in order to achieve compounds having better drug potential. The antibacterial activity of these synthesized derivatives are also studied in N, N' dimethyl formamide and dimethyl sulphoxide against some Gram positive and Gram negative bacteria by agar well diffusion method.

## 2. MATERIALS AND METHODS

### 2.1 Materials:

All the chemicals and solvents were of LR grade and were used without purification for synthesis. For antibacterial studies, DMF and DMSO were purified by fractional distillation using standard method [10].

### 2.2 Synthesis:

### 2.2.1 Synthesis of 2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5-benzo diazepine.

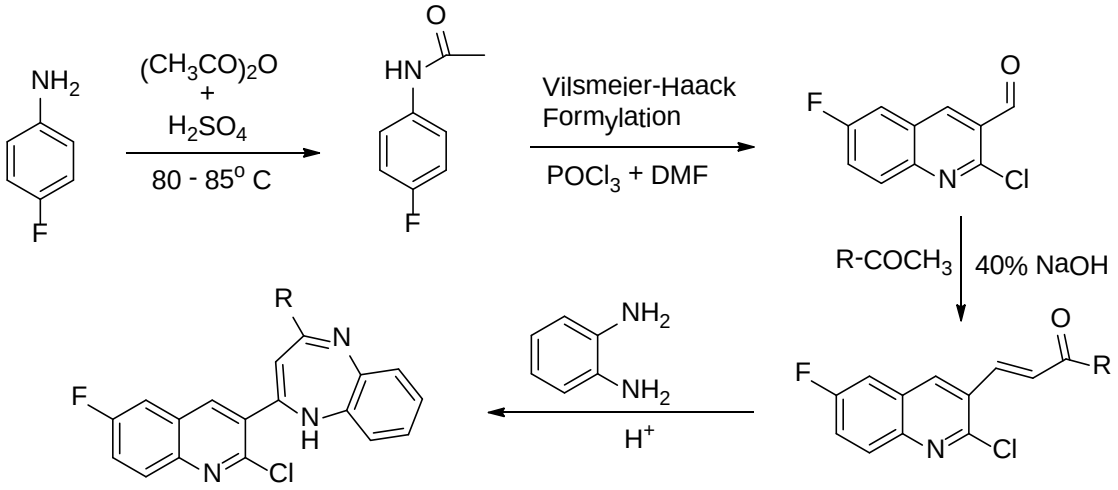
**[A]** ***Synthesis of N-(4-fluorophenyl)acetamide*****:** A mixture of 4-fluoroaniline (0.01M) and acetic anhydride (0.01M) in absolute ethanol (20 ml) was refluxed in water bath for 2-3 hrs using $H_2SO_4$ as catalyst. The crude product was isolated and crystallized from absolute ethanol.

**[B]** ***Synthesis of 2-chloro-6-fluoroquinoline-3-carbaldehyde:*** *N*- (4-fluorophenyl) 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 2ml DMF) and refluxed for 27 hrs. The reaction mixture was poured into ice followed by neutralization using sodium bicarbonate. The crude product was isolated and crystallized from ethanol.

**[C]** ***Synthesis of (2E)- 3- (2-chloro-6-fluoroquinolin-3-yl) -1- (4- methoxyphenyl) prop-2-en-1- one:*** To a well stirred solution of 2-chloro-6-fluoroquinoline-3-carbaldehyde (0.01M) and p-methoxy-acetophenone (0.01M) in ethanol (25 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 ethanol.

**[D]** ***Synthesis of of 2- (2-chloro-6-fluoroquinolin-3-yl) - 4- (4- methoxyphenyl)- 1H-1,5-benzodiazepine:*** A mixture of (2*E*) -3-(2-chloro-6-fluoroquinolin-3-yl) -1-(4- methoxy phenyl) prop-2-en-1- one, o-phenylenediamine (0.01 M) in ethanol (20ml) and glacial $CH_3COOH$ (3-4 drops) was refluxed for 8-10 hrs. The resulting mixture was poured on crushed ice. The product obtained was filtered and crystallized from ethanol.

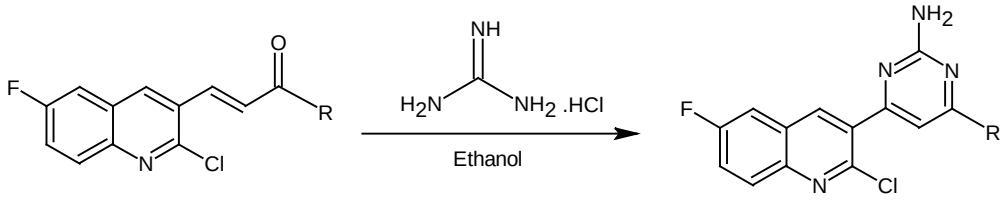
Similarly, other substituted benzodiazepines have been prepared. Overall, ten different benzodiazepines are synthesized by the following scheme.




***2.2.2 Synthesis of Aminopyrimidines:***

**Synthesis of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydro pyrimidin -2-amine:** Synthesis of *N*-(4-fluorophenyl) acetamide, 2-chloro-6-fluoroquinoline-3-carbaldehyde and (2*E*)-3-(2-chloro-6-fluoroquinolin-3-yl)-1-(4- methoxy phenyl)prop-2-en-1- one are given above.

A mixture of (2*E*) -3- ( 2- chloro- 6- fluoroquinolin – 3 – yl)-1-(4- methoxy phenyl) prop-2-en-1- one (0.01M) and guanidine hydrochloride (0.01M) in presence of potassium hydroxide (1 g) was refluxed in ethanol (20 ml) for 8-10 hours. The resulting mixture was poured on crushed ice. The product obtained was filtered and crystallized from ethanol. The reaction is as follows:




Similarly, ten other substituted aminopyrimidines have been prepared.

The characterization of all the synthesized compounds was done by IR, $^1$H NMR and mass spectra. The Infrared spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 cm-1 by KBr powder method. The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. The Mass spectra were recorded by GCMS-SHIMADZU-QP2010.

All the synthesized compounds were re-crystallized prior to use. The antibacterial activities of all synthesized compounds were studied in DMF and DMSO against some Gram positive and Gram negative bacterial strains by agar well diffusion method.

**2.3 Test Microorganisms:**

The synthesized compounds were tested for its antibacterial activity against Gram positive bacteria viz. *Bacillus cereus* ATCC11778, *Micrococcus flavus* ATCC10240, *Staphylococcus epidermidis* ATCC12228, and *Staphylococcus aureus* ATCC29737 and Gram negative bacteria viz. *Proteus mirabilis* NCIM2241, *Salmonella typhimurium* ATCC23564, *Citrobacter freundii* ATCC10787 and *Klebsiella pneumoniae* NCIM2719.

Microorganisms were obtained from National Chemical Laboratory (NCL), Pune, India and were maintained at 4°C on nutrient agar slants.

**2.4 Preparation of test compounds:**

The solutions were prepared at a concentration of 1 mg/μl for all the compounds.

**2.5 Preparation of the plates and microbiological assay:**

The antibacterial evaluation was done by agar well diffusion method [11], using Mueller Hinton Agar No.2 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. [12]. 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 Mueller Hinton 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. 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

The physical constants of synthesized benzodiazepine and amino pyrimidine derivatives are given in Tables 1 and 2 respectively.

**Table 1:** Physical constants of benzodiazepines.

| Sr. No. | Code | R | $R_f$* Value | M.P. °C | Yield % |
|---|---|---|---|---|---|
| **1** | **NBN-1** | 4-$OCH_3$-$C_6H_4$- | 0.59 | 198 | 54 |
| **2** | **NBN-2** | 4-$NH_2$-$C_6H_4$- | 0.51 | 175 | 59 |
| **3** | **NBN-3** | 4-Br-$C_6H_4$- | 0.66 | 232 | 49 |
| **4** | **NBN-4** | 4-$NO_2$-$C_6H_4$- | 0.49 | 202 | 62 |
| **5** | **NBN-5** | 3-$NO_2$-$C_6H_4$- | 0.64 | 215 | 57 |
| **6** | **NBN-6** | 4-OH-$C_6H_4$- | 0.74 | 248 | 61 |
| **7** | **NBN-7** | 4-$CH_3$-$C_6H_4$- | 0.82 | 186 | 55 |
| **8** | **NBN-8** | 4-Cl-$C_6H_4$- | 0.59 | 232 | 52 |
| **9** | **NBN-9** | 2-OH-$C_6H_4$- | 0.63 | 177 | 58 |
| **10** | **NBN-10** | $C_6H_5$- | 0.70 | 182 | 62 |

* Ethyl acetate:Hexane: 2:8

**Table 2:** Physical constants of aminopyrimidines.

| Sr. No. | Code | R | $R_f$* Value | M.P. °C | Yield % |
|---|---|---|---|---|---|
| **1** | **NAP-1** | 4-$OCH_3$-$C_6H_4$- | 0.68 | 165 | 65 |
| **2** | **NAP-2** | 4-$NH_2$-$C_6H_4$- | 0.58 | 172 | 68 |
| **3** | **NAP-3** | 4-Br-$C_6H_4$- | 0.55 | 181 | 62 |
| **4** | **NAP-4** | 4-$NO_2$-$C_6H_4$- | 0.71 | 202 | 71 |
| **5** | **NAP-5** | 3-$NO_2$-$C_6H_4$- | 0.63 | 241 | 74 |
| **6** | **NAP-6** | 4-OH-$C_6H_4$- | 0.52 | 218 | 59 |
| **7** | **NAP-7** | 4-$CH_3$-$C_6H_4$- | 0.59 | 197 | 67 |
| **8** | **NAP-8** | 4-Cl-$C_6H_4$- | 0.62 | 168 | 63 |
| **9** | **NAP-9** | 2-OH-$C_6H_4$- | 0.68 | 174 | 68 |
| **10** | **NAP-10** | $C_6H_5$- | 0.71 | 194 | 72 |

* Acetone:Benzene: 2:8

**3.1 Spectral data:**

***3.1.1 1,5-Benzodiazepines (NBN-1 to NBN-10):***

**NBN-1** ***IR (cm$^{-1}$, KBr)*****:** 2935.76 (asym. C-H str.), 2841.24 (sym. C-H str.), 1458.23 (asym. C-H def.), 1346.36 (sym. C-H def.), 3072.71 (sym. aromatic C-H str.), 1496.81 (aromatic C=C str.), 1118.75 1660.77 (C=N str.), 1303.92 (C-N str.), 3317.67 (N-H str.), 1602.90 (N-H def.), 1259.56 (asym. C-O-C str.), 1020.38 (sym. C-O-C str.), 1224.84 (C-F str.), 738.76 (C-Cl str.). ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*****:** 3.86 (3H, singlet, -$OCH_3$), 4.54 (1H, singlet, -H of benzodiazepine ring), 7.44-7.49 (1H, triplet, Ar-CH), 7.61-7.65 (1H, triplet, Ar-CH), 7.67-7.74 (4H, multiplet, Ar-CH), 7.80-7.82 (1H, triplet, Ar-CH), 7.91-7.93 (1H, doublet, Ar-CH), 7.97-7.99 (1H, doublet, Ar-CH), 8.04-8.10 (2H, doublet, Ar-CH), 8.38 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 429.9

**NBN-2** ***IR (cm$^{-1}$, KBr)*****:** 2935.77 (asym. C-H str.), 2840.10 (sym. C-H str.), 1457.20 (asym. C-H def.), 1344.23 (sym. C-H def.), 3071.70 (sym. aromatic C-H str.), 1495.11 (aromatic C=C str.), 1660.20 (C=N str.), 1303.12 (C-N str.), 3315.07 (N-H str.), 1604.03 (N-H def.), 1256.90 (asym. C-O-C str.), 1024.05 (sym. C-O-C str.), 1221.14 (C-F str.), 736.32 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*****:** 4.54 (1H, singlet, -H of benzodiazepine ring), 7.44-7.49 (1H, triplet, Ar-CH), 7.61-7.65 (1H, triplet, Ar-CH), 7.67-7.74 (4H, multiplet, Ar-CH), 7.80-7.82 (1H, triplet, Ar-CH), 7.91-7.93 (1H, doublet, Ar-CH), 7.97-7.99 (1H, doublet, Ar-CH), 8.04-8.10 (2H, doublet, Ar-CH), 8.38 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 414.9

**NBN-3** ***IR (cm$^{-1}$, KBr)*****:** 2935.29 (asym. C-H str.), 2837.35 (sym. C-H str.), 1451.22 (asym. C-H def.),

1338.30 (sym. C-H def.), 3073.64 (sym. aromatic C-H str.), 1493.53 (aromatic C=C str.), 1659.97 (C=N str.), 1308.95 (C-N str.), 3316.97 (N-H str.), 1602.25 (N-H def.), 1258.52 (asym. C-O-C str.), 1021.38 (sym. C-O-C str.), 1223.84 (C-F str.), 735.83 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 4.56 (1H, singlet, -H of benzodiazepine ring), 7.48-7.49 (1H, triplet, Ar-CH), 7.59-7.61 (1H, triplet, Ar-CH), 7.67-7.71 (4H, multiplet, Ar-CH), 7.79-7.80 (1H, triplet, Ar-CH), 7.90-7.92 (1H, doublet, Ar-CH), 7.95-7.98 (1H, doublet, Ar-CH), 8.01-8.08 (2H, doublet, Ar-CH), 8.34 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 478.7

**NBN-4** ***IR (cm$^{-1}$, KBr)*:** 2935.77 (asym. C-H str.), 2840.28 (sym. C-H str.), 1458.33 (asym. C-H def.), 1346.49 (sym. C-H def.), 3072.73 (sym. aromatic C-H str.), 1496.49 (aromatic C=C str.), 1660.67 (C=N str.), 1303.52 (C-N str.), 3317.69 (N-H str.), 1602.90 (N-H def.), 1258.58 (asym. C-O-C str.), 1020.28 (sym. C-O-C str.), 1224.86 (C-F str.), 738.77(C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 4.51 (1H, singlet, -H of benzodiazepine ring), 7.41-7.45 (1H, triplet, Ar-CH), 7.60-7.63 (1H, triplet, Ar-CH), 7.65-7.72 (4H, multiplet, Ar-CH), 7.82-7.84 (1H, triplet, Ar-CH), 7.90-7.92 (1H, doublet, Ar-CH), 7.96-7.98 (1H, doublet, Ar-CH), 8.03-8.07 (2H, doublet, Ar-CH), 8.29 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 444.8

**NBN-5** ***IR (cm$^{-1}$, KBr)*:** 2935.24 (asym. C-H str.), 2841.24 (sym. C-H str.), 1458.23 (asym. C-H def.), 1346.36 (sym. C-H def.), 3072.71 (sym. aromatic C-H str.), 1496.81 (aromatic C=C str.), 1660.77 (C=N str.), 1303.92 (C-N str.), 3317.67 (N-H str.), 1602.90 (N-H def.), 1259.56 (asym. C-O-C str.), 1020.38 (sym. C-O-C str.), 1224.84 (C-F str.), 738.76 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 4.54 (1H, singlet, -H of benzodiazepine ring), 7.40-7.43 (1H, triplet, Ar-CH), 7.58-7.60 (1H, triplet, Ar-CH), 7.62-7.64 (1H, singlet, Ar-CH), 7.70-7.72 (3H, multiplet, Ar-CH), 7.82-7.84 (1H, triplet, Ar-CH), 7.92-7.94 (1H, doublet, Ar-CH), 7.98-7.99 (1H, doublet, Ar-CH), 8.07-8.09 (2H, doublet, Ar-CH), 8.37 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 444.8

**NBN-6** ***IR (cm$^{-1}$, KBr)*:** 2935.14 (asym. C-H str.), 2841.23 (sym. C-H str.), 1458.24 (asym. C-H def.), 1346.37 (sym. C-H def.), 3072.61 (sym. aromatic C-H str.), 1496.71 (aromatic C=C str.), 1660.79 (C=N str.), 1303.94 (C-N str.), 3317.58 (N-H str.), 1602.54 (N-H def.), 1259.89 (asym. C-O-C str.), 1020.37 (sym. C-O-C str.), 1224.73 (C-F str.), 738.75 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*** **:** 3.86 (3H, singlet, -$OCH_3$), 4.54 (1H, singlet, -H of benzodiazepine ring), 7.44-7.49 (1H, triplet, Ar-CH), 7.61-7.65 (1H, triplet, Ar-CH), 7.67-7.74 (4H, multiplet, Ar-CH), 7.80-7.82 (1H, triplet, Ar-CH), 7.91-7.93 (1H, doublet, Ar-CH), 7.97-7.99 (1H, doublet, Ar-CH), 8.04-8.10 (2H, doublet, Ar-CH), 8.38 (1H, singlet, Ar-CH), 9.29 (1H, singlet, -OH), ***MS*: *(m/z)*** = 415.8

**NBN-7** ***IR (cm$^{-1}$, KBr)*:** 2935.46 (asym. C-H str.), 2841.54 (sym. C-H str.), 1457.13 (asym. C-H def.), 1346.14 (sym. C-H def.), 3072.23 (sym. aromatic C-H str.), 1496.74 (aromatic C=C str.), 1660.70 (C=N str.), 1303.87 (C-N str.), 3317.63 (N-H str.), 1602.92 (N-H def.), 1259.53 (asym. C-O-C str.), 1020.37 (sym. C-O-C str.), 1224.82 (C-F str.), 738.78(C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 2.402 (3H, singlet, -$CH_3$), 4.50 (1H, singlet, -H of benzodiazepine ring), 7.41-7.47 (1H, triplet, Ar-CH), 7.63-7.67 (1H, triplet, Ar-CH), 7.70-7.71 (4H, multiplet, Ar-CH), 7.83-7.85 (1H, triplet, Ar-CH), 7.90-7.92 (1H, doublet, Ar-CH), 7.96-7.98 (1H, doublet, Ar-CH), 8.03-8.05 (2H, doublet, Ar-CH), 8.39 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 413.9

**NBN-8** ***IR (cm$^{-1}$, KBr)*:** 2935.76 (asym. C-H str.), 2841.24 (sym. C-H str.), 1458.23 (asym. C-H def.), 1346.36 (sym. C-H def.), 3072.71 (sym. aromatic C-H str.), 1496.81 (aromatic C=C str.), 1660.77 (C=N str.), 1303.92 (C-N str.), 3317.67 (N-H str.), 1602.90 (N-H def.), 1259.56 (asym. C-O-C str.), 1020.38 (sym. C-O-C str.), 1224.84 (C-F str.), 738.76 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 3.86 (3H, singlet, -$OCH_3$), 4.54 (1H, singlet, -H of benzodiazepine ring), 7.44-7.49 (1H, triplet, Ar-CH), 7.61-7.65 (1H, triplet, Ar-CH), 7.67-7.74 (4H, multiplet, Ar-CH), 7.80-7.82 (1H, triplet, Ar-CH), 7.91-7.93 (1H, doublet, Ar-CH), 7.97-7.99 (1H, doublet, Ar-CH), 8.04-8.10 (2H, doublet, Ar-CH), 8.32 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 434.4

**NBN-9** ***IR (cm$^{-1}$, KBr)*:** 2935.74 (asym. C-H str.), 2841.35 (sym. C-H str.), 1458.20 (asym. C-H def.), 1346.30 (sym. C-H def.), 3072.75 (sym. aromatic C-H str.), 1496.89 (aromatic C=C str.), 1660.77 (C=N str.), 1303.94 (C-N str.), 3317.67 (N-H str.), 1602.93 (N-H def.), 1259.57 (asym. C-O-C str.), 1020.37 (sym. C-O-C str.), 1224.87 (C-F str.), 738.73 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.40-7.43 (1H, triplet, Ar-CH), 7.63-7.65 (1H, triplet, Ar-CH), 7.68-7.72 (4H, multiplet, Ar-CH), 7.81-7.84 (1H, triplet, Ar-CH), 7.92-7.95 (1H, doublet, Ar-CH), 7.98-8.01 (1H, doublet, Ar-CH), 8.08-8.11 (2H, doublet, Ar-CH), 8.39 (1H, singlet, Ar-CH), 9.30 (1H, singlet, -OH), ***MS*: *(m/z)*** = 415.8

**NBN-10** ***IR (cm$^{-1}$, KBr)*:** 2935.26 (asym. C-H str.), 2841.23 (sym. C-H str.), 1458.24 (asym. C-H def.), 1346.35(sym. C-H def.), 3072.74 (sym. aromatic C-H str.), 1496.81 (aromatic C=C str.), 1660.71 (C=N str.), 1303.94 (C-N str.), 3317.69 (N-H str.), 1602.95 (N-H def.), 1259.54 (asym. C-O-C str.), 1020.37 (sym. C-O-C str.), 1224.87 (C-F str.), 738.79 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 4.50 (1H, singlet, -H of benzodiazepine ring), 7.39-7.41 (1H, triplet, Ar-CH), 7.59-7.63 (1H, triplet, Ar-CH), 7.65-7.72 (4H, multiplet, Ar-CH), 7.81-7.83(1H, triplet, Ar-CH), 7.89-7.90 (1H, doublet, Ar-CH), 7.97-7.99 (1H, doublet, Ar-CH), 8.04-8.10 (2H, doublet, Ar-CH), 8.35 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 399.8

### *3.1.2 Aminopyrimidines (NPA-1 to NPA-10):*

**NPA-1** ***IR (cm$^{-1}$, KBr)*:** 2929.97 (asym. C-H str.), 2837.38 (sym. C-H str.), 1452.45 (asym. C-H def.), 1359.86 (sym. C-H def.), 3120.93 (sym. aromatic C-H str.), 1506.46 (aromatic C=C str.), 1670.41 (C=N str.), 1257.63 (C-N str.), 3315.74 (N-H str.), 1539.25 (N-H

def.), 1259.56 (asym. C-O-C str.), 1020.38 (sym. C-O-C str.), 1224.84 (C-F str.), 738.76 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 3.94 (3H, singlet, -$OCH_3$), 7.03-7.05 (2H, doublet, Ar-CH), 7.28 (1H, singlet, Ar-CH), 7.34-7.40 (2H, multiplet, Ar-CH), 7.64-7.68 (1H, doublet, Ar-CH), 7.84 (2H, singlet, -$NH_2$), 8.10-8.12 (2H, doublet, Ar-CH), 8.16 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 380.8

**NPA-2** ***IR (cm$^{-1}$, KBr)*:** 2929.93 (asym. C-H str.), 2837.35 (sym. C-H str.), 1452.42 (asym. C-H def.), 1359.82 (sym. C-H def.), 3120.91 (sym. aromatic C-H str.), 1506.47 (aromatic C=C str.), 1670.41 (C=N str.), 1257.67 (C-N str.), 3315.64(N-H str.), 1539.35 (N-H def.), 1259.76 (asym. C-O-C str.), 1020.72 (sym. C-O-C str.), 1224.73 (C-F str.), 738.77 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.02-7.07 (2H, doublet, Ar-CH), 7.21 (1H, singlet, Ar-CH), 7.35-7.39 (2H, multiplet, Ar-CH), 7.62-7.63 (1H, doublet, Ar-CH), 7.85 (4H, singlet, -$NH_2$), 8.08-8.10 (2H, doublet, Ar-CH), 8.15 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 365.8

**NPA-3** ***IR (cm$^{-1}$, KBr)*:** 2929.91 (asym. C-H str.), 2837.28 (sym. C-H str.), 1452.35 (asym. C-H def.), 1359.76 (sym. C-H def.), 3120.73 (sym. aromatic C-H str.), 1506.36 (aromatic C=C str.), 1670.41 (C=N str.), 1257.67 (C-N str.), 3315.74 (N-H str.), 1539.27 (N-H def.), 1259.56 (asym. C-O-C str.), 1020.35 (sym. C-O-C str.), 1224.84 (C-F str.), 738.16 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.01-7.03 (2H, doublet, Ar-CH), 7.25 (1H, singlet, Ar-CH), 7.33-7.47 (2H, multiplet, Ar-CH), 7.61-7.65 (1H, doublet, Ar-CH), 7.87 (2H, singlet, -$NH_2$), 8.12-8.14 (2H, doublet, Ar-CH), 8.10 (1H, singlet, Ar-CH).

**NPA-4** ***IR (cm$^{-1}$, KBr)*:** 2929.67 (asym. C-H str.), 2837.58 (sym. C-H str.), 1452.32 (asym. C-H def.), 1359.45 (sym. C-H def.), 3120.24 (sym. aromatic C-H str.), 1506.74 (aromatic C=C str.), 1670.71 (C=N str.), 1257.63 (C-N str.), 3315.64 (N-H str.), 1539.35 (N-H def.), 1259.46 (asym. C-O-C str.), 1020.37 (sym. C-O-C str.), 1224.47 (C-F str.), 738.55 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.04-7.06 (2H, doublet, Ar-CH), 7.27 (1H, singlet, Ar-CH), 7.31-7.35 (2H, multiplet, Ar-CH), 7.67-7.69 (1H, doublet, Ar-CH), 7.81 (2H, singlet, -$NH_2$), 8.06-8.07 (2H, doublet, Ar-CH), 8.16 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 395.8

**NPA-5** ***IR (cm$^{-1}$, KBr)*:** 2929.45 (asym. C-H str.), 2837.37 (sym. C-H str.), 1452.43 (asym. C-H def.), 1359.84 (sym. C-H def.), 3120.20 (sym. aromatic C-H str.), 1506.28(aromatic C=C str.), 1670.34 (C=N str.), 1257.63 (C-N str.), 3315.57 (N-H str.), 1539.40 (N-H def.), 1259.74 (asym. C-O-C str.), 1020.37 (sym. C-O-C str.), 1224.24 (C-F str.), 738.36 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.01-7.04 (2H, doublet, Ar-CH), 7.10 (1H, multiplet, Ar-CH), 7.22 (1H, singlet, Ar-CH), 7.32-7.38 (2H, multiplet, Ar-CH), 7.60-7.62 (1H, doublet, Ar-CH), 7.89 (2H, singlet, -$NH_2$),7.93 (1H, singlet, Ar-CH), 8.14 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 395.8

**NPA-6** ***IR (cm$^{-1}$, KBr)*:** 2929.12 (asym. C-H str.), 2837.27 (sym. C-H str.), 1452.36 (asym. C-H def.), 1359.24 (sym. C-H def.), 3120.25 (sym. aromatic C-H str.), 1506.56 (aromatic C=C str.), 1670.43 (C=N str.), 1257.63 (C-N str.), 3315.44 (N-H str.), 1539.45 (N-H def.), 1259.96 (asym. C-O-C str.), 1020.48 (sym. C-O-C str.), 1224.37 (C-F str.), 738.97 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.07-7.09 (2H, doublet, Ar-CH), 7.24 (1H, singlet, Ar-CH), 7.37-7.41 (2H, multiplet, Ar-CH), 7.63-7.67 (1H, doublet, Ar-CH), 7.83 (2H, singlet, -$NH_2$), 8.12-8.18 (2H, doublet, Ar-CH), 8.20 (1H, singlet, Ar-CH), 9.13 (1H, singlet, -OH), ***MS*: *(m/z)*** = 366.8

**NPA-7** ***IR (cm$^{-1}$, KBr)*:** 2929.23 (asym. C-H str.), 2837.74 (sym. C-H str.), 1452.72 (asym. C-H def.), 1359.28 (sym. C-H def.), 3120.36 (sym. aromatic C-H str.), 1506.78 (aromatic C=C str.), 1670.89 (C=N str.), 1257.63 (C-N str.), 3315.87 (N-H str.), 1539.35 (N-H def.), 1259.54 (asym. C-O-C str.), 1020.54 (sym. C-O-C str.), 1224.74 (C-F str.), 738.34 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 1.28 (3H, singlet, -$CH_3$), 7.02-7.04 (2H, doublet, Ar-CH), 7.25 (1H, singlet, Ar-CH), 7.33-7.39 (2H, multiplet, Ar-CH), 7.61-7.67 (1H, doublet, Ar-CH), 7.86 (2H, singlet, -$NH_2$), 8.09-8.11 (2H, doublet, Ar-CH), 8.18 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 364.8

**NPA-8** ***IR (cm$^{-1}$, KBr)*:** 2928.24 (asym. C-H str.), 2837.27 (sym. C-H str.), 1452.35 (asym. C-H def.), 1359.74 (sym. C-H def.), 3120.24 (sym. aromatic C-H str.), 1506.56 (aromatic C=C str.), 1670.74 (C=N str.), 1257.65 (C-N str.), 3315.54 (N-H str.), 1539.35 (N-H def.), 1259.88 (asym. C-O-C str.), 1020.98 (sym. C-O-C str.), 1224.86 (C-F str.), 738.76 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.04-7.06 (2H, doublet, Ar-CH), 7.29 (1H, singlet, Ar-CH), 7.38-7.42 (2H, multiplet, Ar-CH), 7.65-7.69 (1H, doublet, Ar-CH), 7.83 (2H, singlet, -$NH_2$), 8.09-8.11 (2H, doublet, Ar-CH), 8.13 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 385.2

**NPA-9** ***IR (cm$^{-1}$, KBr)*:** 2929.43 (asym. C-H str.), 2837.46 (sym. C-H str.), 1452.35 (asym. C-H def.), 1359.25 (sym. C-H def.), 3120.53 (sym. aromatic C-H str.), 1506.26 (aromatic C=C str.), 1670.41 (C=N str.), 1257.53 (C-N str.), 3315.74 (N-H str.), 1539.55 (N-H def.), 1259.54 (asym. C-O-C str.), 1020.37 (sym. C-O-C str.), 1224.85 (C-F str.), 738.78 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.03-7.05 (2H, doublet, Ar-CH), 7.25 (1H, singlet, Ar-CH), 7.31-7.39 (2H, multiplet, Ar-CH), 7.64-7.68 (1H, doublet, Ar-CH), 7.84 (2H, singlet, -$NH_2$), 8.10-8.12 (2H, doublet, Ar-CH), 8.16 (1H, singlet, Ar-CH), 9.13(1H, singlet, -OH), ***MS*: *(m/z)*** = 366.8

**NPA-10** ***IR (cm$^{-1}$, KBr)*:** 2929.41 (asym. C-H str.), 2837.38 (sym. C-H str.), 1452.43 (asym. C-H def.), 1359.81 (sym. C-H def.), 3120.89 (sym. aromatic C-H str.), 1506.77 (aromatic C=C str.), 1670.41 (C=N str.), 1257.69 (C-N str.), 3315.70 (N-H str.), 1539.20 (N-H def.), 1259.50 (asym. C-O-C str.), 1020.48 (sym. C-O-C str.), 1224.88 (C-F str.), 738.75 (C-Cl str.), ***$^1$H NMR (DMSO-$d_6$) δ(ppm)*:** 7.08-7.10 (2H, doublet, Ar-CH), 7.28 (1H, singlet, Ar-CH), 7.34-7.40 (2H, multiplet, Ar-CH), 7.64-7.68 (1H, doublet, Ar-CH), 7.84 (2H, singlet, -

$NH_2$), 7.98(3H, multiplet, Ar-CH), 8.14 (1H, singlet, Ar-CH), ***MS*: *(m/z)*** = 350.8

**3.2 Antibacterial activity:**

***3.2.1 1,5-Benzdiazepines:***

Figure 1 shows inhibition against Gram positive bacteria in DMSO. It was observed that against *B. cereus*, NBN-10 shows maximum inhibition whereas NBN-6 and NBN-9 exhibited minimum inhibition. NBN-1 and NBN-2 showed no inhibition at all.

All the compounds have the same central moiety but different substitutions as side chain. Thus, in NBN-10, the side chain has no substitution group whereas NBN-6 and NBN-9 possess p-hydroxy and o-hydroxy groups (Table 1). Thus, when there is no substitution group attached to side chain, the compound showed maximum inhibition against *B. cereus*.

For *M. flavus*, again NBN-10 showed maximum inhibition and NBN-9 showed minimum inhibition. Thus, in this case also, absence of any group was most effective and o-hydroxy group was least effective against *S. epidermidis*, only NBN-10 exhibited inhibition. Other compounds had no effect at all. Thus, in DMSO *S. epidermidis* was most resistant bacteria and compound having no substitution group is most effective.

Figure 2 shows inhibition against Gram positive bacteria in DMF. Against *B. cereus* and *M. flavus,* all compounds shows inhibition and maximum was observed for NBN-3 and NBN-5 for *B. cereus* and NBN-10 for *M. flavus* respectively. Thus, for *B. cereus* p-bromo group (as in NBN-3) and m-nitro (as in NBN-5) are most effective whereas for *M. flavus* absence of any group (as in NBN-10) is most effective. For *S. epidermidis*, again only NBN-10 exhibited activity. Other compounds had no effect on this bacterium.

Thus, in DMF also, *S. epidermidis* is most resistant bacteria. For *M. flavus* and *S. epidermidis*, compound having no substitution group is most effective against Gram negative bacteria in DMSO, Figure 3 shows zone of inhibition for the studied compounds. It was evident that all compounds exhibited activity against *P. mirabilis* and activity was maximum for NBN-10 which has no substitution group. Against *S. typhimurium*, again only NBN-10 showed activity. For *K. pneumoniae*, NBN-3 had no effect and maximum is again observed by NBN-10.

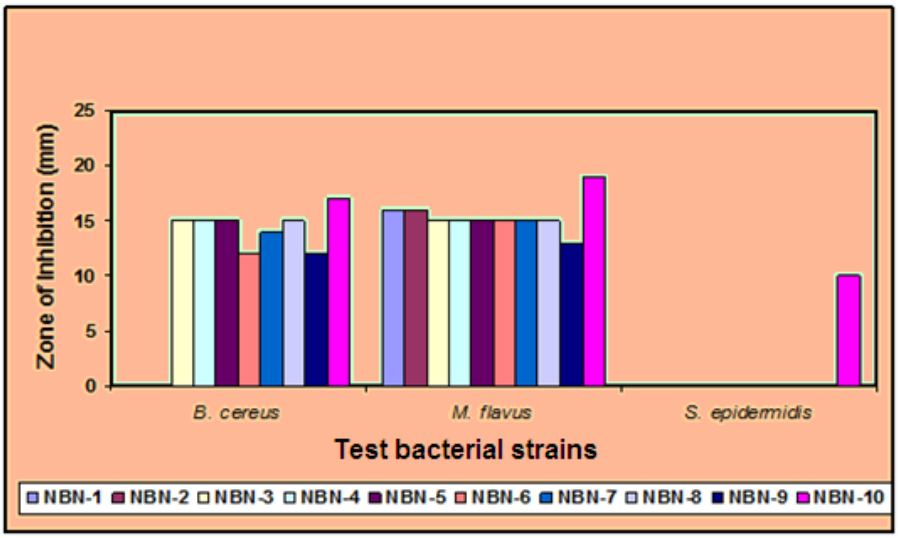



**Figure 1:** Antibacterial activity of benzodiazepines against Gram positive bacteria in DMSO.

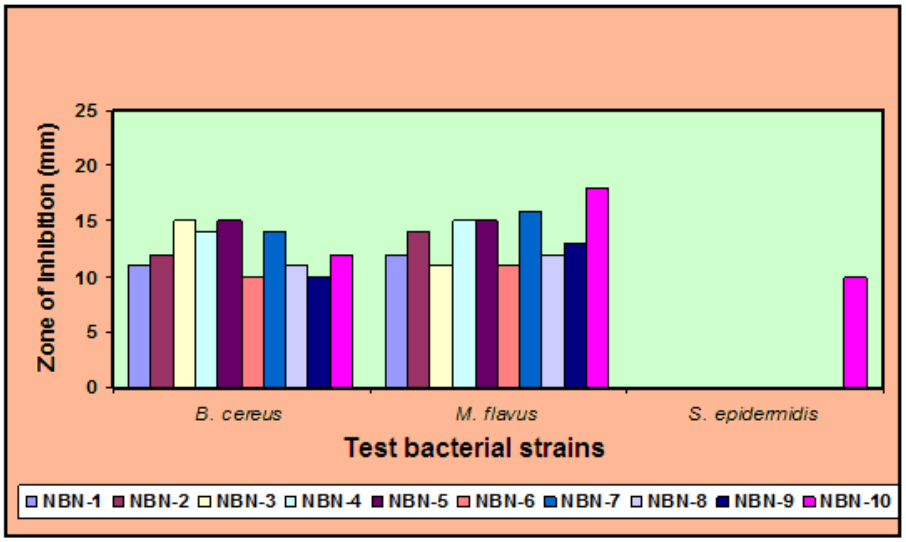



**Figure 2:** Antibacterial activity of benzodiazepines against Gram positive bacteria in DMF.

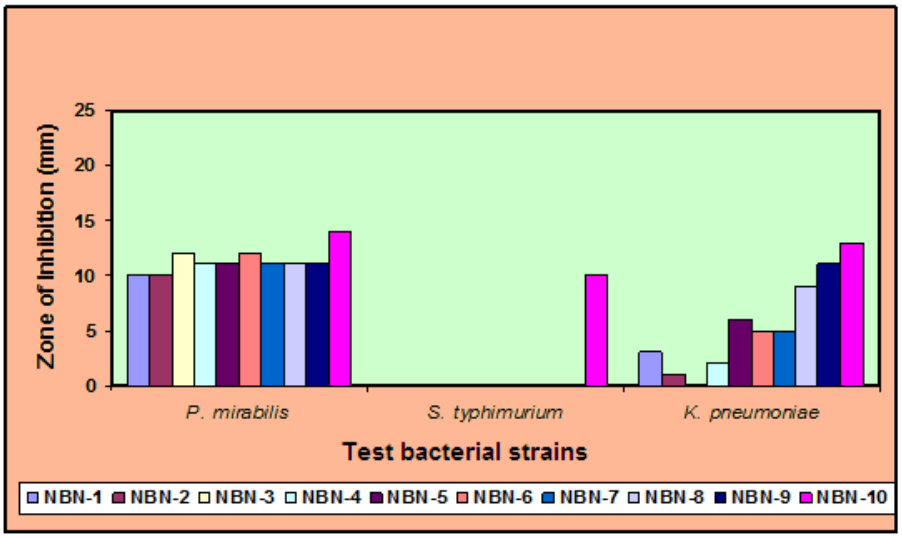



**Figure 3:** Antibacterial activity of benzodiazepines against Gram negative bacteria in DMSO.

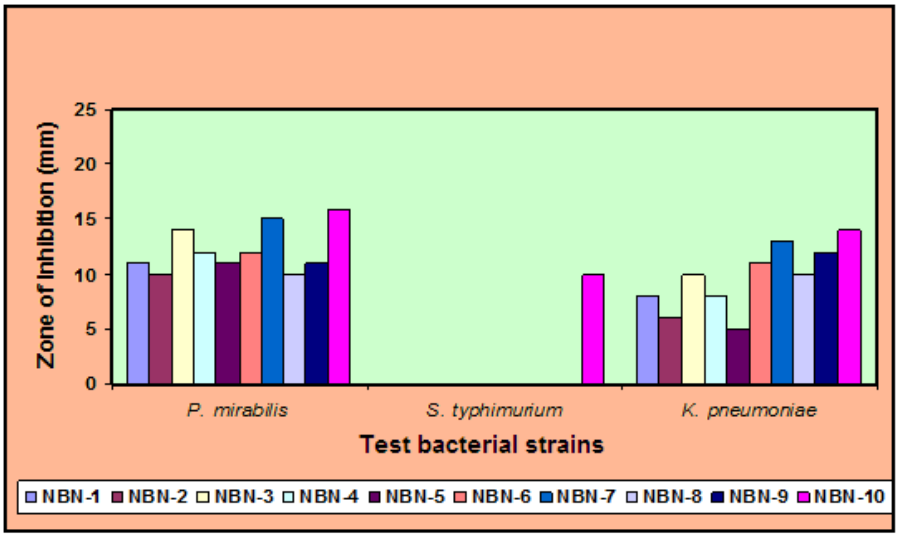



**Figure 4:** Antibacterial activity of benzodiazepines against Gram negative bacteria in DMF.

Thus, for the studied Gram negative bacteria, in DMSO, NBN-10 was most effective and *S. typhimurium* is most resistant bacteria. It is concluded that when there is no group attached to side chain, inhibition is maximum. Figure 4 shows zone of inhibition against Gram negative bacteria in DMF. It was evident that for all the three bacteria, NBN-10 showed maximum activity. Against *P. mirabilis*, minimum was observed by NBN-1 and NBN-2. For *K. pneumoniae,* NBN-5 showed minimum inhibition. For *S. typhimurium,* other compounds had no effect at all. Thus in DMF also, *S. typhimurium* is most resistant bacteria and compound with no substitution group is most effective.

Thus, for the studied benzodiazepine derivatives, although there is slight change in inhibition in the two solvents, the presence of substituent group affects inhibition and when there is no substitution group in the side change, compound exhibited maximum inhibition.

### *3.2.2 Aminopyrimidines:*

Figure 5 shows the zone of inhibition against Gram positive bacteria in DMSO. It was observed that NAP-8 exhibited maximum inhibition against all the studied Gram positive bacteria. Thus, for these compounds also, substitution affects inhibition. NAP-8 contains p-chloro group in side chain (as given in Table 2). Against *B. cereus*, only NAP-6 showed no inhibition. However, against *M. flavus* and S. aureus, many compounds are not effective. Thus, in DMSO for these Gram positive bacteria, p-chloro group in side chain is most effective. and *S. aureus* is most resistant bacteria.

In DMF, Figure 6 shows zone of inhibition against Gram positive bacteria. Again NAP-8 showed maximum inhibition against *B. cereus* and *S. aureus*. However, against *M. flavus,* NAP-9 showed slightly more inhibition. Figures 5 and 6 show inhibition is greater in DMF than in DMSO. In DMF, all the compounds showed inhibition against studied Gram positive bacteria.

Figures 7 and 8 show zone of inhibition against Gram negative bacteria in DMSO and DMF respectively. In DMSO, NAP-4, NAP-6 and NAP-7 showed no inhibition at all and NAP-8 exhibited maximum inhibition. Against *S. typhimurium* and *C. freundii,* only NAP-6 and NAP-2 respectively showed inhibition. Other compounds had

no effect at all. Whereas, in DMF, all the compounds exhibited inhibition against the studied Gram negative bacteria except NAP-7 for *C. freundii*. Against *P. mirabilis,* inhibition is more for NAP-2 and NAP-3. NAP-8 showed maximum inhibition for *S. typhimurium* and NAP-6 showed maximum against *C. freundii*.

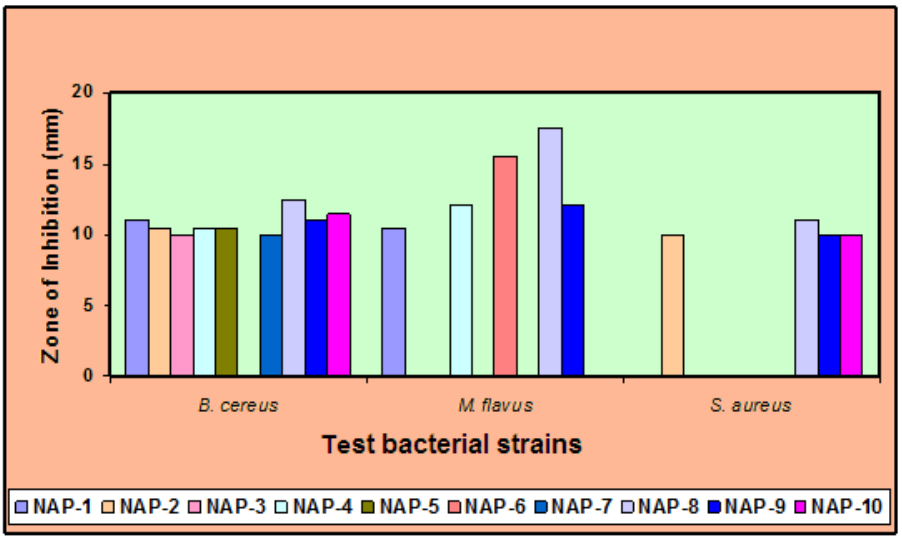



**Figure 5:** Antibacterial activity of aminopyrimidines against Gram positive bacteria in DMSO.

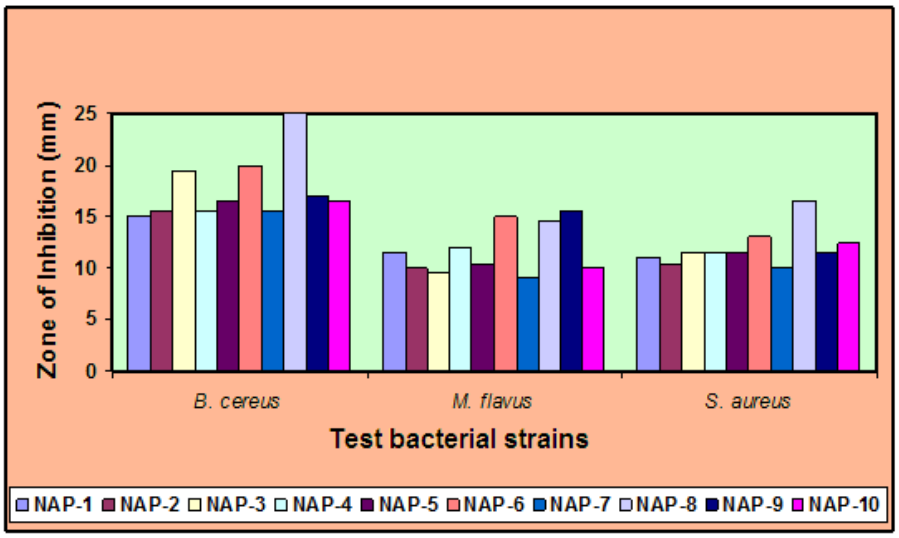



**Figure 6:** Antibacterial activity of aminopyrimidines against Gram positive bacteria in DMF.

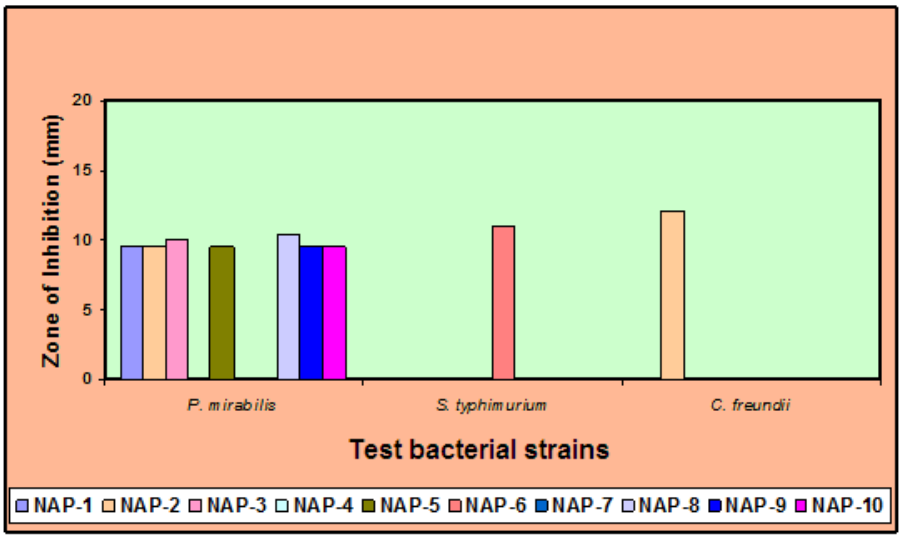



**Figure 7:** Antibacterial activity of aminopyrimidines against Gram negative bacteria in DMSO.

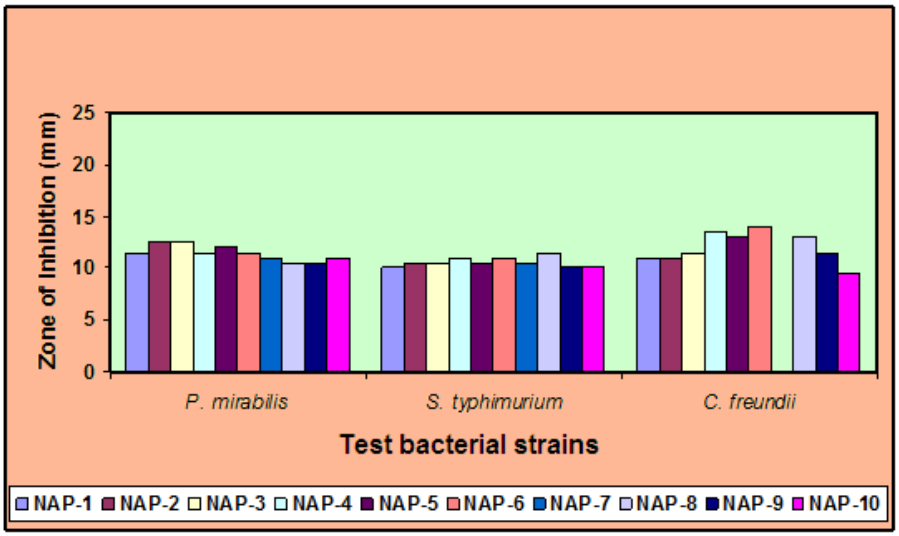



**Figure 8:** Antibacterial activity of aminopyrimidines against Gram negative bacteria in DMF.

Overall, there was not much difference in activity of these compounds against the studied bacteria. Thus, in this series of compounds, solvent and substitution play an important role in inhibition. Against both Gram positive bacteria, DMF is good solvent. p-chloro substitution (as in NAP-8) was found to be most effective in both DMSO and DMF against Gram positive bacteria.

Against Gram negative bacteria also, DMF is found to be good solvent where almost all the substituents were effective. However, p-amino, p- bromo, p-chloro and p-hydroxy groups are proved to be slightly better than others.

## CONCLUSION

For benzodiazepine derivatives, absence of substitution group increases inhibition against both Gram positive and Gram negative bacteria in both DMSO and DMF solvents. Further, in both the solvents, Gram positive bacteria *S. epidermidis* and Gram negative bacteria *S. typhimurium* were most resistant bacterial strains.

Among the synthesized aminopyrimidine derivatives, against Gram positive bacteria p-chloro substitution is most effective in DMSO and *S. aureus* is most resistant bacteria. In DMF also, p-chloro substitution is most effective. However, all the compounds exhibited significant inhibition. Against Gram negative bacteria, in DMSO, S. typhimunium and C. freudii are resistant bacteria whereas in DF, all the compounds showed inhibition. Thus, in aminopyrimidine derivatives, solvent and substitution play an important role in inhibition and DMF is good solvent against both Gram positive and Gram negative bacterial strains.

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