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Research Article

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# Synthesis and antimicrobial activity of pyrazine carboxamide derivatives

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**ABSTRACT**

*A series of pyrazine carboxamide derivatives was synthesized by the condensation of pyrazine-2-carboxylic acid chloride with various substituted amino pyridines. The structures of these derivatives were elucidated on the basis of IR, $^1$H-NMR and mass spectral data. These compounds were further evaluated for their antimycobacterial activity and antifungal activity.*

**Key Words:** Pyrazine carboxamide derivatives, Antimycobacterial activity and Antifungal activity.

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## INTRODUCTION

Pyrazine carboxamide derivatives have been reported to possess diverse pharmacological activities including antimicrobial activity, fungicidal activity, herbicidal activity, antioxidant activity and anti-algal activity [1-8]. A lot of work has been done on pyrazine derivatives for their antimicrobial activity. With a view to achieve better antimicrobial activity, the authors have synthesized pyrazine carboxamide derivatives by the condensation of pyrazine-2-carboxylic acid chloride with various substituted amino pyridines and have evaluated them for their antimicrobial activity.

## EXPERIMENTAL SECTION

The solvents and reagents used were of AR grade. The melting points were determined by capillary tube method. Purity of the compounds was checked by TLC using petroleum ether:ethyl acetate (8:2) and toluene:ethyl acetate:formic acid (5:4:1) as mobile phase. IR spectra were recorded on Perkin Elmer RX1 (KBr disc) spectrometer, $^1$H-NMR spectra were recorded on the Bruker Advance II 400 NMR spectrometer in $D_2O$, $CDCl_3$ and DMSO-$d_6$. Mass spectra were recorded with FAB mass spectrophotometer (Jeol SX-102).

**Synthesis of pyrazine-2-carbonyl chloride:**
A mixture of pyrazine-2-carboxylic acid, (50.0 mmol) and thionyl chloride (5.5 ml, 75.0 mmol) was taken in RBF and to this dry toluene (20 ml) was added. The resulting mixture was refluxed for about 1 hour. Excess of thionyl chloride was removed by repeated evaporation in vacuo with fresh dry toluene. The crude acyl chloride (PA) was collected and recrystallised from aqueous ethanol. Melting point = 160ºC; % Yield = 67%.

**Synthesis of pyrazine-2-carboxylic acid (5-chloro pyridine-2-yl) amide: ($P_1$):**
Pyrazine-2-carbonyl chloride (50.0 mmol) was dissolved in dry acetone (50 ml). This solution was added dropwise to a stirred solution of 2-amino-5-chloro-pyridine (50.0 mmol) in dry pyridine (50 ml) at room temperature. After addition, stirring was continued for 30 minutes. The reaction mixture obtained was poured into cold water (100 ml). The precipitate obtained was filtered to obtain title compound. The compound obtained was recrystallised from aqueous ethanol. IR (KBr; $cm^{-1}$) 3454.95 (N-H), 1625.00 (C=O), 1311.71 (C-Cl), 1395.25 (C-N); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 11.15 (s, 1H, NH), 8.89-9.94 (m, 3H, Ar-H), 5.46-7.38 (m, 3H, Ar-H); MS (m/z): 234 ($M^+$), 212, 191, 166, 154, 139 (100%), 131, 120, 102, 85.

Compounds $P_2$ to $P_8$ were synthesized by using the same method with corresponding substituted amine.

**Pyrazine-2-carboxylic acid (3-hydroxy pyridine-2-yl) amide ($P_2$):**
IR (KBr, $cm^{-1}$) 3432.31 (N-H), 1690.15 (C=O), 3360.23( O-H), 1372.63 (C-N); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 10.42 (s, 1H, NH), 9.28 (s, 1H, OH), 8.804-9.171 (m, 3H, Ar-H), 6.65-7.91 (m, 3H, Ar-H); MS (m/z): 216 ($M^+$, 100%), 205, 149, 138, 78.

**Pyrazine-2-carboxylic acid (5-nitro pyridine-2-yl) amide: ($P_3$):**
IR (KBr, $cm^{-1}$): 3435.26 (N-H), 1672.73 (C=O), 1557.49 and 1348.17 (Ar-$NO_2$); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 10.72 (s, 1H, NH), 9.06-9.34 (m, 3H, Ar-H), 8.43-8.81 (m, 3H, Ar-H); MS (m/z): 245 ($M^+$), 239, 218, 192 (100%), 171, 138, 127, 108, 77.

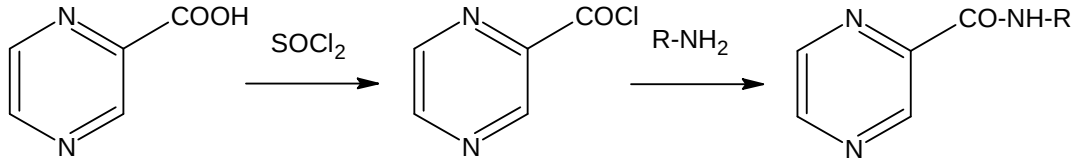
**Pyrazine-2-carboxylic acid (5-methyl pyridine-2-yl) amide ($P_4$):**
IR (KBr, $cm^{-1}$): 3349.66 (N-H), 1693.81 (C=O), 2924.39 (C-H in $CH_3$), 1389.58 (C-N); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 10.18 (s, 1H, NH), 8.79-9.30 (m, 3H, Ar-H), 7.68-8.20 (m, 3H, Ar-H), 2.12-2.27 (d, 3H, $CH_3$); MS (m/z): 214 ($M^+$), 200, 181, 166 (100%), 148, 119, 98, 84.

**Pyrazine-2-carboxylic acid (pyridine-2-yl) amide ($P_5$):**
IR (KBr, $cm^{-1}$): 3347.34 (N-H), 1696.97 (C=O), 1309.70 (C-N); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 10.10 (s, 1H, NH), 8.39-9.32 (m, 3H, Ar-H), 7.15-8.35 (m, 4H, Ar-H); MS (m/z): 200 ($M^+$), 188, 149, 110, 82 (100%).

**Pyrazine-2-carboxylic acid (6-methyl pyridine-2-yl) amide ($P_6$):**
IR (KBr, $cm^{-1}$): 3342.56 (N-H), 1692.41 (C=O), 2911.84 (C-H in $CH_3$), 1378.92 (C-N); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 10.18 (s, 1H, NH), 8.79-9.30 (m, 3H, Ar-H), 7.68-8.21 (m, 3H, Ar-H), 2.12-2.27 (d, 3H, $CH_3$); MS (m/z): 214 ($M^+$), 200, 181, 166 (100%), 148, 119, 98, 84.

**Pyrazine-2-carboxylic acid (pyridine-4-yl) amide ($P_7$):**
IR (KBr, $cm^{-1}$): 3351.64 (N-H), 1687.23 (C=O), 1313.75 (C-N); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 10.20 (s, 1H, NH), 8.79-9.32 (m, 3H, Ar-H), 7.18-8.39 (m, 4H, Ar-H); MS (m/z): 200 ($M^+$), 157, 113, 85 (100%).
.
**Pyrazine-2-carboxylic acid (3-methyl pyridine-2-yl) amide ($P_8$):**
IR (KBr, $cm^{-1}$): 3346.18 (N-H), 1683.74 (C=O), 2896.67 (C-H in $CH_3$), 1390.40 (C-N); $^1$H-NMR ($CDCl_3$, DMSO-$d_6$) δ ppm: 10.17 (s, 1H, NH), 8.77-9.31 (m, 3H, Ar-H), 6.46-8.22 (m, 3H, Ar-H), 2.11-2.26 (d, 3H, $CH_3$); MS (m/z): 214 ($M^+$), 164, 127, 98, 78 (100%).

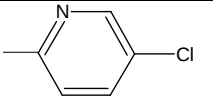
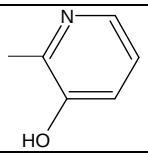
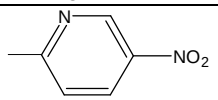
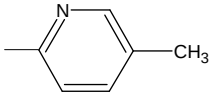
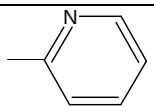
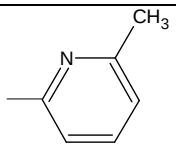
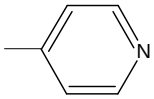
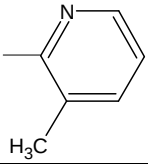
The general scheme for the preparation of pyrazine carboxamide derivatives ($P_1$ to $P_8$) is provided below.




Scheme-1

Physical characterization data and solubility data of pyrazine carboxamide derivatives ($P_1$ to $P_8$) is provided in Table I and Table II respectively.

**Table I: Physical characterization data of pyrazine carboxamide derivatives ($P_1$ to $P_8$)**

| Compound | R | Molecular Formula | M.P. (ºC) | % Yield | $R_f$ Value* |
|---|---|---|---|---|---|
| **$P_1$** |  | $C_{10}H_7ClN_4O$ | 115-117 | 65 | 0.71 |
| **$P_2$** |  | $C_{10}H_8N_4O_2$ | 172-173 | 60 | 0.82 |
| **$P_3$** |  | $C_{10}H_7N_5O_3$ | 233-234 | 45 | 0.52 |
| **$P_4$** |  | $C_{11}H_{10}N_4O$ | 182-183 | 51 | 0.65 |
| **$P_5$** |  | $C_{10}H_8N_4O$ | 131-132 | 53 | 0.43 |
| **$P_6$** |  | $C_{11}H_{10}N_4O$ | 210-211 | 43 | 0.49 |
| **$P_7$** |  | $C_{10}H_8N_4O$ | 140-141 | 48 | 0.55 |
| **$P_8$** |  | $C_{11}H_{10}N_4O$ | 195-196 | 31 | 0.42 |

**$R_f$ value were determined in toluene:ethyl acetate:formic acid (5:4:1)*

**Table II: Solubility data of pyrazine carboxamide derivatives**

| Compound | Solvent | | | | |
|---|---|---|---|---|---|
| | **Water** | **Chloroform** | **Methanol** | **Ethanol** | **Dimethylsulfoxide** |
| **$P_1$** | Insoluble | Soluble | Soluble | Soluble | Soluble |
| **$P_2$** | Sparingly soluble | Sparingly soluble | Soluble | Soluble | Soluble |
| **$P_3$** | Insoluble | Soluble | Soluble | Soluble | Soluble |
| **$P_4$** | Insoluble | Soluble | Sparingly soluble | Soluble | Soluble |
| **$P_5$** | Insoluble | Soluble | Soluble | Sparingly soluble | Soluble |
| **$P_6$** | Insoluble | Sparingly soluble | Soluble | Soluble | Soluble |
| **$P_7$** | Insoluble | Sparingly soluble | Sparingly soluble | Soluble | Soluble |
| **$P_8$** | Insoluble | Insoluble | Soluble | Soluble | Soluble |

The synthesized pyrazine carboxamide derivatives were evaluated for their antimicrobial activity by established procedure [5, 7, 9].

**Antimycobacterial activity:**
Antimycobacterial activity was carried out at the Department of Microbiology, Patel Chest Institute of TB and Chest, Delhi University. Primary screening of all compounds was conducted at 6.25µg/ml against *Mycobacterium tuberculosis* strain H37Rv in Lowenstein-Jensen medium using pyrazinamide as standard drug.

**Antifungal activity:**
Antifungal activity was carried out by disc diffusion technique. All the compounds were tested at 50µg/ml against *Aspergillus niger* and *Candida albicans* using fluconazole as standard drug.

The antimycobacterial activity data and antifungal activity data of pyrazine carboxamide derivatives ($P_1$ to $P_8$) is provided in Table III.

**Table III: Antimycobacterial and antifungal activity of pyrazine carboxamide derivatives**

| Compound | *M. tuberculosis* | *A. niger* | *C. albicans* |
|---|---|---|---|
| **$P_1$** | +++ | + | ++ |
| **$P_2$** | - | + | +++ |
| **$P_3$** | ++ | ++ | ++ |
| **$P_4$** | + | - | + |
| **$P_5$** | ++ | - | - |
| **$P_6$** | + | + | - |
| **$P_7$** | - | - | - |
| **$P_8$** | ++ | + | + |
| **Standard** | +++ | +++ | +++ |
| **Control (Dimethylformamide)** | - | - | - |

*$^{+++}$Excellent, $^{++}$Very good, $^{+}$Good, $^{-}$No activity.*

## RESULTS AND DISCUSSION

The pyrazine carboxamide derivatives ($P_1$ to $P_8$) were synthesized as per Scheme-1 by the condensation of pyrazine-2-carboxylic acid chloride with various substituted amino pyridines. The structures of pyrazine carboxamide derivatives ($P_1$ to $P_8$) were elucidated on the basis of IR, $^1$H-NMR and mass spectral data. Physical characterization data of pyrazine carboxamide derivatives ($P_1$ to $P_8$) is provided in Table I. The solubility data of pyrazine carboxamide derivatives ($P_1$ to $P_8$) is provided in Table II. The pyrazine carboxamide derivatives ($P_1$ to $P_8$) were further evaluated for their antimycobacterial activity and antifungal activity. The antimycobacterial activity data and antifungal activity data of pyrazine carboxamide derivatives ($P_1$ to $P_8$) is provided in Table III. Antimycobacterial activity of pyrazine carboxamide derivatives ($P_1$ to $P_8$) revealed that compound $P_1$ showed highest activity that was comparable to standard drug pyrazinamide. Compounds $P_3$, $P_5$, $P_6$ and $P_8$ also showed activity but to a lesser extent than standard while compounds $P_2$ and $P_7$ were inactive against *M. tuberculosis*. Antifungal activity of pyrazine carboxamide derivatives ($P_1$ to $P_8$) against *C. albicans* revealed that compound $P_2$ showed highest activity that was comparable to standard drug fluconazole. Compounds $P_1$, $P_3$, $P_4$ and $P_8$ also showed activity but to a lesser extent than standard while compounds $P_5$, $P_6$ and $P_7$ were inactive against *C. albicans*. Antifungal activity of pyrazine carboxamide derivatives ($P_1$ to $P_8$) against *A. niger* revealed that compounds $P_1$, $P_2$, $P_3$, $P_6$ and $P_8$ showed activity but to a lesser extent than standard while compounds $P_4$, $P_5$ and $P_7$ were inactive. The combined results of antimycobacterial activity and antifungal activity revealed that compound $P_3$ showed good activity against *M. tuberculosis, C. albicans* as well as *A. niger* while compound $P_7$ was inactive against *M. tuberculosis, C. albicans* as well as *A. niger*.

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