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# Synthesis of Nicotinamide Analogues as Antimicrobial Agents

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## Abstract:

The objectives of the present study is to synthesize nicotinamide analogues and to bring two moieties together i,e. amines and Nicotinyl chloride. Nicotinyl amines derivatives have been employed for various pharmacological activity like analgesic, anti-inflammatory, anti-microbial, anticonvulsant, antcancer and antiviral. Reaction of nicotinic acid with Amines in the presence of thionyl chloride resulted in Nicotinyl Amines derivative. In the light of this information, the present study we have reported the synthesis of some novel heterocyclic derivatives comprising Nicotinyl amines containing moiety. An attempt has already been made by our research to obtain new nicotinamide compounds with improved pharmacological activities. It is our endeavor, to attach nicotinyl chloride with other different moieties by appropriate synthetic routes. The use of antimicrobial agents is critical to successful treatment of infectious diseases. Although there are numerous classes of drugs that are routinely used to treat infections in humans, there are several reasons why the discovery and development of new antimicrobial agents are important. The antibacterial activity of the synthesized compounds was evaluated by cup plate method. The structures of the compounds were elucidated by spectral studies and screened for antibacterial activity against various strains of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi*. The derivatives have shown moderate to good activity when compared with standard antibiotic Ciprofloxacin.

**Keywords:** Nicotinamide, Nicotinic acid, Pyridine, Amines, and Antimicrobial activity.

## Introduction

The pyridine nucleus is an important heteroaromatic class of compounds with a wide range of activities and it is present in many products such as drugs, vitamins, food, flavorings, plants,
dyes, rubber products, adhesives, insecticides and herbicides.[1] In this context, nicotinic acid (pyridine-3-carboxylic acid), also known as niacin and vitamin $B_3$, is found in various plants and animals and has vital roles in such biological processes as production of energy, signal transduction, regulation of gene expression and synthesis of fatty acids, cholesterol and steroids.[2,3] Nicotinic acid derivatives and its isomers have also been investigated as an agent for the prevention or delay of the onset of type 1 diabetes mellitus.[2] They also have anti-bacterial, anti-oxidant, anti-inflammatory and anti-carcinogenic activities, and have putative activity against osteoarthritis and granuloma annulare.[3]

Vitamin $B_3$ is also known as niacin or nicotinic acid. It is an organic compound that has a molecular formula of $C_6H_5NO_2$ and it is also one of the 40-80 of the essential human nutrients. The Nicotinamide are different with niacin in terms of its pharmacological effects. Nicotinamide derivatives can be used in the treatment of tuberculosis, acne, skin cancer, type-I diabetes, hypercholesterolemid and schizophrenia.[3]



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## Materials and Methods

The reaction scheme is given in figure I. Various basic moieties is given in table 1 and final products is given in table 2.

## Reaction Scheme

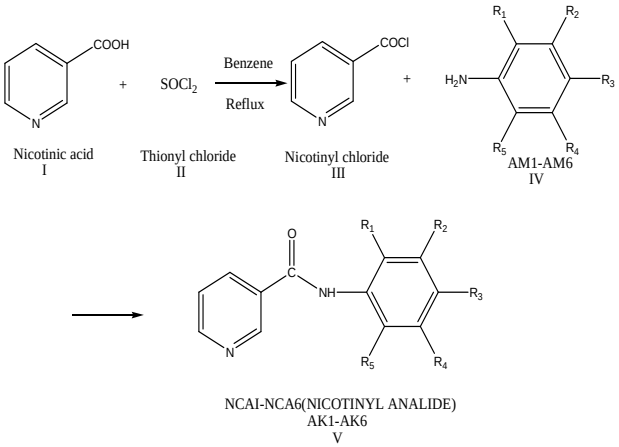


**Figure I** Reaction Scheme

**Various Basic Moities**

| Sr. No | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| AM1 | H | $NO_2$ | H | H | H |
| AM2 | H | H | I | H | H |
| AM3 | H | H | Br | H | H |
| AM4 | H | H | $NO_2$ | H | H |
| AM5 | Br | H | Br | H | Br |
| AM6 | H | H | $SO_3H$ | H | H |

**Table 1** Various Basic Moities

**Nicotinamide Analogous**

| Sr. No | R1 | R2 | R3 | R4 | R5 |
|---|---|---|---|---|---|
| AK1(NAC) | H | $NO_2$ | H | H | H |
| AK2(NAC) | H | H | I | H | H |
| AK3(NAC) | H | H | Br | H | H |
| AK4(NAC) | H | H | $NO_2$ | H | H |
| AK5(NAC) | Br | H | Br | H | Br |
| AK6(NAC) | H | H | $SO_3H$ | H | H |

**Table 2** Nicotinamide Analogous

**N-(3-nitrophenyl) Nicotinamide (AK1):** 1.23 gm (0.01 mol.) of Nicotinic acid was taken in a flask. Then 12.1 ml of thionyl chloride was added to it. It was heated for 45 minutes. Then excess of thionyl chloride was removed by distillation process. Then 1.38 gm (0.01 mol.) of m-Nitroaniline and 25 ml of anhydrous benzene was refluxed for two hours and kept overnight. The solid was filtered and recrystallized from absolute ethanol to give product. 1656(C=O), 3370(-N-H), 1530(C-$NO_2$). 1H NMR (300 MHz, $CDCl_3$-$d_6$): δ= 8.3-8.4(d, 2pyridine), 7.3(s,NH), 8.7 (d,2',benzene). m/z (243) [ $M+H]^+$.[4,5,6,7]

**N-(4-Iodophenyl) Nicotinamide (AK2):** 1.23 gm (0.01 mol.) of nicotinic acid was taken in a flask. Then 12.1 ml of thionyl chloride was added to it. It was heated for 45 minutes. Then excess of thionyl chloride was removed by distillation process. Then 2.18 gm (0.01 mol.) of p-Iodoaniline and 25 ml of anhydrous benzene was refluxed for two hours and kept overnight. The solid was filtered and recrystallized from absolute ethanol to give product.1656(C=O), 3370(-N-H), 550(C-I) $^1$H NMR (300 MHz, $CDCl_3$-$d_6$): δ= 8.3(d, 2-pyridine), 7.4(s,NH), 8.7 (d, 3'-benzene). m/z (324) [ $M+H]^+$.[4,5,6,7]

**N-(4-Bromophenyl) Nicotinamide (AK3):** 1.23 gm (0.01 mol.) of nicotinic acid was taken ina flask. Then 12.1 ml of thionyl chloride was added to it. It was heated for 45 minutes Then excess of thionyl chloride was removed by distillation process. Then 1.71 gm (0.01 mol.) of p-Bromoaniline and 25 ml of anhydrous benzene was refluxed for two hours and kept overnight. The solid was filtered and recrystallized from absolute ethanol to give product.1656(C=O), 3370(-N-H), 705 (C-Br) $^1$H NMR (300 MHz, $CDCl_3$-$d_6$): δ= 8.1(d, 2pyridine), 7.2(s,NH), 7.8 (d,2'-benzene). m/z (263) [ $M+H]^+$.[4,5,6,7]

**N-(4-nitrophenyl) Nicotinamide (AK4):** 1.23 gm (0.01 mol.) of nicotinic acid was taken in a flask. Then 12.1 ml of thionyl chloride was added to it. It was heated for 45 minutes. Then excess of thionyl chloride was removed by distillation process. Then 1.38 gm (0.01 mol.) of p-Nitroaniline and 25 ml of anhydrous benzene was refluxed for two hours and kept overnight. The solid was filtered and recrystallized from absolute ethanol to give



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product. 1656(C=O), 3370(-N-H), 1530(C-$NO_2$). $^1$H NMR (300 MHz, $CDCl_3$-$d_6$): δ= 8.3(d, 2pyridine), 8.7(d,2'benzene), 7.5 (s, NH). m/z(243) [ M+H]$^+$.[4,5,6,7]

**N-(2,4,6-Tribromophenyl) Nicotinamide (AK5):** 1.23 gm (0.01 mol.) of nicotinic acid was taken in a flask. Then 12.1 ml of thionyl chloride was added to it. It was heated for 45 minutes. Then excess of thionyl chloride was removed by distillation process. Then 3.28 gm (0.01 mol.) of 2, 4, 6-tribromoaniline and 25 ml of anhydrous benzene was refluxed for two hours and kept overnight. The solid was filtered and recrystallized from absolute ethanol to give product. 1656(C=O), 3370(-N-H), 705(C-Br). $^1$H NMR (300 MHz, $CDCl_3$-$d_6$): δ= 8.1(d, 4-pyridine), 7.86(s, 3'-benzene), 7.04 (s, NH). m/z (435) [ M+H]$^+$.[4,5,6,7]

**4-(Nicotinamido) Benzenesulphonic acid (AK6):** 1.23 gm (0.01 mol.) of nicotinic acid was taken in a flask. Then 12.1 ml of thionyl chloride was added to it. It was heated for 45 minutes. Then excess of thionyl chloride was removed by distillation process. Then 1.73 gm (0.01 mol.) of sulfonic acid and 25 ml of anhydrous benzene was refluxed for two hours and kept overnight. The solid was filtered and recrystallized from absolute ethanol to give product.1656(C=O), 3370(-N-H), 1708($SO_3$H). $^1$H NMR (300 MHz, $CDCl_3$-$d_6$): δ= 7.9(d, 2-pyridine), 7.9(d , 3'-benzene), 7.6 (s, NH). m/z (278) [ M+H]$^+$.[4,5,6,7]

## Physicochemical data

Physicochemical data is given in Table 3.

| Compound Code | Molecular Formula | Molecular Weight | Colour | Solubility | Melting Point (°C) |
|---|---|---|---|---|---|
| AK1 | $C_{12}H_9O_3N_3$ | 243 | Yellow | Ethanol | 122 |
| AK2 | $C_{12}H_9ON_2I$ | 324 | Black | Ethanol | 68 |
| AK3 | $C_{12}H_9ONBr$ | 263 | Reddish brown | Ethanol | 160 |
| AK4 | $C_{12}H_9O_3N_3$ | 243 | Brown yellow | Ethanol | 74 |
| AK5 | $C_{12}H_7ON_2Br_3$ | 435 | Creamy | Ethanol | 265 |
| AK6 | $C_{12}H_{10}N_2O_4S$ | 278 | Water | water | 230 |

**Table 3:** Physicochemical data

## Antimicrobial Activity

All the synthesized compounds were evaluated in vitro against *Staphylococcus aureus* ,*Escherichia coli, Pseudomonas aeruginosa* and *S. typhi.* using the cup plate method with nutrient agar as the culture medium. A suspension of the bacterial spore was prepared with tween 80 (0.01%) in normal saline. Liquid agar medium was poured (50 ml) into each Petri dish (15 cm diameter). The solid agar medium was inoculated with the bacterial suspension and the plates were then dried in an incubator at 37 °C for 1 h. Wells were made by an agar punch on these seeded agar plates and solutions of the test compounds in DMSO were added into each well, which were labelled previously. Ciprofloxacin was used as standard for comparison of antibacterial activity. Solvent dimethyformamide was used as control. The antibacterial activity of each compound was compared against standard ciprofloxacin and the results are summarized in Table 4.[8]

| Compound Code | Zone of inhibition (in mm) | | | |
|---|---|---|---|---|
| | S. aureus | E. Coli | S. typhi | P. aeruginosa |
| AK1 | 4 | 5 | 6 | 4 |
| AK2 | 4 | 3 | - | 5 |
| AK3 | 2 | 3 | - | 2 |
| AK4 | 3 | 4 | 5 | 4 |
| AK5 | - | - | 4 | 3 |
| AK6 | 3 | - | 6 | 5 |
| DMSO | - | - | - | - |
| Ciprofloxacin (Control) | 12 | 11 | 12 | 12 |

**Table 4**: Antibacterial Activity

## Discussion.

Synthesis of all targeted compounds was confirmed from the result of the spectral and physiochemical analysis of the compounds. Basic moieties were prepared from aniline. The melting points of all the synthesized compounds were recorded. The



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physicochemical properties of the nicotinamide analogues were found to be in agreement with those reported with literature. NMR and IR spectra of selected compounds were recorded. The data was analyzed to confirm structures of all the synthesized compounds. The final synthesized test compounds were screened for their antibacterial activity. DMSO was used as control. Zone of inhibition of the synthesized compounds was compared with ciprofloxacin.

## Conclusion

The present work has been undertaken for the synthesis of nicotinamide analogues. A novel series of analogues were synthesized by refluxing nicotinyl chloride with different aniline derivatives. The yield of synthesized compounds was found to be in a range from 40-55%. All the newly synthesized compounds were characterized on the basis of their physical, spectral and analytical data. The IR spectra and NMR spectra of the compounds were studied and found to be correct. All the compounds showed good to moderate antimicrobial activity for the organism *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Salmonella typhi.*

## Conflict of interest statement

We declare that we have no conflict of interest.

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