J. Environ. Nanotechnol.
Volume 4, No.1 (2015) pp. 19-22
ISSN (Print): 2279-0748
ISSN (Online): 2319-5541
doi: 10.13074/jent.2015.03.144137

Designing and Synthesis of *N*-(6-phenylpyridin-2-yl) Pyridine-2-amine Derivatives as a Novel Antimicrobial Agent

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Received: 20.01.2015 *Accepted: 13.02.2015* *Published: 30-03-2015*

Abstract

A new series of N-(-6-phenylpyridin-2-yl) pyridine-2-amine derivatives were synthesized in satisfactory yield, through simple and greener methodology using 2-Amino, 6-Chloro, Pyridines as a starting material. Some of the newly prepared compounds demonstrate potent inhibitory activity against Gram positive bacteria, Gram negative bacteria and fungai. The results are discussed in terms of structure-activity relationships and an attempt was made to define the structural features required for activity.

Keywords: *Diaryl amino Pyridine; Antibacterial; Antifungal Water.*

1. INTRODUCTION

The rapid development of resistance clinically important Gram positive bacteria represents a serious public health threat (Alaa *et al.* 2005). Staphylococcus aureus is a common cause of many skin and mucpus membrane infection. Many strain have developed resistance and antibiotic treatment option have become more limited(Alaa *et al.* 2005).

Opportunistic infection (OIS) may be caused by fungai, bacteria, viruses, or parasites. Symptoms may vary according to the microorganisms involved and extent of their involvement. Conditions leading to the immunodeficiency, including malnutrition, recurrent infection, immunosuppressive agent for organ transplant recipient, chemotherapy for cancer, acquired immunodeficiency syndrome (AIDS), genetic predisposition, antibiotic treatment, medical procedures and pregnancy among others expose these individuals to the risk of OIS. The most prevalent of these conditions is AIDS and since discovery of AIDS (hiv) IN 1981, A steady increase in the number of people worldwide living with HIV has been reported. This number is according to WHO, has risen from around 8 million in 1990 to about 33 million and is still growing. Since 1981, more than 25 million people have died of AIDS and a large percentage of these individuals mostly die from Opportunistic infection or malignancies associated with the progressive failure of the immune system. In additional to immune-suppressed patients, there are indications in the literature that even immunocompetent individuals may be at risk for some Opportunistic infections. Candida albicans, Cryptococcus neoformans and asper gillus fumigates are three most common fungal pathogens responsible for Opportunistic infections in humans. The current treatment options for the cure of these fungal pathogens are limited by toxicity,resistant development and drug interactions among others**.** Consequently, new drug entities especially those with new mechanism of action are of great need.

Actually, no new class of antibiotics have been introduced in the market in the 37 years between the introduction of nalidixic acid 1962 and linezolid in 2000. All the antibacterials introduced in these period were modifications of the existing molecules. Bacteria have exploited this window of opportunity by developing resistance to all commonly used antibiotics, making the need for new antibiotic more pressing. Therefore, the antifungal and antibacterial properties of substituted pyridines have opened up the possibility of their potential use as a novel class of antimicrobial agents(Barré-Sinoussi *et al.* 1983). 2-Aminopyridens are promising substituted pyridines which have been show to biologically active molecules (Popovic *et al.* 1983; Mitsuya *et al*. 1984). Additionally, because of their chelating abilities, 2-aminopyridines are commonly used as ligands in inorganic and organometallic chemistry (Mitsuya *et al*. 1984). if substituted with optically active groups, they could

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serve as a chiral auxiliaries or chiral ligands in asymmetric reaction. For these reasons,2-aminopyridines derivatives has been extensively reviewed. 2- [substituted amino] pyridines were previously mostly prepared: (1)by reaction of primary or secondary aliphatic amines with 2-halopyridines mary or secondary aliphatic amines with 2-halopyridines or with imidolsilyl ethers derives from the corresponding pyrid-2-ones,14(2)by aminolysis of 2-alkoxypyridines, and (3)by using methodology previously described by katritzky et al.16 of these methods, previously described by high temperatures and high pressure while pathway(2)proceeds with alkoxypyridines containing activating groups in the pyridine ring under strong basic condition, high temperatures, and long reaction time. Method (3)worked reasonably well with simple secondary aminopyridine products when anilines or primary amines were employed as nucleophiles.hence ,a versatile route for the synthesis of nucleophiles .hence ,a versatile route for the synthesis of n-substituted 2-aminopyridines utilizing primary and secondary amines as nucleophiles under mild condition is highly desirable. In a recent paper we have reported the synthesis of *N*-(-6-phenylpyridin-2-yl) pyridine-2-amine derivatives from substituted 2-amino pyridines. *N*-substitution of 2-aminopyridines utilizing primary and secondary aryl amine has done in acid. All synthesized derivatives has treat against gram positive and gram negative bacteria, fungai, result has discussed in terms of structure activity relationship.

2. RESULTS AND DISCUSSION

2.1 A Biological activity

We have developed synthesis of *N*-(6-phenylpyridin-2-yl) pyridine-2-amines using seffer route (scheme1). The starting material required for for the synthesis of biodynamic scaffolds are easily available and details regarding the synthesis given as below.

2.2 Scheme 1 Synthesis of *N*-(6-phenylpyridin-2-yl) pyridine-2-amine

Synthesis of pyridine derivatives from 2-Amino 6-chloro pyridine (**1**) was done with Coupling of Phenyl boronic acid with 2-amino 6-chloro pyridine (**1**) was carried out in 1-4 - dioxanes by using 10% Pd/C as catalyst gave intermediate (**2**) in 82% yield. Obtained amine intermediate (**2**) was coupled with 2-Chloro5-substituted pyridine to get various DAPY (diaryl amino pyridine) series of compounds **3**(A-J). Compounds **3**(A-J) were further methylated with MeI in THF **4**(A-J). It is noteworthy to mention that the key step for the syhthesis of Diaryl amino pyridine derivaties is N-arylation of aromatic amine **(2)** with verrious substituted pyridines(3A-3J).

N-arylation of compound **2** was done with verrious 2-Chloro-5-substituted pyridine derivaties in water. It was found that reaction goes smoothly on the substituted pyridine derivaties. We observed that as electron withdrawing capacity substitutent on 5 position of pyridine increases the reaction rate and yield. We belived that this is the novel, simple and greener methodology for *N* arylation of aromatic compound.

Reaction of Aromatic amine (2) with 2-chloro-5-nitro pyridine goes at rt in water within 30 min. solid was fall out as reaction progress.

We have carried the reaction of Compound (2) with substituted pyridines (without nitro group at 5 position) at reflux in water for 3 hr. from this it was noticed that prolonged reaction time required for the completion of reaction. Keeping these result in mind we have attempted above reaction by adding catalytic amount of aq. HCl.

It was observed that reaction completed within 30 – 45 min. with better yield of Diaryl amino pyridine derivatives.

In such type of reaction we can inhanced reaction rate either increase nucleophilicity of Aromatic Amine (2) or increase electron deficiency at 2-position of substituted pyridine derivatives. We had kept amine (compound2) constant and change was made on substituted pyridine derivatives to make electron deficiency at 2 position.

2-position of pyridine derivatives can be made electron deficient by keeping electron withdrawing substittent at 5 position. These reaction *N*-arylation or SNAri reaction works well with electron withdrawing group such as nitro, and cyno group. Long reaction time and low yield was observed in case of substitutent having electron donating group.

In Such cases to felicitate reaction rate and inhanced yield we have added 1-2 drops of Aq. HCl in catalytic amount. Addition of Aq. HCl result in inhanced reaction rate and yield in case of electron donating substituent on pyridine ring.

Reaction rate might be inhanced due to reaction of aq. HCl with pyridine nitrogen result in to salt formation which increases solubility in aq medium and make 2-position of pyridine derivatives electron deficient.

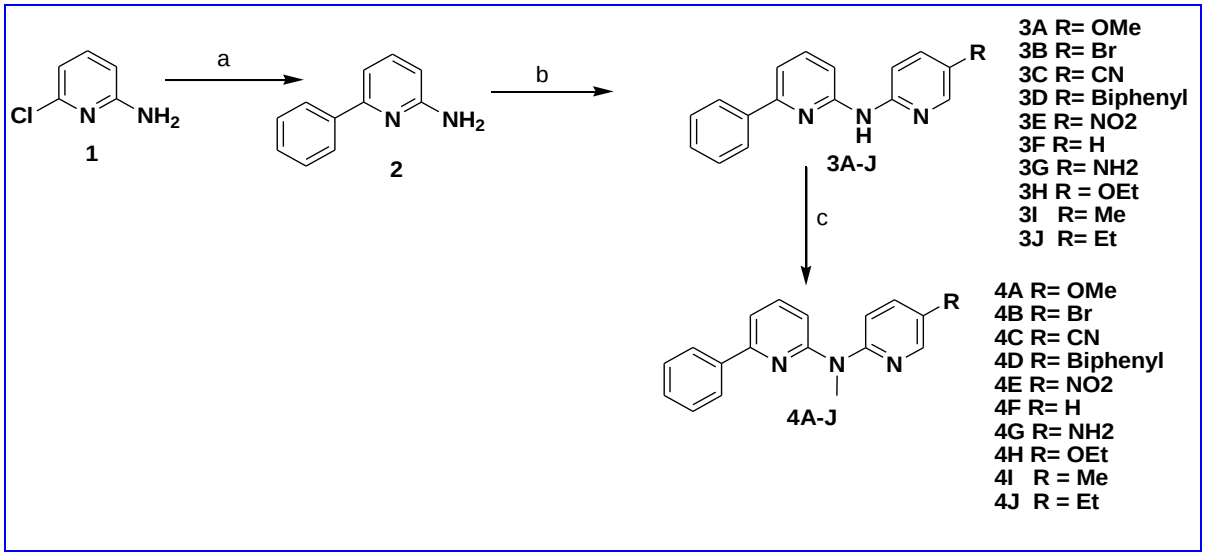

Fig. 1: Reactions and conditions: (a) Dioxane, Phenyl Boronic Acid, 10% Pd/C, K_2CO_3, 100 ^{0}C, 2h, 82%; (b) water,(1-2ml of dil HCl) 110 ^{0}C, 1h, 58%; (c) THF, NaH, MeI, rt, 1h, 90%

2.2 B Biological Activity

In order to search for the potent compound, the newly synthesized compounds **(3A-JJ) and (4A-4J)** were evaluated for their antibacterial and antifungal activity against various Gram-positive, Gram-negative bacteria and fungal strains using agar well diffusion method. The antimicrobial evaluation data is represented in Table 1. As can be seen from our results, many compounds from the newly synthesized series found to be potent antibacterial and antifungal agents. Thus the compounds **3A**, **3G, 3H, 3F and 3I,** (Table 1) exhibited more potent antibacterial and antifungal activity than the standard Streptomycin and Nystatin respectively, against all the tested bacteria or fungi.

While Compounds 3B, 3C, 3D, 3E (Table 2) exhibited Comparable antibacterial and antifungal activity than the standard Streptomycin and Nystatin respectively, against all the tested bacteria or fungi.

Compound 4A, - 4J and 3I, was found to be less potent antibacterial and antifungal activity than the standard Streptomycin and Nystatin respectively, against all the tested bacteria or fungi.

Free amine derivatives (3A-3J) were found to be more potent in antifungal activity and antibacterial activity than n-protected (4A-4J) derivatives. Which indicate free nitrogen are essential for activity.

From SAR study of above derivaties it was observed that as electron donating capacity of substitutent group on phenyl group increases then antibacterial and antifungal activity increase. The increase Activity order of substitutent was found to be NO2 < CN < Biphenyl < H < Br < Me < Et < OMe < OEt < NH2.

The twenty Diaryl aminopyridine derivatives (**3A–3J**) and (4A-4J) were synthesized evaluated for their antimicrobial activity. Out of the synthesized compounds seven analogues have shown MIC in the range of 5.25-6.5 µg/mL. The compounds **3A**, **3G, 3H, 3I, and 3J** were found to more potent antibacterial and antifungal agents than standard Streptomycin. Thus the presence of aromaticity and lipophilicity found to have strong relevance to the antimicrobial activity. These identified Diaryl amino pyridine analog molecules are very useful for further optimization work in microbial chemotherapy.

CONCLUSION

We have developed convenient synthetic route for the synthesis of new diaryl pyridines using environmental benign and ecosustanable protocol. The starting materials required for the synthesis are easily available. Some of these synthesized derivatives were found to be potent Antimicrobial agent.

ACKNOWLEDGMENT

The authors acknowledge the financial support from UGC, [F. No. 39-774/2010 (SR)], New Delhi and

are grateful to Principal of S.C.S. College, Omerga for providing the necessary laboratory facilities.

FUNDING

This research received grant from UGC, New Delhi, India [F. No. 39-774/2010 (SR)].

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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