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# A facile synthesis and antimicrobial activity of some new 2-subsituted benzimidazole derivatives carrying pyridine

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**ABSTRACT**

*Some new 2-amino-6-(1H-benzimidazol -2-yl)-4- phenyl pyridine -3- carbonitriles have been synthesized and evaluated for antimicrobial activity. 2-Acetyl Benzimidazoles (1) were reacted with appropriately substituted benzaldehydes (2) in presence of ethanol to furnish substituted chalcones (3a-f). These chalcones were further treated with Malononitrile & Ammonium Acetate to afford substituted 2-amino-6-(1H-benzimidazol -2-yl)-4- phenyl pyridine -3- carbonitriles (4a-f). The structure of newly synthesized compounds (4a-f) has been confirmed on the basis of spectral data and elemental analysis. All the compounds were screened for their antibacterial activity against K. pneumonae, B. subtilis, E. coli and P. pseudomonas and for antifungal activity against C. albicans and A. niger. The compounds exhibited good antibacterial and moderate antifungal activities.*

**Keywords:** Benzimidazole, Malononitrile, Ammonium Acetate, Antibacterial, Antifungals.

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## INTRODUCTION

Chemistry is critical to drug discovery, especially at the lead optimization phase, but methods for the synthesis of organic compounds have remained essentially unchanged for decades. Since lead optimization time is usually very long with a very high manpower requirement, new ways to improve the efficiency, output and quality in this phase are always needed.

Life-threatening infections caused by pathogenic fungi are becoming increasingly common, especially in individuals with suppressed immune systems such as cancer chemotherapy or AIDS patients. However, there are only a limited number of pharmacological compounds available for such infections, which leads to a strong need to develop new classes of compounds having antifungal activities.

Small ring heterocycles containing nitrogen, sulfer, and oxygen have been under investigation for a long time because of their important medicinal properties[1]. Compounds bearing benzimidazole moiety are reported to possess a number of interesting biological activities such as antitubercular[2], anticancer[3,4], anthelmintic[5], antiallergic[6,7], antioxidant[8−10], antihistaminic[11] and antimicrobial[12−18]. Also 2-pyrazolines have been reported to possess a variety of significant and diverse pharmacological activities such as antibacterial[19-21], antifungal[22,23] antiviral[24], antitubercular[25,26], antidepressant[27,28], antiamoebic[29,30], anti-inflammatory[31], anticonvulsant[32], analgesic[33] and anticancer[34], activities. In light of these finding, it was felt worthwhile to synthesize some new 2-subsituted benzimidazolyl derivatives and evaluate them for their antimicrobial potential.

## MATERIALS AND METHODS

### General

Starting material and reagents were procured from commercial chemical suppliers. All the chemicals and solvents used were of laboratory grade. Melting points were determined in open capillary tubes and are uncorrected. IR spectra (KBr, $cm^{-1}$) were recorded on Perkin Elmer FTIR Spectrometer, $^{1}H$ NMR Spectra was recorded on a Brucker 300 MHz NMR spectrometer using TMS as an internal standard. Mass spectra were taken on a Jeol-SX-DA-600 Mass spectrometer. The purity of compounds were ascertained by thin layer chromatography coated with silica gel G (Merck) using ethyl acetate benzene (1:1) as eluent. All the reactions were carried out in a Samsung domestic microwave oven (2450 MHz output, 800 watt power).

### Method

The title compounds were prepared in the following steps:

### Microwave assisted process

### General procedure for synthesis of chalcones (3a-f)

A solution of 2-Acetyl benzimidazole (0.01 mol) and variously substituted aryl aldehyde (0.012 mol) in methanol were taken in beaker. Potassium hydroxide 4.0 gm was added and the reaction mixture was irradiated in microwave oven for 30 seconds to 3 minutes at 300 watts and then cooled at room temperature. It was then poured in ice cold water. The product obtained was filtered and washed with water followed by recrystalization from ethanol and acetone. The purity of the compounds was checked by TLC using silica gel G.

### Synthesis of 2-amino-6-(1*H*-benzimidazol -2-yl)-4- phenyl pyridine -3- carbonitriles (4a-f)

A mixture of chalcone (3a-f) (0.01 mol), malononitrile (0.01 mole) and ammonium acetate (0.08 mole) was irradiation in a microwave oven for 5 to 6 min at 800 watts, After completion of reaction the mixture was decomposed by pouring in crushed ice, neutralized with dil. HCl. The solid separated was filtered and crystallized from ethanol to give analytical samples of (4a-f).

### Conventional process

### General procedure for synthesis of chalcones(3a-f)

Benzimidazole (0.01 mol) and variously substituted aryl aldehyde (0.012 mol) in methanol were taken in flask. Potassium hydroxide 4.0 gm was added to it and the reaction mixture was refluxed

on water bath for 3 to 4 hours. It was then cooled at room temperature and poured in ice cold water. The product obtained was filtered and washed with water. It was crystallized from ethanol and acetone. The purity of the compounds was checked by TLC using silica gel G.

**Synthesis of 2-amino-6-(1*H*-benzimidazol -2-yl)-4- phenyl pyridine -3- carbonitrile (4a-f)**
A mixture of chalcone (3a-f) (0.01 mol), malononitrile (0.01 mole) and ammonium acetate (0.08 mole) in methanol was refluxed on water bath for 8 to 10 hours, After cooling the mixture was decomposed in crushed ice, neutralized with dil. HCl. The separated solid was crystallized from ethanol to give (4a-f).
*1-(Benzimidazol-2-yl) -3- phenyl prop-2-en-1- one (3a):*
IR (KBr): 3264-3444 (N-H str.), 3080 (C-H Str., Ar-H), 1667 (C=O Str.), 1597 $cm^{-1}$ (C=N Str.); $^1H$ NMR ($CDCl_3$): δ 9.32 (S, 1H, NH), 7.8-7.1 (m, 9H, Ar-H), 5.6 (d, 1H, =CH-Ar).

*1-(Benzimidazol-2-yl) -3(-4 methoxy phenyl) prop-2-en-1- one (3b):*
IR (KBr): 3400 (N-H str.), 1654 (C=O Str.), 1575 (C=N Str.), 1088 $cm^{-1}$ (C=O Str.); $^1H$ NMR ($CDCl_3$): δ 9.08 (S, 1H, NH), 7.88-7.32 (m, 8H, Ar-H), 5.57 (d,1H, =CH-Ar) 3.3(S,3H, $OCH_3$).

*1-(Benzimidazol-2-yl) -3[-4 (dimethylamino) phenyl] prop-2-en-1- one (3f):*
IR (KBr): 3430 (N-H str.), 2913 (C-H Str., $CH_3$), 1663 (C=O Str.), 1601 $cm^{-1}$ (C=N Str.); $^1H$ NMR ($CDCl_3$): δ 9.21 (S, 1H, NH), 7.79-7.27 (m,8H, Ar-H), 5.61 (d,1H, =CH-Ar) 3.19 (S,6H, $N(CH_3)_2$).

*2-Amino-6-(1H-benzimidazol-2-yl)-4-phenyl pyridine-3-carbonitrile (4a):*
IR (KBr, $cm^{-1}$): 3378 (N-H Str.), 3051 (Ar-C-H Str.), 2940 (C-H Str.), 2235 (C≡N Str.), 1528 (C=C Str.); $^1H$ NMR ($CDCl_3$): 5.83 (s, 2H-$NH_2$), 6.91 (m, 5H, Ar-H),7.85 (s,1H, pyridine –C-H).

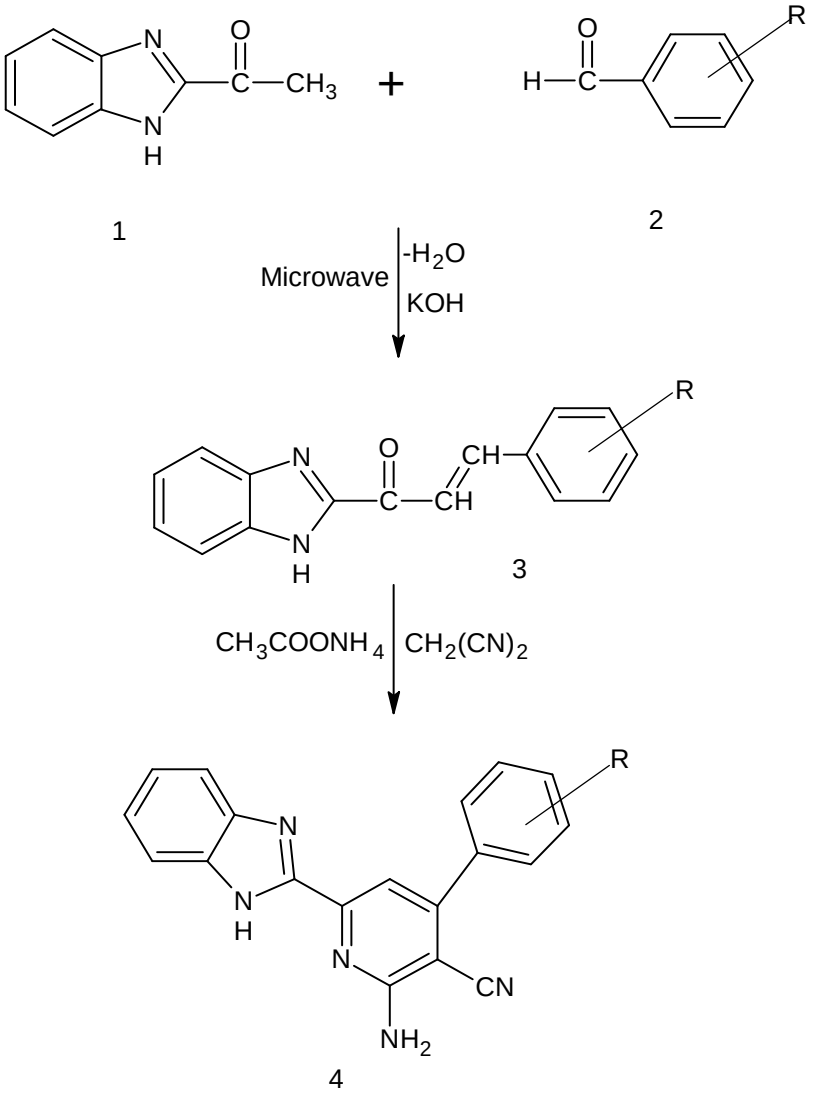
*2-Amino-6-(1H-benzimidazol-2-yl)-4-(4-methoxyphenyl) pyridine-3-carbonitrile (4b):*
IR (KBr, $cm^{-1}$): 3359 (N-H Str.), 3062 (Ar-C-H Str.), 2938 (C-H Str.), 2236 (C≡N Str.), 1495 (C=C Str.); $^1H$ NMR ($CDCl_3$): 3.98 (s, 3H, -$OCH_3$), 5.45 (s, 2H-$NH_2$), 7.50 (m, 4H, Ar-H), 6.97 (s,1H, pyridine –C-H).

*2-Amino-6-(1H-benzimidazol-2-yl)-4-(3,4-dimethoxyphenyl) pyridine-3-carbonitrile (4c):*
IR (KBr, $cm^{-1}$): 3372 (N-H Str.), 3053 (Ar-C-H Str.), 2946 (C-H Str.), 2240 (C≡N Str.), 1515 (C=C Str.); $^1H$ NMR ($CDCl_3$): 3.95 (s, 6H, -$OCH_3$), 5.63 (s, 2H-$NH_2$), 6.91 (m, 3H, Ar-H), 7.73 (s,1H, pyridine –C-H).

*2-Amino-6-(1H-benzimidazol-2-yl)-4-(3,4,5-trimethoxyphenyl) pyridine-3-carbonitrile (4d):*
IR (KBr, $cm^{-1}$): 3375 (N-H Str.), 3050 (Ar-C-H Str.), 2950(C-H Str.), 2244 (C≡N Str.), 1520 (C=C Str.); $^1H$ NMR ($CDCl_3$): 3.92 (s, 9H, -$OCH_3$), 5.68 (s, 2H-$NH_2$), 6.88 (m, 3H, Ar-H), 7.75 (s,1H, pyridine –C-H).

*2-Amino-6-(1H-benzimidazol-2-yl)-4-(4-chlorophenyl) pyridine-3-carbonitrile (4e):*
IR (KBr, $cm^{-1}$): 3361 (N-H Str.), 3031 (Ar-C-H Str.), 2937 (C-H Str.), 2212 (C≡N Str.), 1561 (C=C Str.); $^1H$ NMR ($CDCl_3$): 6.02 (s, 2H-$NH_2$), 7.16 (m, 4H, Ar-H), 7.85 (s,1H,pyridine –C-H).

**SCHEME-1**




*2-Amino-6-(1H-benzimidazol-2-yl)-4-[4-(dimethylamino) phenyl] pyridine-3-carbonitrile (4f):*
IR (KBr, $cm^{-1}$): 3355 (N-H Str.), 3046 (Ar-C-H Str.), 2954 (C-H Str.), 2224 (C≡N Str.), 1536 (C=C Str.); $^1$H NMR ($CDCl_3$): 3.08 (s, 6H, -N($CH_3$)$_2$), 5.89 (s, 2H-$NH_2$), 7.10 (m, 4H, Ar-H), 7.92 (s,1H, pyridine –C-H).

Physical data of synthesized compounds are presented in table 1.

**Biological Activity**

The antimicrobial activity was determined using disc diffusion method by measuring the inhibition zone in mm. All the synthesized compounds i.e. (4a-f) were screened in vitro for their antimicrobial activity at a concentration of 500 µg/mL. Cifuroxacin HCl was used as a standard drug for antibacterial screening and fluconazole was used as a standard for antifungal screening.

All the synthesized compound exhibited moderate antibacterial activities and significant antifungal activities.

## RESULTS AND DISCUSSION

Chalcones (3a-f) were prepared by the both conventional and MWI methods [35] and were treated with malononitrile to yield 2-amino-6-(1H-benzimidazol -2-yl)-4- phenyl pyridine -3-carbonitriles (4a-f). The synthetic procedure for preparation of title compounds is given in scheme 1. The assigned structure and molecular formula of the newly synthesized compounds (4a-f) were confirmed on the basis of their elemental and $^1$H NMR, MASS and IR spectral analysis. The compounds were screened in vitro for their antibacterial and antifungal activities by disc diffusion assay against selected pathogenic bacteria and human pathogenic fungi. The results of antibacterial and antifungal activities expressed in term of Zone of inhibition are reported in table 2.

**Table 1 Physical data of compounds 3&4.**

| Compd | R | Molecular Formula | MP | Yield | | Reaction Time | | %N |
|---|---|---|---|---|---|---|---|---|
| | | | °c | Conv | MWI | Conv(Hrs) | MWI(min) | |
| 3a | H | $C_{16}H_{12}N_2O_1$(248) | 205 | 77 | 82 | 4.0 | 3.0 | 11.29 |
| 3b | 4-$OCH_3$ | $C_{17}H_{14}N_2O2$(278) | 225 | 75 | 80 | 4.3 | 3.2 | 10.07 |
| 3c | 3, 4-$OCH_3$ | $C_{18}H_{16}N_2O3$(308) | 212 | 76 | 85 | 4.1 | 3.0 | 9.09 |
| 3d | 3, 4,5-$OCH_3$ | $C_{19}H_{18}N_2O4$(338) | 217 | 73 | 84 | 4.2 | 3.5 | 8.28 |
| 3e | 4-Cl | $C_{16}H_{11}N_2O_1Cl$(282) | 224 | 75 | 85 | 4.4 | 3.1 | 9.92 |
| 3f | 4-$N(CH_3)_2$ | $C_{18}H_{17}N_3O_1$(291) | 260 | 73 | 80 | 4.2 | 3.3 | 14.43 |
| 4a | H | $C_{19}H_{13}N_5$(311) | 155 | 76 | 78 | 8.2 | 5.0 | 22.20 |
| 4b | 4-$OCH_3$ | $C_{20}H_{15}N_5O$(341) | 145 | 78 | 79 | 9.4 | 5.2 | 20.52 |
| 4c | 3, 4-$OCH_3$ | $C_{21}H_{17}N_5O_2$(371) | 148 | 72 | 75 | 9.3 | 5.4 | 17.86 |
| 4d | 3, 4,5-$OCH_3$ | $C_{22}H_{19}N_5O_3$(401) | 152 | 78 | 80 | 9.5 | 5.1 | 17.45 |
| 4e | 4-Cl | $C_{19}H_{12}N_5Cl$(345.5) | 156 | 85 | 87 | 10.1 | 5.3 | 20.26 |
| 4f | 4-$N(CH_3)_2$ | $C_{21}H_{18}N_6$(354) | 170 | 79 | 82 | 10.3 | 5.4 | 23.72 |

**Table 2 Biological Screening results compounds 4 Zone of inhibition (mm)**

| Compd | Antibacterial | | | | Antifungal | |
|---|---|---|---|---|---|---|
| | E. coli | K. pneumoniae | B. subtilis | P.pseudomonas | Candida Albicans | Aspergillus Niger |
| 4a | 25 | 27 | 30 | 30 | 16 | 14 |
| 4b | 27 | 25 | 20 | 32 | 12 | 15 |
| 4c | 32 | 20 | 21 | 27 | 14 | 17 |
| 4d | 27 | 22 | 19 | 30 | 13 | 12 |
| 4e | 25 | 25 | 27 | 28 | 21 | 16 |
| Standard Drug Cifuroxacin HCl | 40 | 40 | 40 | 40 | - | - |
| Standard Drug Fluconazole | - | - | - | - | 30 | 30 |

### Antimicrobial activity

Newly synthesized compounds were screened for their antibacterial against *E.coli, P. pseudomonas, B.subtilis, K. pneumoniae* and antifungal agents *Candida albicans* and *Aspergillus*

*niger in vitro* at a concentration 500 µg/ml. standard drug were used cifuroxacin HCl and Fluconazole respectively. The screening results have been tabulated in table 2.

## CONCLUSION

All the transformation were carried out using conventional and microwave irradiation method under solvent less condition which lead to considerable time saving, better yields and environmentally profitable procedure. The solvent less condition diminish the problem of waste disposal and is eco friendly. Some of synthesized compounds have shown significant antimicrobial activity.

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