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# SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5, 6-DIHYDRO-3-ARYLNAPHTHO [1,2-b] [1,8] NAPHTHYRIDINE AND THEIR DERIVATIVES

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## ABSTRACT

2-Aminopyridine-3-carboxaldehyde **(1)** on condensation with 3,4-dihydro-6-methoxynaphthalen-1(2H)-one **(2)** afforded 5,6-dihydro-3-methoxynaphtho[1,2-b][1,8] naphthyridine **(3)** in very good yields. It underwent demethylation with aqueous hydrobromic acid to furnish 5,6-dihydronaphtho[1,2-b][1,8]naphthyridin-3-ol **(4)**, followed by treatment with trifluoromethane sulfonic anhydride yielded 5,6-dihydronaphtho[1,2-b][1,8]naphthyridin-3-yl trifluoromethane sulfonate **(5).** The compound **(5)** on further treatment with various aromatic boronic acids gave 5,6-dihydro-3-arylnaphtho[1,2-b][1,8]naphthyridine and their derivative **(6a-f)**.The structures of these new compounds were established by spectral data. All the new compounds have been screened for their antimicrobial activity.

**Key words**: Synthesis, 5,6-Dihydro-3-methoxynaphtho[1,2-b][1,8]naphthyridine, 5,6-Dihydronaphtho [1,2-b][1,8]naphthyridin-3-yl trifluoromethane sulfonate, Antifungal activity.

## INTRODUCTION

1,8-Naphthyridines is an important class of pharmaceutically active compounds as they have excellent and diverse biological activities such as diuretic[1], antimalarial[2], anti-inflammatory[3], antihypertensive[4] and antibacterial[5,6]. Nalidixic acid, 1,8-naphthyridine derivative is being used for chronic urinary track infection caused by gram negative bacteria[7]. Another 1,8-naphtheridine derivative, gemifloxacin is also found to be an antibacterial agent[8]. However, it is known that (E) - and (Z)-O-(diethylamino) ethyl oximes of 1,8-

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naphthyridine series are potential drugs for local anesthesia[9] and 1-(2-fluorobenzyl)-3-(2-tolyl)- 1,8-naphthyridin-2(1H)-one is used for the treatment of memory disorders, particularly for Alzheimer's disease[10].

## EXPERIMENTAL

Melting points were determined on a capillary Buchi melting point apparatus and are uncorrected. The $^{1}H$ NMR and $^{13}C$ spectra were recorded in the indicated solvent on a Varian 500 MHz and 200 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) are reported in ppm from internal TMS. The mass spectra were measured on a GC/MS-QP1000EX (EI, 70 eV) mass spectrometer. Infrared spectra were recorded in KBr on Schimadzu 470 spectrophotometer. Column chromatography was performed on silica gel (Merck 60-120 mesh).All compounds were recrystalised from ethanol.

A few 1,8-naphthyridine derivatives also react with adenosine receptors of subtypes $A_1$ and $A_2$[11]. In continuation of our work on 1,8-naphthyridines, the synthesis of 5,6-dihydro-3-arylnaphtho (1,8) naphthyridines **(6a-f)** and their antimicrobial activity is being reported. The sequential pathway leading to the formation of the title products is shown in **Scheme 1**. The required starting intermediate 5, 6-dihydro-3-methoxy naphtho[1,2-b] [1,8] naphthyridine **(3)** was obtained by the condensation of 2-amino pyridine-3-carboxaldehyde (**1**) with 3,4-dihydro-6-methoxynaphthalen-1(2H)-one **(2)** on refluxing with ethanol in the presence of few drops of aqueous potassium hydroxide. Compound **(3)** in aqueous hydrobromic acid, when heated under reflux, underwent demethylation to furnish 5,6-dihydronaphtho[1,2-b][1,8]naphthyridin-3-ol **(4)** in (91%) yield. Compound **(4)** on further treatment with trifluoromethane sulfonic anhydride ($Tf_2O$) in dichloromethane and triethyl amine as a base afforded 5,6-dihydronaphtho[1,2-b][1,8]naphthyridin-3-yl trifluoromethanesulfonate **(5)**, which on further treatment with various aromatic boronic acids furnished the 5,6-dihydro-3-phenylnaphtho[1,2-b] [1,8]naphthyridines **(6a-f)** in appreciable yields (78-91%).

These compounds were characterized by their elemental analyses and their spectral data. The IR spectra of the obtained compound **(4)** showed strong absorption band in the 3193 $cm^{-1}$ region corresponding to OH functional group. In the $^{1}H$ NMR spectra, the signal for two aliphatic $CH_2$ protons of **(3-6a-f)** ring recorded between 2.91-3.42 ppm and the O-methyl protons of **(3)** appeared as singlet at 3.82 ppm. The $^{13}C$ NMR spectra show the expected resonance signals of the different carbons, especially the signal two aliphatic $CH_2$ protons between 35-56 ppm.

**Preparation of 5, 6-dihydro-3-methoxynaphtho[1,2-b] [1,8] naphthyridine (3)**

To a stirred solution of 8.19 µ moles of 2-amino-pyridine-3-carboxaldehyde **(1)** in 10 µL ethanol, 9.83 µ moles of 3,4-dihydro-6-methoxynaphthalen-1(2H)-one **(2)** was added. To this reaction mixture, few drops of aqueous potassium hydroxide solution were added and then allowed to reflux for 6 hours. The resulting mixture was poured into ice-cold water, the light yellow crude solid thus obtained was filtered and washed with excess of water and dried and recrystallised from ethyl alcohol affording pure product **(3) (Scheme 1).** Yield 92%, mp. 264$^0$C, $^1$H NMR (DMSO-$d_6$) (δ/ppm): 2.91-3.19 (4H, m, 2 x -$CH_2$ ), 3.82 (3H, s, -$OCH_3$), 6.92-8.98 (7H, m, Ar-H), MS: m/z 262 ($M^+$, 100%).

**Preparation of 5,6-dihydronaphtho[1,2-b][1,8]naphthyridin-3-ol (4)**

The solution of 5.84 µ moles of 5,6-dihydro-3-methoxynaphtho[1,2-b][1,8] naphthyridine **(3)** in 10 µL 48% aqueous hydrobromic acid was refluxed for 24 hours. The reaction mixture was cooled to room temperature and poured into 20 µL of ice-cold water. The yellow colored solid obtained, was filtered and washed with excess of water and dried and recrystallised from ethyl alcohol furnising pure product **(4) (Scheme 1**).Yield 91%, mp. 267 $^0$C, $^1$H NMR (DMSO-$d_6$) (δ/ppm): 2.91-3.19 (4H, m, 2 x -$CH_2$), 6.92-7.62 (3H, m, Ar-H), 8.19 (1H, s, Ar-OH), 8.32-9.18 (4H, m, Ar-H), MS: m/z 248 ($M^+$, 100%).

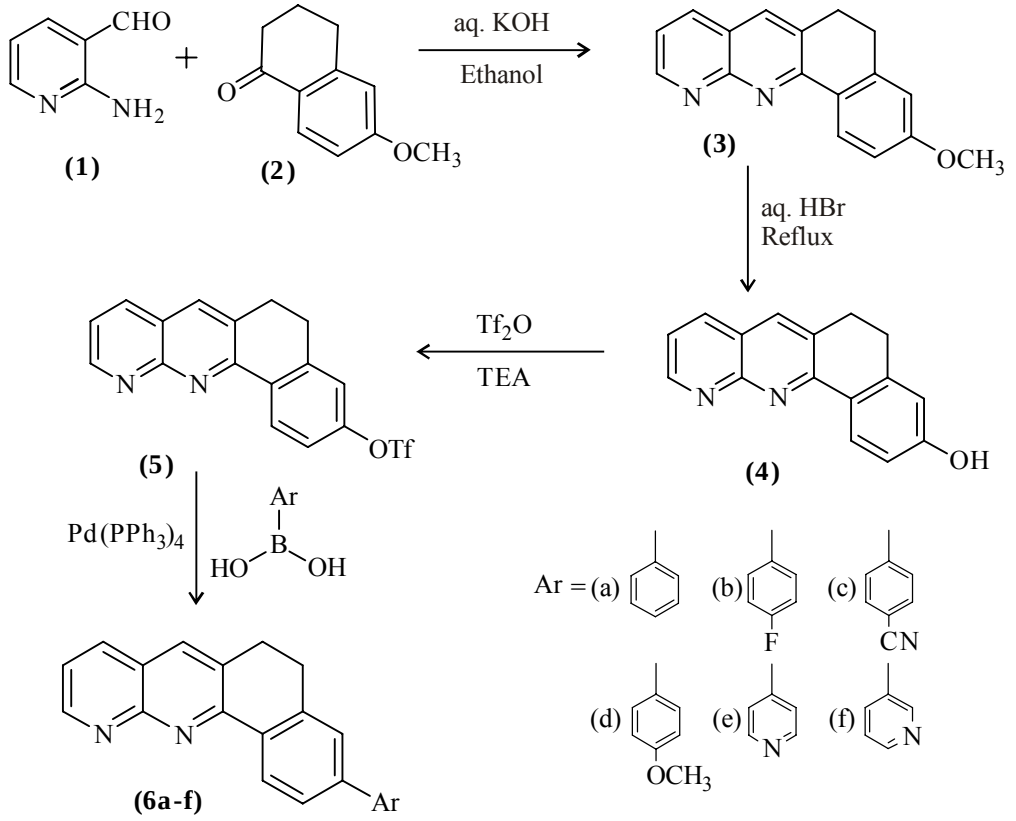
**Preparation of 5,6-dihydronaphtho[1,2-b][1,8]naphthyridin-3-yl-trifluoro methane sulfonate (5)**

To a solution of 5.40 µ moles of 5,6-dihydronaphtho[1,2-b][1,8]naphthyridin-3-ol **(4)** in 20 µ L dry dichloromethane, 10.81 µ moles of triethylamine and 10.81 µ moles of trifluoromethanesulfonic anhydride were added dropwise over a period of 10 min at 0°C. The resulting solution was stirred for 6 hours at room temperature. The reaction mixture was quenched with 10 µL aqueous $NH_4Cl$ solution; then extracted with ethyl acetate and the organic solvent was dried over anhydrous $Na_2SO_4$ followed by evaporation of the solvent to dryness in vacuum to afford a solid product. The resulting crude compound was purified by column chromatography by using 60-120 mesh silica gel, eluted with dichloromethane in methanol (9 : 1) to yield compound (**5)** as light yellow solid **(Scheme 1)**. Yield 91% mp.245 $^0$C, $^1$H NMR (DMSO-$d_6$) (δ/ppm): 3.16-3.36 (4H, m, 2 X -$CH_2$), 6.82 -9.25(7H, m, Ar-H), MS: m/z 380 ($M^+$, 100%).

**General procedure for the preparation of 5,6-dihydro-3-arylnaphtho[1,2-b] [1,8] naphthyridines and their derivatives (6a-f)**

To a solution of 4.95 µ moles of compound **(5)** in 10 µL dry toluene, 14.85 µ moles

of aryl boronic acid and 2 µL of 2N aqueous $Na_2CO_3$ solution were added. The resulting solution was purged with argon for 1 hr; then catalytic amount of Pd $(PPh_3)_4$ was added and purged with argon for 1 hr at room temperature. The resulting suspension was allowed to reflux for 16 hrs. Then the solvent was removed under reduced pressure and crude was dissolved in 20 µL ethyl acetate and washed with water twice. The organic solvent was dried over anhydrous $Na_2SO_4$ followed by evaporation of the solvent to dryness in vacuum to afford a solid product. The resulting crude compound was purified by column chromatography by using 60-120 mesh silica gel, eluted with dichloromethane in methanol (9 : 1) and further recrystallisation by ethanol yielded compound **(6a)**. Several title compounds were synthesized using different aryl boronic acid in the presence of Pd (0) to yield compound (**6a-f)**. The chemical and spectral data of the compounds **(6a-f)** are given in Tables 1 and 2.




**Scheme 1: Synthesis of 5,6-dihydro-3-arylnaphtho [1,2-b] [1,8] naphthyridines and their derivatives (6a-f)**

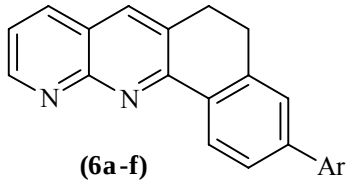
**Table 1: Chemical data of compounds (6a-f)**

| Comp. | Ar | m.p ($^{o}$C) | Yield (%) |
|---|---|---|---|
| **6a** | $C_6H_5$ | 267 | 91 |
| **6b** | $C_6H_4F$ | 247 | 91 |
| **6c** | $C_7H_4N$ | 266 | 78 |
| **6d** | $C_7H_7O$ | 268 | 82 |
| **6e** | $C_5H_4N$ | 238 | 81 |
| **6f** | $C_5H_4N$ | 242 | 80 |

Elemental analyses for C, H, N are within ± 0.3% of the theoretical values

*Solvent for crystallization: Ethyl alcohol for **(6a-f)**

**Table 2: Spectral data of the compounds (6a-f)**




**(6a-f)**

| Compd. | $^{1}$H NMR (DMSO-$d_6$, ppm) |
|---|---|
| **6a** | 3.19-3.42 (4H, m, 2 x $CH_2$), 6.91-7.58 (8H, m, Ar-H), 8.21 (1H, s, Ar-H), 8.31-8.43 (2H, t, Ar-H) 8.95-9.04 ((1H, d, Ar-H) |
| **6b** | 3.19-3.42 (4H, m, 2 x $CH_2$),7.02-8.18 (7H, m, Ar-H), 8.23-8.27 (2H, dd, Ar-H), 9.15-9.20 (2H, dd, Ar-H) |
| **6c** | 3.29-3.42 (4H, m, 2 x $CH_2$), 7.12-8.28 (7H, m, Ar-H), 8.25-8.29 (2H, dd, Ar-H), 9.14-9.19 (2H, dd, Ar-H) |
| **6d** | 3.29-3.42 (4H, m, 2 x $CH_2$), 3.82 (3H, s, $OCH_3$), 7.12-8.28 (7H, m, Ar-H), 8.25- 8.29 (2H, dd, Ar-H), 9.14-9.19 (2H, dd, Ar-H) |

Cont...

| Compd. | $^1$H NMR (DMSO-$d_6$, ppm) |
|---|---|
| **6e** | 3.29-3.42 (4H, m, 2 x $CH_2$), 7.12-8.28 (7H, m, Ar-H), 8.25-8.29 (2H, dd, Ar-H), 9.14-9.19 (2H, dd, Ar-H) |
| **6f** | 3.29-3.42 (4H, m, 2 x $CH_2$), 7.04-8.19 (7H, m, Ar-H), 8.23-8.32 (2H, dd, Ar-H), 9.18-9.22 (2H, dd, Ar-H) |

s, singlet; d, doublet ; dd, doublet of doublets; m, multiplet

## RESULTS AND DISCUSSION

The antimicrobial activity was observed by adopting the glass slide humid chamber technology[12]. The compounds were screened *in vitro* for their antifungal activity against *Alternaria alternate*, *Fusarium oxysporum* and *Curvularia lunata* using griseofulvin as standared for comparison. Compounds **(5)** and **(6b)** showed promising activity against all the three organisms used. Compounds **(6c)**, **(6e)** and **(6f)** were active against *Fusarium oxysporum* and *Curvularia lunata*. Compound **(6a)** was active against *Alternaria alternate*. Compounds **(3)**, **(4)** and **(6d)** exhibited feeble activity. None of the compounds were found to exhibit significant antibacterial activity against *Bacillus subtilis*, *Streptococcus fecalis* and *Psuedomonas aeruginosa*.

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