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# SYNTHESIS OF AND CHARACTERIZATION OF INDOLYL-1,8-NAPHTHYRIDIN-3-CARBONITRILES MOITIES

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**Abstract:**

In the present study novel synthesis of 2-amino-4-(2-methoxynapthylen-6'-yl)-6-(4-chlorophenyl)-pyridin-3-carbonitriles **1a** and (5'-chloro-2'-phenyl-1*H*-indol-3'-yl)-acrylonitrile **2a** underwent cyclization in presence of metallic sodium in refluxing 1,4-dioxane to afford 4-amino-5-(2'-methoxynaphthylen-6'-yl)-7-(4-chlorophenyl)-2-(5'-chloro-2'-phenyl-1*H*-indol-3'-yl)-1,8-naphthyridin-3-carbonitrile (**3a-i)** in good yield. The structures of all these unknown compounds have been confirmed with the help of physical data and spectral data like IR, $^{1}$H NMR and mass spectroscopy.

**Keywords:** Synthesis, Indole, 1,8-Naphthyridine derivatives

## Introduction

Among all the nitrogen containing heteroycles, the 1,8-maphthyridine scaffold has recently gained an immense amount of curiosity from numerous researcher across fields of medicinal chemistry and drug discovery[1-6]. This is new attention can be also it's ascribed to its versatility synthesis, its creativeness and the variety of biological activities it has exhibited[8-10]. Over the past half-decade, numerous diverse biological evaluations have been conducted on 1,8-naphtyridine and its derivatives in a quest to unravel novel pharmacological facets to this scaffold.

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1,8-naphtyridine and its derivatives exhibited numerous pharmacological activities like antimicrobial[11-13], anticancer[14], antiviral[15], antioxidant[16-18], anti-HIV[19] and antidepressant[20] etc., In view of the above observations and in continuation of our research on the synthesis of biologically active molecules[21-25]. Encouraged by the diverse biological activities of indole and pyrimidine heterocyclic compounds and it was decided to prepare a new series of indolyl-napthyridine derivatives **(3a-c)**. Literature survey revealed that incorporation of different groups in one frame i.e., indole, and naphthyridine, heterocycles it may leads enhanced antimicrobial activity.

**RESULTS AND DISCUSSION**

In view of all these findings and in continuation of our research work on 4-substituted-thiazole-2-amines and their derivatives, we hereby report the synthesis of some new 4-amino-5-(2'-methoxynaphthylen-6'-yl)-7-(4-chlorophenyl)-2-(5'-chloro-2'-phenyl-1*H*-indol-3'-yl)-1,8-naphthyridin-3-carbonitrile **3a**. The starting compounds (5'-substituted-2'-phenyl-1H-indol-3'-yl)-acrylonitriles were synthesized by reacting 2-phenyl 5-substituted indole-3-carboxaldehydes with malanonitrile in alcohol containing catalytic amount of piperidine under reflux temperature by using literature method[26]. 2-Amino-4-(2-methoxynapthylen-6'-yl)-6-(4-chlorophenyl)-pyridin-3-carbonitriles **1a** and (5'-chloro-2'-phenyl-1*H*-indol-3'-yl)-acrylonitrile **2a** underwent cyclization in presence of metallic sodium in refluxing 1,4-dioxane to afford 4-amino-5-(2'-methoxynaphthylen-6'-yl)-7-(4-chlorophenyl)-2-(5'-chloro-2'-phenyl-1*H*-indol-3'-yl)-1,8-naphthyridin-3-carbonitrile **3a**. The IR spectrum of this compound showed characteristic absorption peaks at 3192 and 3028 $cm^{-1}$ which corresponds to the $NH_2$/NH functions, respectively. The absorption peak at 2205 $cm^{-1}$ was observed due to the cyano function. In the $^1H$ NMR spectrum of a singlet resonated at δ 3.95 was attributed to three protons of methoxy group of naphthalene ring. The multiplet resonated between δ 6.95-8.33 integration of which corresponds to nineteen aromatic protons and two protons of amino group of naphthyridine ring. The down field singlet appeared at δ 12.66 integrating for one proton was assigned to indole NH. The mass spectrum of this compound **showed** molecular ion peaks $M^+$ at m/z 661, $M^+$+2 at m/z 663 and $M^+$+4 at m/z 665 corresponding to its molecular weight. The physical data and elemental analyses are tabulated in **Table-1**. Spectral data are tabulated in **Table-2**

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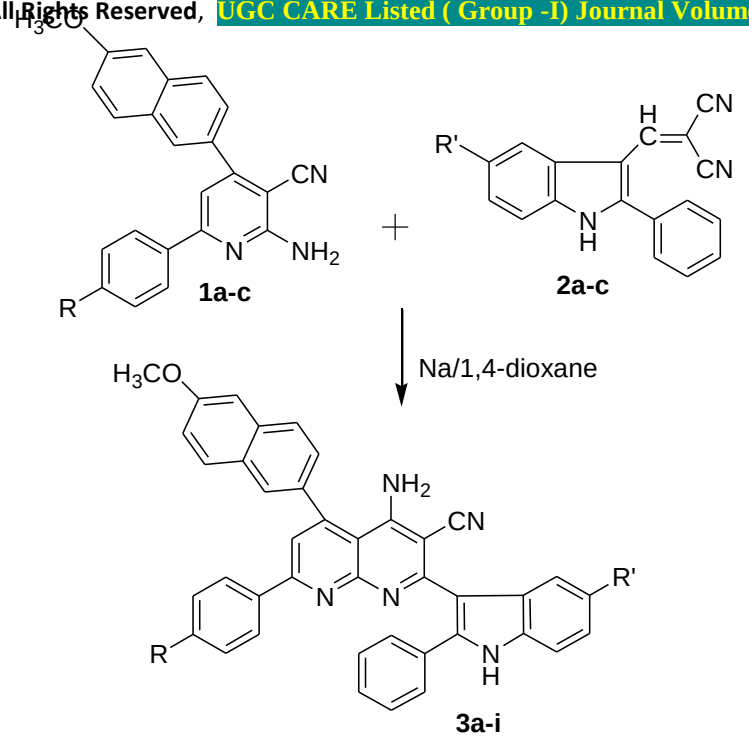


**Scheme-I:** Shematic route for the synthesis of naphthyridin-3-carbonitrile derivatives **(3a-i)**

**Table 1:- Physical and elemental data of 4-amino-5-(2-aryl-4 or 6'-yl)-7-(4-substituted phenyl)-2-(5'-substituted-2'-phenyl-1*H*-indol-3'-yl)-1,8-naphthyridin-3-carbonitriles (3a-i)**

| Comp. | Yield (in %) | M. P. (°C) | Nature (Solvent) | Mol. Formula | Analysis in % found (calcd) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| 3a | 69 | 113-14 | Yellow crystals (ethanol) | $C_{40}H_{25}N_5OCl_2$ | 72.62 (72.79) | 3.78 (3.83) | 10.59 (10.66) |
| 3b | 61 | 150-51 | Yellow crystals (ethanol) | $C_{41}H_{28}N_5OCl$ | 76.76 (76.84) | 4.37 (4.40) | 10.92 (10.98) |
| 3c | 59 | 167-68 | Yellow crystals (ethanol) | $C_{40}H_{26}N_5OCl$ | 76.56 (76.64) | 4.15 (4.20) | 11.16 (11.26) |
| 3d | 69 | 160-61 | Yellow crystals (ethanol) | $C_{41}H_{28}N_5OCl$ | 76.76 (76.89) | 4.37 (4.46) | 10.92 (10.98) |
| 3e | 58 | 152-53 | Pale yellow crystals (ethanol) | $C_{42}H_{31}N_5O$ | 81.16 (81.24) | 5.00 (5.07) | 11.27 (11.32) |
| 3f | 68 | 136-37 | Yellow crystals (ethanol) | $C_{41}H_{29}N_5O$ | 81.05 (81.13) | 4.78 (4.83) | 11.53 (11.58) |
| 3g | 55 | 155-56 | Yellow crystals | $C_{40}H_{26}N_5OCl$ | 76.55 | 4.15 | 11.64 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | (ethanol) | | (76.64) | (4.20) | (11.71) |
| 3h | 66 | 144-45 | Pale yellow crystals (ethanol) | $C_{41}H_{29}N_5O$ | 81.05 (81.11) | 4.78 (4.85) | 11.53 (11.60) |
| 3i | 66 | 163-64 | Pale yellow crystals (ethanol) | $C_{40}H_{27}N_5O$ | 80.94 (80.98) | 4.55 (4.61) | 11.80 (11.88) |

**Table 2:- Spectral data of 4-amino-5-(2-methoxynaphthylen-6'-yl)-7-(4-substituted phenyl)-2-(5'-substituted-2'-phenyl-1*H*-indol-3'-yl)-1,8-naphthyridin-5-carbonitriles (3a-i)**

| Comp. | IR (KBr) ($cm^{-1}$) | $^1$H NMR (δ ppm) | Mass m/z ($M^+$) |
|---|---|---|---|
| 3a | 3192 ($NH_2$), 3028 (NH), 2919 (C-H stretching), 2205 (C=N), 1171 (C-O-C), 772 (C-Cl). | 12.66 (s, 1H, indole NH), 6.95- 8.33 (m, 21H, 19-ArH and $NH_2$), 3.95 (s, 3H, $OCH_3$). | 661, 663, 665 |
| 3b | 3206 ($NH_2$), 3168 (NH), 2955 (C-H stretching), 2204 (C=N), 1172 (C-O-C), 757 (C-Cl). | 12.43 (s, 1H, indole NH), 6.96- 8.22 (m, 21H, 19-ArH and $NH_2$), 3.99 (s, 3H, $OCH_3$), 2.54 (s, 3H, $CH_3$). | 641, 643 |
| 3c | 3206 ($NH_2$), 3168 (NH), 2955 (C-H stretching), 2204 (C=N), 1174 (C-O-C), 744 (C-Cl). | 12.41 (s, 1H, indole NH), 8.19 (s, 2H, $NH_2$), 7.19-8.12 (m, 20H, ArH), 4.01 (s, 3H, $OCH_3$). | 627, 629 |
| 3d | 3198 ($NH_2$), 3041 (NH), 2916 (C-H stretching), 2209 (C=N), 1170 (C-O-C). | 12.60 (s, 1H, indole NH), 6.90- 8.30 (m, 21H, 19-ArH and $NH_2$), 3.94 (s, 3H, $OCH_3$), 2.51 (s, 3H, $CH_3$). | -- |
| 3e | 3207 ($NH_2$), 3173 (NH), 2950 (C-H streching), 2208 (C=N), 1173 (C-O-C). | 12.40 (s, 1H, indole NH), 6.93- 8.18 (m, 21H, 19-ArH and $NH_2$), 3.98 (s, 3H, $OCH_3$), 2.71 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$). | -- |
| 3f | 3218 ($NH_2$), 3180 (NH), 2916 (C-H streching), 2204 (C=N), 1170 (C-O-C). | 12.39 (s, 1H, indole NH), 8.15 (s, 2H, $NH_2$), 7.08-8.04 (m, 20H, ArH), 4.01 (s, 3H, $OCH_3$), 2.51 (s, 3H, $CH_3$). | -- |
| 3g | 3226 ($NH_2$), 3196 (NH), 2915 (C-H stretching), 2208 (C=N), 1178 (C-O-C). | 12.38 (s, 1H, indole NH), 8.14 (s, 2H, $NH_2$), 7.16-8.08 (m, 20H, ArH), 3.88 (s, 3H, $OCH_3$). | -- |
| 3h | 3212 ($NH_2$), 3173 (NH), 2946 (C-H stretching), 2207 (C=N), 1181 (C-O-C). | 12.40 (s, 1H, indole NH), 6.91- 8.16 (m, 22H, 20-ArH and $NH_2$), 3.96 (s, 3H, $OCH_3$), 2.76 (s, 3H, $CH_3$). | -- |
| 3i | 3216 ($NH_2$), 3175 (NH), 2919 (C-H stretching), 2209 (C=N), 1178 (C-O-C). | 12.36 (s, 1H, indole NH), 8.14 (s, 2H, $NH_2$), 7.02-8.06 (m, 21H, ArH), 4.01 (s, 3H, $OCH_3$). | -- |

## EXPERIMENTAL SECTION

Materials and Methods

All the reagents were obtained commercially and used by further purification using standard procedures. Melting points were determined by an open capillary method and are

 

uncorrected. Purity of the compounds was checked by thin layer chromatography using silica gel-G coated Al plates (Merck) and spots were visualized by exposing the dry plates in iodine vapors. The IR (KBr pellet) spectra were recorded on a Perkin-Elmer (Spectrum ONE) FT-IR Spectrometer. The $^{1}H$ and $^{13}C$ NMR (DMSO-$d_6$) spectra were recorded with a BRUKER NMR 500 and 125 MHz spectrometers, and the chemical shift values are expressed in ppm (δ scale) using tetramethylsilane as an internal standard. The mass spectral measurements were carried out by Electron Impact method on JEOL GC mate spectrometer at 70 eV. Elemental analyses were performed on flash EA 1112 series elemental analyzer.

**General procedure for the synthesis of (5'-substituted-2'-phenyl-1*H*-indol-3'-yl)-acrylonitriles (2)**: A solution of 2, 5-disubstituted indole-3-carboxaldehydes **(20a-c)** (0.0056 mol), malanonitrile (0.0056 mol) in dry ethanol (18 ml) containing 3-4 drops of piperidine was refluxed for 1 hr. It was then cooled to room temperature and poured into ice cold water. The separated solid was filtered, washed with cold water, dried and recrystallized from ethanol.

**General procedure for the synthesis of 1-(4-substitutedphenyl)-3-(2-methoxynaphthalen-6-yl)prop-2-en-1-one:** To a solution of acetophenone (1.2 g, 0.01 mol) and substituted benzaldehyde (1.40 g, 0.01 mol) in ethanol (10 ml) potassium hydroxide (10 ml, 60%) solution was added drop wise at 0 °C. The reaction mixture was stirred at 0 °C for 24 hrs. Reaction mixture was then neutralized with cold acetic acid. The yellow precipitate formed was collected, washed with water and recrystalized from ethanol.

**General procedure for the synthesis of 2-amino-4-(2-methoxynapthyl-6'-yl)-6-(4-substituted phenyl)-pyridin-3-carbonitriles (2a-c):**

A mixture of malanonitrile (0.0352 mol), ammonium acetate (0.0352 mol) and 3-(2-methoxynaphthalen-6-yl)-phenyl-prop-2-ene-1-one (**2a-e)** (0.0352 mol) was heated for 7 hr, and left at room temperature overnight. The solid mass formed was diluted with methanol and poured into ice cold water. The product thus separated was filtered, washed with cold water, dried and recrystalized from ethanol.

**General procedure for the synthesis of 4-amino-5-(2-methoxynaphthylen-6'-yl)-7-(4-substituted aryl)-2-(5'-substituted-2'-phenyl-1*H*-indol-3'-yl)-1,8-naphthyridin-5-carbonitriles (3a-i):**

A mixture of compounds (**27a-c)** (0.01 mol) and compounds (**25a-c)** (0.01 mol) in sodium/1,4-dioxane solution (30 ml) [prepared by dissolving (0.01 mol) of sodium in 1,4-

 

dioxane] was refluxed for 4 hr. The reaction mixture was cooled to room temperature poured into ice-cold water, and neutralized with dilute hydrochloric acid. Thus the solid product formed was filtered, washed with cold water, dried and recrystalized from ethanol. Physical and spectral data are tabulated in **Table-1** and **2**.

## CONCLUSION:

In the present study novel synthesis of 2-amino-4-(2-methoxynapthylen-6'-yl)-6-(4-chlorophenyl)-pyridin-3-carbonitriles **1a** and (5'-chloro-2'-phenyl-1*H*-indol-3'-yl)-acrylonitrile **2a** underwent cyclization in presence of metallic sodium in refluxing 1,4-dioxane to afford 4-amino-5-(2'-methoxynaphthylen-6'-yl)-7-(4-chlorophenyl)-2-(5'-chloro-2'-phenyl-1*H*-indol-3'-yl)-1,8-naphthyridin-3-carbonitrile (**3a-i)** in good yield.

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