Synthesis of 2,6-Diaryl-4-Indolylpyridines as Novel 5-LOX Inhibitors

**Abstract**

A series of 2,6-diaryl substituted -4-indolylpyridines have been synthesized from indole-3-carboxaldehyde and acetophenones and all the compounds are characterized by spectroscopic techniques. 5-Lipoxygenase enzyme inhibitory activities were performed for all the compounds. Among the 2, 6-diaryl substituted -4-indolylpyridine derivatives give name and give name showed good activity.

**Keywords:** Indolylpyridine; 5-LOX; Indole-3-carboxaldehyde

# Introduction

3-Substituted indole is a privileged structural motif found in many biologically active compounds and natural products [1]. 3-Substituted indole derivatives exhibit several biological activities such as antibacterial [2-6], anti-inflammatory [7-10], antitumor [11-

13], anticancer [14-18], anti-hypertensive [19], anti-depressant [20,21] and antiviral [22-25] activities. On the other hand, the molecules having pyridine nucleus possess a large spectrum of biological activities like anti-prion [26], anti-hepatitis B virus [27], antibacterial [28], anticancer [29] and antimalarial [30] activities. Therefore, the combined molecules of 3-Substituted indole and pyridine frame works, indolylpyridines, are the valuable starting material for the synthesis of structurally diverse biologically active agents. Indolylpyridines have been reported to exhibit several biological activities such as anti-cancer and anti-inflammatory activities [31,32]. However, 5-lipoxygenase enzyme inhibitory activity (5-LOX) of indolylpyridines has not been

in dry DMF (187.4 mmol) in an ice-salt bath, POCl3 (47.1 mmol) was subsequently added with stirring over a period of 30 min. After completion of addition, the temperature was raised to 40°C, the syrup was stirred for 1.5 h at the same temperature. At the end of the reaction (as indicated by TLC) 25 g crushed ice was added to the reaction mixture. The obtained solution was transferred into 250 mL RB flask, NaOH (470 mmol) dissolved in 50 mL water was added with constant stirring and the resultant suspension was heated rapidly to the boiling point and allowed to cool to room temperature. The mixture was allowed to stand in refrigerator overnight. The precipitate was filtered off, washed thrice with 100 mL water, yielding 1*H*-indole-3-carboxaldehydes (1a or 1b).

**1H-Indole-3-carboxaldehyde (1a):** Brownish yellow solid, Yield: 92%, Mp: 196-198°C, 1H NMR (DMSO-*d*6, 400 MHz): δ=9.52 (s, 1H),

8.12 (s, 1H), 7.62 (d, 1H), 7.52 (s, 1H), 7.34 (d, 1H), 7.22 (t, 1H), 7.14 (t,

1H). 13C NMR (DMSO-*d*6, 100 MHz): δ=1882.7, 137.2, 131.82, 127.7,

122.4, 120.5, 119.4, 118.0, 111.4.

**Bromo-1H-indole-3-carboxaldehyde (1b):** Cream coloured solid, Yield: 90%, Mp: 192°C, 1H NMR (DMSO-*d* , 400 MHz): δ=9.94 (s, 1H)***,***

fully explored. 5-Lipoxygenase is the key enzyme for the biosynthesis

of leukotrienes, the important mediators for inflammatory, allergic,

6

8.32 (s, 1H), 8.25 (s, 1H), 7.75 (s, 1H), 7.43 (d, 1H), 7.34 (d, 1H).

13C

and obstructive processes. 5-LOX inhibitors have potential in treating asthma and various inflammatory disorders [33,34]. Therefore, herein we report the synthesis of a series of 2,6-diaryl-4-indolylpyridines from substituted acetophenones and 1*H*-indole-3-carbaldehydes using ammonium acetate as a nitrogen source in the presence of acetic acid and 5-LOX activities of several 2, 6-diaryl-4-indolylpyridines.

# Experimental Section

## General

All chemicals used were of synthetic grade procured from Sigma Aldrich. Completion of the reactions was monitored by analytical thin layer chromatography (TLC) using E-Merck 0.25 mm silica gel plates using ethyl acetate/hexane as solvent system, visualization was accomplished with UV light (256 nm) and iodine chamber. Synthesized compounds were purified by column chromatography (silica gel 100- 200 mesh) using a mixture of hexane and ethyl acetate. Melting points were measured in open capillary tubes and were uncorrected; all the 1H

and 13C spectra were recorded in CDCl3 solvent (400 MHz for 1H and 100 MHz for 13C) relative to tetramethylsilane (TMS) internal standard, proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q)

and multiplet (m). The electron ionization mass spectra were recorded on Agilent 1100.

## General experimental procedure for the synthesis of 1*H*-indole-3-carboxaldehydes (1a or 1b)

To a solution of substituted indole (42.6 mmol) (or 5-bromo indole)

NMR (DMSO-*d*6, 100 MHz): δ=183.9, 144.4, 136.7, 135.2, 125.6, 123.1,

117.3, 114.8, 113.0.

## General experimental procedure for synthesis of 2,6-diaryl- 4-indolylpyridines

A mixture of 1*H*-indole-3-carboxaldehyde (1**)** (1.0 mmol) and acetophenone (2) (2.0 mmol) in the presence of AcONH4 (5 mol%) and acetic acid was heated in an oil bath at reflux for about 5 h. After the completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature and partitioned between water and ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulphate and concentrated under vacuum to afford the crude compound. The crude compound was purified with silica gel column chromatography using hexane/EtOAc as eluent to afford the pure product (3) (Supplementary Figures 1-18).

## Characterization of 2,6-diaryl-4-indolylpyridines

**3-(2,6-di (Phenylpyridin-4-yl)-1*H*-indole (3aa):** Colorless solid, Yield: 80%, Mp: 178-180°C, 1H NMR (400 MHz, CDCl3): δ=8.71 (d, 1H), 8.23 (d, 4H), 8.08 (d, 1H), 7.99 (s, 2H), 7.60 (d, 1H), 7.55 (m, 4H),

7.48 (d, 3H), 7.31 (t, 2H). 13C NMR (100 MHz, CDCl3): δ=157.3, 145.1,

**2-[2,6-di(Thiophen-2-yl)pyridin-4-yl]-1*H*-indole(3ai):** Colorless solid, Yield: 70%, Mp: 169–171°C, 1H NMR (400 MHz, CDCl3): δ=9.12 (d, 1H), 8.19 (s, 1H), 8.07 (s, 2H), 7.54 (d, 1H), 7.49 (d, 1H), 7.32 (d, 2H), 7.23 (m, 1H), 7.15 (m, 5H). 13CNMR (100 MHz, CDCl3): δ=152.2,

146.2, 137.4, 135.1, 129.9, 128.7, 128.3, 126.3, 122.9, 121.1, 119.2, 118.7,

111.6, 101.8. HRMS (ESI): m/z [M+H]+ calcd for C H N S : found:

139.6, 136.9, 129.0, 128.7, 127.2, 125.3, 123.6, 122.9, 121.1, 119.6, 117.1,

116.0, 111.9. HRMS (ESI): m/z [M+H]+ calcd for C25H18N2: found:

359. 7.

21 14 2 2

347.2.

**3-[2,6-di(*p*-Tolyl)pyridin-4-yl]-1*H*-indole** (**3ab**): Colorless solid, Yield: 75%, Mp: 218–220°C, 1H NMR (400 MHz, CDCl3): δ=8.63 (d, 1H), 8.24 (d, 4H), 7.91 (d, 1H), 7.82 (d, 1H), 7.35 (s, 2H), 7.28 (d, 4H),

7.22 (d, 1H), 7.16 (t, 2H), 2.3 (d, 6H). 13C NMR (100 MHz, CDCl3):

δ=155.6, 144.5, 138.3, 135.5, 135.3, 129.0, 128.1, 126.6, 126.0, 124.5,

120.0, 116.9, 115.5, 112.3, 111.0, 21.3. HRMS (ESI): m/z [M+H]+ calcd

for C27H22N2: found: 375.8.

**3-[2,6-bis(4-Methoxyphenyl)pyridin-4-yl]-1*H*-indole** (**3ac**): Colorless solid, Yield: 80%, Mp: 230–232°C, 1H NMR (400 MHz, CDCl3): δ=8.65 (d, 1H), 8.25 (d, 4H), 7.94 (d, 1H), 7.86 (d, 1H), 7.39 (s,

2H), 7.29 (d, 4H), 7.25 (d, 1H), 7.18 (t, 2H), 3.8 (s, 6H). 13C NMR (100

**5-Bromo-3-(2,6-di(Phenylpyridin-4-yl))-1*H*-indole (3ba):** White Solid, Yield: 72%, Mp: 185-187°C, 1H NMR (400 MHz, CDCl3): δ=8.68 (d, 1H), 8.23 (d, 4H), 8.14 (s, 1H), 7.90 (s, 2H), 7.59 (t, 4H), 7.51 (d, 3H), 7.39 (t, 1H), 7.28 (t, 1H).13C NMR (100 MHz, CDCl3): δ=157.6,

144.2, 139.8, 135.4, 129.0, 128.7, 127.2, 127.0, 125.9, 124.4, 122.2, 117.1,

115.9, 114.4, 113.2. HRMS (ESI): m/z [M+H]+ calcd for C25H17N2Br2:

found: 426.9.

**3-(2,6-bis(4-Methoxyphenyl)pyridin-4-yl)-5-bromo-1*H*- indole(3bc):** Colorless solid, Yield: 80% Mp: 230–232°C, 1H NMR (400 MHz, CDCl3): δ=8.64 (d, 1H), 8.26 (d, 4H); 7.92 (s, 1H), 7.86 (s, 2H),

7.31 (d, 2H), 7.29 (d, 1H), 7.17 (d, 4H), 3.7 (s, 6H). 13C NMR (100 MHz,

CDCl ): δ=156.7, 144.3, 138.2, 135.6, 135.0, 130.6, 129.1, 126.9, 125.4,

MHz, CDCl ): δ=156.2, 144.1, 137.6, 135.2, 134.9, 130.6, 128.5, 126.8, 3 +

3

125.1, 122.8, 119.6, 115.5, 114.9, 112.7, 111.2, 55.8. HRMS (ESI): m/z

[M+H]+ calcd for C27H22N2O2: found: 407.8.

**3-[2,6-bis(4-Chlorophenyl)pyridin-4-yl]-1*H*-indole (3ad):** White solid, Yield: 84%, Mp: 186-188°C, 1H NMR (400 MHz, CDCl3): δ=8.61 (d, 1H), 8.21 (d, 4H), 7.93 (d, 1H), 7.88 (d, 1H), 7.40 (s, 2H),

7.32 (d, 4H), 7.29 (d, 1H), 7.21 (t, 2H). 13C NMR (100 MHz, CDCl3):

123.2, 119.6, 115.8, 115.1, 112.8, 111.5, 55.8. HRMS (ESI): m/z [M+H]

calcd for C27H21N2O2: found: 486.8.

**3-(2,6-bis(4-Chlorophenyl)pyridin-4-yl)-5-bromo-1*H*- indole(3bd):** White Solid, Yield: 81%, mp 120-122°C, 1H NMR (400 MHz, CDCl3): δ=8.64 (d, 1H), 8.14 (d, 4H), 8.11- 8.09 (s, 1H), 7.85

(s, 2H), 7.57 (d, 1H), 7.42 (d, 4H), 7.40 (d, 2H). 13C NMR (100 MHz,

CDCl ): δ=156.4, 144.5, 137.9, 135.4, 135.2, 128.9, 128.3, 126.9, 126.0,

δ=155.8, 144.5, 138.2, 135.4, 135.2, 128.9, 128.3, 126.9, 126.0, 124.2, 3 +

120.1, 116.9, 115.8, 112.5, 111.2. HRMS (ESI): m/z [M+H]+ calcd for

C25H16N2Cl2: found: 416. 7.

**3-[2,6-bis(4-Bromophenyl)pyridin-4-yl]-1*H*-indole (3ae):** Colorless solid, Yield: 82%, Mp: 216–217°C, 1H NMR (400 MHz, CDCl3): δ=8.58 (d, 1H), 8.07 (d, 4H); 7.86 (d, 1H) 7.59 (d, 4H), 7.52

(s, 2H), 7.45 (d, 1H) 7.39 (d, 1H), 7.21 (t, 2H). 13C NMR (100 MHz,

CDCl3): δ=156.6, 144.7, 138.6, 134.6, 130.8, 129.1, 125.8, 124.2, 122.8,

119.7, 119.1, 117.3, 118.5, 115.5, 113.4. HRMS (ESI): m/z [M+H]+ calcd

for C25H16N2Br2: found: 505.7.

**3-(2,6-bis(4-Fluorophenyl)pyridin-4-yl)-1*H*-indole (3af):** White Solid, Yield: 75%, Mp: 175-177°C, 1H NMR (400 MHz, CDCl3): δ=8.51 (d, 1H), 8.22 (d, 4H), 8.19 (d, 1H), 7.95 (s, 2H), 7.65 (d, 1H), 7.52 (d, 1H), 7.33 (t, 2H), 7.29 (d, 4H). 13C NMR (100 MHz, CDCl3): δ=164.8,

156.4, 145.0, 136.8, 135.9, 128.9, 125.2, 123.3, 121.2, 119.6, 116.6, 116.1,

115.7, 115.4, 111.8. HRMS (ESI): m/z [M+H]+ calcd for C25H16N2F2:

124.4, 122.1, 116.9, 115.6, 114.5, 113.2. HRMS (ESI): m/z [M+H] calcd

for C25H15N2Cl2Br: found: 494.8.

**3-(2,6-bis(4-Bromophenyl)pyridin-4-yl)-5-bromo-1*H*-indole (3be):** White Solid, Yield: 83%, Mp: 225-227°C, 1H NMR (400 MHz, CDCl3): δ=8.57 (d, 1H), 8.10 (d, 4H), 8.05 (s, 1H), 7.87 (s, 2H), 7.67

(d, 4H), 7.59 (d, 1H), 7.43 (d, 1H), 7.41 (d, 1H). 13C NMR (100 MHz,

CDCl3): δ=156.5, 144.5, 138.3, 135.4, 131.9, 128.6, 126.9, 126.1, 124.4,

123.6, 122.1, 117.0, 115.7, 114.5, 113.2. HRMS (ESI): m/z [M+H]+ calcd

for C25H15N2Br3: found: 584.5.

**3-(2,6-bis(4-Fluorophenyl)pyridin-4-yl)-5-bromo-1*H*-indole (3bf):** White Solid, Yield: 73%, Mp: 219-221°C, 1H NMR (400 MHz, CDCl3): δ=8.59 (d, 1H), 8.21 (d, 4H), 8.18 (s, 1H), 7.85 (s, 2H), 7.61 (d,

1H), 7.43 (d, 2H), 7.25 (d, 4H). 13C NMR (100 MHz, CDCl3): δ=164.8,

156.5, 144.4, 135.7, 135.4, 128.9, 126.9, 126.0, 124.3, 122.1, 116.6, 115.9,

115.7, 114.5, 113.2. HRMS (ESI): m/z [M+H]+ calcd for C H N BrF :

found: 383.

found: 462.8.

25 15 2 2

**3-[2,6-di(Pyridin-4-yl)pyridin-4-yl]-1*H*-indole (3ag):** Colorless solid, Yield: 63%, Mp: 378–380°C, 1H NMR (400 MHz, CDCl3): δ=9.24 (d, 1H), 8.77 (d, 4H), 8.42 (d, 4H), 8.40 (s, 2H), 7.93 (s, 1H), 7.61 (d, 1H), 7.50 (m, 1H), 7.22 (m, 2H).13C NMR (100 MHz, CDCl3): δ=155.5,

151.1, 146.4, 145.8, 137.2, 129.7, 127.0, 122.3, 121.1, 120.4, 119.1, 118.1,

113.0, 102.8. HRMS (ESI): m/z [M+H]+ calcd for C23H16N4: found:

349.8.

**3-[2,6-di(Furan-2-yl)pyridin-4-yl]-1*H*-indole(3ah):** White solid, Yield: 80%, Mp:153–155°C, 1H NMR (400 MHz, CDCl3): δ=9.38 (d, 1H); 8.15 (m, 1H); 7.90 (s, 2H); 7.62 (s, 1H); 7.56 (m, 2H); 7.45 (m,

1H); 7.30 (m, 2H); 7.21 (d, 2H); 6.56 (m, 2H). 13C NMR (100 MHz,

CDCl3): δ=158.9, 156.3, 148.0, 142.3, 135.5, 131.3, 128.2, 122.2, 120.2,

119.4, 118.5, 111.3, 108.1, 105.3, 102.3. HRMS (ESI): m/z [M+H]+ calcd

for C21H14N2O2: found: 327.6.

## General experimental procedure for biological activity

**5-Lipoxygenase enzyme inhibitory activity:** The indolylpyridines were screened for their 5-LOX inhibitory potential using colorimetric method. The assay mixture contained 50 mM phosphate buffer, pH 6.3, 5-lipoxygenase, various concentrations of test substances in dimethylsulfoxide, and linoleic acid (80 mM) in a total volume of 0.5 mL, after 5 min incubation of the above reaction mixture, 0.5 mL ferric xylenol orange reagent (in perchloric acid) was added and absorbance was measured after two minutes at 585 nm on a spectrophotometer. Controls were run along with test in a similar manner, except using vehicle instead of test substance solution. Percent inhibition was calculated by comparing the absorbance values of the test solution with that of control. All the tests were run in triplicate and averaged.

# Result and Discussion

## Chemistry

1*H*-Indole-3-carboxaldehydeand 5-bromo-1*H*-indole-3- carboxaldehyde were prepared from indole using phosphorus oxychloride in DMF. The general synthesis of 2,6-diaryl-4- indolylpyridines (3aa-3bf) is illustrated in Scheme 1. The reaction of indole-3-carboxaldehyde (1a-b) with substituted acetophenones (2a-i) in the presence of ammonium acetate in acetic acid at reflux conditions furnished 2,6-diaryl-4-indolylpyridines (3aa-3bf) in 63-84% yield. Based on this protocol we have prepared 14 derivatives of and all the compounds were purified by column chromatography on silica gel. The chemical structures of the target compounds were confirmed by 1H NMR, 13C NMR, and MS spectra (Table 1).

## Biological activity

**5-Lipoxnase enzyme inhibitory activity:** All the synthesized 2,6-diaryl-4-indolylpyridines (3aa-3bf) were screened for their 5-lipoxygenase enzyme inhibitory activity using colorimetric method

[35] at different concentrations and found to have significant 5-LOX inhibitory activity with IC50 range 14.40 to 32.78 μg/mL (Table 2). Among all the compounds chloro substituted 2,6-diaryl-4- indolylpyridine (3ad) (IC50; 14.40 μg/mL) and unsubstituted 2,6-diaryl- 4-indolylpyridine (3aa) (IC50; 17.40 μg/mL) showed very good activity whereas the compounds 3bd, 3ba, 3bc, 3be, 3ae, 3bf, 3ab and 3ac showed moderate activity. The compounds 3ag, 3ai and 3ah showed the least activity. In conclusion, we have synthesized a series of 2,6-diaryl substituted -4-indolylpyridine derivatives using commercially available

**Scheme 1:** Synthesis of substituted 2, 6-diaryl-4-indolylpyridines.

R = H, Br

R,

N

**3**

R,

**2**

R,

N H

**1**

AcONH4

AcOH, reflux

+

R

NH

R

O

H

O

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry** | **indole** | **ketone** | **product** | **Yield (%)** b |
| 1 | O HN**1a** H | OCH3**2a** | NHN**3aa** | 80 |
| 2 | **1a** | OCH3H3C**2b** | NHN**3ab**H3C CH3 | 75 |
| 3 | **1a** | OCH3MeO**2c** | NHN**3ac**MeO OMe | 80 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 4 | **1a** | OCH3Cl**2d** | NHNCl **3ad** Cl | 84 |
| 5 | **1a** | OCH3Br**2e** | NHNBr **3ae** Br | 82 |
| 6 | **1a** | OCH3F**2f** | NHN**3af**F F | 75 |
| 7 | **1a** | OCH3N**2g** | NHNN **3ag** N | 63 |
| 8 | **1a** | OOCH3**2h** | NHN OO **3ah** | 80 |
| 9 | **1a** | OSCH3**2i** | NHN SS **3ai** | 70 |
| 10 | O HBrN**1b** H | **2a** | NHBrN**3ba** | 72 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 11 | **1b** | **2c** | NHBrNMeO **3bc** OMe | 81 |
| 12 | **1b** | **2d** | NHBrNCl **3bd** Cl | 80 |
| 13 | **1b** | **2e** | NHBrNBr **3be** Br | 83 |
| 14 | **1b** | **2f** | NHBrNF **3bf** F | 73 |

b Isolated yields

|  |  |  |  |
| --- | --- | --- | --- |
| **Entry** | **Compound** | **Test items** | **IC50 µM** |
| 1 | 3aa | LNO-17-0001 | 17.40 |
| 2 | 3ab | LNO-17-0002 | 32.95 |
| 3 | 3ac | LNO-17-0003 | 33.14 |
| 4 | 3ad | LNO-17-0004 | 14.40 |
| 5 | 3ae | LNO-17-0005 | 29.94 |
| 6 | 3af | LNO-17-0006 | >100 |
| 7 | 3ag | LNO-17-0007 | 34.56 |
| 8 | 3ah | LNO-17-0008 | 42.62 |
| 9 | 3ai | LNO-17-0009 | 38.65 |
| 10 | 3ba | LNO-17-0010 | 24.83 |
| 11 | 3bc | LNO-17-0011 | 25.21 |
| 12 | 3bd | LNO-17-0012 | 21.05 |
| 13 | 3be | LNO-17-0013 | 25.78 |
| 14 | 3bf | LNO-17-0014 | 32.78 |
| Standard \* | 36.49 |

\*Nordihydroguaiaretic acid

**Table 1:** Synthesis of 2,6-diaryl-4-indolylpyridines b.

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**Table 2**: IC50 values obtained from in vitro 5-lipoxygenase inhibition assay for the compounds (3aa–3bf).

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