Medicinal chemistry
ISSN: 2161-0444

Tekluu et al., Med Chem (Los Angeles) 2017, 7:5
DOI: 10.4172/2161-0444.1000449

Research Article OMICS International

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

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Abstract

A series of 2,6-diaryl substituted -4-indolylpyridines have been synthesized from indole-3-carboxaldehyde and acetophenones and all the compounds characterized by spectroscopic techniques. 5-Lipoxygenase enzyme inhibitory activities were performed for all the compounds. Among the 2, 6-diaryl substituted -4-indolylpyridine derivatives 3ad and 3aa 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 fully explored. 5-Lipoxygenase is the key enzyme for the biosynthesis of leukotrienes, the important mediators for inflammatory, allergic, 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 1H-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 the 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 ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ solvent (400 MHz for ^{1}H and 100 MHz for ^{13}C) relative to 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 1H-indole-3-carboxaldehydes (1a or 1b)

To a solution of substituted indole (42.6 mmol) (or 5-bromo indole) in dry DMF (187.4 mmol) in an ice-salt bath, $POCl_3$ (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 same temperature. At the end of the reaction (as indicated by TLC) 25 gms 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 1H-indole-3-carboxaldehydes (1a or 1b).

1H-Indole-3-carboxaldehyde (1a): Brownish yellow solid, Yield: 92%, Mp: 196-198°C, ^{1}H 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). ^{13}C 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, ^{1}H NMR (DMSO-d_6, 400 MHz): δ=9.94 (s, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 7.75 (s, 1H), 7.43 (d, 1H), 7.34 (d, 1H). ^{13}C 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 1H-indole-3-carboxaldehyde (1) (1.0 mmol) and acetophenone (2) (2.0 mmol) in the presence of $AcONH_4$ (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 eluents to afford the pure product (3) (Supplementary Figures 1-18).

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Received May 24, 2017; **Accepted** May 27, 2017; **Published** May 31, 2017

Citation: Tekluu B, Kadiri SK, Vidavalur S (2017) Synthesis of 2,6-Diaryl-4-Indolylpyridines as Novel 5-LOX Inhibitors. Med Chem (Los Angeles) 7: 894-899. doi: 10.4172/2161-0444.1000449

Characterization of 2,6-diaryl-4-indolylpyridines

3-(2,6-di (Phenylpyridin-4-yl)-1H-indole (3aa): Colorless solid, Yield: 80%, Mp: 178-180°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.3, 145.1, 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 $C_{25}H_{18}N_2$: found: 347.2.

3-[2,6-di(p-Tolyl)pyridin-4-yl]-1H-indole (3ab): Colorless solid, Yield: 75%, Mp: 218–220°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{27}H_{22}N_2$: found: 375.8.

3-[2,6-bis(4-Methoxyphenyl)pyridin-4-yl]-1H-indole (3ac): Colorless solid, Yield: 80%, Mp: 230–232°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.2, 144.1, 137.6, 135.2, 134.9, 130.6, 128.5, 126.8, 125.1, 122.8, 119.6, 115.5, 114.9, 112.7, 111.2, 55.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{22}N_2O_2$: found: 407.8.

3-[2,6-bis(4-Chlorophenyl)pyridin-4-yl]-1H-indole (3ad): White solid, Yield: 84%, Mp: 186-188°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.8, 144.5, 138.2, 135.4, 135.2, 128.9, 128.3, 126.9, 126.0, 124.2, 120.1, 116.9, 115.8, 112.5, 111.2. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{16}N_2Cl_2$: found: 416. 7.

3-[2,6-bis(4-Bromophenyl)pyridin-4-yl]-1H-indole (3ae): Colorless solid, Yield: 82%, Mp: 216–217°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{16}N_2Br_2$: found: 505.7.

3-(2,6-bis(4-Fluorophenyl)pyridin-4-yl)-1H-indole (3af): White Solid, Yield: 75%, Mp: 175-177°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{16}N_2F_2$: found: 383.

3-[2,6-di(Pyridin-4-yl)pyridin-4-yl]-1H-indole (3ag): Colorless solid, Yield: 63%, Mp: 378–380°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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).^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{23}H_{16}N_4$: found: 349.8.

3-[2,6-di(Furan-2-yl)pyridin-4-yl]-1H-indole(3ah): White solid, Yield: 80%, Mp:153–155°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{21}H_{14}N_2O_2$: found: 327.6.

2-[2,6-di(Thiophen-2-yl)pyridin-4-yl]-1H-indole(3ai): Colorless solid, Yield: 70%, Mp: 169–171°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}CNMR (100 MHz, $CDCl_3$): 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 $C_{21}H_{14}N_2S_2$: found: 359. 7.

5-Bromo-3-(2,6-di(Phenylpyridin-4-yl))-1H-indole (3ba): White Solid, Yield: 72%, Mp: 185-187°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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).^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{17}N_2Br_2$: found: 426.9.

3-(2,6-bis(4-Methoxyphenyl)pyridin-4-yl)-5-bromo-1H-indole(3bc): Colorless solid, Yield: 80% Mp: 230–232°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.7, 144.3, 138.2, 135.6, 135.0, 130.6, 129.1, 126.9, 125.4, 123.2, 119.6, 115.8, 115.1, 112.8, 111.5, 55.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{21}N_2O_2$: found: 486.8.

3-(2,6-bis(4-Chlorophenyl)pyridin-4-yl)-5-bromo-1H-indole(3bd): White Solid, Yield: 81%, mp 120-122°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.4, 144.5, 137.9, 135.4, 135.2, 128.9, 128.3, 126.9, 126.0, 124.4, 122.1, 116.9, 115.6, 114.5, 113.2. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{15}N_2Cl_2Br$: found: 494.8.

3-(2,6-bis(4-Bromophenyl)pyridin-4-yl)-5-bromo-1H-indole (3be): White Solid, Yield: 83%, Mp: 225-227°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{15}N_2Br_3$: found: 584.5.

3-(2,6-bis(4-Fluorophenyl)pyridin-4-yl)-5-bromo-1H-indole (3bf): White Solid, Yield: 73%, Mp: 219-221°C, ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{15}N_2BrF_2$: found: 462.8.

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.

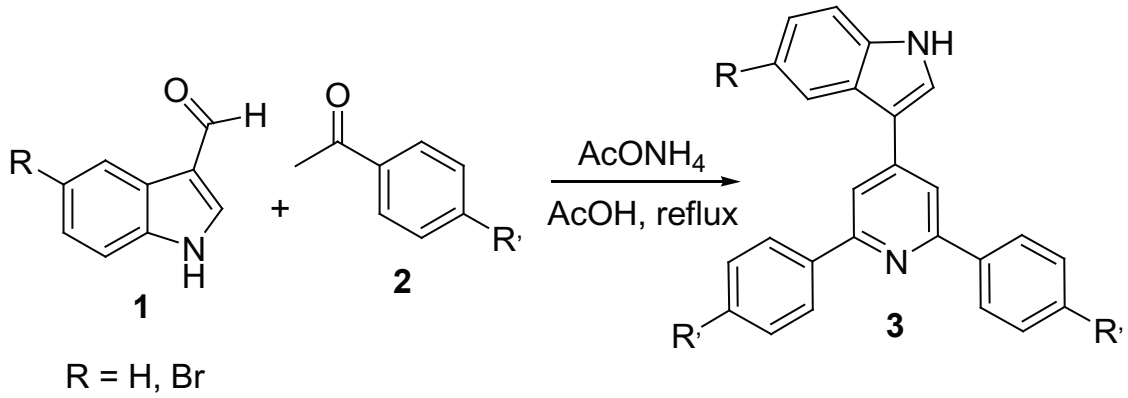
Result and Discussion

Chemistry

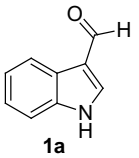
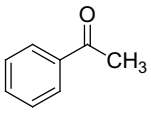
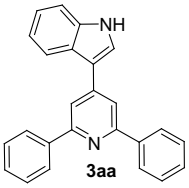
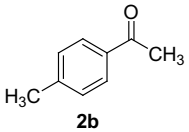
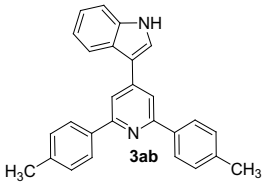
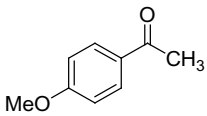
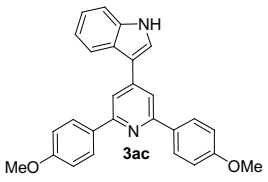
1H-Indole-3-carboxaldehyde and 5-bromo-1H-indole-3-carboxaldehyde were prepared from indole using phosphorus oxychloride in DMF. The general synthesis of 2,6-diaryl-4-indolylpyridines (3aa-3bf) is illustrated in Scheme 1. The reaction of indole-3-carboxaldehyde (1a-b) with substituted acetophenones (2a-i) 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 ^{1}H NMR, ^{13}C NMR, and MS spectra (Table 1).

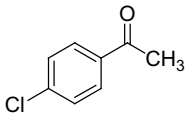
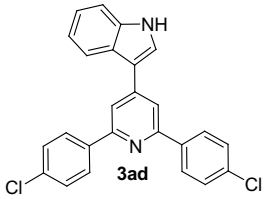
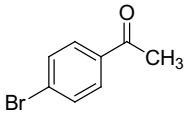
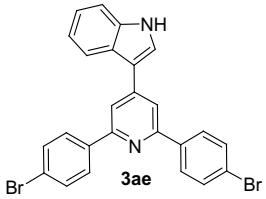
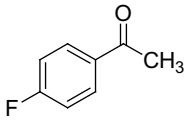
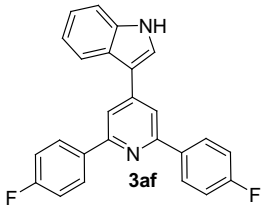
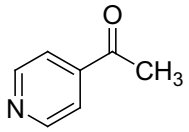
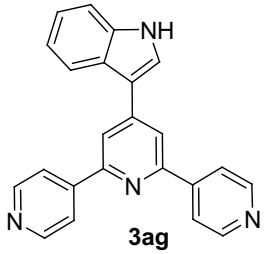
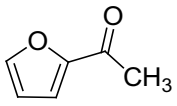
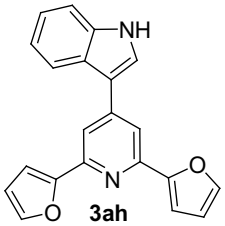
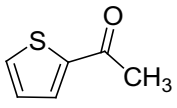
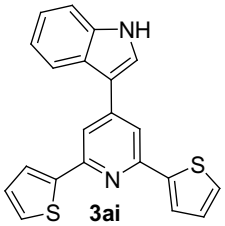
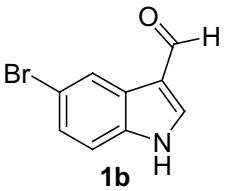
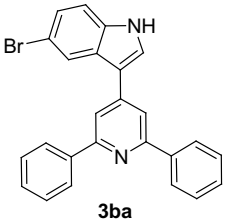
Biological activity

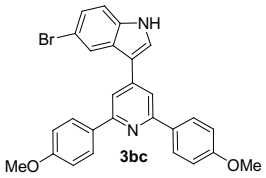
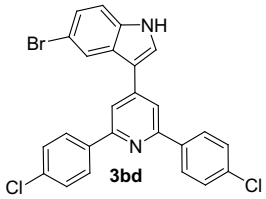
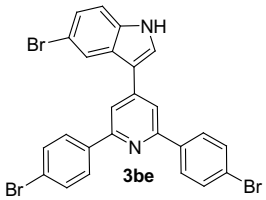
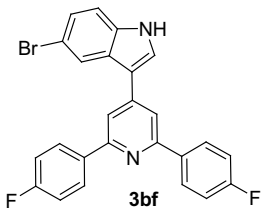
5-Lipoxnase enzyme inhibitory activity: All the synthesized 2,6-diaryl-4-indolylpyridines (3aa-3bf) were screened for their 5-lipoxygenase enzyme inhibitory activity using colorimetric method [35] at different concentrations and found to have significant 5-LOX inhibitory activity with IC_{50} range 14.40 to 32.78 µg/ml (Table 2). Among all the compounds chloro substituted 2,6-diaryl-4-indolylpyridine (3ad) (IC_{50}; 14.40 µg/ml) and unsubstituted 2,6-diaryl-4-indolylpyridine (3aa) (IC_{50}; 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.

Entry	indole	ketone	product	Yield (%)[b]
1	 **1a**	 **2a**	 **3aa**	80
2	**1a**	 **2b**	 **3ab**	75
3	**1a**	 **2c**	 **3ac**	80

4	**1a**	 **2d**	 **3ad**	84
5	**1a**	 **2e**	 **3ae**	82
6	**1a**	 **2f**	 **3af**	75
7	**1a**	 **2g**	 **3ag**	63
8	**1a**	 **2h**	 **3ah**	80
9	**1a**	 **2i**	 **3ai**	70
10	 **1b**	**2a**	 **3ba**	72

11	**1b**	**2c**	 **3bc**	81
12	**1b**	**2d**	 **3bd**	80
13	**1b**	**2e**	 **3be**	83
14	**1b**	**2f**	 **3bf**	73

[b] Isolated yields

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

Entry	Compound	Test items	IC_{50} 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 2: IC_{50} values obtained from in vitro 5-lipoxygenase inhibition assay for the compounds (3aa–3bf).

starting materials. 5-Lipoxygenase (5-LOX) enzyme inhibitory activities were performed for all the synthesized compounds. Among the tested compounds 3ad and 3aa showed good 5-lipoxygenase enzyme inhibitory activity.

Acknowledgement

The authors thank CSIR, New Delhi for financial assistance (through a project 02(0197)/14/EMR-II) and the Ministry of Education, Ethiopia, for financial support to B. T. G.

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Citation: Tekluu B, Kadiri SK, Vidavalur S (2017) Synthesis of 2,6-Diaryl-4-Indolylpyridines as Novel 5-LOX Inhibitors. Med Chem (Los Angeles) 7: 894-899. doi: 10.4172/2161-0444.1000449