

Facile synthesis of biologically important indole based quinoxalines

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Abstract

Condensation of 1,2-phenylenediamine with a variety of indole based aldehydes, prepared from the corresponding acid chloride in presence of HSnBu_3 , furnishes (1*H*-indol-3-yl)quinoxalines. In addition, 1,2-phenylenediamines substituted with a strong electron-withdrawing group at the *para* position, provides 6-substituted (1*H*-indol-3-yl)quinoxalines. Several biologically important quinoxalines were prepared in the same way. The yields are good to excellent in all cases. However, 1,2-phenylenediamine substituted with the weakly electron-donating methyl group, gives an inseparable mixture of 6-methyl and 7-methyl isomers of (1*H*-indol-3-yl)quinoxaline. All the compounds were characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy.

Keywords: Oxoacetaldehyde, quinoxalines, indole, oxoacetyl chloride

Introduction

Numerous quinoxaline derivatives have important biological activity such as antibacterial, antifungal, anticancer, antidepressant and anti-inflammatory agents.¹⁻³ Several groups have reported on the biological effects of “plated-derived-growth-factor” (PDGF) tyrosin kinase blockers from the indole-containing blockers,⁴ quinoxaline blockers.^{5,6} In addition, some piperazinylquinoxalines behave as 5-HT₃ receptor antagonists.^{7a}

The quinoxaline antibiotics of octadepsipeptide type, e.g., echinomycin (Figure 1), show activity against gram-positive bacteria and certain animal tumors and also are potent inhibitors of RNA synthesis.^{7b} Some of the marine sponge bis(indole) alkaloids of the topsentin class (Figure 1) have received considerable attention because of their potent biological properties such as antitumor, antiviral, and anti-inflammatory activities.^{7c} Consequently, we decided to synthesize some indole based quinoxaline derivatives with the aim of investigating their antimicrobial and neuroprotecting properties. In this present study we report the synthesis of several indole based quinoxalines.

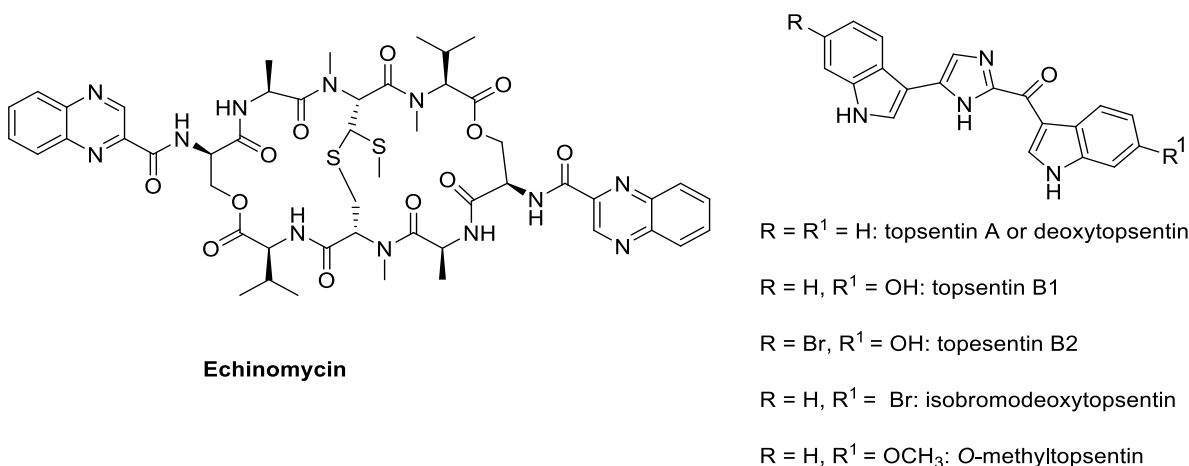
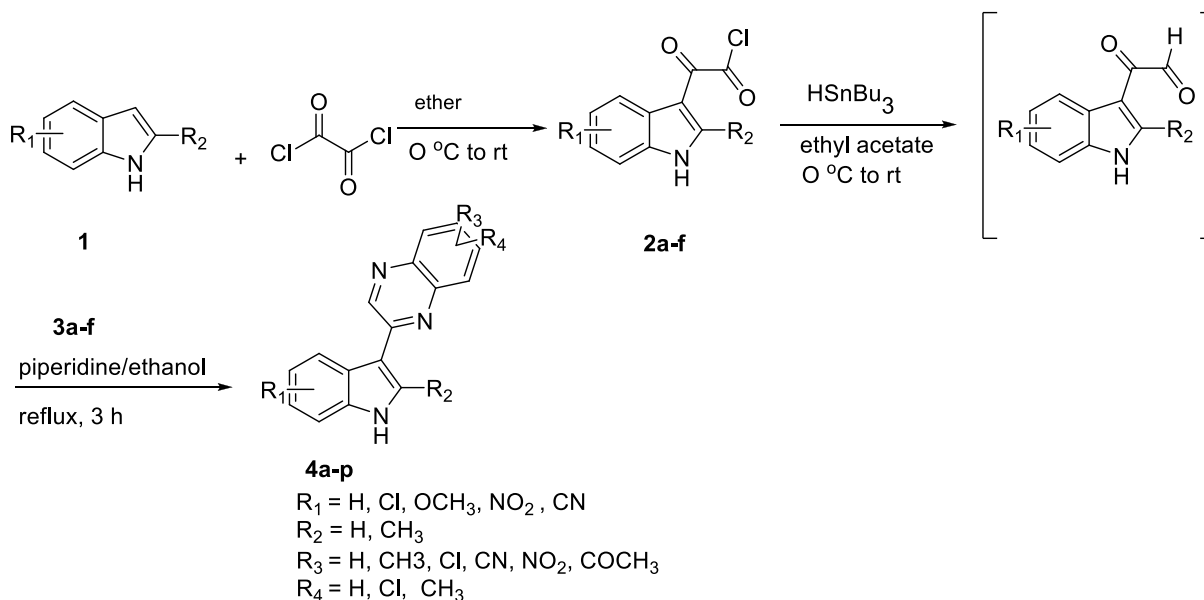


Figure 1

Results and Discussion

The quinoxalines **4a-p** were prepared according to Scheme-1. 3-Indolyl- α -oxoacetyl chloride derivatives **2a-f** were first prepared by the reaction of corresponding indoles with oxalyl chloride in ether.⁸ All the acid chlorides were isolated and characterized by ¹H NMR, ¹³C NMR and IR spectroscopy. Some of the acid chlorides were previously reported.^{9,10} Treatment with Bu₃SnH in ethyl acetate gave the corresponding aldehyde intermediates¹¹ which because of their instability were immediately treated with suitably substituted 1,2-phenylenediamines **3a-f** in presence of base to afford the expected (1*H*-indol-3-yl)quinoxalines **4a-p**. We studied the reaction in different bases and solvents with 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde (Entry 1, Table 2) and 1,2-phenylenediamine **3a** and found that piperidine-ethanol combination gave the best yields of (1*H*-indol-3-yl)quinoxaline **4a**. The results are summarized in Table 1.



Scheme 1. Schematic representation for the synthesis of indole based quinoxalines.

Table 1. Reaction of 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde with 1,2-phenylenediamine in different solvents and bases at 90 °C

Entry	Base (3 equiv.)	Solvent (15 ml)	% Yield
1	KOH	Water	46
2	KOH	Ethanol	51
3	----	Ethanol	Trace
4	NaOH	Water	40
5	Piperidine	Ethanol	88
6	Triethylamine	Ethanol	78
7	DBU	Ethanol	40
8	<i>N</i> -Methylpiperidine	Ethanol	78
9	Piperidine	Benzene	60
10	Pyridine	Ethanol	20
11	Pyridine	----	30
12	Piperidine	----	50

The workup procedure is simple. The crude reaction mixture was allowed to cool at room temperature. In some reactions, the crude product precipitated from solution and was collected by filtration and washed several times with dichloromethane/hexane mixture (60:40, v/v) and give the pure product after recrystallization from ethanol. In those reactions in which the product did not precipitate from solution, the excess solvent (ethanol) was removed in vacuum and the solid product obtained was triturated with dichloromethane/hexane mixture and give the pure product after recrystallization from ethanol.

Further evaluation of the data in Table 2 reveal that condensation of symmetrically substituted 1,2-phenylenediamine **3a-c** with a variety of indole based aldehydes, prepared from the corresponding acid chloride **2a-f** in presence of HSnBu_3 , furnishes (1*H*-indol-3-yl)quinoxalines **4a**, **4h**, **4i**, and **4k**, and 6,7-disubstituted 1*H*-indol-3-yl)quinoxalines **4b-g**, **4j**, **4l** and **4m** respectively. In addition, 1,2-phenylenediamines substituted with the strong electron-withdrawing group (EWG) carbethoxy, nitro, or cyano at the *para* position **3d-f**, provides the corresponding 6- substituted-2-(1*H*-indol-3-yl)quinoxalines **4n-p**. Direct electronic delocalization occurs between the 4-EWG substituent and 1-amino group. This decreases the basicity and hence nucleophilicity of the 1-amine, thus it is the 2-amino group that is the active nucleophile in these reactions.

However, the difference in nucleophilicity of the two amino groups in 1,2-phenylenediamine substituted with the weakly electron-donating methyl group **3g** is not so large which results in the production of an inseparable mixture of the 6-methyl- **6** and 7-methyl isomers **5** of (1*H*-indol-3-yl)quinoxaline (see Scheme 2). The ^1H NMR shows two different peaks at δ 11.53 ppm, δ 11.51 ppm for two NH protons and at δ 9.16 ppm, δ 9.13 ppm for two N=CH protons.

Table 2. Synthesis of indole based quinoxalines **4a-p**

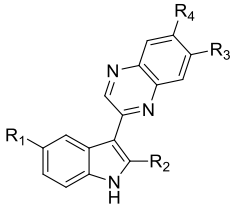
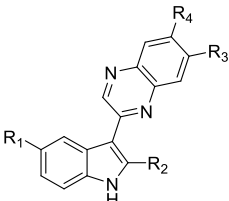
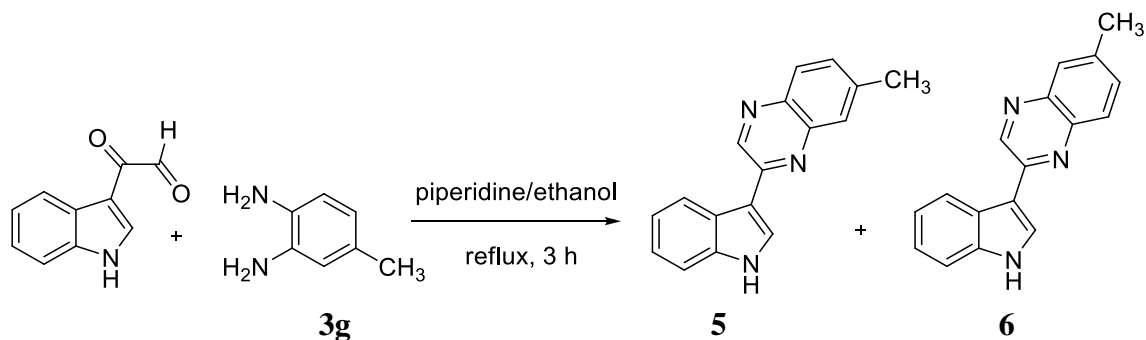
Entry	Acid chlorides 2a-f	1,2-Diamines 3a-f	Quinoxalines 4a-p ^a	
				% Yield ^b
1	R ₁ = R ₂ = H 2a	R ₃ = R ₄ = H 3a	R ₁ = R ₂ = R ₃ = R ₄ = H 4a	88
2	R ₁ = R ₂ = H 2a	R ₃ = R ₄ = CH ₃ 3b	R ₁ = R ₂ = H; R ₃ = R ₄ = CH ₃ 4b	93
3	R ₁ = R ₂ = H 2a	R ₃ = R ₄ = Cl 3c	R ₁ = R ₂ = H; R ₃ = R ₄ = Cl 4c	80
4	R ₁ = OCH ₃ , R ₂ = H 2b	R ₃ = R ₄ = CH ₃ 3b	R ₁ = OCH ₃ , R ₂ = H; R ₃ = R ₄ = CH ₃ 4d	95
5	R ₁ = Cl, R ₂ = H 2c	R ₃ = R ₄ = CH ₃ 3b	R ₁ = Cl, R ₂ = H; R ₃ = R ₄ = CH ₃ 4e	90
6	R ₁ = CN, R ₂ = H 2d	R ₃ = R ₄ = CH ₃ 3b	R ₁ = CN, R ₂ = H; R ₃ = R ₄ = CH ₃ 4f	91
7	R ₁ = NO ₂ , R ₂ = H 2e	R ₃ = R ₄ = CH ₃ 3b	R ₁ = NO ₂ , R ₂ = H; R ₃ = R ₄ = CH ₃ 4g	85
8	R ₁ = Cl, R ₂ = H 2c	R ₃ = R ₄ = H 3a	R ₁ = Cl; R ₂ = R ₃ = R ₄ = H 4h	89
9	R ₁ = CN, R ₂ = H 2d	R ₃ = R ₄ = H 3a	R ₁ = CN, R ₂ = R ₃ = R ₄ = H 4i	85
10	R ₁ = CN, R ₂ = H 2d	R ₃ = R ₄ = Cl 3c	R ₁ = CN, R ₂ = H; R ₃ = R ₄ = Cl 4j	90
11	R ₁ = OCH ₃ , R ₂ = CH ₃ 2f	R ₃ = R ₄ = H 3a	R ₁ = OCH ₃ , R ₂ = CH ₃ ; R ₃ = R ₄ = H 4k	88
12	R ₁ = OCH ₃ , R ₂ = CH ₃ 2f	R ₃ = R ₄ = CH ₃ 3b	R ₁ = OCH ₃ , R ₂ = R ₃ = R ₄ = CH ₃ 4l	90
13	R ₁ = OCH ₃ , R ₂ = CH ₃ 2f	R ₃ = R ₄ = Cl 3c	R ₁ = OCH ₃ ; R ₂ = CH ₃ R ₃ = R ₄ = Cl 4m	88
14	R ₁ = OCH ₃ , R ₂ = CH ₃ 2f	R ₃ = H, R ₄ = COOCH ₃ 3d	R ₁ = OCH ₃ , R ₂ = CH ₃ ; R ₃ = H, R ₄ = COOCH ₃ 4n	91

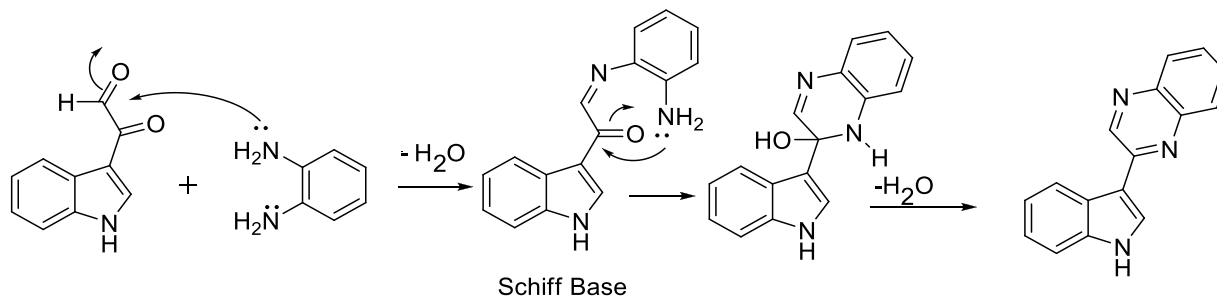
Table 2. Continued

Entry	Acid chlorides 2a-f	1,2-Diamines 3a-f	Quinoxalines 4a-p ^a	% Yield ^b
				
15	R ₁ = OCH ₃ , R ₂ = CH ₃ 2f	R ₃ = H, R ₄ = NO ₂ 3e	R ₁ = OCH ₃ , R ₂ = CH ₃ ; R ₃ = H, R ₄ = NO ₂ 4o	89
16	R ₁ = R ₂ = H 2a	R ₃ = H, R ₄ = CN 3f	R ₁ = R ₂ = H; R ₃ = H, R ₄ = CN 4p	78

^aAll the compounds were characterized by ¹H NMR, ¹³C NMR, IR and HRMS analysis. ^bIsolated yield.

**Scheme 2.** Reaction of 2-(1H-indol-3-yl)-2-oxoacetaldehyde with 4-methyl-1,2-phenylenediamine.

Finally, a possible mechanism for the synthesis of quinoxaline is shown in Scheme 3.

**Scheme 3.** Mechanism for the formation of quinoxaline.

As shown, the aldehydes and diamines react to give a Schiff base that undergoes successive intramolecular cyclisation and dehydration to give **4a**.

Conclusions

In summary we have successfully developed an easy access to novel series of indole based biologically important quinoxalines. This method is more efficient than previously reported.¹² We are currently investigating the synthesis of a number of other quinoxaline-based drug molecules by this method and work is in progress for the detail biological activity (antibacterial, antifungal, anticancer and neuroprotective kinase inhibitor activity) of these important compounds. Results in these areas will be presented in due course.

Experimental Section

General. The ¹H and ¹³C NMR spectra were recorded on 500 MHz Jeol multinuclear NMR spectrometer; chemical shifts were referenced to tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were obtained on a Varian 3100 Fourier transform (FT) IR Spectrometer. Melting points were taken on a Meltemp apparatus. All chemicals and reagents were purchased from commercial sources. Mass spectra was obtained from Washington University, St. Louis.

General procedure for the synthesis of acid chlorides (2a-f)

To a solution of appropriate indole (1 equiv) in anhydrous diethyl ether (120 mL) at 0 °C, oxalyl chloride (1.3 equiv.) was added drop wise over 30 min. The reaction mixture was stirred at 0 °C for 3 h, then allowed to warm at room temperature and stirred for 1 h. The resulting solid products were collected by filtration, washed with cold anhydrous diethyl ether (100 mL) and dried under vacuum to yield **2a-f**. All the compounds were well characterized with ¹H NMR, ¹³C NMR and IR.

2-(1*H*-Indol-3-yl)-2-oxoacetyl chloride (2a). Obtained as yellow crystals. Yield = 90%. Decomposition point: 117-119 °C. All the chemical and physical data are identical to previously reported.¹⁰

2-(5-Methoxy-1*H*-indol-3-yl)-2-oxoacetyl chloride (2b). Obtained as bright orange solid. Decomposition point: 238-239 °C. Yield = 80%. IR (KBr, cm⁻¹): 3194, 1778, 1617 which are in accordance with those previously reported.¹¹ ¹H NMR (DMSO-*d*₆) δ 12.31 (brs, 1H, NH), 8.29 (d, *J* = 5.7 Hz, 1H, Ar-CH), 7.63 (d, *J* = 5.7 Hz, 1H, Ar-CH), 7.41 (d, *J* = 8.5 Hz, 1H, Ar-CH), 6.87 (dd, *J* = 5.7 Hz, 8.5 Hz, 1H, Ar-CH), 3.75 (s, 3H, OCH₃). ¹³C NMR (DMSO-*d*₆) δ 181.1 (C=O), 165.8 (C=O), 156.5 (C), 138.3 (CH), 131.9 (C), 127.0 (C), 114.0 (CH), 113.7 (C), 112.6 (C), 103.5 (C), 55.8 (OCH₃).

2-(5-Chloro-1*H*-indol-3-yl)-2-oxoacetyl chloride (2c). Obtained as yellow powder. Yield = 88%. Decomposition point: 157-158 °C. All the chemical and physical data were identical to those previously reported.¹⁰

2-(5-Cyano-1*H*-indol-3-yl)-2-oxoacetyl chloride (2d). Obtained as brick red solid. Yield = 93%. Decomposition point: 184-185 °C. IR (KBr, cm⁻¹): 3202, 2220, 1733, 1648. ¹H NMR (DMSO-*d*₆) δ 12.02 (brs, 1H, NH), 8.60 (d, *J* = 2.8 Hz, 1H, Ar-CH), 8.48 (s, 1H, Ar-CH), 7.70 (d, *J* = 8.6 Hz, 1H, Ar-CH), 7.63 (dd, *J* = 2.8 Hz, 8.6 Hz, 1H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 181.1 (C=O), 164.9 (C=O), 140.6 (C), 139.0 (C), 127.1 (CH), 126.4 (CH), 126.0 (CH), 120.1 (CH), 114.7 (CN), 112.9 (C), 105.3 (C).

2-(5-Nitro-1*H*-indol-3-yl)-2-oxoacetyl chloride (2e). Obtained as pale yellow solid. Yield = 91%. Decomposition point: 250-252 °C. IR (KBr, cm⁻¹): 3201, 1743, 1647, 1508. ¹H NMR (DMSO-*d*₆) δ 12.09 (brs, 1H, NH), 8.94 (d, *J* = 2.3 Hz, 1H, Ar-CH), 8.65 (d, *J* = 2.3 Hz, 1H, Ar-CH), 8.10 (dd, *J* = 2.3 Hz, 8.5 Hz, 1H, Ar-CH), 7.69 (d, *J* = 8.5 Hz, 1H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 181.2 (C=O), 164.8 (C=O), 143.7 (C), 141.7 (CH), 140.3 (C), 125.6 (C), 119.5 (CH), 117.8 (CH), 114.0 (CH).

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)-2-oxoacetyl chloride (2f). Obtained as dark red solid. Decomposition point: 131-133 °C. Yield = 88%. IR (KBr, cm⁻¹): 3200, 1797, 1738, 1575. ¹H NMR (DMSO-*d*₆) δ 12.32 (brs, 1H, NH), 7.45 (d, *J* = 2.8 Hz, 1H, Ar-CH), 7.29 (d, *J* = 9.1 Hz, 1H, Ar-CH), 6.78 (dd, *J* = 2.8 Hz, 9.1 Hz, 1H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 183.6 (C=O), 168.7 (C=O), 156.1 (C), 147.6 (C), 130.2 (C), 127.9 (C), 112.8 (CH), 112.5 (CH), 108.6 (C), 103.1 (CH), 55.7 (OCH₃), 13.8 (CH₃).

General procedure for the synthesis of suitably substituted 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde

To a suspension of oxoacetyl chloride (25 mmol) in ethyl acetate (80 mL) at 0 °C was added a solution of tributyltin hydride (25 mmol). The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature and then stirred for an additional 15 h. Hexane (100 mL) was added and the resulting solid was collected by filtration, washed with copious amounts of hexane, then dried under vacuum to give ketoaldehyde (60% yield) which was immediately subjected to the next step without further purification.

General procedure for the synthesis of quinoxalines using preparation of (4a) as typical example

To a solution of keto aldehyde obtained from **2a** (0.4 g, 2.31 mmol) and 1,2-phenylenediamine (0.27 g, 2.31 mmol) in 15 mL of ethanol at 90 °C was added piperidine (0.98 g, 11.5 mmol). After stirring at 90 °C for 3 hr, the reaction mixture was allowed to cool at room temperature. The solid formed was collected by filtration, washed with cold ethanol (50 mL), dichloromethane/hexane mixture (50 mL, 60:40, v/v) to afford the desired product **4a** which was recrystallized from ethanol.

2-(1*H*-Indol-3-yl)quinoxaline (4a). This compound was obtained as yellow powder. Mp 203-204 °C (lit¹² m.p. 202-203 °C).

2-(1*H*-Indol-3-yl)-6,7-dimethylquinoxaline (4b). This compound was obtained as light yellow crystalline solid. Mp 279-281 °C. IR (KBr, cm⁻¹): 3432 (NH). ¹H NMR (DMSO-*d*₆): δ 12.21 (brs, 1H, NH), 9.33 (s, 1H, Ar-CH), 8.74 (dd, *J* = 3.1 Hz, 7.8 Hz, 1H, Ar-CH), 8.50 (s, 1H, Ar-CH), 7.81 (s, 1H, Ar-CH), 7.71 (s, 1H, Ar-CH), 7.20-7.19 (m, 1H, Ar-CH), 7.19-7.18 (m, 2H, Ar-CH),

2.42 (s, 3H, CH₃), 2.39 (s, 3H, CH₃). ¹³C NMR (DMSO-*d*₆) δ 150.6 (C), 143.9 (CH), 141.1 (C), 140.4 (C), 138.7 (C), 138.0 (C), 137.8 (C), 129.09 (CH), 128.3 (CH), 128.1 (CH), 122.9 (CH), 122.8 (CH), 121.1 (CH), 111.2 (CH), 20.3 (CH₃), 20.1 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₈H₁₅N₃: 274.1339. Found: 274.1347.

6,7-Dichloro-2-(1*H*-indol-3-yl)quinoxaline (4c). This compound was obtained as bottle green solid. Mp 220-222 °C. IR (KBr, cm⁻¹): 3335 (NH). ¹H NMR (DMSO-*d*₆) δ 12.31 (brs, 1H, NH), 9.49 (s, 1H, Ar-CH), 8.68 (d, *J* = 8.5 Hz, 1H, Ar-CH), 8.30 (s, 2H, Ar-CH), 7.50-7.22 (m, 4H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 150.6 (C), 143.9 (C), 141.18 (C), 140.4 (C), 138.0 (C), 137.8 (C), 128.3 (CH), 128.1 (CH), 122.9 (CH), 122.8 (CH), 121.1 (CH), 111.2 (CH). HRMS: Calcd [M+H]⁺ for C₁₆H₉N₃Cl₂: 314.0255. Found: 314.0248.

2-(5-Methoxy-1*H*-indol-3-yl)-6,7-dimethylquinoxaline (4d). This compound was obtained as bright yellow powder. Mp 277-280 °C. IR (KBr, cm⁻¹): 3431 (NH). ¹H NMR (DMSO-*d*₆) δ 12.01 (brs, 1H, NH), 9.30 (s, 1H, Ar-CH), 8.45 (s, 1H, Ar-CH), 8.29 (d, *J* = 2.5 Hz, 1H, Ar-CH), 7.79 (s, 1H, Ar-CH), 7.70 (s, 1H, Ar-CH), 7.37 (s, 1H, Ar-CH), 6.85-6.83 (m, 1H, Ar-CH), 2.99 (s, 3H, -OCH₃), 2.42 (s, 3H, CH₃), 2.39 (s, 3H, CH₃). ¹³C NMR (DMSO-*d*₆) δ 155.07 (C), 150.84 (C), 143.90 (CH), 141.16 (C), 140.31 (C), 138.63 (C), 137.8 (C), 133.13 (C), 129.79 (C), 128.37 (CH), 128.13 (CH), 112.57 (CH), 104.81 (CH), 55.90 (OCH₃), 20.30, (CH₃), 20.15 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₉H₁₇N₃O: 304.1444. Found: 304.1457.

2-(5-Chloro-1*H*-indol-3-yl)-6,7-dimethylquinoxaline (4e). This compound was obtained as brownish yellow powder. Mp 296-297 °C. IR (KBr, cm⁻¹): 3337 (NH). ¹H NMR (DMSO-*d*₆) δ 11.98 (brs, 1H, NH), 9.31 (s, 1H, Ar-CH), 8.73 (d, *J* = 2.3 Hz, 1H, Ar-CH), 8.58 (s, 1H, Ar-CH), 7.81 (s, 1H, Ar-CH), 7.70 (s, 1H, Ar-CH), 7.54-7.52 (m, 1H, Ar-CH), 7.20 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 2.42 (s, 3H, CH₃), 2.39 (s, 3H, CH₃). ¹³C NMR (DMSO-*d*₆) δ 150.20 (C), 143.80 (CH), 141.04 (C), 140.58 (C), 138.8 (C), 138.2 (C), 136.7 (C), 131.05 (CH), 128.37 (CH), 128.12 (C), 125.6 (C), 122.7 (CH), 121.7 (CH), 114.4 (CH), 113.0 (C), 20.23 (CH₃), 20.15 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₈H₁₄N₃Cl: 308.0949. Found: 308.0963.

3-(6,7-Dimethylquinoxalin-2-yl)-1*H*-indole-5-carbonitrile (4f). This compound was obtained as brownish solid. Mp 275-277 °C. IR (KBr, cm⁻¹): 3438 (NH), 2221 (CN). ¹H NMR (DMSO-*d*₆) δ 12.32 (brs, 1H, NH), 9.16 (s, 1H, Ar-CH), 8.97 (s, 1H, Ar-CH), 7.65-7.54 (m, 4H, Ar-CH), 7.00 (s, 1H, Ar-CH), 2.27 (s, 3H, CH₃), 2.24 (s, 3H, CH₃). ¹³C NMR (DMSO-*d*₆) δ 154.8 (C), 150.6 (C), 138.5 (C), 134.8 (CH), 132.4 (C), 131.5 (C), 128.4 (CH), 128.3 (CH), 126.3 (C), 125.8 (CH), 121.24 (C), 115.5 (CH), 113.7 (CH), 112.3 (C), 103.3 (C), 20.2 (CH₃), 19.4 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₉H₁₄N₄: 299.1298. Found: 299.1311.

6,7-Dimethyl-2-(5-nitro-1*H*-indol-3-yl)quinoxaline (4g). This compound was obtained as light yellow solid. Mp > 300 °C. IR (KBr, cm⁻¹): 3370 (NH). ¹H NMR (DMSO-*d*₆) δ 12.41 (brs, 1H, NH), 9.58 (s, 1H, Ar-CH), 8.70 (s, 1H, Ar-CH), 8.57 (s, 1H, Ar-CH), 8.07 (s, 2H, Ar-CH), 7.76-7.62 (m, 2H, Ar-CH), 2.47 (s, 3H, CH₃), 2.43 (s, 3H, CH₃). ¹³C NMR (DMSO-*d*₆): δ 149.2 (C), 143.6 (CH), 140.8 (C), 140.6 (C), 139.1 (C), 138.9 (C), 137.3 (CH), 131.9 (CH), 128.4 (CH), 119.6 (CH), 118.7 (CH), 118.3 (CH), 115.4 (CH), 113.0 (CH), 20.16 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₈H₁₄N₄O₂: 319.1190. Found: 319.1192.

2-(5-Chloro-1*H*-indol-3-yl)quinoxaline (4h). This compound was obtained as dark brown solid. Mp 225-227 °C. IR (KBr, cm⁻¹): 3330 (NH). ¹H NMR (DMSO-*d*₆) δ 12.19 (brs, 1H, NH), 9.47 (s, 1H, ArCH), 8.75 (s, 1H, Ar-CH), 8.67 (s, 1H, Ar-CH), 7.97 (dd, *J* = 2.5, 8.5 Hz, 2H, Ar-CH), 7.69 (dd, *J* = 2.6, 7.8 Hz, 2H, Ar-CH), 7.51 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.23 (d, *J* = 2.8 Hz, 1H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 150.6 (C), 144.3 (C), 142.1 (CH), 139.6 (C), 136.0 (C), 130.3 (CH), 128.8 (CH), 128.7 (C), 128.2 (C), 127.0 (C), 126.2 (C), 123.0 (CH), 121.9 (CH), 113.7 (CH), 112.9 (C). HRMS: Calcd [M+H]⁺ for C₁₆H₁₀N₃Cl: 280.0643. Found: 280.0651.

3-(Quinoxalin-2-yl)-1*H*-indole-5-carbonitrile (4i). This compound was obtained as pale yellow solid. Mp 331-335 °C. IR (KBr, cm⁻¹): 3439 (NH), 2220 (CN). ¹H NMR (DMSO-*d*₆) δ 12.23 (brs, 1H, NH), 9.20 (s, 1H, Ar-CH), 9.02 (s, 1H, Ar-CH), 7.94 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.65-7.57 (m, 3H, Ar-CH), 7.41 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.31-7.29 (m, 2H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 154.7 (C), 151.9 (C), 138.6 (C), 135.4 (CH), 132.7 (C), 130.8 (C), 129.2 (CH), 128.5 (CH), 126.0 (CH), 123.9 (CH), 121.21 (C), 115.3 (CH), 114.0 (CH), 112.19 (C), 103.5 (C). HRMS: Calcd [M+H]⁺ for C₁₇H₁₀N₄: 271.0985. Found: 271.0986.

3-(6,7-Dichloroquinoxalin-2-yl)-1*H*-indole-5-carbonitrile (4j). This compound was obtained as bottle green powder like solid. Mp > 300 °C. IR (KBr, cm⁻¹): 3303 (NH), 2228 (CN). ¹H NMR (DMSO-*d*₆) δ 12.19 (brs, 1H, NH), 9.10 (s, 1H, Ar-CH), 8.98 (s, 1H, Ar-CH), 8.26 (s, 1H, Ar-CH), 7.60-7.51 (m, 3H, Ar-CH), 7.33 (s, 1H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 154.3 (CH), 152.7 (C), 138.6 (C), 136.1 (C), 132.4 (C), 130.6 (CH), 129.3 (C), 128.5 (CH), 126.1 (CH), 125.4 (CH), 120.9 (CH), 116.3 (CN), 113.8 (CH), 111.9 (C), 103.8 (C). HRMS: Calcd [M+H]⁺ for C₁₇H₈N₄Cl₂: 339.0206. Found: 339.0208.

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)quinoxaline (4k). This compound was obtained as yellow powder. Mp 195-197 °C. IR (KBr, cm⁻¹): 3438 (NH). ¹H NMR (DMSO-*d*₆) δ 11.54 (brs, 1H, NH), 9.21 (s, 1H, Ar-CH), 8.02-7.99 (m, 2H, Ar-CH), 7.80-7.77 (m, 2H, Ar-CH), 7.69 (dd, *J* = 3.1, 7.8 Hz, 1H, Ar-CH), 7.27 (d, *J* = 7.8 Hz, 1H, Ar-CH), 6.78 (dd, *J* = 3.1 Hz, 7.8 Hz, 1H, Ar-CH), 3.79 (s, 3H, OCH₃), 2.75 (s, 3H, CH₃). ¹³C NMR (DMSO-*d*₆) δ 155.0 (C), 151.9 (C), 145.5 (CH), 142.6 (C), 139.6 (C), 139.5 (C), 130.6 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 112.2 (CH), 111.5 (C), 109.7 (C), 102.8 (CH), 55.7 (OCH₃), 14.8 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₈H₁₅N₃O: 290.1288. Found: 290.1301.

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)-6,7-dimethylquinoxaline (4l). This compound was obtained as bright yellow powder. Mp 233-235 °C. IR (KBr, cm⁻¹): 3438 (NH). ¹H NMR (DMSO-*d*₆) δ 11.46 (brs, 1H, NH), 9.08 (s, 1H, Ar-CH), 7.79 (s, 1H, Ar-CH), 7.75-7.65 (m, 2H, Ar-CH), 7.26 (d, *J* = 7.8 Hz, 1H, Ar-CH), 6.77 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 3.78 (s, 3H, OCH₃), 2.72 (s, 3H, CH₃), 2.41 (s, 6H, CH₃). ¹³C NMR (DMSO-*d*₆): δ 154.9 (C), 151.0 (C), 144.5 (CH), 141.4 (C), 140.6 (C), 138.8 (C), 138.5 (C), 130.9 (C), 128.2 (CH), 128.0 (CH), 127.9 (C), 112.1 (CH), 111.3 (CH), 109.9 (C), 102.8 (CH), 55.8 (OCH₃), 20.3 (CH₃), 20.2 (CH₃), 14.7 (CH₃). HRMS: Calcd [M+H]⁺ for C₂₀H₁₉N₃O: 318.1601. Found: 318.1613.

6,7-Dichloro-2-(5-methoxy-2-methyl-1*H*-indol-3-yl)quinoxaline (4m). This compound was obtained as greenish crystalline solid. Mp 219-221 °C. IR (KBr, cm⁻¹): 3438 (NH). ¹H NMR (DMSO-*d*₆) δ 11.61 (brs, 1H, NH), 9.15 (s, 1H, Ar-CH), 8.17 (s, 1H, Ar-CH), 8.14 (s, 1H, Ar-CH), 7.8 (s, 1H, Ar-CH), 7.25 (s, 1H, Ar-CH), 6.77 (s, 1H, Ar-CH), 3.79 (s, 3H, OCH₃), 2.70 (s, 3H,

CH₃). ¹³C NMR (DMSO- *d*₆) δ 155.2 (C), 152.9 (C), 146.5 (CH), 141.6 (C), 140.6 (C), 138.2 (C), 133.0 (C), 130.8 (C), 130.4 (C), 129.9 (CH), 129.5 (CH), 127.9 (C), 112.2 (CH), 111.7 (CH), 109.3 (C), 103.3 (CH), 55.8 (OCH₃), 15.2 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₈H₁₃N₃Cl₂O: 358.0508. Found: 358.0525.

Methyl-2-(5-methoxy-2-methyl-1*H*-indol-3-yl)quinoxaline-6-carboxylate (4n). This compound was obtained as bright yellow solid. Mp 224-226 °C. IR (KBr, cm⁻¹): 3337 (NH), 1728 (CO). ¹H NMR (DMSO-*d*₆) δ 11.68 (brs, 1H, NH), 9.29 (s, 1H, Ar-CH), 8.49 (s, 1H, Ar-CH), 8.18 (d, *J* = 8.0 Hz, 1H, Ar-CH), 8.07 (d, *J* = 8.0 Hz, 1H, Ar-CH), 7.89 (s, 1H, Ar-CH), 7.28 (d, *J* = 8.0 Hz, 1H, Ar-CH), 6.78 (d, *J* = 8.0 Hz, 1H, Ar-CH), 3.91 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 2.77 (s, 3H, CH₃). ¹³C NMR (DMSO-*d*₆): δ 166.2 (C=O), 155.2 (C), 153.6 (C), 146.5 (C), 145.1 (C), 141.0 (C), 138.4 (C), 131.1 (C), 130.9 (CH), 129.6 (C), 128.0 (CH), 112.3 (CH), 111.9 (CH), 109.6 (CH), 103.3 (C), 55.8 (OCH₃), 53.0 (OCH₃), 15.3 (CH₃). HRMS: Calcd [M+H]⁺ for C₂₀H₁₇N₃O₃: 348.1350. Found: 348.1351.

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)-6-nitroquinoxaline (4o). This compound was obtained as orange red solid. Mp 229-131 °C. IR (KBr, cm⁻¹): 3373 (NH). ¹H NMR (DMSO- *d*₆) δ 11.76 (brs, 1H, NH), 9.30 (s, 1H, Ar-CH), 8.66 (s, 1H, Ar-CH), 8.37 (d, *J* = 9.0 Hz, 1H, Ar-CH), 8.07 (d, *J* = 9.0 Hz, 1H, Ar-CH), 7.88 (s, 1H, Ar-CH), 7.25 (d, *J* = 8.6 Hz, 1H, Ar-CH), 6.77 (d, *J* = 8.6 Hz, 1H, Ar-CH), 3.80 (s, 3H, OCH₃), 2.76 (s, 3H, CH₃); ¹³C NMR (DMSO-*d*₆) δ 155.4 (C), 154.2 (C), 147.3 (CH), 145.7 (C), 142.2 (C), 137.5 (C), 130.9 (C), 130.2 (CH), 128.1 (C), 125.1 (CH), 123.9 (CH), 112.2 (CH), 111.9 (CH), 109.5 (C), 103.8 (CH), 55.8 (OCH₃), 15.4 (CH₃). HRMS: Calcd [M+H]⁺ for C₁₈H₁₄N₄O₃: 335.1146. Found: 335.1149.

2-(1*H*-Indol-3-yl)quinoxaline-6-carbonitrile (4p). This compound was obtained as light yellow solid. Mp 297-299 °C. IR (KBr, cm⁻¹): 3438 (NH), 2221 (CN). ¹H NMR (DMSO-*d*₆) δ 11.98 (brs, 1H, NH), 9.53 (s, 1H, Ar-CH), 8.78-8.52 (m, 2H, Ar-CH), 8.26-8.08 (m, 2H, Ar-CH), 7.56-7.50 (m, 2H, Ar-CH), 7.42-7.23 (m, 2H, Ar-CH). ¹³C NMR (DMSO-*d*₆) δ 152.2 (CH), 145.8 (CH), 143.8 (C), 139.1 (C), 137.7 (C), 133.4 (C), 130.3 (CH), 129.2 (CH), 128.7 (CH), 126.6 (C), 123.5 (CH), 123.0 (CH), 121.6 (CH), 113.3 (CN), 112.7 (CH). HRMS: Calcd [M+H]⁺ for C₁₇H₁₀N₄: 271.0985. Found: 271.0986.

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