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An Efficient One Pot Synthesis and Biological Activities of 6*H*-Indolo[2,3-*b*]quinoxalines Promoted by Palladium Acetate as Catalyst

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A multi-component one pot protocol for the synthesis of quinoxalines derivatives by condensation reaction of substituted isatin with substituted *o*-phenylene diamine in presence palladium acetate as catalyst in strong base such as triphenylphosphine under conventional method has been reported. The molecular structures of the newly synthesized compounds were characterized by elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and LCMS spectral data. The presented method is mild, inexpensive, highly atom economy and easy work up to give the products in good to excellent yields. All the synthesized compounds were also evaluated for *in vitro* antibacterial assay against Gram-negative (*Escherichia coli* and *Staphylococcus aureus*), Gram-positive (*Salmonella typhi* and *Bacillus subtilis*) and fungi (*Aspergillus niger* and *Candida albicans*) pathogenic bacteria in comparison to the standards streptomycin and fluconazole.

Keywords: Substituted isatin, 6*H*-Indolo[2,3-*b*]quinoxalines, Palladium acetate, Biological activity.

INTRODUCTION

In recent years, a vast diversity of synthetic transformations with various functionalities has been well known in organic chemistry as well as medicinally as ways to obtained quinoxalines framework [1,2]. The wide range of synthetic approaches like oxidative cyclization metal-catalyzed, condensation, selective synthesis and green reagents have been applied to synthesize quinoxalines heterocycles and related molecules over the recent time [3,4]. The significant therapeutic potential, including antimicrobial [5-8], antibacterial, antifungal [9], antiviral [10,11], cytotoxicity [12-15], antituberculosis [16,17], anti-inflammatory, antioxidant and anti-nociceptive [18,19], *etc.* has been exhibited by quinoxalines derivatives.

The synthesis of quinoxalines derivatives can be accomplished in a conventional route including the condensation of 1,2-diamines with α-diketone, 1,4-addition of 1,2-diamines to diazinyl butenes, the cyclization oxidation of phenacyl bromides and the oxidative coupling of epoxides with ene-1,2-diamines [2,4]. The previous reports revealed that the different catalysts were used to synthesize quinoxalines derivatives and it's preparation have been accomplished by different methods. *viz.* multicomponent synthesis, one pot synthesis, microwave method *etc.* [20-25].

Recent research has been described to show that transition-metal catalyst reactions that were an effective and ecologically friendly method for innovation of heterocyclic molecules. Therefore, they have become a major and exciting field in synthetic organic chemistry as well as medicinal chemistry and compared to organic reaction transferred to utilize transition metal catalysts, they have several advantages [26,27]. The synthesis of quinoxalines and its derivatives with the use of transition metals has therefore experienced great growth during the past decade [28]. Based on their interesting activities and our main focus on the synthesis and structural elucidation of 6*H*-indolo-[2,3-*b*]quinoxalines promoted by palladium catalyst, we report the one-pot synthesis of 6*H*-indolo[2,3-*b*]quinoxalines from substituted isatin with substituted *o*-phenylene diamine in the presence palladium acetate as a catalyst in strong base such as triphenylphosphine under conventional method and also evaluated in biological activity.

EXPERIMENTAL

The Merck Chemical Company provided all the chemicals, reagents and solvents utilized in this work. No additional purification was conducted and used as such. The Gallenkamp melting point apparatus set limits on the melting points of synthesized compounds. Tetra methyl silane (TMS) was used as an internal standard and ^{1}H NMR, 400 MHz and ^{13}C NMR, 100 MHz were recorded on Bruker DRX-400 AVANCE spectrometer. An Agilent mass spectrometer for liquid chromatography/ mass spectrometry (LCMS) was used to measure the mass spectra. Using a Perkin-Elmer 2400 elemental analyzer, the C, H and N were microanalyzed.

Synthesis of 6*H*-indolo[2,3-*b*]quinoxalines analogous: Substituted *o*-phenylenediamine (10 mmol), substituted isatin (10 mmol) were mixed and dissolved in ethanol (30 mL) in a 100 mL four necked RBF and fitted on the magnetic stirrer. The catalytic amount of palladium acetate (2.0 mmol) slowly added and the reaction mixture was vigorously stirred for 5 h at reflux. The reaction was continuously checked by TLC in ethyl acetate and *n*-hexane (5:5) system to confirm the completion of the reaction. After completion, the reaction mixture was poured into ethyl acetate and washed twice with a solution of saturated $NaHCO_3$ (**Scheme-I**). The ethyl acetate layer was separated from water and then distilled off under vacuumed. The crude separated by coloumn chromotogrphy using eluent ethylacetate and *n*-hexane (5:5). Final product was obtained by recrystalli-zation from absolute ethanol.

6*H*-Indolo[2,3-*b*]quinoxalines (3A$_1$): Pale brown solid, yield: 87%, m.p.: 187-189 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.732 (1H, N-H, s), 7.928 (Ar-H, d, *J* = 7.2 Hz, 1H), 7.784-7.272 (Ar-H, 7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.29, 144.04, 141.62, 140.36, 139.65, 129.55, 128.88, 123.73, 121.44, 120.02, 117.36, 112.68; Mass (*m/z*): 218.69 (M-H); Elemental analysis of $C_{14}H_9N_3$; calcd. (found) %: C, 76.70 (76.72); H, 4.14 (4.13), N, 19.17 (19.24).

6*H*-Indolo[2,3-*b*]quinoxalin-2-ol (3A$_2$): White solid, yield: 90%, m.p.: 178-180 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.536 (1H, N-H, s), 9.825 (-OH, 1H, s), 8.024 (Ar-H, 1H, s), 7.627 (1H, Ar-H, s), 7. 593-7.298 (Ar-H, 5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.29, 145.68, 143.37, 142.02, 140.09, 139.17, 130.02, 127.66, 125.24, 122.04, 120.96, 119.36, 112.05, 110.46; Mass (*m/z*): 236.36 (M-H); Elemental analysis of $C_{14}H_9N_3O$; calcd. (found) %: C, 71.48 (71.41); H, 3.86 (3.85); N, 17.86 (17.92).

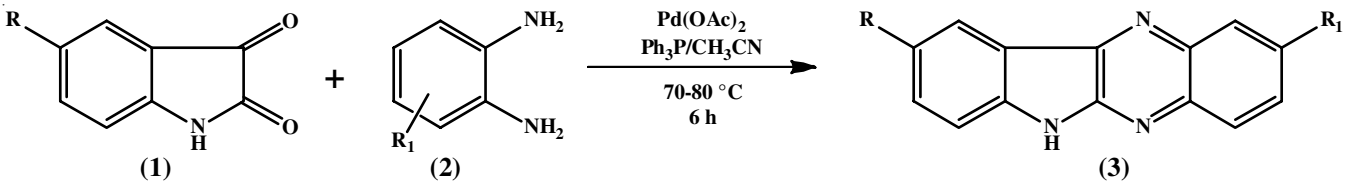
2-Methoxy-6*H*-indolo[2,3-*b*]quinoxalines (3A$_3$): Pale brown solid, yield: 82%, m.p.: 174-176 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.125 (1H, N-H, s), 7.978 (Ar-H, 1H, s), 7.656 (1H, Ar-H, s), 7.614-7.313 (Ar-H, 5H, m), 3.774 (3H, OCH_3, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.09, 148.32, 144.77, 143.02, 141.67, 139.85, 137.04, 129.11, 128.05, 124.28, 120.07, 119.35, 117.62, 113.09, 104.67, 54.71; Mass (*m/z*): 250.48 (M+H); Elemental analysis of $C_{15}H_{11}N_3O$; calcd. (found) %: C, 72.28 (72.23); H, 4.45 (4.44); N, 16.86 (16.92).

2,3-Dimethoxy-6*H*-indolo[2,3-*b*]quinoxalines (3A$_4$): Pale brown solid, yield: 92%, m.p.: 194-196 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10. 894 (1H, NH, s), 8.109 (Ar-H, 1H, s), 7.664-7.335 (Ar-H, 5H, m), 3.684 ((OCH_3)$_2$, 6*H*, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.74, 150.01, 145.33, 144.24, 142.92, 141.05, 140.41, 123.56, 121.04, 120.65, 118.92, 112.02, 106.65, 54.27; Mass (*m/z*): 279.52 (M^+); Elemental analysis of $C_{16}H_{13}N_3O_2$; calcd. (found) %: C, 68.81 (68.75); H, 4.69 (4.67); N, 15.05 (15.12).

2-(Trifluoromethyl)-6*H*-indolo[2,3-*b*]quinoxalines (3A$_5$): Pale Yellow solid, yield: 91%, m.p.: 157-159 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.124 (1H, N-H, s), 8.118 (1H, Ar-H, s), 7.955 (1H, Ar-H, s), 7.820 (Ar-H, d, *J* = 8.0 Hz, 1H), 7.734 (Ar-H, d, *J* = 8.8 Hz, 1H), 7.761-7.294 (3H, Ar-H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.22, 145.38, 144.04, 143.48, 140.65, 131.75, 129.17, 128.66, 127.05, 124.55, 123.49, 122.05, 120.33, 119.15, 112.44; Mass (*m/z*): 288.37 (M+H); Elemental analysis of $C_{15}H_8N_3F_3$; calcd. (found) %: C, 62.72 (62.66); H, 2.81 (2.80); N, 14.63 (14.69).

2-Bromo-6*H*-indolo[2,3-*b*]quinoxalines (3A$_7$): Pale red solid, yield: 90%, m.p.: 169-171 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.546 (1H, N-H, s), 8.128 (1H, Ar-H, s), 7.932 (Ar-H, d, *J* = 5.6 Hz, 1H), 7.846 (Ar-H, *J* = 11.6 Hz, d, 1H), 7.725 (Ar-H, *J* = 8.0 Hz, 1H, d), 7.427 (Ar-H, *J* = 8.8 Hz, 2H, d), 7.363 (Ar-H, *J* = 8.4 Hz, d, 1H), 7.285 (Ar-H, *J* = 7.6 Hz, d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 143.28, 142.56, 140.09, 138.41, 136.65, 130.77, 129.48, 128.85, 128.45, 127.27, 123.66, 121.72, 119.35, 112.26; Mass (*m/z*): 298.57 (M+2); Elemental analysis of $C_{14}H_8N_3Br$; calcd. (found) %: C, 56.90 (56.84); H, 2.70 (2.68); N, 14.09 (14.16).

2-Nitro-6*H*-indolo[2,3-*b*]quinoxalines (3A$_8$): Pale brown solid, yield: 88%, m.p.: 151-153 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.357 (1H, N-H, s), 8.374 (1H, Ar-H, s), 8.210 (Ar-H, *J* = 7.2 Hz, d, 1H), 7.965 (Ar-H, *J* = 8.0 Hz, 1H, d), 7.873 (Ar-H, *J* = 11.6 Hz, d, 1H), 7.585 (Ar-H, *J* = 8.8 Hz, t, 2H), 7.520 (Ar-H, *J* = 13.2 Hz, 1H, d) 7.222 (Ar-H, d, *J* = 8.0



R = H (A), CH_3 (B), F (C)
R_1 = H (1), 4-OH (2), 4-OCH_3 (3), 3,4(OCH_3)$_2$ (4), CF_3 (5), Cl (6), Br (7), NO_2 (8)

Scheme-I: Synthesis of titled compounds

Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.65, 146.35, 144.16, 142.78, 140.02, 138.58, 128.77, 124.18, 122.37, 121.09, 119.25, 117.88, 110.02; Mass (*m/z*): 264.38 (M+2); Elemental analysis of $C_{14}H_8N_4O_2$; calcd. (found) %: C, 63.64 (63.57); H, 3.05 (3.04); N, 21.20 (21.26).

9-Methyl-6*H*-indolo[2,3-*b*]quinoxalines (3B$_1$): White solid, yield: 90%, m.p.: 204-206 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.745 (1H, N-H, s), 7.867 (1H, Ar-H, s), 7.764-7.356 (Ar-H, 6*H*, m), 2.046 (, 3H, -CH_3, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.09, 145.65, 143.75, 141.21, 140.35, 129.17, 128.77, 128.39, 124.64, 122.84, 120.88, 117.62, 20.75; Mass (*m/z*): 234.47 (M+2); Elemental analysis of $C_{15}H_{11}N_3$; calcd. (found) %: C, 77.23 (77.17); H, 4.75 (4.74); N, 18.01 (18.09).

9-Methyl-6*H*-indolo[2,3-*b*]quinoxalin-2-ol (3B$_2$): White powder, yield: 89%, m.p.: 191-193 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.042 (1H, N-H, s), 9.146 (1H, N-H, s), 7.815 (1H, Ar-H, s), 7.692 (1H, Ar-H, s), 7.502-7.384 (Ar-H, 3H, m), 1.914 (3H, -CH_3, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.73, 146.54, 145.06, 143.38, 140.04, 138.25, 130.07, 128.62, 123.33, 121.05, 120.08, 115.76, 108.68, 20.62; Mass (*m/z*): 250.32 (M+H); Elemental analysis of $C_{15}H_{11}N_3O$; calcd. (found) %: C, 72.28 (72.34); H, 4.45 (4.43); N, 16.86 (16.92).

2-Methoxy-9-methyl-6*H*-indolo[2,3-*b*]quinoxalines (3B$_3$): Brown solid, yield: 87%, m.p.: 210-212 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.974 (1H, N-H, s), 7.809 (1H, Ar-H, s), 7.624 (Ar-H, d, *J* = 8.8 Hz, 1H), 7.584 (1H, Ar-H, s), 7.452 (Ar-H, d, *J* = 6.4 Hz, 1H), 7.365 (Ar-H, d, *J* = 8.0 Hz, H), 7.284 (Ar-H, d, *J* = 10.6 Hz, 1H), 3.698 (3H, CH_3, s), 1.841 (3H, CH_3, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.58, 148.07, 145.88, 143.65, 141.05, 138.24, 135.11, 132.58, 128.74, 128.44, 124.03, 122.44, 115.94, 109.65, 21.24; Mass (*m/z*): 264.64 (M+H); Elemental analysis of $C_{16}H_{13}N_3O$; calcd. (found) %: C, 72.99 (72.91); H, 4.98 (4.67); N, 15.96 (16.06).

2,3-Dimethoxy-9-methyl-6*H*-indolo[2,3-*b*]quinoxalines (3B$_4$): Pale-yellow powder, yield: 94%, m.p.: 197-199 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.897 (1H, N-H, s), 7.881 (1H, Ar-H, s), 7.578-7.412 (Ar-H, 4H, m), 3.710 (6*H*, s, $(OCH_3)_2$), 1.975 (3H, -CH_3, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.76, 144.28, 141.72, 140.38, 137.96, 129.72, 128.36, 128.02, 124.02, 121.73, 120.28, 118.32, 54.64, 20.36; Mass (*m/z*): 294.29 (M+H); Elemental analysis of $C_{17}H_{15}N_3O_2$; calcd. (found) %: C, 69.91 (69.85); H, 5.15 (5.13); N, 14.33 (14.38).

9-Methyl-2-nitro-6*H*-indolo[2,3-*b*]quinoxalines (3B$_8$): Brown compound, yield: 86%, m.p.: 184-186 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.095 (1H, N-H, s), 8.566 (1H, Ar-H, s), 8.224 (Ar-H, *J* = 7.6 Hz, d, 1H), 7.912 (Ar-H, *J* = 7.2 Hz, d, 1H), 7.736 (1H, Ar-H, s), 7.496 (Ar-H, *J* = 8.0 Hz, d, 1H) 7.316 (Ar-H, *J* = 9.6 Hz, d, 1H), 2.146 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.56, 145.07, 144.75, 142.31, 140.17, 138.35, 128.82, 128.18, 124.57, 123.15, 121.44, 120.19, 118.78, 117.57, 110.02, 20.43; Mass (*m/z*): 279.31 (M+H); Elemental analysis of $C_{15}H_{10}N_4O_2$; calcd. (found) %: C, 64.74 (64.68); H, 3.62 (3.61); N, 20.13 (20.20).

9-Fluoro-2,3-dimethoxy-6*H*-indolo[2,3-*b*]quinoxalines (3C$_4$): Brown powder, yield: 91%, m.p.: 202-204 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.945 (1H, N-H, s), 8.056 (1H, Ar-H, s), 7.894 (1H, Ar-H, s), 7.805 (1H, Ar-H, s), 7.517 (Ar-H, d, *J* = 7.6 Hz, 1H), 7.364 (Ar-H, *J* = 8.8 Hz, d, 1H), 3.694 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.76, 150.64, 148.83, 143.02, 140.66, 139.96, 128.84, 121.55, 117.27, 114.38, 110.45, 107.66, 54.62; Mass (*m/z*): 299.56 (M+2); Elemental analysis of $C_{16}H_{12}N_3O_2F$; calcd. (found) %: C, 64.64 (64.70); H, 4.07 (4.05); N, 14.13 (14.20).

2-Chloro-9-fluoro-3-methoxy-6*H*-indolo[2,3-*b*]-quinoxalines (3C$_6$): Brown compound, yield: 89%, m.p.: 214-216 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.046 (1H, N-H, s), 8.132 (1H, Ar-H, s), 7.815 (1H, Ar-H, s), 7.678 (1H, Ar-H, s), 7.546 (Ar-H, *J* = 6.6 Hz, d, 1H), 7.327 (Ar-H, *J* = 11.6 Hz, d, 1H), 3.708 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.04, 144.23, 141.06, 137.19, 129.41, 129.05, 128.34, 121.76, 118.57, 115.64, 110.38, 107.74, 54.35; Mass (*m/z*): 303.47 (M+2); Elemental analysis of $C_{15}H_9N_3OClF$; calcd. (found) %: C, 59.72 (59.67); H, 3.01 (3.00); N, 13.93 (13.99).

2-Bromo-9-fluoro-6*H*-indolo[2,3-*b*]quinoxalines (3C$_7$): Brown powder, yield: 86%, m.p.: 224-226 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.467 (1H, N-H, s), 8.196 (1H, Ar-H, s), 7.927 (Ar-H, d, *J* = 8.0 Hz, 1H), 7.765 (Ar-H, *J* = 4.8 Hz, d, 1H,), 7.572 (Ar-H, d, *J* = 8.0 Hz, 1H), 7.406 (Ar-H, d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.94, 149.02, 143.66, 141.20, 138.04, 131.04, 130.05, 129.12, 128.44, 127.26, 120.26, 117.62, 115.65, 104.39; Mass (*m/z*): 316.07 (M+2); Elemental analysis of $C_{14}H_7N_3BrF$; calcd. (found) %: C, 53.19 (53.11); H, 2.23 (2.21); N, 13.29 (13.35).

9-Fluoro-2-nitro-6*H*-indolo[2,3-*b*]quinoxalin-3-ol (3C$_8$): Brown compound, yield: 91%, m.p.: 207-209 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.372 (1H, N-H, s), 8.8376 (1H, s, Ar-H), 7.964 (1H, Ar-H, s), 7.835 (1H, Ar-H, s), 7.429 (Ar-H, d, *J* = 8.8 Hz, 1H), 7.297 (Ar-H, d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.76, 148.24, 146.08, 144.28, 140.39, 138.07, 130.33, 128.79, 126.02, 122.36, 117.62, 113.02, 110.84, 108.59; Mass (*m/z*): 300.61 (M+H); Elemental analysis of $C_{14}H_7N_4O_2F$; calcd. (found) %: C, 56.38 (56.31); H, 2.37 (2.36); N, 18.79 (18.76).

Biological activity

Antibacterial activity: Using the cup and plate method, the *in vitro* antibacterial screening of all the synthesized quinoxalines derivatives was assessed by the Gram-positive (*S. aureus* and *E. coli*) and Gram-negative (*S. typhi* and *B. subtilis*) bacteria. The bacteria were maintained using nutritional agar slants, which were dispersed uniformly in a petridish and allowed to settle for 30 min. In the petri dish, four equal-distance (10 mm) bores were created and filled with streptomycin and test compounds at varying doses (50 and 100 µg/mL), separately. The chloroform was used as a negative control and tested in the same manner. The petri plates were placed in an incubator and kept at 37 ºC for a 24 h following a 2 h cold incubation period. Using a vernier scale, the petri plates were measured for the zone of inhibition following incubation period.

Antifungal activity: Using the disc diffusion method, the antifungal properties of newly synthesized compounds were evaluated against *A. niger* and *C. albicans*. Target chemicals were employed in a different range of concentrations, with an

average value and DMSO serving as solvent. Ketoconazole was used as antifungal standard drug.

RESULTS AND DISCUSSION

We commenced our exploration with substituted isatin with substituted *o*-phenylene diamine to synthesized 6*H*-indolo-[2,3-*b*]-quinoxalines promoted by palladium catalyst in the presence strong base such as triphenylphosphine under conventional method. This method is multicomponent process and having several advantages. The reaction's generality was investigated for several substrates and it was carried out under ideal reaction conditions with a transition metal catalyst present. Palladium acetate served as a catalyst in the reaction between the several substituted isatin derivatives and *o*-phenylene diamine, which was stirred at room temperature (**Scheme-I**). Using acetonitrile as solvent, several types of palladium catalysts, including Pd-C, $PdCl_2$, $Pd(OAc)_2$ and palladium triflate were used and both the time factor and the yield percentage were noted. Palladium acetate has the greatest effect among the palladium moieties when compared to other palladium compounds as shown in Table-1. It was observed that the reaction for the synthesis of the required product could be efficiently catalyzed by 2.0 mol% of $Pd(OAc)_2$. Moreover, the reaction required a certain amount of catalyst; without it, the reaction would not have proceeded and also the product yield decreased significantly at 1 mol% catalyst. Moreover, if the catalyst was increased to 2.0 mol gradually, the reaction progressed slowly and produced a excellent 94% yield. Beyond using excess catalyst, the intended product yield could not be increased (Table-2).

TABLE-1
OPTIMIZATION OF CATALYST FOR THE SYNTHESIS OF DERIVATIVES (**3A$_1$**)

Entry	Catalyst	Time (h)	Yield (%)
1	Pd-C	12	71
2	$PdCl_2$	8	80
3	$Pd(OAc)_2$	6	94
4	$Pd(OTf)_3$	10	65

TABLE-2
OPTIMIZATION OF LOADED CATALYST FOR THE SYNTHESIS OF DERIVATIVES (**3A$_1$**)

Entry	Amount of catalyst	Time (min)	Yield (%)
1	1.0 mol	180	25
2	1.5 mol	150	57
3	2.0 mol	60	94
4	2.5 mol	90	94
5	3.0 mol	120	92

Various solvents were also employed at the same reaction temperature to synthesize 6*H*-indolo[2,3-*b*]quinoxalines and found that varying reaction times resulted in variable yields (Table-3). The reaction can proceed under different solvents such as water, ethanol, acetonitrile, toluene and dichloromethane. However, in conventional synthesis, acetonitrile produces the highest yield with a short reaction time. The presence of electron withdrawing groups, such as fluorine, on isatin was found to have no impact on the yield of products. It was found that the substrates must contain either an electron donating group or an electron attracting group individually in order to achieve a moderate to good yield. However, the titled analogous compound, which contains an isatin with an electron donating group and *o*-phenyl diamine with an electron releasing group, resulted in an excellent yield.

TABLE-3
SOLVENT OPTIMIZATION FOR THE SYNTHESIS OF TITLED DERIVATIVES (**3A$_1$**)

Entry	Solvent	Time (h)	Yield (%)
1	H_2O	12	25
2	C_2H_5OH	8	57
3	CH_3CN	6	92
4	Toluene	10	69
5	CH_2Cl_2	9	74

Biological activities: The antimicrobial activity data of the titled compounds are shown in Table-4. It was observed that compounds containing the electron-donating and electron-withdrawing groups exhibited different levels of potent activity against bacterial and fungal strains. However, compared to molecules with electron-releasing groups, those with electron-withdrawing groups showed less antimicrobial efficacies.

Conclusion

To summarize, a simple and uncluttered one-pot reaction using three components for the synthesis of indolo[2,3-*b*]-quinoxalines is developed. Using a 2.0 mol% catalytic quantity of $Pd(OAc)_2$ in acetonitrile under reflux conditions at room temperature, 6*H*-indolo[2,3-*b*]-quinoxalines were synthesized from substituted isatin and substituted 1,2-diphenylamine compounds in a straightforward, practical and effective manner. Using spectrum techniques, all the compounds' structures were established (^{1}H NMR, ^{13}C NMR and LCMS) and few of the compounds containing electron-donating have similar biological activities as compared to standard drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-4
ANTIMICROBIAL SCREENING OF TITLED COMPOUNDS

Compound	R	R_1	Zone of inhibition (mm)					
			Bacteria				Fungi	
			S. aureus	*E. coli*	*S. typhi*	*B. substill*	*A. niger*	*C. albicans*
$3A_1$	H	H	07	05	04	07	04	05
$3A_2$	H	4-OH	07	10	09	08	07	08
$3A_3$	H	4-OCH_3	15	16	15	15	11	13
$3A_4$	H	3,4$(OCH_3)_2$	14	17	16	15	13	14
$3A_5$	H	CF_3	21	20	21	15	17	15
$3A_7$	H	Br	19	20	19	18	16	17
$3A_8$	H	NO_2	08	10	09	04	09	11
$3B_1$	CH_3	H	08	03	08	07	07	06
$3B_2$	CH_3	4-OH	08	07	05	09	07	08
$3B_3$	CH_3	4-OCH_3	14	14	15	14	12	12
$3B_4$	CH_3	3,4$(OCH_3)_2$	15	15	13	10	12	13
$3B_8$	CH_3	NO_2	07	08	08	05	05	07
$3C_4$	F	3,4$(OCH_3)_2$	08	07	05	09	07	06
$3C_6$	F	Cl	20	19	13	21	15	17
$3C_7$	F	Br	19	20	18	18	16	17
$3C_8$	F	NO_2	17	17	16	15	14	15
Streptomycin			25	25	22	22	NA	NA
Ketoconazole			NA	NA	NA	NA	20	20
DMSO			–	–	–	–	–	–

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