Synthesis of Biologically Active Coupled Quinoxaline Derivatives by Fitting Reaction

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Abstract
Quinoxaline and its derivatives are an important class of heterocyclic compounds which found to possess wide spectrum of biological activities. An efficient and eco-friendly method have been developed for the synthesis of coupled quinoxaline derivatives via the condensation of diaryl halides with phase transfer catalyst using suitable solvent. 2-(6H-indolo[2,3-b]quinoxalin-yl)-6H-indolo[2,3-b] quinoxaline 1a have been synthesized by enhanced Fittig method. 2-(2,3-di(furan-2yl) quinoxalin-6-yl)-6H-indolo[2,3-b] quinoxaline 1b were synthesized with suitable solvent by Fittig method. All the synthesized compounds were characterized and confirmed by various instrumental techniques viz, FTIR, ¹HNMRS, ¹³CNMR and Mass spectroscopy. To examine the antibacterial activity of all the synthesized compounds against pathogens like Staphylococcous aureus and Escherichia coli by zone of inhibition method using ciprofloxacin as a reference. The result showed that the synthesized compounds exhibit good antibacterial activity with respect to Ciprofloxacin selected as reference. Evaluation of anti-fungal activity against pathogens like Aspergillus niger by zone of inhibition method by using Amphotericin-B as a reference. The result shows that the synthesized compounds exhibit good anti-fungal activity.

Keywords
Phasetransfer catalyst, Quinoxaline, Amphotericin-B, 2-(2-3-diphenylquinoxaline- 7-yl)-6H-indolo[2-3-b] quinoxaline.

INTRODUCTION
Quinoxaline is also called as benzopyrazine. It is heterocyclic compound containing benzene ring and pyrazine ring. Pyrazine are stable, colourless compound which are soluble in water. Methoxy pyrazine are very important compound of aroma of many fruits and vegetable such as Peas and Capsicum peppers and also of wines. Quinoxaline and its derivatives are an important class of heterocyclic compounds that differ from chemical and physical properties based on the type and position of functional groups present. Generally, quinoxaline derivatives exhibit biological activity anti-viral, anti-bacterial, anti-inflammatory, anti-protozoal and anti-HIV, anti-cancer (colon cancer therapies) and kinase inhibitors. They are also used in the agricultural field.
as fungicides, herbicides and insecticides.\[^6\] In addition, quinoxaline derivatives have also found applications in dyes,\[^9\] efficient electron luminescence materials\[^10\] and organic semiconductors.\[^11\]

**EXPERIMENTAL SECTION**

**MATERIALS AND METHODS**

All the chemicals were used as Avra synthesis, Sigma-Aldrich, Finar chem, Alfa Aesar, CDH, Nice chem. Solvents and reagents were obtained for commercial sources. The melting points of synthesized compound were determined by an open capillary tube using an X-ray diffractometer. Wells were cut from the agar plate for antibacterial testing. To prepare TLC, clean and dry glass plates were taken. Uniform slurry of silica gel-G in hot water was prepared in ratio 1:2. The plates were prepared manually by spread plate method and spotting was done using iodine/UVP lamp. FTIR Spectra were recorded on a Perkin Elmer FTIR Spectroscopy using KBr pellets. The \(^1\)H NMR and \(^13\)C NMR Spectra were recorded in DMSO (ds) using 400 MHz with a Bruker Avance Spectrometer and TMS used as internal standard.


The synthesis of 2-(6H-indolo[2,3-b]quinoxalin-2-yl)-6H-indolo[2,3-b]quinoxaline from 6H-indolo[2,3-b]quinoxaline (1mmol, 0.2192g) and potassium hydroxide (1mmol, 0.5611g) using DMSO as a solvent were taken in a round bottom flask and the reaction mixture was allowed to stir 10 minutes. After, 2-chloro-6H-indolo[2,3-b]quinoxaline (1mmol, 0.2536g) and pinch of phase transfer catalyst were added to a mixture. Then the reaction mixture was refluxed for about 48 hours due to the completion of reaction. The progress of the reaction was monitored by TLC. The reaction mixture was poured into crushed ice-cold water with few drops of concentrated hydrochloric acid were added to neutralize the mixture. The formed precipitate was filtered off, washed with water and dried. The crude product was purified by recrystallization from hot ethanol.

IR (KBr, cm\(^{-1}\)): 3427 (N-H str.), 3108 (Ar=C=O), 1721 (C=C bend), 1614 (Ar=C=O), 1486 (C=C ring str.), 1402 (N-H bend), 1334 (C-N), 1068 (Ar-C-O), 860 (Ar-C-H bend), \(^1\)H NMR (DMSO): 12.0 (s, 1H, N-H), 7.9-8.1 (dd, 4H, quinoxaline ring str.), 7.6 (m, 2H, -O-CH), 7.4 (m, 2H indole), 8.3 (s, 2H, Ar-H), 6.6 (m, 4H difuryl ring), 7.3 (d, 2H indole). GCMS m/z, 478.6 [M^+].

**EVALUATION OF ANTIMICROBIAL ACTIVITY**

Antimicrobial analysis was followed by using standard agar well diffusion method to study the anti-bacterial activity compounds. [Perez et al., 1990; Erdemoglu et al., 2003; Bagamboula et al., 2004]. Each bacterial isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately \(10^5\) colony forming unit (CFU) per ml. The test organisms were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30\(\mu\)l (50\(\mu\)g compound in 1 ml of solvent-Ethanol) of the sample solution were poured into the wells. The plates were incubated for 18 hours at 37ºC bacteria. Antibacterial activity was evaluated by measuring the diameter of the zone inhibition in mm against the test microorganism. DMSO was used as solvent control. Ciprofloxacin was used as reference antibiotic agent. The tests were carried out in triplicate.
RESULT AND DISCUSSION

SYNTHESIS OF 2-(6H-INDOLO[2,3-B] QUINOXALIN-2YL)-6H-INDOLO[2,3-B] QUINOXALINE (1a)

Synthesis of 2-(6H-indolo[2,3-b]quinoxalin-2yl)-6H-indolo[2,3-b]quinoxaline 1a from 6H-indolo[2,3-b]quinoxaline (1mmol) and 2-chloro-6H-indolo[2,3-b]quinoxaline (1mmol), potassium hydroxide and there using DMSO as a solvent. The product has analyzed FTIR spectrum of compound 1a have shown in Fig. 1. The broad peak appeared at 3397 cm\(^{-1}\) due to the N-H stretching vibration. A peak at 3078 cm\(^{-1}\) due to the aromatic =C-H stretching frequency. A peak at 1614 cm\(^{-1}\) was due to C=N ring stretching, a peak at 1554 cm\(^{-1}\) for aromatic C=C stretching frequency. The frequency appeared at 1410 cm\(^{-1}\) corresponds to N-H bending vibration. The frequency observed at 1342 cm\(^{-1}\) was assigned to the C-N stretching vibration. \(^1\)H NMR spectrum of compound 1a have shown in Fig. 2. The chemical shift value at 12.0 ppm due to the N-H proton. The quinoxaline protons two doublet signal appeared at 7.9-8.1 ppm. The indole proton multiplet signal appeared at 7.3 ppm. The compound 1a was also confirmed by \(^13\)C NMR spectrum have shown in Fig. 3. The carbon atom appeared at 140 ppm attribute the carbon neighbouring to the nitrogen atom. The values appeared at 129 ppm, 126 ppm, 121 ppm and 119 ppm for aromatic carbon atoms. The value appeared at 139 ppm due to bridged carbon atoms.\(^{[12]}\)
SPECTRAL ANALYSIS FOR THE SYNTHESIZED COMPOUNDS

Fig. 1: FTIR spectrum of 2-(6H-indolo[2,3-b] quinoxalin-2yl)-6H-indolo[2,3-b] quinoxaline.

Fig. 2: $^1$H NMR spectrum of 2-(6H-indolo[2,3-b] quinoxalin-2yl)-6H-indolo[2,3-b] quinoxaline

Fig. 3: $^{13}$C NMR spectrum of 2-(6H-indolo[2,3-b] quinoxalin-2yl)-6H-indolo[2,3-b] quinoxaline
Fig. 4 Mass spectrum of 2-(6H-indolo[2,3-b] quinoxalin-2yl)-6H-indolo[2,3-b] quinoxaline

Fig. 5 FTIR Spectrum of 2-(2,3-di(furan-2-yl) quinoxalin-6-yl)-6H-indolo[2,3-b] quinoxaline

Fig. 6 $^1$H NMR Spectrum of 2-(2,3-di(furan-2-yl) quinoxalin-6-yl)-6H-indolo[2,3-b] quinoxaline
SYNTHESIS OF 2-(2,3-DI(FURAN-2-YL) QUINOXALIN-6-YL)-6H-INDOLO[2,3-B] QUINOXALINE (1b)

FTIR spectrum of 2-(2,3-di(furan-2-yl) quinoxalin-6-yl)-6H-indolo[2,3-b] quinoxaline 1b have shown in Fig. 5. The broad peak at 3427 cm$^{-1}$ observed due to the N-H, a peak at 1614 cm$^{-1}$ was due to the aromatic C=N ring and a peak at 1068 for aromatic C-O stretching. The $^1$H NMR spectrum of compound 1b has shown in Fig. 6. The value appeared at 12.0 ppm was attributed to the N-H indole ring and 7.6 ppm denoted as 2,3-difuryl protons. LC Mass spectrums of compound 1b have shown in Fig. 7. The molecular ion peak observed at m/z 478.6 and calculated value m/z 479.

ANTIBACTERIAL ACTIVITY

The results of antibacterial activity of synthesized compounds 1a and 1b have shown in Table 1. The zone of inhibition was indicated the nature of antibacterial activity. The synthesized compounds were subjected to Staphylococcus aureus, Escherichia coli. The compound 1a shows less zone of inhibition against Aspergillus niger (Fungi).

Fig. 7 Mass spectrum of 2-(2,3-di(furan-2-yl) quinoxalin-6-yl)-6H-indolo[2,3-b] quinoxaline
Antimicrobial activity (Zone of inhibition)

Staphylococcus aureus  Escherichia coli

Aspergillus niger (Fungi)

Fig. 8 zone of inhibition of synthesized compounds.
Staphylococcus aureus, Escherichia coli compared with compound 1b.

Anti-fungal activity

The zone of inhibition was indicated the nature of the anti-fungal activity for synthesized compounds were subjected to Aspergillus niger. The synthesized compounds all are found to possess good anti-fungal activity. The compound 1a and 1b found to excellent anti-fungal activity compared with reference Amphotericin-B. The result of anti-fungal activity for the synthesized compounds 1a and 1b have shown in Table 2

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Antibacterial activity</th>
<th>Gram positive Staphylococcus aureus</th>
<th>mm %</th>
<th>Gram negative Escherichia coli</th>
<th>mm %</th>
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<tr>
<td>Ciprofloxacin</td>
<td></td>
<td>20</td>
<td>100</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>1a</td>
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<td>20</td>
<td>7</td>
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<tr>
<td>1b</td>
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<td>8</td>
<td>40</td>
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Antifungal activity

Zone of inhibition of synthesized compounds

Table: 2

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<tr>
<th>Compounds</th>
<th>Zone of inhibition % Aspergillus niger</th>
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<tr>
<td>Amphotericin-B10</td>
<td>100</td>
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<tr>
<td>Compound 1a</td>
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<tr>
<td>Compound 1b</td>
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CONCLUSION

Quinoxaline derivatives 1a and 1b have been synthesized by simple and efficient Fitting reaction using suitable solvent like Methanol, Dimethyl sulfoxide, dichloromethane and Ethanol, with a pinch of phase transfer catalyst. The suitable solvent selected for reaction condition and temperature. The formations of the various compounds were identified using thin layer chromatography and purified by column chromatography. All the synthesized compounds have been confirmed by various spectral techniques viz FTIR, $^{13}$C NMR, $^1$H NMR and mass spectroscopy. The synthesized compounds found good antibacterial and anti-fungal activity.

CONFLICT OF INTEREST

This article contains no conflict of interest.

REFERENCE