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Synthesis, Characterisation and Antibacterial Activity of 2,3-Difurylquinoxalin-6-Vinyl-Benzaldehyde

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ABSTRACT

Quinoxaline derivatives exhibit a wide range of biological activities and electron transport properties. The presence of electron withdrawing quinoxaline ring has been used in π-conjugated structures to fabricate the OLED materials. In the present investigation, vinyl benzaldehyde capped quinoxaline derivatives were synthesized using 6-methyl-2,3-difurylquinoxaline with terephthaldicarboxaldehyde via Wittig reaction. The structures of synthesised compounds were confirmed by FT-IR, ^{1}H, ^{13}C, ^{31}P-NMR spectral data. The results of the antibacterial activity reveals that the target compound found to have considerable antibacterial activity with respect to gram positive and gram negative pathogens of present investigation.

Keywords: p-Phenylene vinylene, Quinoxaline derivatives, Antibacterial activity, Wittig reaction

INTRODUCTION

Over the past decades, π-conjugated polymers have received lots of attention due to their applications in fabricating organic optical and electronic devices [1-5]. Many quinoxaline derivatives have a wide application as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents [6-11]. The conjugated polymers have attracted substantial awareness due to their application in the field of photodiodes [12], photovoltaic cells [13], nonlinear optics [14] and laser devices [15]. Since, the first report of light emitting PPV [16] an massive number of novel conjugated polymers, such as poly(phenylene vinylene)s (PPVs), polyfluorenes (PFs), have been synthesized for light emitting diodes.

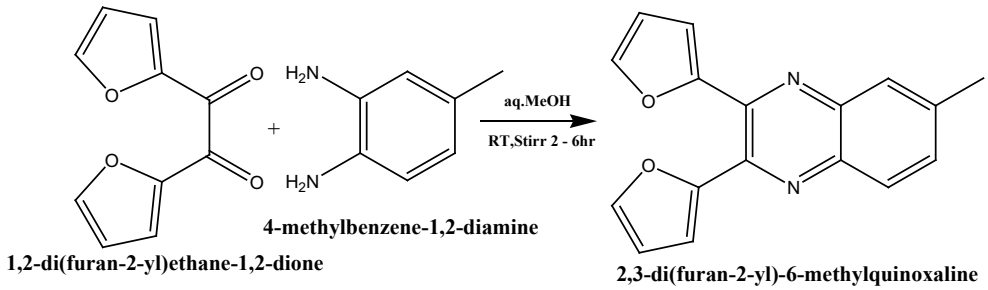
Since, the first report [16] of light-emitting diodes (LEDs) based on poly(*p*-phenylenevinylene) (PPV), much work [17] has been carried out with the objective of tuning the emission color and improving quantum efficiency and stability. In LED investigations, tunability of the emission gamut to any desired color including white colour is of motivating challenges. Up to now five methods have been reported for tuning the emission of polymer LEDs: changing the main-chain molecular structure [18,19], changing the side-chain molecular structure [20], unification of an electroluminescent polymer with a second active polymer [21,22] or with low molecular weight organic [23] or inorganic molecules [24], doping [25] and use multilayer device architectures [26]. The most emissive conjugated polymers such as PPVs has much superior hole mobility than electron mobility followed by low electron affinities, inequity in charge injection, and thus poor exterior quantum efficiencies from single layer OLEDs [27-31] The inclusion of electron transporting moieties (ET), such as nitrile group [32], 1,3,4-oxadiazole [33], quinoxaline [34] in the conjugated stamina is another well-known technique to improve the electron affinity of a light emitting polymer.

Antimicrobial agents are largely used in treatment and prevention of microorganism infections. Among others, the misuse and, especially, the abusive use of this kind of drugs, in human health, veterinary and animal production, led to the development of drug-resistant and multidrug-resistant (MDR) microorganisms [35].

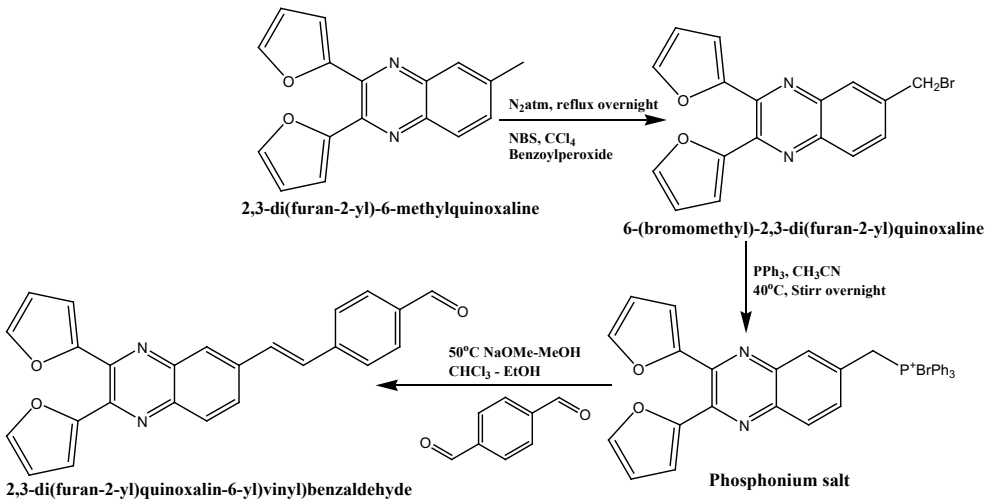
The multidrug-resistant (MDR) bacteria are increasing worldwide human kind deals with the urgent need of development of new drugs with enhanced antimicrobial activity able to fight pathogens with no adverse effects [36]. Compounds

containing the quinoxaline nucleus exhibited a broad spectrum of biological activity such as antibacterial [37-39], antifungal [40,41], antiviral [42,43], anticancer [44], antituberculosis [45], antimalarial [46] and anti-inflammatory properties [47]. Efforts to prepare antibacterial agents from quinoxaline have resulted in compounds used against a wide variety of disorders, including cancer, diabetes, diabetic retinopathy, rheumatoid arthritis, hemangioma and Kaposi's sarcoma, which are related to vasculogenesis and angiogenesis [48]. The quinoxaline ring moiety is part of the chemical structure of various antibiotics such as echinomycine, levomycine and actinoleutine [49,50] that are known to inhibit growth of Gram-positive bacteria.

Based on the careful analysis of available literature with lack of furyl containing quinoxaline, the present investigation aimed in fulfilling the synthesis of p-phenylene vinylene capped furyl containing quinoxaline derivatives via Wittig reaction and found to encompass an antibacterial activity comparable with standard Ampicilin (**Scheme 1 and Scheme 2**).



Scheme 1: Synthesis of 2,3-difuryl-6-methylquinoxaline



Scheme 2: Synthesis of 2,3-difurylquinoxalin-6-vinyl-benzaldehyde

MATERIALS AND METHODS

The chemicals 1,2-difuryl-ethane-1,2-dione, 3,4-diaminotoluene, N-Bromosuccinimide, benzoylperoxide, triphenylphosphine, terephthaldicarboxaldehyde were purchased from Avra, Chennai, India. Silica gel (TLC and Column grade) were purchased from Merck. Methanol, ethanol, acetone, chloroform, acetic acid, acetonitrile were purchased from SD fine-Chem, India and solvents were purified by according to standard procedure. UV spectra were also recorded using Alpha Bruker UV spectrophotometer. FTIR spectra were recorded in KBr disk on an Alpha Bruker FTIR spectrophotometer. ^{1}H, ^{13}C, and ^{31}P NMR was assayed using Bruker Advanced 300MHz NMR spectrometer, TMS was used as internal standard and $CDCl_3$, DMSO as solvent. Mass spectroscopy was recorded on ES-FIGIEAN ionization mass spectrometer.

Experimental study

Synthesis of 6-methyl-2,3-difurylquinoxaline

The synthesis of 6-methyl-2,3-difurylquinoxaline as follows: (0.3803 g) 2 mmol of furil and (0.2443 g) 2 mmol of

4-methylbenzene-1,2-diamine were dissolved in 10 ml of methanol each in a separate reaction flask and made them homogeneous by vigorous stirring at room temperature in 100 ml round bottom flask. The progress of the reaction was monitored by TLC until the completion of reaction. Methanol was evaporated and the solid product thus formed [51] was recrystallized from ethanol (yield 80%).

UV(λmax, nm): 255-288 nm (π-π*) 378 nm (n- π*); FTIR (KBr, cm^{-1}): 3111 Aliphatic C-H, st 3433 (Aromatic C-H, st) 1220 (C-O, st) 1018 (C-O-C, st) 1570 (C=N, st) 1300 (C-N, st); ^{1}H NMR($CDCl_3$, ppm): 2.5 δ (3H, s) 8.0 δ (2H, s) 7.6 δ (1H, s) 7.2 δ (2H, m) 6.6 δ (4H, m) Mass(m/z): Calculated M.W 276.29, Observed M.W 276.0.

Synthesis of 6-bromomethyl-2,3-difurylquinoxaline

To 0.2763 g (0.01 mol) of 6-methyl-2,3-difurylquinoxaline 0.1780 g (0.01 mol) N-bromosuccinimide in 30 ml of CCl_4 containing 0.08 g (0.0003 mol) benzoyl peroxide as radical initiator were refluxed overnight. After the achievement of reaction, the solid by-product was removed by filtration. Further, the filtrate was washed with CCl_4, evaporated to get reddish-brown solid product. (Yield 72%) FT-IR (KBr, cm^{-1}): 1689 (C=N, st), 1479 (C=C, st), 1328 (C-N, st), 1244 (C-O, st), 2926 (C-H, st), 752 (C-Br, st), 1008 (C-O-C, st); 1H-NMR (DMSO, ppm): 3.4 δ (2H,s) 8.1 δ (2H, m) 7.9 δ (1H, d) 7.8 δ (2H, m) 6.7 δ (4H, m); 13C-NMR (DMSO, ppm): 29.79 δ (methyl carbon), 112.05 δ, 113.34 δ, 115.09 δ, 127.71 δ, 128.40 δ, 129.34 δ, 130.18 δ, 133.10 δ, 144.16 δ, 150.50 δ Mass(m/z): Calculated M.W 355.21, Observed M.W 357.0 (M+2).

Synthesis of 6-triphenylphosphonium-bromomethyl-2,3-difurylquinoxaline

6-bromomethyl-2,3-difurylquinoxaline (0.355 g, 1 mmol) and triphenylphosphine (0.26 g, 1 mmol) were dissolved together in acetonitrile (20 ml). The solution was stirred overnight at 40°C. The major precipitate was recrystallized from toluene-methanol mixture (2:1) to yield phosphonium ylide compound. (Yield 76%) ^{1}H-NMR (DMSO, ppm): 2.7 δ (2H, s) (Methyl protons) 7.2 - 8.1 δ (Aromatic protons) ^{31}P-NMR (DMSO, ppm): 25.62 δ.

Synthesis of 2,3-difurylquinoxalin-6-vinyl-benzaldehyde

The phosphonium salt (0.618 g, 1 mmol) and terephthaldicarboxaldehyde (0.135 g, 1 mmol) were dissolved in a mixture of absolute ethanol and dry chloroform (12 ml, 3+1 v/v) under N_2 atmosphere. In additional, the stoichiometric amount (25 wt% in methanol, 1.3 ml, 56 mmol) of sodium methoxide was added and stirred at 50° C overnight. The product was washed with methanol and reprecipitated from dichloromethane-methanol (1:1) followed by dissolving in acetonitrile - chloroform mixture (1:1) and dried under vacuum to yield 80% of brown colour solid product as 2,3-difurylquinoxalin-6-vinyl-benzaldehyde (**Figure 1**).

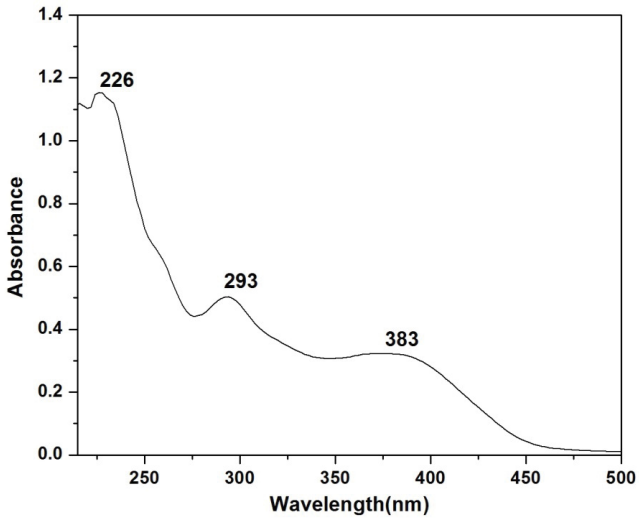


Figure 1: UV spectrum of 2,3-difurylquinoxalin-6-vinyl-benzaldehyde.

FT-IR (KBr, cm^{-1}); 1693 (C=O,st) 1586 (C=N, st) 1416 (C=C, st) 1363(C-N, st) 1182 (C-O, st) 2847 (C-H, st) 3403 (O-H, st); ^{1}H-NMR ($CDCl_3$, ppm): 10.1 δ (1H,s) 8.2 δ (2H,m) 7.9 δ (1H,m) 7.8 δ (2H,m) 7.7 δ (2H,m) 7.6 δ (2H,m) 7.4 δ (4H,m) 6.6 δ (2H,d)(J-Values 6.3); ^{13}C-NMR($CDCl_3$, ppm): 193.64(C=O), 127.71, 128.16, 128.71, 129.24, 129.86, 130.32, 130.73, 132.85, 133.09, 139.95, 141.96, 145.46, 152.68, 154.04; UV(λmax, nm): 226 nm (π-π*) 294 nm (n-π*).

RESULTS AND DISCUSSION

The 2,3-difurylquinoxalin-6-vinyl-benzaldehyde have been prepared similar to our earlier report [52-54]. The p-phenylene vinylene substituted quinoxaline derivatives have been synthesised in a four step.

Step 1: N-heterocyclic compound were prepared by condensation reaction between diamine and diketone.

Step 2: Substitute bromo group in methyl by NBS in CCl_4

Step 3: Formation of phosphonium ylide from 6-bromo-methyl N-heterocyclic compound.

Step 4: The target compound obtained through Wittig reaction between phosphonium salt of N-heterocyclic compound with terephthaldehyde.

The first stage 2,3-difuryl-6-methylquinoxaline compound was confirmed by FTIR, ^{1}H-NMR and GC-MASS. From the FTIR spectrum the transmittance peaks at 2924.09 - 3433.2 due to C-H stretching frequency. The peak at 1018.4 for C-O stretching and peak at 1570.0 for C=N functional group. The ^{1}H NMR spectrum depicts the signal at 2.5 δ for methyl protons and signals at 6.550 - 8.036 δ due to aromatic ring protons. The molecular weight was found from the GC-MASS spectrum. The molecular ion peak was observed at 276 value found to be agreed well with the theoretical value of 276 m/z.

The second stage bromo compound was confirmed by FTIR, ^{1}H-NMR, GC-MASS. The presence of bands at 594-752, 2800-3105 cm^{-1} in the FTIR spectrum clearly indicated the functional groups of C-Br and C-H stretching. Further, the appearance of downfield region signal at 3.416 δ in ^{1}H NMR established the CH_2 protons attached the heterocyclic and bromo group. The molecular ion peak observed in GC-MASS at 357(M+2) this value agreed well with the theoretical value.

The structure of the phosphonium ylide was confirmed by appearance of strong band at 692-752 and 540 cm^{-1} for P-Br and C-P stretching frequency in FTIR spectra. From the ^{1}H NMR spectrum the methylene proton signal of 3.416 δ shifted to 2.61-2.77 δ indicates methylene group attached with phosphonium salt was confirmed. Further, the signal appeared at 25.62 δ in ^{31}P NMR spectrum indicate the single phosphorus inserted in the ylide compound.

The vinyl benzaldehyde capped quinoxaline derivatives were prepared through Wittig reaction. The quinoxaline possessed electron deficient nitrogen atom and act as acceptor component in conjugated vinyl benzaldehyde system. From, the FTIR spectrum a transmittance peak for the aldehyde carbonyl-stretching appeared at 1689 cm^{-1}. The ^{1}H NMR spectrum depicts that the signal at 10.09-10.13 δ due to aldehyde CH proton. The aromatic ring proton signals appeared at 7.27-8.20 δ and the vinylene protons signal at 6.55-6.62 δ. The J-values of vinylene proton signal found to be 6.3 Hz. The molecular weight was originated from the GC-MASS spectrum. The molecular ion peak was observed at 392 found to be decided well with the theoretical value.

Anti-bacterial activity

The anti-bacterial activity of the synthesised 2,3-difurylquinoxalin-6-vinyl-benzaldehyde was evaluated using two-Gram positive (Bacillus substilis and Staphylococccus aureus) and two-Gram negative (*Escherichia Coli* and Pseudomonas auroginosa) bacteria. Ampicillin is used as positive control. The MIC values of the compound were determined by broth dilution method. Extract was dissolved in 10% DMSO. The initial concentration of extract was 2 mg ml^{-1} and end with 0.125 mg/ml concentration. The initial test concentration was serially diluted two-fold. Each well was inoculated with 5 µl of suspension containing 108 colony-forming units CFU ml-1 of bacteria. The antibacterial agent was incubated for 24 h at 37°C for bacteria. The culture intensity of each well was read at 600 nm and compared with the untreated control. The MIC of extract was determined as the lowest concentration of the extract inhibiting the visual growth of the test cultures. Among the tested micro-organism the 2,3-difurylquinoxalin-6-vinyl-benzaldehyde compound exhibited the best antibacterial activity, with a MIC value of 0.12 mg against Gram-negative *Escherichia Coli* bacteria (**Tables 1 and 2**).

Table 1: Antibacterial study of the p-phenylene vinylene substituted quinoxaline compound.

Concentrations (PPV-QUI)	*Bacillus substilis*		*Staphylococccus aureus*		*Escherichia coli*		*Pseudomonas auroginosa*	
	OD	% of inhibition	OD	% of inhibition	OD	% of inhibition	OD	% of inhibition
2 mg	0.346	60.77098	0.12	85.96491	0.16	78.23129	0.148	80.77922
1 mg	0.582	34.01361	0.317	62.92398	0.262	64.35374	0.24	68.83117
0.5 mg	0.698	20.86168	0.42	50.87719	0.348	52.65306	0.5	35.06494
0.25 mg	0.773	12.35828	0.646	24.44444	0.461	37.27891	0.701	8.961039
0.125 mg	0.875	0.793651	0.846	1.052632	0.508	30.88435	0.752	2.337662
Control	0.882	0.00	0.855	0.00	0.735	0.00	0.77	0.00

Table 2: MIC (Minimum inhibitory concentration) values of PPV-QUI compound.

Compound	*Bacillus substilis*	*Staphylococccus aureus*	*Escherichia coli*	*Pseudomonas auroginosa*
2,3-difurylquinoxalin-6-Vinyl-benzaldehyde	0.25 mg	0.25 mg	0.125 mg	0.25 mg
Ampicilin	0.12 mg	0.12 mg	0.12 mg	0.12 mg

CONCLUSION

The 2,3-difurylquinoxalin-6-vinyl-benzaldehyde compound was synthesised through Wittig reaction using phosphonium salt and terephthaldehyde. The resulting compound was characterised by FTIR, ^{1}H, ^{13}C, ^{31}P NMR and GC-MASS spectral studies. Anti-bacterial activities of the synthesised compound were studied using Gram positive and Gram negative bacteria. In comparison with positive control ampicillin, the compound show moderately good anti-bacterial activity against Gram-negative *Escherichia coli* bacteria.

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