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Synthesis of quinoxaline quinones and regioselectivity in their Diels-Alder cycloadditions

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A facile synthesis of quinoxaline quinones is reported. The regioselectivity in their Diels-Alder cycloaddition reactions has been investigated at AM1 level using Gaussian 98 and MOPAC 6 programs. The products have been characterized from their spectral data.

Keywords: Quinoxaline quinone, Diels-Alder cycloaddition, regioselectivity, AM1, spectral characterization

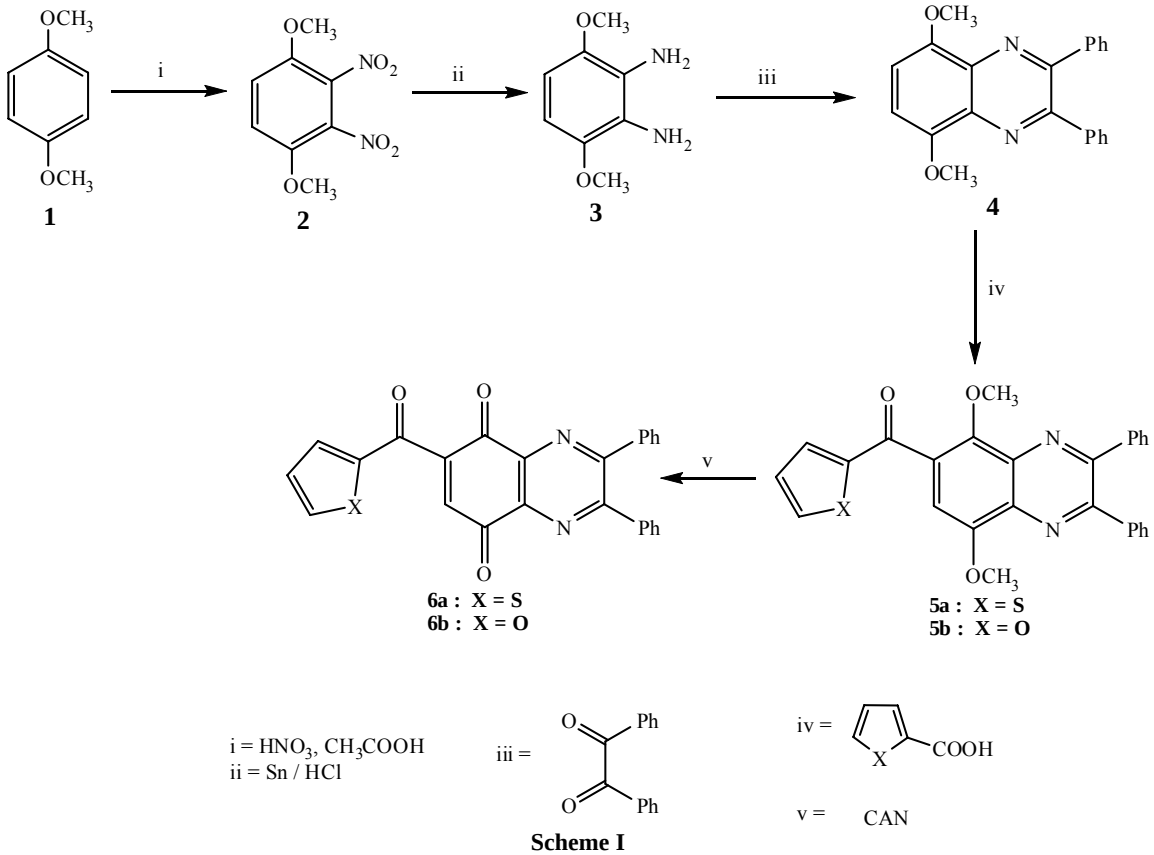
Quinoxaline derivatives are a very important class of nitrogen containing compounds. Quinoxaline ring moiety constitutes a part of chemical structure of various antibiotics[1]. They have also been employed to prepare porphyrins which resemble the arrangement of chromophores in the natural system[2]. Apart from this, some of the quinoxaline derivatives are effective electroluminescent materials[3]. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines[4-11]. Wong and co-workers have studied quinoxaline derivatives theoretically[12].

The quinones derived from alkyl-5,8-quinoxalines have been proved to be potential inhibitors of Coenzyme Q. In particular alkyl-mercapto-5,8-quinoxaline quinones have shown effective antimalarial activity[13]. A number of 6,7-modified 5,8-quinoxalinedione derivatives containing nitrogen, sulfur and oxygen have exhibited cytotoxic effects on human lung, gastric and colon adenocarcinoma cells when compared with *cis*-platin and adriamycin, the commonly used anticancer drugs[14]. Diels-Alder reaction of substituted-5,8-quinoxalinediones provide an attractive approach to the synthesis of cycloadducts that are useful building blocks for the synthesis of various natural products and in the medicinal field[15,16]. Computational calculations in modeling regioselectivity in the [4+2]-cycloaddition reactions of heteroacyl-1,4-quinones have shown[17] that quinoxaline quinones could serve as useful dienophiles for investigating the regiospecific attack at the quinonoid ring or the heterocyclic ring. The synthesis of benzoquinone derivatives and their subsequent cycloaddition with dienes and 1,5-sigmatropic rearrangement of adducts has already been reported[18,19]. In continuation to this work a facile synthesis of the title quinones has been worked out and their cycloaddition reactions have been investigated. The results are presented herein.

Results and Discussion

The key step in the synthesis of quinoxaline quinones is the oxidative demethylation of the corresponding dimethoxyketone **5a**, **5b**. The 5,8-dimethoxy-2,3-diphenylquinoxaline **4** has been prepared from 1,4-dimethoxybenzene **1** by known literature methods[20,21] as depicted in **Scheme I**. Thus nitration of 1,4-dimethoxybenzene **1** with nitrating mixture (HNO_3 / CH_3COOH) afforded 2,3-dinitro derivative **2** in 92% yield. Its reduction with Sn/HCl gave 2,3-diamino-1,4-dimethoxybenzene **3** which on condensation with benzyl afforded 5,8-dimethoxy-2,3-diphenylquinoxaline **4** in 80% yield.

Condensation of **4** with thiophene(furan)-2-carboxylic acid in polyphosphoric acid at 70-80°C furnished thienoyl and furanoyl derivatives **5a, 5b** in 72 and 76% yield, respectively. The dimethoxyketone **5a, 5b** has been converted to target quinone **6a, 6b** directly by oxidative demethylation with ceric ammonium nitrate[22] in acetonitrile for 4 hr in 82 and 74% yield, respectively. The structure of quinoxaline



Scheme I

quinone **6a, 6b** has been ascertained from its spectral data. In the IR spectrum of **6a**, the free and quinonoid C=O group appeared at 1770 and 1700 cm^{-1}, aromatic stretching frequency appeared in the region of 1560-1400 cm^{-1}, a weak band in the region of 690 cm^{-1} was characteristic of C-S-C linkage. In the ^1H NMR spectrum, the H-3 quinonoid proton appeared as a singlet at δ 6.67, two triplets and a doublet at δ 7.05 (*J*=7.0 Hz), 7.39 (*J*=7.0 Hz) and 7.21 (*J*=1.5 Hz) have been assigned to *meta*, *ortho* and *para* phenyl protons, H-3′ appeared as doublet at δ 7.78 (*J*=1.5 Hz), H-5′ as doublet at δ 7.85 (*J*=4.0 Hz) and H-4′ as double doublet at δ 7.56 (J_1=1.5 Hz, J_2=4.0 Hz). In ^{13}C NMR spectrum the free carbonyl group appeared at δ 189.7 while quinonoid C=O appeared at δ 186.9 and 181.5. The thiophene ring carbons appeared at δ 136.5, 136.1, 134.1 and 131.0 while the phenyl ring carbons appeared in the range of δ 129.5-113.3. Mass spectrum showed molecular ion peak at *m/z* 422 (20%). Other main fragments were formed by the cleavage on either side of keto group *i.e. m/z* 111 (42%) and *m/z* 339 (100%). These fragments produced daughter nuclei at *m/z* 83 (14%) and *m/z* 311 (33%) by the loss of carbonyl moiety. Further a loss of two bezonitrile moieties produced daughter ion peak at *m/z* 105 (5%). A peak at *m/z* 230 (15%) was assigned to $C_{16}H_{10}N_2$ formed by the loss of two carbonyl groups and acetylene moiety. The structures of all other precursors **4-6** have also been ascertained from their spectral data as well as literature reports[23-26] (**Tables I** and **II**).

Theoretical Studies

The Diels-Alder reaction of the quinoxaline quinones **6a, 6b** was studied in detail by AM1 quantum chemical method using Gaussian 98 and MOPAC 6 program[27,28]. The aim of these studies was to probe the regiospecificity of the reaction and modeling selectivity in their cycloaddition reactions *i.e.* to ascertain whether the diene addition takes place at quinonoid ring or at thieonyl/furanoyl ring. For this purpose, three different dienes bearing electron donating or electron withdrawing groups namely isoprene, 2,3-dimethyl-1,3-butadiene and perchloro-butadiene have been chosen (**Scheme II**).

For modeling regioselectivity of the Diels-Alder reaction, calculations were performed on all the compounds. **Figure 1** presents the optimized geometry of **6a**.

Table I — Physical characterization data and elemental analysis of compounds

Compd	Physical state	m.p. (°C)	Yield (%)	Mol. Formula	Found (Calcd) %		
					C	H	N
4	Buff colored solid	217	80	$C_{22}H_{18}O_2N_2$	77.00 (77.19	5.20 5.26	8.08 8.18)
5a	Light brown solid	110	76	$C_{27}H_{20}O_3N_2S$	71.20 (70.68	4.02 4.42	6.82 6.19)
5b	Creamish solid	94	72	$C_{27}H_{20}O_4N_2$	74.21 (74.31	4.28 4.28	6.34 6.42)
6a	Yellow solid	95	82	$C_{25}H_{14}O_3N_2S$	71.29 (71.09	3.24 3.32	6.52 6.63)
6b	Grey powder	120-122	74	$C_{25}H_{24}O_4N_2$	72.09 (73.89	3.82 3.44	6.48 6.89)

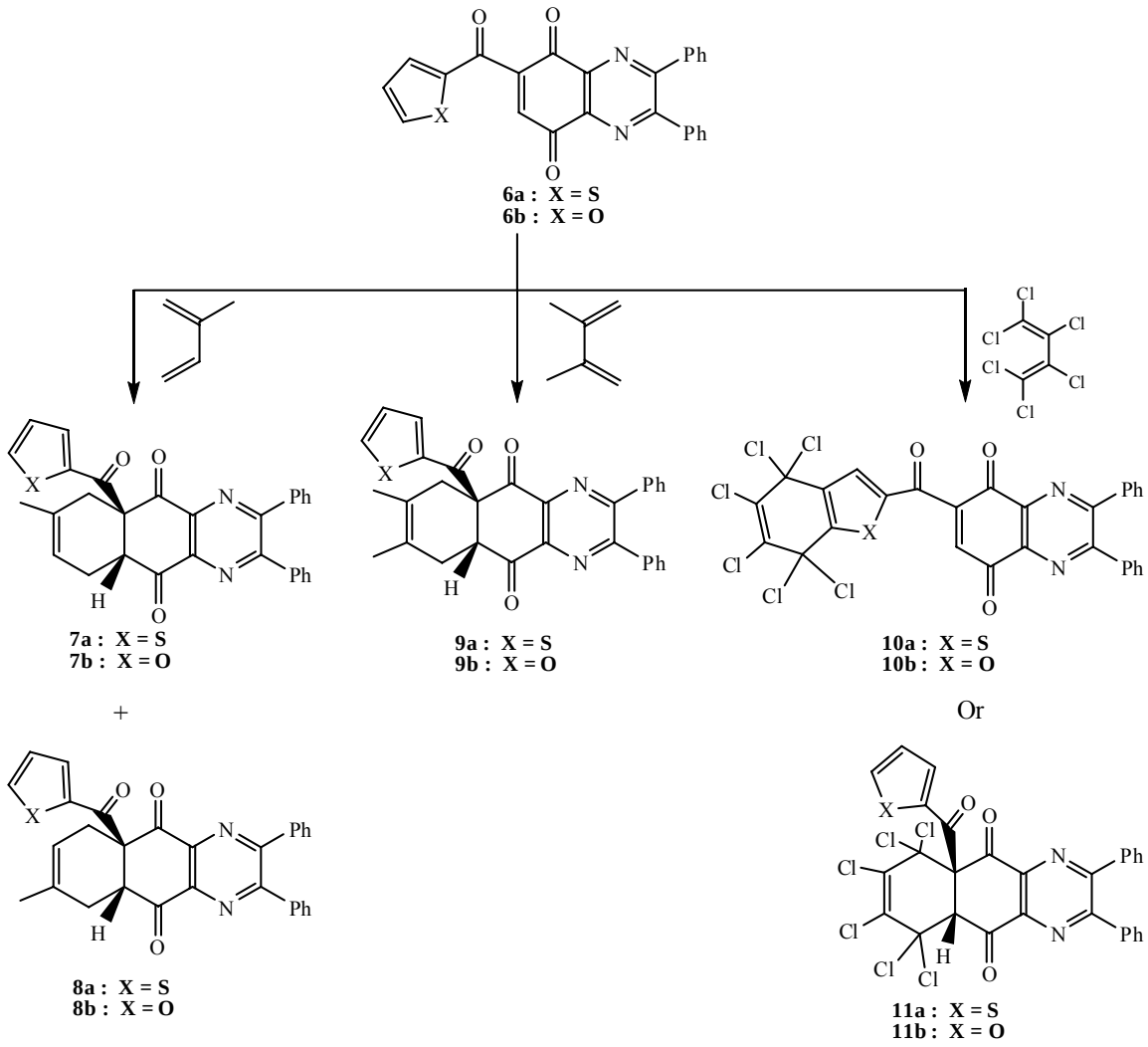
Table II — ^{1}H and ^{13}C NMR data of the compounds

	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
4	3.99 (s, 6H, 2×OCH_3), 7.21 (d, 2H, 2×ArH), 7.44 (t, 4H, 4× *m*-ArH), 7.59 (t, 2H, 2×*p*-ArH), 7.91 (d, 2H, 4× *o*-ArH)	145.2 (C2,C3), 143.0 (C4a,C8a), 134.8 (C5,C8), 138.1 (C6,C7), 132.2, 130.1, 128.5, 125.2 (2 × C_6H_5), 66.4, 66.9 (2 ×OCH_3)
5a	3.85 (s, 6H, 2×OCH_3), 7.05 (s, 1H, H-7), 7.3-7.8 (m, 10H, 2×C_6H_5), 7.8-8.2 (m, 3H, H-3′ + H-4′ + H-5′)	169.4 (C=O), 151.8, 150.3, 143.8, 141.3, (C2'+ C3'+C4'+C5'), 137.6, 136.3, 135.6, 132.9, 132.5, 131.5, 130.3, 128.7 (8×Ar-C), 128.3-119.7 (2×C_6H_5), 60.0, 57.6 (2×OCH_3)
5b	3.45 (s, 6H, 2×OCH_3), 6.85 (s, 1H, H-7), 7.0-7.7 (m, 10H, 2×C_6H_5), 7.7-8.1 (m, 3H, H-3′ + H-4′ + H-5′)	-
6a	6.67 (s, 1H, H-3), 7.05 (t, *J*=7.0 Hz, 4H, 4× *m*-ArH), 7.21 (d, *J*=1.5 Hz, 2H, 2× *p*-ArH), 7.39 (t, *J*=7.0 Hz, 4H, 4× *o*-ArH), 7.56 (dd, J_1=1.5 Hz, J_2=4.0 Hz, 1H, H-4′), 7.78 (d, *J*=1.5 Hz, 1H, H-3′), 7.85 (d, *J*=4.0 Hz, 1H, H-5′)	189.7, 186.9, 181.5 (3×C=O), 141.3, 138.8, 137.7, 137.5, (6 Ar-C), 136.5, 136.1, 134.1, 131.0 (C-2'+C-3'+C-4'+C-5'),129.5-113.3 (2×C_6H_5)
6b	6.52 (s, 1H, H-3), 7.10-7.4 (m, 10H, 2×C_6H_5), 7.62 (dd, J_1=4.0 Hz, J_2=1.5 Hz, 1H, H-4′), 7.75 (d, *J*=15 Hz, 1H, H-3′), 7.95 (d, *J*=4.0 Hz, H-5′)	-

Frontier orbital theory suggests that the bond formation is energetically favored by the overlap of HOMO of the diene with the LUMO of the quinone because of the lower energy gap. This is true for isoprene and 2,3-dimethyl-1,3-butadiene for which $HOMO_{diene}$-$LUMO_{quinone}$ energy gap is lower than $HOMO_{quinone}$-$LUMO_{diene}$ gap. Besides, for isoprene and 2,3-dimethyl-1,3-butadiene the orbital coefficients indicate that the LUMO of quinoxaline quinone **6a, 6b** resides on C_2-C_3 bond (**Table III**) and it is this bond where diene adds to give the cycloadduct **7a-9b**. Hence, these dienes should add to the quinone moiety of the quinoxalinoquinone. However, the case of perchlorobutadiene is a bit different as $HOMO_{diene}$-$LUMO_{quinone}$ and $HOMO_{quinone}$-$LUMO_{diene}$ energy gap difference is not very large and hence it may add either to the heterocyclic part **10a, 10b** or to the quinonoid part **11a, 11b** of the quinone.

In order to ascertain the formation of cycloadduct **10** over cycloadduct **11**, the ground state geometries of quinone **6a**, perchlorobutadiene as well as corresponding cycloadducts **10a, 11a** and their transition state geometries have been optimized. Cycloaddition of quinone **6a** with perchlorobutadiene may result in the formation of products **10a** or **11a** *via* two different transition states TS-1 and TS-2 respectively. Transition state calculations indicated that formation of cycloadduct **10a** through TS-1 is exothermic (6.26 Kcal/mol) with an energy barrier of 12.12 Kcal/mol. Similarly, formation of cycloadduct **11a** through TS-2 is also exothermic (5.17 Kcal/mol) with an energy barrier of 18.15 Kcal/mol at AM1 level. The results of above calculations are summarized in **Table IV** and **Figure 2**.

A careful look at **Table IV** reveals that activation energy required for the formation of **11a** is higher



Scheme II

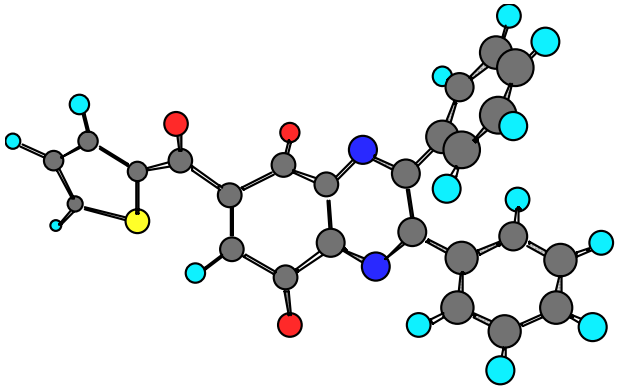


Figure 1 — Optimized geometry of **6a**

than that required for **10a**. Hence, the adduct **10a** should be formed in excess. Therefore, perchlorobutadiene will probably add on the heterocyclic part of quinone **6a**.

Experimental Section

Melting points of the newly synthesized compounds were determined in open glass capillary and are uncorrected. The IR spectra were recorded on Nicolet Magna IR spectrometer Model 550 in KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Jeol 300 MHz model with tetramethylsilane as internal standard. Chemical shifts are given in δ, ppm. Elemental analysis was performed by Perkin-Elmer Series C, H, N, O, S, Analyser 2400. Solvents were purified by standard procedures[29,30].

Computational Details

All calculations have been carried out at AM1 Hamiltonian using the Gaussian 98 and MOPAC 6 program[27,28]. Harmonic vibration frequencies of all stationary points have been computed to characterize

Table III — ΔH_f, orbital energies and energy gaps for quinoxaline quinones and dienes

	ΔH_f (Kcal/mol)	Orbital energies (eV) HOMO	LUMO	Energy gaps (eV)* H-L		L-H	
6a	80.59	-9.47	-1.88				
6b	59.43	-9.43	-1.84				
Isoprene	23.88	-9.18	0.47	**6a**	7.30	**6a**	9.94
				6b	7.34	**6b**	9.90
Dimethyl-1,3-butadiene	16.88	-9.21	0.66	**6a**	7.33	**6a**	10.13
				6b	7.37	**6b**	10.09
Perchloro-1,3-butadiene	-7.51	-10.07	-0.60	**6a**	8.19	**6a**	8.87
				6b	8.23	**6b**	8.83

*Here H-L = $HOMO_{diene}$-$LUMO_{quinone}$, L-H = $LUMO_{diene}$-$HOMO_{quinone}$

Table IV — ΔH_f-R, ΔH_f-TS, ΔH_f-P, Ea and Stabilization Energy for the formation of **10a** and **11a** from the Diels-Alder reaction of **6a** and perchlorobutadiene

Product	ΔH_f-R (Kcal/mol)	ΔH_f-TS (Kcal/mol)	ΔH_f-P (Kcal/mol)	E_a (Kcal/mol)	Stabilization Energy (Kcal/mol)
10a	73.08	85.20	66.22	12.12	6.26
11a	73.08	91.23	67.91	18.15	5.17

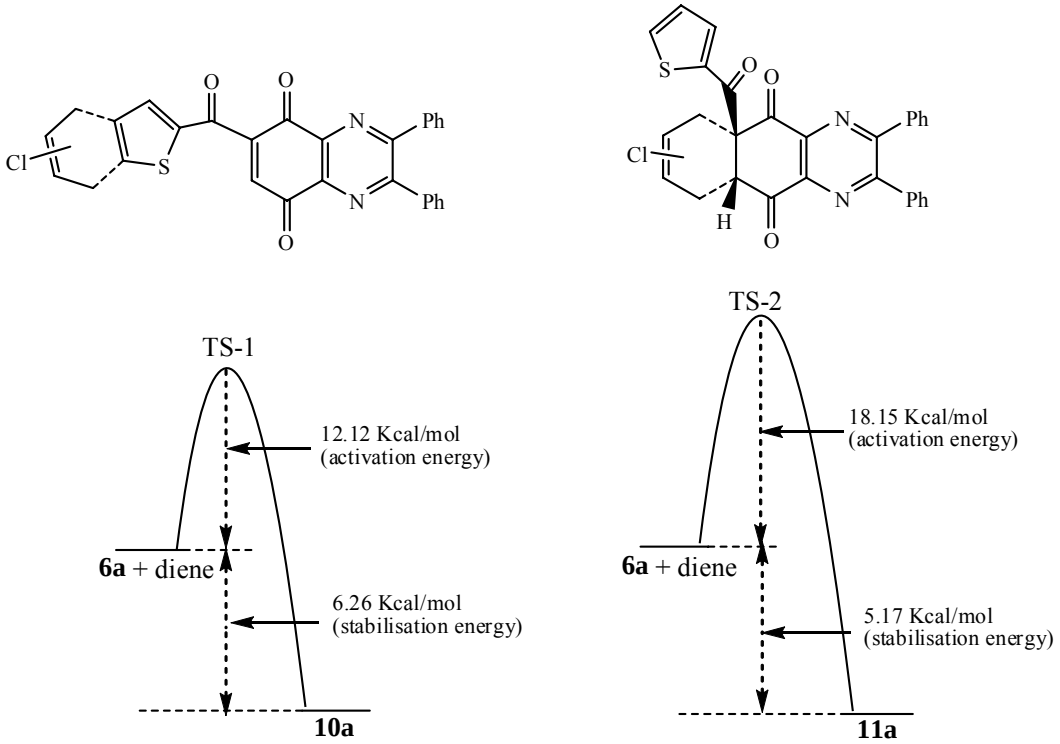


Figure 2 — Energy profile diagram for Diels-Alder reaction of **6a** and perchlorobutadiene

them as energy minima (all frequencies are real) or transition states (one and only one imaginary frequency).

Synthesis of 5,8-dimethoxy-2,3-diphenylquinoxaline, 4

This intermediate was prepared by known literature methods[20,21]. (1.35g, 80%), m.p. 217°C (lit.[22] m.p. 227°C).

Synthesis of 5,8-dimethoxy-2,3-diphenyl-6-thienoylquinoxaline, 5a

A mixture of thiophene-2-carboxylic acid (0.5 g, 4.0 mmole) and the quinoxaline derivative **4** (1.37 g, 4.0 mmole) was heated in the presence of polyphosphoric acid (20 mL) at 70-80°C with vigorous mechanical stirring on an oil bath for 5 hr. After completion of the reaction, as monitored by

TLC, the reaction mixture was poured into warm water (250 mL) and allowed to cool. It was then extracted with ether (4×25 mL) and the combined extract was washed with saturated sodium bicarbonate solution (2×25 mL), distilled water (2×25 mL) and dried over anhydrous sodium sulphate (15 hr). Removal of solvent afforded crude product **5a** as brownish mass, which was purified by column chromatography over silica gel using solvents of rising polarity. The petroleum ether (60-80°C)-chloroform (1:3) fraction afforded the compound **5a** as light brown solid (1.37 g, 76%), m.p.110°C.

Synthesis of 5,8-dimethoxy-2,3-diphenyl-6-furanoyl-quinoxaline, 5b

A mixture of furan-2-carboxylic acid (0.45 g, 4.0 mmole) and the quinoxaline derivative **4** (1.37 g, 4.0 mmole) were heated in the presence of polyphosphoric acid (20 mL) at 70-80°C with vigorous mechanical stirring on an oil bath for 5 hr. After completion of the reaction, as monitored by TLC, the reaction mixture was poured into warm water (250 mL) and allowed to cool. It was then extracted with ether (4×25 mL) and the combined extract was washed with saturated sodium bicarbonate solution (2×25 mL) and dried over anhydrous sodium sulphate (15 hr). Removal of solvent afforded crude product **5b** as brownish mass, which was purified by column chromatography over silica gel using solvents of rising polarity. The petroleum ether (60-80°C)-chloroform (1:3) fraction afforded the compound **5b** as light brown solid (1.26 g, 72%), m.p. 94°C .

Synthesis of 2,3-diphenyl-6-thienoyl-5,8-quinoxalino-quinone, 6a

To a solution of ketone **5a** (0.16 g, 0.35 mmole) in acetonitrile (20 mL) was added a solution of ceric ammonium nitrate (0.42 g in 2 mL water) and the resulting solution was stirred at RT for 30 min. The reaction mixture was diluted with water (100 mL) and extracted with chloroform (4×50 mL). It was washed with brine (NaCl solution) and dried over sodium sulphate. Removal of solvent afforded yellow brown solid, which was purified by crystallization from chloroform-ethyl acetate (3:1) solvent to afford **6a** as yellow solid (0.12 g, 82%), m.p. 95°C.

Synthesis of 2,3-diphenyl-1,6-furanoyl-5,8-quino-xalinoquinone, 6b

To a solution of ketone **5b** (0.153 g, 0.35 mmole) in acetonitrile (20 mL) was added a solution of ceric ammonium nitrate (0.42 g in 2 mL water) and the resulting solution was stirred at RT for 30 min. The reaction mixture was diluted with water (100 mL) and extracted with chloroform (5×50 mL). It was washed with brine (NaCl solution) and dried over sodium sulphate. Removal of solvent afforded yellow brown solid, which was purified by crystallization from chloroform-ethyl acetate (1:1) solvent to afford **6b** as pale yellow solid (0.11 g, 74%), m.p. 120-22°C.

Conclusion

The thienoyl and furanoyl substituted 5,8-dimethoxyquinoxaline quinones have been prepared in good yields from readily available starting materials. The modelling regioselectivity in the Diels-Alder cycloaddition reaction with various dienes has been investigated theoretically. Results of the computational study reveal that by choosing appropriate diene such as an electron-withdrawing diene, it is possible to reverse the course of cycloaddition from quinonoid ring to the heterocyclic moiety.

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