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One-step Approach for Synthesis of Functionalized Quinoxalines Mediated by T3P® - DMSO or T3P® via Tandem Oxidation – Condensation or Condensation Reaction

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Kachigere B. Harsha,[a#] Kanchugarkoppal S. Rangappa.[a]*

An easy and efficient propyl phosphonic anhydride (T3P®) - DMSO or T3P® mediated oxidation-condensation or condensation reaction for the synthesis of quinoxalines from the interaction of different arrays of condensing partners with ortho-phenylene diamines (*o*-PDs) under simple and mild reaction conditions in one step has been reported for the first time.

Introduction

The new synthetic organic transformation for the synthesis of functionalized N-containing heterocyclic small molecules from simple starting materials is of great importance in the field of synthetic organic chemistry. Quinoxalines or benzopyrazines in particular have been studied as antibacterial, antiviral, anthelmentic, antiinflamatory, kinase inhibitory and anticancer activities [1] and quinoxalines have a wide array of other applications. [2] In addition, quinoxaline nucleus contains some important antibiotics such as olaquindox, carbadox, echinomycin, levomycin and actinoleutin. Owing to their wide range of biological and technical interest, number of synthetic strategies have been developed for the synthesis of various substituted quinoxalines. Out of several methods of synthesis, the oxidation-condensation or condensation reaction is one of the major synthetic stratergies for the synthesis of bioactive quinoxaline nucleus from readily available precursors like *o*-PDs and α-hydroxy ketones.[3] And also several methods are available for the synthesis of quinoxalines from phenacyl bromides,[4] 1,2-diketones,[5] alkynes,[6] epoxides,[7] aryliminooximes[8] with *o*-PDs.

Most of the methods reported above suffer from one or more disadvantages such as poor substrate scope, harsh reaction condition, laborious and complex work-up procedure, expensive and moisture sensitive reagents, undesirable side products and unsatisfactory yield. During the course of investigation, our research group, found that T3P® (propane phosphonic anhydride) is being used in the synthesis of peptides,[9] synthesis of polysubstituted quinolines and naphthyridines,[10] β-lactams,[11] pyrimidinones in Biginelli reaction,[12] 1,2,4-oxadiazoles and 1,3,4-oxadiazoles and 1,3,4-thiadiazoles[13] Fischer indole.[14] Due to its significant properties like water scavenger, oxidation-cyclization recently we have been reported several one pot tandem approaches for the synthesis of benzimidazoles and benzothiazoles,[15a] 4-thiazolidinones[15b] and imidazo [1, 2-a] pyridines[15c] from alcohols, using DMSO-propylphosphonic anhydride (T3P®) media as an oxidizing as well as cyclodehydrating agent. In continuation of our research interest in the synthesis of various heterocycles,[16] we report herein a new strategic one-step method for the synthesis of quinoxalines from α-hydroxy ketone, α-haloketone and 1,2-diketones with *o*-PDs by using DMSO:Propylphosphonic anhydride (T3P®) or propylphosphonic anhydride (T3P®) in EtOAc as a solvent under room temperature and reaction underwent via oxidation followed by condensation or by simple condensation reaction. To optimize the reaction conditions, Initially we selected the reaction between *o*-PD **1a** and 2-hydroxy 1,2-diphenylethanone **2a** (scheme1) in EtOAc:DMSO in the ratio 2:1 as a solvent mixture followed by adding 1 equivalent of T3P®(50% solution in ethyl acetate) under stirring at O^0C-RT for 10 hs which afforded the desired 2,3-diphenylquinoxaline **3e** in 25% yield. The same reaction we checked different equivalents T3P® could affect the course of reaction and yield of **3e.** Therefore, we carried out the oxidation-condensation by using various equivalents of T3P®. The best result was obtained when reaction between 1,2-diphenylethanone and *o*-PDs with 2.0 equivalent of T3P® in presence of DMSO was stirred at RT for 6 h. We also studied by keeping the equivalent of T3P® (2.0 eq) at constant and by varying the temperature and time . Finally we were not able to achieve maximum percentage yield compared to yield obtained in RT

[a] DOS In Chemistry, University Of Mysore, Mysuru-570006, India.
[b] * Corresponding authors
[c] E-mail:rangappaks@gmail.com,rangappaks@yahoo.com
[d] Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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Scheme 1. Synthesis of 2,3-diphenyl quinoxaline (3e) from α-hydroxy ketone.

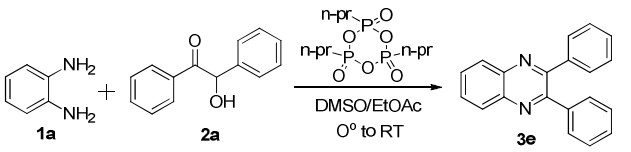


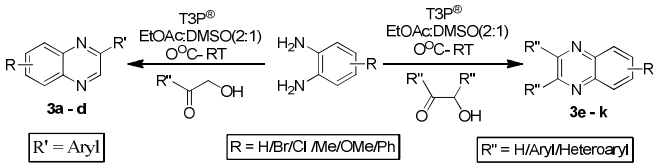
Table 1. T3P®-DMSO mediated synthesis of **3e** under different reaction conditions.

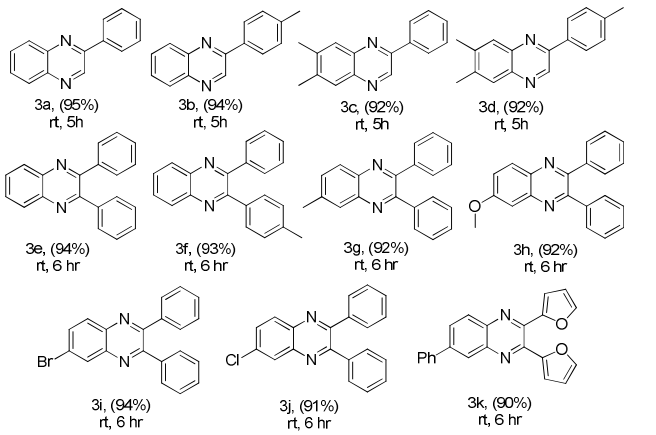
Entry.	Solvent[a]	T3P®(equiv)[b]	Time(h)	T [^{0}C]	Yield[c](%)of **3e**
1.	EtOAc	1.0	10	0-25	25
2.	EtOAc	1.5	6	0-25	54
3.	**EtOAc**	**2.0**	**6**	**0-25**	**94**
4.	EtOAc	2.5	6	0-25	94
5.	EtOAc	3.0	6	0-25	93
6.	EtOAc	3.5	6	0-25	93
7.	CH_2Cl_2	2.5	6	0-25	48
8.	$CHCl_3$	2.5	6	0-25	44
9.	CH_3CN	2.5	6	0-25	55
10.	THF	2.5	6	0-25	49
11.	Toluene	2.5	6	0-25	58
12.	Dioxane	2.5	6	0-25	56
13.	Benzene	2.5	6	0-25	40
14.	EtOAc	2.5	5.5	50	87
15.	EtOAc	2.5	5	60	86
16.	EtOAc	2.5	4	65	88
17.	EtOAc	2.5	3	75	80

[a] Reactions were performed with solvent and DMSO were taken in 2:1 volume ratio, 1mmol of **1a**, 1.2 mmol of **2a** in case of **3e**.
[b] T3P® (50% solution in EtOAc) was used to carry out the reactions.
[c] Isolated yield after purified by column chromatography.

condition. The optimization results are summarized in table 1. Thus, the clear optimization of the reaction conditions to obtain quinoxalines from α-hydroxyl ketone with *o*-PDs was revealed from our studies which had used 2.0 equivalent of T3P® and stirring the reaction mixtures for 6 h at 0°C to RT, the product was isolated initially washing the reaction mixture with water then followed with brine and purified by the column chromatography by using 60:120 silica gel. The oxidation-condensation or cyclodehydrating property of the T3P® helps to generalize the reaction procedure. Next we carried out the reactions with electronically diversified α-hydroxy

Scheme 2: Synthesis of quinoxalines from α- hydroxy ketones.





T3P®(2.0 mmol), α-hydroxy ketone (1.2 mmol), 1,2 Diamine (1.0 mmol).

ketones and *o*-PDs mediated by the T3P® in DMSO:EtOAc as a solvent mixture to obtain the desired quinoxalines **(3a-k)**. The *o*-PD and α-hydroxy ketone without substitution afford good yield and also α-hydroxy ketone containing electron-donating group favours the formation of desired quinoxalines in high yield when compared to *o*-PD contains electron-withdrawing group. The results are summarized in scheme 2. The scope of the reaction was successfully extended to other substrates such as electronically demanding α-bromo ketones with *o*-PD or substituted *o*-PDs which also underwent the title reaction under RT condition to obtain corresponding quinoxalines **(4a-x).** Similarly, here also α-halo ketone and *o*-PD containing without substitution favour the formation of a slightly higher yield. when compared to substituted α-halo ketones or *o*-PDs. The results are summarized in scheme 3. We extended our studies to further increase the substrate scope. We carried out the condensation of 1,2-dicarbonyl compounds with *o*-PD under mild reaction condition at RT in presence of T3P® to produce the desired quinoxaline derivatives **(5a-p).** Interestingly, the reaction between aliphatic diketone and *o*-PD underwent the title reaction to afford desired quinoxaline in lower yield. when compared to aromatic 1,2-diketones. In the case of both aromatic starting materials containing without substitution favour the formation of quinoxalines in higher yield. The results are summarized in scheme 4**.**

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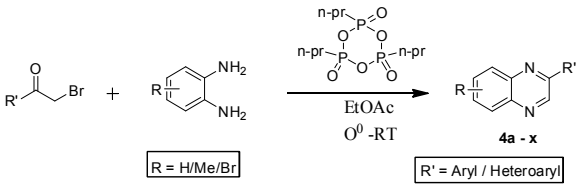
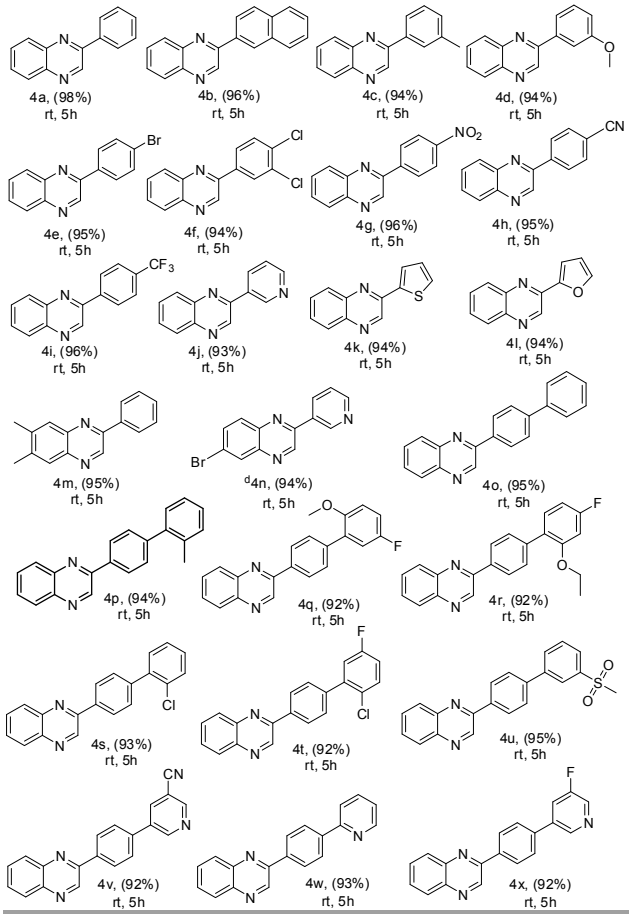
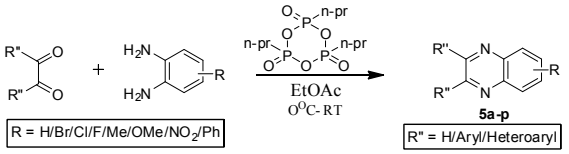
Scheme 3: Synthesis of quinoxalines from α-halo ketone.

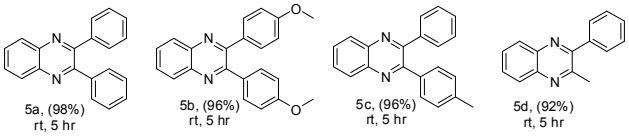


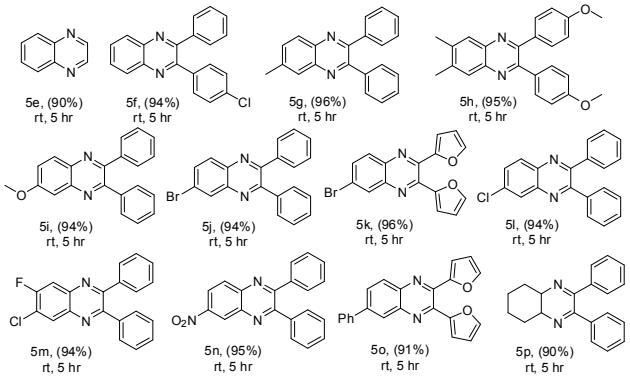


T3P® (2.0 mmol), α-bromoketone(1.2 mmol), diamine(1.0 mmol)
[d] Mixture of regioisomers.

Scheme 4: Synthesis of quinoxalines from 1,2-diketone.







[a] T3P®(2.0 mmol), 1,2-diketone (1.2 mmol), diamine(1.0 mol).

Selected quinoxaline compounds from schemes **1** and **3,** such as **3k, 4o, 4p, 4q, 4r, 4s, 4t, 4u, 4v, 4w, 4x** were evaluated as cytotoxic agents against A549 human lung carcinoma cells, which have frequently been choosen by our group,[17] as a suitable cell culture to perform cytotoxicity assays. Therefore, concentration-response experiments were performed to establish the cytotoxicity activity of each selected compound (fig 1).

Table 2. IC_{50} (μM) inhibitory concentrations with human lung carcinoma cells (A549).

quinoxaline	3k	4o	4p	4q	4r	4s	4t	4u	4v	4w	4x
IC_{50} (μM)	2.14	2.11	27.3	17.4	19.4	2.8	20.3	10.3	5.3	33.2	30.3

We observed that quinoxalines 3k,4o,4s,4v,4u are the most efficient cytotoxic agent when a high concentration (25μM) was used resulting in the death of 74% of the A549 cells in case of 4o. IC_{50} values expressed in μM, summarized in table 2, establish the relative order of effectiveness for the quinoxalines cytotoxicities: 3k ≈ 4o > 4s > 4v > 4u > 4q > 4r > 4t > 4p > 4x > 4w. From these results we can conclude that the observed slight difference in cytotoxicity might be due to differences in the nature of substituents present in the core moiety and percentage uptake of the compounds by the cells.

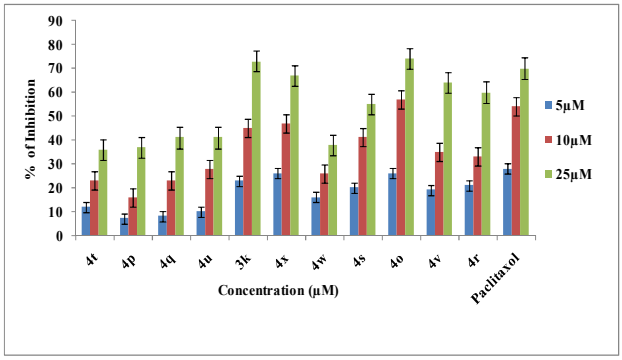


Figure 1. Bar graph showing cytotoxicity activity of quinoxalines on A549 cell line.

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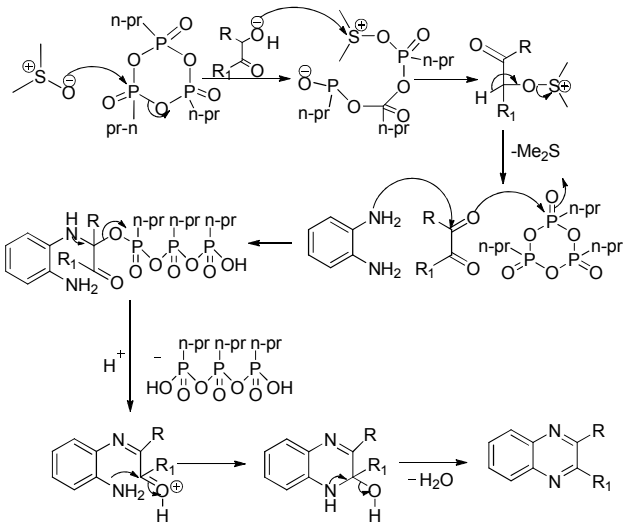
Conclusion:

This synthetic methodology constitutes a versatile, one-step protocol for the preparation of libraries of quinoxalines with broad substrate scope and high yield. The preliminary investigations in to the cytotoxic effects of the studied quinoxalines compounds against A-549 cancer cells, the lowest IC-50 value was observed with the phenyl substituted *o*-PD part of the quinoxaline **3k** and phenyl substituted α-haloketone part of the quinoxaline **4o.** These promising results shows that application of DMSO-T3P® or T3P® Mediated reactions gives new chemical space in the field of synthetic organic chemistry and also in the exploration of new synthetic strategies for the synthesis of biologically active heterocyclic small molecules in the field of medicinal chemistry.



Scheme 5: Proposed mechanism for the formation of quinoxalines in **scheme 1.**

Experimental Section

Materials and Instruments

Purification of reaction products was carried out by normal column chromatography using Sorbent Technologies Standard Grade silica gel (60-120 mesh). Analytical thin layer chromatography was performed on merk silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}HNMR) were recorded on Agilent-400 MHz and are reported in ppm using $CDCl_3$ as the internal standard (7.24 ppm). Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Agilent-100 MHz and reported in ppm using $CDCl_3$ as the internal standard (77.0 ppm). Mass spectra were recorded on Waters' mass spectrum.

General procedure for the synthesis of quinoxalines from α-hydroxyketones:

The stirred suspension of α-Hydroxy ketone (1.2mmol) in DMSO:EtOAc as a solvent mixture in the ratio (2:1) was added to ortho-phenylene diamine (1mmol). It was followed by the addition of T3P® (2.0 mmol) under 0 ^{0}C then reaction mixture was next kept under RT for 6 hrs. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by ice cold water and the extracted reaction mixture with EtOAc (×2), collected organic layer was washed with brine solution and dried over anhydrous sodium sulphate, organic layer was removed under reduced pressure to afford desired quinoxalines which were purified by column chromatography using hexane : ethylacetate as an eluent.

General procedure for the synthesis of quinoxalines from α-haloketone and 1,2-diketone:

Stirred reaction mixture of α-bromoketone or 1,2-diketone (1.2mmol) and ortho phenyl diamine (1mmol) in ethyl acetate followed by the addition of T3P® (2mmol) under O^{0}C. Then, the reaction mixture was kept under RT for 5 hr. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by ice cold water reaction mixture with EtOAc (×2) was extracted. The collected organic layer was washed with brine solution and dried over anhydrous sodium sulphate. Organic layer was removed under reduced pressure to afford the desired quinoxalines which were purified by column chromatography using hexane : ethylacetate as an eluent.

2-phenylquinoxaline (3a or 4a): Pale yellow solid; yield 95%; (Rf = 0.48 in hexanes/ EtOAc 95:05 v/v); MP 75-77 ^{O}C ; IR (KBr): 3055, 1545, 1480, 1445, 1312, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.33 (s, 1H), 8.21-8.11 (m, 4H), 7.81-7.73 (m, 2H), 7.59-7.52 (m, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{14}H_{10}N_2$ 207.0877 found 207.0876

2-(p-tolyl)quinoxaline (3b) : Yellow solid; yield 94%; (Rf = 0.46 in hexanes/ EtOAc 95:05 v/v); MP 92-94 ^{O}C; IR (KBr): 3058, 1615, 1554, 1475, 1445, 1310, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.40 (s, 1H), 8.55–8.38 (m, 4H), 8.37–8.20 (m, 2H), 7.88 (d, *J* = 8 Hz, 2H), 2.40 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{15}H_{12}N_2$ 221.1034 found 221.1035

6,7-dimethyl-2-phenylquinoxaline (3c or 4m): Yellow solid; yield 92%; (Rf = 0.54` in hexanes/ EtOAc 95:05 v/v); MP 129-130 ^{O}C; IR (KBr): 3055, 3040, 2965, 1535, 1480, 1445, 1310, 1210, 1020, 1005 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 9.22 (s, 1H), 8.20 (d, *J* = 11.2 Hz, 2H), 7.89 (s, 1H), 7.88 (s, 1H), 7.65–7.36 (m, 3H), 3.41 (s, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{16}H_{14}N_2$ 235.1190 found 235.1191

6,7-dimethyl-2-(p-tolyl)quinoxaline (3d): Yellow solid; yield 92%; (Rf = 0.62 in hexanes/ EtOAc 95:05 v/v); MP 113-115 ^{O}C; IR (KBr): 3025, 2973, 1605, 1530, 1480, 1442, 1315, 1045, 1025, 860, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.36 (s, 1H), 8.13 (d, *J* = 7.2 Hz, 2H), 8.12 (s, 1H), 7.82 (s, 1H), 7.81 (s, 1H), 7.09 (d, *J* = 8 Hz, 2H), 2.63 (s,

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3H), 2.33 (s, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{17}H_{16}N_2$ 249.13862 found 249.13858

2, 3-diphenylquinoxaline (3e or 5a): Yellow solid; yield 94%; (Rf = 0.58 in hexanes/ EtOAc 95:05 v/v); MP 116-118 ^{O}C; IR (KBr): 3056, 1635, 1475, 1440, 1345, 1075, 1055, 770, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (dd, *J* = 6.8 Hz, 3.2 Hz, 2H), 7.77 (dd, *J* = 3.6 Hz, 3.2 Hz, 2H), 7.53–7.50 (m, 4H), 7.38–7.31 (m, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{14}N_2$ 283.1230 found 283.1231

2-phenyl-3-p-tolylquinoxaline (3f or 5c): Yellow solid; yield 93%; (Rf = 0.62 in hexanes/ EtOAc 95:05 v/v); MP 110-112 ^{O}C ; IR (KBr): 3055, 2915, 1614, 1553, 1519, 1470, 1438, 1388, 1345, 1056, 1020, 974, 754, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz,): δ = 8.26–8.14 (m, 2H), 7.99–7.95 (m, 2H), 7.83–7.78 (m, 2H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.69–7.40 (m, 3H), 7.13 (d, *J* = 6.8 Hz, 2H), 2.42 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{16}N_2$ 297.1386 found 297.1387

6-methyl-2,3-diphenylquinoxaline (3g or 5g): White solid; yield 92%; (Rf = 0.54 in hexanes/ EtOAc 95:05 v/v); MP 111-113 ^{O}C; IR (KBr): 3054, 2938, 1617, 1485, 1444, 1200, 1056, 1021, 812. 768, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz,): δ = 8.10 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 7.92 (dd, *J* = 9.6 Hz, 1.6 Hz, 1H), 7.78–7.69 (m, 4H), 7.68–7.31 (m, 6H), 2.77 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{16}N_2$ 297.1386 found 297.1387

6-methoxy-2,3-diphenylquinoxaline (3h or 5i): White solid; yield 92%; (Rf = 0.52 in hexanes/ EtOAc 95:05 v/v); MP 160-162 ^{O}C ; IR (KBr): 2965, 2936, 1756, 1617, 1482 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.04 (d, *J* = 8.8 Hz, 1H), 7.95–7.92 (m, 4H), 7.91 (d, *J* = 2Hz, 1H), 7.59 (dd, *J* = 9.2 Hz, 2.8 Hz, 1H), 7.37–7.34 (m, 6H), 3.83 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{16}N_2O$ 313.1296 found 313.1295

6-bromo-2,3-diphenylquinoxaline (3i or 5j): Yellow solid; yield 94%; (Rf = 0.48 in hexanes/ EtOAc 95:05 v/v); MP 117-119 ^{O}C ; IR (KBr); 3040, 1588, 1542, 1466, 1442, 1390, 1318, 1182, 1060, 1022, 973, 914, 828, 764, 694 cm-^{1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.35 (s, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 6.8 Hz, 4H), 7.39–7.31 (m, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{13Br}N_2$ 361.0335 found 361.0334

6-chloro-2,3-diphenylquinoxaline (3j or 5l): White solid; yield 80%; (Rf = 0.46 in hexanes/ EtOAc 95:05 v/v); MP 118-120 ^{O}C ; IR (KBr): 3047, 1602, 1548, 1464, 1442, 1338, 1068, 828, 800, 764, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 1H), 7.90–7.64 (m, 5H), 7.60–7.34 (m. 6H), 2.77 (s, 3H), 2.48 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{16}N_2$ 317.0840 found 317.0841

2,3-di(furan-2-yl)-6-phenylquinoxaline (3k or 5o): White solid; yield 91%; (Rf = 0.55 in hexanes/ EtOAc 95:05 v/v); MP 131-133 ^{O}C; IR (KBr): 3356, 1614, 1538, 1438, 1081, 835, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.31 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.94 (t, *J* = 4 Hz, 1H), 7.92 (t, *J* = 3.6 Hz, 1H), 7.65-7.64 (m, 2H), 7.59 (dd, *J* = 7.2 Hz, 2.8 Hz, 2H), 7.39-7.34 (m, 1H), 7.17 (t, *J* = 9.6 Hz, 1H), 6.72-6.69 (m, 2H), 6.59-6.58 (m, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_{22}H_{14}N_2O_2$ 339.1088 found 339.1089

(naphthalen-2-yl)quinoxaline(4b); Yellow solid; yield 94%; (Rf = 0.60 in hexanes/ EtOAc 95:05 v/v); MP 136-138 ^{O}C; IR (KBr): 3038, 1546, 1488, 1306, 1196 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.47(s, 1H), 8.65 (s,1H), 8.37-8.34 (dd, *J* = 10.8 Hz, 2 Hz, 1H), 8.21-8.13 (m, 2H), 8.03-7.99 (m, 2H), 7.90 (t, *J* = 3.6 Hz, 1H), 7.82-7.73 (m, 2H), 7.54-7.50 (m, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_{18}H_{12}N_2$ 257.1072 found 257.1072

2-(m-tolyl)quinoxaline (4c) : Yellow solid; yield 94%; (Rf = 0.52 in hexanes/ EtOAc 95:05 v/v); MP 92-94 ^{O}C ; IR (KBr): 3054, 1612, 1542. 1308 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.33 (s, 1H), 8.19–8.13 (m, 2H), 8.04 (s, 1H), 7.97 (d, *J* = 8 Hz, 1H), 7.98–7.75 (m, 2H), 7.47 (t, *J* = 8 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 2.51 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{15}H_{12}N_2$ 221.1034 found 221.1034

2-(3-methoxyphenyl)quinoxaline (4d): Pale yellow solid; yield 92%; (Rf = 0.46 in hexanes/ EtOAc 95:05 v/v); MP 96-98 ^{O}C ; IR (KBr): 1604, 1539, 1442, 1186, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.32 (s, 1H), 8.18-8.11 (m, 2H), 7.81-7.73 (m, 4H), 7.47 (t, *J* = 8 Hz, 1H), 7.07 (dd, *J* = 10.4 Hz, 2 Hz, 1H), 3.94 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{15}H_{12}N_2O$ 237.0983 found 237.0982

2-(4-bromophenyl)quinoxaline (4e): Pale yellow solid; yield 94%; (Rf = 0.56 in hexanes/ EtOAc 95:05 v/v); MP 136-138 ^{O}C; IR (KBr): 1588, 1536, 1480, 1122, 1068, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.29 (s, 1H), 8.15-8.07 (m, 4H), 7.81-7.73 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_{14}H_{10}BrN_2O$ 285.0023 found 285.0022

2-(3,4-dichlorophenyl)quinoxaline (4f): Yellow solid; yield 90%; (Rf = 0.58 in hexanes/ EtOAc 95:05 v/v); MP 186-188 ^{O}C; IR (KBr): 1540, 1474, 1308, 1146, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.31 (s, 1H), 8.43 (s, 1H), 8.09 (t, *J* = 6 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.80–7.72 (m, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_{14}H_9Cl_2N_2$ 275.0135 found 275.0135

2-(4-nitrophenyl)quinoxaline (4g): Colorless solid; yield 92%; (Rf = 0.64 in hexanes/ EtOAc 95:05 v/v); MP 191-193 ^{O}C ; IR (KBr): 3056, 1529, 1352, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.11 (s, 1H), 8.40–8.37 (m, 4H), 8.21–7.84 (m , 2H), 7.83 (d, *J* = 8Hz, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_{14}H_9N_3O_2$ 252.0728 found 252.0727

4-(quinoxalin-2-yl)benzonitrile (4h): Pale yellow solid; yield 93%; (Rf = 0.60 in hexanes/ EtOAc 95:05 v/v); MP 114-116 ^{O}C ; IR (KBr): 3058, 2230, 1548, 1480, 1435, 1322, 1036; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.36 (s, 1H), 8.35 (d, *J* = 8.8 Hz, 2H), 8.19–8.15 (m, 2H), 7.88-7.80 (m, 4H); HRMS (ESI) $[M+H]^+$ calculated $C_{15}H_9N_3$ 232.0830 found 232.0831

2-(4-(trifluoromethyl) phenyl) quinoxaline (4i): Pale yellow solid; yield 92%; (Rf = 0.40 in hexanes/ EtOAc 95:05 v/v); MP 142-143 ^{O}C ; IR (KBr): 3036, 1545, 1488, 1315, 1120, 645, 554 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.33 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 2H), 8.12–8.10 (m, 2H), 7.88–7.76 (m, 4H); HRMS (ESI) $[M+H]^+$ calculated $C_{15}H_{10}N_2F_3$ 275.0796 found 275.0798

2-(pyridin-3-yl)quinoxaline (4j): White solid; yield 90%; (Rf = 0.44 in hexanes/ EtOAc 95:05 v/v); MP 110-112 ^{O}C; IR (KBr): 3052, 1612, 1588, 1542, 1491 1370, 1025, 1312; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.35 (s, 1H), 9.34 (s, 1H), 8.77 (dd, *J* = 6 Hz, 1.2 Hz, 1H), 8.54 (dt, *J* = 12.4 Hz, 2 Hz, 1H), 8.20–8.12 (m, 2H), 7.85–7.77 (m, 2H), 7.53 – 7.50

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(m, 1H); HRMS (ESI) $[M+H]^+$ calculated $C_{13}H_9N_3$ 208.0830 found 208.0832

2-(thiophen-2-yl) quinoxaline (4k): Pale yellow solid; yield 94%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); MP 116-118 ^{O}C; IR (KBr): 3120, 3056, 1546, 1424, 1328, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.16 (s, 1H), 8.08–7.87 (m, 2H), 7.78–7.68 (m, 3H), 7.58 (d, *J* = 4 Hz, 1H), 7.56 (dd, *J* = 6.4 Hz, 1.6 Hz, 1H); HRMS (ESI) $[M+H]^+$ calculated $C_{12}H_9N_2S$ 213.0483 found 213.0482

2-(furan-2-yl)quinoxaline (4l): Pale yellow solid; yield 93%; (Rf = 0.46 in hexanes/ EtOAc 95:05 v/v); MP 131-133 ^{O}C; IR (KBr): 3134, 3118, 1608, 1548, 1444, 1296, 1225, 1126, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.25 (s, 1H), 8.11-8.06 (m, 2H), 7.78-7.68 (m, 3H), 7.31 (d, *J* = 4 Hz, 1H), 6.63 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H); HRMS (ESI) $[M+H]^+$ calculated $C_{12}H_8N_20$ 197.0670 found 197.0672

6-bromo-2-(pyridin-3-yl)quinoxaline (Regio isomers) (4n): A mixture of two region-isomers (**1**) and (**2**), not separable by column chromatography, was obtained as white solid. The NMR spectra indicated that it is a mixture.White solid; yield 92%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); IR (KBr): 3066, 1608, 1548, 1490, 1318, 648 cm-^{1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.46 (s,1H), 9.38 (s, 1H), 8.83 (s, 1H), 8.57-8.56 (t, *J* = 3.6 Hz, 1H), 8.36 (t, *J* = 2 Hz, 1H), 8.08-8.03 (m, 1H), 7.94-7.88 (m, 1H), 7.58-7.54 (m, 1H)

2-([1,1'-biphenyl]-4-yl)quinoxaline (4o): Colorless solid; yield 95%; (Rf = 0.44 in hexanes/ EtOAc 95:05 v/v); MP 132-134 ^{O}C; IR (KBr): 3060, 1534, 1486, 1420, 1317, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.38 (s, 1H), 8.33 (d, *J* = 8Hz, 2H), 8.19–8.13 (m, 2H), 7.95 (t, *J* = 6.4 Hz, 2H), 7.83–7.75 (m, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.47–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.99, 142.96, 142.36, 141.81, 141.57, 14.50, 140.67, 136.70, 132.19, 130.72, 130.47, 130.01, 129.63, 129.04, 128.24, 127.90, 126.43, 125.83, 121.04, 119.17; HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{14}N_2$ 283.1190 found 283.1191

2-(2'-methylbiphenyl-4-yl)quinoxaline (4p) : White solid; yield 94%; (Rf = 0.46 in hexanes/ EtOAc 95:05 v/v); MP 128-130 ^{O}C; IR (KBr): 3065, 2910, 1560, 1480, 1415, 1312, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.39 (s, 1H), 8.26 (dd, *J* = 2 Hz, 8.4 Hz, 2H), 8.19-8.13 (m, 2H), 7.83-7.75 (m, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.32-7.29 (m, 4H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.7, 144.0, 143.3, 141.5, 141.0, 135.3, 135.2, 130.5, 130.1, 129.6, 129.5, 129.1, 127.6, 127.3, 125.9, 20.5; HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{16}N_2$ 297.1347 found 297.1346

2-(5'-fluoro-2'-methoxybiphenyl-4yl)quinoxaline (4q) : White solid; yield 92%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); MP 134-136^{O}C ; IR (KBr): 3058, 2858, 1528, 1482, 1418, 1145, 1315, 1052, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.38 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 2H), 8.19-8.12 (m, 2H), 7.82-7.77 (m, 2H), 7.76-7.72 (m, 2H), 7.13 (dd, *J* = 2.8 Hz, 8.8 Hz, 1H), 7.07-6.93 (m, 2H), 3.8 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.3, 155.9, 152.7, 151.5, 143.3, 142.3, 141.5, 139.4, 135.6, 130.3, 130.1, 129.6, 129.5, 129.1, 127.2, 56.2; HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{16}N_2$ 331.1202 found 331.1201

2-(2'-ethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)quinoxaline (4r): White solid; yield 92%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); MP 136-138 ^{O}C ; IR (KBr): 3052, 2890, 1532, 1483, 1427, 1319, 1055, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.37 (s, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 8.15 (d, *J* =6.8 Hz, 2H), 8.14–8.05 (m, 2H), 8.04 (d, *J* = 8 Hz, 2H), 7.81–7.31 (m, 3H), 7.05 (dd, *J* = 11.6 Hz, 2.8 Hz, 1H), 3.99 (q, *J* = 16 Hz, 7.2 Hz, 2H), 1.58 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz); 157.47, 152.02, 141.81, 141.57, 140.67, 136.50, 132.29, 130.89, 130.47, 129.04, 128.24, 127.90, 126.53, 125.73, 121.04, 114.27, 110.08, 68.64, 15.47; HRMS (ESI) $[M+H]^+$ calculated $C_{22}H_{17}FN_2O$ 345.1358 found 345.1356

2-(2'-chloro-[1,1'-biphenyl]-4-yl)quinoxaline (4s): White solid; yield 93%; (Rf = 0.50 in hexanes/ EtOAc 95:05 v/v); MP 133-135 ^{O}C; IR (KBr): 3052, 1528, 1480, 1476, 1416, 1312, 1051, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.37 (s, 1H), 8.27 (d, *J* = 12 Hz, 2H), 8.17–8.11 (m, 2H), 7.77 (m, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.40–7.29 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ = 151.4, 143.2, 142.3, 141.6, 141.3, 139.7, 136.0, 132.5, 131.2, 130.2, 130.0, 129.6, 129.5, 129.1, 128.9, 127.2, 126.9; HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{13}ClN_2$ 318.0737 found 318.0738

2-(2'-chloro-5'-fluorobiphenyl-4-yl)quinoxaline (4t) : White solid; yield 90%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); MP 141-143 ^{O}C ; IR (KBr): 3060, 1532, 1484, 1416, 1316, 1050, 734, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.37 (s, 1H), 8.26 (dd, *J* = 2 Hz, 8.8 Hz, 2H), 8.18-8.12 (m, 2H), 7.81-7.72 (m, 2H), 7.13 (dd, *J* = 2.8 Hz, 12 Hz, 1H), 7.06-7.02 (m, 1H), 6.94 (dd, *J* = 4 Hz, 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.3, 155.9, 152.7, 151.52, 143.3, 141.5, 139.4, 135.6, 130.3, 130.2, 129.6, 129.5, 129.1, 127.2; HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{12}ClFN_2$ 336.0643 found 336.0643

2-(3'-(methylsulfonyl) biphenyl-4-yl) quinoxaline (4u): Pale yellow solid; yield 95%; (Rf = 0.48 in hexanes/ EtOAc 95:05 v/v); MP 137-139 ^{O}C ; IR (KBr): 3062, 2886, 1530, 1488, 1414, 1317,1112, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.39 (s, 1H), 8.34 (d, *J* = 8.8 Hz, 2H), 8.24 (t, *J* = 4 Hz, 1H), 8.21-8.14 (m, 2H), 7.99-7.95 (m, 2H), 7.83 (d, *J* = 8 Hz, 2H), 7.81-7.78 (m, 2H), 7.71 (t, *J* = 12 Hz, 1H), 7.48-7.40 (m, 2H), 3.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.9, 151.0, 143.0, 142.3, 141.7, 140.6, 136.6, 132.2, 130.7, 129.0, 128.2, 127.9, 126.4, 125.8, 121.1, 44.5; HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{16}N_2O_2S$ 361.0966 found 361.0965

4'-(quinoxalin-2-yl)-[1,1'-biphenyl]-3-carbonitrile (4v): White solid; yield 90%; (Rf = 0.46 in hexanes/ EtOAc 95:05 v/v); MP 129-131 ^{O}C ; IR (KBr): 3056, 2228, 1531, 1482, 1417, 1319, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 9.57 (s, 1H), 9.37 (s, 1H), 9.21 (s, 1H), 8.50 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 2H), 8.18–8.12 (m, 2H), 7.79 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.6, 162.2, 150.9, 145.9, 145.9, 145.84, 142.3, 141.6, 139.7, 139.6, 138.3, 136.5, 134.0, 130.4, 129.6, 128.2, 115.6, 109.8, 109.4; HRMS (ESI) $[M+H]^+$ calculated $C_{21}H_{13}N_2$ 308.1143 found 308.1144

2-(4-(pyridin-4-yl)phenyl)quinoxaline (4w) : White solid; yield 91%; (Rf = 0.44 in hexanes/ EtOAc 95:05 v/v); MP 138-140 ^{O}C ; IR (KBr): 3056, 1529, 1486, 1418, 1315, 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.39 (s, 1H), 8.7 (d, *J* = 7.2 Hz, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.36 (dt, *J* = 2 Hz, 8.8 Hz, 2H), 8.20-8.14 (m, 2H), 7.83 (dd, *J* = 1.6 Hz, 8.4 Hz, 1H), 7.82–7.76 (m, 4H), 7.68 (dt, *J* = 2.8 Hz, 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.8, 144.0, 143.0, 142.32, 141.7, 138.0, 137.0, 130.4, 129.6, 129.1, 128.3, 127.9, 121.1, 120.9; HRMS (ESI) $[M+H]^+$ calculated $C_{19}H_{13}N_3$ 284.1143 found 284.1142

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2-(4-(5-fluoropyridin-3-yl)phenyl)quinoxaline (4x): White solid; yield 90%; (Rf = 0.46 in hexanes/ EtOAc 95:05 v/v); MP 139-141 ^{O}C ; IR (KBr): 3056, 1528, 1489, 1413, 1316, 1048, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.38 (s,1H), 8.52 (d, *J* = 2 Hz, 1H)), 8.34 (d, *J* = 8.4 Hz, 2H), 8.20-8.13 (m, 2H), 8.09-8.05 (m, 1H), 7.84-7.78 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 3.2 Hz, 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 150.9, 145.9, 145.8, 143.0, 141.6, 139.3, 136.5, 134.0, 130.5, 129.6, 129.1, 128.1, 128.2, 127.7, 109.8, 109.5; HRMS (ESI) $[M+H]^+$ calculated $C_{19}H_{12}FN_3$ 302.1048 found 302.1047

2,3-bis(4-methoxyphenyl)quinoxaline (5b): White solid; yield 96%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); MP 146-148 ^{O}C ; IR (KBr): 3008, 2964, 2842, 1604, 1508, 1460, 1392, 1346, 1286, 1240, 1172, 1024, 828, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz,): δ = 8.14–7.91 (m, 2H), 7.6–7.37 (m, 3H), 7.34 (d, *J* = 8.4 Hz, 4H), 7.33 (d, *J* = 7.2 Hz, 4H), 3.82 (s, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{22}H_{18}N_20_2$ 343.1441 found 343.1440

2-methyl-3-phenylquinoxaline (5d): White solid; yield 92%; (Rf = 0.44 in hexanes/ EtOAc 95:05 v/v); MP 54-56 ^{O}C ; IR (KBr): 3122, 1510, 1461, 1318, 1054, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.25–8.11 (m, 2H), 7.73–7.17 (m, 4H), 7.5–7.51 (m, 3H), 2.73 (s, 3H); HRMS (ESI) $[M+H]^+$ calculated $C_{15}H_{12}N_2$ 221.1034 found 221.1033

quinoxaline (5e): White solid; yield 90%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); MP 30-32 ^{O}C ; IR (KBr); 1498, 1364, 1202, 1128, 1028, 956 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.82 (s, 2H), 8.12 (d, *J* = 8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_8H_6N_2$ 131.0564 found 131.0565

2-(4-chlorophenyl)-3-phenylquinoxaline (5f): White solid; yield 94%; (Rf = 0.40 in hexanes/ EtOAc 95:05 v/v); MP 135-137 ^{O}C ; IR (KBr): 3058, 2926, 1724, 1588, 1490, 1472, 1440, 1398,1342, 1087, 1056, 1012, 966, 848, 806, 760, 696 cm-^{1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.20-8.13 (m, 2H), 8.09–8.07 (m, 2H), 8.05–7.82 (m, 4H), 7.80–7.78 (m, 3H), 7.75 (d, *J* = 8.4 Hz, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{13}Cl_2N_2$ 317.0840 found 317.0841

2,3-bis(4-methoxyphenyl)-6,7-dimethylquinoxaline (5h): Yellow solid; yield 95%; (Rf = 0.42 in hexanes/ EtOAc 95:05 v/v); MP 122-124 ^{O}C ; IR (KBr): 2930, 2833, 1603, 1508, 1455, 1417, 1340, 1298, 1172, 1023, 965, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 2H), 7.60 (d, *J* = 8.4 Hz, 4H), 7.10 (d, *J* = 7.6 Hz, 4H), 3.92 (s, 6H), 2.42 (s, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{24}H_{22}Cl_2N_2O_2$ 371.1754 found 371.1754

6-bromo-2,3-di(furan-2-yl)quinoxaline (5k) : White solid; yield 96%; (Rf = 0.54 in hexanes/ EtOAc 95:05 v/v); MP 132–134 ^{O}C; IR (KBr): 3359, 1541, 1428, 1071, 835, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.36 (d, *J* = 1.6 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 2.4 Hz, 2.4 Hz, 1H), 7.68 (t, *J* = 1.6 Hz, 2H), 6.76–6.75 (m, 2H), 6.63-6.61 (m.2H); HRMS (ESI) $[M+H]^+$ calculated $C_{16}H_9BrN_2O_2$ 341.9826 found 341.9824

6-chloro-7-fluoro-2,3-diphenylquinoxaline (5m): White solid; yield 94%; (Rf = 0.58 in hexanes/ EtOAc 95:05 v/v); MP 158-160 ^{O}C; IR (KBr): 3418, 1466, 1344, 1216, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.80–7.28 (m, 4H), 7.14–7.01 (m, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{12}Cl_2N_2FCl$ 335.0746 found 335.0748

6-nitro-2,3-diphenylquinoxaline (5n): Yellow solid; yield 95%; (Rf = 0.52 in hexanes/ EtOAc 95:05 v/v); MP 183-185 ^{O}C; IR (KBr): 3080, 3057, 1612, 1518, 1398, 1340, 1054, 1023, 810, 767, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.08 (d, *J* = 2.4 Hz, 1H), 8.54 (dd, *J* = 11.6 Hz, 2.4 Hz, 1H), 8.30 (d, *J* = 9.2 Hz, 1H), 7.58–7.54 (m, 4H), 7.43–7.36 (m, 6H); HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{13}Cl_2N_3O_2$ 328.1081 found 328.1082

2,3-diphenyl-4a,5,6,7,8,8a-hexahydroquinoxaline (5p): White solid; yield 90%; (Rf = 0.48 in hexanes/ EtOAc 95:05 v/v); MP 171–176 ^{O}C; IR (KBr): 3048, 2936, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.55-7.49 (m, 4H), 7.28-7.20 (m, 6H), 2.84 (t, *J* = 9.2 Hz, 2H), 2.50 (d, *J* = 13.6 Hz, 2H), 1.89 (d, *J* = 9.2 Hz, 2H), 1.64–1.62 (m, 2H), 1.47-1.39 (m, 2H); HRMS (ESI) $[M+H]^+$ calculated $C_{20}H_{20}N_2$ 289.1660 found 289.1661

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One-step Approach for Synthesis of Functionalized Quinoxalines Mediated by T3P® - DMSO or T3P® via Tandem Oxidation – Condensation or Condensation Reaction

Kachigere B. Harsha,[a#] Kanchugarkoppal S. Rangappa.[a]*