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Efficient synthesis of quinoxalines with hypervalent iodine as a catalyst

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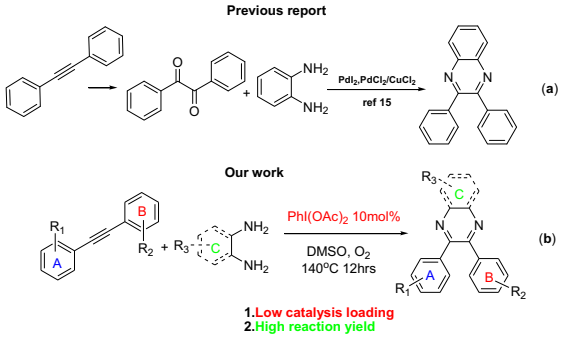
ABSTRACT

Various biologically important quinoxalines were efficiently synthesized in excellent yields via one-pot reaction between 1,2-diaminobenzenes and internal alkynes. The method utilizes inexpensive and readily available hypervalent iodine source, such as (diacetoxyiodo)benzene ($PhI(OAc)_2$) and proved to be a better alternative as compared to expensive transition metal catalysts. Quinoxaline **4i** [(2-phenyl-3-(3,4,5-trimethoxy phenyl)quinoxaline)] was evaluated for leukemia cancer cell lines and turned out to be a good candidate.

1. Introduction

Diversely substituted quinoxalines are important biological agents and therefore a significant development of research has been directed towards the synthesis of this class of compounds.[1] In particular, they are used as anti-tumor,[2] antibacterial,[3] antifungal,[4] antiviral,[5] anti-inflammatory,[6] anti-tubercular,[7] anticonvulsant,[8] antimalarial,[9] antileishanial,[10] and trypanocidal[11] agents. A number of reliable synthetic strategies have been developed in the recent past for the synthesis of various substituted quinoxalines[12,13] The most common method is the condensation of 1,2-diamino benzenes with 1,2-dicarbonyl compounds.[14] However, most of these methods suffer from harsh reaction conditions, tedious isolation procedures, and unsatisfactory yields. Moreover, recent report of one-pot strategy has been developed to construct quinoxalines from internal alkyne with 1,2-diaminobenzene using expensive metal catalysts, such as PdI_2 or $PdCl_2/CuCl_2$ (Scheme 1a).[15] Therefore, these disadvantages and the cost effectiveness of the methodology brought us an attention to develop an affordable alternative catalyst system for this conversion.



Scheme 1. Synthesis of 2,3-diphenylquinoxaline derivatives.

In recent years, hypervalent iodine reagents have received considerable attention due to their low toxicity, ready availability, easy handling, and reactivity similar to those of heavy metal reagents.[16]

To the best of our knowledge, there is no literature precedence to synthesize quinoxaline derivatives in one-pot using hypervalent iodine as a catalyst. Herein we report a novel one-pot transition metal free approach to construct quinoxaline derivatives with high structural diversity using $PhI(OAc)_2$ as a catalyst under mild reaction condition. Mechanistically, the 1,2-diketo compound

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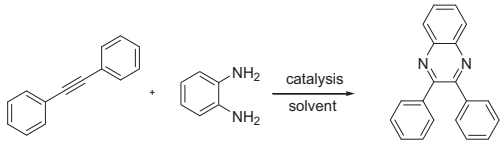
would be generated in situ from internal alkynes in the presence of hypervalent iodine reagent and the subsequent reaction with 1,2-diaminobenzenes leading to the formation of target product in one-pot fashion (Scheme 1b).

2. Results and discussion

At first, we initiated the optimization of reaction conditions with the model substrates of alkyne **1a** and diaminobenzene **2a** to furnish the corresponding product **4a**. The effect of various oxidants, additives at different temperature was studied and the results are summarized in Table 1. The reaction of alkyne **1a** with diaminobenzene **2a** was carried out using stoichiometric amounts of different oxidants viz., $PhI(OAc)_2$, $KMnO_4$, and CAN in the presence of an additive PivOH in DMSO at room temperature (entries 1–3). The use of $PhI(OAc)_2$ afforded the desired compound **4a** in 27% yield (entry 1); whereas, $KMnO_4$ and ceric (IV) ammonium nitrate (CAN) did not produce the desired product (entries 2 and 3). We thought if iodine coupled with an oxidizing reagent might exhibit anticipated product. We, therefore tested the reaction using stoichiometric amounts of *N*-iodosuccinamide (a mild source of molecular iodine) ICl and PIFA (phenyliodine bis(trifluoroacetate)), which produced the required product in low yields (entries 4–6). Further studies were conducted with $PhI(OAc)_2$ at elevated temperatures and the formation of compound **4a** was obtained in 93% yield (entry 7). Furthermore, the reaction of **1a** and **2a** in the presence of $KMnO_4$ and CAN at 140 °C was unsuccessful in generating the desired product (entries 8 and 9). When the reaction was carried out at 140 °C with ICl, NIS, and PIFA produced the desired product in 51%, 77%, and 60%, respectively (entries 10–12). The stoichiometric amount of $PhI(OAc)_2$ afforded the desired compound **4a** in 39% yield when AcOH was used as an additive (entry 13). Among various solvents used to check the feasibility of the reaction, (entries 14–17) DMSO was found to be the better solvent to obtain the desired product in excellent yield (entry 7).

Table 1
Optimization of reaction conditions to synthesize compound **4a**[a]



1a **2a** **4a**

Entry	Catalysis	Solvent	Additive	*T* (°C)	Yield[b]
1	$PhI(OAc)_2$	DMSO	PivOH	rt	**4a**, 27%
2	$KMnO_4$	DMSO	PivOH	rt	n.r.
3	CAN	DMSO	PivOH	rt	n.r.
4	NIS	DMSO	PivOH	rt	**4a**, 13%
5	ICl	DMSO	PivOH	rt	**4a**, 21%
6	PIFA	DMSO	PivOH	rt	n.r.
7	$PhI(OAc)_2$	DMSO	PivOH	140 °C	**4a**, 93%
8	$KMnO_4$	DMSO	PivOH	140 °C	n.r.
9	CAN	DMSO	PivOH	140 °C	Trace
10	NIS	DMSO	PivOH	140 °C	**4a**, 51%
11	ICl	DMSO	PivOH	140 °C	**4a**, 77%
12	PIFA	DMSO	PivOH	140 °C	**4a**, 6%
13	$PhI(OAc)_2$	DMSO	AcOH	140 °C	**4a**, 39%
14	$PhI(OAc)_2$	DMF	PivOH	140 °C	**4a**, 33%
15	$PhI(OAc)_2$	MeCN	PivOH	140 °C	n.r.
16	$PhI(OAc)_2$	PhCl	PivOH	140 °C	n.r.
17	$PhI(OAc)_2$	$CHCl_3$	PivOH	140 °C	n.r.
18	$PhI(OAc)_2$	DMSO	PivOH	100 °C	**4a**, 60%
19[c]	$PhI(OAc)_2$	DMSO	PivOH	140 °C	**4a**, 88%
20[d]	**$PhI(OAc)_2$**	**DMSO**	**PivOH**	**140 °C**	**4a, 90%**
21[e]	$PhI(OAc)_2$	DMSO	PivOH	140 °C	**4a**, 67%
22[f]	$PhI(OAc)_2$	DMSO	PivOH	140 °C	**4a**, 63%
23[g]	$PhI(OAc)_2$	DMSO	PivOH	140 °C	**4a**, 11%

The bold value signifies the reaction condition described in entry **20** (10 mol % of $PhI(OAc)_2$ in DMSO) and can be considered as a standard protocol for this transformation.

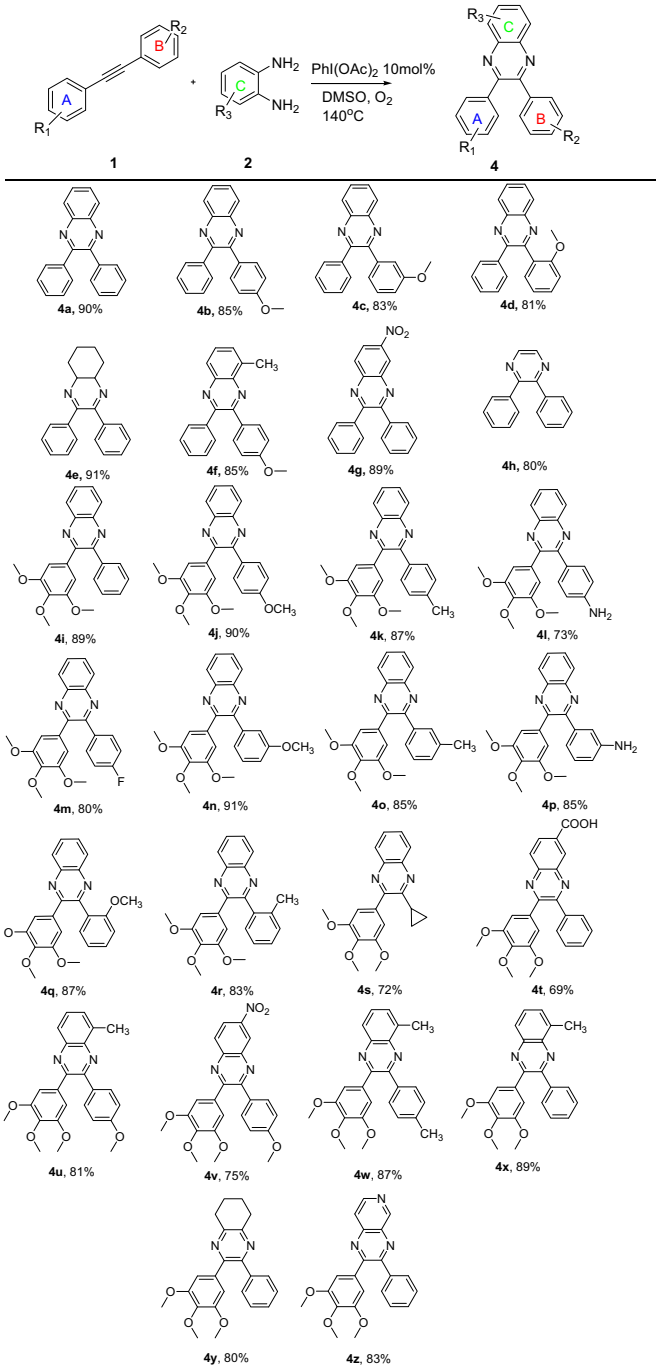
[a] Reactions were performed with **1a** (1.0 mmol), oxidant (1.0 mmol), additive (3.0 mmol), solvent (5 ml) at 140 °C under 1 atm O_2 for 12 h.
[b] Isolated yield.
[c] Catalysis (50 mol %).
[d] Catalysis (10 mol %).
[e] Catalysis (5 mol %).
[f] Under air.
[g] Under N_2.

Since the reaction was successful with stoichiometric amount of $PhI(OAc)_2$, our next efforts were devoted for making this reaction catalytic in nature. Interestingly, it was found that the loading of $PhI(OAc)_2$ had an important effect on reaction yield at different concentrations. Thus, the product **4a** was obtained in 89% yield, when 50 mol % of $PhI(OAc)_2$ was used. Even 10 mol % of $PhI(OAc)_2$ worked well to furnish **4a** in 90% yield (entries 19 and 20). However, further decrease in the catalyst loading to 5 mol % has an adverse effect on the reaction yield of **4a** (67%, entry 21). The effect of O_2 also had a significant effect on reaction yield. Thus, the formation of product in 63% and 11% was obtained under air and N_2, respectively (entries 22 and 23). Therefore, the reaction condition described in entry 20 (10 mol % of $PhI(OAc)_2$ in DMSO) can be considered as a standard protocol for this transformation.

With the optimized reaction conditions, we have studied the reaction scope and limitations. Various 1,2-diaminobenzenes and internal alkynes (Fig. 1) were selected to execute this one-pot approach for the synthesis of wide range of quinoxalines bearing various substituents, including electron-withdrawing and electron-donating on the aromatic core moiety of compounds **4a**–**g**. Non aromatic diamines, such as *cis*-1,2-ethyldiamine also underwent smooth conversion under the standard reaction condition afforded the corresponding substituted pyrazine **4h** in good yield. The cyclization reactions proceeded smoothly irrespective of the electron-donating or electron-withdrawing substituents at R_2 and R_3 along with the ring **A** bearing 3,4,5-trimethoxy groups to furnish products **4i**–**z** in moderate to good yields. These products (**4i**–**z**) were made with this strategy because the structural activity relationship of Combretastatin A4 (CA-4)[17] indicates that the presence of the 3,4,5-trimethoxy phenyl group is fundamental for antitubulin and its anticancer activity (vide infra). It is remarkable that the aryl fluorinated product **4m** was a compatible substrate given its important synthetic application since it could be further functionalized via metal-catalyzed cross-coupling reactions. We were delighted to observe that the replacement of ring **B** with cyclopropane also worked well under the standard conditions to afford corresponding product **4s** in 72% yield. Our additional attempts to expand the scope of our methodology by replacing 1,2-diamino benzenes with cyclohexyl- and pyridinyl diamino compounds was successful to produce various quinoxaline analogues (**4e** and **4y**) and pyrido–pyrazine derivative **4z** in moderate to good yields. The structure of **4i** was unambiguously confirmed by single crystal X-ray analysis (Fig. 2).

We could also able to construct bis-quinoxaline skeleton from 1,4-bis(phenylethynyl)benzene **5** and 1,2-diaminobenzene **2a** to furnish 1,4-bis(3-phenylquinoxalin-2-yl)benzene (**6**) in 88% yield (Scheme 2).

In order to gain insight into the reaction mechanism, we carried out few control experiments. Initially, we performed a reaction between diphenylacetylene **1a** and diaminobenzene **2a** in presence of PIDA (10 mol %) and PivOH in DMSO for 6 h. We observed the formation of **4a** as a major product and the benzil product **3** as a minor component (Scheme 3, reaction **A**). Formation of the benzil product **3** was further evidenced by performing a control experiment with alkyne **1a** in the absence of diaminobenzene **2a** (Scheme 3, reaction **B**). Based on these observations, we confirmed that the benzil product **3** might be an intermediate during this transformation. Based on the previous literature,[18] we envision that the



[a]Reactions were performed with **1** (1.0 mmol), **2** (1.0mmol), $PhI(OAc)_2$ (10 mol%) and PivOH (3.0 mmol) in DMSO (5 ml) at 140°C under O_2.[b] Isolated yield.

Fig. 1. The series of quinoxaline derivatives.[a,b]

iodobenzene might be a byproduct during the reaction. To our delight, when 30 mol % iodobenzene was used instead of PIDA, desired compound **4a** was obtained in 75% yield (Scheme 3, reaction **C**). Furthermore, in absence of PivOH the reaction was unsuccessful (Scheme 3, reaction **D**).

Based on our observations and previous literature reports,[15a,19] a plausible mechanism was outlined in Scheme 4. Initially formed $PhI(OPiv)_2$ from PIDA and PivOH[20] react with compound **1a** to produce oxidized compound **3** with the expulsion of iodobenzene. The compound **3** will then undergo subsequent condensation with 1,2-diaminobenzene to afford desired compound **3a**. The

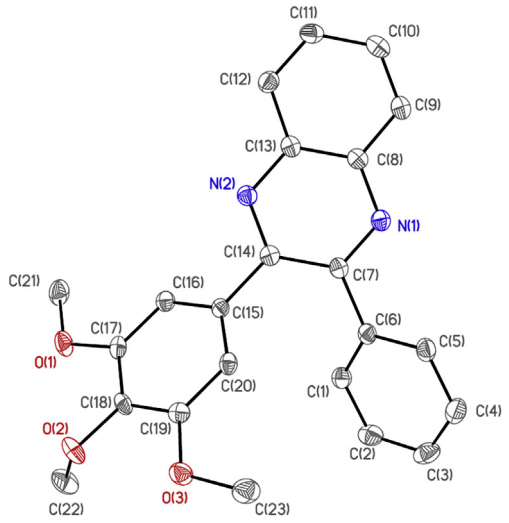
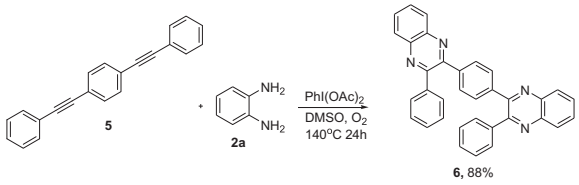
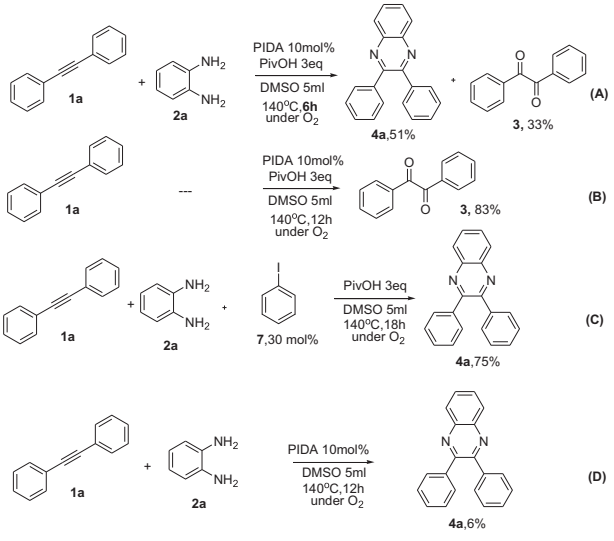


Fig. 2. ORTEP diagram of **4i**.

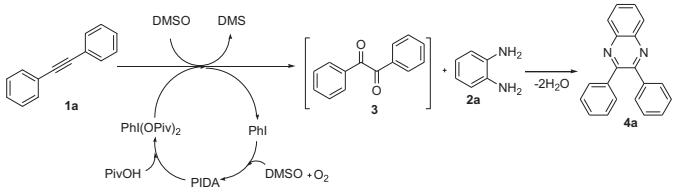


[a]Reaction were performed with **5** (1.0 mmol), **2a** (2.0 mmol), $PhI(OAc)_2$ (0.1 mmol), PivOH (3.0 mmol), DMSO (5 ml) at 140°C under O_2 for 24hrs.[b] Isolated yield.

Scheme 2. Synthesis of bis-quinoxaline derivative.[a,b]



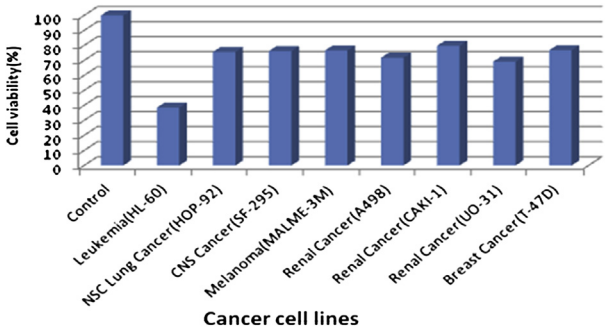
Scheme 3. Control experiments.



Scheme 4. Proposed reaction mechanism for the PIDA-promoted construction of quinoxaline.

iodobenzene will then undergo oxidation[18] in presence of oxygen in DMSO followed by the reaction with pivalic acid to regenerate $PhI(OPiv)_2$ in the catalytic cycle.

After examining scope and limitation of this method we thought of evaluating the biological potential of the synthesized quinoxaline products. In particular, we have chosen **4i** as a model substrate for evaluating its activity against various cancel lines because of its structural similarity with CA-4. Since the cis configuration[21] of the olefinic bridge and the presence of 3,4,5-trimethoxy phenyl group at ring **A** are fundamental for anti-tubulin activity,[22] we envisioned compound **4i** would serve as a potential candidate. Accordingly, **4i** was submitted to NCI for screening against 60 cancer cell lines. Indeed, the compound showed promising results with leukemia cancer cell lines (HL-60) in a highly selective manner (Fig. 3).



[a] Cells were cultured with agents at a concentration of 10μ M for 24 h before growth and viability were assessed using the MTT assay.
[b] NSC Lung cancer= Non-small cell lung cancer.

Fig. 3. NCI screening against human cancer cell line.[a,b]

3. Conclusion

In conclusion, we described a simple, efficient, and one-pot methodology for the synthesis of quinoxaline analogues from various internal alkynes and 1,2-diaminobenzenes using inexpensive and readily available $PhI(OAc)_2$ as an oxidant. High reaction rates, excellent product yields, and easy work up procedures made this methodology as an alternative platform to replace the conventional transition metal catalyzed processes. Biological evaluation was carried out for the compound **4i** against 60 cancer cell lines, which showed promising results with leukemia cancer (HL-60). This study exhibited that proper structure–activity relationship studies of this structure might generate a compound useful for therapeutic applications. Further biological work is in progress and will be reported in due course.

4. Experimental section

4.1. General experimental procedures

$PhI(OAc)_2$ oxidant annulation reactions were performed in mild condition. All other reactions, unless otherwise indicated, were carried out under ambient atmosphere in single-neck, round bottom flasks fitted with a stopcock or condenser, equipped with a magnetic stir bar. Air- or water- sensitive solvents were transferred via syringe. When required, solvents were degassed by bubbling of nitrogen through a needle. Organic solutions were concentrated by rotary evaporation at 25–40 °C under reduced pressure (15–30 Torr, house vacuum). Analytical Thin Layer Chromatography (TLC) was performed using pre-coated UV 254 plates (0.2 mm) from EM Separations. Visualization of the spots was rendered visible either by shining with a 254 nm UV light source, or by charring the plates with potassium permanganate ($KMnO_4$) or anisaldehyde solutions.

4.2. Instrumentation

^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. ^1H NMR chemical shifts are referenced to TMS or $CDCl_3$ (0; 7.26 ppm). ^{13}C NMR was referenced to $CDCl_3$ (77.0 ppm). Mass spectra and high-resolution mass spectra (HRMS) were measured using the Electrospray Ionization (ESI, 70 eV, ion trap) technique. Flash chromatography was carried out on silica gel 60 (40–63 mesh). Spectral data are represented in the following order: chemical shift; multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, td=triplet of doublets, m=multiplet); coupling constant (*J*, Hertz); number of protons.

4.3. Materials

Unless otherwise noted, all reagents, and catalysts were purchased from commercial sources. Dimethyl sulfoxide was purified by distillation under nitrogen immediately prior to use. All other solvents were used as supplied without further purification.

4.4. General procedure for the synthesis of quinoxaline derivatives

The starting material 1,2-diphenylalkyne derivatives (1.0 mmol) was dissolved in dry dimethyl sulfoxide (DMSO, 5 ml), followed by 10 mol % of $PhI(OAc)_2$, then the 1,2-diaminobenzene derivatives (1.0 mmol) were charged to the reaction mixture and stirred at 140 °C for 8–24 h under O_2. Reaction was monitored by TLC and the reaction mixture was poured into a rapidly stirred ice cooled saturated $NaHCO_3$ solution (10 ml) and the aqueous phase was extracted with ethylacetate (2×200 ml), and the combined organic layers were washed with water (2×200 ml), brine (1×200 ml) and dried over Na_2SO_4, filtered and the volatiles were removed under reduced pressure. The product was purified by column chromatography over silica gel 40–63 mesh (gradient eluent ethylacetate/hexane). Purified quinoxaline derivatives **4a**–**z**, **6** (yield 69–91%).

*4.4.1. 2,3-Diphenylquinoxaline (**4a**).*[23] The title compound was prepared according to the general procedure and purified by column chromatography to obtain a white solid 142.6 mg (90%). Mp=125–128 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.19 (d, *J*=7.2 Hz, 2H), 7.79 (d, *J*=7.2 Hz, 2H), 7.53 (d, *J*=7.6, 1.6 Hz, 4H), 7.38–7.31 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 153.4 (2C), 141.2 (2C), 139.0 (2C), 129.9 (2C), 129.8 (4C), 129.1 (2C), 128.7 (2C), 128.2 (4C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{15}N_2$ 283.1230; found 283.1234.

*4.4.2. 2-(4-Methoxyphenyl)-3-phenylquinoxaline (**4b**).*[24] The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid 127.4 mg (85%). Mp=120–122 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.02 (d, *J*=7.2 Hz, 2H), 7.58 (d, *J*=7.2 Hz, 2H), 7.42–7.40 (m, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.21–7.20 (m, 3H), 6.71 (d, *J*=8.8 Hz, 2H), 3.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 160.4, 153.6 (2C), 153.2, 141.2 (2C), 139.6, 131.9, 131.6, 131.6, 130.1, 130.0, 129.8, 129.3, 129.2, 129.0, 128.5 (2C), 113.9 (2C), 55.5. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ $C_{21}H_{17}N_2O$ 313.1335; found 313.1344.

*4.4.3. 2-(3-Methoxyphenyl)-3-phenylquinoxaline (**4c**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a colorless oil 124.4 mg (83%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.09 (d, *J*=7.2 Hz, 2H), 7.66 (d, *J*=7.2 Hz, 2H), 7.44–7.42 (m, 2H), 7.25–7.23 (m, 3H), 7.12 (t, *J*=8.0 Hz, 1H), 6.99–6.97 (m, 2H), 6.81 (d, *J*=8.0 Hz, 1H), 3.57

(s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 159.2, 153.1 (2C), 141.1, 141.0, 140.1 (2C), 139.0 (2C), 129.9, 129.8, 129.6 (2C), 129.2, 129.0, 128.7, 128.1, 122.3, 115.1, 114.7, 55.1. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{17}N_2O$ 313.1335; found 313.1340.

*4.4.4. 2-(2-Methoxyphenyl)-3-phenylquinoxaline (**4d**).*[25] The title compound was prepared according to the general procedure and purified by column chromatography to obtain a white solid 121.4 mg (81%) Mp=91–95 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.20 (d, *J*=7.2 Hz, 2H), 7.76 (d, *J*=7.2 Hz, 2H), 7.66 (dd, *J*=7.6, 2.0 Hz, 1H), 7.50–7.47 (m, 2H), 7.39 (t, *J*=8.2 Hz, 1H), 7.28–7.25 (m, 3H), 7.13 (t, *J*=8.0 Hz, 1H), 6.70 (d, *J*=8.4 Hz, 1H), 3.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 156.3, 154.6, 152.2 (2C), 141.2, 141.1, 139.1, 130.9, 130.6, 129.6, 129.4, 129.1, 129.0, 128.7, 128.5, 128.3, 127.6 (2C), 121.2, 110.9, 54.6. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{17}N_2O$ 313.1335; found 313.1342.

*4.4.5. 2,3-Diphenyl-4a,5,6,7,8,8a-hexahydroquinoxaline (**4e**).*[26] The title compound was prepared according to the general procedure and purified by column chromatography to obtain a white solid 147.2 mg (91%). Mp=170–176 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.40 (d, *J*=6.0 Hz, 4H), 7.25 (d, *J*=2.8 Hz, 4H), 7.24 (t, *J*=1.2 Hz, 2H), 3.05–3.04 (m, 4H), 1.96–1.95 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 150.3 (2C), 149.3 (2C), 138.8 (2C), 129.4 (4C), 128.0 (4C), 127.9 (2C), 31.6 (2C), 22.6 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{19}N_2$ 287.1543; found 287.1548.

*4.4.6. 3-(4-Methoxyphenyl)-5-methyl-2-phenylquinoxaline (**4f**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a colorless oil 133.2 mg (85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.88 (d, *J*=8.4 Hz, 1H), 7.52–7.49 (m, 2H), 7.48–7.37 (m, 5H), 7.27–7.23 (m, 2H), 6.76–6.73 (m, 2H), 3.70 (s, 3H), 2.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C. 160.0, 152.6, 151.2, 140.8, 140.0, 139.6 (2C), 137.3 (2C), 131.6, 131.5, 131.2, 129.9, 129.6, 129.4 (2C), 126.8 (2C), 113.5 (2C), 55.2, 17.0. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{19}N_2O$ 327.1492; found 327.1498.

*4.4.7. 6-Nitro-2,3-diphenylquinoxaline (**4g**).*[27] The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light brown solid 163.4 mg (89%). Mp=190–196 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.97 (s, 1H), 8.43 (d, *J*=9.2 Hz, 1H), 8.23 (m, *J*=8.8 Hz, 1H), 7.55–7.52 (m, 4H), 7.39 (dt, *J*=7.2, 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 155.9, 155.3, 147.5, 143.2, 139.6, 137.8, 137.7, 130.5 (2C), 129.7, 129.6, 129.5, 129.4, 129.1, 128.4, 128.2, 127.8 (2C), 125.3, 122.9. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{14}N_3O_2$ 328.1081; found 328.1083.

*4.4.8. 2,3-Diphenylpyrazine (**4h**).*[28] The title compound was prepared according to the general procedure and purified by column chromatography to obtain a white solid 104.2 mg (80%). Mp=120–122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.58 (s, 2H), 7.46–7.43 (m, 4H), 7.33 (dt, *J*=7.2, 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 152.6 (2C), 141.9 (2C), 138.4 (2C), 129.5 (4C), 128.5 (4C), 128.1 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{13}N_2$ 233.1073; found 233.1081.

*4.4.9. 2-Phenyl-3-(3,4,5-trimethoxyphenyl)quinoxaline (**4i**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow solid 123.5 mg (89%). Mp=150–152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.19 (d, *J*=7.2 Hz, 2H), 7.78 (d, *J*=7.2 Hz, 2H), 7.55 (d, *J*=3.2 Hz, 2H), 7.38–7.37 (m, 3H), 6.76 (s, 2H), 3.85 (s, 3H), 3.67 (s, 6H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 153.7 (2C), 152.8 (2C), 141.1, 141.0, 139.3, 138.7, 133.8, 130.0 (2C), 129.9, 129.5, 129.1, 129.0, 128.7 (2C), 128.3, 107.6 (2C), 61.1, 55.8 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{21}N_2O_3$ 373.1474; found 373.1553.

*4.4.10. 2-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)quinoxaline (**4j**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow solid 121.4 mg (90%). Mp=114–118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.16 (d, *J*=7.2 Hz, 2H), 7.76 (d, *J*=7.2 Hz, 2H), 7.48 (d, *J*=8.8 Hz, 2H), 6.88 (d, *J*=9.2 Hz, 2H), 6.77 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.71 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 160.4, 153.3, 153.2 (2C), 141.4, 141.1, 138.9, 134.5 (2C), 131.8, 131.3 (2C), 130.1, 129.9, 129.2 (2C), 114.0 (2C), 107.5 (2C), 61.1, 56.2 (2C), 55.6. HRMS (ESI-ion trap, *m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{22}N_2O_4Na$ 425.1425; found 425.1475.

*4.4.11. 2-p-Tolyl-3-(3,4,5-trimethoxyphenyl)quinoxaline (**4k**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow solid 119.0 mg (87%). Mp=116–120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.17 (d, *J*=7.2 Hz, 2H), 7.77 (d, *J*=7.2 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.16 (d, *J*=8.0 Hz, 2H), 6.76 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 153.8, 153.2, 153.1, 141.4, 141.2, 139.0 (2C), 138.9, 136.7, 134.3, 130.0, 129.7, 129.3, 129.2, 129.2, 129.0, 128.5, 111.0, 107.6 (2C), 61.1, 56.1 (2C), 21.5. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ $C_{24}H_{23}N_2O_3$ 387.4431; found 387.1706.

*4.4.12. 4-(3-(3,4,5-Trimethoxyphenyl)quinoxalin-2-yl)benzenamine (**4l**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a brown solid 99.8 mg (73%). Mp=170–180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.11 (d, *J*=7.2 Hz, 2H), 7.73 (d, *J*=7.2 Hz, 2H), 7.34 (d, *J*=8.8 Hz, 2H), 6.80 (s, 2H), 6.62 (d, *J*=8.8 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 153.4 (2C), 152.9, 152.9, 147.2 (2C), 141.2, 140.6, 138.5, 134.6, 131.0 (2C), 129.7, 129.3, 128.9, 128.9, 114.5, 114.1, 107.1 (2C), 60.9, 55.9 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{22}N_3O_3$ 388.1661; found 388.1662.

*4.4.13. 2-(4-Fluorophenyl)-3-(3,4,5-trimethoxy phenyl)quinoxaline (**4m**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain light yellow solid 109.0 mg (80%). Mp=88–96 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.07 (d, *J*=7.2 Hz, 2H), 7.67 (d, *J*=7.2 Hz, 2H), 7.45–7.41 (m, 2H), 6.98 (d, *J*=8.4 Hz, 2H), 6.64 (s, 2H), 3.76 (s, 3H), 3.60 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 164.5, 162.0, 153.2, 152.5, 141.3, 141.2, 139.0, 135.5, 135.5, 134.0, 131.9, 131.8, 130.3, 130.3, 129.2, 129.0, 115.7, 115.4, 107.5 (2C), 61.1, 56.2 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{20}FN_2O_3$ 391.1380; found 391.1372.

*4.4.14. 2-(3-Methoxyphenyl)-3-(3,4,5-trimethoxy phenyl)quinoxaline (**4n**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid 122.7 mg (91%). Mp=102–108 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.19 (d, *J*=7.2 Hz, 2H), 7.79 (d, *J*=7.2 Hz, 2H), 7.28 (s, 1H), 7.11–7.09 (m, 2H), 6.94 (d, *J*=8.0 Hz, 1H), 6.78 (s, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 3.70 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 159.4, 153.2, 152.8, 152.8, 141.0, 140.9, 140.5, 138.7, 133.8 (2C), 130.0, 129.9, 129.4, 129.1, 129.0, 122.0, 114.8, 114.6, 107.2 (2C), 60.8, 55.9 (2C), 55.2. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4$ 403.1580; found 403.1586.

*4.4.15. 2-m-Tolyl-3-(3,4,5-trimethoxy phenyl)quinoxaline (**4o**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow solid 116.3 mg (85%). Mp=84–92 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.18 (d, *J*=7.2 Hz, 2H), 7.74 (d, *J*=7.2 Hz, 2H), 7.42 (s, 1H), 7.25–7.19 (m, 3H), 6.79 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H), 2.34 (s, 3H). ^{13}C NMR

($CDCl_3$, 100 MHz): δ_C 153.4 (2C), 152.5 (2C), 140.8 (2C), 139.0, 138.5, 137.8, 133.6 (2C), 129.8 (2C), 129.6 (2C), 128.8, 127.9, 126.5, 107.2 (2C), 60.6, 55.6 (2C), 21.1. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3$ 387.1703; found 387.1710.

*4.4.16. 3-(3-(3,4,5-Trimethoxyphenyl)quinoxalin-2-yl)benzenamine (**4p**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow solid 116.2 mg (85%). Mp=167–172 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.17 (d, *J*=7.2 Hz, 2H), 7.78 (d, *J*=7.2 Hz, 2H), 7.25 (s, 1H), 7.14 (t, *J*=8.2 Hz, 1H), 6.92–6.91 (m, 1H), 6.83 (s, 2H), 6.71–6.68 (m, 1H), 3.86 (s, 3H), 3.72 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 153.9, 153.0 (2C), 146.8 (2C), 141.3, 141.2, 140.6 (2C), 134.1, 130.2, 130.1, 129.5, 129.3, 129.3, 120.3, 116.0, 115.6, 107.6 (2C), 61.1, 56.2 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{22}N_3O_3$ 388.1583; found 388.1585.

*4.4.17. 2-(2-Methoxyphenyl)-3-(3,4,5-trimethoxy phenyl)quinoxaline (**4q**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow oil 117.3 mg (87%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.12 (d, *J*=7.2 Hz, 2H), 7.74 (d, *J*=7.2 Hz, 2H), 7.62 (d, *J*=5.4 Hz, 1H), 7.32 (t, *J*=4.4 Hz, 1H), 7.08 (t, *J*=4.2 Hz, 1H), 6.77 (s, 2H), 6.64 (s, 1H), 3.76 (s, 3H), 3.56 (s, 6H), 3.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 156.4, 153.8, 152.3 (2C), 151.9, 141.0 (2C), 140.9, 138.2, 134.4, 130.5 (2C), 129.7, 129.4, 129.0, 128.9, 121.5, 110.9, 105.9 (2C), 60.7, 55.6 (2C), 54.8. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4$ 403.1580; found 403.1590.

*4.4.18. 2-o-Tolyl-3-(3,4,5-trimethoxy phenyl)quinoxaline (**4r**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid 113.6 mg (83%). Mp=132–134 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.23 (d, *J*=7.2 Hz, 2H), 7.82 (d, *J*=7.2 Hz, 2H), 7.41 (d, *J*=8.8 Hz, 1H), 7.34–7.28 (m, 2H), 7.21 (d, *J*=8.4 Hz, 1H), 6.80 (s, 2H), 3.84 (s, 3H), 3.66 (s, 6H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 154.1, 152.6 (2C), 141.2 (2C), 140.6, 139.3, 138.6, 135.8, 133.2, 130.4, 130.0, 129.7, 129.5, 129.0, 129.0, 128.7, 126.1, 106.8 (2C), 60.7, 55.7 (2C), 19.5. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3$ 387.1630; found 387.1624.

*4.4.19. 2-Cyclopropyl-3-(3,4,5-trimethoxy phenyl)quinoxaline (**4s**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow oil 104.2 mg (72%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.09 (d, *J*=8.0 Hz, 1H), 7.97 (d, *J*=8.0 Hz, 1H), 7.69–7.65 (m, 2H), 7.02 (s, 2H), 3.94 (s, 6H), 3.92 (s, 3H), 1.42–1.40 (m, 2H), 1.25 (s, 1H), 1.09–1.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 156.6, 154.4, 153.4 (2C), 141.6 (2C), 140.3, 134.4, 129.7, 129.2, 128.8, 128.5, 106.9 (2C), 61.1, 56.4 (2C), 15.8, 12.0 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{21}N_2O_3$ 337.1547; found 337.1555.

*4.4.20. 3-Phenyl-2-(3,4,5-trimethoxyphenyl)quinoxaline-6-carboxylic acid (**4t**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow oil 107.1 mg (69%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.90 (s, 1H), 8.38 (d, *J*=8.8 Hz, 1H), 8.19 (d, *J*=8.4 Hz, 1H), 7.53–7.51 (m, 2H), 7.37–7.35 (m, 3H), 6.75 (s, 2H), 3.83 (s, 3H), 3.64 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 168.6, 155.0, 154.3, 153.6, 152.7 (2C), 142.9, 140.1, 138.7 (2C), 133.1, 132.0, 131.4, 129.6 (2C), 129.4, 128.9, 128.3 (2C), 107.3 (2C), 60.8, 55.8 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{21}N_2O_5$ 417.1445; found 417.1453.

*4.4.21. 3-(4-Methoxyphenyl)-5-methyl-2-(3,4,5-trimethoxyphenyl)quinoxaline (**4u**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow oil 113.0 mg (81%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.98 (d, *J*=8.4 Hz, 1H), 7.64 (t, *J*=4.0 Hz, 1H), 7.59 (d, *J*=8.4 Hz, 2H), 7.50 (d, *J*=8.4 Hz, 1H), 6.94 (d, *J*=6.0 Hz, 2H), 6.84 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.71 (s, 6H), 2.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 160.1 (2C), 152.8 (2C), 151.2, 140.8 (2C), 140.0, 137.3, 137.2, 134.6, 131.7, 131.3, 129.6, 129.5 (2C), 129.3, 126.7, 113.7, 107.4 (2C), 60.8, 55.2 (2C), 17.0. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4$ 417.1809; found 417.1814.

*4.4.22. 3-(4-Methoxyphenyl)-6-nitro-2-(3,4,5-trimethoxy phenyl) quinoxaline (**4v**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow oil 108.7 mg (75%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 9.02 (s, 1H), 8.49 (d, *J*=9.2 Hz, 1H), 8.25 (d, *J*=9.2 Hz, 1H), 7.57 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 6.83 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.73 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 160.9, 160.7, 155.6, 155.1, 153.0, 147.6, 143.5, 143.1, 139.8, 139.4, 133.1, 131.3, 131.2, 130.4, 125.2, 123.0, 122.8, 113.8, 107.2 (2C), 60.9 (2C), 55.9, 55.3. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{22}N_3O_6$ 448.1503; found 448.1502.

*4.4.23. 5-Methyl-3-p-tolyl-2-(3,4,5-trimethoxy phenyl)quinoxaline (**4w**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid 123.4 mg (87%). Mp=140–144 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.99 (d, *J*=8.0 Hz, 1H), 7.65 (t, *J*=8.4 Hz, 1H), 7.58 (d, *J*=6.8 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 2H), 7.19 (d, *J*=7.8 Hz, 2H), 6.82 (s, 2H), 3.87 (s, 3H), 3.67 (s, 6H), 2.86 (s, 3H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 152.9, 152.7 (2C), 151.2 (2C), 141.0, 140.1, 138.6 (2C), 137.3, 136.7, 134.3, 129.7, 129.5, 129.4 (2C), 129.0, 126.8, 107.6 (2C), 60.9, 55.8 (2C), 21.2, 17.0. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_3$ 401.1860; found 401.1872.

*4.4.24. 5-Methyl-3-phenyl-2-(3,4,5-trimethoxy phenyl)quinoxaline (**4x**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid 128.1 mg (89%). Mp=180–184 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.00 (d, *J*=8.8 Hz, 1H), 7.66 (t, *J*=7.2 Hz, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.55–7.53 (m, 2H), 7.38–7.37 (m, 3H), 6.82 (s, 2H), 3.87 (s, 3H), 3.66 (s, 6H), 2.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 152.8, 152.7, 151.0 (2C), 140.9, 140.2, 139.6, 138.6, 137.3 (2C), 134.0, 129.8, 129.6, 129.5, 128.5 (2C), 128.3, 126.8, 107.6 (2C), 60.8, 55.8 (2C), 17.0. HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{23}O_3N_2$ 387.1703; found 387.1715.

*4.4.25. 2-Phenyl-3-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydroquinoxaline (**4y**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow oil 98.2 mg (70%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.39 (d, *J*=8.0 Hz, 2H), 7.31–7.24 (m, 3H), 6.62 (s, 2H), 3.81 (s, 3H), 3.63 (s, 6H), 3.06–3.05 (m, 4H), 1.99–1.98 (t, *J*=5.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 152.8 (2C), 150.4 (2C), 149.5, 149.0, 139.2, 138.1, 133.9, 129.4 (2C), 128.2 (2C), 128.0, 107.0 (2C), 60.8, 55.8 (2C), 31.8 (2C), 22.7 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{25}N_2O_3$ 377.1860; found 377.1868.

*4.4.26. 3-Phenyl-2-(3,4,5-trimethoxyphenyl)pyrido[3,4-b]pyrazine (**4z**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid 115.5 mg (83%). Mp=156–164 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 9.62 (s, 1H), 8.92–8.76 (m, 1H), 8.03–7.91 (m, 1H), 7.55 (d, *J*=7.6 Hz, 2H), 7.45–7.38 (m, 3H), 6.79 (s, 2H), 3.87 (s, 3H), 3.68 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.0, 157.3, 155.5, 154.8, 153.0, 152.9 (2C), 147.1, 143.5, 139.5, 138.6, 132.8, 129.6, 129.5, 129.3,

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128.5, 121.4, 107.5 (2C), 60.9, 55.9 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{20}N_3O_3$ 374.1499; found 374.1509.

*4.4.27. 1,4-Bis(3-phenylquinoxalin-2-yl)benzene(1,4-quinoxaline-dimer) (**6**).* The title compound was prepared according to the general procedure and purified by column chromatography to obtain a light yellow oil 153.8 mg (88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.20 (d, *J*=7.2 Hz, 4H), 7.82 (d, *J*=7.2 Hz, 4H), 7.54–7.52 (m, 4H), 7.51–7.50 (m, 4H), 7.33–7.30 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 153.3 (4C), 152.6 (4C), 141.1 (4C), 139.3 (2C), 138.8 (2C), 130.0 (4C), 129.8 (2C), 129.7 (4C), 129.1 (4C), 128.8 (2C), 128.2 (2C). HRMS (ESI-ion trap, *m*/*z*): $[M+H]^+$ calcd for $C_{34}H_{22}N_4$ 487.1844; found 487.1846.

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Supplementary data

Experimental details, spectra data for the products, and X-ray crystallographic data (CIF file of **4i**: CCDC 897279) are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.027.

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