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Visible light-induced metal-free synthesis of quinoxalines using Rose Bengal as a photocatalyst

Jeshma Kovvuri,*[a] Burri Nagaraju,[b] and Angajala Kishore Kumar[c]

[a]*Department of Chemistry, Anurag University, Hyderabad, Telangana, 500088 India*
[b]*Discovery Chemistry Solutions Division SSS organics Pvt Ltd, Hyderabad, Telangana, 500079 India*
[c]*Vardhaman College of Engineering (Autonomous), Hyderabad, 501218, India*
Email: dr.jeshmakovvuri@gmail.com

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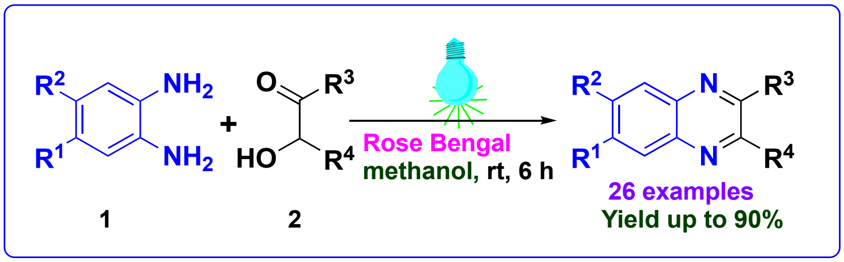
Abstract

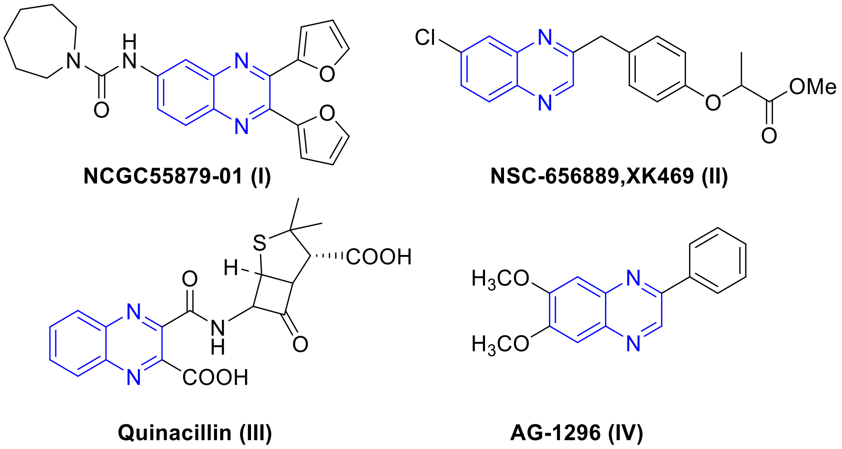
An efficient eco-friendly photocatalytic method was developed for the synthesis of pharmaceutically highly sought-after quinoxalines. This route is a simple condensation between *o*-phenylenediamine and an α-hydroxy ketone in methanol at room temperature in the presence of the organic dye Rose Bengal (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein) as a photocatalyst. Using this protocol, a library of examples with various *o*-phenylenediamines and α-hydroxy ketones was prepared. This is a practically useful method for the development of quinoxaline derivatives of biological importance in good to excellent yields.



Keywords: Quinoxaline, metal-free, photocatalyst, Rose Bengal, visible light.

Introduction

Heterocyclic compounds possess a highest priority in organic synthesis due to their diversified applications. Among them, quinoxalines is one of the most important classes of nitrogen-containing heterocyclic scaffolds which attracts researchers for their many activities. They are considered privileged scaffolds in the new drug discovery process.[1,2] Quinoxaline derivatives are reported to have a varied range of biological properties, such as anticancer,[3] anti-malarial, anti-HIV,[4] antagonist and antibacterial properties.[5] Some of the quinoxaline-containing derivatives that exhibit biological activities are: NCGC55879-01 (**I**) (Figure 1) which acts as a BRCA1 inhibitor,[6] NSC-656889, XK 469 (**II**) is an antineoplastic agent[7] and other quinoxaline derivatives like quinacillin (**III**) is a semi-synthetic penicillin with antibacterial activity[8] and AG-1296 (**IV**), is a protein tyrosine kinase inhibitor.[9] In addition to their medicinal importance they are also commonly used as an electron-acceptor unit, when combined with electron-donor units, these combined materials have efficient applications in photovoltaics, OLDED and dye-sensitized solar cells (DSSCs).[10] Moreover, many quinoxaline derivatives have already found applications as organic semiconductors in thin film transistors.[11,12]



NCGC55879-01 (I)

NSC-656889,XK469 (II)

Quinacillin (III)

AG-1296 (IV)

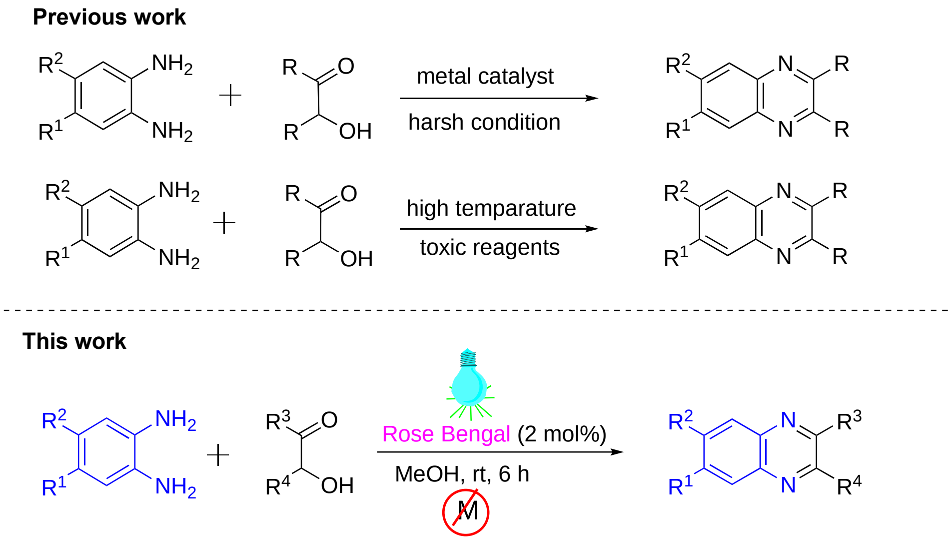
Figure 1. Biologically important molecules containing a quinoxaline scaffold.

In view of their diverse utilization, several methods have been developed for the synthesis of quinoxalines.[13,14] Previous approaches for the synthesis of quinoxalines make use *o*-phenylenediamines and α-hydroxy ketones or diketones or diol compounds with various promoting agents such as $CuCl_2$,[15] ceric ammonium nitrate (CAN), HgI_2,[16] MnO_2,[17] FeMPA,[18] TiO_2,[19] [P_4-VP]-PdNPs][20] or Ru/N-C[21] and manganese octahedral molecular sieves[22] as well as microwave technology. However, these methods are associated with some drawbacks such as harsh reaction conditions, use of hazardous solvents, low yields, use of toxic and expensive reagents and longer reaction times (Table 1). Therefore, the development of eco-friendly methods for the synthesis of quinoxalines is greatly needed.

In the past few years, visible light photoredox catalysis has emerged as a powerful platform for chemists due to its fascinating features like mild, safe reaction conditions, and inexpensive, abundant renewable energy sources.[23-25] It is a powerful tool to accomplish novel organic chemical transformations via a single-electron-transfer pathway.[26,27] Continuing our efforts towards the synthesis of heterocyclic scaffolds herein, we developed a visible-light-driven environmentally benign process for the synthesis of quinoxalines (Scheme 1) from readily available *o*-phenylenediamines and α-hydroxy ketones at room temperature under open air by using organic dye such as Rose Bengal as a photocatalyst

Table 1. Comparison of the new method with existing methods for synthesis of quinoxalines

S. No	Reactants	Reagents & Solvents	Temperature	Time	Yield
1	*o*-phenylenediamines and diketones	2.0 eq Iodine, 1.2 eq K_2CO_3, DMSO[28]	100 °C	12 h, Open air	69-85%
2	*o*-phenylenediamines and α-hydroxy ketones	10 eq MnO_2, DCM[29]	reflux	4h	64-88%
3	*o*-phenylenediamines and α-hydroxy ketones	Cu-Mn/HT, EtOH[30]	70 °C	6 h	75-90%
4	*o*-phenylenediamines and α-hydroxy ketones	$KMnO_4/CuSO_4$[31]	reflux	2 h	80-89%
5	*o*-phenylenediamines and α-hydroxy ketones	2 mol % $Pd(OAc)_2$ or $RuCl2(PPh_3)_3$-TEMPO/ toluene, THF, NEt_3[32]	reflux	14 h	64-88%
6	*o*-phenylenediamines and α-hydroxy ketones	Rose Bengal, MeOH	room temp.	6 h	52-90%



Scheme 1. Visible light-driven synthesis of quinoxaline derivatives.

Results and Discussion

With the aim to develop an efficient new photocatalytic method for the synthesis of quinoxalines from o-phenylenediamines and α-hydroxy ketones, our initial attempt at the Rhodamine B (2 mol%) catalysed reaction of *o*-phenylenediamine (**1**) with α-hydroxy ketone (**2**) using 15 W LED bulb at room temperature for 6 hours resulted in the production of desired quinoxaline **3** was obtained in a 74% yield (Table 2, entry 1).

To investigate more reaction conditions, various photocatalysts like Rose Bengal, Eosin-y, methylene blue, Ru- and Ir-complexes were screened (Table 2, entries 2-6). Among these, Rose Bengal was found to be the most effective. In addition, the reaction was checked in different solvents such as water, acetone, dichloroethane (DCE), methanol, ethanol, chloroform, 2-propanol, acetonitrile, hexane, ethyl acetate and dichloromethane (DCM) (Table 2, entries 7-22) with 2 mol % of photocatalyst in the presence of white LED bulb (15 W) in which, Rose Bengal in methanol was found to be the best conditions, resulting in a 90% yield of **3** in a reaction time of 6 hours (Table 2, entry 6). Once Rose Bengal has been identified as the best photocatalyst for promoting this reaction, we turned our consideration towards optimization of the amount of photocatalyst essential for obtaining a high yield of quinoxaline. A series of trials were conducted using different quantities of Rose Bengal wherein it was observed that the use of 2 mol % catalyst gave the best result. Reducing the amount of catalyst resulted in a poorer yield. Moreover, the advantage of the Rose Bengal is its reusability,[33] the catalyst can be reused for up to three cycles with the almost same results, as shown in Figure 2.

Furthermore, we studied the reaction conditions by conducting control experiments, including the effect of photocatalyst, light and atmospheric oxygen. In these experiments, reaction in the absence of a photocatalyst, light (Table 2, entries 23-26) and switch on-off trials, revealed that both the catalyst and light were essential. Poor yields were obtained under inert conditions (Table 2, entry 27).

Having established optimal reaction conditions in hand, we extended the scope of the present photocatalytic method using various substituted *o*-phenylenediamines and α-hydroxy ketones for the synthesis of corresponding products. The reaction was successful with various *o*-phenylenediamines (e.g. substituted with H, Cl, Br, Me, F, NO_2, I, dimethyl, and dichloro) and α-hydroxy-1,2-diphenylmethane in moderate to good yields (Figure 3, 70-90 %). Moreover, the optimized conditions were also successfully applied to heteroaryl α-hydroxy ketones which generated the corresponding heterocycle-substituted products in moderate yields (Figure 3). Notably, aliphatic and unsymmetrical α-hydroxy ketones also worked smoothly under the current conditions to afford the desired quinoxalines.

Various *o*-phenylenediamines, with different aromatic substituents, both electron-withdrawing and electron-donating, afforded the substituted quinoxalines **3** in good to excellent yields. The electronic effects of the substituents did not show much effect on the yield of the products. After separation of the product, Rose Bengal was eluted by using a polar solvent mixture (chloroform/methanol) that allows the catalyst to be reused subsequent to evaporation of the solvent under vacuum.

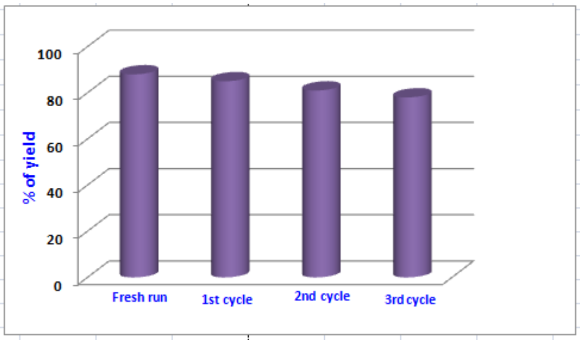
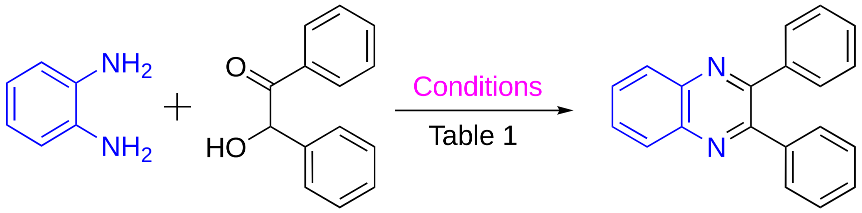


Figure 2. Graph representing reusability of the catalyst.

Table 2. Optimization of photocatalytic synthesis of quinoxalines[a]



1 **2** **3**

Entry	Photocatalyst	T (°C)/ t (h)	Solvent	Yield (%)[b]
1	Rhodamine B	rt /6	methanol	74
2	$Ru(bpy)_3Cl_2.6H_2O$	rt /6	methanol	80
3	Eosin-y	rt /6	methanol	65
4	methylene blue	rt /6	methanol	52
5	$Ir(ppy)_3$	rt /6	methanol	78
6	Rose Bengal	rt/6	methanol	90
7	$Ru(bpy)_3Cl_2.6H_2O$	rt /6	acetonitrile	60
8	$Ru(bpy)_3Cl_2.6H_2O$	rt /6	ethanol	65
9	Eosin-y	rt /6	acetone	56
10	$Ir(ppy)_3$	rt /6	DCM	43
11	Rhodamine B	rt /6	ethanol	60
12	Rhodamine B	rt /6	acetonitrile	50
13	Rose Bengal	rt /6	water	45
14	Rose Bengal	rt /6	DCM	40
15	Rose Bengal	rt /6	2-propanol	60
16	Rose Bengal	rt /6	acetonitrile	55
17	Rose Bengal	rt /6	DCE	58
18	Rose Bengal	rt /6	acetone	48
19	Rose Bengal	rt /6	ethanol	60
20	Rose Bengal	rt/6	hexane	30
21	Rose Bengal	rt /6	ethyl acetate	59
22	Rose Bengal	rt /6	chloroform	47
23[c]	-	rt/12	methanol	10
24[c]	-	rt /12	Water	12
25[c]	-	rt /12	acetonitrile	15
26[d]	Rose Bengal	rt /6	methanol	ND
27[e]	Rose Bengal	rt /6	methanol	30

[a]Reaction conditions: **1a** (1 equiv.), **2a** (1 equiv.), solvent (12 mL) and a 15 W white LED bulb kept at a distance of 10 cm (approx.) from the reaction vessel. [b]Yields of the isolated products after column chromatography. [c]Absence of the photocatalyst. [d]The reaction was run in the dark. [e]Inert condition, ND = the desired product was not detected on TLC.

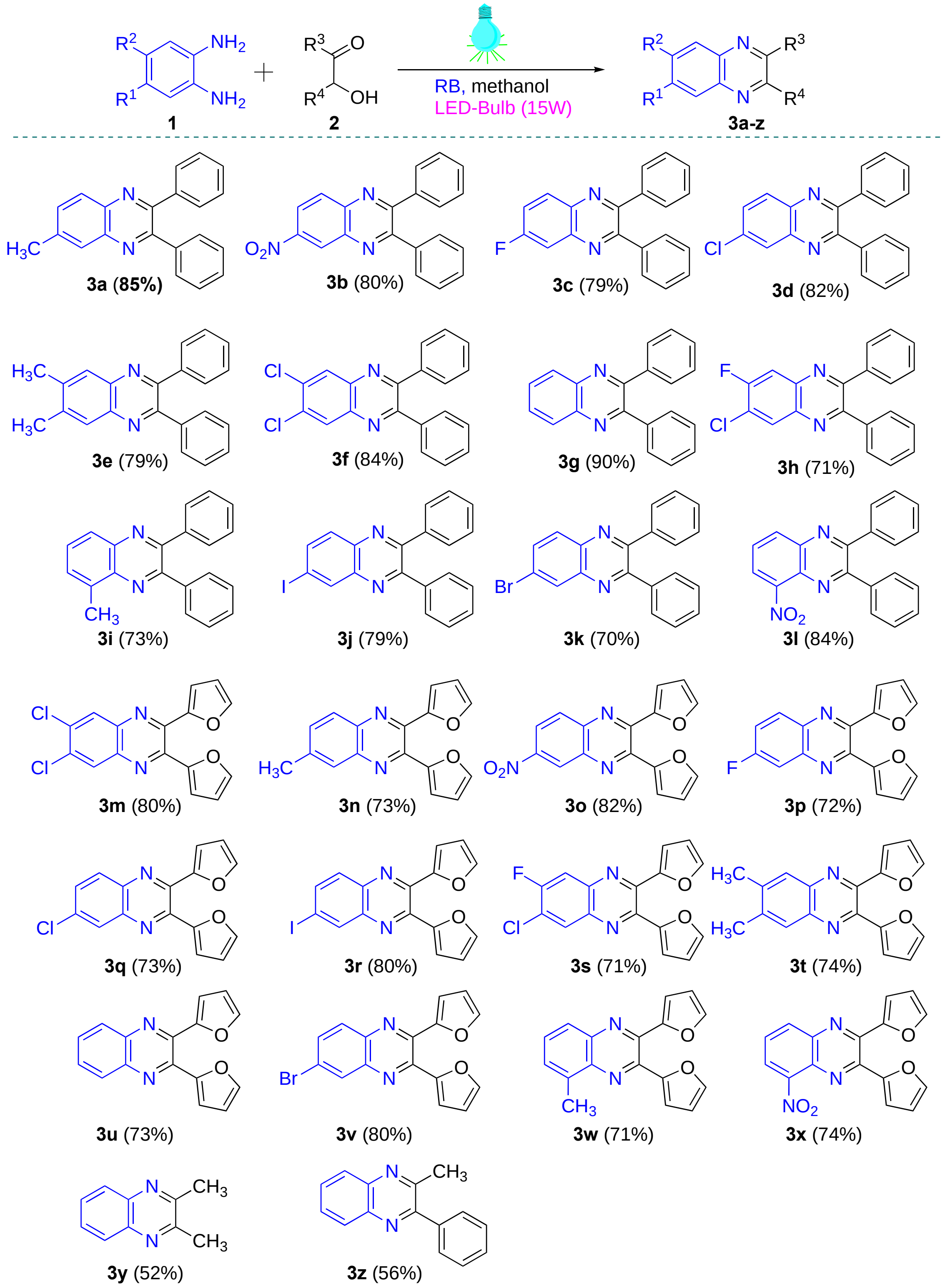


Figure 3. Scope of the substrates.

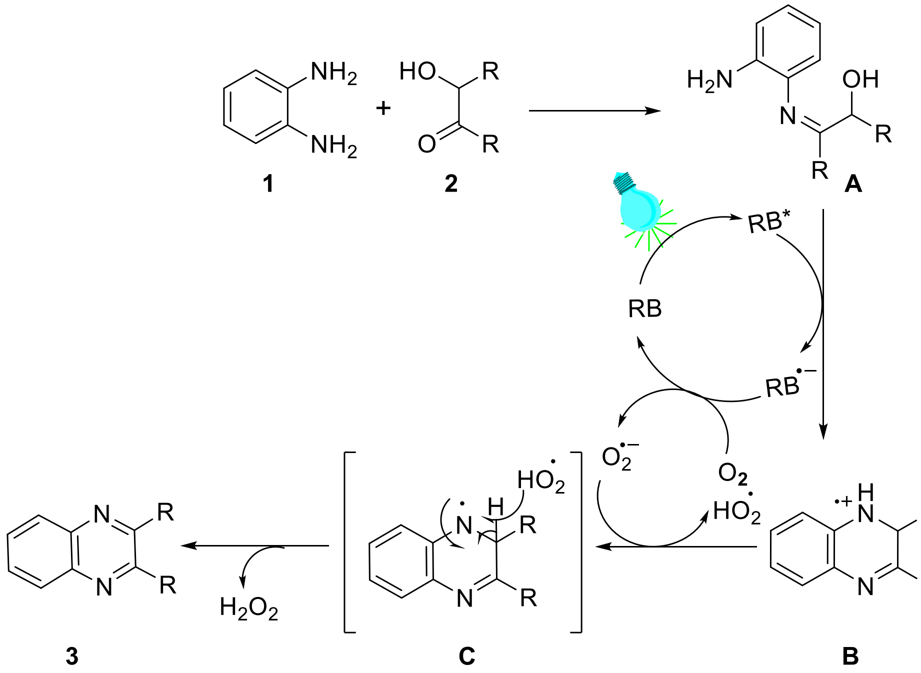


Figure 4. Plausible mechanism.

A plausible pathway for the synthesis of quinoxaline from *o*-phenylenediamine and α-hydroxy ketones is depicted in Figure 4. Initially, the reaction between the *o*-phenylenediamine (**1**) and α-hydroxy ketone (**2**) gives the imine **A**, which on single-electron extraction by the visible-light-excited Rose Bengal (RB*) via an SET process results in the formation of Rose Bengal radical anion (RB•−) and radical cation **B**. Transfer of an electron to O_2 to form the superoxide radical anion, and regeneration of Rose Bengal completes the photoredox cycle. Finally, the abstraction of hydrogen by hydroxyl radical (HOO·) from **C** results in the formation of the desired quinoxaline product (**3**). The elimination of hydrogen peroxide (H_2O_2) was identified by starch iodide paper, an observation that provides support to the above mechanism. [26]

Conclusions

We have disclosed a new, one-pot protocol for the synthesis of quinoxalines (**3a-z**) by employing α-hydroxy ketone and *o*-phenylenediamine as the starting materials. This protocol utilizes visible light as an inexpensive, green and eco-sustainable energy source, cheap and commercially available starting materials, Rose Bengal as a metal-free photoredox catalyst and molecular oxygen (open-air) as an oxidant at ambient temperature. This protocol tolerates a wide variety of substrates such as aromatic, aliphatic and unsymmetrical α-hydroxy ketones and various substituted *o*-phenylenediamines. It is expected that this procedure will offer wide practical utility.

Experimental Section

General. All chemicals, reagents and photocatalysts were purchased from commercial sources and were used without further purification. Reactions were monitored by TLC on a silica gel glass plate containing 60 GF-254, and visualization was done by UV light and iodine vapor. ^{1}H and ^{13}C NMR spectra were recorded on Bruker UXNMR/XWIN-NMR (300 MHz) or InovaVarian-VXR-unity (400, 500 MHz) instruments. Chemical shifts were expressed in parts per million (δ in ppm) downfield from TMS expressed as internal standard and coupling constants are expressed in Hz. ^{1}H NMR spectral data were reported in the following order: multiplicity (s, singlet; brs, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet), coupling constants in Hz, and the number of protons. ESI mass spectra were recorded on a Micromass Quattro LC using ESI+ software with a capillary voltage 3.98 kV and an ESI mode positive ion trap detector. High-resolution mass spectra were recorded on a QSTAR XL Hybrid MS-MS mass spectrometer. Melting points were determined with an electrothermal digital melting point apparatus IA9100 and are uncorrected. All reactions were conducted in glass vials and using the following procedure and and an LED bulb (15W) reaction set-up.

General procedure for the synthesis of quinoxalines

In a 30 mL clear glass vial with 12 mL of MeOH, was added *o*-phenylenediamine (1 equiv.), α-hydroxy ketone (1 equiv.) and 2 mol % of Rose Bengal photocatalyst, then the reaction mixture was placed nearby the 15W LED bulb in photochemical reactor box under open air, and stirred until the starting materials were completely consumed, monitored by TLC analysis. After completion of the reaction, the solvent was removed under vacuum and the final compound was purified by the column chromatography (silica gel 60:120 mesh) by using EtOAc and hexane as eluent to afford the desired products in good to excellent yields. After isolation of the product, Rose Bengal was eluted by $CHCl_3$/MeOH which can be reused after evaporation of the solvent under vacuum.

6-Methyl-2,3-diphenylquinoxaline (3a). Brown solid; yield 90%; mp 121-124 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 8.023 (d, *J* = 8.5 Hz, 1H), 7.91 (s, 1H), 7.59 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 4H), 7.36 – 7.27 (m, 6H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 152.2, 152.1, 151.4, 148.1, 148.9, 141.8, 140.2, 139.5, 138.7, 138.3, 131.4, 129.0, 127.8, 127.7, 127.3, 127.0, 21.0; HRMS (ESI): calculated for $C_{21}H_{17}N_2$ $[M+H]^+$ 297.1386, found 297.1388.

6-Nitro-2,3-diphenylquinoxaline (3b). Light yellow solid; yield 80%; mp 143-145 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (d, *J* = 2.5 Hz, 1H), 8.54 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.30 (d, *J* = 9.2 Hz, 1H), 7.60 – 7.54 (m, 4H), 7.46 – 7.35 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 155.7, 147.9, 143.6, 140.0, 138.1, 138.0, 130.8, 129.9, 129.9, 128.5, 127.5, 127.4, 125.7, 123.3; HRMS (ESI): calculated for $C_{20}H_{14}N_3O_2$ $[M+H]^+$ 328.1081, found 328.1083.

6-Fluoro-2,3-diphenylquinoxaline (3c). Light brown solid; yield 79%; mp 104-106 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 9.2, 5.7 Hz, 1H), 7.80 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.51 (dd, *J* = 6.6, 3.9 Hz, 4H), 7.39 – 7.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2 (d, *J*=252.48 Hz); 161.1, 154.2, 152.8, 142.0, 138.7, 138.6, 131.3, 131.1, 129.8, 129.0, 128.4, 120.4, 120.1, 112.7, 112.3; HRMS (ESI): calculated for $C_{20}H_{14}FN_2$ $[M+H]^+$ 301.1136, found 301.1138.

6-Chloro-2,3-diphenylquinoxaline (3d). White solid; yield 82%; mp 120-122 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.3 Hz, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 7.70 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 4H), 7.39 – 7.37 (m, 1H), 7.36 (dd, *J* = 3.3, 1.7 Hz, 1H), 7.35 (s, 1H), 7.33 (d, *J* = 1.8 Hz, 2H), 7.32 (t, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 153.5, 141.4, 139.4, 138.6, 138.6, 134.3, 130.9, 130.4, 129.8, 129.2, 129.0, 129.0, 128.3, 128.0, 127.9; HRMS (ESI): calculated for $C_{20}H_{14}ClN_2$ $[M+H]^+$ 317.0840, found 317.0842.

6,7-Dimethyl-2,3-diphenylquinoxaline (3e). Light white solid; yield 79%; mp 169-172 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.49 (d, *J* = 9.4 Hz, 4H), 7.32 (q, *J* = 5.62, 3.01 Hz, 6H), 2.51 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 140.6, 140.2, 139.4, 129.9, 128.6, 128.2, 20.5; HRMS (ESI): calculated for $C_{22}H_{19}N_2$ $[M+H]^+$ 311.1546, found 311.1548.

6,7-Dichloro-2,3-diphenylquinoxaline (3f). Dirty white solid; yield 84%; mp 140-144 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.26 (s, 1H), 8.22 (s, 1H), 8.17 (s, 3H), 7.56 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 154.0, 139.4, 137.8, 133.7, 129.3, 129.3, 128., 127.8; HRMS (ESI): calculated for $C_{20}H_{13}Cl_2N_2$ [M+H]$^+$ 351.0450, found 351.0452.

2,3-Diphenylquinoxaline (3g). White solid; yield 90%; mp: 122-124 ˚C[27] (lit. mp 127-128); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (m, 2H), 7.79 – 7.76 (dd, *J* = 2.26, 7.50 Hz, 2H), 7.53 (q, *J* = 3.02, 6.04 Hz, 4H), 7.35 – 7.26 (q, *J* = 3.02, 6.04 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1, 140.0, 137.9, 128.9, 128.7, 128.0, 127.7, 127.1; HRMS (ESI): calculated for $C_{20}H_{15}N_2$ [M+H]$^+$ 283.1230, found 283.1232.

6-Chloro-7-fluoro-2,3-diphenylquinoxaline (3h). Light brown solid; yield 71%; mp 151-154 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 9.3 Hz, 1H), 7.50 (s, 1H), 7.49 (s, 2H), 7.48 (d, *J* = 1.5 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.35 (s, 1H), 7.33 (s, 2H), 7.31 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (d, *J* = 158.6 Hz), 157.2, 154.4, 153.8, 138.4, 130.4, 129.8, 129.8, 129.3, 129.2, 128.4, 113.9, 113.7; HRMS (ESI): calculated for $C_{20}H_{13}N_2ClF$ [M+H]$^+$ 335.0746, found 335.0748.

5-Methyl-2,3-diphenylquinoxaline (3i). Dirty white solid; yield 73%; mp 119-123 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.62 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 4H), 7.36 – 7.27 (m, 6H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 152.4, 151.6, 140.5, 139.7, 138.9, 138.5, 131.6, 129.2, 128.0, 127.5, 121.2, 21.3; HRMS (ESI): calculated for $C_{21}H_{17}N_2$ [M+H]$^+$ 297.1386, found 297.1388.

6-Iodo-2,3-diphenylquinoxaline (3j). White solid; yield 79%; mp 147-151 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.3 Hz, 1H), 8.13 – 8.09 (m, 1H), 7.71 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.52 (dd, *J* = 6.9, 1.0 Hz, 4H), 7.36 (t, *J* = 8.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 154.5, 153.8, 141.7, 139.9, 138.9, 138.8, 135.84, 131.4, 130.6, 130.0, 130.0, 129.2, 128.5, 128.3; HRMS (ESI): calculated for $C_{20}H_{14}IN_2$ [M+H]$^+$ 409.0196, found 409.0198.

6-Bromo-2,3-diphenylquinoxaline (3k). Light white solid; yield 70%; mp 152-156 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.3 Hz, 1H), 8.12 – 8.08 (m, 1H), 7.70 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.51 (dd, *J* = 6.9, 1.0 Hz, 4H), 7.39 – 7.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 154.0, 153.3, 141.1, 139.4, 138.4, 138.3, 135.3, 130.6, 130.1, 129.5, 128.8, 128.7, 128.1, 127.4; HRMS (ESI): calculated for $C_{20}H_{14}BrN_2$ [M+H]$^+$ 361.0335, found 361.0337.

5-Nitro-2,3-diphenylquinoxaline (3l). White solid; yield 84%; mp 142-146 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.6 Hz, 1H), 7.89 (s, 1H), 7.51 (dd, *J* = 4.2, 2.5 Hz, 3H), 7.40 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.38 (d, *J* = 1.4 Hz, 1H), 7.36 – 7.34 (m, 3H), 7.33 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 154.0, 153.3, 141.1, 139.4, 138.4, 135.3, 130.6, 130.1, 129.5, 129.5, 128.8, 128.7, 128.1, 127.7; HRMS (ESI): calculated for $C_{20}H_{14}N_3O_2$ [M+H]$^+$ 328.1081, found 328.1083.

6,7-Dichloro-2,3-di(furan-2-yl)quinoxaline (3m). Light brown solid; yield 80%; mp 135-139 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 2H), 7.64 (d, *J* = 1.1 Hz, 2H), 6.74 (d, *J* = 3.4 Hz, 2H), 6.59 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-*d*$_6$) δ 149.6, 144.1, 142.6, 138.5, 133.8, 128.9, 113.4, 111.6; HRMS (ESI): calculated for $C_{16}H_9Cl_2N_2O_2$ [M+H]$^+$ 331.0036, found 331.0038.

2,3-Di(furan-2-yl)-6-methylquinoxaline (3n). Light brown solid; yield 73%; mp 129-132 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.82 (s, 1H), 7.58 – 7.48 (m, 3H), 6.51 (d, *J* = 16.5 Hz, 4H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 150.7, 143.9, 143.8, 142.31, 141.6, 140.9, 140.5 138.8, 132.6, 128.4, 127.7, 112.7, 112.4, 111.8, 21.8; HRMS (ESI): calculated for $C_{17}H_{13}N_2O_2$ [M+H]$^+$ 277.0971, found 277.0973.

2,3-Di(furan-2-yl)-6-nitroquinoxaline (3o). White solid; yield 82%; mp 153-156 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, *J* = 2.4 Hz, 1H), 8.50 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.24 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 6.1 Hz, 2H), 6.86 (dd, *J* = 16.9, 3.5 Hz, 2H), 6.62 (td, *J* = 3.9, 1.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 149.19, 146.86, 144.62, 144.2, 143.1, 142.0, 138.1, 129.6, 124.1, 122.6, 114.5, 113.6, 111.7; HRMS (ESI): calculated for $C_{16}H_{10}N_3O_4$ [M+H]$^+$ 308.0665, found 308.0668.

6-Fluoro-2,3-di(furan-2-yl)quinoxaline (3p). Brown solid; yield 72%; mp; 104-109 ˚C; ^{1}H NMR (300MHz, $CDCl_3$): δ 6.56-6.58 (m, 2H), 6.66 (dd, *J* = 9.80, 3.02 Hz, 2H), 7.52 (d, *J* = 9.06, 3.02 Hz, 1H), 7.62 – 7.65 (m, 2H), 7.75 (dd, *J* = 9.06, 3.02 Hz, 1H), 8.10 (q, *J* = 9.06, 6.04 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (d, *J* = 252.53 Hz), 149.6, 149.6, 148.7, 143.6 (d, *J* = 252.53 Hz), 140.4 (d, *J* = 13.20 Hz), 136.7, 130.3, 130.2, 123.6, 119.7 (d, *J* = 26.40 Hz), 112.8, 112.3, 112.0, 111.6, 111.3, 111.2 (d, *J* = 8.80 Hz); HRMS (ESI): calculated for $C_{16}H_{10}N_2O_2F$ $[M+H]^+$ 281.0720, found 281.0722.

6-Chloro-2,3-di(furan-2-yl)quinoxaline (3q). Light brown solid; yield 73%; mp 138-142 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 2.3 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.66 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.63 – 7.61 (m, 2H), 6.69 (t, *J* = 3.4 Hz, 2H), 6.57 (dd, *J* = 3.5, 1.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 144.5, 144.3, 143.2, 142.6, 140.8, 139.0, 136.1, 131.3, 127.8, 113.6, 113.3, 112.0, 111.9; HRMS (ESI): calculated for $C_{16}H_{10}ClN_2O_2$ $[M+H]^+$ 297.0425, found 297.0427.

2,3-Di(furan-2-yl)-6-iodoquinoxaline (3r). White solid; yield 80%; mp 150-153 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.3 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.68 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.65 – 7.64 (m, 2H), 6.72 – 6.70 (m, 2H), 6.58 (dd, *J* = 3.5, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 150.7, 144.7, 144.6, 143.4, 142.8, 141.0, 139.2, 136.2, 131.5, 130.4, 128.1, 113.9, 113.5, 112.3, 112.2; HRMS (ESI): calculated for $C_{16}H_{10}N_2O_2I$ $[M+H]^+$ 388.9781, found 388.9783.

6-Chloro-7-fluoro-2,3-di(furan-2-yl)quinoxaline (3s). Brown solid; yield 71%; mp: 139-144 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 – 6.58 (m, 2H), 6.70 (dd, *J* = 18.76, 3.35 Hz, 2H), 7.62 (dd, *J* = 5.18, 1.06 Hz, 2H), 7.83 (d, *J* = 9.30 Hz, 1H), 8.17 (d, *J* = 7.62 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 157.6, 150.6, 150.5, 145.0, 143.5, 142.9, 140.3, 137.9, 130.4, 126.3, 114.3, 113.9, 113.7, 112.3; HRMS (ESI): calculated for $C_{16}H_9N_2O_2ClF$ $[M+H]^+$ 315.0331, found 315.0333.

2,3-Di(furan-2-yl)-6,7-dimethylquinoxaline (3t). Cream solid; yield 74%; mp: 127-131 ˚C; ^{1}H NMR (300MHz, $CDCl_3$): δ 6.61 (d, *J* = 16.42 Hz, 3H), 7.59 (t, *J* = 8.87 Hz, 3H), 7.89 (s, 1H), 7.99 (d, *J* = 8.49 Hz, 1H), 2.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 159.7, 152.6, 151.9, 139.7, 139.2, 132.1, 131.6, 130.9, 130.9, 128.2, 127.5, 114.0, 113.4, 55.0, 21.6; HRMS (ESI): calculated for $C_{18}H_{15}N_2O_2$ $[M+H]^+$ 291.1128, found 291.1130.

2,3-Di(furan-2-yl)quinoxaline (3u). Cream solid; yield 88%; mp: 132-135 ˚C; ^{1}H NMR (300MHz, $CDCl_3$): δ 6.66 (q, *J* = 3.21, 1.70 Hz, 2H), 6.56 (dd, *J* = 3.39, 0.56 Hz, 2H), 7.26 (dd, *J* = 1.70, 0.56 Hz, 2H), 7.77 (q, *J* = 6.42, 3.58 Hz, 2H), 8.13 (q, *J* = 6.42, 3.58 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 146.2, 144.0, 143.5, 141.4, 137.5, 128.9, 123.5, 122.0, 113.9, 113.0, 111.0, 110.9; HRMS (ESI): calculated for $C_{16}H_{11}N_2O_2$ $[M+H]^+$ 263.0815, found 263.0817.

6-Bromo-2,3-di(furan-2-yl)quinoxaline (3v). White solid; yield 70%; mp 151-155 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.08 (d, *J* = 8.9 Hz, 1H), 7.71 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.68 – 7.66 (m, 2H), 6.75 – 6.73 (m, 2H), 6.61 (dd, *J* = 3.5, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 150.2, 144.2, 144.1, 142.9, 142.3, 140.5, 138.7, 135.8, 131.0, 129.9, 127.6, 113.3, 113.0, 111.7, 111.7; HRMS (ESI): calculated for $C_{16}H_{10}BrN_2O_2$ $[M+H]^+$ 340.9920, found 340.9922.

2,3-Di(furan-2-yl)-5-methylquinoxaline (3w). Light brown solid; yield 74%; mp 127-132 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.90 (s, 1H), 7.68 – 7.54 (m, 3H), 6.59 (d, *J* = 16.5 Hz, 4H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 150.4, 143.7, 143.5, 142.0, 141.3, 140.7, 140.2, 138.6, 132.4, 128.1, 127.4, 112.4, 112.2, 111.5, 21.5; HRMS (ESI): calculated for $C_{17}H_{13}N_2O_2$ $[M+H]^+$ 277.0972, found 277.0974.

2,3-Di(furan-2-yl)-5-nitroquinoxaline (3x). Light yellow solid; yield 82%; mp 153-155 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.3 Hz, 1H), 8.03 (d, *J* = 8.9 Hz, 1H), 7.66 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.63 – 7.62 (m, 2H), 6.70 – 6.68 (m, 2H), 6.56 (dd, *J* = 3.5, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 149.5, 147.2, 144.9, 144.5, 144.0, 143.5, 142.3, 138.5, 129.9, 124.5, 122.9, 114.8, 114.0, 112.0, 111.8; HRMS (ESI): calcd for $C_{16}H_{10}N_3O_4$ $[M+H]^+$ 308.0666, found 308.0668.

2,3-Dimethylquinoxaline (3y). White solid; yield 56%; mp 105-107 ˚C[28]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.50-7.48 (d, *J* = 2.13 Hz, 2H), 2.50 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 140.2, 139.9, 139.1, 128.2, 127.9, 20.1; HRMS (ESI): calculated for $C_{10}H_{11}N_2$ $[M+H]^+$ 159.0917, found 159.0919.

2-Methyl-3-phenylquinoxaline (3z). Brown solid; yield 59%; mp 119-124 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 8.02 (d, *J* = 8.49 Hz, 1H), 7.50, (1H), 7.53 (d, *J* = 7.17 Hz, 1H), 7.48 (d, *J* = 6.79 Hz, 3H), 7.30 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-*d*$_6$) δ 152.5, 151.8, 140.6, 139.84 139.0, 138.6, 131.8, 129.3, 128.2, 127.6, 127.4, 21.4; HRMS (ESI): calculated for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1073, found 221.1075.

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Supplementary Material

Supplementary material related to this article, including Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) figures for some compounds.

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