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Cerium oxide nanoparticle-catalyzed three-component protocol for the synthesis of highly substituted novel quinoxalin-2-amine derivatives and 3,4-dihydroquinoxalin-2-amines in water†

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The syntheses of novel quinoxalin-2-amine derivatives were conducted in water using CeO_2 nanoparticle catalyzed three-component reactions of 1,2-diamines with aldehydes and isocyanides. A variety of 3,4-dihydroquinoxalin-2-amine derivatives were also synthesized by reactions between 1,2-diamines, ketones and isocyanides. This new method offers an environmentally benign and effective approach for the synthesis of quinoxalin-2-amines and 3,4-dihydroquinoxalin-2-amines.

Introduction

One of the central goals in organic synthesis is to discover and identify reactions that enable processes to proceed in an environmentally benign and sustainable way.[1] The use of nanocatalysis and green chemistry holds the answer of sustainability.[2] The main focus of green chemistry concerns the avoidance of volatile organic solvents or their replacement with non-flammable, non-volatile, non-toxic, and inexpensive green alternatives.[3] Water is the reaction medium used by nature for biosynthesis, and has the advantage of being abundantly available, non-hazardous, non-flammable, redox-stable, and cheap. Thus, water is regarding as being an ideal green solvent, and preferable to alternatives like ionic liquids.[4] In addition, water facilitates solvation and molecular assembly processes that modulate reactivity and selectivity.[5] On the other hand, catalysis lies at the heart of innumerable chemical reactions,[6] due to their unique properties and nano-catalysts have considerably expanded the available possibilities.[7]

In particular, nano-catalysts have been widely used to construct synthetic routes that are environmentally compatible, safe, and high-yielding.[8] Furthermore, metal oxide nanoparticles recently provide sustainable alternatives to conventional catalysts in the organic chemistry sphere.[9] Their recyclability and ease of separation further increase their potentials.[10]

Molecules bearing a quinoxaline moiety are commonly found in natural and synthetic materials (Fig. 1),[11] and they have been shown to possess a range of significant biological and pharmacological properties.[12] For example, compounds **A** and **B** were isolated from beer,[13] and the synthesized compound **C** showed anti-leishmanial activity *in vitro*.[14] In addition, compounds **D**, (2-(4-(7-chloroquinoxalin-2-yl)-phenoxy]propionic acid (XK469), and **E** chloroquinoxaline-sulfonamide (CQS) are well known topoisomerase IIβ inhibitors[15] and anticancer reagents.[16] Compound **F** has high RhoA inhibitor activity and offers a basis for the development of new therapies for cardiovascular diseases.[17] In addition, naturally occurring antibiotics such as echinomycin, actinomycin, and levomycin with a quinoxaline skeleton show Gram-positive bacterial and various transplantable tumor activities.[18]

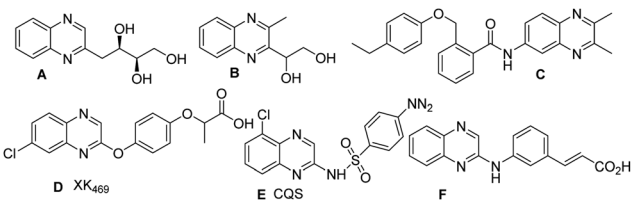
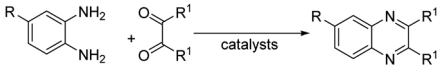


Fig. 1 Selected natural and synthetic molecules bearing quinoxalines.

Quinoxaline derivatives are also used as dyes, organic semiconductors, and other materials.[19] Due to their varied biological activities and industrial applications, several synthetic strategies have been developed for the preparation of quinoxalines[20] and dihydroquinoxalines.[21] As shown in Scheme 1, the general method used to synthesize quinoxalines is catalyzed aryl 1,2-amine to 1,2-dicarbonyl condensation; the catalysts used include gallium(III) triflate,[22] montmorillonite K10,[23]



Scheme 1 Reported general method for the synthesis of quinoxalines.

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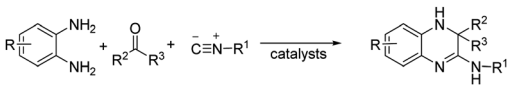
† Electronic supplementary information (ESI) available: Depiction of ^1H, ^{13}C NMR spectra for all products **5a–5q**, **7a–7i** and **14a–14b**. See DOI: 10.1039/c4ra00717d

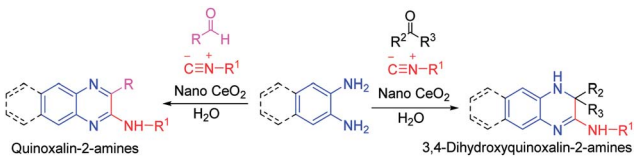
sulfamic acid,[24] cupric sulphate pentahydrate,[25] Zn (L-proline),[26] I_2,[27] cellulose sulphuric acid,[28] and zirconium tetrakis(dodecyl sulphate).[29]

The three-component reactions between aryl 1,2-amines, carbonyls, and isocyanides in the presence of a suitable catalyst such as *p*-TsOH,[30] $Fe(ClO_4)$,[31] ceric ammonium nitrate (CAN),[32] or Amberlyst-15 (Scheme 2)[33] provide any alternative means of synthesizing dihydroquinoxalines. In fact, we previously described the EDTA-catalyzed syntheses of a series of 3,4-dihydroquinoxalin-2-amine derivatives involving three-component coupling using one-pot condensation reactions.[34] Importantly, in these reactions, quinoxalin-2-amines were not produced.

Despite their own merits, many existing methods for the synthesis of quinoxalines and dihydroquinoxalines suffer from shortcomings including toxic organic solvents, long reaction times, the necessity of large amounts of expensive catalysts, and harsh reaction conditions. Therefore, more environmentally benign and efficient arsenals are still needed improving on these shortcomings, which prompt us to develop new approaches relying on the use of green catalysts.



Scheme 2 Reported method for the synthesis of 3,4-dihydroquinoxalin-2-amines.



Scheme 3 Three-component reactions for the synthesis of quinoxalin-2-amines and 3,4-dihydroxyquinoxalin-2-amines.

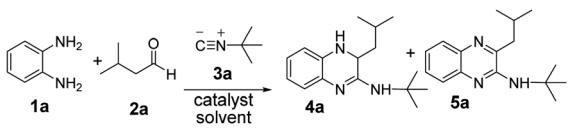
Cerium oxide nanoparticles (CeO_2-NPs) are environmentally benign and economically feasible heterogeneous catalysts that offer several advantages, such as, sustainability in water, low cost, high catalytic reactivity, ease of handling, non-toxicity, reusability, and experimental simplicity.[35] Because of their importance, CeO_2-NPs have been extensively used as catalysts,[35] catalyst supports,[36] sunscreens,[37] gas sensors,[38] and fluorescent materials,[39] and have been used as automotive catalysts,[40] fuel cells,[41] and heterogeneous catalytic ozonation reagents.[42]

To the best of our knowledge, no report has been issued on the synthesis of quinoxaline-2-amines using CeO_2-NPs as a reusable heterocatalyst. Recently, in water medium, we have described environmentally benign and facile synthesis of 2*H*-pyrans.[43] In continuation with our studies on the development of a new methodology in water medium, we report herein an efficient and facile one-pot synthesis of quinoxalin-2-amines and 3,4-dihydroquinoxalin-2-amines *via* a three-component condensation of diamines with aldehydes/ketones, and isocyanides in the presence of catalytic amounts of CeO_2 nanoparticles (Scheme 3).

Results and discussion

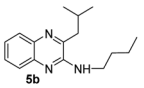
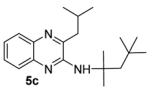
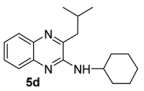
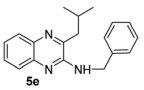
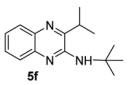
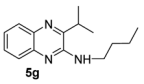
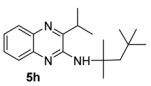
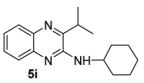
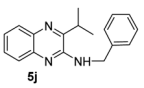
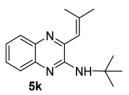
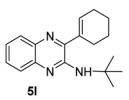
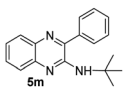
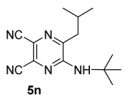
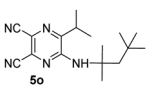
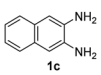
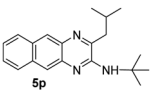
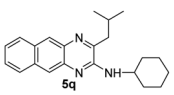
To afford quinoxaline-2-amines, treatment of *o*-phenylenediamine (**1a**) with isovaleraldehyde (**2a**) and *tert*-butyl isocyanide (**3a**) was first attempted under several conditions. In the absence of a catalyst at 80 °C for 12 h in water, only a trace amount of product **5a** was formed and most of starting material was recovered (entry 1, Table 1). With $InCl_3$ or $CeCl_3 \cdot 7H_2O$ as catalysts, the product **5a** was isolated in 58 and 64% yield, respectively (entries 2 and 3). With ceric ammonium nitrate (CAN), **5a** was isolated in 70% yield (entry 4). With CeO_2-nanoparticles, further reactions were investigated under several solvents. Interestingly, the best yield (92%) was obtained in the presence of 5 mol% or 10 mol% of CeO_2-NPs in water (entry 7). Importantly, in this reaction, only **5a** was formed and the

Table 1 Optimization of reaction conditions for the synthesis of **5a**



Entry	Catalyst	Solvent	Temp.	Time (h)	Yield (%) 4a	5a
1	—	H_2O	80 °C	12	0	Trace
2	$InCl_3$ (10 mol%)	H_2O	80 °C	8	0	58
3	$CeCl_3 \cdot 7H_2O$ (10 mol%)	H_2O	80 °C	6	0	64
4	$(NH_4)_2Ce(NO_3)_6$ (10 mol%)	H_2O	80 °C	4	0	70
5	CeO_2-NPs (2 mol%)	H_2O	80 °C	2	0	78
6	CeO_2-NPs (5 mol%)	H_2O	80 °C	2	0	92
7	CeO_2-NPs (10 mol%)	H_2O	80 °C	2	0	92
8	CeO_2-NPs (5 mol%)	Toluene	100 °C	9	0	35
9	CeO_2-NPs (5 mol%)	Ethanol	78 °C	6	0	54
10	CeO_2-NPs (5 mol%)	CH_3CN	80 °C	4	0	68

Table 2 Additional reactions of 1,2-diamines with several aldehydes and isocyanides[a]

Entry	1,2-Diamine	Aldehyde	Isocyanide	Time (h)	Product	Yield[b] (%)
1			 3b	2	 5b	81
2		 2a	 3c	2	 5c	86
3	 1a		 3d	2	 5d	76
4			 3e	2	 5e	84
5			**3a**	2	 5f	91
6			**3b**	2	 5g	76
7	 1a	 2b	**3c**	2	 5h	82
8			**3d**	2	 5i	82
9			**3e**	2	 5j	87
10		 2c		2	 5k	71
11		 2d	**3a**	2	 5l	67
12		 2e		12	 5m	0
13	 1b	**2a**	**3a**	2	 5n	81
14		**2b**	**3c**	2	 5o	77
15	 1c	**2a**	**3a**	2	 5p	67
16		**2a**	**3d**	2	 5q	66

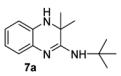
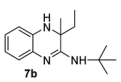
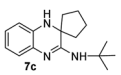
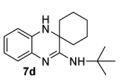
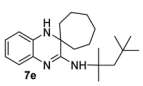
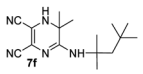
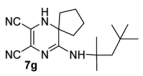
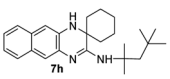
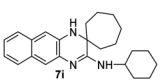
[a] Reaction conditions: 1,2-diamines (1.0 mmol), aldehyde (1.0 mmol), and isocyanide (1.0 mmol) catalyst CeO_2-NPs (5 mol%), water (3.0 mL), 80 °C.
[b] Isolated yields after column chromatography.

expected **4a** was not produced. The structure of **5a** was determined by ^{1}H NMR, which showed 4 aromatic protons on a quinoxaline ring at δ_H 7.78 (1H, dd, J = 8.1, 0.9 Hz), 7.65 (1H, dd, J = 8.1, 0.9 Hz), 7.46 (1H, td, J = 6.9, 1.5 Hz), and 7.30 (1H, td, J = 6.9, 1.5 Hz) ppm. In the ^{13}C NMR spectrum of **5a**, 8 carbon peaks on a quinoxaline showed at δ_C 150.2, 147.5, 140.9, 136.0, 128.4, 128.0, 126.2, and 123.7 ppm.

Additional reactions between various 1,2-diamines, aldehydes, and isocyanides were carried out to determine the generality and efficiency under optimized conditions (Table 2). Reactions between *o*-phenylenediamine (**1a**), isovaleraldehyde (**2a**), and *n*-butyl isocyanide (**3b**), 1,1,3,3-tetramethyl butyl isocyanide (**3c**), cyclohexyl isocyanide (**3d**), or benzyl isocyanide (**3e**) in the presence of 5 mol% of CeO_2-NPs in water at 80 °C for 2 h afforded the corresponding quinoxalin-2-amine derivatives **5b–5e** in 76–86% yield (Table 2, entries 1–4). Furthermore, treatment of **1a** with isobutyraldehyde (**2b**) and isocyanides **3a–3e** for 2 h provided the expected products **5f–5j** in 76–91% yield (Table 2, entries 5–9). With α,β-unsaturated aldehydes like 3-methyl-2-butenal (**2c**) or 1-cyclohexene-1-carboxaldehyde (**2d**), the desired products **5k** and **5l** were formed in 71 and 67% yield, respectively (entries 10 and 11). However, when benzaldehyde was used, the desired product **5m** was not formed (entry 12). To investigate the scope and limitations of this cyclization, three-component reactions using diaminomaleonitrile (**1b**) or diaminonaphthalene (**1c**) were next attempted. Reaction of **1b** with isovaleraldehyde (**2a**) and *tert*-butyl isocyanide (**3a**) afforded **5n** in 81% yield (entry 13), whereas reaction between **1b** with **2b** and **3c** provided **5o** in 77% yield (entries 14). In addition, reaction between diaminonaphthalene (**1c**) with **2a** and **3a** or **3d** afforded **5p** and **5q** in 67 and 66% yield, respectively (entries 15 and 16). Accordingly, these reactions were found to provide a rapid route to the synthesis of a variety of quinoxaline-2-amine derivatives in good yield.

The generality and usefulness of this aqueous approach utilizing CeO_2-NPs as a catalyst were further demonstrated by reactions between 1,2-diamines, ketones, and isocyanides to form the corresponding 3,4-dihydroquinoxalin-2-amine derivatives. Further reactions between 1,2-diamines **1**, various ketones **6**, and several isocyanides **3** were carried out in the presence of 5 mol% of CeO_2 in water. Results are summarized in Table 3. All reactions were highly regioselective and no other products were observed. Reactions between *o*-phenylenediamine (**1a**), acetone (**6a**) or propanone (**6b**), and *tert*-butyl isocyanide (**3a**) in water at 80 °C for 2 h provided the 3,4-dihydoquinoxalin-2-amines **7a** and **7b** in 94 and 93% yield, respectively (Table 3, entries 1 and 2). When cyclopentanone, cyclohexanone, or cycloheptanone were used, the products **7c–7e** were produced in 91, 89, and 83% yield, respectively (entries 3–5). Interestingly, when diaminomalenonitrile (**1b**) and diaminonaphthalene (**1c**) were used, the products **7f–7i** were obtained in 79–94% yield (entries 6–9). Accordingly, these

Table 3 Additional reactions of 1,2-diamines with several ketones and isocyanides[a]

Entry	1,2-Diamine	Ketone	Isocyanide	Time (h)	Product	Yield[b] (%)
1				2		94
2				2		93
3				2		91
4				2		89
5				2		83
6		**6a**		2		93
7		**6c**		2		94
8		**6d**		2		81
9		**6e**		2		79

[a] Reaction conditions: 1,2-diamines (1.0 mmol), ketone (1.0 mmol), and isocyanide (1.0 mmol) catalyst CeO_2-NPs (5 mol%), water (3.0 mL), 80 °C.
[b] Isolated yields after column chromatography.

reactions were found to provide rapid synthetic routes to a variety of 3,4-dihydroquinoxalin-2-amine derivatives.

The aqueous nano-catalyzed three-component protocol described above results in a potential medicinal scaffold, conforms to the principles of green chemistry, and offers a potential means of developing combinatorial libraries. Green aspects of this reaction include high atom economy, its multi-component nature, and the use of water as the reaction medium. The movement of green chemistry has developed a series of metrics to support and reinforce behaviour change in both industry and academia in the move towards green and more sustainable chemistry.[44] Two most common green metrics including atom economy and atom efficiency are calculated below.

Atom economy (A. Eco) is calculated below for:

(i) compound **5a**

% A. Eco = molecular mass of desired product/(molecular mass of all reactants) × 100 = 257.37/(108.14 + 86.13 + 83.13) × 100 = 92.78%

(ii) compound **7a**

% A. Eco = molecular mass of desired product/(molecular mass of all reactants) × 100 = 231.33/(108.14 + 58.07 + 83.13) × 100 = 92.77%

Atom efficiency is calculated below for:

(i) compound **5a**

% Atom efficiency = (yield × A. Eco)/100 = (92% × 92.78%)/100 = 85.35%

(ii) compound **7a**

% Atom efficiency = (yield × A. Eco)/100 = (94% × 92.77%)/100 = 87.20%

Catalyst recyclability is an essential aspect of green chemistry. After completing reactions under optimized conditions, the catalyst was recovered by filtering reaction mixtures, washing residues with dichloromethane and/or water, and drying at 80 °C. The recovered catalyst was then reused to perform the same reactions with fresh raw materials under identical conditions. We found the effectiveness of CeO_2-NPs was not significantly affected up to the fourth cycle, but product yields were slightly reduced during the fifth cycle. A chart of the catalytic potential of recycled CeO_2-NPs is provided in Fig. 2.

A possible reaction mechanism is suggested as shown in Scheme 4.We suggest that the carbonyl group of aldehyde **2** is activated by coordination with oxygen of CeO_2-NPs to give the

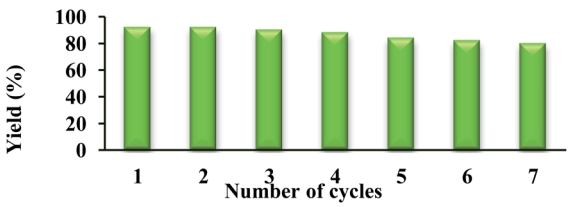
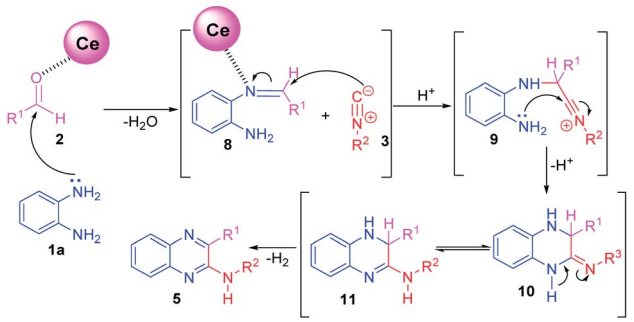
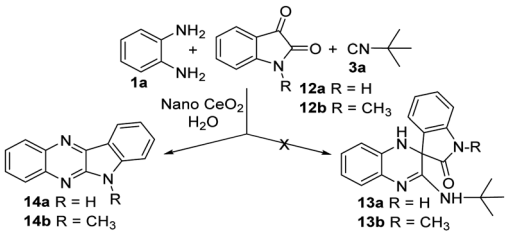


Fig. 2 Recovery and reuse of CeO_2-NPs for the synthesis of **5a**.



Scheme 4 Proposed mechanism for the formation of product **5**.



Scheme 5 Reaction of **1a** with isatins **12a–12b** and isocyanide **3a** for the synthesis of compounds **14a–14b**.

iminium ion **8**. Nucleophilic addition of isocyanide **3** to **8** would give the intermediate **9**, which undergoes intramolecular cycloaddition to afford other intermediate **10**. Isomerization of **10** followed by subsequent oxidation would give the final product **5**.

Finally, to investigate further use of CeO_2-NPs, reactions between 1,2-diamine **1a**, isatins, and isocyanides were also attempted (Scheme 5). For example, the reaction between **1a**, isatin (**12a**) or *N*-methylisatin (**12b**), and *tert*-butyl isocyanide (**3a**) afforded **14a** and **14b** in 94 and 95% yield, respectively, without any formation of desired **13a** and **13b**. The structures of compounds **14a** and **14b** were determined by comparing with spectral data of previously reported results.[45]

Conclusions

In summary, we have developed a novel one-pot three-component reaction to the synthesis of quinoxalin-2-amine and 3,4-dihydroquinoxaline-2-amine derivatives starting from various simple and readily available 1,2-diamines, diverse carbonyl compounds, and isocyanides. This multi-component reaction allows the synthesis of medicinally important indophenazines, which should find various applications in the synthesis of pharmaceuticals. This methodology offers several advantages, including high product yield, ease of experimental procedure, and an environmentally benign character.

Experimental section

All experiments were carried out under nitrogen. Merck pre-coated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR and ^{13}C

NMR spectra were recorded at 25 °C on Bruker Avance DPX 300 MHz spectrometer or a Varian VNS 300 MHz spectrometer in $CDCl_3$, DMSO-d_6 as solvent. Multiplicities are abbreviated as s = singlet, d = doublet, t = triplet, m = multiplet. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. All melting points (uncorrected) were obtained on a Fischer-Johns melting point apparatus. HRMS was carried out at the Korean Basic Science Institute.

General procedure for the synthesis of quinoxalin-2-amine derivatives (5a–5q)

To a solution of 1,2-diamine (1.0 mmol), aldehyde (1.0 mmol), and isocyanide (1.0 mmol) in 3 mL of water was added CeO_2-NPs (5 mol%). The resulting mixture was gently heated at 80 °C. Reaction completion was monitored by TLC. The crude product was dissolved in ethyl acetate and purified by silica gel column chromatography using hexane–ethyl acetate (9 : 1) as eluent to afford the desired compounds **5a–5q**.

***N-tert*-Butyl-3-isobutylquinoxalin-2-amine (5a).** Solid (237 mg, 92%), mp 47–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.78 (1H, dd, J = 8.1, 0.9 Hz), 7.65 (1H, dd, J = 8.1, 0.9 Hz), 7.46 (1H, td, J = 6.9, 1.5 Hz), 7.30 (1H, td, J = 6.9, 1.5 Hz), 4.66 (1H, br s, NH), 2.61 (2H, d, J = 6.9 Hz), 2.34–2.20 (1H, m), 1.54 (9H, s), 1.01 (6H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 150.2, 147.5, 140.9, 136.0, 128.4, 128.0, 126.2, 123.7, 51.9, 43.0, 28.8, 26.9, 22.8; IR (KBr): 3456, 2959, 2870, 1942, 1673, 1576, 1518, 1456, 1362, 1215, 1169, 1098, 943, 759 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{16}H_{23}N_3$: 257.1892, found 257.1894.

***N*-Butyl-3-isobutylquinoxalin-2-amine (5b).** Liquid (208 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.80 (1H, d, J = 8.1 Hz), 7.66 (1H, d, J = 8.1 Hz), 7.47 (1H, t, J = 6.9 Hz), 7.31 (1H, td, J = 8.1, 0.6 Hz), 4.72 (1H, br s, NH), 3.57 (2H, q, J = 6.3 Hz), 2.63 (2H, d, J = 6.6 Hz), 2.34–2.25 (1H, m), 1.71–1.62 (2H, m), 1.50–1.38 (2H, m), 0.95 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 150.7, 147.2, 141.2, 136.5, 128.2, 128.0, 126.0, 123.3, 42.7, 40.9, 31.4, 26.8, 26.5, 21.8, 20.2, 13.8; IR (neat): 3459, 2956, 2868, 1943, 1762, 1666, 1575, 1521, 1463, 1371, 1165, 1102, 948, 758 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{16}H_{23}N_3$: 257.1892, found 257.1894.

3-Isobutyl-*N*-(2,4,4-trimethylpentan-2-yl)quinoxalin-2-amine (5c). Liquid (270 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.77 (1H, dd, J = 9.0, 0.9 Hz), 7.64 (1H, dd, J = 9.0, 0.9 Hz), 7.46 (1H, td, J = 6.9, 1.5 Hz), 7.29 (1H, td, J = 6.9, 1.5 Hz), 4.71 (1H, br s, NH), 2.60–2.58 (2H, m), 2.35–2.22 (1H, m), 2.00 (2H, s), 1.59 (6H, s), 1.02–0.99 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 150.2, 147.4, 140.9, 135.9, 128.4, 128.0, 126.2, 123.6, 55.9, 51.5, 43.1, 31.8, 31.4, 29.3, 29.1, 26.6; IR (neat): 3469, 3057, 2955, 1762, 1670, 1576, 1517, 1465, 1365, 1237, 1163, 1056, 941, 757 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{20}H_{31}N_3$: 313.2518, found 313.2520.

***N*-Cyclohexyl-3-isobutylquinoxalin-2-amine (5d).** Semi solid (216 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.79 (1H, dd, J = 9.0, 0.9 Hz), 7.64 (1H, dd, J = 9.0, 0.9 Hz), 7.47 (1H, td, J = 8.1, 1.5 Hz), 7.30 (1H, td, J = 8.1, 1.5 Hz), 4.62 (1H, d, J = 7.2 Hz, NH), 4.21–4.09 (1H, m), 2.62 (2H, d, J = 6.9 Hz), 2.35–2.22 (1H, m), 2.14–2.09 (2H, m), 1.78–1.64 (3H, m), 1.55–1.42 (2H, m), 1.31–1.18 (3H, m), 1.01 (6H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 149.9, 147.2, 141.2, 136.5, 128.6, 128.1, 125.8, 123.7, 49.0, 42.7, 33.0, 26.8, 25.8, 24.8, 22.8; IR (KBr): 3454, 2929, 2857, 1574, 1515, 1458, 1337, 1264, 1164, 1093, 1019, 890, 757 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{18}H_{25}N_3$: 283.2048, found 283.2047.

***N*-Benzyl-3-isobutylquinoxalin-2-amine (5e).** Liquid (245 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.84 (1H, d, J = 8.1 Hz), 7.70 (1H, d, J = 8.1 Hz), 7.52 (1H, t, J = 7.2 Hz), 7.39–7.29 (6H, m), 5.03 (1H, br s, NH), 4.79 (2H, d, J = 4.5 Hz), 2.65 (2H, d, J = 6.9 Hz), 2.37–2.28 (1H, m), 1.00 (6H, d, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 150.4, 147.1, 140.9, 139.0, 136.9, 128.8, 128.7, 128.2, 127.9, 127.4, 125.9, 124.2, 45.4, 42.6, 26.7, 22.7; IR (neat): 3453, 3385, 3060, 2956, 1673, 1575, 1519, 1461, 1322, 1231, 1165, 1103, 1024, 948, 757 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{19}H_{21}N_3$: 291.1735, found 291.1735.

***N-tert*-Butyl-3-isopropylquinoxalin-2-amine (5f).** Solid (221 mg, 91%), mp 94–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.81 (1H, d, J = 8.1 Hz), 7.66 (1H, d, J = 8.1 Hz), 7.47 (1H, dd, J = 8.1, 1.2 Hz), 7.31 (1H, dd, J = 8.1, 1.2 Hz), 4.76 (1H, br s, NH), 3.02–2.93 (1H, m), 1.57 (9H, s), 1.37 (6H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 151.9, 149.2, 140.6, 136.1, 128.3, 128.2, 126.1, 123.6, 51.9, 30.7, 28.9, 20.3; IR (KBr): 3444, 3071, 2964, 1517, 1458, 1317, 1214, 1080, 944, 758 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{15}H_{21}N_3$: 243.1735, found 243.1732.

***N*-Butyl-3-isopropylquinoxalin-2-amine (5g).** Solid (185 mg, 76%), mp 52–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.81 (1H, dd, J = 8.1, 0.9 Hz), 7.65 (1H, dd, J = 8.1, 0.9 Hz), 7.47 (1H, td, J = 8.4, 1.5 Hz), 7.31 (1H, td, J = 8.4, 1.5 Hz), 4.81 (1H, br s, NH), 3.59 (2H, q, J = 6.9 Hz), 3.06–2.97 (1H, m), 1.70–1.63 (2H, m), 1.49–1.42 (2H, m), 1.37 (6H, d, J = 6.6 Hz), 1.00–0.93 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 151.8, 149.8, 140.9, 136.6, 128.6, 128.3, 125.7, 123.8, 41.0, 31.5, 30.5, 29.6, 20.3, 14.1; IR (KBr): 3402, 3061, 2926, 2861, 1573, 1521, 1465, 1311, 1229, 1090, 949, 805, 762 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{15}H_{21}N_3$: 243.1735, found 243.1732.

3-Isopropyl-*N*-(2,4,4-trimethylpentan-2-yl)quinoxalin-2-amine (5h). Solid (246 mg, 82%), mp 77–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.80 (1H, dd, J = 8.1, 0.9 Hz), 7.66 (1H, dd, J = 8.1, 0.9 Hz), 7.47 (1H, td, J = 8.4, 1.5 Hz), 7.30 (1H, td, J = 8.4, 1.5 Hz), 4.81 (1H, br s, NH), 3.01–2.92 (1H, m), 2.04 (2H, s), 1.62 (6H, s), 1.37 (6H, d, J = 6.6 Hz), 1.02 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 151.9, 149.2, 140.6, 136.0, 128.3, 128.2, 126.1, 123.5, 55.8, 51.5, 31.7, 31.6, 30.6, 29.3, 20.5; IR (KBr): 3459, 3064, 2959, 2872, 1944, 1572, 1517, 1468, 1420, 1306, 1220, 1127, 1081, 940, 755 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{19}H_{29}N_3$: 299.2361, found 299.2364.

***N*-Cyclohexyl-3-isopropylquinoxalin-2-amine (5i).** Solid (222 mg, 82%), mp 98–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.80 (1H, dd, J = 8.1, 0.9 Hz), 7.63 (1H, dd, J = 8.1, 0.9 Hz), 7.45 (1H, td, J = 8.1, 1.2 Hz), 7.39 (1H, td, J = 8.1, 1.2 Hz), 4.71 (1H, d, J = 6.9 Hz), 4.27–4.09 (1H, m), 3.05–2.96 (1H, m), 2.15–2.11 (2H, m), 1.78 (8H, m), 1.37 (6H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 151.7, 148.9, 141.0, 136.5, 128.5, 128.3, 125.7, 123.6, 49.0, 33.1, 30.5, 29.6, 25.8, 24.8, 20.3; IR (KBr): 3406, 2968, 2370, 1522, 1463, 1321, 1078, 915, 726 cm^{-1}; HRMS (EI$^+$): m/z: calcd for $C_{17}H_{23}N_3$: 269.1892, found 269.1893.

***N*-Benzyl-3-isopropylquinoxalin-2-amine (5j).** Solid (241 mg, 87%), mp 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.85 (1H, dd, J = 8.1, 0.9 Hz), 7.69 (1H, dd, J = 8.1, 0.9 Hz), 7.50 (1H, td, J = 8.1, 1.5 Hz), 7.43–7.27 (6H, m), 5.10 (1H, br s, NH), 4.80 (2H, d,

$J = 5.1$ Hz), 3.07–2.98 (1H, m), 1.37 (6H, d, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 151.7, 149.4, 140.7, 139.0, 136.9, 128.7, 128.3, 128.0, 127.4, 125.8, 124.1, 45.5, 40.9, 30.5, 20.4; IR (KBr): 3409, 2970, 2368, 1519, 1461, 1318, 1075, 915, 734 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{18}H_{19}N_3$: 277.1579, found 277.1581.

***N*-*tert*-Butyl-3-(2-methylprop-1-enyl)quinoxalin-2-amine (5k).** Liquid (181 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.78 (1H, d, $J = 8.1$ Hz), 7.64 (1H, d, $J = 8.1$ Hz), 7.47 (1H, t, $J = 8.1$ Hz), 7.29 (1H, t, $J = 8.1$ Hz), 6.12 (1H, s), 4.87 (1H, br s, NH), 1.99 (3H, s), 1.85 (3H, s), 1.53 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 150.2, 145.2, 145.1, 141.0, 136.0, 128.7, 128.3, 126.2, 123.7, 119.2, 51.8, 28.7, 26.3, 19.9; IR (neat): 3430, 2969, 2316, 1763, 1644, 1567, 1516, 1452, 1313, 1242, 1056, 759 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{16}H_{21}N_3$: 255.1735, found 255.1737.

***N*-*tert*-Butyl-3-cyclohexenylquinoxalin-2-amine (5l).** Solid (188 mg, 67%), mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.78 (1H, dd, $J = 8.1$, 0.9 Hz), 7.62 (1H, dd, $J = 8.1$, 0.9 Hz), 7.46 (1H, td, $J = 6.9$, 1.5 Hz), 7.28 (1H, td, $J = 6.9$, 1.5 Hz), 6.12 (1H, m), 5.20 (1H, br s, NH), 2.40–2.37 (2H, m), 2.24–2.21 (2H, m), 1.83–1.71 (4H, m), 1.51 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 149.4, 149.3, 141.1, 135.9, 135.9, 129.7, 128.8, 128.4, 126.1, 123.7, 51.7, 28.9, 28.6, 27.4, 25.2, 22.6, 21.7; IR (KBr): 3430, 3061, 2937, 2372, 1518, 1454, 1410, 1359, 1315, 1220, 1138, 1014, 940, 756 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{18}H_{23}N_3$: 281.1892, found 281.1889.

5-(*tert*-Butylamino)-6-isobutylpyrazine-2,3-dicarbonitrile (5n). Semi solid (224 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.11 (1H, br s, NH), 2.43 (2H, d, $J = 6.9$ Hz), 2.28–2.20 (1H, m), 1.47 (9H, s), 0.98 (6H, d, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 151.8, 147.7, 129.6, 118.8, 114.8, 114.0, 53.6, 41.7, 28.3, 25.8, 22.6; IR (KBr): 3411, 2963, 2925, 2229, 1769, 1658, 1565, 1460, 1397, 1213, 1106, 805, 692 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{14}H_{19}N_5$: 257.1640, found 257.1642.

5-Isobutyl-6-(2,4,4-trimethylpentan-2-ylamino)pyrazine-2,3-dicarbonitrile (5o). Liquid (231 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.29 (1H, br s, NH), 2.84–2.75 (1H, m), 1.85 (2H, s), 1.52 (6H, s), 1.25 (6H, d, $J = 6.6$ Hz), 0.98 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 149.0, 117.3, 114.4, 112.9, 108.3, 57.2, 57.1, 51.2, 42.2, 31.6, 31.4, 29.3, 28.8, 28.7, 18.7, 18.0; IR (neat): 3380, 2963, 2879, 2228, 1768, 1653, 1583, 1533, 1389, 1259, 1120, 1025, 803, 739 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{17}H_{25}N_5$: 299.2110, found 299.2108.

***N*-*tert*-Butyl-3-isobutylbenzo[*g*]quinoxalin-2-amine (5p).** Semi solid (206 mg, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.32 (1H, s), 8.11 (1H, s), 7.92 (2H, t, $J = 9.3$ Hz), 7.44–7.33 (2H, m), 4.82 (1H, br s, NH), 2.66–2.64 (2H, d, $J = 6.9$ Hz), 2.39–2.30 (1H, m), 1.59 (9H, s), 1.06 (6H, d, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 150.2, 149.4, 135.0, 133.9, 130.5, 128.3, 127.3, 126.3, 125.7, 124.0, 122.3, 52.1, 43.3, 29.7, 28.9, 27.0, 22.9; IR (KBr): 3463, 3051, 2924, 2857, 2354, 1676, 1581, 1510, 1455, 1359, 1262, 1218, 1095, 1030, 877, 742 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{20}H_{25}N_3$: 307.2048, found 307.2051.

***N*-Cyclohexyl-3-isobutylbenzo[*g*]quinoxalin-2-amine (5q).** Semi solid (220 mg, 66%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.34 (1H, s), 8.11 (1H, s), 7.90–7.89 (2H, m), 7.44–7.33 (2H, m), 4.80 (1H, d, $J = 6.9$ Hz, NH), 4.27–4.12 (1H, m), 2.68 (2H, d, $J = 7.2$ Hz), 2.40–2.31 (1H, m), 2.19–2.15 (2H, m), 1.80–1.68 (3H, m), 1.54–1.46 (2H, m), 1.30–1.22 (3H, m), 1.07–1.04 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 149.9, 149.2, 138.8, 135.3, 133.9, 130.5, 128.3, 127.3, 126.4, 125.8, 124.0, 121.9, 49.0, 42.9, 33.0, 29.6, 26.8, 25.8, 24.8, 22.8; IR (KBr): 3454, 3050, 2925, 2369, 1929, 1673, 1581, 1509, 1372, 1261, 1097, 877, 742 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{22}H_{27}N_3$: 333.2205, found 333.2202.

General procedure for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives (7a–7i)

To a solution of 1,2-diamine (1.0 mmol), ketone (1.0 mmol), and isocyanide (1.0 mmol) in 3 mL of water was added CeO_2-NPs (5 mol%). The resulting mixture was gently heated at 80 °C. Reaction completion was monitored by TLC. The crude product was dissolved in ethyl acetate and purified by silica gel column chromatography using hexane–ethyl acetate (7 : 3) as eluent to afford the desired compounds **7a–7i.**

***N*-*tert*-Butyl-3,3-dimethyl-3,4-dihydroquinoxalin-2-amine (7a).** Solid (218 mg, 94%), mp 90–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.03 (1H, m), 6.80–6.71 (2H, m), 6.52 (1H, m), 4.18 (1H, br s, NH), 3.42 (1H, br s, NH), 1.46 (9H, s), 1.25 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 157.4, 135.4, 134.7, 123.8, 122.5, 119.3, 113.4, 51.5, 50.4, 28.9, 26.0; IR (KBr): 3438, 3370, 3047, 2869, 1619, 1585, 1511, 1229, 748 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{14}H_{21}N_3$: 231.1735, found 231.1736.

***N*-*tert*-Butyl-3-ethyl-3-methyl-3,4-dihydroquinoxalin-2-amine (7b).** Solid (228 mg, 93%), mp 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.99 (1H, d, $J = 6.9$ Hz), 6.76–6.69 (2H, m), 6.48 (1H, d, $J = 7.5$ Hz), 4.13 (1H, br s, NH), 3.45 (1H, br s, NH), 1.58–1.50 (2H, m), 1.45 (9H, s), 1.27 (3H, s), 0.90 (3H, t); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 156.6, 135.0, 134.7, 123.7, 122.5, 118.9, 112.9, 53.5, 51.5, 31.2, 29.0, 24.1; IR (KBr): 3451, 3349, 2965, 1613, 1514, 1267, 748 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{15}H_{23}N_3$: 245.1892, found 245.1896.

***N*-*tert*-Butyl-1′*H*-spiro[cyclopentane-1,2′-quinoxalin]-3′-amine (7c).** Solid (233 mg, 91%); mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.03 (1H, dd, $J = 7.2$, 1.5 Hz), 6.75–6.71 (2H, m), 6.51 (1H, dd, $J = 7.2$, 1.5 Hz), 4.16 (1H, br s, NH), 3.61 (1H, br s, NH), 1.76–1.68 (8H, m), 1.46 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 157.1, 136.4, 135.0, 123.8, 122.3, 119.5, 113.6, 61.6, 51.5, 36.9, 28.9, 24.0; IR (KBr): 3462, 3297, 2960, 2879, 2343, 1614, 1582, 1518, 1472, 1359, 1263, 1223, 1098, 1037, 803, 746 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{16}H_{23}N_3$: 257.1892, found 257.1894.

***N*-*tert*-Butyl-1′*H*-spiro[cyclohexane-1,2′-quinoxalin]-3′-amine (7d).** Solid (242 mg, 89%), mp 106–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.06 (1H, dd, $J = 7.2$, 1.5 Hz), 6.85–6.75 (2H, m), 6.63 (1H, dd, $J = 7.2$, 1.5 Hz), 4.36 (1H, br s), 4.13 (1H, br s), 1.84–1.80 (2H, m), 1.74–1.60 (3H, m), 1.50 (9H, s), 1.45–1.39 (4H, m), 1.29–1.20 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 157.4, 135.5, 133.9, 123.6, 122.2, 119.3, 113.6, 51.5, 51.4, 31.6, 28.9, 25.0, 20.7; IR (KBr): 3435, 2928, 2859, 1612, 1574, 1512, 1219, 741 cm^{-1}; HRMS (EI$^+$): *m*/*z*: calcd for $C_{17}H_{25}N_3$: 271.2048, found 217.2046.

***N*-(2,4,4-Trimethylpentan-2-yl)-1′*H*-spiro[cycloheptane-1,2′-quinoxalin]-3′-amine (7e).** Solid (284 mg, 83%), mp 79–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.01 (1H, dd, $J = 6.9$, 1.5 Hz), 6.80–6.71 (2H, m), 6.54 (1H, dd, $J = 6.9$, 1.5 Hz), 4.27 (1H, br s, NH), 3.78 (1H, br s, NH), 1.91 (2H, s), 1.76–1.71 (4H, m), 1.58–1.52 (14H, m), 1.03 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 158.1,

135.7, 134.3, 123.5, 122.2, 119.2, 113.6, 55.7, 55.5, 52.0, 36.1, 31.6, 30.5, 29.1, 22.8; IR (KBr): 3465, 3371, 2919, 2363, 1613, 1511, 1366, 1211, 1074, 738 cm^{-1}; HRMS (EI^+): *m*/*z*: calcd for $C_{22}H_{35}N_3$: 341.2831, found 341.2828.

6,6-Dimethyl-5-(2,4,4-trimethylpentan-2-ylamino)-1,6-dihydropyrazine-2,3-dicarbonitrile (7f). Solid (267.2 mg, 93%), mp 150–151 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 4.69 (1H, br s, NH), 3.87 (1H, br s, NH), 1.77 (2H, s), 1.42 (6H, s), 1.21 (6H, s), 0.96 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 153.0, 116.8, 114.1, 113.5, 108.6, 57.0, 49.1, 32.4, 31.6, 30.6, 28.9, 23.8, 23.1; IR (KBr): 3414, 3346, 2962, 2369, 2217, 1552, 1454, 1360, 1316, 1222, 1133, 1033, 848, 711 cm^{-1}; HRMS (EI^+): *m*/*z*: calcd for $C_{16}H_{25}N_5$: 287.2110, found 287.2111.

10-(2,4,4-Trimethylpentan-2-ylamino)-6,9-diazaspiro[4.5]deca-7,9-diene-7,8-dicarbonitrile (7g). Solid (295 mg, 94%), mp 146–147 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 4.71 (1H, br s), 4.04 (1H, br s), 1.77–1.67 (10H, m), 1.42 (6H, s), 0.95 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 151.7, 117.0, 114.4, 114.3, 108.5, 56.9, 51.2, 35.4, 31.6, 31.5, 31.4, 28.7, 28.6, 23.1; IR (KBr): 3436, 3343, 2964, 2214, 1676, 1552, 1469, 1362, 1298, 1220, 1149, 1034, 978, 858, 701 cm^{-1}; HRMS (EI^+): *m*/*z*: calcd for $C_{18}H_{27}N_5$: 313.2266, found 313.2263.

***N*-(2,4,4-Trimethylpentan-2-yl)-1*H*-spiro[benzo[*g*]quinoxaline-2,1′-cyclohexan]-3-amine (7h).** Solid (306 mg, 81%), mp 140–142 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.58 (1H, d, $J = 7.5$ Hz), 7.47 (1H, d, $J = 7.5$ Hz), 7.35 (1H, s), 7.17–7.06 (2H, m), 6.85 (1H, s), 4.44 (1H, br s, NH), 4.41 (1H, br s, NH), 1.88 (2H, s), 1.88–1.54 (8H, m), 1.50 (6H, s), 1.40–1.33 (2H, m), 0.97 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 159.0, 136.1, 135.0, 130.8, 129.5, 126.5, 124.8, 123.3, 121.9, 119.2, 107.5, 55.4, 51.7, 51.6, 41.6, 32.0, 31.4, 31.4, 28.9, 26.6, 24.7, 24.6, 20.4; IR (KBr): 3479, 3349, 2943, 1740, 1584, 1522, 1472, 1359, 1225, 1163, 867, 759 cm^{-1}; HRMS (EI^+): *m*/*z*: calcd for $C_{25}H_{35}N_3$: 377.2831, found 377.2831.

***N*-Cyclohexyl-1*H*-spiro[benzo[*g*]quinoxaline-2,1′-cycloheptan]-3-amine (7i).** Solid (286 mg, 79%), mp 155–157 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.56 (1H, d, $J = 8.1$ Hz), 7.45 (1H, d, $J = 8.1$ Hz), 7.35 (1H, s), 7.15–7.05 (2H, m), 6.79 (1H, s), 4.40 (1H, d, $J = 6.6$ Hz, NH), 4.04–4.02 (2H, m), 2.01–1.95 (2H, m), 1.80–1.33 (16H, m), 1.22–1.06 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 161.7, 136.4, 135.7, 131.2, 129.7, 126.9, 125.0, 123.8, 122.2, 119.5, 107.9, 56.3, 48.2, 36.8, 32.9, 30.3, 25.7, 24.6, 22.8; IR (KBr): 3400, 3046, 2923, 2852, 1631, 1569, 1525, 1466, 1284, 1203, 1095, 1020, 875, 746 cm^{-1}; HRMS (EI^+): *m*/*z*: calcd for $C_{24}H_{31}N_3$: 361.2518, found 361.2515.

Synthesis of indophenazine (14a) and its derivative (14b)

To a solution of *o*-phenylenediamine (1.0 mmol), isatin (1.0 mmol), or *N*-methyl isatin (1.0 mmol), and isocyanide (1.0 mmol) in 3 mL of water was added CeO_2-NPs (5 mol%). The resulting mixture was gently heated at 80 °C. Reaction completion was monitored by TLC. The organic layer was extracted with ethyl acetate (2 × 5 mL) and dried over Na_2SO_4. Solvent was removed using a rotary evaporator and the crude compounds were crystallized from hot ethyl acetate to give pure compound **14a** and **14b**.

6*H*-Indolo[2,3-*b*]quinoxaline (14a). Solid (202 mg, 94%), mp 264–265 °C; ^1H NMR (300 MHz, DMSO) δ_H: 11.96 (1H, s), 8.32 (1H, d, $J = 7.5$ Hz), 8.21 (1H, d, $J = 8.1$ Hz), 8.04 (1H, d, $J = 8.1$ Hz), 7.77–7.63 (3H, m), 7.55 (1H, d, $J = 8.1$ Hz), 7.33 (1H, t, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, DMSO) δ_C: 145.8, 143.9, 140.1, 139.7, 138.5, 131.1, 128.9, 128.6, 127.4, 128.8, 122.1, 120.5, 118.9, 111.9; IR (KBr): 3154, 2363, 1950, 1610, 1465, 1407, 1207, 1131, 1011, 751 cm^{-1}; HRMS (EI^+): *m*/*z*: calcd for $C_{14}H_9N_3$: 219.0796, found 219.0794.

6-Methyl-6*H*-indolo[2,3-*b*]quinoxaline (14b). Solid (220 mg, 95%), mp 146–148 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.45 (1H, d, $J = 7.8$ Hz), 8.27 (1H, d, $J = 8.1$ Hz), 8.11 (1H, d, $J = 8.1$ Hz), 7.76–7.63 (3H, m), 7.42 (1H, d, $J = 8.1$ Hz), 7.36 (1H, t, $J = 7.5$ Hz), 3.94 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 145.6, 144.7, 140.4, 139.9, 139.0, 130.8, 129.2, 128.6, 127.5, 125.8, 122.5, 120.8, 119.1, 109.0, 27.3; IR (KBr): 3423, 3057, 2926, 1923, 1609, 1469, 1431, 1253, 1117, 753 cm^{-1}; HRMS (EI^+): *m*/*z*: calcd for $C_{15}H_{11}N_3$: 234.1031, found 234.1029.

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Notes and references

1 F.-X. Zhu, W. Wang and H.-X. Li, *J. Am. Chem. Soc.*, 2011, **133**, 11632.
2 V. Polshettiwar and R. S. Varma, *Green Chem.*, 2010, **12**, 743.
3 F. M. Kerton and R. Marriot, *Alternative Solvents for Green Chemistry*, RSC Green Chemistry Book Series, RSC Publishing, Cambridge, UK, 2nd edn, 2013.
4 (*a*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (*b*) N. Shapiro and A. Vigalok, *Angew. Chem.*, 2008, **120**, 2891; (*c*) C.-J. Li and T.-H. Chan, in *Comprehensive Organic Reactions in Aqueous Media*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2nd edn, 2007; (*d*) C. Wei and C.-J. Li, *Green Chem.*, 2002, **4**, 39; (*e*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*f*) A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725; (*g*) K. H. Shaughnessy, *Chem. Rev.*, 2009, **109**, 643.
5 (*a*) V. K. Ahluwalia and R. S. Varma, *Green Solvents for Organic Synthesis*, Alpha Science International, Abingdon, UK, 2009; (*b*) A. Modak, J. Mondal, M. Sasidharan and A. Bhaumik, *Green Chem.*, 2011, **13**, 1317.
6 R. A. van Santen and M. Neurock, *Molecular Heterogeneous Catalysis: A Conceptual and Computational Approach*, Wiley-VCH, Weinheim, 2007.
7 V. Polshettiwar, B. Baruwati and R. S. Varma, *ACS Nano*, 2009, **3**, 728.
8 Y. Xia, P. Yang, Y. Sun, Y. Wu, B. Mayers, B. Gates, Y. Yin, F. Kim and H. Yan, *Adv. Mater.*, 2003, **15**, 353.
9 (*a*) P. Pratim Ghosh and A. R. Das, *J. Org. Chem.*, 2013, **78**, 6170; (*b*) N. V. Suramwar, S. R. Thakare, N. N. Karade and N. T. Khaty, *J. Mol. Catal. A: Chem.*, 2012, **359**, 28; (*c*) M. A. Ghasemzadeh, J. Safaei-Ghomi and H. Molaei, *C. R. Chim.*, 2012, **15**, 969; (*d*) S. E. Davis, M. S. Ide and

R. J. Davis, *Green Chem.*, 2013, **15**, 17; (*e*) V. Polshettiwar and R. S. Varma, *Org. Biomol. Chem.*, 2009, **7**, 37; (*f*) S. Luo, X. Zheng and J.-P. Cheng, *Chem. Commun.*, 2008, 5719.

10 (*a*) M. J. Jacinto, P. K. Kiyohara, S. H. Masunaga, R. F. Jardim and L. M. Rossi, *Appl. Catal., A*, 2008, **338**, 52; (*b*) H. Woo, H. Kang, A. Kim, S. Jang, J. C. Park, S. Park, B.-S. Kim, H. Song and K. H. Park, *Molecules*, 2012, **17**, 13235; (*c*) N. Yan, C. Xiao and Y. Kou, *Coord. Chem. Rev.*, 2010, **254**, 1179.

11 (*a*) L. E. Seitz, W. J. Suling and R. C. Reynolds, *J. Med. Chem.*, 2002, **45**, 5604; (*b*) D. J. Brown, *Quinoxalines, Supplement II, the chemistry of heterocyclic compounds*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2004, vol. 61; (*c*) S. Gobec and U. Urleb, in *Science of Synthesis*, ed. Y. Yamamoto, Thieme Chemistry, 2007, ch. 16.15, pp. 845–912.

12 (*a*) M. M. Ali, M. M. F. Ismail, M. S. A. EI-Gaby, M. A. Zahran and Y. A. Ammar, *Molecules*, 2000, **5**, 864; (*b*) R. Sarges, H. R. Howard, R. G. Browne, L. A. Lebel and P. A. Seymour, *J. Med. Chem.*, 1990, **33**, 2240; (*c*) G. Sakata, K. Makino and Y. Kurasawa, *Heterocycles*, 1988, **27**, 2481; (*d*) A. Gomtsyan, E. K. Bayburt, R. G. Schmidt, G. Z. Zheng, R. J. Perner, S. Didomenico, J. R. Koenig, S. Turner, T. Jinkerson, I. Drizin, S. M. Hannick, B. S. Macri, H. A. McDonald, P. Honore, C. T. Wismer, K. C. Marsh, J. Wetter, K. D. Stewart, T. Oie, M. F. Jarvis, C. S. Surowy, C. R. Faltynek and C.-H. Lee, *J. Med. Chem.*, 2005, **48**, 744; (*e*) A. Jaso, B. Zarranz, I. Aldana and A. Monge, *J. Med. Chem.*, 2005, **48**, 2019.

13 A. Bravo, J. C. Herrera, E. Scherer, Y. Ju-Nam, H. Rübsam, J. Madrid, C. Zufall and R. Rangel-Aldao, *J. Agric. Food Chem.*, 2008, **56**, 4134.

14 X. Hui, J. Desrivot, C. Bories, P. M. Loiseau, X. Franck, R. Hocquemiller and B. Figadère, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 815.

15 H. Gao, E. F. Yamasaki, K. K. Chan, L. L. Shen and R. M. Snapka, *Mol. Pharmacol.*, 2003, **63**, 1382.

16 (*a*) R. H. Shoemaker, *Cancer Treat. Rep.*, 1986, **70**, 9; (*b*) F. Valeriote, T. Corbett, M. Edelstein and L. Baker, *Cancer Invest.*, 1996, **14**, 124.

17 J. Deng, E. Feng, S. Ma, Y. Zhang, X. Liu, H. Li, H. Huang, J. Zhu, W. Zhu, X. Shen, L. Miao, H. Liu, H. Jiang and J. Li, *J. Med. Chem.*, 2011, **54**, 4508.

18 (*a*) A. Dell, D. H. William, H. R. Morris, G. A. Smith, J. Feeney and G. C. K. Roberts, *J. Am. Chem. Soc.*, 1975, **97**, 2497; (*b*) C. Bailly, S. Echepare, F. Gago and M. J. Waring, *Anticancer Drug Des.*, 1999, **14**, 291; (*c*) S. Sato, O. Shiratori and K. Katagiri, *J. Antibiot.*, 1967, **20**, 270.

19 (*a*) L. Marin, L. Lutsen, D. Vanderzande and W. Maes, *Org. Biomol. Chem.*, 2013, **11**, 5866; (*b*) S. Achelle, C. Baudequin and N. Plé, *Dyes Pigm.*, 2013, **98**, 575; (*c*) T. Kono, T. N. Murakami, J. Nishida, Y. Yoshida, K. Hara and Y. Yamashita, *Org. Electron.*, 2012, **13**, 3097; (*d*) X. Lu, Q. Feng, T. Lan, G. Zhou and Z.-S. Wang, *Chem. Mater.*, 2012, **24**, 3179.

20 (*a*) M. Shamsi, M. M. Baradarani, A. Afghan and J. A. Joule, *ARKIVOC*, 2011, 252; (*b*) D.-M. Cui, D.-W. Zhuang, Y. Chen and C. Zhang, *Beilstein J. Org. Chem.*, 2011, **7**, 860; (*c*) S. A. Raw, C. D. Wilfred and R. J. K. Taylor, *Chem. Commun.*, 2003, 2286; (*d*) S. Sithambaram, Y. Ding, W. Li, X. Shen, F. Gaenzler and S. L. Suib, *Green Chem.*, 2008, **10**, 1029; (*e*) S. V. More, M. N. V. Sastry and C.-F. Yao, *Green Chem.*, 2006, **8**, 91.

21 (*a*) A. Shaabani, A. Maleki, H. Mofakham and H. R. Khavasi, *J. Comb. Chem.*, 2008, **10**, 323; (*b*) H. Mofakham, Z. Hezarkhani and A. Shaabani, *J. Mol. Catal. A: Chem.*, 2012, **360**, 26; (*c*) A. Shaabani, F. Hajishaabanha, H. Mofakham, M. Mahyari and B. Lali, *Helv. Chim. Acta*, 2012, **95**, 246; (*d*) R. Ghorbani-Vaghei, M. Amiri, R. Karimi-Nami, Z. Toghraei-Semiromi and M. Ghavidel, *Mol. Diversity*, 2013, **17**, 251.

22 J.-J. Cai, J.-P. Zou, X.-Q. Pan and W. Zhang, *Tetrahedron Lett.*, 2008, **49**, 7386.

23 T.-K. Huang, R. Wang, L. Shi and X.-X. Lu, *Catal. Commun.*, 2008, **9**, 1143.

24 Z. Li, W. Li, X. Ren, Y. Sun, Y. Shi and P. Ouyang, *Heterocycl. Commun.*, 2011, **13**, 125.

25 M. M. Heravi, S. Taheri, K. Bakhtiari and H. A. Oskooie, *Catal. Commun.*, 2007, **8**, 211.

26 M. M. Heravi, M. H. Tehrani, K. Bakhtiari and H. A. Oskooie, *Catal. Commun.*, 2007, **8**, 1341.

27 D. Bandyopadhyay, S. Mukherjee, R. R. Rodriguez and B. K. Banik, *Molecules*, 2010, **15**, 4207.

28 B. Suresh Kuarm, P. A. Crooks and B. Rajitha, *Green Chem. Lett. Rev.*, 2013, **6**, 228.

29 A. Hasaninejad, A. Zare, M. A. Zolfigol and M. Shekouhy, *Synth. Commun.*, 2009, **39**, 569.

30 A. Shaabani, A. Maleki and J. Moghimi-Rad, *J. Org. Chem.*, 2007, **72**, 6309.

31 M. M. Heravi, B. Baghernejad and H. A. Oskooie, *Tetrahedron Lett.*, 2009, **50**, 767.

32 J. Li, Y. Liu, C. Li and X. Jia, *Tetrahedron Lett.*, 2009, **50**, 6502.

33 J.-Y. Liu, J. Liu, J.-D. Wang, D.-Q. Jiao and H.-W. Liu, *Synth. Commun.*, 2010, **40**, 2047.

34 S. R. Kolla and Y. R. Lee, *Tetrahedron*, 2010, **66**, 8938.

35 (*a*) M. Tamura, K. Noro, M. Honda, Y. Nakagawa and K. Tomishige, *Green Chem.*, 2013, **15**, 1567; (*b*) R. Shelkar, S. Sarode and J. Nagarkar, *Tetrahedron Lett.*, 2013, **54**, 6986; (*c*) A. Gharib, B. R. H. Khorasani, M. Jahangir, M. Roshani and R. Safaee, *Org. Chem. Int.*, 2013, 1; (*d*) B. Akhlaghinia, H. Ebrahimabadi, E. K. Goharshadi, S. Samiee and S. Rezazadeh, *J. Mol. Catal. A: Chem.*, 2012, **357**, 67; (*e*) M. Honda, S. Sonehara, H. Yasuda, Y. Nakagawa and K. Tomishige, *Green Chem.*, 2011, **13**, 3406.

36 A. Tanaka, K. Hashimoto and H. Kominami, *ChemCatChem*, 2011, **3**, 1619.

37 B. Faure, G. Salazar-Alvarez, A. Ahniyaz, I. Villaluenga, G. Berriozabal, Y. R. De Miguel and L. Bergström, *Sci. Technol. Adv. Mater.*, 2013, **14**, 1.

38 N. Shehata, K. Meehan and D. Leber, *J. Fluoresc.*, 2013, **23**, 527.

39 K. Woan, Y.-Y. Tsai and W. Sigmund, *Nanomedicine*, 2010, **5**, 233.

40 R. Di Monte and J. Kašpar, *J. Mater. Chem.*, 2005, **15**, 633.

41 M. Mogensen, N. M. Sammes and G. A. Tompsett, *Solid State Ionics*, 2000, **129**, 63.
42 T. L. R. Hewer, L. S. Soeira, G. E. S. Brito and R. S. Freire, *J. Mater. Chem. A*, 2013, **1**, 6169.
43 E. J. Jung, B. H. Park and Y. R. Lee, *Green Chem.*, 2010, **12**, 2003.
44 P. J. Dunn, *Chem. Soc. Rev.*, 2012, **41**, 1452.
45 B. Malapel-Andrieu and J.-Y. Mérour, *Tetrahedron*, 1998, **54**, 11095.