Synthesis of Quinoxalin-2(1*H*)-ones and Hexahydroquinoxalin-2(1*H*)-ones via Oxidative Amidation–Heterocycloannulation

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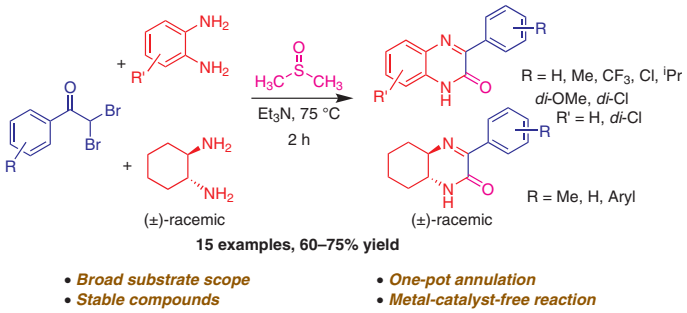

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Abstract A metal-catalyst-free synthesis of substituted quinoxalin-2-ones from 2,2-dibromo-1-arylethanone by employing an oxidative amidation–heterocycloannulation protocol is reported. The substrate scope of the reaction has been demonstrated and a possible mechanism for this reaction has also been proposed.

Key words oxidative amidation, heterocycloannulation, quinoxalin-2(1*H*)-one, 2,2-dibromo-1-arylethanone

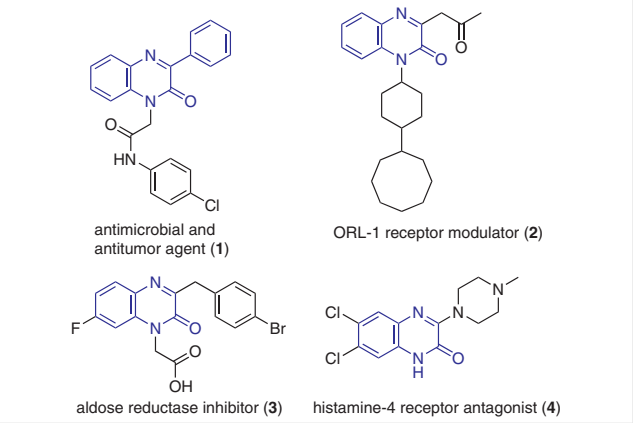


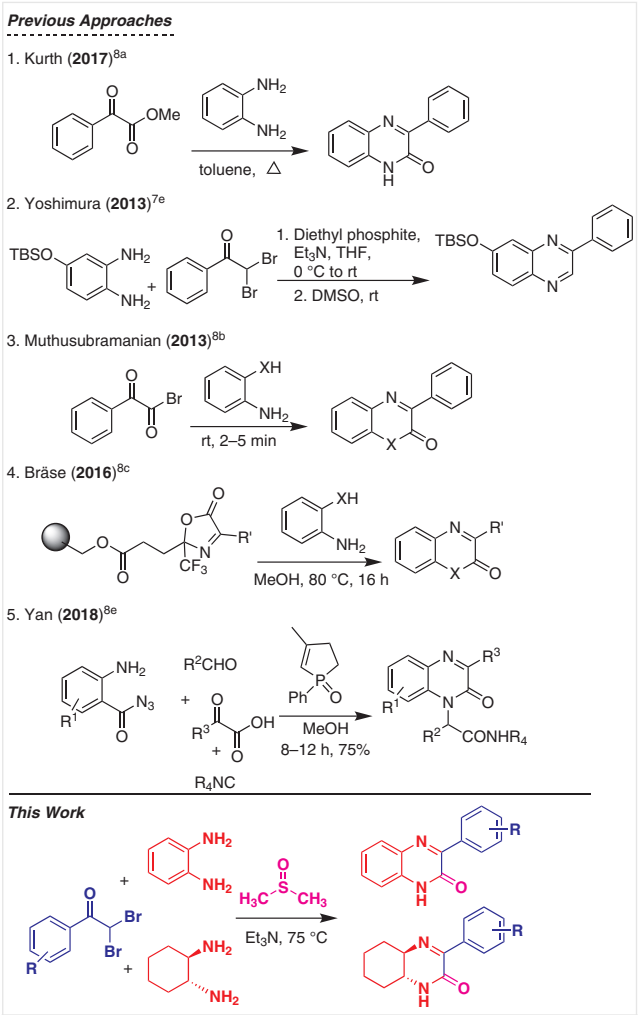
Figure 1 Representative medicinally important quinoxalin-2-ones

Due to their diverse biological activity and applications in pharmaceutical industry, the efficient preparation of quinoxalin-2-one derivatives is highly desirable for drug discovery. Quinoxalinones have gained much recent attention as an important pharmacophore in a family of biologically active heterocyclic compounds, and several antimicrobial and antitumor drugs (**1**) possess the quinoxalinone unit in their structural framework (Figure 1).[1,2]

Other quinoxalinone derivatives demonstrate aldose reductase inhibition (**3**), histamine-4 receptor antagonism (**4**), and ORL-1 receptor modulation (**2**) (Figure 1).[1] Furthermore, related compounds prevent the growth of Gram-positive bacteria or are active against various transplantable tumors. In addition, quinoxalin-2-one derivatives have been used as a fluorophores in HPLC for the analysis of carboxylic acids, alcohols and amines.[3,4] Moreover, quinoxalin-2-one derivatives have been used to sense alkali metal ions in the presence of aza-crown ethers.[5]

A number of synthetic strategies have been developed for the preparation of substituted quinoxalinones (Scheme 1).[6–8] The most common approach involves the condensation of aryl-1,2-diamines with 1,2-dicarbonyl compounds.[7a] Other noteworthy synthetic approaches towards quinoxalines include multicomponent reactions (MCR).[7b] In addition, Ping et al. have reported the reaction of α-bromo ketones and 1,2-diamines to afford 2-substituted quinoxalines using $Ga(ClO_4)_3$ as a catalyst in good yields.[7c]

Yan et al. developed a method utilizing a sequential Ugi reaction/catalytic aza-Wittig cyclization sequence to synthesize multi-substituted quinoxalin-2(1*H*)-ones in a one-pot procedure.[7d] Similarly Yoshimura et al. demonstrated a metal catalyst-free synthesis of 2-substituted quinoxalines using α-bromo ketones and 1,2-diamines in dimethyl sulfoxide (DMSO; Scheme 1).[7e] Kurth and co-workers synthesized a range of arylquinoxalinones by condensing *o*-phenylenediamines with substituted phenyloxoacetates.[8a]

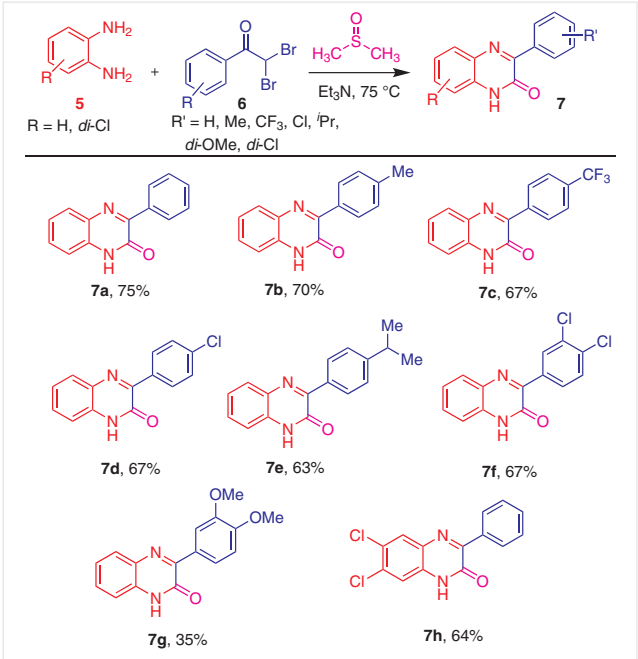


Scheme 1 Reported methods for the synthesis of quinoxalin-2-ones

Muthusubramanian and co-workers reported the preparation of novel quinoxalinones from 2-oxo-2-arylacetyl bromide as a precursor.[8b] Another interesting invention from the Bräse group uses immobilized oxazolones in combination with difunctional nucleophiles as cleavage agent.[8c] Despite these notable efforts, the development of an efficient methodology for the synthesis of highly functionalized quinoxalin-2-ones is still an important challenge for organic chemists.

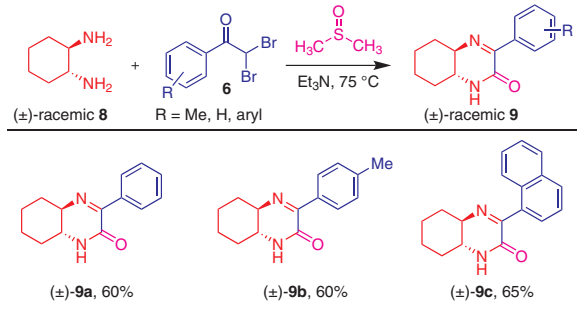
In a continuation of our ongoing research,[9] we herein report a one-pot oxidative amidation strategy for the synthesis a range of quinoxalin-2-ones. As reported in our earlier report,[10] the key intermediate **10** is formed during the oxidation of aryldibromoethanone **6a** with DMSO (see Scheme 5 below). Compound **10** behaves like a masked α-keto ester or α-keto acid chloride equivalent and can react readily with aryl-1,2-diamine to give quinoxalin-2-ones.

Initially, the reaction conditions were optimized by taking 2,2-dibromo-1-phenylethanone (**6a**) and aryl-1,2-diamine (**5a**) as a model substrates in dimethyl sulfoxide as solvent. The reaction was screened with different bases at different temperatures and, to our satisfaction, the reaction occurred efficiently at 75 °C using triethylamine as a base to form the arylquinoxalin-2-one in good yield. Indeed, the reaction of 2,2-dibromo-1-phenylethanone (**7a**) in dimethyl sulfoxide gives oxosulfonium intermediate that further reacts with thearyl-1,2-diamine in one pot to form quinoxalin-2-one (**7a**), as confirmed by spectroscopic analysis. The substrate scope of the reaction was then studied with different substituted 2,2-dibromo-1-phenylethanones **6a–h** and aryl-1,2-diamines **5a–b** to obtain the corresponding quinoxalin-2-ones **7a–h** (Scheme 2). Furthermore 2,2-dibromo-1-phenylethanone with racemic 1,2-diaminocyclohexane produced hexahydroquinoxaline-2-ones **9a–c** (Scheme 3) in good yields. However, the reaction of dibromoethanone and 1,2-diaminoethane in DMSO was not successful under similar conditions. Furthermore, during the course of the investigation, the dimethoxyaryldibromoethanone (**7g**) underwent competitive demethylation during the oxidation, which resulted in low yield of product.



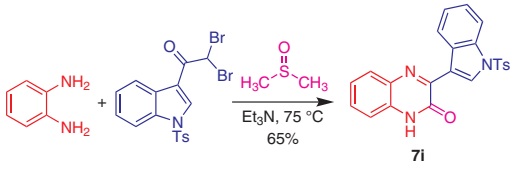
Scheme 2 Substrate scope of the reaction. *Reagents and conditions*: aryl-1,2-diamine **5** (1 mol), dibromoketone **6** (1 mol), triethylamine (3 mol), DMSO (6 mL), 75 °C, 2 h.

In a continuation of our investigations, we also studied the regioselectivity of various quinoxalin-2-ones by the reaction of 2,2-dibromo-1-phenylethanone (**6a**) with unsymmetrically substituted aryldiamines **5b–d** (Table 1). Gratifyingly, when an electron-withdrawing group was present at the *meta*-position of aryl-1,2-diamines, the reaction occurs



Scheme 3 Substrate scope of the reaction. *Reagents and conditions*: dibromoketone **6** (1 mol), cyclohexyl-1,2-diamine **8** (1 mol), triethylamine (3 mol), DMSO (6 mL), 75 °C, 2 h.

with high regioselectivity and can provide insights into the reaction mechanism. The amine functionality at the *meta*-position to the electron-withdrawing group can form either an imine (Path A) or an amide bond (Path B), followed by cyclization to provide the quinoxalin-2-one (see Scheme 5 below). The dibromoethanones **6a–g** were synthesized from the corresponding ketones by following our reported procedure.[10] To demonstrate the efficiency of this protocol further, a gram-scale reaction was performed on toluenesulfonyl-indole-dibromoethanone and it was possible to reproduce the same yields of **7i** as obtained in the smaller-scale reaction (Scheme 4).



Scheme 4 Gram-scale reaction

A detailed investigation of regioisomer formation was carried out by NOE spectroscopic analysis. Reaction of aryl-1,2-diamine **5c** with dibromoethanone (**6a**) provides the two regioisomeric quinoxalin-2-ones (**7ma**; 95%) and (**7mb**; 5%) (Table 1). From the NOE enhancements it can be concluded that the H_b proton is spatially close to H_a and also showed H_c in a neighboring environment (Figure 2). The formation of quinoxalin-2-one **7ma** as the major product indicates that the reaction proceeds through the imine mechanism rather than via an amide intermediate in the first step. Furthermore, 1-chloro-3,4-diaminobenzene (**5d**) also showed a similar reactivity pattern and the structure of the major product was again confirmed by NOE studies. However, no regioselectivity (1:1 ratio of products) was observed, when 4-methyl-1,2-diaminobenzene (**5e**) was used.

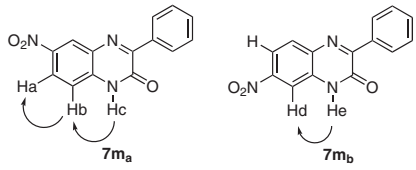


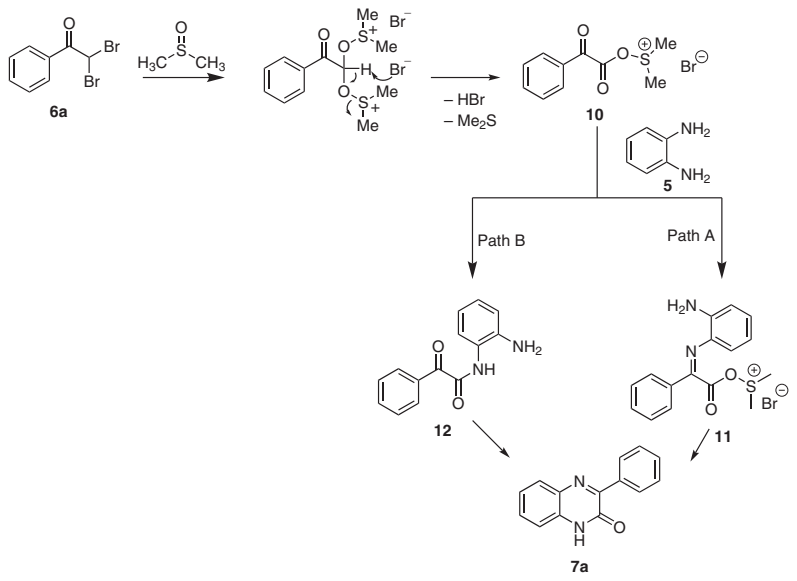
Figure 2 NOE studies

The mechanism for the formation of 3-phenylquinoxalin-2-one (**7a**) from aryldibromoethanone (**6a**) might proceed either via Path A or B (Scheme 5). The reaction of aryldibromoethanone (**6a**) in dimethylsulfoxide gives oxosulfonium intermediate **10** that reacts further with the aryl-1,2-diamine to form 3-phenylquinoxalin-2-one **7a**.

Finally, to explore the general synthetic applicability of quinoxalin-2-ones, we have synthesized a range of quinoxalin-2-one derivatives with potential application in drug discovery. Initially, quinoxalin-2-one **7a** was converted into 2-chloro-3-phenylquinoxaline (**13**) by treatment with $POCl_3$ under neat conditions at elevated temperature[11] and

Table 1 Regioselectivity of Quinoxalin-2(1*H*)-ones

Substrate	Amine	Quinoxalin-2(1*H*)-one		Yield (%)	Ratio
6a	**5c**	**7ma**	**7mb**	64	95:5
6a	**5d**	**7na**	**7nb**	68	90:10
6a	**5e**	**7oa**	**7ob**	62	50:50

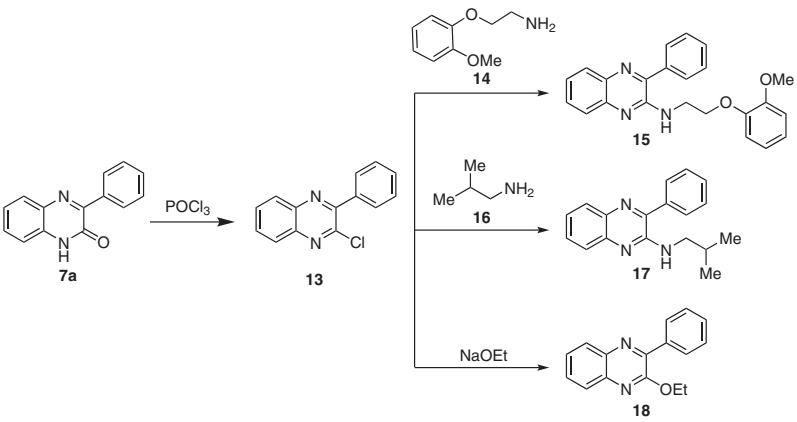


Scheme 5 Proposed mechanism for the formation of 3-phenylquinoxalin-2-one

then **13** was coupled with 2-(2-methoxyphenoxy)ethanamine (**14**) to form *N*-[2-(2-methoxyphenoxy)ethyl]-3-phenylquinoxalin-2-amine (**15**). Similarly, 2-chloro-3-phenylquinoxaline (**13**) was coupled with 2-methylpropan-1-amine (**16**) to obtain *N*-isobutyl-3-phenylquinoxalin-2-amine (**17**) and 2-ethoxy-3-phenylquinoxaline (**18**) was then obtained by treating 2-chloro-3-phenylquinoxaline (**13**) with NaOEt in EtOH (Scheme 6).

In conclusion, we have developed a novel and efficient one-pot method for the synthesis of substituted arylquinoxalin-2-ones and hexahydroquinoxalin-2-ones in moderate to good yields. In addition, the regioselectivity of quinoxalin-2-ones has been demonstrated. Several quinoxaline derivatives have also been prepared and a possible mechanism for the formation of the arylquinoxalin-2-ones has been proposed.

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reaction mixtures were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized with ultraviolet light or by treatment with a spray of Pancaldi's reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O}. Chromatographic purification of products was carried out by flash column chromatography on silica gel (60–120 mesh). Melting points were determined with an electrothermal melting point apparatus. Infrared spectra were recorded with a Perkin–Elmer 1650 Fourier transform spectrophotometer. ^1H NMR spectra were measured in $CDCl_3$, DMSO-d_6 (all with TMS as internal standard) with a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts (δ) are



Scheme 6 Synthesis of quinoxaline derivatives

reported in ppm, and coupling constants (*J*) are in Hz. The following abbreviations are used for the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded with a HP-5989A quadrupole mass spectrometer.

Synthesis of 2,2-Dibromo-1-phenylethanone

Bromine (2.90 g, 18 mmol) was added dropwise to anhydrous 1,4-dioxane (15 mL) in a round-bottom flask under nitrogen at room temperature over a period of 20 minutes, and the mixture stirred for 30 minutes. A solution of acetophenone (1.00 g, 8.0 mmol) in 1,4-dioxane (10 mL) was added and the mixture was stirred for another 2 h. The reaction was quenched with ice cold water (100 mL) and the resultant solid was filtered off followed by washing the filter cake with hexane (2 × 10 mL) to give pure 2,2-dibromo-1-phenylethanone (**1a**; 2.10 g, 90%).

Synthesis of 3-Phenylquinoxalin-2-(1*H*)-one

A solution of dibromoketone (**1a**; 1.00 g, 3.6 mmol) in anhydrous dimethyl sulfoxide (6 mL) was stirred at 75 °C for 14 h under a nitrogen atmosphere and the reaction mass was slowly cooled to 55 °C. To the above mixture, a solution of benzene-1,2-diamine (0.4 g, 3.6 mol) and triethylamine (1.1 g, 10 mmol) in anhydrous dimethyl sulfoxide (4 mL) was added and the mixture was stirred for 15 min. The temperature was increased to 80 °C and stirring was continued for 5 h. After completion of reaction, the mixture was cooled to 35 °C, water (20 mL) was added and the mixture was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with water (3 × 15 mL), brine (15 mL) and dried over anhydrous sodium sulfate. After filtration, the organic extract was concentrated under reduced pressure and the crude product was subjected to column chromatography to obtain pure 3-phenylquinoxalin-2(1*H*)-one (**2a**).

3-Phenylquinoxalin-2-(1*H*)-one (7a)[10]

Yield: 0.44 g (75%); yellow solid; mp 247–249 °C.

IR (KBr): 2836, 1664, 1431, 1285, 1007, 908, 765, 689 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.5 (s, NH), 8.29–8.31 (m, 2 H), 7.84 (m, 1 H), 7.49–7.52 (m, 4 H), 7.33 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.5, 154.0, 135.5, 131.9, 130.2, 130.0, 129.1, 128.6 (2C), 127.7, 123.3, 114.9.

MS: *m*/*z* (%) = 223 [M + 1], 245 [M + 23].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0865.

3-(*p*-Tolyl)quinoxalin-2(1*H*)-one (7b)

Yield: 0.56 g (70%); yellow solid; mp 233–235 °C.

IR (KBr): 2854, 1660, 1487, 1444, 1270, 880, 813, 759, 689 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.8 (s, NH), 8.0 (d, *J* = 8 Hz, 2 H), 7.56–7.57 (m, 2 H), 7.37 (d, *J* = 8 Hz, 2 H), 7.18 (dd, *J* = 2.8, 2.4 Hz, 2 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.5, 154.0, 135.5, 131.9, 130.2, 130.0, 129.1, 128.6, 127.7, 123.3, 114.9, 20.9.

MS: *m*/*z* (%) = 237 [M + 1].

3-(4-(Trifluoromethyl)phenyl)quinoxalin-2-(1*H*)-one (7c)

Yield: 0.56 g (67%); pale-yellow solid; mp 210–212 °C.

IR (KBr): 2848, 1662, 1478, 1329, 1109, 1071, 852, 759, 577 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.7 (s, NH), 8.5 (d, *J* = 8.4 Hz, 2 H), 7.86–7.89 (m, 3 H), 7.57–7.59 (m, 1 H), 7.36–7.38 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.8, 154.5, 152.8, 139.3, 132.3, 131.9, 130.9, 129.8, 129.0, 124.7, 124.7, 123.6, 115.2.

MS: *m*/*z* (%) = 291[M + 1].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{10}F_3N_2O$: 291.0745; found: 291.0741.

3-(4-Chlorophenyl)quinoxalin-2(1*H*)-one (7d)

Yield: 0.55 g (67%); yellow solid; mp 213–214 °C.

IR (KBr): 2836, 1661, 1593, 1477, 1280, 1091, 1005, 887, 750 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.6 (s, NH), 8.3 (d, *J* = 8.8 Hz, 2 H), 7.76–7.86 (m, 1 H), 7.54–7.58 (m, 3 H), 7.33–7.36 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.5, 152.7, 135.0, 134.3, 132.1, 131.9, 130.9, 130.5, 128.8, 127.9, 123.5, 115.1.

MS: *m*/*z* (%) = 257 [M + 1].

3-(4-Isopropylphenyl)quinoxalin-2-(1*H*)-one (7e)

Yield: 0.52 g (63%); yellow solid; mp 181–184 °C.

IR (KBr): 2836, 1664, 1593, 1477, 1282, 1093, 1005, 888, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.8 (s, NH), 8.3 (d, *J* = 8.4 Hz, 1 H), 7.97–7.99 (m, 2 H), 7.64–7.67 (m, 1 H), 7.47–7.49 (m, 1 H), 7.35–7.37 (m, 3 H), 2.94–2.98 (m, 1 H), 1.27 (d, *J* = 8.8 Hz, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.6, 150.8, 133.3, 132.0, 131.9, 130.1, 129.3, 128.6, 126.8, 126.5, 125.8, 123.3, 121.9, 115.0, 33.4, 23.7.

MS: *m*/*z* (%) = 265 [M + 1].

3-(3,4-Dichlorophenyl)quinoxalin-2-(1*H*)-one (7f)

Yield: 0.56 g (67%); yellow solid; mp 250–252 °C.

IR (KBr): 2842, 1665, 1594, 1477, 1282, 1096, 1005, 889, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ = 12.6 (s, 1 H), 7.8 (d, *J* = 6.4 Hz, 1 H), 7.49–7.53 (m, 3 H), 7.40–7.41 (m, 2 H), 7.32–7.38 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.2, 153.6, 134.6, 134.4, 133.3, 132.5, 132.3, 131.6, 131.1, 128.9, 128.7, 127.2, 123.5, 115.5.

MS: *m*/*z* (%) = 291 [M + 1].

3-(3,4-Dimethoxyphenyl)quinoxalin-2-(1*H*)-one (7g)

Yield: 0.29 g (35%); yellow solid; mp 238–240 °C.

IR (KBr): 2835, 1661, 1598, 1474, 1282, 1092, 1015, 887, 745 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.48 (s, 1 H), 8.15–8.18 (m, 1 H), 8.03 (s, 1 H), 7.8 (d, *J* = 8.4 Hz, 1 H), 7.49–7.53 (m, 1 H), 7.32–7.34 (m, 2 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 3.8 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.7, 152.7, 150.9, 148.0, 131.9, 131.7, 129.7, 128.5, 128.2, 123.3 (2C), 114.9, 112.3, 110.8, 55.5 (2C).

MS: *m*/*z* (%) = 283 [M + 1].

6,7-Dichloro-3-phenylquinoxalin-2-(1*H*)-one (7h)

Yield: 0.67 g (64%); pale-yellow solid.

IR (KBr): 2832, 1650, 1444, 1285, 1011, 948, 756, 691 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.6 (s, NH), 8.24–8.28 (m, 2 H), 8.08 (s, 1 H), 7.46–7.54 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.5, 154.1, 134.9, 132.1, 131.8, 131.3, 130.6, 129.4, 129.3, 127.8, 125.0, 115.9.

MS: *m*/*z* (%) = 291 [M].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9Cl_2N_2O$: 291.0092; found: 291.0090.

3-(1-Tosyl-1*H*-indol-3-yl)quinoxalin-2(1*H*)-one (7i)

Yield: 5.7 g (65%); yellow solid.

IR (KBr): 2842, 1665, 1594, 1477, 1282, 1096, 1005, 889, 756 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.72 (s, 1 H), 9.25 (s, 1 H), 8.87–8.89 (m, 1 H), 7.96–8.18 (m, 3 H), 7.24–7.56 (m, 8 H), 2.3 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 161.1, 142.7, 139.4, 135.9, 135.4, 134.8, 131.7, 130.0, 129.1, 128.2, 127.4, 126.3, 125.9, 123.6, 121.6, 119.8, 115.4, 114.5, 112.2, 21.3.

MS: *m*/*z* (%) = 416.20 [M + 1].

3-Phenyl-4a,5,6,7,8,8a-hexahydroquinoxalin-2-(1*H*)-one (9a)

Yield: 0.49 g (60%); pale-yellow solid.

IR (KBr): 2832, 1650, 1444, 1285, 1011, 948, 756, 691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.8 (dd, *J* = 6.4 Hz, 2 H), 7.39–7.41 (m, 3 H), 3.21–3.26 (m, 2 H), 2.45 (s, 1 H), 1.82–1.99 (m, 3 H), 1.39–1.45 (m, 5 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 157.3, 135.4, 129.8, 128.7, 127.6, 62.3, 53.3, 31.6, 30.1, 24.7, 23.3.

MS: *m*/*z* (%) = 229.1 [M + 1].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O$: 229.1341; found: 229.1340.

3-(*p*-Tolyl)-4a,5,6,7,8,8a-hexahydroquinoxalin-2-(1*H*)-one (9b)

Yield: 0.49 g (60%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.5 (s, 1 H, NH), 7.8 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 3.06–3.22 (m, 2 H), 2.35 (s, 3 H), 2.22–2.26 (m, 1 H), 1.92–1.98 (m, 1 H), 1.70–1.88 (m, 2 H), 1.39–1.48 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 140.6, 133.9, 163.6, 128.8, 128.8, 63.0, 54.0, 31.8, 31.1, 25.2, 23.7, 21.4.

MS: *m*/*z* (%) = 279.1501 [M + Na].

3-(Naphthalen-1-yl)-4a,5,6,7,8,8a-hexahydroquinoxalin-2-(1*H*)-one (9c)

Yield: 0.55 g (65%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.63 (s, 1 H, NH), 7.96–7.98 (m, 2 H), 7.8 (d, *J* = 8 Hz, 1 H), 7.46–7.51 (m, 4 H), 3.36–3.37 (m, 2 H), 2.19–2.27 (m, 1 H), 1.98–2.04 (m, 1 H), 1.74–1.79 (m, 2 H), 1.39–1.54 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.6, 157.6, 134.5, 132.8, 130.9, 128.9, 128.1, 126.8, 126.2, 125.8, 125.1, 124.9, 62.7, 53.8, 31.5, 30.2, 24.8, 23.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O$: 279.1497; found: 279.1501.

7-Nitro-3-phenylquinoxalin-2-(1*H*)-one (7ma)

Yield: 0.61 g (64%); yellow solid.

IR (KBr): 2855, 1668, 1520, 1337, 948, 756, 688 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.63 (s, NH), 8.27–8.29 (m, 2 H), 7.50–7.53 (m, 1 H), 7.48–7.49 (m, 3 H), 7.33–7.34 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.3, 154.1, 135.3, 134.2, 133.0, 130.7, 130.3, 129.2, 127.8, 125.0, 123.4, 114.3.

MS: *m*/*z* (%) = 268 [M + 1].

3-(4-Chlorophenyl)quinoxalin-2-(1*H*)-one (7na)

Yield: 0.63 g (68%); yellow solid.

IR (KBr): 2851, 1664, 1480, 1284, 1009, 936, 754, 686 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.63 (s, NH), 8.27–8.29 (m, 2 H), 7.83–7.85 (m, 1 H), 7.48–7.53 (m, 3 H), 7.32–7.36 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.5, 154.3, 135.3, 134.3, 133.0, 130.7, 130.4, 129.2, 127.8, 123.5, 114.3.

MS: *m*/*z* (%) = 257 [M + 1].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}ClN_2O$: 257.0482; found: 257.0493.

7-Methyl-3-phenylquinoxalin-2-(1*H*)-one (7oa)

Yield: 0.53 g (62%); yellow solid.

IR (KBr): 2852, 1671, 1435, 1287, 1011, 908, 767, 690 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.63 (s, NH), 8.28–8.30 (m, 2 H), 7.72 (d, *J* = 6.4 Hz, 1 H), 7.48–7.53 (m, 3 H), 7.23–7.25 (m, 2 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.5, 154.0, 135.5, 134.4, 131.9, 130.2, 130.0, 129.1, 128.6, 127.7, 123.3, 114.9, 20.9.

MS: *m*/*z* (%) = 237 [M + 1], 259 [M + Na].

2-Chloro-3-phenylquinoxaline (13)

Yield: 0.91 g (85%); yellow solid; mp 127–129 °C.

IR (KBr): 3035, 1667, 1560, 1444, 1339, 1088, 980, 764, 687 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18–8.19 (m, 1 H), 8.07–8.12 (m, 1 H), 7.90–7.96 (m, 2 H), 7.84–7.86 (m, 2 H), 7.52–7.57 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152, 145.6, 140.4, 140.3, 136.5, 131.4, 130.9, 129.6, 129.6, 128.8, 128.1, 127.7.

MS: *m*/*z* (%) = 241 [M + 1].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0533; found: 241.0527.

***N*-(2-(2-Methoxyphenoxy)ethyl)-3-phenylquinoxalin-2-amine (15)**

Yield: 0.67 g (90%); viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.92 (m, 1 H), 7.73–7.75 (m, 3 H), 7.51–7.55 (m, 5 H), 6.85–6.98 (m, 4 H), 5.81 (s, 1 H, NH), 4.35 (d, *J* = 7.0 Hz, 2 H), 4.0 (d, *J* = 6.8 Hz, 2 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 149.6, 147.9, 146.8, 141.5, 137.1, 136.7, 129.6, 129.5, 129.2, 128.9, 128.5, 125.9, 124.5, 121.7, 120.6, 114.7, 111.9, 67.8, 55.7, 40.5.

MS: *m*/*z* (%) = 372.20 [M + 1].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}N_3O_2$: 372.1712; found: 372.1711.

***N*-Isobutyl-3-phenylquinoxalin-2-amine (17)**

Yield: 0.52 g (90%); viscous liquid.

IR (KBr): 3452, 3035, 1667, 1560, 1444, 1339, 1088, 980, 764, 687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.92 (m, 1 H), 7.72–7.74 (m, 3 H), 7.52–7.58 (m, 4 H), 7.35–7.37 (m, 1 H), 5.13 (s, NH), 3.37–3.39 (t, *J* = 6.8 Hz, 2 H), 1.93–1.96 (m, 1 H), 0.96 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.1, 150.3, 146.7, 141.8, 136.9, 129.6, 129.6, 129.3, 128.8, 128.4, 125.9, 124.2, 48.7, 31.9, 20.4.

MS: *m*/*z* (%) = 278.2 [M + 1].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3$: 278.1657; found: 278.1645.

2-Ethoxy-3-phenylquinoxaline (18)

Yield: 0.47 g (90%); viscous liquid.

IR (KBr): 2852, 1671, 1435, 1287, 1011, 908, 767, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.16 (m, 2 H), 8.11–8.12 (m, 1 H), 7.83–7.85 (m, 1 H), 7.64–7.67 (m, 1 H), 7.52–756 (m, 4 H), 4.63 (q, *J* = 7.7 Hz, 2 H), 1.49 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 146.6, 139.9, 138.8, 136.2, 129.7, 129.5, 128.9, 128.1, 126.6, 126.5, 62.5, 14.4.

MS: *m*/*z* (%) = 251 [M + 1].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$: 251.1184; found: 251.1185.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707203.

References

(1) (a) Shi, L.-L.; Zhou, H.; Wu, J.-F.; Li, X. *Mini-Rev. Org. Chem.* **2015**, *12*, 96. (b) Carta, A.; Piras, S.; Loriga, G.; Paglietti, G. *Mini-Rev. Med. Chem.* **2006**, *6*, 1179. (c) Li, X.; Yang, K.; Li, W.; Xu, W. *Drugs Future* **2006**, *31*, 979. (d) Akins, P. T.; Atkinson, R. P. *Curr. Med. Res. Opin.* **2002**, *18*, 9. (e) Vega, A. M.; Gil, M. J.; Basilio, A.; Giraldez, A.; Fernandez-Alvarez, E. *Eur. J. Med. Chem.* **1986**, *21*, 251.

(2) (a) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Kim, H.-S.; Wataya, Y.; Harayama, T. *Tetrahedron* **2001**, *57*, 1213. (b) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193.

(3) (a) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510. (b) Tekeuchi, Y.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **1999**, *47*, 905. (c) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833.

(4) (a) McQuaid, L. A.; Smith, E. C. R.; South, K. K.; Mitch, C. H.; Schoepp, D. D.; True, R. A.; Calligaro, D. O.; Malley, P. J. O.; Lodge, D.; Ornstein, P. L. *J. Med. Chem.* **1992**, *35*, 3319. (b) Iwata, T.; Yamagushi, M.; Hara, S.; Nakamura, M.; Ohkura, Y. *J. Chromatogr.* **1986**, *362*, 209.

(5) (a) Bourson, J.; Pouget, J.; Valeur, B. *J. Phys. Chem.* **1993**, *97*, 4552. (b) Ahmad, A. R.; Mehta, L. K.; Parrick, J. *Tetrahedron* **1995**, *51*, 12899.

(6) (a) Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. *J. Med. Chem.* **2008**, *51*, 2457. (b) de la Fuente, J. R.; Canete, A.; Zanocco, A. L.; Saitz, C.; Jullian, C. *J. Org. Chem.* **2000**, *65*, 7949. (c) Nunez-Rico, J. L.; Vidal-Ferran, A. *Org. Lett.* **2013**, *13*, 2066. (d) Murthy, S. N.; Madhav, B.; Nageswar, Y. V. D. *Helv. Chim. Acta* **2010**, *93*, 1216. (e) Wiedermannová, I.; Slouka, J. *J. Heterocycl. Chem.* **2001**, *38*, 1465. (f) Zielinski, U.; Weber, F. G.; Tonew, M.; Tonew, E. *Pharmazie* **1977**, *32*, 570. (g) Gobec, S.; Urleb, U. *Science of Synthesis, Vol. 16*, Houben-Weyl Methods of Molecular Transformations, category 2; Georg Thieme: Stuttgart, **2004**, 845.

(7) (a) Brown, D. J. *Quinoxalines Supplement II*, In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C.; Wipf, P., Ed.; John Wiley & Sons: Hoboken, **2004**. (b) Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. *Tetrahedron Lett.* **2009**, *50*, 767. (c) Ji, Y-F.; Chen, T.-M.; Mao, H.-F.; Zou, J.-P. *Chem. Res. Chin. Univ.* **2012**, *28*, 642. (d) Yan, Y.-M.; Li, H.-Y.; Ren, J.; Wang, S.; Ding, M.-W. *Synlett* **2018**, *29*, 1447. (e) Yoshimura, M.; Ono, M.; Matsumura, K.; Watanabe, H.; Kimura, H.; Cui, M.; Nakamoto, Y.; Togashi, K.; Okamoto, Y.; Ihara, M.; Takahashi, R.; Saji, H. *ACS Med. Chem. Lett.* **2013**, *4*, 596.

(8) (a) Son, J.-H.; Zhu, J. S.; Phuan, P.-W.; Cil, O.; Teuthorn, A. P.; Ku, C. K.; Lee, S.; Verkman, A. S.; Kurth, M. J. *J. Med. Chem.* **2017**, *6*, 2401. (b) Nagaraj, M.; Sathiyamoorthy, S.; Boominathan, M.; Muthusubramanian, S.; Bhuvanesh, N. *J. Heterocycl. Chem.* **2013**, *50*, 1146. (c) Gräßle, S.; Vanderheiden, S.; Hodapp, P.; Bulat, B.; Nieger, M.; Jung, N.; Bräse, S. *Org. Lett.* **2016**, *18*, 3598. (d) Dutta, N. B.; Bhuyan, M.; Baishya, G. *RSC Adv.* **2020**, *10*, 3615. (e) Yan, Y.-M.; Li, H.-Y.; Ren, J.; Wang, S.; Ding, M.-W. *Synlett* **2018**, *29*, 1447.

(9) (a) Murthy, V. N.; Satish, N. P.; Krishnaji, T.; Madhubabu, M. V.; Rao, J. S.; Rao, L. V.; Raghunadh, A. *RSC Adv.* **2018**, *8*, 22331. (b) Kumar, S. P.; Murthy, V. N.; Ganesh, K. R.; Rao, G. S.; Krishnaji, T.; Raghunadh, A. *ChemistrySelect* **2018**, *3*, 6836. (c) Jaganmohan, C.; Kumar, K. P. V.; Reddy, G. S.; Mohanty, S.; Kumar, J.; Rao, B. V.; Krishnaji, T.; Raghunadh, A. *Synth. Commun.* **2018**, *48*, 168. (d) Venkateshwarlu, R.; Murthy, V. N.; Krishnaji, T.; Satish, P. N.; Rajesh, J.; Vidavalur, S.; Madhu, M. V.; Mohana, B. H. R.; Raghunadh, A. *RSC Adv.* **2020**, *10*, 9486. (e) Jaganmohan, Ch.; Kumar, K. P. V.; Venkateshwarlu, R.; Mohanty, S.; Kumar, J.; Rao, B. V.; Raghunadh, A.; Krishnaji, T. *Synth. Commun.* **2020**, *14*, 2163.

(10) Raghunadh, A.; Babu, M. S.; Kumar, N. A.; Kumar, G. S.; Rao, L. V.; Kumar, U. K. S. *Synthesis* **2012**, *44*, 283.

(11) Makhloufi, A.; Baitiche, M.; Merbah, M.; Benachour, D. *Synth. Commun.* **2011**, *41*, 3532.