Synthesis of Quinoxaline Analogues

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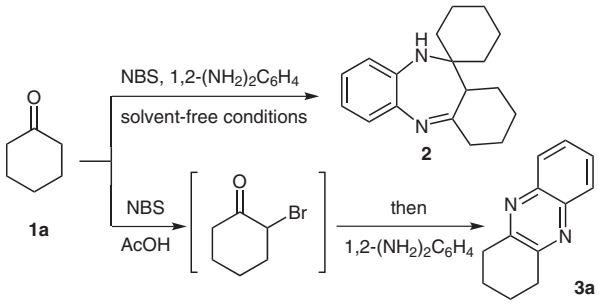
Abstract: Substituted tricyclic or tetracyclic quinoxalines, tricyclic pyridoquinoxalines and bis-quinoxalines were synthesized in high yields starting from cyclic ketones by the α-bromination of cyclic ketones with *N*-bromosuccinimide (NBS) followed by condensation of the resulting α-bromo ketones with 1,2-diaminobenzene, 3,4-diaminopyridine, or 3,3′-diaminobenzidine.

Key words: condensation, halogenation, tandem reactions, heterocycles, arenes

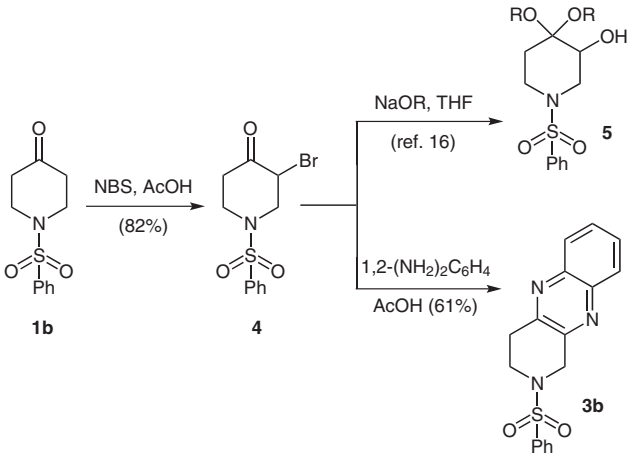
Quinoxaline heterocycles are important benzoheterocycles in combinatorial drug discovery libraries.[1] There are a number of processes available to generate the structural skeleton of quinoxalines, but they are generally synthesized by the condensation of 1,2-dicarbonyls with 1,2-diamines in either acetic acid or ethanol heated to reflux.[2] Some recent reactions of 1,2-diaminobenzene with α-dicarbonyl equivalents are described as follows: (1) epoxides in the presence of Bi(0) and acid derivatives,[3] (2) ketones and potassium hydroxide in PEG 400,[4] (3) α-bromo ketones in an aqueous media system[5] or by use of solid phase chemistry,[6] (4) hydroxylimino ketones under microwave irradiation,[7] (5) α-hydroxyketones[8] by the use of iodine,[9] sulfamic acid,[10] nanoparticles,[11] metal complex-mediated tandem oxidation process,[12] and other notable approaches.[13] Although a great number of quinoxalines and their derivatives with this specific substitution pattern have been developed, new methods for their preparation are needed. Since the above-mentioned procedures are almost all multi-step reactions, we wanted to explore a one-pot methodology[14] for the preparation of tricyclic or tetracyclic quinoxaline skeletons by the α-bromination of cyclic ketones with *N*-bromosuccinimide (NBS) in acetic acid, followed by the addition of different aryl-1,2-diamines (e.g., 1,2-diaminobenzene; 3,4-diaminopyridine or 3,3′-diaminobenzidine).

Recently, Yao et al. reported that NBS (10 mol%) promoted the synthesis of 1,5-benzodiazepine **2** through the reaction of cyclohexanone (**1a**; 4.0 mmol) with 1,2-diaminobenzene (1.0 mmol) either at r.t. or at 40 °C under solvent-free conditions.[15] Three components were added almost simultaneously for the one-pot reaction. However, our concise synthesis of quinoxaline **3a** with the ordinal addition sequence was achieved from the reaction of cyclohexanone (**1a**; 1.0 mmol) with NBS (1.05 mmol) in acetic acid (5 mL), followed by the addition of the resulting α-bromo ketone with 1,2-diaminobenzene (1.1 mmol), as shown in Scheme 1. The major difference between the construction of the two frameworks of benzodiazepine **2** and quinoxaline **3a**[8b] is the sequence of addition of the reagents [NBS, cyclohexanone (**1a**), then 1,2-diaminobenzene].



Scheme 1 NBS-mediated synthetic strategies toward benzodiazepine **2** and quinoxaline **3a** from ketone **1a**. For benzodiazepine **2**: **1** (4.0 mmol), NBS (10%), 1,2-diaminobenzene (1.0 mmol). For quinoxaline **3a**: **1** (1.0 mmol), NBS (1.05 mmol), 1,2-diaminobenzene (1.1 mmol).

In previous studies, we have explored the synthetic application of *N*-benzenesulfonyl-3-bromopiperidin-4-one (**4**) to generate the structural framework of 4,4-dialkoxy-3-piperidinol **5** with a range of sodium alkoxides (Scheme 2).[16] Furthermore, treatment of compound **4**



Scheme 2 Synthetic application of α-bromopiperidin-4-one **4**

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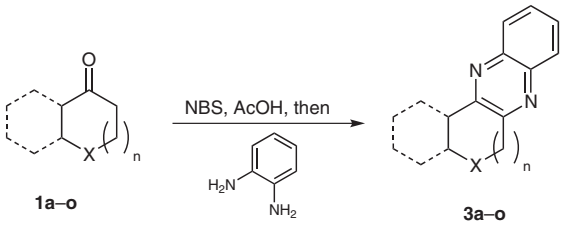
with 1,2-diaminobenzene in acetic acid gave compound **3b** in 61% yield. The total yield of the two-step protocol was 50%. Because acetic acid was used as the solvent in both the bromination and condensation, the combination of the two reactions was worthy of further study. Initially, compound **1b** (1.0 mmol) was chosen as the starting material for the one-pot tandem reaction of quinoxaline with NBS (1.05 equiv) and 1,2-diaminobenzene (1.1 equiv), as shown in Table 1.

Table 1 Synthesis of Substituted Quinoxaline Analogues[a]



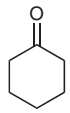
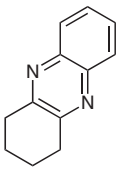
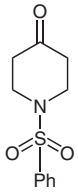
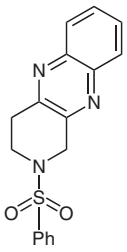
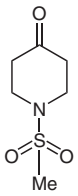
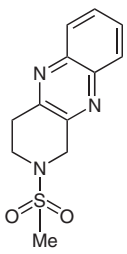
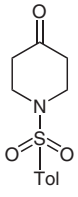
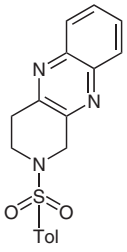
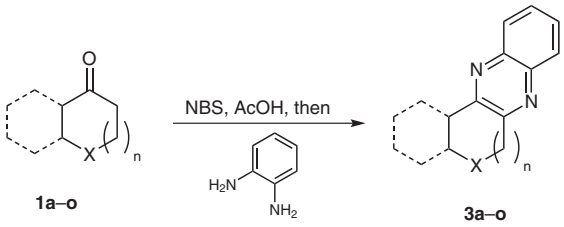
Entry	Reactant	Product	Yield (%)
1	 **1a**	 **3a**	74
2	 **1b**	 **3b**	72
3	 **1c**	 **3c**	66
4	 **1d**	 **3d**	67

Table 1 Synthesis of Substituted Quinoxaline Analogues[a] (continued)



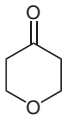
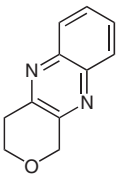
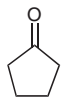
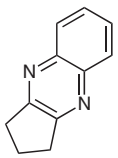
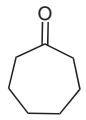
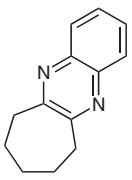
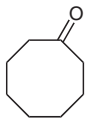
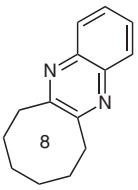
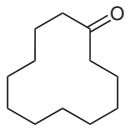
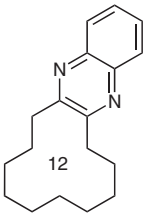
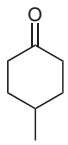
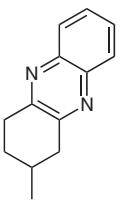
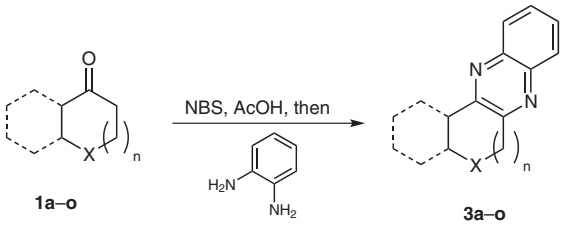
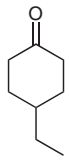
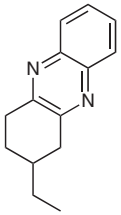
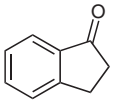
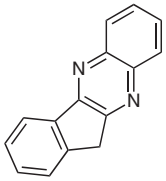
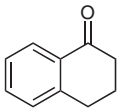
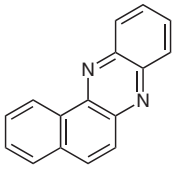
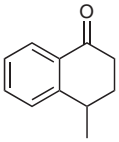
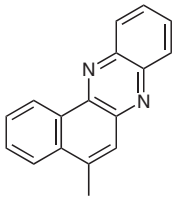
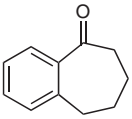
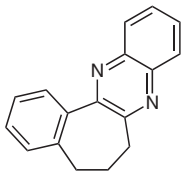
Entry	Reactant	Product	Yield (%)
5	 **1e**	 **3e**	70
6	 **1f**	 **3f**	52
7	 **1g**	 **3g**	79
8	 **1h**	 **3h**	80
9	 **1i**	 **3i**	92
10	 **1j**	 **3j**	66

Table 1 Synthesis of Substituted Quinoxaline Analogues[a] (continued)



Entry	Reactant	Product	Yield (%)
11	 **1k**	 **3k**	62
12	 **1l**	 **3l**	60
13	 **1m**	 **3m**	79
14	 **1n**	 **3n**	80
15	 **1o**	 **3o**	82

[a] The products were >95% pure as judged by ^{1}H NMR analysis.

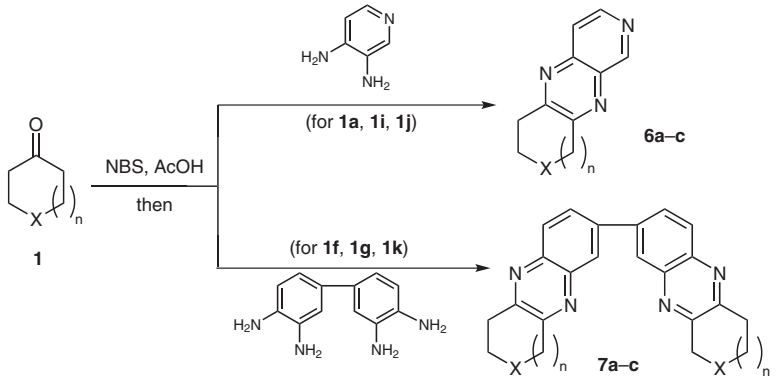
The synthetic strategy was first applied to the synthesis of a series of tricyclic or tetracyclic quinoxaline analogues. Cyclic ketones, in particular, were examined because fewer tricyclic quinoxalines have been reported.[4,13] Under the above conditions, compound **3b** was obtained in 72% yield. The elevated yields should be a major advantage of the convenient, one-pot reaction. Furthermore, we were able to present an atom-economic, green procedure. Since replacing NBS with either NCS or NIS did not improve the yields, further studies were conducted only with NBS. In order to evaluate the effect of the solvent on the reaction, a range of solvents, such as methanol, acetonitrile, and dichloromethane, were examined. Among the different solvents, acetic acid proved to be the best medium for this reaction. Next, a one-pot reaction of cyclic ketones **1a–o** (*N*-sulfonyl-piperidin-4-ones, tetrahydropyran-4-one, cycloalkanones, and benzocycloalkanones) with NBS and 1,2-diaminobenzene provided compounds **3a–o**. The total synthetic procedure could be monitored by TLC until the reaction was complete (within 8 h).

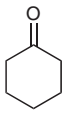
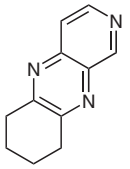
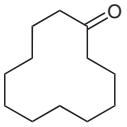
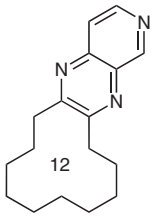
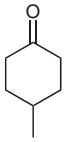
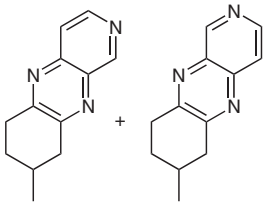
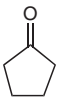
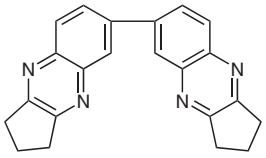
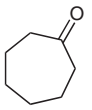
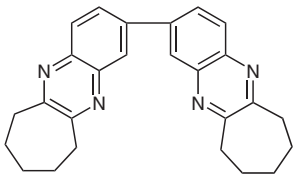
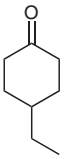
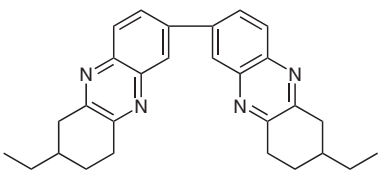
According to the procedure, the skeleton of quinoxaline with a range of functional groups was also synthesized in moderate yields. Eleven tricyclic quinoxaline analogues **3a–k** (52–92% yields) and four tetracyclic quinoxaline analogues **3l–o** (60–82% yields) were generated. In comparison to the isolated yields of quinoxaline products with different ring sizes, it was found that the larger-ring compounds were more suitable. Attempts to extend this reaction to cyclobutanone were unsuccessful. A possible reason might be that ring strain was a key factor affecting the distribution of yields. In Table 1, entries 13 and 14, when the benzocyclohexanone skeleton was chosen as the reactant, benzo[*a*]phenazines **3m** and **3n** were isolated by using the in situ aromatization procedure. The skeleton of β-lapachone benzo[*a*]phenazine has attracted considerable attention because of its interesting biological activities,[17] including anti-malarial[18] and anti-hepatitis C viral replication properties.[19] The structural frameworks of compounds **3b**, **3h**, **3m**, and **3o** were determined by using single-crystal X-ray analysis (Figure 1 and Figure 2).[20]

With these results in hand, other aromatic diamines were further investigated. The reaction of ketone **1a**, **1i** or **1j** with NBS (1.05 equiv) and 3,4-diaminopyridine (1.1 equiv) was examined, as shown in Table 2. The pyridoquinoxaline analogues **6a–c** were also afforded in 66–90% yields. For Table 2, entry 3, product **6c** was generated as an isomeric mixture with a ratio of nearly 1:1. We then further expanded the scope of the double-condensation strategy to the skeleton of bis-quinoxaline through the use of 3,3′-diaminobenzidine instead of 1,2-diaminobenzene or 3,4-diaminopyridine. Three bis-quinoxaline analogues **7a–c,** with a five-, seven-, and six-membered ring, respectively, were afforded in 43–80% yields by treatment of compounds **1f**, **1g** or **1k** (1.0 mmol) with NBS (1.05 equiv) and 3,3′-diaminobenzidine (0.5 equiv). This present methodology is the simplest and perhaps quickest synthesis of quinoxaline, pyridoquinoxaline, and bis-quinoxaline derivatives available.

To increase the synthetic potential, an acyclic ketone was also submitted to the facile one-pot methodology. Thus, 2-phenylquinoxaline was provided in 87% yield via treatment of acetophenone with NBS followed by addition of 1,2-diaminobenzene under the conditions described above.

Table 2 Synthesis of Quinoxaline Analogues **6** and **7**[a]



Entry	Reactant	Product	Yield (%)
1	 **1a**	 **6a**	66
2	 **1i**	 **6b**	90
3	 **1j**	 **6c**	70
4	 **1f**	 **7a**	43
5	 **1g**	 **7b**	80
6	 **1k**	 **7c**	78

[a] The isolated products were >95% pure as judged by ^{1}H NMR analysis.

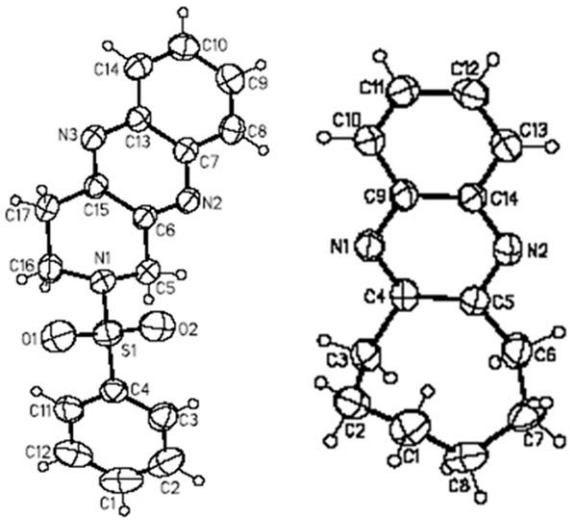


Figure 1 X-ray crystal structures of compounds **3b** and **3h**

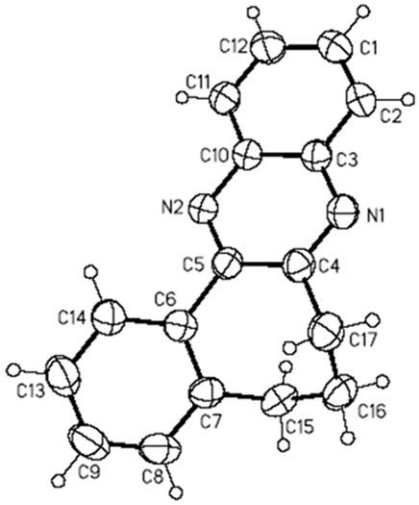


Figure 2 X-ray crystal structure of compound **3o**

In summary, a straightforward, one-pot, concise synthesis of the polycyclic quinoxaline analogues **3a–o**, **6a–c**, and **7a–c** from treatment of cyclic ketones **1a–o** with NBS in acetic acid followed by condensation by addition of 1,2-diaminobenzene, 3,4-diaminopyridine or 3,3′-diaminobenzidine has been developed. Further investigation is required to establish the structure–activity relationships of the polycyclic quinoxaline analogues.

THF was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with an SMP3 melting-point apparatus. Infrared spectra were recorded with a Perkin–Elmer 100 series FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian INOVA-400 spectrometer operating at 200/400 and at 50/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in hertz. High-resolution mass spectra (HRMS) were measured with a Finnigan/Thermo Quest MAT 95XL mass spectrometer. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN-OS-Rapid Analyzer or Elementar Vario EL III instruments.

Synthesis of Skeleton 3; General Procedure

NBS (94 mg, 0.53 mmol) was added to a stirred solution of **1a–o** (0.5 mmol) in AcOH (5 mL) at r.t. and the reaction mixture was stirred at reflux for 2–4 h and then cooled to r.t.. 1,2-Diaminobenzene (59 mg, 0.55 mmol) was added at r.t. and the reaction mixture was further stirred at reflux for 2–4 h and then again cooled to r.t. CH_2Cl_2 (20 mL) and sat. aq $NaHCO_3$ (10 mL) were added to the reaction mixture, which was cooled in an ice bath. The residue was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (3 × 10 mL), dried, filtered and evaporated to afford the crude product. Purification on silica gel (hexanes–EtOAc, 4:1→1:1) afforded compounds **3a–o**.

1,2,3,4-Tetrahydrophenazine (3a)

Compound **3a** is a known compound and the analytical data are consistent with those reported in the literature.[8b]

Yield: 68 mg (74%); mp 92–93 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 2:1).

IR ($CHCl_3$): 3008, 2937, 1578, 1459, 1423, 1384, 1330, 1291, 1238 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.98–7.96 (m, 2 H), 7.62–7.56 (m, 2 H), 3.19–3.17 (br s, 4 H), 2.06–2.03 (br s, 4 H).

^{13}C NMR (100 MHz): δ = 154.19 (2×), 141.20 (2×), 128.95 (2×), 128.28 (2×), 33.32 (2×), 22.79 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{12}H_{13}N_2$: 185.1079; found: 185.1081.

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.49; H, 6.86; N, 15.42.

2-Benzenesulfonyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline (3b)

Yield: 117 mg (72%); mp 179–180 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 2957, 1559, 1491, 1449, 1368 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.96–7.93 (m, 2 H), 7.80–7.76 (m, 2 H), 7.71–7.68 (m, 2 H), 7.63–7.51 (m, 3 H), 4.54 (s, 2 H), 3.60 (t, *J* = 6.0 Hz, 2 H), 2.51 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 149.74, 147.88, 141.43, 140.96, 134.15, 133.11, 129.96, 129.77, 129.26 (2×), 128.46, 128.45, 127.39 (2×), 45.76, 43.71, 32.19.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{16}N_3O_2S$: 326.0963; found: 326.0966.

Anal. Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 63.02; H, 4.90; N, 13.10.

Single-Crystal X-ray Structure of 3b

Grown by slow diffusion of EtOAc into a solution of compound **3b** in CH_2Cl_2 to yield a colorless prism. The compound crystallizes in the triclinic crystal system; space group $P\bar{1}$; *a* = 6.7112(2) Å, *b* = 10.0918(2) Å, *c* = 11.1626(3) Å; *V* = 720.59(3) Å^3; *Z* = 2; d_{calcd} = 1.389 g/cm^3; *F*(000) = 320, 2θ range 1.85–26.38°, *R* indices (all data) *R*1 = 0.0539, *wR*2 = 0.1470.

2-Methanesulfonyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline (3c)
Yield: 87 mg (66%); mp 166–167 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 2955, 1548, 1482, 1440, 1361 cm^{-1}.

^1H NMR (400 MHz): δ = 7.96–7.93 (m, 2 H), 7.80–7.76 (m, 2 H), 4.50 (s, 2 H), 3.52 (t, *J* = 6.0 Hz, 2 H), 2.78 (s, 3 H), 2.26 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 149.96, 146.87, 142.08, 141.19, 129.53, 129.47, 128.09, 128.07, 46.11, 44.07, 34.46, 30.01.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{12}H_{14}N_3O_2S$: 264.0807; found: 264.0808.

Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.96; H, 5.23; N, 16.08.

2-(4-Methylphenyl)sulfonyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline (3d)
Yield: 114 mg (67%); mp 189–190 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 2963, 1555, 1444, 1339 cm^{-1}.

^1H NMR (400 MHz): δ = 7.99–7.93 (m, 2 H), 7.77–7.65 (m, 4 H), 7.33–7.29 (m, 2 H), 4.52 (s, 2 H), 3.58 (t, *J* = 6.0 Hz, 2 H), 2.40 (s, 3 H), 2.21 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 149.80, 148.00, 144.17, 141.40, 140.96, 129.93, 129.86 (2×), 129.76, 129.00, 128.45 (2×), 128.41, 127.75, 50.56, 43.71, 32.19, 21.47.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{18}N_3O_2S$: 340.1120; found: 340.1122.

Anal. Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.92; H, 5.25; N, 12.49.

3,4-Dihydro-1*H*-pyrano[3,4-*b*]quinoxaline (3e)
Yield: 65 mg (70%); mp 88–89 °C (recrystallized from hexanes and EtOAc); R_f = 0.3 (hexanes–EtOAc, 2:1).

IR ($CHCl_3$): 2945, 1610, 1422, 1341 cm^{-1}.

^1H NMR (400 MHz): δ = 8.02–7.97 (m, 2 H), 7.74–7.69 (m, 2 H), 5.01 (s, 2 H), 4.21 (t, *J* = 6.0 Hz, 2 H), 3.29 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 151.24, 150.52, 141.68, 141.16, 129.55, 129.49, 128.60, 128.58, 70.31, 65.61, 32.43.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{11}N_2O$: 187.0871; found: 187.0871.

Anal. Calcd for $C_{11}H_{10}N_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.30; H, 5.72; N, 14.89.

2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxaline (3f)
Yield: 44 mg (52%); mp 93–94 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2948, 1633, 1432, 1349 cm^{-1}.

^1H NMR (400 MHz): δ = 8.01–7.97 (m, 2 H), 7.67–7.63 (m, 2 H), 3.19 (t, *J* = 7.6 Hz, 4 H), 2.29 (quint., *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 160.54 (2×), 141.49 (2×), 128.71 (2×), 128.68 (2×), 32.34 (2×), 21.24.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{11}N_2$: 171.0922; found: 171.0924.

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.46; H, 6.12; N, 16.80.

7,8,9,10-Tetrahydro-6*H*-cyclohepta[*b*]quinoxaline (3g)
Yield: 78 mg (79%); mp 74–75 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2951, 1612, 1439, 1355 cm^{-1}.

^1H NMR (400 MHz): δ = 7.96–7.92 (m, 2 H), 7.64–7.60 (m, 2 H), 3.19–3.16 (m, 4 H), 1.94–1.88 (m, 2 H), 1.82–1.77 (m, 4 H).

^{13}C NMR (100 MHz): δ = 158.84 (2×), 140.61 (2×), 128.79 (2×), 128.27 (2×), 38.70 (2×), 31.89, 26.82 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{13}H_{15}N_2$: 199.1235; found: 199.1234.

Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.97; H, 7.45; N, 14.25.

6,7,8,9,10,11-Hexahydro-cycloocta[*b*]quinoxaline (3h)
Compound **3a** is a known compound and the analytical data are consistent with those reported in the literature.[4a,b]

Yield: 85 mg (80%); mp 118–119 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2954, 1638, 1436, 1332 cm^{-1}.

^1H NMR (400 MHz): δ = 8.01–7.97 (m, 2 H), 7.67–7.63 (m, 2 H), 3.20–3.17 (m, 4 H), 1.93–1.87 (m, 4 H), 1.45–1.40 (m, 4 H).

^{13}C NMR (100 MHz): δ = 157.74 (2×), 141.36 (2×), 128.77 (2×), 128.41 (2×), 34.94 (2×), 30.91 (2×), 26.02 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{14}H_{17}N_2$: 213.1392; found: 213.1394.

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.45; H, 7.93; N, 13.41.

Single-Crystal X-ray Structure of 3h
Grown by slow diffusion of EtOAc into a solution of compound **3h** in CH_2Cl_2 to yield a prism. The compound crystallizes in the orthorhombic crystal system; space group $P2_12_12_1$; *a* = 8.842(5) Å, *b* = 10.429(5) Å, *c* = 12.574(6) Å; *V* = 1159.6(10) Å^3; *Z* = 4; d_{calcd} = 1.216 g/cm^3; *F*(000) = 456, 2θ range 3.24–26.49°, *R* indices (all data) *R*1 = 0.1096, *wR*2 = 0.1181.

6,7,8,9,10,11,12,13,14,15-Decahydro-5,16-diaza-cyclododeca[*b*]naphthalene (3i)
Yield: 123 mg (92%); mp 81–82 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2934, 1641, 1429, 1333 cm^{-1}.

^1H NMR (400 MHz): δ = 7.98–7.96 (m, 2 H), 7.65–7.63 (m, 2 H), 3.05 (t, *J* = 7.6 Hz, 4 H), 1.98–1.92 (m, 4 H), 1.54–1.38 (m, 12 H).

^{13}C NMR (100 MHz): δ = 157.28 (2×), 140.96 (2×), 128.77 (2×), 128.33 (2×), 32.44 (2×), 27.95 (2×), 26.39 (2×), 25.48 (2×), 23.06 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{25}N_2$: 269.2018; found: 269.2019.

Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.77; H, 9.32; N, 10.76.

2-Methyl-1,2,3,4-tetrahydrophenazine (3j)
Yield: 65 mg (66%); oil; R_f = 0.2 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2937, 1618, 1449, 1312 cm^{-1}.

^1H NMR (400 MHz): δ = 7.97–7.92 (m, 2 H), 7.65–7.61 (m, 2 H), 3.26–3.20 (m, 2 H), 3.10 (ddd, *J* = 6.0, 11.6, 17.6 Hz, 1 H), 2.73 (dd, *J* = 10.8, 17.6 Hz, 1 H), 2.18–2.06 (m, 2 H), 1.70–1.58 (m, 1 H), 1.16 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz): δ = 155.74, 153.68, 141.13, 141.10, 128.76, 128.84, 128.30, 128.26, 41.49, 32.31, 30.78, 29.13, 21.52.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{13}H_{15}N_2$: 199.1235; found: 199.1233.

Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.95; H, 7.39; N, 14.42.

2-Ethyl-1,2,3,4-tetrahydrophenazine (3k)
Yield: 66 mg (62%); oil; R_f = 0.2 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2926, 1635, 1432, 1351 cm^{-1}.

^1H NMR (400 MHz): δ = 7.91–7.86 (m, 2 H), 7.59–7.54 (m, 2 H), 3.13 (ddt, *J* = 2.0, 4.8, 17.6 Hz, 2 H), 3.01 (ddt, *J* = 6.4, 11.6, 17.6 Hz, 1 H), 2.66 (dd, *J* = 11.2, 17.6 Hz, 1 H), 2.11–2.04 (m, 1 H), 1.84–1.75 (m, 1 H), 1.59–1.49 (m, 1 H), 1.46–1.37 (m, 2 H), 0.96 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz): δ = 153.81, 153.66, 140.96, 140.94, 128.72, 128.70, 128.13, 128.11, 39.19, 35.60, 32.18, 28.66, 28.37, 11.29.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{14}H_{17}N_2$: 213.1392; found: 213.1394.

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.42; H, 7.81; N, 13.42.

11*H*-Indeno[1,2-*b*]quinoxaline (3l)
Yield: 65 mg (60%); mp 131–132 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2980, 1520, 1420, 1329, 1231 cm^{-1}.

^1H NMR (400 MHz): δ = 8.25–8.23 (m, 1 H), 8.17–8.14 (m, 1 H), 8.10–8.06 (m, 1 H), 7.76–7.69 (m, 2 H), 7.66–7.63 (m, 1 H), 7.57–7.49 (m, 2 H), 4.13 (s, 2 H).

^{13}C NMR (100 MHz): δ = 159.42, 154.59, 143.46, 141.98, 141.17, 137.95, 131.11, 129.22, 129.14, 128.90, 128.79, 128.01, 125.77, 122.65, 35.90.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{11}N_2$: 219.0822; found: 219.0823.

Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found: C, 82.68; H, 4.87; N, 13.02.

Benzo[*a*]phenazine (3m)
Yield: 91 mg (79%); mp 144–145 °C (recrystallized from hexanes and EtOAc); R_f = 0.3 (hexanes–EtOAc, 2:1).

IR ($CHCl_3$): 3043, 1354, 1024, 767 cm^{-1}.

^1H NMR (400 MHz): δ = 9.32–9.29 (m, 1 H), 8.28 (ddt, *J* = 0.5, 3.2, 10.0 Hz, 1 H), 8.22 (ddt, *J* = 0.5, 3.2, 10.0 Hz, 1 H), 7.91 (d, *J* = 9.2 Hz, 1 H), 7.87 (d, *J* = 9.2 Hz, 1 H), 7.82–7.78 (m, 3 H), 7.75–7.67 (m, 2 H).

^{13}C NMR (100 MHz): δ = 143.37, 142.47, 142.40, 141.75, 133.12, 133.02, 130.90, 129.87, 129.66, 129.62, 129.57, 128.97, 128.01, 127.75, 126.93, 125.20.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{16}H_{11}N_2$: 231.0922; found: 231.0923.

Anal. Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.80; H, 4.67; N, 12.42.

Single-Crystal X-ray Structure of 3m
Grown by slow diffusion of EtOAc into a solution of compound **3m** in CH_2Cl_2 to yield a prism. The compound crystallizes in the monoclinic crystal system; space group P1n1; *a* = 7.1628(15) Å, *b* = 5.0923(12) Å, *c* = 15.510(3) Å; *V* = 565.7(2) Å^3; *Z* = 2; d_{calcd} = 1.352 g/cm^3, *F*(000) = 240, 2θ range 2.63–26.47°, *R* indices (all data) *R*1 = 0.0566, *wR*2 = 0.0883.

5-Methyl-benzo[*a*]phenazine (3n)
Yield: 98 mg (80%); mp 174–175 °C (recrystallized from hexanes and EtOAc); R_f = 0.3 (hexanes–EtOAc, 2:1).

IR ($CHCl_3$): 3033, 1331, 1033, 781 cm^{-1}.

^1H NMR (400 MHz): δ = 9.44–9.40 (m, 1 H), 8.33–8.29 (m, 1 H), 8.24–8.21 (m, 1 H), 8.02–7.98 (m, 1 H), 7.84–7.76 (m, 5 H), 2.76 (s, 3 H).

^{13}C NMR (100 MHz): δ = 143.54, 142.80, 142.32, 141.64, 140.02, 133.54, 130.93, 129.79, 129.71, 129.65, 129.28, 128.98, 127.59, 126.40, 125.58, 124.46, 20.28.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{13}N_2$: 245.1083; found: 245.1084.

Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.82; H, 5.12; N, 11.62.

6,7-Dihydro-5*H*-8,13-diazabenzo[3,4]cyclohepta[1,2-*b*]naphthalene (3o)
Yield: 101 mg (82%); mp 92–93 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 2:1).

IR ($CHCl_3$): 3023, 1376, 1107 cm^{-1}.

^1H NMR (400 MHz): δ = 8.18–8.14 (m, 1 H), 8.11–8.07 (m, 1 H), 7.86–7.84 (m, 1 H), 7.73–7.69 (m, 2 H), 7.47–7.40 (m, 2 H), 7.29–7.27 (m, 1 H), 2.96 (t, *J* = 7.2 Hz, 2 H), 2.64 (t, *J* = 7.2 Hz, 2 H), 2.41–2.34 (m, 2 H).

^{13}C NMR (100 MHz): δ = 155.62, 154.95, 141.74, 141.18, 139.11, 138.11, 129.89, 129.28, 129.22, 128.99 (2x), 128.59, 128.36, 127.08, 33.80, 30.77, 30.51.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{15}N_2$: 247.1235; found: 247.1236.

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.12; H, 5.98; N, 11.55.

Single-Crystal X-ray Structure of 3o
Grown by slow diffusion of EtOAc into a solution of compound **3o** in CH_2Cl_2 to yield a prism. The compound crystallizes in the monoclinic crystal system; space group C12/c1; *a* = 11.5698(3) Å, *b* = 12.8032(4) Å, *c* = 18.2009(5) Å; *V* = 2573.69(13) Å^3; *Z* = 8; d_{calcd} = 1.271 g/cm^3; *F*(000) = 1040, 2θ range 2.34–26.39°, *R* indices (all data) *R*1 = 0.0718, *wR*2 = 0.1731.

Synthesis of Skeleton 6; General Procedure
NBS (94 mg, 0.53 mmol) was added to a stirred solution of compound **1a**, **1i**, or **1j** (0.5 mmol) in AcOH (5 mL) at r.t., and the reaction mixture was stirred at reflux for 2–4 h and then cooled to r.t. 3,4-Diaminopyridine (60 mg, 0.55 mmol) was added at r.t. and the reaction mixture was further stirred at reflux for 2–4 h and then cooled to r.t. again. CH_2Cl_2 (20 mL) and sat. aq $NaHCO_3$ (10 mL) were added to the reaction mixture, which was cooled in an ice bath. The residue was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (3 × 10 mL), dried, filtered, and evaporated to afford the crude product. Purification on silica gel (hexanes–EtOAc,2:1→1:2) afforded compounds **6a–c**.

6,7,8,9-Tetrahydropyrido[3,4-*b*]quinoxaline (6a)
Yield: 61 mg (66%); mp 79–80 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 2938, 1422, 1381, 1329, 1272 cm^{-1}.

^1H NMR (400 MHz): δ = 9.41 (s, 1 H), 8.73 (d, *J* = 5.6 Hz, 1 H), 7.81 (d, *J* = 6.0 Hz, 1 H), 3.23–3.19 (m, 4 H), 2.11–2.05 (m, 4 H).

^{13}C NMR (100 MHz): δ = 159.58, 156.50, 153.52, 146.42 (2×), 120.82 (2×), 33.31 (2×), 22.51 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{12}N_3$: 186.1031; found: 186.1030.

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.49; H, 6.21; N, 22.78.

6,7,8,9,10,11,12,13,14,15-Decahydro-2,5,16-triaza-cyclododeca[*b*]naphthalene (6b)
Yield: 121 mg (90%); mp 96–97 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 2944, 1429, 1363, 1281 cm^{-1}.

^1H NMR (400 MHz): δ = 9.50 (s, 1 H), 8.72 (d, *J* = 5.6 Hz, 1 H), 7.82 (d, *J* = 6.0 Hz, 1 H), 3.32–3.22 (m, 4 H), 1.98–1.91 (m, 4 H), 1.53–1.30 (m, 12 H).

^{13}C NMR (100 MHz): δ = 160.12, 156.14, 153.54, 146.44 (2×), 120.82 (2×), 32.43 (2×), 27.95 (2×), 26.38 (2×), 25.48 (2×), 23.05 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{24}N_3$: 270.1970; found: 270.1971.

Anal. Calcd for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.60. Found: C, 76.02; H, 8.79; N, 15.49.

Mixture of 8-Methyl-6,7,8,9-tetrahydropyrido[3,4-*b*]quinoxaline and 7-Methyl-6,7,8,9-tetrahydropyrido[3,4-*b*]quinoxaline (6c)
Yield: 70 mg (70%); R_f = 0.2 (hexanes–EtOAc, 1:1).

^1H NMR (400 MHz): δ = 9.39 (s, 1 H), 8.71 (d, *J* = 5.6 Hz, 1 H), 7.79 (d, *J* = 6.0 Hz, 1 H), 3.33–3.26 (m, 2 H), 3.19–3.10 (m, 1 H), 2.78 (dd, *J* = 10.8, 18.0 Hz, 1 H), 2.21–2.10 (m, 2 H), 1.74–1.63 (m, 1 H), 1.20 (d, *J* = 6.4 Hz, 3/2 H), 1.19 (d, *J* = 6.4 Hz, 3/2 H).

^{13}C NMR (100 MHz): δ = 159.19 (1/2×), 159.16 (1/2×), 156.12 (1/2×), 156.08 (1/2×), 153.55 (1/2×), 153.52 (1/2×), 146.44 (1/2×), 146.41 (1/2×), 143.71 (1/2×), 143.68 (1/2×), 136.54 (1/2×), 136.50 (1/2×), 120.81 (1/2×), 120.78 (1/2×), 41.94 (1/2×), 41.59 (1/2×), 32.84 (1/2×), 32.46 (1/2×), 30.55 (1/2×), 30.45 (1/2×), 29.02 (1/2×), 28.93 (1/2×), 21.47.

Synthesis of Skeleton 7; General Procedure
NBS (187 mg, 1.05 mmol) was added to a stirred solution of compound **1f**, **1g**, or **1k** (1.0 mmol) in AcOH (5 mL) at r.t., and the reaction mixture was stirred at reflux for 2–4 h. The reaction was cooled to r.t. and 3,3′-diaminobenzidine (110 mg, 0.5 mmol) was added to the reaction mixture at r.t. The reaction mixture was further stirred at reflux for 2–4 h and then cooled to r.t. again. CH_2Cl_2 (20 mL) and sat. aq $NaHCO_3$ (10 mL) were added to the reaction mixture, which was cooled in an ice bath. The residue was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (3 × 10 mL), dried, filtered, and evaporated to afford the crude product. Purification on silica gel (hexanes–EtOAc, 2:1→1:2) afforded compounds **7a–c**.

2,3-Dihydro-6-(2,3-dihydro-1*H*-cyclopenta[*b*]quinoxalin-7-yl)-1*H*-cyclopenta[*b*]quinoxaline (7a)
Yield: 73 mg (43%); mp >230 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 3043, 2944, 1631, 1438, 1343 cm^{-1}.

^1H NMR (400 MHz): δ = 8.34 (s, 2 H), 8.08 (s, 4 H), 3.27–3.24 (m, 8 H), 1.99–1.95 (m, 4 H).

^{13}C NMR (100 MHz): δ = 159.69 (2×), 159.25 (2×), 140.99 (2×), 140.51 (2×), 140.36 (2×), 129.03 (2×), 128.46 (2×), 126.68 (2×), 32.45 (2×), 32.00 (2×), 21.29 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{22}H_{19}N_4$: 339.1610; found: 339.1612.

Anal. Calcd for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 15.56. Found: C, 78.26; H, 5.45; N, 15.73.

7,8,9,10-Tetrahydro-2-(7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoxalin-3-yl)-6*H*-cyclohepta[*b*]quinoxaline (7b)
Yield: 158 mg (80%); mp >230 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 3032, 1582, 1410, 1324 cm^{-1}.

^1H NMR (400 MHz): δ = 8.34 (s, 2 H), 8.09 (s, 4 H), 3.27–3.24 (m, 8 H), 1.99–1.95 (m, 4 H), 1.90–1.82 (m, 8 H).

^{13}C NMR (100 MHz): δ = 159.67 (2×), 159.25 (2×), 140.96 (2×), 140.49 (2×), 140.34 (2×), 129.02 (2×), 128.46 (2×), 126.67 (2×), 38.86 (2×), 38.84 (2×), 31.99 (2×), 26.96 (2×), 26.93 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{26}H_{27}N_4$: 395.2236; found: 395.2238.

Anal. Calcd for $C_{26}H_{26}N_4$: C, 79.16; H, 6.64; N, 14.20. Found: C, 79.38; H, 6.84; N, 14.51.

2-Ethyl-7-(2-ethyl-1,2,3,4-tetrahydrophenazin-7-yl)-1,2,3,4-tetrahydrophenazine (7c)
Yield: 165 mg (78%); mp 129–130 °C (recrystallized from hexanes and EtOAc); R_f = 0.2 (hexanes–EtOAc, 1:1).

IR ($CHCl_3$): 3066, 2897, 1587, 1465, 1359 cm^{-1}.

^1H NMR (400 MHz): δ = 8.32 (s, 2 H), 8.07 (s, 4 H), 3.37–3.24 (m, 4 H), 3.18–3.09 (m, 2 H), 2.77 (ddd, *J* = 2.4, 10.8, 13.2 Hz, 2 H), 2.23–2.16 (m, 2 H), 1.96–1.87 (m, 2 H), 1.72–1.62 (m, 2 H), 1.57–1.49 (m, 4 H), 1.05 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz): δ = 154.79, 154.66, 154.38, 154.24, 141.40, 141.37, 140.81 (2×), 140.37, 140.34, 128.98 (2×), 128.47 (2×), 126.53 (2×), 39.45 (2×), 35.81 (2×), 32.42 (2×), 28.84 (2×), 28.54 (2×), 11.46 (2×).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{28}H_{31}N_4$: 423.2549; found: 423.2550.

Anal. Calcd for $C_{28}H_{30}N_4$: C, 79.59; H, 7.16; N, 13.26. Found: C, 79.87; H, 7.39; N, 13.41.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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