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Synthesis of novel substituted naphthoquino[*b*]-benzo[*e*][1,4]diazepines via Pictet–Spengler cyclization

Xiao Lei Wang, Xiu Fang Zheng, Ren He Liu, John Reiner* and Jun Biao Chang*

School of Pharmaceutical Science and Technology, Tianjin University, 300072 Tianjin, PR China

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Abstract—Synthesis of novel 4,5-dihydro-1*H*-1,4-naphthoquino[*b*]-benzo[*e*][1,4]diazepine derivatives via Pictet–Spengler cyclization is reported. Reaction of 2,3-diamino-naphthoquinones with aldehydes in the presence of $BF_3 \cdot Et_2O$ gives benzodiazepine-naphthoquinones in good yields.

1. Introduction

Benzodiazepines have been investigated extensively because of their anti-convulsant, anti-anxiety, analgesic, sedative, anti-depressive, and hypnotic activities in the central nervous system.[1] Medicinal chemistry efforts in this field have led to the discovery of many CNS drugs. Heterocyclic scaffolds containing the benzodiazepine moiety, which show additional bioactivities are also interesting compounds.[2]

Additionally, heterocyclic naphthoquinones such as imidazole,[3] pyrrole,[4] triazole,[5] and quinoline[6] fused derivatives of naphthoquinones are common in a variety of nature products and are associated with anti-malarial, anti-bacterial, and anti-tumor activities. In most cases, the biological activity is related to the ability of quinones to accept one or two electrons to form the corresponding radical anion or dianion species, due to the electron attracting or donating substituents at the quinone moiety. So the heterocycles fused on the quinone moiety also play an important role in the bioactivity of the compounds. Benzodiazepine-naphthoquinones are therefore potential pharmacological active. However, a careful survey of the literature revealed such compounds not having been synthesized before that stimulated us to search for an efficient synthesis of such compounds. We became attracted to the Pictet–Spengler[7] reaction due to its new application in preparing seven-membered heterocyclic ring system,[8] although application of this reaction to aromatic amines linked to an activated aromatic nucleus was not as well documented.[9] Herein, a convenient approach for the synthesis of novel 4,5-dihydro-1*H*-1,4-naphthoquino[*b*]-benzo[*e*][1,4]diazepine derivatives from readily accessible 2,3-diamino-1,4-naphthoquinones[10] using Pictet–Spengler reaction as a key step is described.

2. Results and discussion

We speculate that the reaction takes place through a Pictet–Spengler cyclization mechanism, which includes formation of iminium ion intermediate and then cyclization to afford a seven-membered ring (Scheme 1). $BF_3 \cdot Et_2O$ was found to efficiently promote the condensation reaction of diamino-naphthoquinones with both alkyl and aryl aldehydes (as shown in Table 1). Reactions of 2,3-diamino-1,4-naphthoquinones with alkyl aldehydes required shorter reaction times and gave higher yields (Table 1, compare entries 1 and 2 with 8–10), which may be due to alkyliminium ions being more electrophilic than aryliminium ions.[7] Slightly lower yield and prolonged reaction time detected in the synthesis of **9** and **10**, which applied bulky aldehyde may indicate that steric hindrance plays an important role in the cyclization reaction (Table 1, entries 3 and 4). A slightly lower yield of **16** was obtained when 3,4,5-trimethoxybenzaldehyde was applied, which can be rationalized by the electrophilicity of the trimethoxyphenyliminium ion intermediate (Table 1, entry 10). When 2-(4-nitro-anilino)-3-anilino-1,4-naphthoquinone was explored to react with propionaldehyde, the reaction took place so slowly that only trace amount of product can be detected even after three days of reaction time (experiment not reported). This may due to the strong electron-withdrawing property of the 4-nitro group, which inhibit the formation of iminium ion **g′** and also deactivate the nucleophilic ability of the nitro substituted aromatic ring in **g**. Although **6** reacted with paraformaldehyde successfully and produced **20** in moderate

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* Corresponding authors. Tel.: +86 22 27404386; fax: +86 22 27890968; e-mail: jreiner@tju.edu.cn

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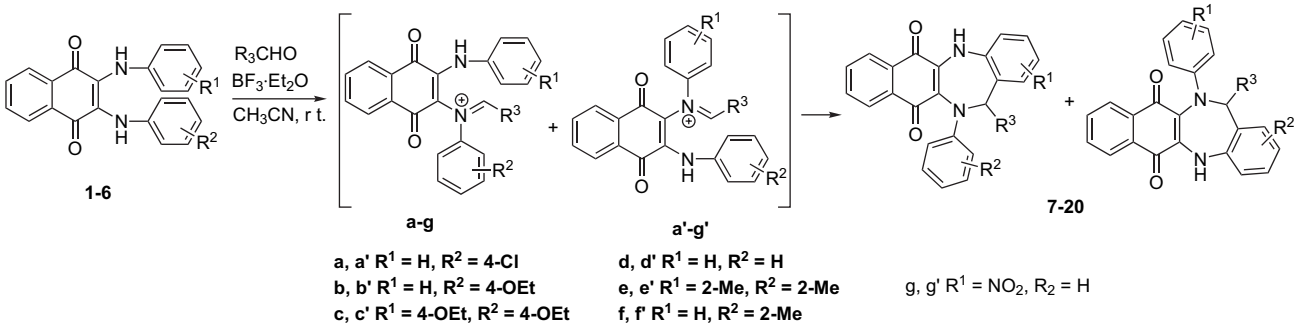
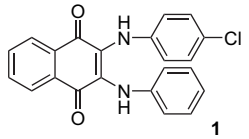
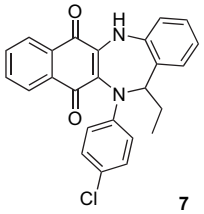
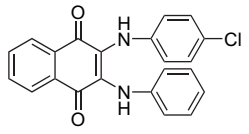
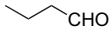
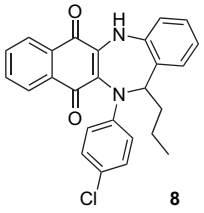
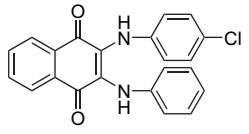
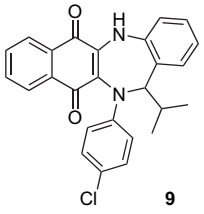
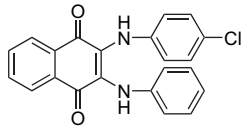
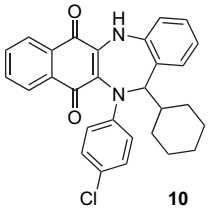
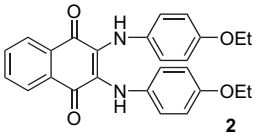
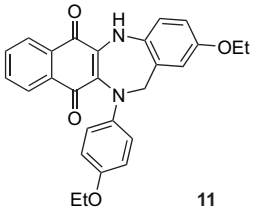
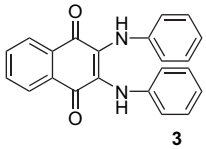
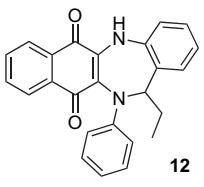


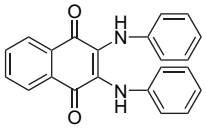
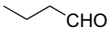
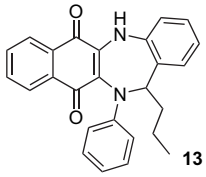
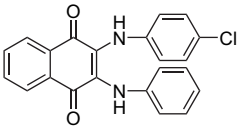
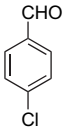
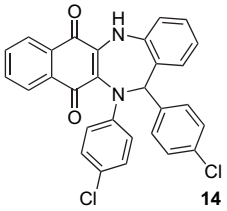
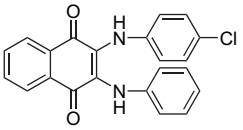
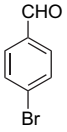
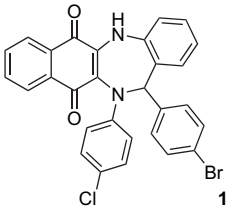
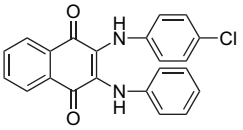
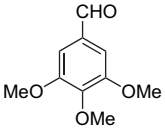
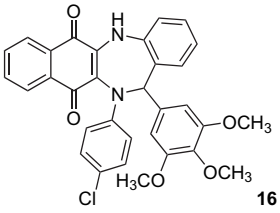
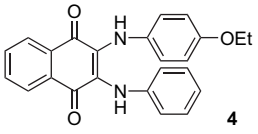
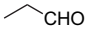
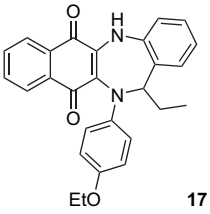
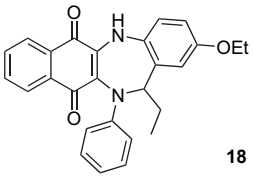
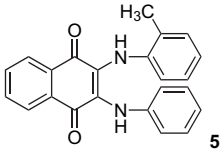
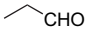
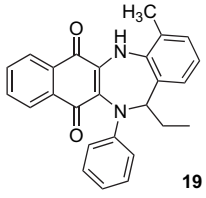
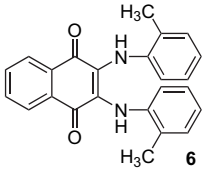
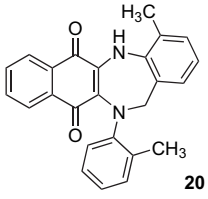
Scheme 1.

Table 1. Synthesis of naphthoquino[*b*]-benzo[*e*][1,4]-diazepines via Pictet–Spengler reaction

Entry	Diaminonaphthoquinone	Aldehyde	Product	Time (h)	Yield[a] (%)
1	 **1**		 **7**	3	92
2			 **8**	4	90
3			 **9**	48	88
4			 **10**	72	74
5	 **2**	$(HCHO)_n$	 **11**	3	83
6	 **3**		 **12**	3	92

(*continued*)

Table 1. (*continued*)

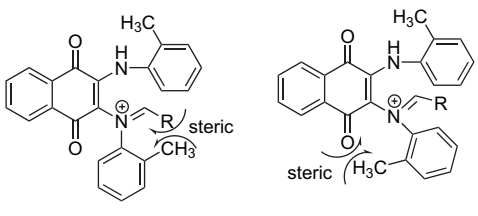
Entry	Diaminonaphthoquinone	Aldehyde	Product	Time (h)	Yield[a] (%)
7			 **13**	4	90
8			 **14**	10	82
9			 **15**	6	81
10			 **16**	15	70
11	 **4**		 **17**	3	73
			 **18**		18
12	 **5**		 **19**	24	70
13	 **6**	$(HCHO)_n$	 **20**	3	65

[a] Isolated yield.

65% yield (Table 1, entry 13), its reaction with propionaldehyde occurred very slowly, even with a high concentration of $BF_3 \cdot Et_2O$ and additional equivalent of aldehyde, and only trace amount of the cyclization product was obtained (experiment not reported). That may due to the steric effect between the *ortho*-CH_3 and quinone carbonyl or the R group (as shown in Fig. 1), which inhibited the formation of iminium ion intermediate as well as the cyclization.[9c] Doing the reaction at 50 °C in order to promote the reaction induced the product to disappear, leaving polar spots at the bottom of the TLC plate. That may be because of the benzodiazepine-naphthoquinone products being unstable at the acidic and 50 °C condition.

It was noteworthy that when asymmetric diaminonaphthoquiones such as **1**, **4**, and **5** were applied, two possible regioisomers should be formed. However, only one regioisomer was obtained (Table 1, entries 1–4, 8–10, and 12) or one of the two isolated regioisomers was major (Table 1, entry 12) that suggested a high regioselectivity of this reaction. The high regioselectivity in case of **1** can be explained by two factors: iminium ion intermediate **a** being more electronically active than **a′**[7] and the nucleophilic aromatic ring in **a** being more active than in **a′**[9c] due to the electron-withdrawing chloride substitute. In the case of **4**, compound **17** was obtained as the major product and **18** as the minor one that may be due to iminium ion intermediate **b** being generated more easily and cyclized more quickly than **b′**. Additionally, when **5** was explored, the high regioselectivity may be attributed to the steric effect similar to the case of **6**, which induced **f′** as the only iminium ion intermediate. However, a long reaction time was required that may because one of the two *ortho* positions in one aniline part is substituted, which has less nucleophilic opportunity.

The structures of these benzodiazepine-naphthoquinones were identified on the basis of their ^{1}H NMR and ^{13}C NMR spectra. As expected for such an asymmetric system, four naphthalene protons with different chemical shifts and one amino proton as a singlet in the ^{1}H NMR spectra, and two carbonyl carbon peaks in the ^{13}C NMR spectra are detected. The configuration of compounds **7**–**10** and **14**–**19**, which were obtained from asymmetric 2,3-diamino-1,4-naphthoquinones (**1**, **4**, and **5**) were verified by analyzing chemical shift and spin coupling constants of ^{1}H NMR data, which have proven to be consistent with these structures. Taking **7** and **8** as examples, the four benzodiazepine benzene protons appear as double doublet (or doublet), triple doublet (or triplet), triple doublet (or triplet), and double doublet (or doublet) splitting. The four *N*-aryl benzene protons appear as double doublet (or doublet) with only two different chemical shifts.



e

Figure 1.

3. Conclusions

In conclusion, we have developed an efficient synthesis of novel 4,5-dihydro-1*H*-1,4-naphthoquino[*b*]-benzo[*e*]-[1,4]diazepine derivatives by coupling of 2,3-diarylamino-1,4-naphthoquinones with aldehydes in the presence of $BF_3 \cdot Et_2O$. Utilizing this method, a series of benzodiazepine-naphthoquinones, which was previously unavailable were now obtained.

4. Experimental section

4.1. General

CH_3CN was distilled from CaH_2. All aldehydes and $BF_3 \cdot Et_2O$ were commercially available and were used without further purification. 2,3-Diamino-1,4-naphthoquinones were synthesized via palladium catalyzed coupling of 2-amino-3-chloro-1,4-naphthoquinones with amines.[10d] ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Inova 500 MHz instrument or Varian Unityplus 400 MHz instrument. IR spectra were recorded on Bio-Red Merlin FTS 3000 instrument. High-resolution mass spectra (HRMS) were recorded on Q-TOF micro (water) apparatus.

4.2. General experimental procedure

4.2.1. Synthesis of 2,3-diarylamino-1,4-naphthoquinones. A mixture of 2-arylamino-3-chloro-1,4-naphthoquinone (200 mg), *t*-BuONa (1.5 equiv), $PdCl_2$(dppf) (5 mol %), dppf (5 mol %), and the corresponding aryl amine (1.5 equiv) in 5 mL toluene in oven-dried round bottom flask was heated at 100 °C under an atmosphere of nitrogen with magnetic stirring. After TLC (ethyl acetate/petrol ether) indicated that the reaction has finished, the reaction mixture was concentrated in vacuo. The crude mixture was then purified by chromatography (5–20% ethyl acetate/petrol ether) to give the corresponding 2,3-diarylamino-1,4-naphthoquinone.

4.2.2. Synthesis of 4,5-dihydro-1*H*-1,4-naphthoquino[*b*]-benzo[*e*][1,4]diazepines. A solution of 2,3-diamino-1,4-naphthoquinone (200 mg, 1.0 equiv), aldehyde (1.1 equiv), and $BF_3 \cdot Et_2O$ (2.0 equiv) in CH_3CN (5 mL) was stirred at room temperature. After completion of the reaction (TLC), the reaction mixture was concentrated and the product purified by column chromatography.

4.2.2.1. Compound 7. Dark green solid; mp 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J=7.5, 1.0 Hz, 1H), 8.07 (dd, J=7.5, 1.0 Hz, 1H), 7.86 (s, 1H), 7.73 (td, J=7.5, 1.5 Hz, 1H), 7.67 (td, J=7.5, 1.5 Hz, 1H), 7.17 (td, J=7.5, 1.0 Hz, 1H), 7.06–7.10 (m, 3H), 6.94 (dd, J=8.0, 1.0 Hz, 1H), 6.87 (td, J=7.5, 1.5 Hz, 1H), 6.78–6.81 (m, 2H), 4.85 (t, J=8.0 Hz, 1H), 1.98–2.04 (m, 1H), 1.70–1.76 (m, 1H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.22, 178.98, 147.16, 138.99, 137.87, 134.85, 132.84, 132.72, 132.63, 130.20, 129.95, 129.12, 128.45, 127.07, 126.40, 125.16, 122.65, 122.10, 120.76, 119.18, 67.61, 53.44, 27.45, 11.58; IR (KBr): 3324, 2965, 1650, 1609, 1593, 1575, 1524, 1492, 1378, 1289, 1252, 752, 723 cm^{-1}; HRMS calcd for $C_{25}H_{20}ClN_2O_2$ $(M+H)^+$: requires 415.1208, found: 415.1227.

4.2.2.2. Compound 8. Dark green solid; mp 149–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J=6.5 Hz, 1H), 8.07 (d, J=6.5 Hz, 1H), 7.88 (s, 1H), 7.72 (t, J=7.0 Hz, 1H), 7.66 (t, J=7.0 Hz, 1H), 7.14 (t, J=7.5 Hz, 1H), 7.05–7.09 (m, 3H), 6.93 (d, J=7.0 Hz, 1H), 6.85 (t, J=7.5 Hz, 1H), 6.79 (d, J=9.0 Hz, 2H), 4.96 (t, J=7.5 Hz, 1H), 1.93–2.00 (m, 1H), 1.63–1.70 (m, 1H), 1.43–1.49 (m, 1H), 1.30–1.37 (m, 1H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.20, 178.94, 147.05, 139.00, 137.89, 134.80, 132.81, 132.72, 132.68, 130.19, 129.82, 129.09, 128.39, 127.03, 126.38, 125.07, 122.72, 122.07, 120.78, 119.08, 65.60, 36.35, 20.02, 13.90; IR (KBr): 3322, 2958, 1652, 1612, 1589, 1517, 1490, 1386, 1293, 1251, 744, 716 cm^{-1}; HRMS calcd for $C_{26}H_{22}ClN_2O_2$ $(M+H)^+$: requires 429.1364, found: 429.1375.

4.2.2.3. Compound 9. Dark green solid; mp 200–201 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J=7.5 Hz, 1H), 8.02 (d, J=7.5 Hz, 1H), 7.79 (s, 1H), 7.69 (td, J=7.5, 1.0 Hz, 1H), 7.64 (td, J=7.5, 1.0 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.09 (d, J=9.0 Hz, 2H), 6.91–6.95 (m, 2H), 6.84 (d, J=9.0 Hz, 2H), 6.81 (t, J=7.5 Hz, 1H), 4.43 (d, J=11.0 Hz, 1H), 2.04–2.32 (m, 1H), 1.17 (d, J=6.5 Hz, 3H), 0.70 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.99, 178.64, 147.81, 138.36, 138.14, 134.62, 132.74, 132.60, 132.22, 130.69, 130.10, 129.04, 128.42, 126.93, 126.18, 125.51, 123.24, 121.67, 120.62, 120.38, 74.27, 30.78, 20.93, 20.81; IR (KBr): 3326, 2959, 1651, 1616, 1590, 1520, 1492, 1292, 1255, 1058, 971, 753, 726 cm^{-1}; HRMS calcd for $C_{26}H_{22}ClN_2O_2$ $(M+H)^+$: requires 429.1364, found: 429.1372.

4.2.2.4. Compound 10. Dark green solid; mp 203–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J=6.5 Hz, 1H), 8.04 (d, J=6.5 Hz, 1H), 7.87 (s, 1H), 7.68 (td, J=7.5, 1.5 Hz, 1H), 7.62 (td, J=7.5, 1.5 Hz, 1H), 7.10–7.16 (m, 3H), 6.89–6.96 (m, 4H), 6.81 (t, J=7.5 Hz, 1H), 4.58 (d, J=11.0 Hz, 1H), 2.25–2.27 (m, 1H), 1.98–2.05 (m, 1H), 1.74–1.77 (m, 1H), 1.62–1.65 (m, 2H), 1.10–1.21 (m, 4H), 0.85–0.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.33, 179.07, 148.46, 138.72, 138.39, 134.91, 133.06, 132.94, 132.21, 131.05, 130.47, 129.38, 128.74, 127.29, 126.51, 126.03, 123.85, 121.89, 121.20, 120.93, 73.84, 39.99, 31.68, 31.58, 26.64, 26.32, 26.31; IR (KBr): 3311, 2926, 1645, 1606, 1575, 1523, 1492, 1290, 1247, 725 cm^{-1}; HRMS calcd for $C_{29}H_{26}ClN_2O_2$ $(M+H)^+$: requires 469.1677, found: 469.1689.

4.2.2.5. Compound 11. Dark green solid; mp 159–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (dd, J=7.5, 1.0 Hz, 1H), 8.01 (dd, J=7.5, 1.0 Hz, 1H), 7.57–7.66 (m, 3H), 6.79–6.81 (m, 3H), 6.71 (d, J=9.0 Hz, 2H), 6.64 (dd, J=8.5, 3.0 Hz, 1H), 6.59 (s, 1H), 4.68 (s, 2H), 3.90 (q, J=7.0 Hz, 4H), 1.30–1.34 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.74, 178.12, 154.03, 153.43, 141.16, 138.25, 134.52, 133.64, 132.83, 132.37, 131.70, 130.18, 127.25, 126.85, 126.13, 120.75, 119.85, 115.98, 115.20, 113.94, 63.69, 63.56, 55.82, 14.94, 14.76; IR (KBr): 3317, 2974, 1659, 1641, 1604, 1573, 1504, 1363, 1293, 1248, 1111, 1050, 719 cm^{-1}; HRMS calcd for $C_{27}H_{25}N_2O_4$ $(M+H)^+$: requires 441.1809, found: 441.1793.

4.2.2.6. Compound 12. Dark green solid; mp 195–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J=7.5, 1.0 Hz, 1H), 8.06 (dd, J=7.5, 1.0 Hz, 1H), 7.83 (s, 1H), 7.71 (td, J=7.5, 1.5 Hz, 1H), 7.66 (td, J=7.5, 1.5 Hz, 1H), 7.16–7.12 (m, 3H), 7.07 (d, J=7.5 Hz, 1H), 6.92 (d, J=8.0 Hz, 1H), 6.88 (d, J=8.0 Hz, 2H), 6.83 (t, J=7.5 Hz, 1H), 6.79 (t, J=7.5 Hz, 1H), 4.92 (t, J=7.5 Hz, 1H), 2.07–1.99 (m, 1H), 1.70–1.78 (m, 1H), 1.01 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.28, 179.18, 148.52, 138.81, 138.13, 134.67, 132.95, 132.88, 132.59, 130.29, 129.98, 129.17, 128.27, 127.06, 126.28, 123.43, 121.82, 120.56, 120.38, 118.18, 67.44, 27.59, 11.65; IR (KBr): 3287, 2961, 1687, 1638, 1597, 1529, 1493, 1379, 1286, 1254, 1128, 973, 869, 745, 721, 684 cm^{-1}; HRMS calcd for $C_{25}H_{21}N_2O_2$ $(M+H)^+$: requires 381.1598, found: 381.1595.

4.2.2.7. Compound 13. Dark green solid; mp 157–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J=7.0, 1.0 Hz, 1H), 8.06 (dd, J=7.0, 1.0 Hz, 1H), 7.84 (s, 1H), 7.72 (td, J=7.0, 1.0 Hz, 1H), 7.66 (td, J=7.0, 1.0 Hz, 1H), 7.12–7.16 (m, 3H), 7.06 (d, J=7.5 Hz, 1H), 6.92 (d, J=7.0 Hz, 1H), 6.77–6.88 (m, 4H), 5.02 (t, J=7.5 Hz, 3H), 1.95–2.03 (m, 1H), 1.64–1.72 (m, 1H), 1.43–1.52 (m, 1H), 1.31–1.39 (m, 1H), 0.91 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.30, 179.19, 148.44, 138.82, 138.15, 134.67, 132.99, 132.92, 132.59, 130.29, 129.87, 129.17, 128.23, 127.06, 126.29, 123.51, 121.81, 120.58, 120.34, 118.08, 65.44, 36.51, 20.10, 13.95; IR (KBr): 3266, 2931, 1669, 1643, 1604, 1525, 1494, 1375, 1293, 1253, 1130, 748, 720 cm^{-1}; HRMS calcd for $C_{26}H_{23}N_2O_2$ $(M+H)^+$: requires 395.1754, found: 395.1746.

4.2.2.8. Compound 14. Dark blue solid; mp 165–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97–7.99 (m, 2H), 7.73 (s, 1H), 7.66 (td, J=7.5, 1.5 Hz, 1H), 7.59 (td, J=7.5, 1.5 Hz, 1H), 7.29 (td, J=7.5, 1.5 Hz, 1H), 7.12–7.15 (m, 5H), 7.07–7.09 (m, 2H), 7.02 (dd, J=8.0, 1.0 Hz, 1H), 6.96 (td, J=7.5, 1.0 Hz, 1H), 6.92 (dd, J=7.0, 2.0 Hz, 2H), 6.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.75, 178.78, 146.87, 139.18, 138.76, 138.38, 134.78, 133.46, 132.68, 132.43, 131.02, 129.90, 129.58, 129.48, 129.34, 128.84, 128.70, 126.93, 126.37, 125.84, 123.98, 122.63, 120.88, 119.44, 68.87; IR (KBr): 3313, 1665, 1611, 1524, 1492, 1331, 1291, 969, 877, 811, 752, 720 cm^{-1}; HRMS calcd for $C_{29}H_{19}Cl_2N_2O_2$ $(M+H)^+$: requires 497.0818, found: 497.0843.

4.2.2.9. Compound 15. Dark blue solid; mp 182–184 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J=8.0 Hz, 2H), 7.73 (s, 2H), 7.67 (td, J=7.5, 1.5 Hz, 1H), 7.59 (td, J=7.5, 1.5 Hz, 1H), 7.27–7.31 (m, 3H), 7.13–7.16 (m, 3H), 7.01–7.03 (m, 3H), 6.96 (td, J=7.5, 1.0 Hz, 1H), 6.92 (dd, J=7.0, 2.0 Hz, 2H), 6.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.73, 178.78, 146.87, 139.18, 138.93, 138.73, 134.78, 132.68, 132.42, 131.79, 131.02, 129.90, 129.50, 129.49, 129.33, 129.05, 126.93, 126.37, 125.86, 123.96, 122.63, 121.73, 120.89, 119.47, 68.94; IR (KBr): 3315, 1664, 1612, 1524, 1490, 1333, 1291, 969, 810, 751, 727 cm^{-1}; HRMS calcd for $C_{29}H_{19}BrClN_2O_2$ $(M+H)^+$: requires 541.0313, found: 541.0294.

4.2.2.10. Compound 16. Dark green solid; mp 246–247 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99–8.01 (m, 2H), 7.77 (s, 1H), 7.67 (td, J=7.5, 1.0 Hz, 1H), 7.60 (td, J=7.5, 1.0 Hz, 1H), 7.29 (td, J=8.0, 1.5 Hz, 1H), 7.21

(dd, J=7.5, 1.0 Hz, 1H), 7.13 (dd, J=7.0, 2.0 Hz, 2H), 7.02 (dd, J=8.0, 1.0 Hz, 1H), 6.99 (td, J=7.5, 1.0 Hz, 1H), 6.90 (dd, J=7.0, 2.0 Hz, 2H), 6.37 (s, 1H), 6.34 (s, 1H), 3.73 (s, 3H), 3.60 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 180.83, 178.95, 153.24, 146.65, 139.21, 138.91, 137.08, 135.93, 134.87, 132.72, 132.60, 131.29, 129.94, 129.75, 129.37, 129.29, 126.72, 126.45, 125.26, 124.14, 122.47, 120.80, 118.46, 104.19, 68.77, 60.72; IR (KBr): 3308, 1666, 1646, 1612, 1592, 1525, 1493, 1414, 1330, 1291, 1255, 1125, 998, 884, 756, 719 cm^{-1}; HRMS calcd for $C_{32}H_{26}ClN_2O_5$ (M+H)$^+$: requires 553.1525, found: 553.1506.

4.2.2.11. Compound 17. Dark green solid; mp 182–183 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J=7.5 Hz, 1H), 7.99 (d, J=7.5 Hz, 1H), 7.74 (s, 1H), 7.60–7.68 (m, 2H), 7.13 (t, J=7.5 Hz, 1H), 6.95 (d, J=7.0 Hz, 1H), 6.88–6.90 (m, 3H), 6.77 (t, J=7.5 Hz, 1H), 6.72 (d, J=7.5 Hz, 2H), 4.66 (t, J=7.0 Hz, 2H), 3.91 (q, J=7.0 Hz, 2H), 2.09 (m, 1H), 1.76 (m, 1H), 1.33 (t, J=7.0 Hz, 3H), 1.02 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.07, 179.54, 153.82, 142.89, 138.84, 137.84, 134.37, 133.22, 132.81, 132.49, 130.34, 129.67, 128.23, 126.80, 126.05, 124.77, 121.46, 120.28, 115.10, 69.64, 63.48, 27.50, 14.91, 11.77; IR (KBr): 3332, 2975, 1657, 1612, 1506, 1389, 1326, 1287, 1236, 1050, 969, 750, 722 cm^{-1}; HRMS calcd for $C_{27}H_{25}N_2O_3$ (M+H)$^+$: requires 425.1860, found: 425.1852.

4.2.2.12. Compound 18. Dark green solid; mp 169–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J=7.5, 1.5 Hz, 1H), 8.08 (dd, J=7.5, 1.5 Hz, 1H), 7.77 (s, 1H), 7.71 (td, J=7.5, 1.5 Hz, 1H), 7.64 (td, J=7.5, 1.5 Hz, 1H), 7.14 (t, J=7.5 Hz, 2H), 6.83–6.87 (m, 3H), 6.77 (t, J=7.5 Hz, 1H), 6.65–6.68 (m, 2H), 4.88 (t, J=7.5 Hz, 1H), 3.92–3.99 (m, 2H), 1.99–2.05 (m, 1H), 1.72–1.77 (m, 1H), 1.37 (t, J=7.0 Hz, 3H), 1.01 (t, J=7.0 Hz, 3H); IR (KBr): 3281, 2969, 1674, 1603, 1573, 1522, 1495, 1367, 1245, 1124, 1042, 870, 753, 722 cm^{-1}; HRMS calcd for $C_{27}H_{25}N_2O_3$ (M+H)$^+$: requires 425.1860, found: 425.1845.

4.2.2.13. Compound 19. Dark green solid; mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J=7.6 Hz, 1H), 8.07 (d, J=7.6 Hz, 1H), 7.98 (s, 1H), 7.72 (t, J=6.8 Hz, 1H), 7.66 (t, J=7.2 Hz, 1H), 7.16 (t, J=7.5 Hz, 2H), 7.04 (d, J=7.6 Hz, 1H), 6.95 (d, J=7.6 Hz, 1H), 6.91 (dd, J=8.0, 1.2 Hz, 2H), 6.80 (t, J=7.6 Hz, 1H), 6.76 (t, J=7.6 Hz, 1H), 4.93 (t, J=7.6 Hz, 1H), 2.39 (s, 3H), 2.02–2.09 (m, 1H), 1.72–1.79 (m, 1H), 1.02 (t, J=7.6 Hz, 3H); IR (KBr): 3336, 2924, 1742, 1660, 1643, 1612, 1520, 1288, 1010, 720, 665 cm^{-1}; HRMS calcd for $C_{26}H_{23}N_2O_2$ (M+H)$^+$: requires 395.1754, found: 395.1757.

4.2.2.14. Compound 20. Dark blue solid; mp 201–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, J=6.0, 3.2 Hz, 1H), 7.87 (dd, J=6.0, 3.2 Hz, 1H), 7.69 (s, 1H), 7.58–7.60 (m, 2H), 7.26 (d, J=6.8 Hz, 1H), 7.08 (d, J=7.2 Hz, 1H), 7.04 (t, J=7.2 Hz, 1H), 6.97 (t, J=7.2 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 6.66 (t, J=7.6 Hz, 1H), 6.61 (d, J=6.8 Hz, 1H), 4.51 (s, 2H), 2.47 (s, 3H), 2.41 (s, 3H); IR (KBr): 3347, 2926, 1744, 1649, 1598, 1571, 1511, 1363, 1336, 1291, 1108, 962, 752, 723 cm^{-1}; HRMS calcd for $C_{25}H_{21}N_2O_2$ (M+H)$^+$: requires 381.1598, found: 381.1606.

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