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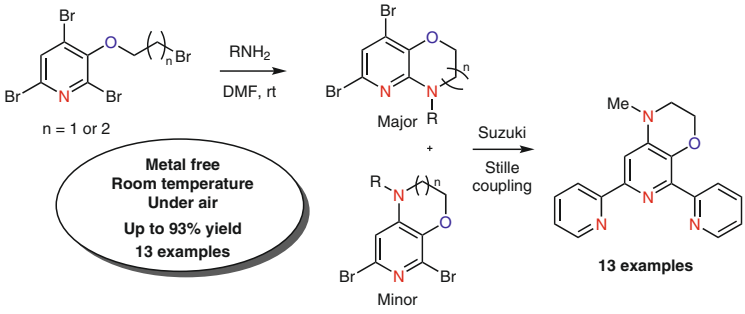
Synthesis of Substituted Pyrido-oxazine through Tandem S_N2 and S_NAr Reaction

Mosim Amin Pathan
Faiz Ahmed Khan*

Department of Chemistry, Indian Institute of Technology Hyderabad, Kandi, Sangareddy, Telangana, 502 285, India
faiz@iith.ac.in



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Abstract Pyrido-oxazine derivatives have been synthesized by employing tandem S_N2 and S_NAr reaction between 2,4,6-tribromo-3-(2-bromoethoxy)pyridine or 2,4,6-tribromo-3-(3-bromopropoxy)pyridine and a variety of primary amines. Moderate to good regioselectivity in favor of cyclization at the 2-position is observed. Pyrido-oxazine products thus generated are converted into biarylated pyrido-oxazine and terpyridine ligands.

Key words pyridine, terpyridine, pyrido-oxazines, Suzuki coupling, Stille coupling

Pyridine is an important heterocycle that is frequently encountered in natural products, bioactive molecules, and therapeutic drugs and serves also as a common synthetic building block.[1] There is a demand for reactions that allow direct functionalization of pyridine. Phenanthroline, bipyridine, terpyridine (Figure 1) and their derivatives have been extensively used as organic ligands with a variety of metals to perform important synthetic transformations.[2] Pyrido-oxazines are a class of heterocycles in which one of the carbon atoms in benzoxazine is replaced with nitrogen, and such compounds have shown promising biological activity.[3] Halo-pyridines are important building blocks in organic synthesis because they easily react with various nucleophiles. This reactive nature can be attributed to the high electronegativity of the halogen atom, which makes carbon–halogen bonds prone to nucleophilic aromatic substitutions (S_NAr). In general, substituted 2- and 4-halopyridines are attractive intermediates in synthetic and medicinal chemistry and they are extensively used for the construction of various pyridine-based heterocycles including *N*-fused heterocycles.[4] This electrophilic character of halopyridines has also been used in pyrido-oxazines syntheses.[5] Several other synthetic protocols are also available in the literature.[6] However there is a need to develop alternative methods in view of the importance of these scaffolds. In a continuation of our ongoing program of synthesizing brominated marine natural product and their analogues,[7] we wish to report a simple strategy for the synthesis of functionalized pyrido-oxazines by employing a tandem S_N2 and S_NAr reaction.

We have recently reported a synthesis of dihydrobenzoxazines and tetrahydrobenzoxazepines by employing complementary ambiphile pairing (CAP) and complementary pairing (CP) method through an interesting *N*-dealkylative S_NAr substitution reaction with activated aromatic halides.[8] We thought of extending the same protocol for the synthesis of pyrido-oxazines. Unlike our previous work,[8] the pyridine moiety does not require an EWG activating group and therefore 2,4,6-tribromopyridin-3-ol (**1**) and 3-chloro-*N*,*N*-dimethylpropan-1-amino hydrochloride (**1ab**) appeared to be a suitable substrate pair for this study.

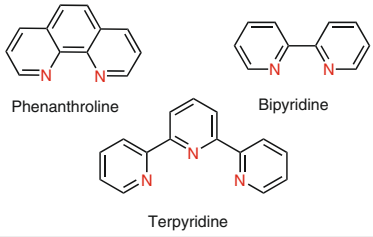
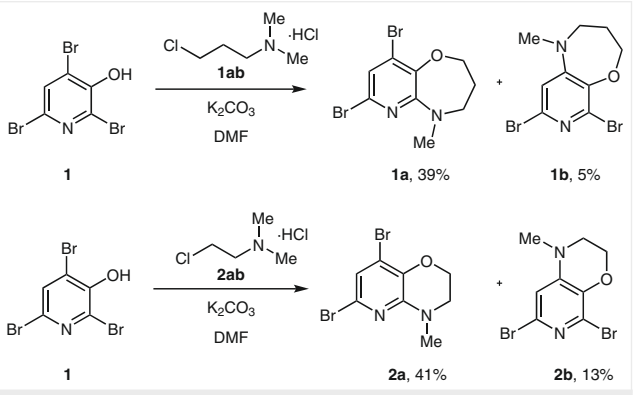


Figure 1 The important pyridine motif

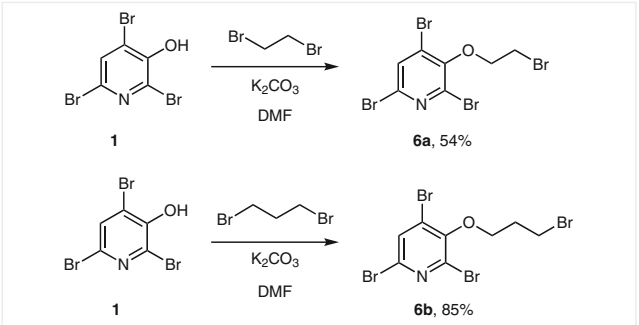
Accordingly, when **1** was treated with **1ab**, we observed the formation of regioisomeric seven-membered *N*-demethylative products **1a** and **1b** in 44% overall yield. Similarly, treatment of **1** with 2-chloro-*N*,*N*-dimethylethanamino hydrochloride (**2ab**) gave **2a** and **2b** in 54% overall yield (Scheme 1).



Scheme 1 N-Dealkylative cyclization

Alternatively, transformation of **1** into **6a** and **6b** would furnish bis-electrophilic species, which, upon treatment with primary amines, would provide the corresponding products, without a *N*-demethylative pathway.[8] Phenol **1**, on treatment with 1,2-dibromoethane, gave bis-electrophile **6a** in 54% yield, and similar treatment of 1,3-dibromopropane gave **6b** in 85% yield (Scheme 2). When **6a** was subjected to aqueous methylamine (**2ba**) in DMF at ambient temperature, cyclized products **2a** and **2b** were obtained in 80% overall yield (Scheme 3). To check the scope of the reaction, **6a** was then subjected to a variety of primary amines. This methodology tolerates functional groups including allyl (**2c**, **2d**), cyclopropyl (**2g**, **2h**), and benzyl (**2o**, **2p**) (Scheme 3). Interestingly the use of a chiral amine afforded the cyclic products **2k**, **2l** in good yield. 2-(Aminomethyl)aniline **2qr**, which has two free NH_2 groups, reacted selectively at the benzyl amino group to give the products **2q** and **2r** in good yield. Biologically important indole derivatives **2u** and **2v** were prepared in good yield. This methodology has also been used to prepare seven-membered pyrido-oxazine derivatives **1a–d** in good yield.

The structural assignment of the two regioisomeric (2- or 4-cyclized) products was based on the characteristic ^{13}C NMR values of methine carbon shifts in the pyridine ring of the two isomers. As depicted in Figure 2, for the 2-cyclized isomer the methine carbon appears in the range δ = 119.6–117.6 ppm and the signal for the 4-cyclized isomer resonates between δ = 110.4–108.1 ppm. An unambiguous confirmation was obtained by single- crystal X-ray analysis of **2p** (Figure 2). A similar difference, δ = 119.8–121.5 ppm for 2-cyclized isomer and δ = 112.4–114.3 ppm for 4-cyclized isomer, allowed assignment of the seven-membered derivatives.



Scheme 2 Synthesis of bis-electrophilic intermediates **6a** and **6b**

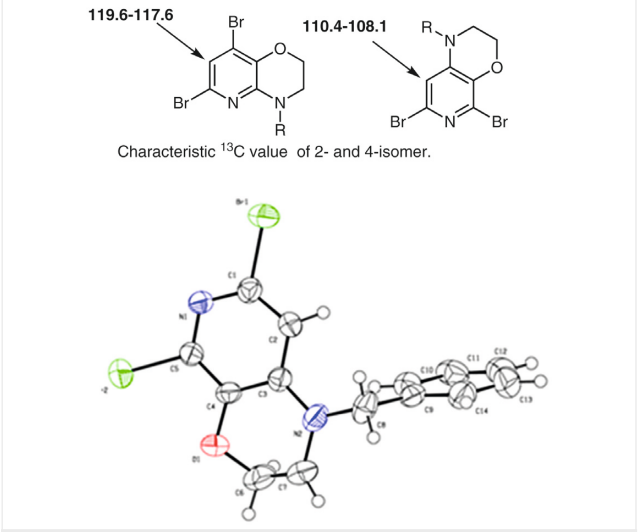
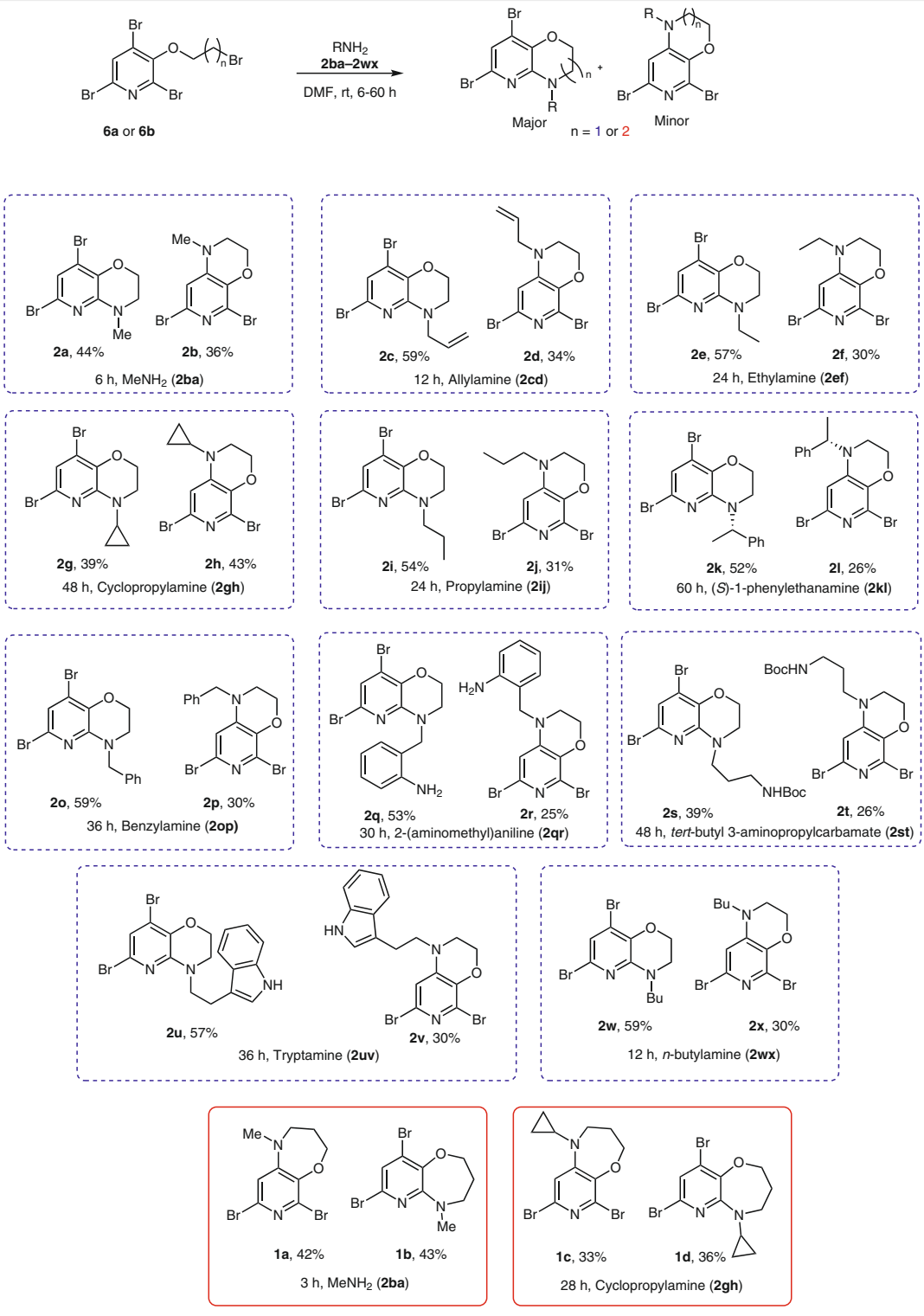
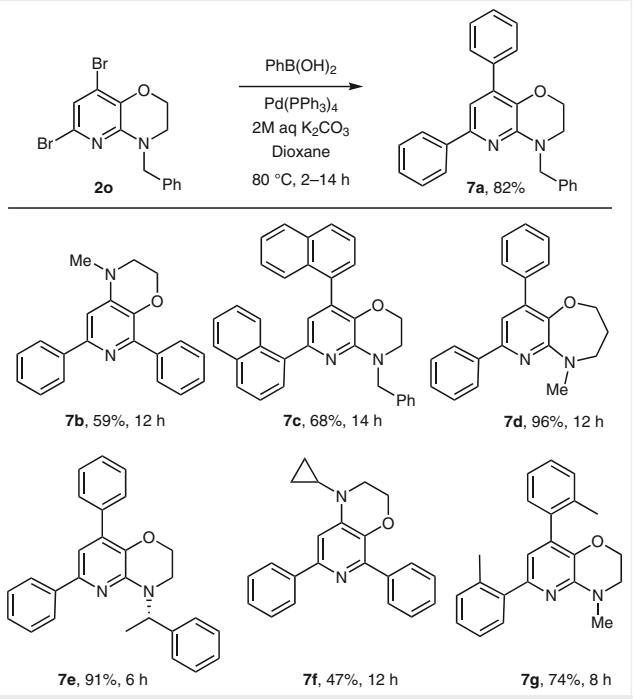


Figure 2 Characteristic ^{13}C NMR shifts of the 2- and 4-isomer and single-crystal X-ray structure of compound **2p** (CCDC 1584958)

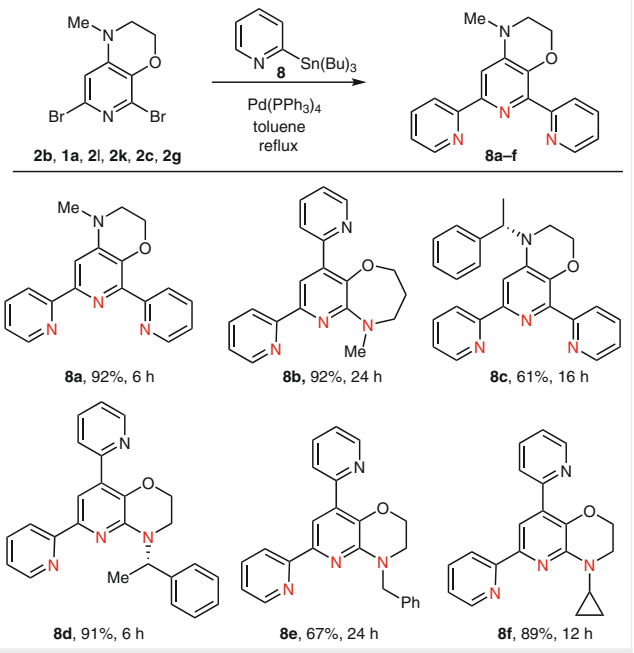
With pyrido-oxazine products in hand, we thought of utilizing bromine atoms at the 2,6- or 4,6-positions for further functionalization through standard procedures. Application of Suzuki–Miyaura reaction furnished biarylated pyrido-oxazine **7a–g** in good yield (Scheme 4). Similarly, Stille coupling between pyrido-oxazine **2b** and 2-(tributylstannyl)pyridine **8** in the presence of $Pd(PPh_3)_4$ gave terpyridine ligand **8a** in good yield (Scheme 5). This reaction was then extended to **1a**, **2l**, **2k**, **2c**, **2g** to obtain terpyridine ligands **8b–f** in good yield.



Scheme 3 Cyclization with primary amines



Scheme 4 Synthesis of biarylated pyrido-oxazine



Scheme 5 Synthesis of terpyridine ligand

In conclusion, we have developed a method for the synthesis of pyrido-oxazine through tandem S_N2 and S_NAr reaction in good yield. We were also able to functionalize pyrido-oxazine to form biarylated pyrido-oxazine and terpyridines using Suzuki and Stille coupling reactions in moderate to good yield.

All starting material and reagents were purchased from standard commercial sources or were prepared in the laboratory. All the glassware were cleaned with soap water followed by acetone and dried in a hot air oven at 100 °C for 2 h. Solvents were distilled prior to use. IR spectra were recorded with a Bruker Tensor 37 (FTIR) spectrophotometer.^{1}H NMR spectra were recorded with a Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ, ppm) and coupling constants (Hz) are reported with reference to either tetramethylsilane (TMS) (δ = 0.00 ppm ppm) or $CHCl_3$ (δ = 7.26 ppm). ^{13}C NMR spectra were recorded with a Bruker Avance 400 (100 MHz) spectrometer at 298 K in $CDCl_3$; chemical shifts (δ, ppm) are reported relative to $CHCl_3$ (δ = 77.00 ppm; central line of triplet). For ^{13}C NMR analysis, the nature of the carbon atoms (C, CH, CH_2, and CH_3) was determined by recording DEPT-135 spectra. In ^{1}H NMR data, the following abbreviations are used throughout: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, and br. s = broad singlet. The assignment of the signals was confirmed by ^{1}H, ^{13}C and DEPT spectra. High-resolution mass spectra (HRMS) were recorded with an Agilent 6538 UHD Q-TOF using multimode source in +ESI method at the Department of Chemistry, Indian Institute of Technology Hyderabad, India. Reactions were monitored by TLC on silica gel (254 mesh) using a combination of hexane and EtOAc as eluents.

2,4,6-Tribromopyridin-3-ol (1)

To a solution of 3-hydroxypyridine (5 g, 52.5 mmol) in H_2O (60 mL) was added bromine (10.84 mL, 210 mmol) at 0 °C and the reaction mixture was stirred at r.t. for 12 h. The formed solid was filtered through suction filter. Solid product **1** was collected and used without further purification.

Yield: 12 g (69%); yellow solid; mp 74–76 °C; R_f = 0.5 (60%, EtOAc/hexane).

IR (neat): 3743, 3677, 3617, 1698, 1540, 1516, 1459 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1 H), 6.02 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 131.1, 129.7, 128.6, 120.8.

HRMS (ESI+): *m*/*z* $[M]^+$ calcd for $C_5H_2Br_3NO$: 330.7666; found: 330.775.

Typical Procedure and Spectral Data for 1a, 1b, 2a, 2b Obtained through N-Dealkylative Cyclization

To a stirred suspension of K_2CO_3 (167 mg, 1.208 mmol) in DMF (1 mL) was added 2,4,6-tribromopyridin-3-ol (**1**; 100 mg, 0.302 mmol) and 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride (**1ab**; 86 mg, 0.604 mmol) and, after stirring for 10 h at 120 °C, water (3 mL) was added. The mixture was extracted with EtOAc (8 × 3 mL) and the organic layer was washed with water (3 mL) and brine (3 mL), dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified over silica gel chromatography (20%, EtOAc/hexane) to give **1a** (38 mg, 39%) and **1b** (5 mg, 5%) as colorless solids.

7,9-Dibromo-5-methyl-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepine (1a)

Yield: 38 mg (39%); white solid; mp 92–94 °C; R_f = 0.5 (10%, EtOAc/hexane).

IR (neat): 2922, 1562, 1522, 1416, 1363, 1192, 1042, 962, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1 H), 4.24 (t, *J* = 6.4 Hz, 2 H), 3.56–3.48 (m, 2 H), 3.06 (s, 3 H), 2.19–2.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 140.5, 131.4, 125.1, 119.8, 70.3, 50.0, 39.5, 28.0.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}Br_2N_2O$: 322.9218; found: 322.9201.

6,8-Dibromo-1-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*][1,4]oxazepine (1b)

Yield: 5 mg (5%); white solid; mp 98–100 °C; R_f = 0.5 (10%, EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (s, 1 H), 4.31–4.22 (m, 2 H), 3.62–3.53 (m, 2 H), 2.99–2.90 (m, 3 H), 2.21–2.09 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7, 141.2, 134.0, 133.9, 112.5, 70.2, 51.9, 40.8, 28.0.

IR (neat): 2925, 1564, 1511, 1426, 1382, 1264, 1196, 1040 cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}Br_2N_2O$: 322.9218; found: 322.9202.

6,8-Dibromo-4-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2a)

Yield: 38 mg (41%); white solid; mp 82–84 °C; R_f = 0.5 (10%, EtOAc/hexane).

IR (neat): 2939, 2892, 1580, 1531, 1510, 1451, 1415, 1357, 1302, 1211, 1051, 922, 778, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 1 H), 4.3 (t, *J* = 4.4 Hz, 2 H), 3.48 (t, *J* = 4.4 Hz, 2 H), 3.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 136.4, 129.7, 118.6, 117.9, 64.4, 47.7, 36.2.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_8H_9Br_2N_2O$: 308.9061; found: 308.9053.

5,7-Dibromo-1-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2b)

Yield: 12 mg (36%); white solid; mp 138–140 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 2945, 2882, 1581, 1509, 1461, 1426, 1352, 1290, 1249, 1217, 1119, 1052, 926, 822, 790 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (s, 1 H), 4.31 (t, *J* = 4.4 Hz, 2 H), 3.43 (t, *J* =4.4 Hz, 2 H), 2.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 136.8, 131.6, 126.9, 108.5, 64.1, 48.0, 37.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}Br_2N_3O$: 308.9061; found: 308.9053.

2,4,6-Tribromo-3-(2-bromoethoxy)pyridine (6a)

To a stirred suspension of K_2CO_3 (4.99 g, 36.15 mmol) in DMF (35 mL) was added 2,4,6-tribromopyridin-3-ol (**1**; 4 g, 12.05 mmol) and the mixture was stirred at 0 °C for 0.5 h. 1,2-Dibromoethane (11.32 g, 60.25 mmol) was added and, after stirring for 12 h at 80 °C, water (100 mL) was added. The mixture was extracted with EtOAc (80 × 2 mL) and the organic layer was washed with water (12 × 3 mL) and brine (20 × 2 mL), dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified over silica gel chromatography (10%, EtOAc/hexane) to give 2,4,6-tribromo-3-(2-bromoethoxy)pyridine **6a**.

Yield: 2.45 g, 46%); colorless solid; mp 60–62 °C; R_f = 0.5 (10%, EtOAc/hexane).

IR (neat): 2924, 1516, 1412, 1310, 985, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1 H), 4.35 (t, *J* = 6.5 Hz, 2 H), 3.72 (t, *J* = 6.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 136.7, 134.8, 131.5, 129.7, 72.9, 28.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_7H_6Br_4NO$: 439.7142; found: 439.7134.

2,4,6-Tribromo-3-(3-bromopropoxy)pyridine (6b)

To a stirred suspension of K_2CO_3 (2.5 g, 18.12 mmol) in DMF (20 mL) was added 2,4,6-tribromopyridin-3-ol (**1**; 2 g, 6.02 mmol) and the mixture was stirred at 0 °C for 0.5 h. 1,3-Dibromopropane (6.08 g, 30.1 mmol) was added and after stirring for 4 h at 80 °C, water (40 mL) was added. The mixture was extracted with EtOAc (30 × 2 mL) and the organic layer was washed with water (20 mL) and brine (20 mL), dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified over silica gel chromatography (20%, EtOAc/hexane) to give 2,4,6-tribromo-3-(3-bromopropoxy)pyridine **6b**.

Yield: 1.67 g (61%); colorless solid; mp 40–42 °C; R_f = 0.7 (20%, EtOAc/hexane).

IR (neat): 2950, 1517, 1416, 1311, 996, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 4.18 (t, *J* = 5.6 Hz, 2 H), 3.70 (t, *J* = 6.4 Hz, 2 H), 2.41 (quin, *J* = 6.4, 5.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 136.9, 134.4, 131.5, 129.8, 71.4, 33.17, 29.5.

HRMS (ESI+): *m*/*z* [M]$^+$ calcd for $C_8H_7Br_4NO$: 452.7220; found: 452.7368.

Typical Procedure and Spectral Data for 2c–x

To a solution of 2,4,6-tribromo-3-(2-bromoethoxy)pyridine (**6a**; 100 mg, 0.228 mmol) in DMF (1 mL) was added benzyl amine (73 mg, 0.684 mmol) and the reaction mixture was stirred at r.t. for 36 h. Water (3 mL) was then added and the mixture was extracted with EtOAc (12 × 3 mL). The combined organic phases were washed with water (3 mL), brine (3 mL), dried over Na_2SO_4 and concentrated in vacuo The resulting crude residue was purified over silica gel column chromatography (10–20%, EtOAc/hexane) to afford product **2o** (52 mg, 59%) and **2p** (26 mg, 30%).

4-Allyl-6,8-dibromo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2c)

Yield: 45 mg (59%); white solid; mp 54–56 °C; R_f = 0.6 (10%, EtOAc/hexane).

IR (neat); 3093, 2939, 1578, 1534, 1502, 1449, 1418, 1357, 1305, 1255, 1213, 1094, 1040, 992, 925, 806, 673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 1 H), 5.89–5.72 (m, 1 H), 5.27–5.16 (m, 2 H), 4.27 (t, *J* = 4.4 Hz, 2 H), 4.21 (d, *J* = 5.9 Hz, 2 H), 3.44 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 135.1, 131.7, 128.5, 117.6, 117.2, 117.1, 63.4, 49.1, 43.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}Br_2N_2O$: 334.9218; found: 334.9212.

1-Allyl-5,7-dibromo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2d)

Yield: 26 mg (34%); white solid; mp 78–80 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 3086, 2874, 1576, 1528, 1503, 1454, 1402, 1352, 1287, 1246, 1211, 1167, 1070, 1035, 925, 822, 796, 700, 662 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (s, 1 H), 5.78 (tdd, *J* = 5.0, 10.4, 17.2 Hz, 1 H), 5.33–5.11 (m, 2 H), 4.3 (t, *J* = 4.4 Hz, 2 H), 3.91 (td, *J* = 1.7, 5.0 Hz, 2 H), 3.46 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 136.7, 131.7, 130.2, 127.5, 118.1, 108.7, 64.0, 52.8, 46.3.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}Br_2N_2O$: 334.9218; found: 334.9212.

6,8-Dibromo-4-ethyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2e)

Yield: 42 mg (57%); white solid; mp 82–84 °C; R_f = 0.6 (10%, EtOAc/hexane).

IR (neat): 2932, 1578, 15051443, 1358, 1209, 1058, 930, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 4.31–4.23 (m, 2 H), 3.64 (q, *J* = 7.2 Hz, 2 H), 3.53–3.44 (m, 2 H), 1.17 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 136.1, 129.7, 118.0, 117.9, 64.3, 44.7, 42.7, 11.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}Br_2N_2O$: 322.9218; found: 322.9209.

5,7-Dibromo-1-ethyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2f)

Yield: 22 mg (30%); white solid; mp 78–80 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 2932, 1578, 1505, 1423, 1358, 1209, 1058, 930, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1 H), 4.32–4.24 (m, 2 H), 3.46–3.42 (m, 2 H), 3.36 (q, *J* = 7.3 Hz, 2 H), 1.27–1.12 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 136.8, 131.7, 127.4, 108.1, 63.9, 45.5, 45.0, 10.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}Br_2N_2O$: 322.9218; found: 322.9209.

6,8-Dibromo-4-cyclopropyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2g)

Yield: 30 mg (39%); white solid; mp 91–93 °C; R_f = 0.5 (10%, EtOAc/hexane).

IR (neat): 2979, 1575, 1485, 1443, 1354, 1219, 1118, 1023 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (s, 1 H), 4.31–4.23 (m, 2 H), 3.51–3.43 (m, 2 H), 2.68 (tt, *J* = 3.5, 7.0 Hz, 1 H), 0.93–0.82 (m, 2 H), 0.68–0.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 136.6, 129.5, 119.6, 117.9, 65.3, 45.7, 30.5, 7.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}Br_2N_2O$: 334.9218; found: 334.9214.

5,7-Dibromo-1-cyclopropyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2h)

Yield: 33 mg (43%); white solid; mp 142–144 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 2958, 1574, 1487, 1451, 1348, 1251, 1116, 1026, 823 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (s, 1 H), 4.28 (br. s., 2 H), 3.42 (br. s., 2 H), 2.48 (br. s., 1 H), 0.99–0.88 (m, 2 H), 0.69 (br. s., 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 137.2, 131.1, 127.1, 110.4, 64.9, 45.7, 31.1, 8.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}Br_2N_2O$: 334.9218; found: 334.9211.

6,8-Dibromo-4-propyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2i)

Yield: 41 mg (54%); gummy solid; R_f = 0.5 (10%, EtOAc/hexane).

IR (neat): 2927, 1578, 1504, 1423, 1357, 1300, 1211, 1061, 938, 746.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (s, 1 H), 4.29–4.22 (m, 2 H), 3.59–3.43 (m, 4 H), 1.70–1.55 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1, 135.8, 131.5, 129.6, 117.9, 64.3, 49.6, 45.5, 20.1, 11.4.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{13}Br_2N_2O$: 336.9374; found: 336.9365.

5,7-Dibromo-1-propyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2j)

Yield: 24 mg (31%); white solid; mp 67–69 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 2933, 1505, 1403, 1065, 939, 797 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (s, 1 H), 4.32–4.23 (m, 2 H), 3.49–3.42 (m, 2 H), 3.28–3.19 (m, 2 H), 1.65 (sext, *J* = 7.4 Hz, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, 400 MHz, $CDCl_3$): δ = 143.1, 136.6, 131.7, 127.4, 108.1, 63.8, 52.3, 46.5, 19.5, 11.4.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{13}Br_2N_2O$: 336.9374; found: 336.9383.

(*S*)-6,8-Dibromo-4-(1-phenylethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2k)

Yield: 47 mg (52%); gummy solid; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 2938, 1574, 1488, 1415, 1353, 1211, 1064, 775, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 6.87 (s, 1 H), 6.20 (q, *J* = 7.0 Hz, 1 H), 4.25–4.16 (m, 1 H), 4.03 (ddd, *J* = 2.9, 7.5, 10.6 Hz, 1 H), 3.32 (ddd, *J* = 3.2, 7.5, 12.8 Hz, 1 H), 3.04 (ddd, *J* = 2.7, 4.5, 12.8 Hz, 1 H), 1.61–1.50 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 140.2, 136.0, 131.5, 129.5, 128.5, 127.5, 127.4, 118.3, 72.9, 64.6, 51.0, 39.3, 28.6, 15.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}Br_2N_2O$: 398.9531; found: 398.9521.

(*S*)-5,7-Dibromo-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2l)

Yield: 24 mg (26%); white solid; mp 106–108 °C; R_f = 0.3 (10%, EtOAc/hexane).

IR (neat): 2938, 1574, 1488, 1415, 1353, 1211, 1064, 775, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.21 (m, 5 H), 6.80 (s, 1 H), 5.08 (q, *J* = 6.8 Hz, 1 H), 4.31–4.21 (m, 1 H), 4.09 (ddd, *J* = 2.9, 7.7, 10.9 Hz, 1 H), 3.30 (ddd, *J* = 3.2, 7.5, 12.8 Hz, 1 H), 3.17–3.04 (m, 1 H), 1.68–1.52 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 139.0, 136.8, 131.8, 129.0, 128.1, 127.9, 126.8, 108.5, 64.2, 55.0, 40.1, 15.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}Br_2N_2O$: 398.9531; found: 398.952.

4-Benzyl-6,8-dibromo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2o)

Yield: 52 mg (59%); gummy solid; R_f = 0.3 (10%, EtOAc/hexane).

IR (neat): 2836, 2899, 1576, 1533, 1500, 1445, 1417, 1356, 1298, 1210, 1048, 915, 737, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5 H), 6.88 (s, 1 H), 4.80 (s, 2 H), 4.21 (t, *J* = 4.4 Hz, 2 H), 3.37 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 136.9, 136.0, 129.5, 128.7, 128.2, 127.6, 118.8, 118.5, 64.4, 50.9, 44.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}Br_2N_2O$: 384.9374; found: 384.9364.

1-Benzyl-5,7-dibromo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2p)

Yield: 26 mg (30%); white solid; mp 142–144 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 2931, 2874, 1574, 1528, 1501, 1453, 1352, 1246, 1072, 922, 799, 733, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.29 (m, 3 H), 7.24–7.14 (m, 2 H), 6.65 (s, 1 H), 4.51 (s, 2 H), 4.31 (t, *J* = 4.4 Hz, 2 H), 3.48 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 136.7, 135.0, 131.8, 129.2, 128.1, 127.7, 126.8, 108.7, 64.1, 53.9, 46.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}Br_2N_2O$: 384.9374; found: 384.9365.

2-((6,8-Dibromo-2*H*-pyrido[3,2-*b*][1,4]oxazin-4(3*H*)-yl)methyl)aniline (2q)

Yield: 48 mg (53%); white solid; mp 81–83 °C; R_f = 0.7 (10%, EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.04 (m, 2 H), 6.87 (s, 1 H), 6.74–6.63 (m, 2 H), 4.68 (s, 2 H), 4.55 (br. s., 2 H), 4.21 (t, *J* = 4.4 Hz, 2 H), 3.45 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 146.2, 136.2, 131.5, 129.4, 129.2, 119.8, 118.7, 118.6, 117.4, 115.9, 64.3, 49.0, 44.5.

IR (neat): 3450, 3339, 3220, 3010, 2895, 1631, 1575, 1502, 1443, 1354, 1298, 1251, 1206, 1162, 1111, 1041, 908, 747 cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}Br_2N_3O$: 399.9483; found: 399.9473.

2-((5,7-Dibromo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-1-yl)methyl)aniline (2r)

Yield: 23 mg (25%); white solid; mp 164–166 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 3743, 2929, 1572, 1504, 1456, 1401, 1354, 1247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (dt, *J* = 1.2, 7.7 Hz, 1 H), 7.01 (d, *J* = 7.3 Hz, 1 H), 6.82–6.72 (m, 3 H), 4.34 (s, 2 H), 4.3 (t, *J* = 4.4 Hz, 2 H), 3.71 (br. s., 2 H), 3.29 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 143.6, 137.2, 131.7, 129.5, 129.1, 127.7, 119.0, 118.3, 116.4, 109.0, 64.5, 50.9, 44.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}Br_2N_3O$: 399.9483; found: 399.9476.

***tert*-Butyl 3-(6,8-Dibromo-2*H*-pyrido[3,2-*b*][1,4]oxazin-4(3*H*)-yl)propylcarbamate (2s)**

Yield: 40 mg (39%); gummy solid; R_f = 0.3 (25%, EtOAc/hexane).

IR (neat): 3743, 3616, 3346, 2929, 1698, 1577, 1518, 1360, 1167, 1067 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 1 H), 5.56 (br. s., 1 H), 4.25 (t, *J* = 4.4 Hz, 2 H), 3.64 (t, *J* = 6.4 Hz, 2 H), 3.48 (t, *J* = 4.4 Hz, 2 H), 3.10 (q, *J* = 6.4 Hz, 2 H), 1.74 (quin, *J* = 6.1 Hz, 2 H), 1.48–1.40 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 147.3, 135.9, 129.5, 118.4, 78.9, 64.2, 45.5, 45.0, 36.0, 28.5, 27.4.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{21}Br_2N_3NaO_3$: 473.9827; found: 473.9779.

***tert*-Butyl 3-(5,7-Dibromo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-1-yl)propylcarbamate (2t)**

Yield: 27 mg (26%); white solid; mp 121–123 °C; R_f = 0.2 (25%, EtOAc/hexane).

IR (neat): 3343, 2773, 2933, 1694, 1577, 1520, 1459, 1401, 1359, 1281, 1248, 1167, 1065, 930, 796 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (s, 1 H), 4.70 (br. s, 1 H), 4.27 (t, *J* = 4.4 Hz, 2 H), 3.45 (t, *J* = 4.4 Hz, 2 H), 3.33 (t, *J* = 7.3 Hz, 2 H), 3.22–3.15 (m, 2 H), 1.80 (quin, *J* = 7.0 Hz, 2 H), 1.48–1.37 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 142.9, 136.8, 131.6, 127.5, 108.1, 79.7, 63.9, 48.1, 46.5, 38.0, 28.4 (3×CH_3), 27.0.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}Br_2N_3O_3$: 452.0007; found: 451.9996.

4-(2-(1*H*-Indol-3-yl)ethyl)-6,8-dibromo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2u)

Yield: 57 mg (57%); white solid; mp 62–64 °C; R_f = 0.3 (25%, EtOAc/hexane).

IR (neat): 3413, 2932, 1577, 1532, 1504, 1450, 1421, 1357, 1258, 1210, 1088, 1041, 927, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (br. s, 1 H), 7.71 (d, *J* = 7.8 Hz, 1 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 7.16–7.03 (m, 2 H), 6.88 (d, *J* = 2.0 Hz, 1 H), 6.77 (s, 1 H), 4.02–3.93 (m, 2 H), 3.75 (t, *J* = 7.3 Hz, 2 H), 3.27–3.19 (m, 2 H), 2.97 (t, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 136.3, 136.0, 129.9, 127.5, 122.2, 122.0, 119.5, 119.2, 118.1, 117.9, 113.3, 111.2, 64.3, 49.3, 46.3, 22.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}Br_2N_3O$: 437.9640; found: 437.9628.

1-(3-(1*H*-Indol-3-yl)propyl)-5,7-dibromo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2v)

Yield: 30 mg (30%); gummy solid; R_f = 0.1 (25%, EtOAc/hexane).

IR (neat): 3400, 1658, 1578, 1523, 1355, 1247, 1021, 999, 822, 759, 620 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.85 (br. s, 1 H), 7.55 (d, *J* = 7.8 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.20 (d, *J* = 2.4 Hz, 1 H), 7.08 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.02–6.94 (m, 1 H), 6.74 (s, 1 H), 4.11 (t, *J* = 4.4 Hz, 2 H), 3.64 (t, *J* = 7.1 Hz, 2 H), 3.37–3.32 (m, 2 H), 2.96 (t, *J* = 7.1 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.3, 136.2, 136.1, 130.8, 127.0, 126.1, 123.3, 121.0, 118.4, 118.0, 111.5, 110.8, 107.8, 63.5, 50.4, 45.8, 21.4.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}Br_2N_3O$: 437.9640; found: 437.9631.

6,8-Dibromo-4-butyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (2w)

Yield: 47 mg (59%); gummy solid; R_f = 0.4 (10%, EtOAc/hexane).

IR (neat): 2925, 1694, 1513, 1460, 1211 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (s, 1 H), 4.26 (t, *J* = 4.4 Hz, 2 H), 3.58 (t, *J* = 7.1 Hz, 2 H), 3.49 (t, *J* = 4.4 Hz, 2 H), 1.58 (quin, *J* = 7.1, 15 Hz, 2 H), 1.35 (qd, *J* = 7.2, 15.0 Hz, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1, 135.9, 131.5, 129.7, 117.9, 64.3, 47.6, 45.4, 29.0, 20.1, 13.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}Br_2N_2O$: 350.9531; found: 350.9516.

5,7-Dibromo-1-butyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (2x)

Yield: 24 mg (30%); white solid; mp 47–49 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 2956, 2868, 1577, 1505, 1459, 1403, 1354, 1246, 1210, 1066, 920, 818, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (s, 1 H), 4.26 (t, *J* = 4.4 Hz, 2 H), 3.44 (t, *J* = 4.4 Hz, 2 H), 3.27 (t, *J* = 7.8 Hz, 2 H), 1.59 (quin, *J* = 7.3 Hz, 2 H), 1.45–1.29 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 136.6, 131.7, 127.4, 108.1, 63.8, 50.5, 46.5, 28.2, 20.2, 13.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}Br_2N_2O$: 350.9531; found: 350.952.

7,9-Dibromo-5-cyclopropyl-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepine (1c)

Yield: 25 mg (33%); white solid; mp 60–62 °C; R_f = 0.6 (10%, EtOAc/hexane).

IR (neat): 1559, 1526, 1467, 1434, 1370, 1349, 1308, 1278, 1203, 1094, 1061, 1023, 949, 878, 820, 777, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (s, 1 H), 4.16 (t, *J* = 6.1 Hz, 2 H), 3.61–3.52 (m, 2 H), 2.80 (tt, *J* = 3.5, 7.0 Hz, 1 H), 2.01 (quin, *J* = 6.0 Hz, 2 H), 0.87–0.76 (m, 2 H), 0.57–0.48 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 141.3, 131.2, 125.1, 121.5, 70.3, 50.2, 33.8, 29.5, 8.3.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}Br_2N_2O$: 348.9374; found: 348.9365.

6,8-Dibromo-1-cyclopropyl-1,2,3,4-tetrahydropyrido[3,4-*b*][1,4]oxazepine (1d)

Yield: 23 mg (36%); white solid; mp 106–108 °C; R_f = 0.2 (10%, EtOAc/hexane).

IR (neat): 3086, 2956, 1562, 1518, 1444, 1385, 1336, 1281, 1234, 1062, 1025, 990, 951, 836, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (s, 1 H), 4.18 (t, *J* = 5.8 Hz, 2 H), 3.64 (t, *J* = 5.8 Hz, 2 H), 2.55 (tt, *J* = 3.3, 6.7 Hz, 1 H), 2.05 (quin, *J* = 6.0 Hz, 2 H), 0.94–0.83 (m, 2 H), 0.67–0.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 141.5, 133.7, 133.2, 114.3, 70.2, 51.4, 34.0, 29.5, 9.0.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}Br_2N_2O$: 348.9374; found: 348.9366.

Typical Procedure and Spectral Data for 7a–g

To solution of 5,7-dibromo-1-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (**2b**; 40 mg, 0.129 mmol) in dioxane (1 mL) was added $Pd(PPh_3)_4$ (14 mg, 0.0129 mmol), *o*-tolylboronic acid and aq 2 M K_2CO_3 (0.2 mL). The reaction mixture was stirred for 8 h at 80 °C. Water (4 mL) was added and the mixture was extracted with EtOAc (12 × 3 mL). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated in vacuo. The resulting crude material was purified over silica gel column chromatography (10%, EtOAc/hexane) to afford product **7g** (32 mg, 74%).

4-Benzyl-6,8-diphenyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (7a)

Synthesized from **2o** (11 mg).

Yield: 9 mg (82%); white solid; mp 144–146 °C; R_f = 0.5 (10%, EtOAc/hexane).

IR (neat): 1693, 1648, 1515, 1462, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.97 (m, 2 H), 7.63 (dd, *J* = 1.2, 8.6 Hz, 2 H), 7.51–7.23 (m, 11 H), 7.12 (s, 1 H), 5.07 (s, 2 H), 4.26–4.18 (m, 2 H), 3.51–3.42 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 146.8, 139.7, 138.6, 135.6, 135.0, 129.2, 128.6, 128.4, 128.2, 127.9, 127.7, 127.2, 126.2, 111.1, 64.3, 51.0, 45.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{23}N_2O$: 379.1810; found: 379.1796.

1-Methyl-5,7-diphenyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (7b)

Yield: 23 mg (59%); white solid; mp 130–132 °C; R_f = 0.4 (10%, EtOAc/hexane).

IR (neat): 2930, 1589, 1507, 1235, 774, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.8 Hz, 4 H), 7.42 (t, *J* = 7.3 Hz, 4 H), 7.34 (d, *J* = 4.4 Hz, 2 H), 6.91 (s, 1 H), 4.26 (br. s, 2 H), 3.41 (br. s, 2 H), 3.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4, 144.1, 142.9, 140.5, 138.4, 129.6, 128.5, 128.0, 128.0, 127.9, 126.8, 102.4, 64.0, 48.5, 38.2.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found: 303.149.

4-Benzyl-6,8-di(naphthalen-1-yl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (7c)

Synthesized from **2o** (62 mg).

Yield: 52 mg (68%); white solid; mp 170–172 °C; R_f = 0.7 (10%, EtOAc/hexane).

IR (neat): 3051, 1546, 1454, 1358, 1046, 778 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.8 Hz, 1 H), 7.93–7.74 (m, 5 H), 7.69–7.61 (m, 1 H), 7.58–7.21 (m, 12 H), 6.95–6.87 (m, 1 H), 5.10–5.00 (m, 1 H), 4.97–4.85 (m, 1 H), 4.16–4.03 (m, 2 H), 3.50–3.33 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 146.7, 138.9, 138.5, 135.9, 134.9, 134.2, 134.1, 133.6, 131.5, 131.4, 128.6, 128.4, 128.4, 128.3, 128.2, 127.3, 127.2, 126.7, 126.3, 126.2, 125.9, 125.9, 125.6, 125.4, 125.4, 117.4, 64.2, 51.0, 45.4.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{27}N_2O$: 479.2123; found: 479.213.

5-Methyl-7,9-diphenyl-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepine (7d)

Synthesized from **1a** (50 mg).

Yield: 47 mg (96%); white solid; mp 89–91 °C; R_f = 0.7 (10%, EtOAc/hexane).

IR (neat): 2950, 1544, 1497, 1370, 1202, 1036, 952, 762, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.00 (m, 2 H), 7.58–7.53 (m, 2 H), 7.49–7.33 (m, 6 H), 7.17 (s, 1 H), 4.20 (t, *J* = 6.1 Hz, 2 H), 3.60–3.49 (m, 2 H), 3.31–3.19 (m, 3 H), 2.18–2.06 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 148.1, 141.2, 140.6, 139.5, 137.5, 129.2, 128.5, 128.1, 128.0, 127.9, 127.7, 126.4, 126.3, 112.6, 70.3, 50.6, 40.0, 29.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O$: 317.1654; found: 317.1635.

(*S*)-6,8-Diphenyl-4-(1-phenylethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (7e)

Synthesized from **2k** (70 mg).

Yield: 63 mg (91%); white solid; mp 116–118 °C; R_f = 0.5 (15%, EtOAc/hexane).

IR (neat): 2932, 1594, 1484, 1440, 1358, 1207, 1029, 771, 744, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.90 (m, 2 H), 7.55–7.50 (m, 2 H), 7.38–7.13 (m, 11 H), 7.00 (s, 1 H), 6.56 (q, *J* = 6.8 Hz, 1 H), 4.11–4.04 (m, 1 H), 3.95 (ddd, *J* = 2.9, 7.6, 10.5 Hz, 1 H), 3.30 (ddd, *J* = 2.9, 7.7, 12.3 Hz, 1 H), 3.03–2.97 (m, 1 H), 1.54 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 146.5, 141.8, 139.8, 136.9, 135.6, 134.9, 129.2, 128.4, 128.4, 128.2, 127.8, 127.7, 127.5, 127.0, 126.2, 110.7, 64.4, 50.4, 39.5, 15.0.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}N_2O$: 393.1967; found: 393.1956.

1-Cyclopropyl-5,7-diphenyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (7f)

Synthesized from **2h** (35 mg).

Yield: 16 mg (47%); white solid; mp 55–57 °C; R_f = 0.4 (15%, EtOAc/hexane).

IR (neat): 2929, 1583, 1546, 1505, 1358, 1231, 1023, 1023, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.96 (m, 4 H), 7.50–7.41 (m, 5 H), 7.39–7.32 (m, 2 H), 4.38–4.19 (m, 2 H), 3.53–3.38 (m, 2 H), 2.60–2.45 (m, 1 H), 1.03–0.89 (m, 2 H), 0.83–0.66 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 144.3, 143.0, 140.5, 138.4, 137.8, 129.6, 128.5, 127.9, 127.9, 127.8, 126.7, 115.3, 104.0, 64.8, 46.1, 31.3, 8.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}N_2O$: 329.1654; found: 329.1647.

4-Methyl-6,8-di-*o*-tolyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (7g)

Yield: 32 mg (74%); white solid; mp 44–46 °C; R_f = 0.8 (10%, EtOAc/hexane).

IR (neat): 2926, 1601, 1454, 1359, 1206, 1036, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.43 (m, 1 H), 7.29–7.18 (m, 7 H), 6.55 (s, 1 H), 4.27–4.20 (m, 2 H), 3.50–3.42 (m, 2 H), 3.18 (s, 3 H), 2.50 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 147.1, 140.7, 136.7, 136.3, 136.1, 135.5, 134.6, 130.8, 129.9, 129.7, 129.5, 127.9, 127.4, 125.7, 125.6, 115.5, 64.2, 48.2, 36.3, 21.1, 20.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O$: 331.1810; found: 331.1802.

Typical Procedure and Spectral Data for 8a–f

To a solution of (*S*)-5,7-dibromo-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (**2l**; 85 mg, 0.213 mmol) in toluene (2 mL) was added $Pd(PPh_3)_4$ (24 mg, 0.0213 mmol), 2-(tributylstannyl)pyridine **8** and, after degassing under argon, the reaction mixture was stirred for 16 h at reflux. After completion of reaction, which was checked by TLC, the reaction mixture was filtered through a short pad of Celite and concentrated in vacuo. The resulting crude material was purified over 5% KF + silica gel column chromatography with 10% MeOH in CH_2Cl_2, which afforded product **8c** (52 mg, 61%).

1-Methyl-5,7-di(pyridin-2-yl)-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (8a)

Synthesized from **2b** (60 mg).

Yield: 55 mg (92%); white solid; mp 102–104 °C; R_f = 0.2 (80%, EtOAc/hexane).

IR (neat): 2934, 1560, 1501, 1433, 1364, 1203, 1050, 791, 607 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76–8.68 (m, 1 H), 8.63–8.56 (m, 1 H), 8.35–8.28 (m, 1 H), 8.11 (s, 1 H), 7.82–7.78 (m, 1 H), 7.71 (dtd, *J* = 2.0, 7.7, 11.4 Hz, 2 H), 7.24–7.14 (m, 2 H), 4.33–4.26 (m, 2 H), 3.55–3.46 (m, 2 H), 3.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 154.7, 149.5, 148.9, 147.6, 145.8, 138.1, 136.4, 135.8, 133.1, 124.9, 122.4, 122.3, 120.2, 112.0, 64.4, 47.8, 36.3.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_4O$: 305.1402; found: 305.1391.

5-Methyl-7,9-di(pyridin-2-yl)-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepine (8b)

Synthesized from **1b** (48 mg).

Yield: 46 mg (92%); white solid; mp 98–100 °C; R_f = 0.2 (25%, EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (td, *J* = 1.3, 4.8 Hz, 1 H), 8.64–8.57 (m, 1 H), 8.37–8.29 (m, 1 H), 8.11 (s, 1 H), 7.78–7.68 (m, 3 H), 7.28–7.16 (m, 2 H), 4.22 (t, *J* = 6.1 Hz, 2 H), 3.55 (dd, *J* = 5.1, 6.6 Hz, 2 H), 3.23 (s, 3 H), 2.15–2.08 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 155.4, 154.3, 149.4, 148.9, 147.3, 142.9, 139.4, 136.5, 135.8, 125.0, 122.6, 122.4, 120.5, 113.4, 70.3, 50.5, 40.0, 28.8.

IR (neat): 2951, 1699, 1547, 1488, 1428, 1371, 1263, 1198, 1043, 792 cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_4O$: 319.1559; found: 319.1547.

(*S*)-1-(1-Phenylethyl)-5,7-di(pyridin-2-yl)-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine (8c)

Yield: 52 mg (61%); white solid; mp 100–102 °C; R_f = 0.2 (5%, MeOH/CH_2Cl_2).

IR (neat): 1693, 1648, 1515, 1462, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79–8.73 (m, 1 H), 8.62–8.58 (m, 1 H), 8.47 (d, *J* = 8.3 Hz, 1 H), 8.07 (d, *J* = 1.0 Hz, 1 H), 7.93–7.89 (m, 1 H), 7.82–7.70 (m, 2 H), 7.41–7.32 (m, 4 H), 7.31–7.25 (m, 2 H), 7.21 (ddd, *J* = 1.0, 4.9, 7.3 Hz, 1 H), 5.57 (q, *J* = 6.8 Hz, 1 H), 4.25–4.17 (m, 1 H), 4.08 (ddd, *J* = 2.9, 7.5, 10.6 Hz, 1 H), 3.36 (ddd, *J* = 2.9, 7.6, 12.5 Hz, 1 H), 3.14–3.03 (m, 1 H), 1.66 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 156.7, 149.3, 148.9, 148.6, 144.1, 142.2, 140.1, 139.4, 136.6, 136.0, 128.7, 127.6, 127.2, 124.9, 122.8, 122.5, 121.2, 103.1, 64.2, 54.0, 39.8, 15.2;

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{23}N_4O$: 395.1872; found: 395.1867.

(*S*)-4-(1-Phenylethyl)-6,8-di(pyridin-2-yl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (8d)

Yield: 78 mg (91%); white solid; mp 118–120 °C; R_f = 0.2 (30%, EtOAc/hexane).

IR (neat): 2931, 1698, 1300, 1254, 1174, 1060, 789 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.75–8.71 (m, 1 H), 8.60 (td, *J* = 1.0, 4.9 Hz, 1 H), 8.31 (d, *J* = 8.3 Hz, 1 H), 8.11 (s, 1 H), 7.82–7.77 (m, 1 H), 7.71 (tt, *J* = 1.8, 7.8 Hz, 2 H), 7.46–7.41 (m, 2 H), 7.37–7.30 (m, 2 H), 7.28–7.20 (m, 2 H), 7.17 (ddd, *J* = 1.0, 4.9, 7.3 Hz, 1 H), 6.61 (q, *J* = 6.8 Hz, 1 H), 4.25–4.17 (m, 1 H), 4.09 (ddd, *J* = 2.9, 7.5, 10.6 Hz, 1 H), 3.42 (ddd, *J* = 3.2, 7.3, 12.5 Hz, 1 H), 3.15–3.08 (m, 1 H), 1.63 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 154.9, 149.5, 148.9, 146.4, 145.7, 141.6, 137.7, 136.5, 135.9, 133.7, 128.5, 127.4, 127.1, 124.9, 122.5, 122.4, 120.3, 111.7, 64.6, 50.7, 39.3, 15.0.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{23}N_4O$: 395.1872; found: 395.1865.

4-Benzyl-6,8-di(pyridin-2-yl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (8e)

Synthesized from **2o** (96 mg).

Yield: 63 mg (67%); white solid; mp 150–152 °C; R_f = 0.2 (35%, EtOAc/hexane).

IR (neat): 2928, 1560, 1497, 1436, 1362, 1204, 1043, 747 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.77–8.69 (m, 1 H), 8.63–8.56 (m, 1 H), 8.30–8.23 (m, 1 H), 8.14 (s, 1 H), 7.83–7.78 (m, 1 H), 7.69 (dtd, *J* = 2.0, 7.8, 11.7 Hz, 2 H), 7.40–7.35 (m, 2 H), 7.34–7.29 (m, 2 H), 7.28–7.20 (m, 2 H), 7.15 (ddd, *J* = 1.0, 4.8, 7.5 Hz, 1 H), 5.04 (s, 2 H), 4.31–4.17 (m, 2 H), 3.52–3.38 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 154.8, 149.5, 148.9, 146.8, 145.8, 138.4, 137.7, 136.5, 135.9, 133.8, 128.6, 128.1, 127.2, 124.9, 122.5, 122.4, 120.3, 112.1, 64.4, 51.2, 45.0;

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O$: 381.1715; found: 381.1703.

4-Cyclopropyl-6,8-di(pyridin-2-yl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (8f)

Synthesized from **2g** (50 mg).

Yield: 44 mg (89%); white solid; mp 118–120 °C; R_f = 0.3 (40%, EtOAc/hexane).

IR (neat): 2951, 1517, 1416, 1375, 1311, 1247, 997, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.75–8.71 (m, 1 H), 8.60 (td, *J* = 1.2, 5.0 Hz, 1 H), 8.43–8.38 (m, 1 H), 8.18 (s, 1 H), 7.82–7.68 (m, 3 H), 7.25–7.14 (m, 2 H), 4.37–4.19 (m, 2 H), 3.60–3.43 (m, 2 H), 2.80–2.63 (m, 1 H), 1.03–0.87 (m, 2 H), 0.78–0.65 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 154.8, 149.5, 148.8, 147.9, 145.7, 138.3, 136.5, 135.8, 133.3, 124.9, 122.4, 122.3, 120.3, 112.9, 65.4, 46.0, 31.0, 7.8.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{19}N_4O$: 331.1559; found: 331.1546.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591960.

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