Synthesis of substituted pyrido-oxazine *via* tandem S_N2 and S_NAr reaction

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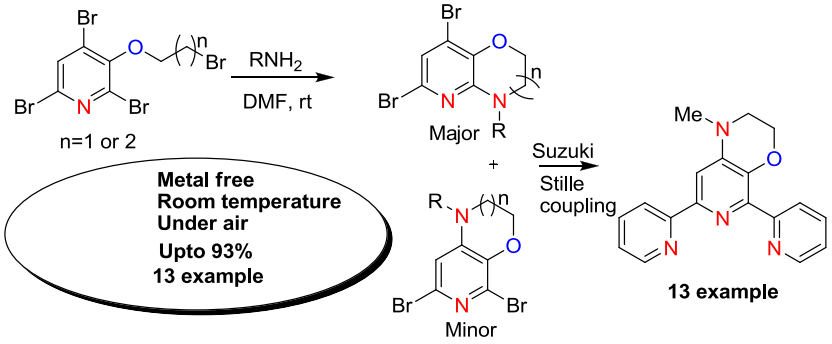

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Abstract Pyrido-oxazine derivatives have been synthesized employing tandem S_N2 and S_NAr reaction between 2,4,6-tribromo-3-(2-bromoethoxy)pyridine or 2,4,6-tribromo-3-(3-bromopropoxy)pyridine and variety of primary amines. Moderate to good regioselectivity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

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

Pyridine is one of the important heterocycles, often encountered in natural products, bioactive molecules, and therapeutic drugs and also serves as 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 variety of metals to perform important synthetic transformations.[2] Pyrido-oxazines are class of heterocycles where one of the carbon in benzoxazine is replaced by nitrogen and they have shown promising biological activity.[3] Halo-pyridines are important building blocks in organic synthesis as they easily react with various nucleophiles. This reactive nature can be attributed to the high electronegativity of halogen atom which makes carbon–halogen bond prone to nucleophilic aromatic substitutions (S_NAr). In general, substituted 2- and 4-halopyridines are attractive intermediates in synthetic and medicinal chemistry and are extensively used for the construction of various pyride-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 continuation with our ongoing program of synthesizing brominated marine natural product and their analogs,[7] we wish to report a simple strategy for synthesis of functionalized pyrido-oxazines 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 via 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] 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 suitable substrate pair for this study.

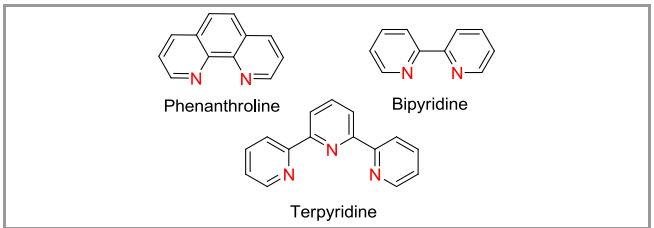
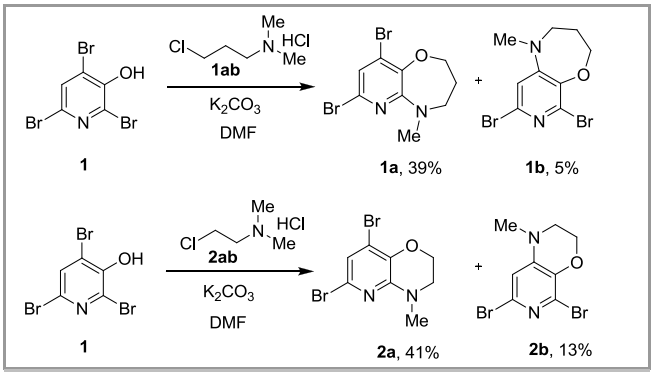


Figure 1 Important pyridine motif.

Accordingly when 2,4,6-tribromopyridin-3-ol **1** was treated with 3-chloro-*N*,*N*-dimethylpropan-1-amino hydrochloride **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 cyclisation

Alternatively, transformation of **1** to **6a,b** would furnish *bis*-electrophilic species which upon treatment with primary amines would provide the corresponding products, sans *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 scope of the reaction **6a** was then subjected to variety of primary amines. This methodology tolerates functional group like Allyl **2c**, **2d** cyclopropyl **2g**, **2h** and benzyl **2o**, **2p** (figure 2). Interestingly chiral amine afforded cyclic product **2k**, **2l** in good yield. 2-(Aminomethyl)aniline **2qr** which has two free –NH_2 groups reacted to give a product with selectively benzyl amino group getting involved in the reaction to give product **2q**, **2r** in good yield. Biologically important indole derivative **2u**, **2v** were prepared in good yield. This methodology has also been used to prepare seven membered pyrido-oxazine **1a**, **1b**, **1c** and **1d** in good yield.

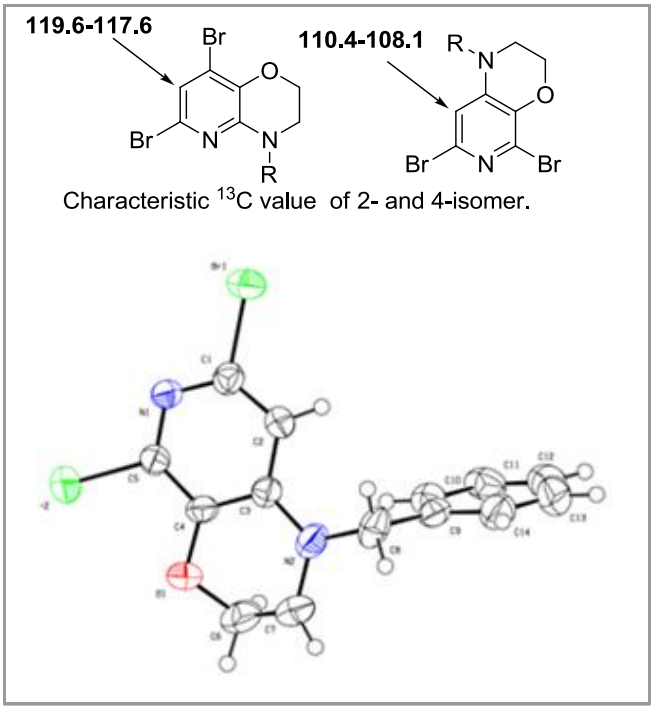
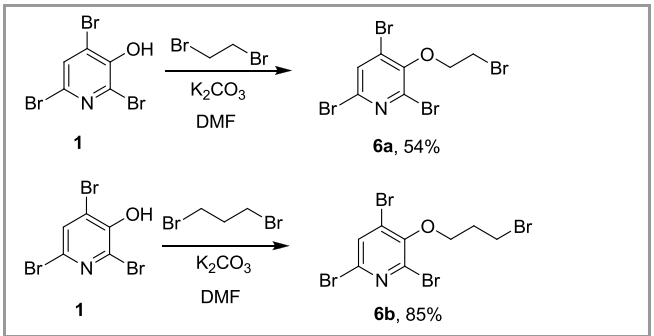
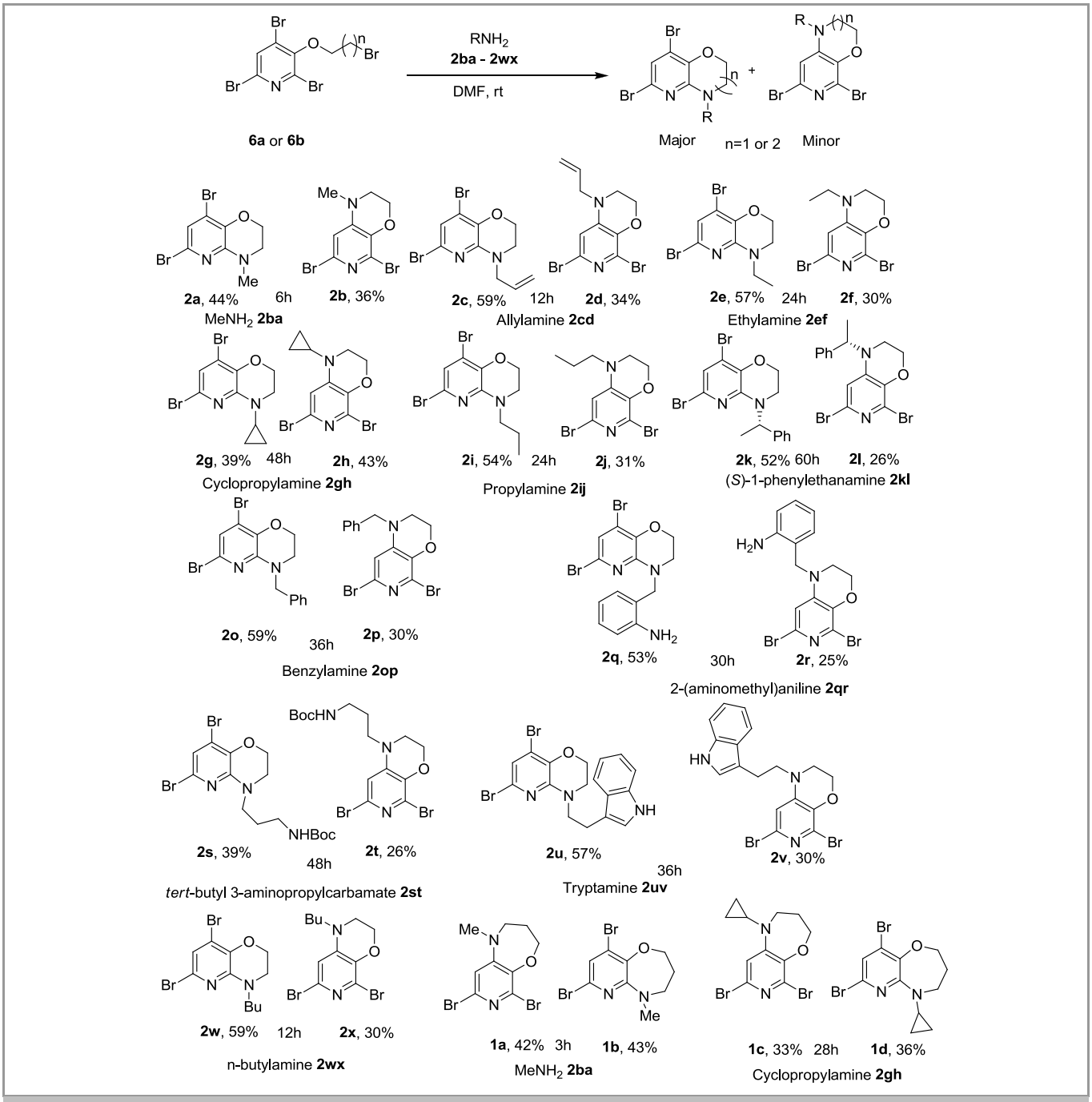


Figure 2 Characteristic ^{13}C value of 2- and 4-isomer and single crystal X-ray structure of compound **2p** (CCDC 1584958)

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

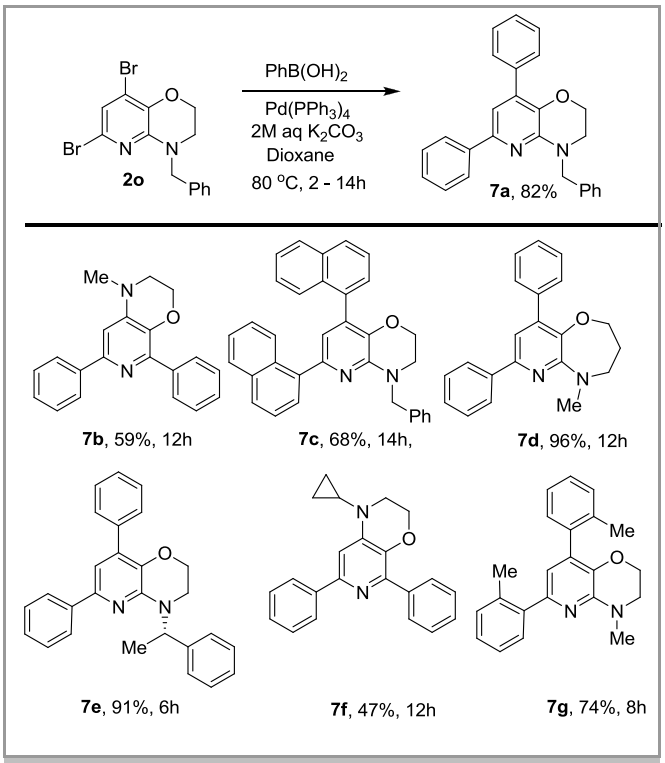


Scheme 2 Synthesis of bis-electrophilic intermediate **6a** and **6b**

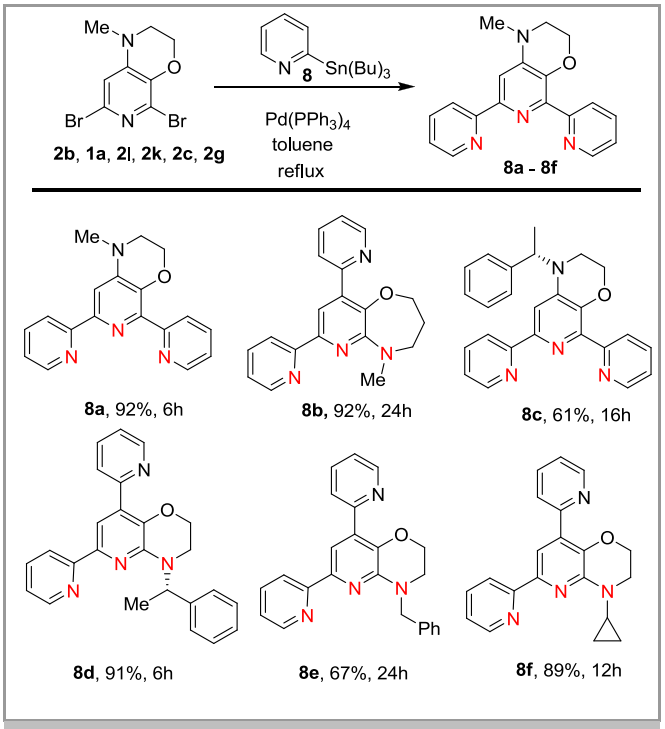


Scheme 3 cyclization with primary amine

After having pyrido-oxazine products in hand we thought of utilizing bromine atoms at 2,6- or 4,6-positions for further functionalisation through standard procedures. Application of Suzuki–Miyaura reaction furnished biarylated pyrido-oxazine **7a**-**7g** in good yield (Scheme 4). Similarly, Stille coupling between pyrido-oxazine **2b** and 2-(tributylstannyl)pyridine **8** in 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**, **8c**, **8d**, **8e**, **8f** in good yield.



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 via tandem S_N2 and S_NAr reaction in good yield. We were successfully able to functionalize pyrido-oxazine formed into biarylated pyrido-oxazine and terpyridines using Suzuki and stille coupling reactions in moderate to good yield

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In this section the preparations of all the compounds that have been made in the course have been discussed. For the experiments, all starting material and reagents are purchased from standard commercial sources or were prepared in laboratory. All the glassware were cleaned with soap water followed by acetone and dried in hot air oven at 100 ˚C for 2h. Solvents were distilled prior to use. IR spectra were recorded on the Bruker Tensor 37 (FTIR) spectrophotometer.^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295K in $CDCl_3$; chemical shifts value (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either tetramethylsilane (TMS) (δ-H = 0.00 ppm) or $CHCl_3$ (δ-H = 7.26 ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at 298K in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [(δ-C = 77.00 ppm) central line of triplet]. In ^{13}C NMR the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT- 135 spectra. In ^{1}H NMR, the following abbreviations were used throughout the experimental; s = singlet, d = doublet, t = triplet, q = quartet, qui = 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 on 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 ethyl acetate as eluents.

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

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

(12 g, 69%); Yellow solid; mp: 74-76 °C; R_f = 0.5 (60% EtOAc in hexane);

IR (neat): 3743, 3677, 3617, 1698, 1540, 1516, 1459;

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

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

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

General procedure and spectral data for compound 1a, 1b, 2a, 2b via *N*-dealkylative cyclisation.

To 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 being stirred for 10 h at 120 °C, to the reaction mixture was then added water (3 mL) and extracted with EtOAc (8x3 mL). The EtOAc layer was washed with water (3 mL) and brine (3 mL) solutions, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified over silica gel chromatography (20% EtOAc in hexane) to give compound **1a** (38 mg, 39%) and **1b** (5 mg, 5%) as colourless solid.

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

(38 mg, 39%); white solid; mp: 92-94 °C; R_f = 0.5 (10% EtOAc in hexane);

IR (neat); 2922, 1562, 1522, 1416, 1363, 1192, 1042, 962, 759;

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

^{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 calculated for $C_9H_{11}Br_2N_2O$ $[M+H]^+$: 322.9218; found: 322.9201.

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

(5 mg, 5%); white solid; mp: 98-100 °C; R_f = 0.5 (10% EtOAc in hexane);

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

^{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;

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

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

(38 mg, 41%); white solid; mp: 82-84 °C; R_f = 0.5 (10% EtOAc in hexane);

IR (neat); 2939, 2892, 1580, 1531, 1510, 1451, 1415, 1357, 1302, 1211, 1051, 922, 778, 695;

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

^{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 calculated for $C_8H_9Br_2N_2O$ $[M+H]^+$: 308.9061; found: 308.9053.

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

(12 mg, 36%); white solid; mp: 138-140 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 2945, 2882, 1581, 1509, 1461, 1426, 1352, 1290, 1249, 1217, 1119, 1052, 926, 822, 790;

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

^{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 calculated for $C_{17}H_{16}Br_2N_3O$ $[M+H]^+$: 308.9061; found: 308.9053.

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

To 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 stirred at 0 °C for 0.5 h. Then added 1,2-dibromoethane (11.32 g, 60.25 mmol) and after being stirred for 12 h at 80 °C to the reaction mix was added water (100 mL) and extracted with EtOAc (80x2 mL). The EtOAc layer was washed with water (12x3 mL) and brine (20x2 mL) solution, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified over silica gel chromatography (10% EtOAc in hexane) to give compound 2,4,6-tribromo-3-(2-bromoethoxy)pyridine **3** (2.45 g, 46%); colourless solid mp: 60-62 °C; R_f = 0.5 (10% EtOAc in hexane);

(IR neat); 2924, 1516, 1412, 1310, 985, 742;

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

^{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 calculated for $C_7H_6Br_4NO$ $[M+H]^+$: 439.7142; found: 439.7134.

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

To 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 stirred at 0 °C for 0.5 h. Then added 1,3-dibromopropane (6.08 g, 30.1 mmol) and after being stirred for 4 h at 80 °C to the reaction mix was added water (40 mL) and extracted with EtOAc (30x2 mL). The EtOAc layer was washed with water (20 mL) and brine (20 mL) solution, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified over silica gel chromatography (20% EtOAc in hexane) to give compound 2,4,6-tribromo-3-(3-bromopropoxy)pyridine **4** (1.67 g, 61%); colourless solid; mp: 40-42 °C; R_f = 0.7 (20% EtOAc in hexane);

(IR neat); 2950, 1517, 1416, 1311, 996, 742;

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

^{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 calculated for $C_8H_7Br_4NO$ $[M]^+$: 452.7220; found: 452.7368.

General Procedure and spectral data for product compounds 2c- 2x

To 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 for 36 h at rt. To the reaction mixture was then added water (3 mL) and extracted with EtOAc (12x3 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 was purified over silica gel column chromatography with 10-20% EtOAc in hexane, which afforded product **2o** (52 mg, 59%) & **2p** (26 mg, 30%).

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

(45 mg, 59%); white solid; mp: 54-56 °C; R_f = 0.6 (10% EtOAc in hexane);

IR (neat); 3093, 2939, 1578, 1534, 1502, 1449, 1418, 1357, 1305, 1255, 1213, 1094, 1040, 992, 925, 806, 673;

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

^{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 calculated for $C_{10}H_{11}Br_2N_2O$ $[M+H]^+$: 334.9218; found: 334.9212.

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

(26 mg, 34%); white solid; mp**:** 78-80 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 3086, 2874, 1576, 1528, 1503, 1454, 1402, 1352, 1287, 1246, 1211, 1167, 1070, 1035, 925, 822, 796, 700, 662;

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

^{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 calculated for $C_{10}H_{11}Br_2N_2O$ $[M+H]^+$: 334.9218; found: 334.9212.

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

(42 mg, 57%); white solid; mp: 82-84 °C; R_f = 0.6 (10% EtOAc in hexane);

IR (neat); 2932, 1578, 15051443, 1358, 1209, 1058, 930, 767;

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

^{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 calculated for $C_9H_{11}Br_2N_2O$ $[M+H]^+$: 322.9218; found: 322.9209.

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

(22 mg, 30%); white solid; mp: 78-80 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 2932, 1578, 1505, 1423, 1358, 1209, 1058, 930, 767;

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

^{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 calculated for $C_9H_{11}Br_2N_2O$ $[M+H]^+$: 322.9218; found: 322.9209.

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

(30 mg, 39%); white solid; mp: 91-93 °C; R_f = 0.5 (10% EtOAc in hexane);

IR (neat); 2979, 1575, 1485, 1443, 1354, 1219, 1118, 1023;

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

^{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 calculated for $C_{10}H_{11}Br_2N_2O$ $[M+H]^+$: 334.9218; found: 334.9214.

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

(33 mg, 43%); white solid; mp: 142-144 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 2958, 1574, 1487, 1451, 1348, 1251, 1116, 1026, 823;

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

^{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 calculated for $C_{10}H_{11}Br_2N_2O$ $[M+H]^+$: 334.9218; found: 334.9211.

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

(41 mg, 54%); gummy solid; R_f = 0.5 (10% EtOAc in hexane);

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

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

^{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 calculated for $C_{10}H_{13}Br_2N_2O$ $[M+H]^+$: 336.9374; found: 336.9365.

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

(24 mg, 31%); white solid; mp: 67-69 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 2933, 1505, 1403, 1065, 939, 797;

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

^{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 calculated for $C_{10}H_{13}Br_2N_2O$ $[M+H]^+$: 336.9374; found: 336.9383.

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

(47 mg, 52%); gummy solid; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 2938, 1574, 1488, 1415, 1353, 1211, 1064, 775, 699;

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

^{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 calculated for $C_{15}H_{15}Br_2N_2O$ $[M+H]^+$: 398.9531; found: 398.9521.

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

(24 mg, 26%); white solid; mp: 106-108 °C; R_f = 0.3 (10% EtOAc in hexane);

IR (neat); 2938, 1574, 1488, 1415, 1353, 1211, 1064, 775, 699;

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

^{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 calculated for $C_{15}H_{15}Br_2N_2O$ $[M+H]^+$: 398.9531; found: 398.952.

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

(52 mg, 59%); gummy solid; R_f = 0.3 (10% EtOAc in hexane);

IR (neat); 2836, 2899, 1576, 1533, 1500, 1445, 1417, 1356, 1298, 1210, 1048, 915, 737, 697;

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

^{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 calculated for $C_{14}H_{13}Br_2N_2O$ $[M+H]^+$: 384.9374; found: 384.9364.

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

(26 mg, 30%); white solid; mp**:** 142-144 °C ; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 2931, 2874, 1574, 1528, 1501, 1453, 1352, 1246, 1072, 922, 799, 733, 697;

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

^{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 calculated for $C_{14}H_{13}Br_2N_2O$ $[M+H]^+$: 384.9374; found: 384.9365.

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

(48 mg, 53%); white solid; mp: 81-83 °C; R_f = 0.7 (10% EtOAc in hexane);

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

^{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;

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

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

(23 mg, 25%); white solid; mp: 164-166 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 3743, 2929, 1572, 1504, 1456, 1401, 1354, 1247;

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

^{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 calculated for $C_{14}H_{14}Br_2N_3O$ $[M+H]^+$: 399.9483; found: 399.9476.

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

(40 mg, 39%); gummy solid; R_f = 0.3 (25% EtOAc in hexane);

IR (neat); 3743, 3616, 3346, 2929, 1698, 1577, 1518, 1360, 1167, 1067;

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

^{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 calculated for $C_{15}H_{21}Br_2N_3NaO_3$ $[M+Na]^+$: 473.9827; found: 473.9779.

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

(27 mg, 26%); white solid; mp: 121-123 °C; R_f = 0.2 (25% EtOAc in hexane);

IR (neat); 3343, 2773, 2933, 1694, 1577, 1520, 1459, 1401, 1359, 1281, 1248, 1167, 1065, 930, 796;

^{1}H NMR (400 MHz, $CDCl_3$) δ =6.55 (s, 1 H), 4.70 (br. s., 1H), 4.27 (t, *J*=4.4 Hz, 2H), 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(3XCH3), 27.0;

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

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

(57 mg, 57%); white solid; mp: 62-64 °C; R_f = 0.3 (25% EtOAc in hexane);

IR (neat); 3413, 2932, 1577, 1532, 1504, 1450, 1421, 1357, 1258, 1210, 1088, 1041, 927, 742;

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

^{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 calculated for $C_{17}H_{16}Br_2N_3O$ $[M+H]^+$: 437.9640; found: 437.9628.

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

(30 mg, 30%); gummy solid; R_f = 0.1 (25% EtOAc in hexane);

IR (neat); 3400, 1658, 1578, 1523, 1355, 1247, 1021, 999, 822, 759, 620;

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

^{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 calculated for $C_{17}H_{16}Br_2N_3O$ $[M+H]^+$: 437.9640; found: 437.9631.

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

(47 mg, 59%); gummy solid; R_f = 0.4 (10% EtOAc in hexane);

IR (neat); 2925, 1694, 1513, 1460, 1211;

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

^{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 calculated for $C_{11}H_{15}Br_2N_2O$ $[M+H]^+$: 350.9531; found: 350.9516.

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

(24 mg, 30%); white solid; mp: 47-49 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 2956, 2868, 1577, 1505, 1459, 1403, 1354, 1246, 1210, 1066, 920, 818, 698;

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

^{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 calculated for $C_{11}H_{15}Br_2N_2O$ $[M+H]^+$: 350.9531; found: 350.952.

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

(25 mg, 33%); white solid; mp: 60-62 °C; R_f = 0.6 (10% EtOAc in hexane);

IR (neat); 1559, 1526, 1467, 1434, 1370, 1349, 1308, 1278, 1203, 1094, 1061, 1023, 949, 878, 820, 777, 689;

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

^{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 calculated for $C_{11}H_{13}Br_2N_2O$ $[M+H]^+$: 348.9374; found: 348.9365.

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

(23 mg, 36%); white solid; mp: 106-108 °C; R_f = 0.2 (10% EtOAc in hexane);

IR (neat); 3086, 2956, 1562, 1518, 1444, 1385, 1336, 1281, 1234, 1062, 1025, 990, 951, 836, 689;

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

^{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 calculated for $C_{11}H_{13}Br_2N_2O$ $[M+H]^+$: 348.9374; found: 348.9366.

General Procedure and spectral data for product compound 7a-7g

To solution of 5,7-dibromo-1-methyl-2,3-dihydro-1H-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 2M K_2CO_3 (0.2 mL). The reaction mixture was stirred for 8 h at 80 °C. To the reaction mixture was then added water (4 mL) and extracted with EtOAc (12x3 mL) The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated in vacuo. The resulting crude was purified over silica gel column chromatography with 10% EtOAc in hexane, which afforded product **7g** (32 mg, 74%)

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

11 mg of **2o** gave (9 mg, 82%); white solid; mp: 144-146 °C; R_f = 0.5 (10% EtOAc in hexane);

IR (neat); 1693, 1648, 1515, 1462, 756;

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

^{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 calculated for $C_{26}H_{23}N_2O$ $[M+H]^+$: 379.1810; found: 379.1796.

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

(23 mg, 59%); white solid; mp: 130-132 °C; R_f = 0.4 (10% EtOAc in hexane);

IR (neat); 2930, 1589, 1507, 1235, 774, 696;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 7.8 Hz, 4H), 7.42 (t, *J* = 7.3 Hz, 4H), 7.34 (d, *J* = 4.4 Hz, 2H), 6.91 (s, 1H), 4.26 (br. s., 2H), 3.41 (br. s., 2H), 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 calculated for $C_{20}H_{19}N_2O$ $[M+H]^+$: 303.1497; found: 303.149.

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

62 mg of **2o** gave (52 mg, 68%); white solid; mp:170-172 °C; R_f = 0.7 (10% EtOAc in hexane);

IR (neat); 3051, 1546, 1454, 1358, 1046, 778;

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

^{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 calculated for $C_{34}H_{27}N_2O$ $[M+H]^+$: 479.2123; found: 479.213.

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

50 mg of **1a** gave (47 mg, 96%); white solid; mp:89-91 °C; R_f = 0.7 (10% EtOAc in hexane);

IR (neat); 2950, 1544, 1497, 1370, 1202, 1036, 952, 762, 696;

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

^{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 calculated for $C_{21}H_{21}N_2O$ $[M+H]^+$: 317.1654; found: 317.1635.

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

70 mg of **2k** gave (63 mg, 91%); white solid; mp: 116-118 °C; R_f = 0.5 (15% EtOAc in hexane);

IR (neat); 2932, 1594, 1484, 1440, 1358, 1207, 1029, 771, 744, 695;

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

^{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 calculated for $C_{27}H_{25}N_2O$ $[M+H]^+$: 393.1967; found: 393.1956.

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

35 mg of **2h** gave (16 mg, 47%); white solid; mp: 55-57 °C; R_f = 0.4 (15% EtOAc in hexane);

IR (neat); 2929, 1583, 1546, 1505, 1358, 1231, 1023, 1023, 776;

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

^{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 calculated for $C_{22}H_{21}N_2O$ $[M+H]^+$: 329.1654; found: 329.1647.

4-methyl-6,8-dio-tolyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (7g)

(32 mg, 74%); white solid; mp: 44-46 °C; R_f = 0.8 (10% EtOAc in hexane);

IR (neat); 2926, 1601, 1454, 1359, 1206, 1036, 759;

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

^{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 calculated for $C_{22}H_{23}N_2O$ $[M+H]^+$: 331.1810; found: 331.1802.

General Procedure and spectral data for compound 8a-8f

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

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

60 mg of **2b** gave (55 mg, 92%); white solid; mp: 102-104 °C; R_f = 0.2 (80% EtOAc in hexane);

IR (neat); 2934, 1560, 1501, 1433, 1364, 1203, 1050, 791, 607;

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

^{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 calculated for $C_{18}H_{17}N_4O$ $[M+H]^+$: 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)

48 mg of **1b** gave (46 mg, 92%); white solid; mp: 98-100 °C; R_f = 0.2 (25% EtOAc in hexane);

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

^{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;

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

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

(52 mg, 61%); white solid; mp: 100-102 °C; R_f = 0.2 (5% MeOH in DCM);

IR (neat); 1693, 1648, 1515, 1462, 754;

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

^{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 calculated for $C_{25}H_{23}N_4O$ $[M+H]^+$: 395.1872; found: 395.1867.

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

(78 mg, 91%); white solid; mp: 118-120 °C; R_f = 0.2 (30% EtOAc in hexane);

IR (neat); 2931, 1698, 1300, 1254, 1174, 1060, 789;

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

^{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 calculated for $C_{25}H_{23}N_4O$ $[M+H]^+$: 395.1872; found: 395.1865.

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

96 mg of **2o** gave (63 mg, 67%); white solid; mp: 150-152 °C; R_f = 0.2 (35% EtOAc in hexane);

IR (neat); 2928, 1560, 1497, 1436, 1362, 1204, 1043, 747;

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

^{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 calculated for $C_{24}H_{21}N_4O$ $[M+H]^+$: 381.1715; found: 381.1703.

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

50 mg of **2g** gave (44 mg, 89%); white solid; mp: 118-120 °C; R_f = 0.3 (40% EtOAc in hexane);

IR (neat); 2951, 1517, 1416, 1375, 1311, 1247, 997, 742;

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

^{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 calculated for $C_{20}H_{19}N_4O$ $[M+H]^+$: 331.1559; found: 331.1546.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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