Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supplementary Information

A regioselective, convergent, and additive-free approach for the synthesis of pyrido[1,4]oxazocines

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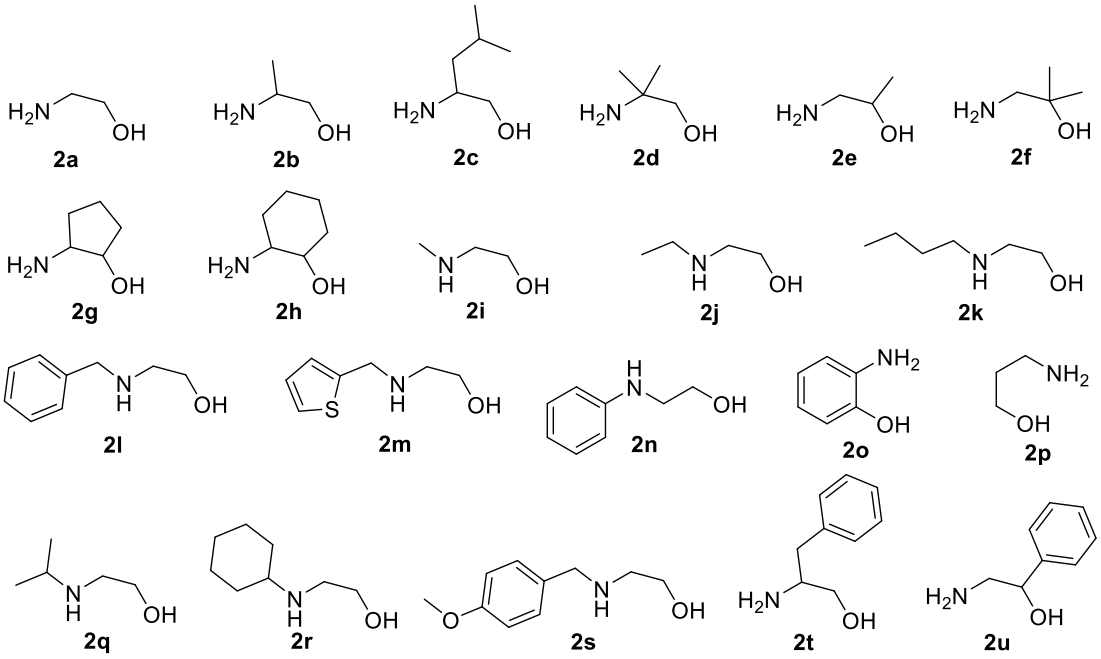
Table of contents: **Page**

1. General Experiment Information

Unless otherwise noted, all the reactions were carried out under ambient atmosphere. All chemicals and solvents were directly used without further purification. Substituted ethanolamines (**2a–2u**) were commercially available.



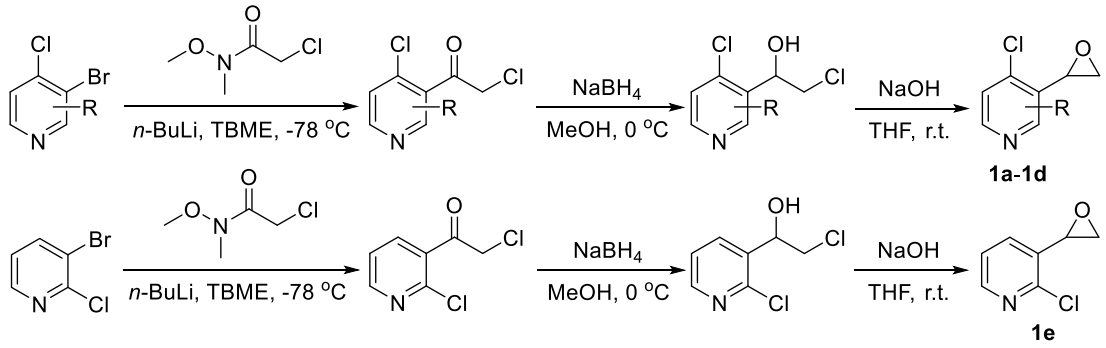
Organic solvents of commercial grade were concentrated under reduced pressure on a EYELA rotary evaporator (Japan). Analytical thin-layer chromatography (TLC) was performed on 0.25 mm commercial silica gel plates (purchased from Aladdin, silica gel GF254), and the compounds were visualized with the UV light at 254 nm and 365 nm, respectively. Column chromatography was performed on silica gel 200−300 mesh (purchased from Qingdao Haiyang Chemical, China). High-resolution mass spectra (HRMS) using electrospray ionization (ESI) as the ion source was performed by LC−MSD TOF using a column of C18 (rapid resolution, 3.5 μm, 2.1 mm × 30 mm) at a flow of 0.40 mL/min.

CD_3OD and $CDCl_3$ was purchased from Innochem (Beijing). ^1H NMR spectra were recorded on the Bruker Ascend^{TM} 400 with 400 MHz frequencies, and ^{13}C NMR spectra were recorded with 100 MHz frequencies. Chemical shifts are given in ppm and coupling constants in Hertz (Hz), respectively. ^1H spectra were calibrated in relation to the reference measurement of TMS (δ_H = 0.000 ppm). ^{13}C spectra were

calibrated in relation to CD_3OD (δ_C = 49.00 ppm) or $CDCl_3$ (δ_C = 77.10 ppm). The following abbreviations were used for ^1H NMR and ^{13}C NMR spectra to indicate the signal multiplicities: bs (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplets), as well as combinations of them.

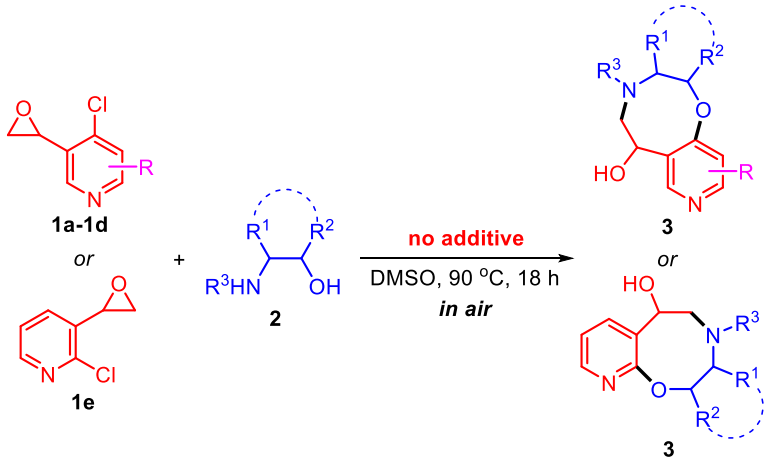
2. General Procedures

(1) General Procedure for the Preparation of 4-Chloro-3-(oxiran-2-yl)pyridines (1a−1d) and 2-Chloro-3-(oxiran-2-yl)pyridine (1e)



4-Chloro-3-(oxiran-2-yl)pyridines (**1a**−**1d**) and 2-chloro-3-(oxiran-2-yl)pyridine (**1e**) were prepared from corresponding 3-bromo-4-chloropyridines or 3-bromo-2-chloropyridine through selective lithium−bromine exchange with *n*-BuLi at −78 ℃ in dry *t*-butyl methyl ether (TBME) with subsequent reaction of the aryllithium with Weinreb amide,[1] $NaBH_4$ reduction,[2] and cyclization under basic conditions[1] according to the literature procedures.

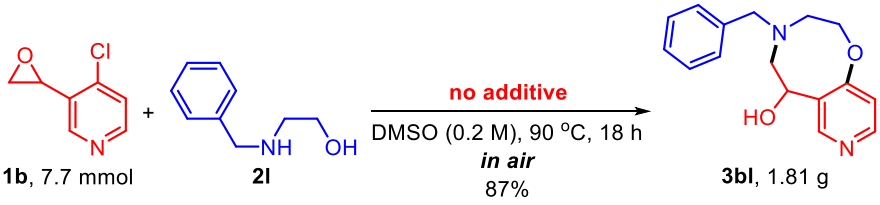
(2) General Procedure for the Synthesis of Pyrido[1,4]oxazocines 3



To a sealed tube (10 mL) equipped with a stirrer bar under ambient atmosphere was added 4-Chloro-3-(oxiran-2-yl)pyridine or 2-chloro-3-(oxiran-2-yl)pyridine (**1**, 0.2 mmol) and substituted ethanolamine (**2**, 0.4 mmol). Then DMSO (2.0 mL, 0.1 M) was added. The tube was sealed and the reaction mixture was stirred at 90 ℃ for 18 h using a Heidolph MR Hei-Tec heating magnetic stirrer (Heidolph Instruments,

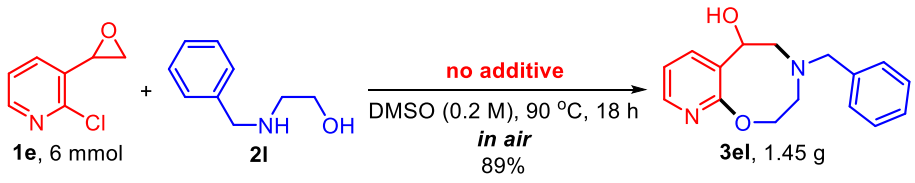
Germany). Upon completion, the reaction mixture was cooled to room temperature and 10 mL of H_2O was added. The mixture was extracted with DCM (3 × 10 mL). The combined organic phases were washed successively with 15 mL of H_2O and 15 mL of saturated brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (DCM/MeOH) to afford the desired product **3**.

(3) Scale-Up Synthesis of 3bl



To a 100 mL of round-bottomed flask equipped with a stir bar under air was added 4-chloro-3-(oxiran-2-yl)pyridine **1b** (7.7 mmol, 1.198 g) and 2-(benzylamino)ethan-1-ol **2l** (15.4 mmol, 2.328 g). Then DMSO (38.5 mL, 0.2 M) was added. The reaction mixture was stirred at 90 ℃ for 18 h using a heating magnetic stirrer. Upon completion, the reaction mixture was cooled to room temperature and 100 mL of H_2O was added. The mixture was extracted with DCM (3 × 50 mL). The combined organic phases were washed successively with 75 mL of H_2O and 75 mL of saturated brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (DCM/MeOH = 150:1) to afford the desired product **3bl** as a brown oil (1.81 g, 87%).

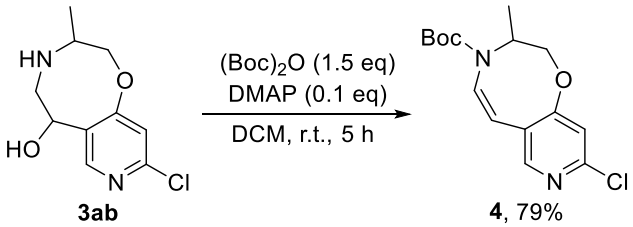
(4) Scale-Up Synthesis of 3el



To a 100 mL of round-bottomed flask equipped with a stir bar under air was added 2-chloro-3-(oxiran-2-yl)pyridine **1e** (6 mmol, 0.933 g) and 2-(benzylamino)ethan-1-ol **2l** (12 mmol, 1.815 g). Then DMSO (30 mL, 0.2 M) was added. The reaction mixture was stirred at 90 ℃ for 18 h using a heating magnetic stirrer. Upon completion, the

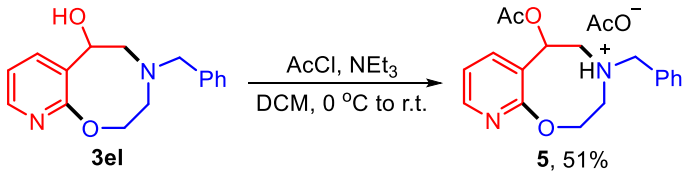
reaction mixture was cooled to room temperature and 100 mL of H_2O was added. The mixture was extracted with DCM (3 × 50 mL). The combined organic phases were washed successively with 75 mL of H_2O and 75 mL of saturated brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (DCM/MeOH = 150:1) to afford the desired product **3el** as a brown oil (1.45 g, 89%).

(5) Synthesis of 4



To a solution of 9-chloro-3-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4] oxazocin-6-ol (**3ab**, 457.4 mg, 2 mmol) in DCM (10 mL) was added di-*tert*-butyl dicarbonate (654.8 mg, 3 mmol) and DMAP (24.4 mg, 0.2 mmol). The mixture was stirred at room temperature for 5 h. Upon completion of the reaction, H_2O (6 mL) was added to the mixture and then extracted. The aqueous phase was extracted with DCM (2 × 6 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (DCM/MeOH = 400:1) to give the target product **4** (491 mg, 79% yield) as a yellow oil.

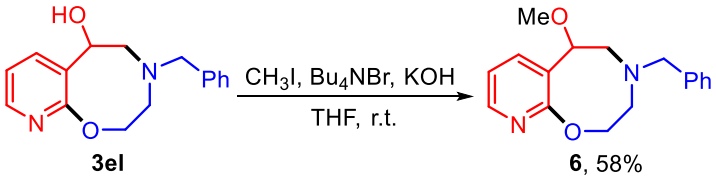
(6) Synthesis of 5



The product **5** was prepared according to the literature procedure.[3] To a stirred solution of **3el** (100.0 mg, 0.37 mmol) and triethyl amine (67 μL, 0.48 mmol) in absolute CH_2Cl_2 (600 μL) was added acetyl chloride (34 μL, 0.48 mmol) at 0 ℃. The reaction mixture was taken slowly to room temparature and stirred overnight. To the

crude reaction mixture was added CH_2Cl_2 (500 μL) and a saturated $NaHCO_3$ solution (500 μL). The organic phase was removed and washed with water (2 × 1 mL). After drying over Na_2SO_4, filtration and evaporation of the solvent, the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 300:1) to afford the desired product **5** as a light-yellow oil, 70.1 mg (51%).

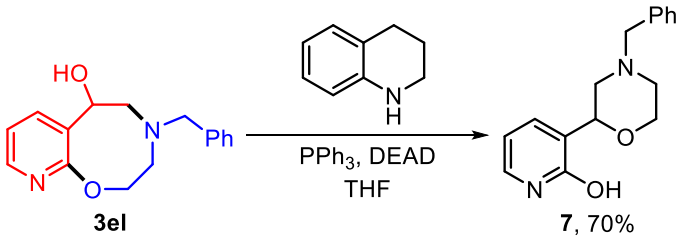
(7) Synthesis of 6



3el **6**, 58%

The product **6** was prepared according to the literature procedure.[4] A mixture of **3el** (162.2 mg, 0.6 mmol), CH_3I (936.5 mg, 6.6 mmol), Bu_4NBr (851.1 mg, 2.6 mmol), and KOH (306.3 mg, 5.5 mmol) in anhydrous THF (10 mL) was stirred for 18 h at room temperature. The mixture was diluted with water and extracted with EA. The extract was washed with water, dried, and evaporated. The residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 300:1) to afford the desired product **6** as a light-yellow oil, 99.1 mg (58%).

(8) Synthesis of 7

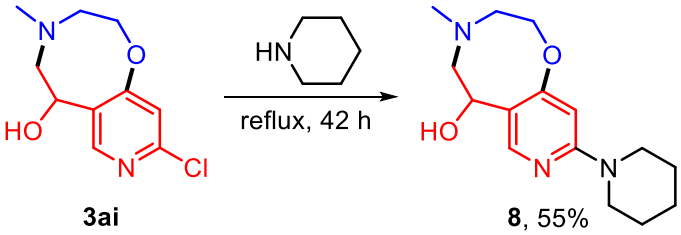


3el **7**, 70%

The product **7** was prepared under the Mistunobu reaction conditions.[5] To a stirred solution of **3el** (100.0 mg, 0.37 mmol), 1,2,3,4-tetrahydroquinoline (98.6 mg, 0.74 mmol), and triphenylphosphine (145.6 mg, 0.56 mmol) in anhydrous THF (10 mL) under atmosphere of N_2 was added DEAD (97.5 mg, 0.56 mmol) in anhydrous THF (5 mL) dropwise at 0 ℃. The reaction mixture was stirred at 0 ℃ for additional 1h. It was then allowed to warm to room temperature and was stirred for an additional 14 h. To the reaction mixture was added hexane (25 mL), and triphenylphosphine oxide

precipitated was filtered off. The solvent was removed in vacuum, and the mixture was diluted with 30 mL of water and the aqueous layer was extracted with EA (3 × 30 mL) and dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of crude product over silica gel (CH_2Cl_2/MeOH = 300:1) furnished the desired product **7** as a light-yellow oil, 70.4 mg (70%).

(9) Synthesis of 8

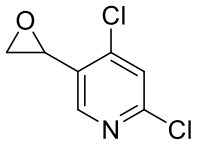


3ai **8**, 55%

3ai (30 mg, 0.13 mmol) was refluxed in piperidine (0.5 mL) for 42 h. The excess of piperidine was distilled off under reduced pressure and the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 300:1) to afford the desired product **8** as a light-yellow oil, 19.8 mg (55%).

3. Characterization of Materials

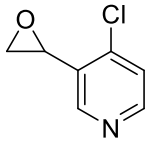
2,4-dichloro-5-(oxiran-2-yl)pyridine (1a)



1a

According to the General Procedure, the product **1a** was obtained as a light-yellow oil (42% yield in three steps) after silica gel chromatography (*n*-hexane/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.38 (s, 1H), 4.14 (ddd, J = 4.0 Hz, 2.4 Hz, 0.8 Hz, 1H), 3.25 (dd, J = 5.2 Hz, 4.0 Hz, 1H), 2.74 (dd, J = 5.2 Hz, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 147.4, 144.9, 130.8, 124.1, 50.5, 48.3; HRMS (ESI-TOF) calcd for $C_7H_6Cl_2NO$ $[M+H]^+$ (189.9826), found 189.9827.

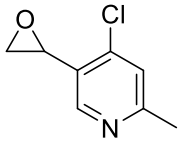
4-chloro-3-(oxiran-2-yl)pyridine (1b)



1b

According to the General Procedure, the product **1b** was obtained as a colorless oil (49% yield in three steps) after silica gel chromatography (*n*-hexane/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.47 (m, 2H), 7.32 (d, J = 5.2 Hz, 1H), 4.19-4.21 (m, 1H), 3.25 (dd, J = 5.6 Hz, 4.4 Hz, 1H), 2.77 (dd, J = 5.6 Hz, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.7, 143.3, 131.5, 124.0, 50.5, 48.7; HRMS (ESI-TOF) calcd for C_7H_7ClNO $[M+H]^+$ (156.0216), found 156.0214.

4-chloro-2-methyl-5-(oxiran-2-yl)pyridine (1c)

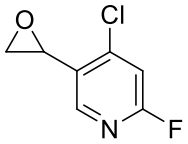


1c

According to the General Procedure, the product **1c** was obtained as a light-yellow oil

(68% yield in three steps) after silica gel chromatography (*n*-hexane/EtOAc = 20:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.30 (s, 1H), 4.06 (dd, *J* = 4.0 Hz, 2.4 Hz, 1H), 3.11 (dd, *J* = 5.6 Hz, 4.0 Hz, 1H), 2.67 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.4, 147.3, 145.4, 130.7, 125.0, 50.8, 49.3, 23.4; HRMS (ESI-TOF) calcd for C_8H_9ClNO $[M+H]^+$ (170.0373), found 170.0370.

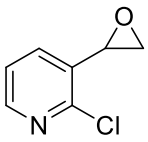
4-chloro-2-fluoro-5-(oxiran-2-yl)pyridine (1d)



1d

According to the General Procedure, the product **1d** was obtained as a light-yellow oil (50% yield in three steps) after silica gel chromatography (*n*-hexane/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 4.13-4.15 (m, 1H), 3.23 (dd, *J* = 5.6 Hz, 4.0 Hz, 1H), 2.75 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, *J* = 239.2 Hz), 146.7 (d, *J* = 10.5 Hz), 145.5 (d, *J* = 16.8 Hz), 129.6 (d, *J* = 5.3 Hz), 110.0 (d, *J* = 40.8 Hz), 50.4, 48.4; HRMS (ESI-TOF) calcd for C_7H_6ClFNO $[M+H]^+$ (174.0122), found 174.0120.

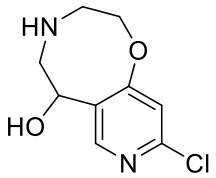
2-chloro-3-(oxiran-2-yl)pyridine (1e)



1e

According to the General Procedure, the product **1e** was obtained as a light-yellow oil (66% yield in three steps) after silica gel chromatography (*n*-hexane/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 4.8 Hz, 2.0 Hz, 1H), 7.59 (dd, *J* = 7.6 Hz, 2.0 Hz, 1H), 7.26 (dd, *J* = 7.6 Hz, 4.8 Hz, 1H), 4.17 (dd, *J* = 4.0 Hz, 2.8 Hz, 1H), 3.24 (dd, *J* = 5.6 Hz, 4.0 Hz, 1H), 2.67 (dd, *J* = 5.6 Hz, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 148.7, 134.7, 132.7, 122.8, 50.7, 49.2; HRMS (ESI-TOF) calcd for C_7H_7ClNO $[M+H]^+$ (156.0216), found 156.0214.

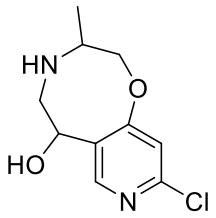
9-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3aa)



3aa

According to the General Procedure, the product **3aa** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 30.9 mg (72%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (s, 1H), 6.44 (s, 1H), 5.12 (dd, *J* = 8.0 Hz, 2.8 Hz, 1H), 3.77 (dd, *J* = 11.6 Hz, 7.6 Hz, 1H), 3.64 (t, *J* = 5.6 Hz, 2H), 3.45 (dd, *J* = 11.6 Hz, 2.8 Hz, 1H), 3.30 (td, *J* = 5.6 Hz, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.5, 152.9, 144.6, 128.6, 101.9, 68.6, 62.5, 60.3, 49.2; HRMS (ESI-TOF) calcd for $C_9H_{12}ClN_2O_2$ $[M+H]^+$ (215.0587), found 215.0588.

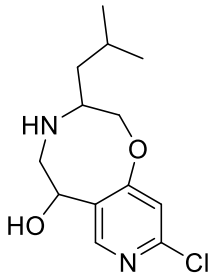
9-chloro-3-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ab)



3ab

According to the General Procedure, the product **3ab** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 32.0 mg (70%). d.r. = 1:1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 6.52 (s, 1H), 5.18 (dd, *J* = 7.6 Hz, 2.4 Hz, 1H), 3.82-3.90 (m, 1H), 3.76 (dd, *J* = 11.6 Hz, 7.6 Hz, 1H), 3.57-3.67 (m, 2H), 3.49 (dd, *J* = 11.6 Hz, 2.4 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.2, 152.9, 144.7, 128.5, 102.1, 68.2, 64.4, 56.6, 53.3, 13.5; HRMS (ESI-TOF) calcd for $C_{10}H_{14}ClN_2O_2$ $[M+H]^+$ (229.0744), found 229.0746.

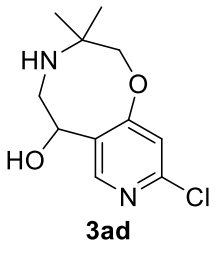
9-chloro-3-isobutyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ac)



3ac

According to the General Procedure, the product **3ac** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 33.0 mg (61%). d.r. = 1:1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (s, 0.47H), 7.72 (s, 0.47H), 6.42 (s, 0.5H), 6.41 (s, 0.5H), 5.08-5.13 (m, 1H), 3.61-3.73 (m, 2H), 3.47-3.57 (m, 2H), 3.38 (dd, *J* = 11.6 Hz, 2.8 Hz, 0.55H), 3.30 (dd, *J* = 11.6 Hz, 2.4 Hz, 0.51H), 1.34-1.60 (m, 2H), 1.14-1.24 (m, 1H), 0.82-0.87 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.9, 160.6, 152.89, 152.86, 144.8, 144.7, 128.2, 101.83, 101.75, 68.2, 68.0, 63.44, 63.41, 56.6, 56.4, 56.1, 55.7, 38.3, 38.1, 25.9, 25.6, 23.8, 23.6, 22.4, 22.2; HRMS (ESI-TOF) calcd for $C_{13}H_{20}ClN_2O_2$ $[M+H]^+$ (271.1213), found 271.1216.

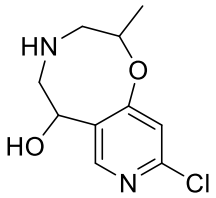
9-chloro-3,3-dimethyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ad)



3ad

According to the General Procedure, the product **3ad** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 20.4 mg (42%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (s, 1H), 6.61 (s, 1H), 4.96 (dd, *J* = 7.2 Hz, 2.4 Hz, 1H), 3.81 (dd, *J* = 11.6 Hz, 7.2 Hz, 1H), 3.55-3.63 (m, 3H), 1.30 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.6, 152.5, 144.7, 130.1, 104.9, 67.7, 67.4, 60.6, 59.3, 23.3, 23.2; HRMS (ESI-TOF) calcd for $C_{11}H_{16}ClN_2O_2$ $[M+H]^+$ (243.0900), found 243.0902.

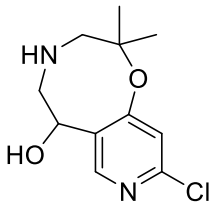
9-chloro-2-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ae)



3ae

According to the General Procedure, the product **3ae** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 29.7 mg (65%). d.r. = 1:1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (s, 1H), 6.43 (s, 1H), 5.11 (d, J = 6.4 Hz, 1H), 3.89-3.96 (m, 1H), 3.72-3.82 (m, 1H), 3.43-3.55 (m, 1H), 3.11-3.16 (m, 2H), 1.10 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.6, 153.0, 152.9, 144.7, 144.6, 128.44, 128.42, 102.0, 101.9, 68.6, 66.8, 66.7, 63.23, 63.20, 54.54, 54.49, 20.93, 20.87; HRMS (ESI-TOF) calcd for $C_{10}H_{14}ClN_2O_2$ $[M+H]^+$ (229.0744), found 229.0746.

9-chloro-2,2-dimethyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3af)

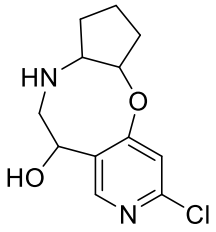


3af

According to the General Procedure, the product **3af** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 33.0 mg (68%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (s, 1H), 6.46 (s, 1H), 5.11 (dd, J = 7.2 Hz, 2.8 Hz, 1H), 3.81 (dd, J = 12.0 Hz, 7.2 Hz, 1H), 3.57 (dd, J = 12.0 Hz, 2.8 Hz, 1H), 3.14 (d, J = 14.8 Hz, 1H), 3.08 (d, J = 14.8 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.2, 152.9, 144.6, 128.3, 102.3, 73.4, 68.6, 65.0, 58.8, 27.50, 27.47; HRMS (ESI-TOF) calcd for $C_{11}H_{16}ClN_2O_2$ $[M+H]^+$ (243.0900), found 243.0902.

2-chloro-5,6,7,7a,8,9,10,10a-octahydrocyclopenta[*b*]pyrido[3,4-*g*][1,4]oxazocin-5-

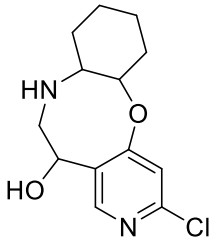
ol (3ag)



3ag

According to the General Procedure, the product **3ag** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 38.2 mg (75%). d.r. = 1:1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (s, 0.43H), 7.72 (s, 0.47H), 6.48 (s, 0.45H), 6.47 (s, 0.48H), 5.07-5.13 (m, 1H), 4.03-4.11 (m, 1H), 3.65-3.76 (m, 2H), 3.36-3.41 (m, 1H), 1.81-1.91 (m, 2H), 1.48-1.78 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.4, 160.3, 152.9, 152.8, 144.6, 144.5, 128.6, 102.4, 75.2, 74.9, 68.2, 68.1, 64.2, 64.1, 57.5, 57.4, 33.0, 32.7, 26.0, 25.5, 20.9, 20.8; HRMS (ESI-TOF) calcd for $C_{12}H_{16}ClN_2O_2$ $[M+H]^+$ (255.0900), found 255.0901.

2-chloro-6,7,7a,8,9,10,11,11a-octahydro-5*H*-benzo[*b*]pyrido[3,4-*g*][1,4]oxazocin-5-ol (3ah)

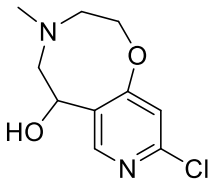


3ah

According to the General Procedure, the product **3ah** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 39.8 mg (74%). d.r. = 1.2:1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (s, 0.38H), 7.70 (s, 0.55H), 6.44 (s, 0.41H), 6.41 (s, 0.59H), 5.12 (dd, J = 7.6 Hz, 2.8 Hz, 0.6H), 5.06 (dd, J = 7.6 Hz, 2.0 Hz, 0.44H), 3.75 (dd, J = 11.2 Hz, 8.0 Hz, 0.6H), 3.67 (dd, J = 11.6 Hz, 7.6 Hz, 0.46H), 3.48-3.56 (m, 1H), 3.42 (dd, J = 11.6 Hz, 2.0 Hz, 0.45H), 3.37 (dd, J = 11.2 Hz, 3.2 Hz, 0.63H), 3.21-3.30 (m, 1H), 1.94-1.97 (m, 1H), 1.66-1.68 (m, 3H), 1.38-1.49 (m, 1H), 1.19-1.37 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.39, 160.38, 152.9, 152.7,

144.7, 144.5, 128.34, 128.32, 102.2, 102.1, 71.34, 71.31, 68.3, 68.1, 61.5, 61.3, 56.81, 56.78, 35.7, 35.3, 29.4, 28.8, 25.9, 25.49, 25.42; HRMS (ESI-TOF) calcd for $C_{13}H_{18}ClN_2O_2$ $[M+H]^+$ (269.1057), found 269.1056.

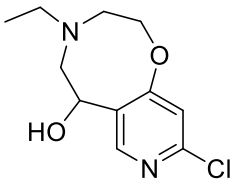
9-chloro-4-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ai)



3ai

According to the General Procedure, the product **3ai** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 32.0 mg (70%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 7.00 (s, 1H), 5.10 (dd, *J* = 9.6 Hz, 4.8 Hz, 1H), 4.30 (ddd, *J* = 12.4 Hz, 6.8 Hz, 3.2 Hz, 1H), 3.94 (ddd, *J* = 12.4 Hz, 6.8 Hz, 3.2 Hz, 1H), 2.99 (dd, *J* = 12.4 Hz, 4.8 Hz, 1H), 2.75 (ddd, *J* = 15.2 Hz, 6.8 Hz, 2.8 Hz, 1H), 2.51-2.57 (m, 1H), 2.42 (dd, *J* = 12.4 Hz, 9.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.1, 151.7, 148.5, 134.9, 118.1, 75.3, 67.0, 66.8, 57.0, 45.6; HRMS (ESI-TOF) calcd for $C_{10}H_{14}ClN_2O_2$ $[M+H]^+$ (229.0744), found 229.0745.

9-chloro-4-ethyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3aj)

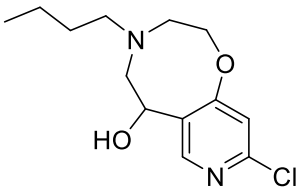


3aj

According to the General Procedure, the product **3aj** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 38.3 mg (79%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.00 (s, 1H), 5.06 (dd, *J* = 9.6 Hz, 5.2 Hz, 1H), 4.25 (ddd, *J* = 12.0 Hz, 5.6 Hz, 3.2 Hz, 1H), 3.81-3.86 (m, 1H), 3.03 (dd, *J* = 12.0 Hz, 5.2 Hz, 1H), 2.77 (ddd, *J* = 15.2 Hz, 7.6 Hz, 2.8 Hz, 1H), 2.59 (ddd, *J* = 15.2 Hz, 5.6 Hz, 2.8 Hz, 1H), 2.49 (q, *J* = 7.2 Hz, 2H), 2.37 (dd, *J* = 12.0 Hz, 9.6 Hz, 1H),

0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.7, 151.6, 148.0, 135.8, 118.2, 76.9, 67.5, 64.5, 55.0, 52.4, 12.7; HRMS (ESI-TOF) calcd for $C_{11}H_{16}ClN_2O_2$ $[M+H]^+$ (243.0900), found 243.0904.

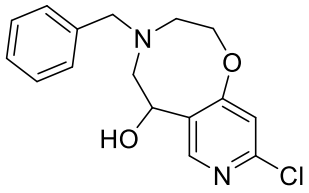
4-butyl-9-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ak)



3ak

According to the General Procedure, the product **3ak** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 43.9 mg (81%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 7.30 (s, 1H), 5.39 (dd, J = 9.6 Hz, 5.2 Hz, 1H), 4.53-4.57 (m, 1H), 4.12-4.17 (m, 1H), 3.29-3.33 (m, 1H), 3.10-3.16 (m, 1H), 2.90-2.94 (m, 1H), 2.61-2.78 (m, 3H), 1.45-1.51 (m, 2H), 1.22-1.31 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.0, 151.6, 147.7, 135.7, 118.0, 76.8, 67.7, 64.6, 58.2, 56.5, 30.8, 20.9, 14.1; HRMS (ESI-TOF) calcd for $C_{13}H_{20}ClN_2O_2$ $[M+H]^+$ (271.1213), found 271.1214.

4-benzyl-9-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3al)

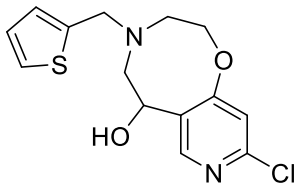


3al

According to the General Procedure, the product **3al** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 41.4 mg (68%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.33 (s, 1H), 7.09-7.14 (m, 5H), 4.96 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.48-3.59 (m, 3H), 2.72-2.78 (m, 2H), 2.58-2.65 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.2, 150.4, 145.0, 140.2, 137.4, 130.1, 129.3, 128.1, 125.2, 68.6, 61.2, 61.0, 60.9, 58.1; HRMS (ESI-TOF)

calcd for $C_{16}H_{18}ClN_2O_2$ $[M+H]^+$ (305.1057), found 305.1051.

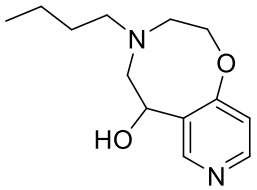
9-chloro-4-(thiophen-2-ylmethyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3am)



3am

According to the General Procedure, the product **3am** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 33.6 mg (54%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 7.39 (s, 1H), 7.16 (dd, J = 4.4 Hz, 2.0 Hz, 1H), 6.80-6.82 (m, 2H), 5.03 (dd, J = 8.0 Hz, 3.6 Hz, 1H), 3.84-3.92 (m, 2H), 3.46-3.56 (m, 2H), 2.80 (dd, J = 13.6 Hz, 3.6 Hz, 1H), 2.69-2.76 (m, 1H), 2.60-2.65 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.3, 150.5, 145.1, 142.8, 137.4, 127.6, 127.4, 126.1, 125.2, 68.6, 61.0, 60.8, 57.4, 54.8; HRMS (ESI-TOF) calcd for $C_{14}H_{16}ClN_2O_2S$ $[M+H]^+$ (311.0621), found 311.0617.

4-butyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bk)

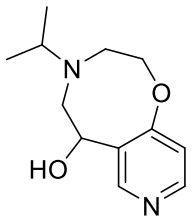


3bk

According to the General Procedure, the product **3bk** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 39.7 mg (84%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.64 (s, 1H), 8.28 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 5.2 Hz, 1H), 5.07 (dd, J = 8.8 Hz, 3.2 Hz, 1H), 3.48-3.58 (m, 2H), 2.70-2.77 (m, 2H), 2.46-2.62 (m, 4H), 1.33-1.41 (m, 2H), 1.14-1.27 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 150.1, 149.8, 143.6, 138.3, 125.8, 68.3, 61.8, 60.6, 57.8, 56.1, 30.0, 21.5, 14.4; HRMS (ESI-TOF) calcd for $C_{13}H_{21}N_2O_2$ $[M+H]^+$ (237.1603), found

237.1602.

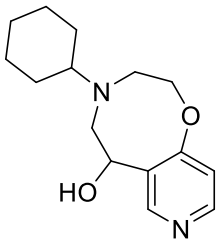
4-isopropyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bq)



3bq

According to the General Procedure, the product **3bq** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 29.3 mg (66%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.64 (s, 1H), 8.29 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 5.2 Hz, 1H), 5.00 (dd, J = 8.8 Hz, 3.2 Hz, 1H), 3.43-3.55 (m, 2H), 2.88-2.99 (m, 1H), 2.46-2.77 (m, 4H), 0.95 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 150.2, 149.8, 143.7, 138.3, 125.8, 68.9, 61.6, 58.1, 53.5, 19.3, 17.3; HRMS (ESI-TOF) calcd for $C_{12}H_{19}N_2O_2$ $[M+H]^+$ (223.1447), found 223.1443.

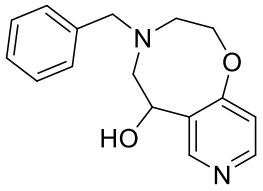
4-cyclohexyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3br)



3br

According to the General Procedure, the product **3br** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 180:1), 26.2 mg (50%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (s, 1H), 8.28 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 5.2 Hz, 1H), 4.98 (dd, J = 8.4 Hz, 3.2 Hz, 1H), 3.41-3.54 (m, 2H), 2.81 (dd, J = 13.6 Hz, 3.2 Hz, 1H), 2.59-2.71 (m, 2H), 2.49-2.56 (m, 1H), 2.35-2.46 (m, 1H), 1.64-1.73 (m, 4H), 0.97-1.22 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 150.2, 149.7, 143.7, 138.4, 125.7, 69.1, 62.6, 61.9, 58.6, 54.1, 30.8, 29.3, 27.3; HRMS (ESI-TOF) calcd for $C_{15}H_{23}N_2O_2$ $[M+H]^+$ (263.1760), found 263.1756.

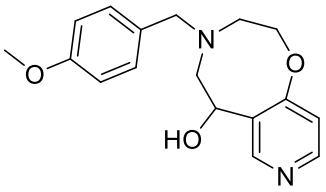
4-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bl)



3bl

According to the General Procedure, the product **3bl** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 43.3 mg (80%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.24 (d, J = 5.2 Hz, 1H), 7.30 (d, J = 5.6 Hz, 1H), 7.09-7.20 (m, 5H), 5.05 (dd, J = 8.4 Hz, 3.6 Hz, 1H), 3.74 (d, J = 13.6 Hz, 1H), 3.61 (d, J = 13.6 Hz, 1H), 3.47-3.58 (m, 2H), 2.72-2.79 (m, 2H), 2.59-2.66 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 150.2, 149.6, 143.7, 140.2, 138.4, 130.2, 129.3, 128.2, 125.8, 68.7, 61.5, 60.9, 57.9; HRMS (ESI-TOF) calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ (271.1447), found 271.1442.

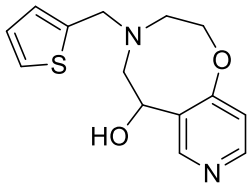
4-(4-methoxybenzyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bs)



3bs

According to the General Procedure, the product **3bs** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 48.7 mg (81%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.24 (d, J = 5.2 Hz, 1H), 7.30 (d, J = 5.2 Hz, 1H), 7.07-7.11 (m, 2H), 6.70-6.74 (m, 2H), 5.02 (dd, J = 8.0 Hz, 3.6 Hz, 1H), 3.63-3.69 (m, 1H), 3.66 (s, 3H), 3.46-3.57 (m, 3H), 2.69-2.76 (m, 2H), 2.57-2.62 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.3, 150.2, 149.6, 143.7, 138.5, 132.0, 131.3, 125.8, 114.7, 68.7, 61.3, 60.9, 60.2, 57.7, 55.7; HRMS (ESI-TOF) calcd for $C_{17}H_{21}N_2O_3$ $[M+H]^+$ (301.1552), found 301.1548.

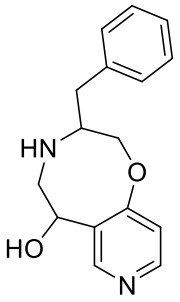
4-(thiophen-2-ylmethyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bm)



3bm

According to the General Procedure, the product **3bm** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 33.2 mg (60%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.26 (d, J = 5.2 Hz, 1H), 7.34 (d, J = 5.2 Hz, 1H), 7.17 (dd, J = 4.8 Hz, 0.8 Hz, 1H), 6.81-6.83 (m, 2H), 5.09 (dd, J = 8.4 Hz, 3.6 Hz, 1H), 3.90 (dd, J = 18.0 Hz, 14.8 Hz, 2H), 3.46-3.56 (m, 2H), 2.80 (dd, J = 13.6 Hz, 3.6 Hz, 1H), 2.69-2.75 (m, 1H), 2.58-2.65 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 150.3, 149.7, 143.7, 142.7, 138.4, 127.7, 127.4, 126.2, 125.8, 68.8, 61.0, 57.2, 54.7; HRMS (ESI-TOF) calcd for $C_{14}H_{17}N_2O_2S$ $[M+H]^+$ (277.1011), found 277.1007.

3-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bt)

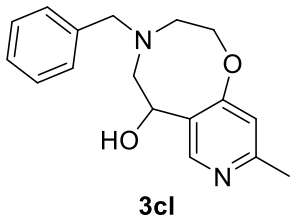


3bt

According to the General Procedure, the product **3bt** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 120:1), 35.7 mg (66%), d.r. = 1:1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.28 (d, J = 5.6 Hz, 1H), 7.36 (d, J = 5.6 Hz, 1H), 7.15-7.19 (m, 2H), 7.06-7.11 (m, 3H), 5.02-5.09 (m, 1H), 3.41-3.47 (m, 1H), 3.28-3.36 (m, 1H), 2.78-2.93 (m, 2H), 2.56-2.70 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 145.0, 149.90, 149.87, 143.64, 143.57, 140.1, 140.0, 138.6, 138.5, 130.3, 129.6, 129.5, 127.40, 127.38, 125.9, 69.1, 68.7, 64.2, 63.9, 62.3, 61.8, 53.9, 53.5, 38.7,

38.5; HRMS (ESI-TOF) calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ (271.1447), found 271.1443.

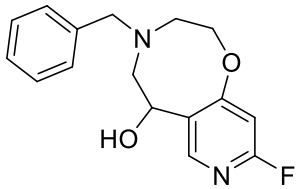
4-benzyl-9-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3cl)



3cl

According to the General Procedure, the product **3cl** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 44.9 mg (79%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 7.35-7.47 (m, 6H), 5.27 (dd, J = 8.4 Hz, 3.6 Hz, 1H), 3.99 (d, J = 13.6 Hz, 1H), 3.85 (d, J = 13.6 Hz, 1H), 3.74-3.85 (m, 2H), 2.98-3.04 (m, 2H), 2.84-2.90 (m, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.3, 149.3, 143.8, 140.2, 135.3, 130.1, 129.3, 128.1, 125.0, 68.5, 61.6, 60.90, 60.86, 57.9, 23.2; HRMS (ESI-TOF) calcd for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ (285.1603), found 285.1599.

4-benzyl-9-fluoro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3dl)

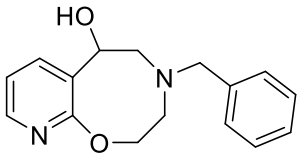


3dl

According to the General Procedure, the product **3dl** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 46.1 mg (80%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 7.08-7.19 (m, 5H), 7.01 (d, J = 2.4 Hz, 1H), 4.97 (dd, J = 8.0 Hz, 3.6 Hz, 1H), 3.70 (d, J = 13.6 Hz, 1H), 3.59 (d, J = 13.6 Hz, 1H), 3.47-3.59 (m, 2H), 2.71-2.78 (m, 2H), 2.58-2.64 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.1 (d, J = 237.4 Hz), 148.2 (d, J = 16.1 Hz), 146.7 (d, J = 10.8 Hz), 140.3, 136.1 (d, J = 5.1 Hz), 130.2, 129.3, 128.1, 110.9 (d, J = 40.5 Hz), 68.5, 61.5, 61.0, 60.9, 58.1; HRMS (ESI-TOF) calcd for $C_{16}H_{18}FN_2O_2$ $[M+H]^+$ (289.1352),

found 289.1347.

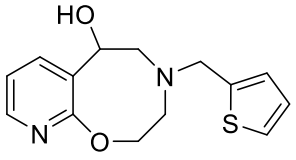
4-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-6-ol (3el)



3el

According to the General Procedure, the product **3el** was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 44.9 mg (83%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (dd, J = 4.8 Hz, 2.0 Hz, 1H), 7.86-7.88 (m, 1H), 7.25 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 7.08-7.21 (m, 5H), 4.96 (dd, J = 8.4 Hz, 3.2 Hz, 1H), 3.73 (d, J = 13.6 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 3.46-3.57 (m, 2H), 2.70-2.77 (m, 2H), 2.50-2.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 149.6, 149.1, 140.3, 139.2, 138.7, 130.1, 129.3, 128.1, 124.5, 69.3, 61.5, 60.9, 60.8, 57.7; HRMS (ESI-TOF) calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ (271.1447), found 271.1442.

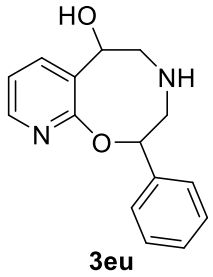
4-(thiophen-2-ylmethyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-6-ol (3em)



3em

According to the General Procedure, the product **3em** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 150:1), 33.7 mg (61%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (dd, J = 4.8 Hz, 2.0 Hz, 1H), 7.93-7.96 (m, 1H), 7.30 (dd, J = 7.6 Hz, 4.8 Hz, 1H), 7.17 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 6.82-6.85 (m, 2H), 5.01 (dd, J = 8.4 Hz, 3.2 Hz, 1H), 3.87-3.95 (m, 2H), 3.48-3.64 (m, 2H), 2.71-2.81 (m, 2H), 2.52-2.64 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 149.6, 149.2, 142.7, 139.2, 138.8, 127.7, 127.4, 126.1, 124.5, 69.4, 61.0, 60.9, 57.1, 54.6; HRMS (ESI-TOF) calcd for $C_{14}H_{17}N_2O_2S$ $[M+H]^+$ (277.1011), found 277.1009.

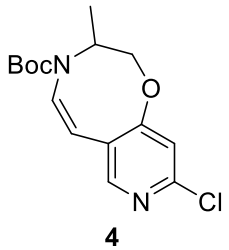
2-phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-6-ol (3eu)



3eu

According to the General Procedure, the product **3eu** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 200:1), 31.8 mg (62%), d.r. = 1:1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.74-7.75 (m, 1H), 7.33-7.40 (m, 3H), 7.22-7.25 (m, 2H), 7.14-7.17 (m, 1H), 6.44-6.47 (m, 1H), 4.98-5.01 (m, 1H), 4.84-4.89 (m, 1H), 3.40-3.66 (m, 3H), 3.24-3.37 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.0, 162.9, 148.1, 144.2, 144.1, 134.34, 134.25, 129.3, 128.6, 127.3, 126.4, 113.49, 113.46,73.6, 73.5, 68.9, 68.8, 60.90, 60.85, 54.45, 54.43; HRMS (ESI-TOF) calcd for $C_{15}H_{17}N_2O_2$ $[M+H]^+$ (257.1290), found 257.1288.

***tert*-butyl (*Z*)-9-chloro-3-methyl-2,3-dihydro-4*H*-pyrido[3,4-*g*][1,4]oxazocine-4-carboxylate (4)**

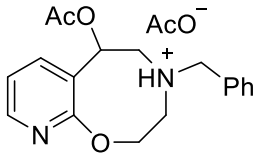


4

The product **4** was obtained as a yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 400:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.55 (s, 1H), 7.53 (d, J = 3.2 Hz, 1H), 6.70 (d, J = 3.2 Hz, 1H), 4.88-4.95 (m, 1H), 4.28-4.38 (m, 2H), 1.58 (d, J = 7.2 Hz, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 154.4, 143.7, 143.1, 143.0, 129.0, 126.4, 106.3, 103.1, 83.2, 70.2, 52.2, 27.8, 16.7; HRMS (ESI-TOF) calcd for $C_{15}H_{20}ClN_2O_3$ $[M+H]^+$ (311.1162), found 311.1158.

6-acetoxy-4-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-4-ium

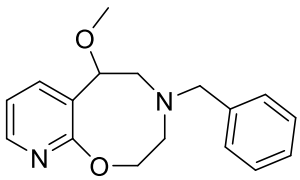
acetate (5)



5

The product **5** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 300:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 4.8 Hz, 2.0 Hz, 1H), 7.58 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 7.12-7.23 (m, 6H), 6.17 (dd, J = 7.2 Hz, 4.8 Hz, 1H), 4.00-4.10 (m, 2H), 3.76 (d, J = 13.6 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 2.71-2.87 (m, 4H), 2.05 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.7, 149.3, 148.9, 138.8, 136.5, 133.7, 128.8, 128.3, 127.2, 122.7, 70.6, 62.5, 59.5, 58.0, 52.7, 21.1, 21.0; HRMS (ESI-TOF) calcd for $C_{18}H_{21}N_2O_3$ $[M\text{-}AcO]^+$ (313.1547), found 313.1556.

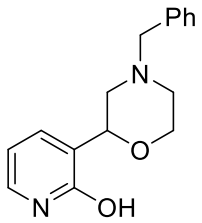
4-benzyl-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocine (6)



6

The product **6** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 300:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (dd, J = 4.8 Hz, 2.0 Hz, 1H), 7.85 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 7.25 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 7.08-7.19 (m, 5H), 4.93 (dd, J = 8.4 Hz, 4.0 Hz, 1H), 3.71 (d, J = 13.6 Hz, 1H), 3.59 (d, J = 13.6 Hz, 1H), 3.32-3.42 (m, 2H), 3.20 (s, 3H), 2.74-2.80 (m, 2H), 2.60-2.67 (m, 1H), 2.52 (dd, J = 13.2 Hz, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 149.7, 149.1, 140.4, 139.2, 138.7, 130.1, 129.3, 128.1, 124.4, 72.1, 69.2, 61.5, 60.8, 58.9, 55.0; HRMS (ESI-TOF) calcd for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ (285.1603), found 285.1606.

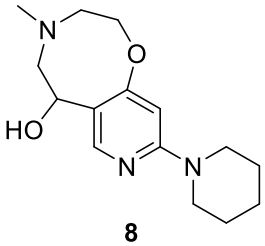
3-(4-benzylmorpholin-2-yl)pyridin-2-ol (7)



7

The product **7** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 300:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (dd, *J* = 4.8 Hz, 2.0 Hz, 1H), 7.86 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.28 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 7.12-7.24 (m, 5H), 4.74 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 3.91 (ddd, *J* = 11.6 Hz, 3.6 Hz, 1.2 Hz, 1H), 3.71 (td, *J* = 11.6 Hz, 2.4 Hz, 1H), 3.45 (s, 2H), 3.00 (dt, *J* = 11.6 Hz, 2.0 Hz, 1H), 2.65-2.68 (m, 1H), 2.18 (td, *J* = 11.6 Hz, 3.6 Hz, 1H), 1.76 (dd, *J* = 11.6 Hz, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 149.6, 149.4, 138.7, 138.1, 136.4, 130.5, 129.4, 128.5, 124.5, 75.4, 68.0, 63.9, 59.1, 53.7; HRMS (ESI-TOF) calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ (271.1447), found 271.1448.

4-methyl-9-(piperidin-1-yl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (8)



8

The product **8** was obtained as a light-yellow oil after silica gel chromatography (CH_2Cl_2/MeOH = 300:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.30 (s, 1H), 4.62 (dd, *J* = 6.4 Hz, 1.2 Hz, 1H), 4.21 (dt, *J* = 11.6 Hz, 6.8 Hz, 1H), 3.99 (dt, *J* = 11.6 Hz, 2.8 Hz, 1H), 3.49 (t, *J* = 4.8 Hz, 4H), 3.07 (dd, *J* = 12.8 Hz, 6.4 Hz, 1H), 2.80 (dd, *J* = 12.8 Hz, 1.6 Hz, 1H), 2.60 (dd, *J* = 6.8 Hz, 2.8 Hz, 2H), 2.56 (s, 3H), 1.78-2.16 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 161.6, 148.3, 122.3, 100.3, 74.7, 69.5, 64.9, 55.6, 47.3, 46.5, 25.6, 24.8; HRMS (ESI-TOF) calcd for $C_{15}H_{24}N_3O_2$ $[M+H]^+$ (278.1869), found 278.1866.

4. References

[1] Bradley, P. A.; Carroll, R. J.; Lecouturier, Y. C.; Moore, R.; Noeureuil, P.; Patel, B.; Snow, J.; Wheeler, S. *Org. Process Res. Dev*. **2010**, *14*, 1326.

[2] Perrone, M. G.; Santandrea, E.; Giorgio, E.; Bleve, L.; Scilimati, A.; Tortorella, P. *Bioorg. Med. Chem*. **2006**, *14*, 1207.

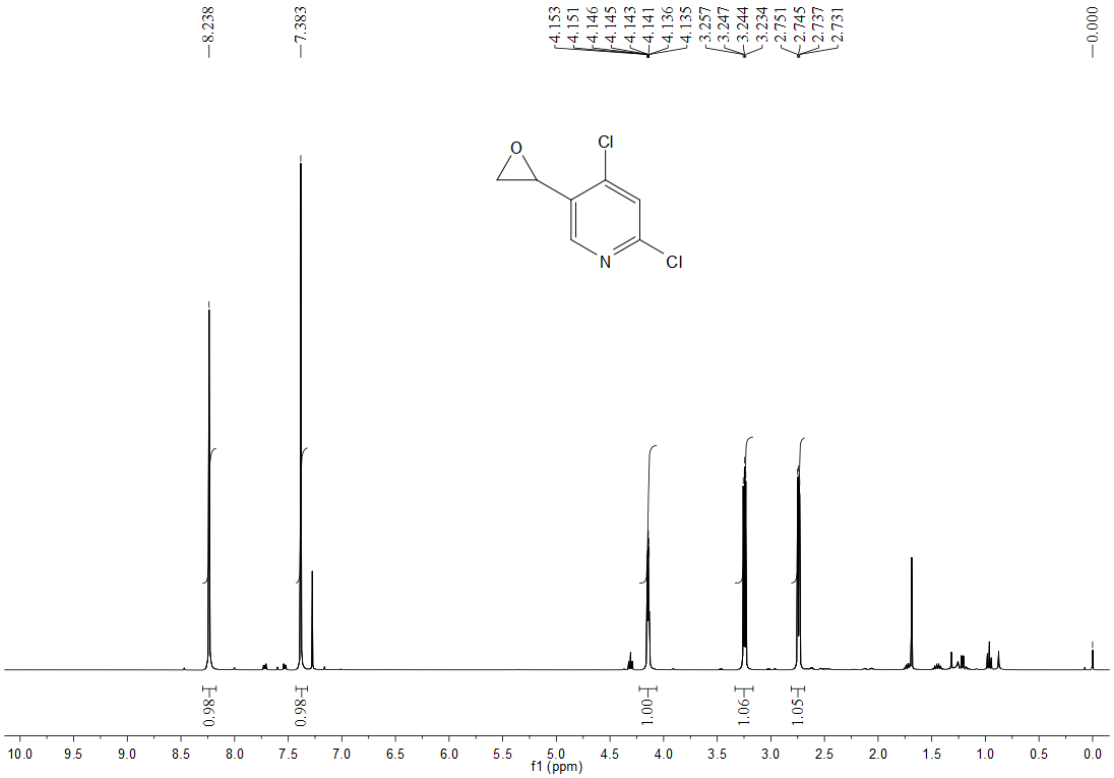
[3] Gärtner, D.; Stein, A. L.; Grupe, S.; Arp, J.; von Wangelin, A. J. *Angew. Chem. Int. Ed*. **2015**, *54*, 10545.

[4] Sano, T.; Toda, J.; Maehara, N. *Can. J. Chem.* **1987**, *65*, 94.

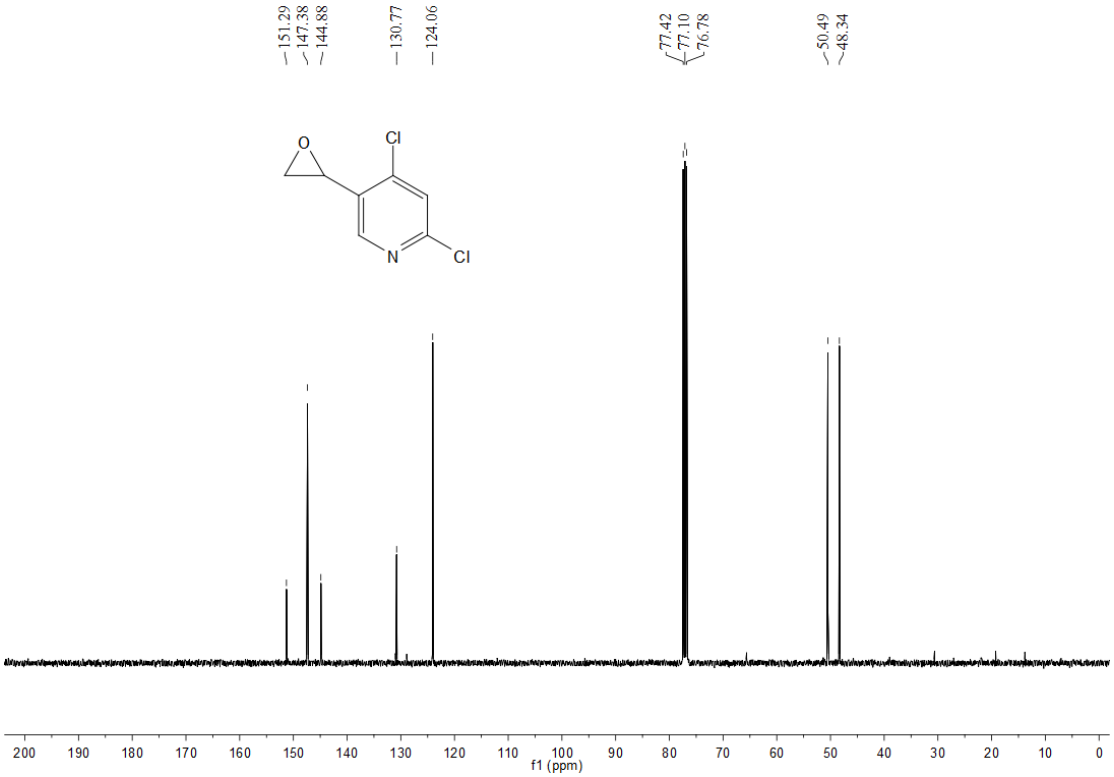
[5] Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244.

5. Copies of NMR Spectra

2,4-dichloro-5-(oxiran-2-yl)pyridine (1a)

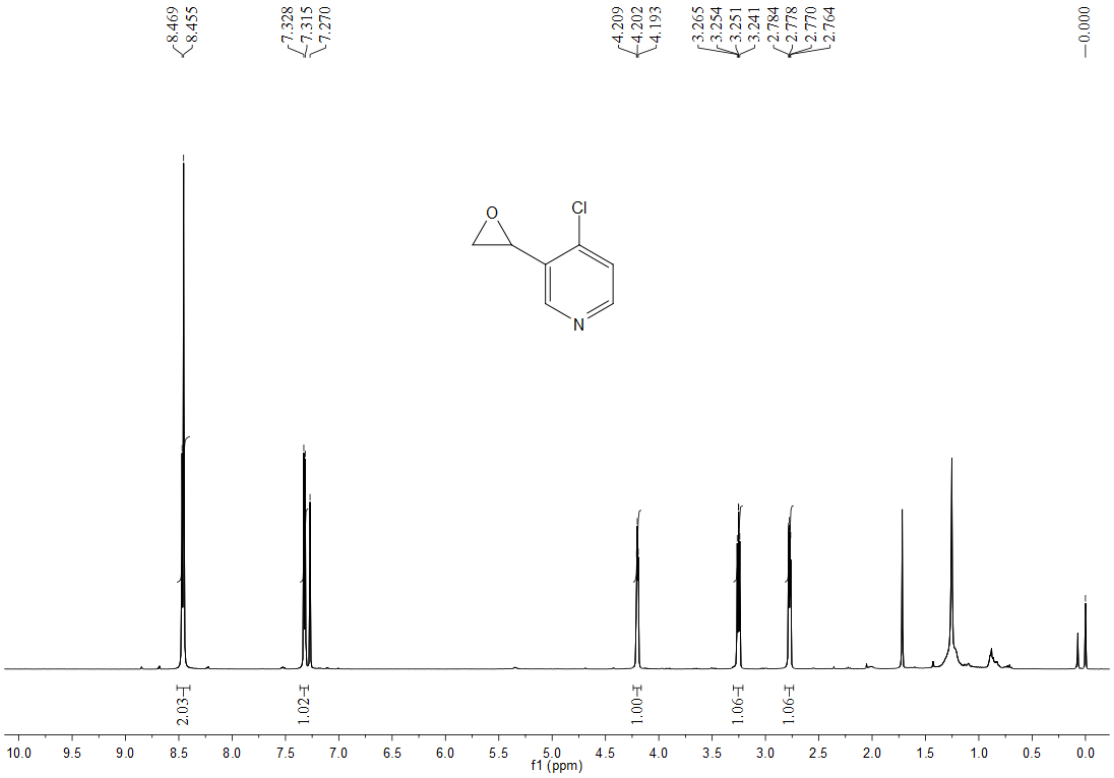


^{1}H NMR (400 MHz, $CDCl_3$) of **1a**

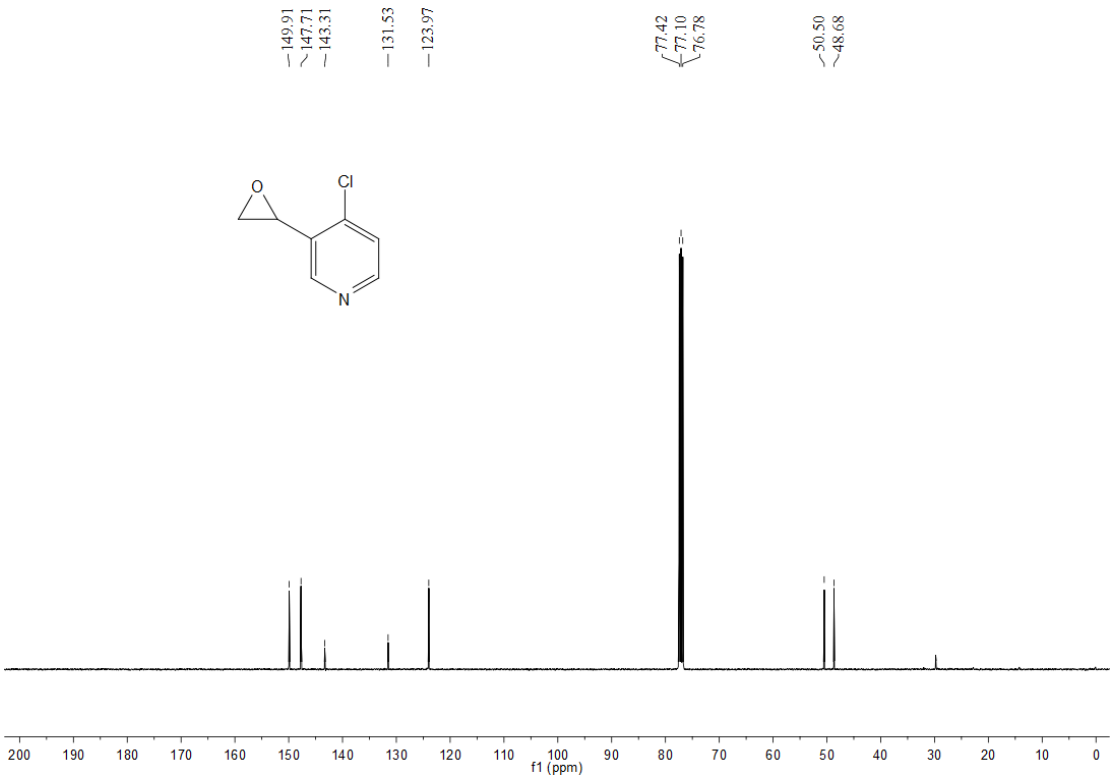


^{13}C NMR (100 MHz, $CDCl_3$) of **1a**

4-chloro-3-(oxiran-2-yl)pyridine (1b)

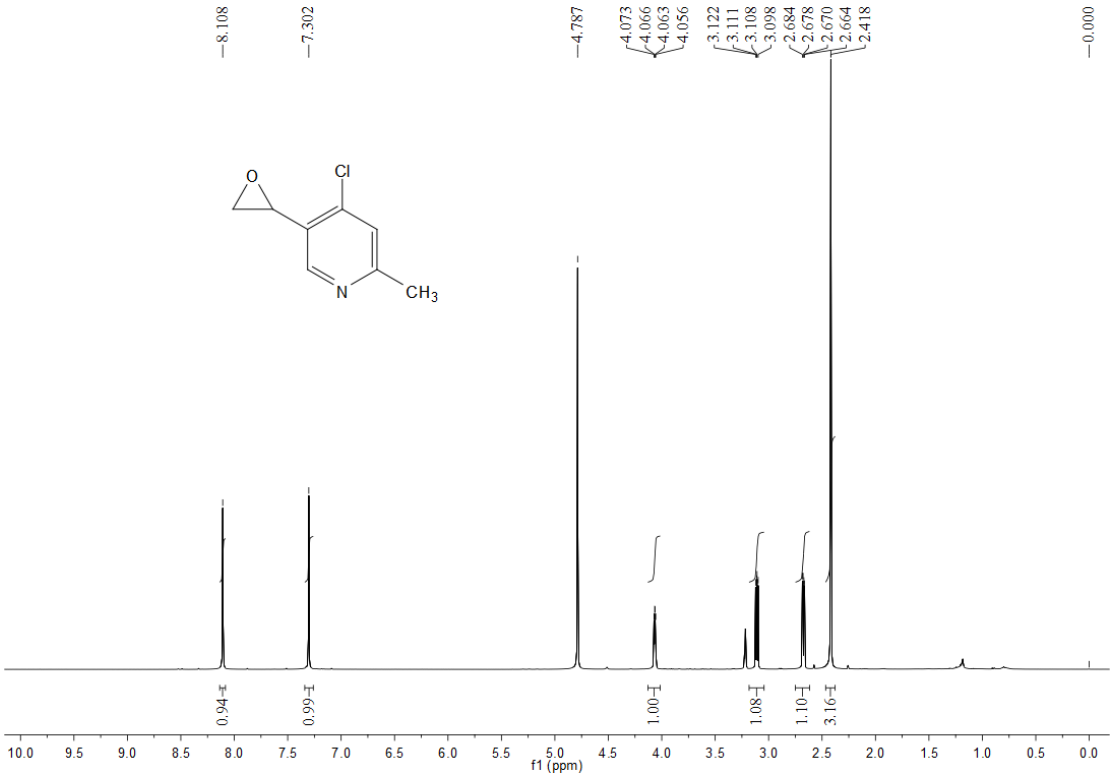


^{1}H NMR (400 MHz, $CDCl_3$) of **1b**

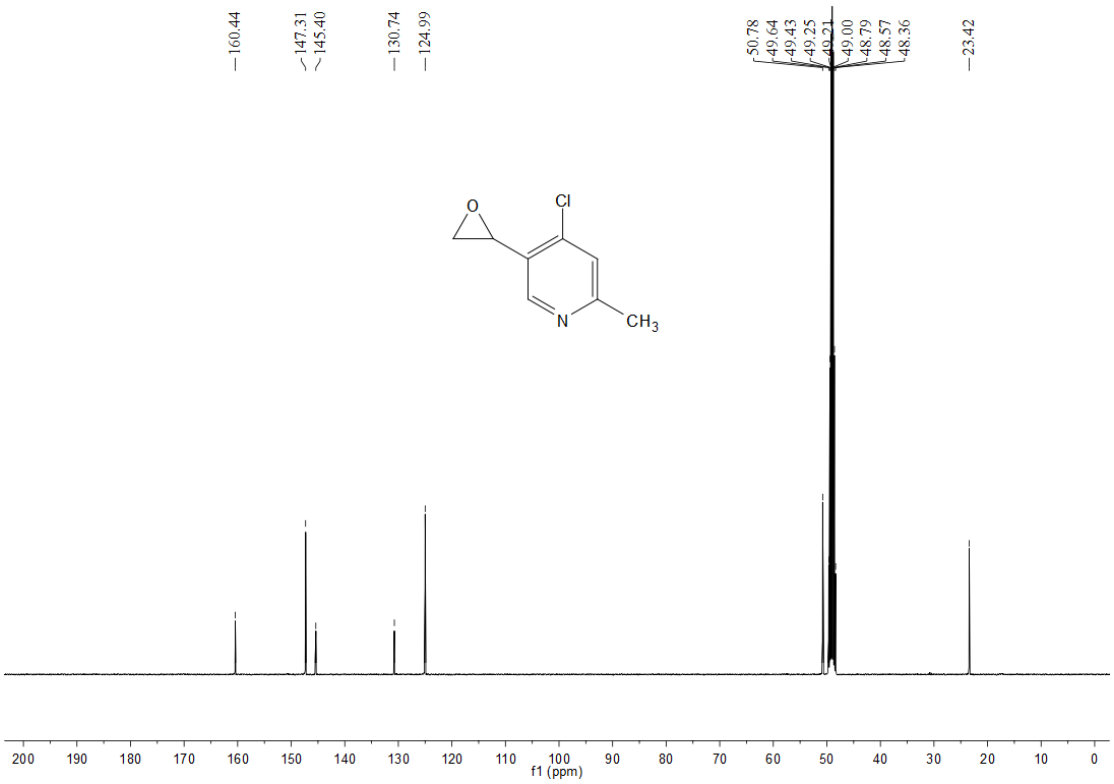


^{13}C NMR (100 MHz, $CDCl_3$) of **1b**

4-chloro-2-methyl-5-(oxiran-2-yl)pyridine (1c)

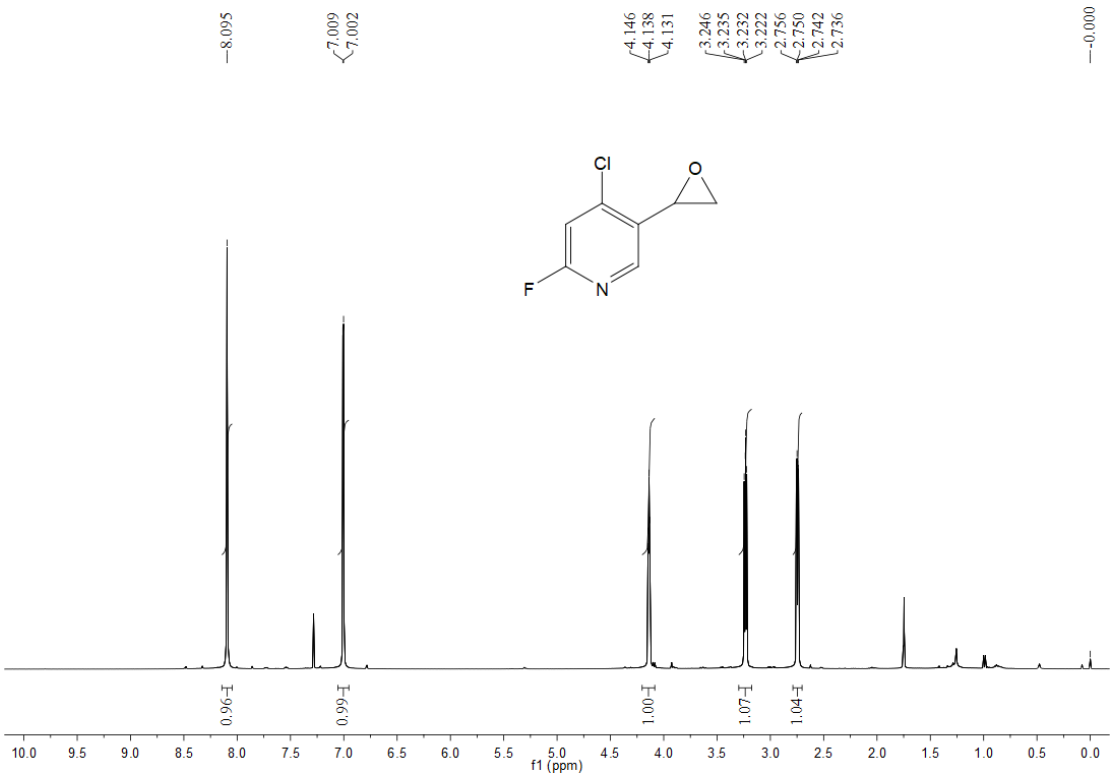


^{1}H NMR (400 MHz, CD_3OD) of **1c**

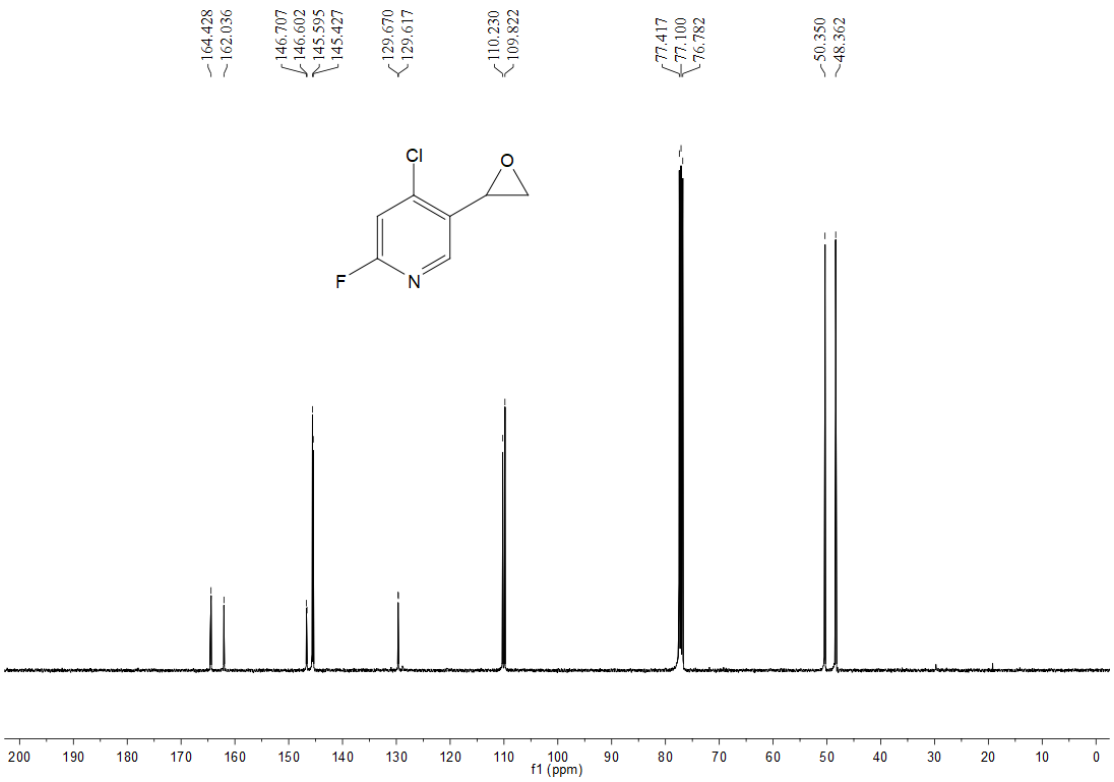


^{13}C NMR (100 MHz, CD_3OD) of **1c**

4-chloro-2-fluoro-5-(oxiran-2-yl)pyridine (1d)

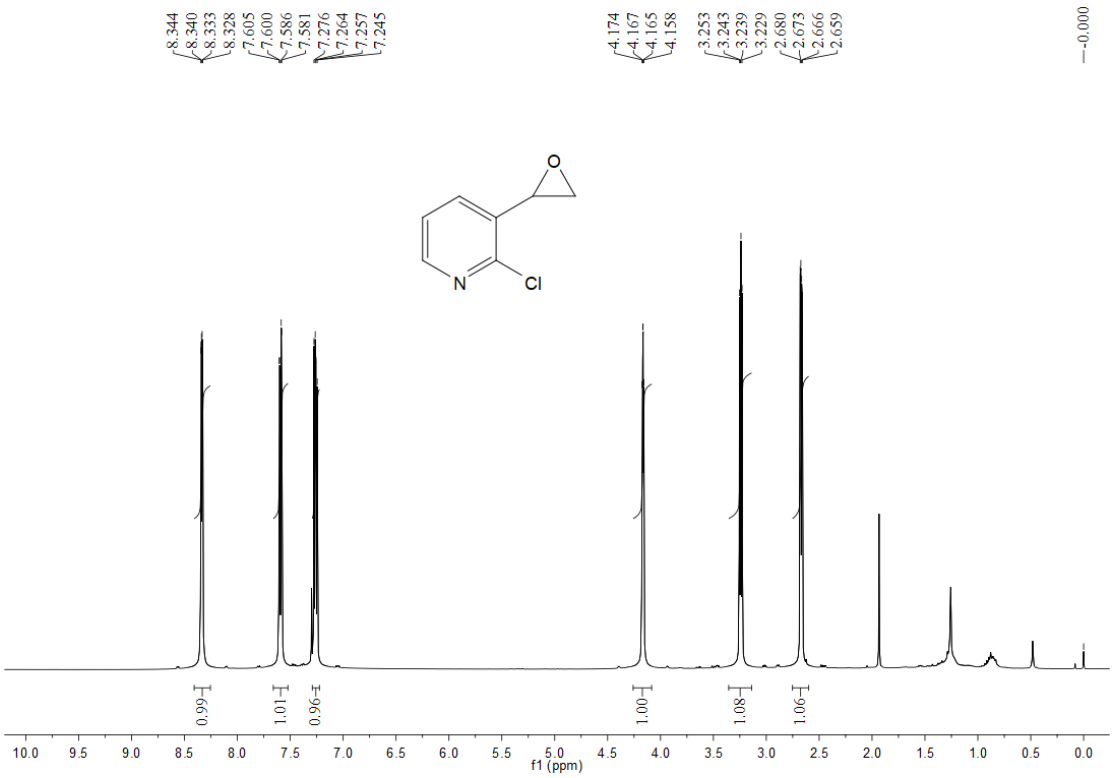


^{1}H NMR (400 MHz, $CDCl_3$) of **1d**

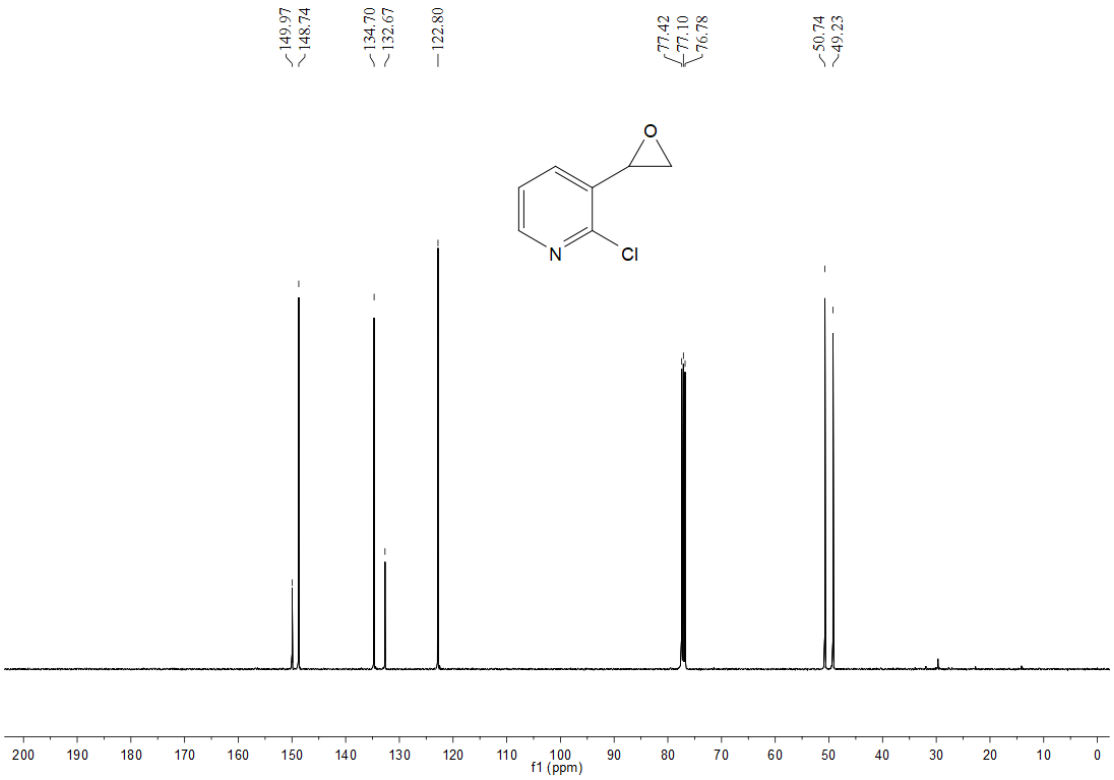


^{13}C NMR (100 MHz, $CDCl_3$) of **1d**

2-chloro-3-(oxiran-2-yl)pyridine (1e)

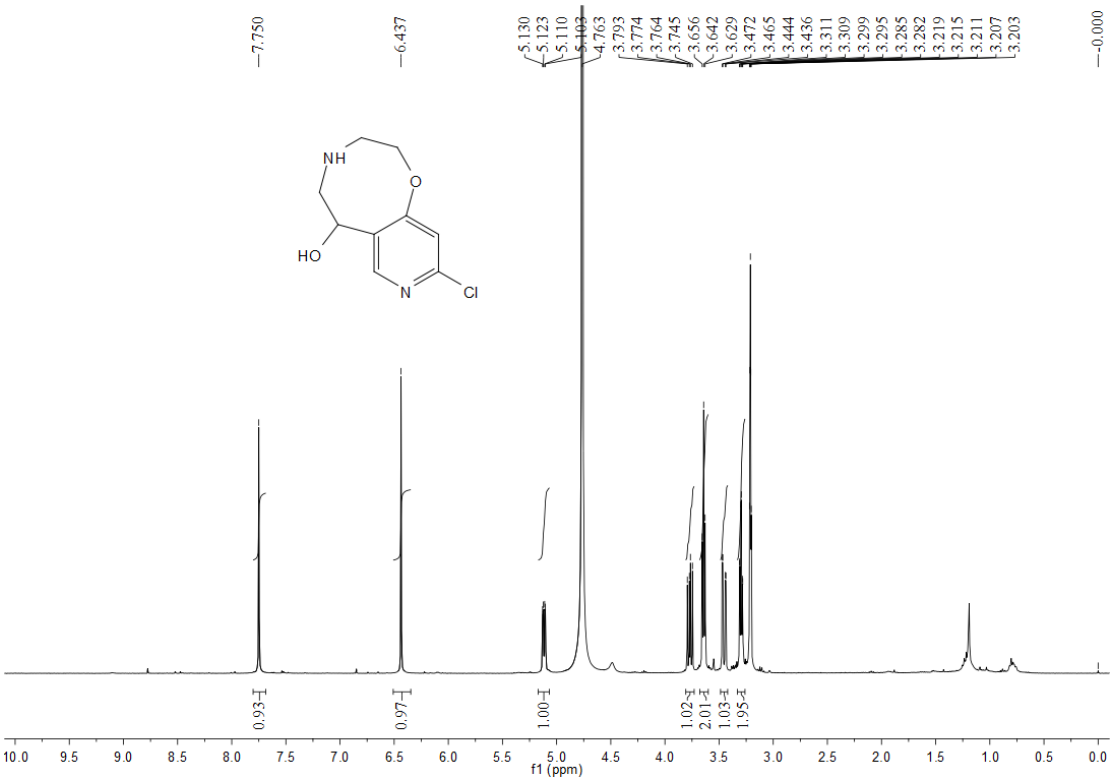


^{1}H NMR (400 MHz, $CDCl_3$) of **1e**

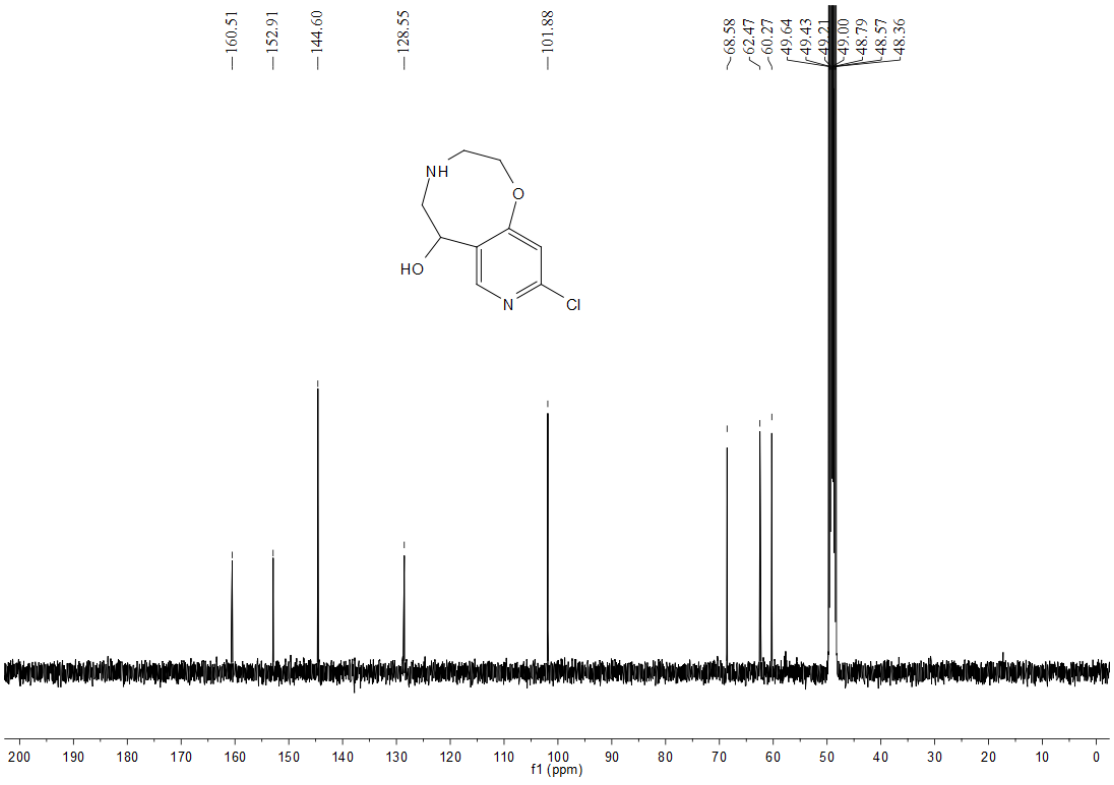


^{13}C NMR (100 MHz, $CDCl_3$) of **1e**

9-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3aa)

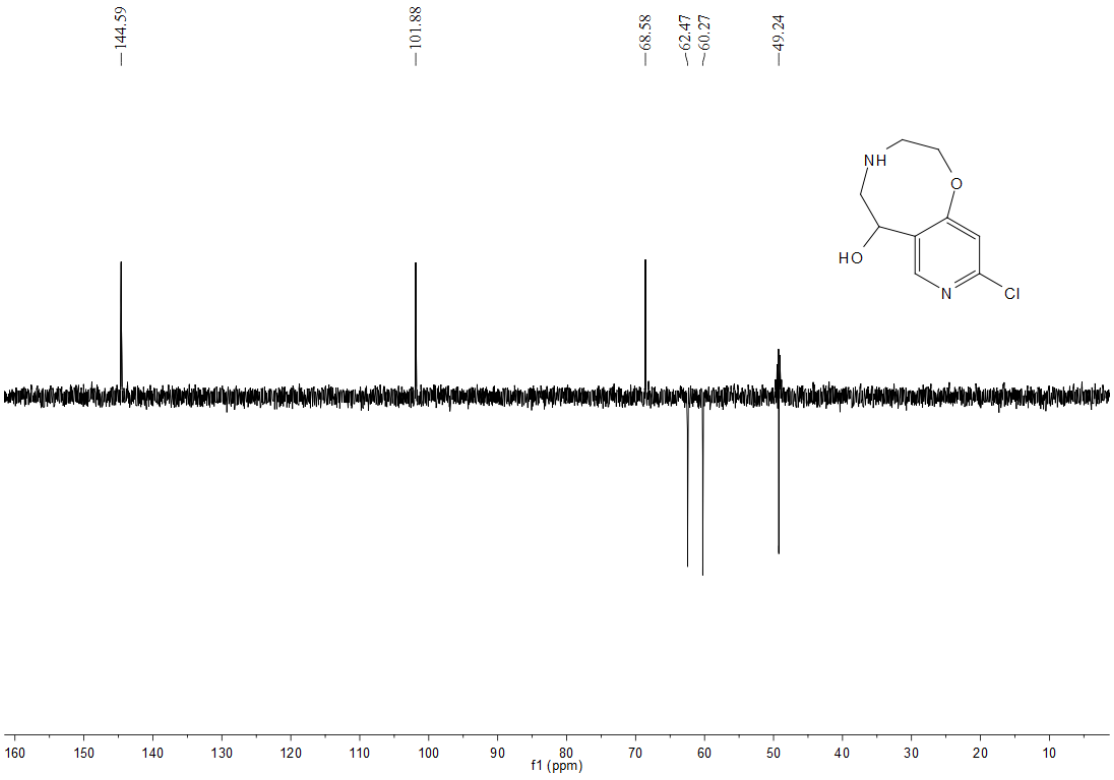


^{1}H NMR (400 MHz, CD_3OD) of **3aa**



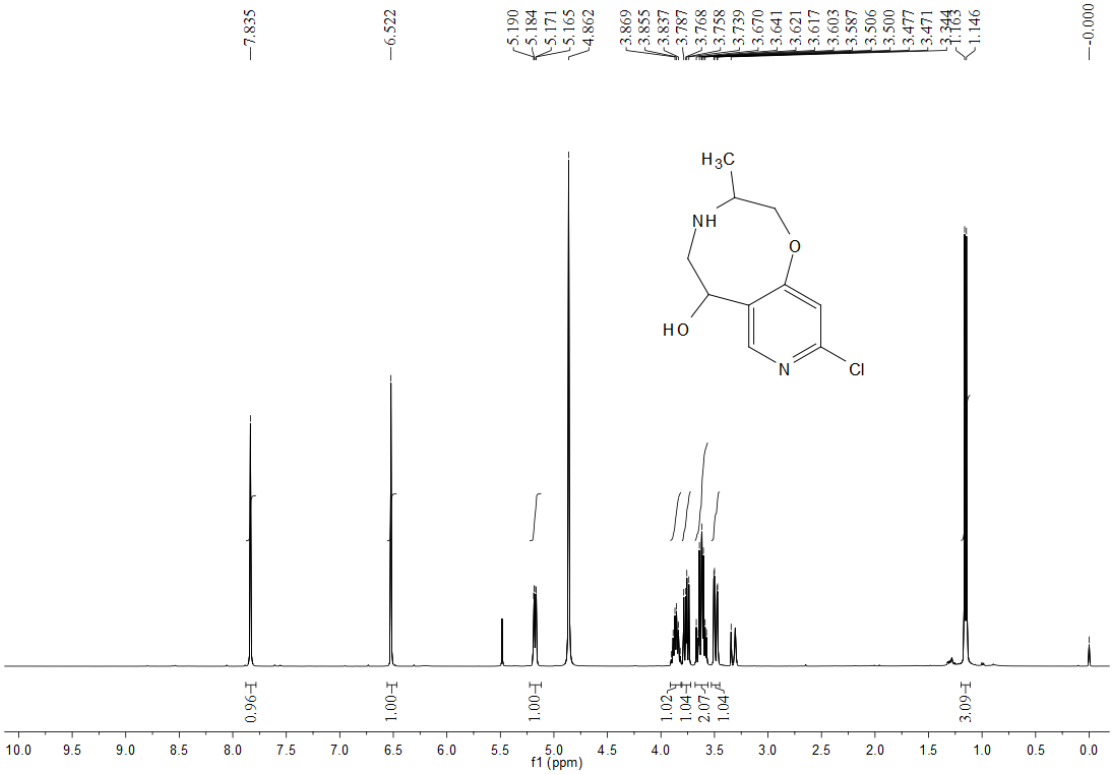
^{13}C NMR (100 MHz, CD_3OD) of **3aa**

9-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3aa)

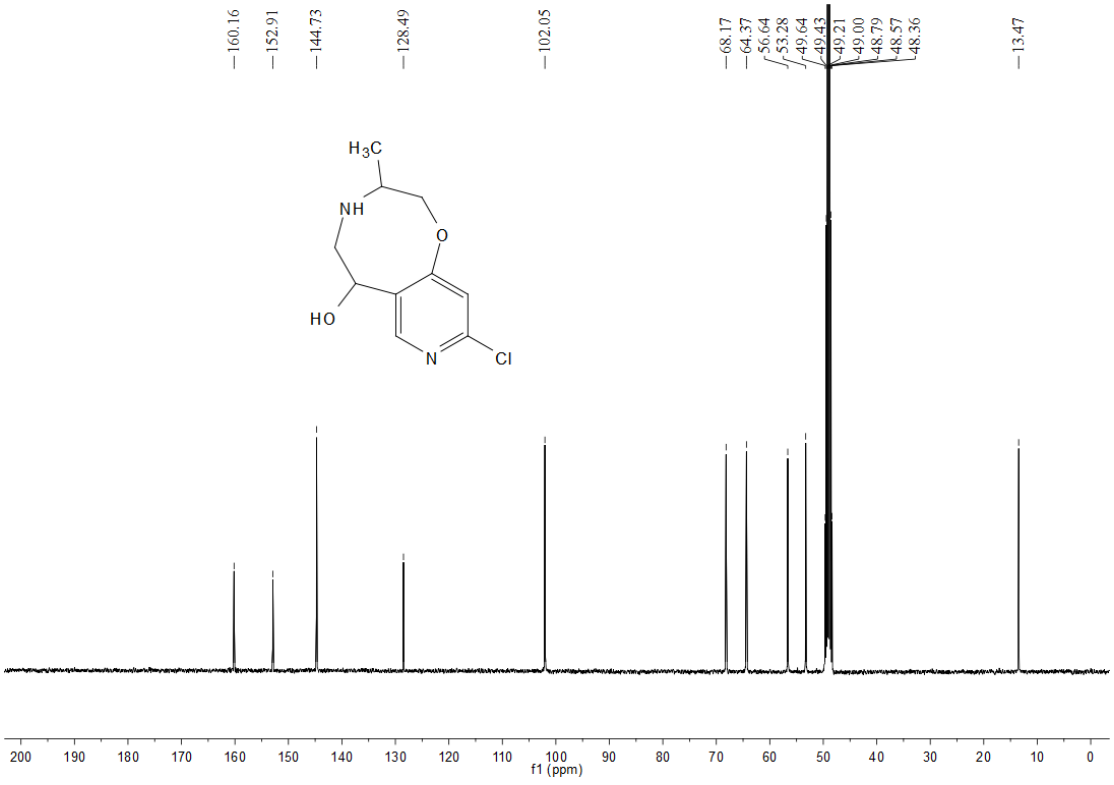


DEPT135 of **3aa**

9-chloro-3-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ab)

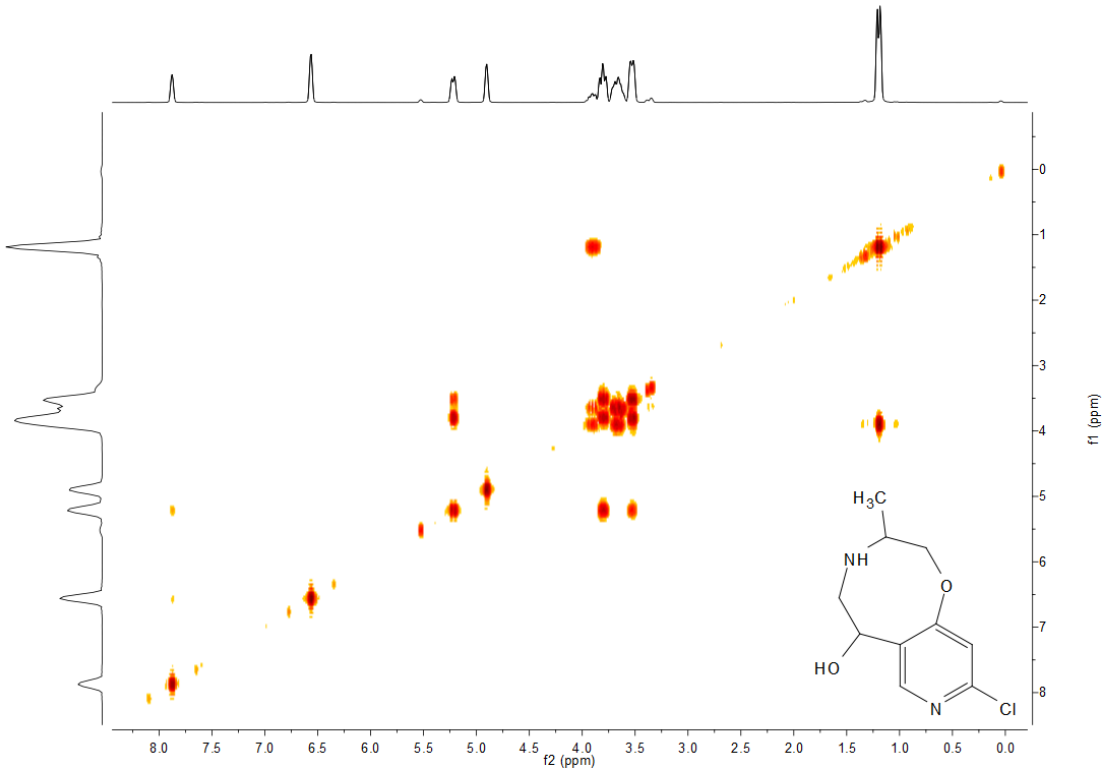


^{1}H NMR (400 MHz, CD_3OD) of **3ab**

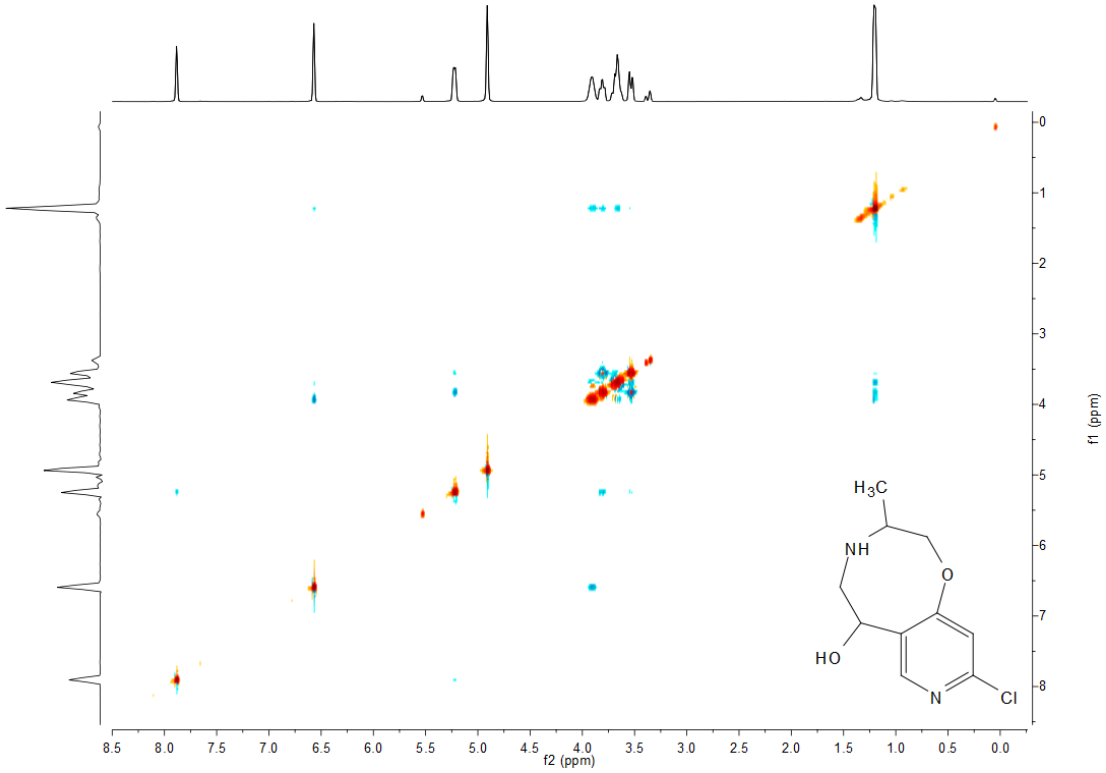


^{13}C NMR (100 MHz, CD_3OD) of **3ab**

9-chloro-3-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ab)

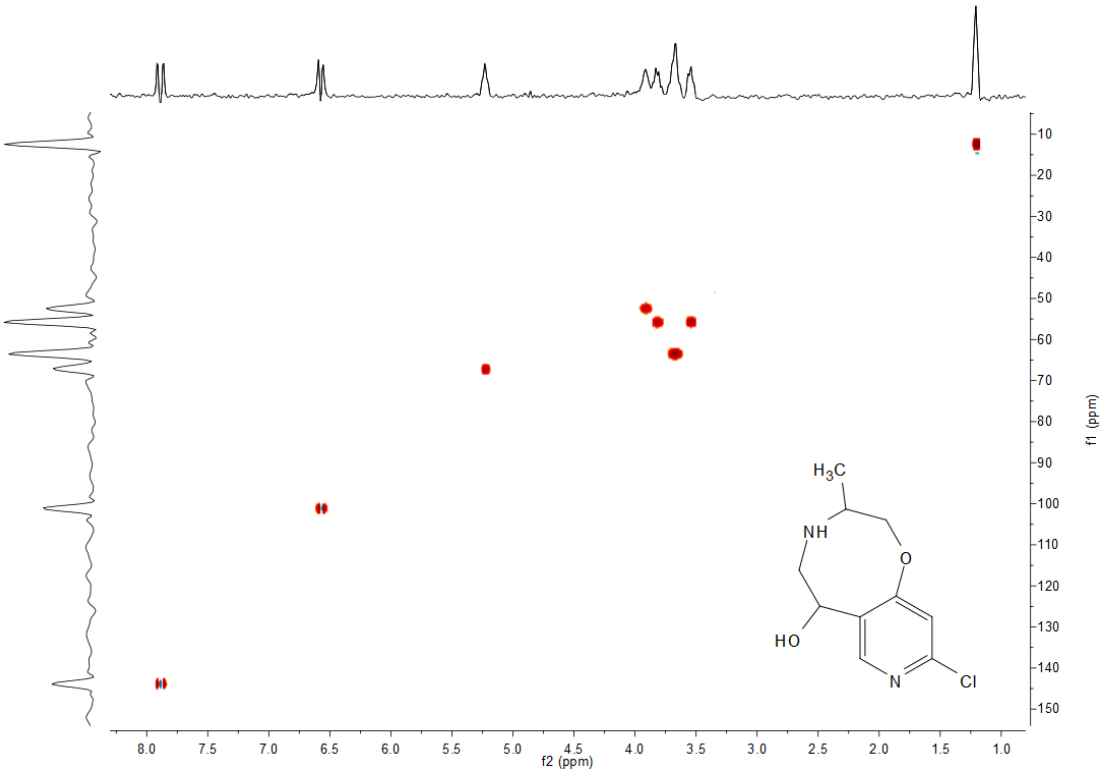


^{1}H-^{1}H COSY of **3ab**



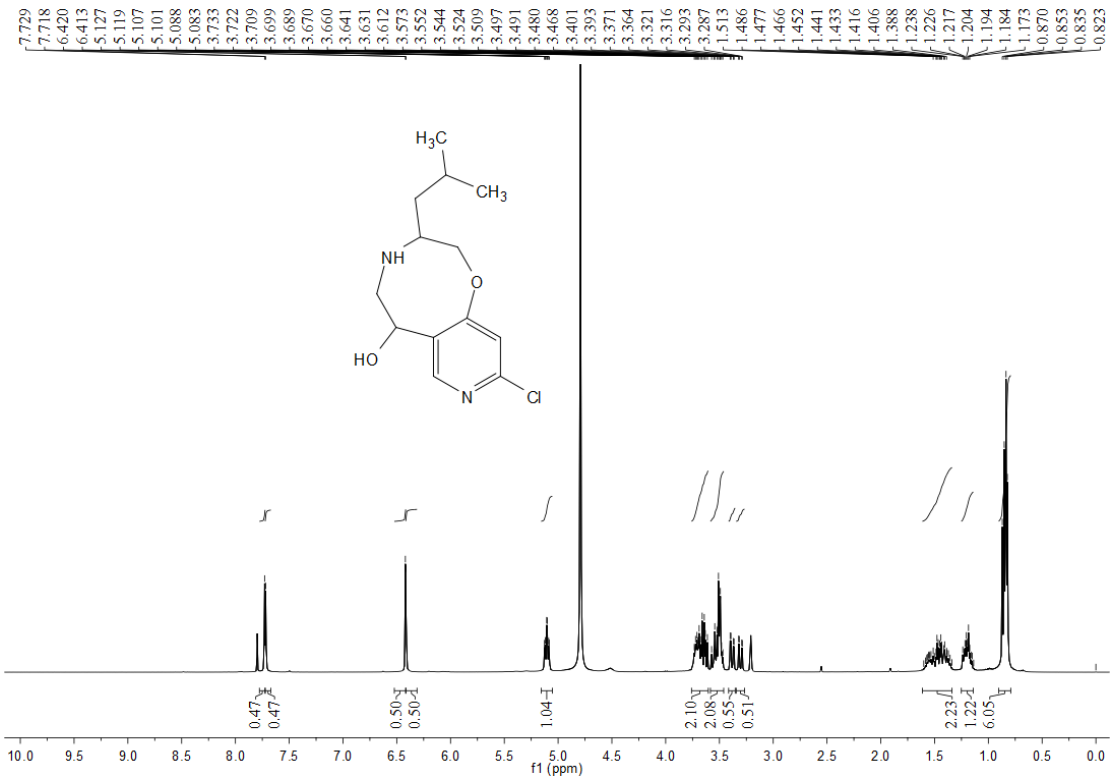
NOESY of **3ab**

9-chloro-3-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ab)

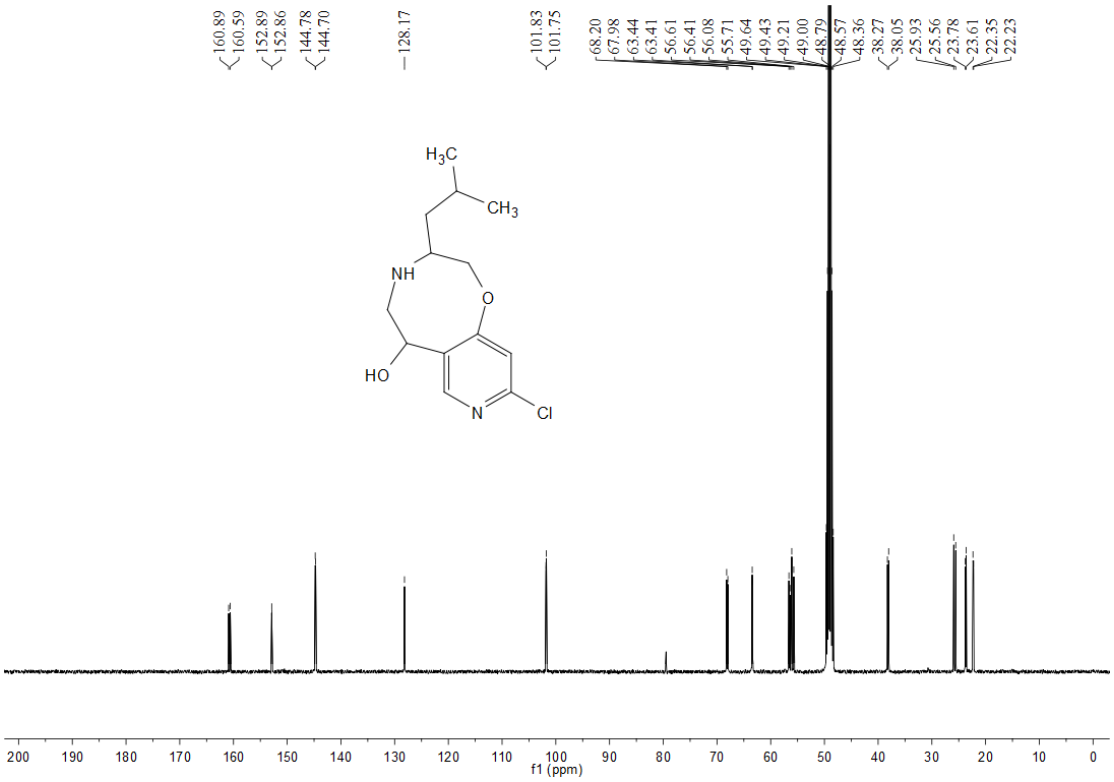


HSQC of **3ab**

9-chloro-3-isobutyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ac)

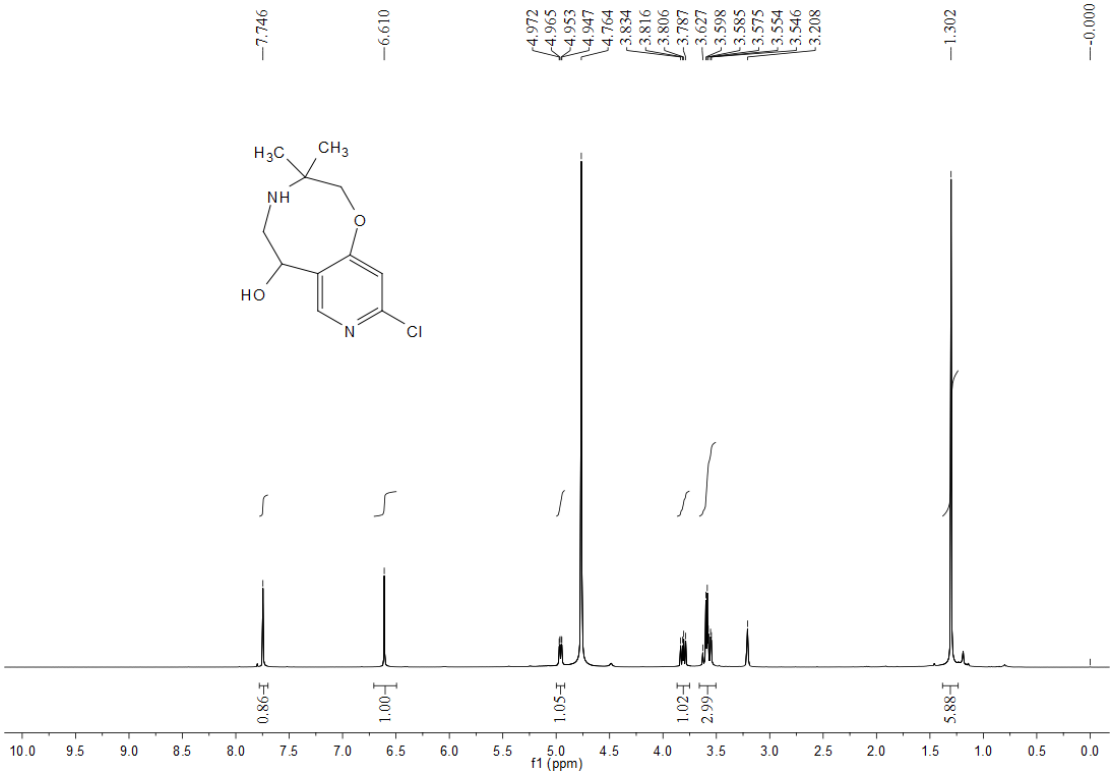


^{1}H NMR (400 MHz, CD_3OD) of **3ac**

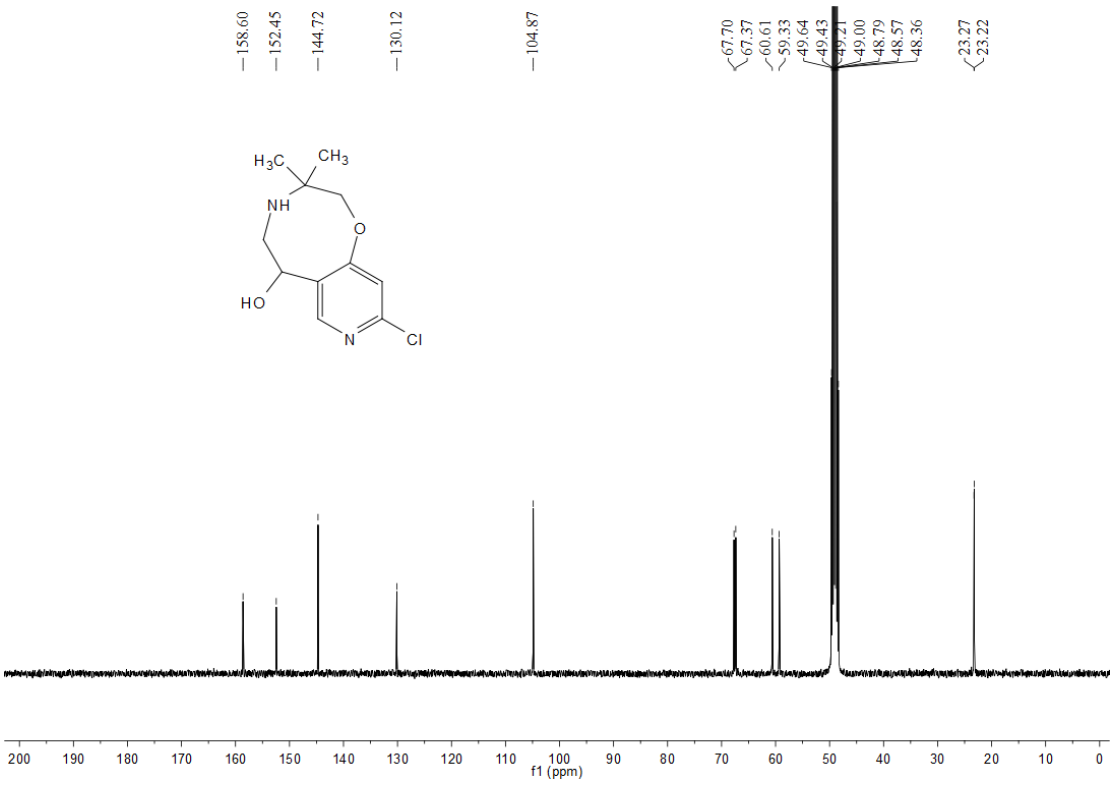


^{13}C NMR (100 MHz, CD_3OD) of **3ac**

9-chloro-3,3-dimethyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ad)

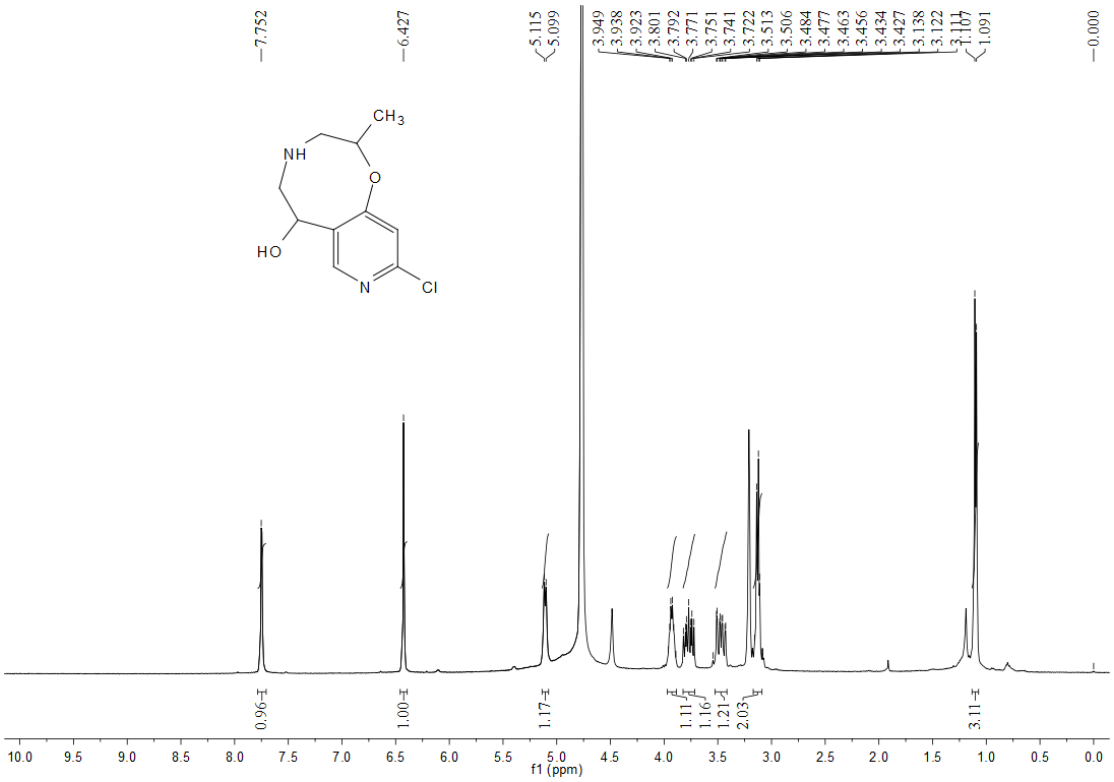


^{1}H NMR (400 MHz, CD_3OD) of **3ad**

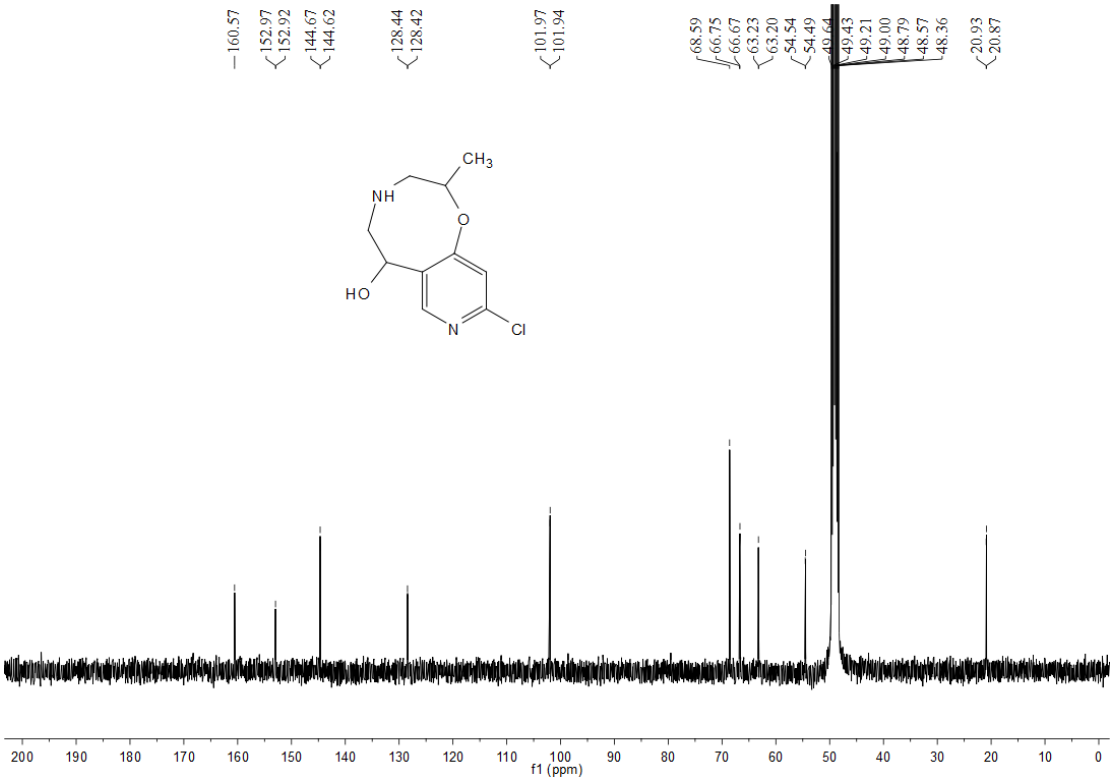


^{13}C NMR (100 MHz, CD_3OD) of **3ad**

9-chloro-2-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ae)

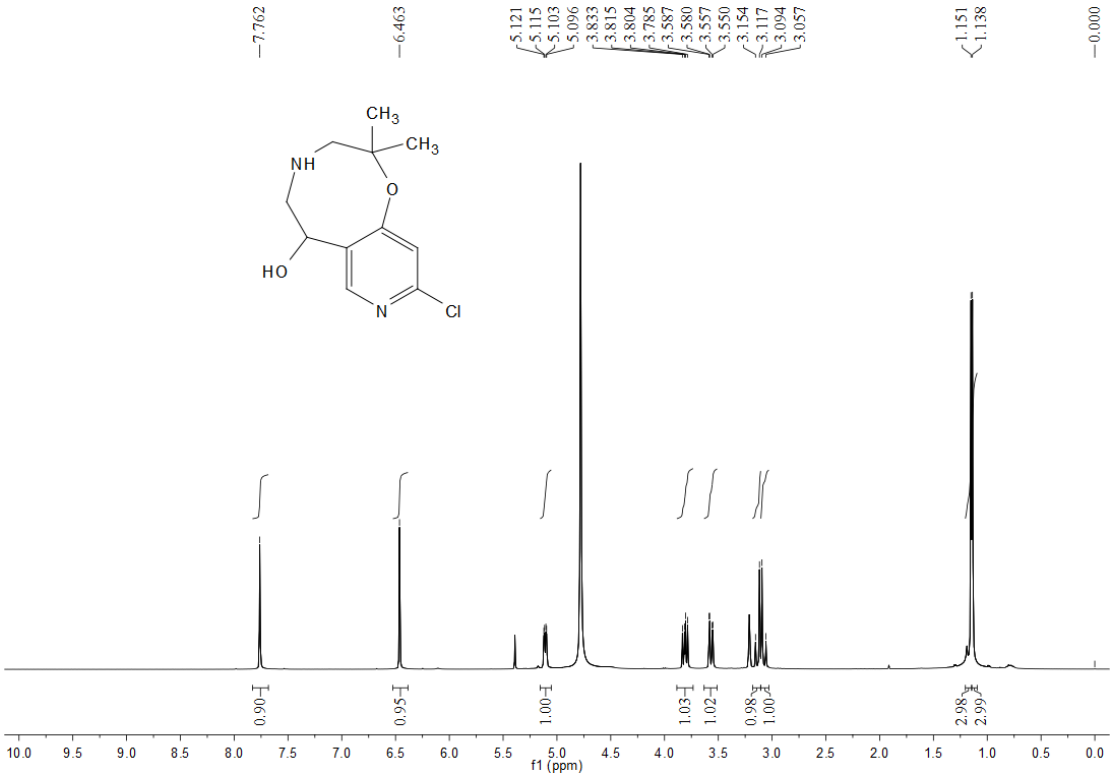


^{1}H NMR (400 MHz, CD_3OD) of **3ae**

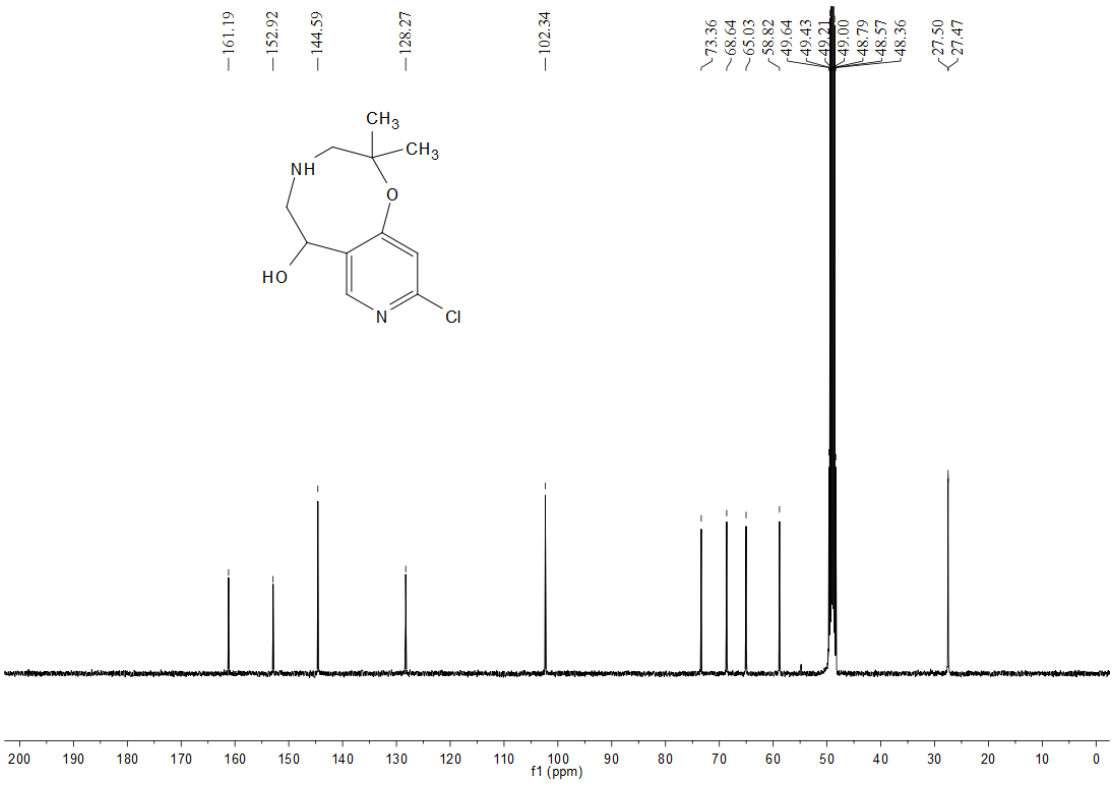


^{13}C NMR (100 MHz, CD_3OD) of **3ae**

9-chloro-2,2-dimethyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3af)

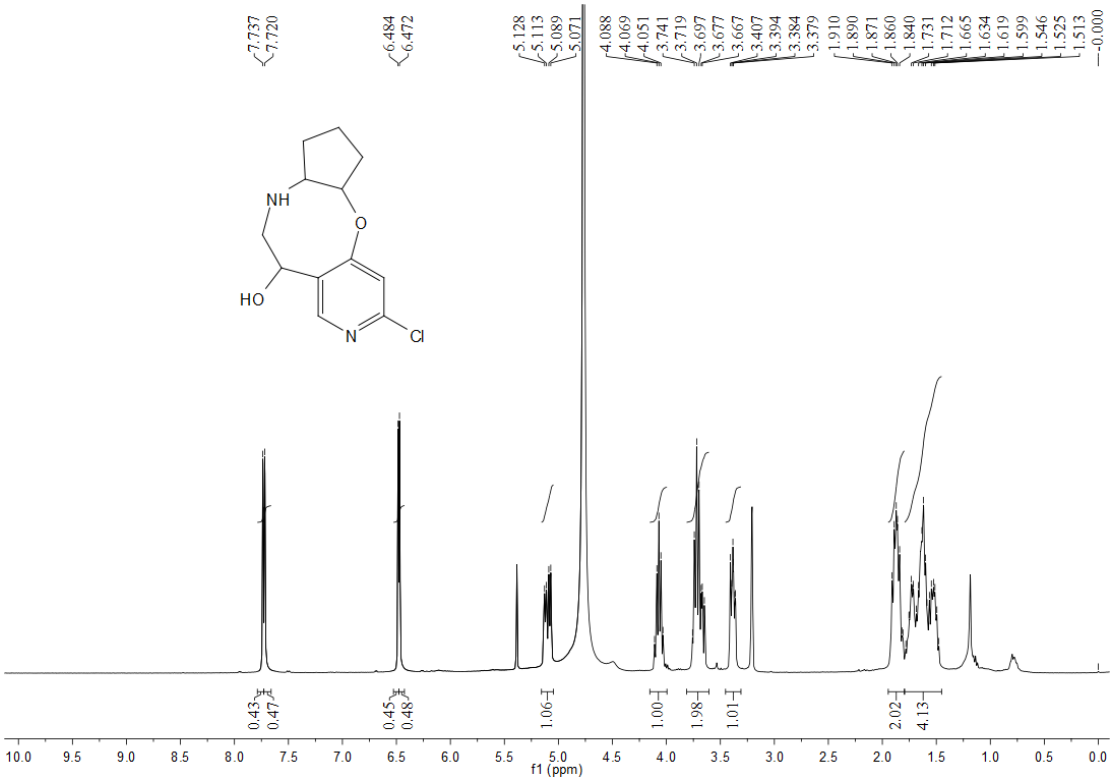


^{1}H NMR (400 MHz, CD_3OD) of **3af**

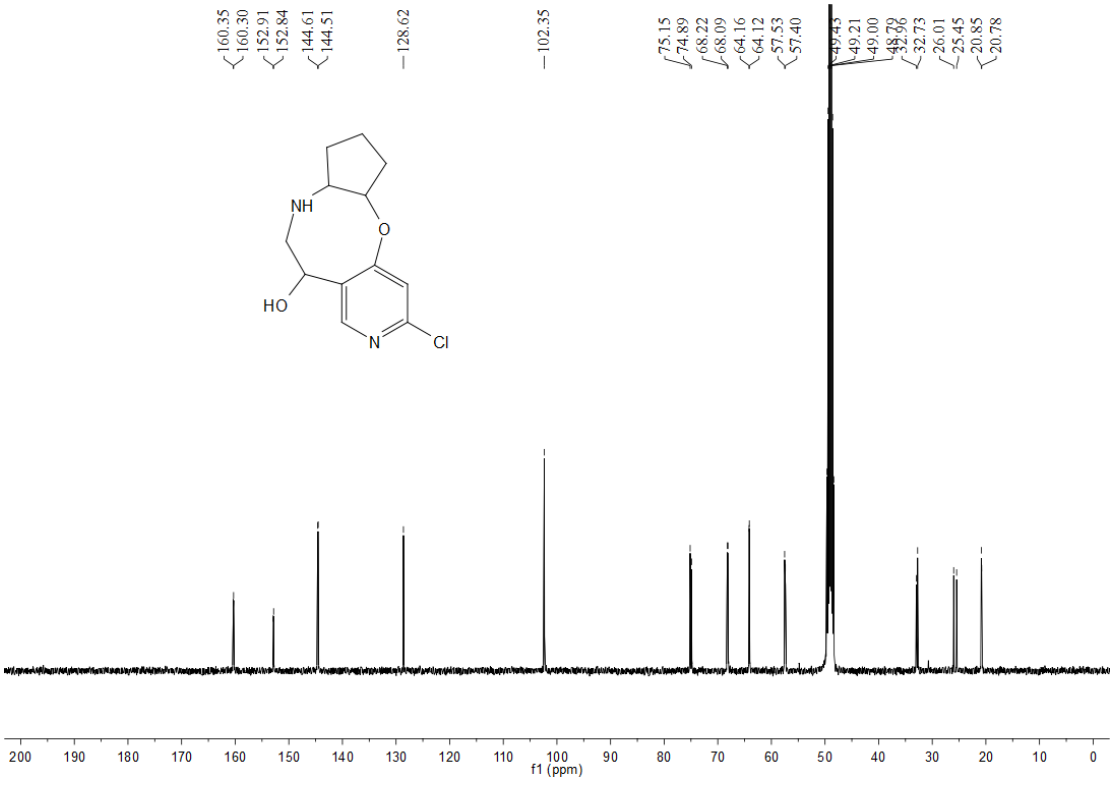


^{13}C NMR (100 MHz, CD_3OD) of **3af**

2-chloro-5,6,7,7a,8,9,10,10a-octahydrocyclopenta[*b*]pyrido[3,4-*g*][1,4]oxazocin-5-ol (3ag)

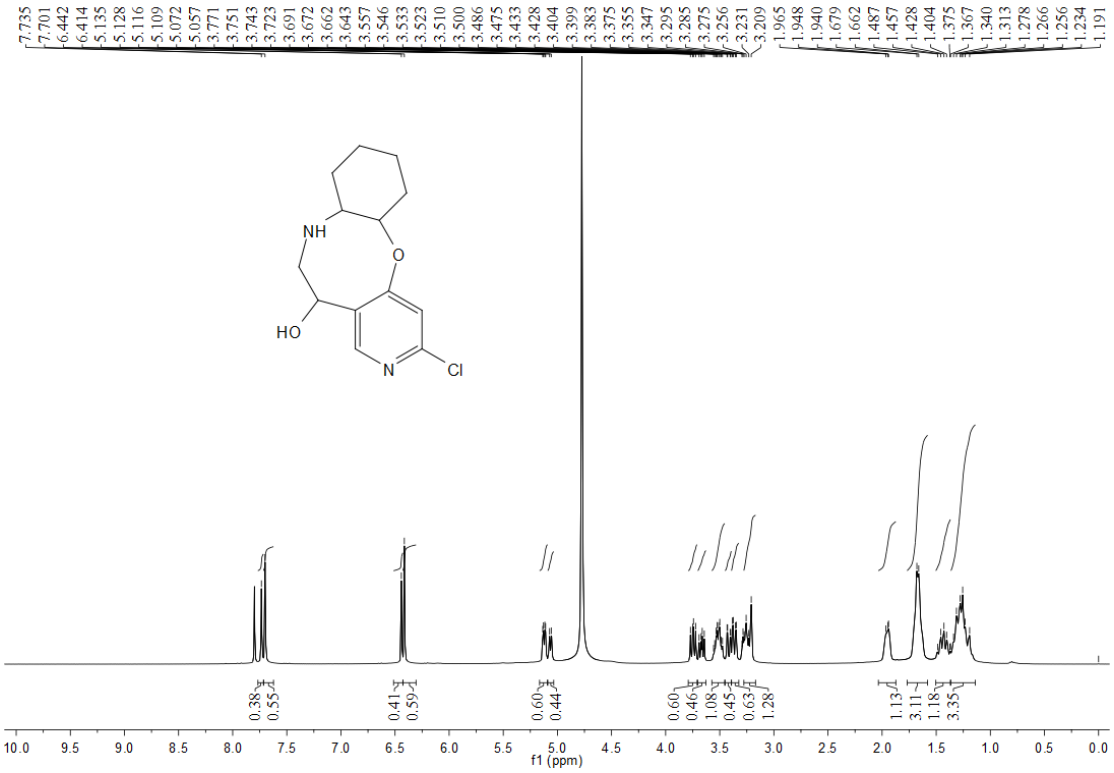


^{1}H NMR (400 MHz, CD_3OD) of **3ag**

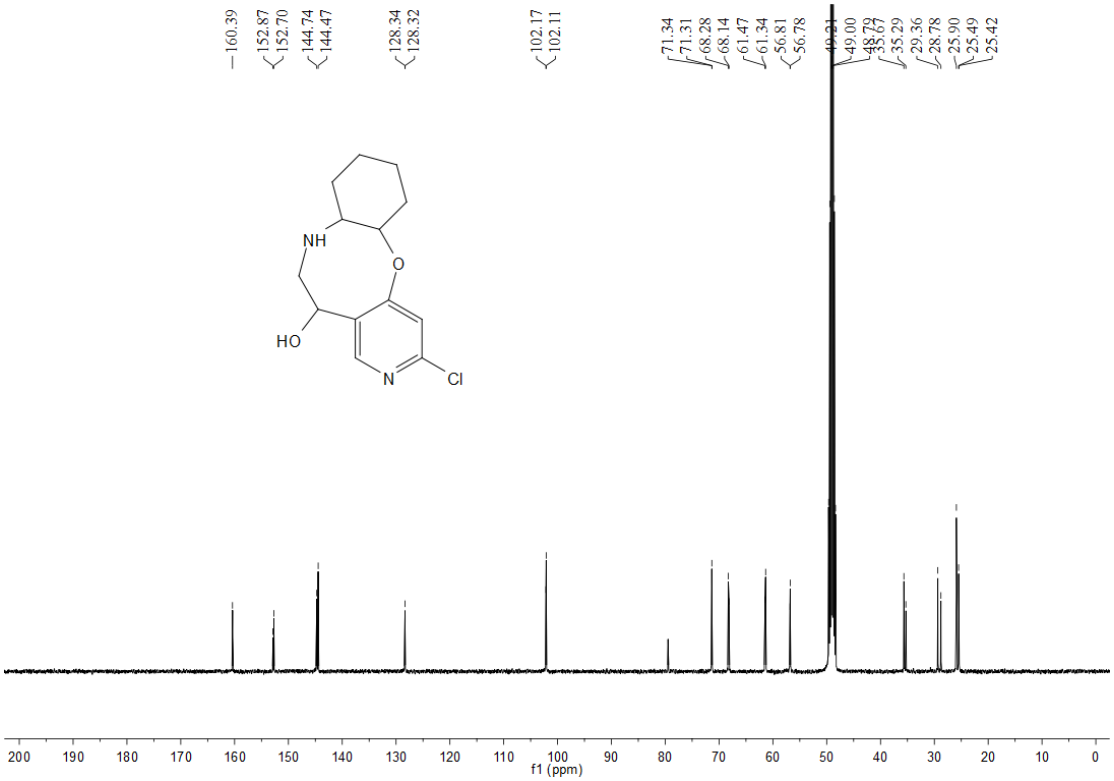


^{13}C NMR (100 MHz, CD_3OD) of **3ag**

2-chloro-6,7,7a,8,9,10,11,11a-octahydro-5*H*-benzo[*b*]pyrido[3,4-*g*][1,4]oxazocin-5-ol (3ah)

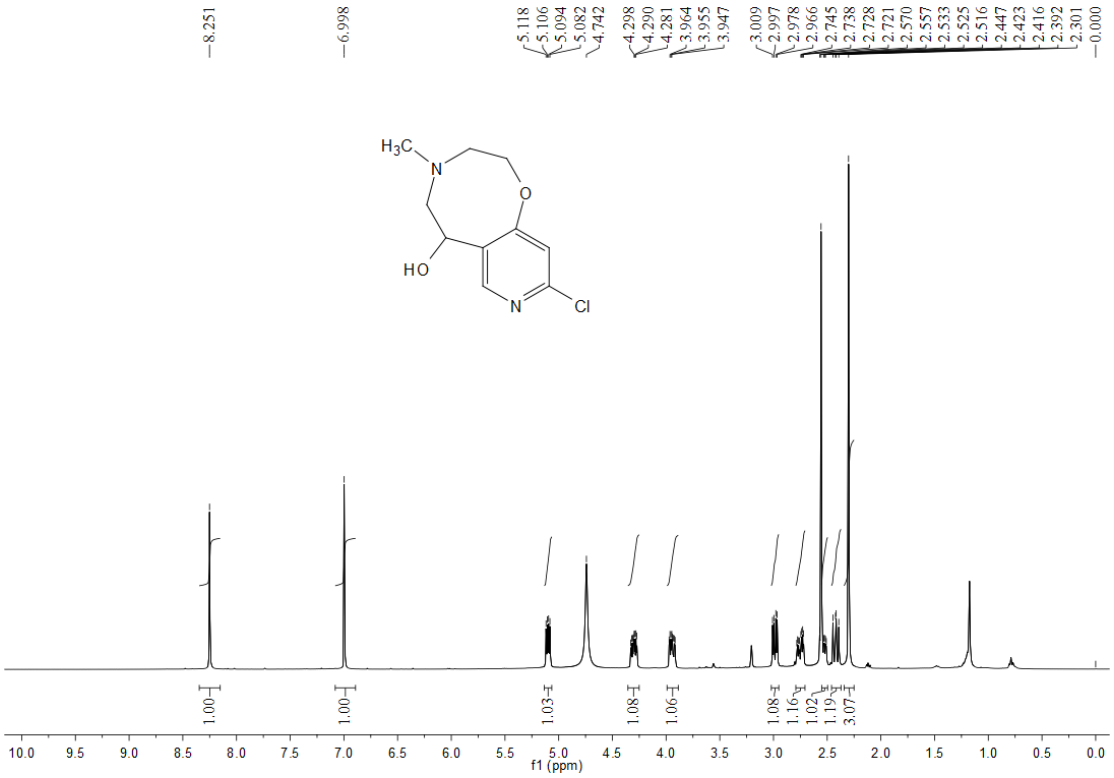


^{1}H NMR (400 MHz, CD_3OD) of **3ah**

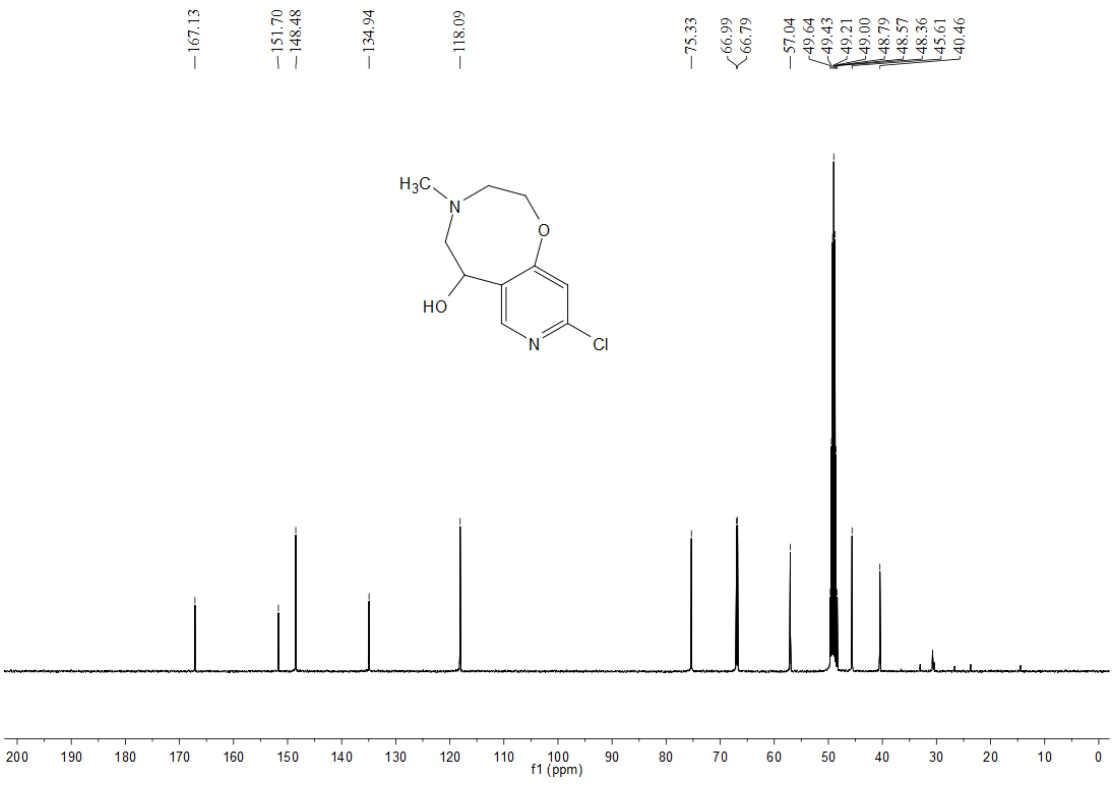


^{13}C NMR (100 MHz, CD_3OD) of **3ah**

9-chloro-4-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ai)

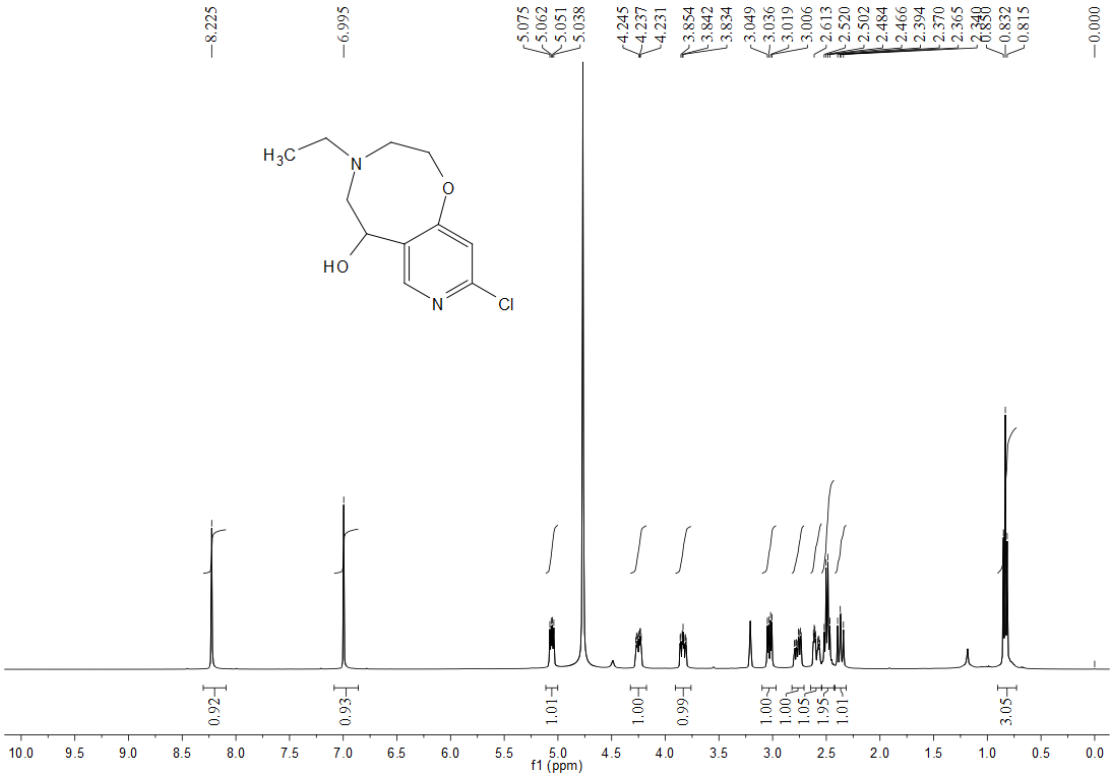


^{1}H NMR (400 MHz, CD_3OD) of **3ai**

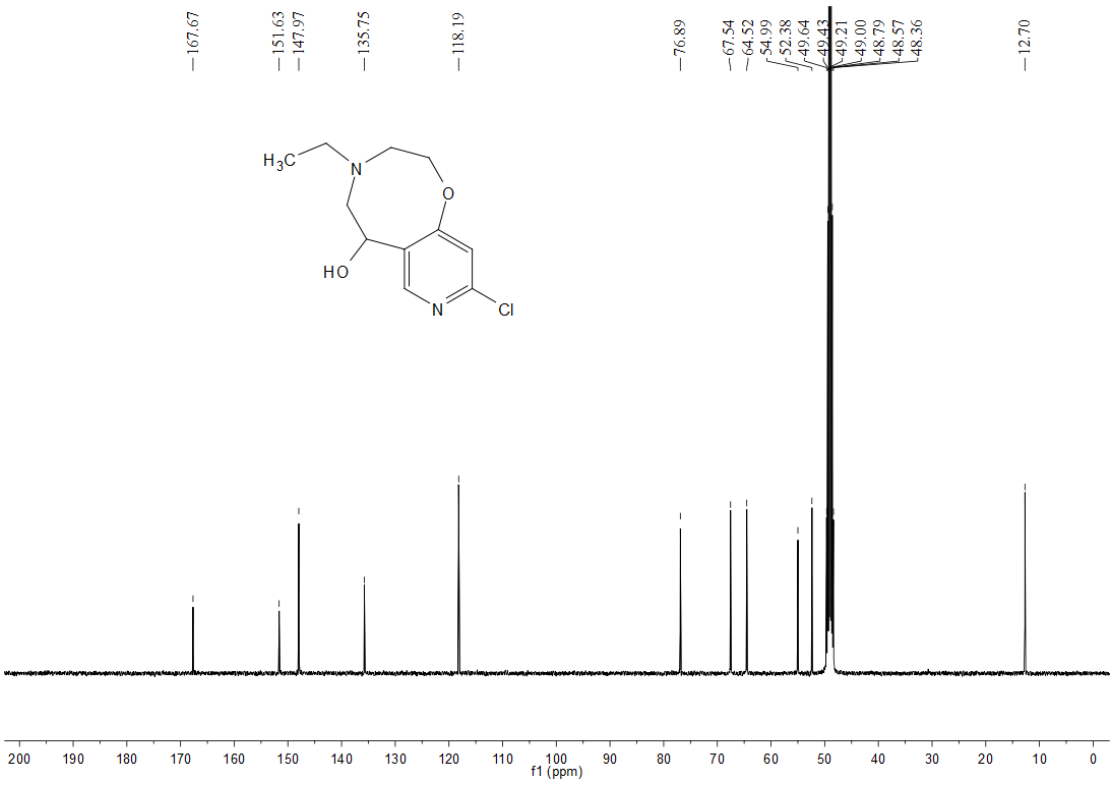


^{13}C NMR (100 MHz, CD_3OD) of **3ai**

9-chloro-4-ethyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3aj)

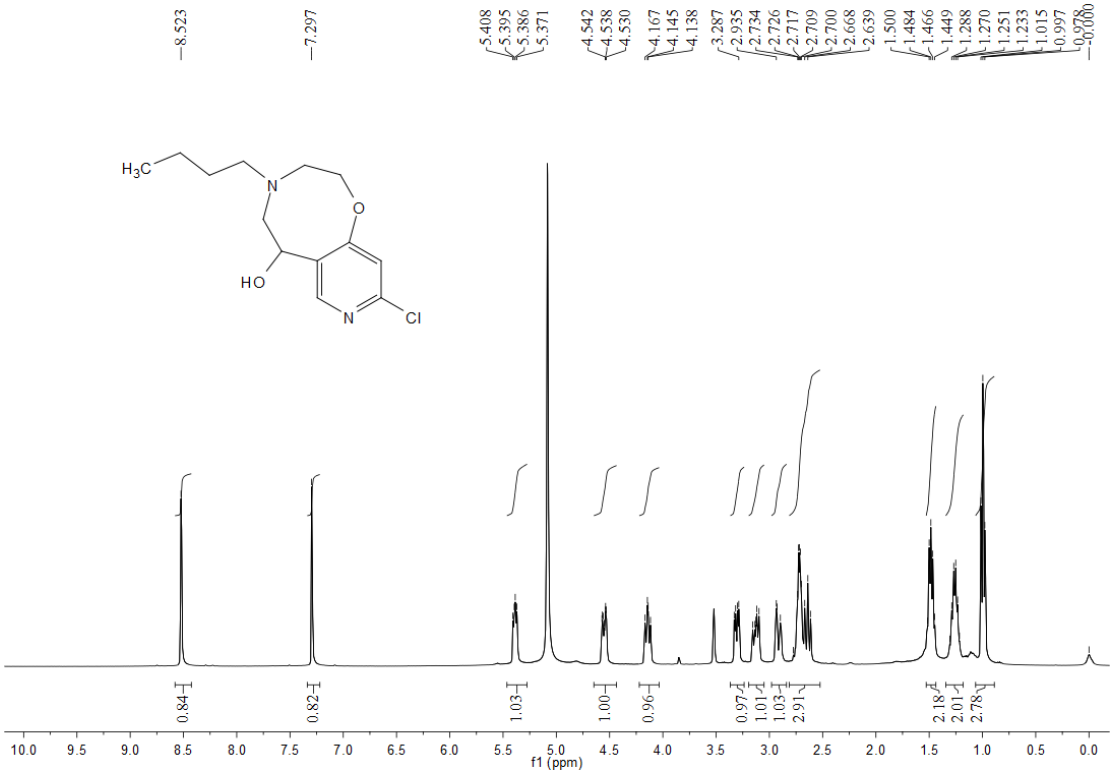


^{1}H NMR (400 MHz, CD_3OD) of **3aj**

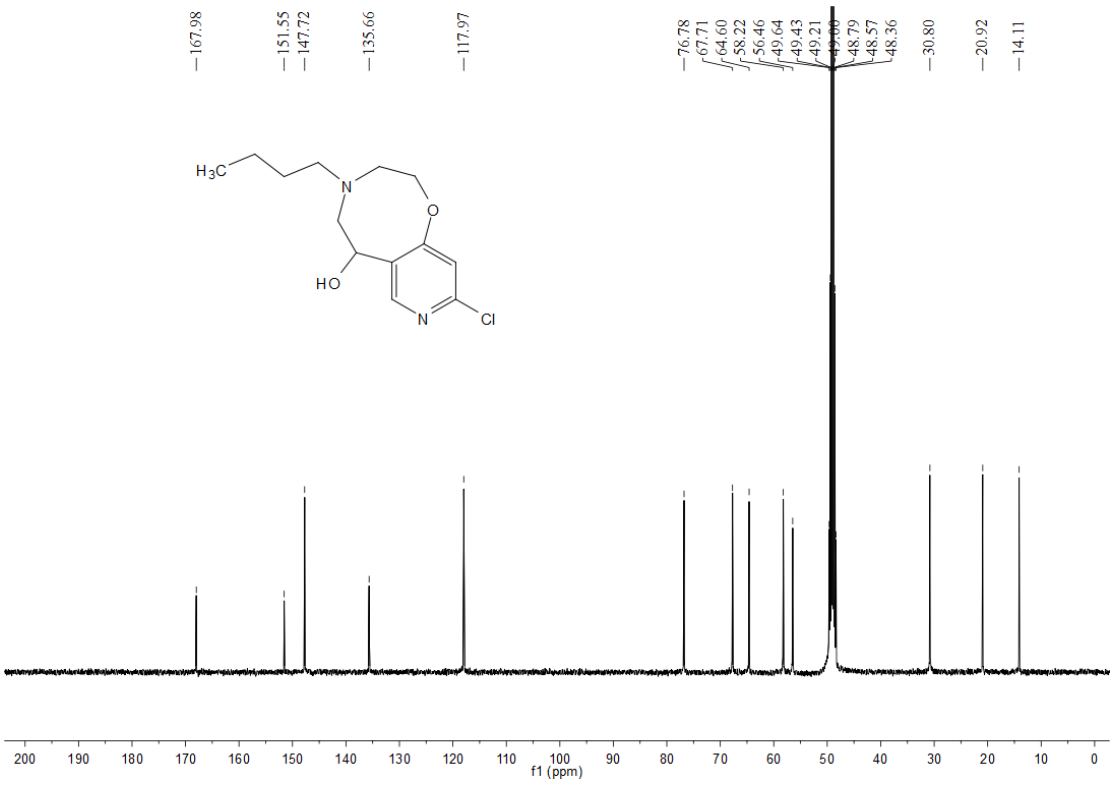


^{13}C NMR (100 MHz, CD_3OD) of **3aj**

4-butyl-9-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3ak)

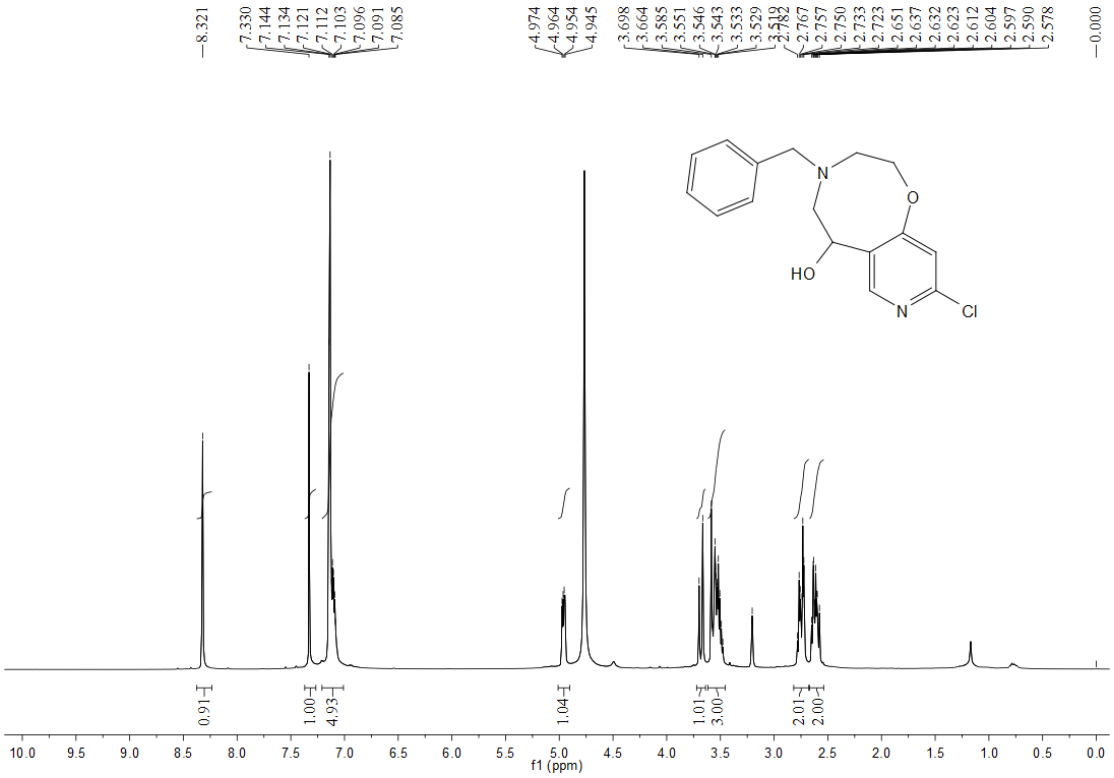


^{1}H NMR (400 MHz, CD_3OD) of **3ak**

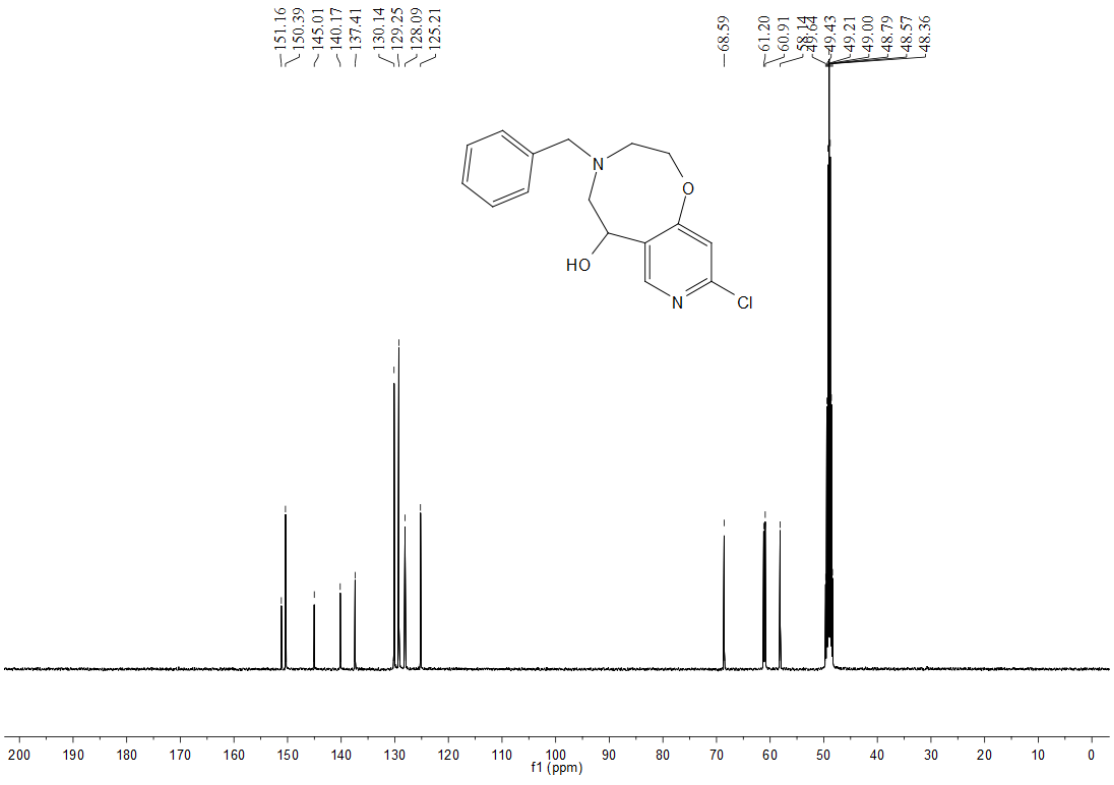


^{13}C NMR (100 MHz, CD_3OD) of **3ak**

4-benzyl-9-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3al)

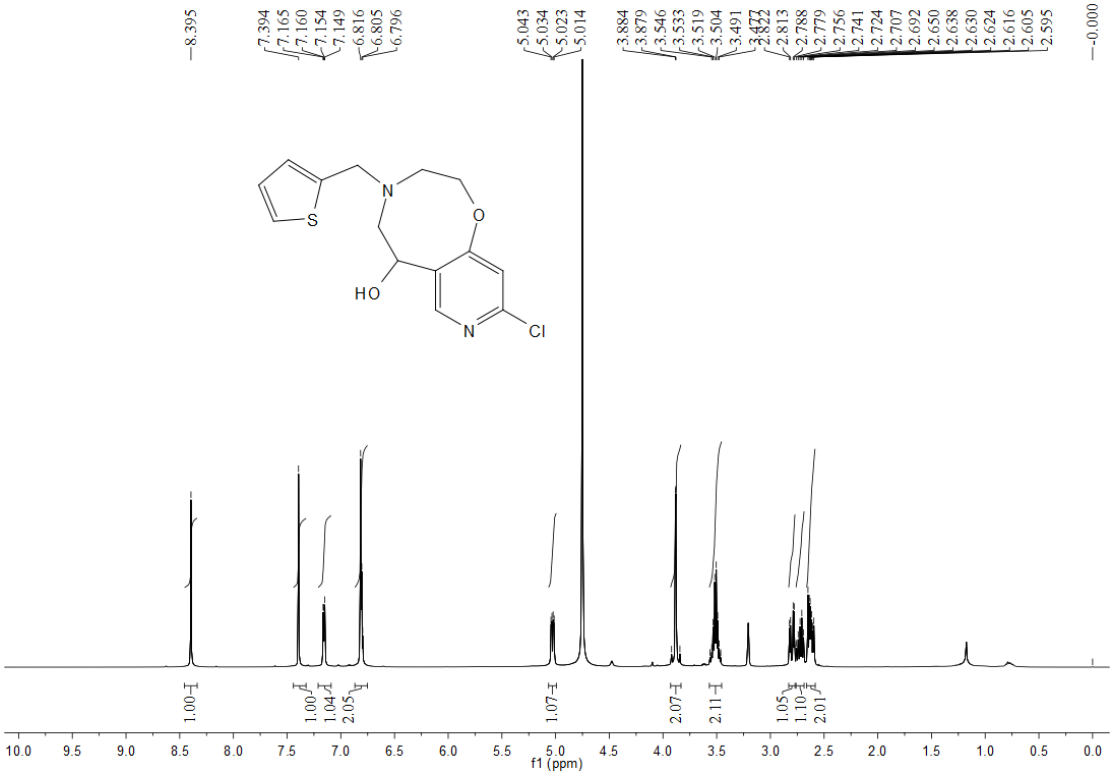


^{1}H NMR (400 MHz, CD_3OD) of **3al**

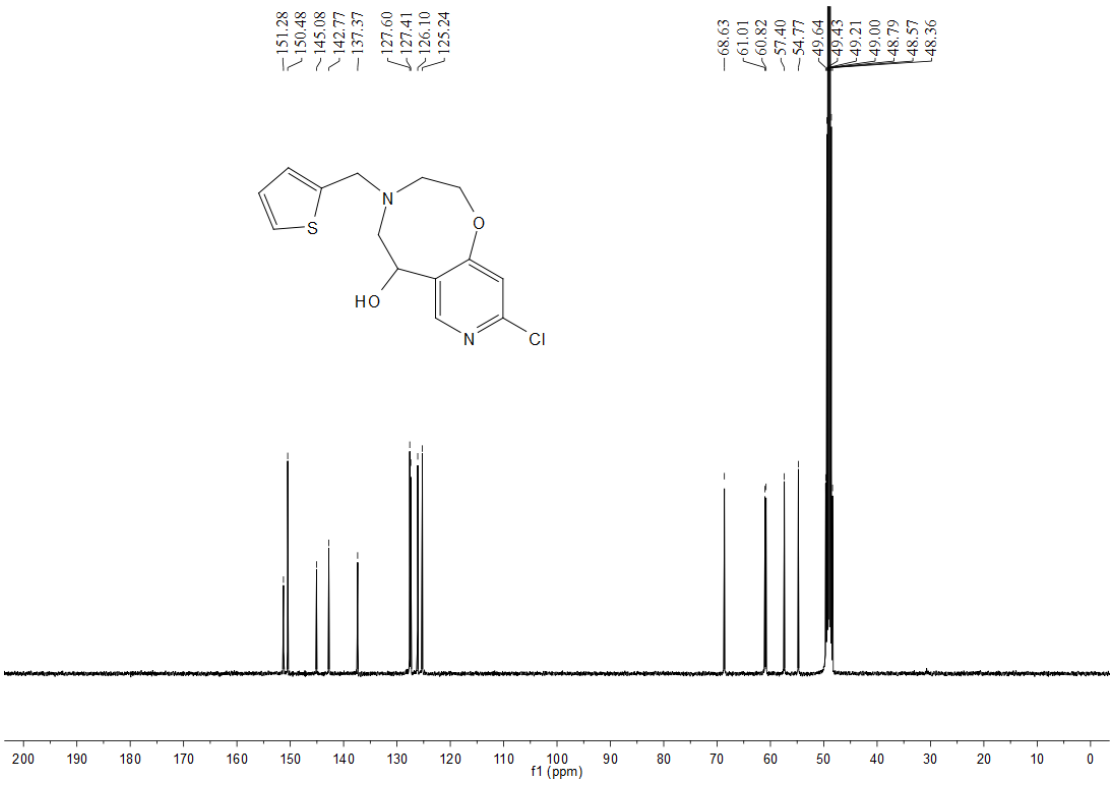


^{13}C NMR (100 MHz, CD_3OD) of **3al**

9-chloro-4-(thiophen-2-ylmethyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazoc in-6-ol (3am)

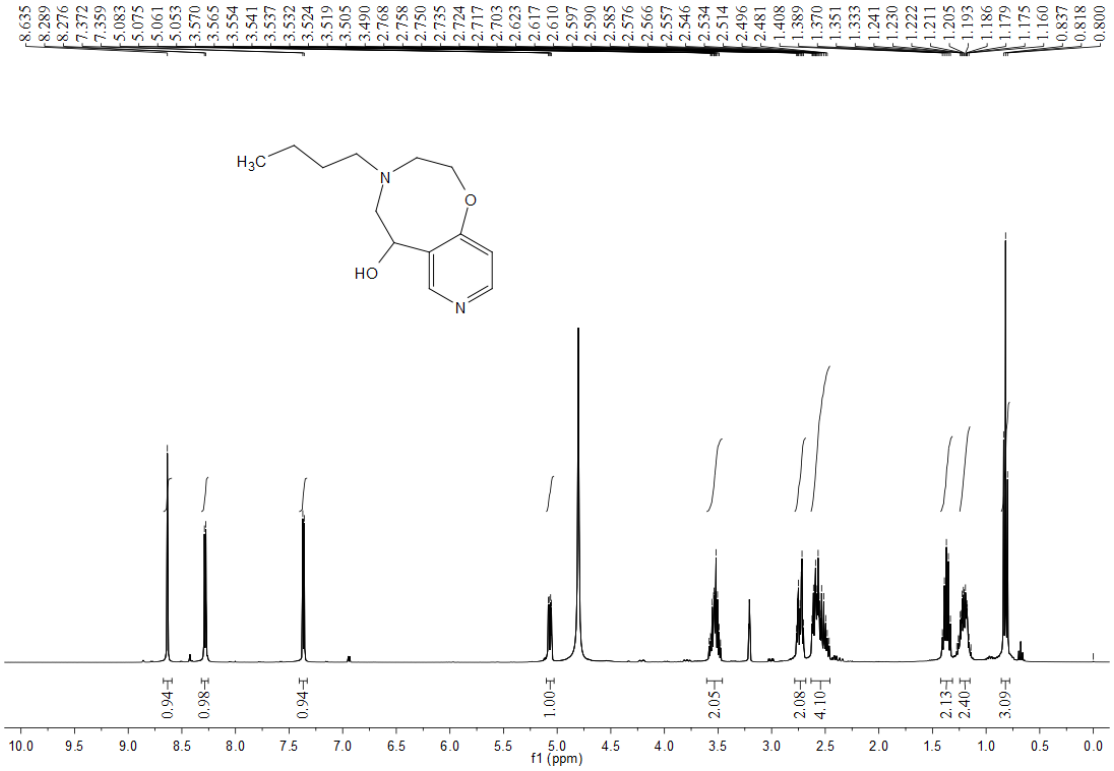


^{1}H NMR (400 MHz, CD_3OD) of **3am**

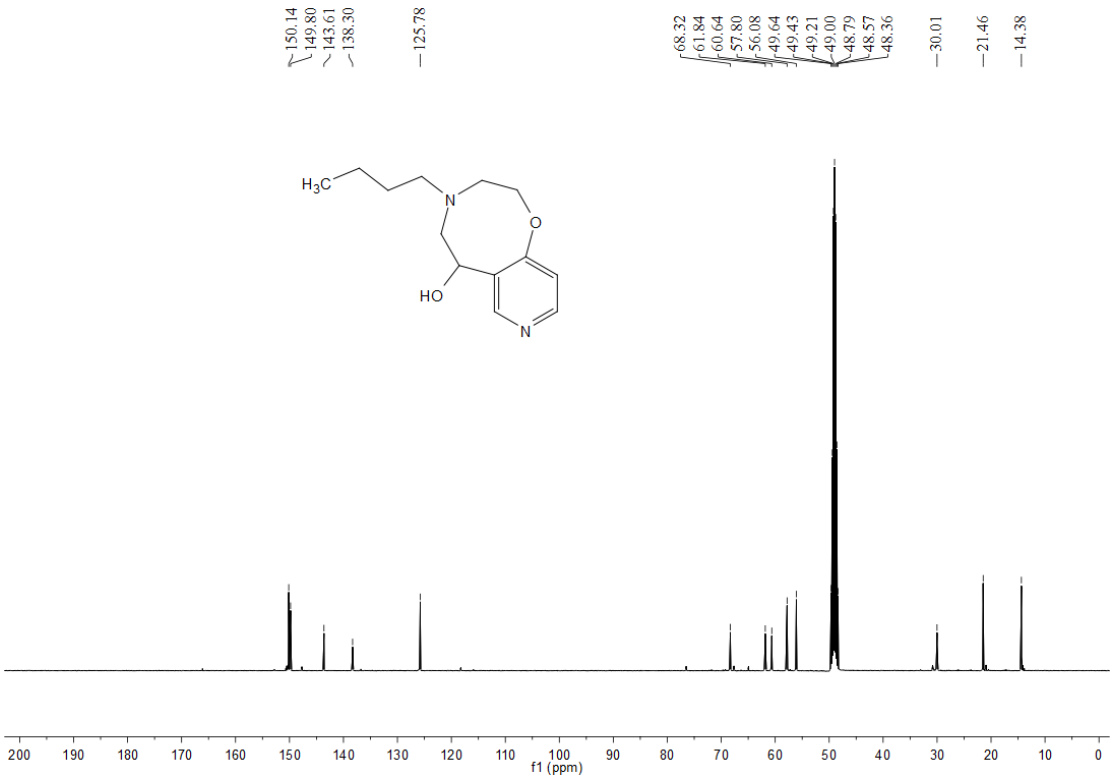


^{13}C NMR (100 MHz, CD_3OD) of **3am**

4-butyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bk)

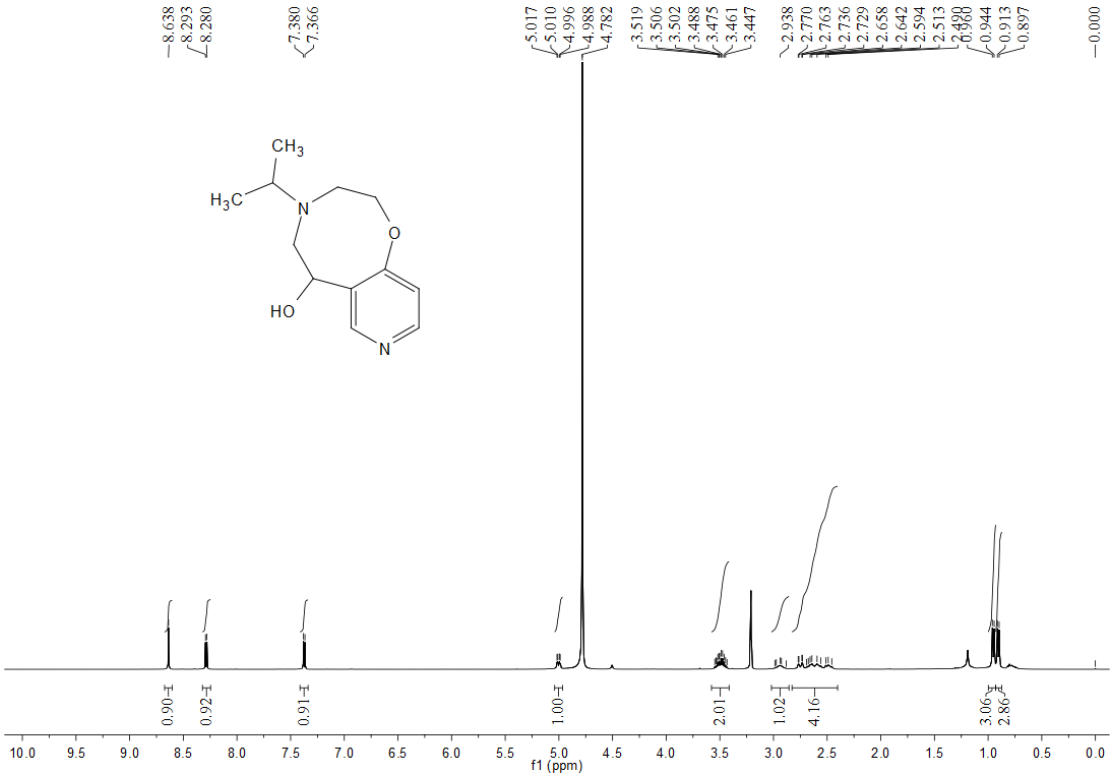


^{1}H NMR (400 MHz, CD_3OD) of **3bk**

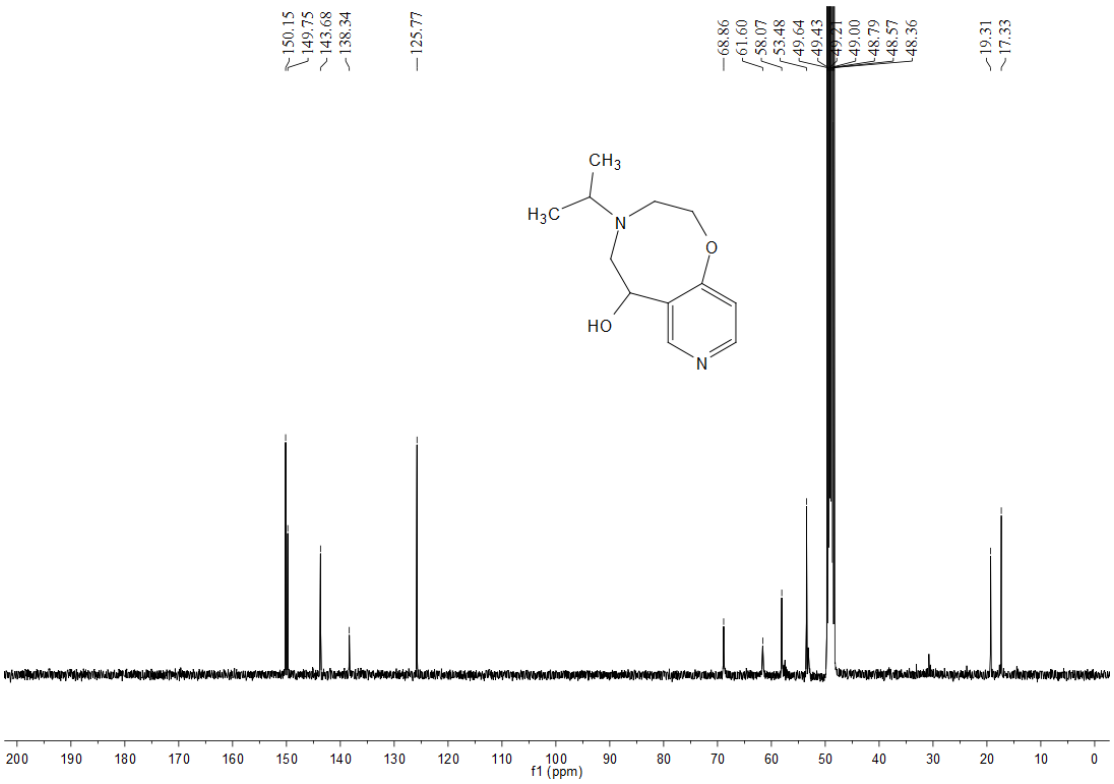


^{13}C NMR (100 MHz, CD_3OD) of **3bk**

4-isopropyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bq)

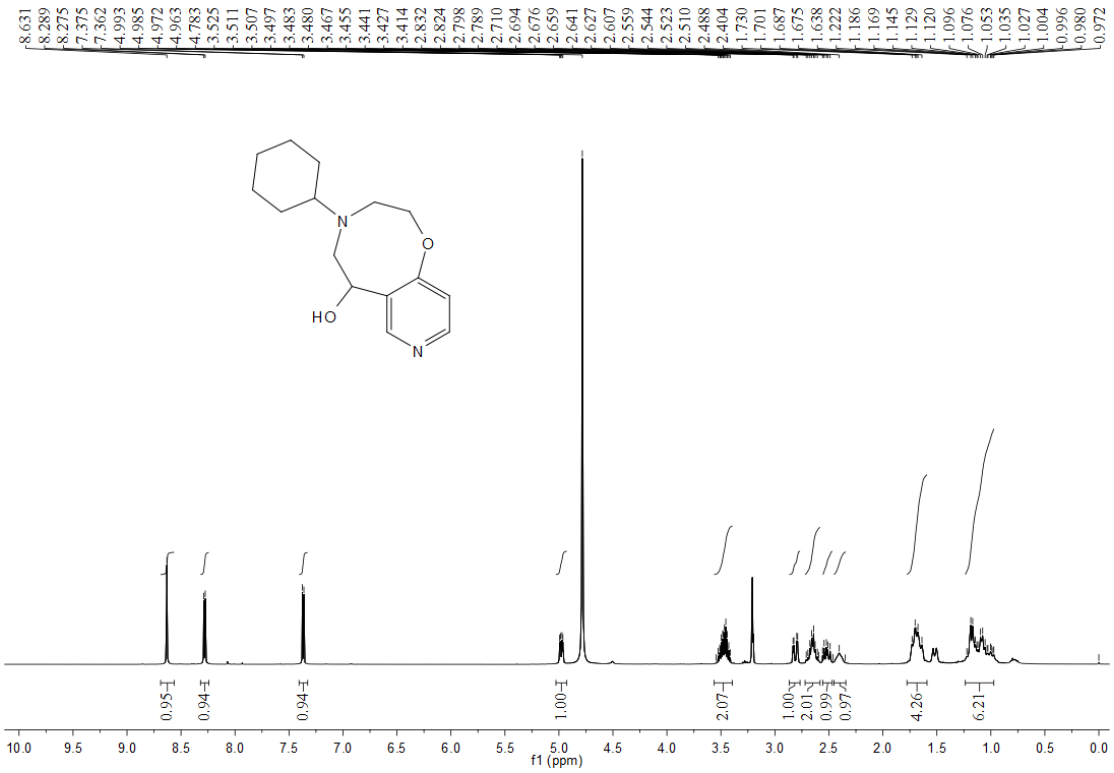


^{1}H NMR (400 MHz, CD_3OD) of **3bq**

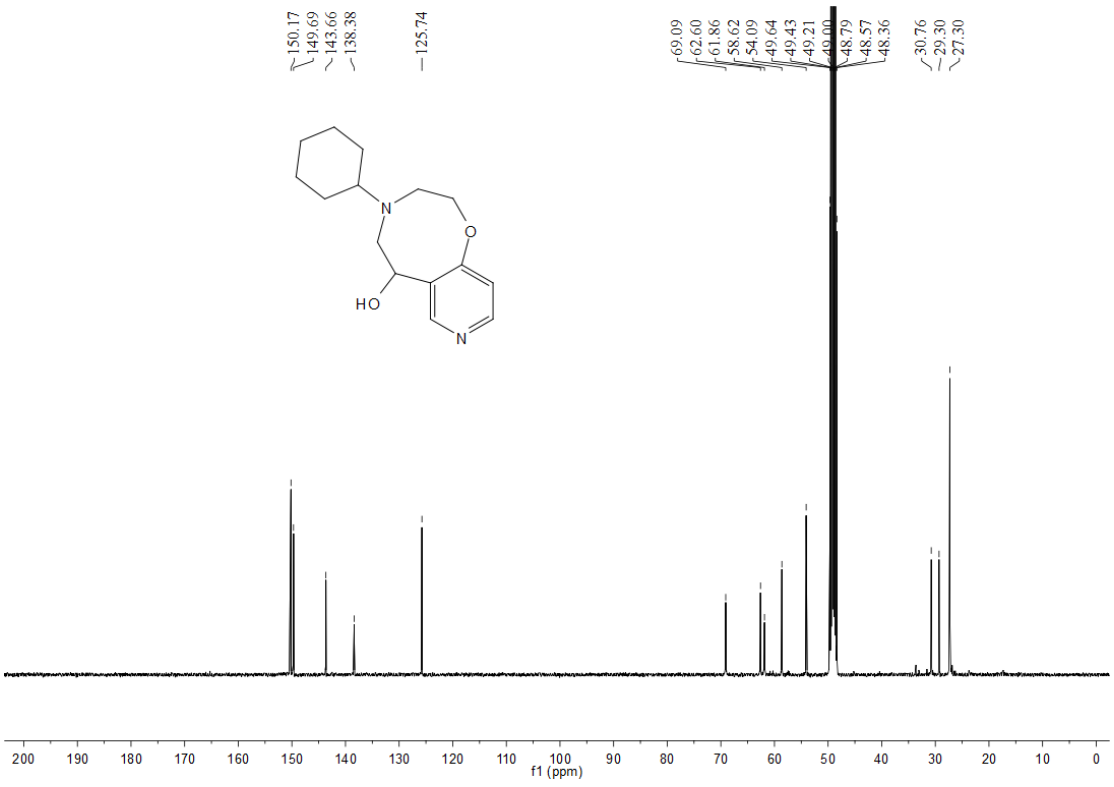


^{13}C NMR (100 MHz, CD_3OD) of **3bq**

4-cyclohexyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3br)

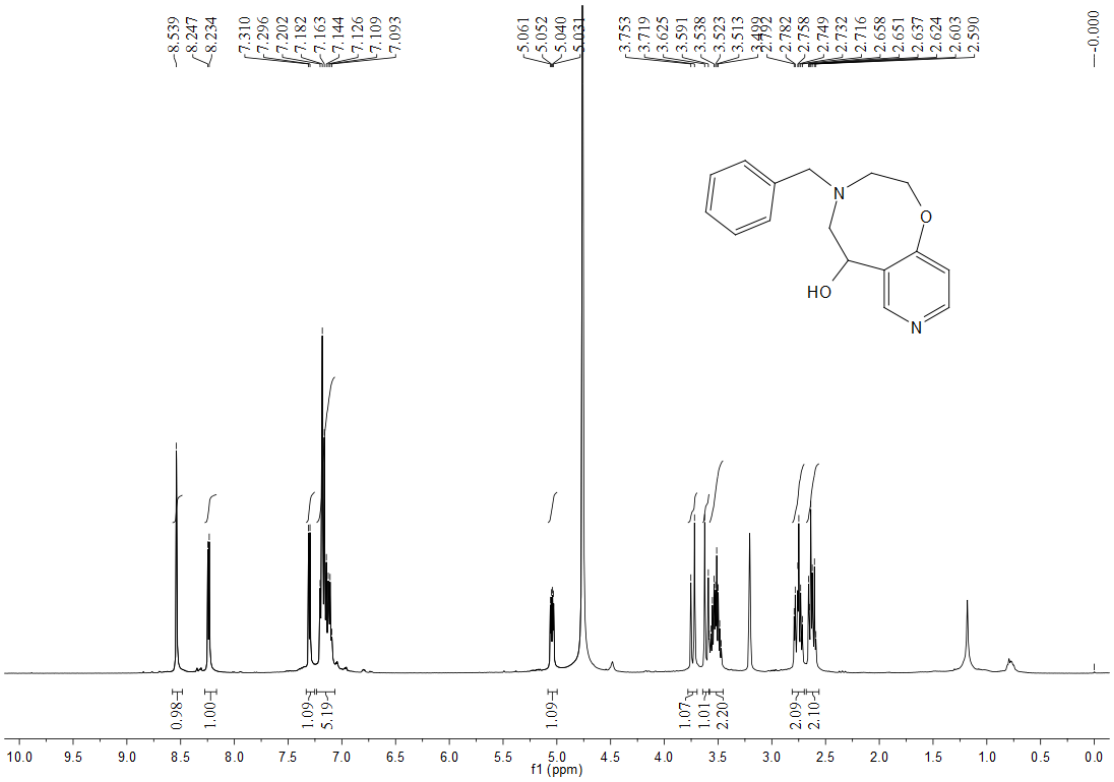


^{1}H NMR (400 MHz, CD_3OD) of **3br**

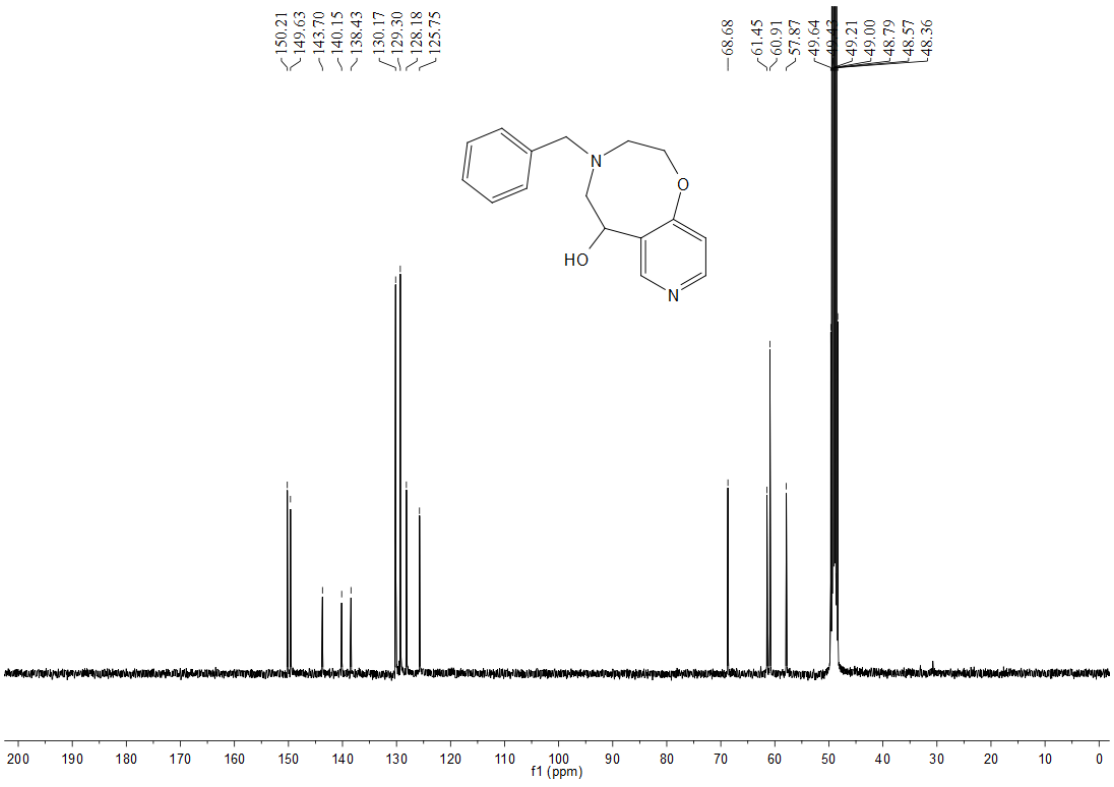


^{13}C NMR (100 MHz, CD_3OD) of **3br**

4-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bl)

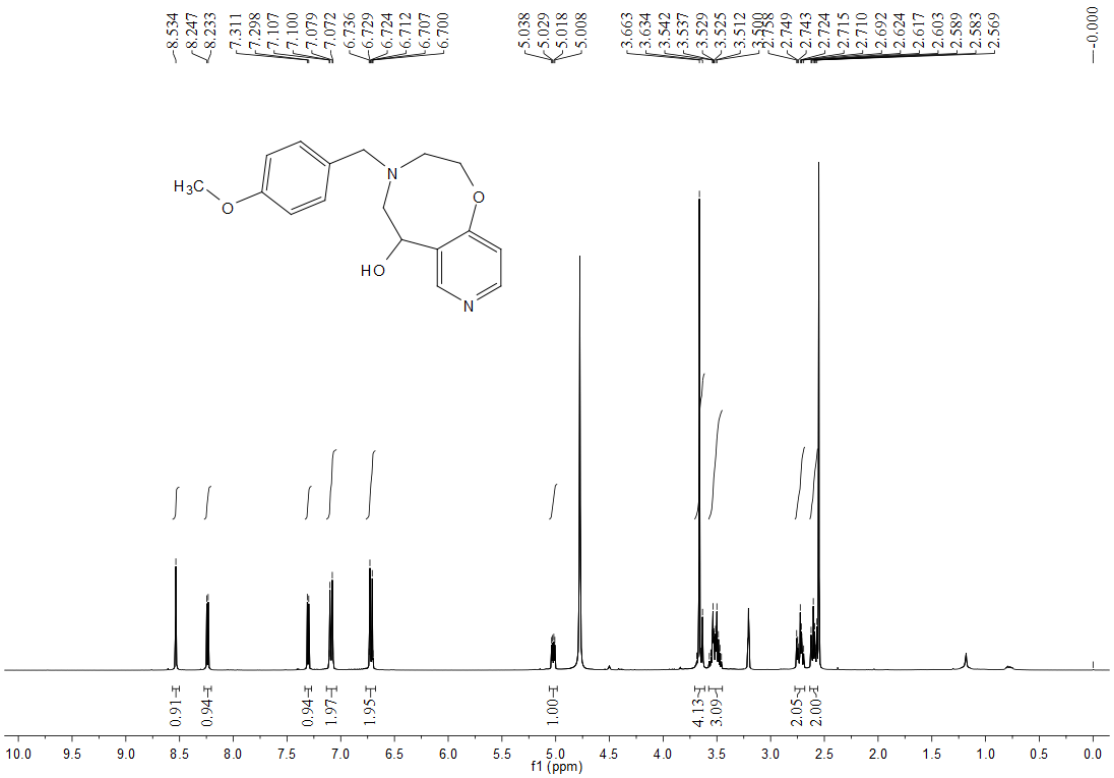


^{1}H NMR (400 MHz, CD_3OD) of **3bl**

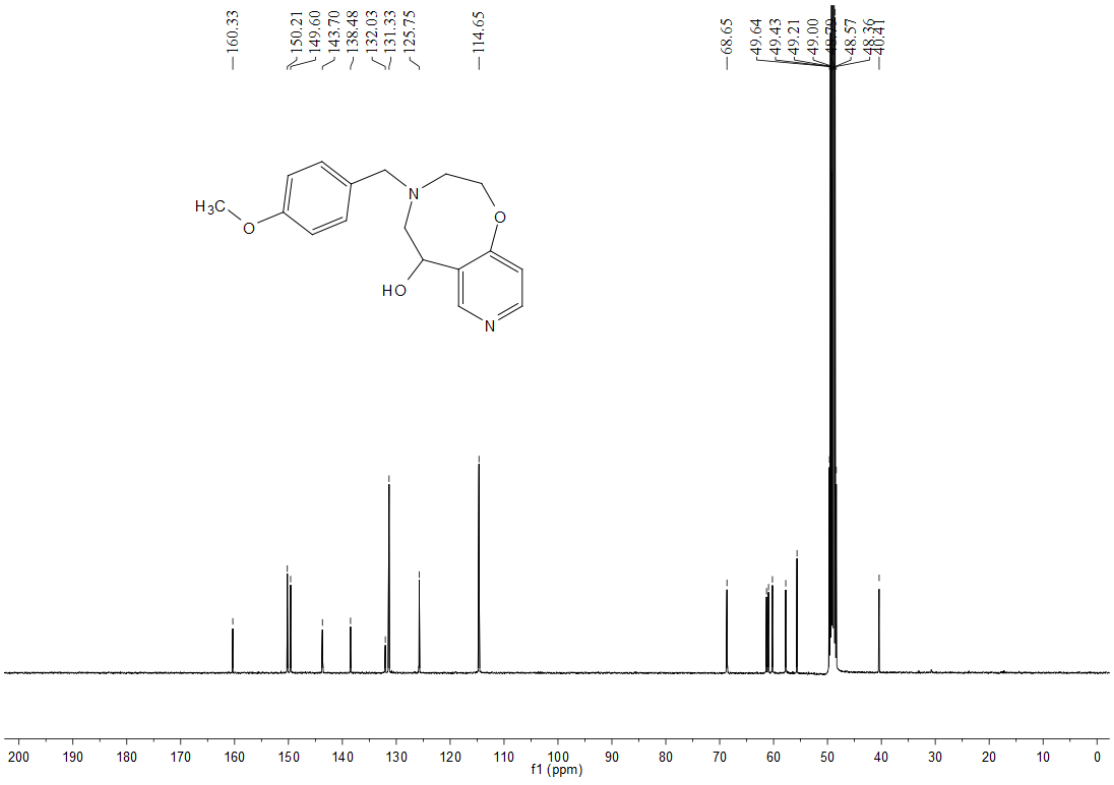


^{13}C NMR (100 MHz, CD_3OD) of **3bl**

4-(4-methoxybenzyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bs)

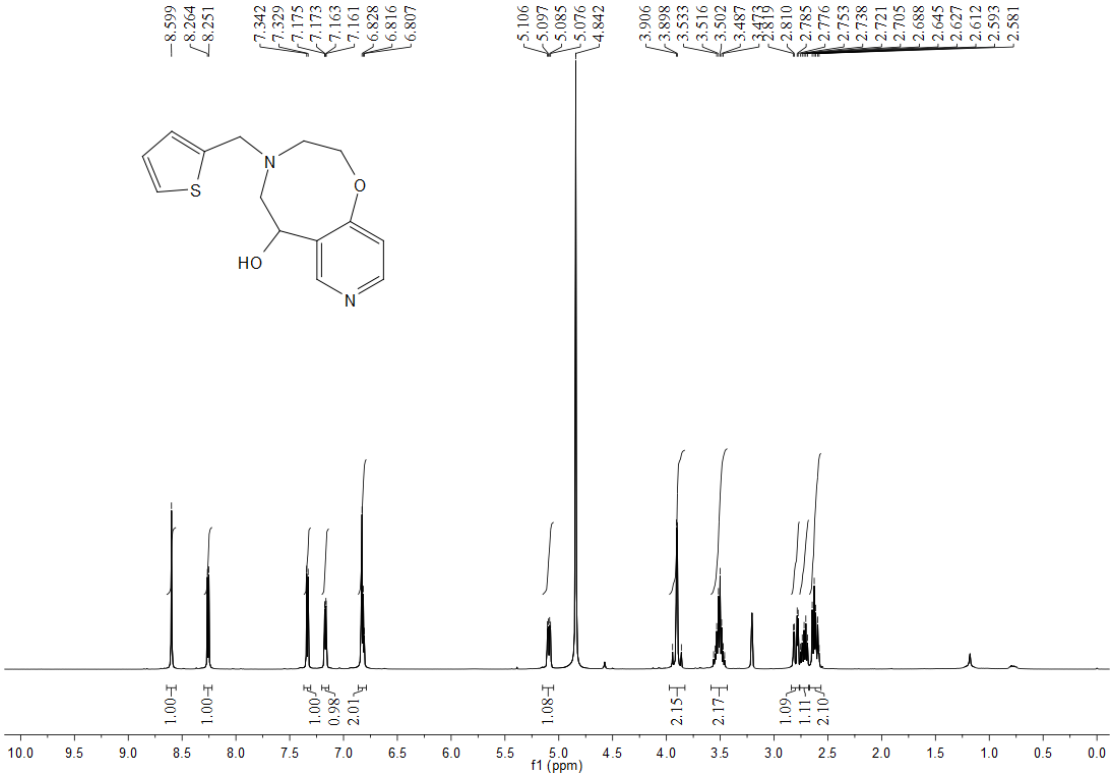


^{1}H NMR (400 MHz, CD_3OD) of **3bs**

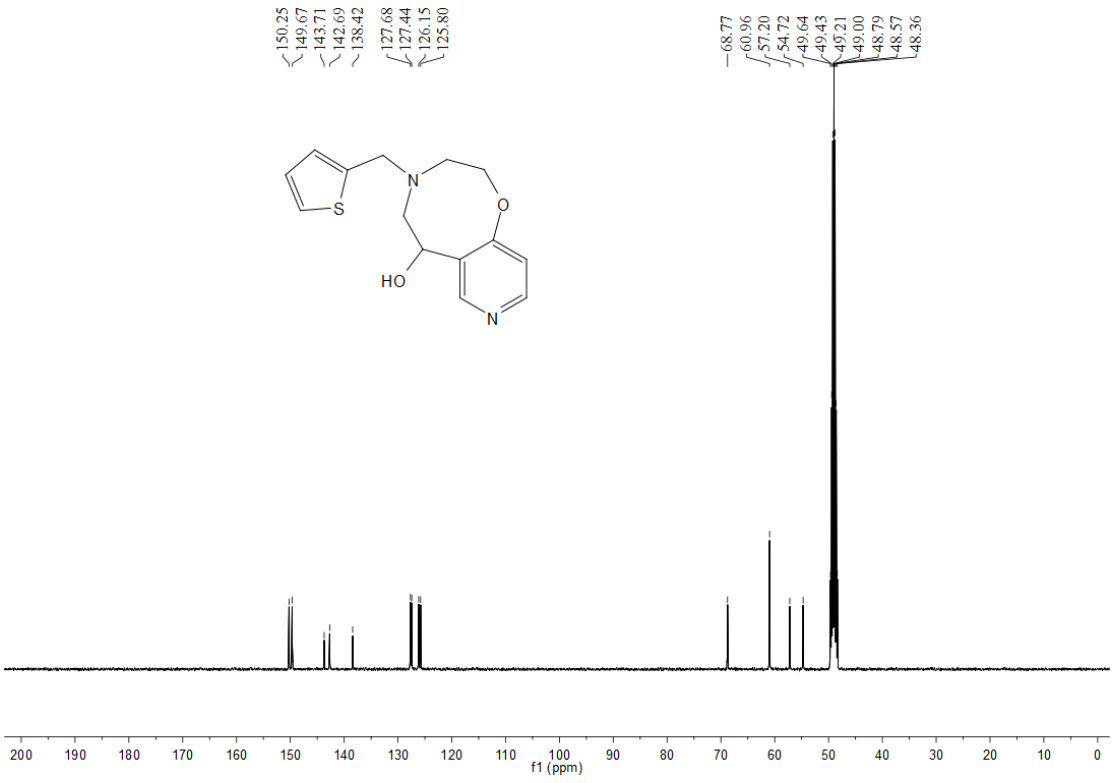


^{13}C NMR (100 MHz, CD_3OD) of **3bs**

4-(thiophen-2-ylmethyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bm)

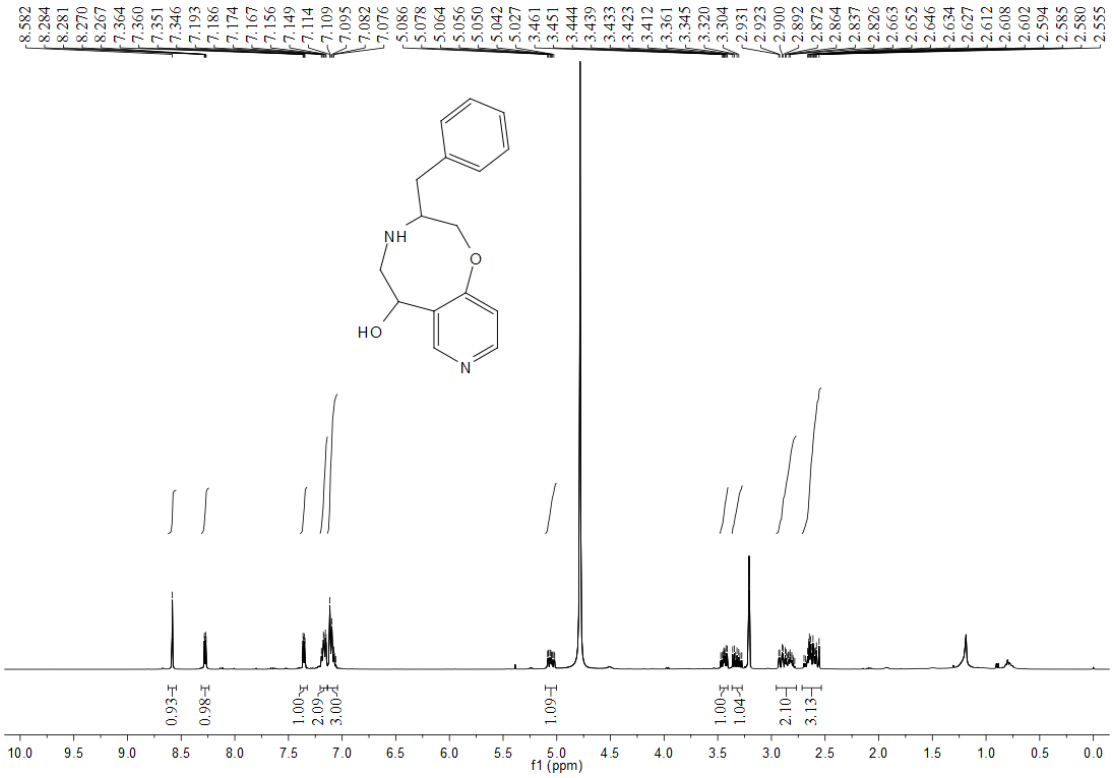


^{1}H NMR (400 MHz, CD_3OD) of **3bm**

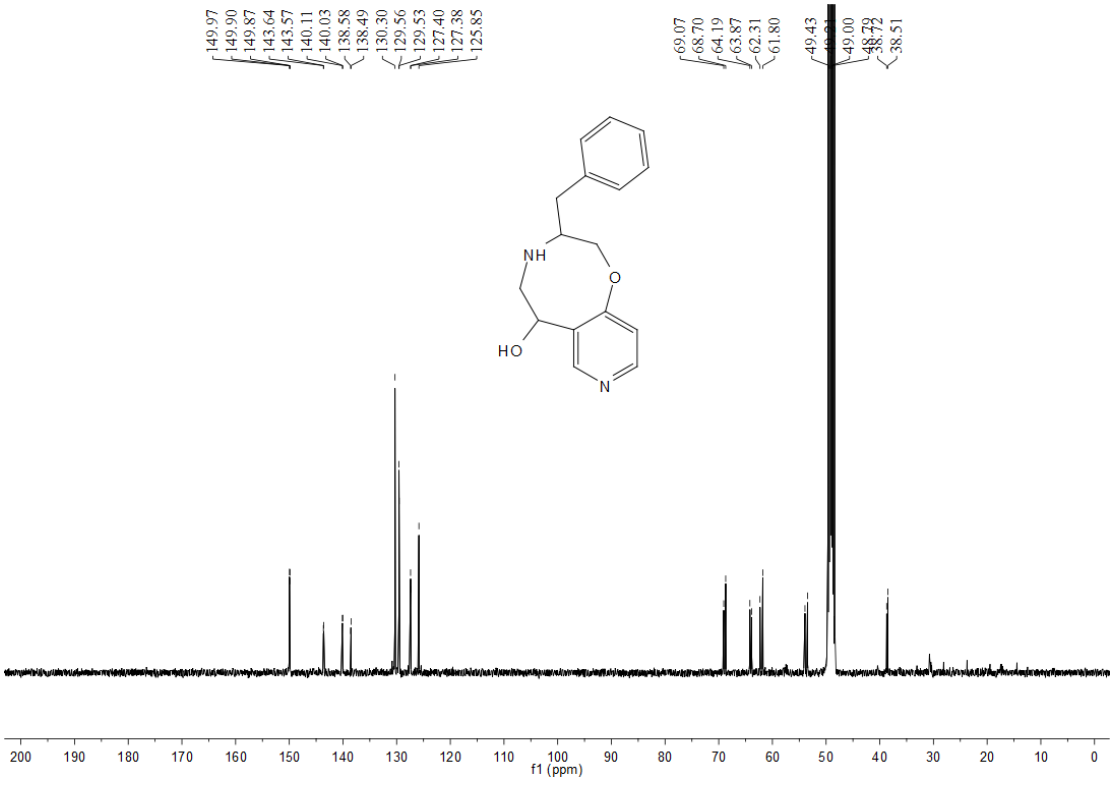


^{13}C NMR (100 MHz, CD_3OD) of **3bm**

3-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3bt)

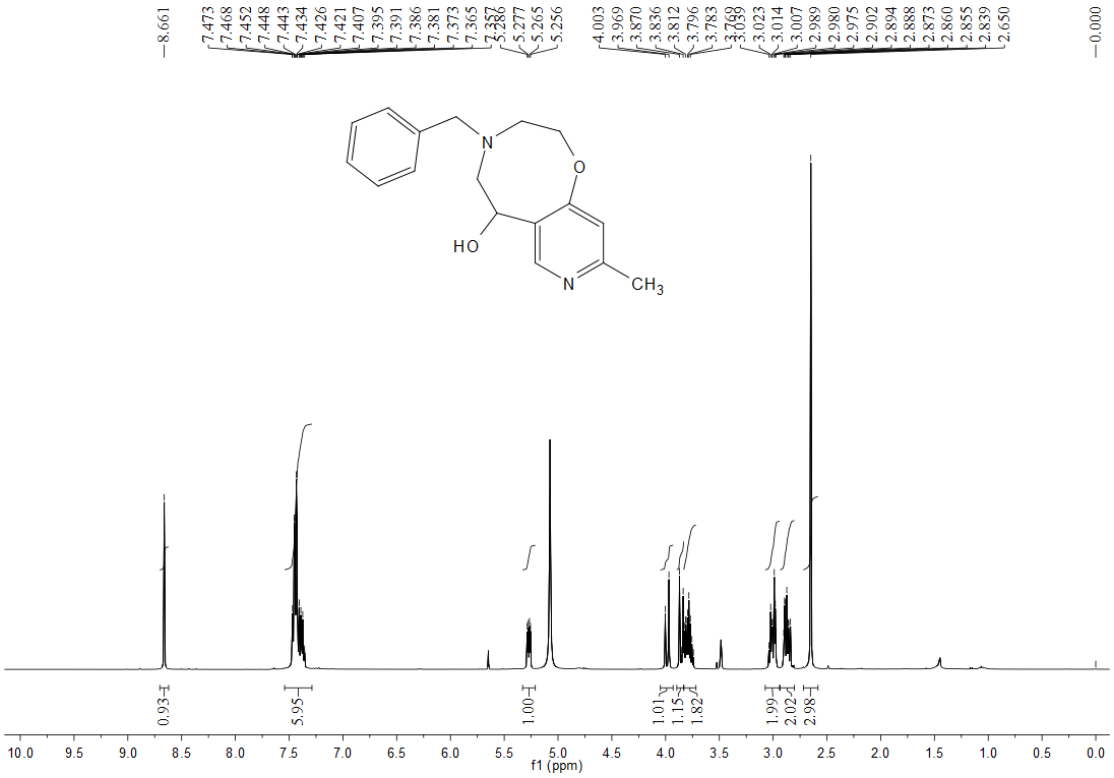


^{1}H NMR (400 MHz, CD_3OD) of **3bt**

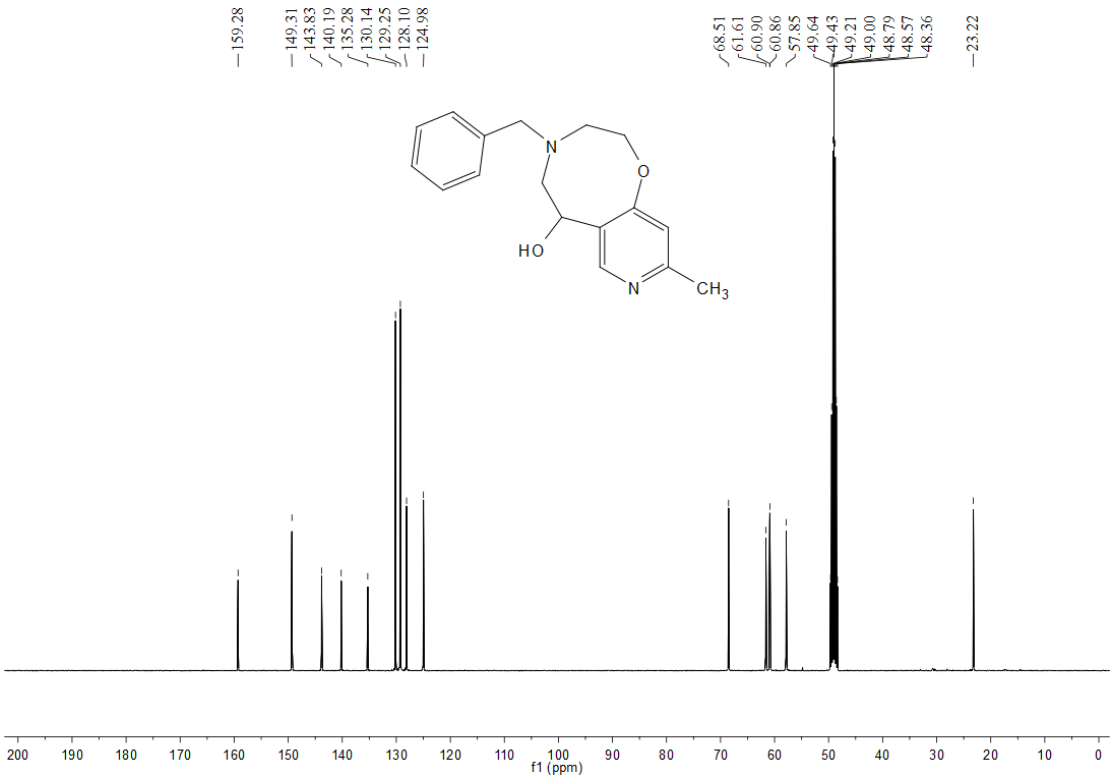


^{13}C NMR (100 MHz, CD_3OD) of **3bt**

4-benzyl-9-methyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3cl)

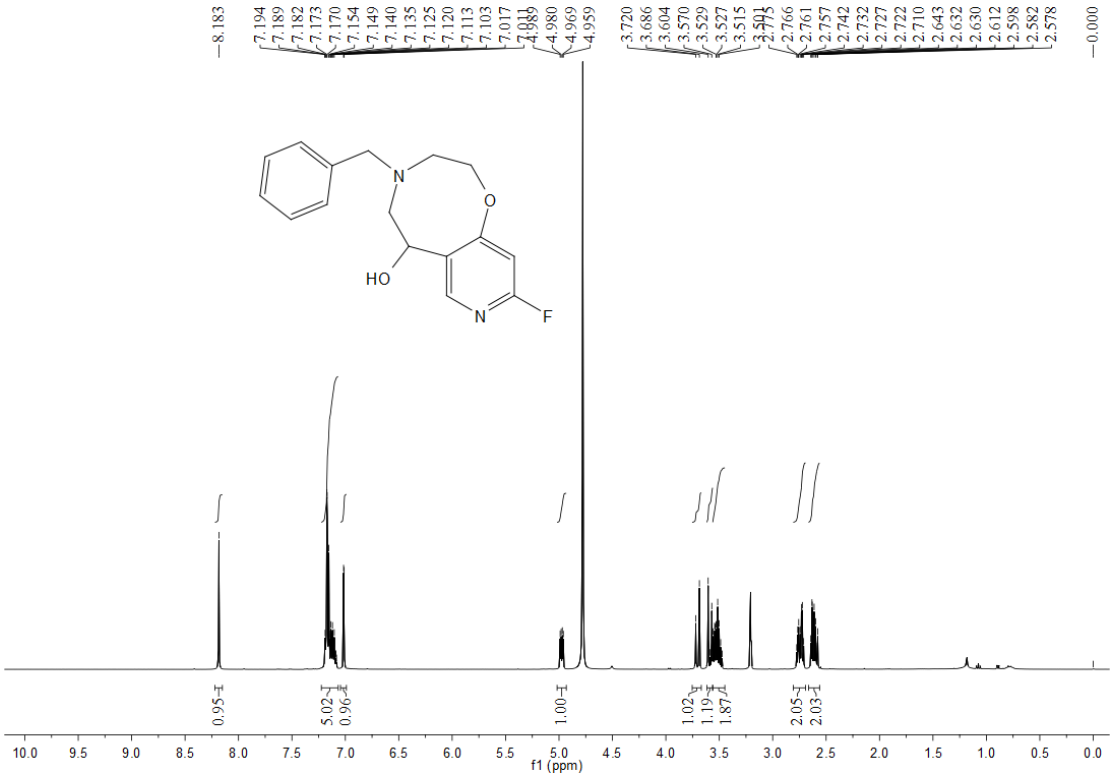


^{1}H NMR (400 MHz, CD_3OD) of **3cl**

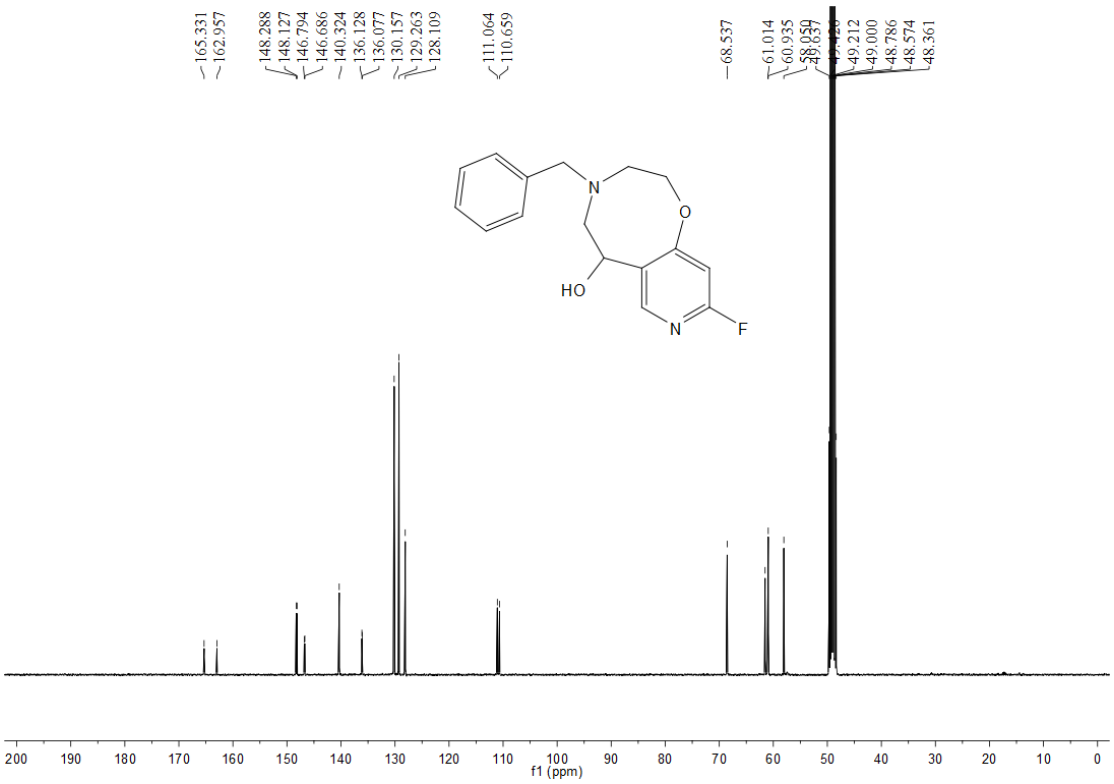


^{13}C NMR (100 MHz, CD_3OD) of **3cl**

4-benzyl-9-fluoro-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (3dl)

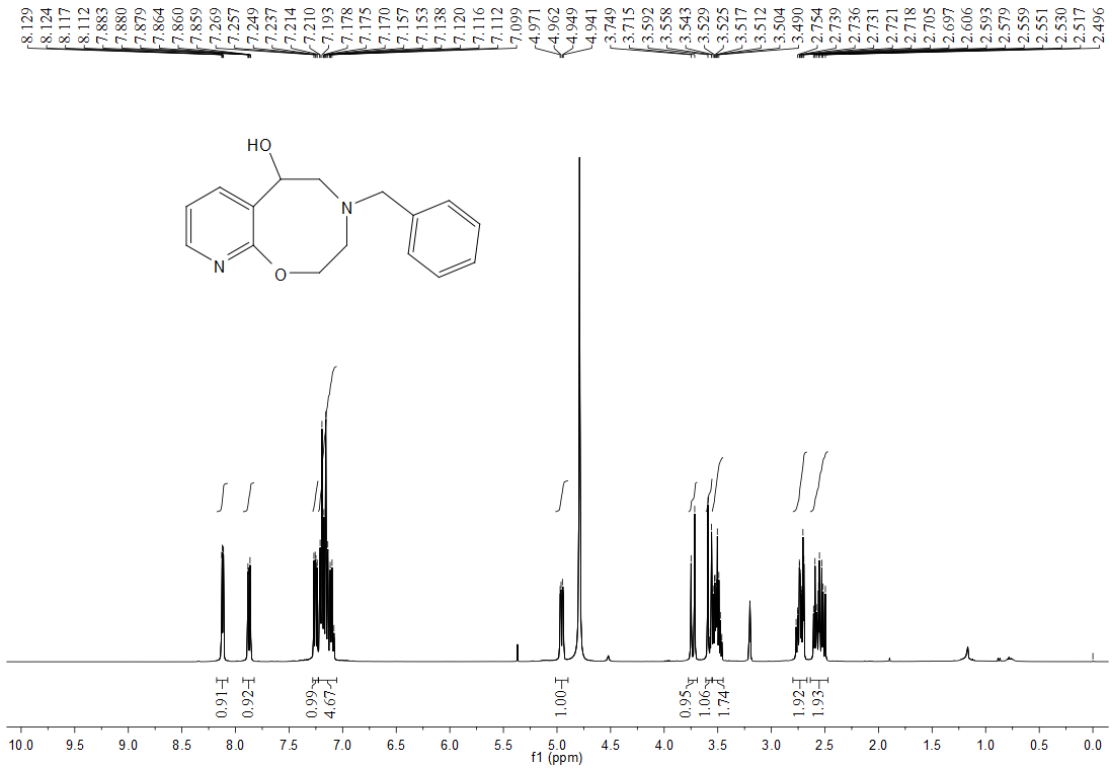


^{1}H NMR (400 MHz, CD_3OD) of **3dl**

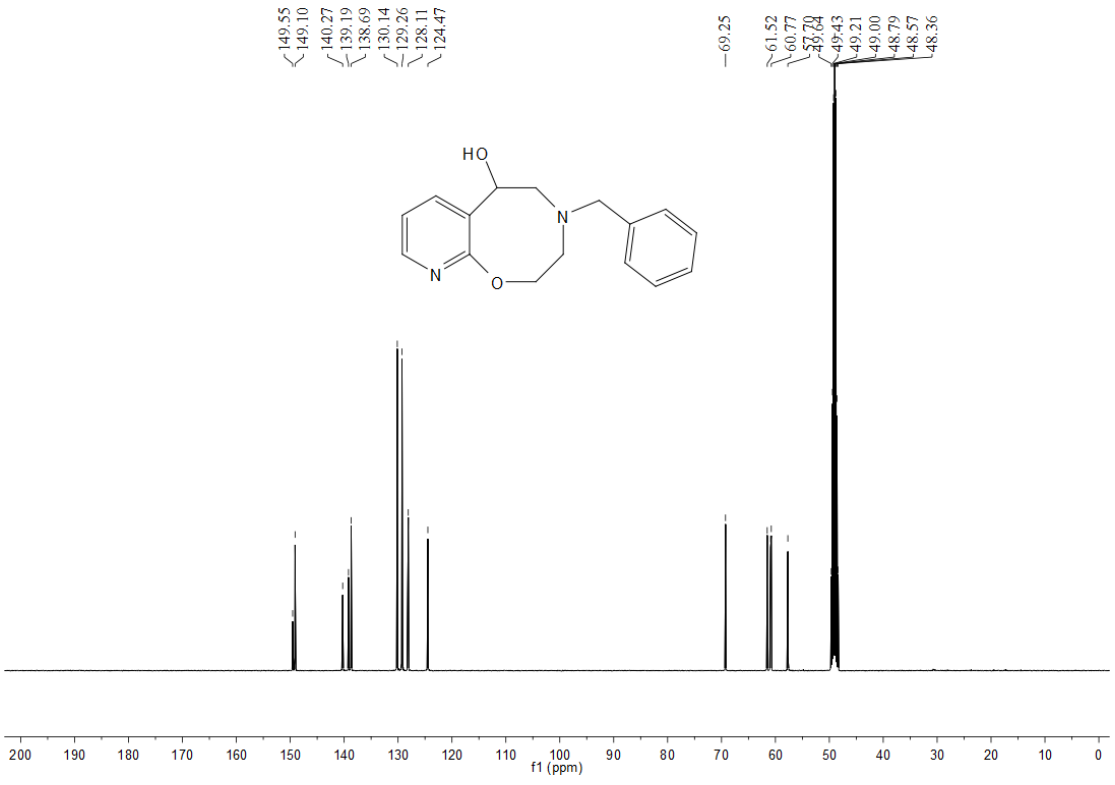


^{13}C NMR (100 MHz, CD_3OD) of **3dl**

4-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-6-ol (3el)

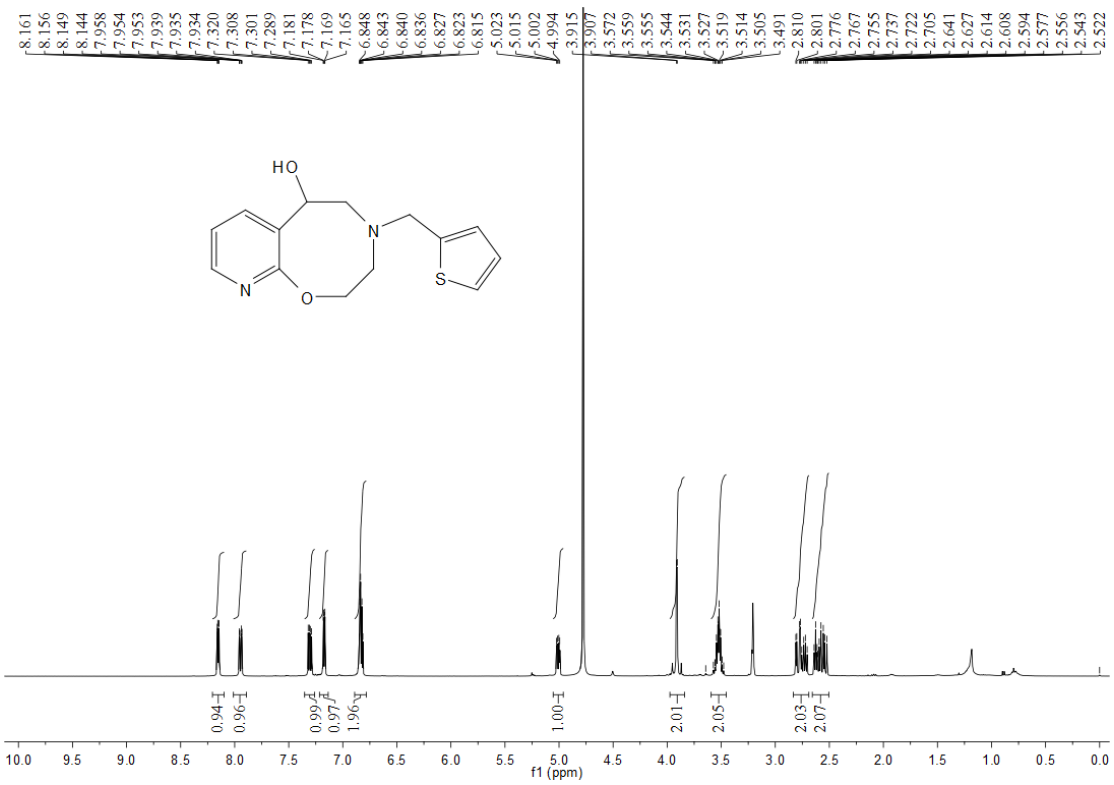


^{1}H NMR (400 MHz, CD_3OD) of **3el**

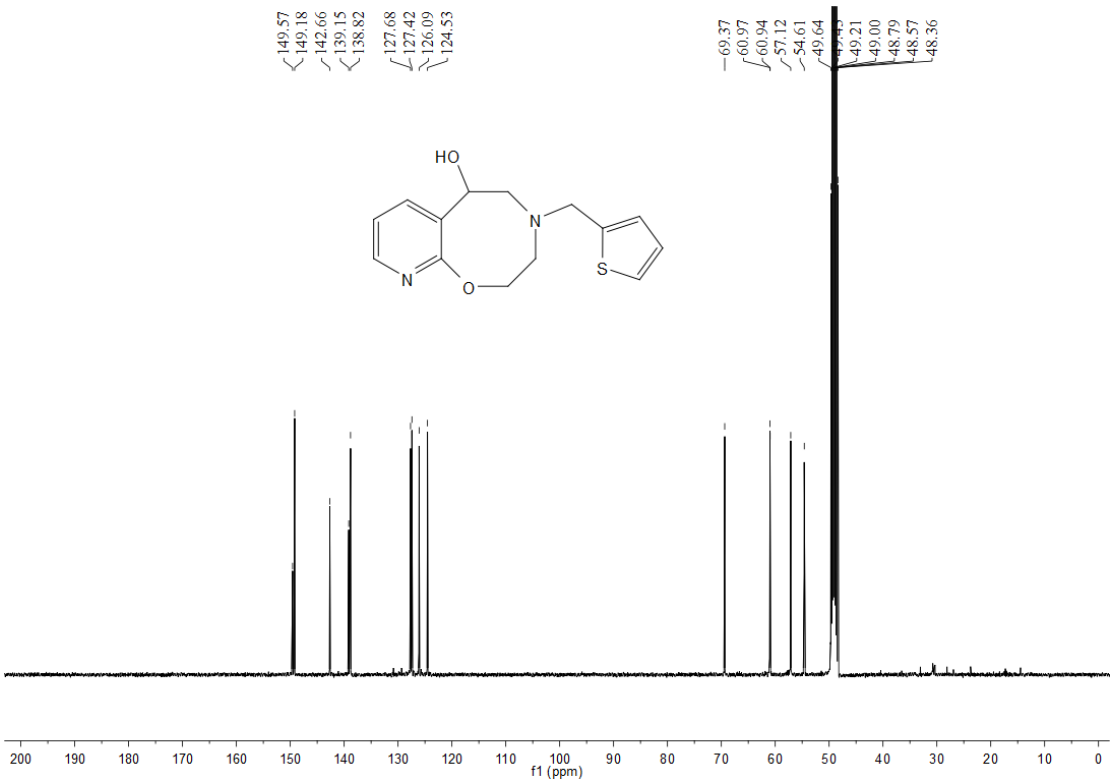


^{13}C NMR (100 MHz, CD_3OD) of **3el**

4-(thiophen-2-ylmethyl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-6-ol (3em)

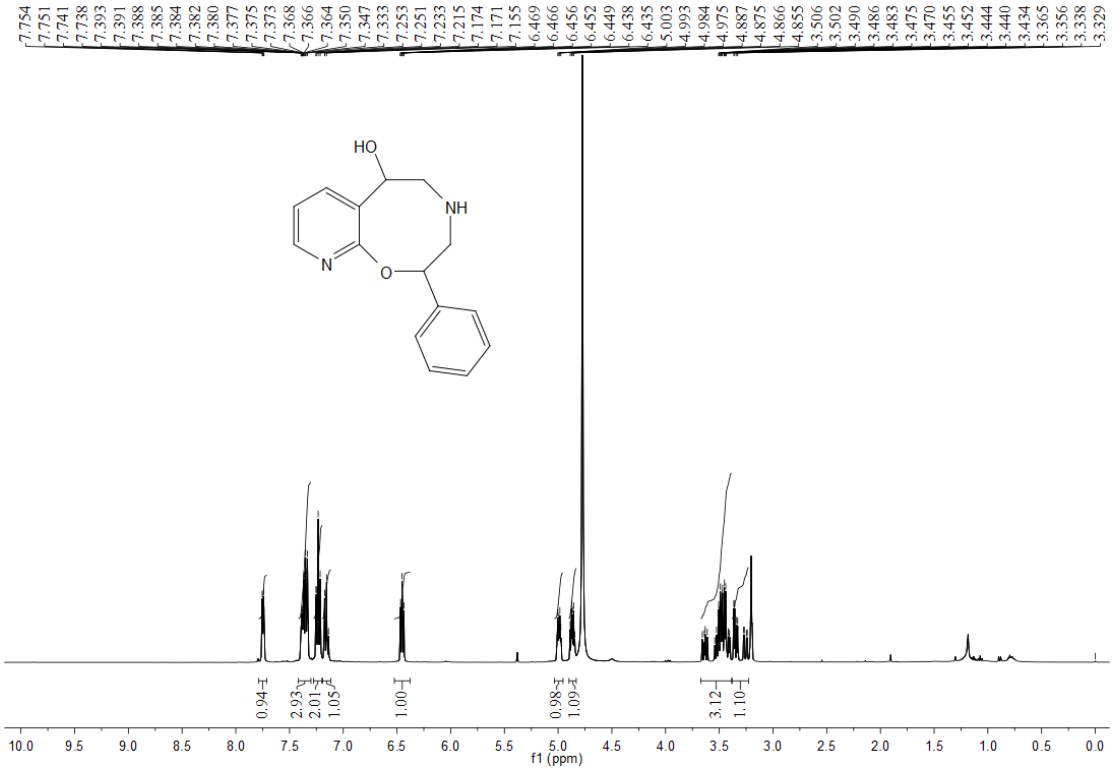


^{1}H NMR (400 MHz, CD_3OD) of **3em**

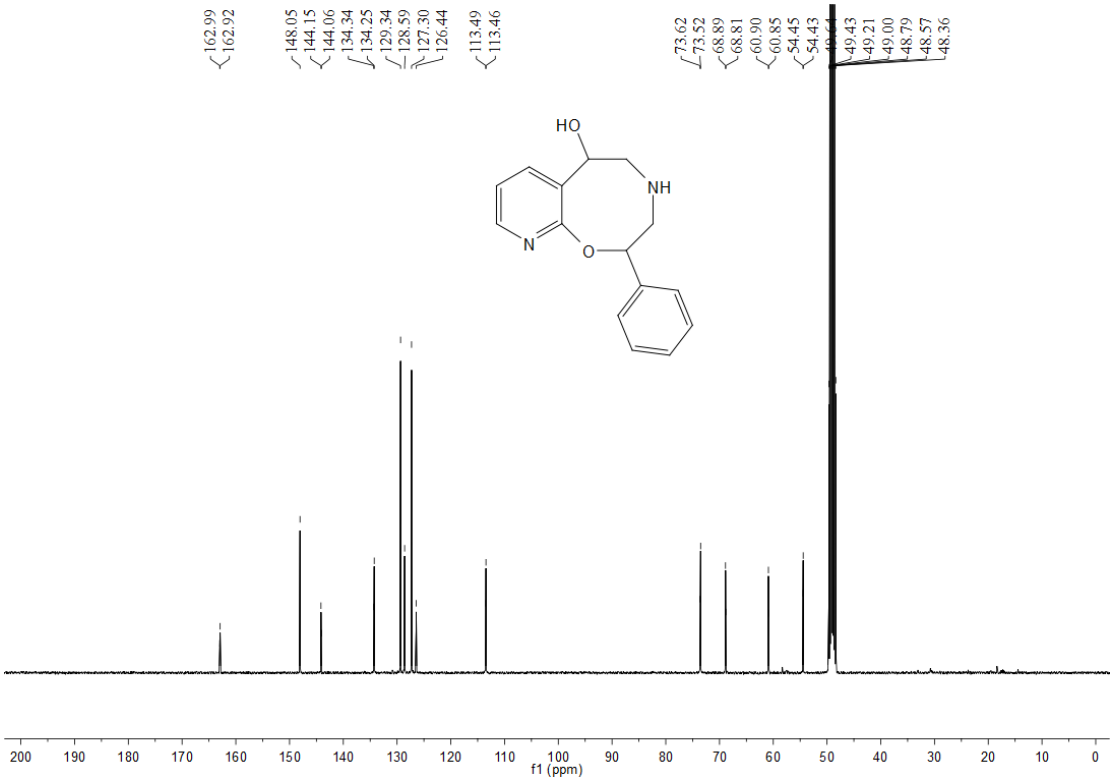


^{13}C NMR (100 MHz, CD_3OD) of **3em**

2-phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-6-ol (3eu)

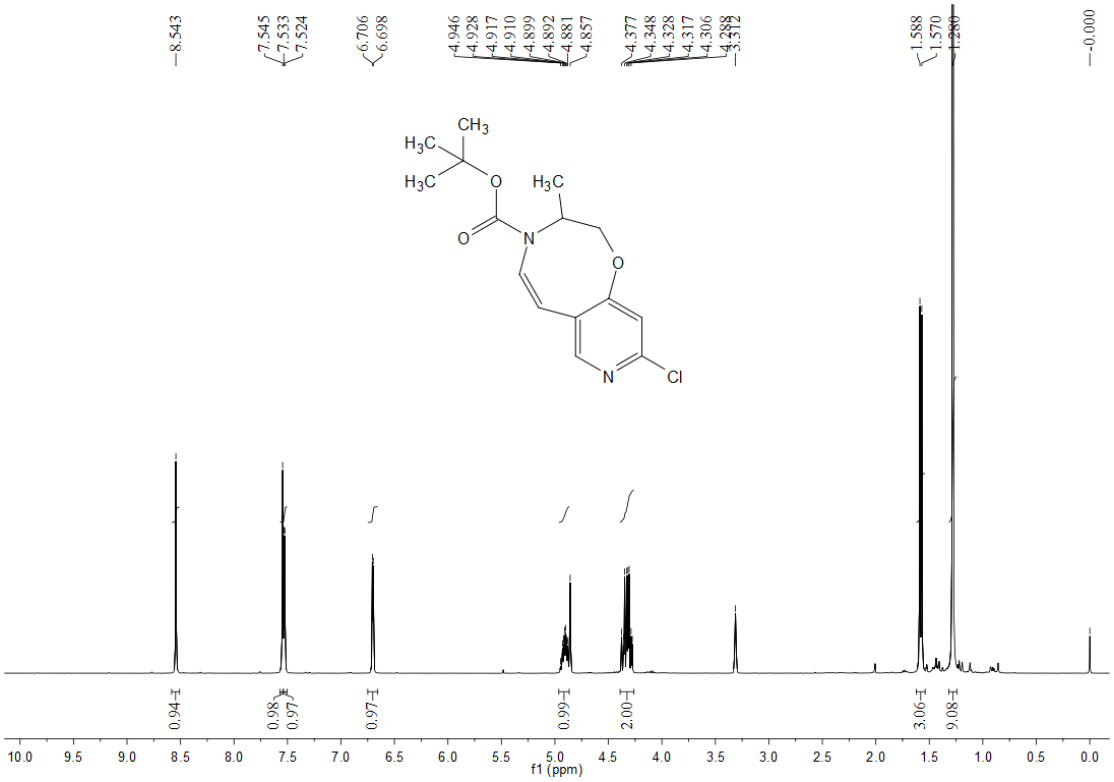


^{1}H NMR (400 MHz, CD_3OD) of **3eu**

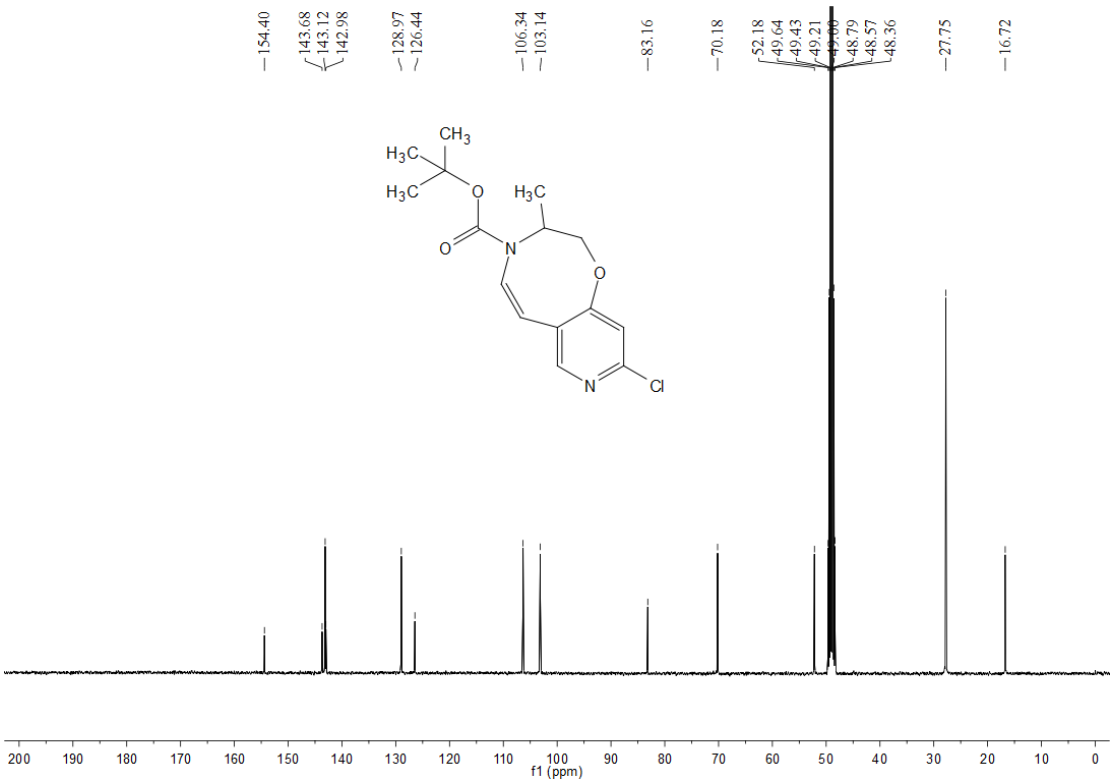


^{13}C NMR (100 MHz, CD_3OD) of **3eu**

***tert*-butyl (*Z*)-9-chloro-3-methyl-2,3-dihydro-4*H*-pyrido[3,4-*g*][1,4]oxazocine-4-carboxylate (4)**

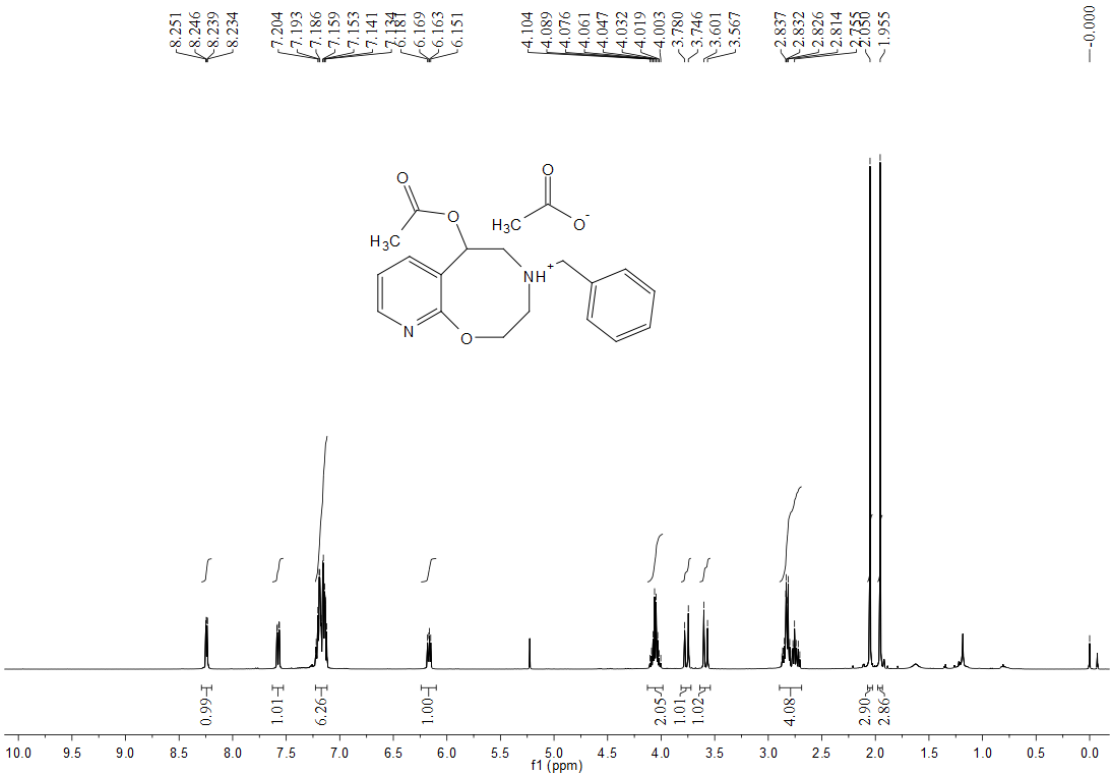


^{1}H NMR (400 MHz, CD_3OD) of **4**

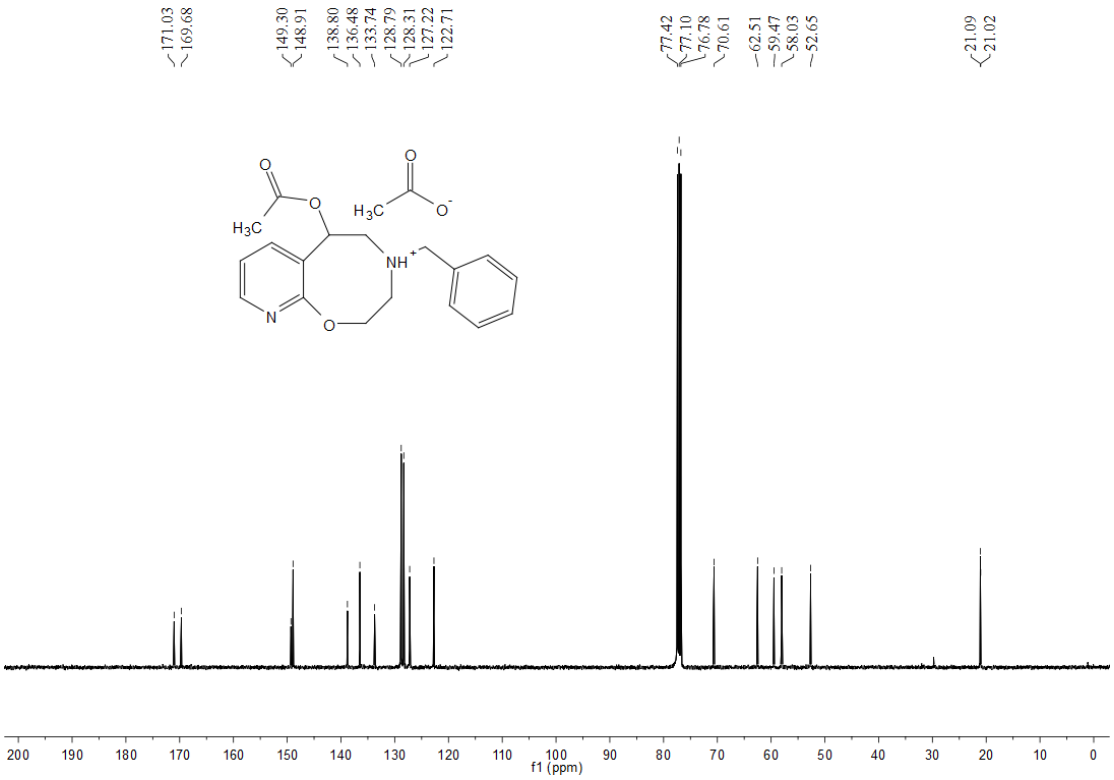


^{13}C NMR (100 MHz, CD_3OD) of **4**

6-acetoxy-4-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-4-ium acetate (5)

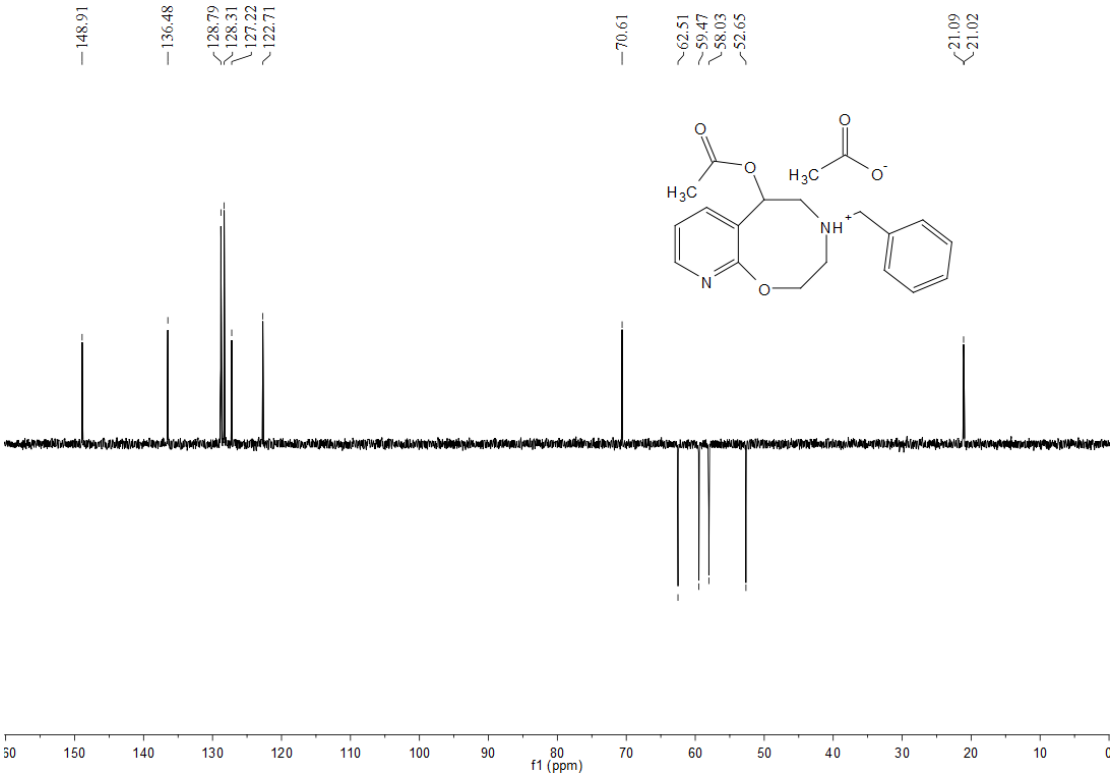


^{1}H NMR (400 MHz, $CDCl_3$) of **5**

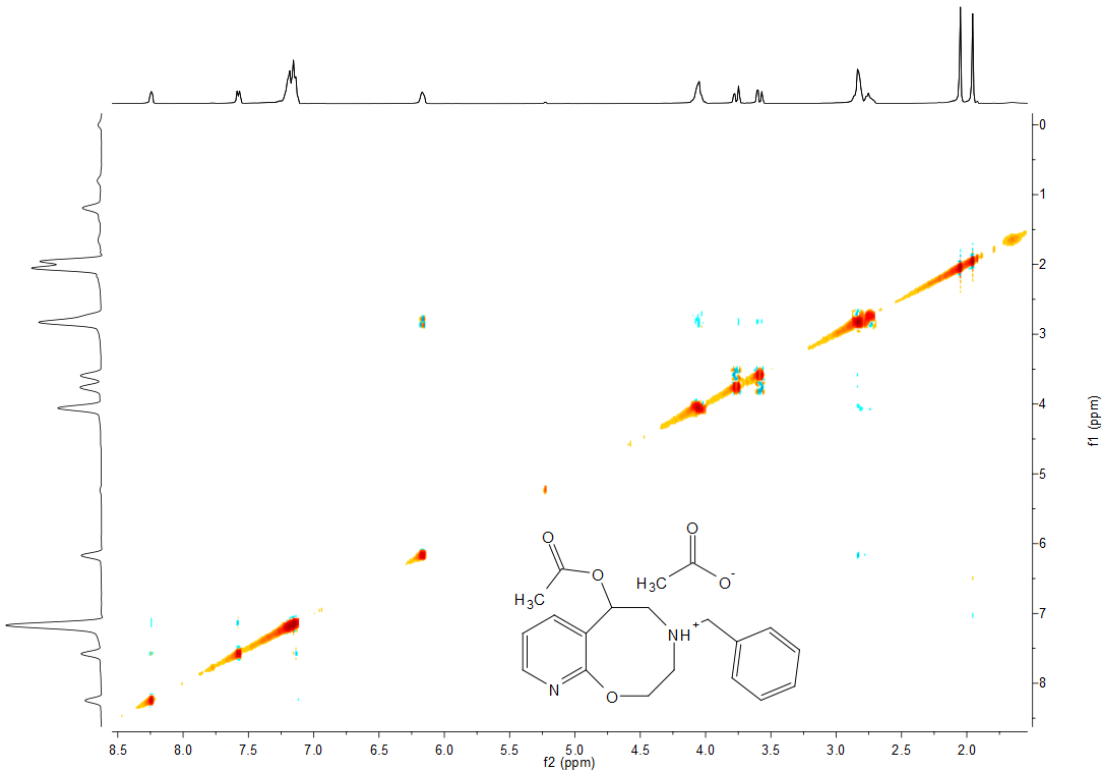


^{13}C NMR (100 MHz, $CDCl_3$) of **5**

6-acetoxy-4-benzyl-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocin-4-ium acetate (5)

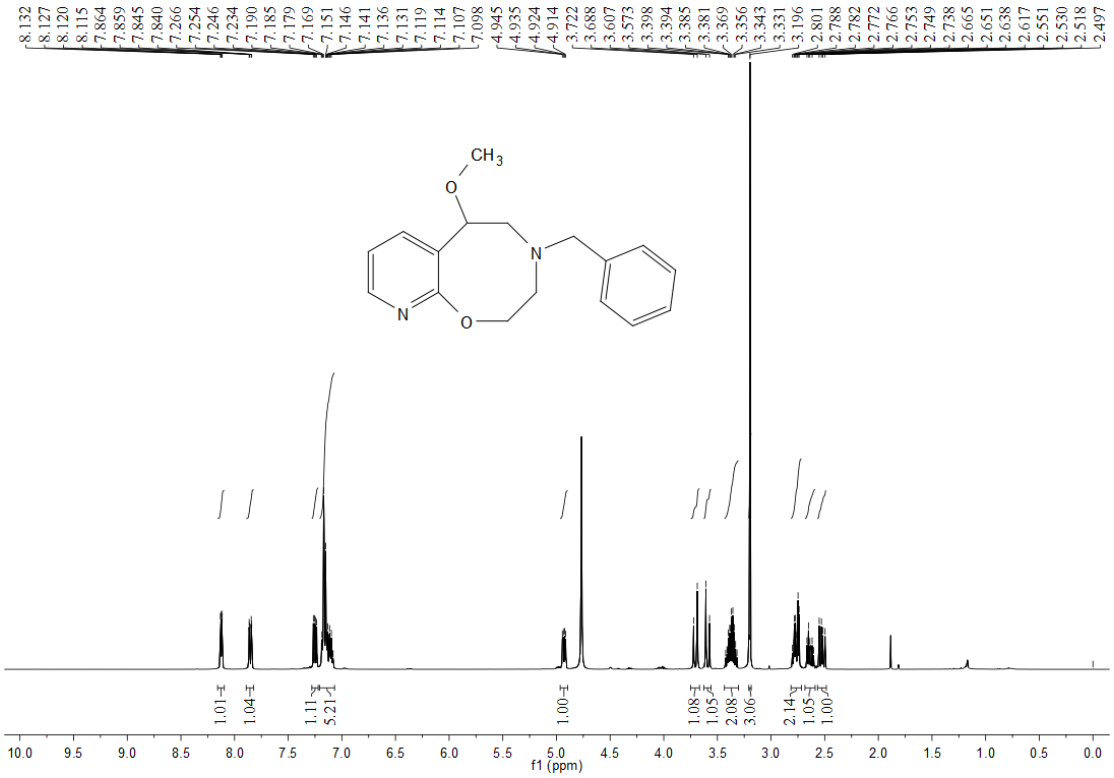


DEPT135 of **5**

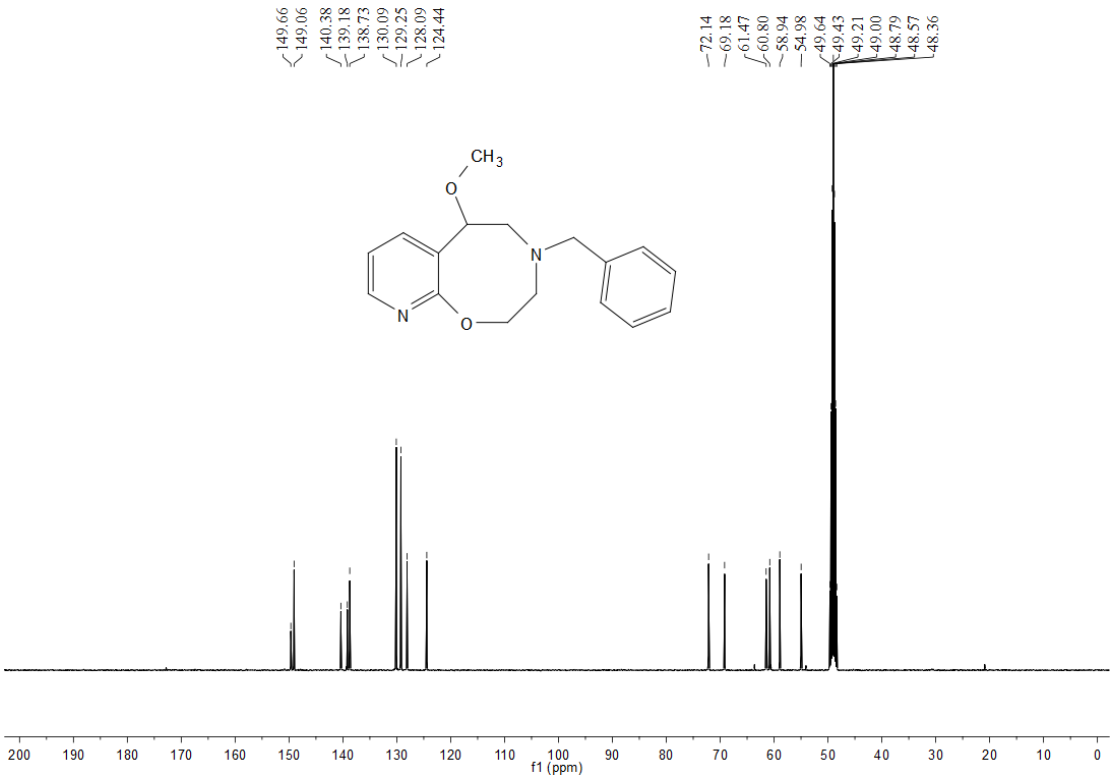


NOESY of **5**

4-benzyl-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*g*][1,4]oxazocine (6)

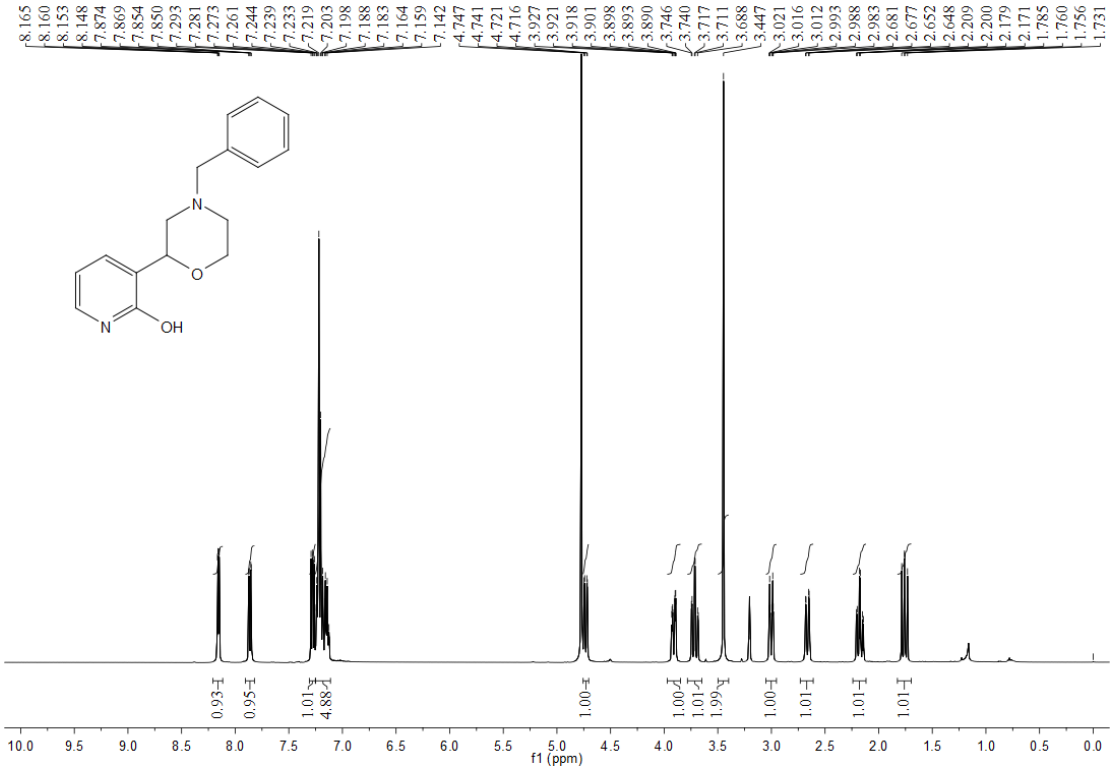


^{1}H NMR (400 MHz, CD_3OD) of **6**

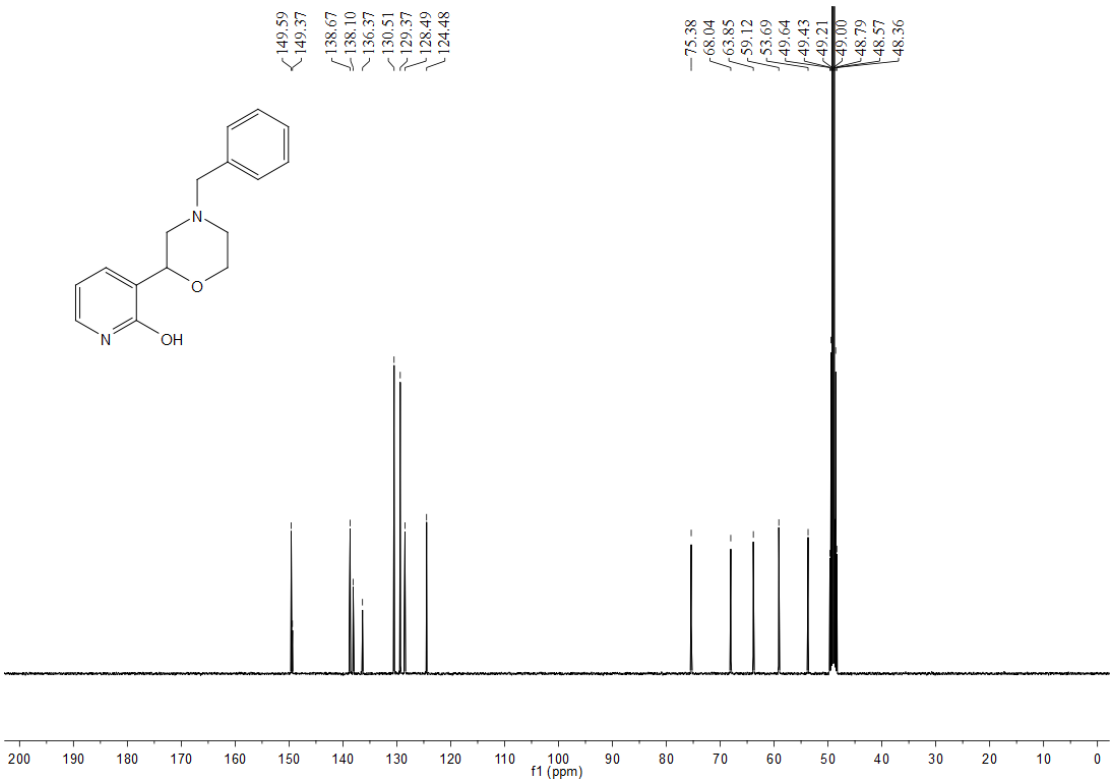


^{13}C NMR (100 MHz, CD_3OD) of **6**

3-(4-benzylmorpholin-2-yl)pyridin-2-ol (7)

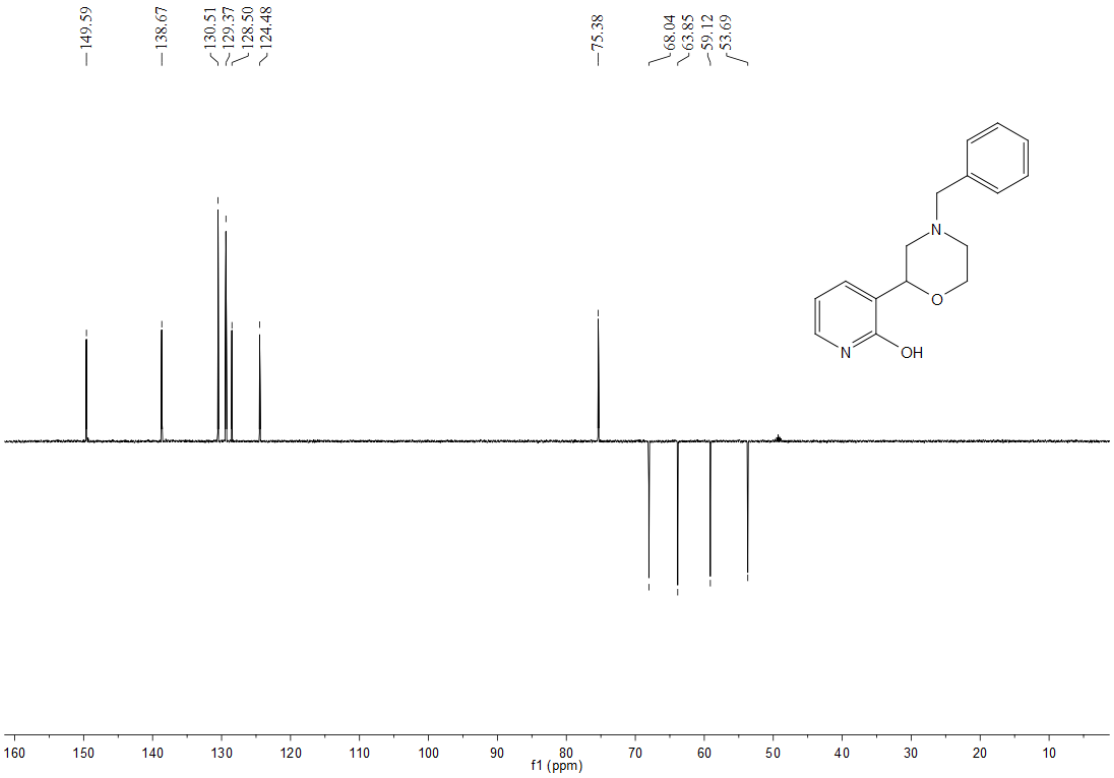


^{1}H NMR (400 MHz, CD_3OD) of **7**

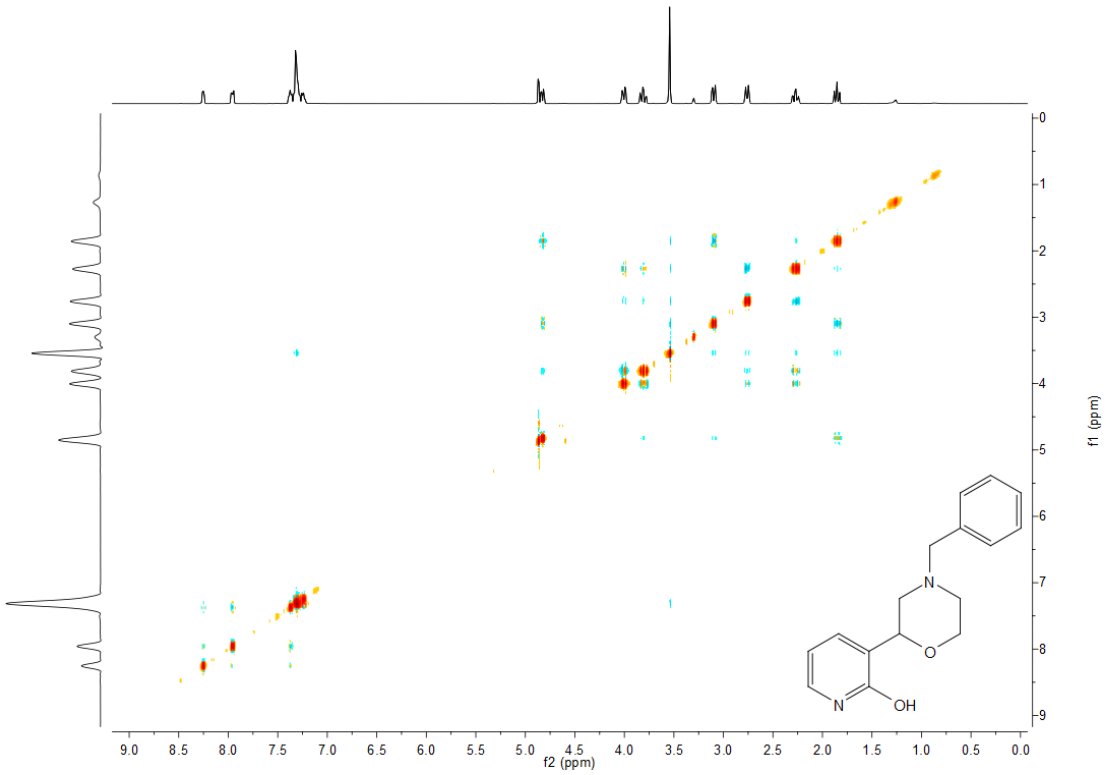


^{13}C NMR (100 MHz, CD_3OD) of **7**

3-(4-benzylmorpholin-2-yl)pyridin-2-ol (7)

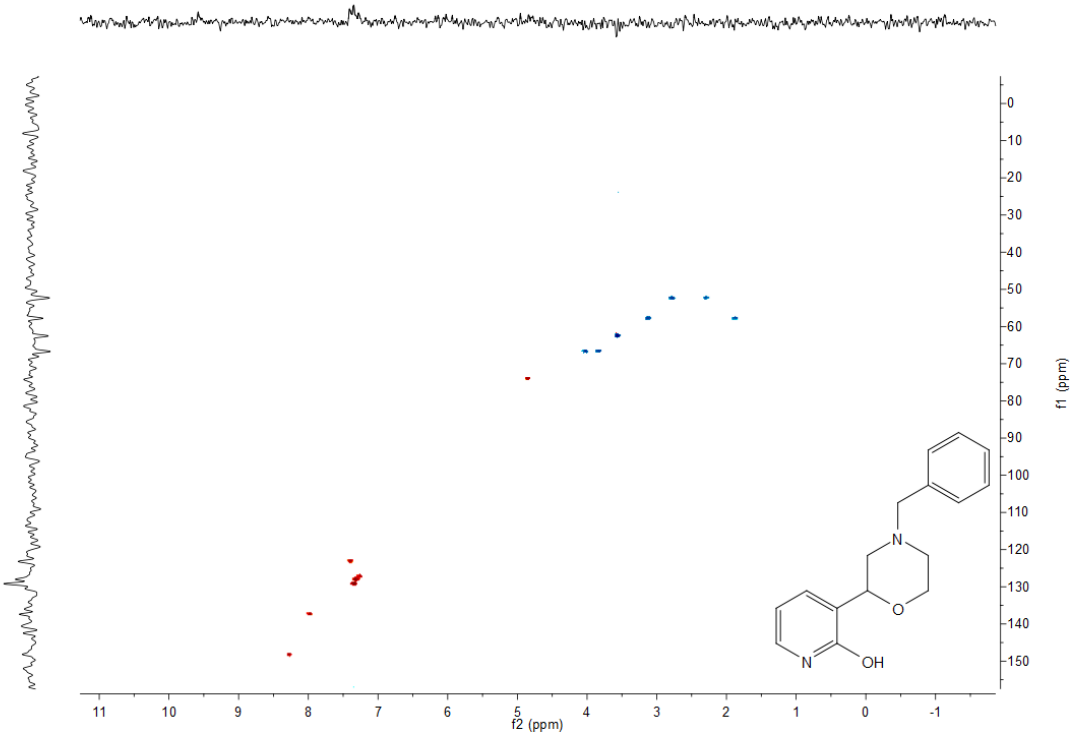


DEPT135 of **7**

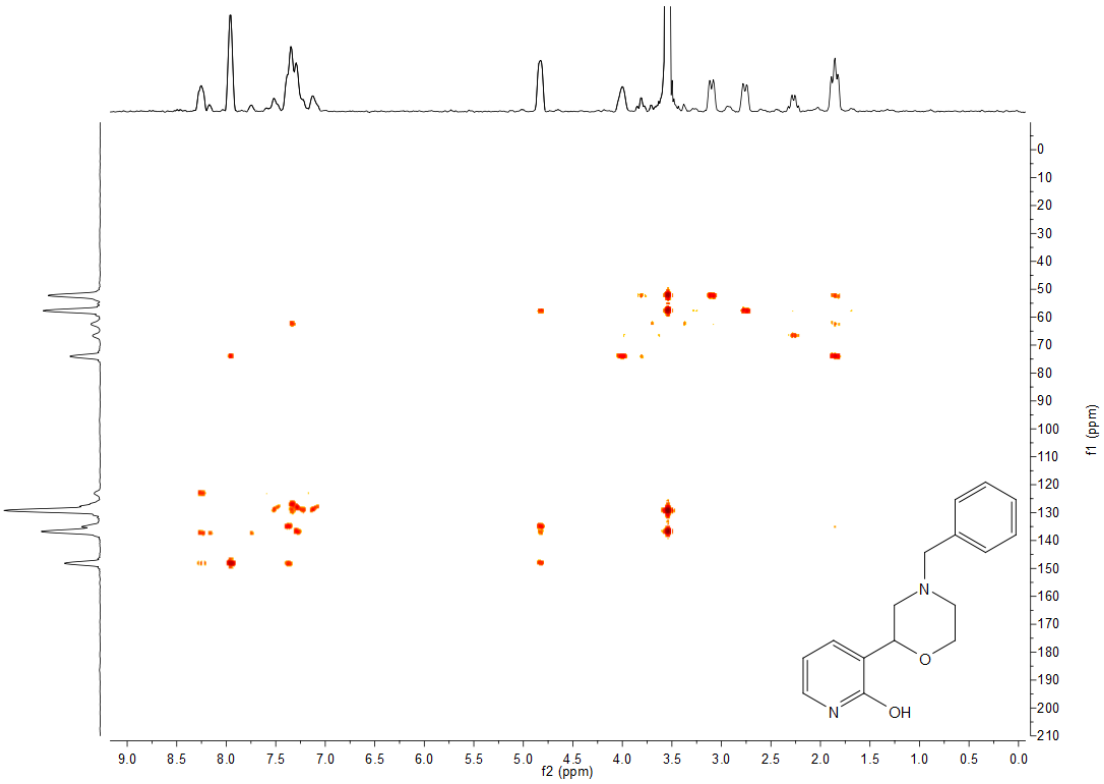


NOESY of **7**

3-(4-benzylmorpholin-2-yl)pyridin-2-ol (7)

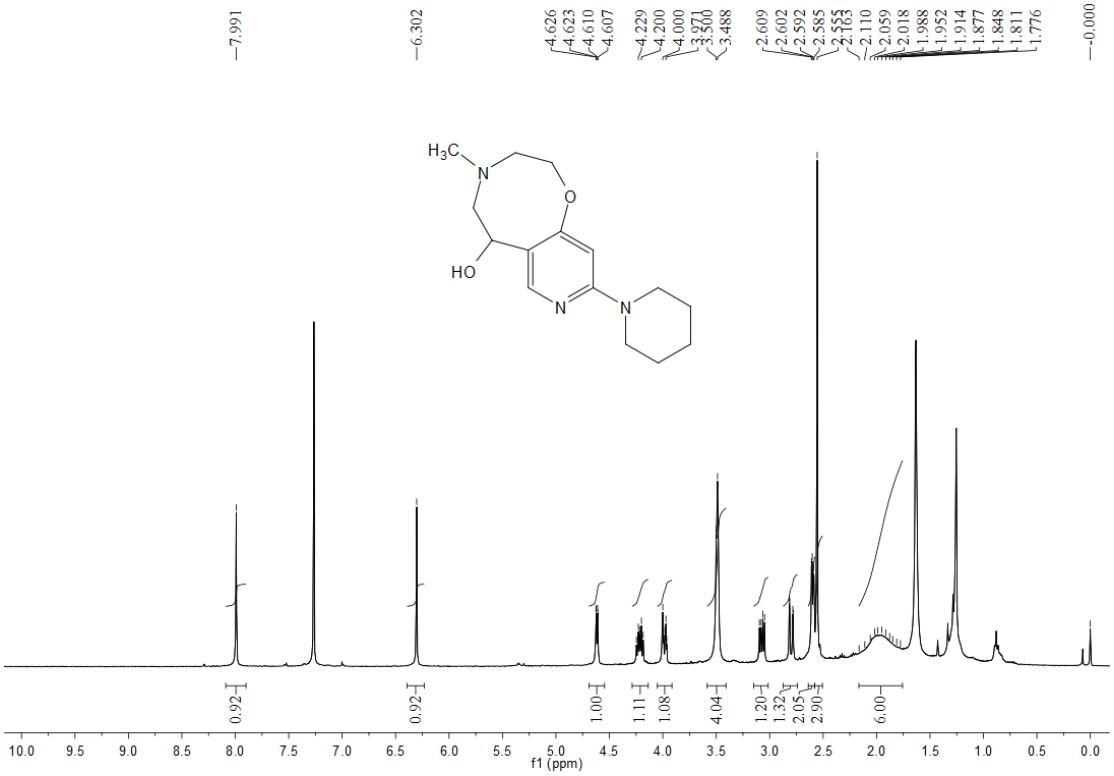


HSQC of **7**

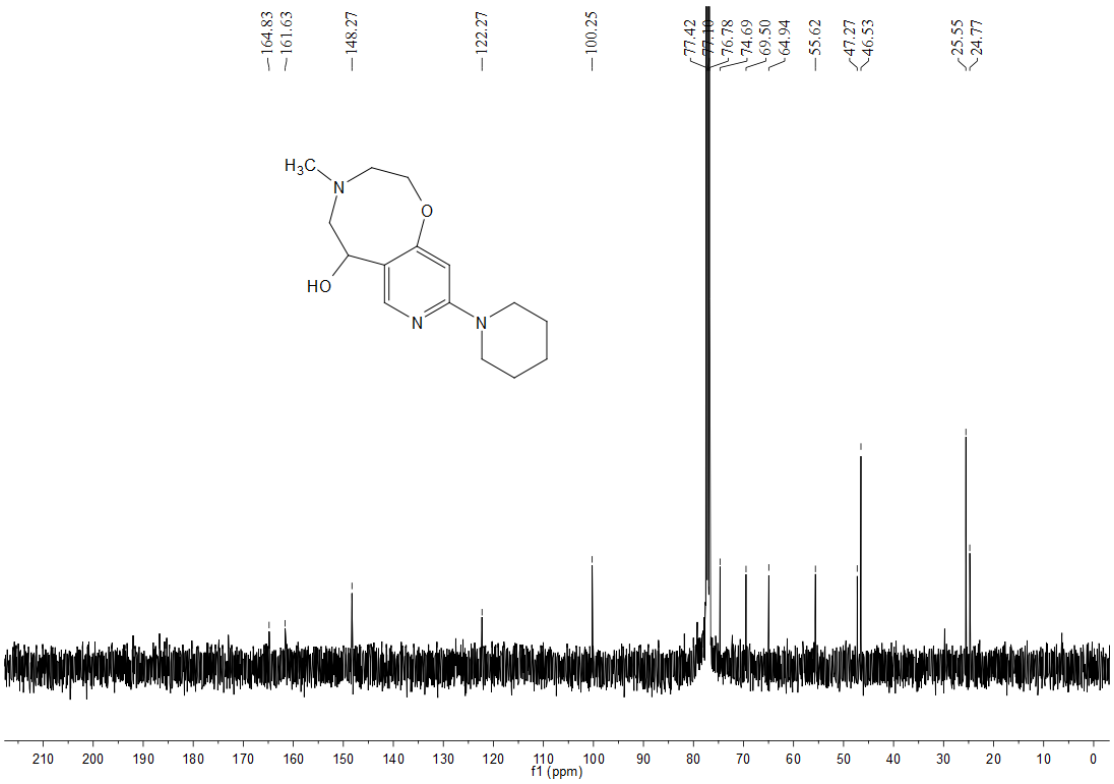


HMBC of **7**

4-methyl-9-(piperidin-1-yl)-3,4,5,6-tetrahydro-2*H*-pyrido[3,4-*g*][1,4]oxazocin-6-ol (8)



^{1}H NMR (400 MHz, $CDCl_3$) of **8**



^{13}C NMR (100 MHz, $CDCl_3$) of **8**