Supporting Information

Hydrogen-bond Guided Reaction of Cyclohexadienone-aldehydes with Amines: Synthesis of Aminal group containing Fused Tetracyclic Framework

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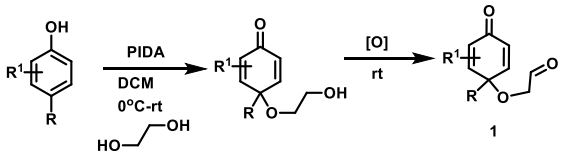
[1] General

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on Bruker Avance III 400 spectrometer at 25 °C. The chemical shifts in ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra are reported in parts per million (ppm) and are referenced to the residual solvent signal as the internal standard; ^{1}H NMR spectra ($CDCl_3$ δ 7.26 ppm), ^{13}C ($CDCl_3$ δ 77.16). Coupling constants (*J*) are quoted in Hz. Splitting patterns are denoted as "s" for singlet; "d" for doublet; "t" for triplet; "q" for quartet; "sext" for sextet; "sept" for septet; "m"formultiplet, "br" for broad; "dt" for doublet of triplets; "td" for triplet of doublets, and "app" for apparent. Assignment of proton signals was assisted by ^{1}H, ^{1}H COSY, HSQC and HMBC experiments. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively using Bruker AVANCE 400. High Resolution Mass Spectra (HRMS) were recorded on Q-TOF mass spectrometer at SAIF department in CSIR-CDRI, Lucknow, India. Column chromatography was done in 60-120Å or 100-200 Å mesh silica gel of Merck Company. All solvents were distilled for purification in column chromatography. Reagents and starting materials were used as received from company. THF and toluene were distilled from sodium benzophenone ketyl and other solvents were distilled under standard procedures. Starting materials were synthesized with the procedure that reported in literature. Wherever, it is noted the reaction under heating conditions; the reaction flask was heated in the oil bath and temperature recorded was corresponds to the temperature of oil bath.

[2] Preparation of starting materials (1):

The general reaction procedure for the preparation of 3-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl) propanal (cyclohexadienone-aldehydes; **1**) were followed the method reported previously.[S1]

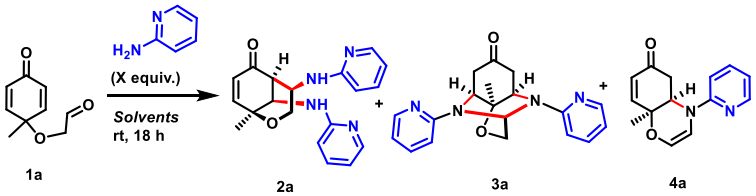


The experimental procedures are followed as below.
A dried 250 mL round bottom flask was charged with substituted phenol (10-20 mmol) and ethylene glycol (300 mmol) the flask was degassed under line vacuum and then refilled with argon. To the reaction flask, 10 mL $CH_2Cl_2$was added. Subsequently, $PhI(OAc)_2$ (11 mmol, dissolved in 20 ml CH_2Cl_2) was added dropwise over an hours and reaction mixture was allowed to stir at ambient temperature for further 1-6hrs (monitored by TLC). The solution was concentrated in vacuo and the residue was subjected to column chromatography (eluated with 25-30%EtOAc in Hexane) to provide cyclohexadienone-alcohol as thick oil(60-75% yield).Formation of the intermediate compound was confirmed with the reported spectral data.[1,2]Cyclohexadienone-alcohol was then subjected to oxidation step using Dess-Martin periodinone (DMP; 1.1 equiv.)in CH_2Cl_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and the stirring was continued for 2-6h. After completion the reaction mixture (monitored by TLC using $KMnO_4$ and PMA; 50% EtOAc in Hexane, comes close to starting material), it was passed through the pad of celite and the organic layer was concentrated and purified on filter silica gel column using 100% CH_2Cl_2 to obtain the pure compound **1** as colorless oil (almost quantitative yield; 55-70% over two steps). The spectral data were completely in match with the reported aldehydes.[S1]

Note: In place of DMP, IBX (1.2 equiv.) also gave the aldehyde **1** in quantitative yield under reflux conditions in ethyl acetate).

[3] Optimization of reaction conditions

Table S1. Optimization Table



run[a]	X equiv.	solvent	add. conditions	yield (%)[b] 2a[c]	3a	4a
1	1.5	Toluene	-	-	40	5
2	1.5	DMSO	-	-	trace	-
3	1.5	Dioxane	-	-	35	5
4	1.5	CH_3CN	-	-	50	10
5	1.5	MeOH	-	-	60	8
6	1.5	CH_2Cl_2	-	-	35	5
7	1.5	MeOH	MS (4 A°)	-	65	10
8	2.2	MeOH	MS (4 A°)	-	71	5
9	2.2	CH_3CN	*p*-TSA	-	65	10
10	2.2	MeOH	-	-	62	15

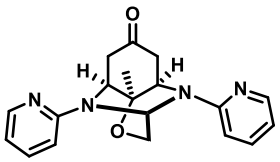
[a]Reaction was conducted at 0.5 mmol scale in 2 mL solvent. [b]Isolated yields are mentioned.[c]"-" means not observed.

General Procedure for optimization: To the reaction vial, cyclohexadienone-aldehyde (**1a**, 83.0 mg, 0.5 mmol), 2-aminopyridine (0.75 to 1.1 mmol) were added in solvent (2 mL) and stirred at room temperature. After the completion of reaction with reference to **1a** (monitored by TLC under UV, iodine and $KMnO_4$), solvent was evaporated under reduced pressure and the further purified by silica gel column chromatography to receive **3a** as a pale yellow solid (R_f 0.3; 30% EtOAc in hexane, eluted at 20%) along with bicyclic product **4a** (R_f 0.7; 30% EtOAc in hexane, eluted at 10%). The structures of these products were confirmed by detail spectral analyses (2D correlation NMRs, representative example shown for compound **3j**, *vide infra*) and X-ray for **3a** and others were assigned by analogy.

[4] Synthesis and spectral data

4A: Reaction with 2-aminopyridines: General Procedure for the synthesis tetracyclic compounds were followed the optimal condition (run 8, Table S1)

(3*S,4a*R**,8*S**,8a*S**)-8a-methyl-4,9-di(pyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3a):** General procedure was followed with **1a** (83 mg, 0.5 mmol), 2-aminopyridine (103 mg, 1.1 mmol) at room temperature for 18 h to furnish **3a** as a white solid (119 mg, 0.35 mmol, 71% yield).

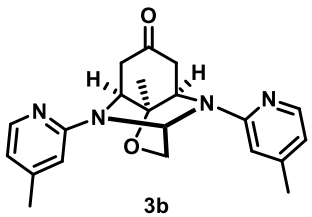


3a

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21(dd, *J* = 5.0, 1.4 Hz, 2H), 7.53 (ddd, *J* = 7.9, 1.9, 1.4 Hz, 2H), 6.85 (s, 1H), 6.69 (dd, *J* = 6.1, 2.3 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.40 (s, 2H), 4.07 (d, *J* = 1.6 Hz, 2H), 3.04 (d, *J* = 16.4 Hz, 2H), 2.68 (dd, *J* = 16.4, 2.9 Hz, 2H), 1.67 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 155.3, 148.2, 137.8, 114.1, 106.9, 70.6, 69.7, 60.4, 57.6, 43.1,21.7.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$calculated for $C_{19}H_{21}N_4O_2$: 337.1665, found: 337.1658.

(3*S,4a*R**,8*S**,8a*S**)-8a-methyl-4,9-bis(4-methylpyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3b):** General procedure was followed with **1a** (83.0 mg, 0.5 mmol), 2-amino-4-methylpyridine (118 mg, 1.1 mmol) at room temperature for 18 h to furnish **3b** as a white solid (109 mg, 0.30 mmol, 60% yield).

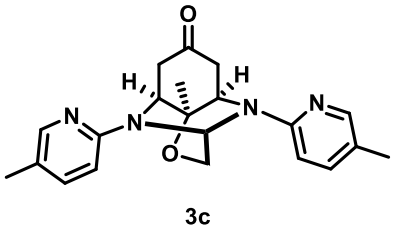


3b

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.50 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 5.2 Hz, 2H), 6.83 (s, 1H), 6.53 (d, *J* = 5.2 Hz, 2H), 6.42 (s, 2H), 4.38 (s, 2H), 4.06 (d, *J* = 1.2 Hz, 2H), 3.03 (d, *J* = 16.4 Hz, 2H), 2.67 (d, *J* = 16.4 Hz, 2H), 2.29 (s, 6H), 1.66 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 155.6, 148.8, 147.8, 115.6, 107.3, 70.5, 69.6, 60.4, 57.7, 43.3, 21.7, 21.4.
HRMS (ESI$^+$: *m/z*: [M + H] $^+$ calculated for $C_{21}H_{25}N_4O_2$: 365.1978, found: 365.1976.

(3*S,4a*R**,8*S**,8a*S**)-8a-methyl-4-(4-methylpyridin-2-yl)-9-(5-methylpyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3c):** General procedure was followed with **1a** (83.0 mg, 0.5 mmol), 2-amino-5-methylpyridine (118 mg, 1.1 mmol) at room temperature for 20 h to furnish **3c** as a white solid (141 mg, 0.39 mmol, 78% yield).

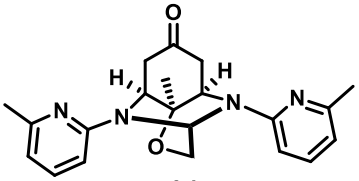


3c

Purification: Silica gel Flash chromatography, eluted with 22% EtOAc in hexane, R_f 0.50 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 6.69 (s, 1H), 6.54 (d, *J* = 8.5 Hz, 2H), 4.36 (s, 2H), 4.05 (s, 2H), 2.99 (d, *J* = 16.2 Hz, 2H), 2.65 (d, *J* = 16.2 Hz, 2H), 2.21 (s, 6H), 1.65 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 153.6, 147.9, 138.7, 122.9, 106.7, 70.5, 69.4, 60.5, 58.0, 43.4, 21.7, 17.3.
HRMS (ESI$^+$): *m/z*: [M+H] $^+$calculated for $C_{21}H_{25}N_4O_2$: 365.1978, found: 365.1974.

(3*S,4a*R**,8*S**,8a*S**)-8a-methyl-4,9-*bis*(6-methylpyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3d):** General procedure was followed with **1a** (83.0 mg, 0.5 mmol), 2-amino-6-methylpyridine (118 mg, 1.1 mmol) at room temperature for 24 h to furnish **3d** as a white solid (118 mg, 0.32 mmol, 65% yield).

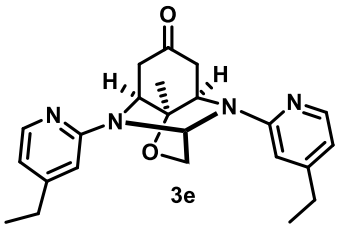


3d

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.50 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.9, 7.9 Hz, 2H), 6.87 (s, 1H), 6.54 (d, *J* = 7.5 Hz, 2H), 6.40 (d, *J* = 8.3 Hz, 2H), 4.40 (s, 2H), 4.06 (d, *J* = 1.3 Hz, 2H), 3.07 (d, *J* = 16.4 Hz, 2H), 2.66 (dd, *J* = 16.4, 3.0 Hz, 2H), 2.41 (s, 6H), 1.66 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 157.1, 154.7, 137.9, 113.1, 103.5, 70.6, 69.8, 60.3, 57.3, 43.1, 24.6, 21.7.
HRMS (ESI$^{+)}$: *m/z*: [M + H] $^+$ calculated for $C_{21}H_{25}N_4O_2$: 365.1978, found: 365.1973.

(3*S,4a*R**,8*S**,8a*S**)-4,9-*bis*(4-ethylpyridin-2-yl)-8a-methylhexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3e):** General procedure was followed with **1a** (83.0 mg, 0.5 mmol), 2-amino-4-ethylpyridine (134 mg, 1.1 mmol) at room temperature for 18 h to furnish **3e** as a white solid (122 mg, 0.31 mmol, 62% yield).



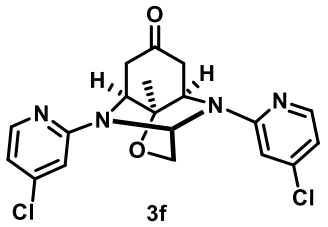
3e

Purification: Silica gel Flash chromatography, eluted with 50% EtOAc in hexane, R_f 0.60 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 4.9 Hz, 2H), 6.84 (s, 1H), 6.56 (d, *J* = 4.3 Hz, 2H), 6.43 (s, 2H), 4.39 (s, 2H), 4.07 (s, 2H), 3.04 (d, *J* = 16.7 Hz, 2H), 2.67 (d, *J* = 16.7 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 4H), 1.66 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 155.6, 154.8, 147.9, 114.3, 106.2, 70.5, 69.7, 60.4, 57.7, 43.3, 28.7, 21.7, 14.5.

HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{23}H_{29}N_4O_2$: 393.2291, found: 393.2286.

(3*S,4a*R**,8*S**,8a*S**)-4,9-bis(4-chloropyridin-2-yl)-8a-methylhexahydro-2H-3,8-epiminobenzo[b][1,4]oxazin-6(5H)-one (3f):** General procedure was followed with **1a** (83.0 mg, 0.5 mmol), 2-amino-4-chloropyridine (140 mg, 1.1 mmol) at room temperature for 18 h to furnish **3f** as a white solid (111 mg, 0.27 mmol, 55% yield).

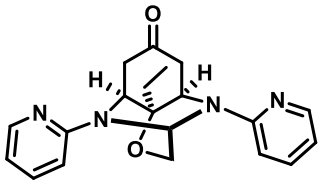


3f

Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane, R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 5.4 Hz, 2H), 6.84 (s, 1H), 6.72 (dd, *J* = 5.5, 1.6 Hz, 2H), 6.58 (d, *J* = 1.3 Hz, 2H), 4.35 (s, 2H), 4.05 (d, *J* = 1.4 Hz, 2H), 3.01 (d, *J* = 16.4 Hz, 2H), 2.68 (d, *J* = 16.4 Hz, 2H), 1.67 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.3, 156.0, 149.2, 145.4, 114.8, 106.7, 70.6, 69.7, 60.6, 57.6, 42.8, 21.6.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{19}H_{19}Cl_2N_4O_2$: 405.0885, found: 405.0876.

(3*S,4a*R**,8*S**,8a*S**)-8a-ethyl-4,9-di(pyridin-2-yl)hexahydro-2H-3,8-epiminobenzo[b][1,4]oxazin-6(5H)-one (3g):** General procedure was followed with **1b** (90.0 mg, 0.5 mmol), 2-aminopyridine (103 mg, 1.1mmol) at room temperature for 18 h to furnish **3g** as a white solid (119 mg, 0.34 mmol, 68% yield).

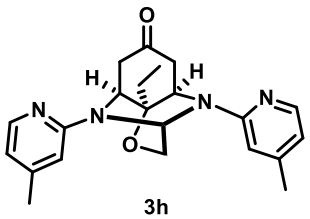


3g

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.50 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 5.0, 1.3 Hz, 2H), 7.53 (td, *J* = 7.9, 1.8, Hz, 2H), 6.83 (s, 1H), 6.69 (dd, *J* = 6.1, 1.8 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 4.45 (s, 2H), 4.07 (d, *J* = 1.4 Hz, 2H), 3.02 (d, *J* = 16.3 Hz, 2H), 2.65 (dd, *J* = 17.1, 3.2 Hz, 2H), 2.03 (q, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 155.3, 148.2, 137.8, 114.0, 107.0, 72.2, 69.5, 58.7, 57.7,42.8, 27.1, 7.2.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{20}H_{23}N_4O_2$: 351.1821, found: 351.1817.

(3*S,4a*R**,8*S**,8a*S**)-8a-ethyl-4,9-*bis*(4-methylpyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5H)-one (3h) :** General procedure was followed with **1b** (90.0 mg, 0.5 mmol), 2-amino-4-methylpyridine (118 mg, 1.1 mmol) at room temperature for 20 h to furnish **3h** as a white solid (113 mg, 0.30 mmol, 60% yield).



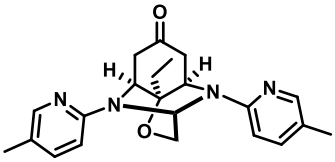
3h

Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane, R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 5.2 Hz, 2H), 6.80 (s, 1H), 6.52 (d, *J* = 5.2 Hz, 2H), 6.42 (s, 2H), 4.42 (s, 2H), 4.05 (d, *J* = 1.4, 2H), 3.01 (d, *J* = 15.8 Hz, 2H), 2.63 (dd, *J* = 16.7, 2.9 Hz, 2H), 2.28 (s, 6H), 2.01 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 155.7, 148.8, 147.8, 115.5, 107.4, 72.2, 69.5, 58.7, 57.7, 42.9, 27.1, 21.4, 7.2.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{21}H_{27}N_4O_2$: 379.2134, found: 379.2126.

(3*S,4a*R**,8*S**,8a*S**)-8a-ethyl-4-(4-methylpyridin-2-yl)-9-(5-methylpyridin-2-yl)hexahydro-2H-3,8-epiminobenzo[b][1,4]oxazin-6(5H)-one (3i):** General procedure was followed with **1b** (90.0 mg, 0.5 mmol), 2-amino-5-methylpyridine (118 mg,1.1 mmol) at room temperature for 18 h to furnish **3i** as a white solid (123 mg, 0.33 mmol, 65% yield).

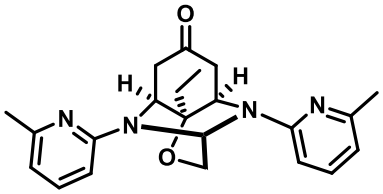


3i

Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane, R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H), 7.35 (dd, *J* = 8.5, 1.9 Hz, 2H), 6.67 (s, 1H), 6.55 (d, *J* = 8.5 Hz, 2H), 4.40 (s, 2H), 4.04 (s, 2H), 2.98 (d, *J* = 16.0 Hz, 2H), 2.62 (d, *J* = 16.0 Hz, 2H), 2.21 (s, 6H), 2.01 (q, *J* = 7.5 Hz, 2H), 1.14 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 153.7, 147.9, 138.6, 122.8, 106.7, 72.1, 69.2, 58.7, 58.0, 43.0, 27.1, 17.3, 7.2.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{22}H_{27}N_4O_2$: 379.2134, found: 379.2129.

(3*S,4a*R**,8*S**,8a*S**)-8a-ethyl-4,9-*bis*(6-methylpyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3j):** General procedure was followed with **1b** (90.0 mg, 0.5 mmol), 2-amino-6-methylpyridine (118 mg, 1.1 mmol) at room temperature for 18 h to furnish **3j** as a white solid (122 mg, 0.32 mmol, 65% yield).

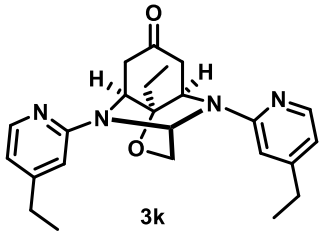


3j

Purification: Silica gel Flash chromatography, eluted with 12% EtOAc in hexane, R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 7.9, 7.9 Hz, 2H), 6.86 (s, 1H), 6.53 (d, *J* = 7.3 Hz, 2H), 6.40 (d, *J* = 8.3 Hz, 2H), 4.43 (s, 2H), 4.05 (d, *J* = 1.3 Hz, 2H), 3.04 (d, *J* = 16.4 Hz, 2H), 2.60 (d, *J* = 16.4Hz, 2H), 2.41 (s, 6H), 2.02 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 157.1, 154.9, 137.9, 113.0, 103.5, 72.3, 69.7, 58.5, 57.3, 42.8, 27.1, 24.6, 7.3.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$calculated for $C_{22}H_{27}N_4O_2$: 379.2134, found: 379.2134.

(3*S,4a*R**,8*S**,8a*S**)-8a-ethyl-4,9-bis(4-ethylpyridin-2-yl)hexahydro-2H-3,8-epiminobenzo[b][1,4]oxazin-6(5H)-one (3k):** General procedure was followed with **1b** (90.0 mg, 0.5 mmol), 2-amino-4-ethylpyridine (134 mg, 1.1 mmol) at room temperature for 22 h to furnish **3k** as a white solid (118 mg, 0.29 mmol, 58% yield).

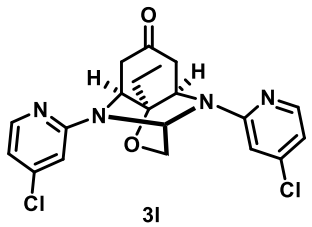


3k

Purification: Silica gel Flash chromatography, eluted with 12% EtOAc in hexane, R_f 0.70 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 5.1 Hz, 2H), 6.82 (s, 1H), 6.56 (d, *J* = 4.6 Hz, 2H), 6.43 (s, 2H), 4.43 (s, 2H), 4.06 (s, 2H), 3.02 (d, *J* = 16.4 Hz, 2H), 2.63 (d, *J* = 17.2 Hz, 2H), 2.58 (q, *J* = 7.8 Hz, 4H), 2.01 (q, *J* = 7.4 Hz, 2H), 1.23 (t, *J* = 7.4 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 155.8, 154.8, 147.9,114.3, 106.2, 72.2, 69.5, 58.7, 57.7, 42.9, 28.7, 27.1, 14.5, 7.2.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{24}H_{31}N_4O_2$: 407.2447, found: 407.2442.

(3*S,4a*R**,8*S**,8a*S**)-4,9-*bis*(4-chloropyridin-2-yl)-8a-ethylhexahydro-2*H*-3,8-epiminobenzo[*b*][1,4] oxazin-6(5*H*)-one (3l):** General procedure was followed with **1b** (90.0 mg, 0.5 mmol), 2-amino-4-chloropyridine (140 mg, 1.1 mmol) at room temperature for 20 h to furnish **3l** as a white solid (125 mg, 0.30 mmol, 60% yield).

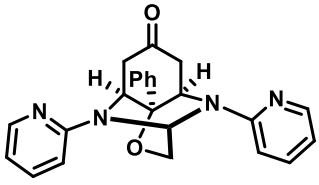


3l

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane, R_f 0.70 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 5.4 Hz, 2H), 6.83 (s, 1H), 6.72 (dd, *J* = 5.4, 1.6 Hz, 2H), 6.58 (d, *J* = 1.4 Hz, 2H), 4.39 (s, 2H), 4.04 (d, *J* = 1.5 Hz, 2H), 2.99 (d, *J* = 16.2 Hz, 2H), 2.65 (dd, *J* = 17.1, 3.0 Hz, 2H), 2.03 (q, *J* = 7.4 Hz, 2H), 1.16 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6, 156.1, 149.2, 145.4, 114.7, 106.7, 72.2, 69.6, 58.8, 57.7, 42.5, 27.0, 7.2.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{20}H_{21}Cl_2N_4O_2$: 419.1042, found: 419.1041.

(3*S,4a*R**,8*S**,8a*S**)-8a-phenyl-4,9-di(pyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3m):** General procedure was followed with **1c** (114.0 mg, 0.5 mmol), 2-aminopyridine (103 mg, 1.1 mmol) at room temperature for 20 h to furnish **3m** as a white solid (121 mg, 0.30 mmol, 61% yield).

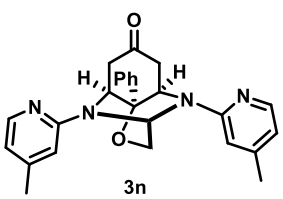


3m

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane R_f 0.60 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, *J* =5.0, 1.3 Hz, 2H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.58 (td, *J* = 7.9, 1.7 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 6.90 (s, 1H), 6.74 (td, *J* = 8.8, 3.0 Hz, 4H), 5.29 (s, 2H), 4.18 (d, *J* = 1.3 Hz, 2H), 3.07 (d, *J* = 15.7 Hz, 2H), 2.63 (d, *J* = 16.3 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 155.4, 148.3, 137.9, 136.9, 129.5, 129.3, 126.9, 114.3, 107.2, 73.7, 70.1, 58.6, 57.9, 43.5.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$calculated for $C_{24}H_{23}N_4O_2$: 399.1821, found: 399.1819.

(3*S,4a*R**,8*S**,8a*S**)-4,9-*bis*(4-Methylpyridin-2-yl)-8a-phenylhexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3n):** General procedure was followed with **1c** (114.0 mg, 0.5 mmol), 2-amino-4-methylpyridine (118 mg, 1.1 mmol) at room temperature for 18 h to furnish **3n** as a white solid (111 mg, 0.26 mmol, 52% yield).



3n

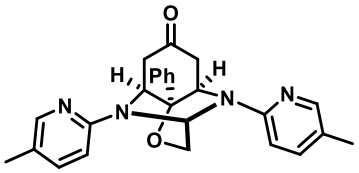
Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 5.1 Hz, 2H), 7.83 (d, *J* = 7.4 Hz, 2H), 7.52 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.45 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.88 (s, 1H), 6.58 (d, *J* = 5.5 Hz, 2H), 6.55 (s, 2H), 5.27 (s, 2H), 4.16 (d, *J* = 1.3 Hz, 2H), 3.06 (d, *J* = 16.0 Hz, 2H), 2.62 (d, *J* = 16.0 Hz, 2H), 2.33 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 155.7, 148.9, 147.9, 137.1, 129.4, 129.3, 126.9, 115.8, 107.6, 73.6, 70.1, 58.6, 57.9, 43.7, 21.5.

HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{26}H_{27}N_4O_2$: 427.2134, found: 427.2129.

(3*S,4a*R**,8*S**,8a*S**)-4,9-*bis*(5-Methylpyridin-2-yl)-8a-phenylhexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3o):** General procedure was followed with **1c** (114.0 mg, 0.5 mmol), 2-amino-5-methylpyridine (118 mg, 1.1 mmol) at room temperature for 18 h to furnish **3o** as a white solid (141mg, 0.33 mmol, 66% yield).



3o

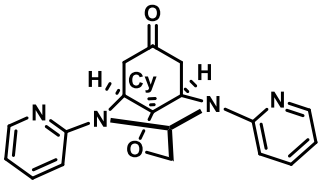
Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 1.6 Hz, 2H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.2 Hz, 2H), 6.73 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 5.25 (s, 2H), 4.15 (d, *J* = 1.3 Hz, 2H), 3.03 (d, *J* = 16.0 Hz, 2H), 2.61 (d, *J* = 16.0 Hz, 2H), 2.24 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 153.7, 148.0, 138.7, 137.1, 129.3, 129.3, 126.9 123.0, 106.9, 73.5, 69.8, 58.7, 58.3, 43.8, 17.4.

HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{26}H_{27}N_4O_2$: 427.2134, found: 427.2129.

(3*S,4a*R**,8*S**,8a*S**)-8a-Cyclohexyl-4,9-di(pyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3p):** General procedure was followed with **1d** (117.0 mg, 0.5 mmol), 2-aminopyridine (103 mg, 1.1 mmol) at room temperature for 20 h to furnish **3p** as white solid (113 mg, 0.28 mmol, 56% yield).



3p

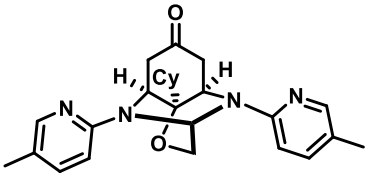
Purification: Silica gel Flash chromatography, eluted with 12% EtOAc in hexane R_f 0.60 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, *J* = 5.1, 1.2 Hz, 2H), 7.52 (ddd, *J* = 7.7, 2.1, 1.5 Hz, 2H), 6.77 (s, 1H), 6.68 (dd, *J* = 5.0, 1.6 Hz, 2H), 6.61 (d, *J* = 8.5 Hz, 2H), 4.64 (s, 2H), 4.03 (d, *J* = 1.4 Hz, 2H), 2.98 (d, *J* = 16.0 Hz, 2H), 2.64 (d, *J* = 14.7 Hz, 2H), 2.01–1.90 (m, 5H), 1.72 (d, *J* = 11.7 Hz, 1H), 1.55–1.45 (m, 2H), 1.31–1.28 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 155.6, 148.2, 137.7, 113.9, 107.0, 73.7, 69.4, 57.1, 56.9, 42.3, 39.1, 26.6, 26.0, 25.9.

HRMS (ESI$^+$): *m/z*: [M + H] $^+$calculated for $C_{24}H_{29}N_4O_2$: 405.2291, found: 405.2284.

(3*S,4a*R**,8*S**,8a*S**)-8a-Cyclohexyl-4,9-bis(5-methylpyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo [*b*][1,4]oxazin-6(5*H*)-one (3q):** General procedure was followed with **1d** (117.0 mg, 0.5 mmol),2-amino-5-methylpyridine (118 mg, 1.1 mmol) at room temperature for 18 h to furnish **3q** as a pink solid (130 mg, 0.30 mmol, 60% yield).

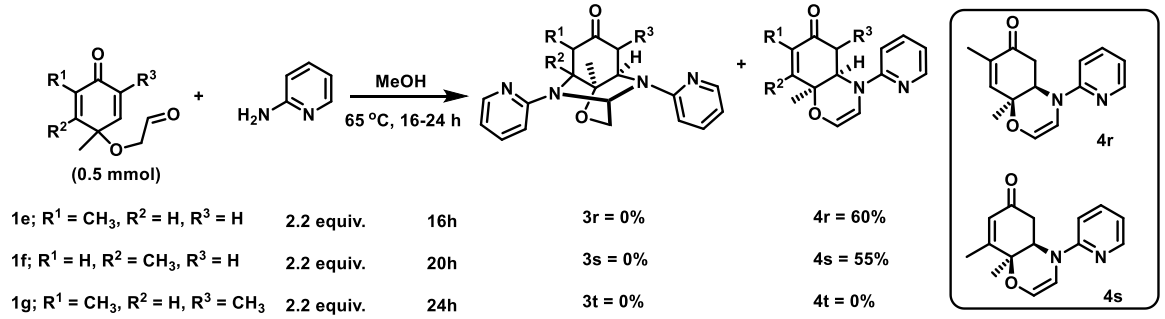


3q

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane R_f 0.60 (30% EtOAc in hexane)

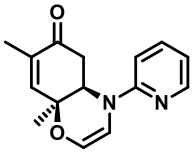
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 2.3 Hz, 2H), 7.33 (dd, *J* = 8.5, 2.3 Hz, 2H), 6.61 (s, 1H), 6.54 (d, *J* = 8.6 Hz, 2H), 4.60 (s, 2H), 3.99 (d, *J* = 1.4 Hz, 2H), 2.95 (d, *J* = 16.1 Hz, 2H), 2.62 (dd, *J* = 17.2, 2.3 Hz, 2H), 2.20 (s, 6H),1.97 (dd, *J* = 11.9, 2.9 Hz, 1H), 1.93–1.87 (m, 5H),1.70 (d, *J* = 11.3 Hz, 1H), 1.54–1.44 (m, 2H), 1.34–1.29 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 153.9, 147.9, 138.5, 122.6,106.7, 73.5, 69.1, 57.5, 57.0, 42.5, 39.1, 26.6, 26.0, 26.0, 17.3.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{26}H_{33}N_4O_2$: 433.2604, found: 433.2595.

Reaction with multi-substituted cyclohexadienone-aldehydes:



1e; R^1 = CH_3, R^2 = H, R^3 = H	2.2 equiv.	16h	3r = 0%	4r = 60%
1f; R^1 = H, R^2 = CH_3, R^3 = H	2.2 equiv.	20h	3s = 0%	4s = 55%
1g; R^1 = CH_3, R^2 = H, R^3 = CH_3	2.2 equiv.	24h	3t = 0%	4t = 0%

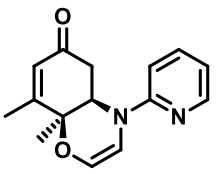
(4a*R,8a*S**)-7,8a-dimethyl-4-(pyridin-2-yl)-4a,8a-dihydro-4H-benzo[b][1,4]oxazin-6(5H)-one (4r):** General procedure was followed with **1e** (90.0 mg, 0.5 mmol), 2-aminopyridine (103 mg, 1.1 mmol) in methanol at 65 °C for 16 h to furnish **4r** as a thick oil (77 mg, 0.30 mmol, 60% yield).
Purification: Silica gel Flash chromatography, eluted with 7% EtOAc in hexane, R_f 0.70 (30% EtOAc in hexane)



4r

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17–8.16 (m, 1H), 7.55–7.51 (m, 1H), 6.72–6.67 (m, 2H), 6.66 (d, *J* = 1.5 Hz, 1H), 6.24 (dd, *J* = 4.9, 1.4 Hz, 1H), 6.13(d, *J* = 4.9 Hz, 1H), 4.82 (ddd, *J* = 10.1, 6.1, 1.3 Hz, 1H), 2.69 (s, 1H), 2.66 (d, *J* = 4.3 Hz, 1H), 1.86 (d, *J* = 1.5 Hz, 3H), 1.36 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 153.5, 148.2, 144.3, 138.6, 138.0, 127.5, 114.6, 105.8, 103.8, 71.2, 51.9, 37.2, 22.4, 15.7.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{15}H_{17}N_2O_2$: 257.1290, found: 257.1283.

(4a*R*,8a*S***)-8,8a-Dimethyl-4-(pyridin-2-yl)-4a,8a-dihydro-4*H*-benzo[*b*][1,4]oxazin-6(5*H*)-one (4s):** General procedure was followed with **1f** (90.0 mg, 0.5 mmol), 2-aminopyridine (103 mg, 1.1 mmol) at 65 °C in methanol for 20 h to furnish **4s** as a thick oil (70 mg, 0.28 mmol, 55% yield).



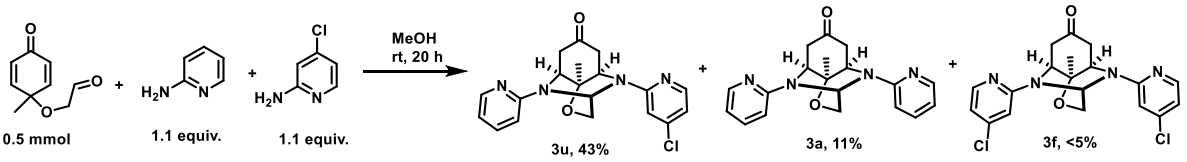
4s

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane, R_f 0.60 (30% EtOAc in hexane)

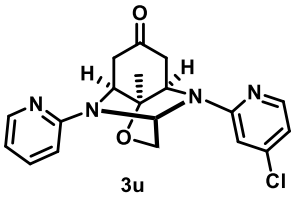
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 4.8, 1.1 Hz, 1H), 7.54 (ddd, *J* = 7.8, 1.8, 1.4 Hz, 1H), 6.73–6.68 (m, 2H), 6.22 (dd, *J* = 4.9, 1.2 Hz, 1H), 6.13 (d, *J* = 5.0 Hz, 1H), 6.0 (s, 1H) 4.88 (dd, *J* = 6.0, 1.0 Hz, 1H), 2.67–2.63 (m, 2H), 2.13 (d, *J* = 1.2 Hz, 3H), 1.37 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 158.3, 153.3, 148.2 138.0, 129.4, 127.5, 114.7, 105.8, 103.7, 72.9, 51.8, 36.8, 19.7, 19.4.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$calculated for $C_{15}H_{17}N_2O_2$: 257.1290, found: 257.1282.

Synthesis of pyridine containing unsymmetrical tetracyclic framework (3u-w)

a) Reaction of **1a** with 2-amino pyridine and 2-amino-4-chloropyridine



(3*S*,4a*R***,8*S***,8a**)-4-(4-chloropyridin-2-yl)-8a-methyl-9-(pyridin-2-yl)hexahydro-2H-3,8-epimino-benzo[b][1,4]oxazin-6(7H)-one (3u):** To the reaction flask containing **1a** (83.0 mg, 0.5 mmol) in 2 mL methanol, solution (mixture of 2-amino pyridine (52 mg, 0.55 mmol) and 2-amino-4-chloropyridine (70 mg, 0.55 mmol) in 1 mL MeOH) was added at room temperature and stirred for 20 h to furnish **3u** as a white amorphous solid (79 mg, 0.22 mmol, 43% yield).[**3a** was isolated in 11% yield (18 mg)].

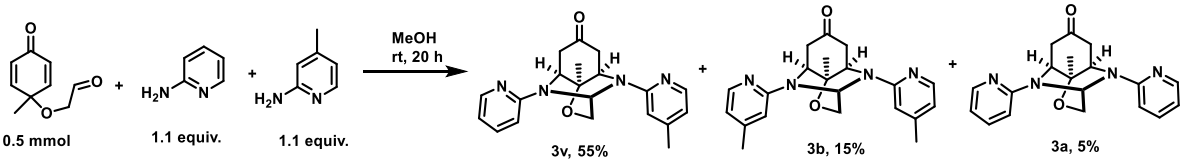


3u

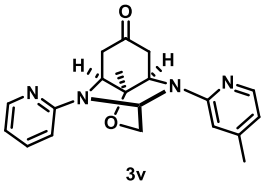
Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane R_f 0.50 (50% EtOAc in hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 3.3 Hz, 1H), 8.10 (d, *J* = 5.4 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 6.84 (s, 1H), 6.71 (t, *J* = 5.5 Hz, 2H), 6.61 (d, *J* = 10.5 Hz, 2H), 4.38 (d, *J* = 15.3 Hz, 2H), 4.06 (s, 2H), 3.02 (t, *J* = 13.7 Hz, 2H), 2.68 (d, *J* = 16.5 Hz, 2H), 1.67 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 156.1, 155.1, 149.1, 148.3, 145.3, 137.8, 114.5, 114.3, 107.0, 106.6, 70.6, 69.7, 60.6, 60.4, 57.7, 43.1, 42.9, 21.7.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{19}H_{20}ClN_4O_2$: 371.1275 found: 371.1269

b) Reaction of **1a** with 2-amino pyridine and 2-amino-4-methylpyridine



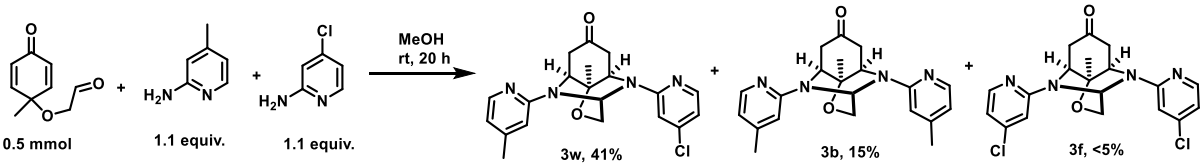
(3*S,4a*R**,8*S**,8a*S**)-8a-Methyl-4-(4-methylpyridin-2-yl)-9-(pyridin-2-yl)hexahydro-2*H*-3,8-epimino-benzo[*b*][1,4]oxazin-6(5*H*)-one (3v):** To the reaction flask containing **1a** (83.0 mg, 0.5 mmol) in 2 mL methanol, solution (mixture of 2-amino pyridine (52 mg, 0.55 mmol) and 2-amino-4-methylpyridine (59 mg, 0.55 mmol) in 1 mL MeOH) was added at room temperature and stirred for 20h to furnish **3v** as white solid (96 mg, 0.28 mmol, 55% yield).[**3a** and **3b** were isolated in 15% (27 mg) and 5% (8mg) yields, respectively].



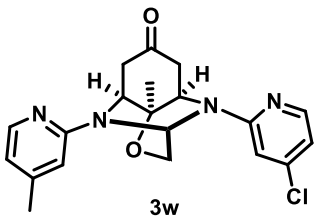
Purification: Silica gel Flash chromatography, eluted with 12% EtOAc in hexane, R_f 0.70 (50% EtOAc in hexane)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21(d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 4.9 Hz, 1H), 7.52 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.83 (s, 1H), 6.69 (t, *J* = 6.0 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 5.1 Hz, 1H), 6.42 (s, 1H), 4.39 (s, 2H), 4.07 (s, 2H), 3.03 (d, *J* = 16.6 Hz, 2H), 2.67 (d, *J* = 16.0 Hz, 2H), 2.29 (s, 3H), 1.66 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 206.3, 155.5, 155.3, 148.8, 148.2, 147.8, 137.8, 115.7, 114.0, 107.3, 107.0, 70.6, 69.6, 60.4, 57.6, 43.3, 43.2, 21.7, 21.4.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{20}H_{23}N_4O_2$: 351.1821, found: 351.1818.

c) Reaction of **1a** with 2-amino-4-chloropyridine and 2-amino-4-methylpyridine



(3*S,4a*R**,8*S**,8a*S**)-4-(4-Chloropyridin-2-yl)-8a-methyl-9-(4-methylpyridin-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (3w):** To the reaction flask containing **1a** (83.0 mg, 0.5 mmol) in 2 mL methanol, solution (mixture of 2-amino-4-chloropyridine (70 mg, 0.55 mmol) and 2-amino-4-methyl-pyridine (59 mg, 0.55 mmol)in 1 mL MeOH) was added at room temperature and stirred for 22 h to furnish **3w** as a white solid (79 mg, 0.20 mmol, 41% yield).[**3b** was isolated in 15% yield (27 mg)].

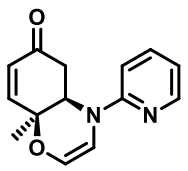


Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.50 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, *J* = 10.4, 5.2 Hz, 2H), 6.83 (s, 1H), 6.69 (d, *J* = 4.9 Hz, 1H), 6.60 (s, 1H), 6.55 (d, *J* = 4.8 Hz, 1H), 6.40 (s, 1H), 4.37 (d, *J* = 9.5 Hz, 2H), 4.05 (s, 2H), 3.02 (t,*J* = 14.3 Hz,

2H), 2.67 (dd, *J* = 16.8, 2.8 Hz, 2H), 2.29 (s, 3H), 1.66 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.8, 156.2, 155.4, 149.1, 148.9, 147.9, 145.3, 115.9, 114.4, 107.4, 106.6, 70.6, 69.7, 60.6, 60.4, 57.7, 43.2, 42.9, 21.7, 21.5.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{20}H_{22}ClN_4O_2$: 385.1431, found: 385.1423.

(4a*R,8a*S**)-8a-Methyl-4-(pyridin-2-yl)-4a,8a-dihydro-4*H*-benzo[*b*][1,4]oxazin-6(5*H*)-one (4a):** Following the general procedure with **1a** (83.0 mg, 0.5 mmol), 2-aminopyridine (103 mg, 1.1 mmol) in methanol for 18 h at room temperature, the bicyclic by-product **4a** was obtained as a thick oil (6 mg, 0.025 mmol, 5% yield).



4a

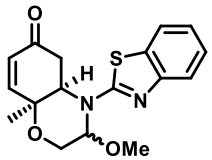
Synthesis from 3a (Scheme 4): Tetracyclic product **3a** (67.0 mg, 0.2 mmol) was heated at 65 °C in MeOH for 12 h in the presence of AcOH (20 mol%) to furnish **4a** as a thick oil (33 mg, 0.14 mmol, 69% yield).

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane, R_f 0.70 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17–8.18 (m, 1H), 7.52–7.57 (m, 1H), 6.88 (d, *J* = 10.0 Hz, 1H), 6.74–6.69 (m, 2H), 6.24 (dd, *J* = 4.9, 1.4 Hz, 1H), 6.14 (dd, *J* = 7.4, 2.5 Hz, 2H), 4.86 (td, *J* = 8.4, 1.4 Hz, 1H), 2.68 (s, 1H), 2.66 (d, *J* = 2.3 Hz, 1H), 1.38 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 153.4, 148.8, 148.2, 138.0, 131.6, 127.5, 114.8, 105.9, 103.9, 70.2, 51.7, 37.3, 21.1.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{14}H_{15}N_2O_2$: 243.1134, found: 243.1126.

4B. Reaction with 2-aminothioazoles: A slightly modified conditions were employed as followed {*conditions 1* (65 °C in MeOH; for **6**, **8** and **9**) and *conditions 2* (65 °C in acetonitrile; for **7**).

(3*R,4a*R**,8a*S**)-4-(Benzo[*d*]thiazol-2-yl)-3-methoxy-8a-methyl-3,4,4a,8a-tetrahydro-2*H*-benzo[*b*]-[1,4]oxazin-6(5*H*)-one (6a):** *Conditions 1*: Cyclohexadienone-aldehyde (**1a**; 83.0 mg, 0.5 mmol) was heated with 2-aminobenzothiazole (165 mg, 1.1 mmol) in MeOH at 65 °C for 16 h to furnish **6a** as a thick oil (107 mg, 0.32 mmol, 65% yield).

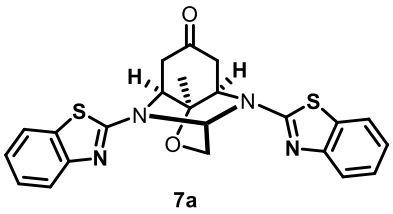


6a

Purification: Silica gel Flash chromatography, eluted with 11% EtOAc in hexane R_f 0.60 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.3, Hz, 1H), 7.15 (dd, *J* = 7.4,7.4 Hz, 1H), 6.69 (d, *J* = 10.2 Hz, 1H), 6.11 (d, *J* = 10.1 Hz, 1H), 5.23 (s, 1H), 4.37 (dd, *J* = 12.7, 4.3 Hz, 1H), 4.12–4.02 (m, 2H), 3.54–3.43 (m, 1H), 3.43 (s, 3H), 2.90 (dd, *J* = 16.0, 4.4 Hz, 1H), 1.53 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 168.0, 151.9, 148.6, 130.3, 129.8, 126.4, 122.4, 120.8, 119.9, 83.8, 69.2, 62.6, 56.3, 56.1, 39.5, 21.4.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$calculated for $C_{16}H_{15}N_2O_2S$: 299.0854, found: 299.0845 (corresponding to eliminated product, **9a**)

(3*S,4a*R**,8*S**,8a*S**)-4,9-bis(benzo[*d*]thiazol-2-yl)-8a-methylhexahydro-2*H*-3,8-epiminobenzo [*b*][1,4]oxazin-6(5*H*)-one (7a):** *Conditions 2*:Cyclohexadienone-aldehyde **1a** (83.0 mg, 0.5 mmol) and 2-aminobenzothiazole (165 mg, 1.1 mmol) were heated at 65 °C in acetonitrile for 18 h to furnish **7a** as a white solid (175 mg, 0.39 mmol, 78% yield).

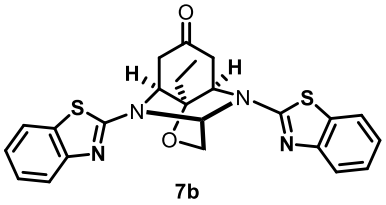


7a

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.50 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (ddd, *J* =7.5, 2.5, 0.9 Hz, 4H), 7.36 (td, *J* = 7.6, 1.3 Hz, 2H), 7.17 (td, *J* = 7.6, 1.0 Hz, 2H), 6.05 (s, 1H), 4.50 (s, 2H), 4.27 (d, *J* = 1.3 Hz, 2H), 3.31 (d, *J* = 16.5 Hz, 2H), 2.73 (dd, *J* = 16.0, 2.2 Hz, 2H), 1.69 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 163.9, 152.0, 130.7, 126.4, 122.5, 121.0, 120.1,70.4, 69.2, 65.4, 63.5, 42.7, 21.2.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{23}H_{21}N_4O_2S_2$: 449.1106, found: 449.1098.

(3*S,4a*R**,8*S**,8a*S**)-4,9-bis(benzo[*d*]thiazol-2-yl)-8a-ethylhexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (7b):** *Conditions 2*:Cyclohexadienone-aldehyde **1b** (90.0 mg, 0.5 mmol) and 2-aminobenzothiazole (165 mg, 1.1 mmol) were heated at 65 °C in acetonitrile for 18 h to furnish **7b** as a white solid (164 mg, 0.36 mmol, 71% yield).

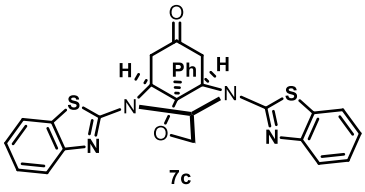


7b

Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane. R_f 0.60 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.7 Hz, 4H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 2H), 6.02 (s, 1H), 4.54 (s, 2H), 4.27 (s, 2H), 3.29 (d, *J* = 16.6 Hz, 2H), 2.69 (d, *J* = 16.5 Hz, 2H), 2.03 (q, *J* = 7.4 Hz, 2H), 1.16 (t, *J* = 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 164.1, 152.1, 130.7, 126.4, 122.5, 121.0, 120.1,72.2, 69.2, 65.5, 61.9, 42.4, 26.7, 7.1.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{24}H_{23}N_4O_2S_2$: 463.1262, found: 463.1258.

(3*S,4a*R**,8*S**,8a*S**)-4,9-bis(benzo[*d*]thiazol-2-yl)-8a-phenylhexahydro-2*H*-3,8-epiminobenzo[*b*] [1,4]oxazin-6(5*H*)-one (7c):** *Conditions 2*:Cyclohexadienone-aldehyde **1c** (114.0 mg, 0.5 mmol) and 2-aminobenzothiazole (165 mg, 1.1 mmol) were heated in acetonitrile at 65 °C for 18 h to furnish **7c** as a pale yellow solid (158 mg, 0.31 mmol, 62% yield).



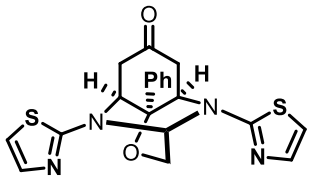
7c

Purification: Silica gel Flash chromatography, eluted with 12% EtOAc in hexane. R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 4H), 7.58–7.50 (m, 3H), 7.38 (t, *J* = 7.6, Hz, 2H), 7.19 (t, *J* = 7.6, Hz, 2H), 6.09 (s, 1H), 5.38 (s, 2H), 4.39 (s, 2H), 3.34 (d, *J* = 16.3 Hz, 2H), 2.70 (d, *J* = 16.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 164.0, 152.1, 135.4, 130.7, 130.0, 129.6, 126.8, 126.4, 122.6, 121.0, 120.2, 73.5, 69.8, 65.7, 61.9, 43.1.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{28}H_{23}N_4O_2S_2$: 511.1262, found: 511.1255.

(3*S,4a*R**,8*S**,8a*S**)-8a-phenyl-4,9-di(thiazol-2-yl)hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6(5*H*)-one (7d):** *Conditions 2*:Cyclohexadienone-aldehyde **1c** (114.0 mg, 0.5 mmol) and 2-aminothiazole (110 mg, 1.1 mmol) were heated in acetonitrile at 65 °C for 16 h to furnish **7d** as a pale yellow solid (166 mg, 0.41 mmol,81% yield).



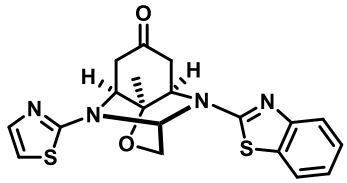
7d

Purification: Silica gel Flash chromatography, eluted with 12% EtOAc in hexane, R_f 0.50 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.0 Hz, 2H), 7.51–7.47 (m, 3H), 7.29 (d, *J* = 3.6 Hz, 2H), 6.72 (d, *J* = 3.6 Hz, 2H), 5.93 (s, 1H), 5.16 (s, 2H), 4.29 (d, *J* = 1.4 Hz, 2H), 3.17 (dd, *J* = 17.6, 1.7 Hz, 2H), 2.63 (d, *J* = 16.2 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 166.9, 139.8, 135.6, 129.9, 129.5, 126.8, 108.7, 73.0, 68.8, 65.6, 62.3, 43.1.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$calculated for $C_{20}H_{19}N_4O_2S_2$: 411.0949, found: 411.0945.

Synthesis of thiazole containing unsymmetrical tetracyclic framework (8)

(3*,4a*R,8*S**,8a*S**)-4-(benzo[d]thiazol-2-yl)-8a-methyl-9-(thiazol-2-yl)hexahydro-2H-3,8-epimino-benzo[b][1,4]oxazin-6(7H)-one (8a) :** To a solution of **6a** (50.0 mg, 0.15 mmol) in acetone, 2-aminothiazole (16 mg, 0.16 mmol) followed by *p*-TSA (25.0 mg, 0.15 mmol) was added and further stirred at 65 ° C for 20 h to furnish **8a** as a white solid (40 mg, 0.10 mmol, 67% yield).

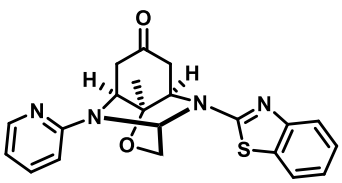


8a

Purification: Silica gel Flash chromatography, eluted with 25% EtOAc in hexane R_f 0.40 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (td, *J* = 7.5, 0.7 Hz, 2H), 7.35 (td, *J* = 7.5, 1.3 Hz, 1H), 7.28 (d, *J* = 3.7 Hz, 1H), 7.16 (td, *J* = 7.6, 1.0 Hz, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 5.99 (s, 1H), 4.51 (q, *J* = 2.8 Hz, 1H), 4.30 (q, *J* = 2.8 Hz, 1H), 4.24 (d, *J* = 1.5 Hz, 2H), 3.31 (dt, *J* = 16.9, 2.7 Hz, 1H), 3.16 (dt, *J* = 16.8, 2.7 Hz, 1H), 2.71 (ddd, *J* = 14.0, 3.4, 2.3 Hz, 2H), 1.68 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 166.8,163.9, 152.1, 139.7, 130.6, 126.3, 122.4, 120.9, 120.0, 108.6, 70.2, 68.8, 65.3, 64.2,63.3, 42.7, 21.3.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{19}H_{19}N_4O_2S_2$: 399.0949 found: 399.0942

(3*,4a*R,8*S**,8a*S**)-4-(benzo[d]thiazol-2-yl)-8a-methyl-9-(pyridin-2-yl)hexahydro-2H-3,8-epimino-benzo[b][1,4]-oxazin-6(7H)-one (8b):** To a solution of **6a** (50.0 mg, 0.15 mmol) in acetone, 2-aminopyridine (15 mg, 0.16 mmol) followed by *p*-TSA (25.0 mg, 0.15 mmol) was added and further stirred for 24 h at 65 ° C to furnish **8b** as a white solid (32 mg, 0.08 mmol, 54% yield).

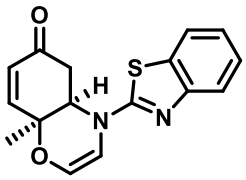


8b

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 3.6 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 2H), 7.56 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.74 (dd, *J* = 6.0, 1.8 Hz, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 6.47 (s, 1H), 4.52 (d, *J* = 2.3 Hz, 1H), 4.37 (d, *J* = 2.4 Hz, 1H), 4.23 (d, *J* = 7.3 Hz, 1H), 4.12 (d, *J* = 7.7 Hz, 1H), 3.33 (d, *J* = 16.7 Hz, 1H), 3.03 (d, *J* = 16.7 Hz, 1H), 2.71 (ddd, *J* = 14.4, 4.9, 3.4 Hz, 2H), 1.68 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1, 164.4, 154.8, 152.3, 148.3, 138.0, 130.7, 126.2, 122.1, 120.9, 119.8, 114.7, 106.7, 70.5,69.4, 63.1, 61.8, 60.8, 43.2, 42.7, 21.5.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{21}H_{21}N_4O_2S$: 393.1385, found: 393.1378.

(4a*R,8a*S**)-4-(Benzo[*d*]thiazol-2-yl)-8a-methyl-4a,8a-dihydro-4*H*-benzo[*b*][1,4]oxazin-6(5*H*)-one (9a):** *Conditions 1* was first followed with **1a** (83.0 mg, 0.5 mmol) and 2-aminobenzothiazole (165 mg, 1.1 mmol)to furnish **6a**. After completion of reaction (monitored with respect to aldehyde), methanol was evaporated and the residue (without purification) was treated with *p*-TSA (20 mol%) in acetone and run for 3 h at room temperature to furnish **9a** as a white solid (86 mg, 0.29 mmol, 58% yield over two steps).

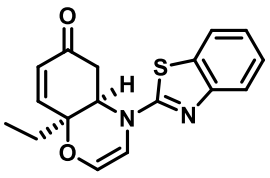


9a

Purification: Silica gel Flash chromatography, eluted with 8% EtOAc in hexane, R_f 0.70 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.59(dd, *J* = 8.1, 0.5 Hz, 1H), 7.34 (ddd, *J* = 7.5, 1.2, 1.1 Hz, 1H) 7.14 (td, *J* = 7.6, 1.1 Hz, 1H), 6.86 (d, *J* = 9.9 Hz, 1H), 6.19–6.16 (m, 2H), 6.09 (dd, *J* = 4.9, 1.2 Hz, 1H), 4.82 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.84 (ddd, *J* = 16.5, 4.7, 0.9 Hz, 1H), 2.69 (dd, *J* = 16.5, 12.1 Hz, 1H), 1.47 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 162.8, 152.0, 147.8, 131.8, 130.6, 128.9, 126.4, 122.4, 121.0, 120.0, 105.5, 70.3, 55.2, 37.2, 22.1.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{16}H_{15}N_2O_2S$: 299.0854, found: 299.0847.

(4a*R,8a*S**)-4-(Benzo[d]thiazol-2-yl)-8a-ethyl-4a,8a-dihydro-4H-benzo[b][1,4]oxazin-6(5H)-one (9b):** *Conditions 1* was first followed with **1b** (90.0 mg, 0.5 mmol) and 2-aminobenzothiazole (165 mg, 1.1 mmol) in MeOH at 65 °C for 18 h to furnish **6b**. After completion of reaction (monitored with respect to aldehyde), methanol was evaporated and the residue (without purification) was treated with *p*-TSA (20 mol%) in acetone and run for 3 h at room temperature to furnish furnish **9b** as a yellow solid (74 mg, 0.24 mmol, 48% yield over two steps).



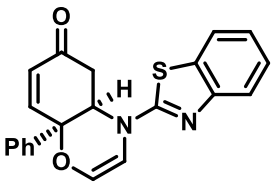
9b

Purification: Silica gel Flash chromatography, eluted with 8% EtOAc in hexane. R_f 0.70 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.60 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.34 (td, *J* = 7.8, 1.3 Hz, 1H), 7.14 (td, *J* = 7.7, 1.2 Hz, 1H), 6.92 (d, *J* = 10.1 Hz, 1H), 6.23 (dd, *J* = 10.1, 0.7 Hz, 1H),

6.21 (d, *J* = 4.8 Hz, 1H), 6.09 (dd, *J* = 4.7, 1.0 Hz, 1H), 4.94 (dd, *J* = 11.8, 5.0 Hz, 1H), 2.84 (ddd, *J* = 16.8, 5.1, 0.8 Hz, 1H), 2.75 (d, *J* = 11.6 Hz, 1H), 1.85–1.75 (m, 2H), 0.95 (t, *J* = 7.5, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 162.7, 152.0, 146.3, 132.8, 130.6, 129.4, 126.4, 122.3, 120.9, 119.9, 105.6, 73.4, 52.6, 37.0, 26.7, 7.7.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{17}H_{17}N_2O_2S$: 313.1011, found: 313.1003.

(4a*R,8a*S**)-4-(Benzo[d]thiazol-2-yl)-8a-phenyl-4a,8a-dihydro-4*H*-benzo[*b*][1,4]oxazin-6(5*H*)-one (9c):** *Conditions 1* was first followed with **1c** (114.0 mg, 0.5 mmol) and 2-aminobenzothiazole (165 mg, 1.1 mmol) in MeOH at 65 °C for 14 h to furnish **6c**. After completion of reaction (monitored with respect to aldehyde), methanol was evaporated and the residue (without purification) was treated with *p*-TSA (20 mol%) in acetone and run for 3 h at room temperature to furnish **9c** as a thick yellow (88 mg, 0.25 mmol, 49% yield over two steps).

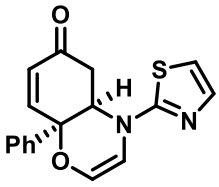


9c

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane. R_f 0.60 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (t, *J* = 7.4 Hz, 2H), 7.43 (d, *J* = 6.7 Hz, 2H), 7.32-7.28 (m, 4H), 7.11 (t, *J* = 6.7 Hz, 1H), 6.84 (d, *J* = 9.8 Hz, 1H), 6.35 (d, *J* = 3.9 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 6.01(s, 1H), 5.63 (brs, 1H), 2.96 (d, *J* = 10.5 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 162.2, 151.9, 148.1, 139.6, 130.8, 130.6, 129.4, 129.0, 128.6, 126.3, 125.4, 122.3, 120.9, 120.0, 107.3, 75.2, 53.7, 37.2.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{21}H_{17}N_2O_2S$: 361.1011, found: 361.1004.

(4a*R,8a*S**)-8a-Phenyl-4-(thiazol-2-yl)-4a,8a-dihydro-4H-benzo[b][1,4]oxazin-6(5H)-one (9d):** *Conditions 1* was first followed with **1c** (114.0 mg, 0.5 mmol) and 2-aminothiazole (110 mg, 1.1 mmol) in MeOH at 65 °C for 16 h to furnish **6d**. After completion of reaction (monitored with respect to aldehyde), methanol was evaporated and the residue (without purification) was treated with *p*-TSA (20 mol%) in acetone and run for 3 h at room temperature to furnish **9d** as a thick yellow (94 mg, 0.30 mmol, 61% yield over two steps).



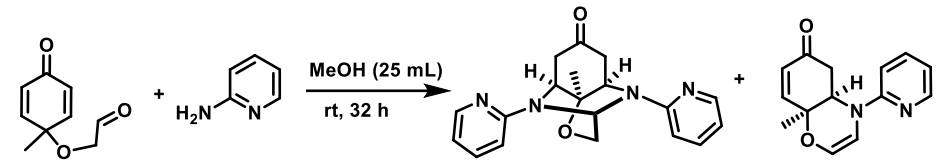
9d

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane R_f 0.60 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.34–7.28 (m, 3H), 7.16 (d, *J* = 3.6 Hz, 1H), 6.81(d, *J* = 9.9 Hz, 1H), 6.55 (d, *J* = 3.6 Hz, 1H), 6.32 (d, *J* = 4.8 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 5.92 (dd, *J* = 4.7, 1.3 Hz, 1H), 5.48 (t, *J* = 8.1 Hz, 1H), 2.92 (d, *J* = 2.1 Hz, 1H), 2.90 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 165.1, 148.2, 139.7, 139.5, 130.7, 128.9, 128.7, 128.5, 125.4, 108.3, 107.8, 75.1, 54.0, 37.1.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{17}H_{15}N_2O_2S$: 311.0854, found: 311.0846.

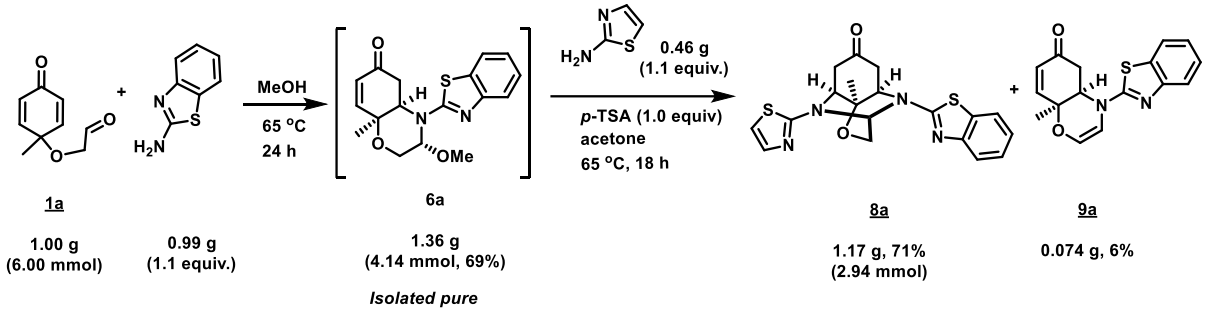
[5] Gram-scale synthesis of 3a and 8a

For symmetrical tetracyclic compound 3a:



To a 100 mL round bottom flask was added a mixture of **1a** (1.08 g, 6.5 mmol) and 2-aminopyridine (1.3 g, 2.2 equiv.) in methanol (25 mL) and allowed to stir at room temperature (monitored by TLC, *ca* 32 h). Methanol was evaporated under vacuum after the completion of reaction and loaded directly on the silica gel for purification. Compound **3a** was obtained as a white solid (1.6 g, 73% yield) along with bicyclic product **4a** (60 mg, 4%). Compound **3a** was further recrystallized with EtOH: $CHCl_3$ (1:1) to obtain colorless crystalline solid (1.57 g).

Gram-scale, two-step synthesis of unsymmetrical tetracyclic compound 8a (from 1a)

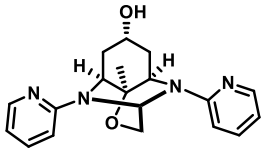


Cyclohexadienone-aldehyde (**1a**; 1.00 g, 6.00 mmol) was heated with 2-aminobenzothiazole (0.99 g, 1.1 equiv.) in MeOH at 65 ºC for 24 h. After the completion of reaction, methanol was evaporated completely under vacuo and loaded directly on the small pad of silica gel to remove excess triazole and other slightly eliminated product (1.36 g, 4.14 mmol, 69% yield).

Compound **6a** was dissolved in acetone (40 mL) and added 2-aminothiazole (0.46 g, 1.1 equiv.) and*p*-TSA (0.7 g, 1.0 equiv.) was added sequentially and stirred further at 65 º C for 18 h. After the completion of reaction, acetone was completely evaporated and diluted with ethyl acetate (30 mL) and washed with saturated $NaHCO_3$ (aq.) solution. Aqueous layer was washed with ethyl acetate (30 X 2) and combined organic layer was extracted with brine. Organic layer was dried on anhyd. Na_2SO_4 and evaporated. The crude residue was further purified by silica gel chromatography to furnish **8a** as a white solid (1.2 g, 71% yield).

[6] Synthetic transformation of 3a

v(3*S,4a*R**,8*S**,8a*S**)-8a-Methyl-4,9-di(pyridin-2-yl)octahydro-2H-3,8-epiminobenzo[b][1,4]oxazin-6-ol (10):** To a stirred solution of compound **3a** (60.0 mg, 0.16 mmol) in MeOH (3 mL) was added $NaBH_4$ (9.0 mg, 0.24 mmol) at 0°C. After completion of the reaction (monitored by TLC), acetone (1 mL) was added to the reaction mixture and almost half of the solvent was evaporated and the mixture was diluted in water (4 mL) and EtOAc (10 mL). Then it was partitioned and aqueous phase was extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography to afford **10** in 89% yield (47 mg) as a white solid (dr = *ca* 7:1; 89% yield for major isomer).



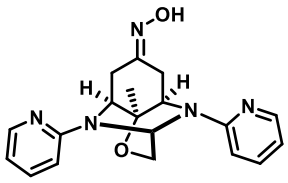
10

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.30 (30% EtOAc in hexane)

NMR of major diastereomer is stated below：

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 4.2, Hz, 2H), 7.56 (t, *J* = 7.2, Hz, 2H), 7.18 (s, 1H), 6.77–6.70 (m, 4H), 4.12 (s, 2H), 4.06 (s, 2H), 3.95 (d, *J* = 10.1 Hz, 1H), 3.72 (d, *J* = 11.5 Hz, 1H) 2.70 (d, *J* = 15.0 Hz, 2H), 1.95 (d, *J* = 14.7 Hz, 2H), 1.39 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 148.3, 137.8, 114.4, 107.3, 70.9, 68.7, 65.6, 59.8, 57.8, 33.8, 21.7.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{19}H_{23}N_4O_2$: 339.1821, found: 339.1821.

(3*S,4a*R**,8*S**,8a*S**)-8a-methyl-4,9-di(pyridin-2-yl)hexahydro-2H-3,8-epiminobenzo[b][1,4]oxazin-6(5H)-one oxime (11):** A stirring solution of **3a** (100 mg, 0.30 mmol), hydroxylamine hydrochloride (31.0mg, 0.45 mmol) and sodium acetate (50 mg, 0.60 mmol) were dissolved in EtOH/H_2O (4:1; 10 mL) and heated for 2 hour at 80 °C. Then the reaction mixture was concentrated and extracted with EtOAc/H2O. The organic phase was separated and dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the corresponding oxime **11** in 87% yield (92 mg) as a white solid.

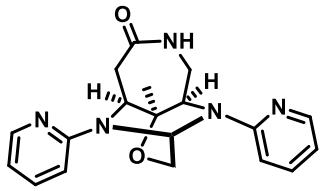


11

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane, R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (t, *J* = 5.1 Hz, 2H), 7.47 (q, *J* = 8.7 Hz, 2H), 6.87 (s, 1H), 6.65–6.58 (m, 4H), 4.16 (d, *J* = 12.5 Hz, 2H), 4.00 (s, 2H), 3.87 (d, *J* = 16.7 Hz, 1H), 2.97 (d, *J* = 15.9 Hz, 1H), 2.44 (d, *J* = 15.9 Hz, 1H), 2.07 (d, *J* = 15.7 Hz, 1H), 1.47 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 155.5, 153.2, 148.1, 137.7, 137.7, 113.6, 106.9, 106.8, 71.2, 69.7, 59.6, 59.4, 57.4, 33.0, 26.4, 21.4.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{19}H_{22}N_5O_2$: 352.1773, found: 352.1767.

(3*S,4a*R**,9*S**,9a*S**)-9a-Methyl-4,10-di(pyridin-2-yl)octahydro-3,9-epimino[1,4]oxazino[3,2-*c*]azepin-7(2*H*)-one (12):** To a stirring solution of the oxime **11** (50 mg, 0.14 mmol, 1.0 equiv.) in dry dioxane (2 mL) was added dropwise with freshly distilled thionyl chloride (70 μL) at room temperature. After the addition, the reaction mixture was stirred further for 6h. The volatile material was removed by evaporation and the residue was purified by silica gel column chromatography to obtain the corresponding lactam product **12** in 55% yield (27.0 mg) as a white solid.

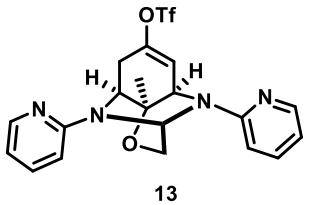


12

Purification: Silica gel Flash chromatography, eluted with 35% acetone in hexane, R_f 0.20 (40% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, *J* =14.5, 3.3 Hz, 2H), 7.55 (q, *J* = 8.2 Hz, 2H), 6.78–6.66 (m, 5H), 5.38 (s, 1H), 4.21 (d, *J* = 5.4 Hz, 1H), 4.13–4.05 (m, 4H), 3.42 (dd, *J* = 16.0, 4.2 Hz, 1H), 3.27 (q, *J* = 7.3 Hz, 1H), 2.74 (d, *J* = 15.0 Hz, 1H), 1.53 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 156.2, 155.6, 148.2, 148.0, 138.0, 137.8, 114.5, 113.8, 107.5, 107.3, 73.5, 69.4, 60.9, 59.3, 59.1, 39.7, 37.0, 21.5.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{19}H_{22}N_5O_2$: 352.1773, found: 352.1767.

(3*S,4a*S**,8*R**,8a*S**)-8a-Methyl-4,9-di(pyridin-2-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazin-6-yl-trifluoromethanesulfonate (13):** A 20 mL Schlenk tube, charged with compound **3a** (336.0 mg, 1.0 mmol) and *N*-phenyl-bis(trifluoromethanesulfonamide) (535.0 mg, 1.5 mmol)and magnetic bar was degassed under vacuo and filled back with argon. Reagents were dissolved in THF (5.0 mL) and cooled at -78 °C. To the reaction solution was added lithium bis(trimethylsilyl)amide (LiHMDS, 0.9 mL, 1.3 M solution in THF) slowly over 10 minutes and then slowly warmed up to room temperature and further stirring for 16 h. The reaction was then quenched with an aqueous saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc. The combined organic solvent was washed by brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and purified by silica gel column chromatography to afforded the corresponding enol-triflate product **13** in 65% yield (304 mg) as a white solid.

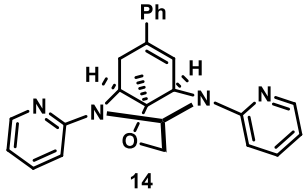


13

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane. R_f 0.60 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (ddd, *J* = 11.4, 4.7, 1.1 Hz, 2H), 7.57–7.51 (m, 2H), 6.76 (s, 1H), 6.73–6.65 (m, 3H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.31 (dd, *J* = 5.8, 2.0 Hz, 1H), 4.52 (d, *J* = 4.5 Hz, 1H), 4.29 (t, *J* = 2.0 Hz, 1H), 4.09 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.01 (d, *J* = 8.2 Hz, 1H), 2.90 (dd, *J* = 18.3, 1.2 Hz, 1H), 2.74 (ddd, *J* = 18.4, 2.5, 1.2 Hz, 1H), 1.45 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 155.1, 149.5, 148.4, 148.3, 137.9, 117.9, 114.5, 113.6, 107.8, 105.9, 70.1, 69.7, 57.4, 57.0, 56.4, 32.6, 20.9.
HRMS (ESI$^+$): *m/z*: [M + H] $^+$ calculated for $C_{20}H_{20}F_3N_4O_4S$: 469.1157, found: 469.1150.

(3*S,4a*S**,8*R**,8a*S**)-8a-Methyl-6-phenyl-4,9-di(pyridin-2-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-3,8-epiminobenzo[*b*][1,4]oxazine (14):** The Schlenk tube containing a solution of enol-triflate **13** (60.0 mg, 0.13 mmol), phenylboronic acid (23 mg, 0.19 mmol), K_2CO_3 (72 mg, 0.52 mmol) in toluene/water/ethanol (5:2:l; *ca* 2 mL) was degassed and continuously purged with nitrogen for 10 minutes. To the reaction mixture was added $Pd(PPh_3)_4$ (10 mol%) at room temperature and it was heated for 15 h at 95 °C. After the completion of reaction (monitored with TLC with respect to **13**), it was cooled to room temperature, diluted with saturated aqueous NH_4Cl (5 mL) solution and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic solvent was dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and purification by column chromatography to afford the corresponding product **14** in 77% yield (40 mg) as a white solid.

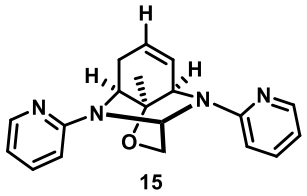


14

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane. R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 4.8, 2.9 Hz, 2H), 7.52 (s, 2H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.26–7.21 (m,3H), 6.94 (s, 1H), 6.72 (dd, *J* = 8.4, 7.2 Hz, 2H), 6.67–6.62 (m, 3H), 4.42 (d, *J* = 4.8 Hz, 1H), 4.34 (s, 1H), 4.14 (d, *J* = 8.0 Hz, 1H), 4.07 (d, *J* = 8.0 Hz, 1H), 3.12 (d, *J* = 18.2 Hz, 1H), 2.77 (d, *J* = 18.3 Hz, 1H), 1.44 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 155.8, 148.3, 148.2, 140.3, 137.6, 137.6, 135.9, 128.3, 127.7, 125.5, 122.8, 113.7, 112.8, 107.9, 106.1, 70.7, 69.9, 57.6, 57.5, 56.4, 32.1, 21.3.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{25}H_{25}N_4O$: 397.2028, found: 397.2024.

(3*S,4a*S**,8*R**,8a*S**)-8a-Methyl-4,9-di(pyridin-2-yl)-3,4,4a,5,8,8a-hexahydro-2H-3,8-epiminobenzo [b][1,4]oxazine (15):** A Schlenk tube was charged with $Pd(OAc)_2$ (1.5 mg, 0.006 mmol), and PPh_3 (3.4 mg, 0.013 mmol) was degassed and refilled with nitrogen. Then a solution of enol-triflate **13** (60 mg, 0.13 mmol) in anhydrous DMF (2 mL) was added slowly through a syringe to the reaction tube. The resulting reaction mixture was added Et_3N (58.0 μL, 0.39 mmol) followed by formic acid (12μL, 0.26 mmol) and was heated for 4h at 65 °C. The reaction mixture was cooled to room temperature, diluted with water, followed by washing with cold ether (3 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography to afford compound **15** in 91% yield (38 mg) as a white solid.

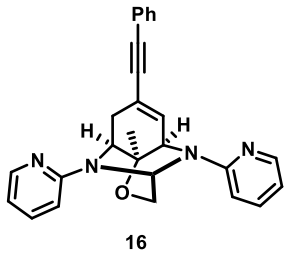


15

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane. R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (ddd, *J* = 12.7, 5.0, 1.2 Hz, 2H), 7.53–7.48 (m, 2H), 6.96 (s, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.66–6.59 (m, 3H), 6.28–6.25 (m, 1H), 5.66–5.63 (m, 1H), 4.22 (d, *J* = 5.0 Hz, 1H), 4.15 (brs, 1H), 4.10 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.04 (dd, *J* = 8.2, 1.0 Hz, 1H), 2.72 (dd, *J* = 18.3, 4.4 Hz, 1H), 2.40 (dd, *J* = 18.8, 3.4 Hz, 1H), 1.38 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 155.8, 148.2, 137.5, 137.5, 126.6, 126.4, 113.6, 112.8, 107.8, 106.1, 70.8, 69.9, 57.3, 56.4, 30.3, 21.1.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{19}H_{21}N_4O$: 321.1715, found: 321.1710.

(3*S,4a*S**,8*R**,8a*S**)-8a-Methyl-6-(phenylethynyl)-4,9-di(pyridin-2-yl)-3,4,4a,5,8,8a-hexahydro-*2H*-3,8-epiminobenzo[*b*][1,4]oxazine (16):** A Schlenk tube, charged with $Pd(PPh_3)_2Cl_2$ (4 mg, 0.006 mmol) and copper (I) iodide (2.5 mg, 0.013 mmol) was degassed and purged with nitrogen for 10 minutes. Then a mixture of THF:TEA (2 mL; 1:1), solution of enol-triflate **13** (60.0 mg, 0.13 mmol) in THF (1 mL)followed by phenylacetylene (16 µL, 0.14 mmol 1.1 equiv.) were added to the reaction mixture via syringe was added at room temperature. The solution was then refluxed for14 h. After completion of the reaction, solvent was removed under reduced pressure and the crude reaction was purified by column chromatography to afford the corresponding product **16** in 73% yield (40 mg) with a thick yellow oil.

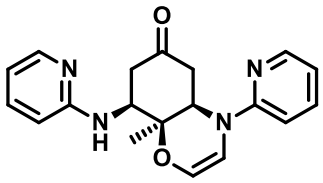


16

Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane, R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (ddd, *J* = 14.4, 4.9, 1.2 Hz, 2H), 7.55–7.49 (m, 2H), 7.37–7.34 (m, 2H), 7.25–7.24 (m, 3H), 6.94 (s, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.69–6.61 (m, 4H), 4.35 (d, *J* = 5.1 Hz, 1H), 4.21 (t, *J* = 2.0 Hz, 1H), 4.10 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.04 (dd, *J* = 8.3, 1.0 Hz, 1H), 2.88 (d, *J* = 18.4 Hz, 1H), 2.60 (tt, *J* = 18.8, 2.8 Hz, 1H), 1.42 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 155.5, 148.3, 137.7, 137.6, 132.2, 131.5, 128.3, 122.9, 120.5, 113.9, 113.1, 107.9, 106.0, 89.4, 89.3, 70.3, 69.8, 57.1, 57.1, 56.4, 34.2, 21.2.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{27}H_{25}N_4O$: 421.2028, found: 421.2020.

(4a*R,8*S**,8a*S**)-8a-methyl-4-(pyridin-2-yl)-8-(pyridin-2-ylamino)-4a,5,8,8a-tetrahydro-4H-benzo[b][1,4]oxazin-6(7H)-one (17):** The compound **3a** (50.0 mg, 0.15 mmol) in methanol (3 mL) was treated with CF_3SO_3H (4.5 µl , 0.05 mmol) and stirred at room temperaturefor 20 h to complete the reaction. Methanol was evaporated and diluted with DCM and work-up with water. Water layer was washed with DCM (10 mL X 3) and combined organic layer was washed with brine, concentrated under vacuo and dried over anhyd. Na_2SO_4. The residue was further purified by column chromatography to furnish **17** as a white solid (38 mg, 0.10 mmol, 75 % yield) and minor product **4a** (2 mg, 6%).



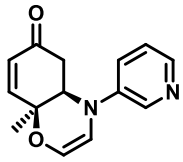
17

Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane R_f 0.40 (50% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 3.7 Hz, 1H), 8.05 (d, *J* = 3.9 Hz, 1H), 7.52 (td, *J* = 7.8, 1.8 Hz, 1H), 7.40 (td, *J* = 7.7, 1.7 Hz, 1H), 6.70 (dd, *J* = 6.0, 1.7 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.57 (dd, *J* = 6.0, 1.1 Hz, 1H), 6.41 (d, *J* = 8.5 Hz, 1H), 6.20 (d, *J* = 3.5 Hz, 1H), 6.10 (d, *J* = 4.8 Hz, 1H), 4.82 (s, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 4.55 (q, *J* = 9.5 Hz, 1H), 2.67 (t, *J* = 9.7 Hz, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 1.29(s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5, 157.3, 153.4, 148.3, 148.0, 138.0, 137.5, 125.4, 114.7, 113.4, 108.1, 105.6, 103.9, 76.0, 69.7, 52.9, 52.3, 43.7, 39.9, 18.9.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{19}H_{21}N_4O_2$: 337.1665 found: 337.1653.

Reaction of 1a with 3-aminopyridine:

(4a*R*,8a*S***)-8a-Methyl-4-(pyridin-3-yl)-4a,8a-dihydro-4*H*-benzo[*b*][1,4]oxazin-6(5*H*)-one (19):** General procedure was followed with **1a** (83.0 mg, 0.5 mmol), 3-aminopyridine (103 mg, 1.1mmol) in methanol. *Reaction of **1a** proceeded with 3-aminopyridine very sluggish yielded **19** after heating* at 65 ºC for 16 h (70 mg, 0.29 mmol, 58% yield).



19

Purification: Silica gel Flash chromatography, eluted with 1.5% Methanol in chloroform, R_f 0.70 (10% Methanol in chloroform)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 2.4 Hz, 1H), 8.15 (dd, *J* = 4.3, 1.6 Hz, 1H), 7.22–7.16 (m, 2H), 6.89 (d, *J* = 9.9 Hz, 1H), 6.22 (d, *J* = 4.7 Hz, 1H), 6.15 (dd, *J* = 10.0, 0.9 Hz, 1H), 5.92 (dd, *J* = 4.7, 1.6 Hz, 1H), 4.05 (ddd, *J* = 12.2, 4.4, 1.5 Hz, 1H), 2.82 (dd, *J* = 16.6, 12.1 Hz, 1H), 2.66 (ddd, *J* = 16.6, 4.4, 0.9 Hz, 1H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 148.9, 141.4, 140.9, 136.3, 131.5, 128.4, 124.0, 120.4, 105.0, 70.0, 55.8, 37.9, 21.9.

HRMS (ESI^+): *m/z*: $[M + H]^+$ calculated for $C_{14}H_{15}N_2O_2$: 243.1134, found: 243.1125.

[7] DFT Calculation Details and Energy profile

DFT calculations employing the B3PW91[S2] functional with D3 version of Grimme's dispersion; London-dispersion correction with Becke-Johnson damping (D3BJ)[S3] were performed with the GAUSSIAN 16 series of programs, B01 version [S4] with 6-311 G(d,p) basis sets. The polarizable continuum model has been used for MeOH as solvent. Full optimizations of geometry without any constraint were performed. Calculations of harmonic vibrational frequencies were performed to determine the nature of each extremum. The nature of the transition states was checked by reaction path be followed by integrating the intrinsic reaction coordinate (IRC method) and the resulting geometries as local minima to ensure the nature of the connected intermediates. The contributions to the Gibbs free energy were taken at T = 298.15 within the harmonic oscillator and rigid rotator approximations.

Local nucleophilic index determination method has been reported previously and compared with experimental Mayr's nucleophilic indexes.[S5]

Nucleophilic Index (N)[S6]

Nucleophilicity index N is defined as the energy difference between the HOMO of the nucleophilic molecule and the tetracyanoethylene (TCE), as the reference molecule. [S5a]

$$N_{(nu)} = HOMO_{(nu)} - HOMO_{(TCE)}$$

Fukui Function

Fukui's function for electrophilic attack on an atom, k, in an N-electron system was introduced by Yang and Mortier[S7]. The condensed Fukui functions of f_k^- are calculated using Natural Population Analysis (NPA) for N-electron and (N-1)-electron system using NBO program, present in Gaussian 16 package.

$$f_k^- = q_k(\mathrm{N}) - q_k(\mathrm{N-1})$$

Local Nucleophilic Index (N_k)[S5c]

Condensed local nucleophilicity index (N_k) is defined as

$$N_k = \mathrm{N} * f_k^-$$

For complete reaction path (Figure 1): The DFT study has been made for the synthesis of **3a**/**4a**, assuming the formation of the imine (resulting from the condensation between amine and aldehyde) is a preliminary step before ring closure processes. The total electronic energy (E) and Gibbs energies (G), in kcal.mol^{-1}, were reported considering the imine and the 2-aminopyridine as the reference system (**A0**). The both reaction pathways leading to ring fused aminal **3a** and the bicyclic product **4a** are exergonic, ΔG = -26.4 and -13.9 kcal.mol^{-1}, respectively. Among the many possibilities[S8] to compare the nucleophilicity of nitrogen, we have selected the condensed local nucleophilicity index (*Nk*). This "*Nk*" index, defined locally for atom k, is correspond to the nucleophilicity index (N) for the overall molecule. N index associated with the condensed local Fukui function (f_k^-) by the following relation $N_k = \mathrm{N} * f_k^-$. The *Nk* values obtained with different aminopyridines are shown in Table 1. Only the relative values are discussed here. Higher is the *Nk* index, better is the nucleophilicity of the nitrogen considered.

Table 1. Nucleophilicity indexes[a]

entry	compound	N	f_k^-	*Nk*
1	2-aminopyridine	2.86	0.269	0.77
2	3-aminopyridine	3.08	0.278	0.86
3	4-chloroaniline	4.13	0.240	0.99
4	**A0**	2.21	0.137	0.30
5	**A1**	3.16	0.288	0.91
6	**A3**	3.36	0.299	1.01

[a]The values rely to the nitrogen involved in nucleophilic attack to the enone or to the imine fragment. (Entry 1-3 and 5: the values for the amine nitrogen, Entry 4: values for imine nitrogen, Entry 6: values for the nitrogen that involved in the ring closure).

Considering the *Nk* values, 4-chloroaniline is a better nucleophile than the 2-aminopyridine and 3-aminopyridine (entries 1–3). This first comparison is in agreement with the synthesis of the bicyclic diamine product **18**, as the first step is the nucleophilic attack at the Cβ position in cyclohexadienone ring. The possibility to form the ring by the imine is unfavorable due to the low nucleophilicity of the imine nitrogen (entry 4, **A0**, *Nk* = 0.30). The possible formation of hydrogen bond, inside the solvation cavity, between 2-aminopyridine and imine is slightly endergonic. This formation enhances the nucleophilicity of the 2-aminopyridine fragment (*Nk* values: 0.77 to 0.91 entry 1 and 5, respectively). The transition state **TS1** is +17.3 kcal.mol^{-1} over **A1**, a H-bonded pre-organized dimer of imine and 2-aminopyridine. An intermediate

A2 close in energy to **TS1** (at the range of calculation energies errors[S9]) has been found. This **A2** intermediate leads to a new intermediate **A3**, resulting from the hydrogen transfer to the pyridine-N. The energy of **A2** is very close to that of **A1** system. The activation associated with the formation of **A3** is the rate-determining step for ring closure. The nitrogen, originally at imine fragment, increases its nucleophilicity dramatically to *Nk* =1.01 (entry 6). This value is in the same order of magnitude as the nitrogen in 4-chloroaniline (*Nk* = 0.99, *cf* entry 3). After rotation of the pyridine fragment to give **A4**, the ring closure could occur in a concerted process involving the formation of the N-C bond and hydrogen transfer (see video, for the connecting **A4** and **A5** via **TS3**). A conformation changes of the six aza-membered ring formed, **A5** to **A6**, is then needed to favorably place the second nitrogen close to the remaining electrophilic Cβ position on cyclohexanone ring. This new conformation allows the ring closure to get ring-fused aminal **3a** (= **A7**), as shown in Figure 1.

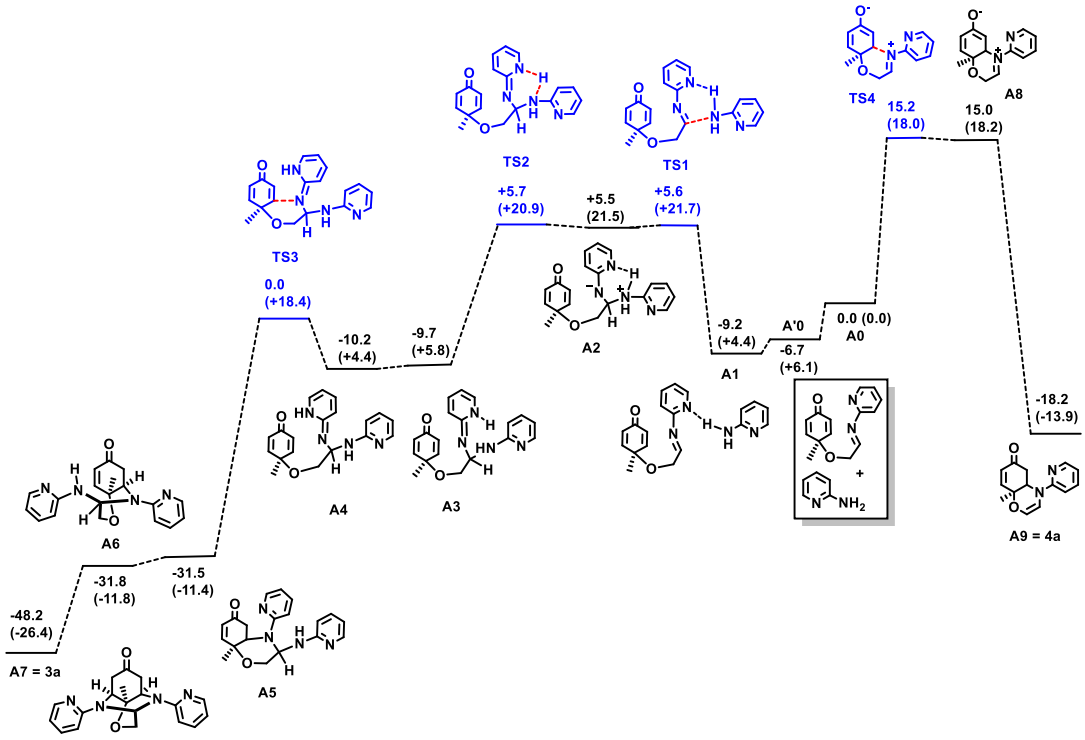


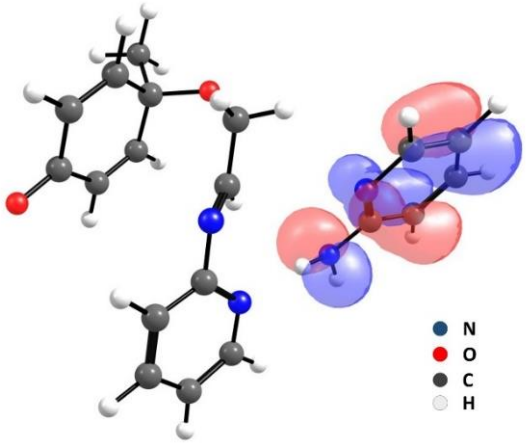
Figure 1. Energy profile E in kcal.mol^{-1}, Parentheses () ΔG in kcal.mol^{-1}. In blue: transition states (TS). In red dotted line: bonds formed and/or broken at the TS. The presented **TS4**, **A8**, and **A9** energy values take account of contribution from one additional free 2-aminopyridine energy values for comparison.

Alternatively, the synthesis of minor product **4a** (= **A9**) has also been investigated by calculation (Fig. S1). A direct amination seems possible (see molecular orbitals frontiers below) with a free energy activation of 18.0 kcal.mol^{-1}, despite the low *Nk* value (0.30). The relative energy position between **A0** and **A1** depends on the determination of the entropic parameter. Calculation involving the presence of the 2-

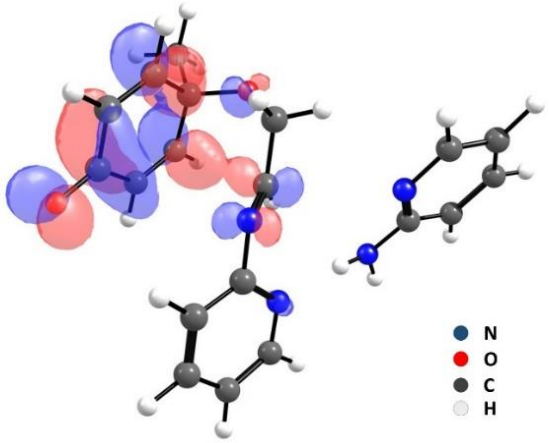
aminopyridine and the imine in the same solvation cavity, without hydrogen bonding, places this latter (**A'0**) above **A1** by ΔG = 1.7 kcal.mol^{-1}.

Molecular orbitals for A1

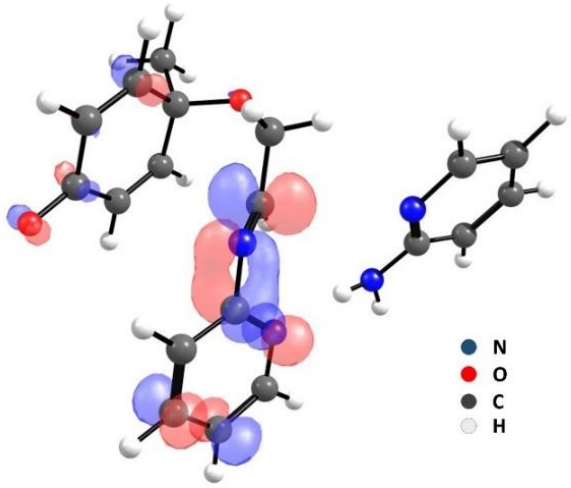
HOMO:



LUMO:



LUMO +1:



Name of compound, E the absolute energy value in Hartree, “One imaginary frequency” is specified when a transition state was found, and Cartesian coordinates xyz

2-AminoPyr E = -303.638740

C	-0.043298	0.064902	-0.085997
C	-0.058845	0.044154	1.294330
C	1.170767	-0.009667	1.979626
N	2.347096	-0.037411	1.339442
C	2.331573	-0.020500	0.002853
C	1.177854	0.029627	-0.762920
N	1.216833	-0.086330	3.349610
H	1.229911	0.044300	-1.844370
H	-0.977295	0.108823	-0.636300
H	-0.991274	0.066948	1.847083
H	2.112311	0.140690	3.754873
H	0.423583	0.269396	3.859304
H	3.307058	-0.044853	-0.477479

A0 E= -801.766504

N	5.079178	-2.280970	-2.058941
C	5.944486	-1.264373	-2.113668
C	6.965877	-1.086362	-1.176216
C	7.107124	-2.021268	-0.162952
C	6.215121	-3.088162	-0.102999
C	5.220278	-3.165794	-1.070354
N	5.817079	-0.300041	-3.129404
C	5.326911	-0.665803	-4.242174
C	5.099466	0.273572	-5.381290
O	5.444088	1.615922	-5.126987
C	4.355952	2.462830	-4.717487
C	3.395643	2.617947	-5.862199
C	2.084245	2.389083	-5.762028
C	1.476325	1.931881	-4.499694
C	2.392540	1.706312	-3.370473
C	3.704072	1.936845	-3.471792
C	5.008070	3.811753	-4.412407
O	0.270469	1.740415	-4.400965
H	1.945521	1.340900	-2.451865
H	1.410808	2.523598	-6.602043
H	3.840022	2.940890	-6.799860
H	4.256378	4.540627	-4.105381
H	5.521068	4.177322	-5.304403
H	5.738265	3.686024	-3.610445
H	5.712121	-0.067763	-6.224841
H	4.376654	1.750580	-2.641959
H	5.050963	-1.709447	-4.435979
H	7.623476	-0.230493	-1.264860

H	7.895111	-1.916199	0.574485
H	6.278991	-3.835693	0.678264
H	4.054684	0.173935	-5.709572
H	4.494916	-3.975036	-1.047723

A0' -1105.415944

C	3.856883	2.062557	-3.449889
C	4.514426	2.510177	-4.723502
C	3.540199	2.707757	-5.849356
C	2.220681	2.562655	-5.715140
C	1.614838	2.152428	-4.438802
C	2.537156	1.905263	-3.319213
O	5.521987	1.566536	-5.130290
C	5.050516	0.260083	-5.363393
C	5.198370	-0.684414	-4.217440
N	5.739925	-0.363157	-3.114356
C	5.776046	-1.327817	-2.091883
N	4.806708	-2.244712	-2.017632
C	4.863939	-3.132280	-1.023077
C	5.873323	-3.155472	-0.068142
C	6.874414	-2.191555	-0.148036
C	6.822334	-1.254561	-1.167782
C	5.277525	3.809860	-4.470809
O	0.403059	2.011182	-4.318834
H	2.088987	1.585336	-2.384256
H	1.538691	2.713023	-6.543429
H	3.978711	2.970255	-6.807749
H	4.593132	4.602934	-4.165206
H	5.792589	4.112186	-5.385063
H	6.017500	3.648811	-3.684132
H	5.615337	-0.144798	-6.211005
H	4.533796	1.859651	-2.627423
H	4.812442	-1.695561	-4.396158
H	7.567356	-0.475453	-1.271452
H	7.678320	-2.166600	0.579234
H	5.865918	-3.899601	0.718923
H	3.998371	0.259276	-5.681535
H	4.055741	-3.858180	-0.984924
N	4.255443	0.612796	-8.723691
H	4.709784	-0.284059	-8.656092
C	2.894844	0.644092	-8.542918
N	2.244599	1.677439	-9.092102
C	0.926469	1.766070	-8.887392
C	0.191612	0.860149	-8.138860
C	0.878914	-0.214581	-7.572002
C	2.239714	-0.334698	-7.771356
H	0.435829	2.618384	-9.351472
H	-0.874205	0.990387	-8.001175

H	0.352807	-0.952234	-6.975854
H	2.797380	-1.163275	-7.350001
H	4.594001	1.197456	-9.472955

A1 E = -1105.419908

N	-2.59787	0.42401	-1.68671
N	0.94095	0.77370	-0.61618
N	-2.99719	0.89003	0.53298
N	-0.32141	2.20976	0.79639
C	-4.33560	-0.39377	-3.13771
C	-3.03107	-0.00805	-2.87385
C	-5.25059	-0.32089	-2.08368
C	0.21022	-1.41493	-1.30124
C	-4.83270	0.12039	-0.84529
C	-3.47997	0.48848	-0.67606
C	2.66323	-2.48982	-0.42977
C	0.15055	-0.20523	-0.42705
C	3.58392	-1.63550	0.02151
C	1.39004	-2.79412	0.30299
C	0.85383	1.86789	0.25603
C	2.03297	2.56789	0.52693
C	1.37207	-4.27552	0.68904
C	3.39623	-0.88184	1.27246
C	1.98826	3.63589	1.40793
C	1.22102	-1.96933	1.54859
C	-0.35533	3.25307	1.62835
C	0.76730	3.99343	1.97309
C	2.14612	-1.12285	2.00829
O	0.24917	-2.62932	-0.55871
O	4.23585	-0.08334	1.67165
H	-4.62633	-0.73447	-4.12344
H	-2.28042	-0.04343	-3.66084
H	-6.28640	-0.60782	-2.23317
H	1.06392	-1.32606	-1.98124
H	-0.70976	-1.47098	-1.88637
H	2.81085	-3.03032	-1.36103
H	4.50531	-1.44867	-0.51957
H	1.47550	-4.88633	-0.20998
H	-5.52144	0.18554	-0.01031
H	2.95382	2.24952	0.05590
H	-0.57737	-0.22501	0.38877
H	-2.08779	1.35801	0.54605
H	0.42024	-4.51205	1.16944
H	-3.66035	1.16609	1.23804
H	2.18767	-4.50305	1.37735
H	2.89087	4.18696	1.64667
H	-1.33084	3.50757	2.03387
H	0.28706	-2.12317	2.08192

H	0.68280	4.82903	2.65682
H	2.00198	-0.55316	2.92002

TS1 E = -1105.396331, One imaginary frequency

N	-1.59241	1.88070	0.42454
N	3.26082	1.79353	1.04838
N	0.94801	1.53990	1.13694
N	-0.87724	-0.18557	1.30460
C	1.66162	-3.32336	-1.97247
C	-0.17584	-1.69560	-1.71599
C	3.13529	2.70831	-1.58120
C	-1.49097	-1.77208	-1.50348
C	4.36116	2.55986	-0.93990
C	0.83908	-2.51635	-0.96729
C	1.97141	2.39777	-0.89331
C	-2.05141	-2.67072	-0.48453
C	0.21719	-3.44613	0.03250
C	-2.59207	2.73482	0.16215
C	-1.09671	-3.52104	0.24692
C	4.37024	2.10356	0.37217
C	-3.91492	2.48351	0.46301
C	2.10352	1.94745	0.41735
C	0.30018	0.04355	0.65320
C	1.37324	-1.01409	0.87358
C	-4.21547	1.26535	1.09735
C	-1.86881	0.68835	1.02650
C	-3.20807	0.37772	1.38558
O	-3.25537	-2.72503	-0.26266
O	1.79753	-1.65439	-0.32393
H	3.08483	3.06417	-2.60356
H	2.16950	-2.63994	-2.65649
H	1.01719	-3.99086	-2.54773
H	0.23389	-1.01819	-2.46046
H	-2.19949	-1.16178	-2.05330
H	5.29102	2.79334	-1.44323
H	2.41124	-3.91381	-1.44191
H	0.99216	2.50423	-1.34374
H	-2.30004	3.66947	-0.31128
H	0.21934	0.30209	-0.41369
H	-4.68500	3.20613	0.22373
H	0.91186	-4.06875	0.59067
H	5.30566	1.97680	0.90852
H	-1.52127	-4.20276	0.97651
H	0.07367	2.08340	0.89986
H	-5.24199	1.02401	1.35530
H	2.28578	-0.57627	1.28130
H	0.97556	-1.73493	1.59354
H	-3.40219	-0.57610	1.85988

H	1.12328	1.50826	2.13865

A2 E = -1105.396432

N	1.30133	1.75849	-1.19662
N	-0.90173	1.04758	-0.75477
N	0.44031	1.56352	1.25024
N	0.59514	1.30419	3.56265
C	0.55739	2.47535	-3.77154
C	1.88837	2.64911	-3.34468
C	-0.37590	1.95198	-2.91390
C	-1.65953	-1.57036	-2.48143
C	2.19260	2.28322	-2.05148
C	-0.36480	-1.95081	-1.89967
C	-2.84112	-1.70379	-1.61179
C	0.00625	1.56843	-1.59609
C	-0.26034	-2.33923	-0.62729
C	-2.73729	-2.09405	-0.34116
C	-1.43134	-2.43639	0.31347
C	-0.37553	0.46528	0.38679
C	-1.49732	-3.85434	0.88012
C	-1.41970	-0.20075	1.27913
C	2.28452	0.27850	2.18842
C	1.14177	1.04616	2.38328
C	2.89187	-0.25436	3.31652
C	2.34019	0.00307	4.56727
C	1.19683	0.78897	4.63857
O	-1.75915	-1.18398	-3.64010
O	-1.21278	-1.59579	1.46407
H	0.27034	2.75191	-4.78150
H	2.64706	3.06101	-3.99823
H	-1.40405	1.79119	-3.21328
H	0.49895	-1.87802	-2.55205
H	-3.79801	-1.45713	-2.05992
H	3.19883	2.41312	-1.65975
H	0.70225	-2.60656	-0.19939
H	-1.62531	-4.58277	0.07720
H	-3.61604	-2.17253	0.29383
H	0.45343	-0.23577	0.19996
H	1.07945	1.86807	0.43957
H	-2.39868	0.00260	0.83676
H	2.67953	0.11666	1.19302
H	-0.57181	-4.07374	1.41700
H	-2.33584	-3.93263	1.57516
H	-0.19570	2.30874	1.52961
H	-1.39805	0.21068	2.28968
H	3.78570	-0.85931	3.21913
H	2.78607	-0.39435	5.47055
H	0.73790	1.01588	5.59579

TS2 E = -1105.396145, One imaginary frequency

N	-3.65384	0.40570	-1.20727
N	0.94498	0.54534	-1.01140
N	-1.43987	1.02648	-0.82159
N	0.33335	2.44734	0.23063
C	-0.60358	-1.33770	-1.23947
C	-4.85592	0.03367	-0.75768
C	2.80546	-2.24217	-0.81757
C	1.67520	-2.94878	-0.82907
C	2.56978	2.27743	-0.63881
C	-0.27741	0.00520	-0.58326
C	1.26382	1.72308	-0.47486
C	-2.71555	0.65254	-0.30269
C	2.87279	3.48978	-0.07982
C	3.11241	-1.28712	0.26126
C	0.62472	-2.84249	0.23686
C	-5.15220	-0.11374	0.59111
C	1.89525	4.20832	0.64338
C	0.64596	3.64568	0.75279
C	0.34817	-4.22469	0.82731
C	-2.90003	0.54675	1.07252
C	2.14097	-1.19763	1.36062
C	1.00789	-1.90219	1.34783
C	-4.15138	0.14977	1.52092
O	-0.63441	-2.43601	-0.33680
O	4.14346	-0.62451	0.25508
H	0.12771	-1.49684	-2.03705
H	-5.60956	-0.15752	-1.51543
H	-1.52030	1.22323	-1.81827
H	1.45502	-3.63957	-1.63900
H	3.54640	-2.33192	-1.60515
H	-1.60337	-1.32426	-1.67677
H	3.30137	1.69873	-1.18798
H	3.87139	3.90079	-0.19168
H	-0.89796	1.89004	-0.26078
H	0.05544	-4.91218	0.03106
H	-6.14174	-0.42410	0.90255
H	-0.33371	-0.11414	0.51089
H	2.11149	5.16965	1.09131
H	1.23668	-4.61211	1.32952
H	-0.15849	4.15496	1.27660
H	-0.46759	-4.15370	1.55032
H	-2.09588	0.77680	1.76008
H	2.38605	-0.51582	2.16815
H	0.28709	-1.82133	2.15710
H	-4.34312	0.05349	2.58326

A3 E = -1105.420743

N	1.32682	-0.44891	0.13043
N	0.24155	1.61006	0.69974
N	-0.67969	3.70696	0.85430
N	2.53728	0.48879	1.94752
C	-1.46084	-1.84851	-4.05970
C	-0.21135	-2.13006	-3.33636
C	-2.68856	-1.76829	-3.24874
C	-0.19996	-2.36834	-2.02183
C	-2.67762	-2.02050	-1.93772
C	-1.44642	-2.43993	-1.18755
C	-1.62794	-3.87825	-0.69157
C	-1.05823	-0.27298	-0.20934
C	3.64123	-0.97622	0.43593
C	0.12879	0.14799	0.64957
C	2.42463	-0.30339	0.80997
C	4.77241	-0.86410	1.18196
C	-1.52909	4.56936	1.41536
C	-0.69977	2.43535	1.27806
C	4.80192	-0.05634	2.35481
C	-2.43895	4.23180	2.40679
C	-1.58675	1.98909	2.27447
C	3.67035	0.61371	2.69145
C	-2.45748	2.90562	2.83578
O	-1.47970	-1.66597	-5.27179
O	-1.30262	-1.65697	-0.00154
H	0.70081	-2.11351	-3.92396
H	-3.59683	-1.49149	-3.77400
H	-1.75383	-4.56275	-1.53177
H	0.72589	-2.51876	-1.47754
H	-3.58517	-1.95382	-1.34340
H	-0.81783	-0.06132	-1.25617
H	3.60213	-1.58683	-0.45706
H	-0.74993	-4.17292	-0.11296
H	-2.50870	-3.93054	-0.04794
H	0.66993	2.01938	-0.12126
H	-1.95010	0.29817	0.06838
H	5.66799	-1.39732	0.88099
H	-1.47744	5.58946	1.04227
H	-0.06140	-0.20037	1.67871
H	1.75607	1.10613	2.13688
H	-3.10826	4.97476	2.82190
H	-1.59035	0.95653	2.59832
H	5.69480	0.03963	2.95631
H	3.59750	1.27508	3.54509
H	-3.15105	2.58468	3.60558

A4 E = -1105.421445

N	-3.25427	-1.86126	-1.42470
N	-1.29244	-0.88793	-0.75200
N	-0.77727	3.29061	-0.53456
N	-0.12051	1.12244	-0.24702
C	-4.33827	-2.59083	-1.16145
C	4.75526	-0.58338	-1.15803
C	3.96300	0.64362	-0.98168
C	-1.62447	4.34365	-0.47134
C	-2.37873	-1.64585	-0.42679
C	4.54101	-1.65445	-0.16919
C	-4.63162	-3.13689	0.08067
C	-2.87832	4.19586	0.03900
C	-1.06660	2.00074	-0.10909
C	3.14038	0.80389	0.05856
C	-0.41455	-0.21220	0.19691
C	-3.25485	2.90531	0.49229
C	-2.39828	1.84617	0.42221
C	0.87932	-1.00139	0.33996
C	3.72836	-1.48734	0.87690
C	-2.57020	-2.17979	0.86435
C	-3.71355	-2.91868	1.10716
C	3.00048	-0.20532	1.16184
C	3.54512	0.40164	2.45913
O	5.53793	-0.71889	-2.09164
O	1.62306	-0.46970	1.42850
H	-5.01578	-2.74234	-1.99902
H	4.06929	1.40138	-1.75124
H	-1.31602	-0.49084	-1.67990
H	-1.23672	5.28149	-0.84683
H	0.15050	3.41692	-0.91624
H	5.07568	-2.58316	-0.33998
H	1.43749	-0.93072	-0.59931
H	-3.55407	5.03763	0.08692
H	-5.53413	-3.71483	0.23450
H	2.51838	1.68642	0.16186
H	0.65067	-2.05538	0.53187
H	-4.24988	2.75528	0.89813
H	-2.71261	0.86767	0.75838
H	-0.90922	-0.21603	1.18078
H	3.56906	-2.28367	1.59923
H	-1.83442	-2.03310	1.64436
H	-3.88279	-3.33442	2.09492
H	4.60548	0.63815	2.35943
H	2.99095	1.31391	2.68978
H	3.40889	-0.31003	3.27631

TS3 E = -1105.405192, One imaginary frequency

N	-0.52342	-0.02412	0.05120

N	-0.94432	2.21642	0.26558
N	1.57035	-0.87487	0.80330
N	3.68605	-0.26215	1.40895
C	-3.44001	-2.35468	-1.46857
C	4.74912	-1.08904	-1.02268
C	1.39110	2.99943	-0.85400
C	-2.08864	-0.36293	-0.90173
C	3.39814	-1.24735	-0.76905
C	1.11715	1.65873	-0.73702
C	-3.08255	0.61107	-0.63603
C	0.46888	3.96969	-0.41872
C	-2.42489	-1.77768	-0.47257
C	5.57566	-0.51960	-0.05599
C	-0.09464	1.22698	-0.14579
C	0.45940	-1.08728	-0.09328
C	-0.70848	3.53779	0.12323
C	-0.23207	-2.38878	0.27321
C	-3.91460	0.50803	0.50841
C	2.89451	-0.79752	0.46627
C	-3.03579	-1.77122	0.90300
C	4.98637	-0.13999	1.14188
C	-3.73868	-0.72178	1.33314
O	-1.31943	-2.67476	-0.57308
O	-4.74920	1.36561	0.87030
H	-3.00199	-2.36970	-2.46968
H	5.15790	-1.42280	-1.97041
H	-1.63614	-0.33213	-1.89207
H	-4.34991	-1.75650	-1.48097
H	2.75655	-1.72452	-1.49821
H	2.32499	3.31231	-1.30720
H	-3.67789	-3.37954	-1.17634
H	-3.15850	1.49991	-1.25215
H	1.81853	0.92603	-1.10869
H	0.83877	-1.15929	-1.12108
H	0.67102	5.02748	-0.50829
H	6.63733	-0.38566	-0.21991
H	0.47257	-3.21495	0.16750
H	-1.49097	4.19694	0.47308
H	-1.84787	1.89586	0.60747
H	-2.96333	-2.69181	1.47644
H	-0.54818	-2.32256	1.32351
H	5.58945	0.29361	1.93621
H	1.34598	-0.49037	1.70992
H	-4.25444	-0.73455	2.28899

A5 E = -1105.455452

N	-0.33602	1.63452	-0.56586
N	-0.09473	-0.67478	-0.37849

N	-0.87101	0.00167	1.81539
N	-1.07986	2.10522	2.68532
C	-1.04964	-1.17732	-3.11082
C	0.38188	-1.35899	-2.65891
C	-2.03747	-2.10531	-2.53951
C	0.38992	-4.26614	-1.55145
C	-1.71081	-2.95383	-1.56143
C	0.46840	-1.76123	-1.18911
C	-0.33132	-3.05789	-0.96384
C	2.40824	2.04080	-0.80928
C	1.53736	3.12317	-0.76978
C	1.88902	0.75988	-0.69914
C	0.17870	2.86347	-0.64605
C	0.50735	0.60261	-0.57080
C	-0.21328	-1.01702	1.05566
C	-1.01734	-2.29825	1.17283
C	-0.24868	1.10573	2.36168
C	1.13531	1.18084	2.58782
C	1.64817	2.33894	3.14148
C	-0.55998	3.20754	3.22726
C	0.79282	3.38844	3.47300
O	-1.36078	-0.33757	-3.93757
O	-0.42623	-3.34448	0.43160
H	0.83186	-2.13912	-3.28116
H	-3.04184	-2.06043	-2.94772
H	0.92826	-0.43804	-2.86231
H	0.49079	-4.19092	-2.63417
H	-0.17943	-5.16839	-1.32049
H	-2.44624	-3.64454	-1.15588
H	1.38124	-4.35415	-1.10093
H	3.47790	2.19155	-0.90462
H	1.89808	4.14248	-0.83614
H	1.51227	-1.98095	-0.91667
H	-0.53644	3.68104	-0.61634
H	2.54573	-0.10178	-0.69419
H	-2.04583	-2.10598	0.83556
H	0.78085	-1.19526	1.48810
H	-1.80878	0.22077	1.50506
H	-1.04122	-2.62034	2.21354
H	1.79328	0.36513	2.32207
H	2.71621	2.42346	3.31101
H	-1.27251	3.99180	3.47193
H	1.16103	4.31060	3.90463

A6 E = -1105.455923

N	-0.77176	-2.38865	-0.23998
N	1.31116	0.22543	-0.23128
N	-0.94363	-0.17873	0.40668

N	3.16162	-0.64465	0.84926
C	-2.05566	1.69900	-1.69754
C	4.71641	-0.29476	-1.43610
C	-0.80498	2.45022	-1.57337
C	3.38437	0.05789	-1.44537
C	-1.29580	-3.60032	-0.42198
C	5.28204	-0.82725	-0.27236
C	-2.73243	1.28271	-0.41041
C	-0.25034	2.67884	-0.37750
C	-2.61785	-3.92160	-0.14780
C	2.63034	-0.13384	-0.26846
C	-3.42257	-2.91868	0.38428
C	-1.55549	-1.41966	0.24843
C	-2.89522	-1.65592	0.59845
C	4.45790	-0.97760	0.82874
C	-1.75149	1.00053	0.73129
C	0.43787	-0.19988	0.85073
C	-0.85442	2.23956	0.93311
C	-1.65608	3.40030	1.52275
C	0.57303	0.66626	2.08776
O	-2.55388	1.44580	-2.78249
O	0.20685	2.01503	1.86319
H	5.31807	-0.15935	-2.32871
H	-0.34497	2.79629	-2.49306
H	2.91416	0.47231	-2.33005
H	0.84676	0.35485	-1.11559
H	-0.61632	-4.35284	-0.81423
H	-3.35478	0.41815	-0.63495
H	-2.99509	-4.92032	-0.32861
H	6.32519	-1.11425	-0.22745
H	0.67318	3.24214	-0.28624
H	-3.41350	2.08831	-0.11811
H	-4.45441	-3.12042	0.65047
H	-2.42124	3.76677	0.83779
H	-3.50362	-0.88731	1.05488
H	0.69575	-1.22312	1.13267
H	4.84979	-1.38897	1.75589
H	-0.96891	4.22054	1.73810
H	-2.30705	0.84430	1.66619
H	-2.12340	3.08414	2.45828
H	1.61219	0.66704	2.41321
H	-0.04810	0.22529	2.87931

A7 E = -1105.482101

N	-1.091208	-0.651122	-2.657984
C	-1.053278	0.513258	-2.048241
C	0.082956	1.284889	-1.856622
C	1.277512	0.773148	-2.350829

C	1.268166	-0.456858	-2.997850
C	0.061098	-1.134672	-3.127440
N	-2.335692	1.041720	-1.577046
C	-3.014889	2.032067	-2.561726
N	-4.083202	2.640653	-1.853305
C	-5.181761	1.681885	-1.512179
C	-4.674601	0.286070	-1.929560
C	-3.370923	0.005715	-1.155281
C	-3.503718	1.255027	-3.753146
O	-4.415143	0.258167	-3.324566
C	-3.549115	0.061159	0.355423
C	-4.357905	1.253426	0.853858
C	-5.518975	1.692022	-0.021810
C	-5.694364	-0.814325	-1.710726
C	-3.696960	3.619138	-0.908917
C	-4.548271	4.666857	-0.573412
C	-4.124894	5.568210	0.390737
C	-2.865528	5.415705	0.964260
C	-2.075737	4.358627	0.546198
N	-2.484984	3.468703	-0.364192
O	-4.105573	1.787734	1.901899
H	-6.617376	-0.557977	-2.233611
H	-5.308264	-1.738503	-2.143453
H	-5.922949	-0.989020	-0.660187
H	-6.070323	1.921843	-2.102200
H	-3.999694	1.948761	-4.438558
H	-6.347764	0.995874	0.143257
H	-2.669080	0.775938	-4.271062
H	-2.971535	-0.950554	-1.489915
H	-5.504903	4.768702	-1.070559
H	-4.085402	-0.840609	0.670305
H	-5.857753	2.666147	0.327848
H	-4.764825	6.393121	0.682129
H	-2.252734	2.765624	-2.820661
H	-2.589956	0.043518	0.878535
H	-2.503837	6.102673	1.718415
H	0.007432	-2.098220	-3.623110
H	0.035279	2.238114	-1.342798
H	-1.086917	4.199085	0.962858
H	2.179555	-0.887786	-3.393296
H	2.200687	1.326851	-2.226398

TS4 E = -801.742345, One imaginary frequency

C	0.451482	-1.760485	-2.453104
C	1.182533	-1.089287	-1.418494
C	0.666652	-1.293916	0.001446
C	-0.838081	-1.268274	0.031987
C	-1.559878	-1.561705	-1.049859

C	-0.941365	-1.940509	-2.356480
O	1.220237	-0.301142	0.881658
C	0.694293	0.981370	0.686533
C	0.592642	1.365980	-0.735853
N	1.018837	0.589225	-1.659559
C	0.951083	1.013749	-3.024912
C	1.957272	0.613536	-3.896178
C	1.887893	1.066520	-5.205064
C	0.829468	1.887824	-5.580211
C	-0.114671	2.229954	-4.620841
N	-0.060502	1.798283	-3.358045
C	1.181427	-2.623814	0.539614
O	-1.683821	-2.413422	-3.247122
H	0.936686	-1.988986	-3.394348
H	2.265387	-1.194693	-1.451038
H	2.273366	-2.606934	0.581918
H	0.858495	-3.439025	-0.107671
H	0.792634	-2.782342	1.547234
H	-2.644784	-1.598706	-1.009379
H	-1.299837	-1.075928	0.997118
H	1.365578	1.693044	1.181131
H	-0.294082	1.108792	1.152152
H	0.156586	2.325524	-1.005902
H	-0.953794	2.871855	-4.870575
H	0.736710	2.257774	-6.593696
H	2.650708	0.783259	-5.920627
H	2.765551	-0.020798	-3.556821

A8 E = -801.742656

C	0.670678	-1.390951	-0.448918
C	1.274305	-1.385336	-1.829746
C	0.400272	-2.185749	-2.800510
C	-0.082469	-3.459038	-2.244041
C	-0.419040	-3.563209	-0.902688
C	-0.104781	-2.394328	-0.037599
O	1.429018	-0.040594	-2.310301
C	0.236809	0.689306	-2.284686
C	-0.933892	-0.074081	-2.753632
N	-0.839402	-1.297063	-3.131687
C	-2.002421	-1.962107	-3.665796
N	-3.160722	-1.603511	-3.145487
C	-4.261943	-2.167641	-3.649797
C	-4.229767	-3.098790	-4.678907
C	-2.996105	-3.446323	-5.220743
C	-1.845705	-2.865250	-4.709169
C	2.679422	-1.966363	-1.801895
O	-0.941477	-4.578265	-0.336765
H	-0.321582	-4.278773	-2.908110

H	-0.492151	-2.429685	0.976177
H	0.961873	-0.578222	0.210941
H	2.642173	-3.015494	-1.508295
H	3.288739	-1.410491	-1.087318
H	3.133405	-1.884147	-2.792668
H	0.356164	1.551306	-2.951264
H	0.927869	-2.288818	-3.749896
H	-1.909411	0.400386	-2.801292
H	-0.867993	-3.101662	-5.107011
H	-2.928177	-4.159145	-6.033725
H	-5.148746	-3.536075	-5.048501
H	0.004940	1.096328	-1.288612
H	-5.202543	-1.860411	-3.204110

A9 E= -801.795540

N	7.407240	1.509125	-5.362214
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C	6.510643	1.898050	-3.171798
C	5.371563	1.183746	-3.501956
C	5.251435	0.629528	-4.773563
C	6.310817	0.808784	-5.652093
N	8.669686	2.787079	-3.897295
C	8.750882	3.742996	-2.791375
C	10.101569	4.493542	-2.864130
O	11.197951	3.578048	-2.955653
C	11.055949	2.710753	-4.009752
C	9.860427	2.346483	-4.474354
C	7.618601	4.766330	-2.899388
C	7.704877	5.591034	-4.164856
C	9.051242	5.887897	-4.668012
C	10.139667	5.385452	-4.079435
C	10.364664	5.294180	-1.596365
O	6.703263	6.018379	-4.712829
H	6.634254	4.303117	-2.875251
H	7.660931	5.450286	-2.046126
H	9.117382	6.533607	-5.537295
H	11.134814	5.621799	-4.445659
H	9.636603	6.093571	-1.462500
H	11.357742	5.741848	-1.661908
H	10.336724	4.630375	-0.729270
H	11.989573	2.356202	-4.422749
H	8.712247	3.224633	-1.825927
H	9.750996	1.669928	-5.307275
H	6.640202	2.285061	-2.170046
H	4.592104	1.043448	-2.761112
H	4.377229	0.062665	-5.067954
H	6.280077	0.372260	-6.647226

[8] Crystal Structure of Compound 3a

The compound **3a** was recrystallized in EtOH:$CHCl_3$ (1:1) at room temperature to obtain the colorless single crystal for X-ray.

Crystal parameters

```
_chemical_formula_moiety           '2(C19 H20 N4 O2)'
_chemical_formula_sum              'C38 H40 N8 O4'
_chemical_formula_weight           672.78
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_space_group_IT_number             14
_space_group_name_H-M_alt          'P 1 21/n 1'
_space_group_name_Hall             '-P 2yn'
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_cell_length_b                     9.4848(13)
_cell_length_c                     20.804(3)
_cell_angle_alpha                  90
_cell_angle_beta                   99.189(4)
_cell_angle_gamma                  90
_cell_volume                       3270.9(7)
_cell_formula_units_Z              4
_cell_measurement_reflns_used      6113
_cell_measurement_temperature      100
_cell_measurement_theta_max        28.353
_cell_measurement_theta_min        2.457
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_exptl_crystal_description         prism
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_exptl_crystal_size_min            0.01
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_diffrn_ambient_temperature        100
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_diffrn_measurement_device_type    'CCD area detector'
_diffrn_radiation_type             MoK\a
_diffrn_radiation_wavelength       0.71073
_reflns_Friedel_coverage           0.000
_reflns_number_gt                  6113
_reflns_number_total               8161
_reflns_special_details
;
 Reflections were merged by SHELXL according to the crystal
 class for the calculation of statistics and refinement.

 _reflns_Friedel_fraction is defined as the number of unique
 Friedel pairs measured divided by the number that would be
 possible theoretically, ignoring centric projections and
 systematic absences.
;
_reflns_threshold_expression       'I > 2\s(I)'
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_refine_ls_extinction_expression
 'Fc^*^=kFc[1+0.001xFc^2^\l^3^/sin(2\q)]^-1/4^'
_refine_ls_extinction_method       'SHELXL-2016/6 (Sheldrick 2016)'
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_refine_ls_matrix_type             full
_refine_ls_number_parameters       454
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_refine_ls_number_restraints       0
_refine_ls_R_factor_all            0.0980
_refine_ls_R_factor_gt             0.0681
_refine_ls_restrained_S_all        1.127
_refine_ls_shift/su_max            0.000
_refine_ls_shift/su_mean           0.000
_refine_ls_structure_factor_coef   Fsqd
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 'w=1/[\s^2^(Fo^2^)+(0.0489P)^2^+2.4198P] where P=(Fo^2^+2Fc^2^)/3'
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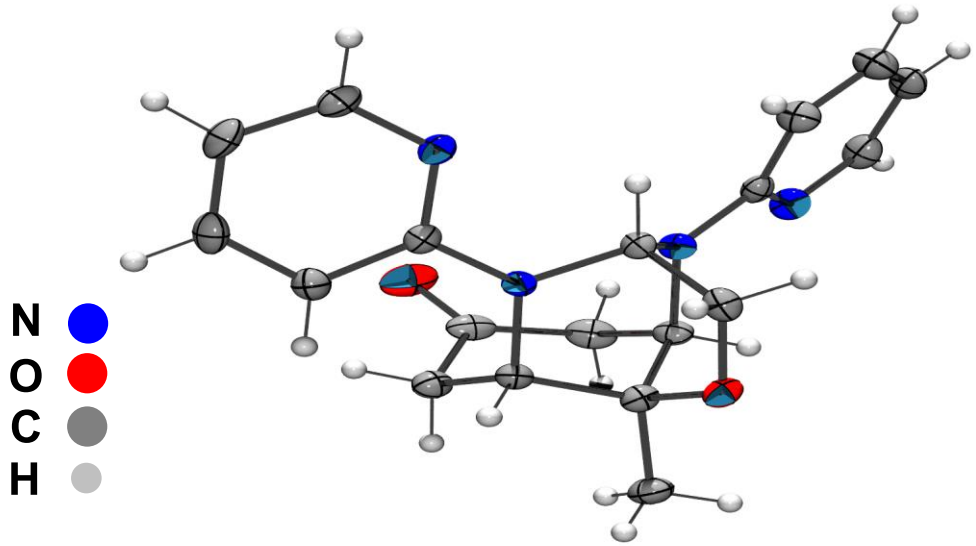
Thermal Ellipsoid Plot



Thermal Ellipsoid structure of **3a** is shown with 50% probability level

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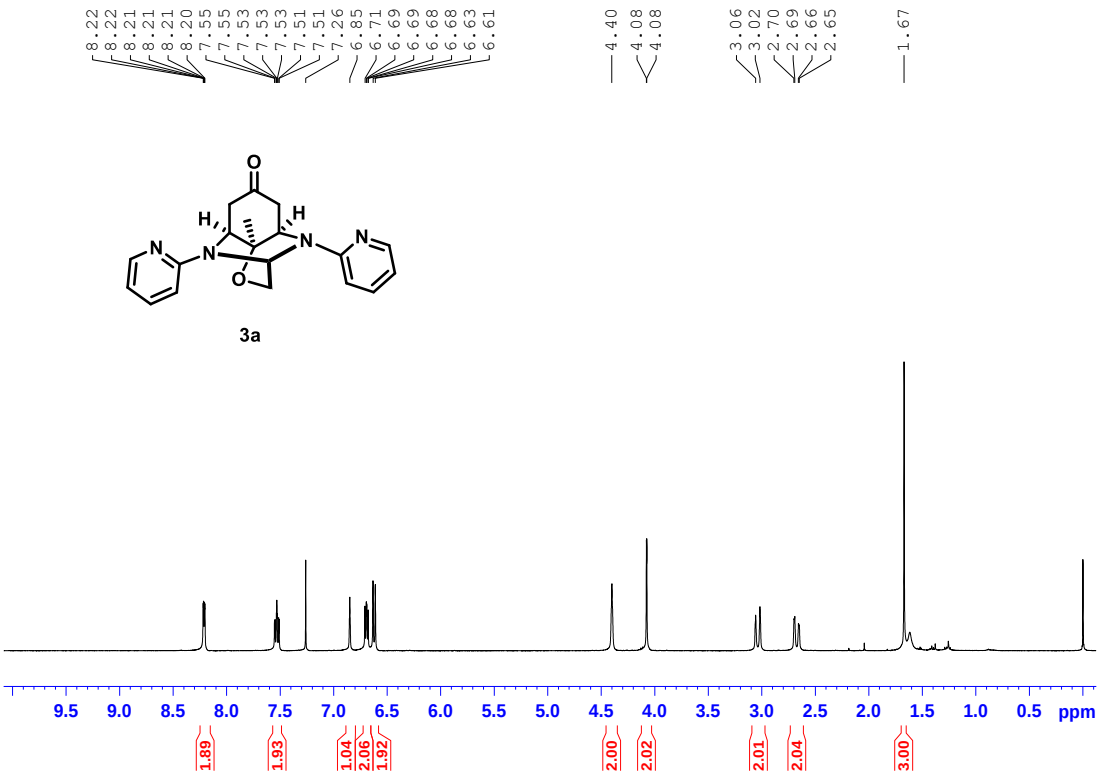
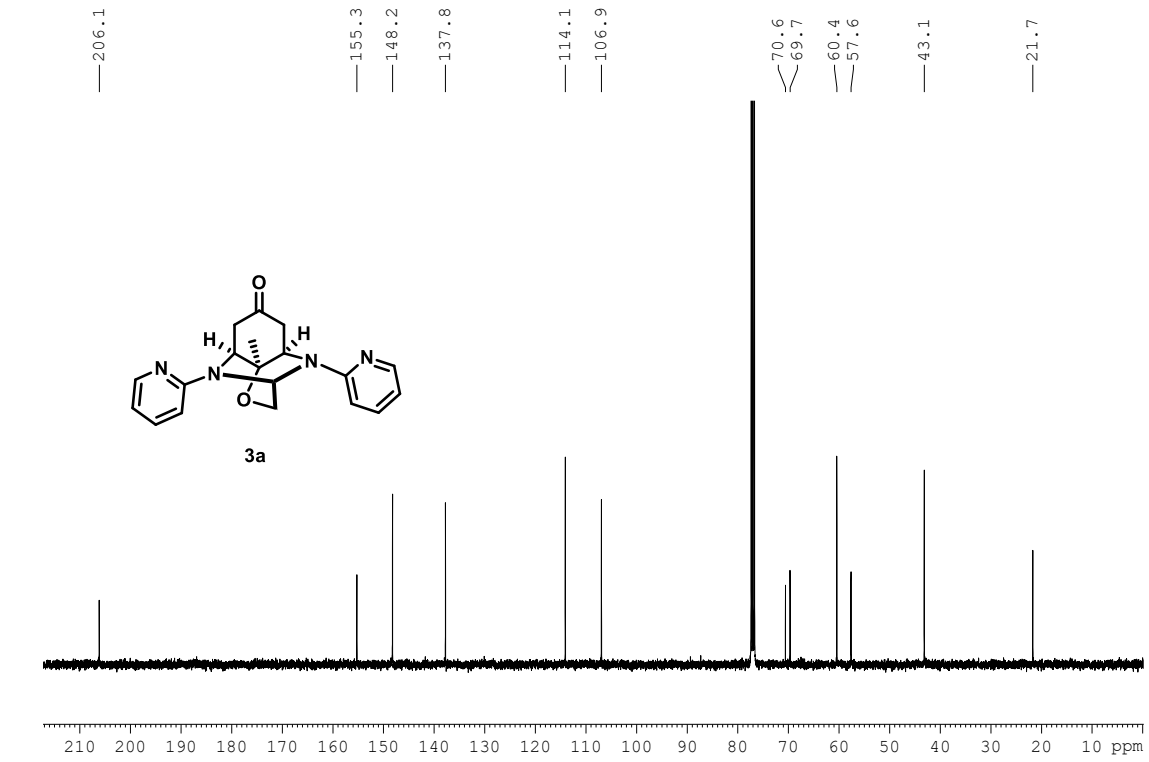
[10] Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) for 3a



^{13}C NMR (100 MHz, $CDCl_3$) for 3a



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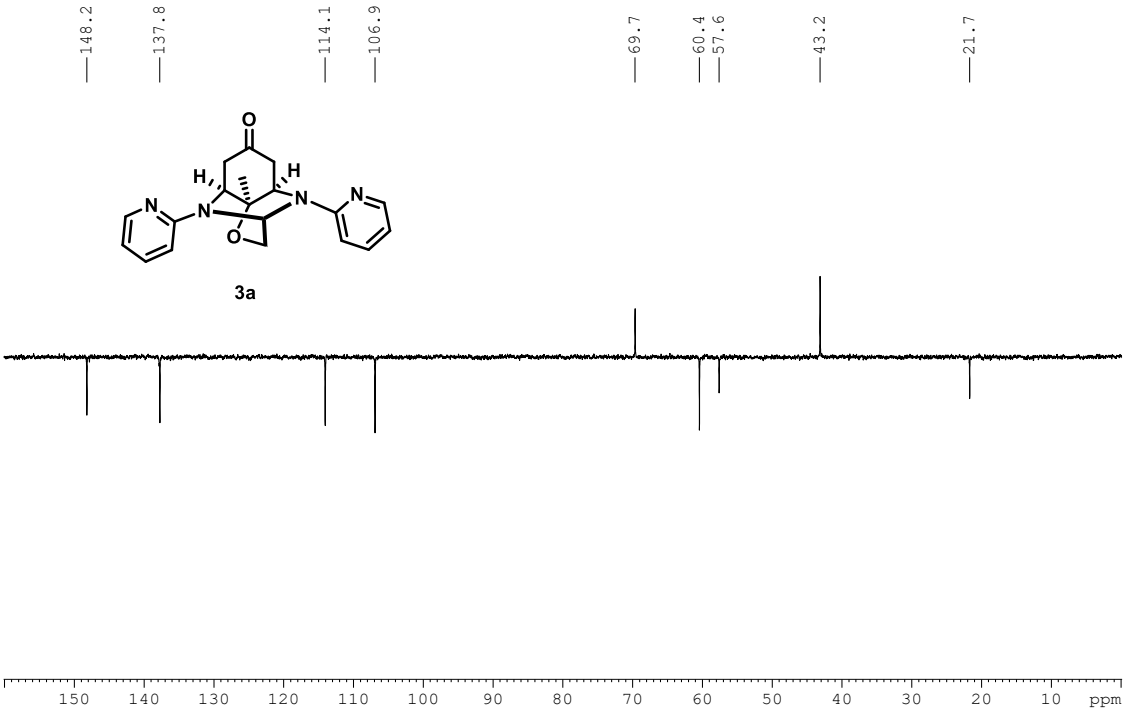

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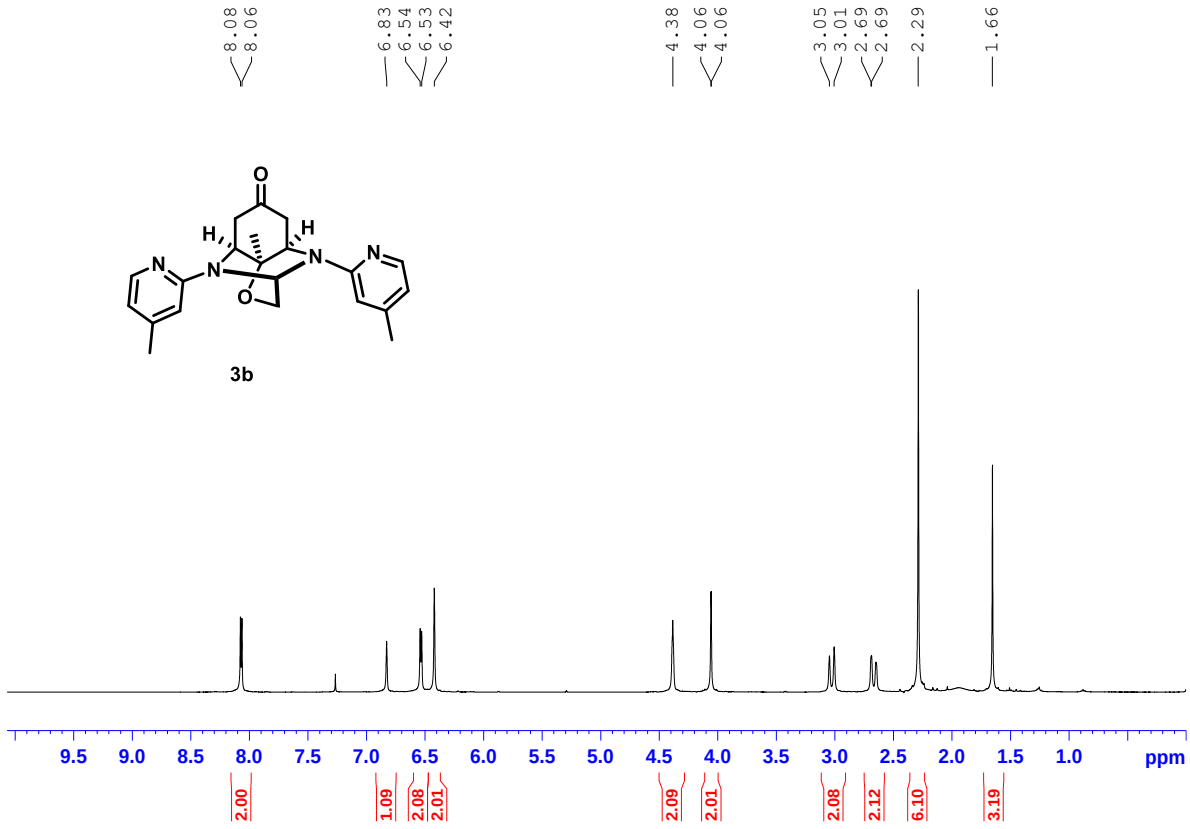

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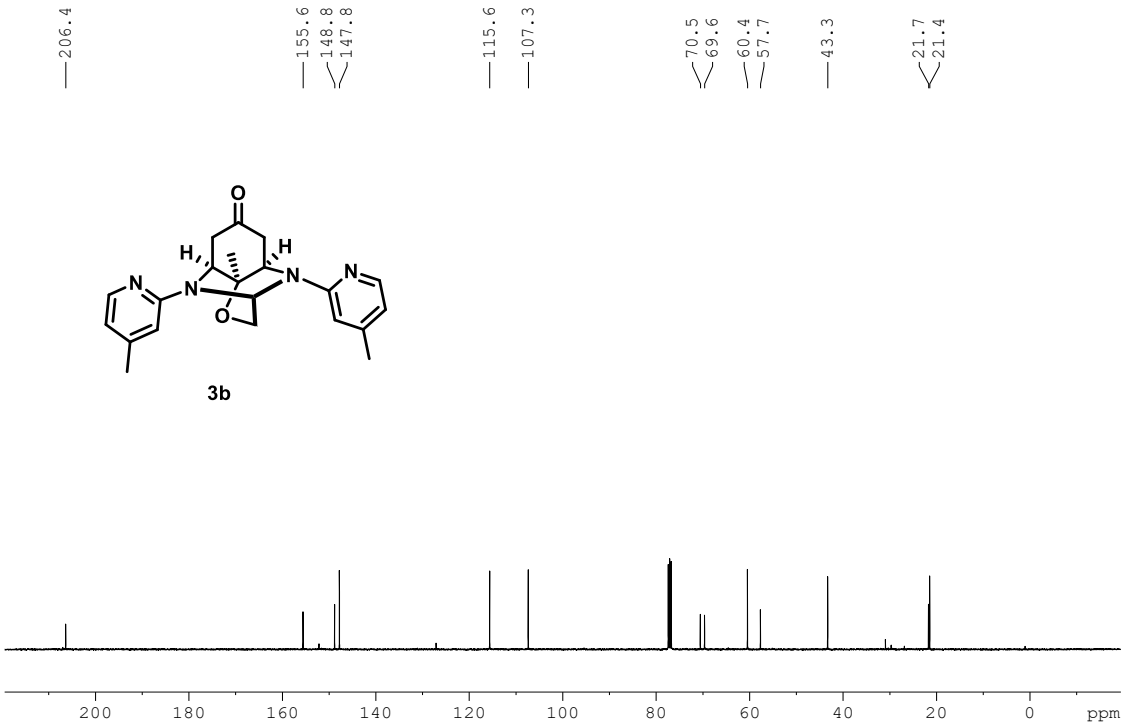

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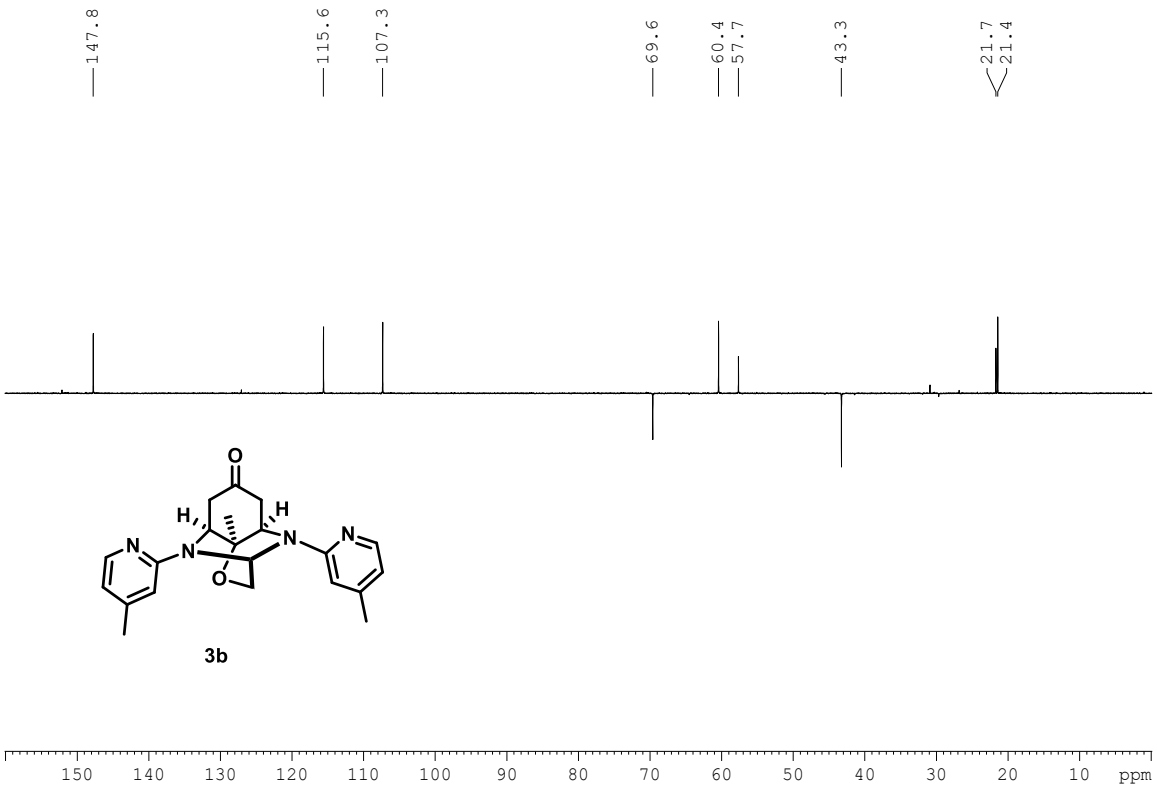

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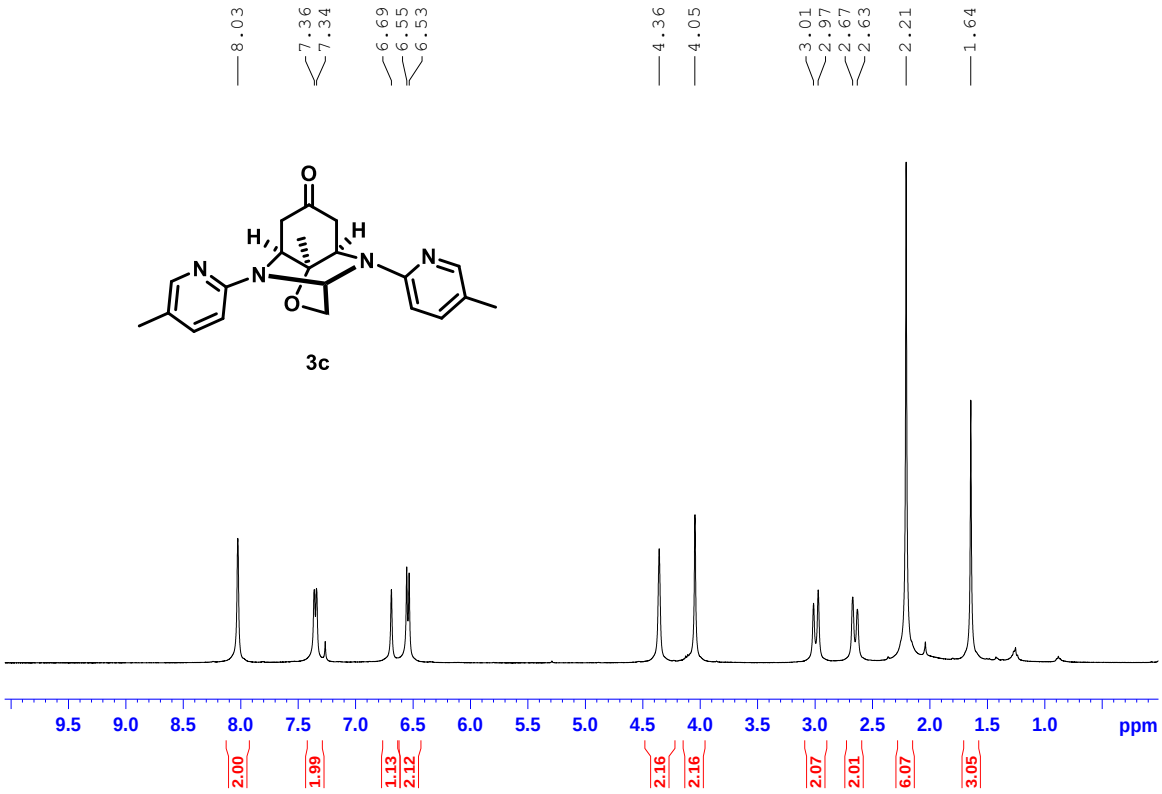

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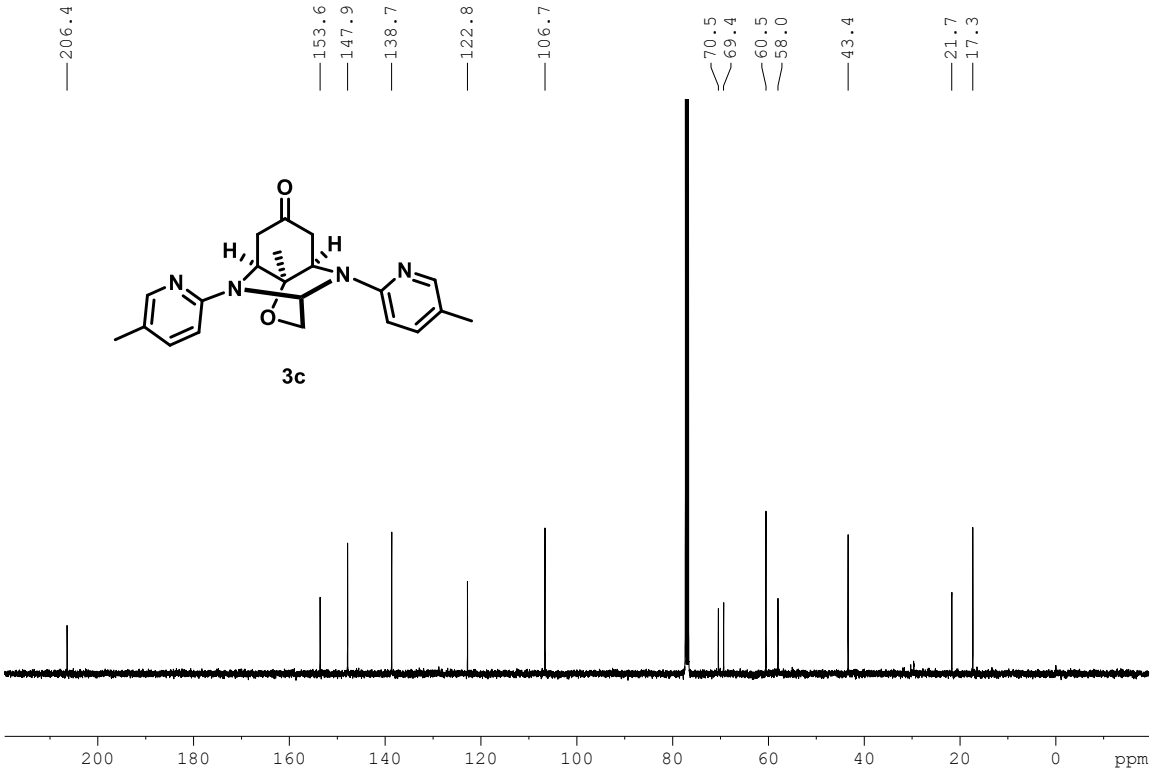
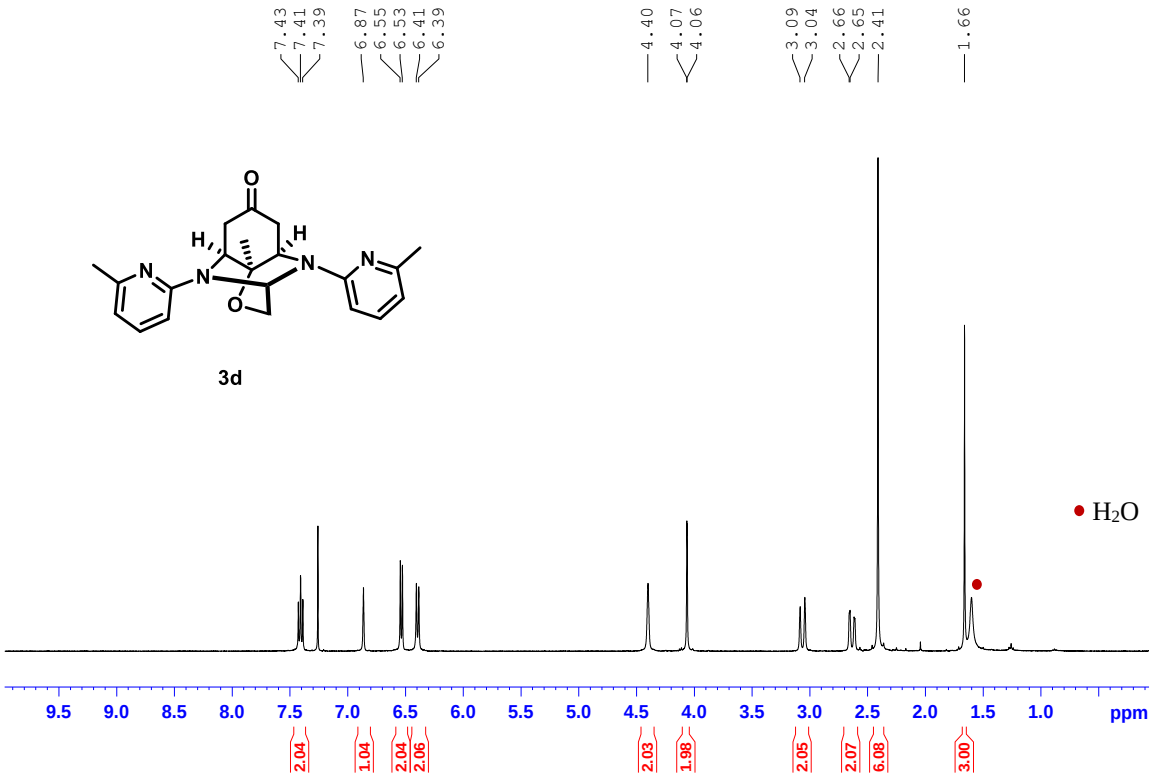


DEPT (100 MHz, $CDCl_3$) for 3c

^{1}H NMR (400 MHz, $CDCl_3$) for 3d



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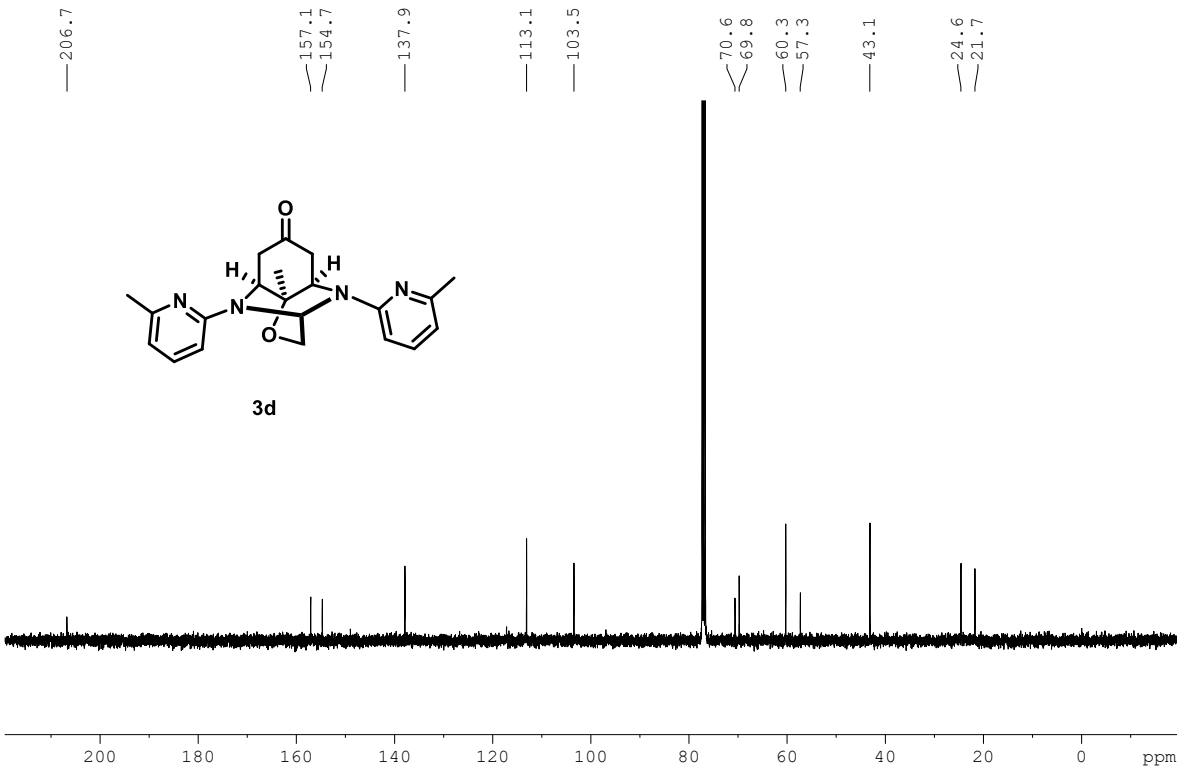
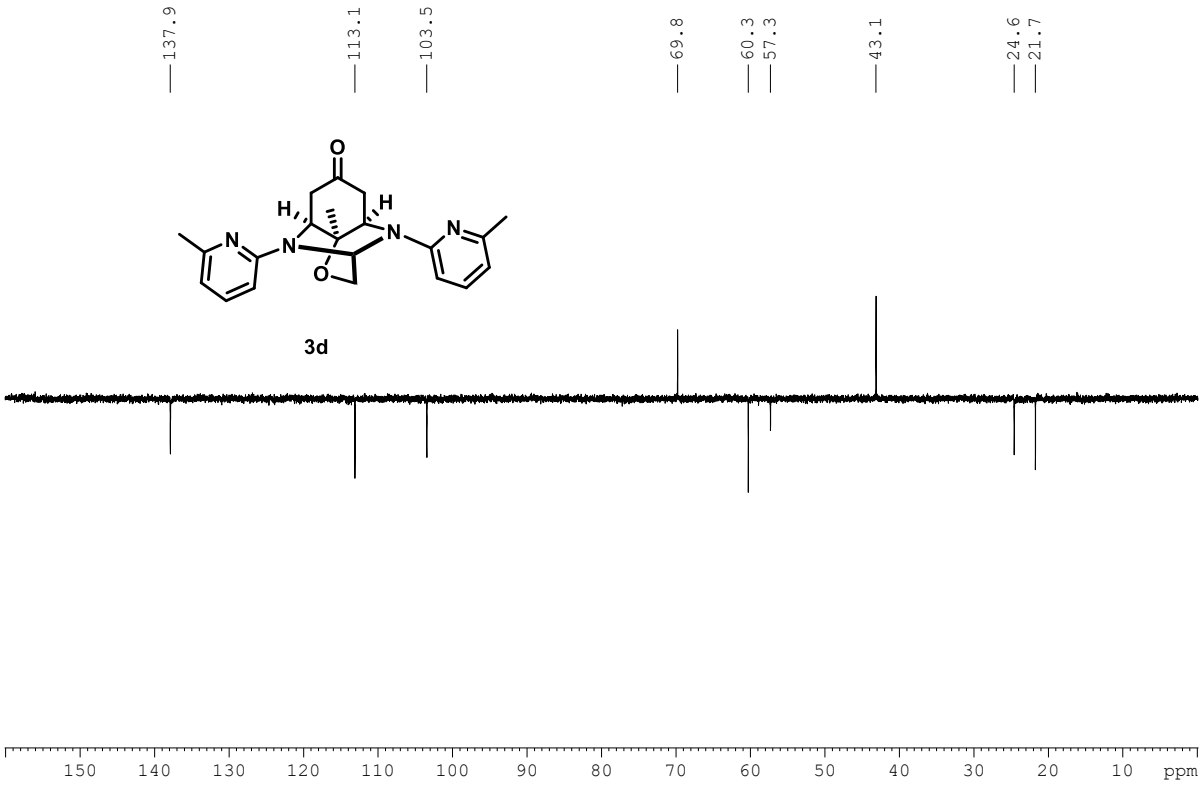


DEPT (100 MHz, $CDCl_3$) for 3d



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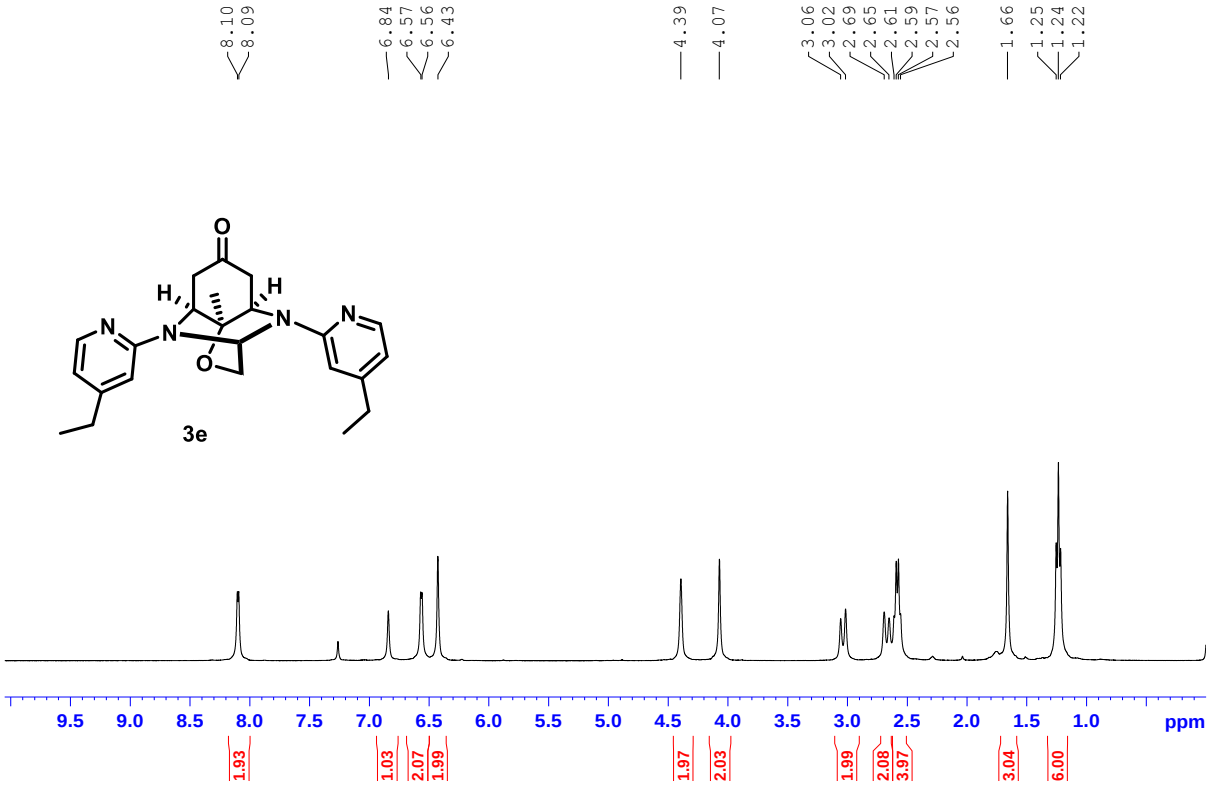

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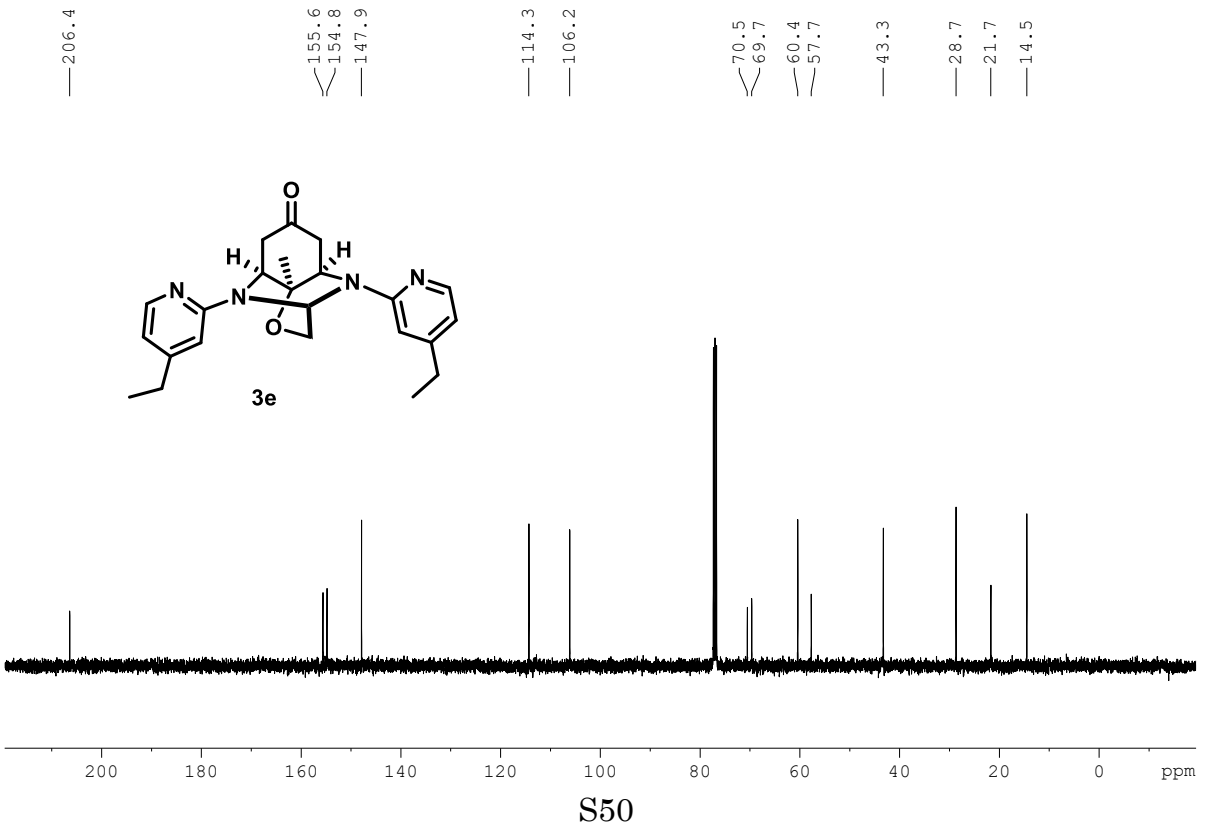

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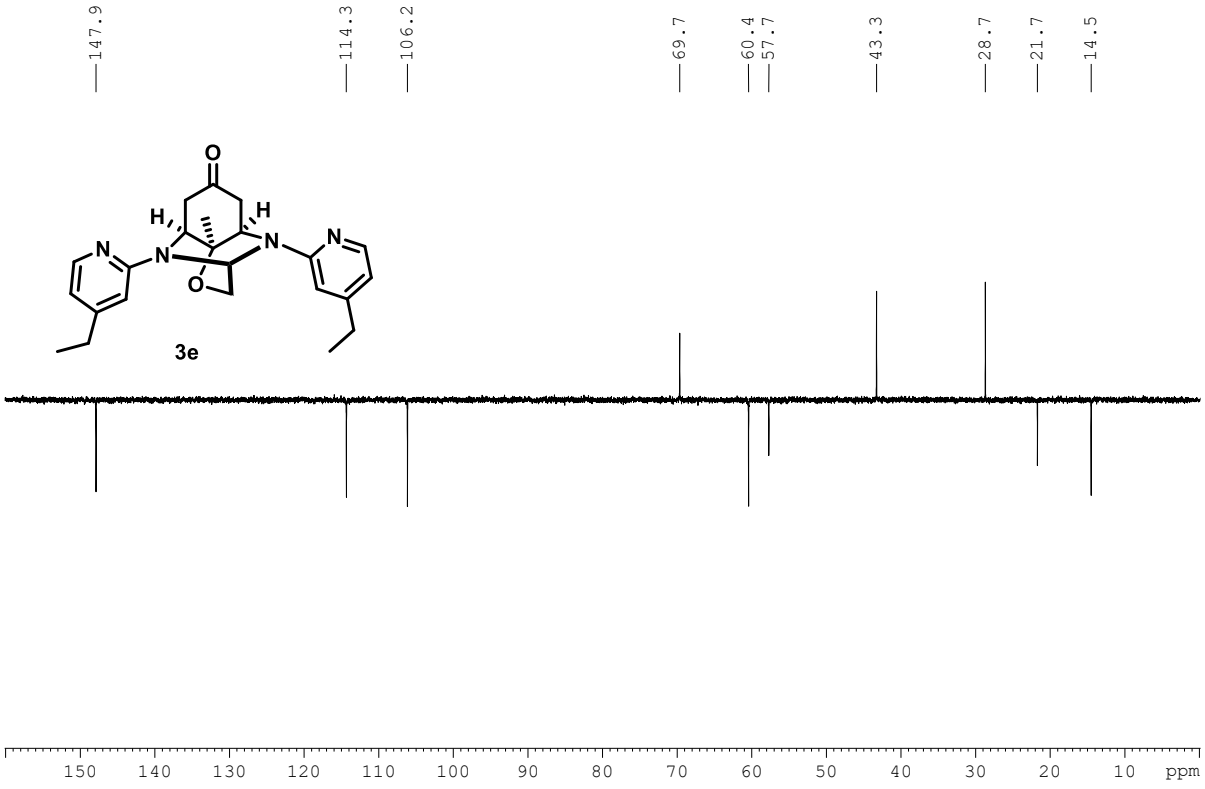

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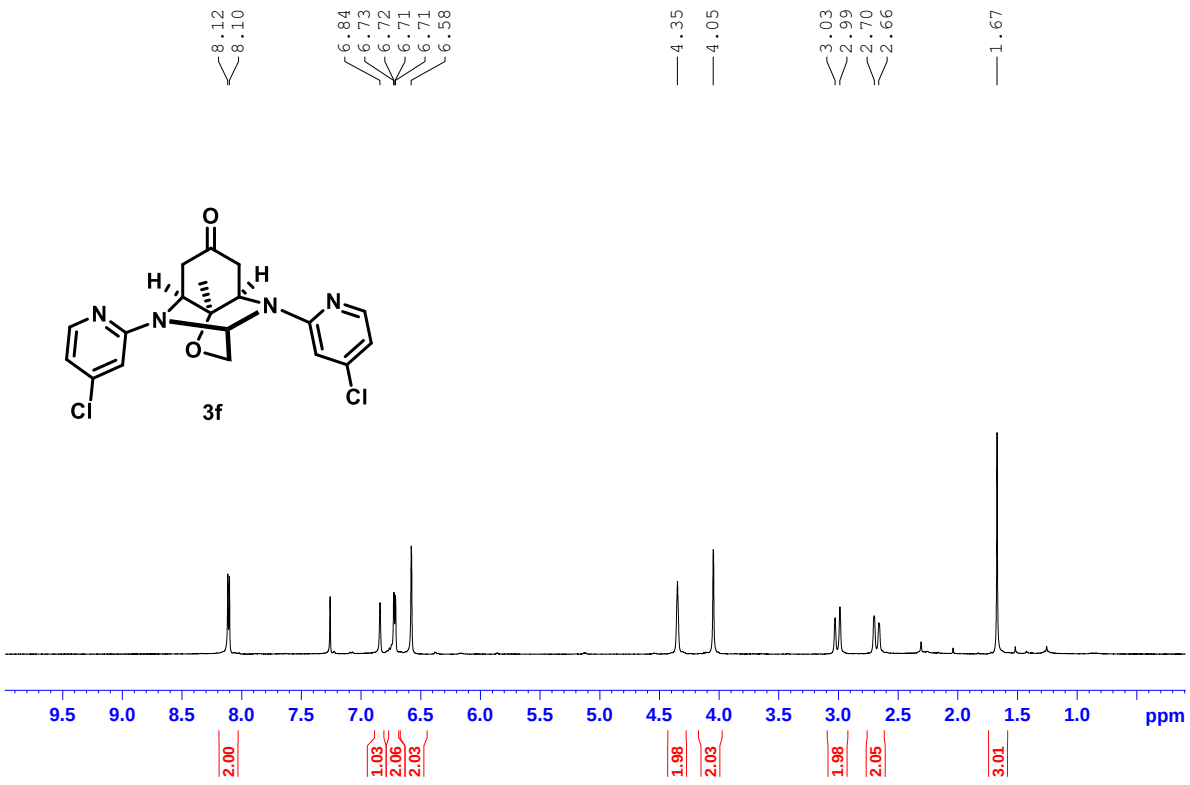

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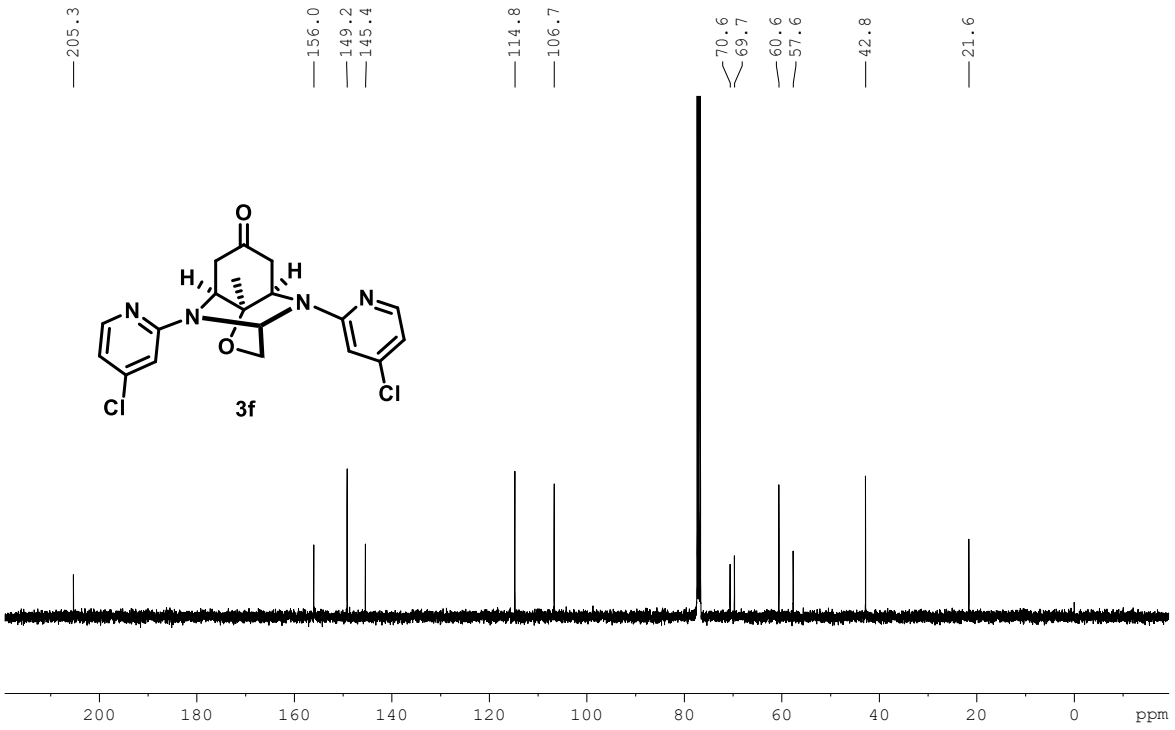

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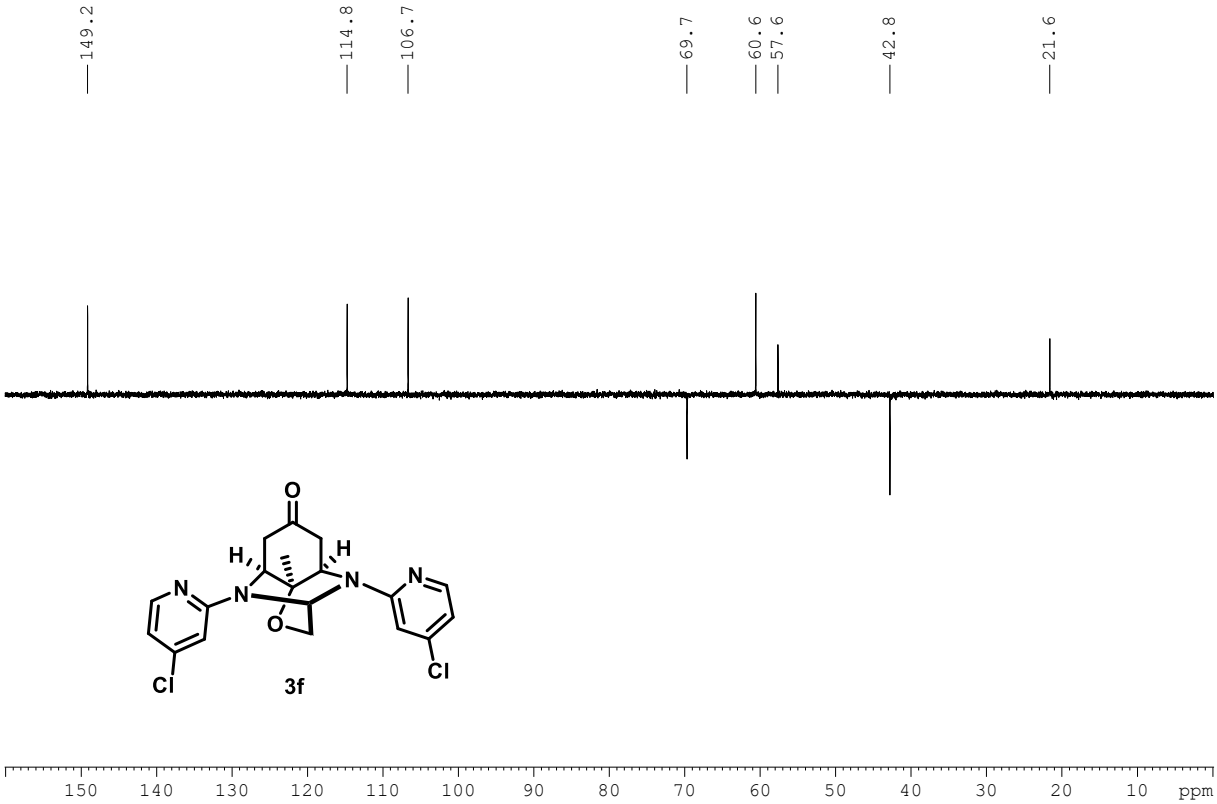

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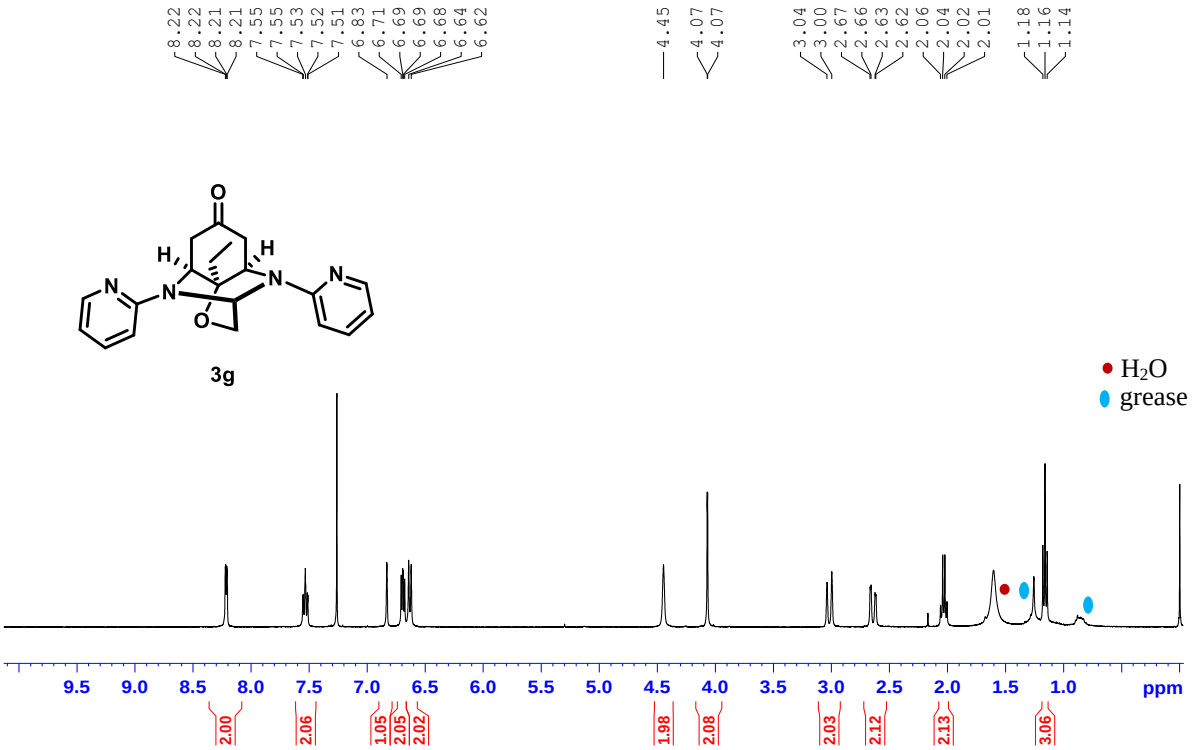

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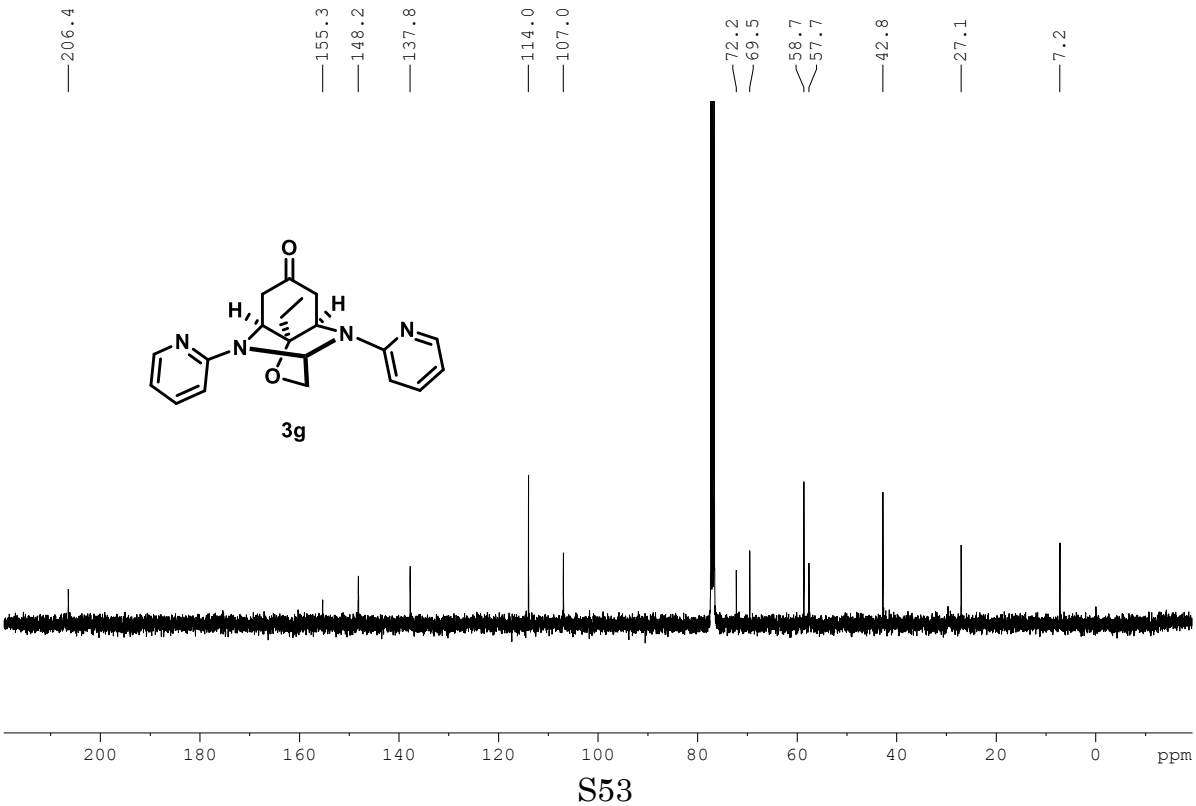
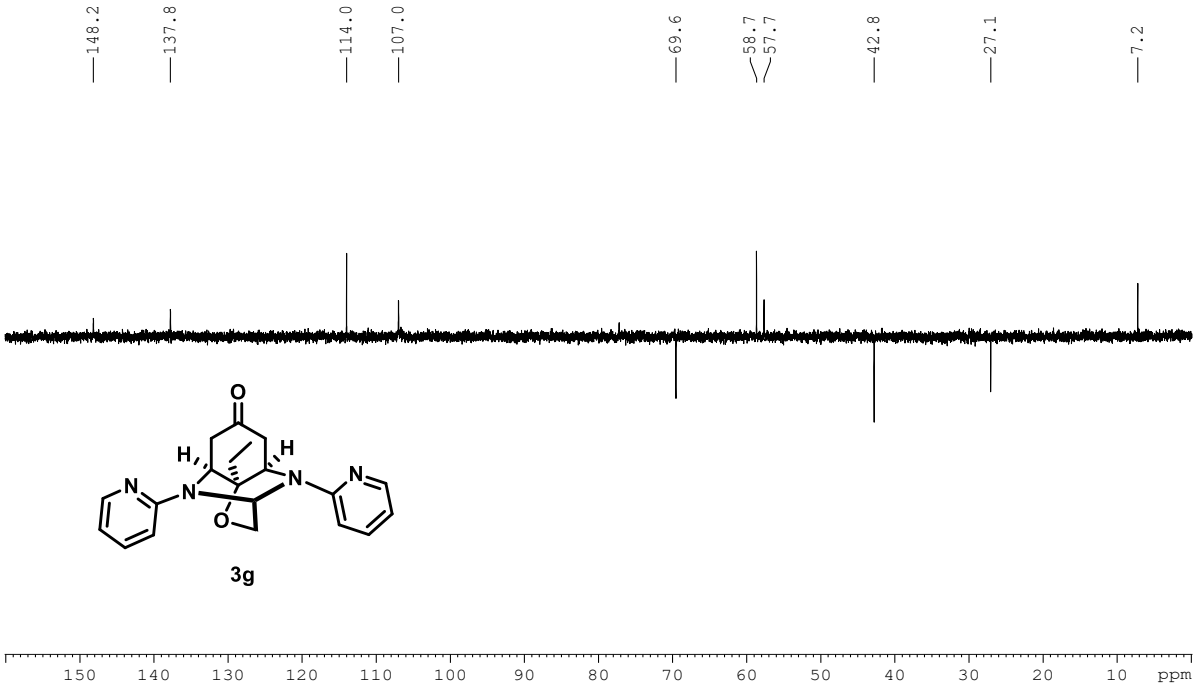
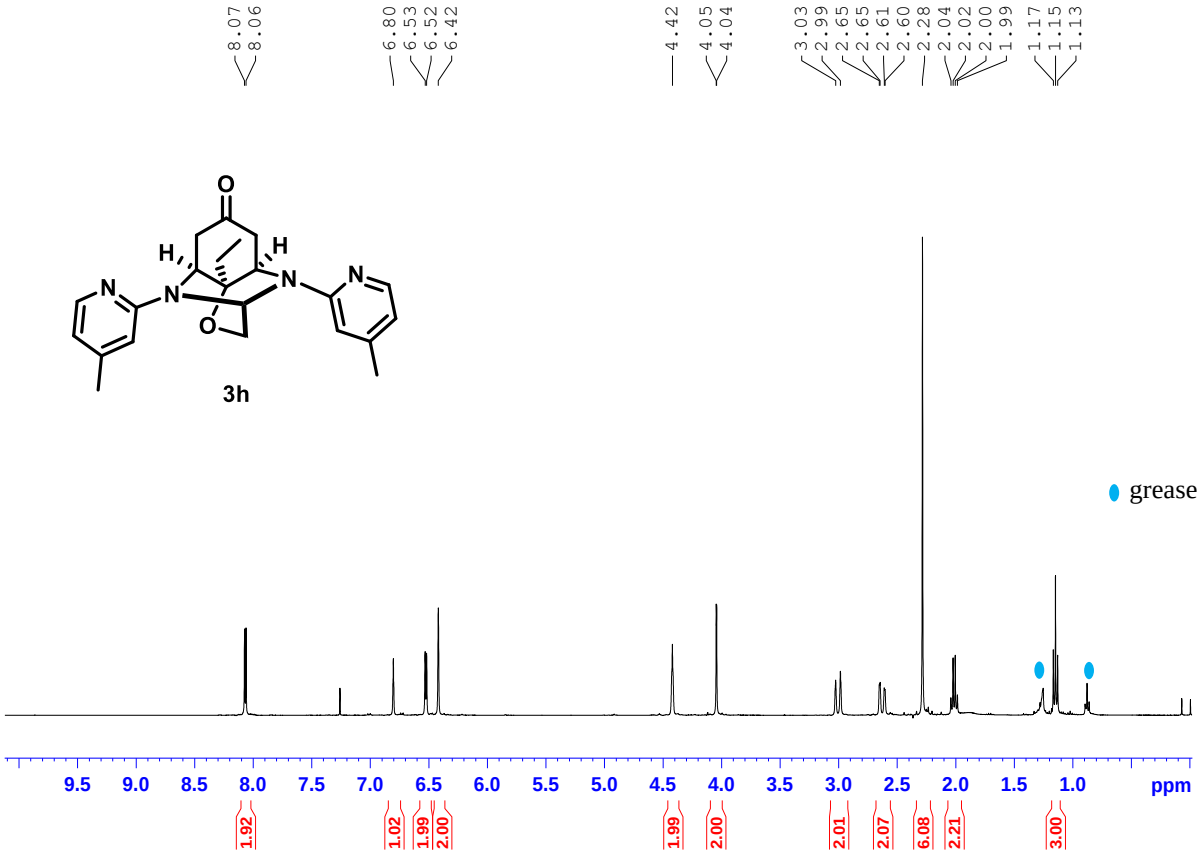


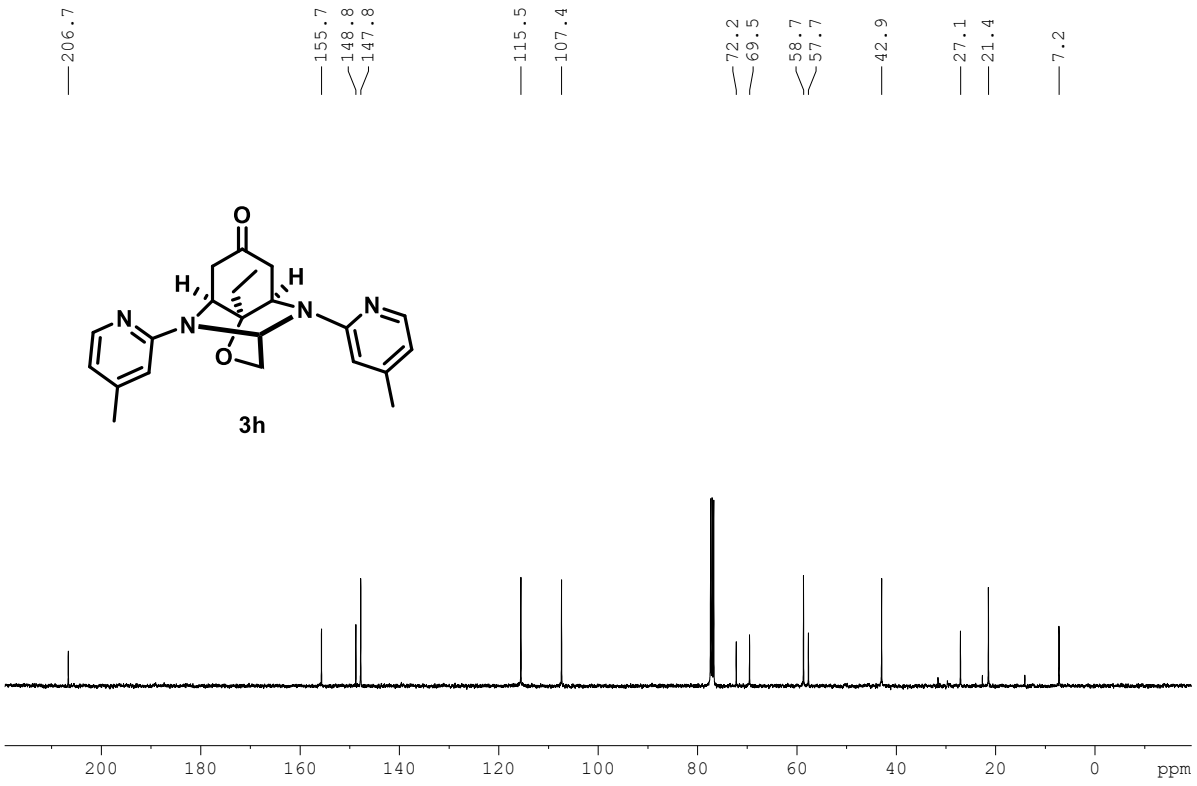
DEPT (100 MHz, $CDCl_3$) for 3g



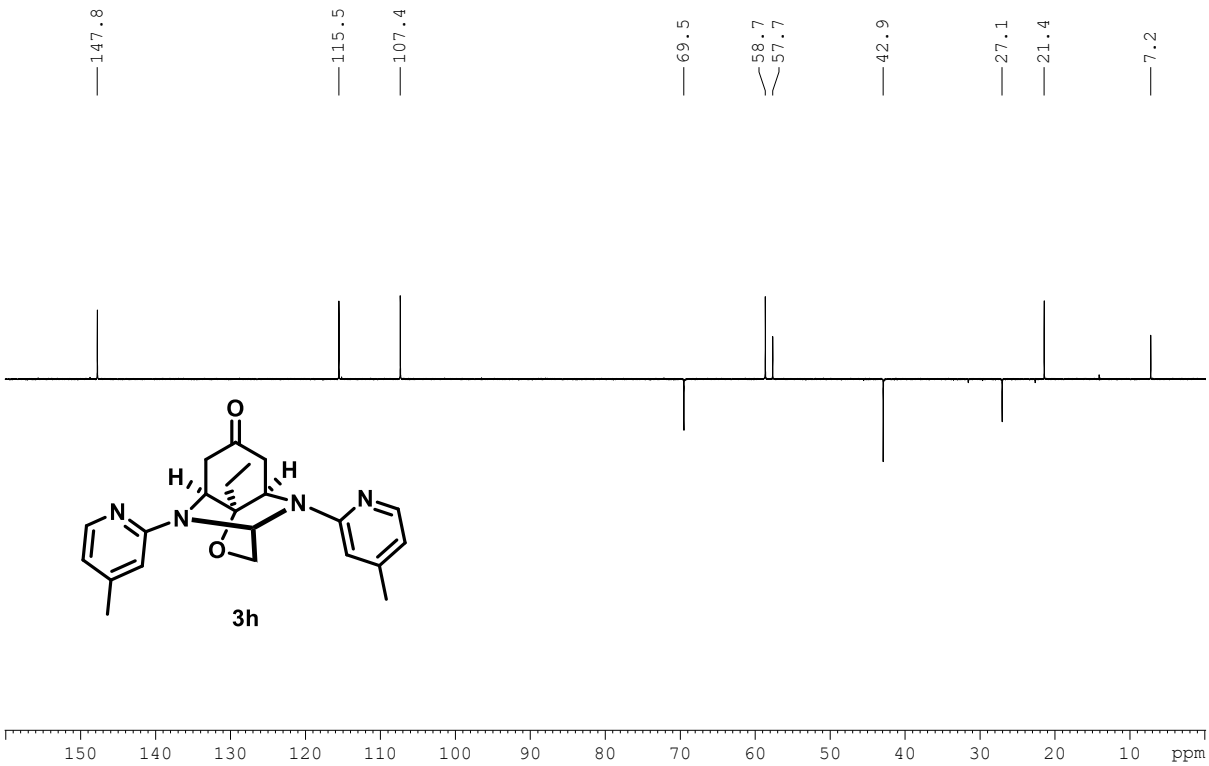
^{1}H NMR (400 MHz, $CDCl_3$) for 3h



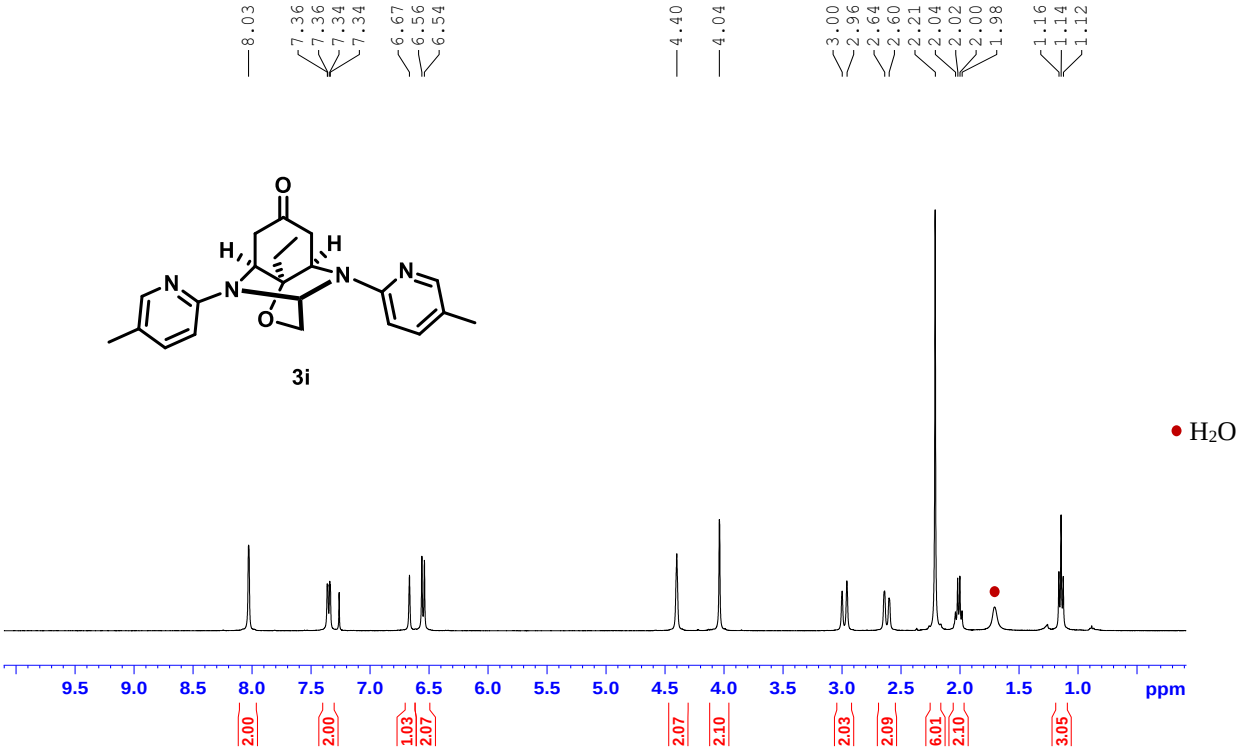
^{13}C NMR (100 MHz, $CDCl_3$) for 3h



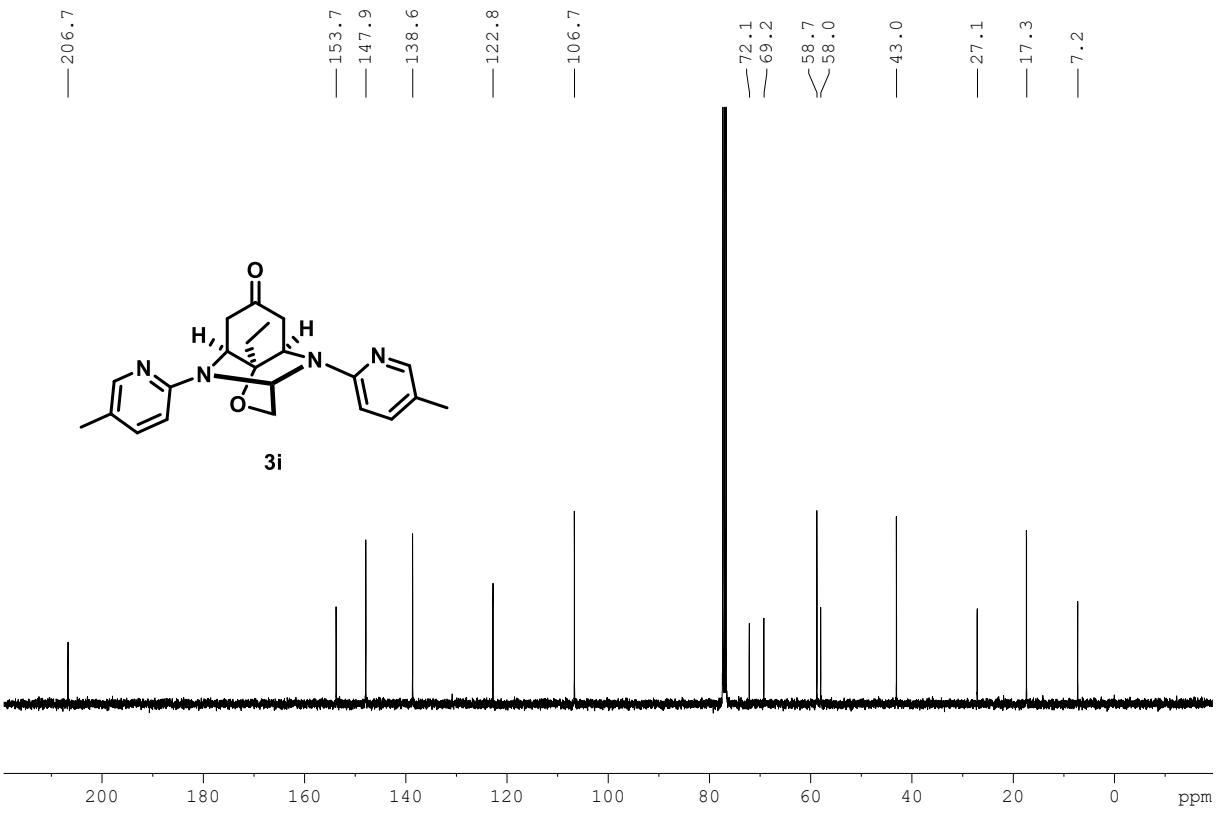
DEPT (100 MHz, $CDCl_3$) for 3h



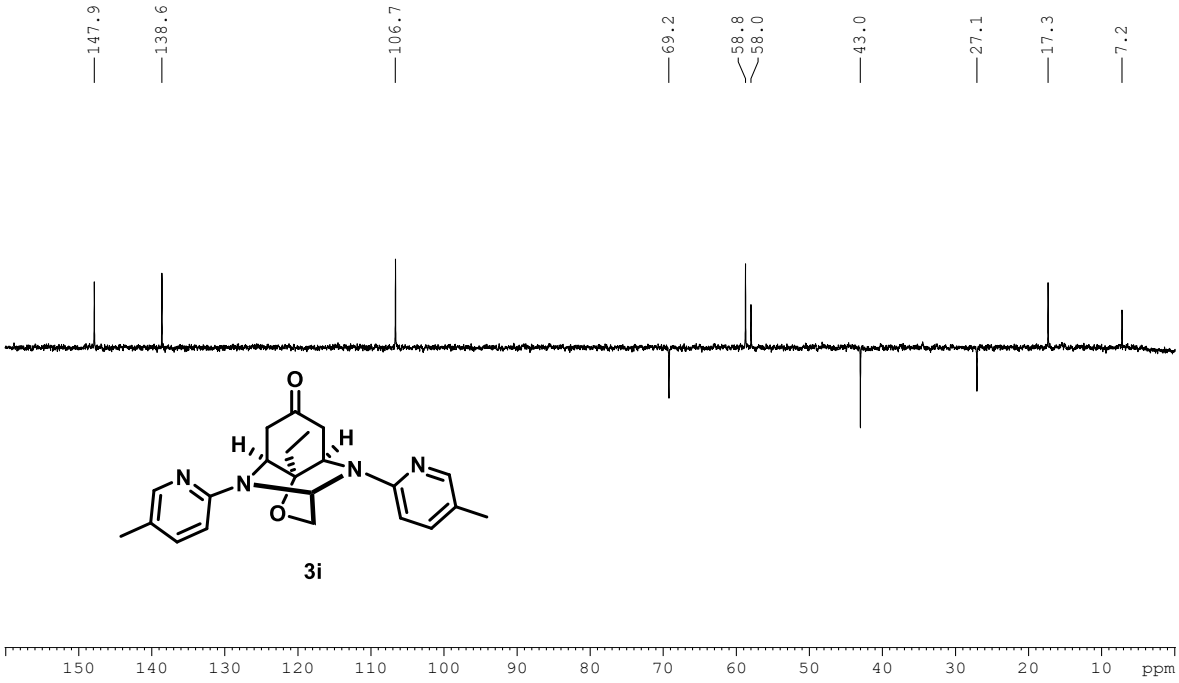
^{1}H NMR (400 MHz, $CDCl_3$) for 3i



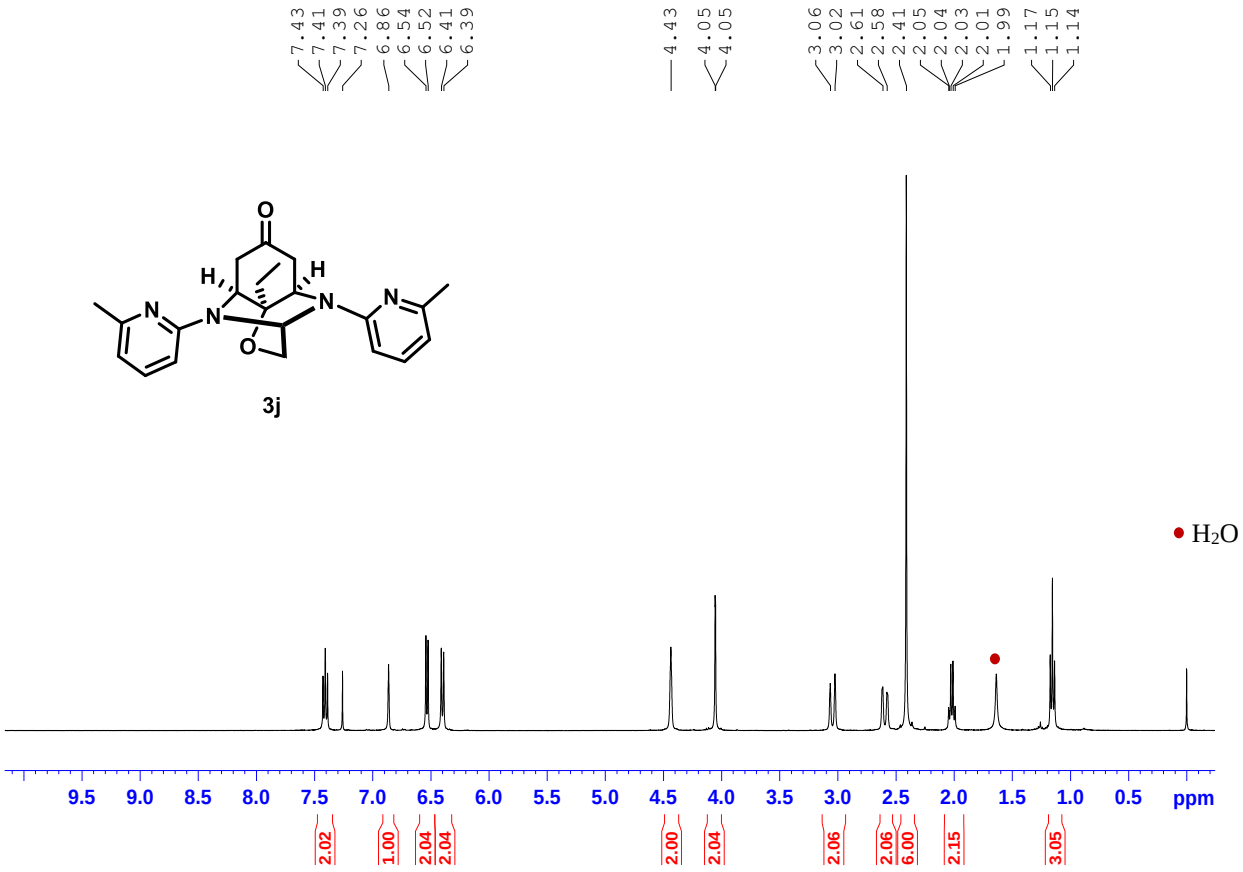
^{13}C NMR (100 MHz, $CDCl_3$) for 3i



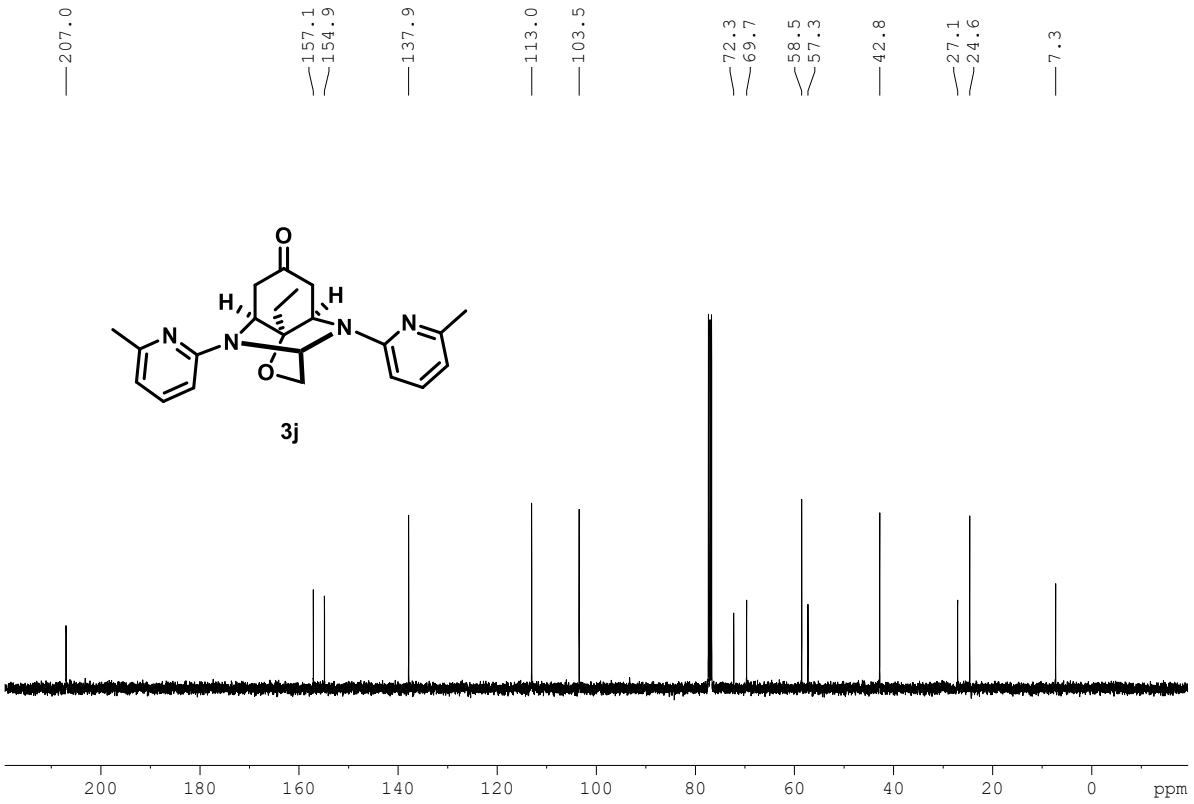
DEPT (100 MHz, $CDCl_3$) for 3i



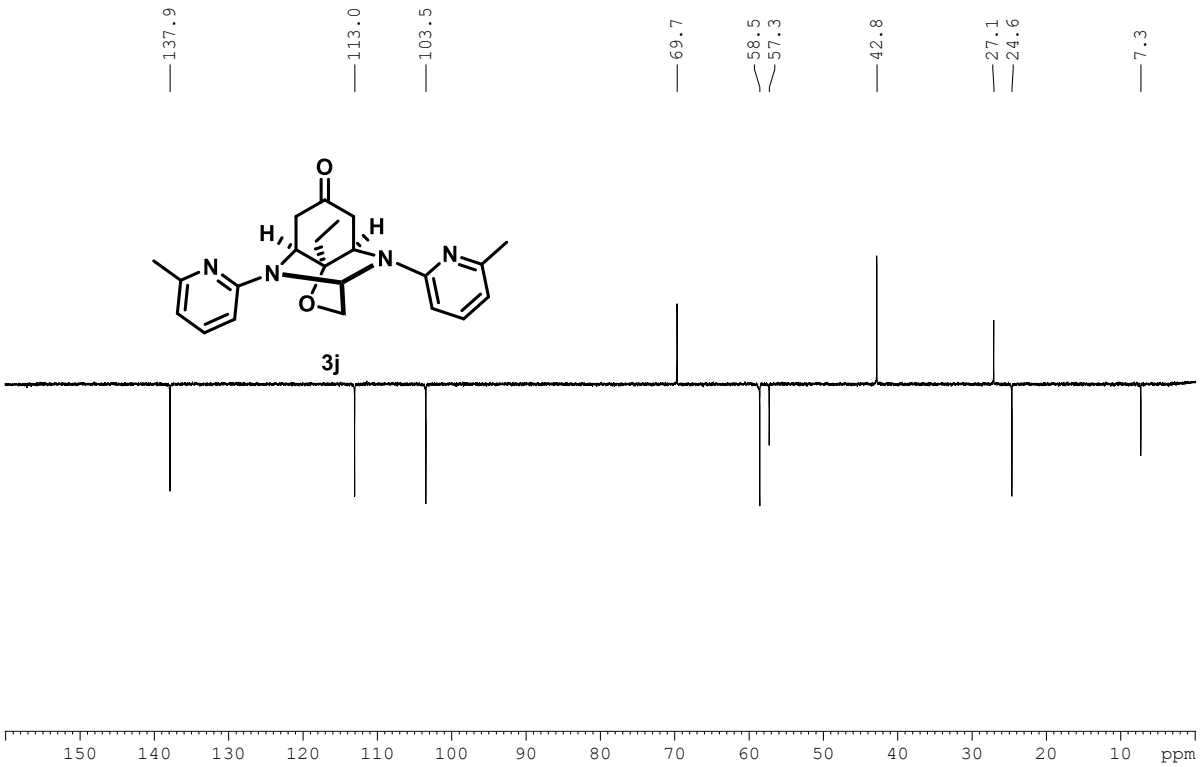
^{1}H NMR (400 MHz, $CDCl_3$) for 3j



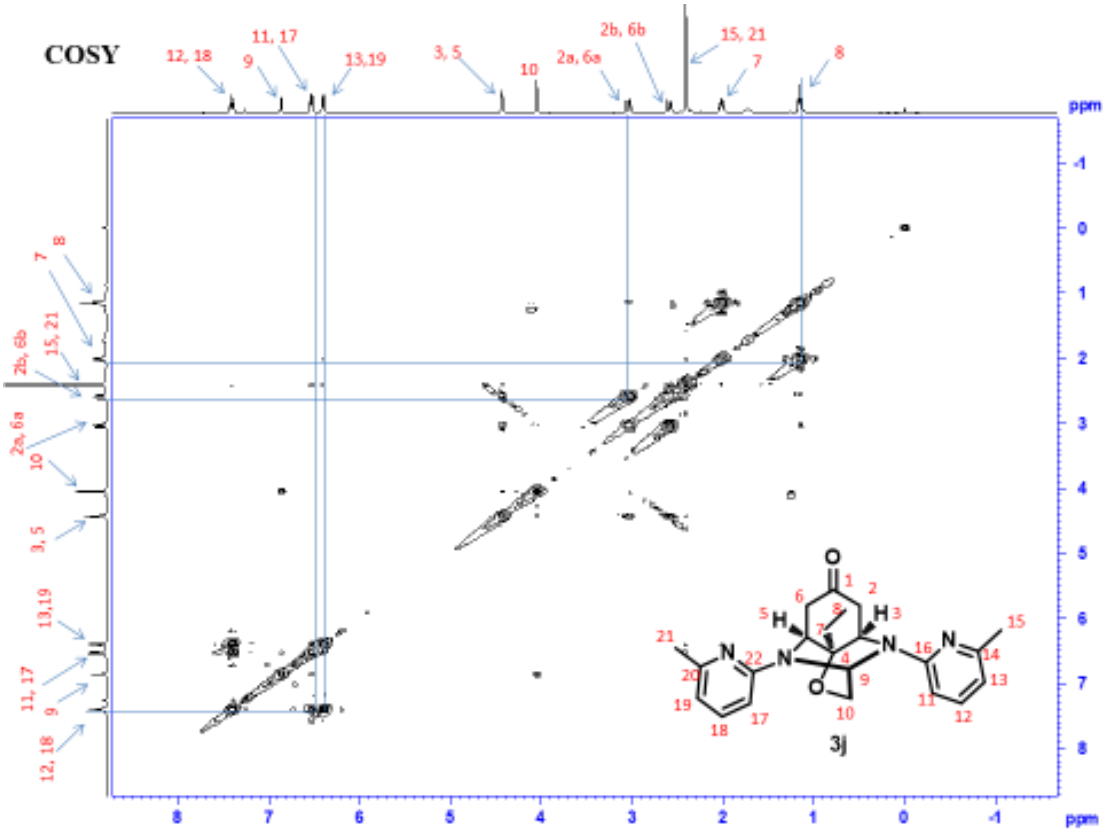
^{13}C NMR (100 MHz, $CDCl_3$) for 3j



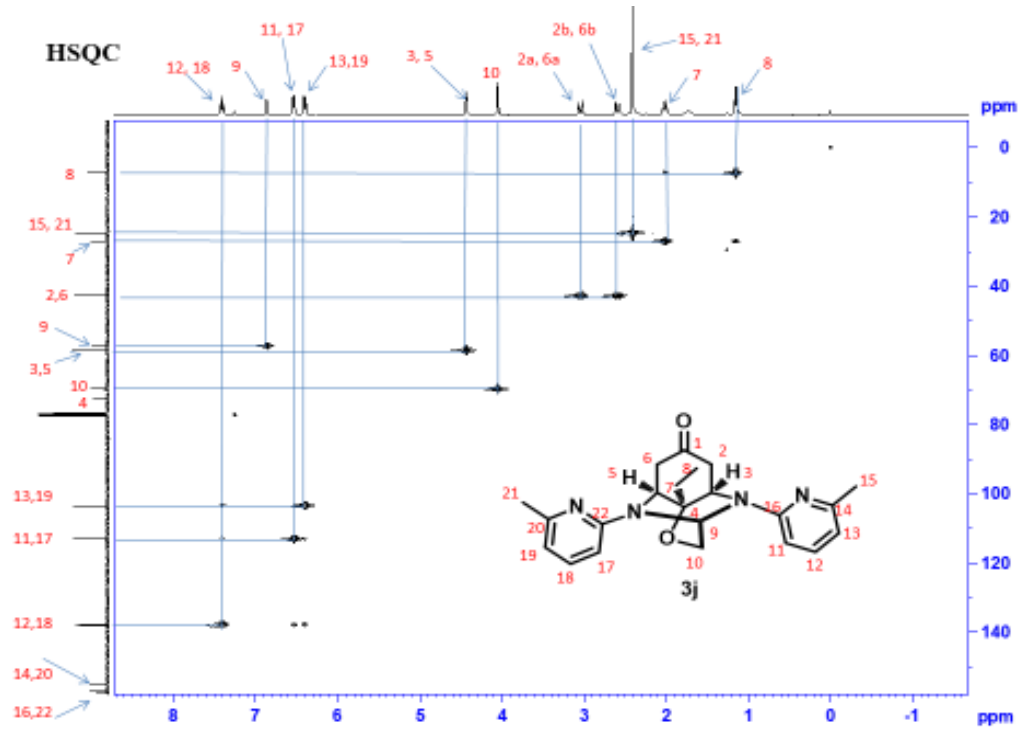
DEPT (100 MHz, $CDCl_3$) for 3j



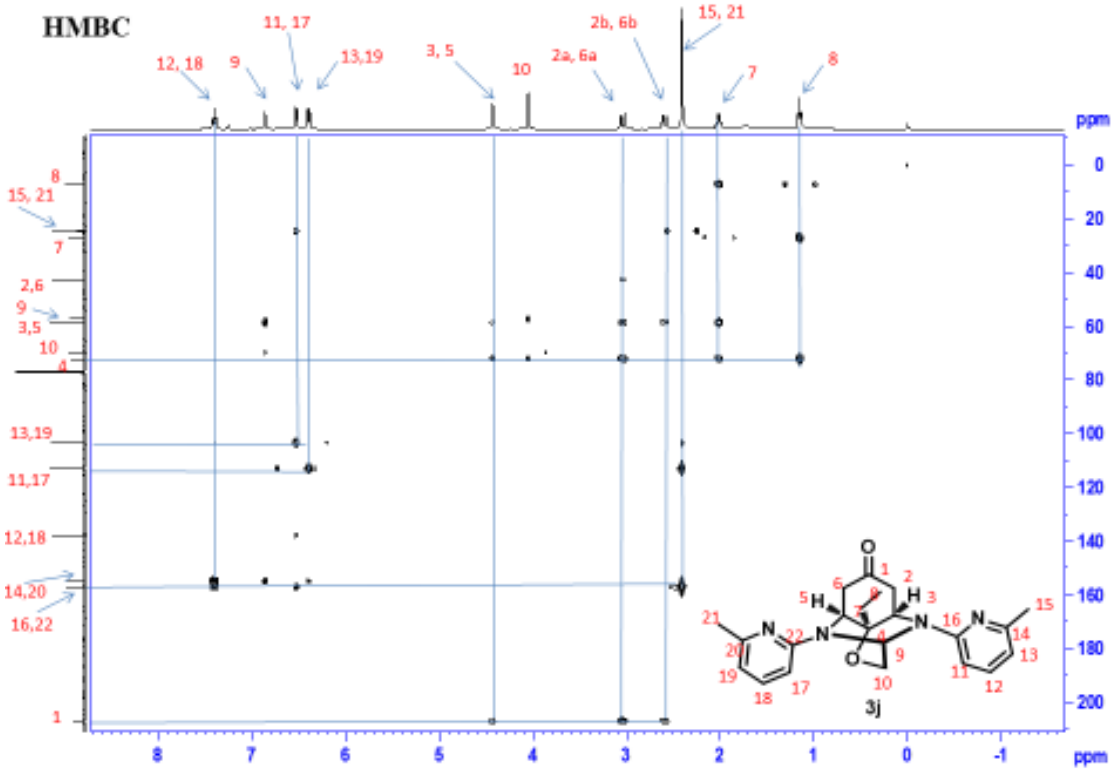
COSY (400 MHz, $CDCl_3$) for 3j



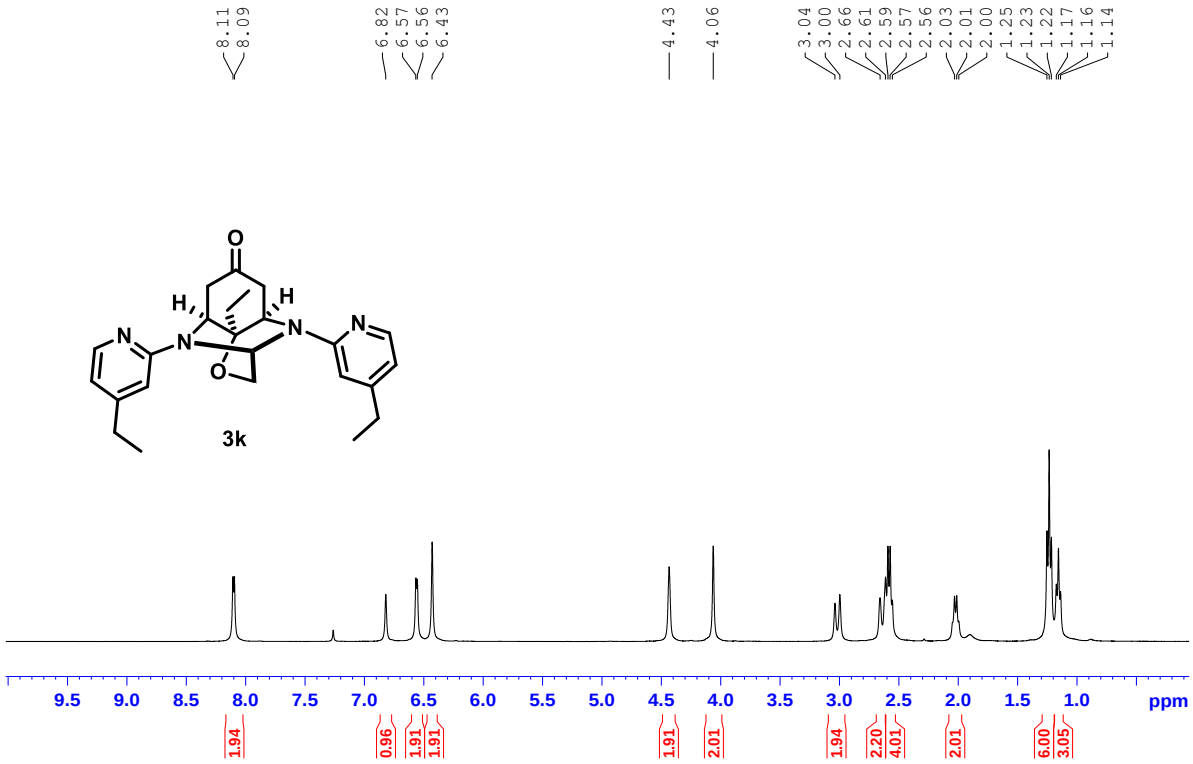
HSQC (400 MHz, $CDCl_3$) for 3j



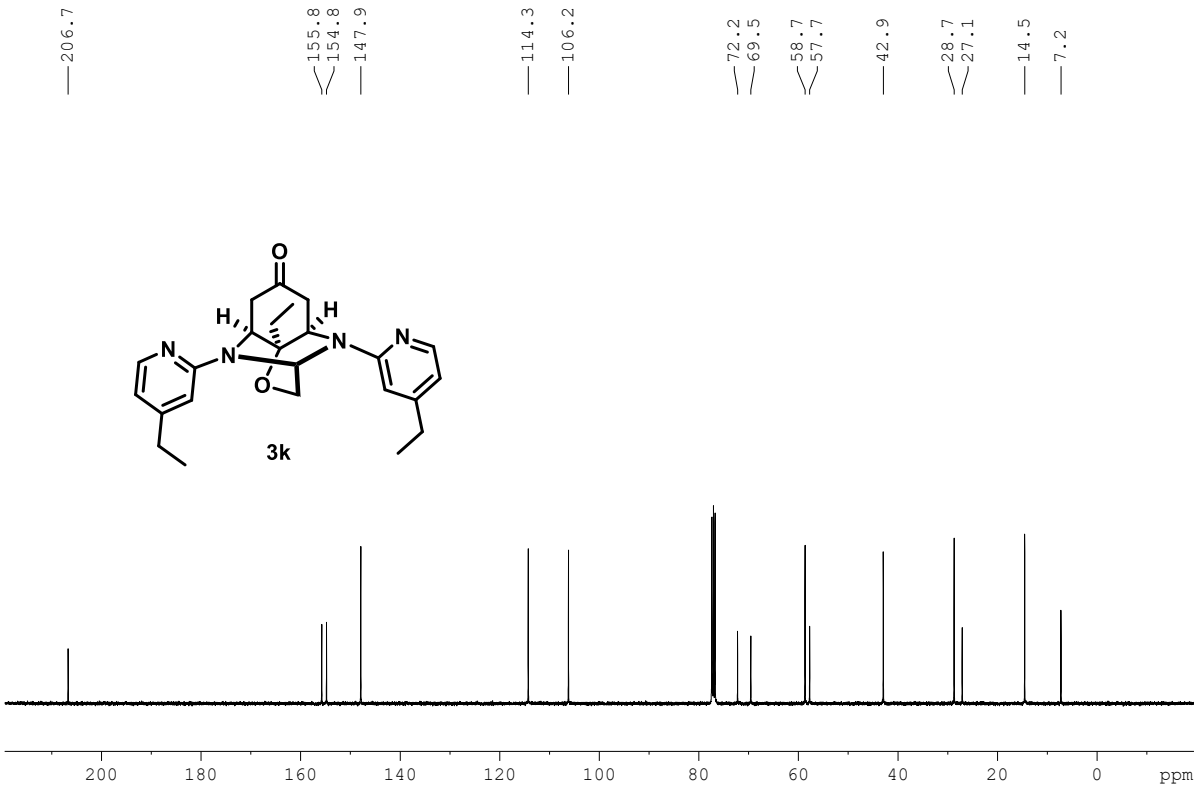
HMBC (400 MHz, $CDCl_3$) for 3j



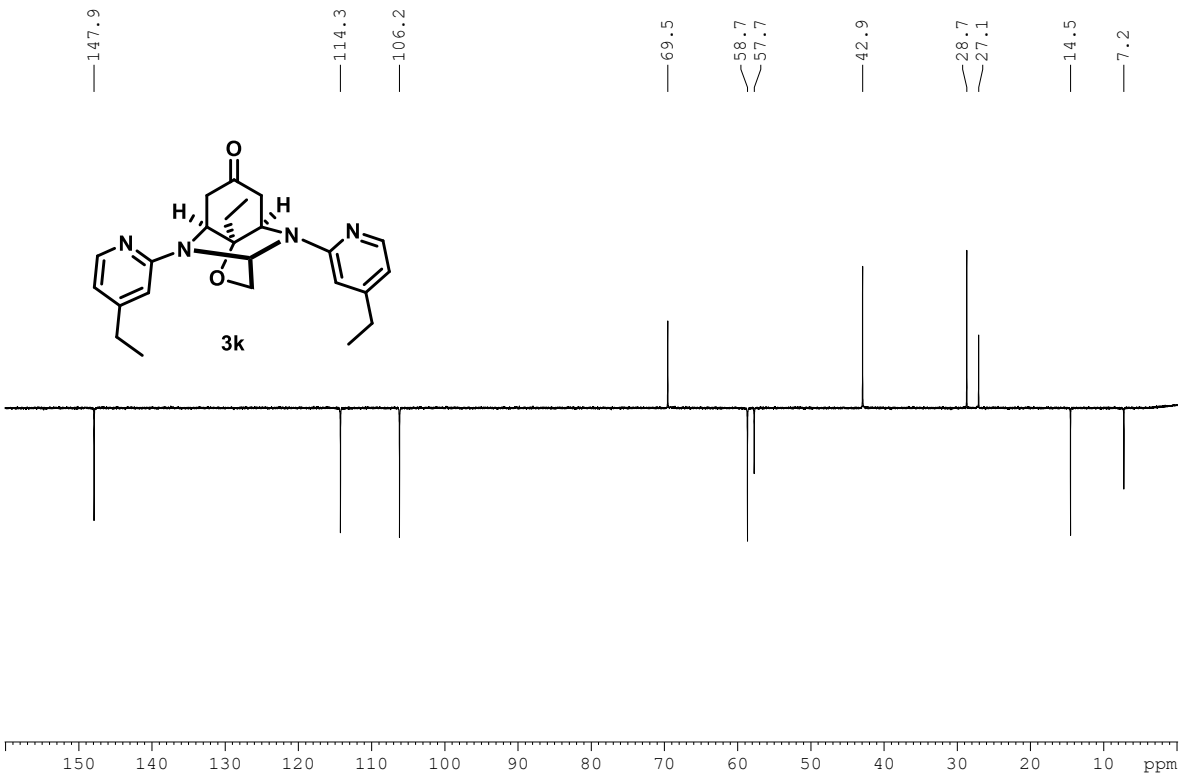
^{1}H NMR (400 MHz, $CDCl_3$) for 3k



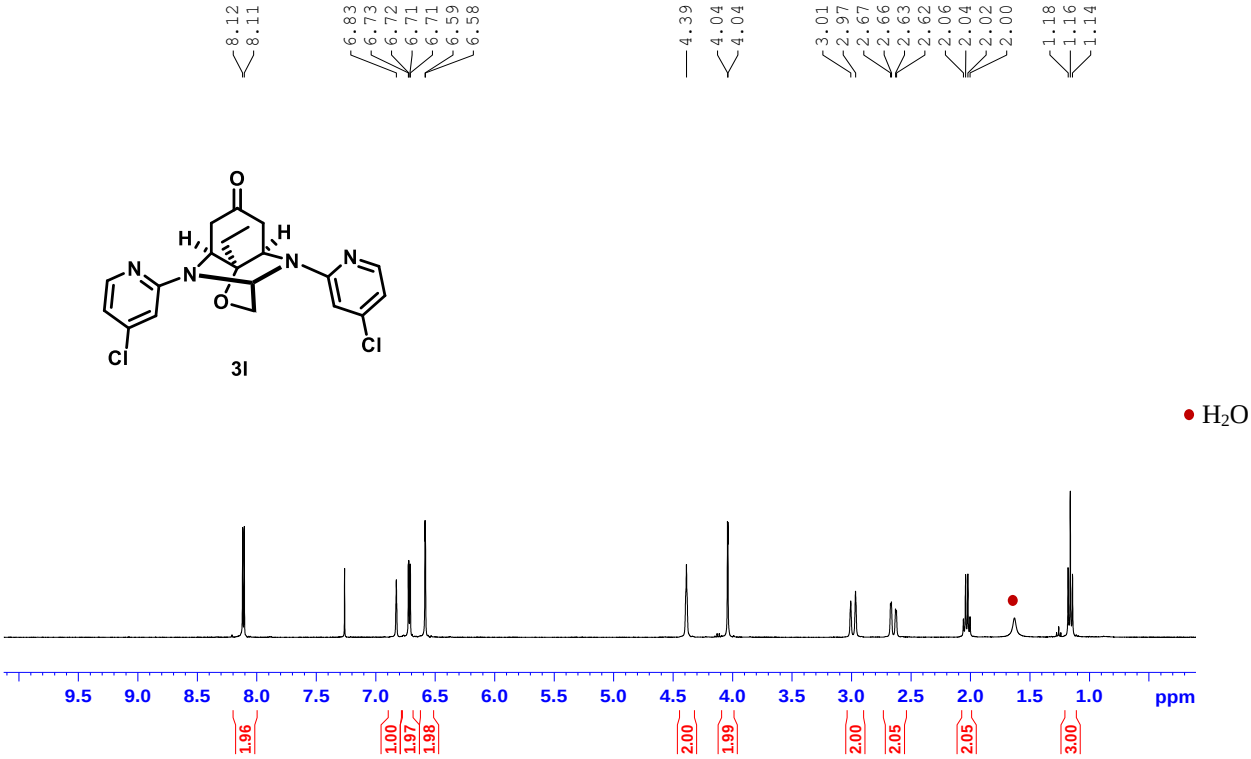
^{13}C NMR (100 MHz, $CDCl_3$) for 3k



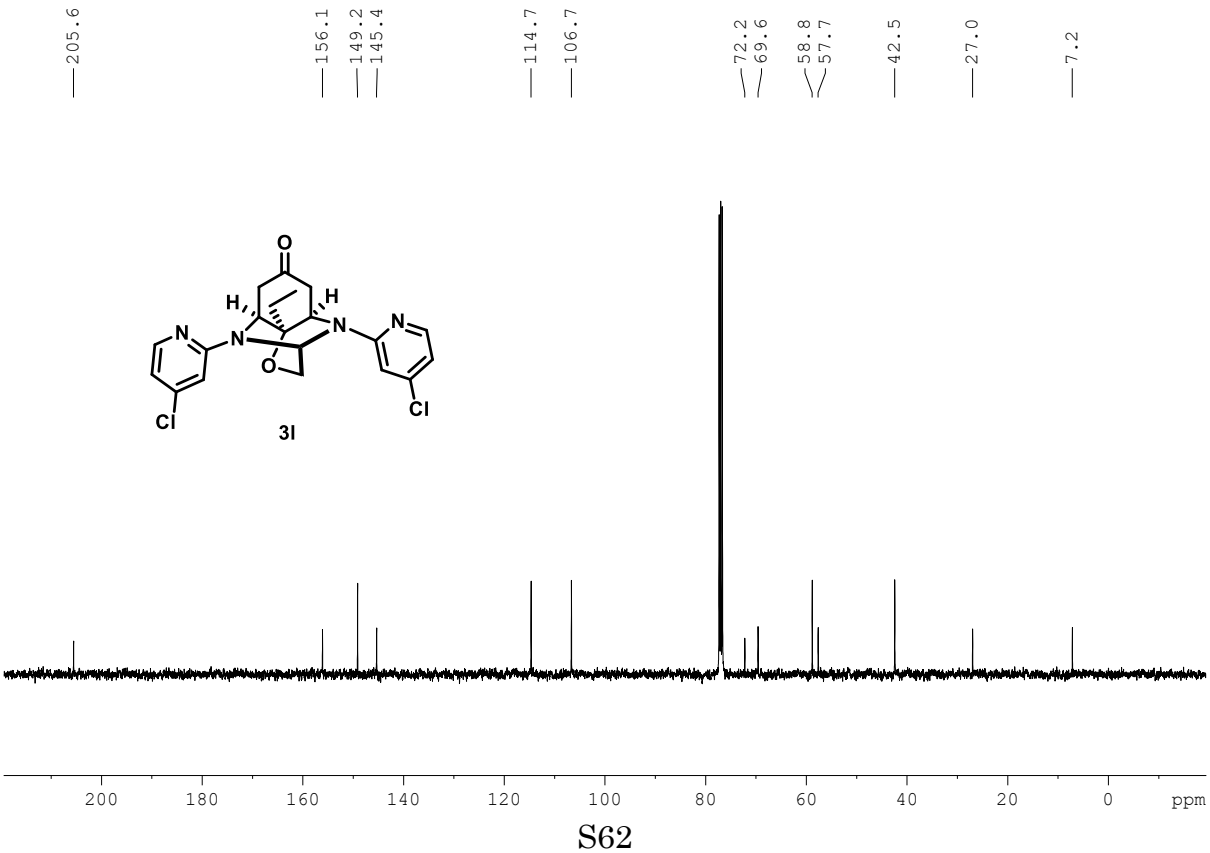
DEPT (100 MHz, $CDCl_3$) for 3k



^{1}H NMR (400 MHz, $CDCl_3$) for 3l

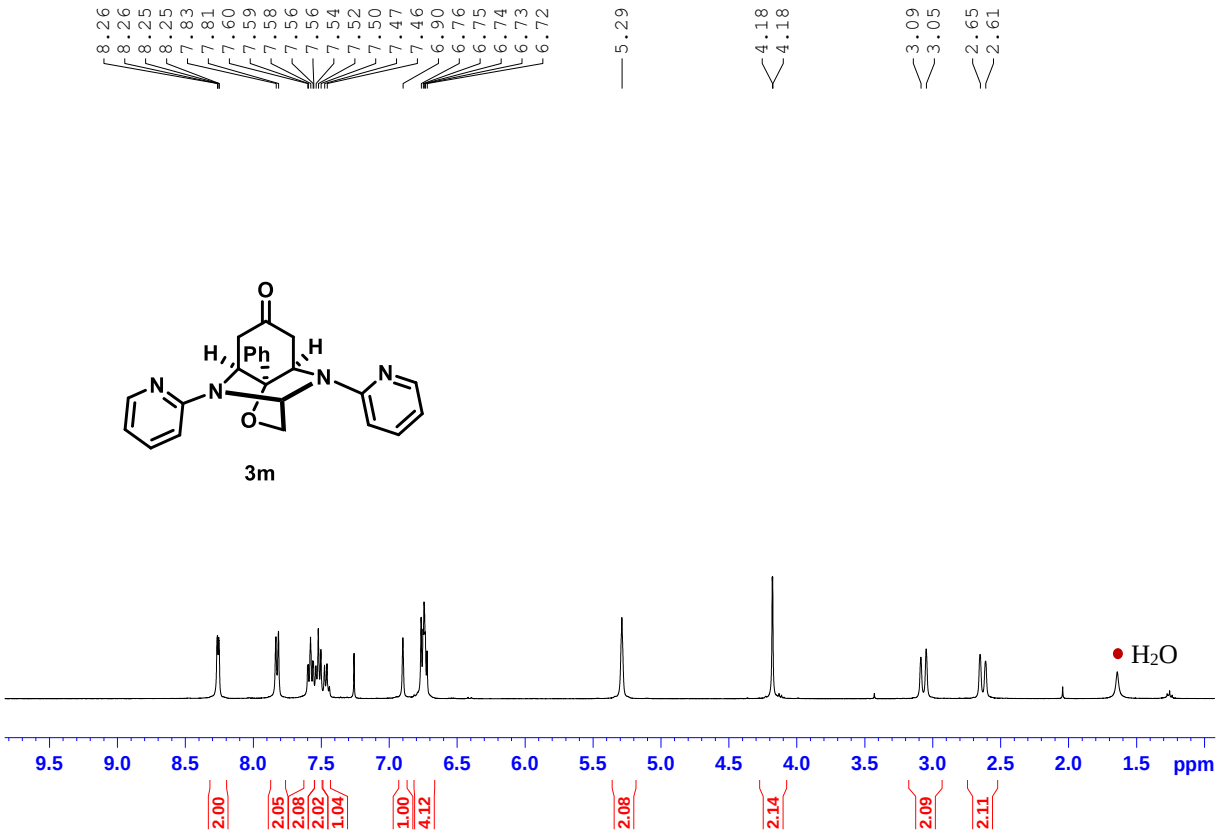


^{13}C NMR (100 MHz, $CDCl_3$) for 3l

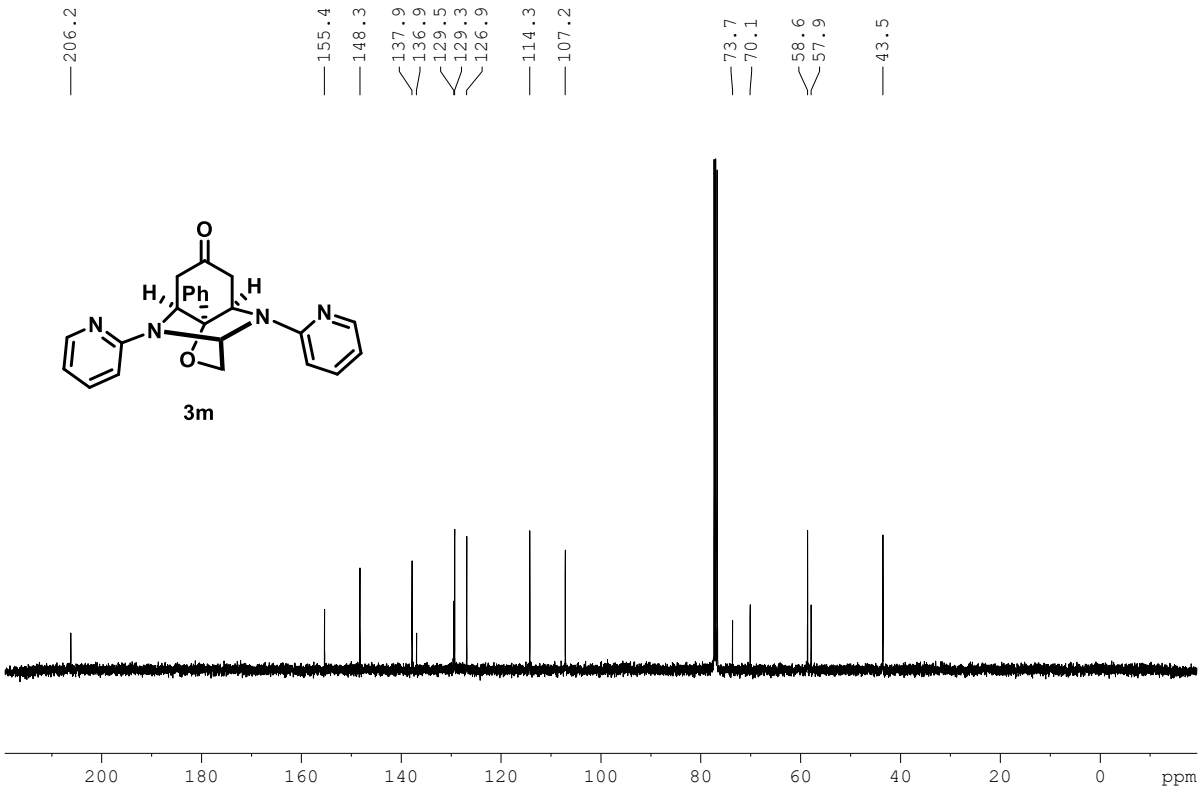


DEPT (100 MHz, $CDCl_3$) for 3l

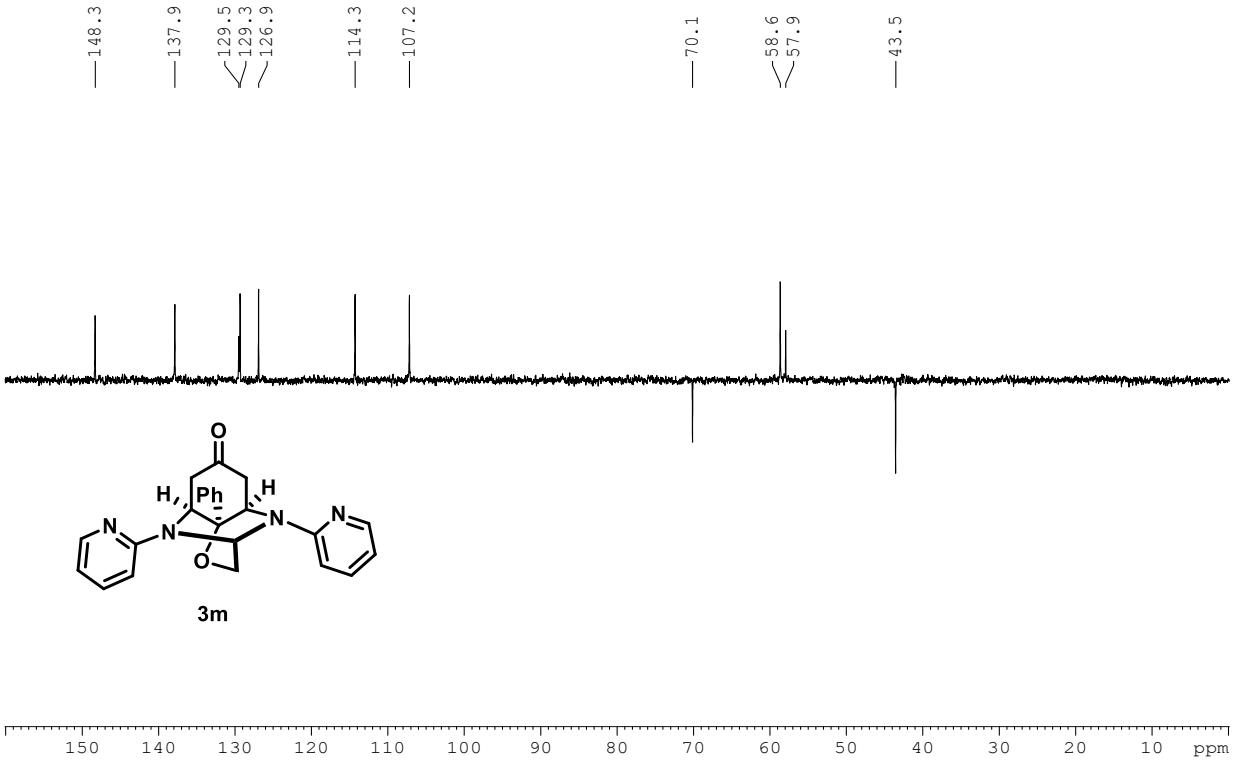
^{1}H NMR (400 MHz, $CDCl_3$) for 3m



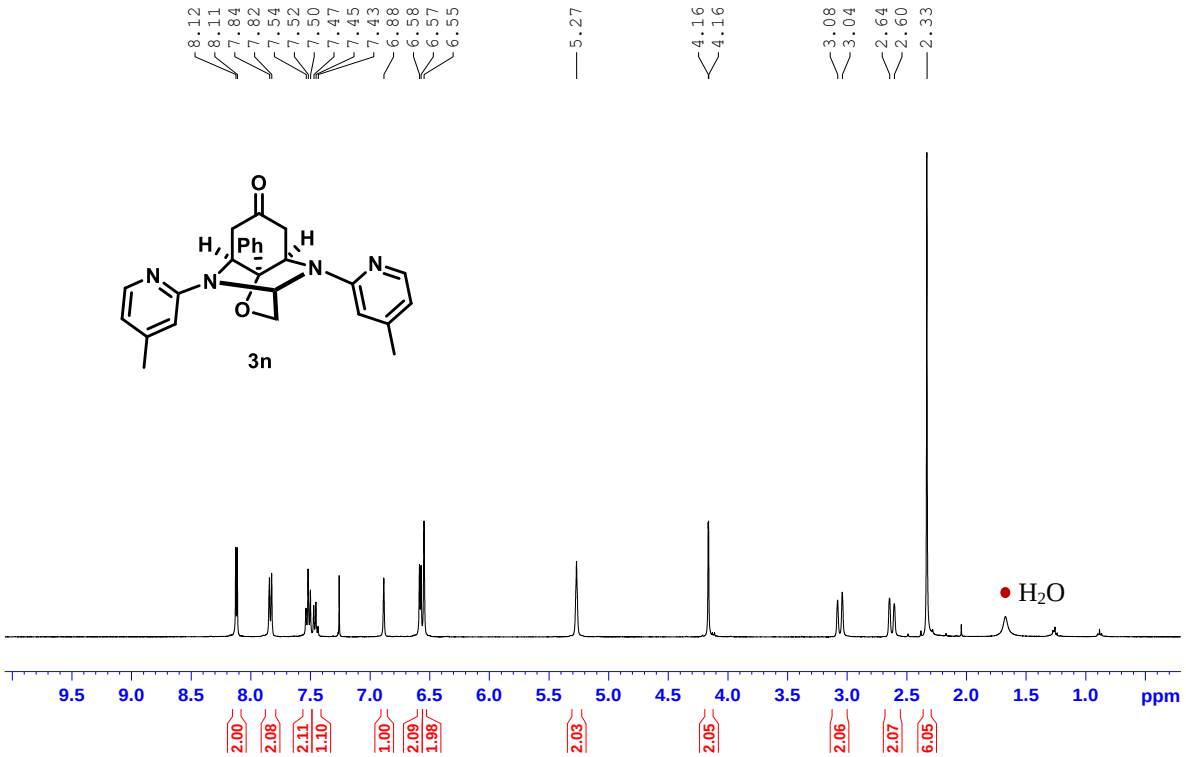
^{13}C NMR (100 MHz, $CDCl_3$) for 3m



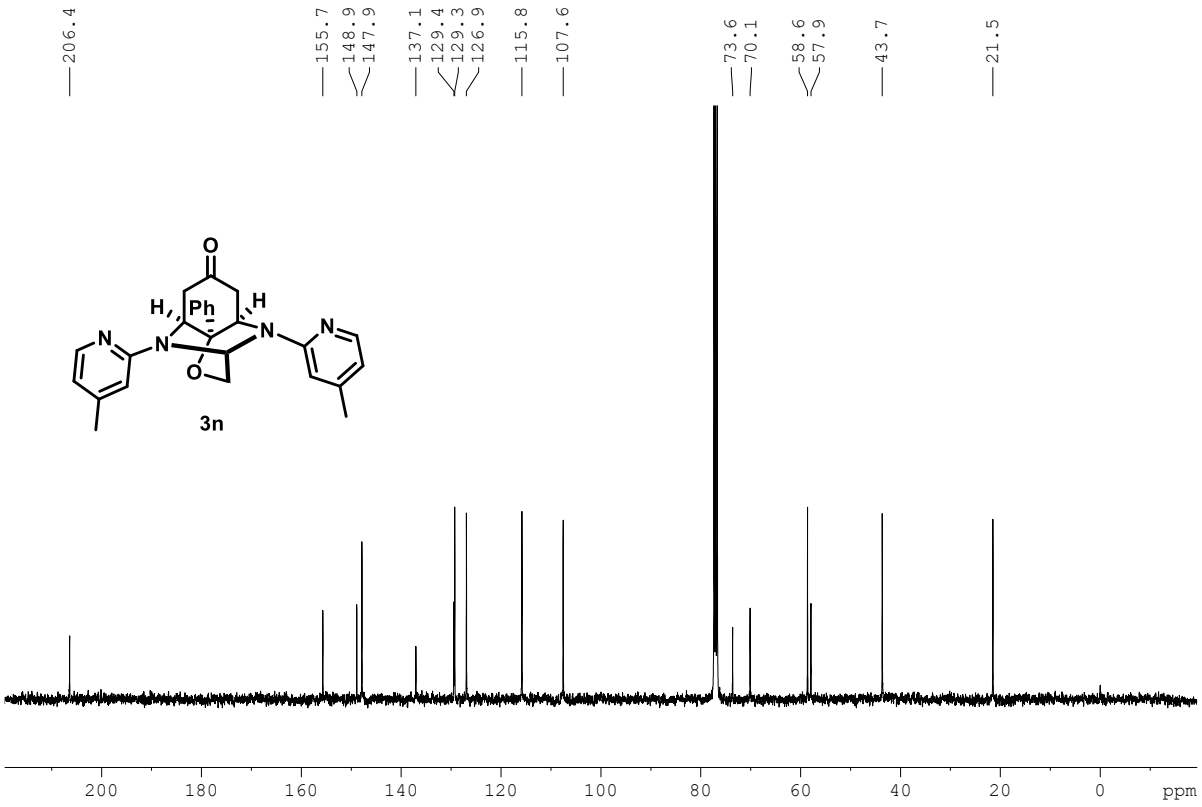
DEPT (100 MHz, $CDCl_3$) for 3m



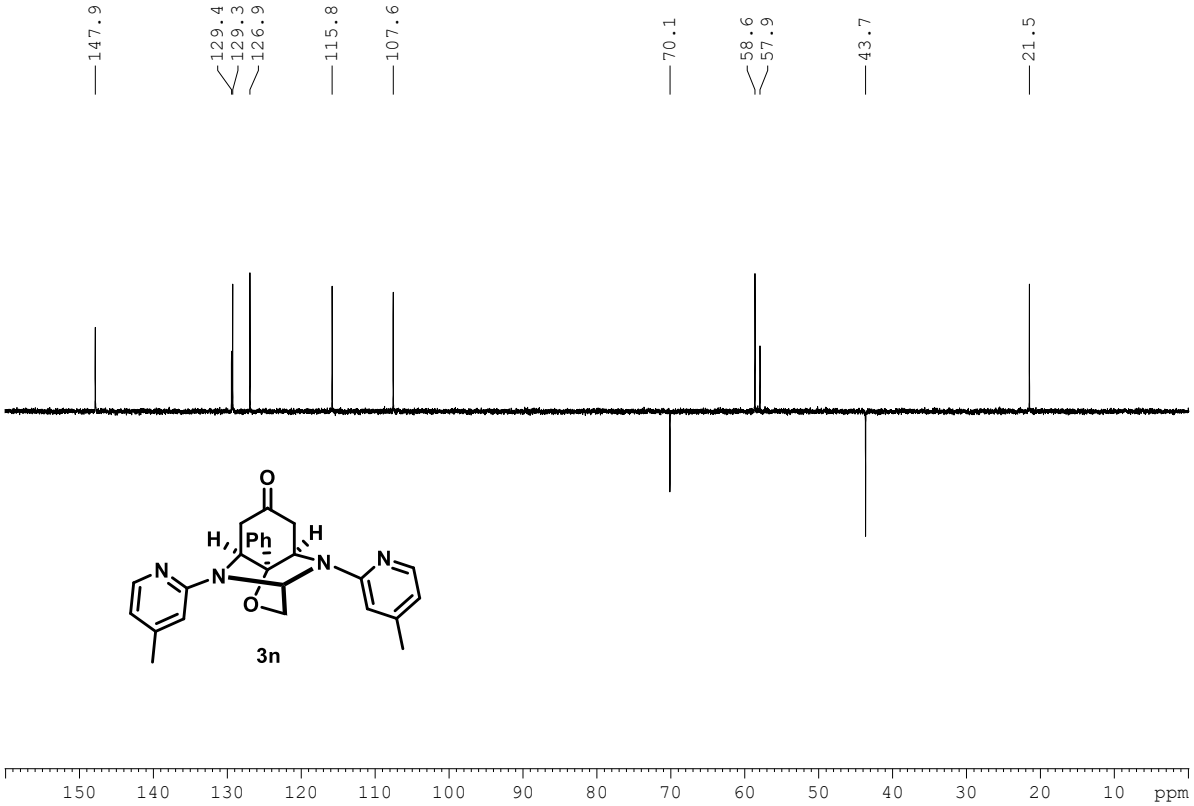
^{1}H NMR (400 MHz, $CDCl_3$) for 3n



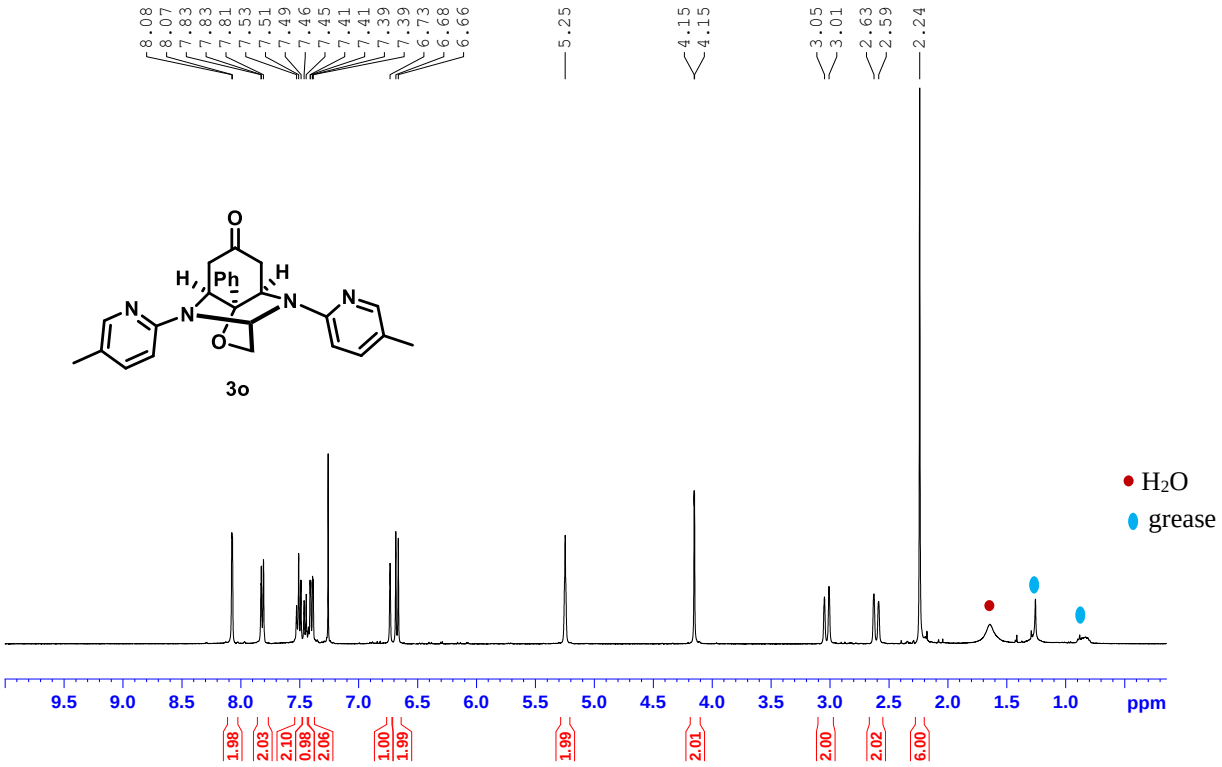
^{13}C NMR (100 MHz, $CDCl_3$) for 3n



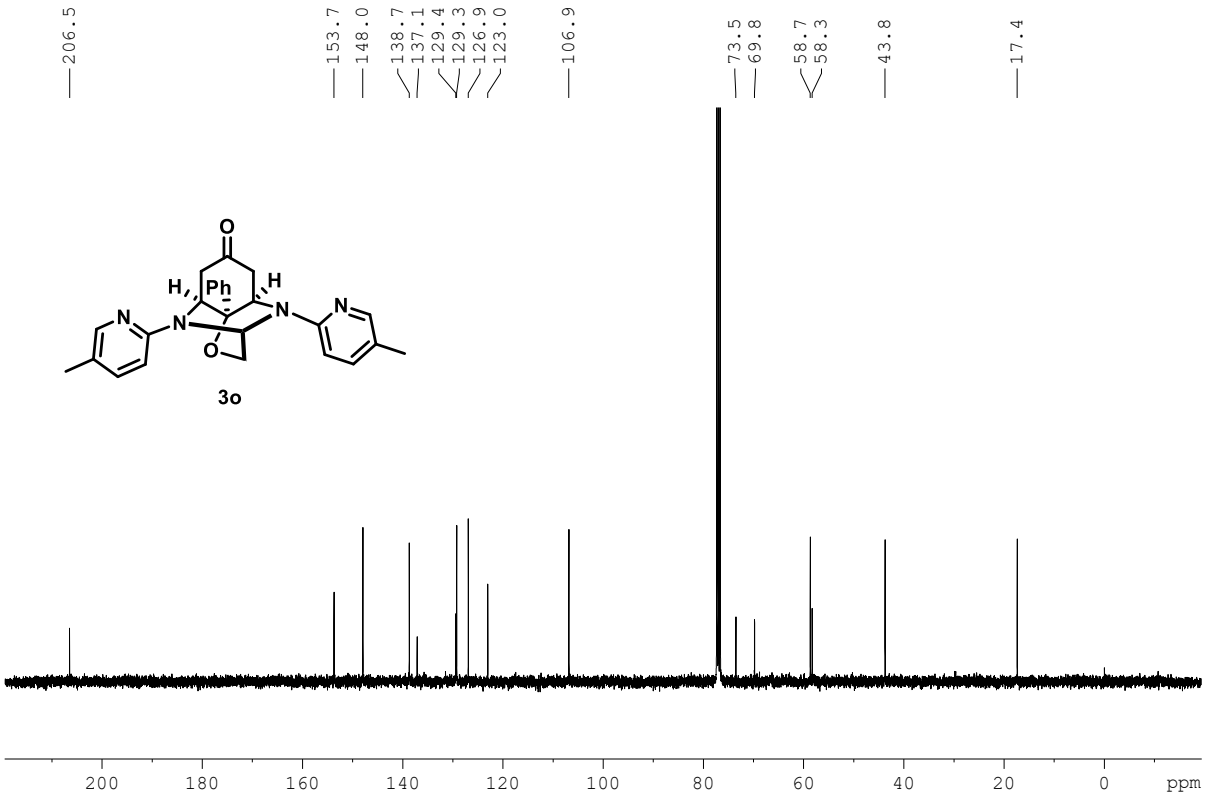
DEPT (100 MHz, $CDCl_3$) for 3n



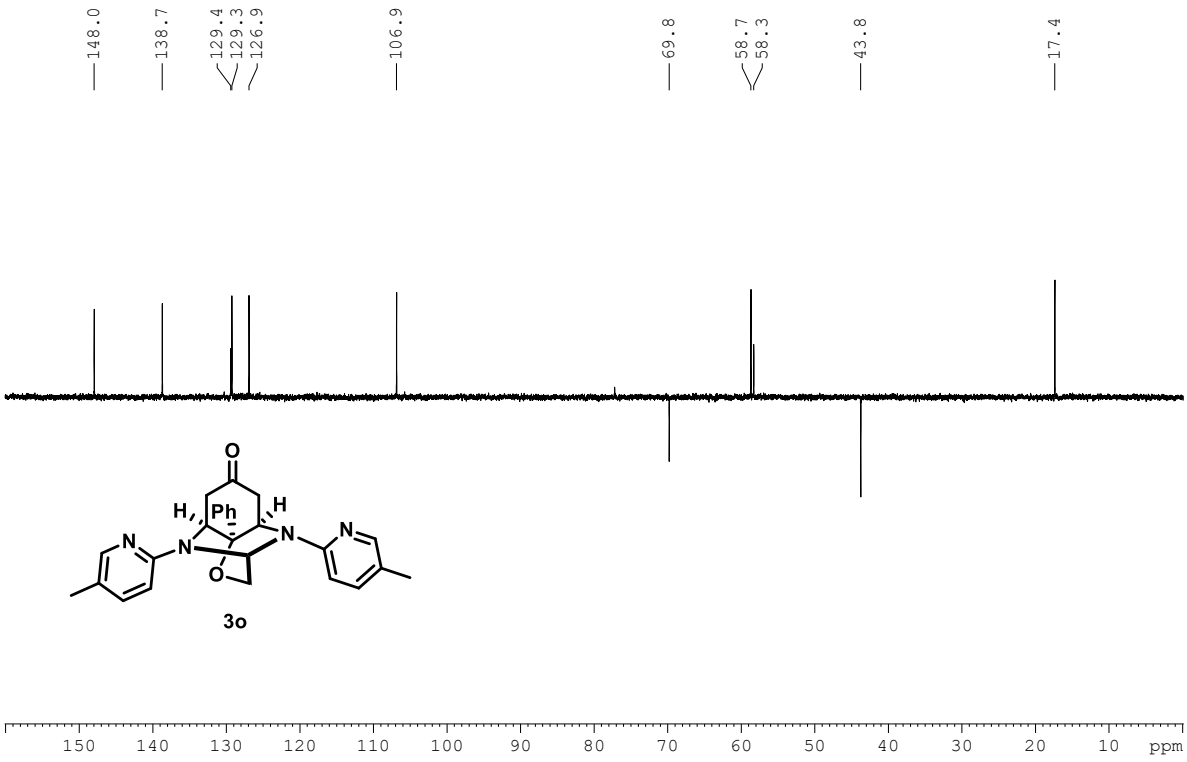
^{1}H NMR (400 MHz, $CDCl_3$) for 3o



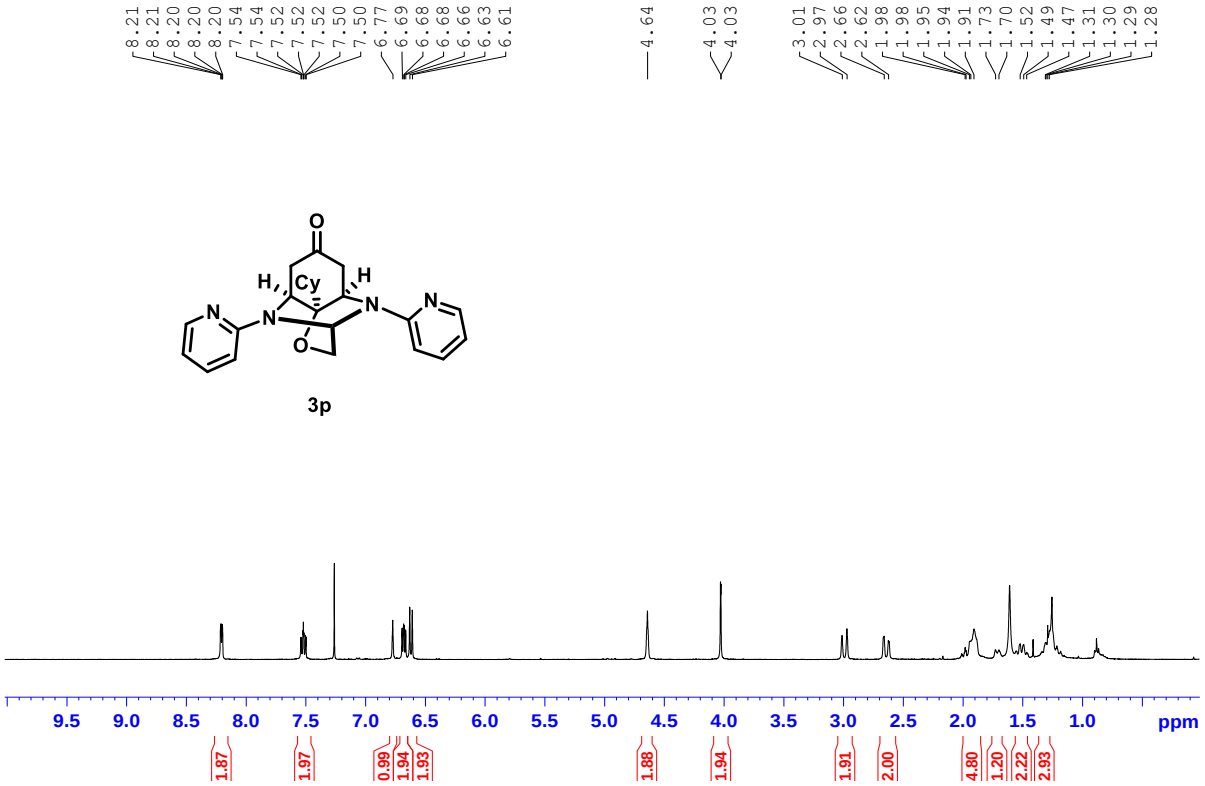
^{13}C NMR (100 MHz, $CDCl_3$) for 3o



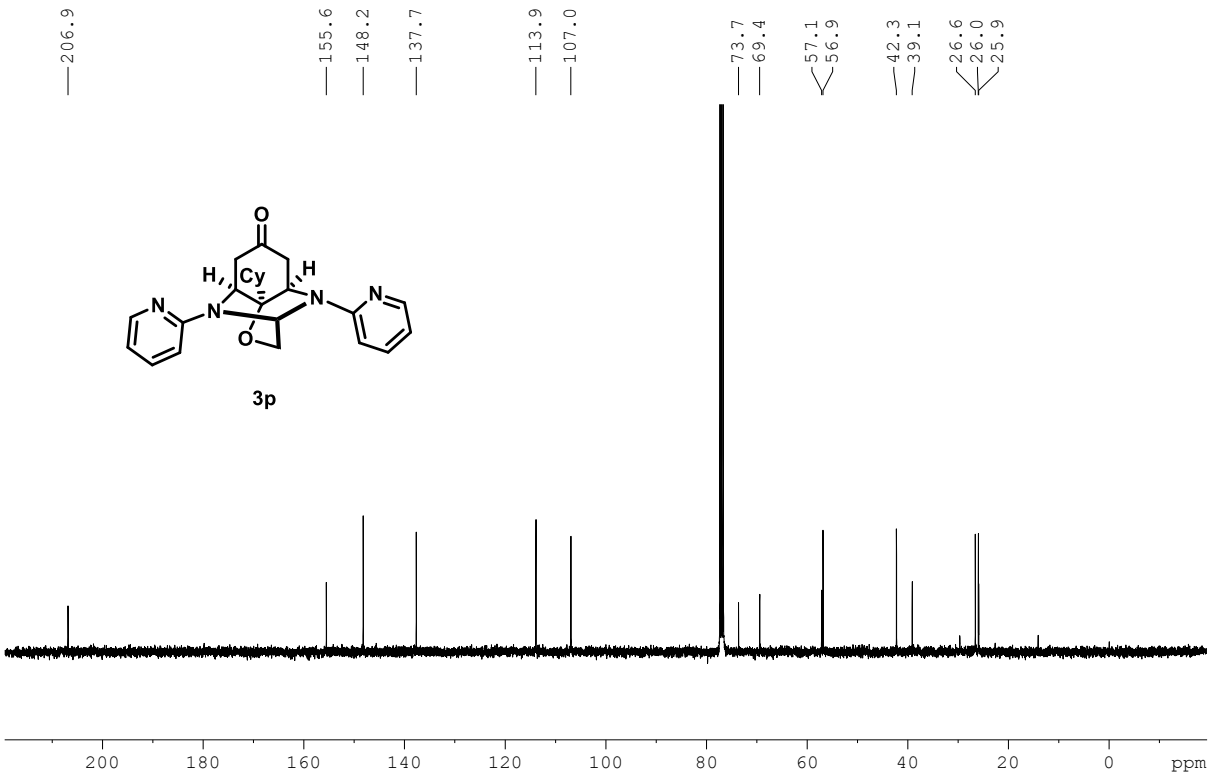
DEPT (100 MHz, $CDCl_3$) for 3o



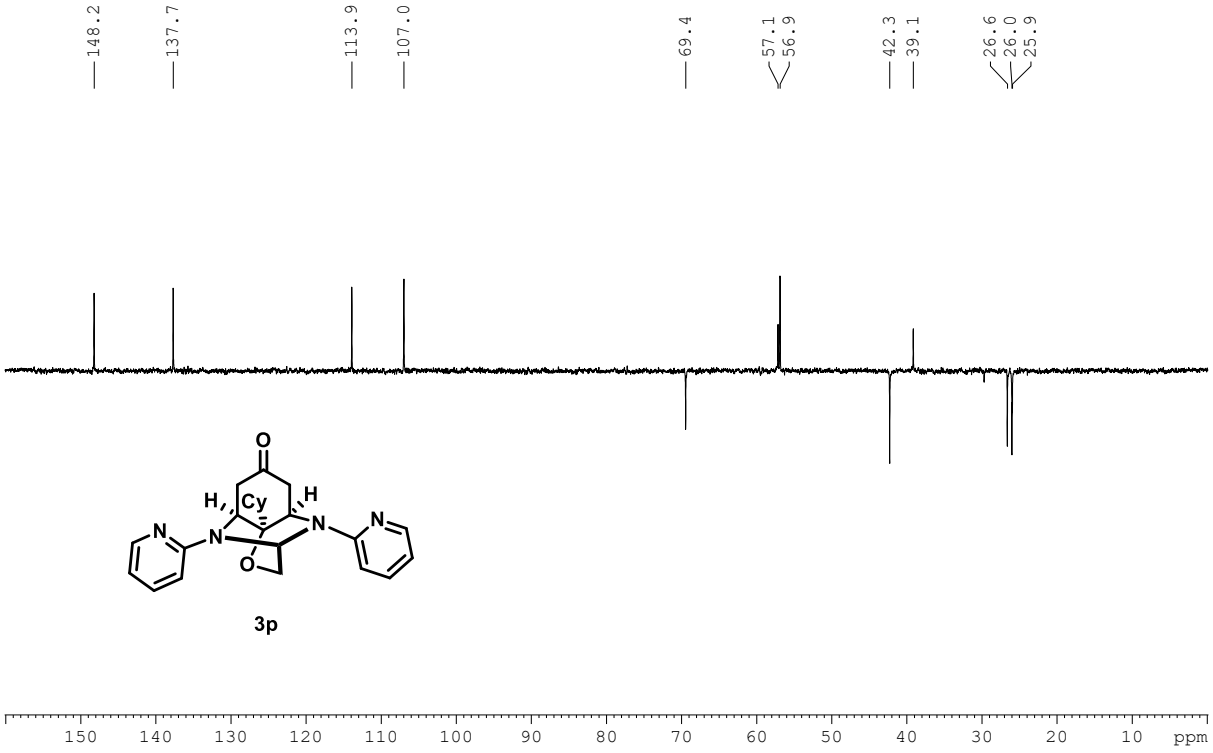
^{1}H NMR (400 MHz, $CDCl_3$) for 3p



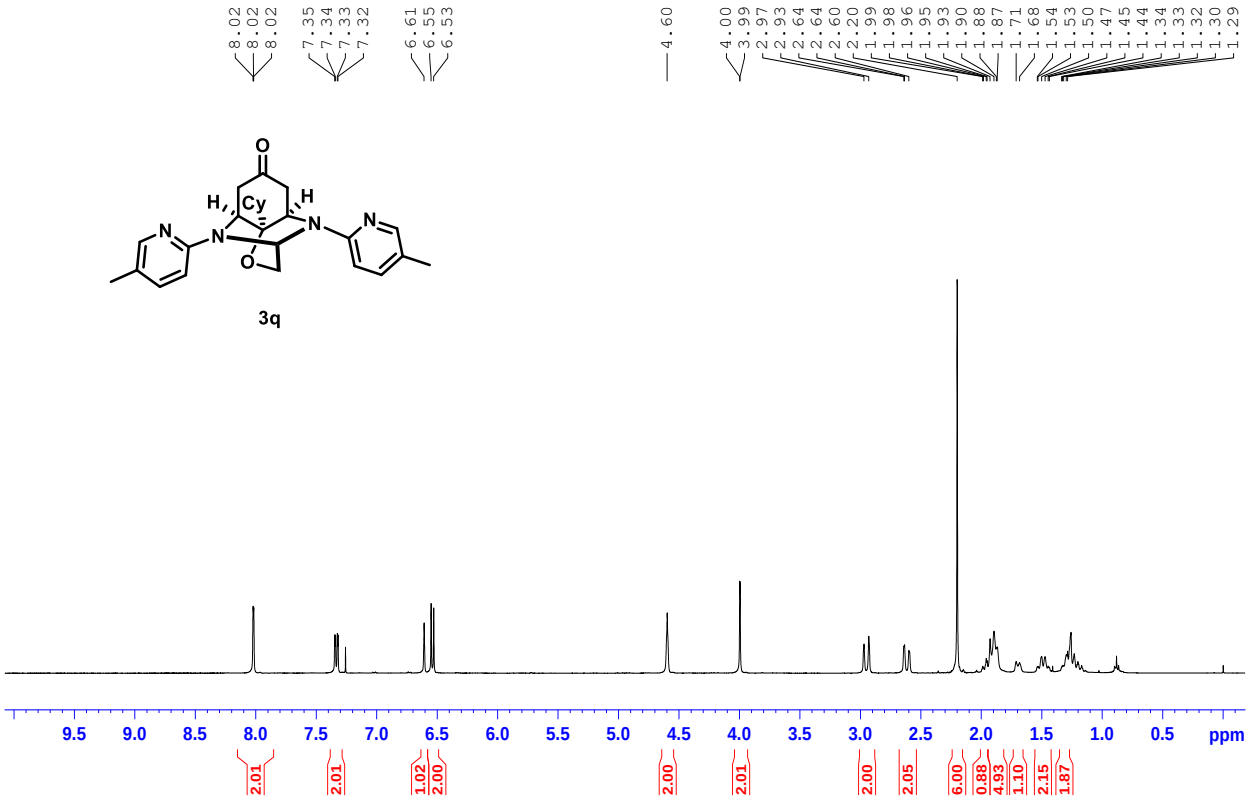
^{13}C NMR (100 MHz, $CDCl_3$) for 3p



DEPT (100 MHz, $CDCl_3$) for 3p

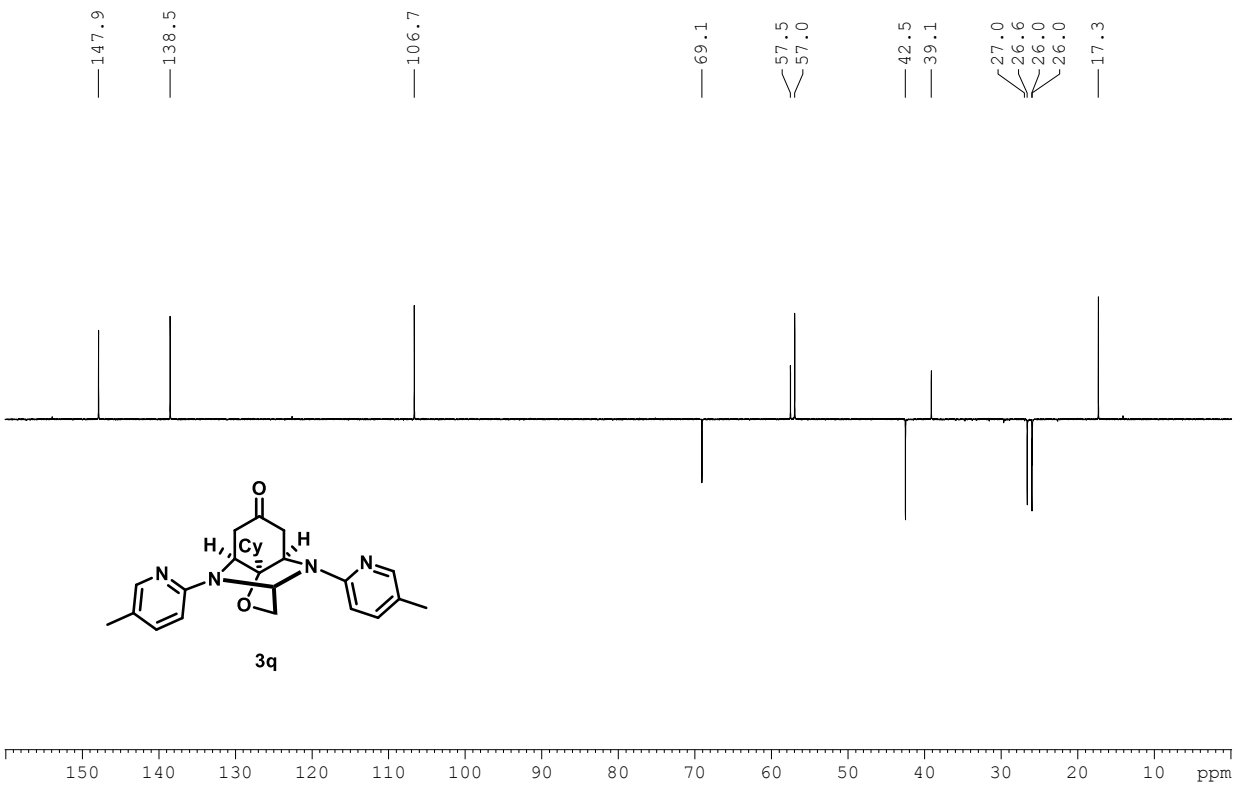


^{1}H NMR (400 MHz, $CDCl_3$) for 3q

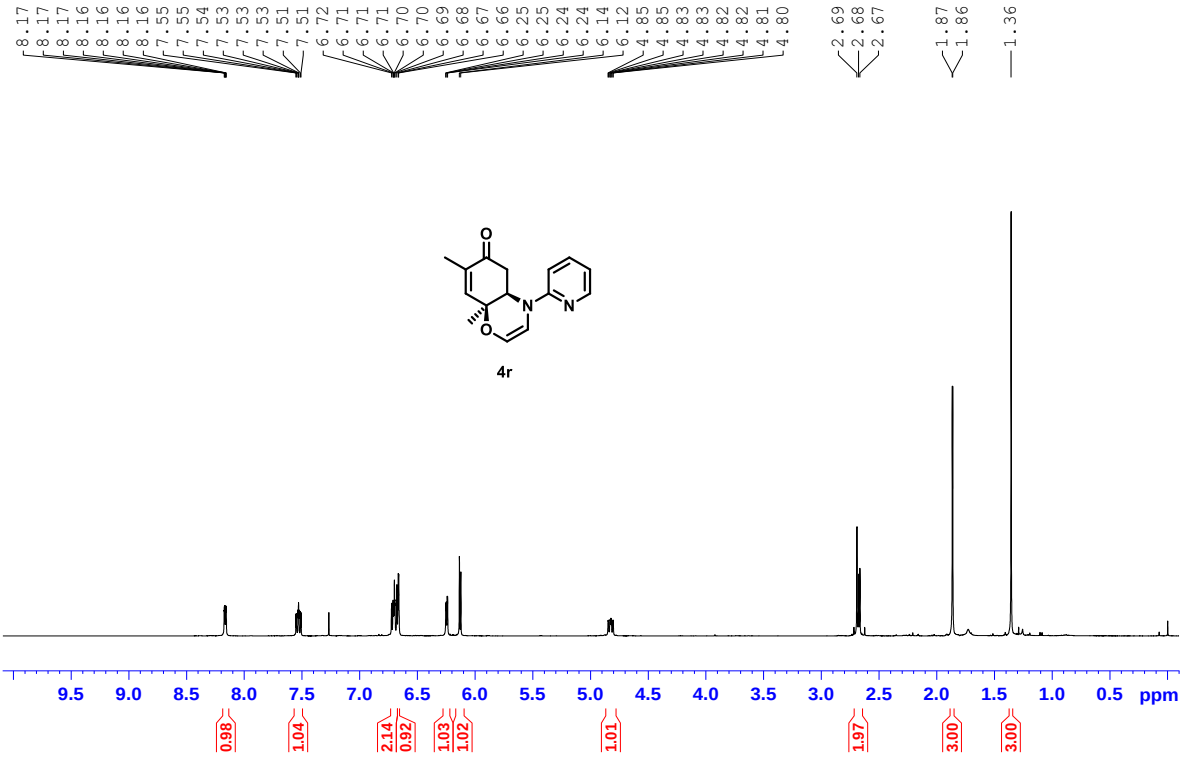


^{13}C NMR (100 MHz, $CDCl_3$) for 3q

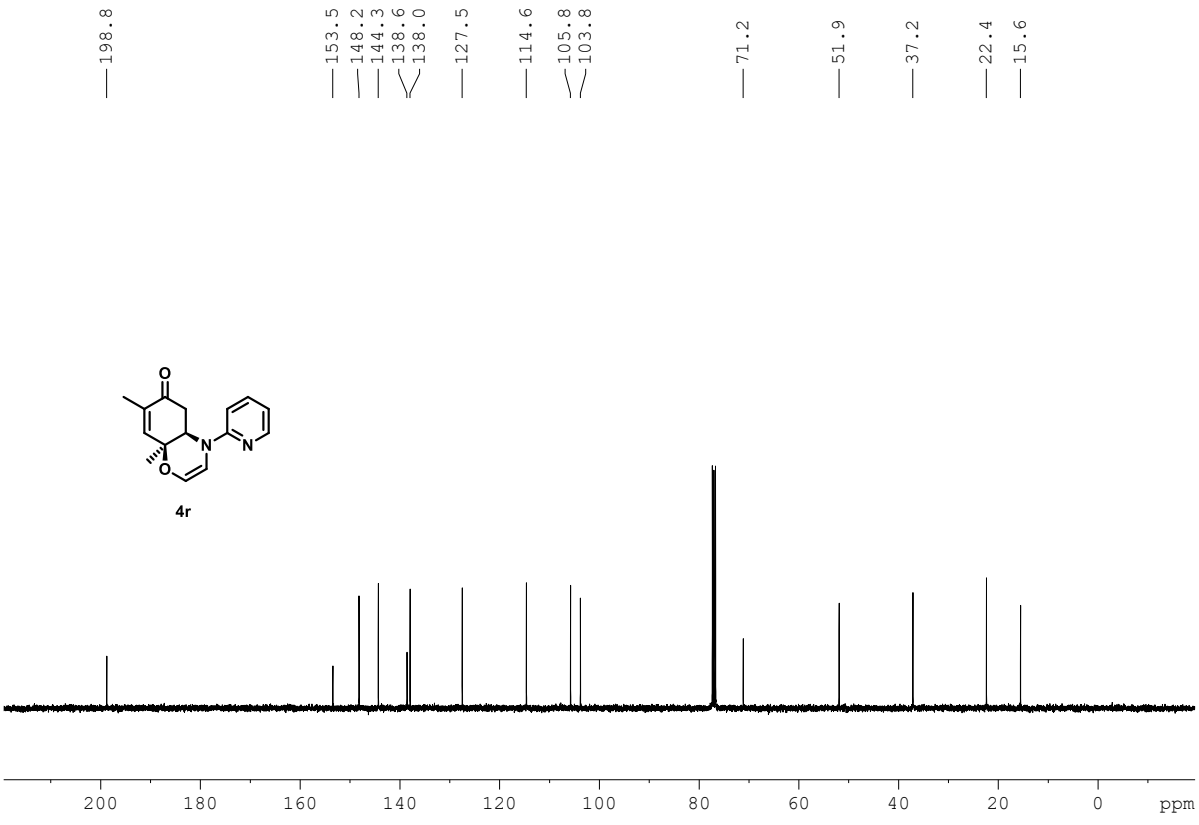
DEPT (100 MHz, $CDCl_3$) for 3q



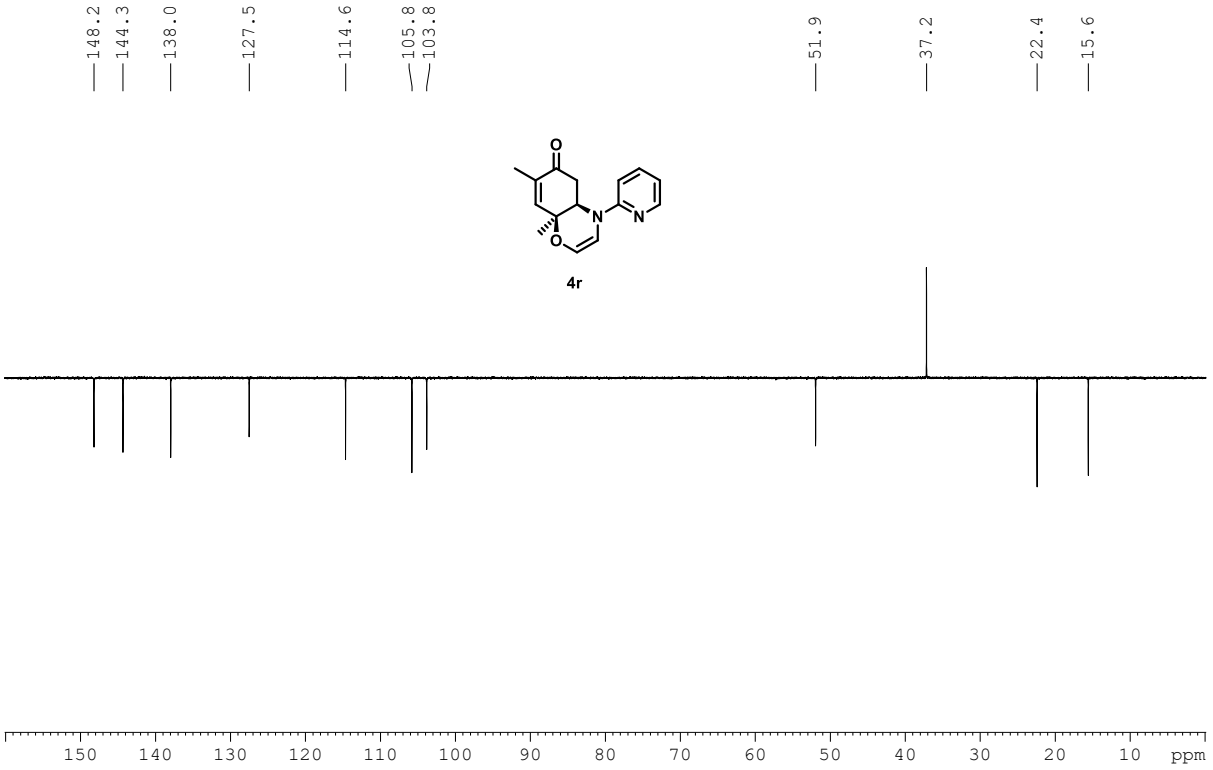
^{1}H NMR (400 MHz, $CDCl_3$) for 4r



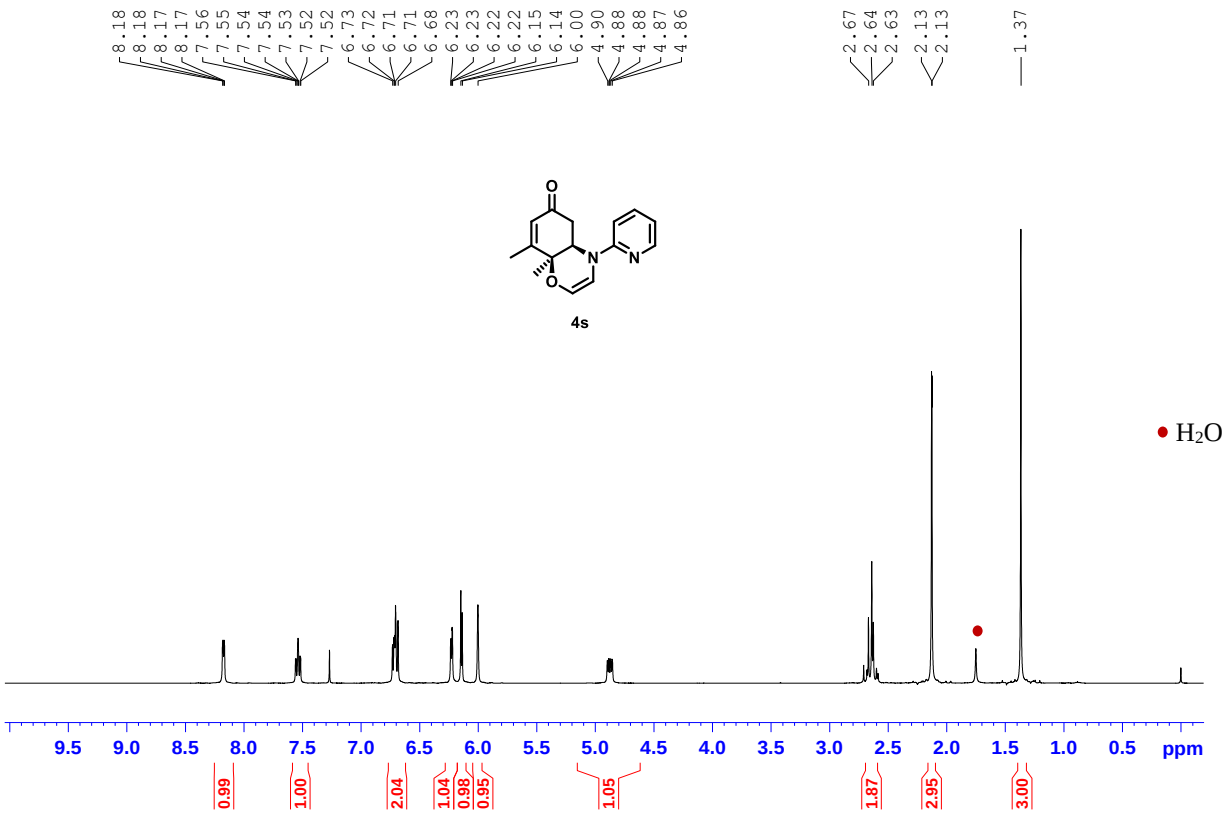
^{13}C NMR (100 MHz, $CDCl_3$) for 4r



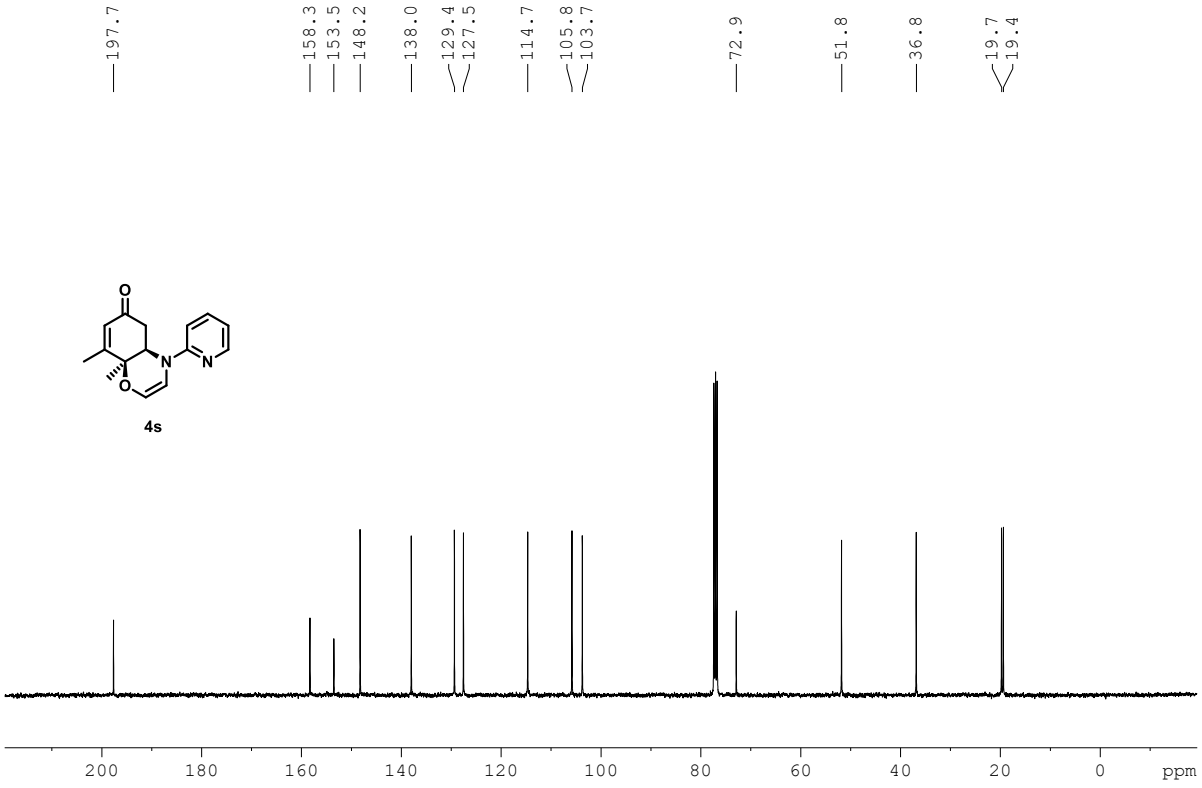
DEPT (100 MHz, $CDCl_3$) for 4r



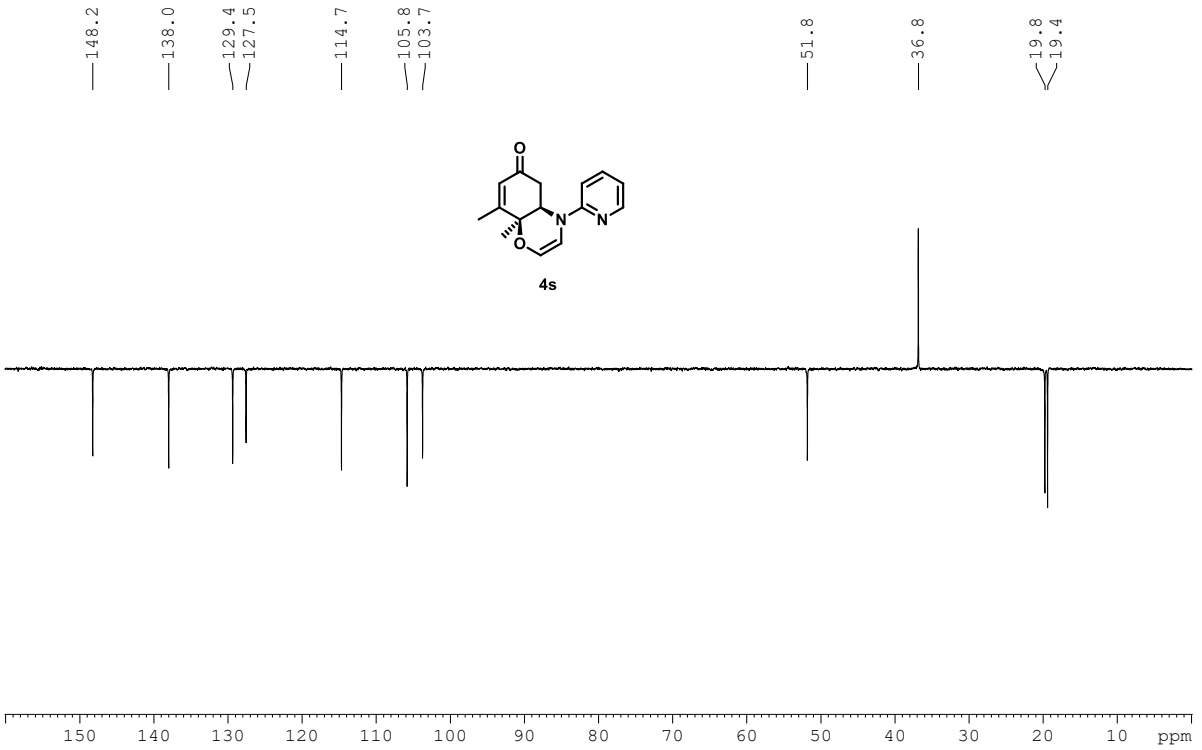
^{1}H NMR (400 MHz, $CDCl_3$) for 4s



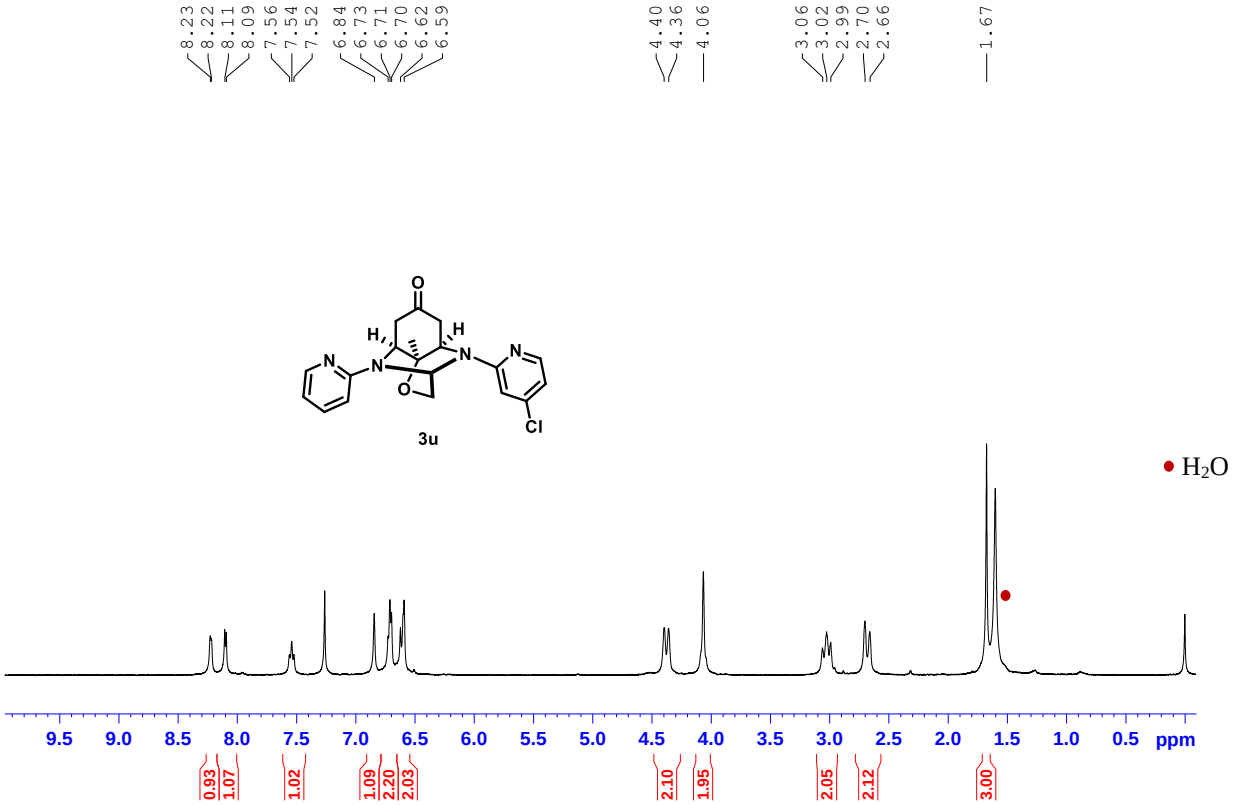
^{13}C NMR (100 MHz, $CDCl_3$) for 4s



DEPT (100 MHz, $CDCl_3$) for 4s

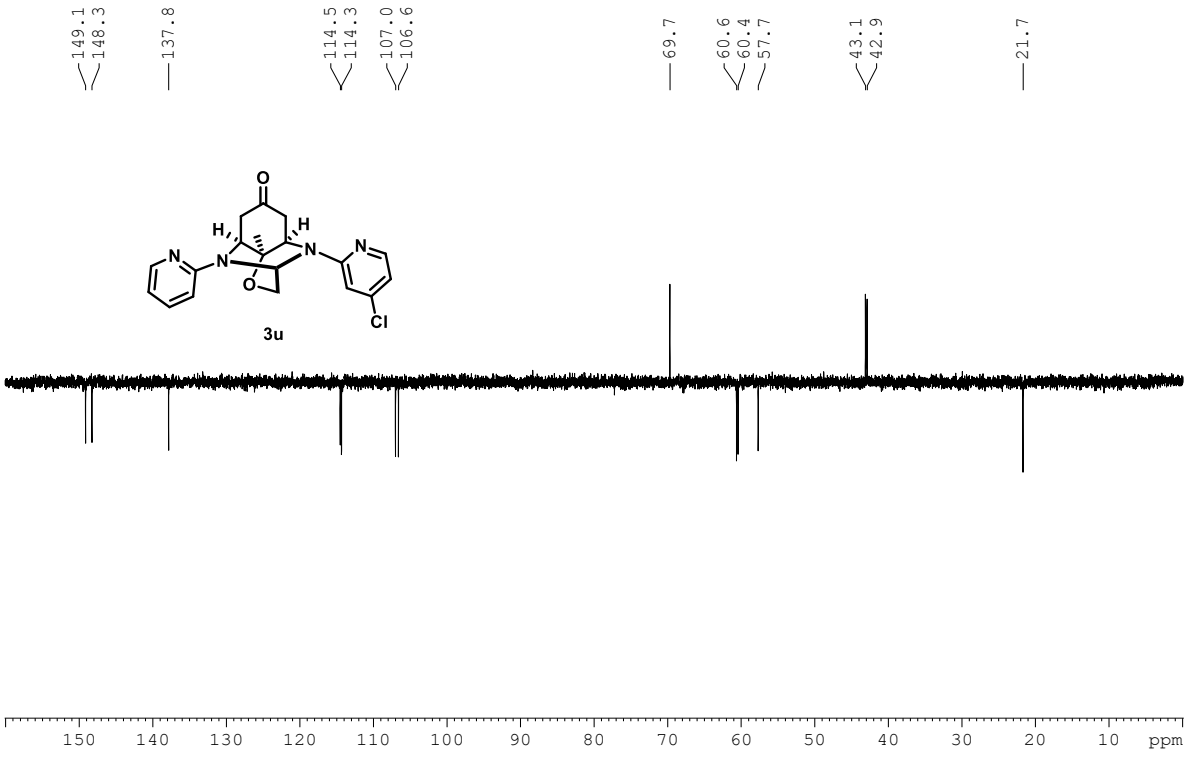


^{1}H NMR (400 MHz, $CDCl_3$) for 3u

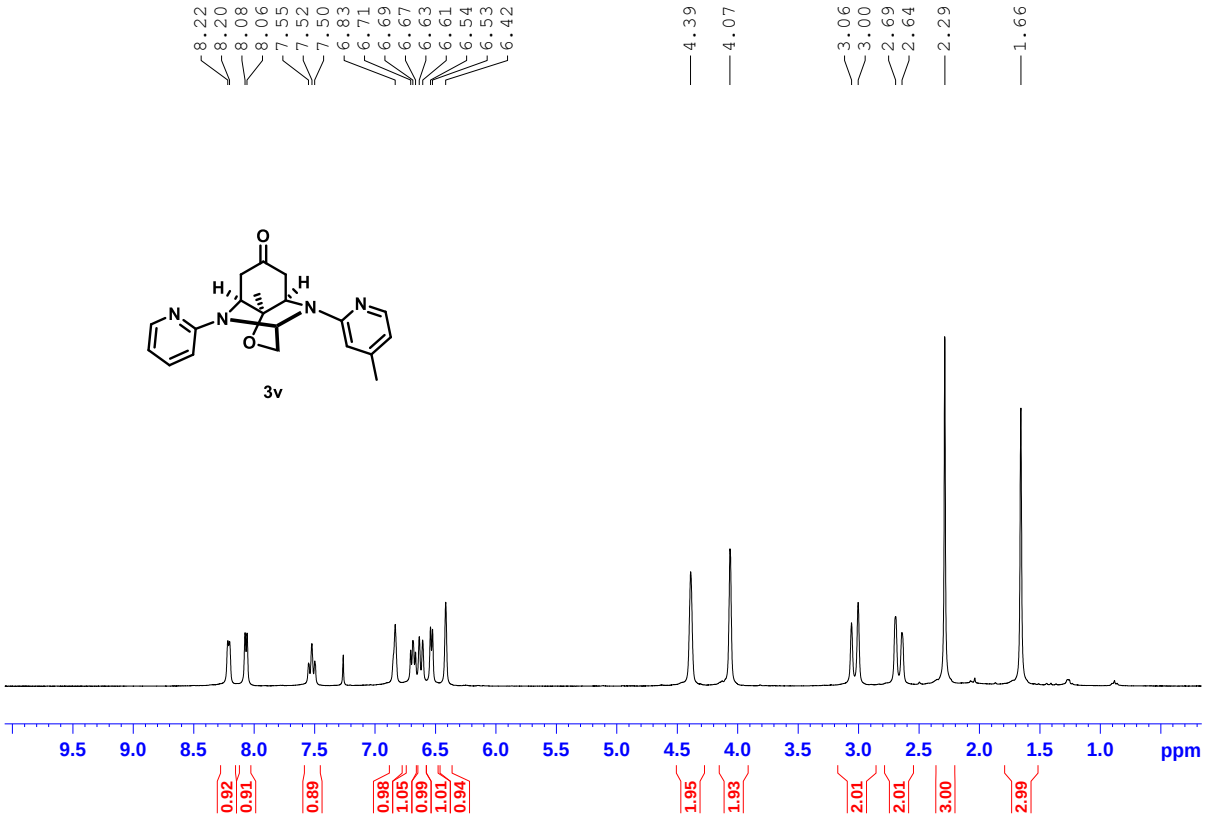


^{13}C NMR (100 MHz, $CDCl_3$) for 3u

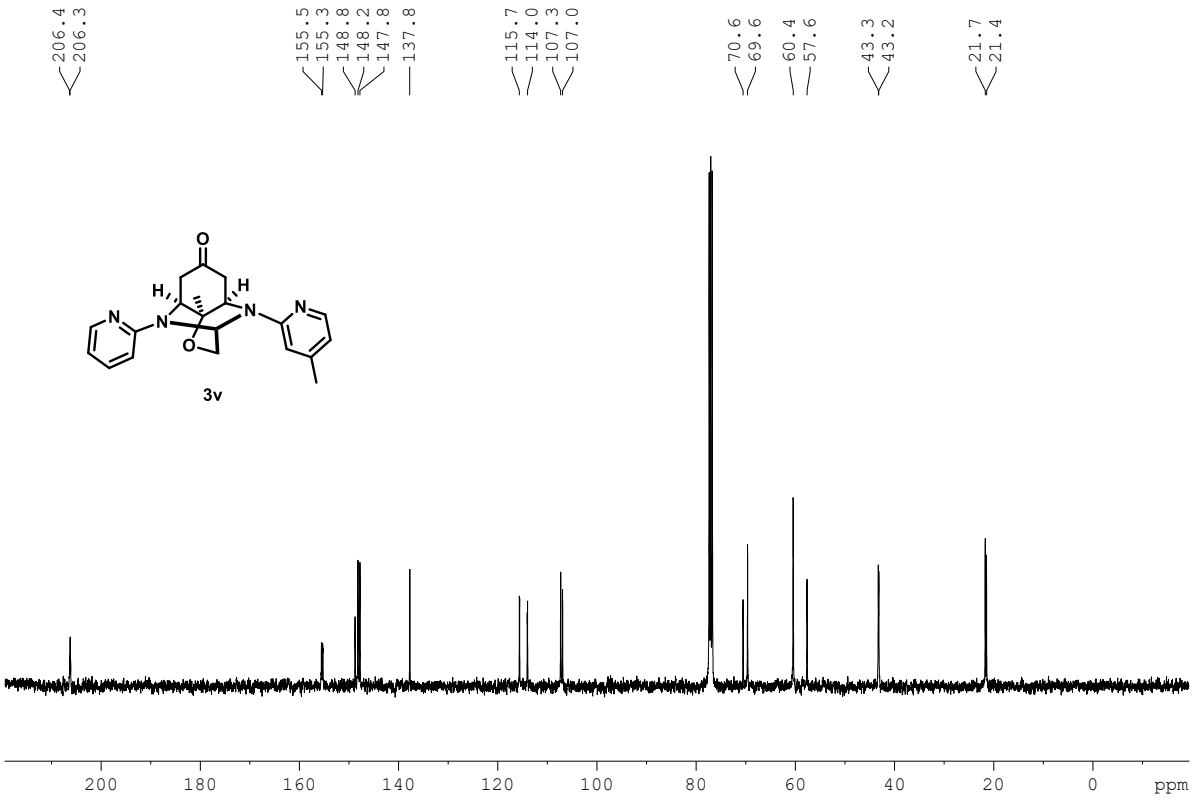
DEPT (100 MHz, $CDCl_3$) for 3u



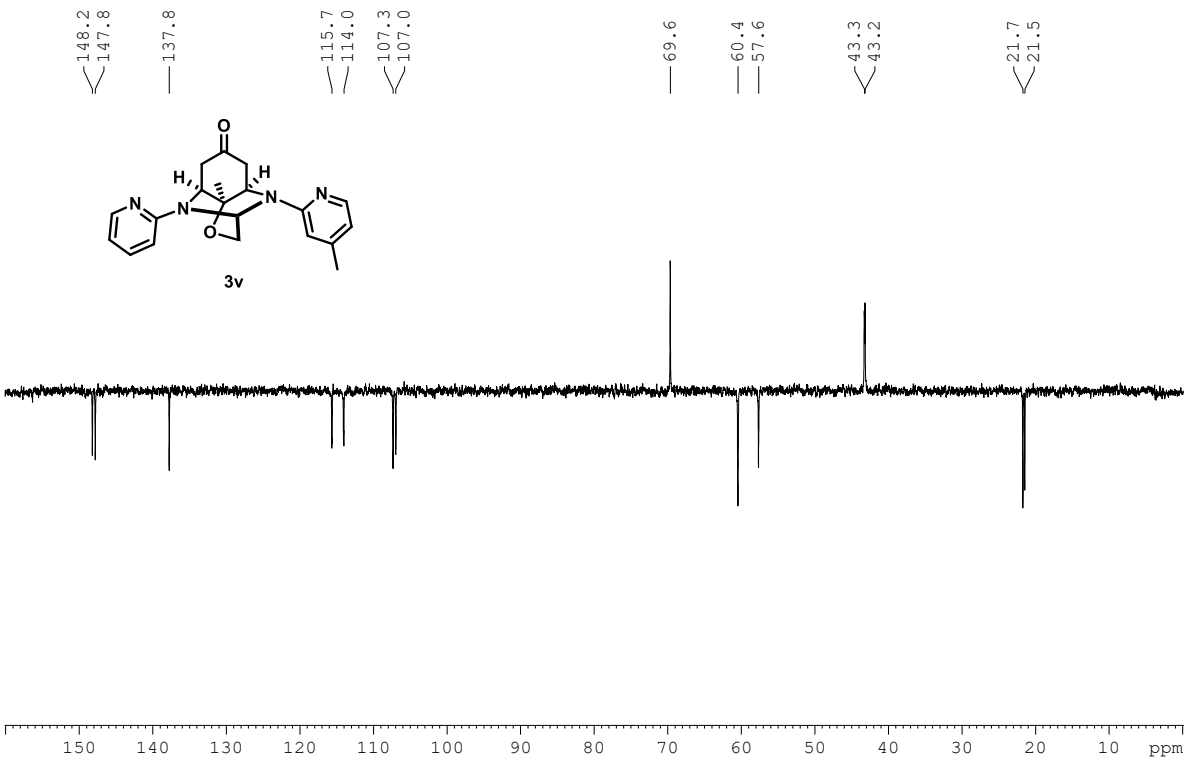
^{1}H NMR (300 MHz, $CDCl_3$) for 3v



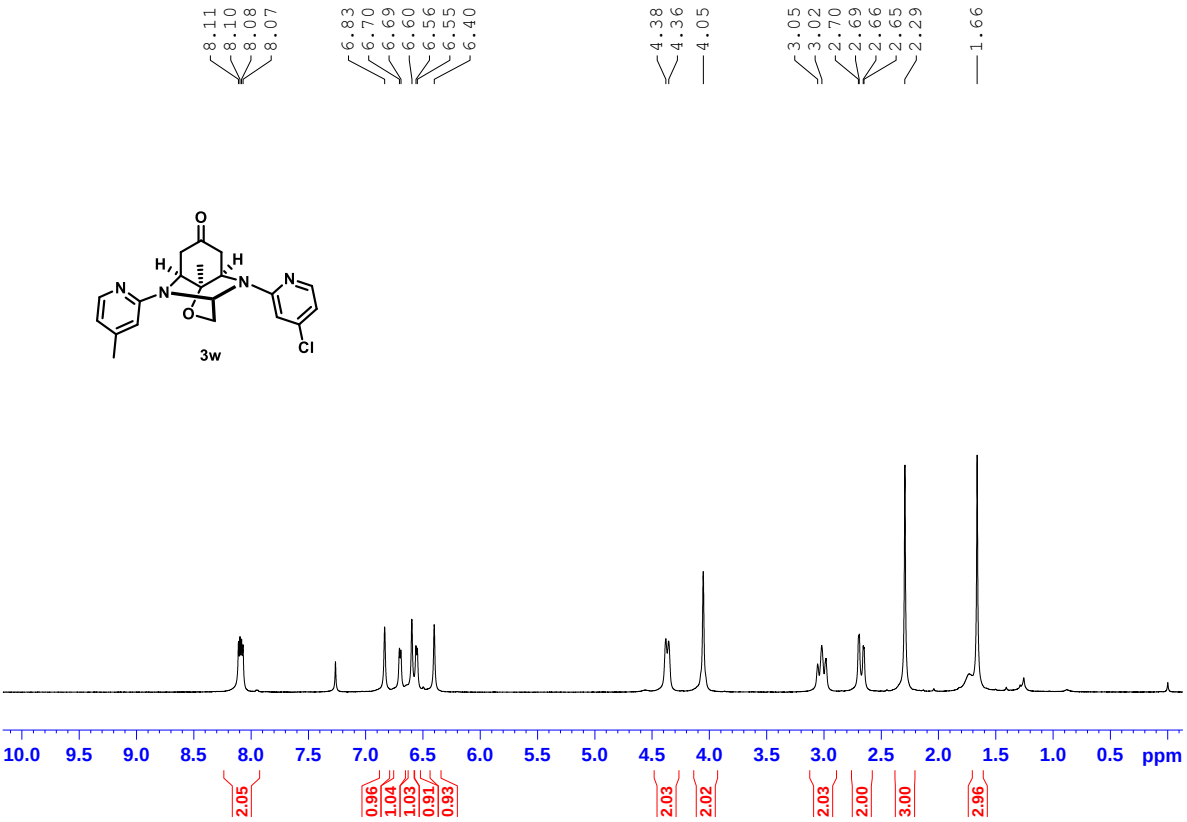
^{13}C NMR (100 MHz, $CDCl_3$) for 3v



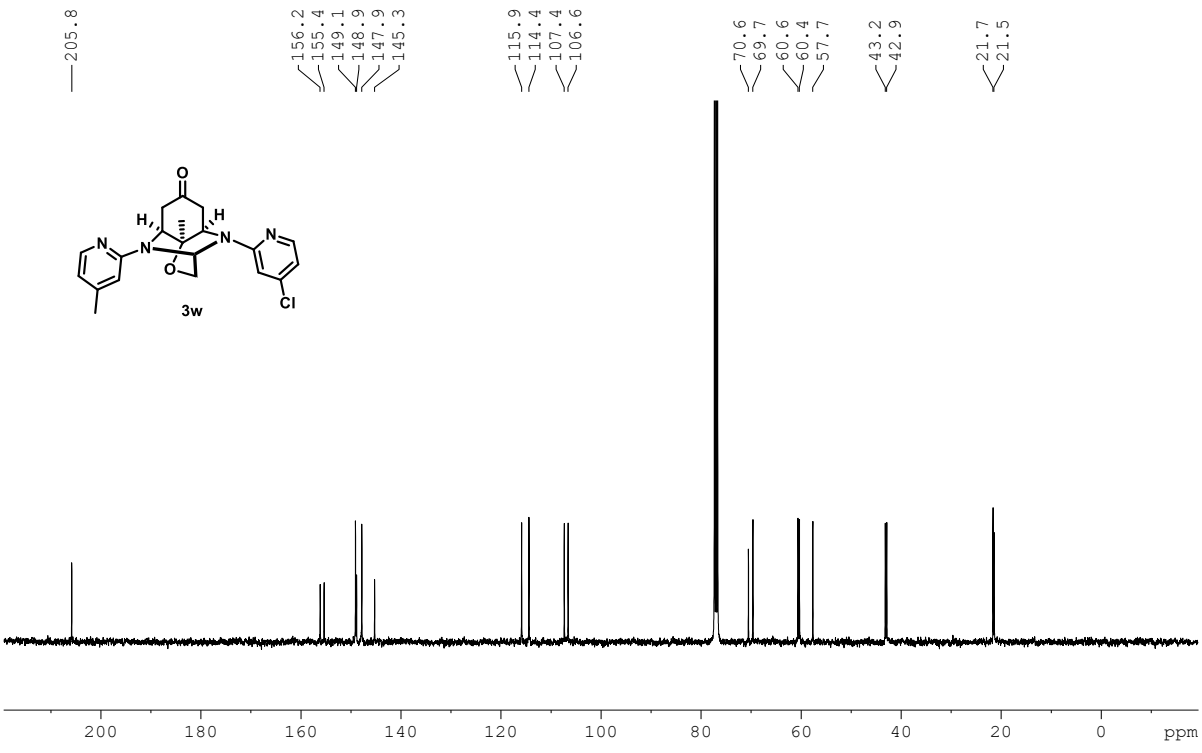
DEPT (100 MHz, $CDCl_3$) for 3v



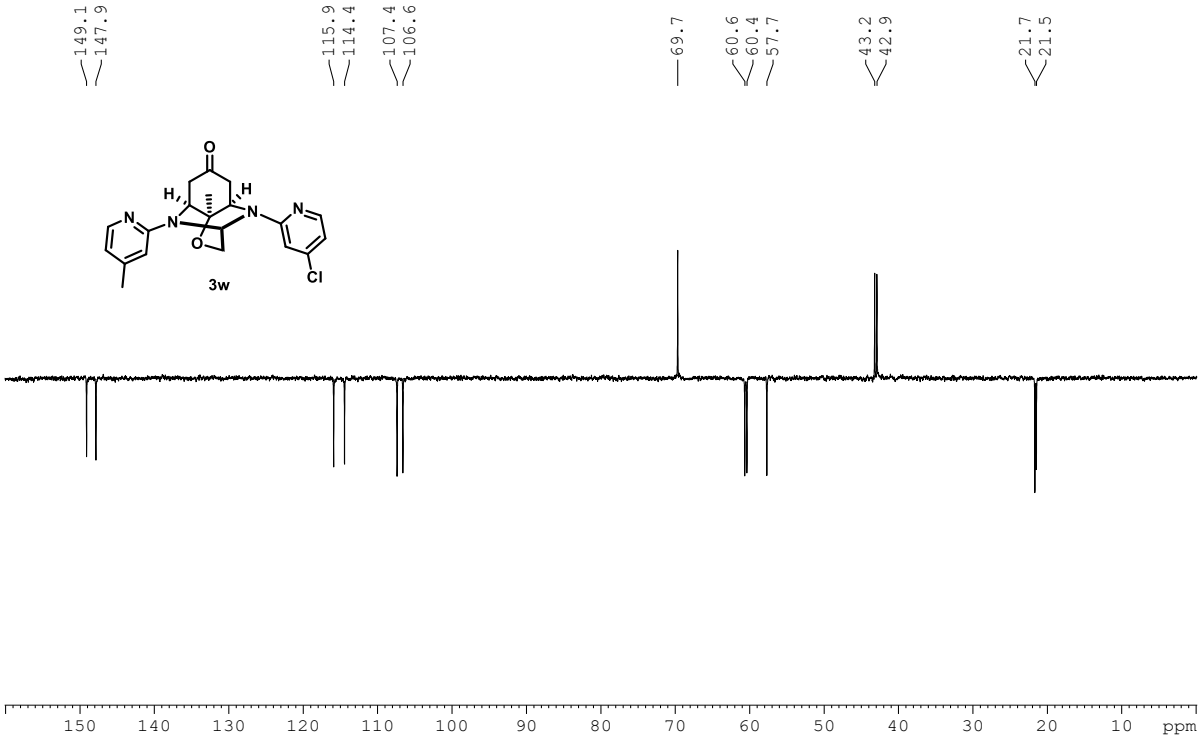
^{1}H NMR (400 MHz, $CDCl_3$) for 3w



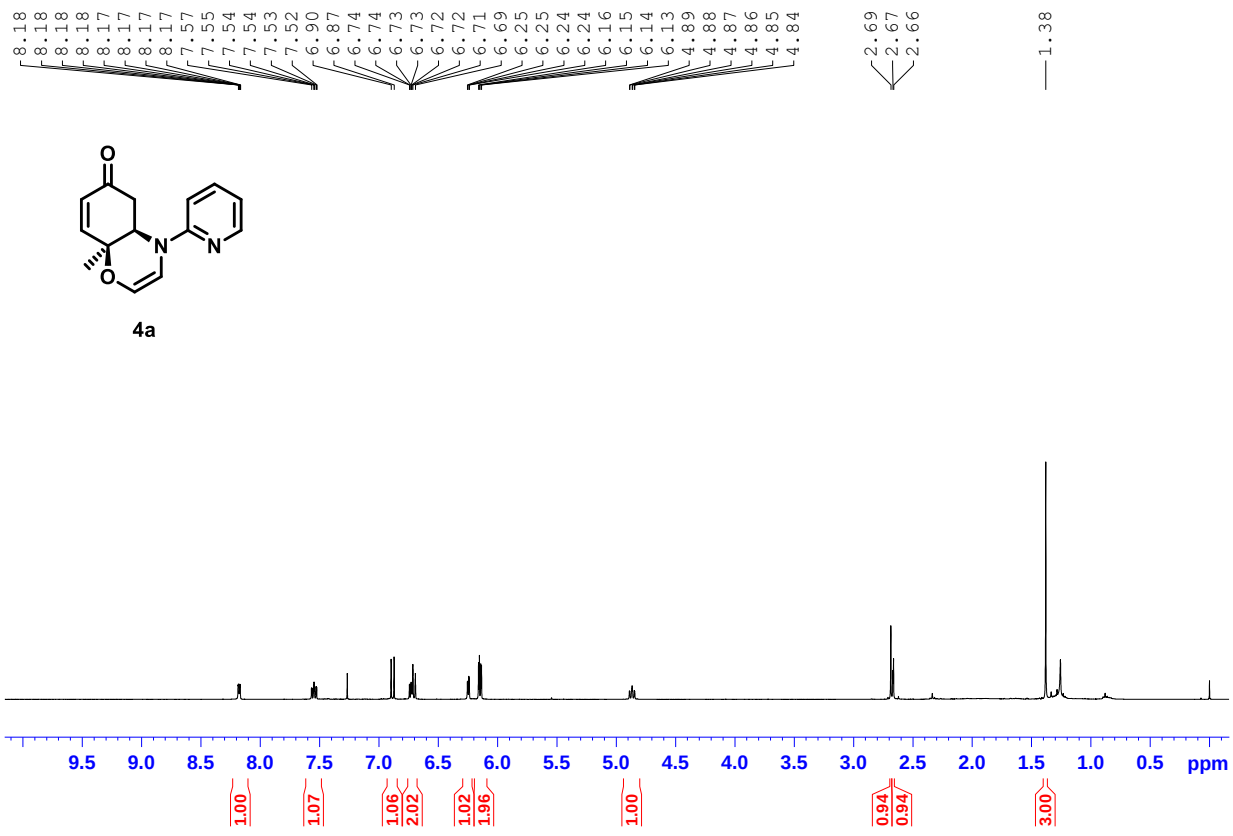
^{13}C NMR (100 MHz, $CDCl_3$) for 3w



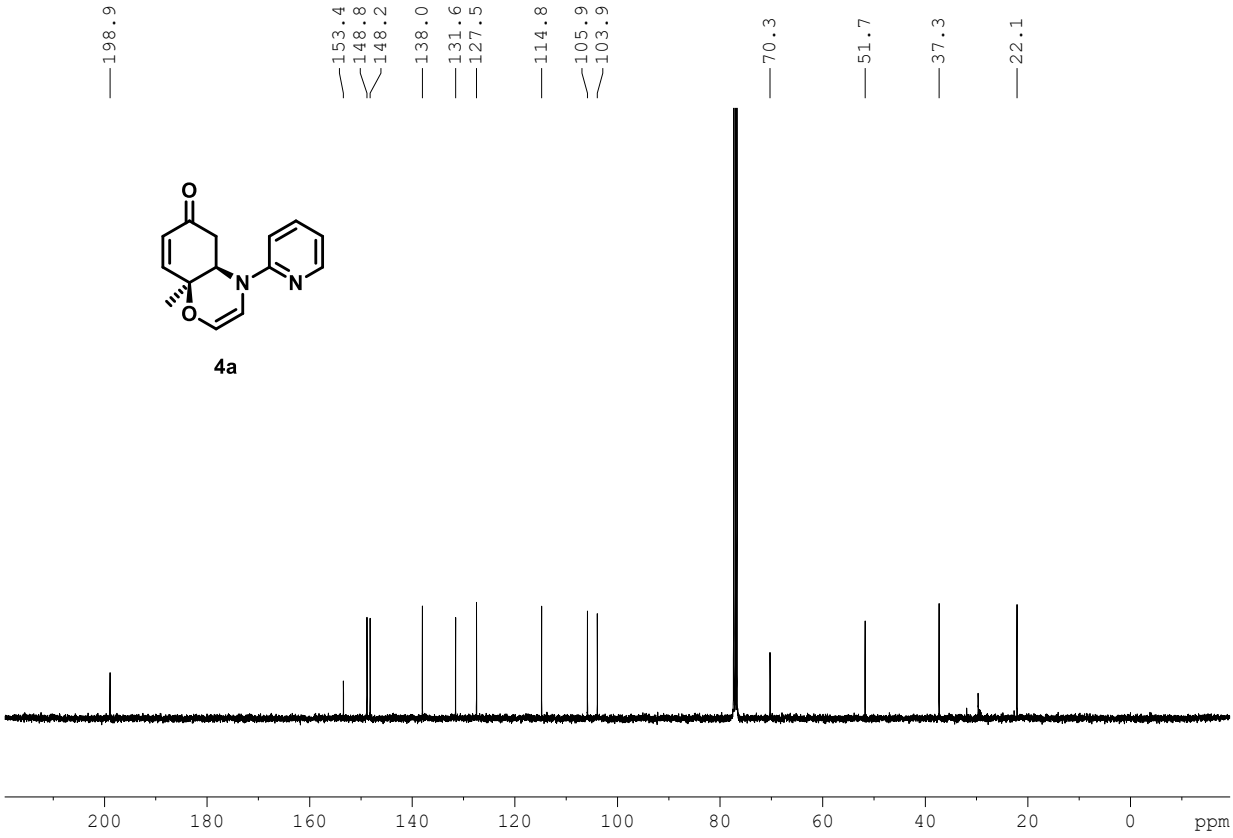
DEPT (100 MHz, $CDCl_3$) for 3w



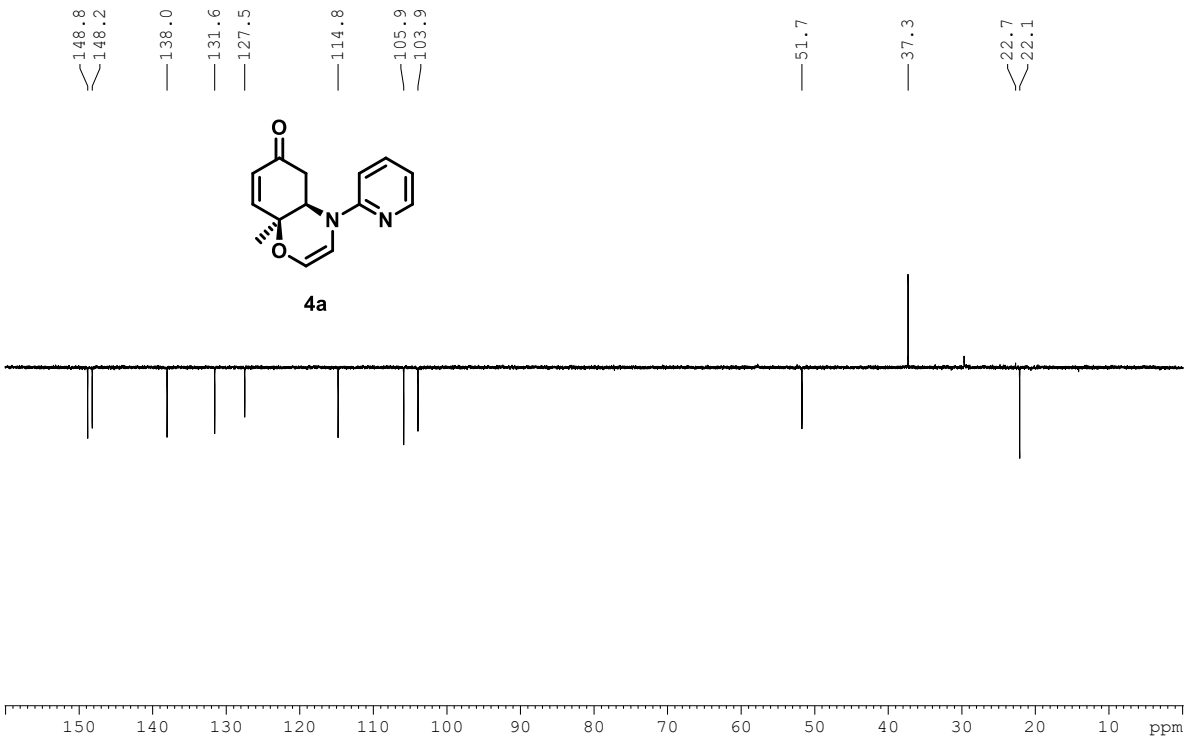
^{1}H NMR (400 MHz, $CDCl_3$) for 4a



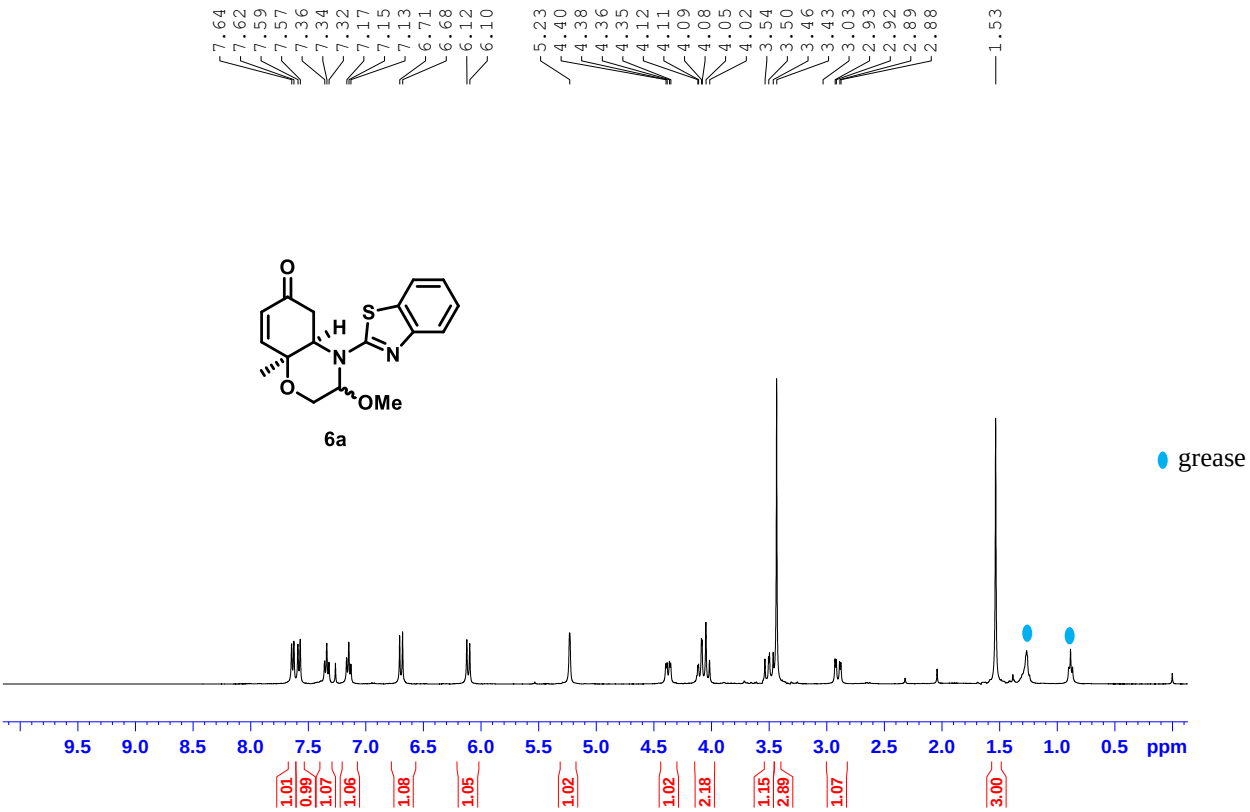
^{13}C NMR (100 MHz, $CDCl_3$) for 4a



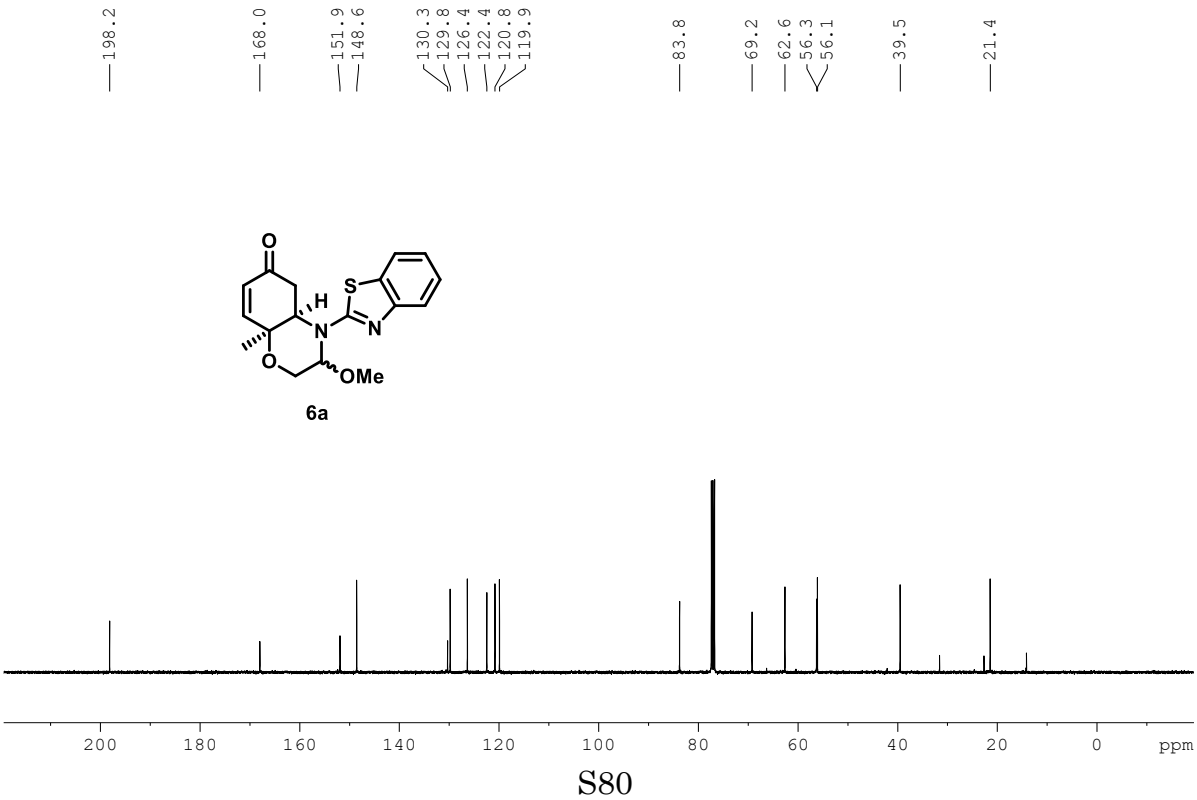
DEPT (100 MHz, $CDCl_3$) for 4a



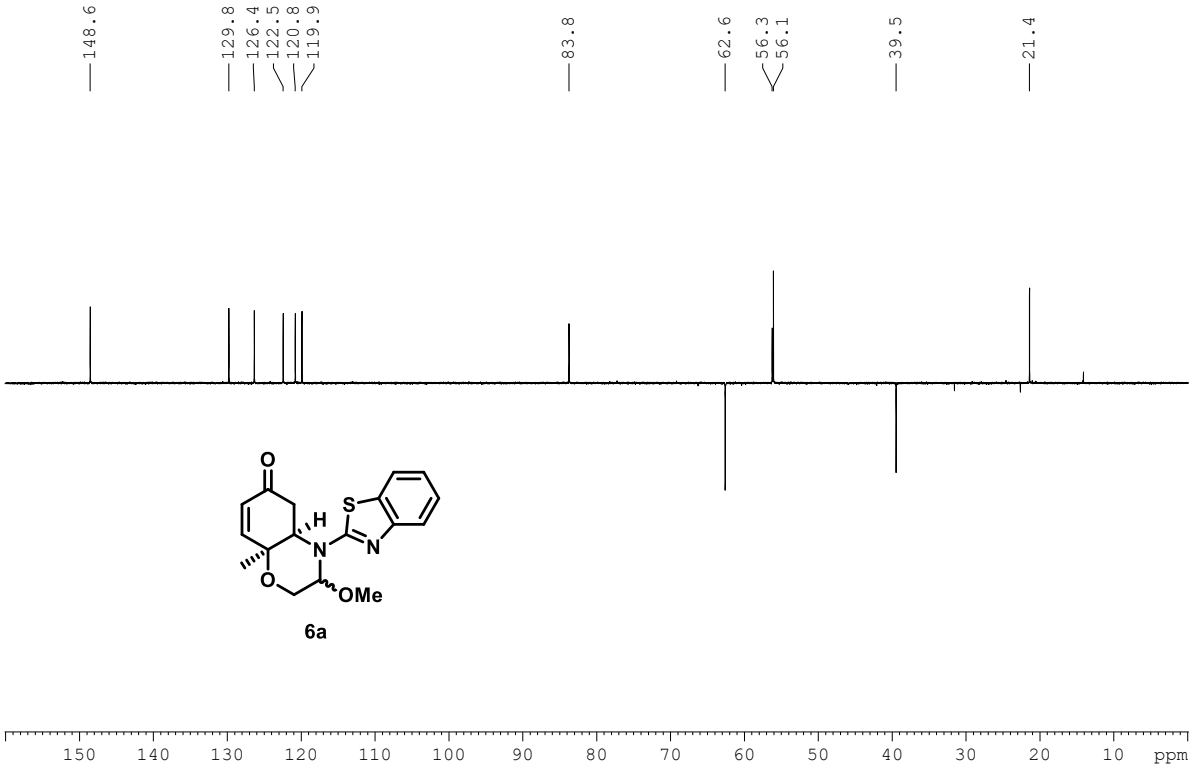
^{1}H NMR (400 MHz, $CDCl_3$) for 6a



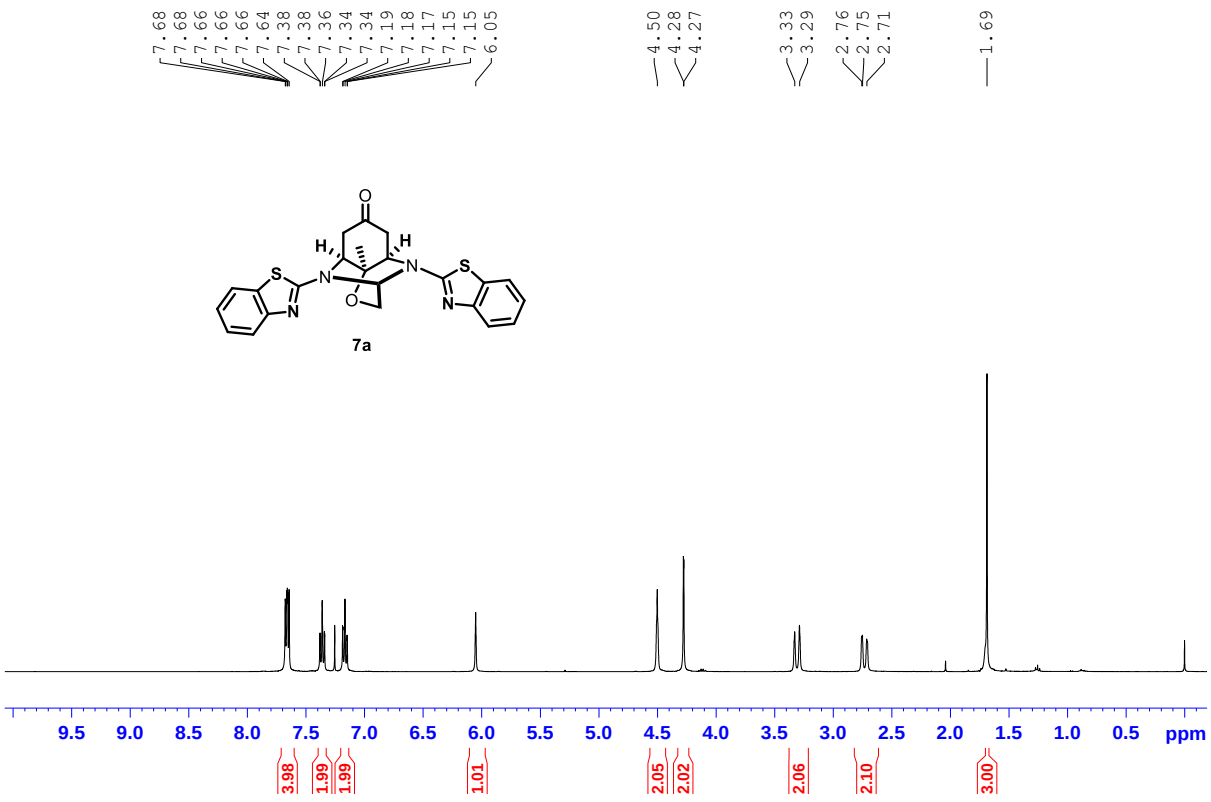
^{13}C NMR (100 MHz, $CDCl_3$) for 6a



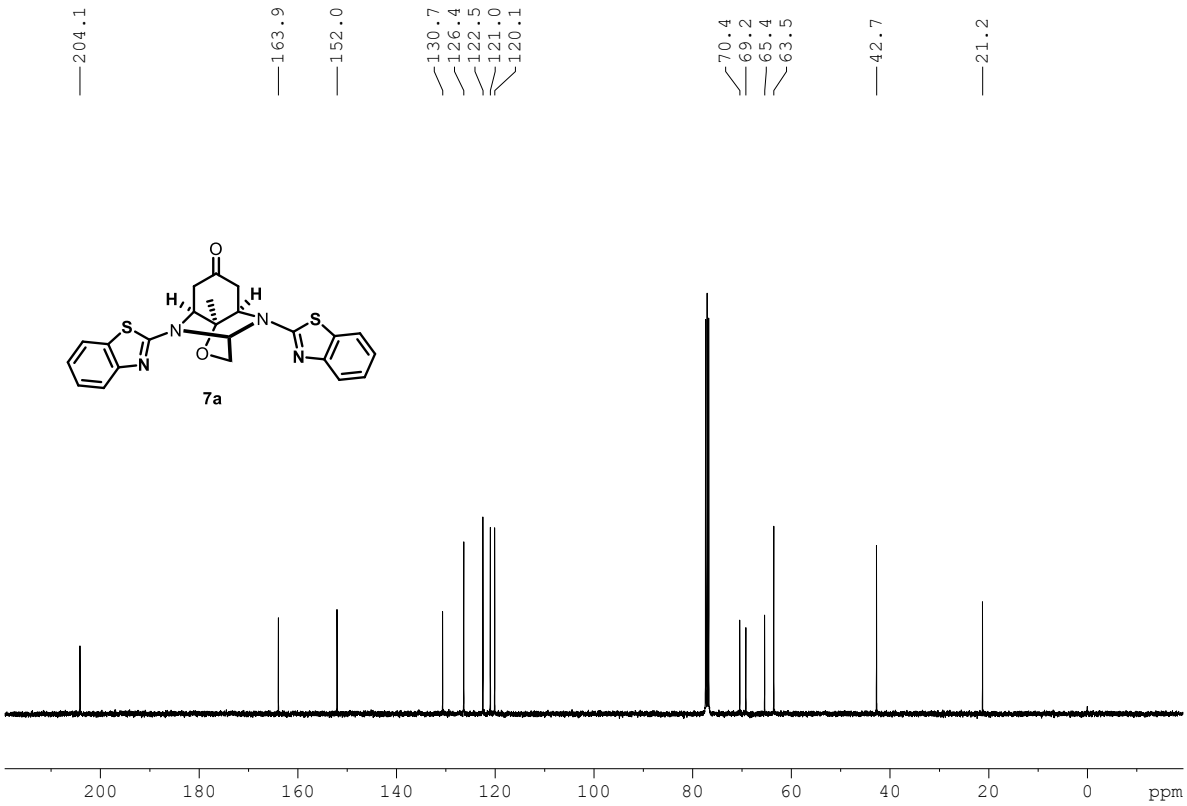
DEPT (100 MHz, $CDCl_3$) for 6a



^{1}H NMR (400 MHz, $CDCl_3$) for 7a

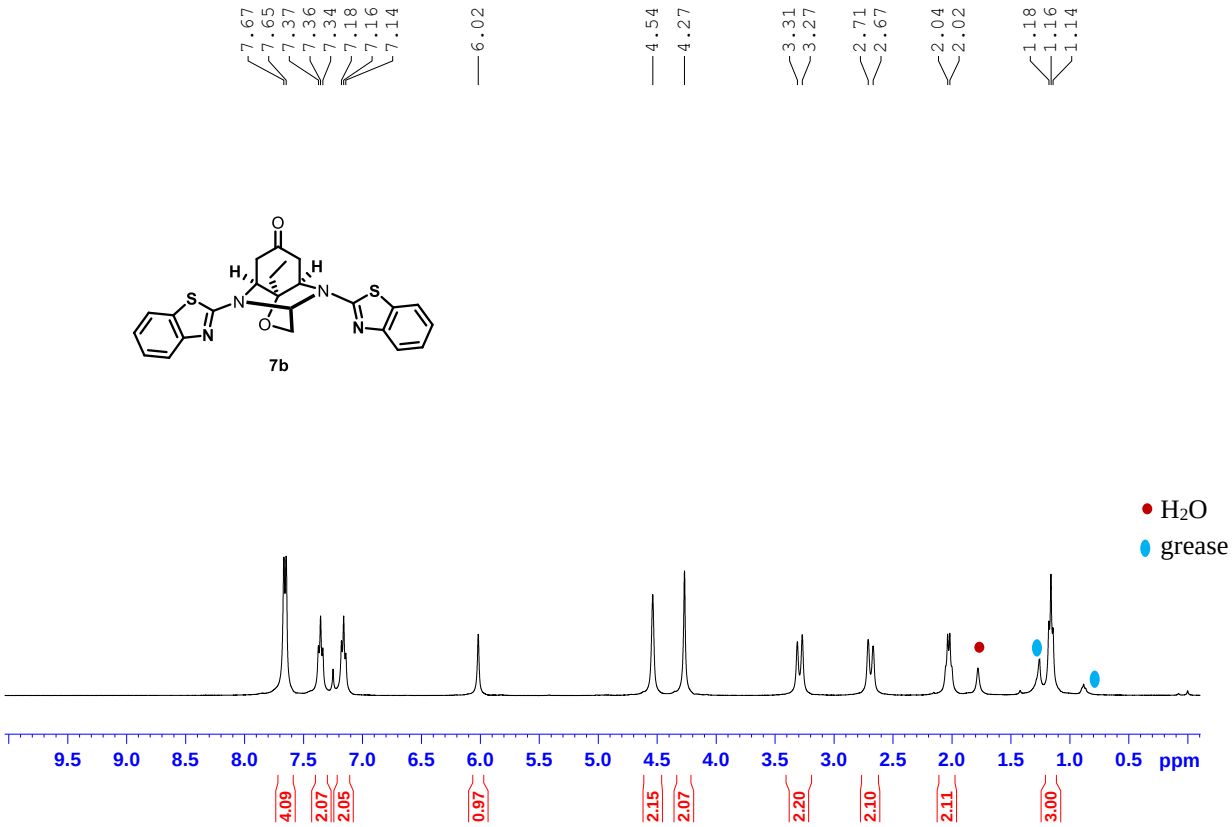


^{13}C NMR (100 MHz, $CDCl_3$) for 7a

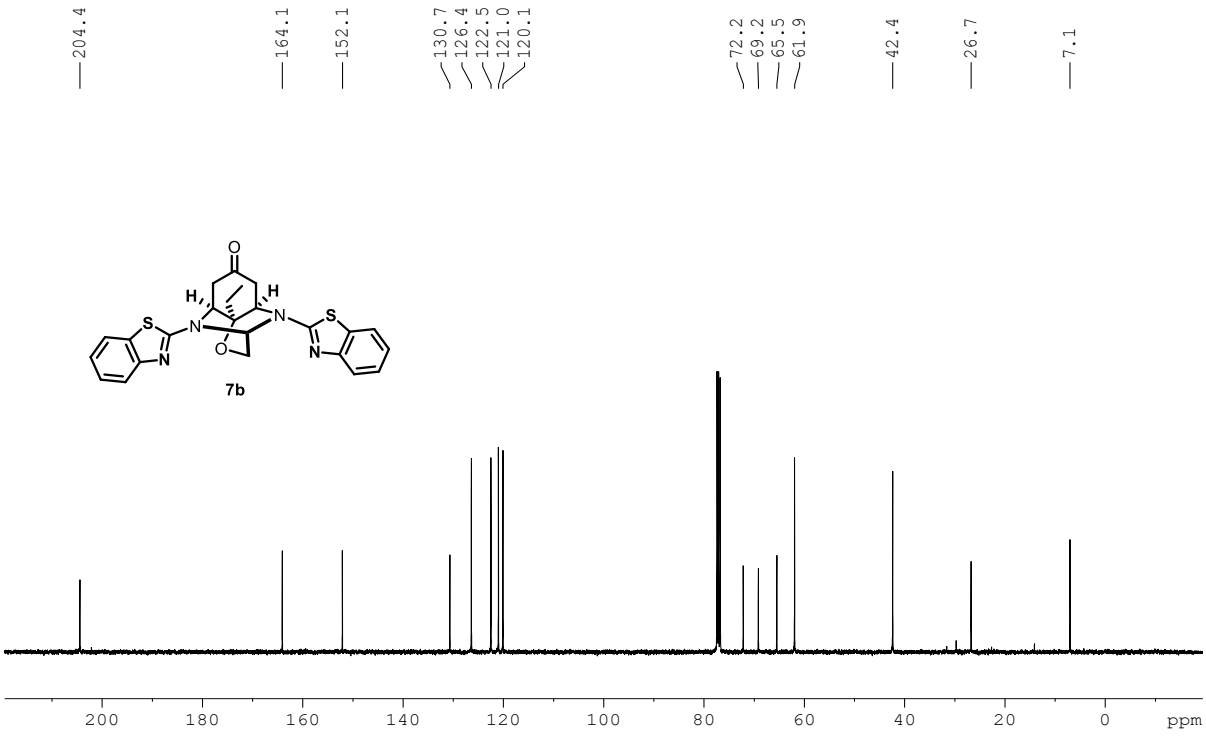


DEPT (100 MHz, $CDCl_3$) for 7a

^{1}H NMR (400 MHz, $CDCl_3$) for 7b

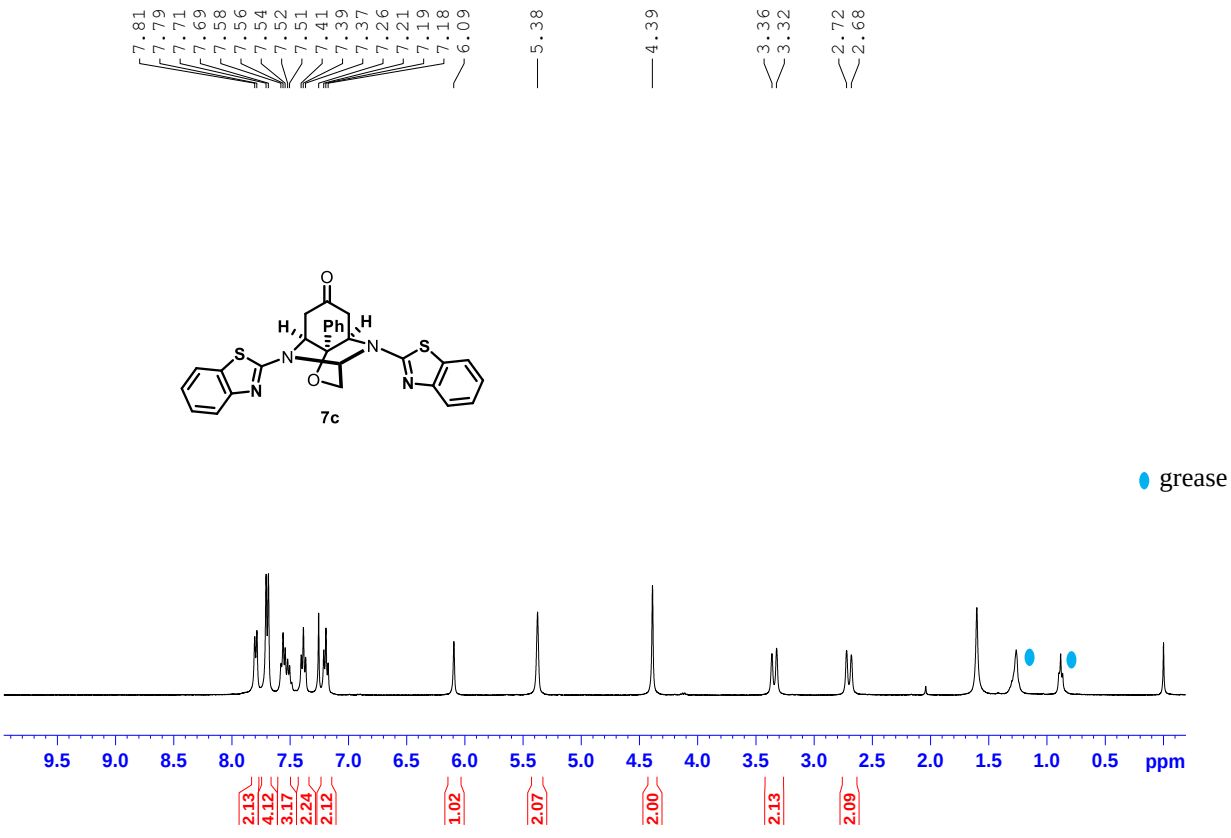


^{13}C NMR (100 MHz, $CDCl_3$) for 7b

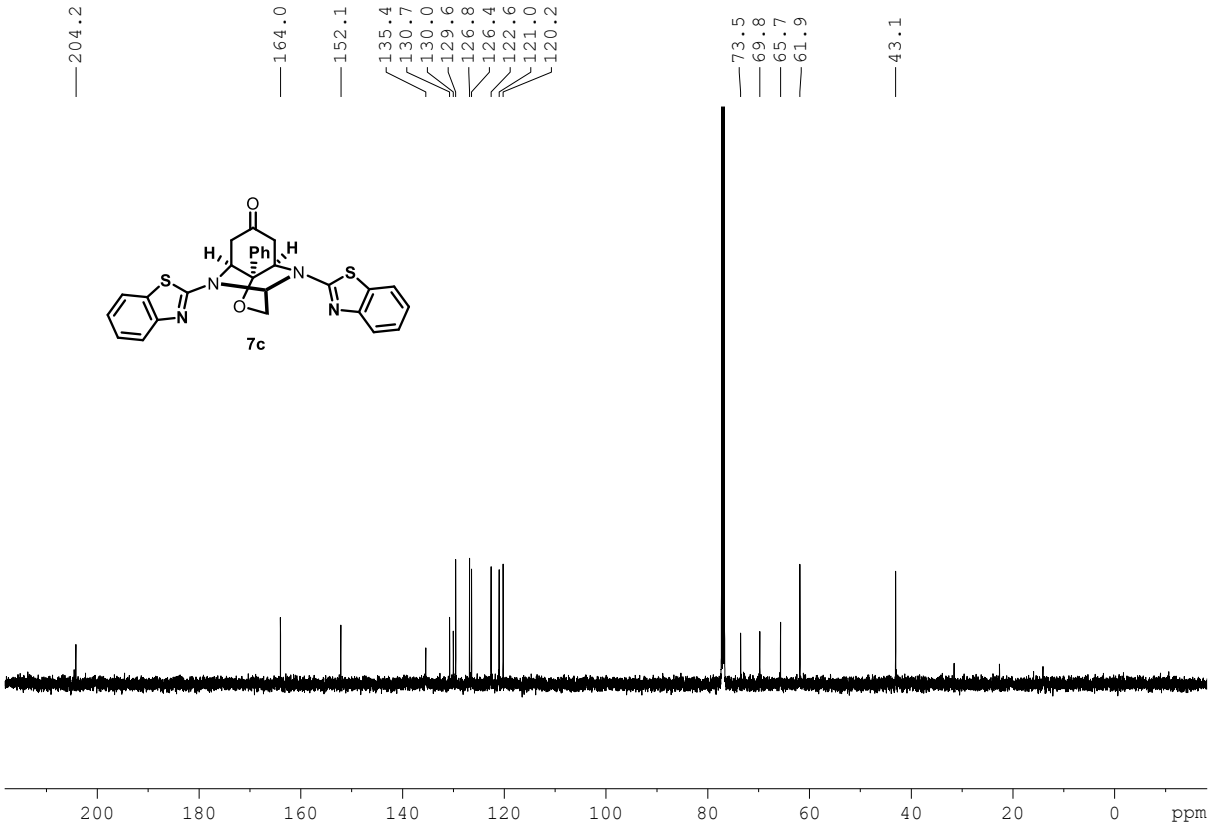


DEPT (100 MHz, $CDCl_3$) for 7b

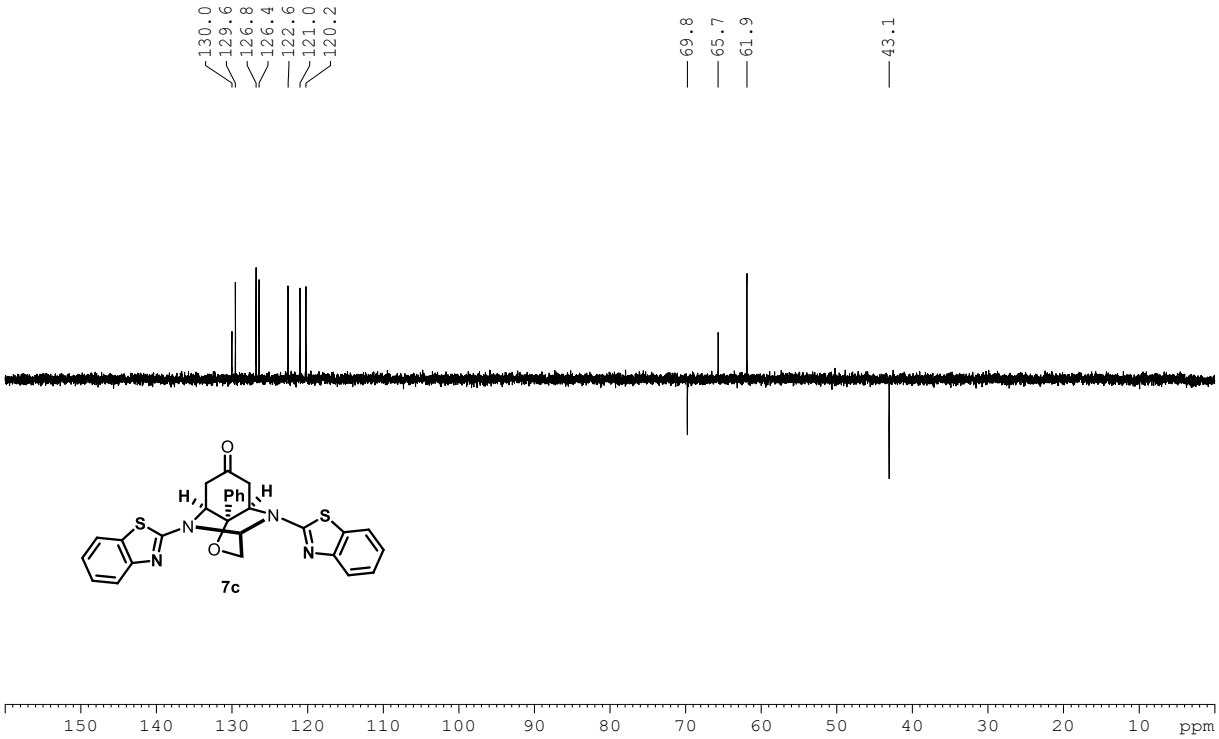
^{1}H NMR (400 MHz, $CDCl_3$) for 7c



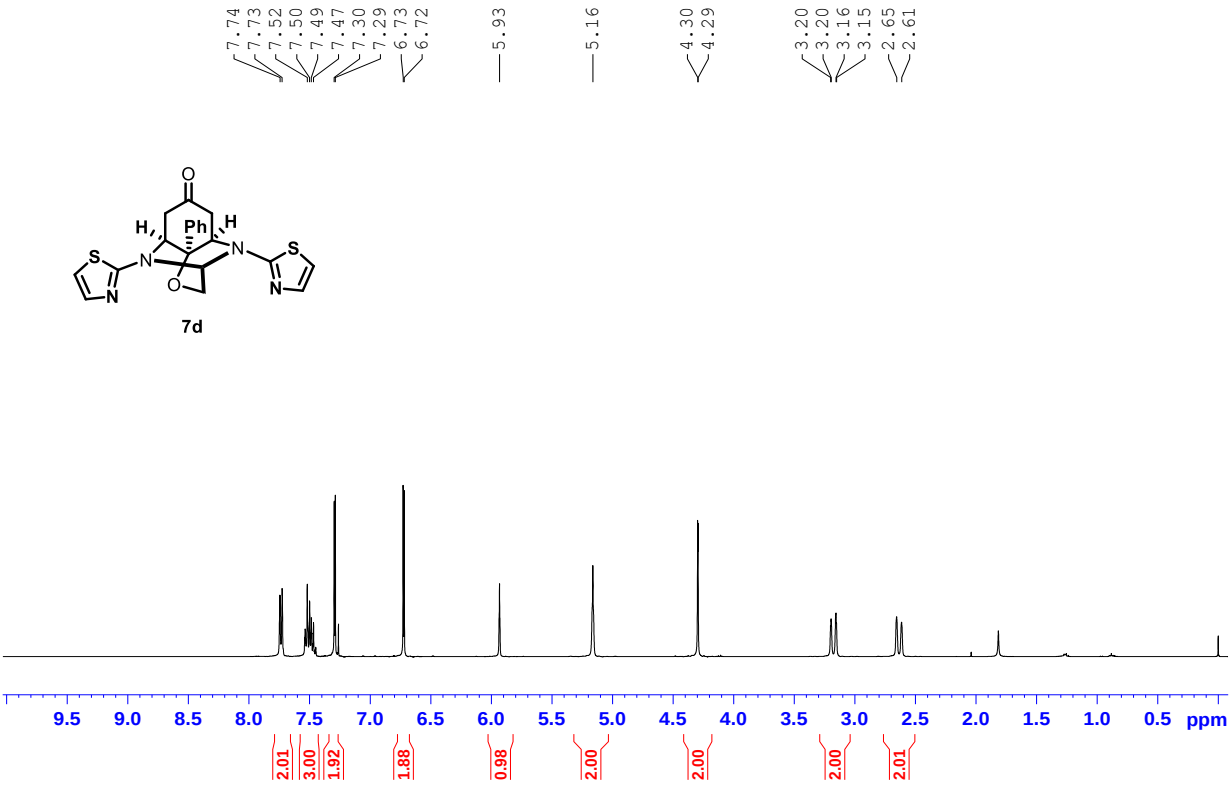
^{13}C NMR (100 MHz, $CDCl_3$) for 7c



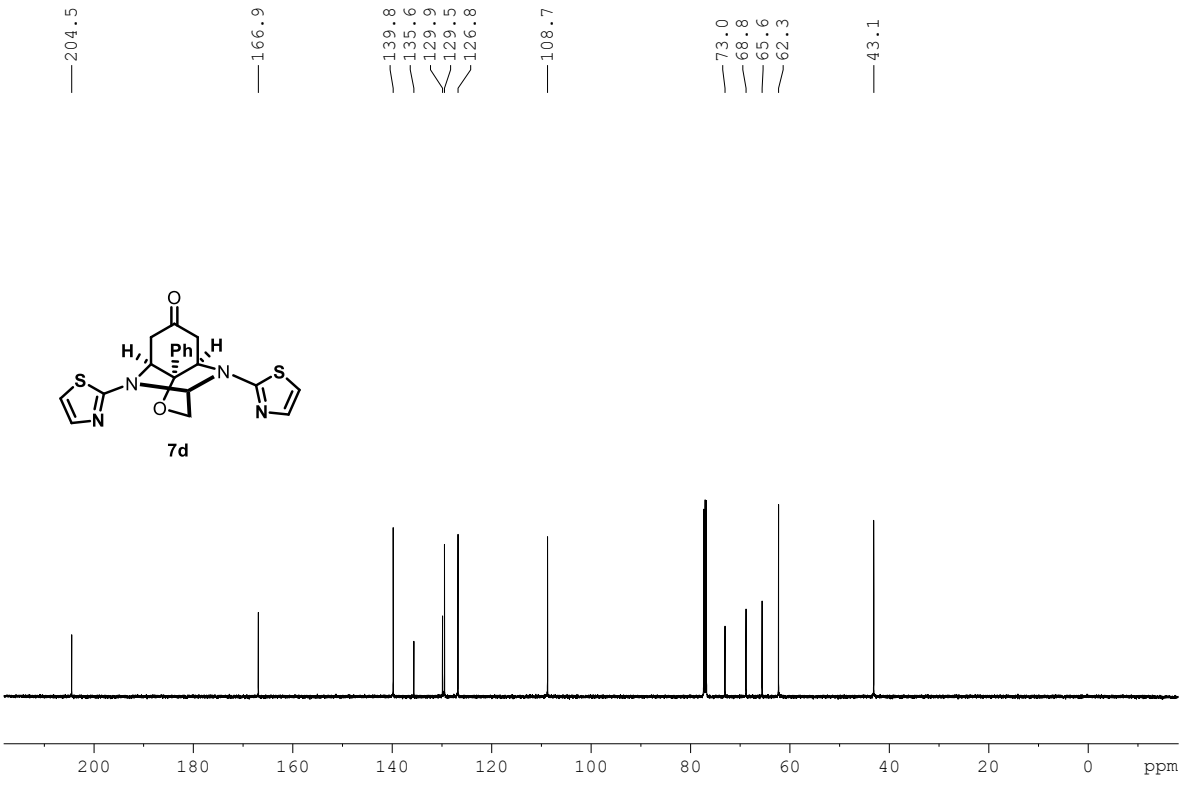
DEPT (100 MHz, $CDCl_3$) for 7c



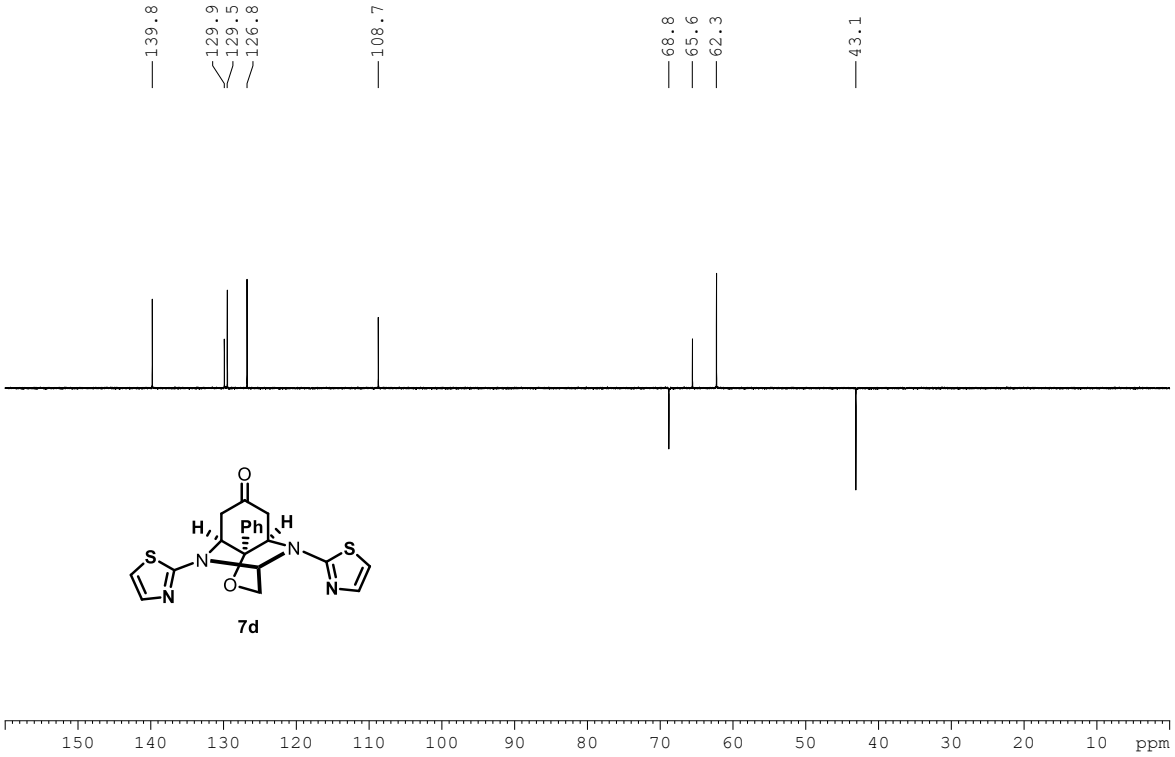
^{1}H NMR (400 MHz, $CDCl_3$) for 7d



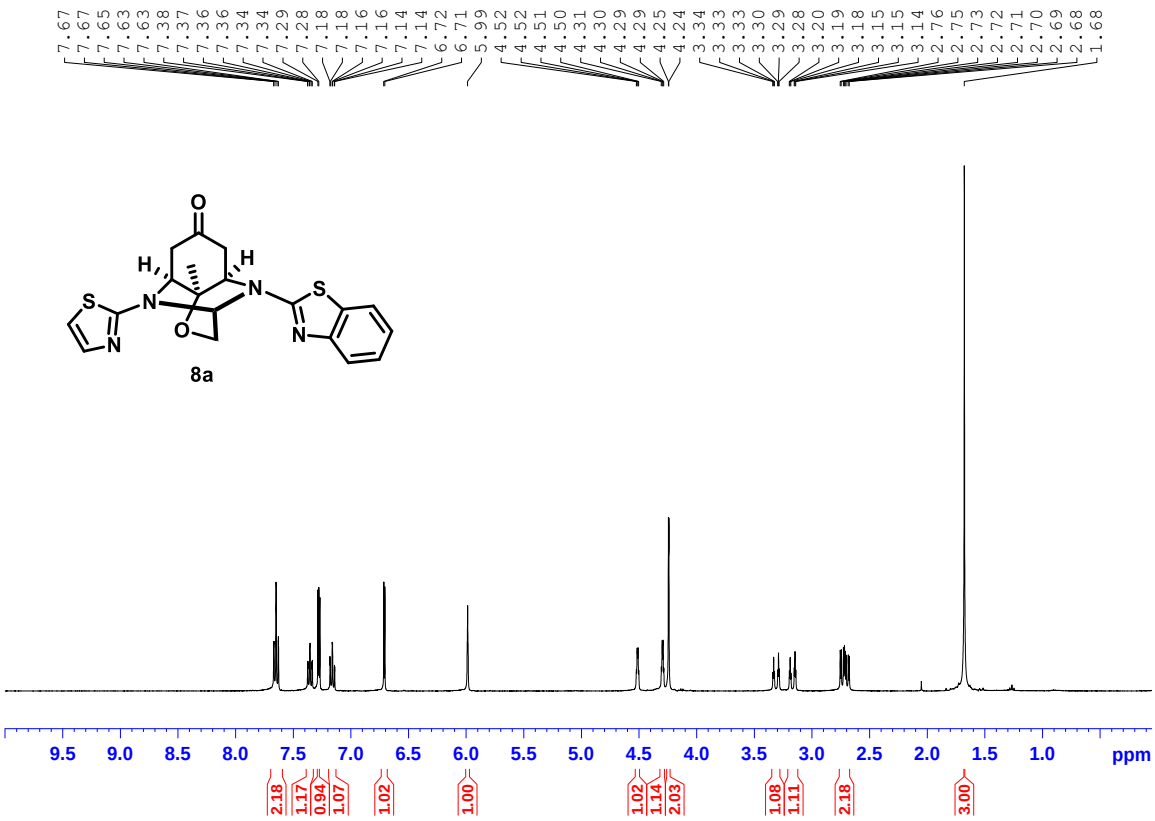
^{13}C NMR (100 MHz, $CDCl_3$) for 7d



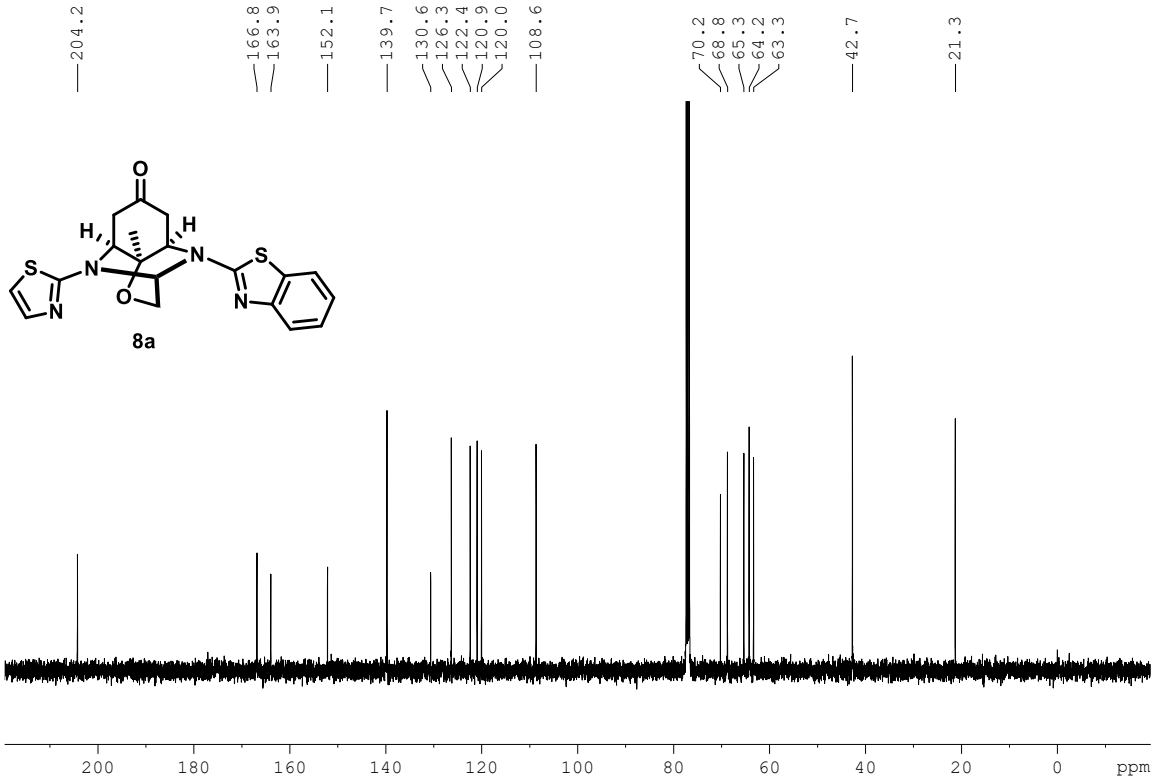
DEPT (100 MHz, $CDCl_3$) for 7d



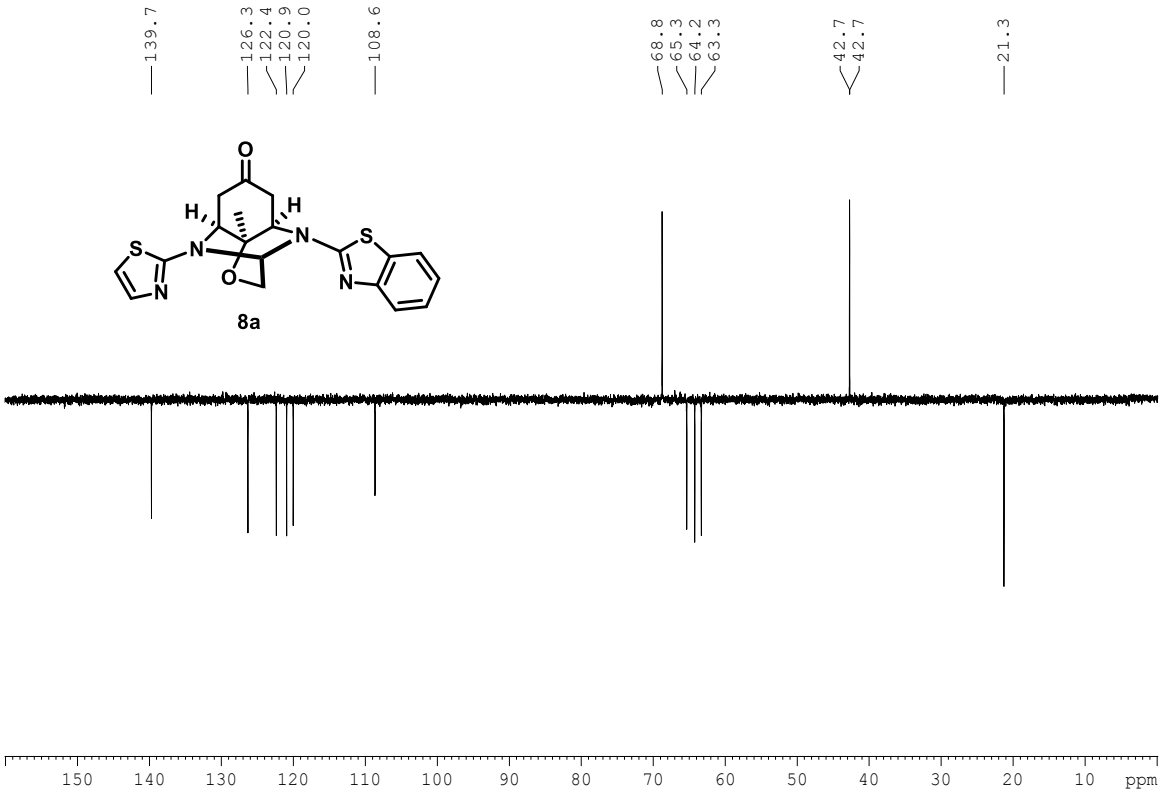
^{1}H NMR (400 MHz, $CDCl_3$) for 8a



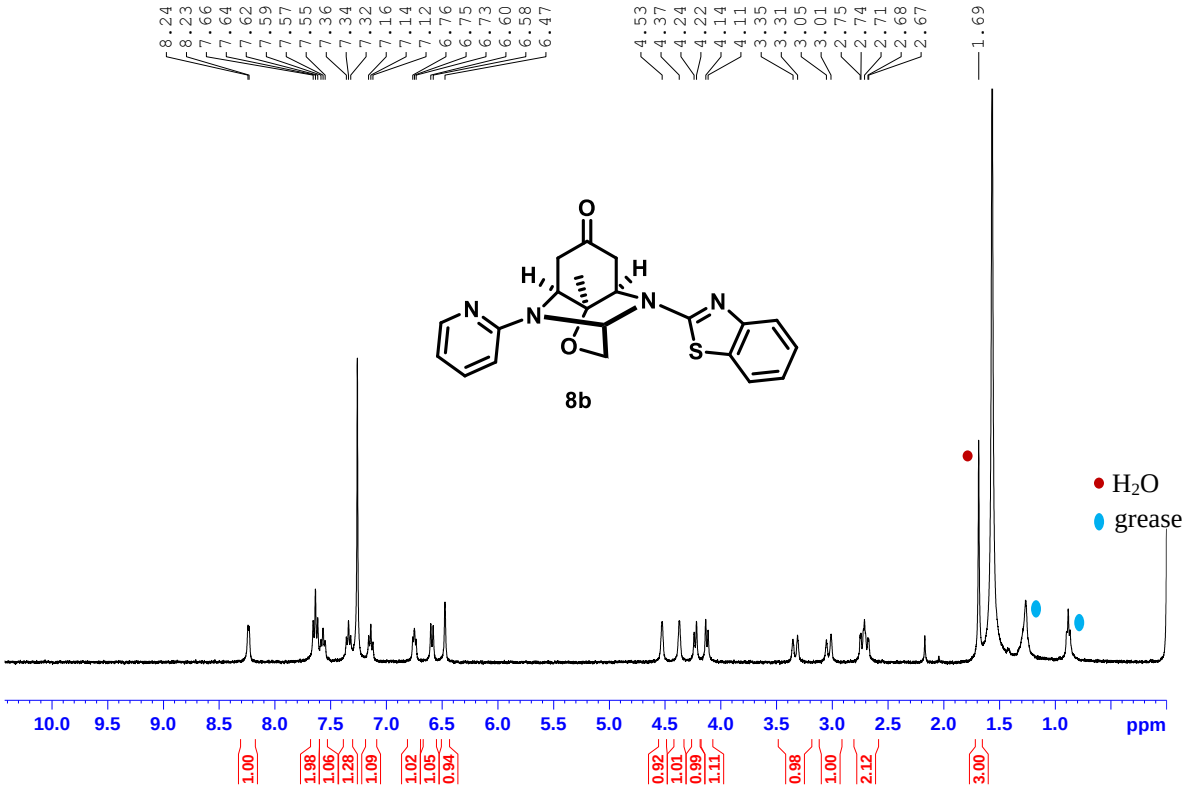
^{13}C NMR (100 MHz, $CDCl_3$) for 8a



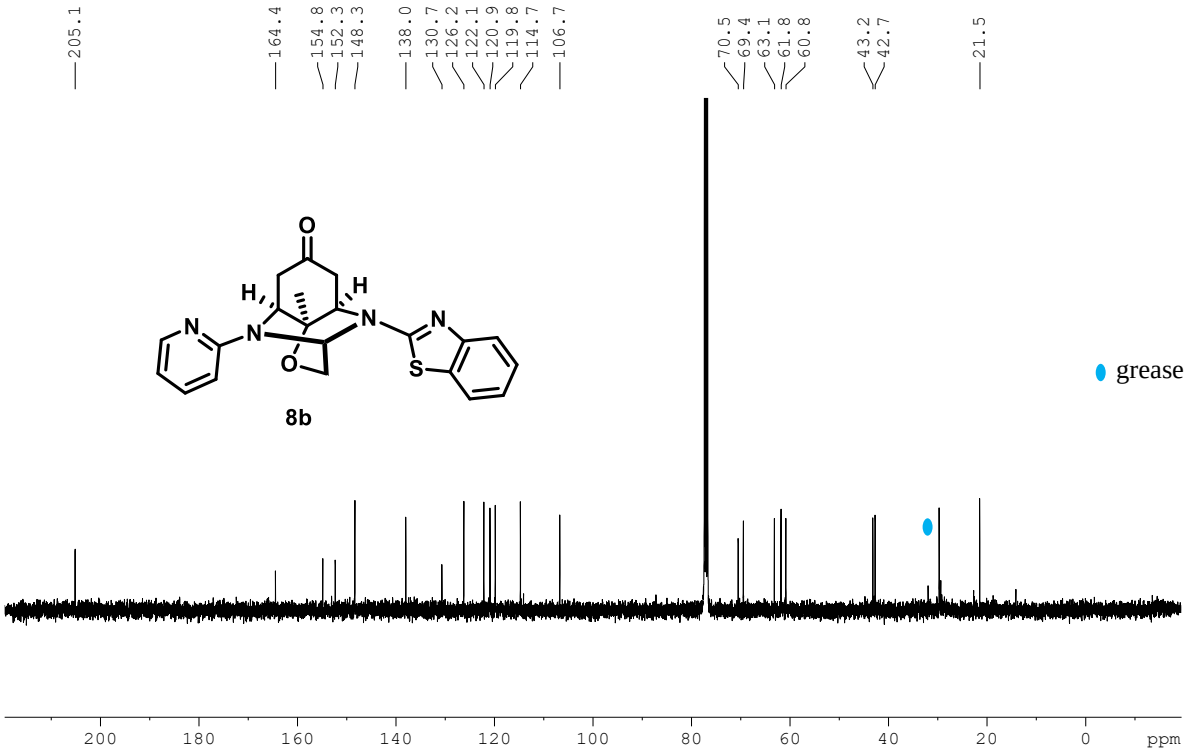
DEPT (100 MHz, $CDCl_3$) for 8a



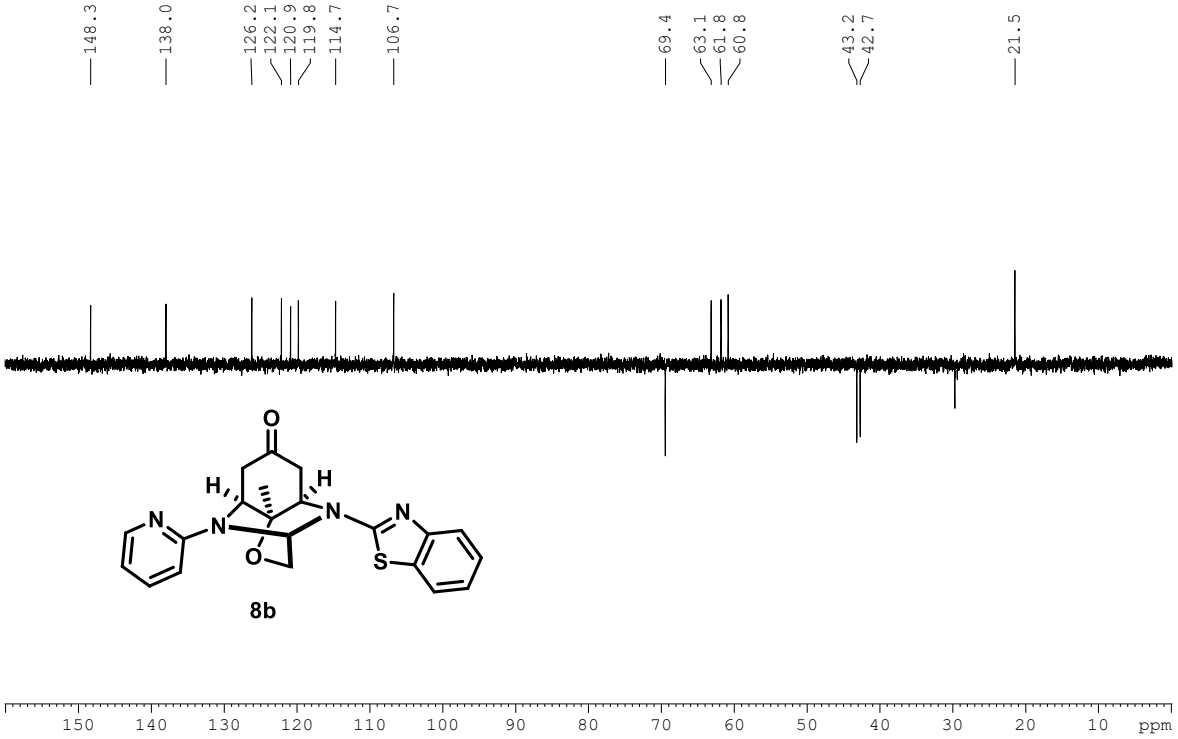
^{1}H NMR (400 MHz, $CDCl_3$) for 8b



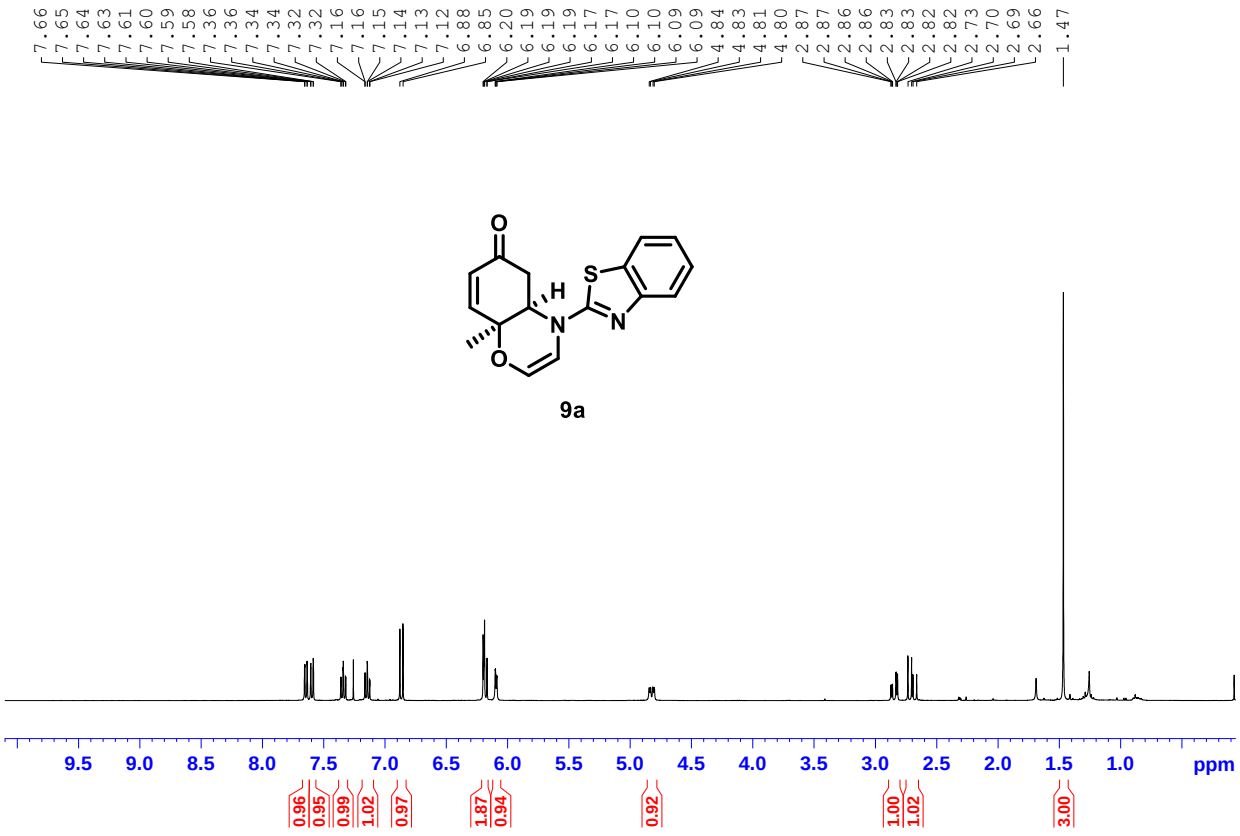
^{13}C NMR (100 MHz, $CDCl_3$) for 8b



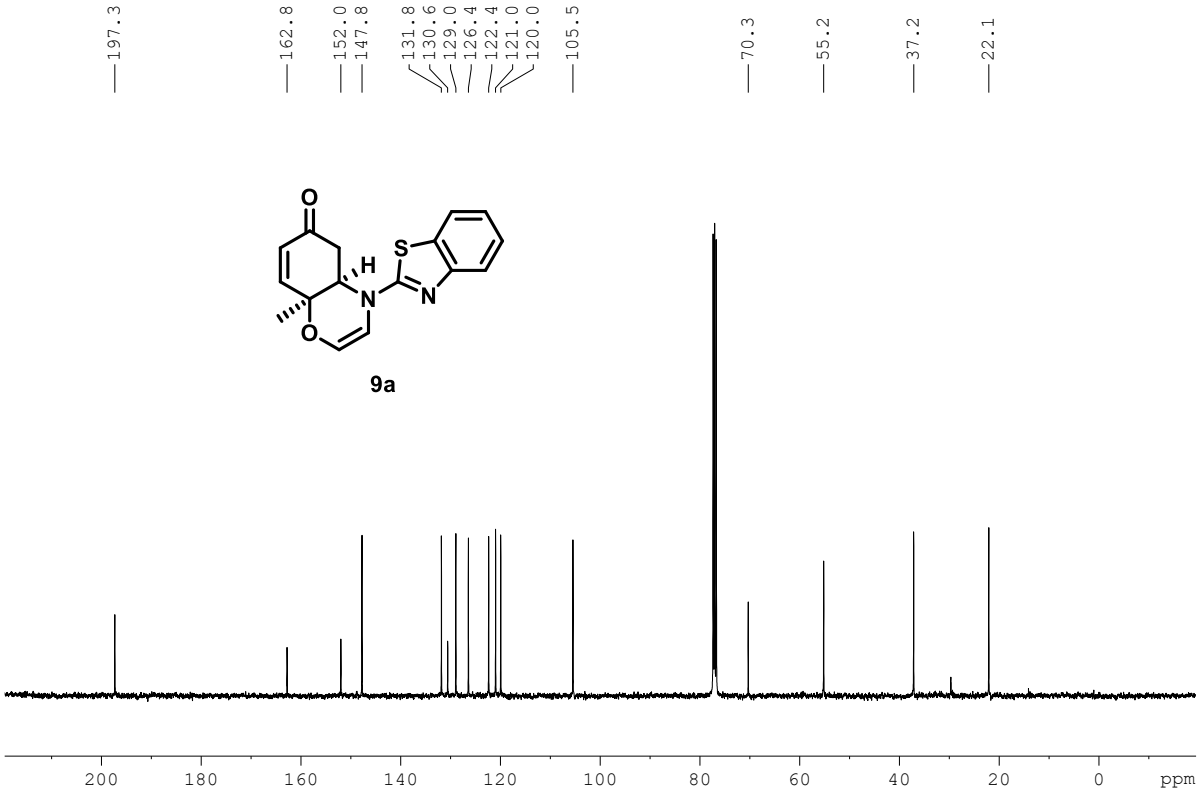
DEPT (100 MHz, $CDCl_3$) for 8b



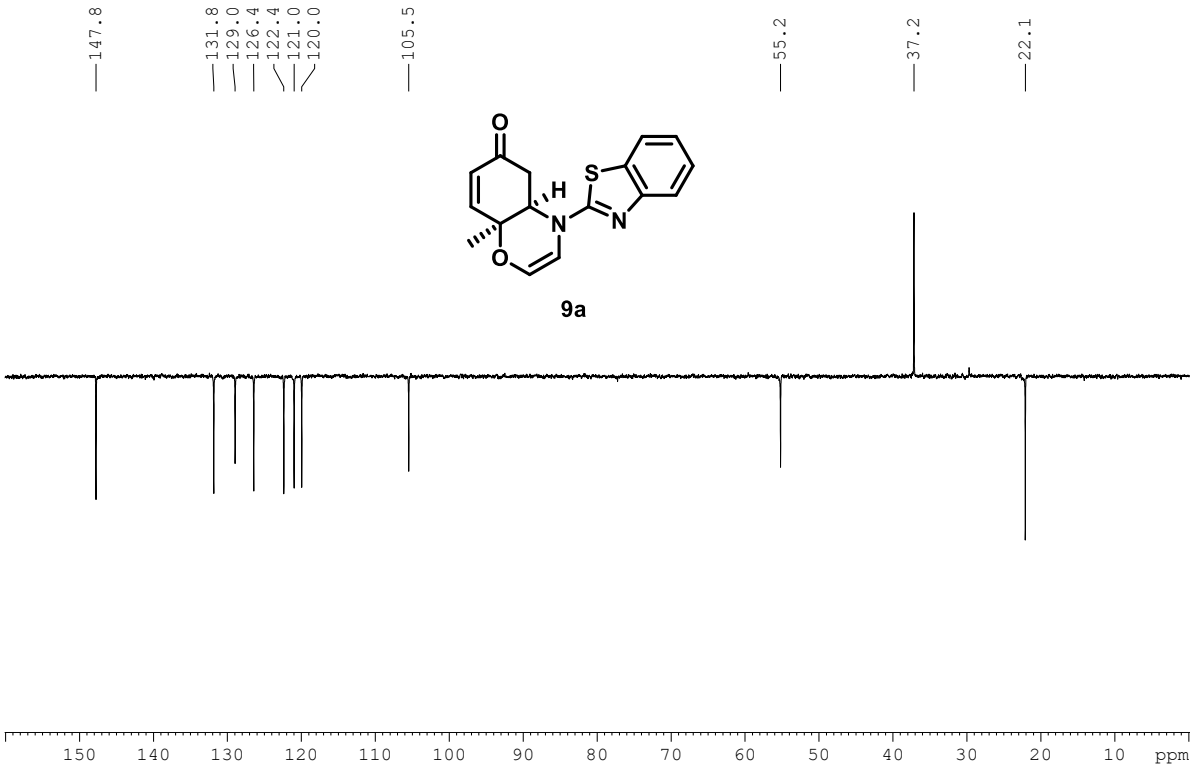
^{1}H NMR (400 MHz, $CDCl_3$) for 9a



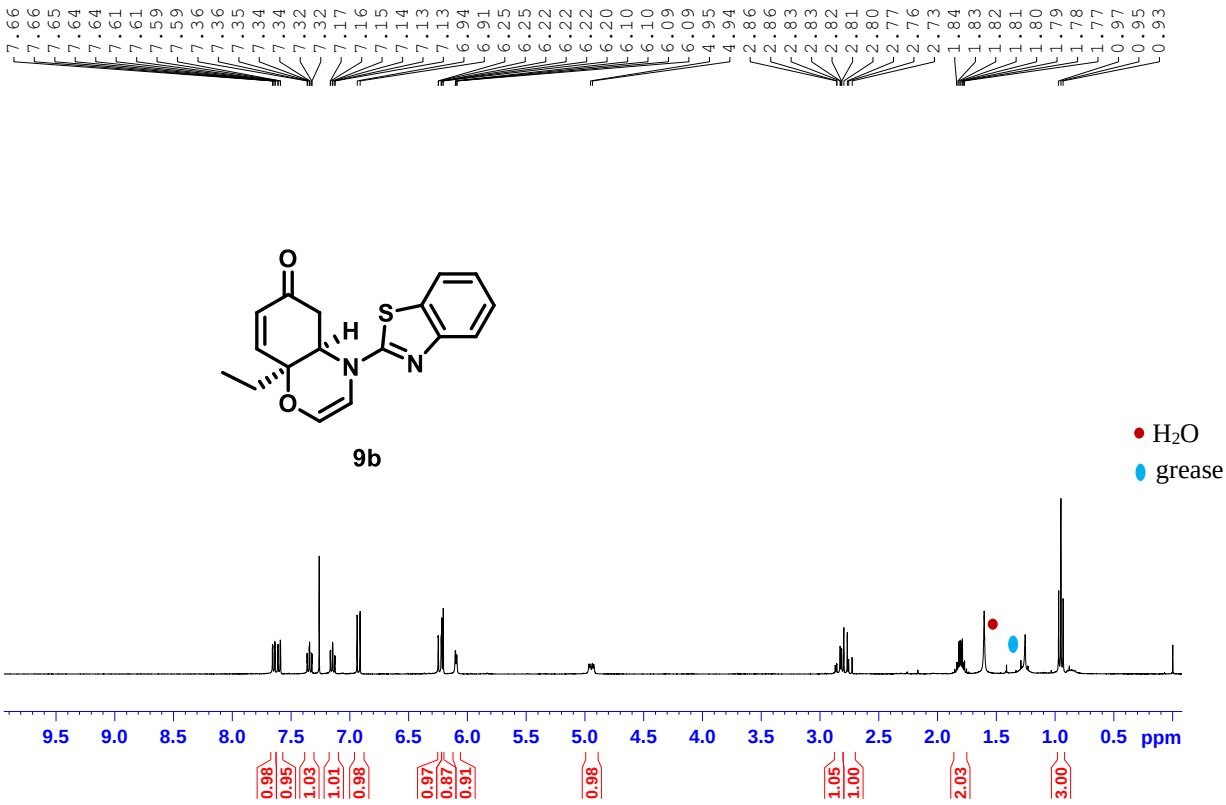
^{13}C NMR (100 MHz, $CDCl_3$) for 9a



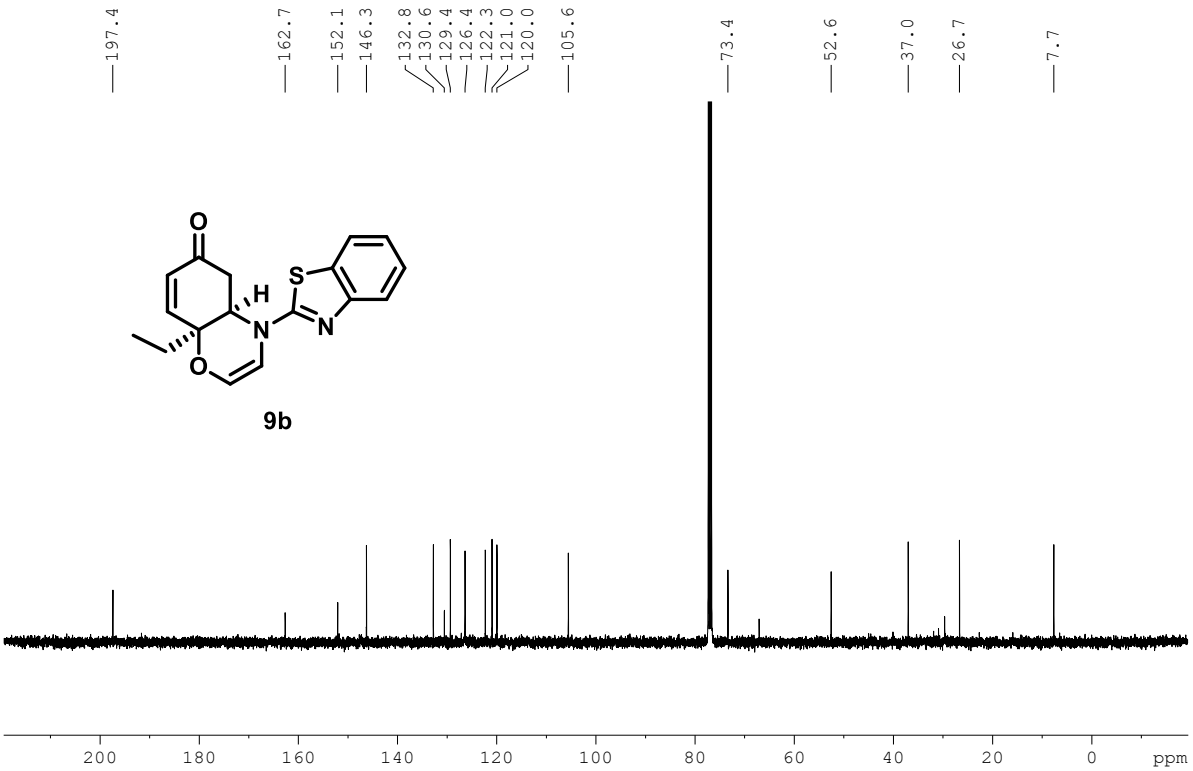
DEPT (100 MHz, $CDCl_3$) for 9a



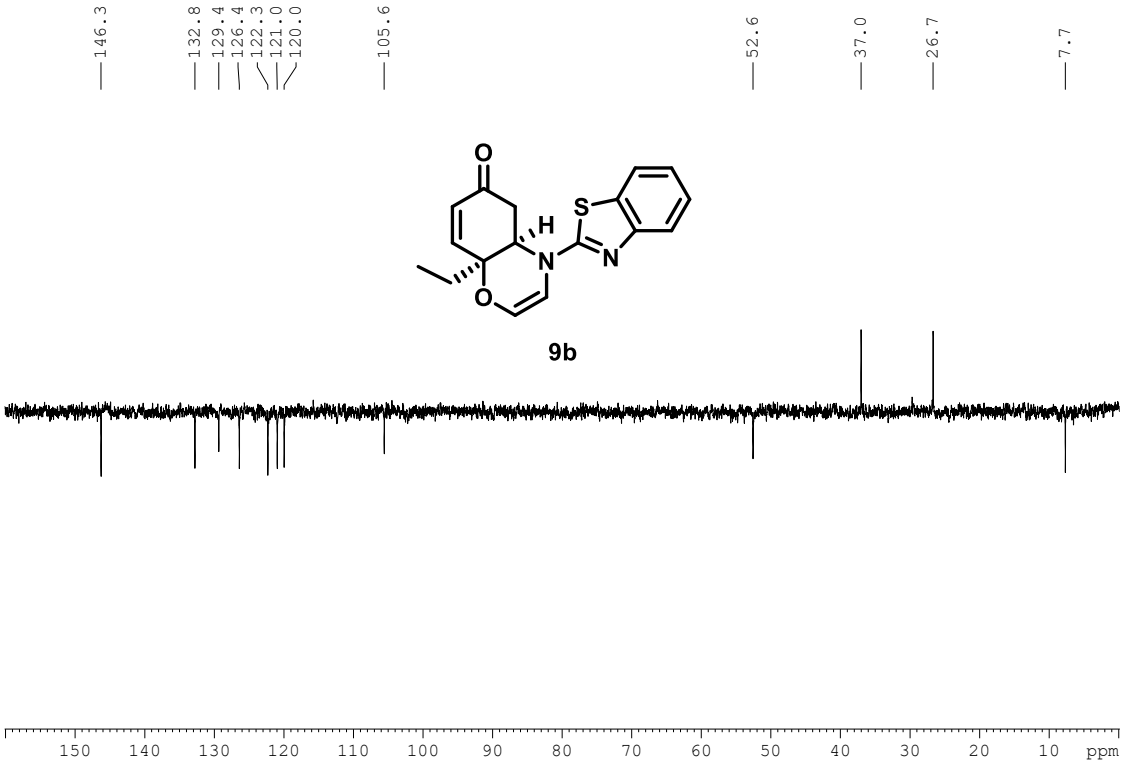
^{1}H NMR (400 MHz, $CDCl_3$) for 9b



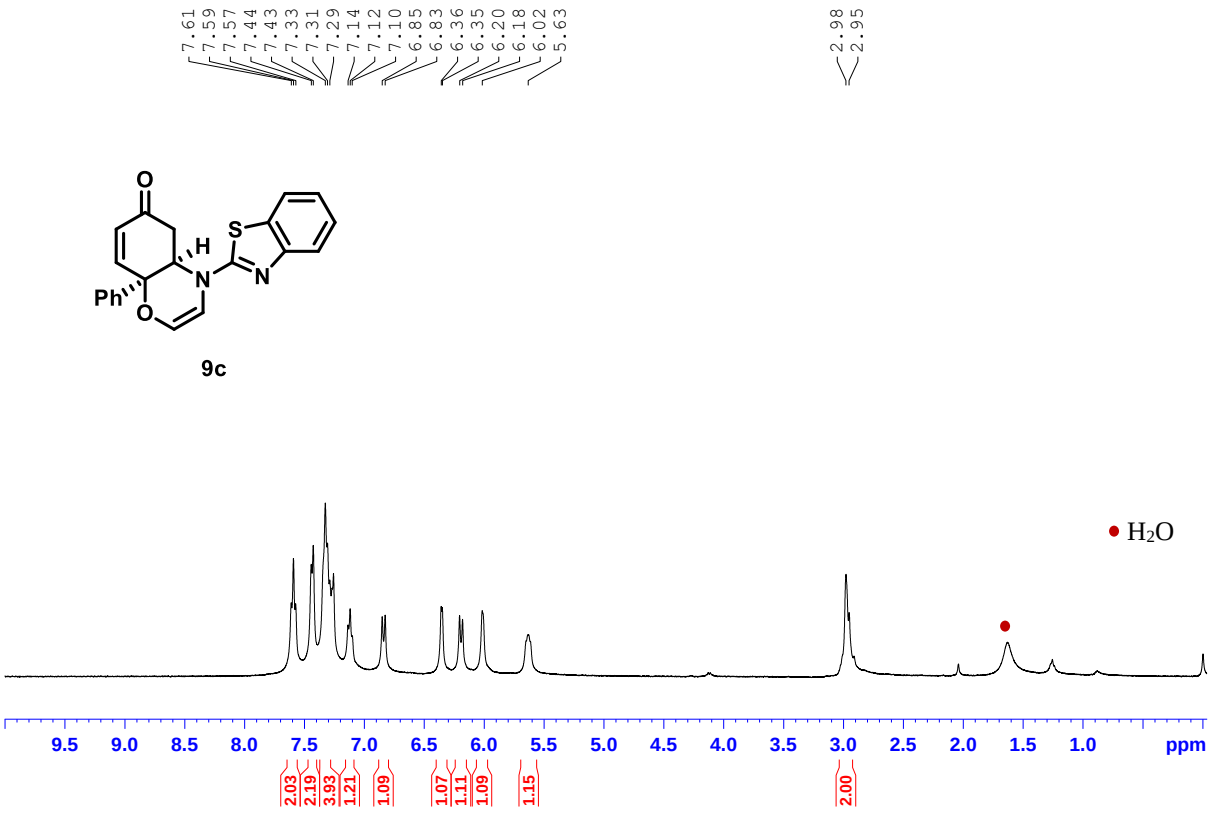
^{13}C NMR (100 MHz, $CDCl_3$) for 9b



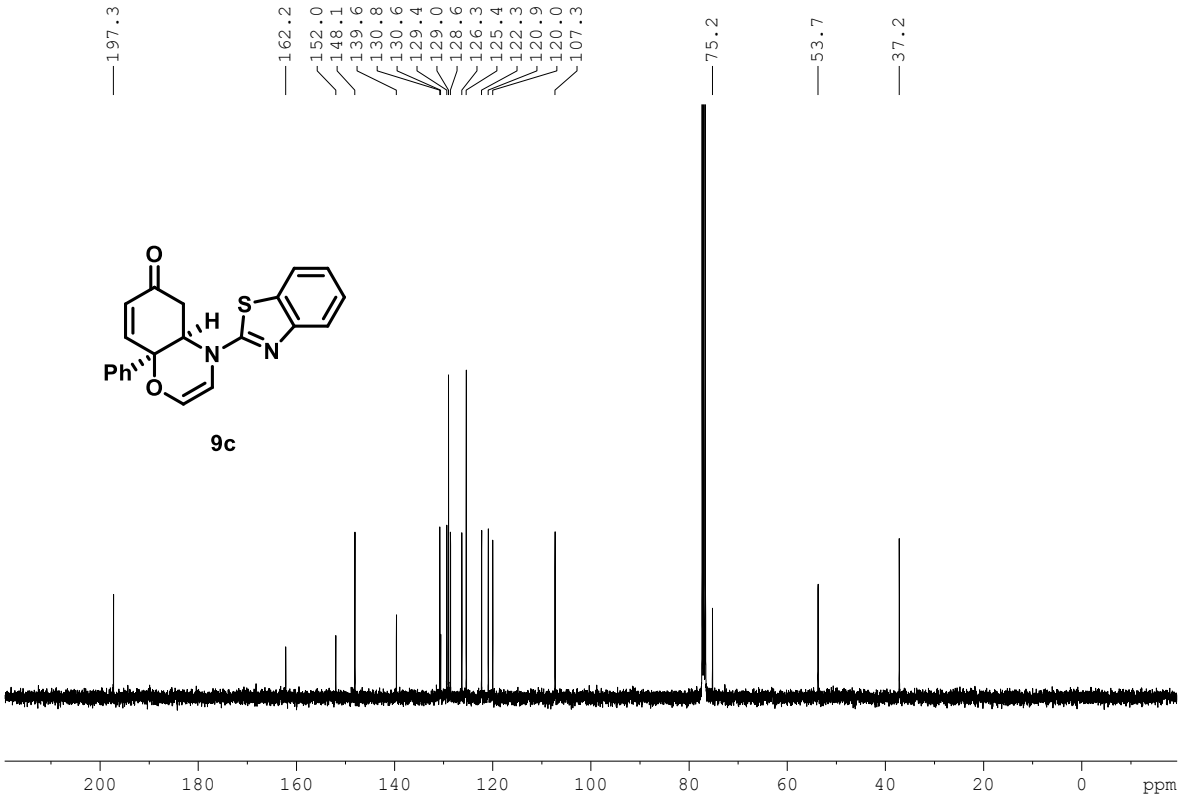
DEPT (100 MHz, $CDCl_3$) for 9b



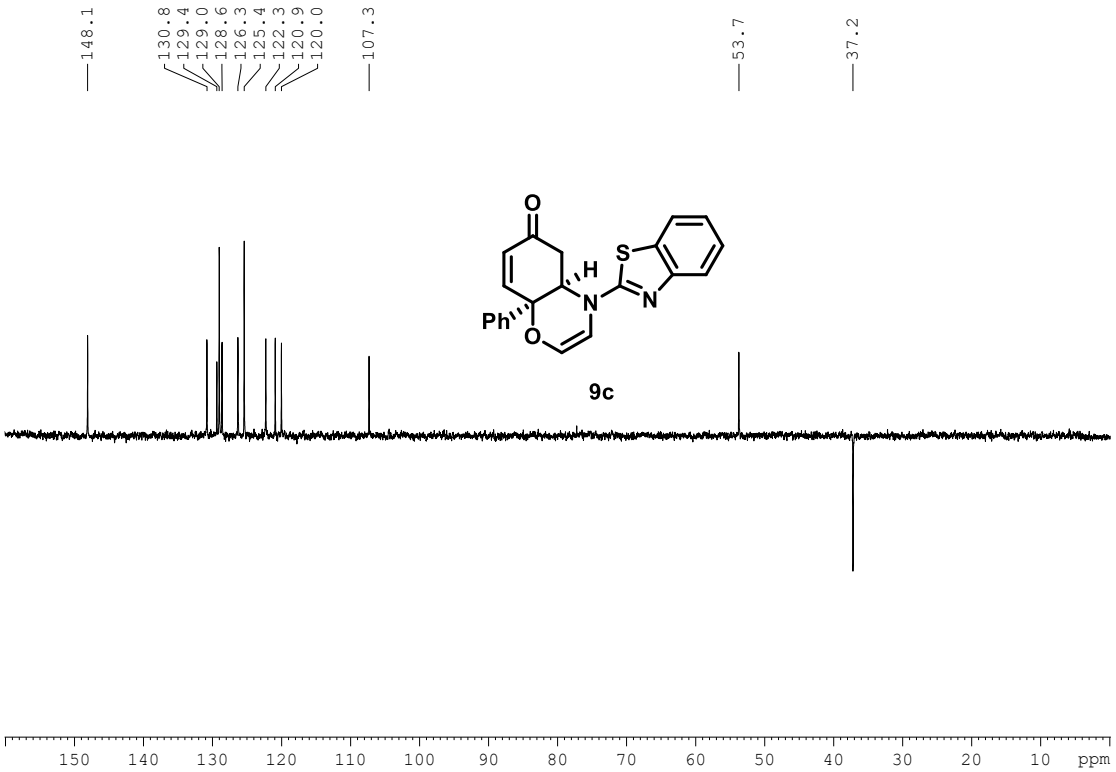
^{1}H NMR (400 MHz, $CDCl_3$) for 9c



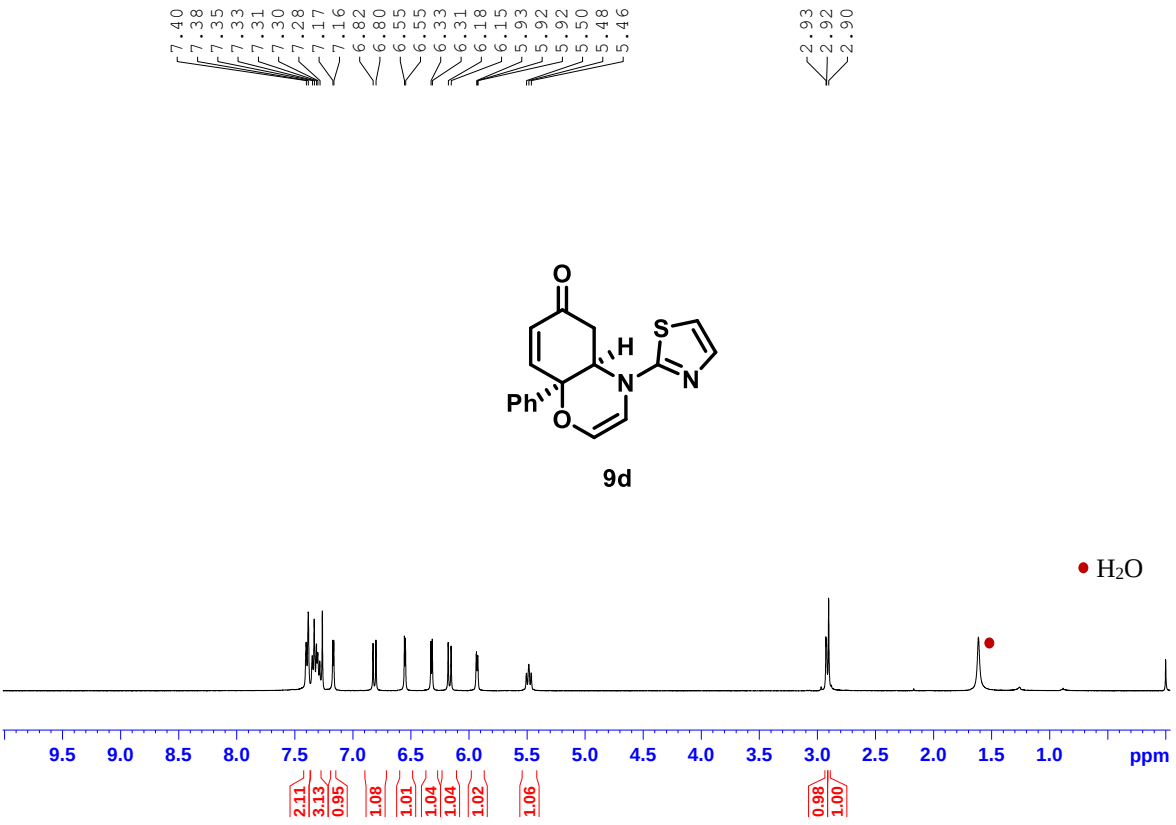
^{13}C NMR (100 MHz, $CDCl_3$) for 9c



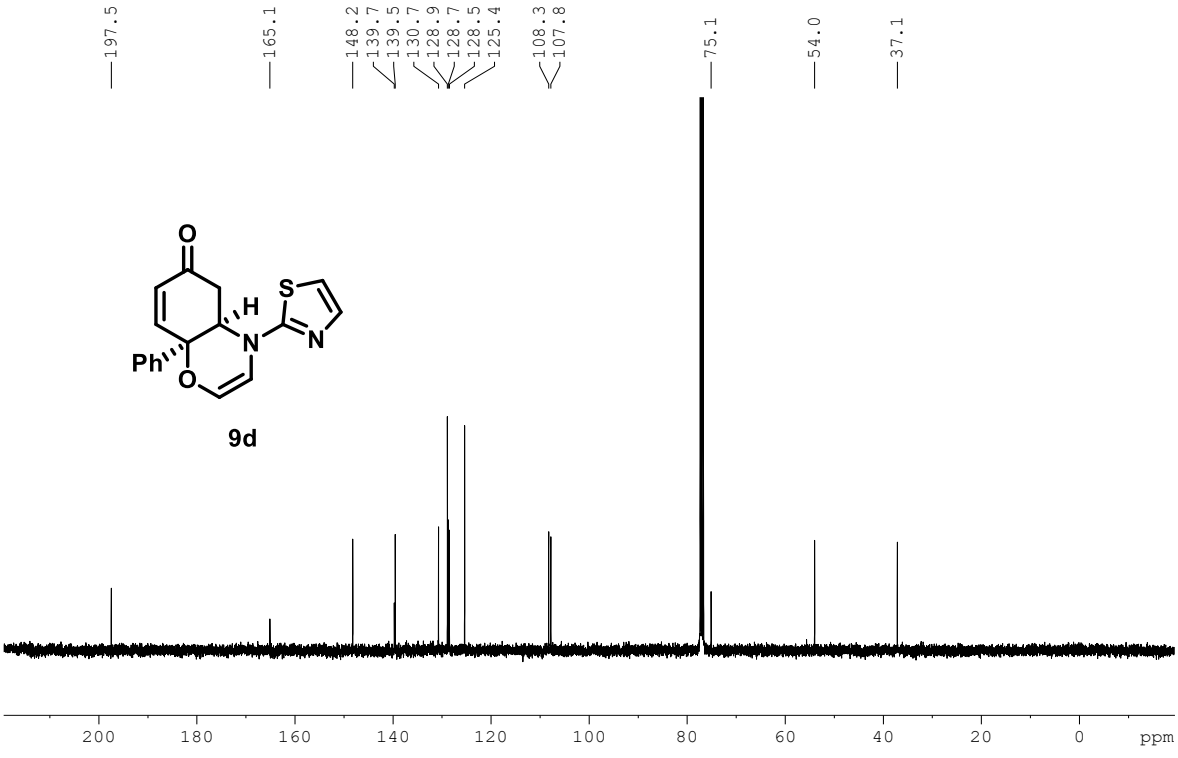
DEPT (100 MHz, $CDCl_3$) for 9c



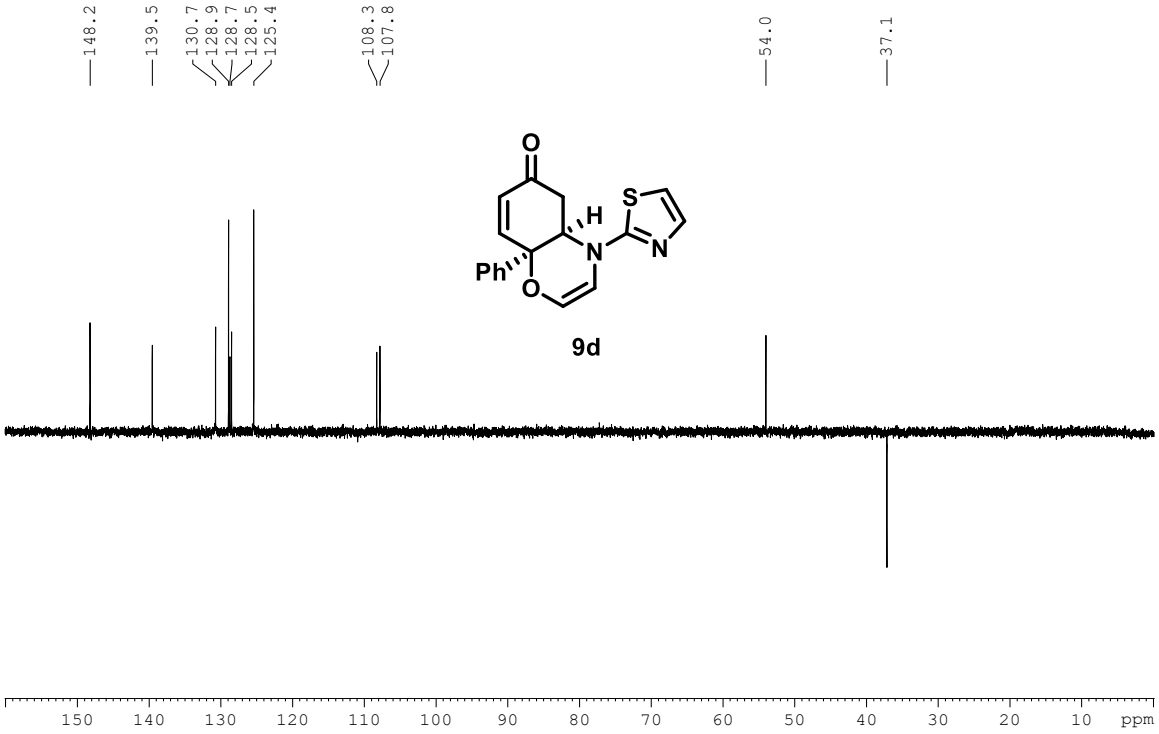
^{1}H NMR (400 MHz, $CDCl_3$) for 9d



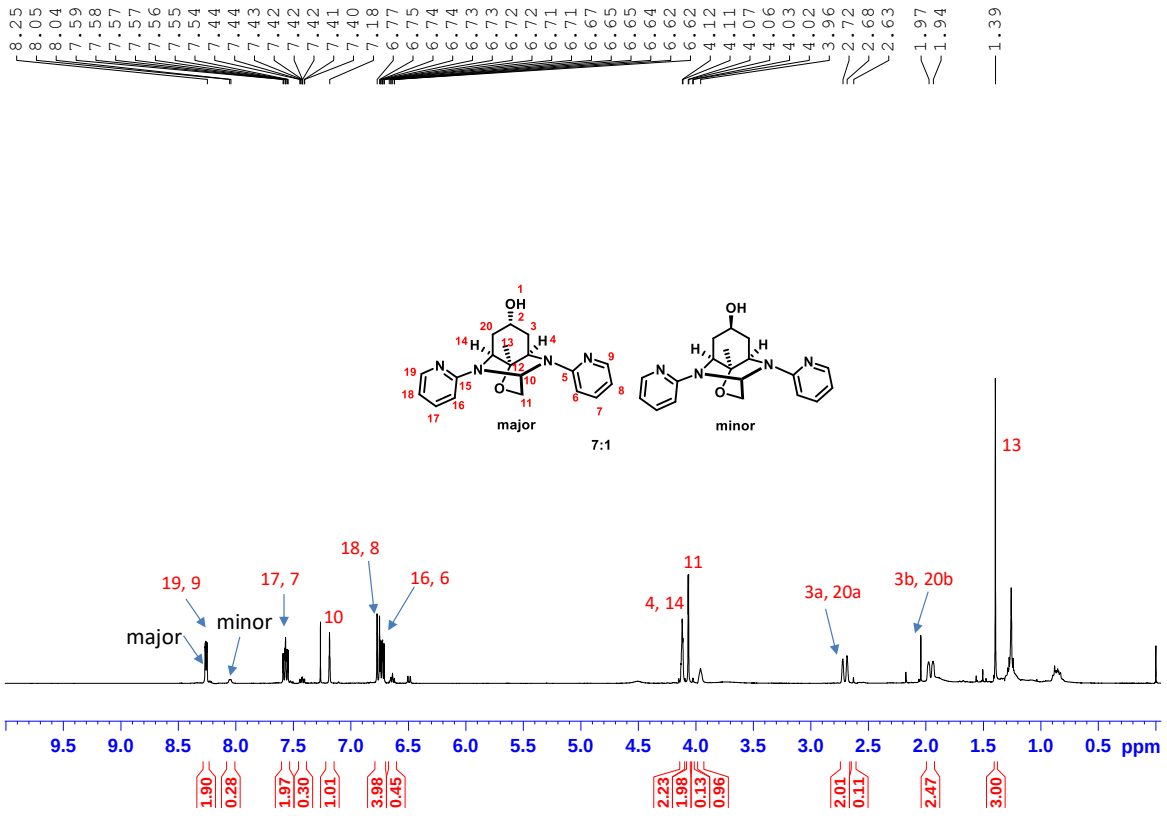
^{13}C NMR (100 MHz, $CDCl_3$) for 9d



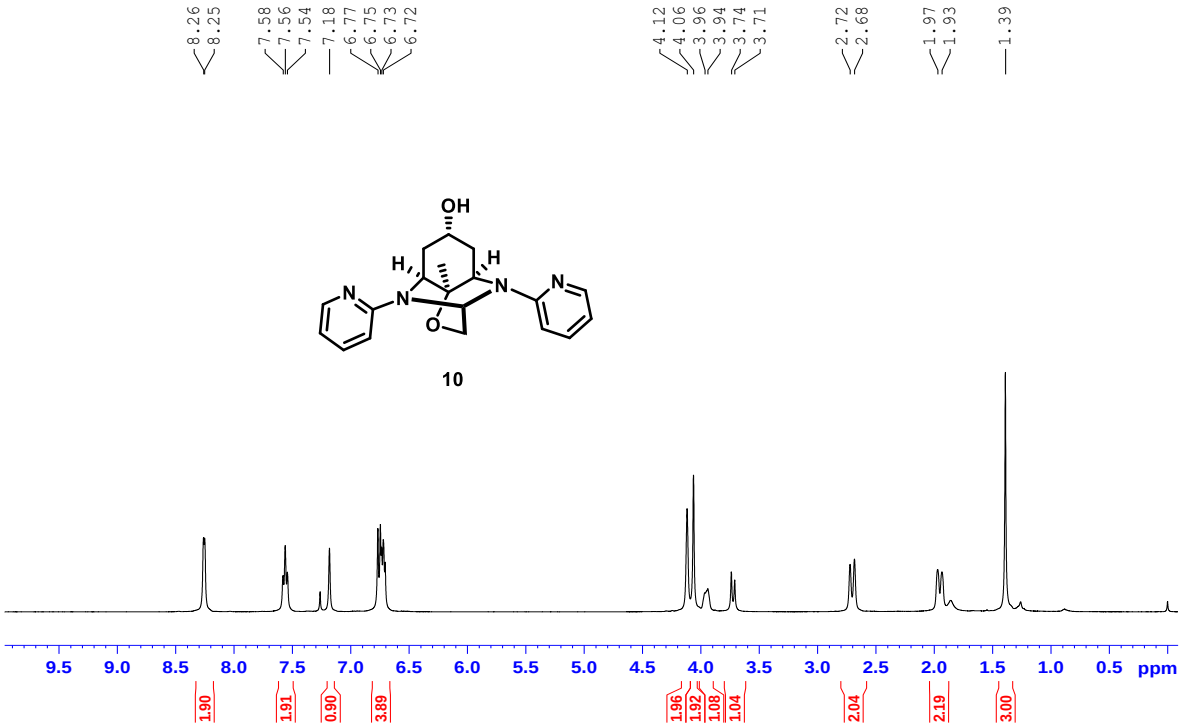
DEPT (100 MHz, $CDCl_3$) for 9d



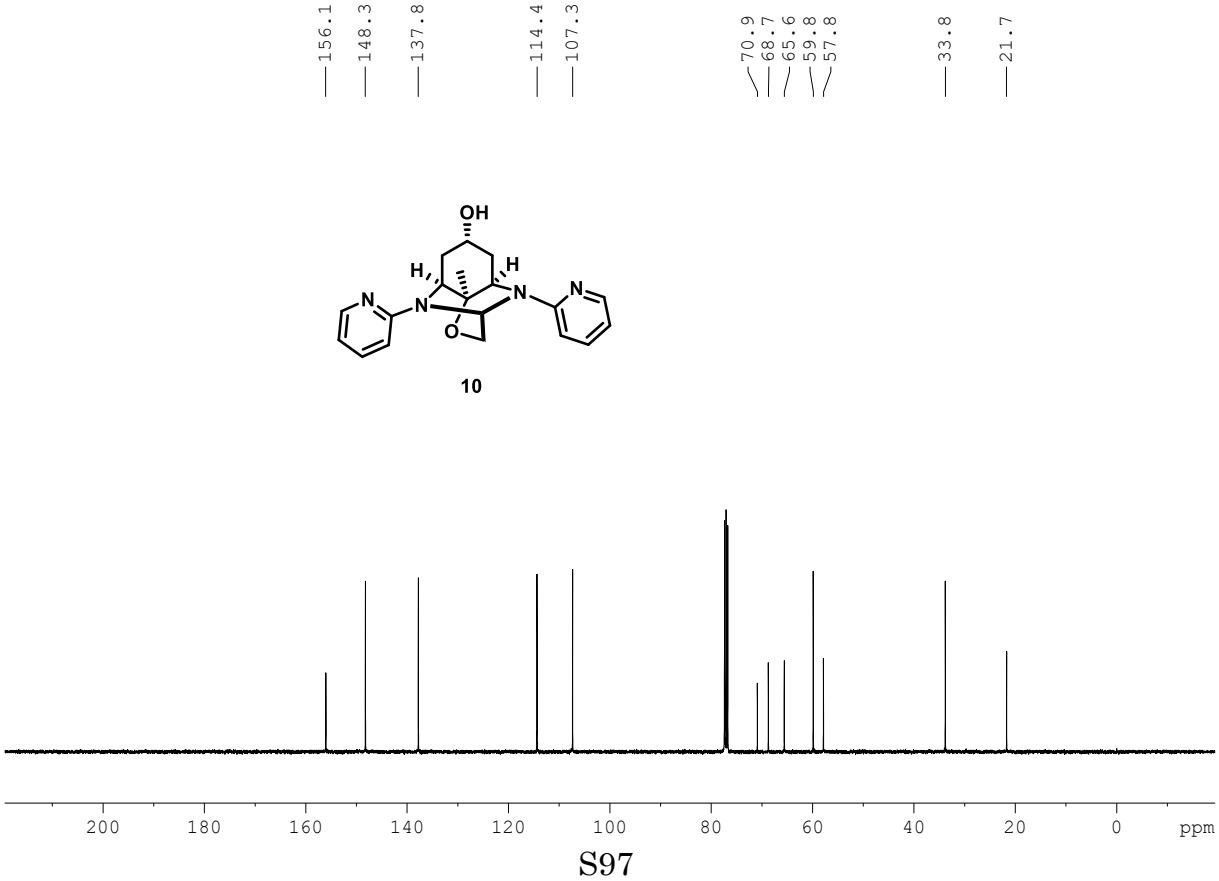
^{1}H NMR (400 MHz, $CDCl_3$) of crude reaction mixture (10)



^{1}H NMR (400 MHz, $CDCl_3$) for 10 (major diastereomer)

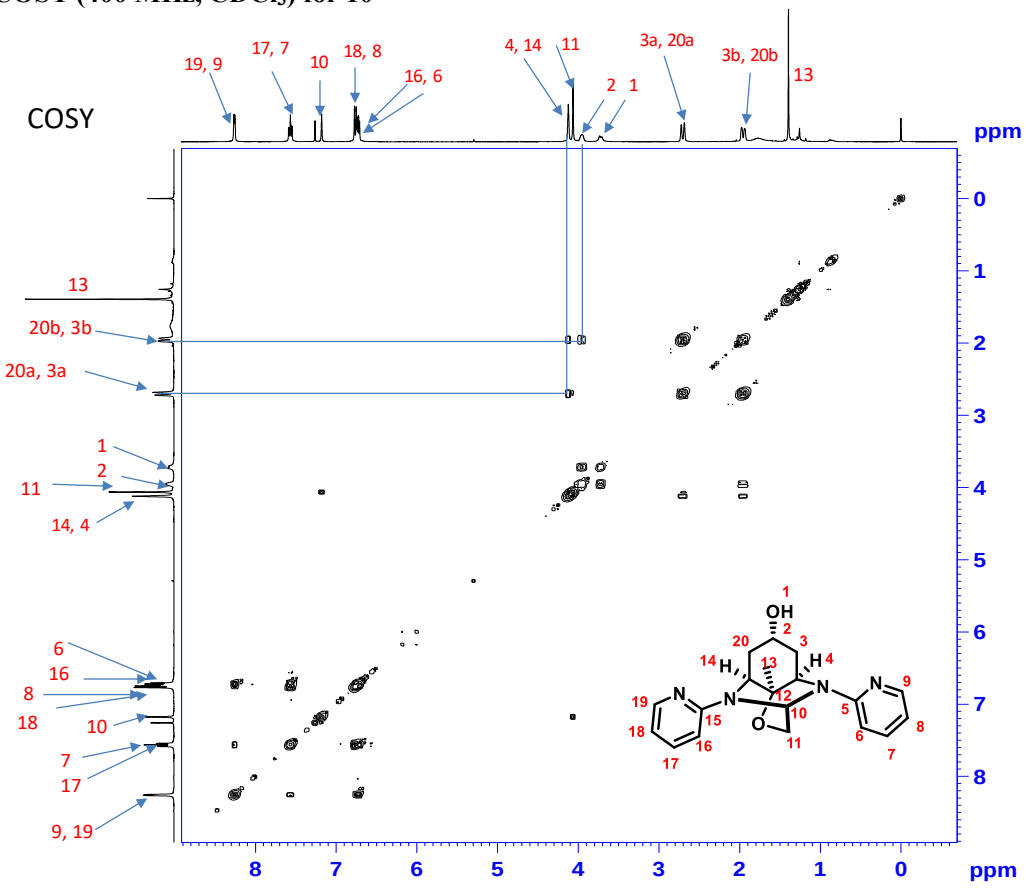


^{13}C NMR (100 MHz, $CDCl_3$) for 10

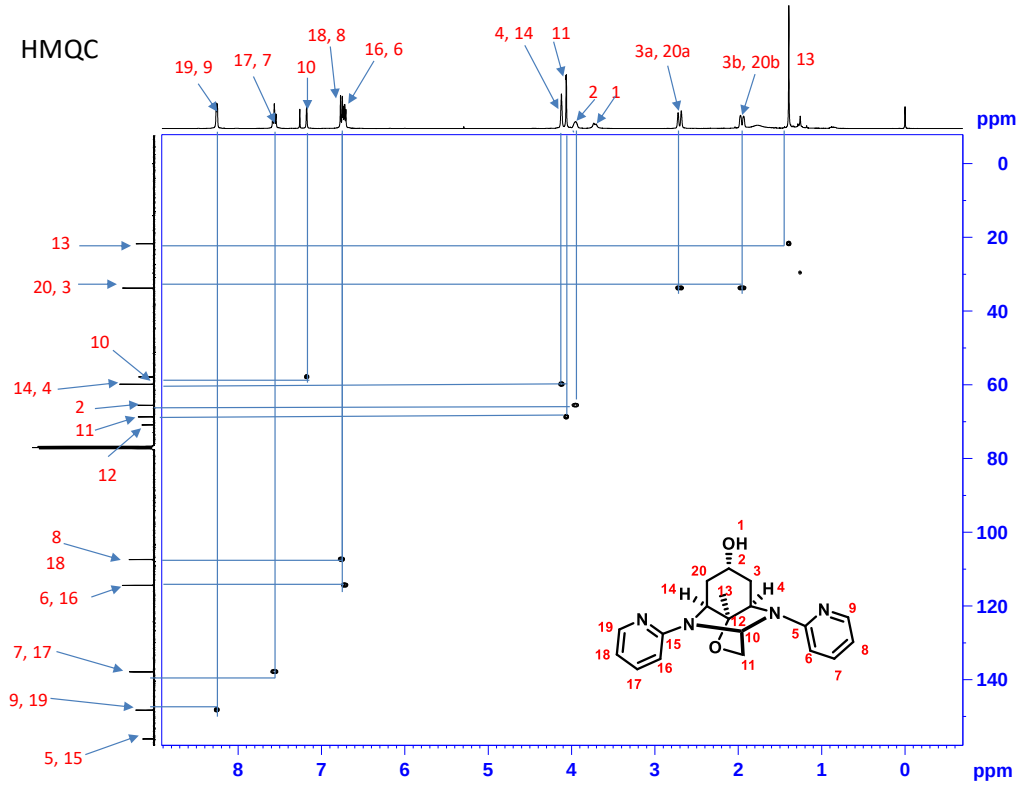


DEPT (100 MHz, $CDCl_3$) for 10

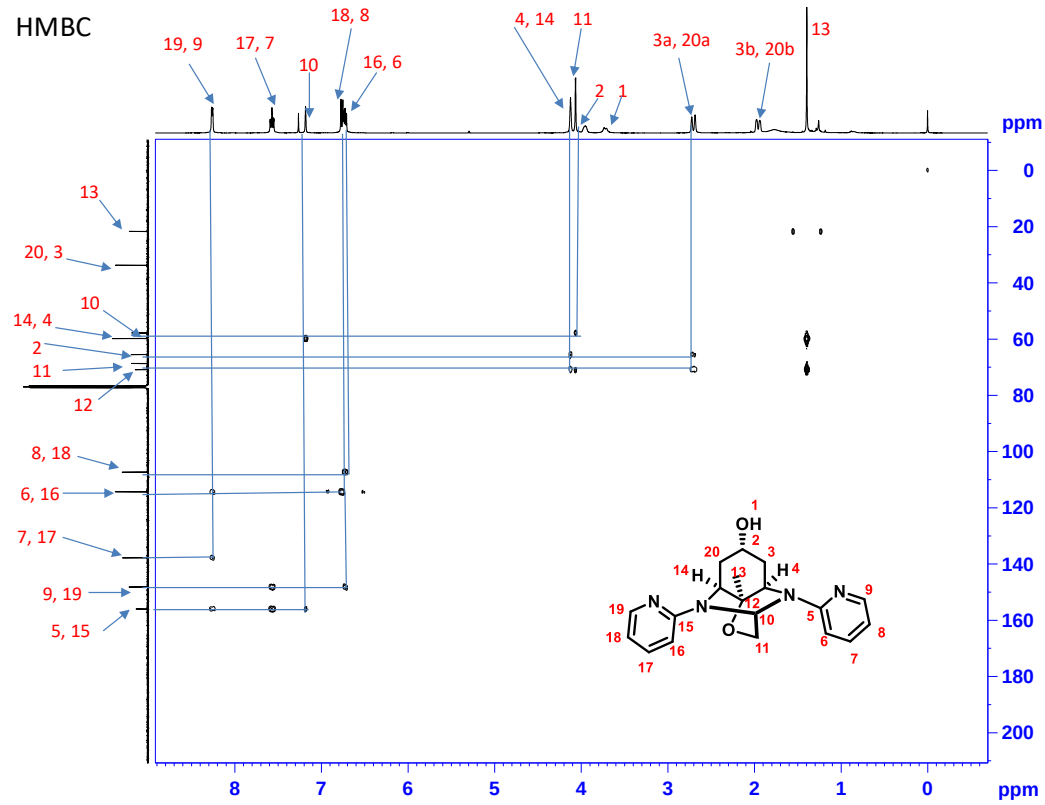
COSY (400 MHz, $CDCl_3$) for 10



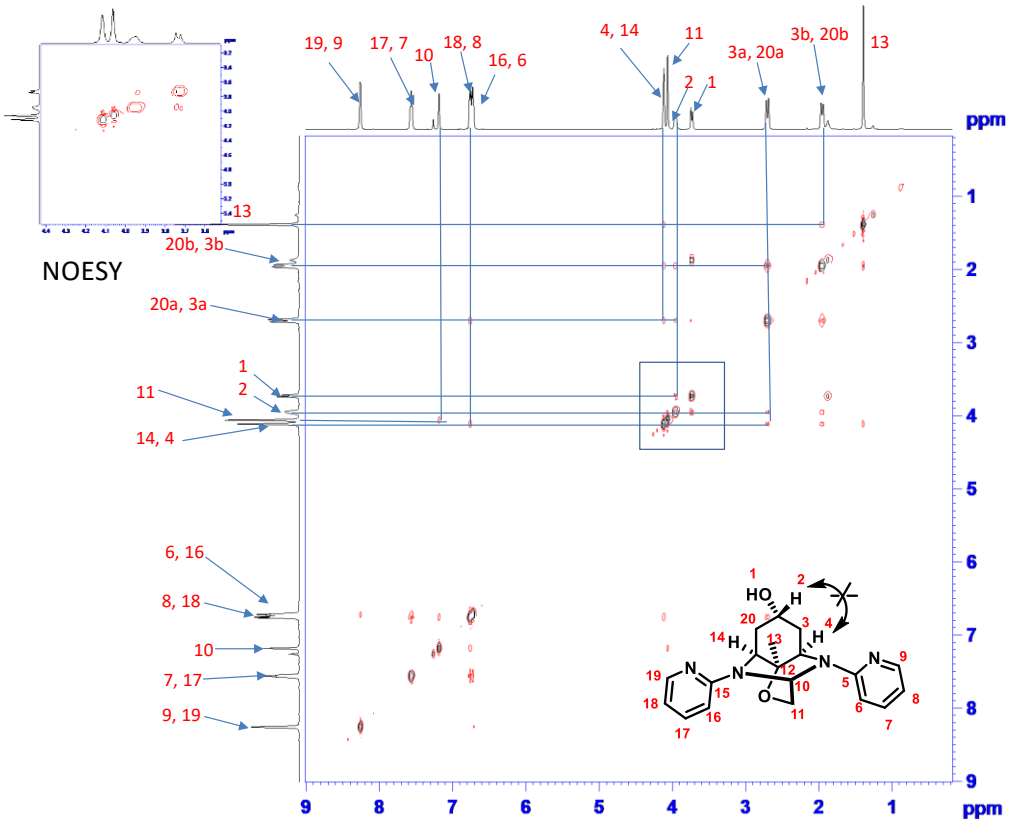
HMQC (400 MHz, $CDCl_3$) for 10



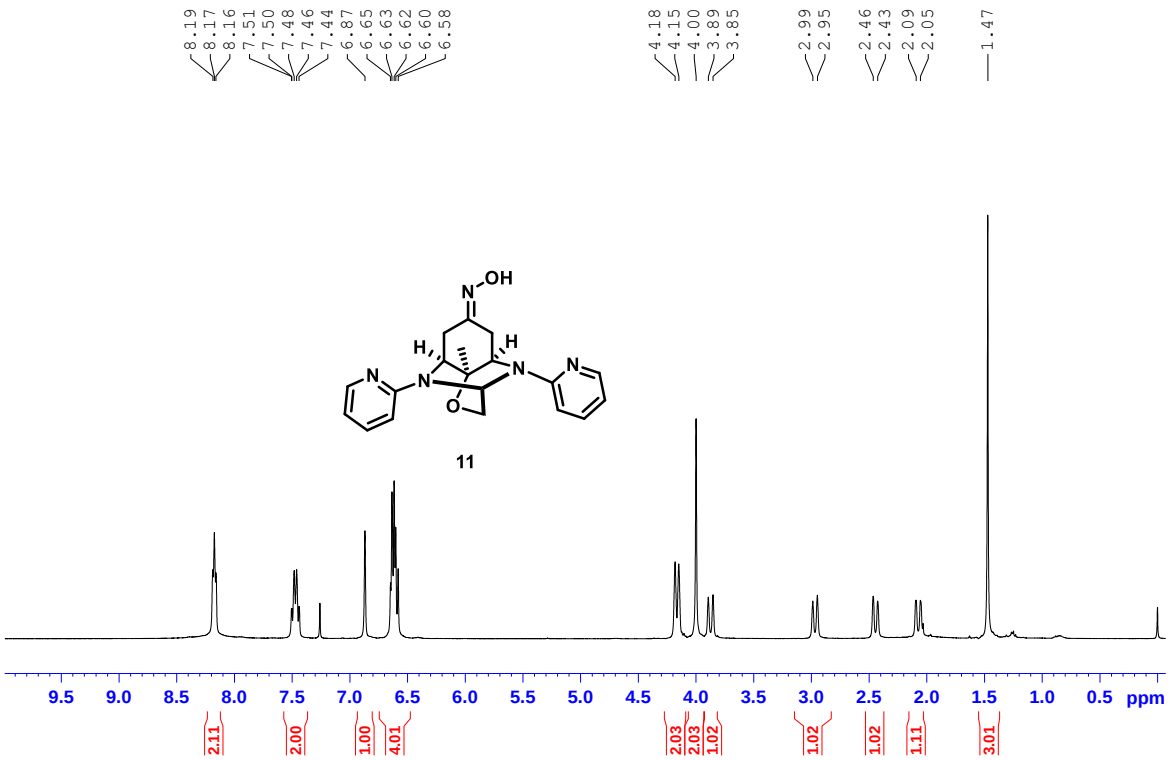
HMBC (400 MHz, $CDCl_3$) for 10



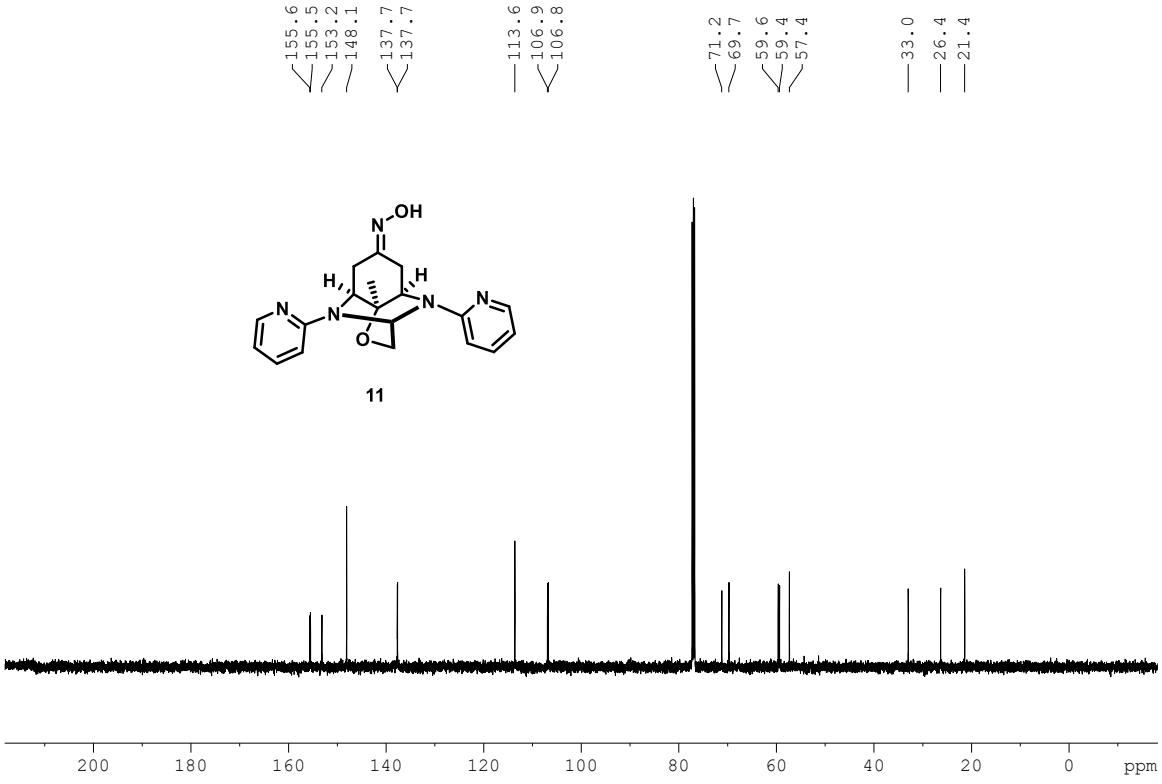
NOESY (500 MHz, $CDCl_3$) for 10



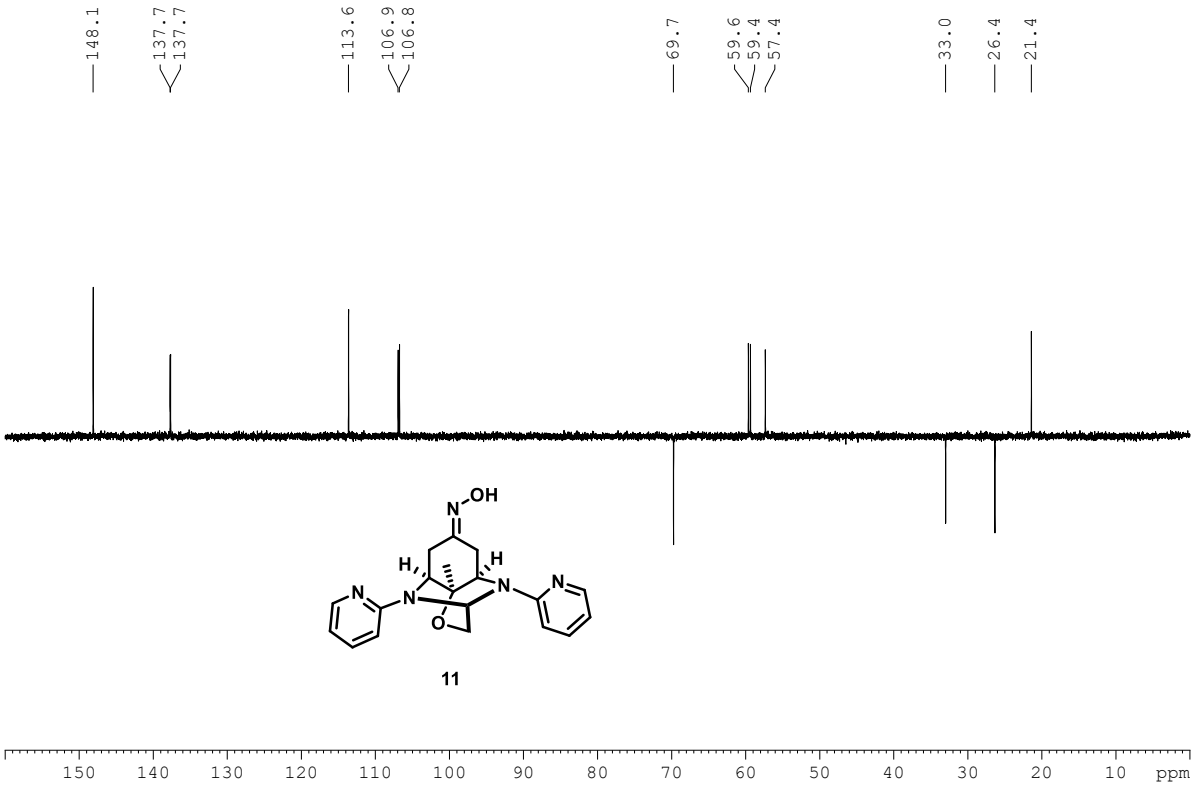
^{1}H NMR (400 MHz, $CDCl_3$) for 11



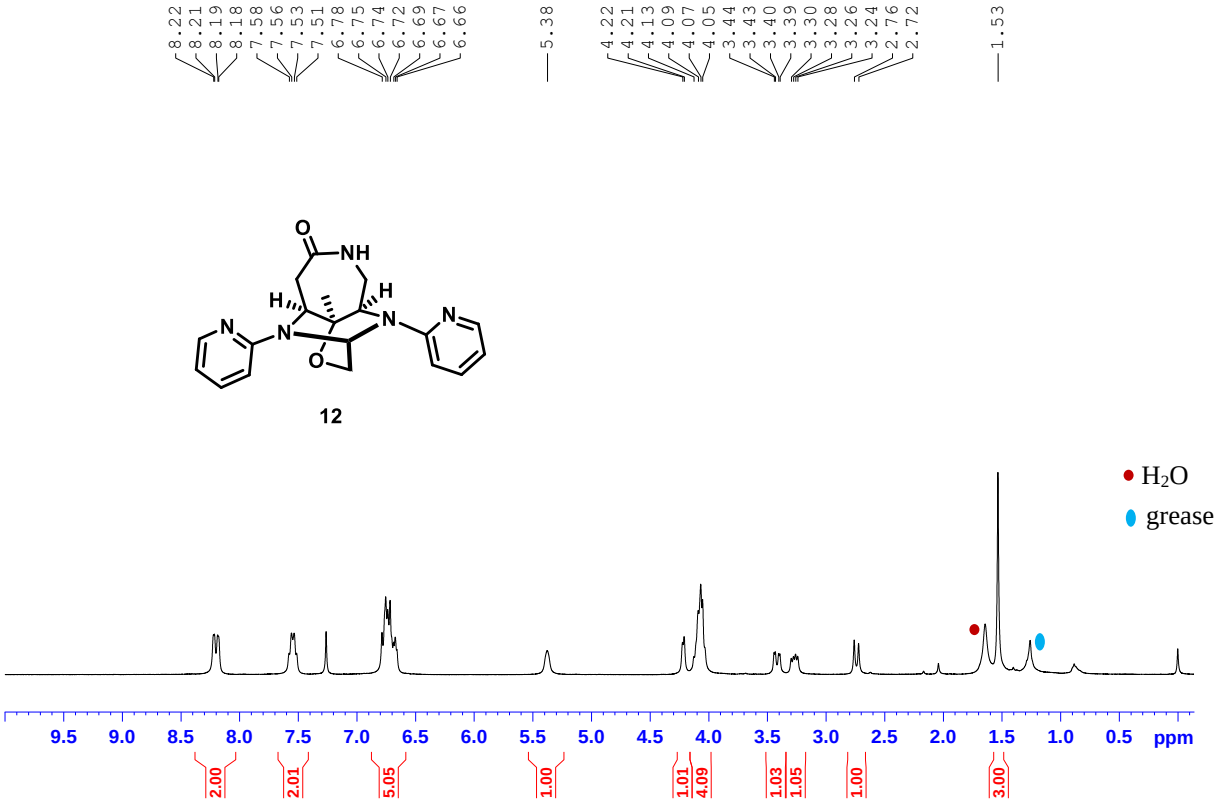
^{13}C NMR (100 MHz, $CDCl_3$) for 11



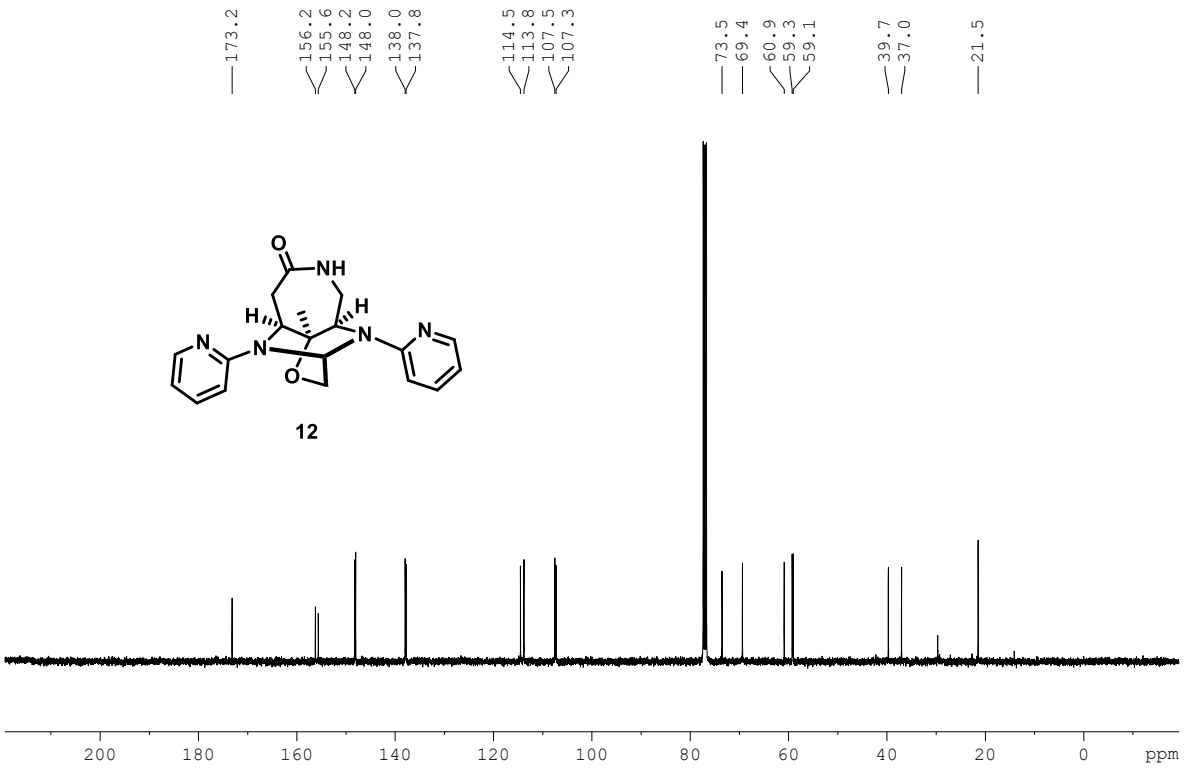
DEPT (100 MHz, $CDCl_3$) for 11



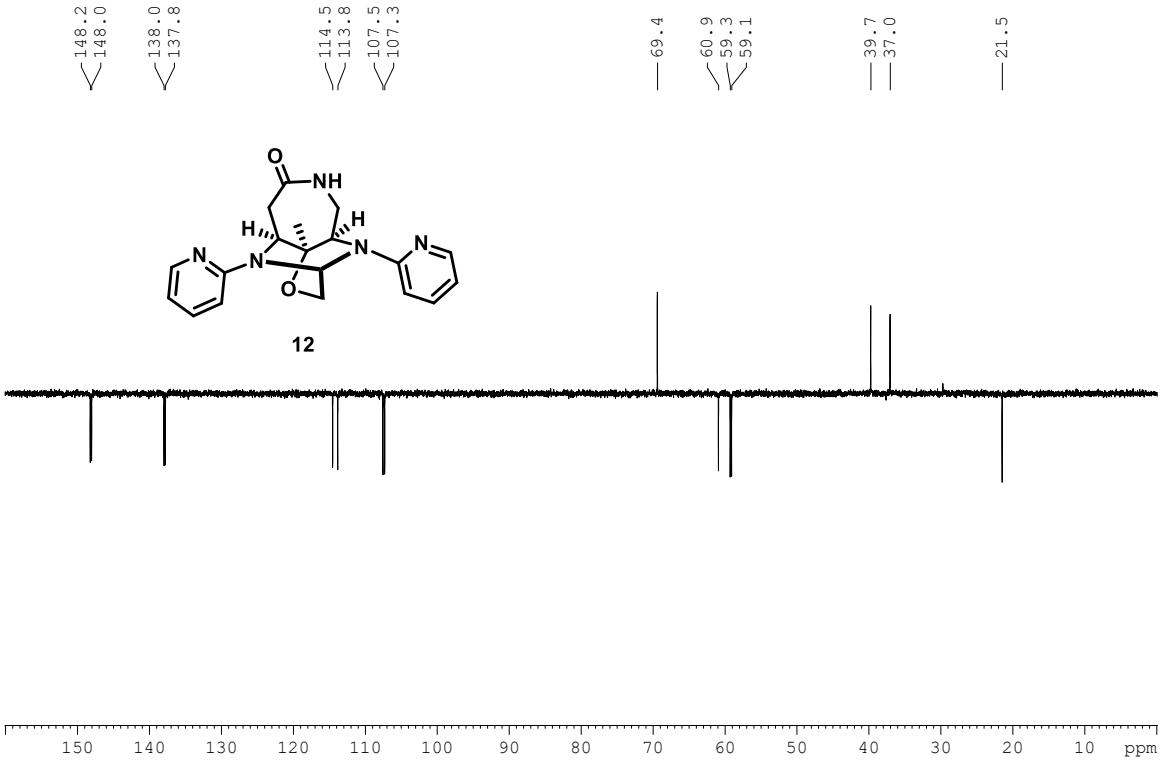
^{1}H NMR (400 MHz, $CDCl_3$) for 12



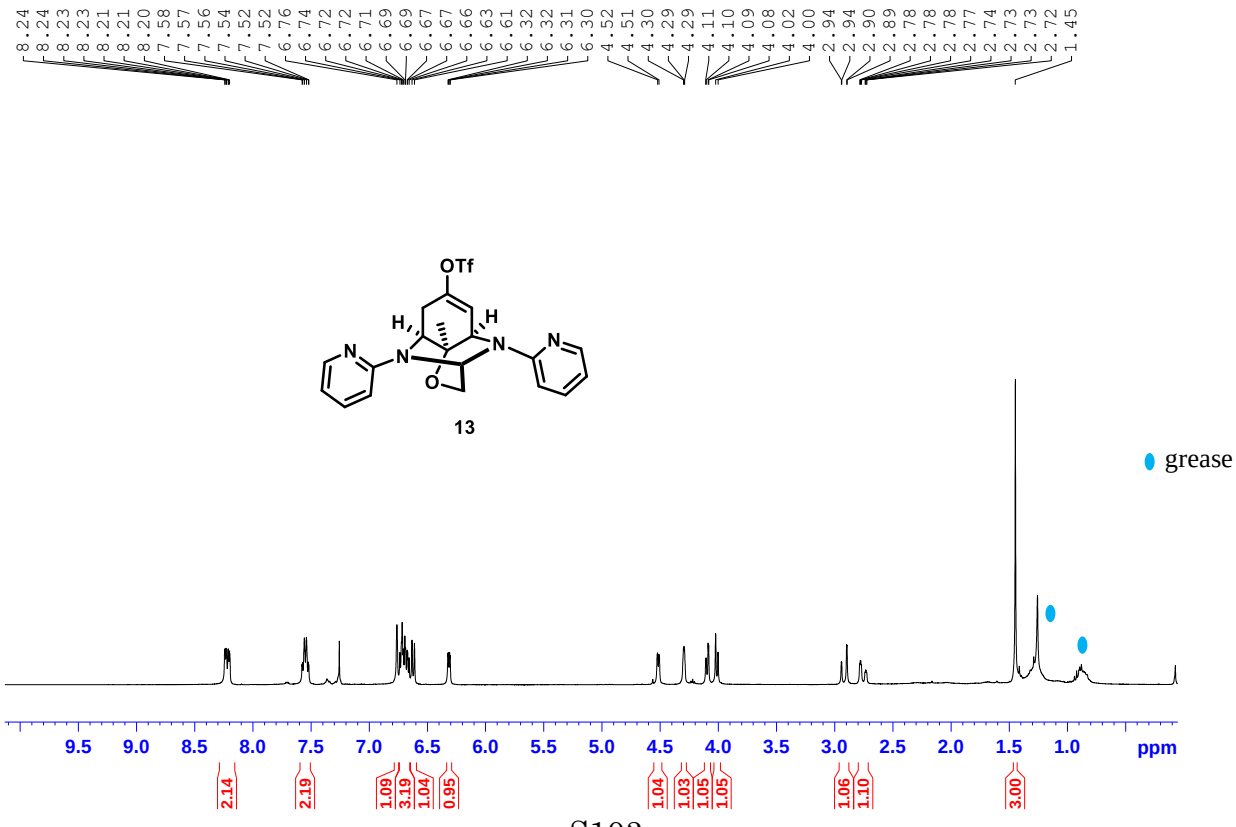
^{13}C NMR (100 MHz, $CDCl_3$) for 12



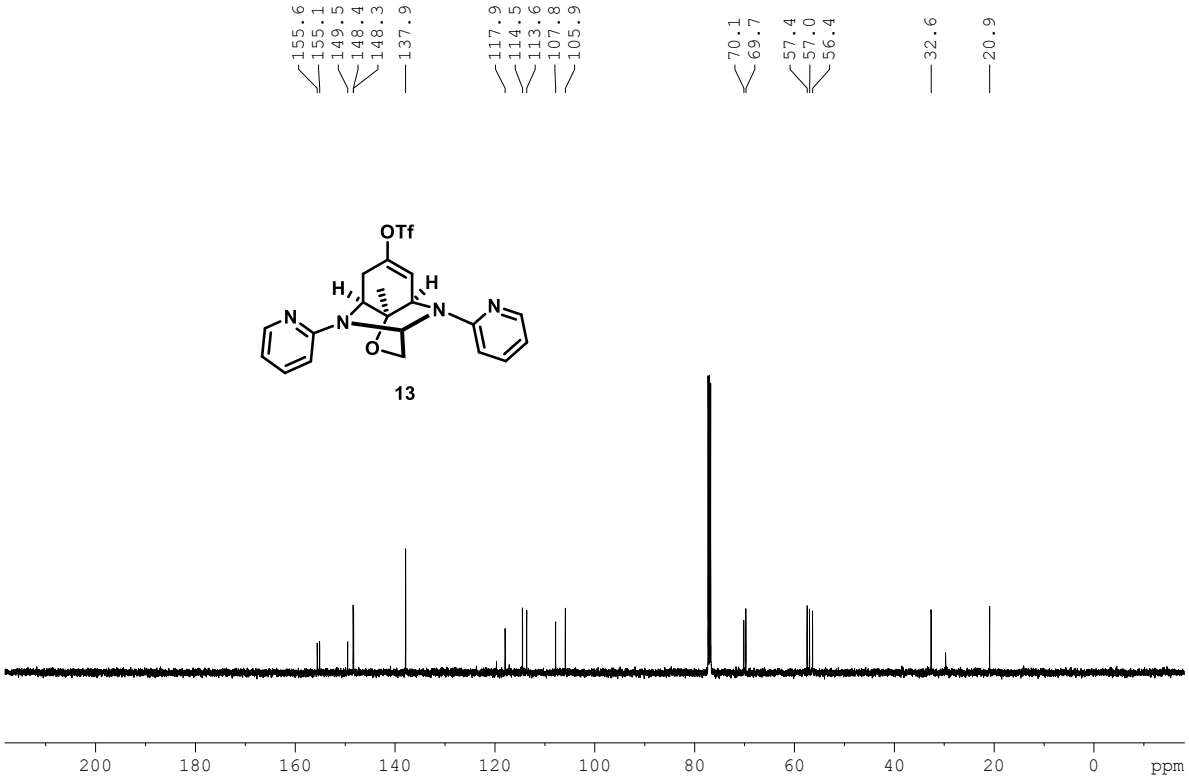
DEPT (100 MHz, $CDCl_3$) for 12



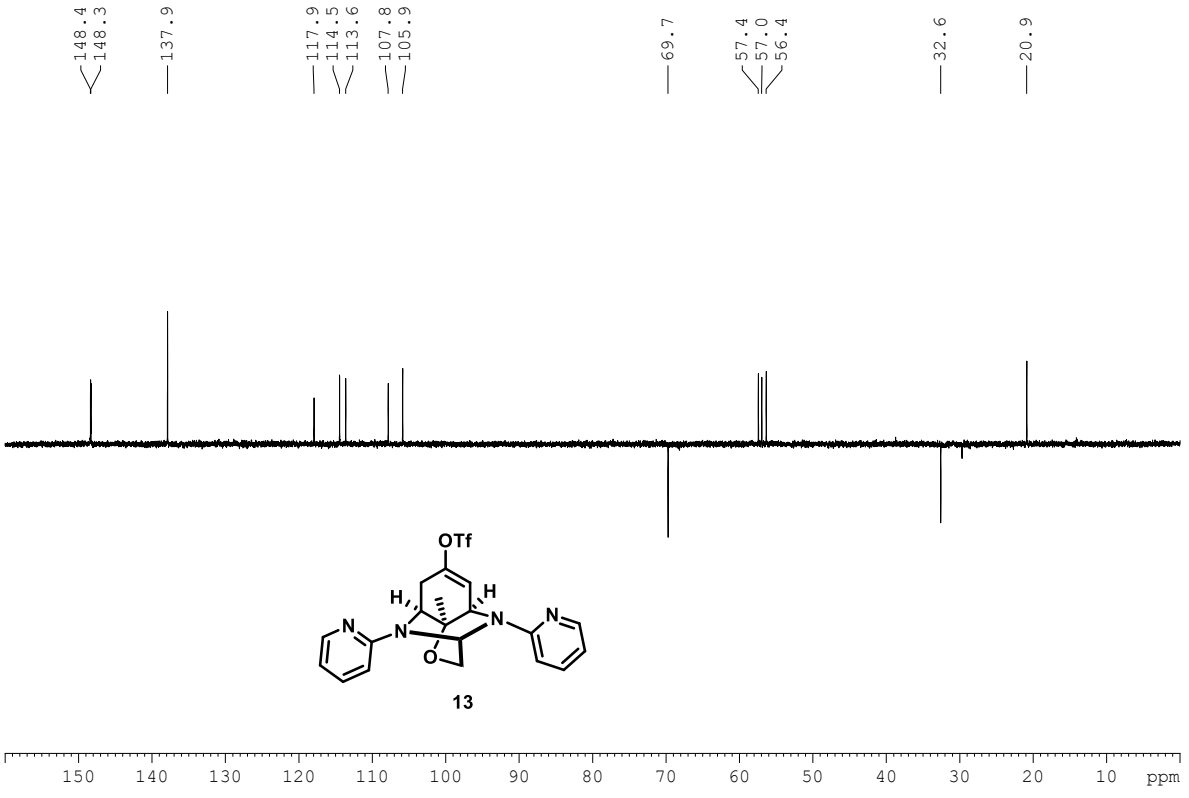
^{1}H NMR (400 MHz, $CDCl_3$) for 13



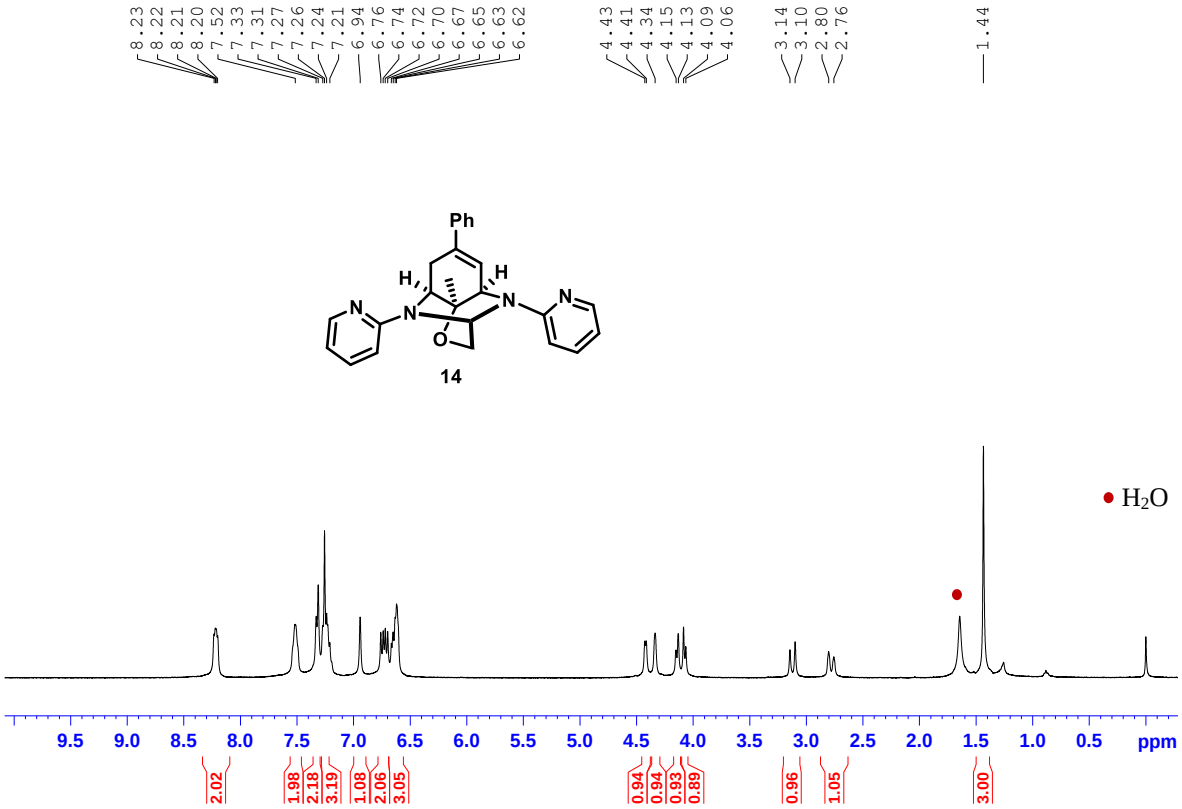
^{13}C NMR (100 MHz, $CDCl_3$) for 13



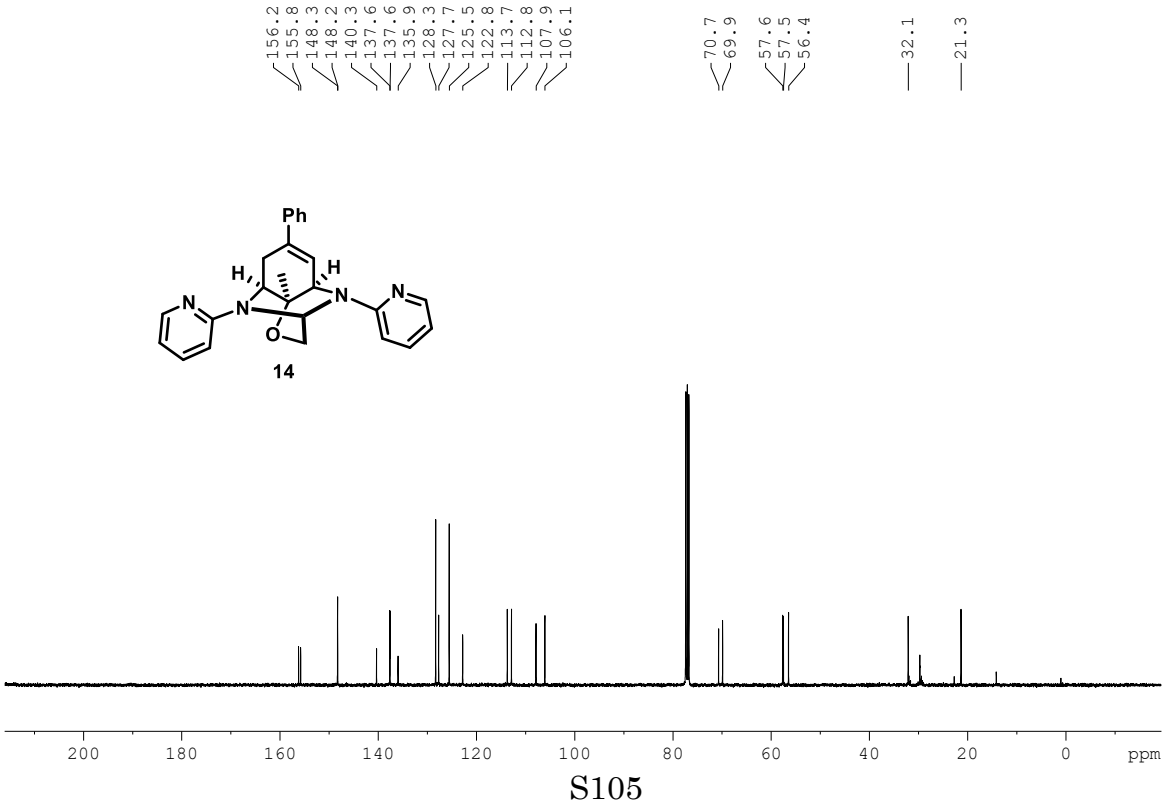
DEPT (100 MHz, $CDCl_3$) for 13



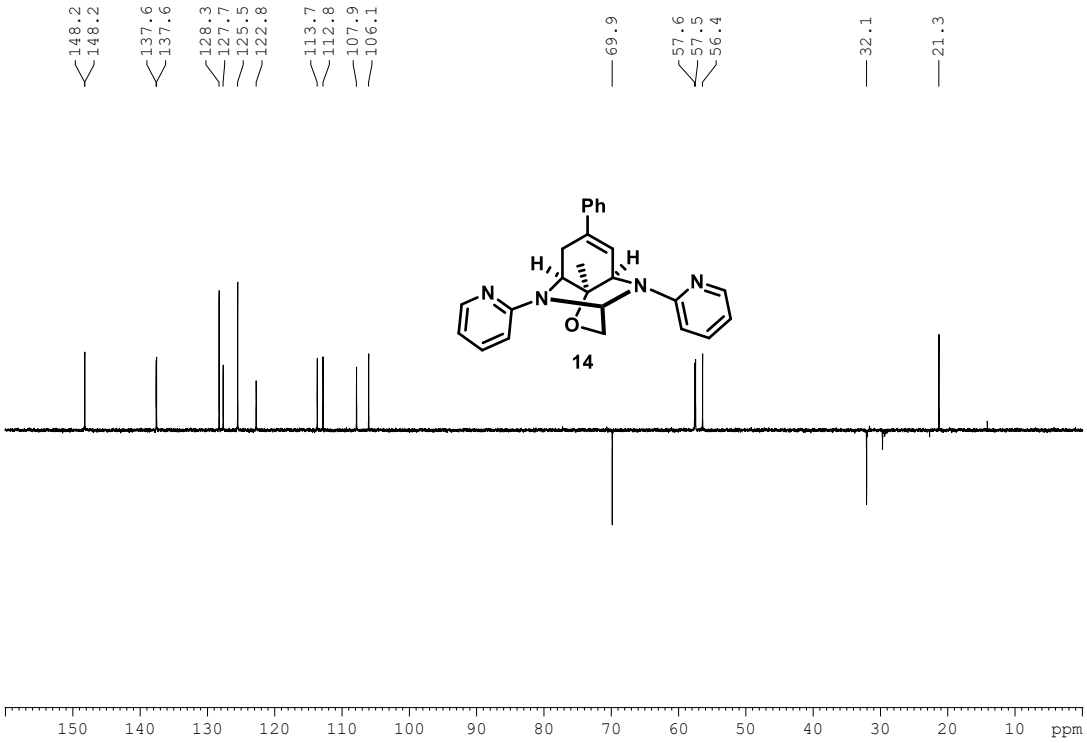
^{1}H NMR (400 MHz, $CDCl_3$) for 14



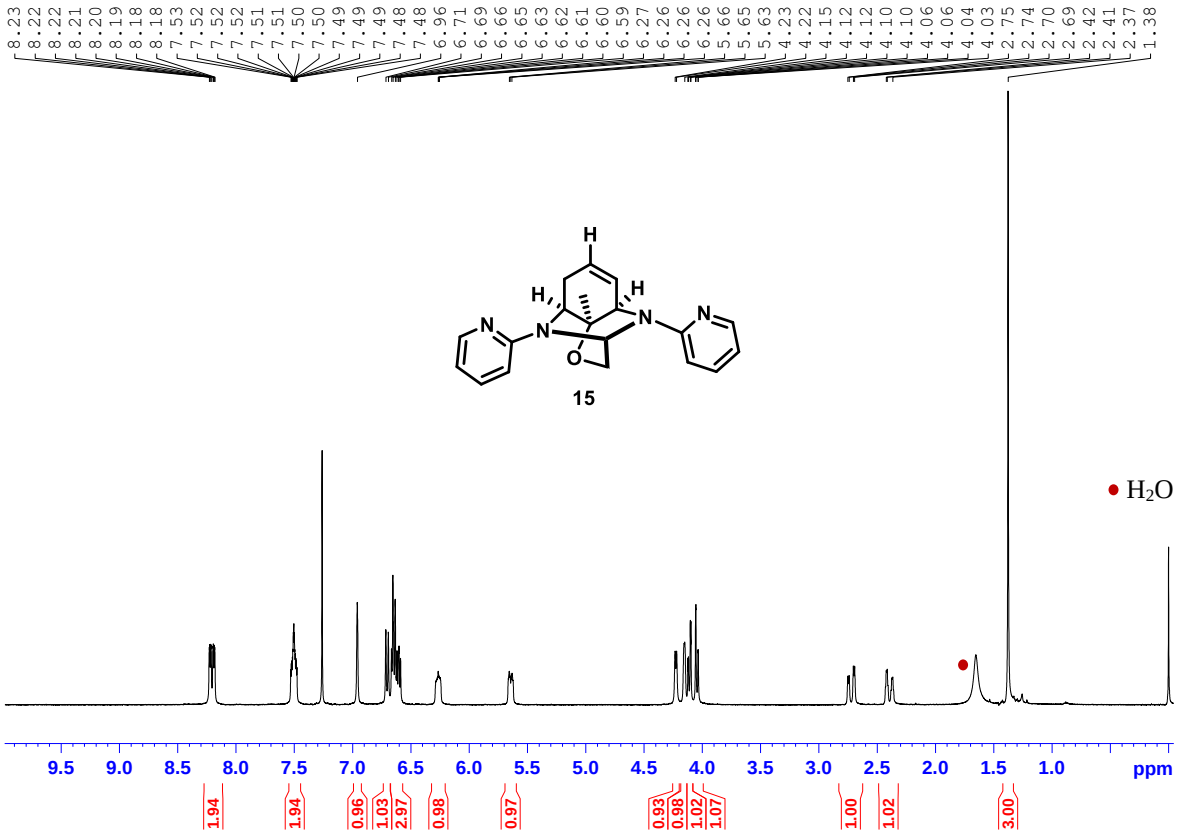
^{13}C NMR (100 MHz, $CDCl_3$) for 14



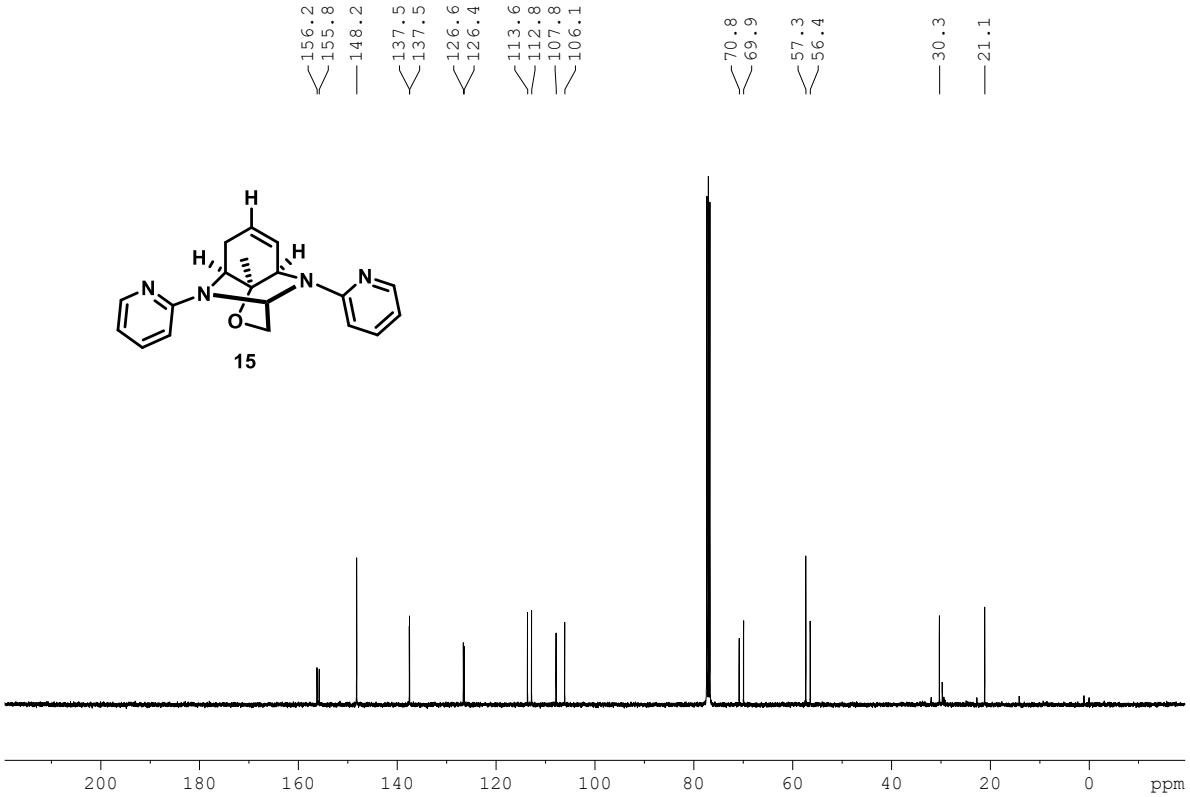
DEPT (100 MHz, $CDCl_3$) for 14



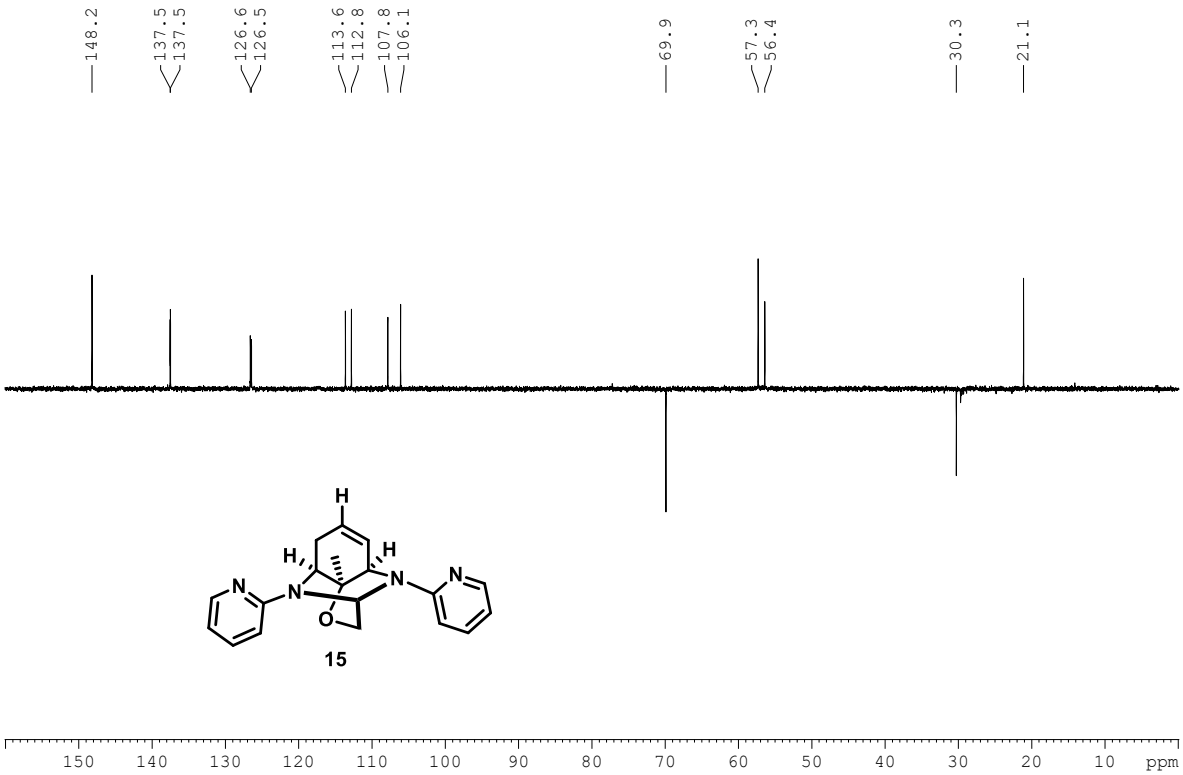
^{1}H NMR (400 MHz, $CDCl_3$) for 15



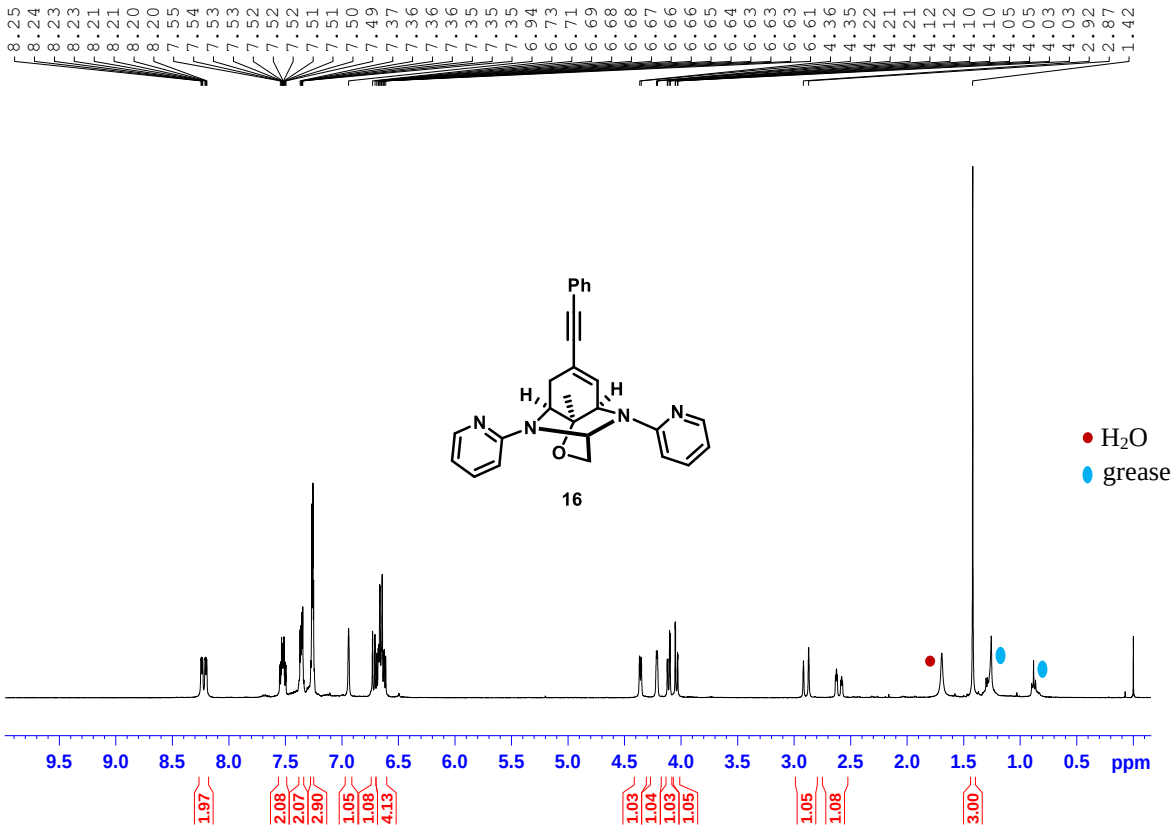
^{13}C NMR (100 MHz, $CDCl_3$) for 15



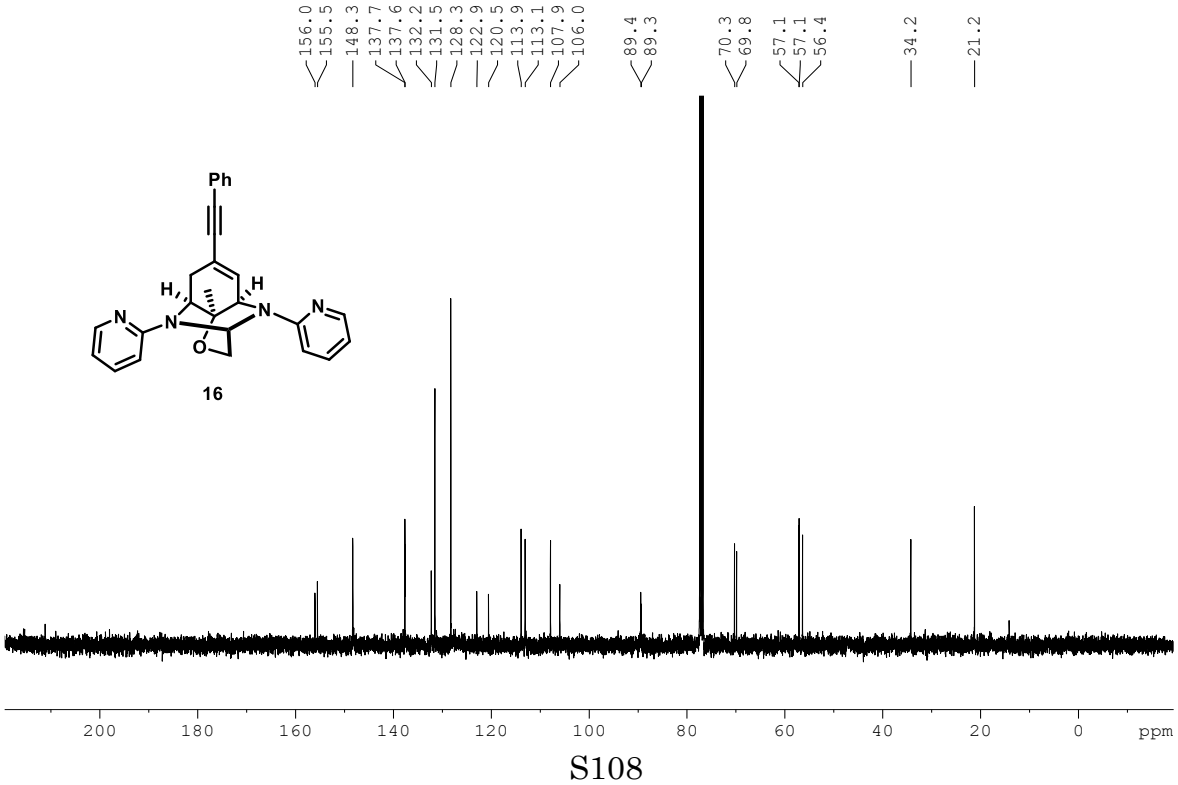
DEPT (100 MHz, $CDCl_3$) for 15



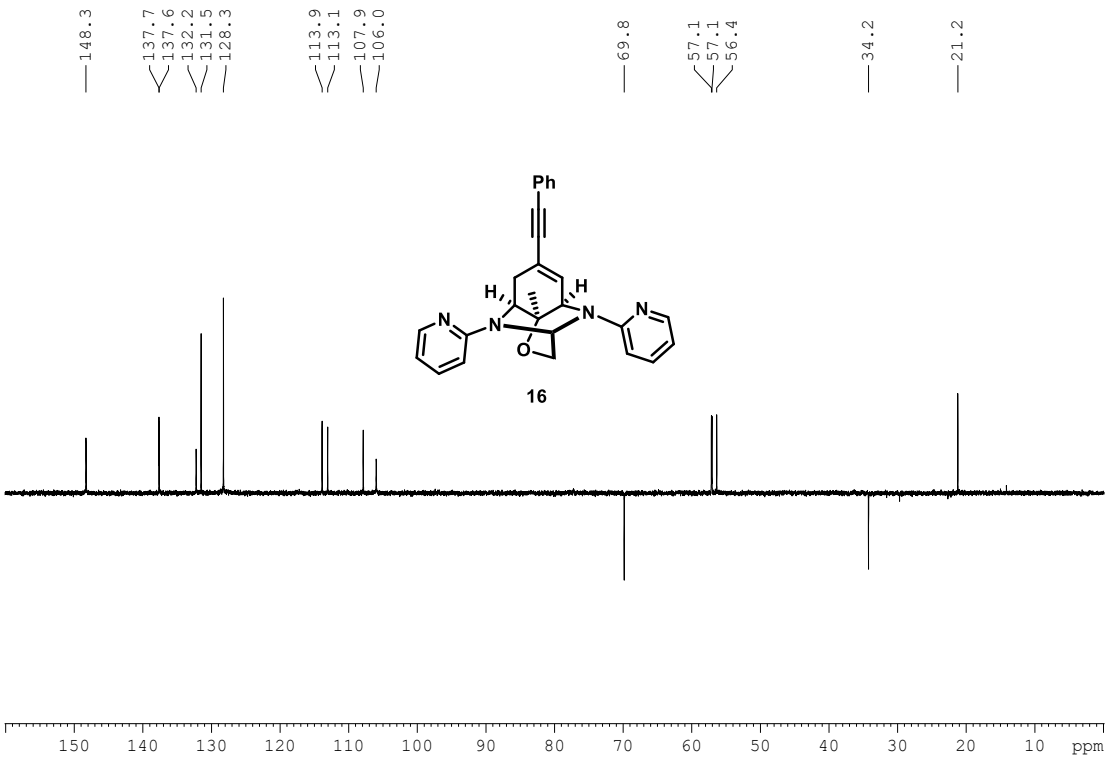
^{1}H NMR (400 MHz, $CDCl_3$) for 16



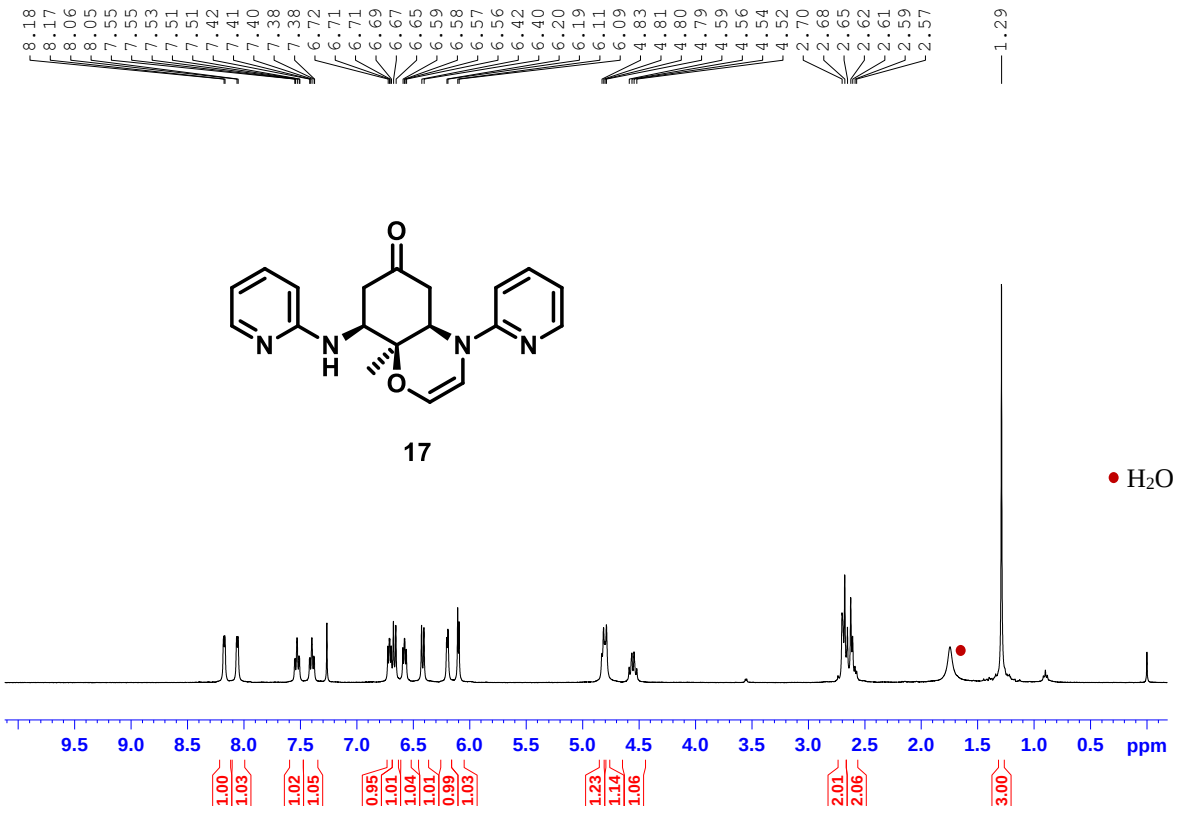
^{13}C NMR (100 MHz, $CDCl_3$) for 16



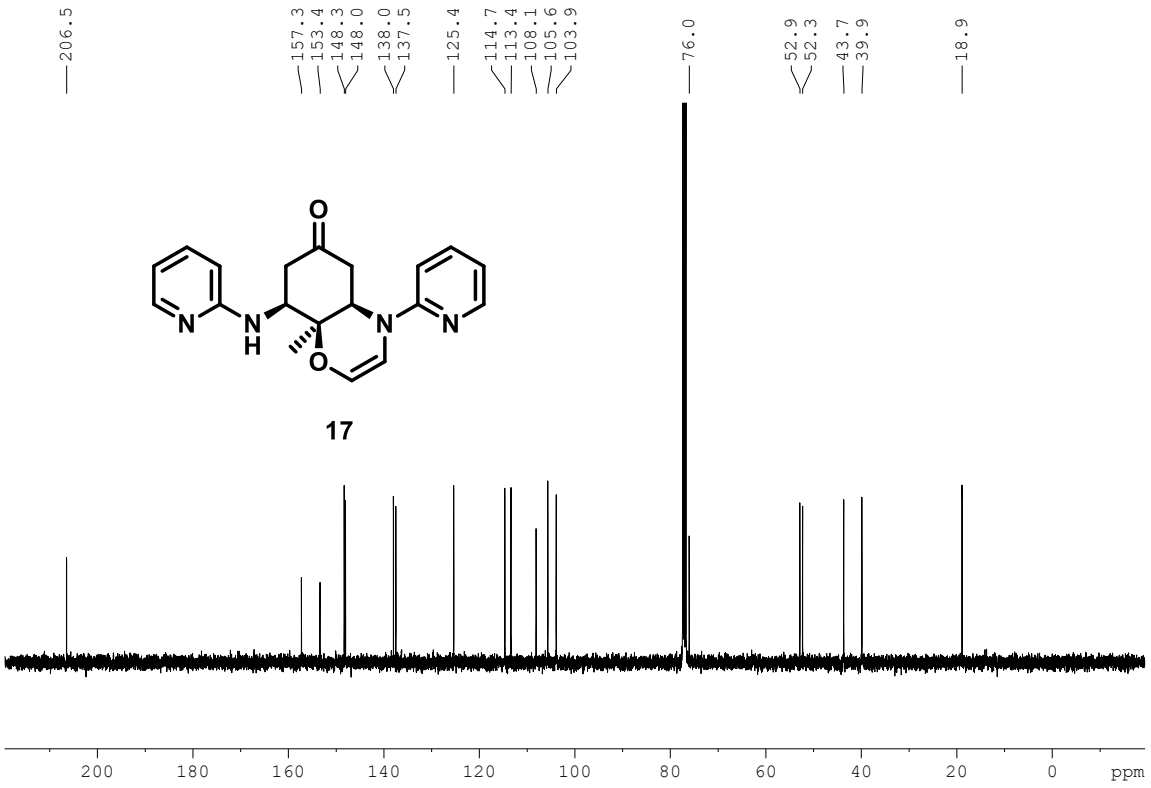
DEPT (100 MHz, $CDCl_3$) for 16



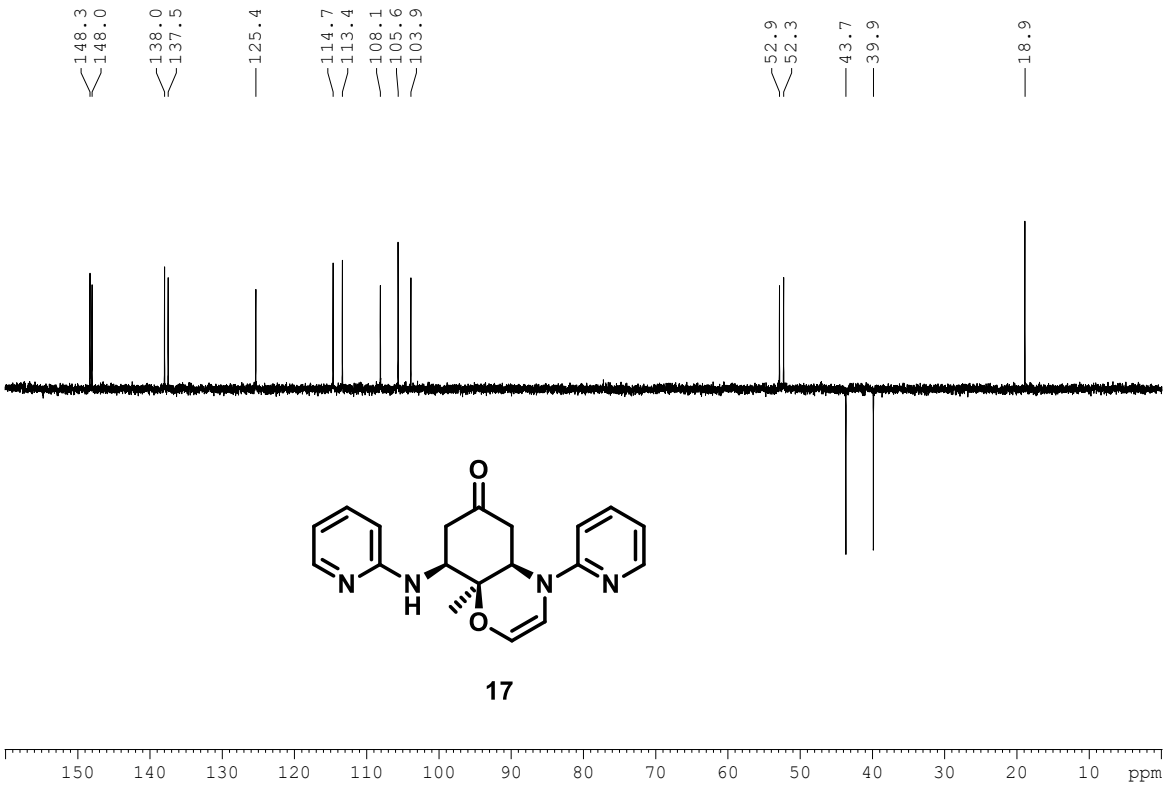
^{1}H NMR (400 MHz, $CDCl_3$) for 17



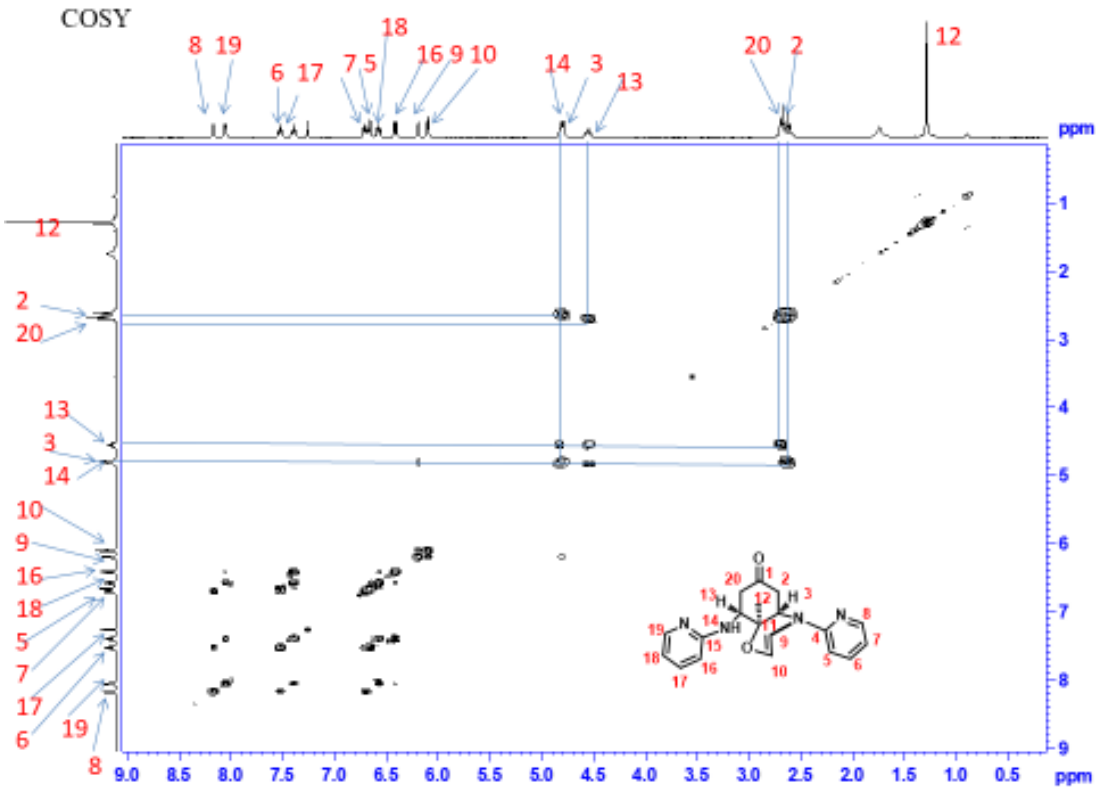
^{13}C NMR (100 MHz, $CDCl_3$) for 17



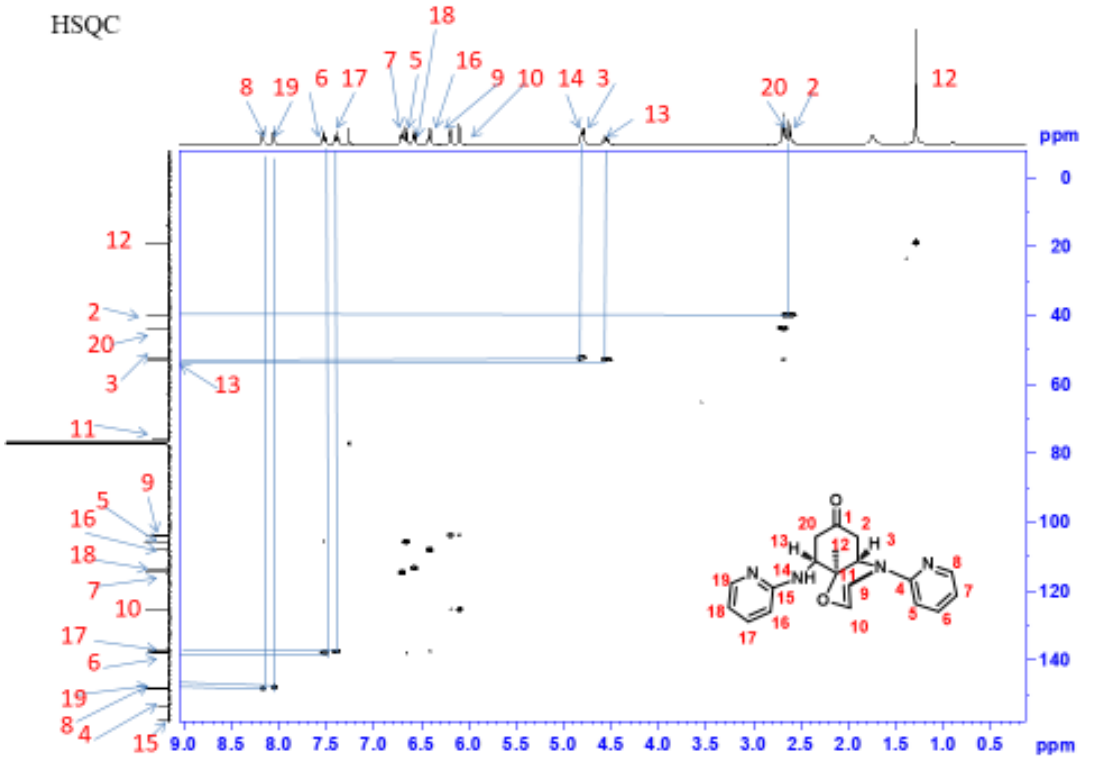
DEPT (100 MHz, $CDCl_3$) for 17



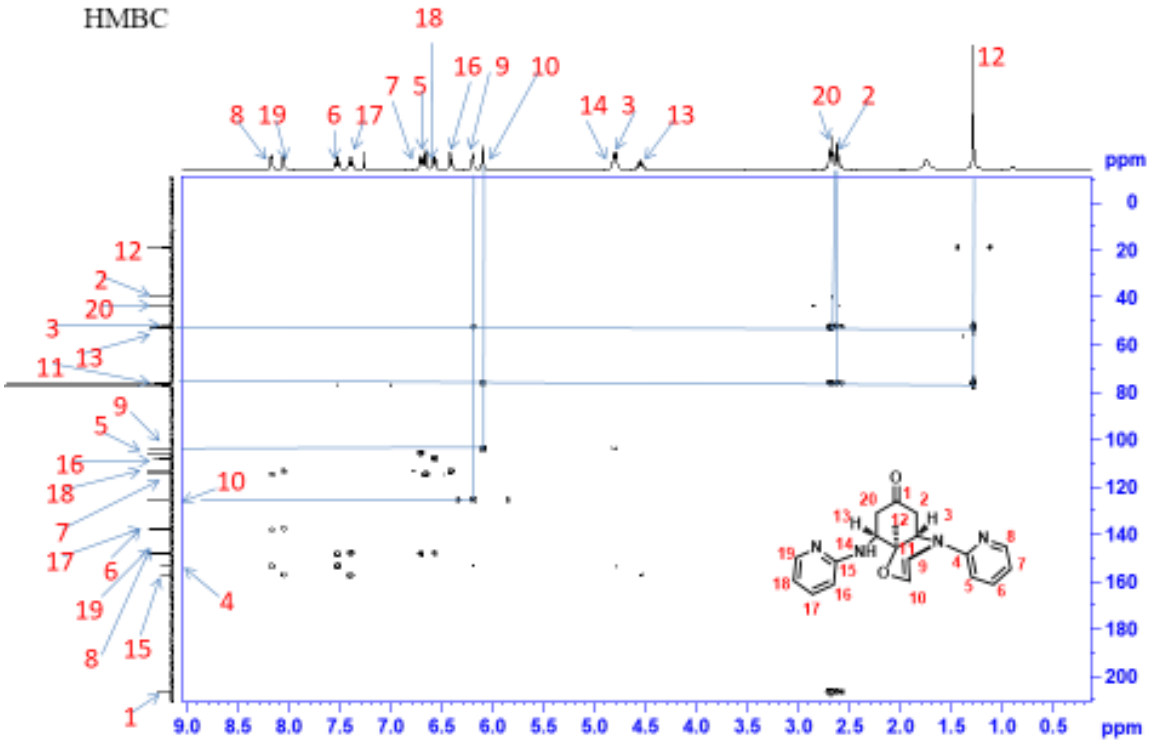
COSY (400 MHz, $CDCl_3$) for 17



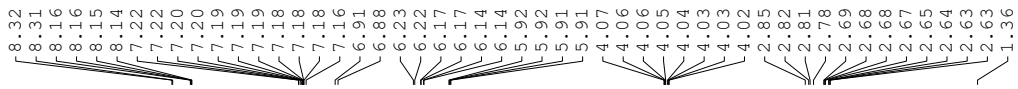
HSQC (400 MHz, $CDCl_3$) for 17

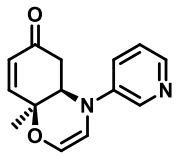


HMBC (400 MHz, $CDCl_3$) for 17



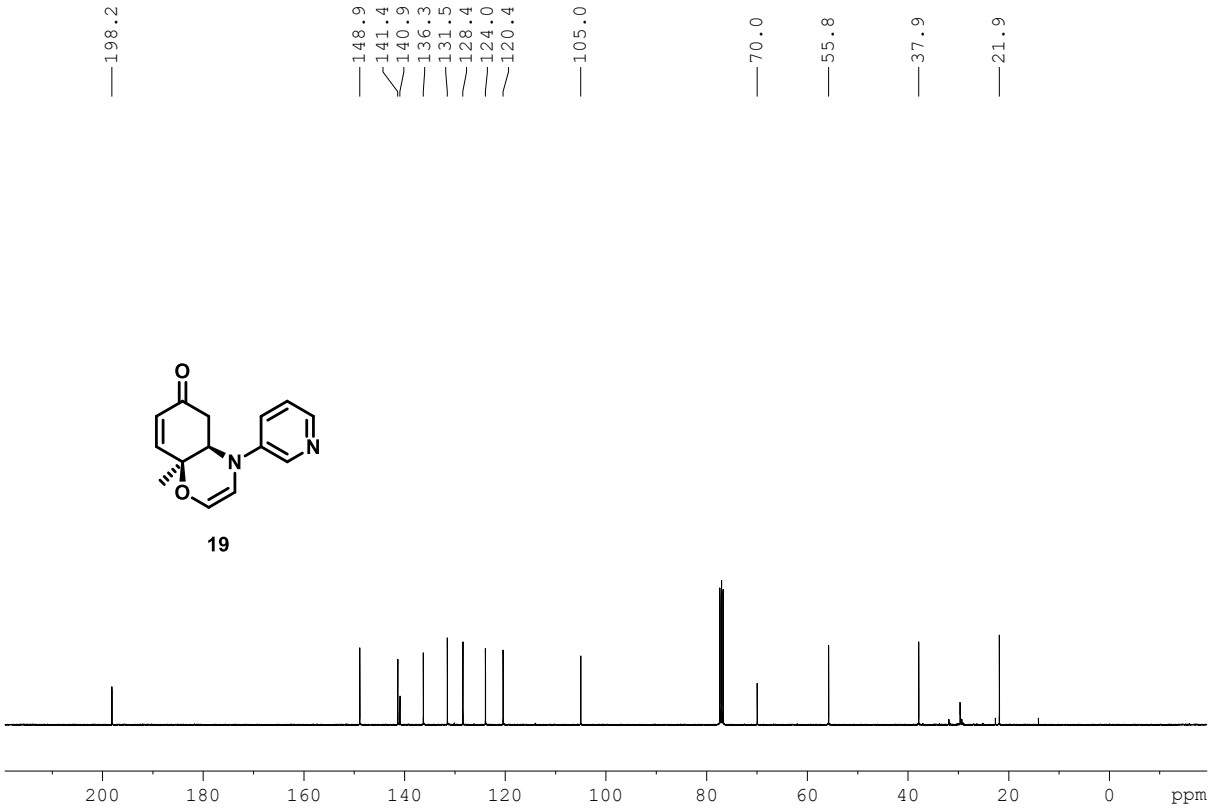
^{1}H NMR (400 MHz, $CDCl_3$) for 19





19

^{13}C NMR (100 MHz, $CDCl_3$) for 19



DEPT (100 MHz, $CDCl_3$) for 19