Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Visible-light-mediated decarboxylative alkylation of 2-pyridone derivatives *via* a C3-selective C–H functionalization

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Supporting Information

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1. General Information

All reactions were performed in a Schlenk tube under an argon atmosphere at room temperature. Heat generated from the LED lamps resulted in warming of the reactions to 35 – 40 ºC, and fan cooling was used to maintain this temperature. Chemicals and photocatalysts were commercially available from chemical suppliers and were used without purification. DMSO and DMA were anhydrous purchased from Sigma-Aldrich. *N*-Hydroxyphthalimide esters were prepared according to literature procedures.[1] 2-Pyridone derivatives was prepared from 2-hydroxypyridines and the appropriate alkylating agents or aryl halides.[2,3] 8 W blue LED bulbs (8 W PAR38 EVE) were purchased from HomePro (https://www.homepro.co.th). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on Bruker AVANCE 300 spectrometer. Chemical shifts were reported in part per million on the scale using TMS (0 ppm) as an internal standard in $CDCl_3$ and solvent signals (2.50 ppm) in DMSO-d_6. The ^{13}C NMR chemical shifts were determined by using solvent signals (77.0 ppm in $CDCl_3$, and 39.5 ppm in DMSO-d_6). Infrared spectra were measured using PerkinElmer FT-IR spectrometer. High resolution mass spectra (HRMS) were obtained using a Thermo Scientific orbitrap Q Exactive Focus mass spectrometer *via* the electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). Melting points were measured on a Thermo Scientific digital melting point apparatus in open capillaries. Flash column chromatography was carried out using silica gel (silica gel 60, size 0.06 – 0.20 mm, 70 – 230 mesh ASTM). TLC-Aluminum sheets on silica gel 60 GF_{254} were used for monitoring the reactions. Optical rotation ($[\alpha]_D^T$) was measured on an automatic polarimeter (BIOBASE BK-P2S) and is quoted in (° mL)(g dm)$^{-1}$.

Photo of reaction setup

Two 8 W blue LED lamps (8 W PAR38 EVE) were purchased from HomePro (https://www.homepro.co.th). The lamps were positioned on opposite sides of the Schlenk tubes at a distance 2 – 3 cm from the tubes. Fan cooling was used to maintain the temperature. With this setup, the temperature near the tubes was at approximately 35 – 40 °C throughout the reaction time of 4 – 24 h.

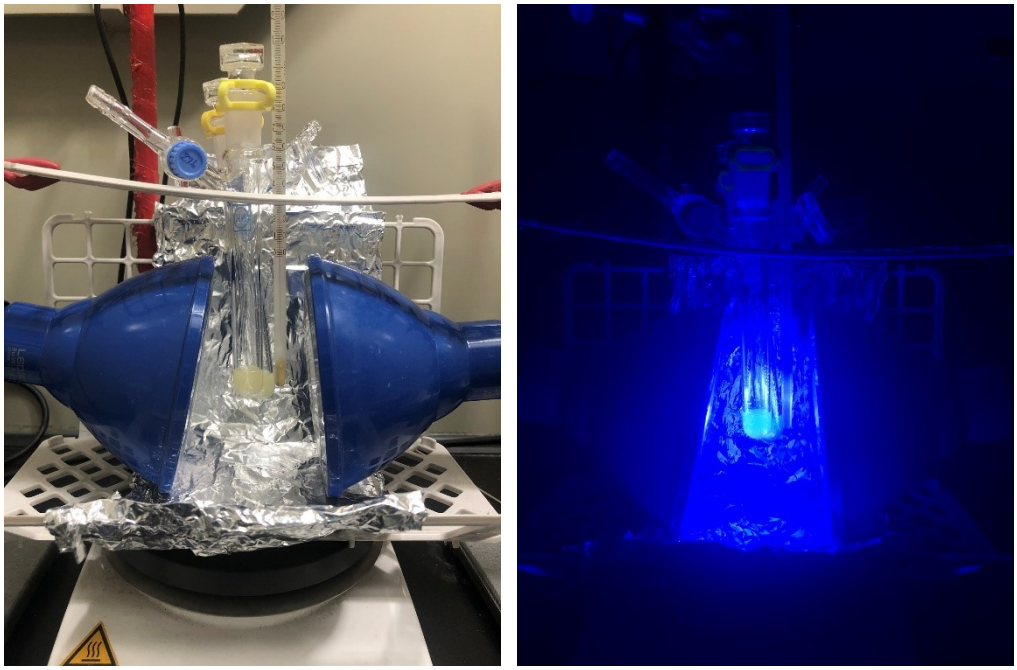
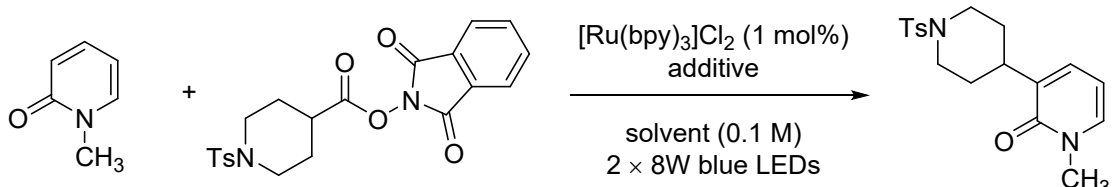


Figure S1. Photo of reaction setup.

2. Reaction optimisation

Under Ar atmosphere, a Schlenk tube was charged with redox active ester **2a** (0.20 mmol, 2.0 eq.), and *fac*-Ir(ppy)$_3$ (1 mol%). Solvent (1.0 mL) and *N*-methyl-2-pyridone **1** (0.10 mmol, 1.0 eq.) were added. The reaction mixture was degassed by ultra-sonication for 1 min and stirred for 4 – 24 h under the irradiation of blue LEDs (8 W × 2, at approximately 2 – 3 cm away from the light source, ca. 35 °C). 2 N NaOH (5 mL) was added. The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. NMR yield of **3a** was determined as described in the tables.

i) Reductive pathway with Ru photocatalyst

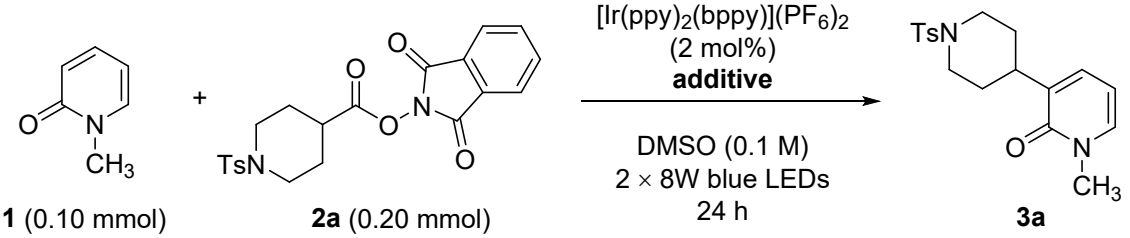


1 (0.10 mmol) **2a** (0.20 mmol) **3a**

Entry	Additive	Solvent	Yield[a]
1	NEt*i*Pr$_2$ (2.0 eq.)	CH_3CN	traces
2[b]	NEt*i*Pr$_2$ (2.0 eq.)	CH_3CN	n.r.
3	NEt*i*Pr$_2$ (0.5 eq.)	CH_3CN	n.r.
4	Ascorbic acid (2.0 eq.)	CH_3CN/H_2O (1:1, 0.2 M)	n.r.

[a]Determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.
[b]**1** (0.50 mmol) and **2a** (0.10 mmol).

ii) Screening of additives with $[Ir(ppy)_2(bppy)](PF_6)_2$



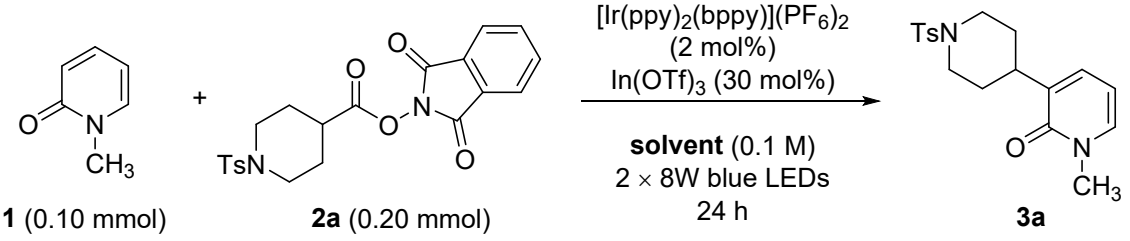
1 (0.10 mmol) **2a** (0.20 mmol) **3a**

Entry	Additive	Yield[a]	Entry	Additive	Yield[a]
1	$Bi(OTf)_3$ (30 mol%)	23%	6	$Ni(dme)_2Cl_2$ (20 mol%)	40%
2	$B(C_6F_5)_3$ (10 mol%)	traces	7	$In(OTf)_3$ (30 mol%)	48%
3	$B(C_6F_5)_3$ (30 mol%)	traces	8	$In(OTf)_3$ (50 mol%)	52%
4	TFA (4.0 eq.)	18%	9	$In(OTf)_3$ (1.0 eq.)	24%
5	$Zn(OAc)_2$ (30 mol%)	16%	10	$In(OTf)_3$ (30 mol%)	20%[b]
6	$Zn(OTf)_2$ (30 mol%)	28%	11	-	n.r.

[a]Determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

[b]The reaction was performed under air atmosphere.

iii) Solvent screening with $[Ir(ppy)_2(bppy)](PF_6)_2$

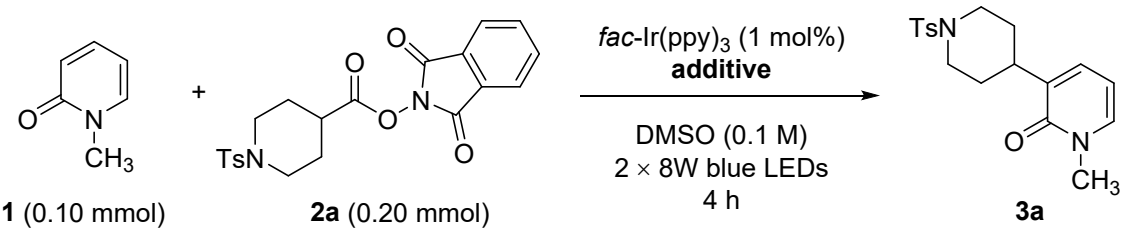


1 (0.10 mmol) **2a** (0.20 mmol) **3a**

Entry	Solvent	Yield[a]	Entry	Solvent	Yield[a]
1	CH_3CN	traces	6	THF	traces
2	CH_3CN	traces	7	DCM	14%
3	DMA	traces	8	toluene	n.r.
4	DMF	traces	9	TFE	13%
5	DMSO	48%	10	MeOH	42%

[a]Determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

iv) Screening of additives with fac-Ir(ppy)$_3$

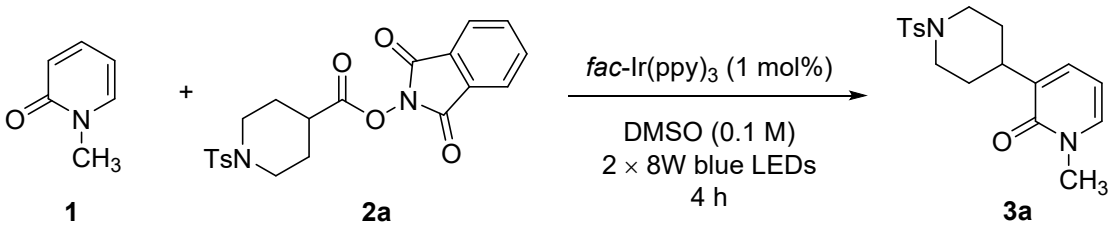


1 (0.10 mmol) **2a** (0.20 mmol) **3a**

Entry	Additive	Yield[a]	Entry	Additive	Yield[a]
1	-	53%	11	$Ni(dme)_2Br_2$ (20 mol%)	43%
2	$In(OTf)_3$ (30 mol%)	53%	12	$Ni(dme)_2Cl_2$ (20 mol%)	45%
3	$Sc(OTf)_3$ (30 mol%)	28%	13	$Ni(dme)_2Cl_2$ (20 mol%) dtbpy (20 mol%)	44%
4	$Cu(OTf)_2$ (20 mol%)	n.r.	14	$Ni(dme)_2Cl_2$ (20 mol%) dtbpy (20 mol%) K_2CO_3 (2.0 eq.)	35%
5	$Mn(OAc)_3$ (20 mol%)	28%	15	Cs_2CO_3 (2.0 eq.)	17%
6	$Zn(OAc)_2$ (1.0 eq.)	42%	16	2,6-lutidine (2.0 eq.)	36%
7	$Fe(NO_3)_3 9H_2O$ (30 mol%)	n.r.	17	Et_3N (2.0 eq.)	15%
8	TFA (2.0 eq.)	40%	18	*t*BuOK (2.0 eq.)	17%
9	Ascorbic acid (2.0 eq.)	27%	19	NaOAc (2.0 eq.)	26%
10	$Pd(OAc)_2$ (5 mol%)	35%	20	KH_2PO_4 (2.0 eq.)	39%

[a]Determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

v) Varying ratios of substrates

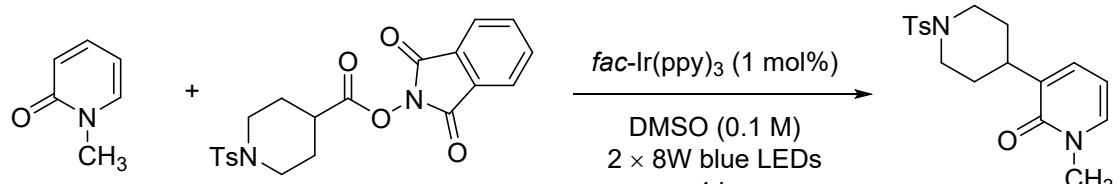


1 **2a** **3a**

Entry	1 (mmol)	2a (mmol)	Yield[a]	Entry	1 (mmol)	2a (mmol)	Yield[a]
1	1.0	2.0	53%	4	5.0	1.0	46%
2	1.0	1.5	36%	5	1.0	5.0	52%
3	2.0	1.0	27%				

[a]Determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

vi) Varying reaction setup



1 (0.10 mmol) **2a** (0.20 mmol) **3a**

Entry	Deviation from above	Yield[a]
1	Using CFL bulbs	5%
2	No fan cooling (55 °C)	38%

[a]Determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

vii) Unsuccessful products.

Attempts were made to prepare the following desired products and these compounds could not be formed in our standard conditions. It can be suggested that corresponding NHPI esters were decomposed or unstable in the reactions. For the reaction with huperzine A, no reaction was observed.

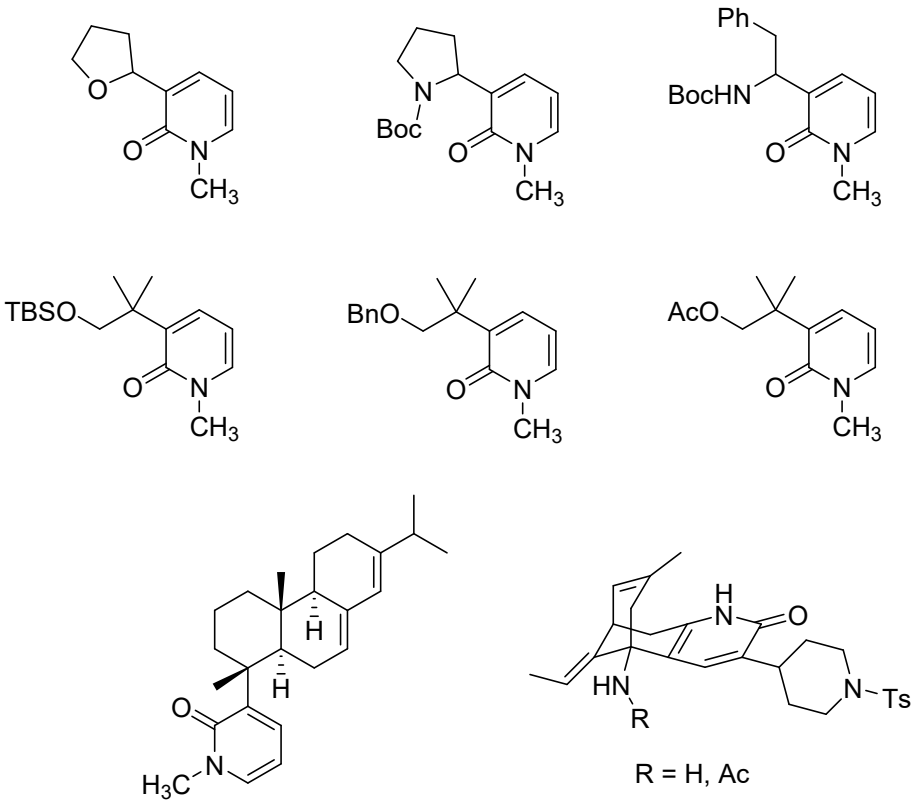


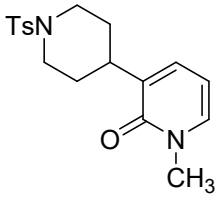
Figure S2. Unsuccessful products.

3. Synthesis of the compounds

General Procedure for the Decarboxylative Alkylation of 2-Pyridones.

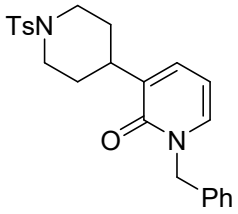
Under Ar atmosphere, a Schlenk tube was charged with redox active ester (0.20 mmol, 2.0 eq.), pyridones (if solid, 0.10 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1 mol%). Anhydrous DMSO (1.0 mL) and pyridones (if liquid, 0.10 mmol, 1.0 eq.) were added. The reaction mixture was degassed by ultra-sonication for 1 min and stirred for 4 – 24 h under the irradiation of blue LEDs (8 W × 2, at approximately 2 – 3 cm away from the light source, ca. 35 °C). 2 N NaOH (5 mL) was added. The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the crude by column chromatography gave the desired product.

Pyridone scope

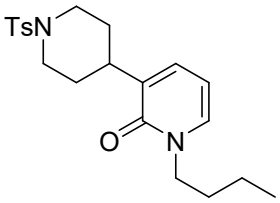


*1-Methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (**3a**).* Flash column chromatography [DCM:Et_2O:Et_3N (90:10:1 – 80:20:1)]; Yellow solid (55%, 19.1 mg). m.p. 130 – 133 °C (DCM). R_f = 0.34 (DCM:Et_2O, 8:2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.74 – 7.62 (m, 2H), 7.40 – 7.30 (m, 2H), 7.19 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.13 (dd, *J* = 6.9, 1.7 Hz, 1H), 6.16 (t, *J* = 6.8 Hz, 1H), 3.99 – 3.84 (m, 2H), 3.54 (s, 3H), 2.80 (tt, *J* = 12.3, 3.4 Hz, 1H), 2.46 (s, 3H), 2.38 (td, *J* = 12.0, 2.5 Hz, 2H), 2.02 – 1.86 (m, 2H), 1.70 – 1.54 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.4, 143.5, 135.9, 133.8, 132.9, 129.6, 127.7, 105.6, 46.9, 37.9, 34.9, 30.5, 21.5. IR (ν/cm^{-1}) 2919, 2846, 1648, 1597, 1561, 1326, 1157, 935, 769. HRMS (ESI+) calcd for $C_{18}H_{23}O_3N_2S$ $[M+H]^+$: 347.1424, found 347.1421.

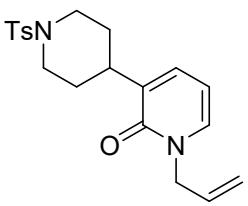
For large-scale synthesis. According to the general procedure, using the NHPI ester (1.7 g, 4.00 mmol), *N*-methyl-2-pyridone (0.20 mL, 2.00 mmol), *fac*-Ir(ppy)$_3$ (1.3 mg, 0.10 mol%), and anhydrous DMSO (20 mL). The product **3a** was obtained in 43% yield.



*1-Benzyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (**3b**).* Flash column chromatography [EtOAc:*n*-hexane (2:3)]; Colourless solid (39%, 16.3 mg). m.p. 160 – 164 °C (EtOAc/*n*-hexane). R_f = 0.21 (EtOAc:*n*-hexane, 2:3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.77 – 7.57 (m, 2H), 7.44 – 7.25 (m, 7H), 7.21 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.16 – 7.06 (m, 1H), 6.16 (t, *J* = 6.8 Hz, 1H), 5.13 (s, 2H), 3.99 – 3.84 (m, 2H), 2.91 – 2.72 (m, 1H), 2.46 (s, 3H), 2.37 (td, *J* = 12.0, 2.5 Hz, 2H), 2.01 – 1.89 (m, 2H), 1.71 – 1.51 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.0, 143.5, 136.4, 136.1, 134.9, 133.7, 132.8, 129.6, 128.9, 128.2, 128.0, 127.7, 105.9, 52.5, 46.9, 35.1, 30.5, 21.5. IR (ν/cm^{-1}) 2934, 2849, 1648, 1597, 1559, 1328, 1159, 921, 764. HRMS (ESI+) calcd for $C_{24}H_{27}O_3N_2S$ $[M+H]^+$: 423.1737, found 423.1737.

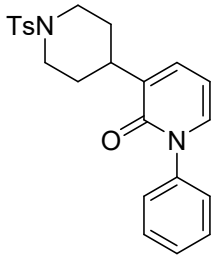


*1-Butyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (**3c**).* Flash column chromatography [EtOAc:*n*-hexane:Et_3N (40:60:1)]; Yellow oil (39%, 15 mg). R_f = 0.38 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.72 – 7.61 (m, 2H), 7.39 – 7.30 (m, 2H), 7.16 (dd, *J* = 6.7, 1.9 Hz, 1H), 7.11 (dd, *J* = 6.9, 1.5 Hz, 1H), 6.15 (t, *J* = 6.8 Hz, 1H), 4.04 – 3.77 (m, 4H), 2.90 – 2.69 (m, 1H), 2.46 (s, 3H), 2.43 – 2.30 (m, 2H), 2.00 – 1.87 (m, 2H), 1.81 – 1.50 (m, 4H), 1.44 – 1.29 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.8, 143.5, 135.8, 135.2, 133.4, 132.9, 129.6, 127.7, 105.5, 50.0, 46.9, 35.0, 31.3, 30.5, 21.5, 19.9, 13.7. IR (ν/cm^{-1}) 2927, 2853, 1724, 1645, 1595, 1558, 1160, 719, 546. HRMS (ESI+) calcd for $C_{21}H_{29}O_3N_2S$ $[M+H]^+$:389.1893, found 389.1892.

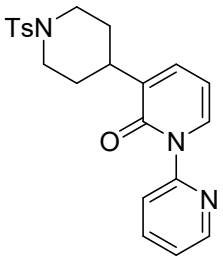


*1-Allyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (**3d**)*. Flash column chromatography [EtOAc:*n*-hexane:Et_3N (60:40:1)]; Yellow oil (27%, 10 mg). R_f = 0.56 (EtOAc). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.22 – 7.03 (m, 2H,),

6.19 (t, *J* = 6.8 Hz, 1H), 6.02 – 5.81 (m, 1H), 5.34 – 5.11 (m, 2H), 4.56 (d, *J* = 5.9 Hz, 2H), 3.99 – 3.80 (m, 2H), 2.89 – 2.71 (m, 1H), 2.46 (s, 3H), 2.42 – 2.26 (m, 2H), 2.00 – 1.87 (m, 2H), 1.70 – 1.51 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.7, 143.5, 136.0, 134.7, 133.7, 132.9, 132.5, 129.6, 127.7, 118.5, 105.8, 51.4, 46.9, 35.0, 30.5, 21.5. IR (ν/cm^{-1}) 2921, 2849, 1648, 1593, 1558, 1330, 1162, 929, 726. HRMS (ESI+) calcd for $C_{20}H_{25}O_3N_2S$ $[M+H]^+$:373.1580, found 373.1581.

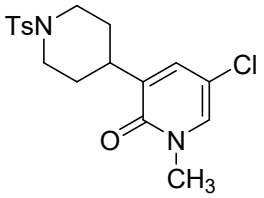


*1-Phenyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (**3e**).* Flash column chromatography [EtOAc:*n*-hexane:Et_3N (40:60:1)]; Colourless solid (55%, 22.6 mg). m.p. 208 – 210 °C (EtOAc/*n*-hexane). R_f = 0.38 (DCM:MeOH, 98:2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 – 7.63 (m, 2H), 7.54 – 7.31 (m, 7H), 7.27 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.21 (dd, *J* = 7.0, 2.0 Hz, 1H), 6.26 (t, *J* = 6.9 Hz, 1H), 4.02 – 3.85 (m, 2H), 2.81 (tt, *J* = 12.1, 3.0 Hz, 2H), 2.45 (s, 3H), 2.37 (td, *J* = 12.0, 2.5 Hz, 2H), 2.06 – 1.95 (m, 2H), 1.76 – 1.58 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.8, 143.5, 141.1, 136.7, 135.6, 134.1, 133.0, 129.6, 129.2, 128.4, 127.7, 126.6, 105.7, 46.9, 35.2, 30.5, 21.5. IR (ν/cm^{-1}) 2921, 2844, 1653, 1606, 1556, 1340, 1161, 929, 698. HRMS (ESI+) calcd for $C_{23}H_{25}O_3N_2S$ $[M+H]^+$: 409.1580, found 409.1577.

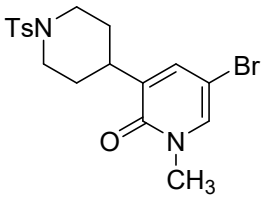


*3-(1-Tosylpiperidin-4-yl)-2H-[1,2'-bipyridin]-2-one (**3f**).* Flash column chromatography [EtOAc:*n*-hexane:Et_3N (70:30:1)]; Yellow solid (59%, 24 mg). m.p. 160 – 162 °C (EtOAc/*n*-hexane). R_f = 0.45 (EtOAc:*n*-hexane, 4:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.57 (d, *J* = 4.6 Hz, 1H), 7.91 – 7.78 (m, 2H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.42 – 7.28 (m, 3H), 7.20 (d, *J* = 6.7 Hz, 1H), 6.30 (t, *J* = 6.9 Hz, 1H), 4.04 – 3.85 (m, 2H), 2.91 – 2.73 (m, 1H), 2.51 – 2.31 (m, 5H), 2.08 – 1.92 (m, 2H), 1.74 – 1.57 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.6, 152.2, 149.0, 143.5, 137.6, 136.7, 134.5, 133.9, 132.9, 129.6, 127.7, 123.2, 121.6, 106.0, 46.9, 35.2, 30.5, 21.5. IR (ν/cm^{-1}) 2920, 2845, 1652, 1605, 1556, 1463,

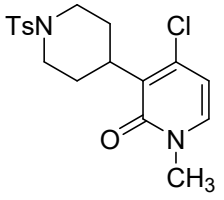
1433, 1344, 1161, 931, 796, 722. HRMS (ESI+) calcd for $C_{22}H_{24}O_3N_3S$ $[M+H]^+$: 410.1533, found 410.1527.



5-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (***3g***). Flash column chromatography [EtOAc:*n*-hexane:Et_3N (80:20:1)]; Colourless solid (33%, 12.6 mg). m.p. 211 – 212 °C (EtOAc/*n*-hexane). R_f = 0.35 (EtOAc:*n*-hexane, 4:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.74 – 7.60 (m, 2H), 7.42 – 7.32 (m, 2H), 7.25 (d, *J* = 2.7 Hz, 1H), 7.07 (d, *J* = 2.6 Hz, 1H), 4.00 – 3.83 (m, 2H), 3.51 (s, 3H), 2.77 (ddd, *J* = 15.3, 7.7, 3.2 Hz, 1H), 2.46 (s, 3H), 2.38 (td, *J* = 12.0, 2.2 Hz, 2H), 2.02 – 1.87 (m, 2H), 1.71 – 1.50 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 160.8, 143.6, 136.9, 135.0, 133.4, 133.0, 129.6, 127.7, 112.0, 46.7, 38.0, 35.2, 30.3, 21.5. IR (ν/cm^{-1}) 3075, 2929, 2826, 1648, 1586, 1557, 1349, 1160, 927, 728. HRMS (ESI+) calcd for $C_{18}H_{22}O_3N_2{}^{35}ClS$ $[M+H]^+$: 381.1034, found 381.1024.

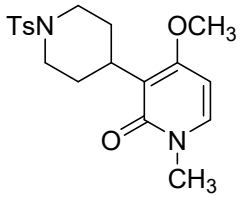


5-Bromo-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (***3h***). Flash column chromatography [EtOAc:Et_3N (99:1)]; Yellow solid (24%, 10 mg). m.p. 217 – 218 °C (EtOAc). R_f = 0.39 (EtOAc). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.30 (m, 3H), 7.20 – 7.07 (m, 1H), 4.03 – 3.82 (m, 2H), 3.52 (s, 3H), 2.86 – 2.67 (m, 1H), 2.47 (s, 3H), 2.43 – 2.29 (m, 2H), 2.01 – 1.85 (m, 2H), 1.66 – 1.49 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 160.9, 143.6, 137.3, 137.1, 135.7, 133.0, 129.6, 127.7, 97.7, 46.7, 37.9, 35.2, 30.3, 21.5. IR (ν/cm^{-1}) 2921, 2847, 1646, 1589, 1551, 1351, 1163, 728. HRMS (ESI+) calcd for $C_{18}H_{22}O_3N_2{}^{79}BrS$ $[M+H]^+$:425.0529, found 425.0531.

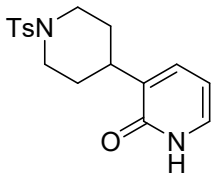


4-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (***3i***). Flash column chromatography [EtOAc:Et_3N (99:1)]; Brown solid (60%, 23 mg). m.p. > 240 °C (decomposed)

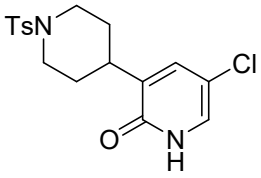
(EtOAc). R_f = 0.44 (EtOAc). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.73 – 7.64 (m, 2H), 7.39 – 7.31 (m, 2H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.16 (d, *J* = 7.3 Hz, 1H), 3.97 – 3.86 (m, 3H), 3.48 (s, 3H), 3.18 – 3.02 (m, 1H), 2.75 – 2.53 (m, 2H), 2.46 (s, 3H), 2.40 – 2.25 (m, 2H), 1.63 – 1.47 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.5, 143.5, 143.3, 135.5, 133.4, 131.1, 129.6, 127.8, 108.3, 46.9, 37.8, 26.8, 21.5. IR (ν/cm^{-1}) 2924, 2856, 1641, 1594, 1328, 1158, 920, 766, 733, 613. HRMS (ESI+) calcd for $C_{18}H_{22}O_3N_2{}^{35}ClS$ [M+H$^+$]: 381.1034, found 381.1037.



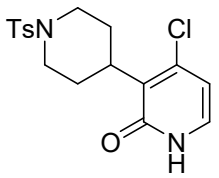
4-Methoxy-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one ***(3j)***. Preparative thin-layer chromatography [DCM:MeOH (95:5)]; Yellow soild (12%, 4.7 mg). m.p. 218 – 220 °C (EtOAc). R_f = 0.58 (DCM:MeOH, 95:5). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.75 – 7.60 (m, 2H), 7.40 – 7.32 (m, 2H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.03 (d, *J* = 7.7 Hz, 1H), 3.92 – 3.79 (m, 5H), 3.49 (s, 3H), 3.16 – 3.02 (m, 1H), 2.47 (s, 3H), 2.43 – 2.25 (m, 4H), 1.61 – 1.48 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.5, 163.4, 143.3, 136.6, 133.1, 129.5, 127.8, 116.3, 94.9, 55.6, 47.4, 37.7, 33.0, 27.8, 21.5. IR (ν/cm^{-1}) 2920, 2849, 1645, 1594, 1351, 1254, 1162, 928, 720. HRMS (ESI+) calcd for $C_{19}H_{25}O_4N_2S$ [M+H$^+$]:377.1530, found 377.1531.



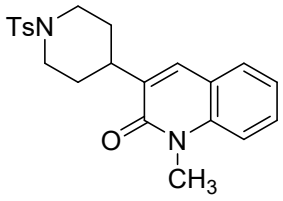
3-(1-Tosylpiperidin-4-yl)pyridin-2(1H)-one ***(3k)***. Flash column chromatography [DCM:MeOH:NH_4OH (97.25:2.5:0.25)]; Colorless solid (49%, 16.4 mg). m.p. 233 – 236 °C (EtOAc). R_f = 0.19 (DCM:MeOH, 97.5:2.5). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.66 (br s, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.16 (m, 2H), 6.42 – 6.10 (m, 1H), 4.00 – 3.84 (m, 2H), 2.87 – 2.68 (m, 1H), 2.48 – 2.26 (m, 5H), 2.03 – 1.84 (m, 2H), 1.78 – 1.58 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.2, 143.5, 135.9, 135.6, 132.9, 132.0, 129.6, 127.8, 106.8, 46.9, 34.5, 30.4, 21.5. IR (ν/cm^{-1}) 3581, 3477, 2916, 2844, 1639, 1619, 1562, 1324, 1164, 930, 776. HRMS (ESI+) calcd for $C_{17}H_{21}O_3N_2S$ [M+H]$^+$:333.1267, found 333.1269.



5-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one ***(3l)***. Flash column chromatography [EtOAc:Et_3N (99:1)]; Yellow solid (22%, 8 mg). m.p. 274 – 276 °C (EtOAc). R_f = 0.39 (EtOAc). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.64 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 2.7 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 4.05 – 3.84 (m, 2H), 2.81 – 2.62 (m, 1H), 2.46 (s, 3H), 2.44 – 2.30 (m, 2H), 2.01 – 1.86 (m, 2H), 1.76 – 1.55 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.7, 143.6, 137.2, 136.9, 132.9, 129.8, 129.6, 127.8, 113.8, 46.7, 34.9, 30.1, 21.5. IR (ν/cm^{-1}) 2922, 2848, 1642, 1610, 1555, 1355, 1332, 1166, 919, 868. HRMS (ESI+) calcd for $C_{17}H_{20}O_3N_2{}^{35}ClS$ $[M+H]^+$: 367.0878, found 367.0875.

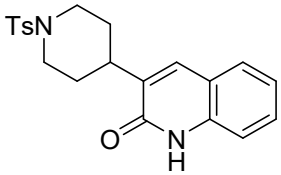


4-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one ***(3m)***. Flash column chromatography [DCM:MeOH:NH_4OH (97.25:2.5:0.25)]; Brown solid (70%, 26 mg). m.p. 236 – 238 °C (DCM). R_f = 0.21 (DCM:MeOH, 97.5:2.5). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.91 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 6.9 Hz, 1H), 6.32 (d, *J* = 7.0 Hz, 1H), 4.04 – 3.80 (m, 2H), 3.11 – 2.95 (m, 1H), 2.83 – 2.64 (m, 2H), 2.47 (s, 3H), 2.37 – 2.19 (m, 2H), 1.65 – 1.48 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.8, 145.6, 143.5, 133.0, 132.4, 131.0, 129.6, 127.8, 109.5, 47.0, 37.1, 26.6, 21.6. IR (ν/cm^{-1}) 2922, 2853, 1628, 1334, 1251, 1157, 944, 923, 786. HRMS (ESI+) calcd for $C_{17}H_{20}O_3N_2{}^{35}ClS$ $[M+H]^+$: 367.0878, found 367.0875.



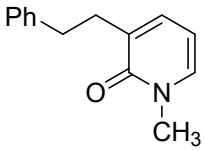
1-Methyl-3-(1-tosylpiperidin-4-yl)quinolin-2(1H)-one ***(3n)***. Flash column chromatography [EtOAc:*n*-hexane (1:1)]; Colorless solid (76%, 30 mg). m.p. 75 – 77 °C (EtOAc). R_f = 0.39 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.75 – 7.64 (m, 2H), 7.60 – 7.50 (m, 2H), 7.47 (s, 1H), 7.42 – 7.31 (m, 3H), 7.30 – 7.21 (m, 1H), 4.05 – 3.86 (m, 2H), 3.73 (s, 3H), 3.00 – 2.79 (m, 1H), 2.53 – 2.36 (m, 5H), 2.09 – 1.95 (m, 2H), 1.81 – 1.62 (m, 2H). ^{13}C

NMR (75 MHz, Chloroform-*d*) δ 161.8, 143.6, 138.8, 136.0, 133.3, 132.9, 129.9, 129.6, 128.5, 127.8, 122.2, 120.4, 113.9, 46.9, 35.3, 30.7, 29.9, 21.6. IR (ν/cm^{-1}) 2924, 2844, 1642, 1623, 1593, 1574, 1351, 1162, 754. HRMS (ESI+) calcd for $C_{22}H_{25}O_3N_2S$ $[M+H]^+$:397.1580, found 397.1576.

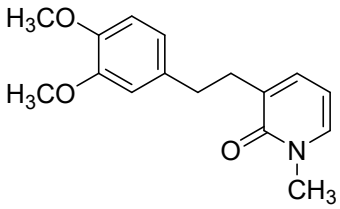


*3-(1-Tosylpiperidin-4-yl)quinolin-2(1H)-one (**3o**).* Flash column chromatography [DCM:MeOH:NH_4OH (97.25:2.5:0.25)]; Colorless solid (89%, 34 mg). m.p. 304 – 305 °C (DCM). R_f = 0.25 (DCM:MeOH, 97.5:2.5). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.78 – 7.56 (m, 4H), 7.56 – 7.38 (m, 3H), 7.32 – 7.23 (m, 1H), 7.22 – 7.11 (m, 1H), 3.87 – 3.71 (m, 2H), 2.77 – 2.59 (m, 1H), 2.43 (s, 3H), 2.36 – 2.21 (m, 2H), 1.97 – 1.83 (m, 2H), 1.75 – 1.52 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.9, 144.0, 138.0, 136.7, 134.6, 133.0, 130.3, 130.0, 128.0 128.0, 122.2, 119.8, 115.1, 47.0, 35.1, 30.3, 21.5. IR (ν/cm^{-1}) 2922, 2848, 1652, 1570, 1349, 1332, 1162, 1091, 935, 817. HRMS (ESI+) calcd for $C_{21}H_{23}O_3N_2S$ $[M+H]^+$: 383.1424, found 383.1422.

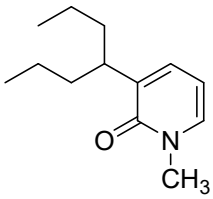
Alkyl NHPI ester scope



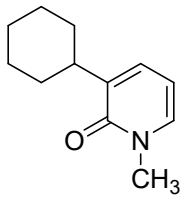
*1-Methyl-3-phenethylpyridin-2(1H)-one (**4a**)*. Flash column chromatography [EtOAc:*n*-hexane (2:3)]; Colourless oil (20%, 8 mg). R_f = 0.31 (EtOAc:*n*-hexane, 2:3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.15 (m, 7H), 7.10 (d, *J* = 6.6 Hz, 1H), 6.08 (t, *J* = 6.8 Hz, 1H), 3.59 (s, 3H), 3.00 – 2.77 (m, 4H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.0, 141.9, 136.5, 135.9, 132.7, 128.6, 128.3, 125.8, 105.5, 37.8, 34.4, 33.1. IR (ν/cm^{-1}) 3022, 2921, 2853, 1647, 1588, 1560, 1453, 754. HRMS (ESI+) calcd for $C_{14}H_{16}ON$ $[M+H]^+$:214.1226, found 214.1231.



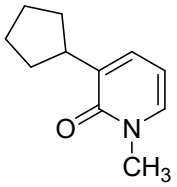
*3-(3,4-Dimethoxyphenethyl)-1-methylpyridin-2(1H)-one (**4b**)*. Flash column chromatography [EtOAc:Et_3N (99:1)]; Brown oil (21%, 11.5 mg). R_f = 0.30 (EtOAc). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 – 7.14 (m, 1H), 7.14 – 7.06 (m, 1H), 6.84 – 6.71 (m, 3H), 6.08 (t, *J* = 6.7 Hz, 1H), 3.86 (s, 6H), 3.58 (s, 3H), 2.94 – 2.78 (m, 4H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.0, 148.7, 147.1, 136.6, 135.9, 134.6, 132.7, 120.4, 111.9, 111.1, 105.5, 55.9, 55.8, 37.8, 34.1, 33.4. IR (ν/cm^{-1}) 2932, 2835, 1646, 1586, 1560, 1514, 1463, 1258, 1236, 1153, 1028, 763. HRMS (APCI+) calcd for $C_{16}H_{20}O_3N$ $[M+H]^+$:274.1438, found 274.1439.



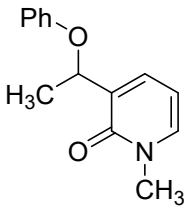
*3-(Heptan-4-yl)-1-methylpyridin-2(1H)-one (**4c**)*. Flash column chromatography [EtOAc:*n*-hexane:Et_3N (80:20:1 – 100:0:1)]; Yellow oil (20%, 8 mg). R_f = 0.32 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 – 7.06 (m, 2H), 6.13 (t, *J* = 6.8 Hz, 1H), 3.56 (s, 3H), 3.03 (p, *J* = 7.1 Hz, 1H), 1.63 – 1.50 (m, 4H), 1.31 – 1.16 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.1, 137.0, 135.3, 134.8, 105.4, 38.4, 37.9, 36.7, 20.5, 14.3. IR (ν/cm^{-1}) 2954, 2928, 2870, 1647, 1596, 1556, 1465, 756. HRMS (ESI+) calcd for $C_{13}H_{22}ON$ $[M+H]^+$: 208.1696, found 208.1691.



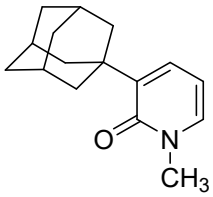
*3-Cyclohexyl-1-methylpyridin-2(1H)-one (**4d**)*. Flash column chromatography [EtOAc:Et_3N (99:1)]; Brown oil (31%, 12 mg). R_f = 0.16 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 – 7.10 (m, 2H), 6.13 (t, *J* = 6.8 Hz, 1H), 3.55 (s, 3H), 2.99 – 2.80 (m, 1H), 1.98 – 1.72 (m, 5H), 1.53 – 1.34 (m, 2H), 1.29 – 1.07 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.8, 138.7, 135.1, 133.4, 105.6, 37.8, 37.5, 32.4, 26.8, 26.4. IR (ν/cm^{-1}) 2921, 2849, 1646, 1590, 1557, 1447, 758. HRMS (APCI+) calcd for $C_{12}H_{18}ON$ $[M+H]^+$:192.1383, found 192.1384.



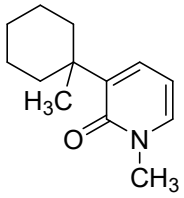
*3-Cyclopentyl-1-methylpyridin-2(1H)-one (**4e**)*. Flash column chromatography [EtOAc:Et_3N (99:1)]; Brown oil (35%, 12.5 mg). R_f = 0.19 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.25 – 7.11 (m, 2H), 6.12 (t, *J* = 6.8 Hz, 1H), 3.56 (s, 3H), 3.24 (p, *J* = 8.3 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.83 – 1.64 (m, 4H), 1.58 – 1.42 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.1, 137.3, 135.2, 133.3, 105.5, 40.2, 37.8, 32.0, 25.3. IR (ν/cm^{-1}) 2949, 2868, 1735, 1646, 1594, 1558, 1241, 1045, 757. HRMS (ESI+) calcd for $C_{11}H_{16}ON$ $[M+H]^+$:178.1226, found 178.1224.



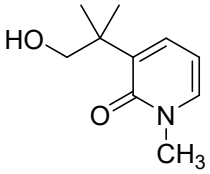
*1-Methyl-3-(1-phenoxyethyl)pyridin-2(1H)-one (**4f**).* Flash column chromatography [EtOAc:*n*-hexane:Et_3N (50:50:1)]; Yellow oil (46%, 21 mg). R_f = 0.16 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 (dd, *J* = 6.9, 1.6 Hz, 1H), 7.28 – 7.18 (m, 3H), 6.95 – 6.83 (m, 3H), 6.16 (t, *J* = 6.8 Hz, 1H), 5.64 (q, *J* = 6.3 Hz, 1H), 3.61 (s, 3H), 1.60 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.4, 157.5, 136.8, 134.7, 133.8, 129.4, 120.6, 115.5, 106.0, 70.1, 37.6, 21.6. IR (ν/cm^{-1}) 2976, 2929, 1650, 1596, 1560, 1493, 1236, 1086, 754. HRMS (ESI+) calcd for $C_{14}H_{16}O_2N$ $[M+H]^+$:230.1176, found 230.1177.



*3-((3r,5r,7r)-Adamantan-1-yl)-1-methylpyridin-2(1H)-one (**4g**)*. Flash column chromatography [EtOAc:*n*-hexane:Et_3N (50:50:1)]; Colourless solid (49%, 24 mg). m.p. 175 – 177 °C (EtOAc). R_f = 0.39 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.26 – 7.12 (m, 2H, H4, H6), 6.12 (t, *J* = 6.9 Hz, 1H, H5), 3.52 (s, 3H, NC$\underline{H}_3$), 2.14 – 2.00 (m, 9H), 1.84 – 1.70 (m, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.1, 140.3, 135.7, 133.9, 105.2, 39.5, 37.8, 37.1, 37.0, 28.8. IR (ν/cm^{-1}) 2900, 2848, 1641, 1582, 1570, 1552, 1342, 1211, 758. HRMS (ESI+) calcd for $C_{16}H_{22}ON$ $[M+H]^+$:244.1696, found 244.1697.

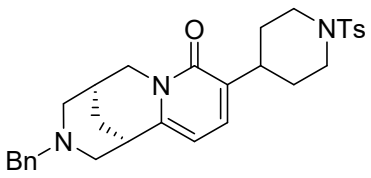


*1-Methyl-3-(1-methylcyclohexyl)pyridin-2(1H)-one (**4h**)*. Flash column chromatography [EtOAc:*n*-hexane:Et_3N (50:50:1)]; Yellow solid (49%, 10 mg). m.p. 70 – 72 °C (EtOAc). R_f = 0.35 (EtOAc:*n*-hexane, 3:7). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.22 (dd, *J* = 6.6, 2.0 Hz, 1H), 6.18 – 6.07 (m, 1H), 3.53 (s, 3H), 2.22 – 2.01 (m, 2H), 1.80 – 1.35 (m, 8H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.4, 139.6, 135.8, 135.1, 105.1, 38.3, 38.0, 35.7, 26.7 (2C), 22.6. IR (ν/cm^{-1}) 2922, 2851, 1646, 1595, 1580, 1448, 1367, 1214, 750. HRMS (ESI+) calcd for $C_{13}H_{20}ON$ $[M+H]^+$:206.1539, found 206.1540.



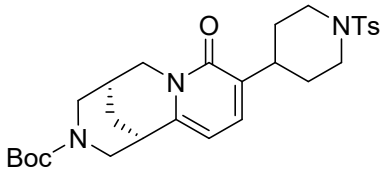
*3-(1-Hydroxy-2-methylpropan-2-yl)-1-methylpyridin-2(1H)-one (**4i**)*. Flash column chromatography [EtOAc:MeOH:Et_3N (99:1:1)]; Colourless solid (17%, 3 mg). m.p. 123 – 124 °C (EtOAc). R_f = 0.38 (DCM:MeOH, 97.5:2.5). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.26 (dd, *J* = 6.5, 2.0 Hz, 1H), 6.29 – 6.16 (m, 1H), 5.04 (s, 1H), 3.80 – 3.66 (m, 2H), 3.58 (s, 3H), 1.36 (s, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.9, 138.4, 136.4, 136.1, 106.3, 72.1, 40.5, 38.4, 24.7. IR (ν/cm^{-1}) 3382, 2957, 2922, 2866, 1636, 1573, 1555, 1384, 1052, 778, 543. HRMS (ESI+) calcd for $C_{10}H_{16}O_2N$ $[M+H]^+$: 182.1176, found 182.1177.

Cytisine scope

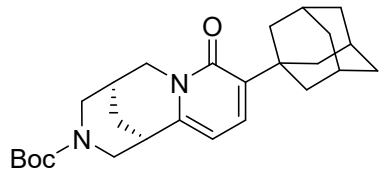


*3-(1-Tosylpiperidin-4-yl)-N-benzyl-(–)-cytisine (**5a**)*. Flash column chromatography [EtOAc:*n*-hexane:Et_3N (40:60:1)]; Amorphous yellow solid (29%, 15 mg). m.p. 80 – 82 °C (EtOAc). R_f = 0.28 (EtOAc). $[\alpha]_D^{27}$ = –122 (*c* 0.97, $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.75 – 7.64 (m, 2H), 7.42 – 7.32 (m, 2H), 7.21 – 7.13 (m, 3H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.99 – 6.89 (m, 2H), 5.92 (d, *J* = 7.2 Hz, 1H), 4.11 (d, *J* = 15.3 Hz, 1H), 4.01 – 3.80 (m, 3H), 3.54 – 3.34 (m, 2H), 3.00 – 2.78 (m, 4H), 2.47 (s, 3H), 2.46 – 2.27 (m, 5H), 2.11 – 1.86 (m, 3H), 1.86 – 1.57

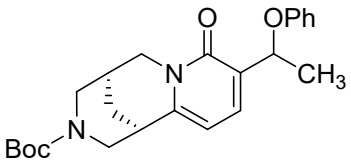
(m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.6, 148.9, 143.5, 138.2, 133.0, 131.2, 129.6, 128.1, 128.1, 127.8, 126.9, 104.2, 61.8, 60.1, 60.0, 50.2, 47.0, 35.4, 34.8, 30.7, 28.2, 26.0, 21.5. IR (ν/cm^{-1}) 2926, 2844, 2797, 1639, 1587, 1559, 1351, 1162, 927, 723, 650. HRMS (ESI+) calcd for $C_{30}H_{36}O_3N_3S$ [M+H]$^+$: 518.2472, found 518.2471.



*3-(1-Tosylpiperidin-4-yl)-N-Boc-(–)-cytisine (**5b**).* Flash column chromatography [EtOAc:Et_3N (99:1)]; Amorphous colourless solid (47%, 25 mg). m.p. 60 – 63 °C (EtOAc). R_f = 0.28 (EtOAc). $[\alpha]_D^{27}$ = –97 (*c* 0.83, $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.76 – 7.56 (m, 2H), 7.47 – 7.30 (m, 2H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.19 – 5.93 (m, 1H), 4.53 – 4.00 (m, 3H), 3.99 – 3.70 (m, 3H), 3.22 – 2.84 (m, 3H), 2.84 – 2.62 (m, 1H), 2.51 – 2.25 (m, 6H), 2.05 – 1.76 (m, 4H), 1.72 – 1.45 (m, 2H), 1.45 – 1.02 (m, 9H).^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.5, 154.4, 146.6 and 146.2 (conformers), 143.5, 133.5, 132.9, 132.0 and 131.7 (conformers), 129.6, 127.7, 105.4 and 104.6 (conformers), 80.2 and 79.6 (conformers), 51.7, 50.6, 49.1, 47.0 and 46.9 (conformers), 34.9, 34.8, 30.5, 30.3, 28.0, 27.7, 26.3, 21.5. IR (ν/cm^{-1}) 2925, 2860, 1688, 1641, 1557, 1424, 1160, 1132, 925, 721, 582. HRMS (ESI+) calcd for $C_{28}H_{38}O_5N_3S$ [M+H]$^+$: 528.2527, found 528.2530.

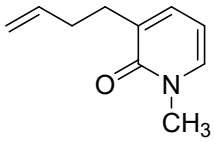


*3-((3r,5r,7r)-Adamantan-1-yl)-N-Boc-(–)-cytisine (**5c**).* Flash column chromatography [EtOAc:Et_3N (99:1)]; Pale yellow solid (31%, 13 mg). m.p. 187 – 190 °C (EtOAc). R_f = 0.24 (EtOAc:*n*-hexane, 1:1). $[\alpha]_D^{27}$ = –124 (*c* 0.72, $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.14 (d, *J* = 7.3 Hz, 1H), 6.12 – 5.94 (m, 1H), 4.50 – 4.05 (m, 3H), 3.81 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.20 – 2.86 (m, 3H), 2.54 – 2.32 (m, 1H), 2.14 – 1.86 (m, 11H), 1.76 (s, 6H), 1.44 – 1.11 (m, 9H).^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.1, 154.5, 145.7, 136.5, 133.5 and 132.8 (conformers), 104.9 and 104.1 (conformers), 80.3 and 79.6 (conformers), 51.8 and 50.7 (conformers), 50.6 and 49.3 (conformers), 48.8, 39.5, 37.1, 36.8, 34.8, 28.8, 28.1, 28.0, 26.4. IR (ν/cm^{-1}) 2900, 2848, 1679, 1637, 1583, 1558, 1453, 1425, 1362, 1238, 1167, 1133. HRMS (ESI+) calcd for $C_{26}H_{37}O_3N_2$ [M+H]$^+$: 425.2799, found 425.2794.



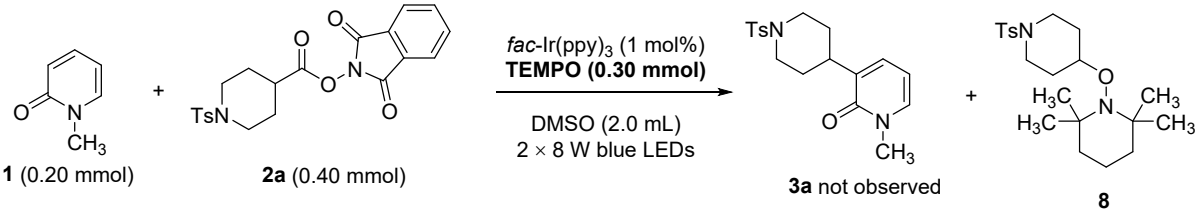
*3-(1-Phenoxyethyl)-N-Boc-(–)-cytisine (**5d**).* Flash column chromatography [EtOAc:Et_3N (99:1)]; Brown oil (10 %, 4 mg). R_f = 0.38 (EtOAc). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 – 7.36 (m, 1H), 7.26 – 7.14 (m, 2H), 6.96 – 6.78 (m, 3H), 6.18 – 5.98 (m, 1H), 5.72 – 5.46 (m, 1H), 4.55 – 4.03 (m, 3H), 3.99 – 3.83 (m, 1H), 3.20 – 2.90 (m, 3H), 2.56 – 2.38 (m, 1H), 2.10 – 1.88 (m, 2H), 1.60 – 1.52 (m, 3H), 1.42 – 1.17 (m, 9H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.5, 157.6, 154.4, 129.4, 120.6, 115.5, 70.6 and 70.1 (conformers), 50.4, 49.1 and 49.0 (conformers), 34.9 and 34.7 (conformers), 28.1, 27.7 and 27.5 (conformers), 26.3 and 26.1 (conformers), 21.7 and 21.5 (conformers), *pyridone carbons and Boc quaternary carbon not observed.* IR (ν/cm^{-1}) 2974, 2918, 2845, 1689, 1641, 1586, 1556, 1454, 1425, 1270, 1238, 1164, 1131, 754. HRMS (ESI+) calcd for $C_{24}H_{31}O_4N_2$ $[M+H]^+$: 411.2278, found 411.2281.

Radical clock experiment



*3-(But-3-en-1-yl)-1-methylpyridin-2(1H)-one (**6**)*. Flash column chromatography [EtOAc:*n*-hexane:Et_3N (80:20:1)]; Brown oil (28%, 9 mg). R_f = 0.22 (EtOAc:*n*-hexane, 1:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.25 – 7.12 (m, 2H), 6.11 (t, *J* = 6.8 Hz, 1H), 5.87 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.14 – 4.92 (m, 2H), 3.56 (s, 3H), 2.73 – 2.57 (m, 2H), 2.46 – 2.30 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.0, 138.2, 136.2, 135.8, 132.8, 115.0, 105.5, 77.5, 37.8, 32.2, 30.2. IR (ν/cm^{-1}) 2919, 2856, 1646, 1586, 1560, 912, 762. HRMS (ESI+) calcd for $C_{10}H_{14}ON$ $[M+H]^+$: 164.1070, found 164.1071.

4. Radical trapping experiment



Under Ar atmosphere, a Schlenk tube was charged with redox active ester (0.20 mmol, 2.0 eq.), TEMPO (0.30 mmol, 3.0 eq.) and $Ir(ppy)_3$ (1 mol%). Anhydrous DMSO (1.0 mL) and *N*-methyl-2-pyridone **1** (0.10 mmol, 1.0 eq.) were added. The reaction mixture was degassed by ultra-sonication for 1 min and stirred for 4 h under the irradiation of blue LEDs (8W × 2, at approximately 2 – 3 cm away from the light source, ca. 35 °C). The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The alkyl-TEMPO adduct **8** was detected by LC-MS (calcd for $C_{21}H_{35}O_3N_2S$ $[M+H]^+$: 395.2363, found 395.2362).

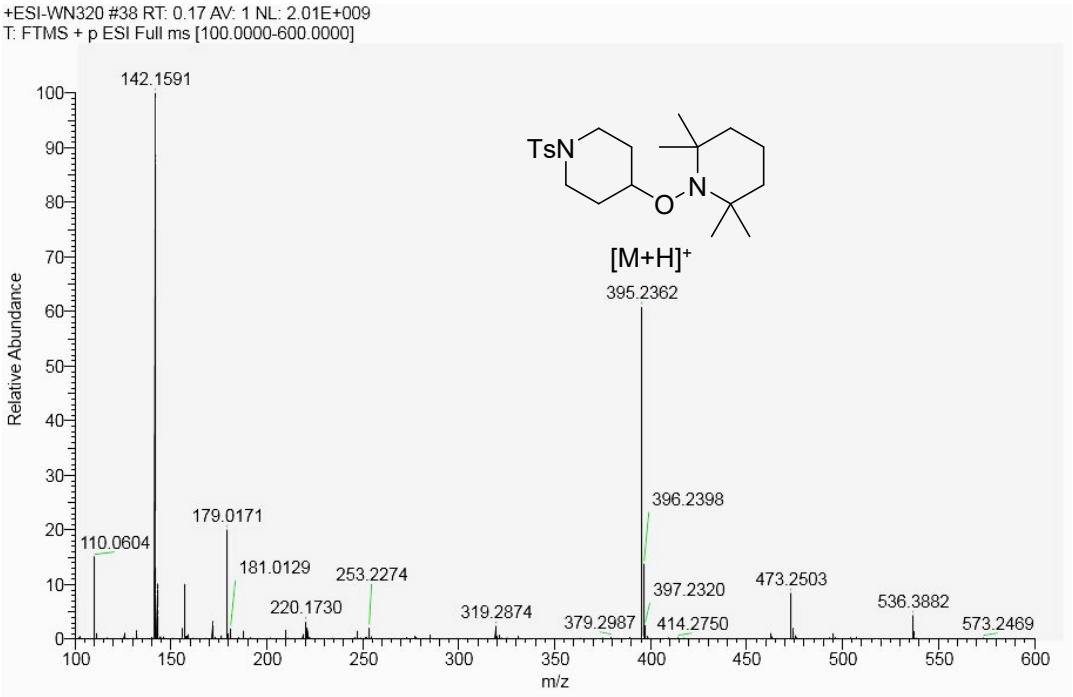


Figure S2. HRMS spectrum of the reaction crude.

5. References

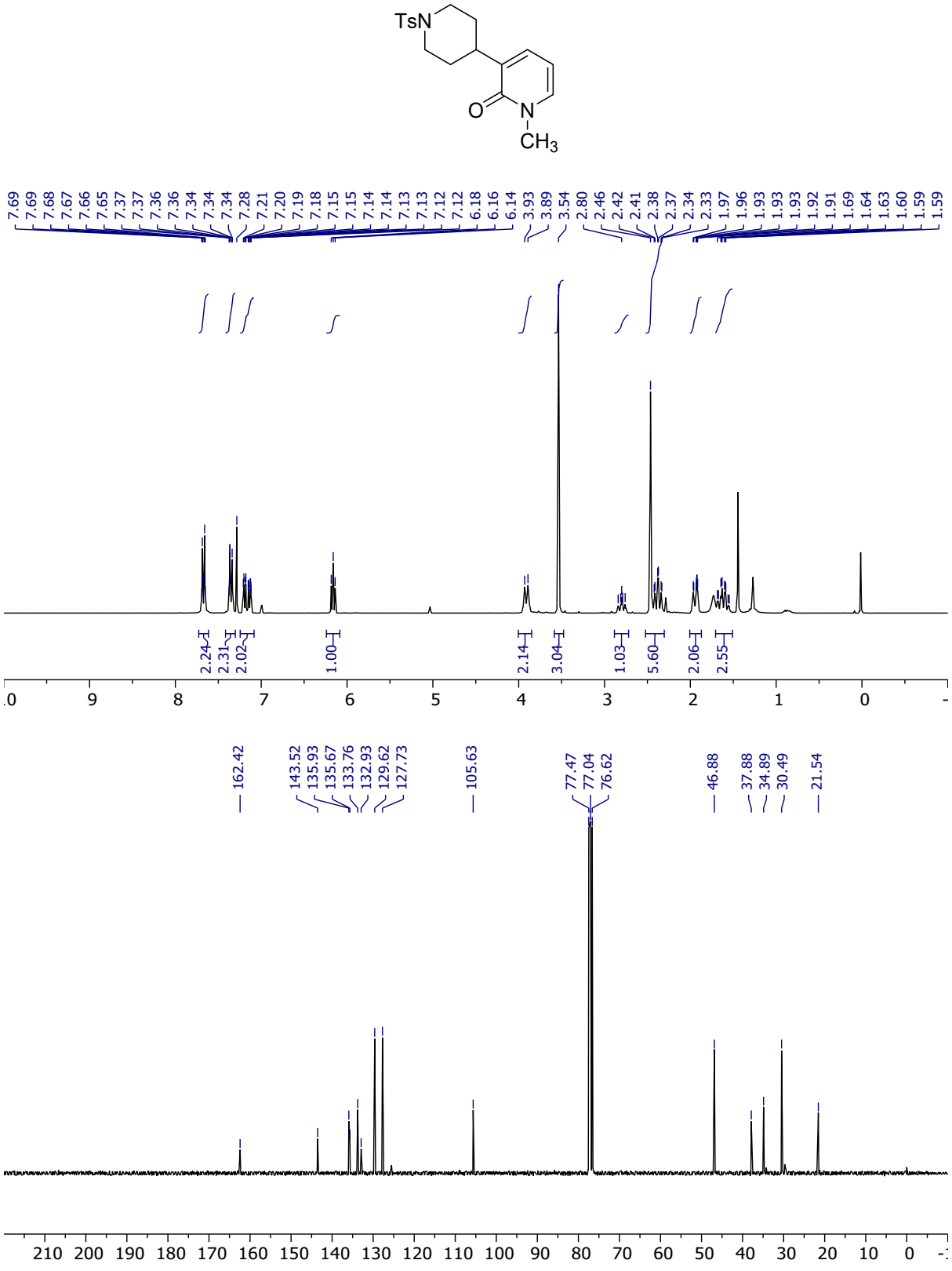
1. (a) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate and P. S. Baran, *Science*, 2016, **352**, 801–805. (b)

2. A. Modak, S. Rana and D. Maiti, *J. Org. Chem.*, 2015, **80**, 296–303.

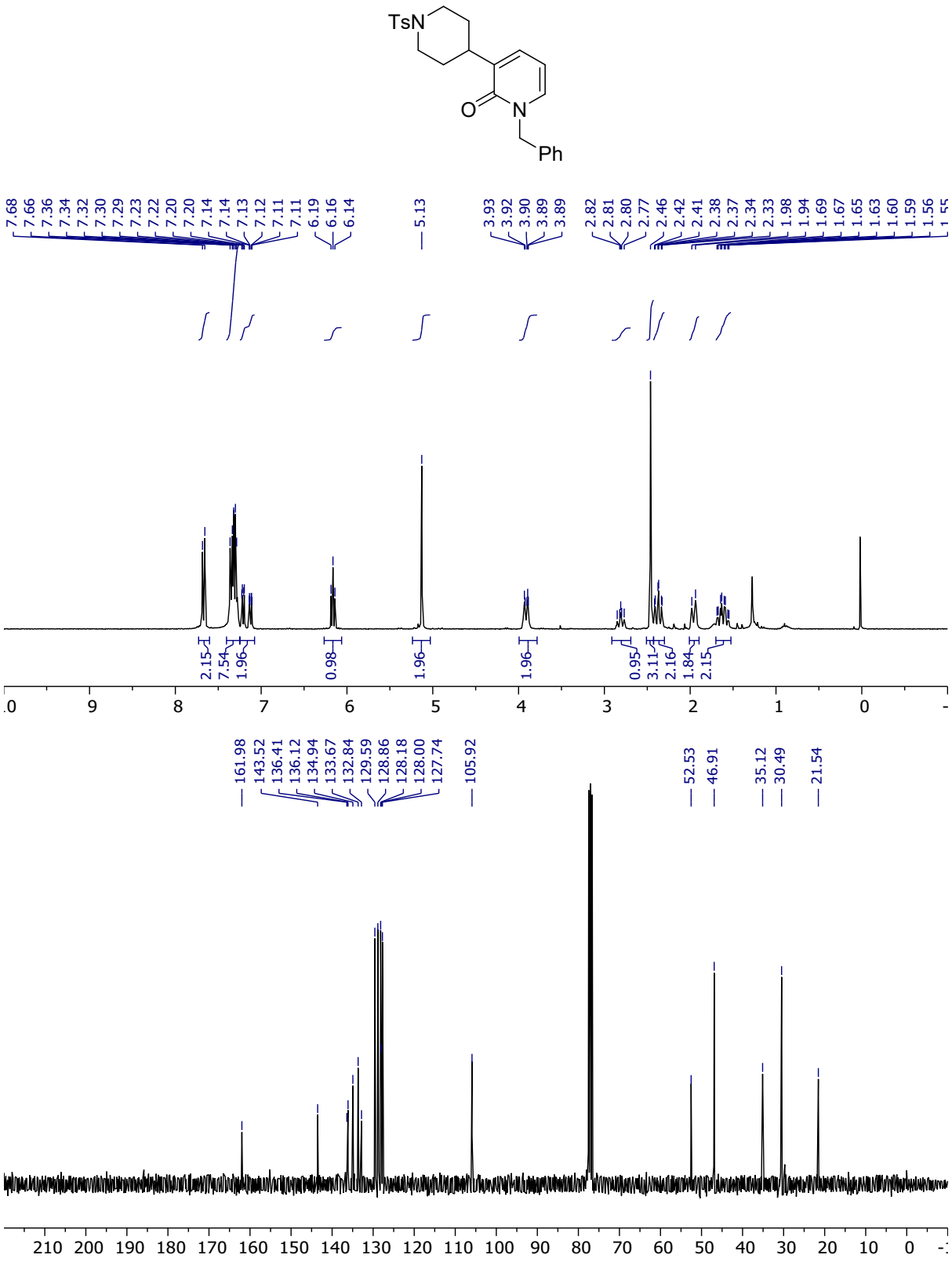
3. D. Das, A. Biswas, U. Karmakar, S. Chand and R. Samanta, *J. Org. Chem.*, 2016, **81**, 842–848.

6. ^{1}H and ^{13}C NMR spectra of all compounds

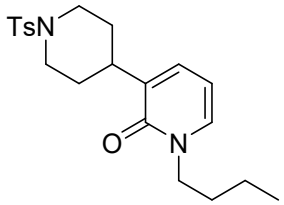
1-Methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3a).

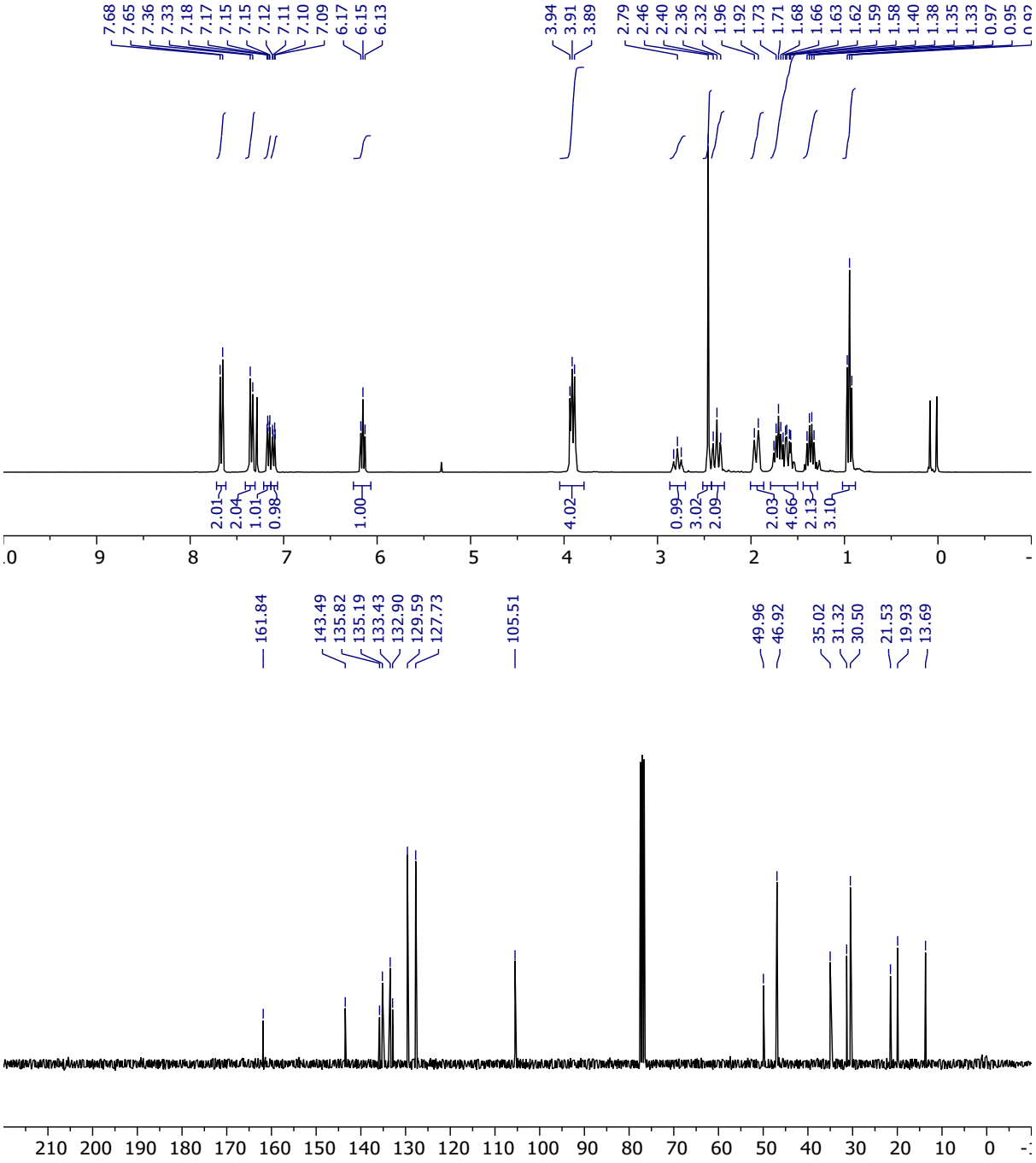


1-Benzyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3b).

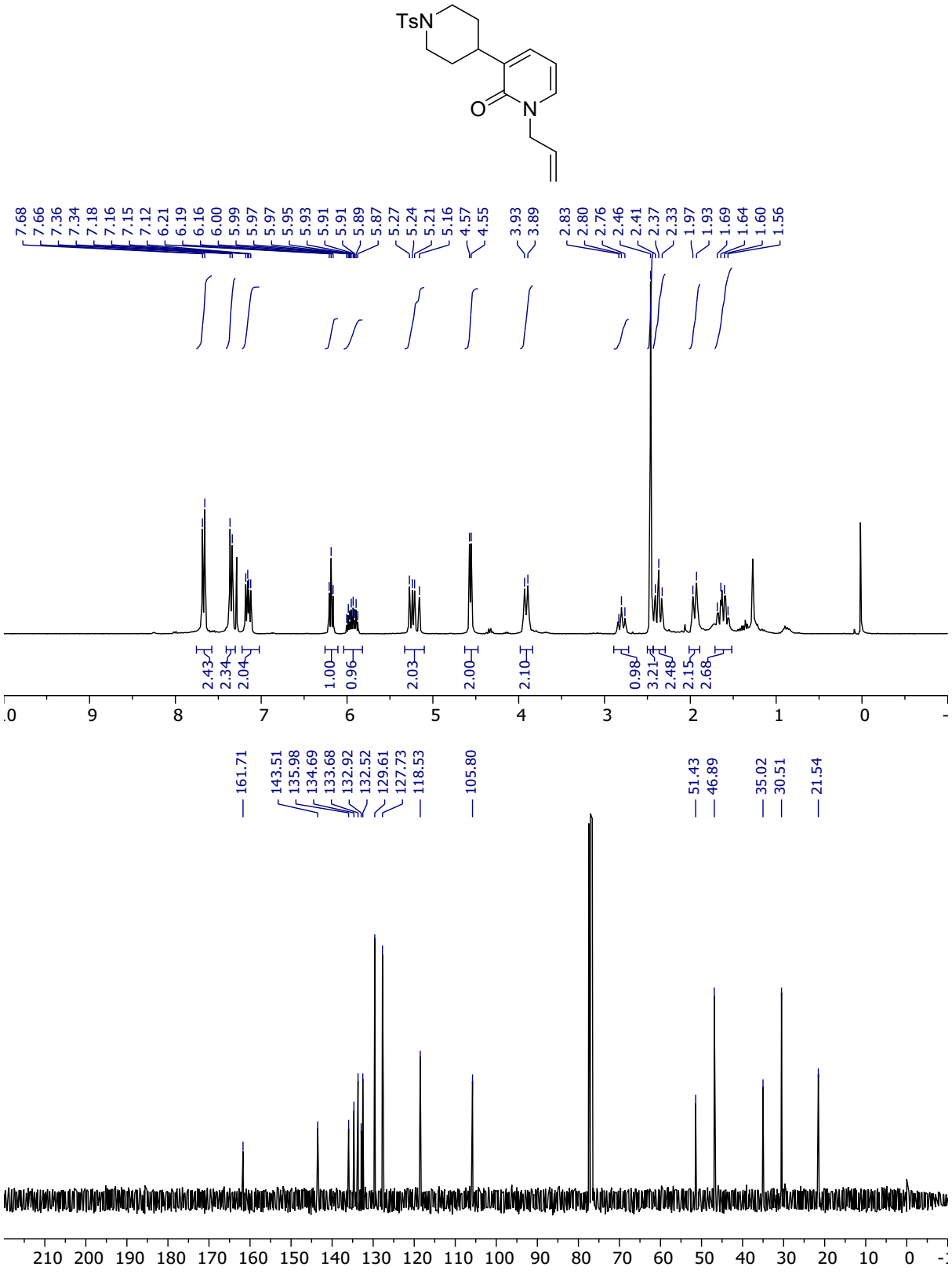


1-Butyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3c)

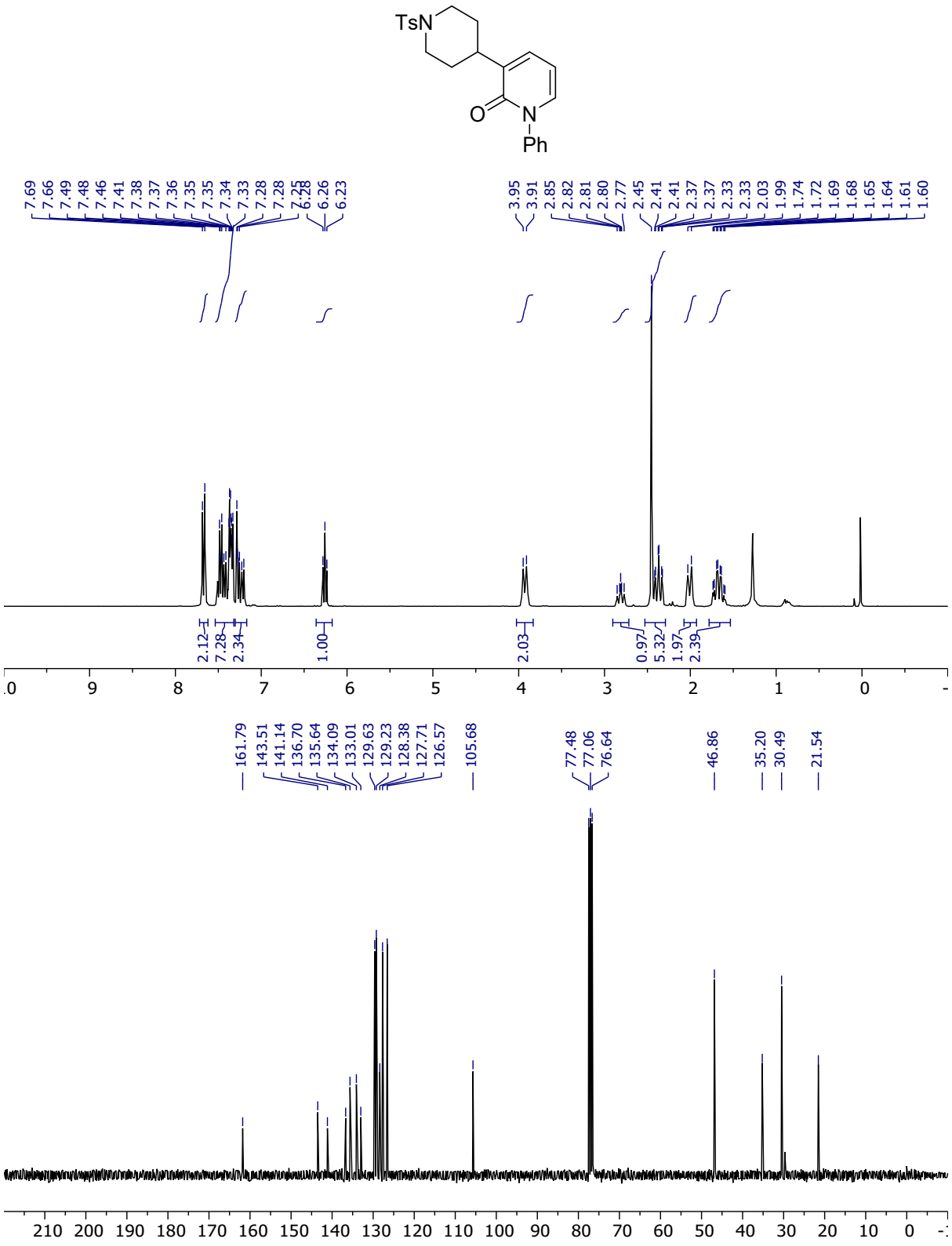




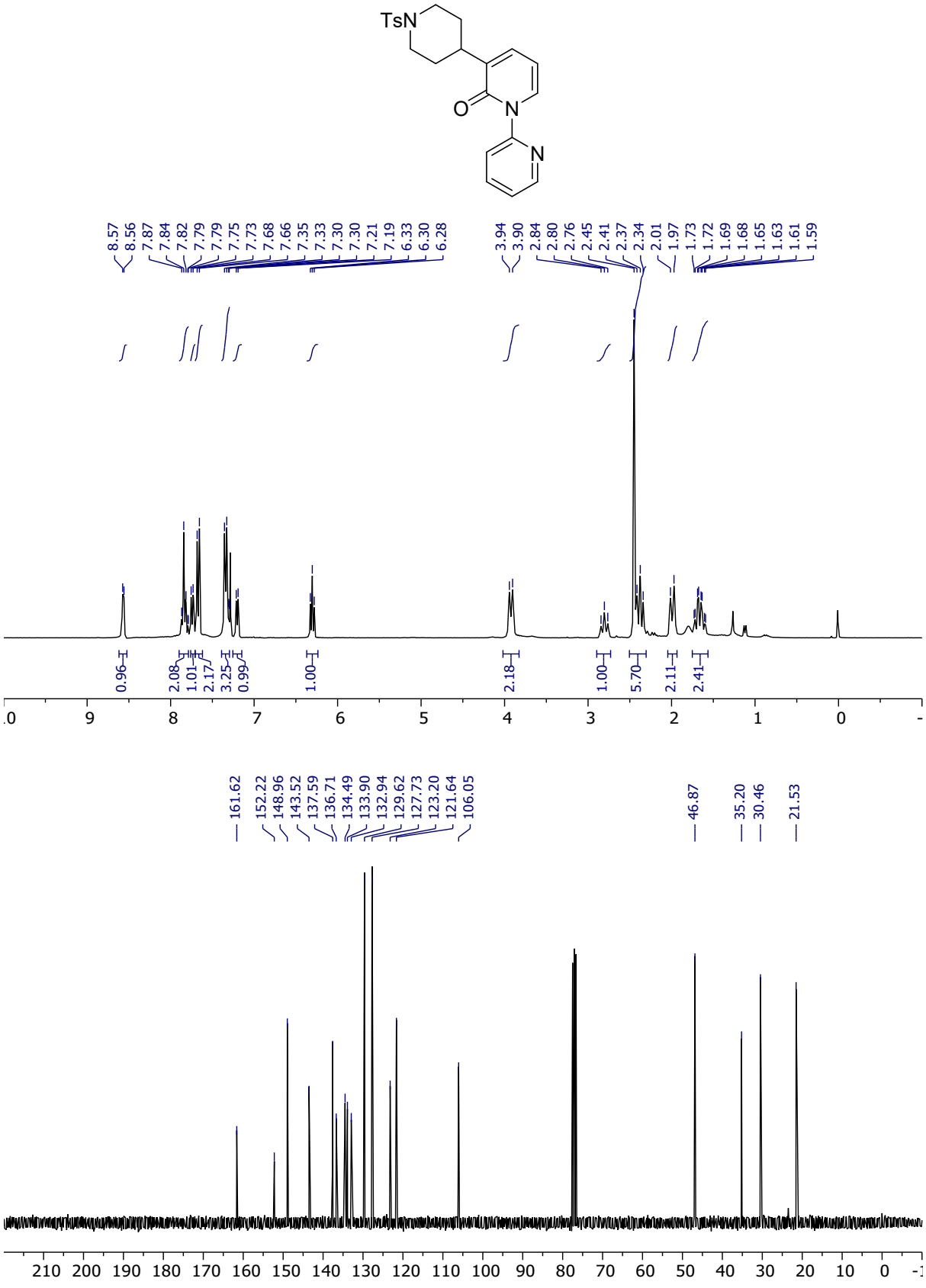
1-Allyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3d)



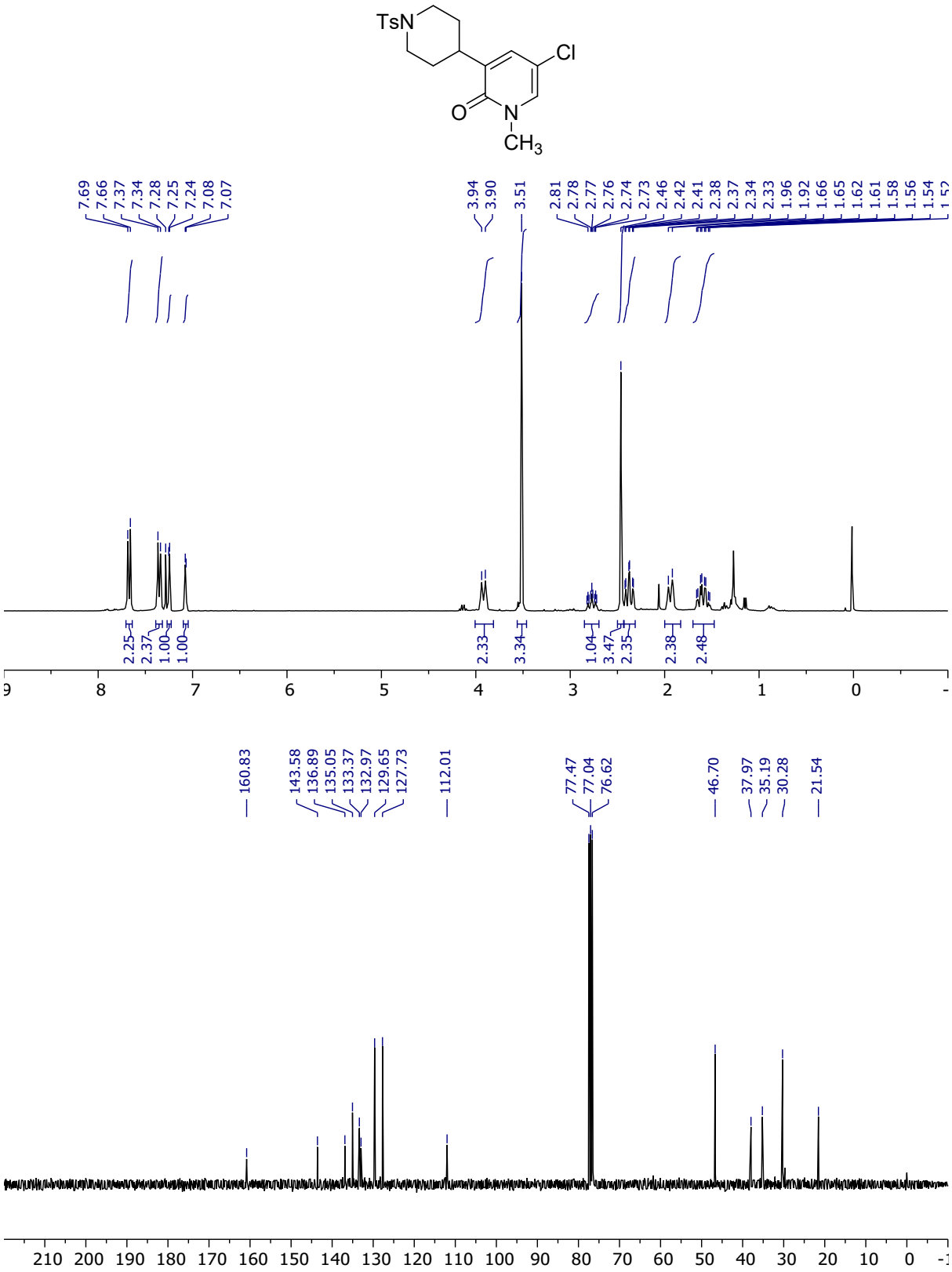
1-Phenyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3e).



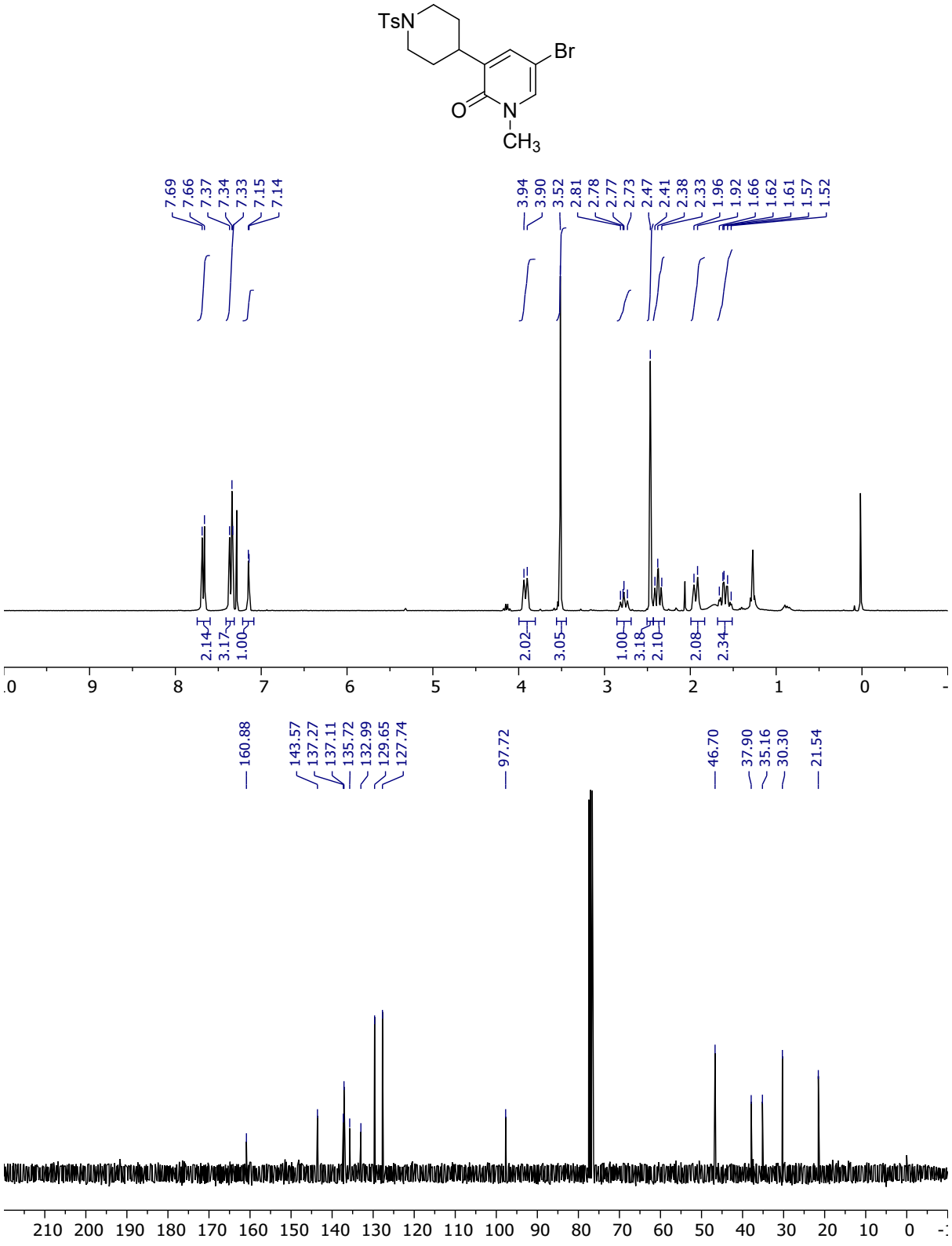
3-(1-Tosylpiperidin-4-yl)-2*H*-[1,2'-bipyridin]-2-one (3f).



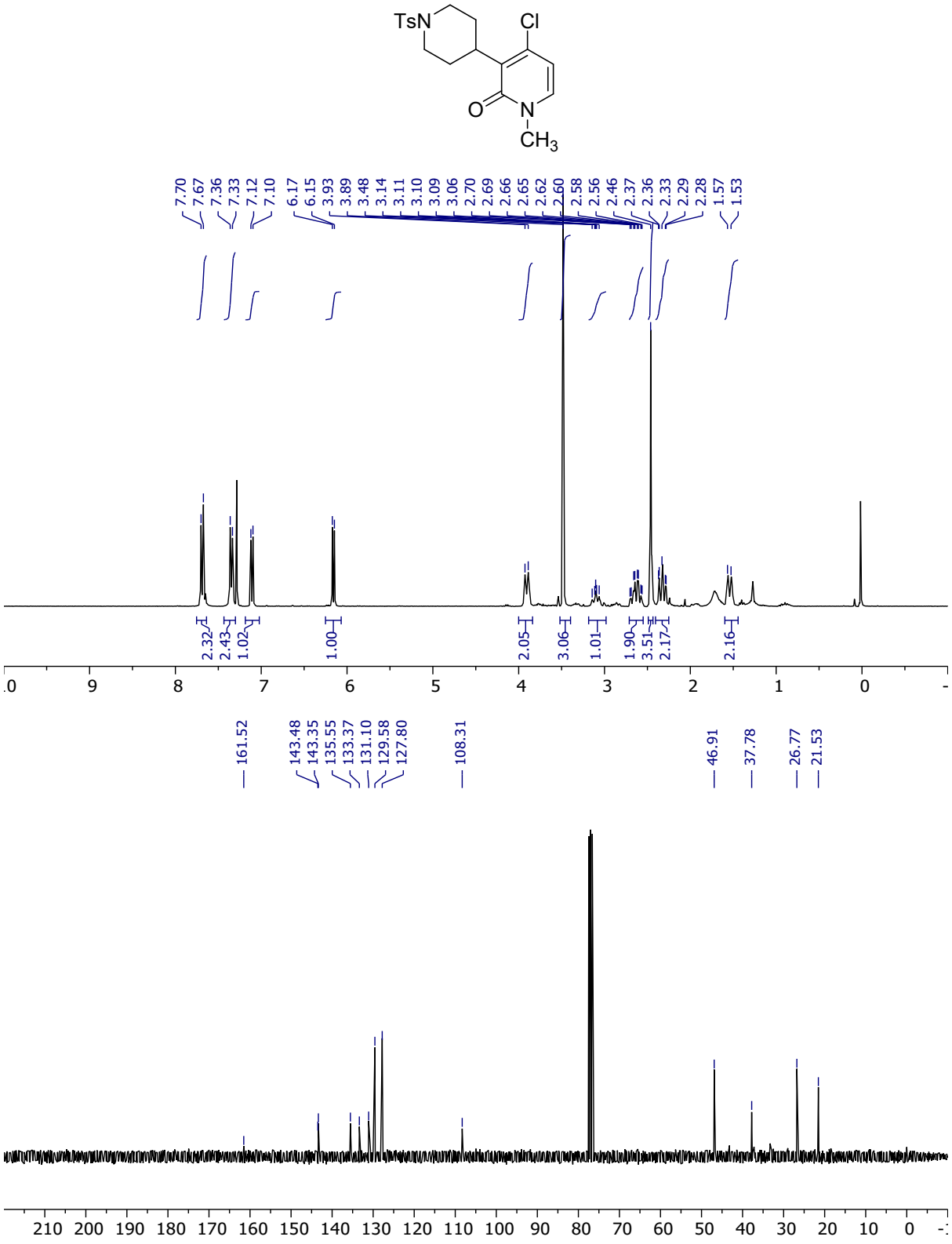
5-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3g).



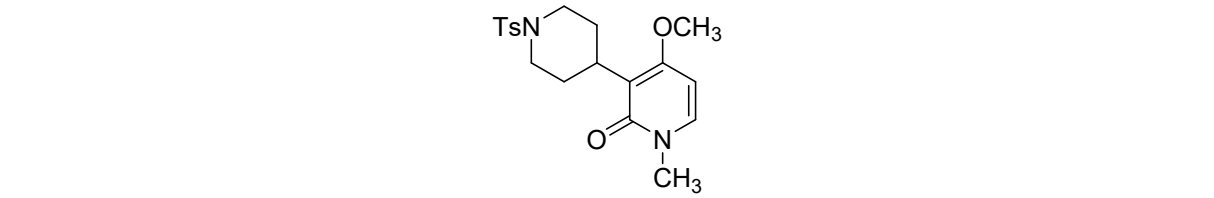
5-Bromo-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3h)

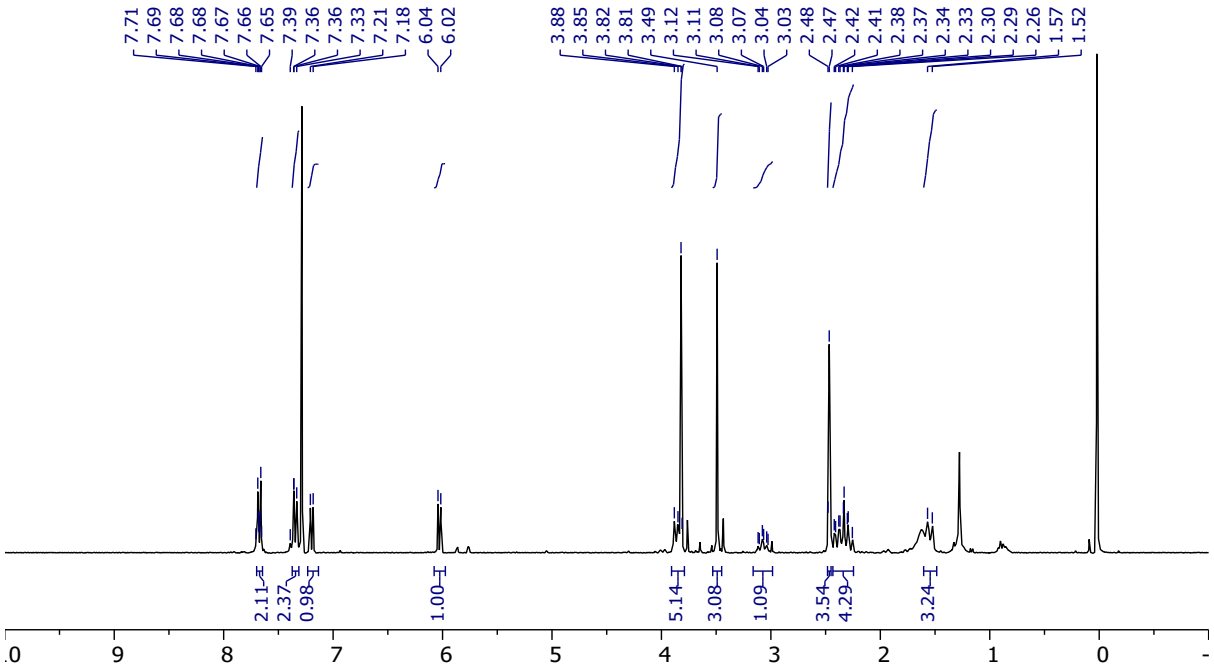


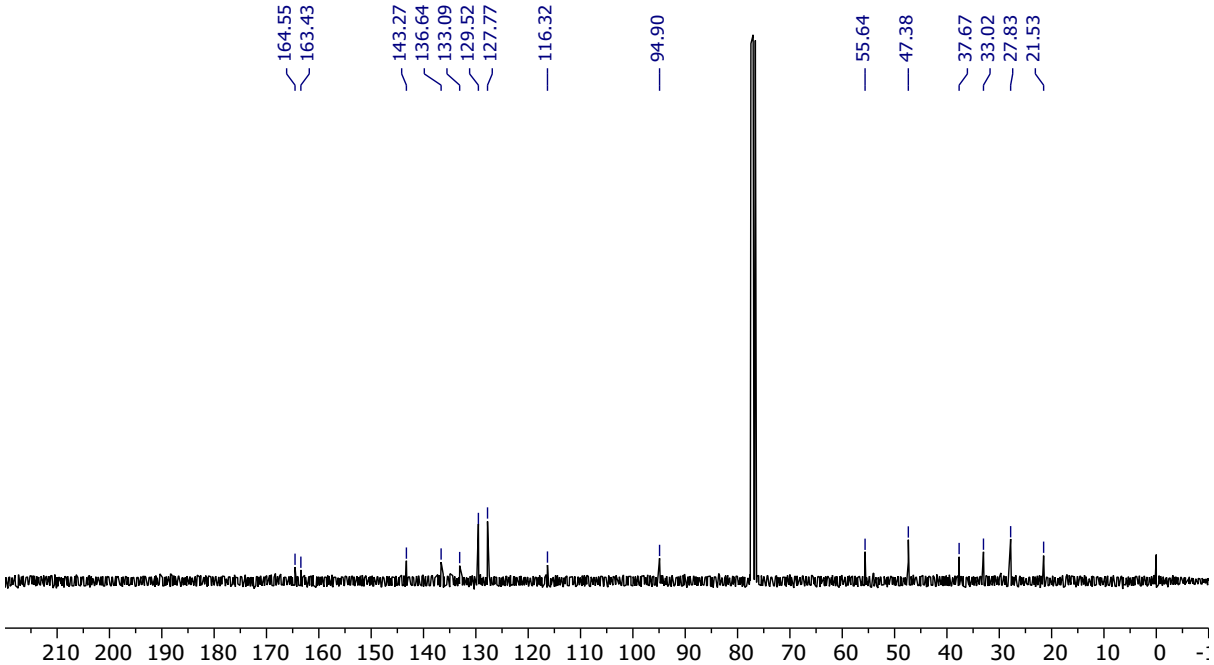
4-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3i)



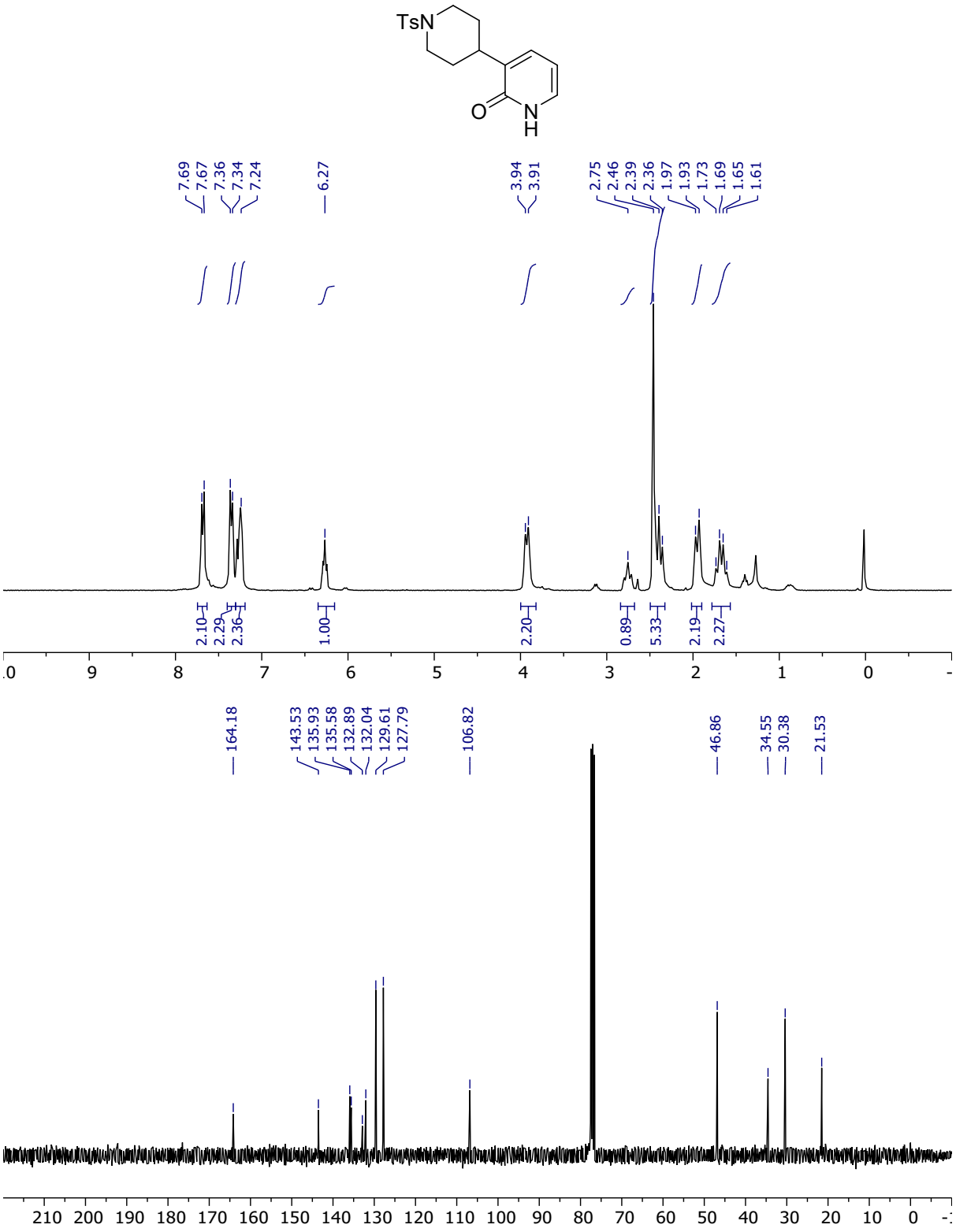
4-Methoxy-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3j)



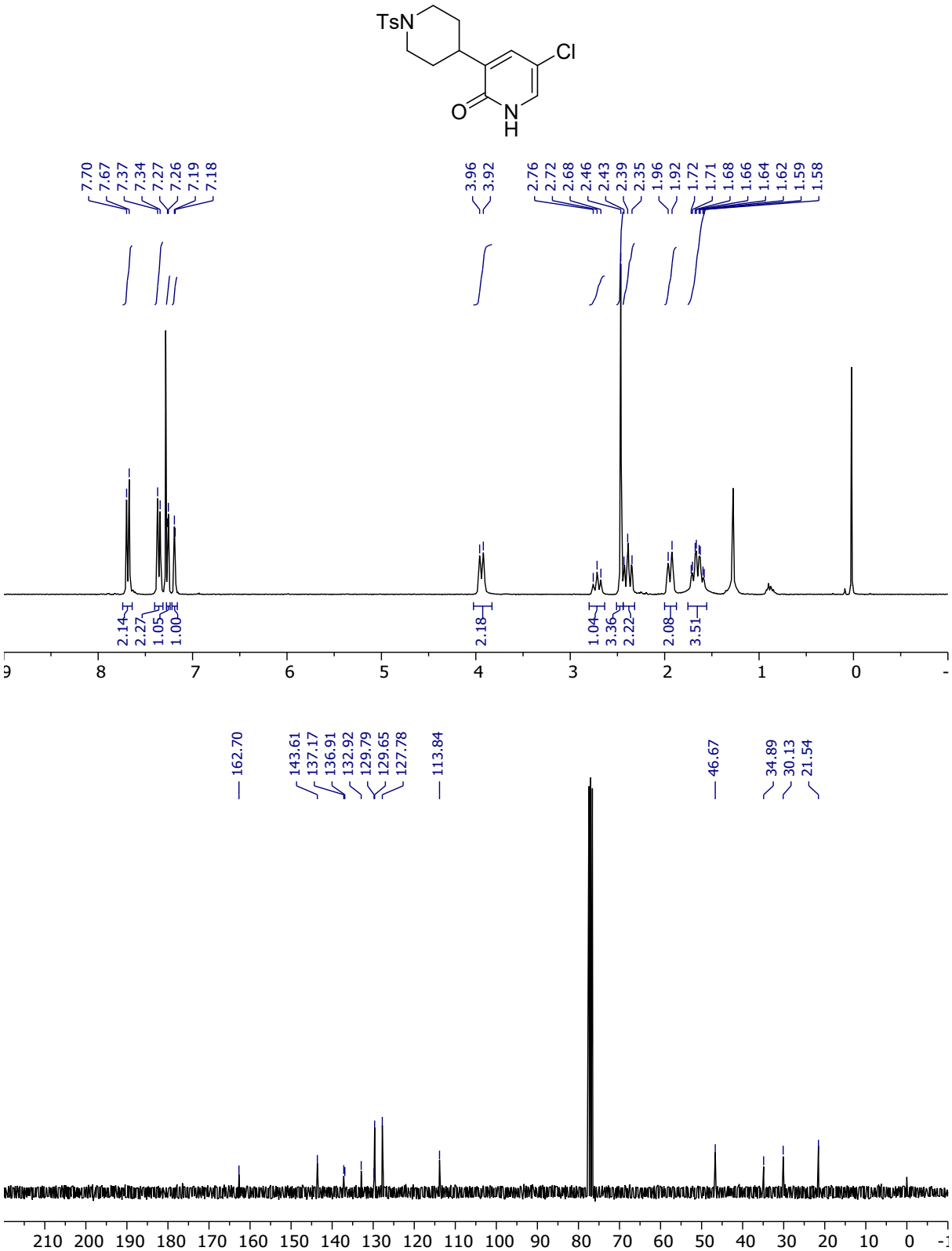




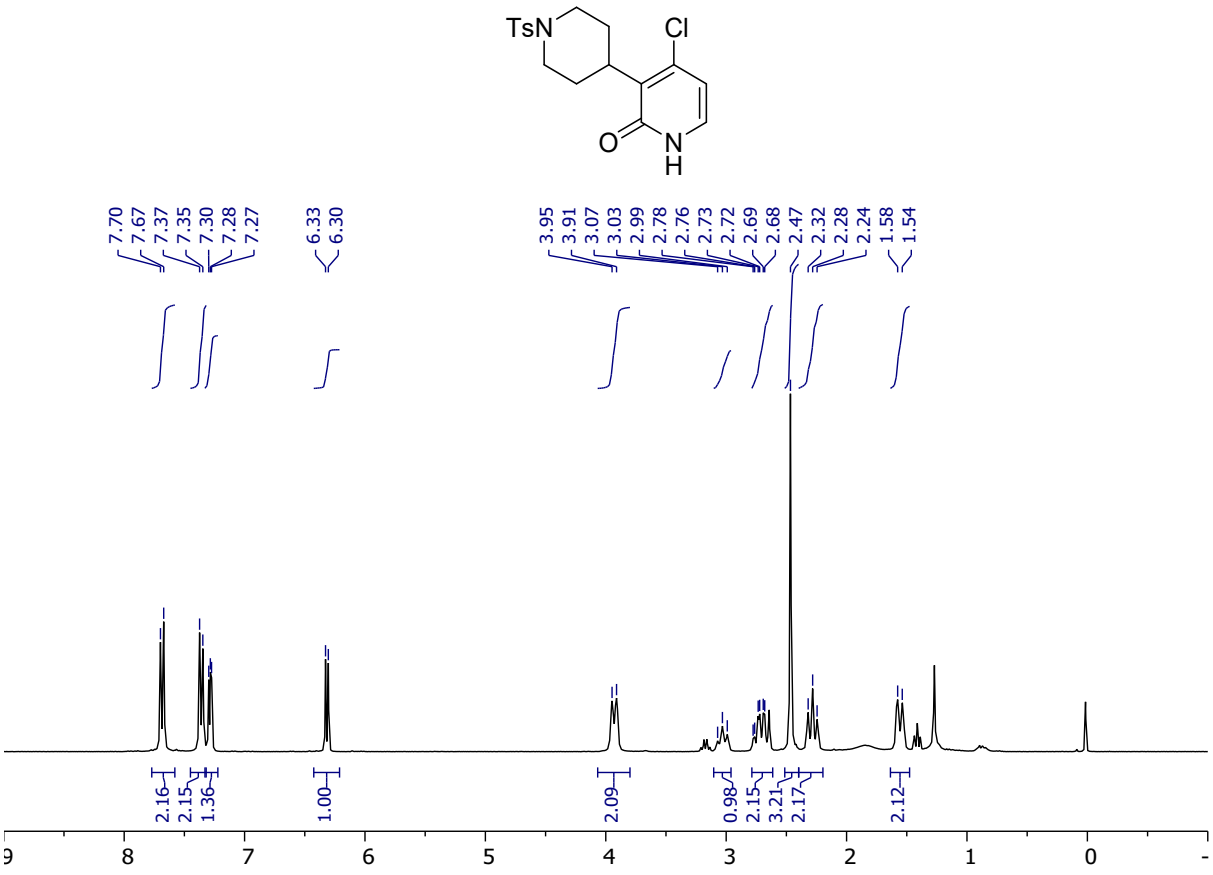
3-(1-Tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3k)

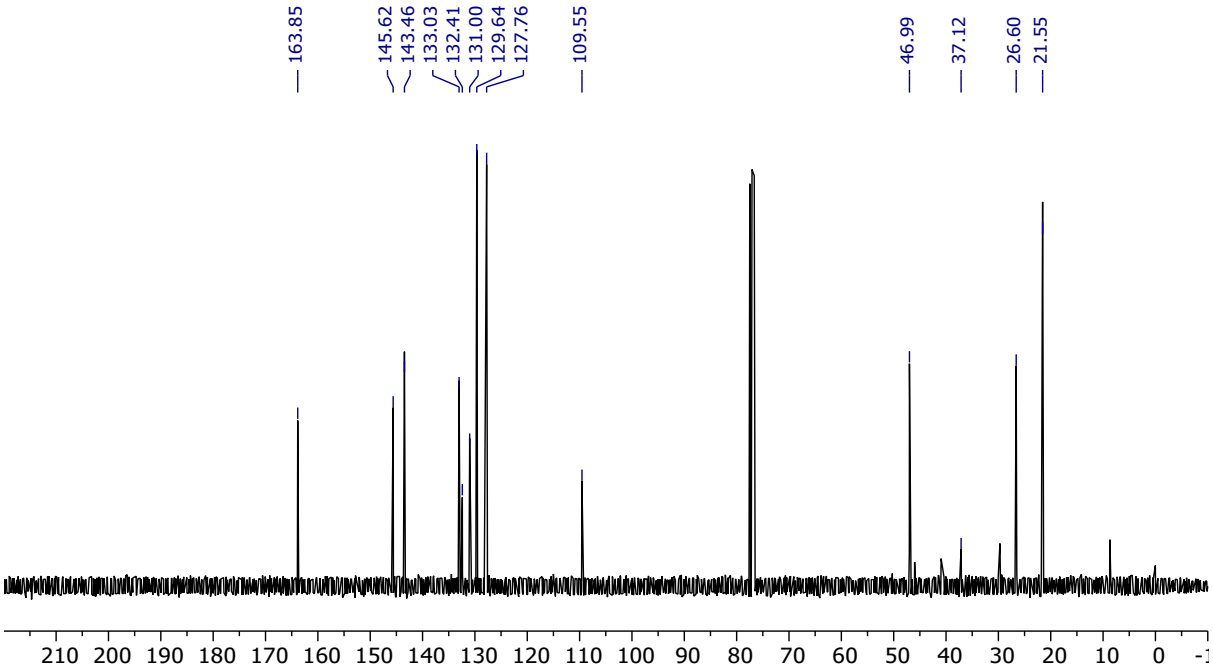


5-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3l).

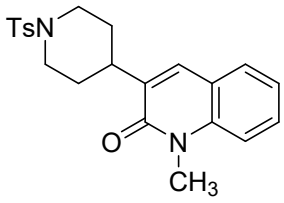


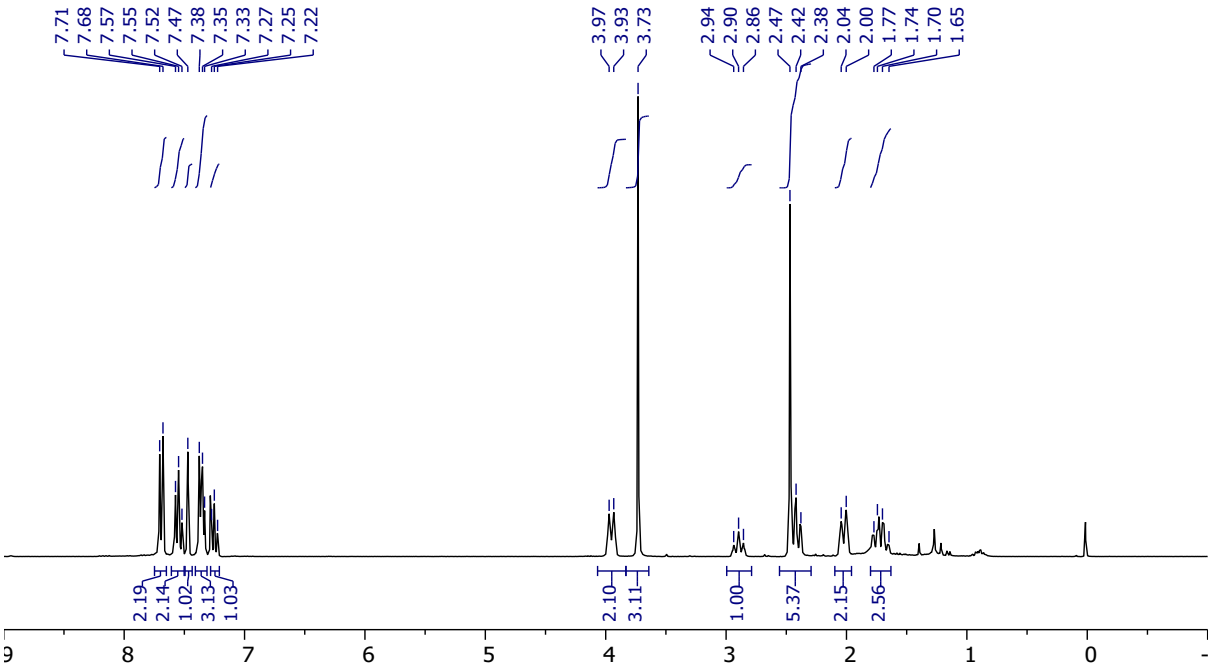
4-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1*H*)-one (3m).

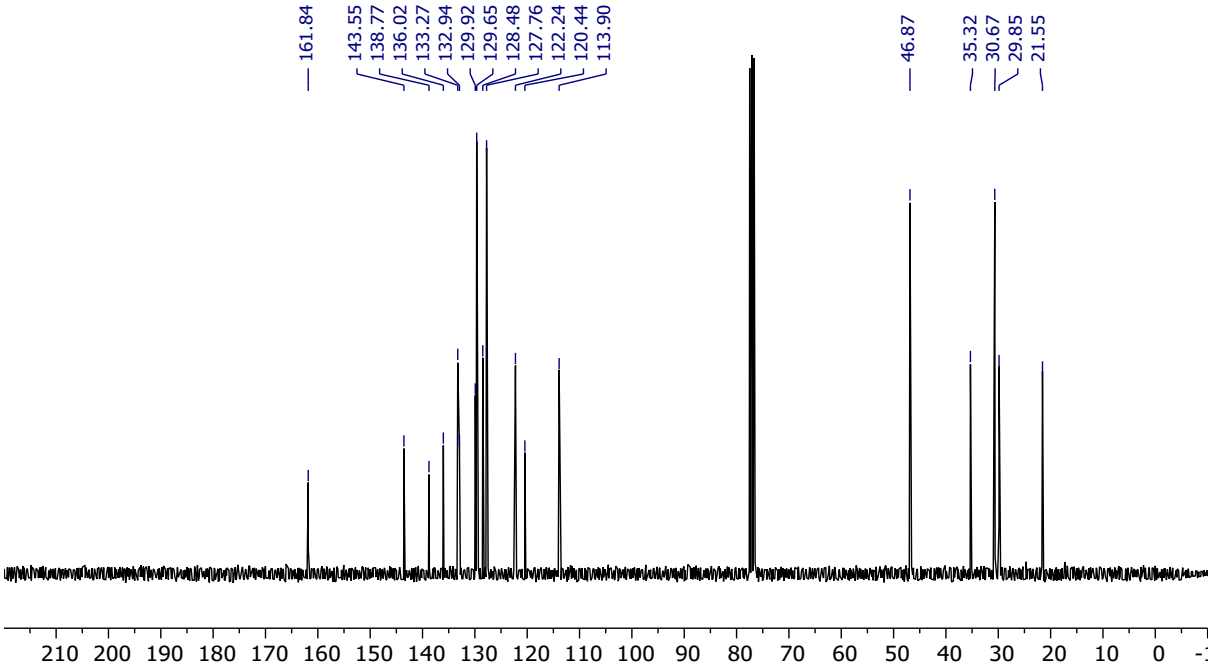




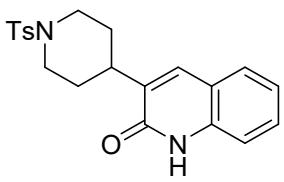
1-Methyl-3-(1-tosylpiperidin-4-yl)quinolin-2(1*H*)-one (3n)

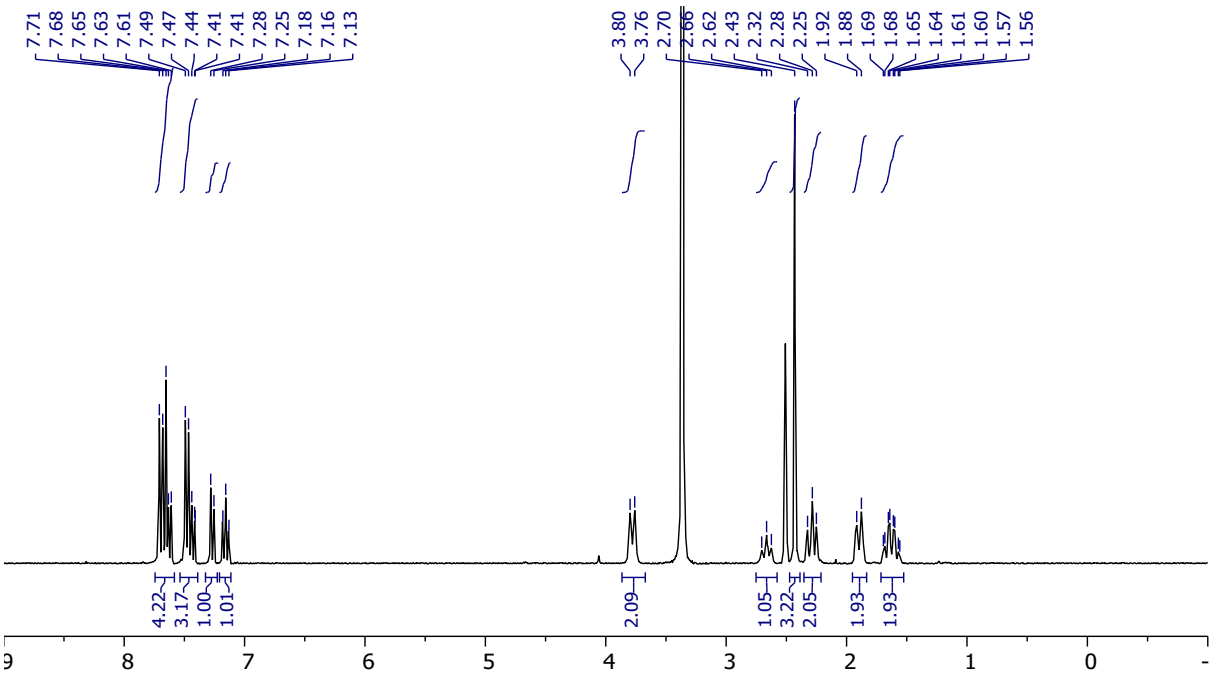


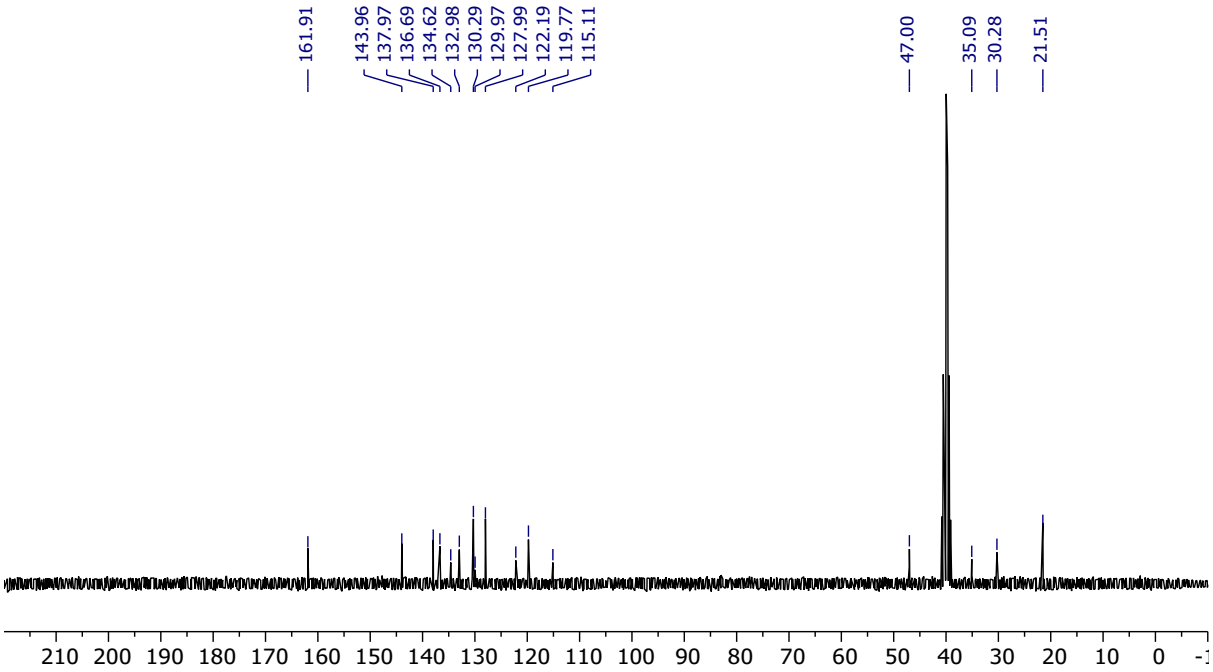




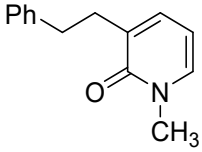
3-(1-Tosylpiperidin-4-yl)quinolin-2(1*H*)-one (3o).

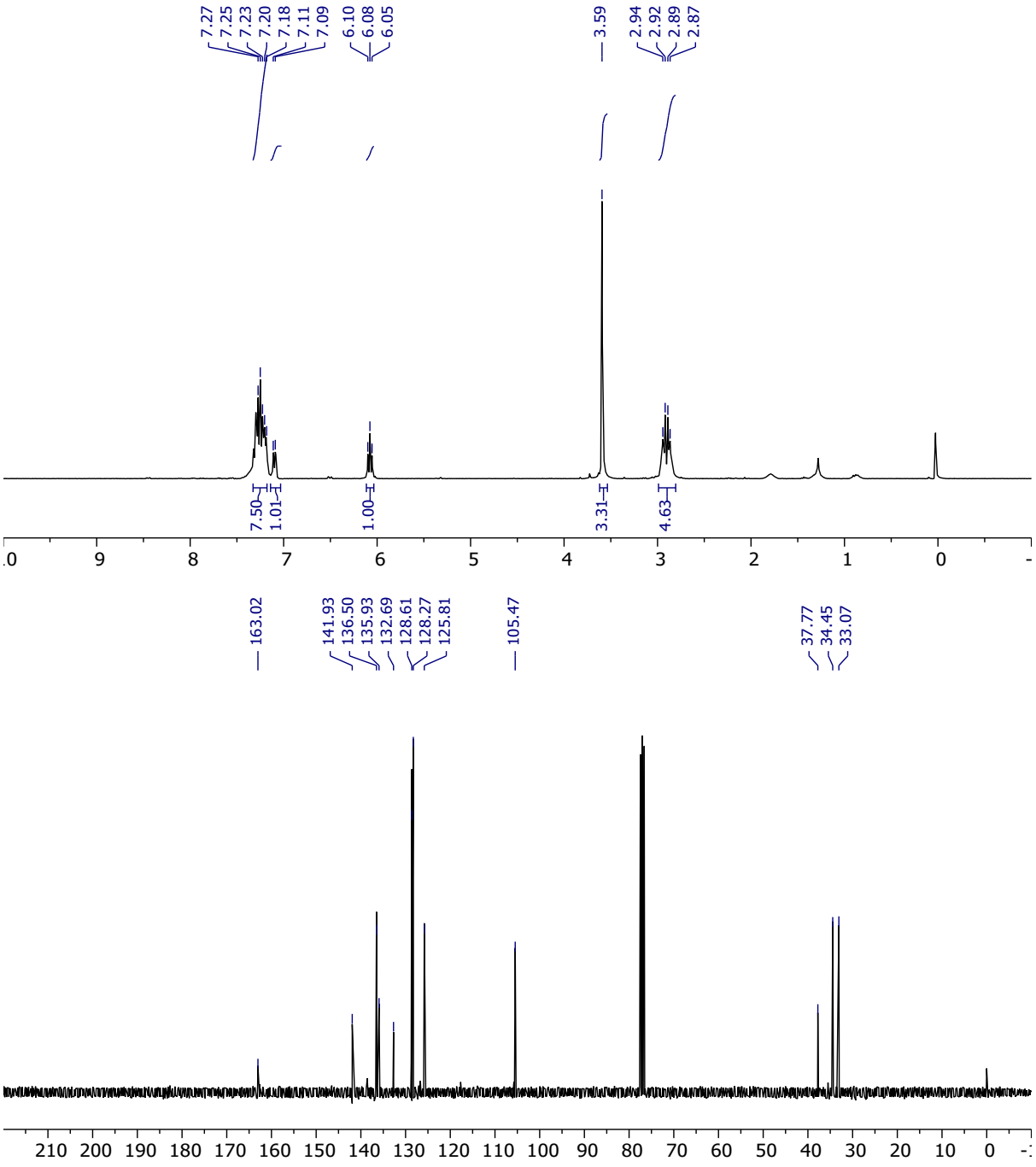




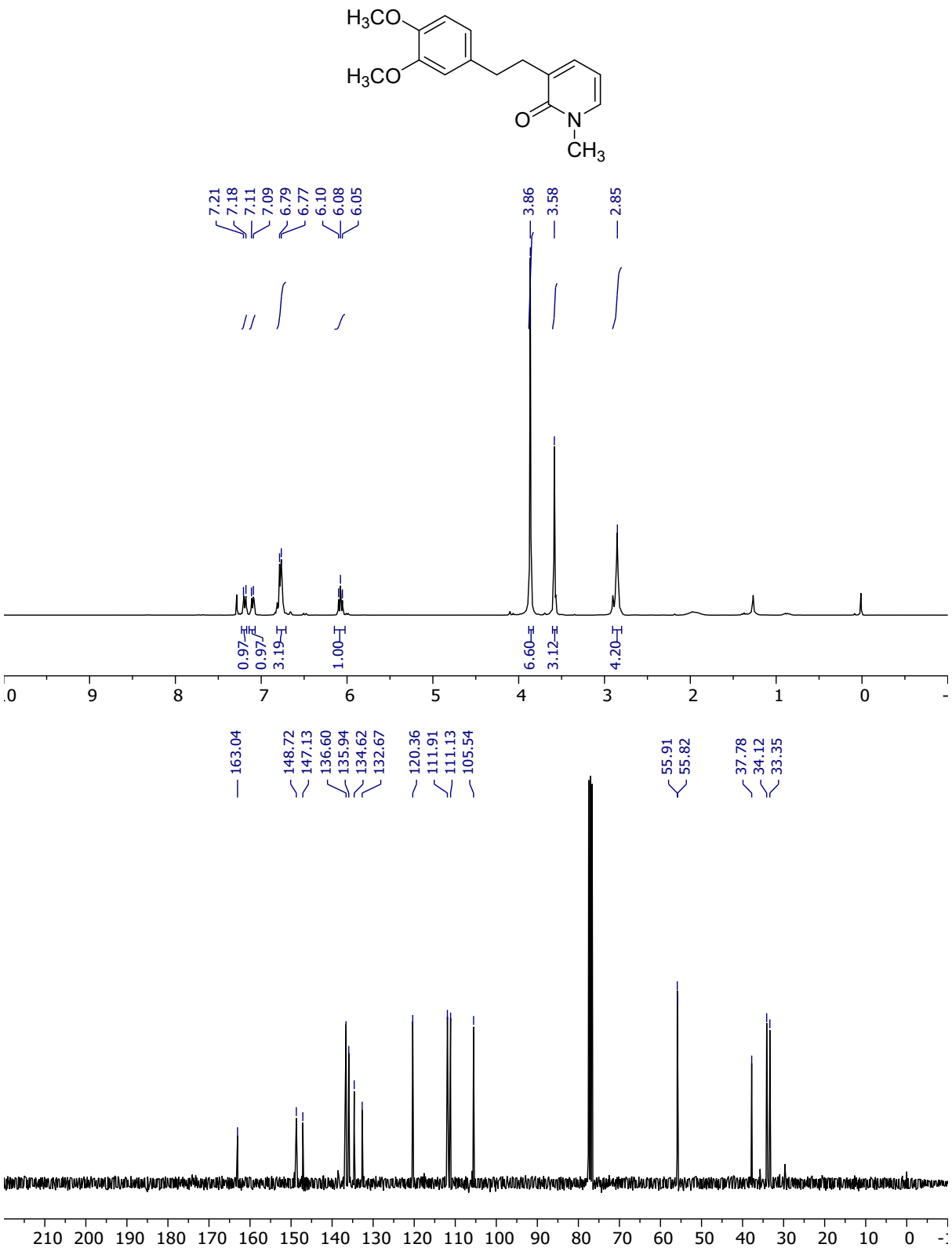


1-Methyl-3-phenethylpyridin-2(1*H*)-one (4a)

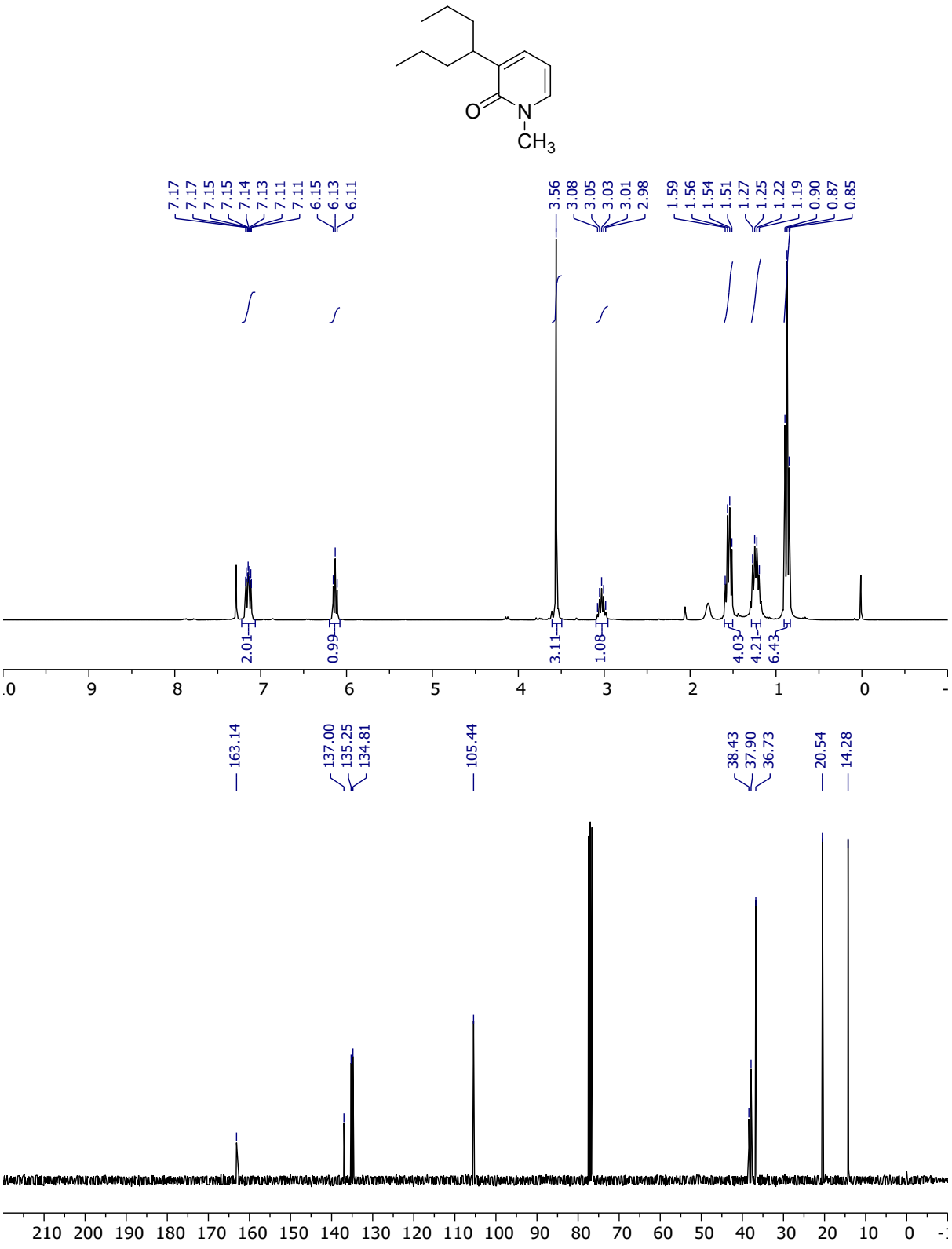




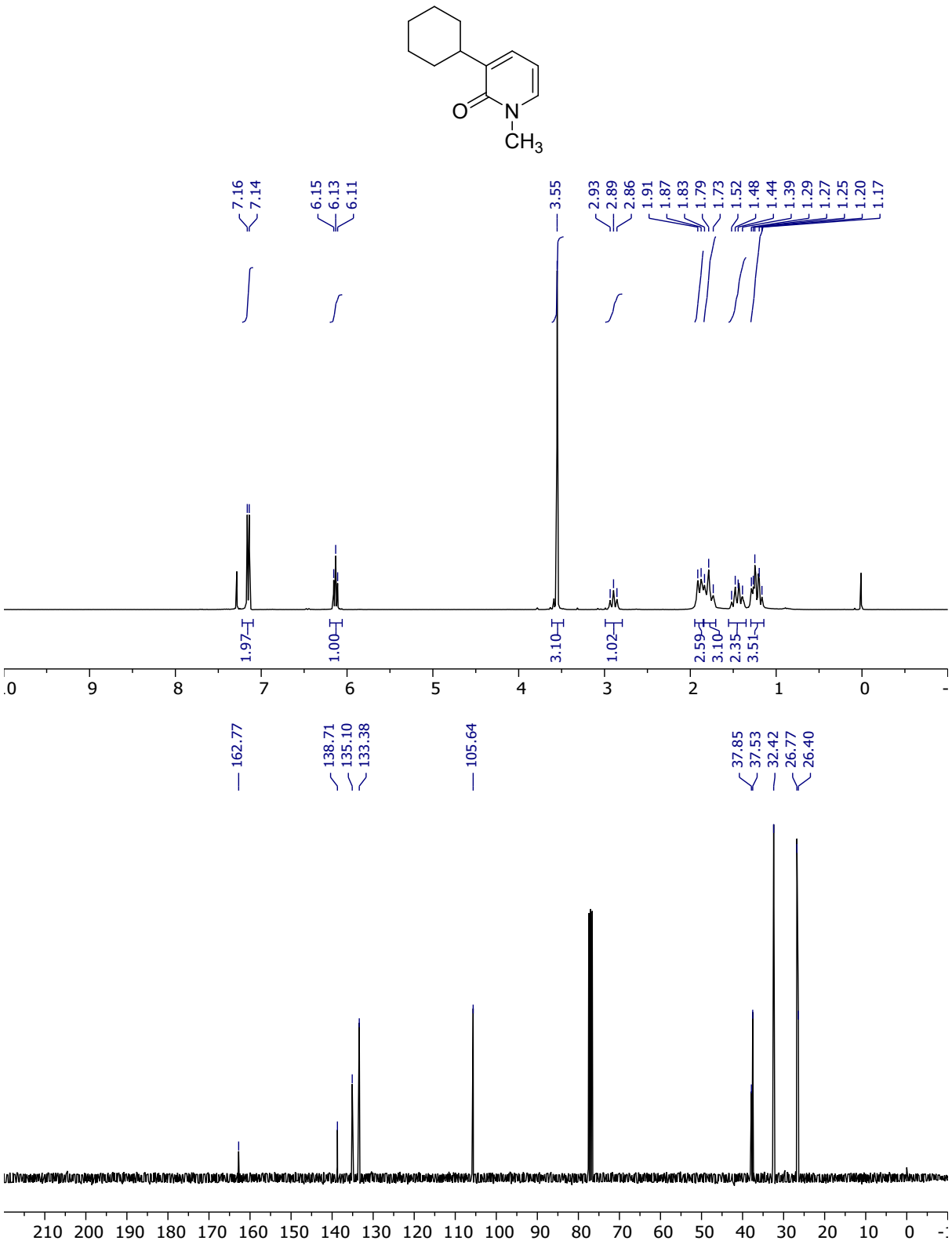
3-(3,4-Dimethoxyphenethyl)-1-methylpyridin-2(1*H*)-one (4b)



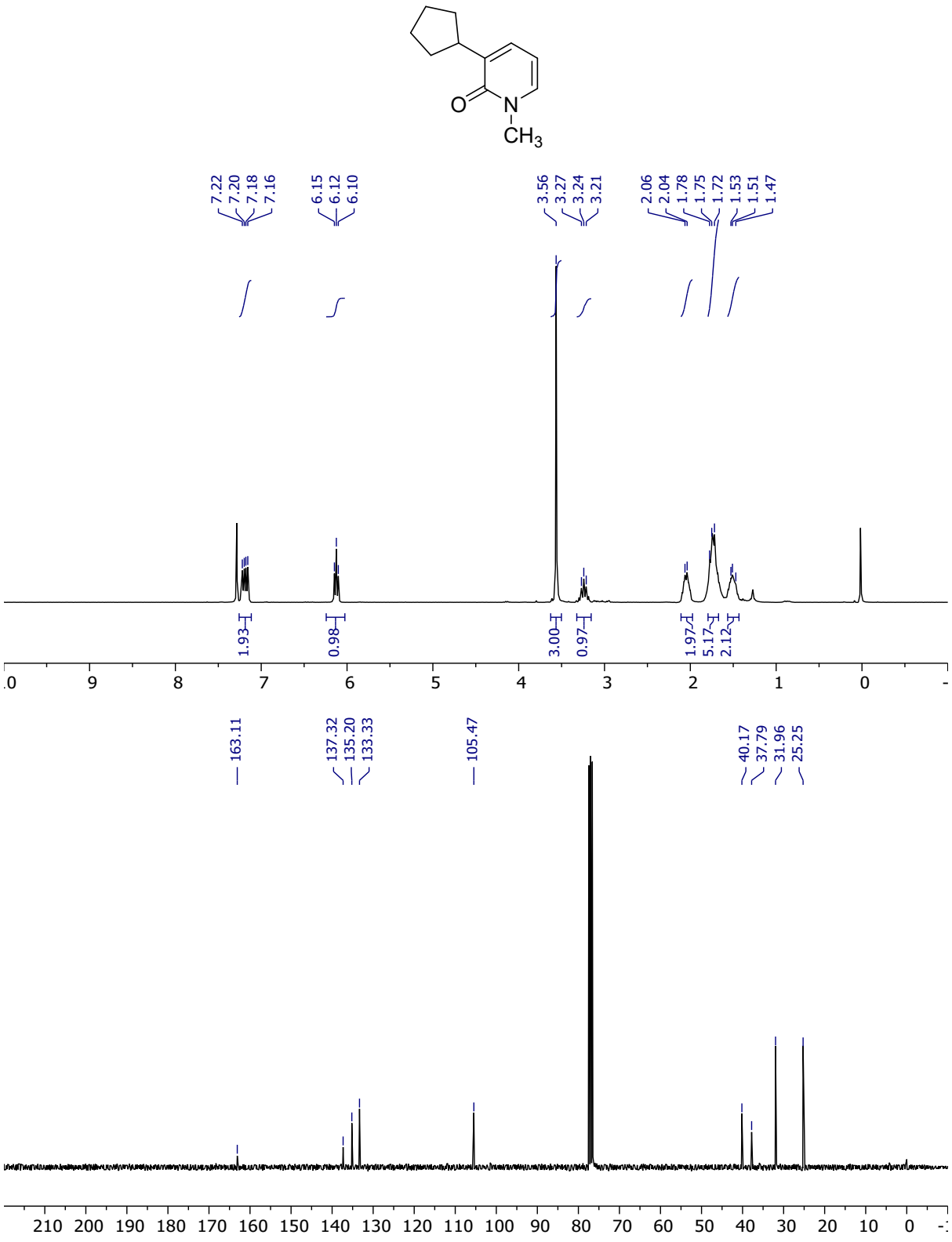
3-(Heptan-4-yl)-1-methylpyridin-2(1*H*)-one (4c)



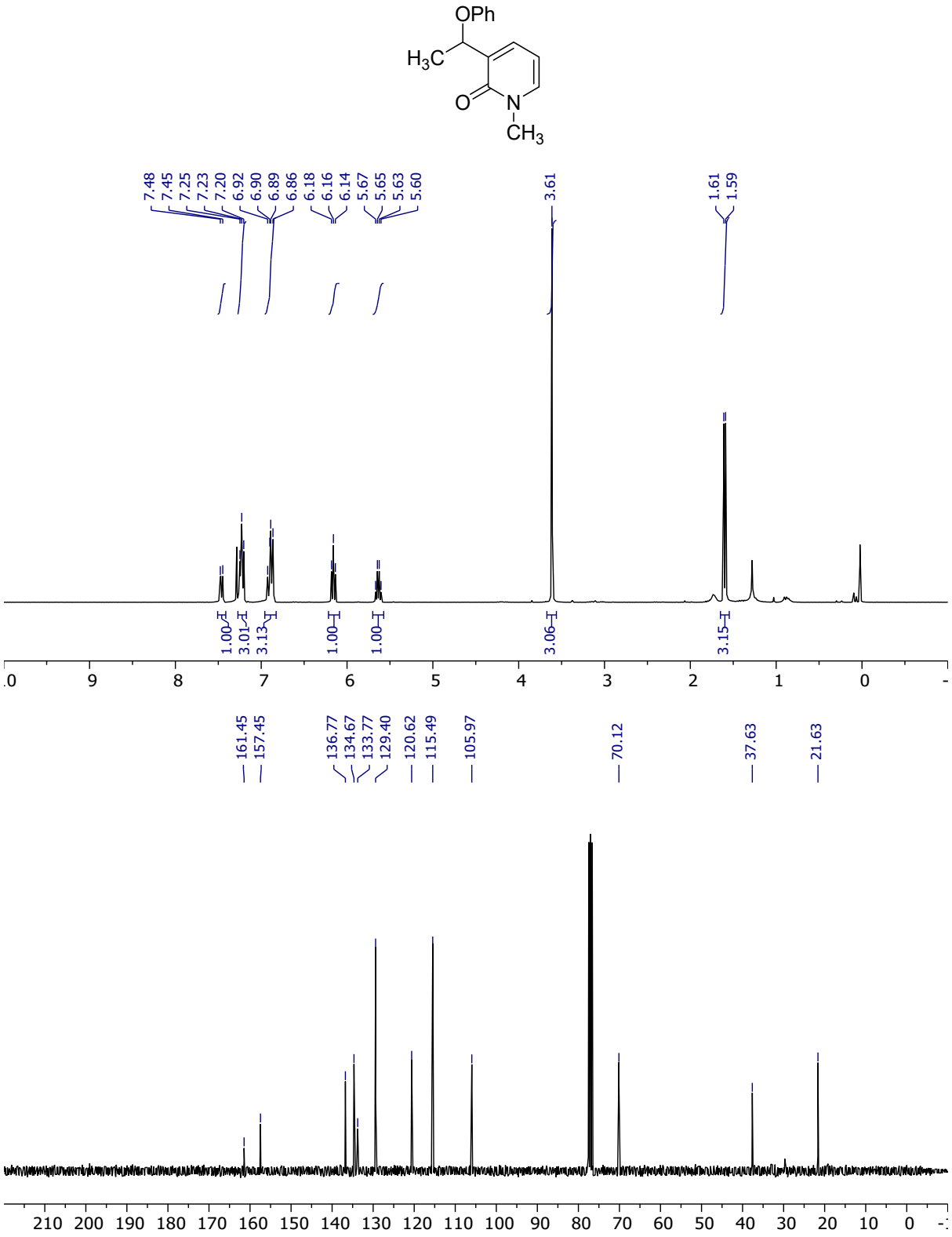
3-Cyclohexyl-1-methylpyridin-2(1*H*)-one 4d)



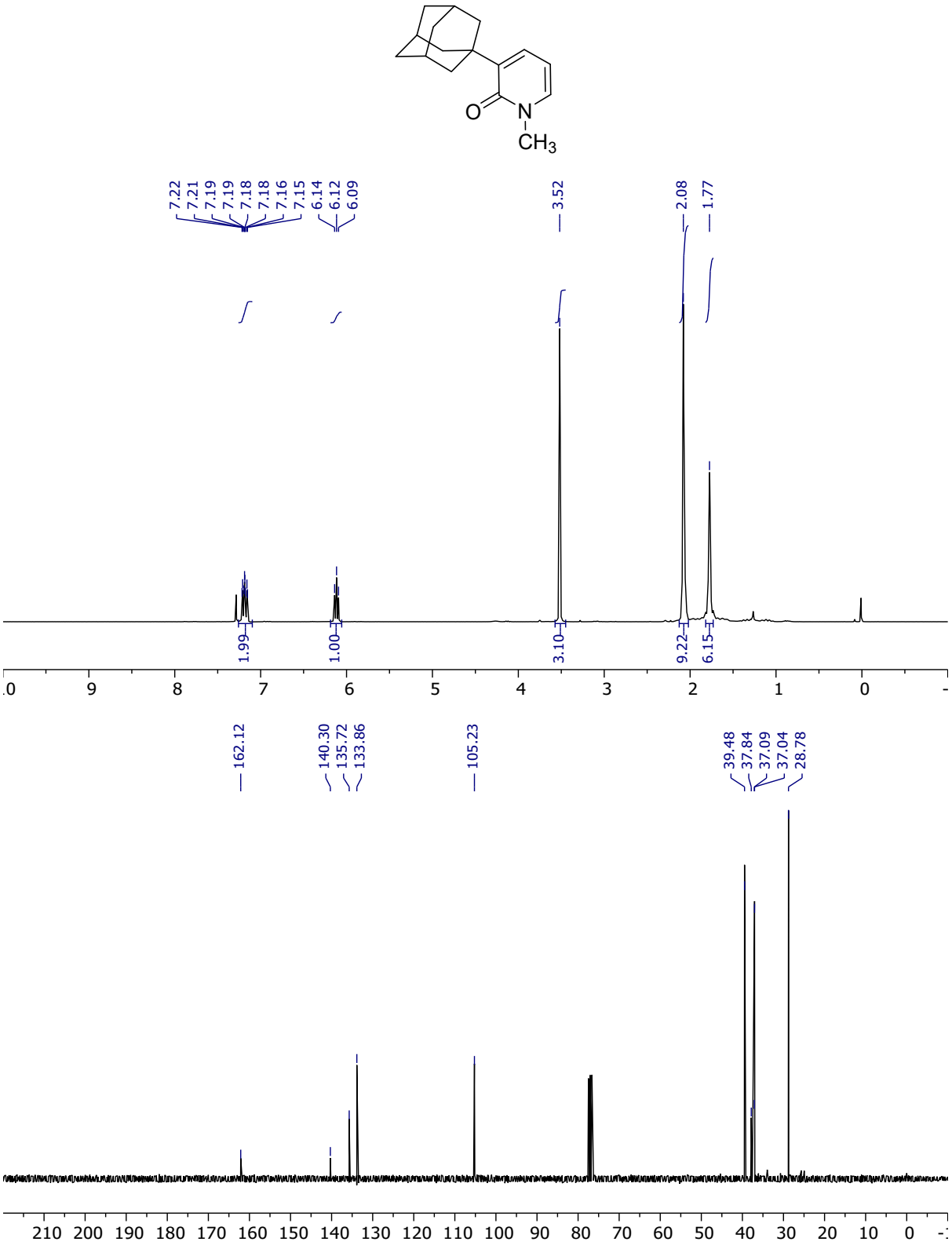
3-Cyclopentyl-1-methylpyridin-2(1*H*)-one (4e)



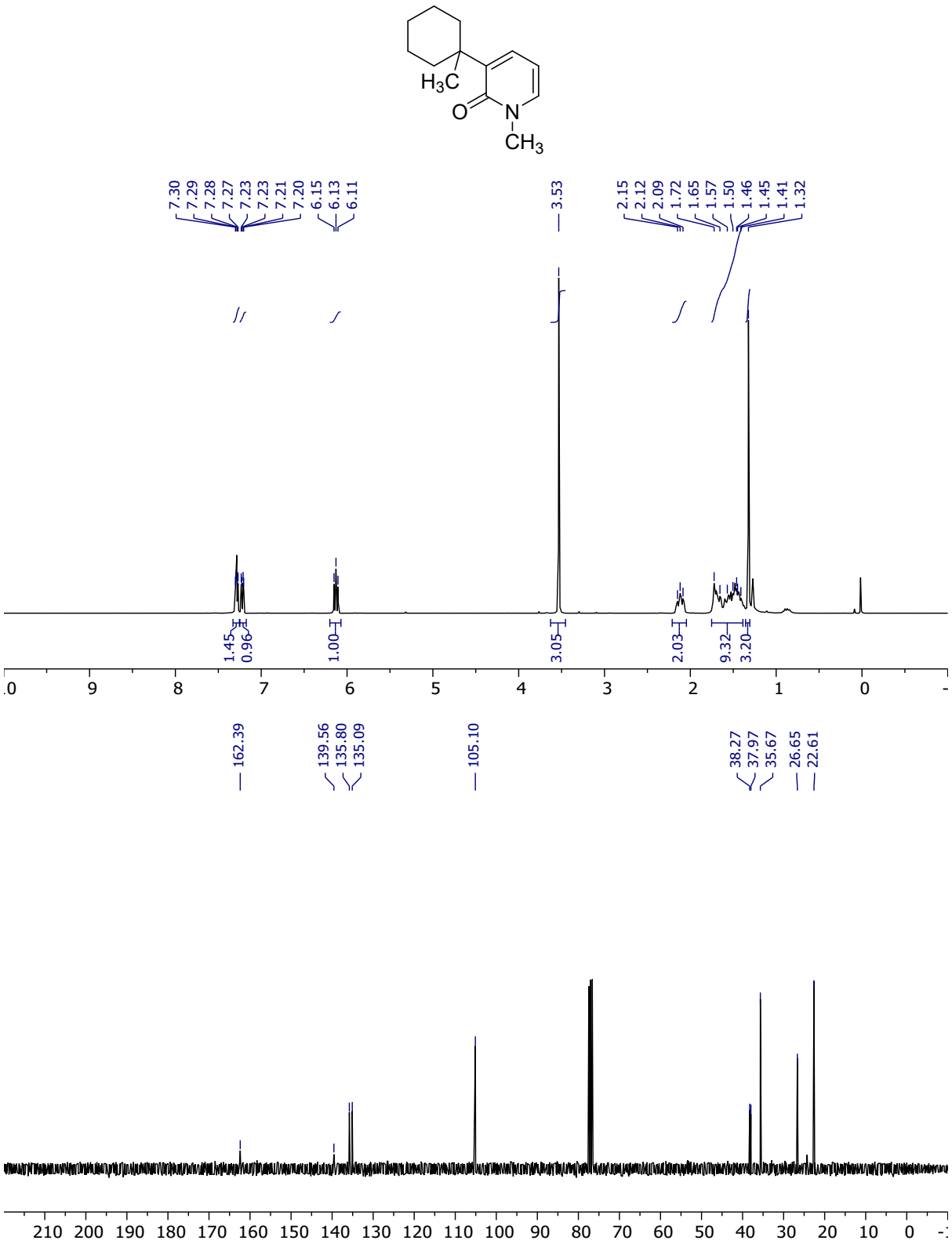
1-Methyl-3-(1-phenoxyethyl)pyridin-2(1H)-one (4f)



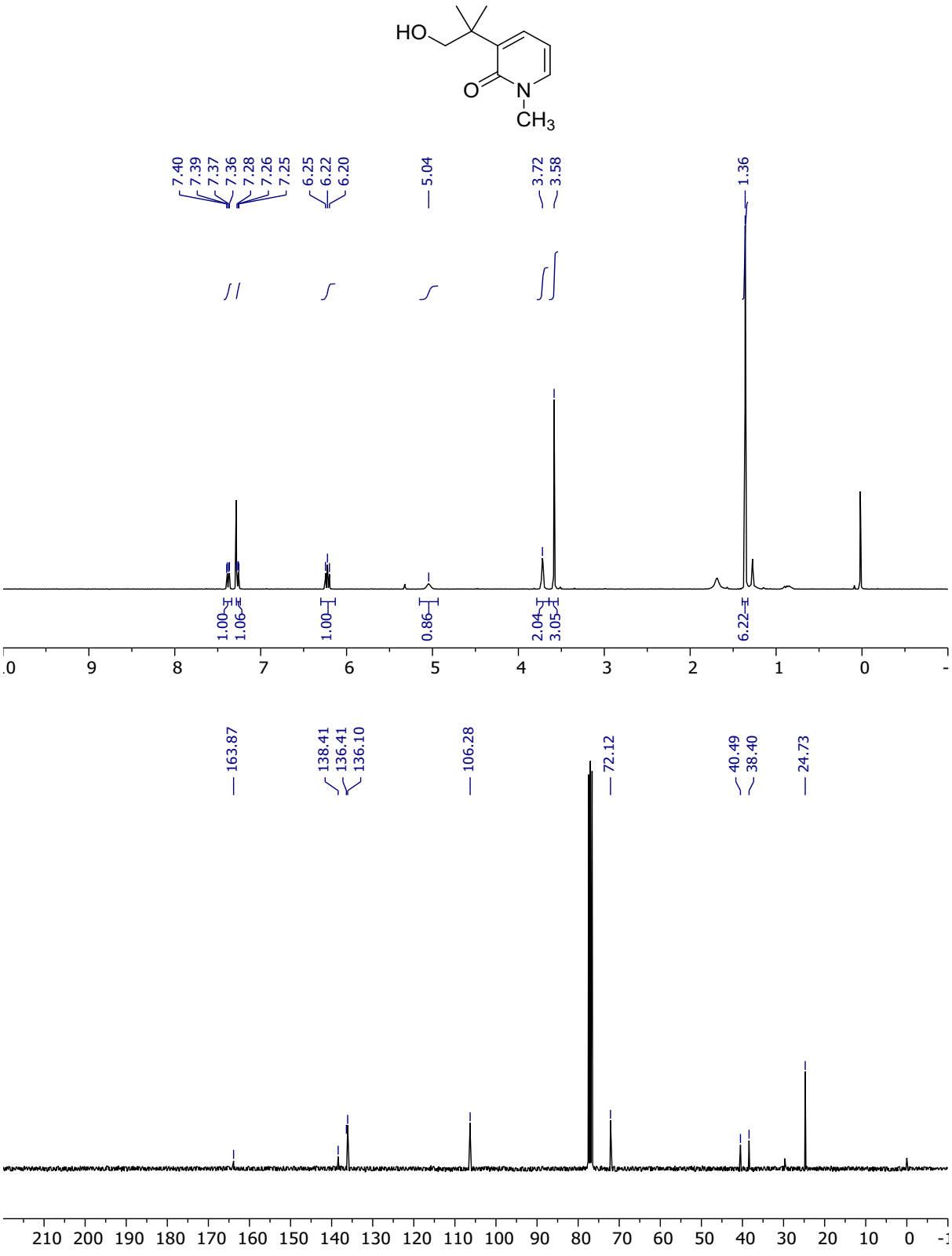
3-((3*r*,5*r*,7*r*)-Adamantan-1-yl)-1-methylpyridin-2(1*H*)-one (4g)



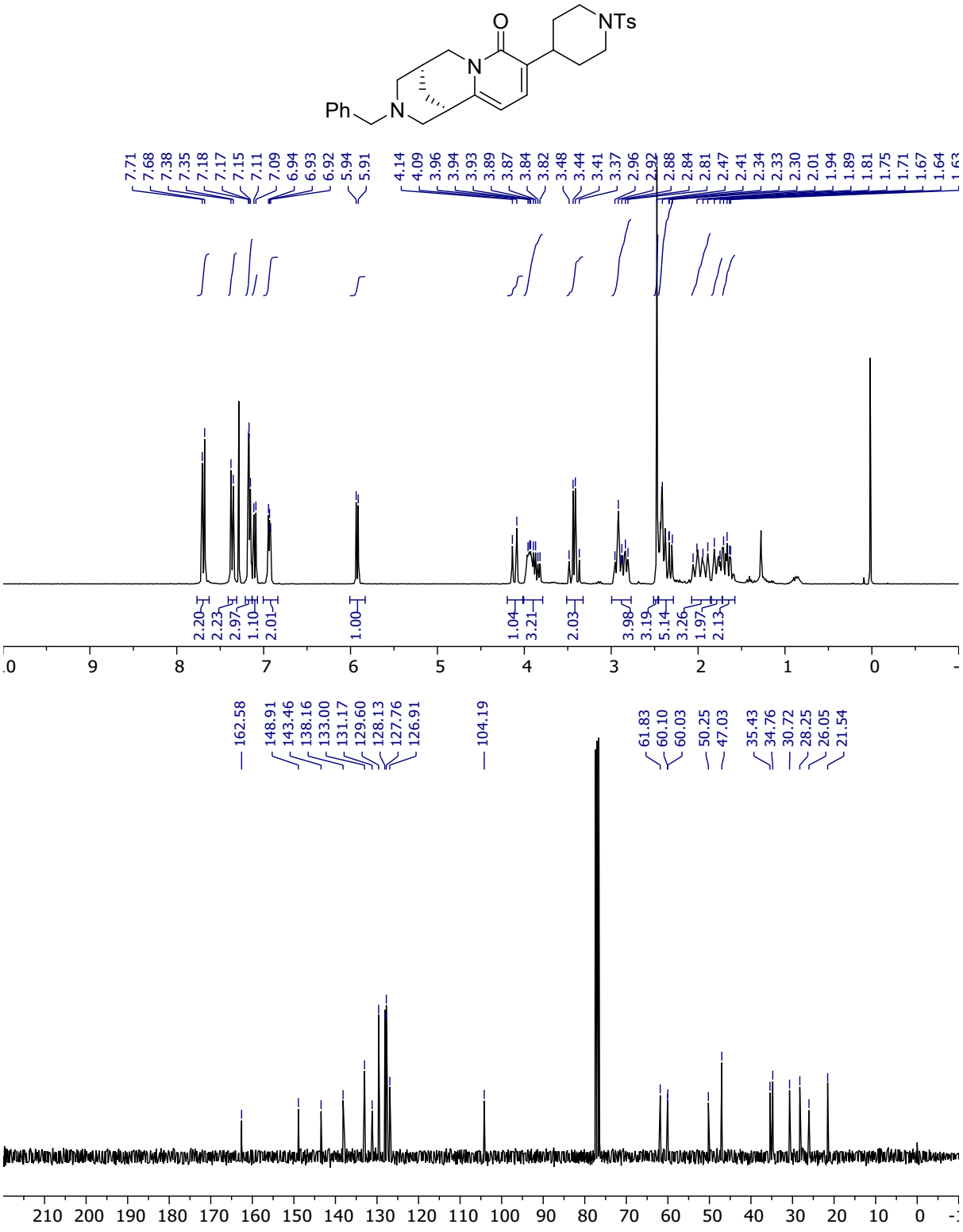
1-Methyl-3-(1-methylcyclohexyl)pyridin-2(1*H*)-one (4h)



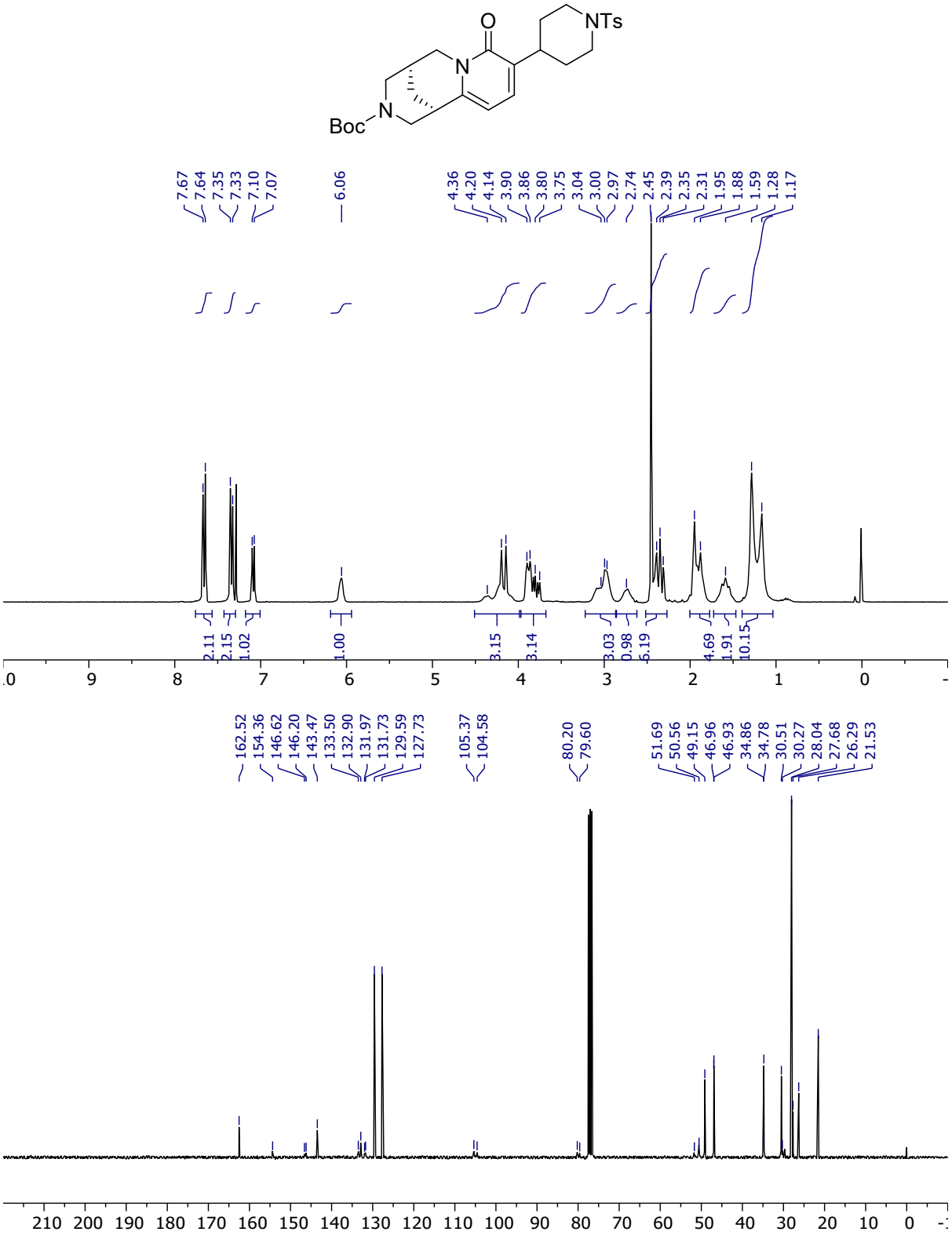
3-(1-Hydroxy-2-methylpropan-2-yl)-1-methylpyridin-2(1*H*)-one (4i).


HO
O
N
CH3
7.40
7.39
7.37
7.36
7.28
7.26
7.25
6.25
6.22
6.20
5.04
3.72
3.58
1.36
1.00
1.06
1.00
0.86
2.04
3.05
6.22
163.87
138.41
136.41
136.10
106.28
72.12
40.49
38.40
24.73

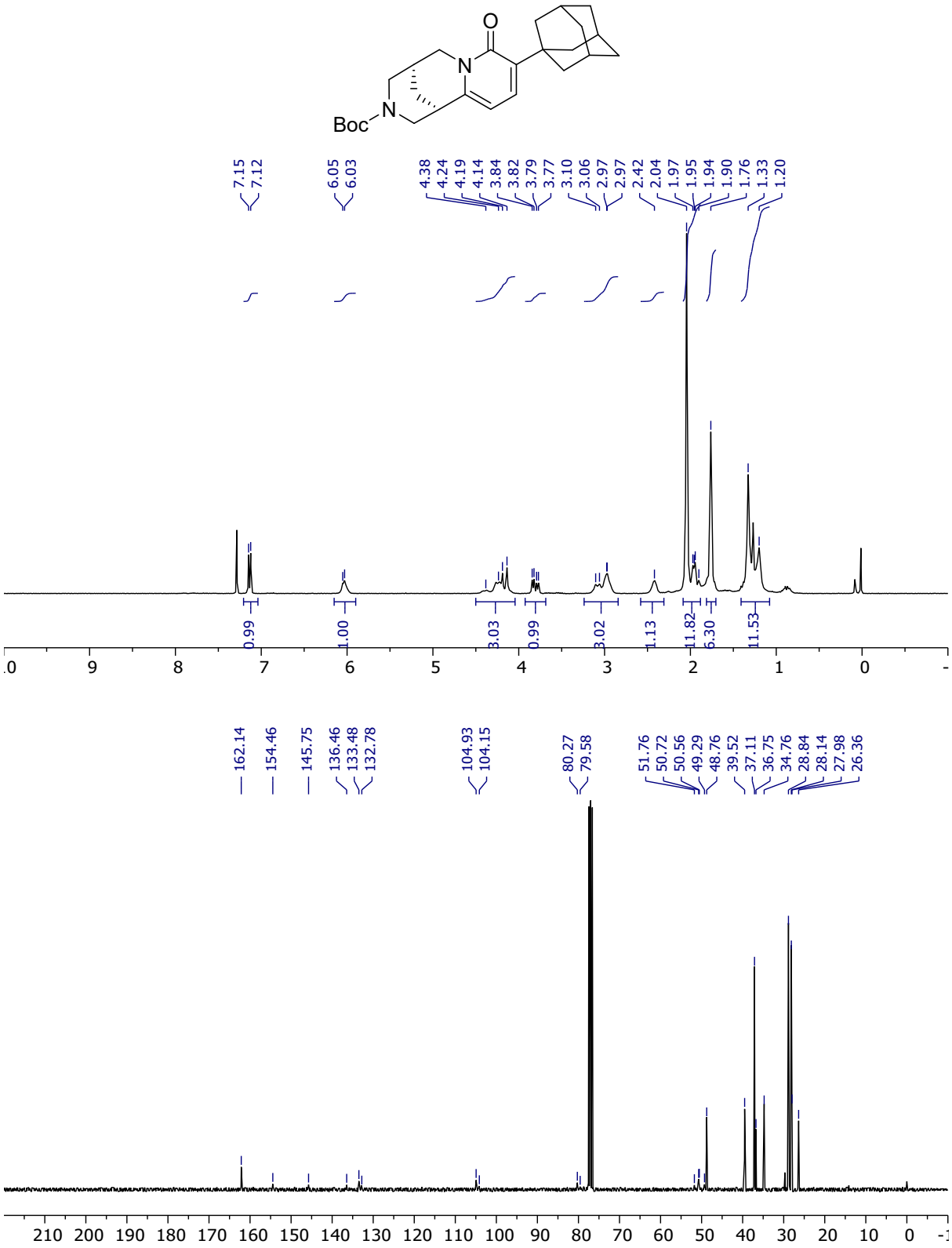
3-(1-Tosylpiperidin-4-yl)-*N*-benzyl-(–)-cytisine (5a).



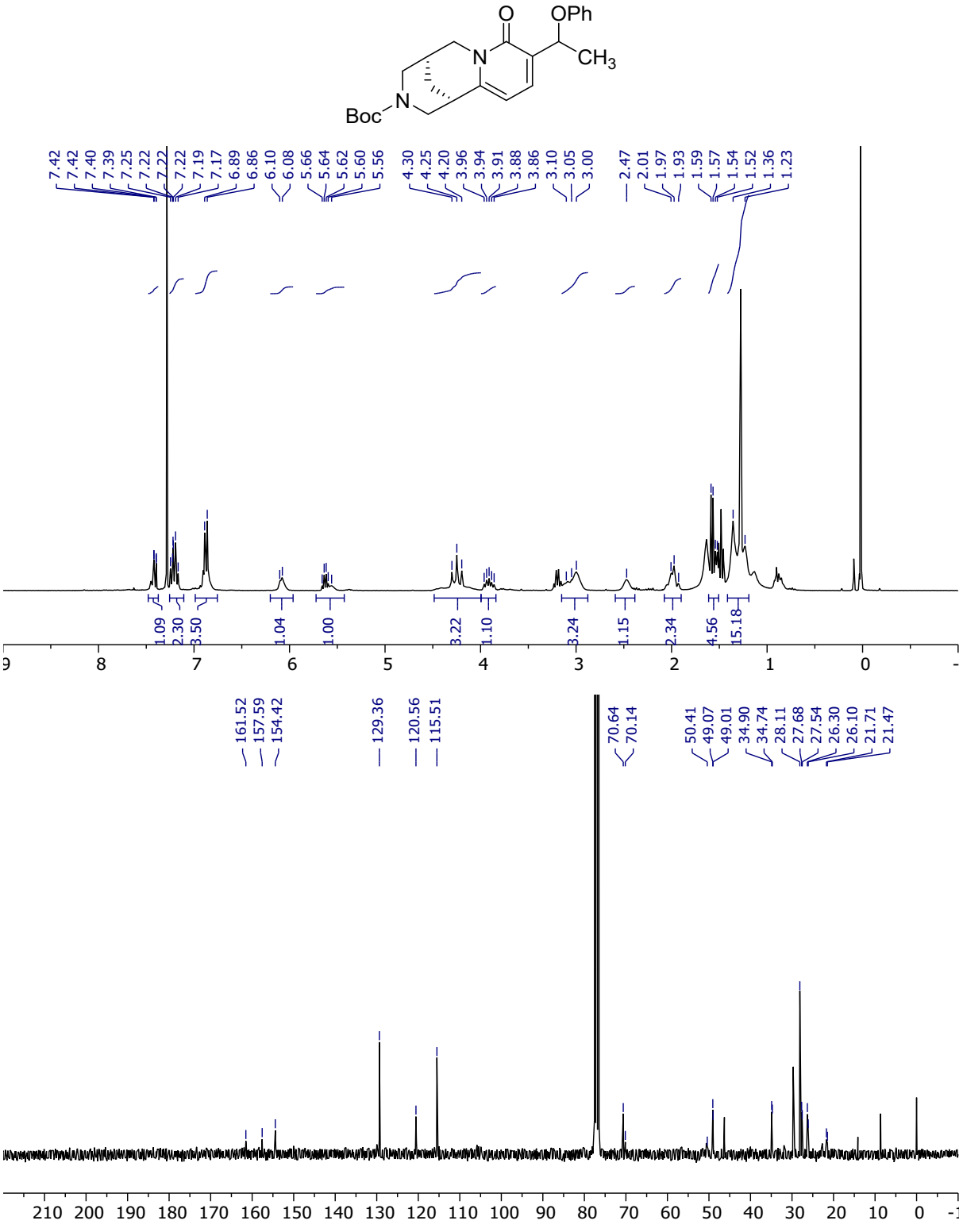
3-(1-Tosylpiperidin-4-yl)-*N*-Boc-(–)-cytisine (5b).



3-((3r,5r,7r)-Adamantan-1-yl)-*N*-Boc-(–)-cytisine (5c).



3-(1-Phenoxyethyl)-*N*-Boc-(–)-cytisine (5d).



3-(But-3-en-1-yl)-1-methylpyridin-2(1*H*)-one (7)