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# Poly(ethylene glycol)-supported chiral pyridine-2,6-bis(oxazoline): synthesis and application as a recyclable ligand to $Cu^{I}$-catalyzed enantioselective direct addition of terminal alkynes to imines

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## 1. Experimental Section

### 1.1. General Information

All commercially available reagents were used without further purification. The solvents were purified by standard procedures. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F254 plates, compounds were visualized by UV. Column chromatography was performed using Merck silica gel 60 (40 – 63 μm).

$^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ on a Bruker Avanve-400 and Agilent 400-MR spectrometers (400.0 and 100.6 MHz for $^{1}H$ and $^{13}C$, respectively). Chemical shifts are given in ppm referenced to the solvent signals ($CDCl_3$, $^{1}H$ δ = 7.25 ppm, $^{13}C$ δ = 77.00 ppm; DMSO-$d_6$, $^{1}H$ δ = 2.48 ppm). Infrared (IR) spectra were recorded on a Thermo Nicolet FTIR-200 in KBr pellets. Elemental analyses were performed on a Carlo Erba 1106 instrument. Enantiomeric excesses were determined by chiral HPLC (Daicel Co. Chiralcel OD-H column, hexane : 2-propanol = 95 : 5, 1.0 ml / min). Optical rotation was measured on a Kruss P8000 polarimeter.

The following compounds were prepared according to literature methods: pybox ligands **9**,[1] **10** and **11**,[2] MeOPEG$_{5000}$-azide **7**,[3] benzyl azide,[4] *N*-benzylideneaniline,[5] racemic *N*-(1,3-diphenylprop-2-yn-1-yl)aniline **12**.[6]

### 1.2. Synthesis of immobilized ligand 1

**Dimethyl 4-hydroxypyridine-2,6-dicarboxylate (3)**[7]

Chelidamic acid monohydrate **2** (4.02 g, 20.0 mmol) was suspended in absolute methanol (100 ml) and concentrated sulfuric acid (0.6 ml) was carefully added at room temperature with vigorous stirring. The resulting mixture was refluxed for 4 h. After cooling to room temperature, the mixture was neutralized with a saturated aqueous $NaHCO_3$ (to pH 7). Methanol was evaporated, the remainder was extracted with $CH_2Cl_2$ (6×100 ml). The combined organic layers were dried with $Na_2SO_4$ and evaporated to give a product **3** as a white solid. Yield 2.74 g (65%),

mp 169-170 °C (lit.[8] mp 169-169.5 °C). $^1$H NMR (DMSO-*d6*): δ = 11.56 (s, 1H, OH), 7.55 (s, 2H, $H_{Py}$), 3.86 (s, 6H, $CH_3$).

**Dimethyl 4-(prop-2-yn-1-yloxy)pyridine-2,6-dicarboxylate (4) (synthesized by the modified method[9])**

To a suspension of dimethyl chelidamate **3** (1.06 g, 5.0 mmol) and $K_2CO_3$ (1.38 g, 10.0 mmol) in DMF (20 ml) was added propargyl bromide solution 80 wt. % in toluene (0.78 g of solution, 5.25 mmol) under argon. The mixture was heated at 90 °C for 4 h and stirred at room temperature overnight. Then the mixture was filtered and the filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography using short column (eluent $CH_2Cl_2$) to afford product **4** as a white solid. Yield 1.15 g (92%), mp 151-152 °C (lit.[9] mp 133-135 °C). $^1$H NMR ($CDCl_3$): δ = 7.88 (s, 2H, $H_{Py}$), 4.86 (d, *J*=2.4 Hz, 2H, $CH_2$), 4.00 (s, 6H, $CH_3$), 2.61 (t, *J*=2.4 Hz, 1H, CH≡). $^{13}$C NMR ($CDCl_3$): δ 165.50, 164.90, 149.80, 114.77, 77.56, 76.12, 56.32, 53.22.

***N*$^2$,*N*$^6$-Bis[(*S*)-2-hydroxy-1-phenylethyl]-4-(prop-2-yn-1-yloxy)pyridine-2,6-dicarboxamide (5)**

A mixture of dimethyl 4-(prop-2-yn-1-yloxy)pyridine-2,6-dicarboxylate **4** (1.00 g, 4.00 mmol) and (*S*)-phenylglycinol (1.37 g, 10.00 mmol) was stirred at 120 C for 6 h under Ar stream. The crude product was purified by column chromatography ($CH_2Cl_2$ : MeOH = 50:1, $R_f$ = 0.07) to afford product **5** as a white solid. Yield 1.22 g (67%), mp 81–83 °C. $[\alpha]_D^{20}$ -64.67 (*c* 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): δ = 8.65 (d, 2H, *J*=7.1 Hz, NH), 7.78 (s, 2H, $H_{Py}$), 7.24-7.33 (m, 10H, Ph), 5.13-5.18 (m, 2H, C*H*Ph), 4.72-4.75 (m, 2H, $CH_2O$), 3.90 (t, 4H, *J*=5.1 Hz, C*H*$_2$OH), 3.29 (br s, 2H, OH), 2.54 (t, 1H, *J*=2.4 Hz, CH≡). $^{13}$C NMR ($CDCl_3$): δ 166.42, 163.46, 150.62, 138.79, 128.82, 127.83, 126.62, 111.58, 77.33, 76.36, 66.07, 56.27, 55.83. $C_{26}H_{25}N_3O_5$. Calcd., %: C 67.96, H 5.48, N 9.14. Found, %: C 67.66, H 5.59, N 8.93.

**(4*S*,4'*S*)-2,2'-[4-(Prop-2-ynyloxy)pyridine-2,6-diyl]bis(4-phenyl-4,5-dihydrooxazole) (6)**

To a solution of 4-(prop-2-yn-1-yloxy)pyridine-2,6-dicarboxylic acid bis[((*S*)-2-hydroxy-1-phenylethyl)amide **5** (1.20 g, 2.61 mmol) in $CH_2Cl_2$ (7 ml), $Et_3N$ (3.2 ml) and TsCl (1.10 g, 5.75 mmol) were added. The resulting mixture was refluxed for 10 h, diluted with $CH_2Cl_2$ (15 ml) and washed with $K_2CO_3$ solution (20 mmol in 15 ml $H_2O$) and water (2×10 ml). The organic phase was dried over $Na_2SO_4$. After evaporation, the crude product was purified by column chromatography using deactivated by $Et_3N$ silica gel (petroleum ether : ethyl acetate = 1:2, $R_f$ = 0.18) to afford a product **6** as a white solid. Yield 0.70 g (63%), mp 146–148 °C. $[\alpha]_D^{20}$ -65.05 (*c* 1, $CH_2Cl_2$).$^1$H NMR ($CDCl_3$): δ = 7.91 (s, 2H, $H_{Py}$), 7.26-7.37 (m, 10H, Ph), 5.43 (dd, *J*=10.2 Hz, 8.8 Hz, 2H, $CH_{2oxazolin}$), 4.90 (dd, *J*=10.4 Hz, 8.7Hz, 2H, $CH_{2oxazolin}$), 4.82 (d, *J*=2.4 Hz, 2H, $CH_2C{\equiv}$), 4.39 (t, *J*=8.6 Hz, 2H, C*H*Ph), 2.57 (t, *J*=2.4 Hz, 1H, CH≡). $^{13}$C NMR ($CDCl_3$): δ = 164.57, 163.39, 148.32, 141.64, 128.77, 127.75, 126.79, 112.96, 77.13, 76.49, 75.53, 70.25, 56.17. $C_{26}H_{21}N_3O_3$. Calcd., %: C 73.74, H 5.00, N 9.92. Found, %: C 73.45, H 4.97, N 9.71.

**MeOPEG$_{5000}$-immobilized ligand (1)**

To a mixture of pybox **6** (0.349 g, 0.825 mmol), MeOPEG$_{5000}$-azide **7** (3.838 g, 0.75 mmol) (average $M_n$ = 5117 was determined by MALDI-TOF method with dithranol as a matrix) and CuI (14.3 mg, 0.075 mmol) in degassed $CH_2Cl_2$ (12 ml), $Et_3N$ (1.1 ml) was added under argon and the reaction mixture was stirred for 72 h at the room temperature. Then $CH_2Cl_2$ (40 ml) was added and the resulting solution was washed with 0.1 M EDTA-$Na_2$ aqueous solution (2×20 ml). The organic phase was dried over $Na_2SO_4$ and evaporated. The crude product was redissolved in $CH_2Cl_2$ (10 ml), $Et_2O$ (500 ml) was added and the resulting mixture was kept at 0 °C overnight. The light-yellow precipitate was filtered, washed with $Et_2O$ (2×15 ml) and dried under vacuum. Yield 4.011 g (97%). $^1$H NMR ($CDCl_3$): δ = 7.94 (br s, 2H, $H_{Py}$), 7.84 (s, 1H, $H_{triazole}$), 7.27-7.36 (m, 10H, Ph), 5.43 (t, *J*=9.2 Hz, 2H, $H_{oxazoline}$), 5.31 (s, 2H, pyboxO$CH_2$), 4.90 (t, *J*=9.2 Hz, 2H, $H_{oxazoline}$), 4.54 (t, *J*=4.8 Hz, 2H, N$CH_2$), 4.39 (t, *J*=8.3 Hz, 2H, $H_{oxazoline}$), 3.86 (t, *J*=4.9 Hz, 2H,

$CH_2O_{PEG}$), 3.79 (t, *J*=4.9 Hz, $CH_2O_{PEG}$), 3.48-3.75 (m, $CH_2O_{PEG}$), 3.44 (t, *J*=4.8 Hz, $CH_2O_{PEG}$), 3.36 (s, 3H, PEGOC*H*$_3$).

**1.3. Synthesis of ligand 8**

**(4*S*,4'*S*)-2,2'-{4-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]pyridine-2,6-diyl}bis(4-phenyl-4,5-dihydrooxazole) (8)**

To a mixture of pybox **6** (212 mg, 0.500 mmol) and CuI (9.5 mg, 0.050 mmol) in degassed $CH_2Cl_2$ (5 ml), $Et_3N$ (0.8 ml) and benzylazide (69 μl, 73.2 mg, 0.550 mmol) were added under argon and the reaction mixture was stirred for 24 h at the room temperature. Then $CH_2Cl_2$ (10 ml) was added and the resulting solution was washed with 0.1 M EDTA-$Na_2$ aqueous solution (2×15 ml). The organic phase was dried over $Na_2SO_4$ and evaporated. The crude product was purified by column chromatography using deactivated by $Et_3N$ silica gel (petroleum ether : ethyl acetate = 1:5, $R_f$ = 0.09) to afford a product **8** as a white solid. Yield 226 mg (81%), mp 203.5-204.5 °C. $[\alpha]_D^{20}$ -27.40 (*c* 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): δ = 7.91 (s, 2H, $H_{Py}$), 7.51 (s, 1H, $H_{triazole}$), 7.23-7.35 (m, 15H, Ph), 5.51 (s, 2H, PhC*H*$_2$N), 5.41 (t, *J*=9.5 Hz, 2H, $H_{oxazoline}$), 5.28 (s, 2H, pyboxO$CH_2$), 4.88 (dd, *J*=10.0 Hz, 9.0 Hz, 2H, $H_{oxazoline}$), 4.38 (t, *J*=8.6 Hz, 2H, $H_{oxazoline}$). $^{13}$C NMR ($CDCl_3$): δ = 165.17, 163.38, 148.36, 142.66, 141.65, 134.17, 129.13, 128.83, 128.73, 128.07, 127.71, 126.76, 122.83, 112.81, 75.49, 70.21, 62.36, 54.24. $C_{33}H_{28}N_6O_3$. Calcd., %: C 71.21, H 5.07, N 15.10. Found, %: C 71.47, H 5.20, N 14.84.

**1.4. General procedure for enantioselective addition of phenylacetylene to *N*-benzylidene-aniline, catalyzed by Cu(I) - pybox (8)-(11) complexes**

Pybox ligand **8,9,10** or **11** (0.0263 mmol) and $Cu(MeCN)_4OTf$ (0.025 mmol, 9.4 mg) in degassed $CH_2Cl_2$ (1 ml) were stirred for 1 h under argon. Then *N*-benzylideneaniline (45.3 mg, 0.25 mmol) and phenylacetylene (41.2 μl, 38.3 mg, 0.375 mmol) were added. The reaction mixture was stirred for 48 h at room temperature, filtered through a plug of silica gel and the latter was washed with $CH_2Cl_2$. The solvent was evaporated under reduced pressure. Conversion and yield of *N*-(1,3-diphenylprop-2-yn-1-yl)aniline **12** were measured by $^1$H NMR spectroscopy.

The crude product was purified by column chromatography (petroleum ether : $CH_2Cl_2$ = 2:1, $R_f$ = 0.34) to afford a compound **12** as a pale yellow solid. The *ee* values were determined by HPLC (Chiralcel OD-H column, hexane : *i*-PrOH = 95 : 5, 1.0 ml / min): $t_1$= 9.3 min (major), $t_2$= 10.6 min (minor). NMR spectra for compound **12** were in agreement with the literature.[6]

**1.5. General procedure for enantioselective addition of phenylacetylene to *N*-benzylidene-aniline, catalyzed by Cu(I) - MeOPEG$_{5000}$-immobilized pybox 1 complex**

Pybox ligand **1** (0.0263 mmol, 146 mg) and $Cu(MeCN)_4OTf$ (0.025 mmol, 9.4 mg) in degassed $CH_2Cl_2$ (1 ml) were stirred for 1 h under argon. Then $CH_2Cl_2$ (1-2 ml, if necessary, see tables 2, 3), *N*-benzylideneaniline (45.3 mg, 0.25 mmol) and phenylacetylene (41.2 μl, 38.3 mg, 0.375 mmol) were added. The reaction mixture was stirred for 2-7 days at room temperature or at 50 °C and concentrated under reduced pressure (if necessary) to 1 ml. Then $Et_2O$ (15 ml) was added. The catalyst was separated by filtration and washed with $Et_2O$ (3×5 ml). The solvent was evaporated under vacuum. Conversion and yield of *N*-(1,3-diphenylprop-2-yn-1-yl)aniline **12** were measured by $^1H$ NMR spectroscopy. The crude product was purified by column chromatography (petroleum ether : $CH_2Cl_2$ = 2:1, $R_f$ = 0.34) to afford compound **12** as a pale yellow solid. The *ee* values were determined by HPLC (Chiralcel OD-H column, hexane : i-PrOH = 95 : 5, 1.0 ml / min): $t_1$= 9.3 min (major), $t_2$= 10.6 min (minor). NMR spectra for compound **12** were in agreement with the literature.[6]

**1.6. Catalyst recycling**

After isolation from the reaction mixture the catalyst was dried under vacuum, fresh portions of reagents and $CH_2Cl_2$ were added and the reaction was performed as described above.

**1.7. Ligand recycling**

After isolation from the reaction mixture the catalyst was dissolved in $CH_2Cl_2$ (10 ml), washed with 0.1 M EDTA-$Na_2$ aqueous solution (3×3 ml), dried over $Na_2SO_4$, evaporated and dried under vacuum. Fresh portion of $Cu(MeCN)_4OTf$ and $CH_2Cl_2$ were added and the mixture was

stirred for 1 h under argon. Then the reactants were added and the reaction was performed as described above.

### 1.8. References


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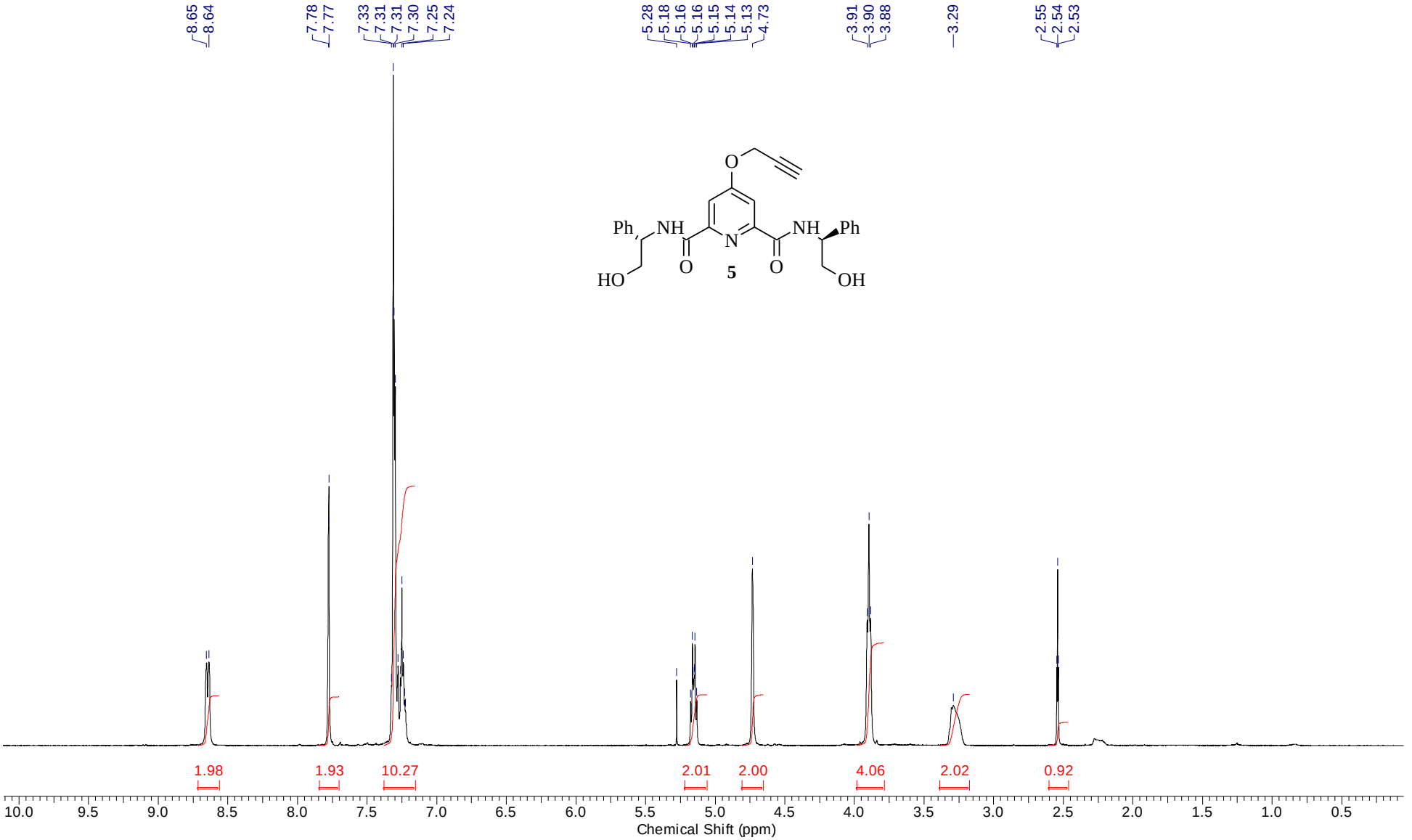
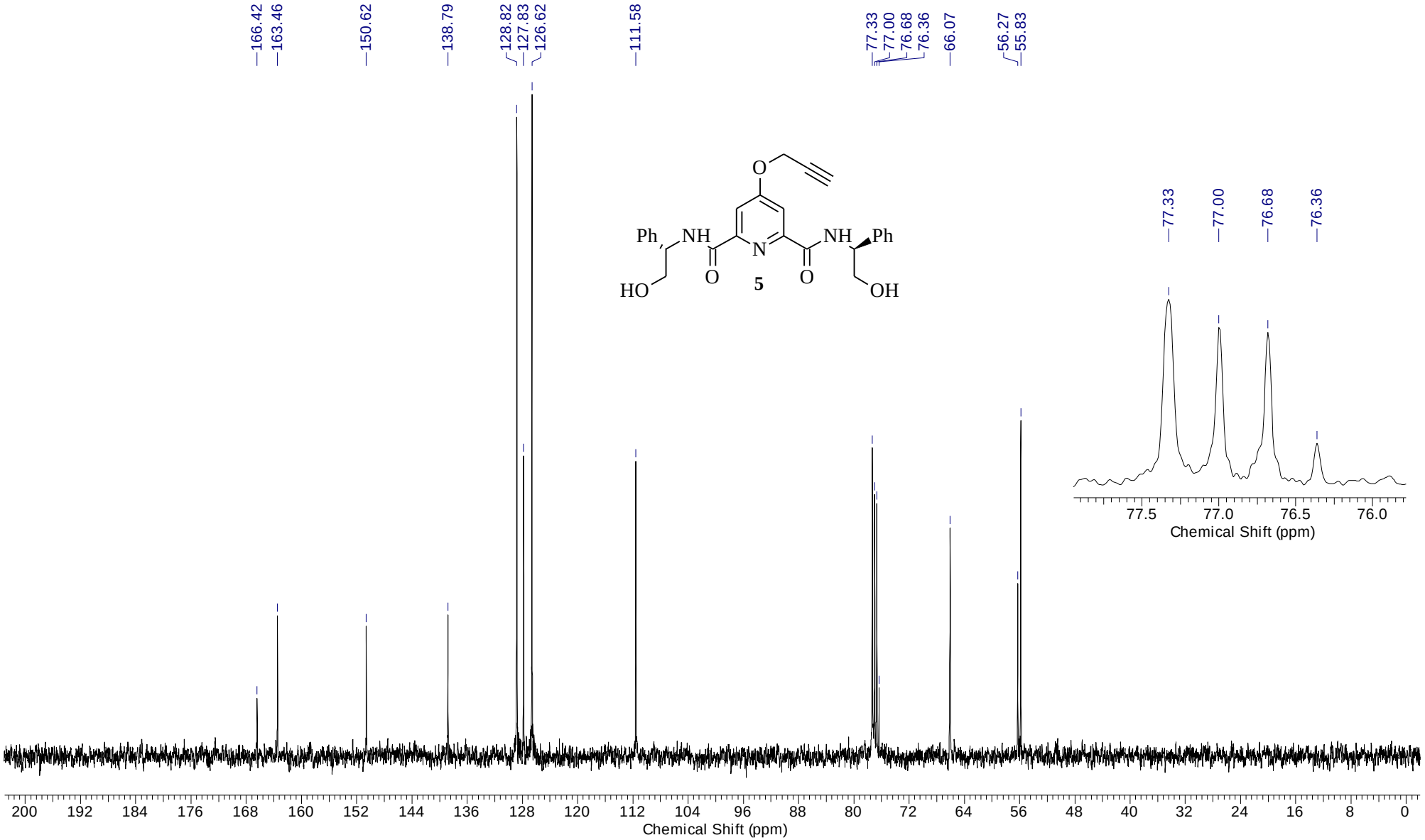
## 2. Spectra

### 2.1. $^{1}H$ NMR and $^{13}C$ NMR spectra of newly synthesized compounds

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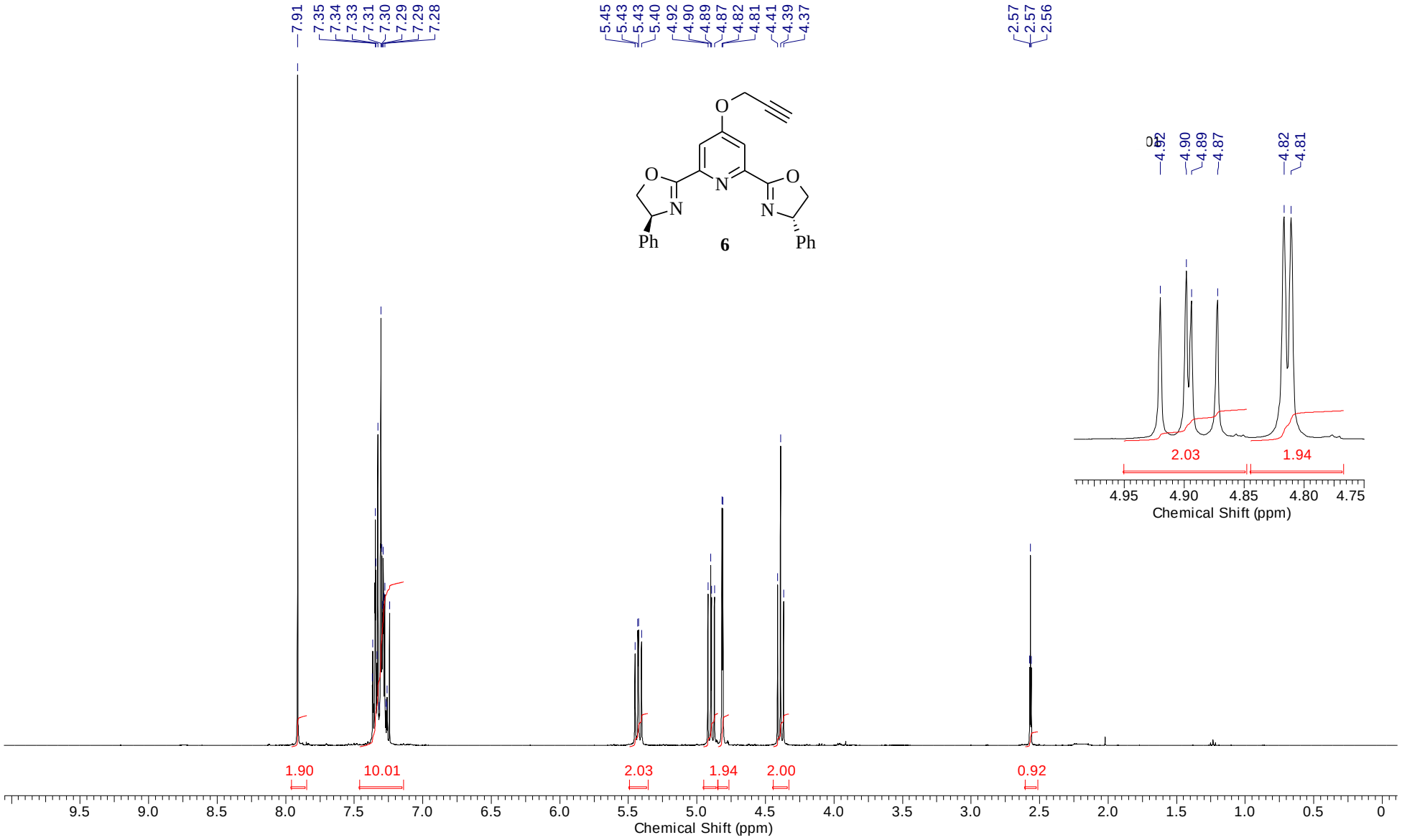
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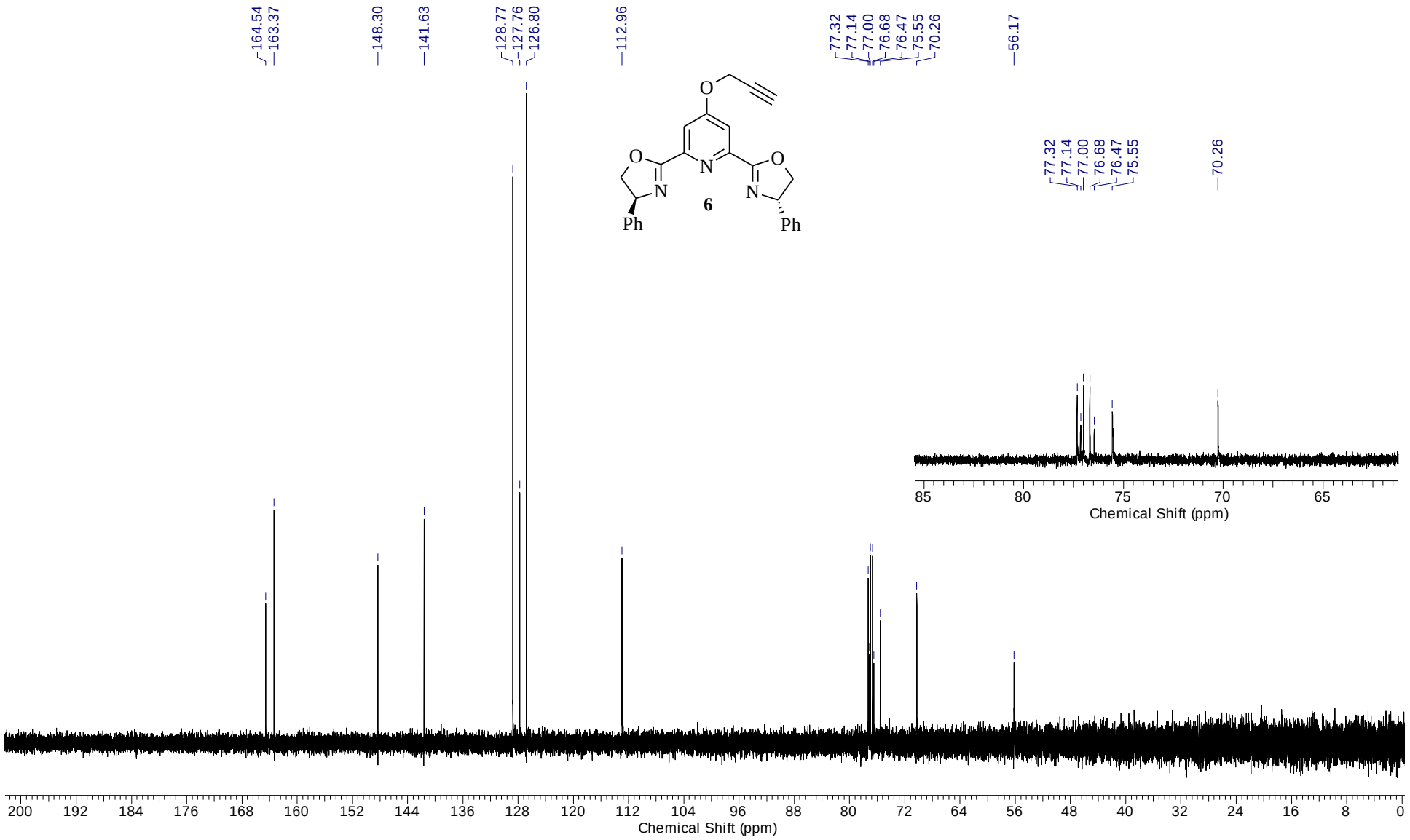
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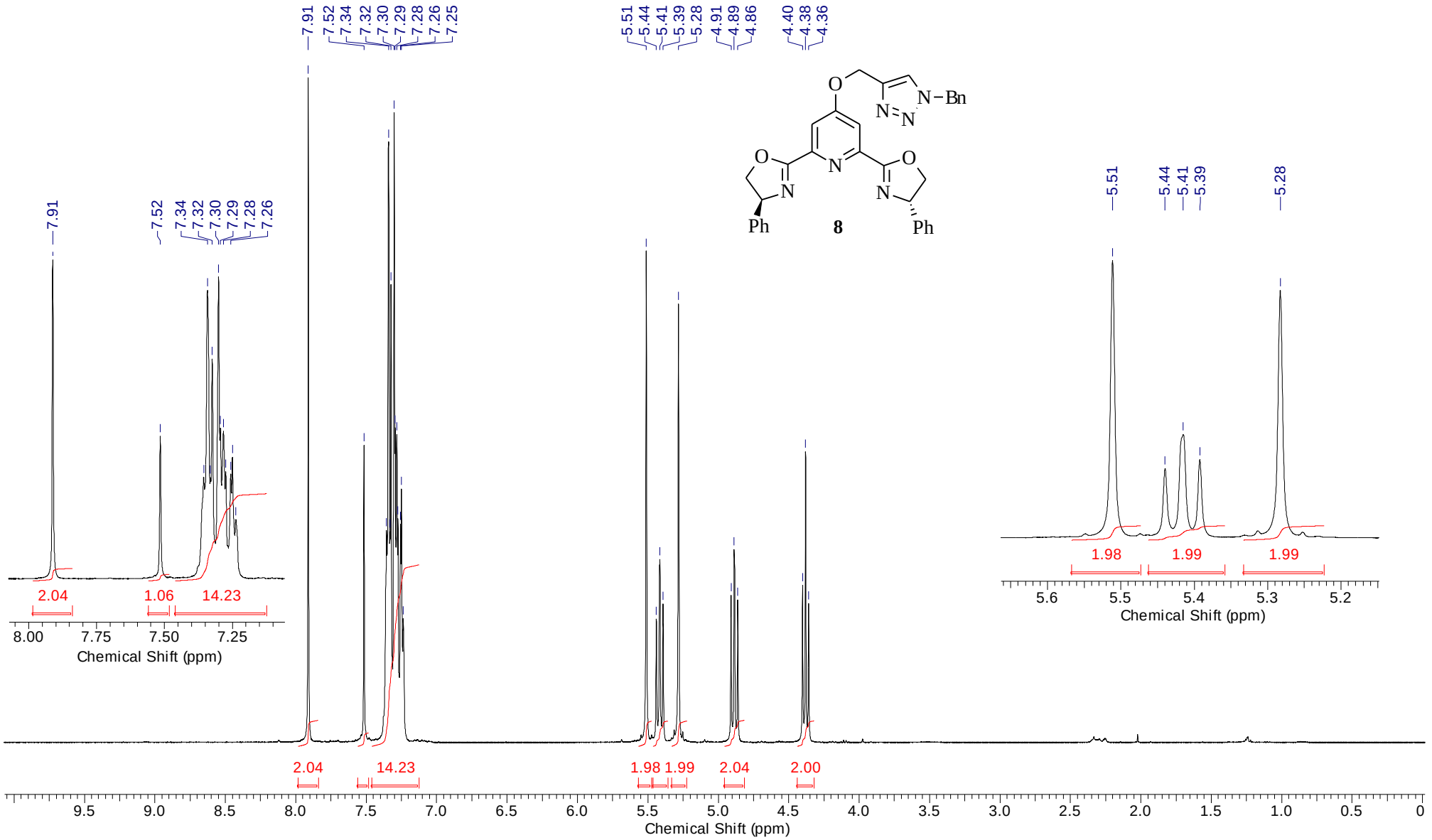
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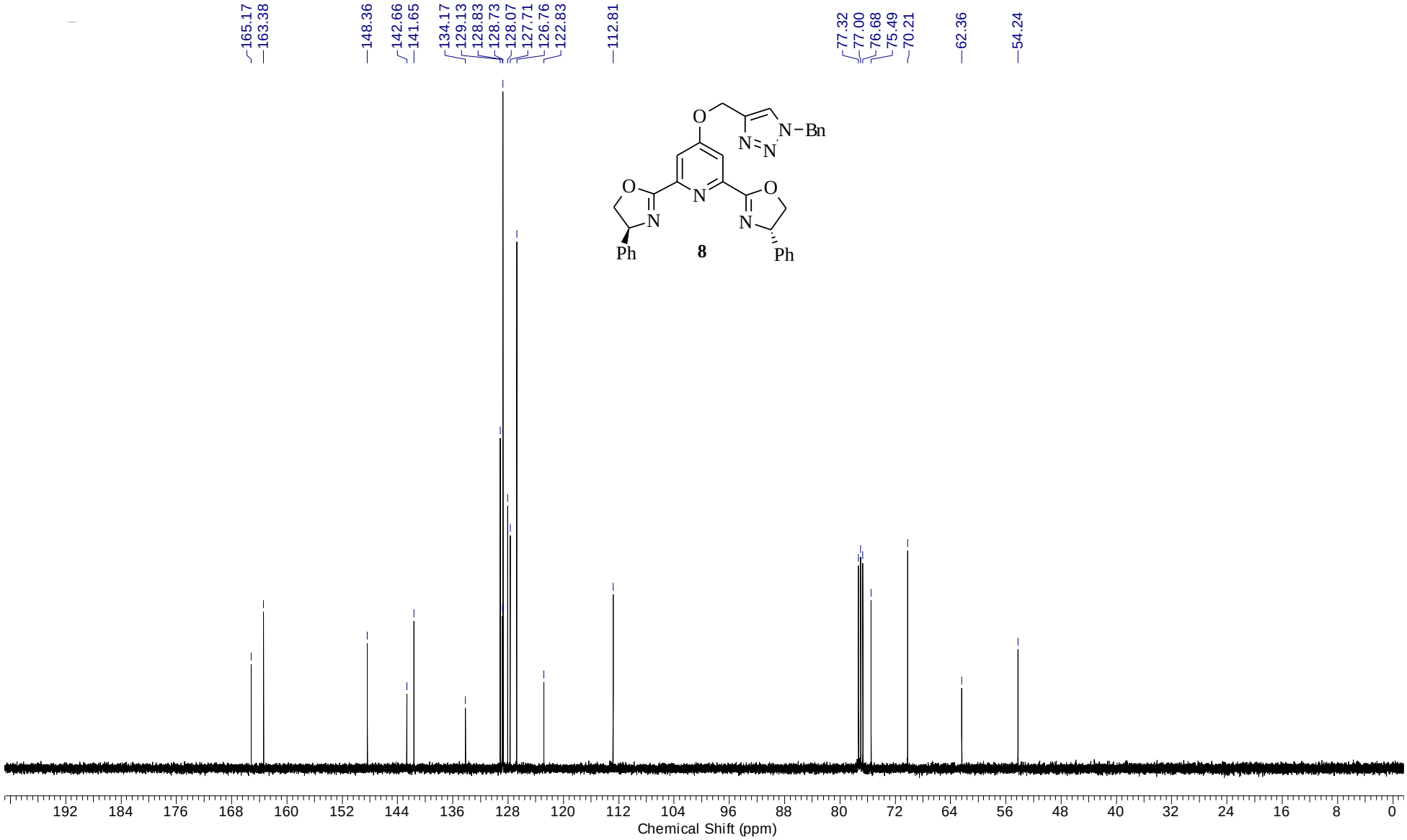
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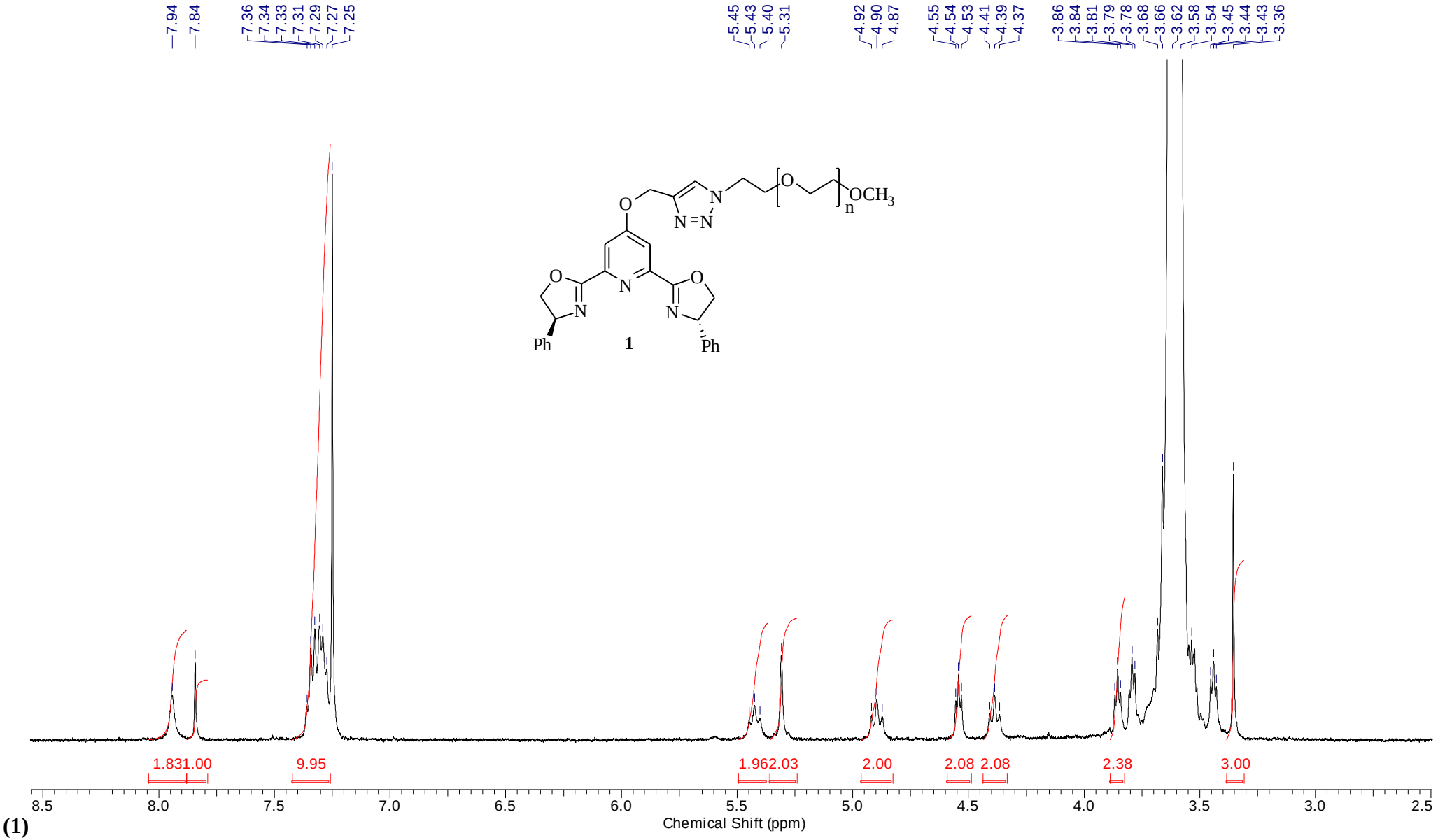
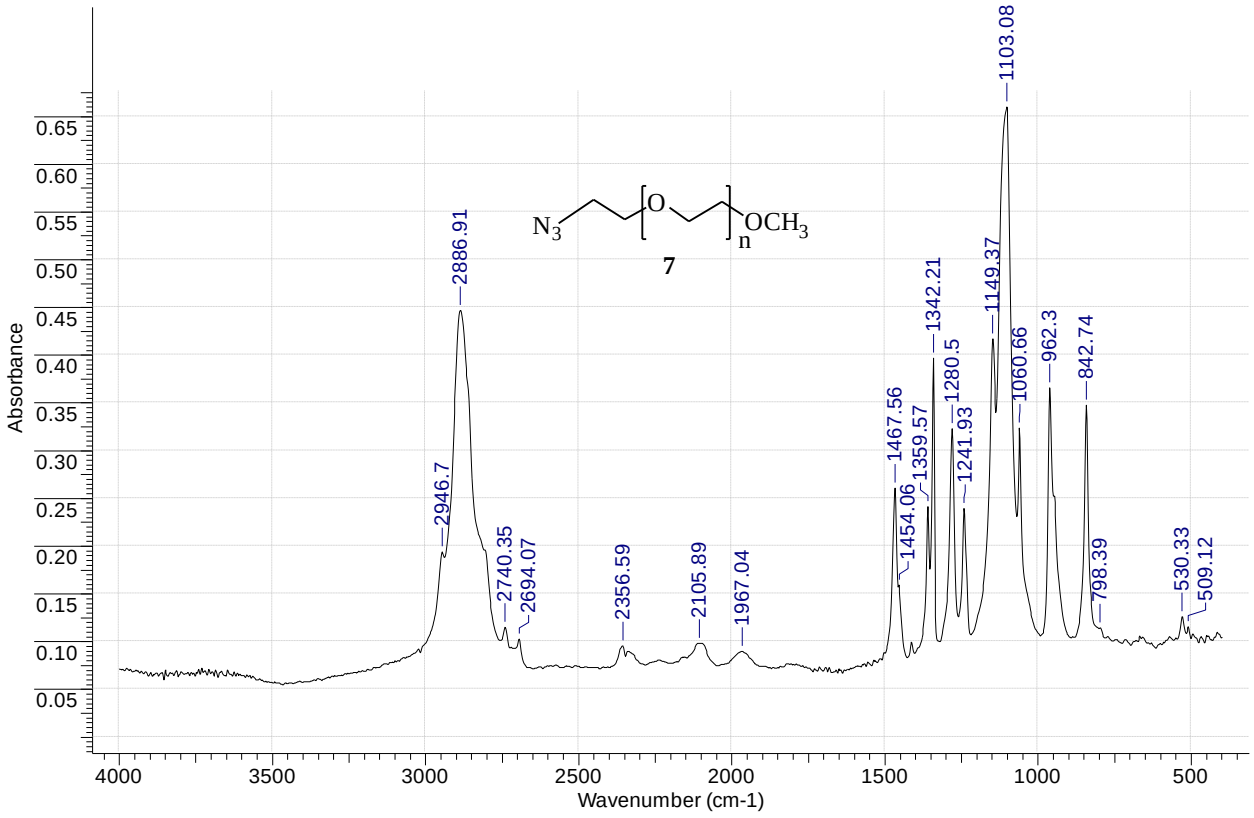
## 2.2. $^1$H NMR spectrum of MeOPEG$_{5000}$-immobilized pybox




**1**

**(1)**

## 2.3. IR-spectrum of MeOPEG$_{5000}$-azide (7)




## IR-spectrum of MeOPEG$_{5000}$-immobilized pybox (1)