Electronic Supporting Information

Continuous Flow Synthesis of Benzoxazoles Derivatives by Manganese-Based Heterogeneous Catalyst.

Francesco Ferlin,[a] Mitchell Van der Hulst,[a] Stefano Santoro,[a] Daniela Lanari,[b] and Luigi Vaccaro[a]*

[a] *Laboratory of Green S.O.C. – Dipartimento di Chimica, biologia e Biotecnologie, Università degli Studi di Perugia, Via Elce di Sotto 8, 06123 – Perugia, Italy. E-mail: luigi.vaccaro@unipg.it; http://www.dcbb.unipg.it/greensoc.*

[b] *Dipartimento di Scienze Farmaceutiche, Università di Perugia, Via del Liceo, 1, 06123 Perugia, Italy*

CONTENTS

General Information

Unless otherwise stated, all solvents and reagents were used as obtained from commercial sources without further purification. GC analyses were performed using a Hewlett-Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm) and a FID detector. GC-EIMS analyses were carried out using a Hewlett-Packard HP 6890N Network GC system/5975 MassSelective Detector equipped with an electron impact ionizer at 70 eV. NMR spectra were recorded on a Bruker DRX-ADVANCE 400 MHz (^{1}H at 400 MHz and ^{13}C at 100.6 MHz). The deuterated solvent used was $CDCl_3$. Elemental analyses were conducted on a Fisons EA1108CHN. Melting points were measured on a Büchi 510. Metal leaching in solution measurements were carried out using an Agilent 4210 MP-AES instrument. Flow procedures were performed using tailored pressure tubes as a reagents reservoir and Supelco HPLC Column Blank as catalyst columns. Characterization data and copies of the ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR are reported below.

Procedures for catalyst synthesis:

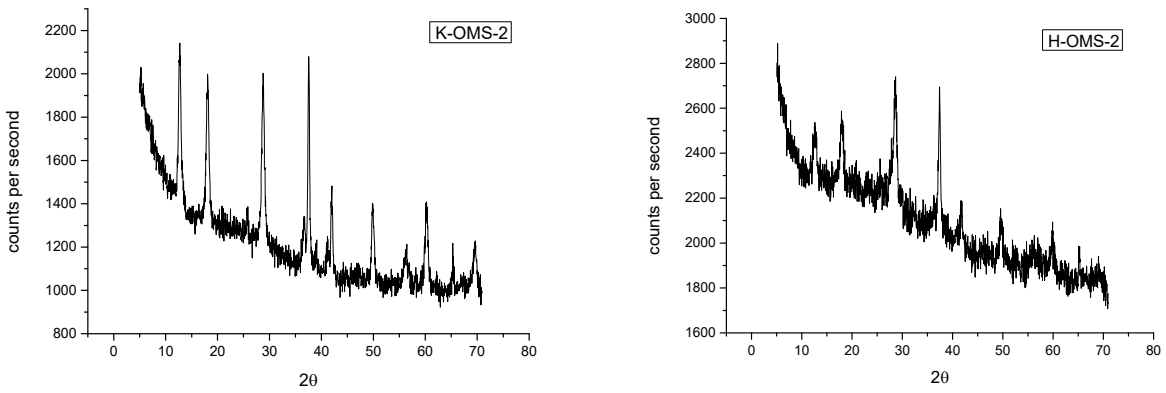
General procedures for K-OMS synthesis:

$MnSO_4$ hydrate (4.4 g, 26.0 mmol) and concentrated HNO_3 (1.5 mL) were dissolved in deionized water (15.0 mL). Then a solution made by dissolving $KMnO_4$ (2.9 g, 18.4 mmol) in deionized water (40.0 mL) was added drop-wise to make a brown slurry. The slurry was then refluxed at 100–110 °C in a 250 mL round-bottom flask for 24 h. The product was washed with copious amounts of deionized water to remove unreacted precursors, filtered, and then dried at 120 °C overnight, yielding 4.2 g of K-OMS. A small aliquot of the resulting material was dissolved in a 10 mL volumetric flask into 5 mL of HCl/HNO_3 solution (3:1, *aqua regia*) and stirred at 50 °C for 30 minutes or until complete dissolution take place. The solution was adjusted to 10 mL with deionized water and then measured with MP-AES instrument. Manganese loading was 62% w/w.

General procedures for H-OMS synthesis:

K-OMS (2 g) from the previous synthesis were stirred in a 1M solution of HNO_3 (20 mL) at 70 °C for 24 h. The product was washed with copious amounts of deionized water to remove unreacted precursors, filtered, and then dried at 120 °C overnight, yielding 1.8 g of H-OMS. A small aliquot of the resulting material was dissolved in a 10 mL volumetric flask into 5 mL of HCl/HNO_3 solution (3:1, *aqua regia*) and stirred at 50 °C for 30 minutes or until complete dissolution take place. The solution was adjusted to 10 mL with deionized water and then measured with MP-AES instrument. Manganese loading was 62% w/w.

XRD of the materials:



General procedures for batch optimization of reaction conditions:

General procedures for benzyl alcohol oxidation in batch with stoichiometric quantity of catalyst:

In a 4 mL screw-capped vial equipped with a magnetic stirring bar, benzyl alcohol (**1**) (1 mmol, 103 µL), the desired solvent (0.25 M, 4 mL), and catalyst (100 mol%) were consecutively added, and the resulting mixture was left under stirring at reflux temperature for 30 minutes. The reaction mixture was then removed from the heating plate and cooled to room temperature. An aliquot of the reaction mixture was filtered through a short pad of celite and analyzed by GLC to determine the conversion, using samples of pure compounds as reference.

General procedures for benzyl alcohol oxidation in batch with catalytic quantity of catalyst:

In a 4 mL screw-capped vial equipped with a magnetic stirring bar, benzyl alcohol (**1**) (1 mmol, 103 µL), the desired solvent (0.25 M, 4 mL), and catalyst (20 mol%) were consecutively added, and the resulting mixture was left under stirring at reflux temperature for 24 h. The reaction mixture was then removed from the heating plate and cooled to room temperature. An aliquot of the reaction mixture was filtered through a short pad of celite and analyzed by GLC to determine the conversion, using samples of pure compounds as reference.

General procedures for imine (5) formation:

In a 4 mL screw-capped vial equipped with a magnetic stirring bar, benzaldehyde (**2**) (0.4 mmol, 41 µL), *o*-aminophenol (**4**) (0.2 mmol, 21.8 mg) and CPME (0.1 M, 2 mL), were consecutively added, and the resulting mixture was left under stirring at the temperature indicated (Table 3 of main text) for 10 minutes. The reaction mixture was then removed from the heating plate and cooled to room temperature. An aliquot of the reaction mixture was taken and analyzed by GLC to determine the conversion, using samples of pure compounds as reference.

General procedures for the synthesis of 6 *via* oxidative cyclization of 5 with stoichiometric quantity of catalyst:

In a 4 mL screw-capped vial equipped with a magnetic stirring bar, imine (**5**) (1 mmol, 197.2 mg), the desired solvent (0.25 M, 4 mL), and catalyst (100 mol%) were consecutively added, and the resulting mixture was left under stirring at reflux temperature for 30 minutes. The reaction mixture was then removed from the heating plate and cooled to room temperature. An aliquot of the reaction mixture was filtered through a short pad of celite and analyzed by GLC to determine the conversion, using samples of pure compounds as reference.

General procedures for the synthesis of 6 *via* oxidative cyclization of 5 with catalytic quantity of catalyst:

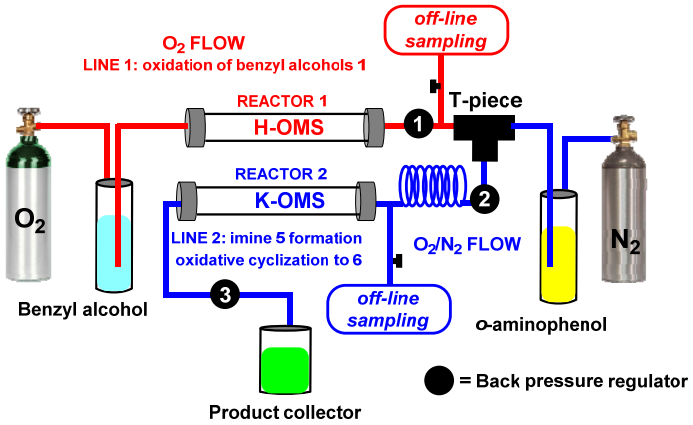
In a 4 mL screw-capped vial equipped with a magnetic stirring bar, imine (**5**) (1 mmol, 197.2 mg), the desired solvent (0.25 M, 4 mL), and catalyst (20 mol%) were consecutively added, and the resulting mixture was left under stirring at reflux temperature for 24 h. The reaction mixture was then removed from the heating plate and cooled to room temperature. An aliquot of the reaction mixture was filtered through a short pad of celite and analyzed by GLC to determine the conversion, using samples of pure compounds as reference.

General multistep procedure and E-factor calculation for the synthesis of 6 in batch conditions:

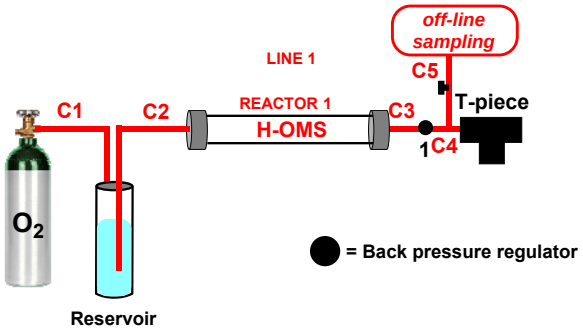
In a 4 mL screw-capped vial equipped with a magnetic stirring bar, benzyl alcohol (**1**) (0.4 mmol, 41 µL), CPME (0.1 M, 2 mL), and H-OMS (100 mol%, 0.4 mmol of Mn, 35.4 mg) were consecutively added, and the resulting mixture was left under stirring at 106 °C for 30 minutes. The reaction mixture was then removed from the heating plate and cooled to room temperature. The heterogeneous mixture was filtered over sintered glass funnel into a 4 mL screw-capped vial containing *o*-aminophenol (0.2 mmol, 21.8 mg). The resulting yellowish solution was vigorously stirred at 106 °C for 10 minutes and K-OMS (100 mol%, 0.2 mmol, 17.7 mg) was then added. The resulting mixture was left under stirring at 106 °C for 30 minutes. A small aliquot of the reaction mixture was subjected to MP-AES analysis to determine the manganese leaching. The heterogeneous mixture was finally filtered over sintered glass funnel and washed with CPME (2x2mL). The solvent was distilled under reduced pressure and recovered as pure (98 % of the total amount, confirmed by ^{1}H-NMR), 2 mL of EtOH was added and then evaporated to remove unreacted benzaldehyde furnishing the pure product as white crystals (0.18 mmol, 36.7 mg) in 94 % yield.

E-factor: [5.16 g (CPME) + 0.035 g (H-OMS) + 0.043 g (benzyl alcohol) + 0.022 g (o-aminophenol) + 0.017 g (K-OMS) + 1.58 g (EtOH)] – [0.035 g (H-OMS) + 0.017 g (K-OMS) + 5.05 (CPME recovered) + 0.037 g (product, 94 % yield)]/ 0.037 g (product, 94 % yield)] = **46.4**

General procedure for multistep continuous flow protocol for the synthesis of 6



Description of Flow system:



LINE 1:

C1: Stainless steel tube 6mm (supplied by Nordival srl), 20 cm

C2: PTFE tube (1/16''), Internal Diameter (ID): 1 mm. Length: 30 cm

C3: PTFE tube (1/16''), ID: 1 mm. Length: 2 cm

C4: PTFE tube (1/16''), ID: 1 mm. Length: 2 cm

C5: PTFE tube (1/16''), ID: 1 mm. Length: 3 cm connected to a needle valve (supplied by Nordival srl) used for off-line analysis

PTFE tube (1/16'') has been supplied by ABreg srl.

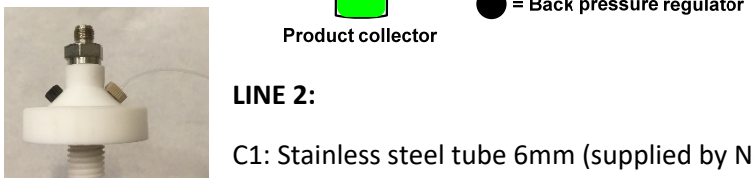
Reactor 1: Supelco HPLC Column Blank 20 cm

Back Pressure Regulator 1: 75 psi BPR (supplied by Upchurch)

T-Piece: stainless steel T-piece 6mm with 6mm – 1/16'' reducer (supplied by Nordival srl)

Reservoir: tailor made PTFE reservoir end capped tailor made PTFE plug (Fig. S1) with 6mm Tube adapter (supplied by Nordival srl).

Figure. S1. Tailor made PTFE plug



LINE 2:

C1: Stainless steel tube 6mm (supplied by Nordival srl), 20 cm

Reservoir: tailor made PTFE reservoir end capped tailor made PTFE plug (Fig. S1) with 6mm Tube adapter (supplied by Nordival srl).

C2: PTFE tube (1/16''), Internal Diameter (ID): 1 mm. Length: 20 cm

T-Piece: stainless steel T-piece 6mm with 6mm – 1/16'' reducer (supplied by Nordival srl)

C3: PTFE tube (1/16''), ID: 1 mm. Length: 2 cm

Back Pressure Regulator 2: 75 psi BPR (supplied by Upchurch)

C4: PTFE tube (1/16''), ID: 1 mm. Length: 2 cm

C4: PTFE tube (1/16''), ID: 1 mm. Length: 60 cm (loop)

Reactor 2: Supelco HPLC Column Blank 20 cm

C5: PTFE tube (1/16''), ID: 1 mm. Length: 5 cm

Back Pressure Regulator 2: 40 psi BPR (supplied by Upchurch)

C6: PTFE tube (1/16''), ID: 1 mm. Length: 5 cm

C7: PTFE tube (1/16''), ID: 1 mm. Length: 3 cm connected to a needle valve (supplied by Nordival srl) used for off-line analysis

PTFE tube (1/16'') has been supplied by ABreg srl.

Product collector: graduated cylinder.

General information: reactor 1, reactor 2 and loop have been thermostated into a stainless steel box. All the connection between 1/16'' tubes, BPRs and reactors have been realized with PTFE HPLC peek (supplied by ABreg srl).

Small scale continuous flow procedures and E-factor calculation (4 mmol):

Reservoir 1 was charged with 4 mL of CPME and benzyl alcohol (4 mmol, 0.432 g, 414 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6** (3.6 mmol, 0.708 g) in 98% yield.

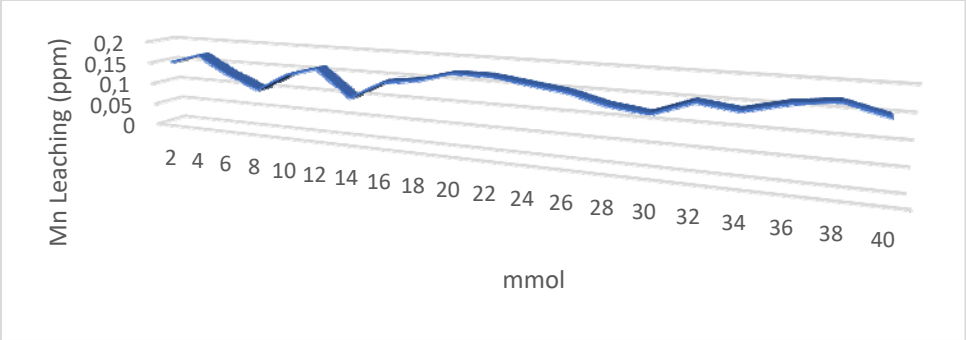
E-factor = [24 g (CPME) + 0.432 g (benzyl alcohol) + 0.404 g (o-aminophenol) + 3.9 g (EtOH)] – [23.5 (CPME recovered) + 0.708 g (product, 98 % yield)]/ 0.708 g (product, 98 % yield)] = **6.4**

Multi-gram scale continuous flow procedures and E-factor calculation (280 mmol):

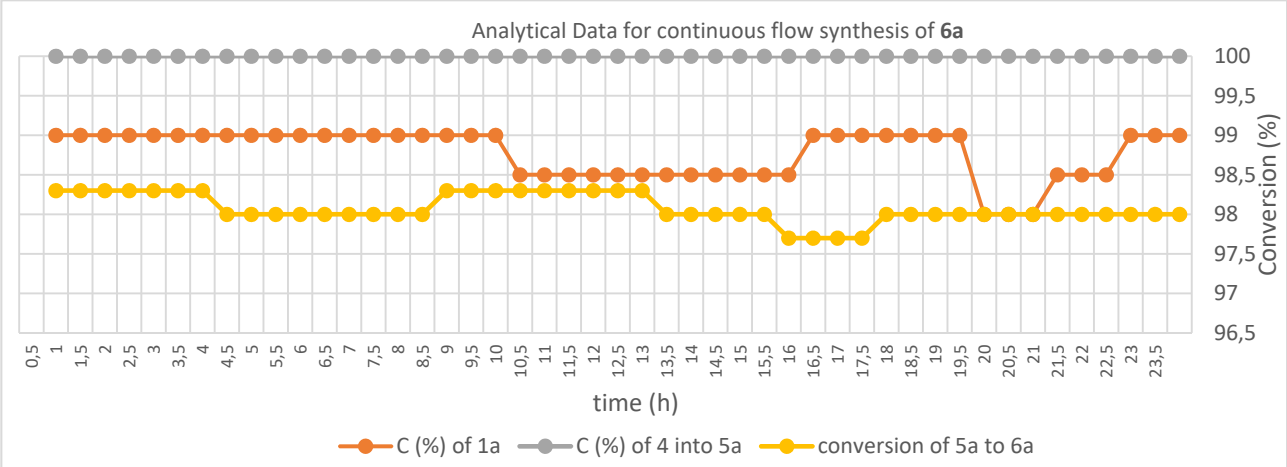
Reservoir 1 was charged with 1M CPME (300 mL) solution of benzyl alcohol (308 mmol, 33.3 g, 32 mL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the o-aminophenol solution (280 mmol, 30.5 g in 300 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 55 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered via distillation under reduced pressure (98% of the total amount, confirmed by 1H-NMR) and the residue was washed with 90 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product 6 (274.4 mmol, 53.5 g) in 98% yield with a productivity of 2.3 g/h after steady state was reached.

E-factor = [610 g (CPME) + 33.3 g (benzyl alcohol) + 30.5 g (o-aminophenol) + 71 g (EtOH)] – [598 (CPME recovered) + 53.5 g (product, 98 % yield)]/ 53.5 g (product, 98 % yield)] = **1.7**

Leaching of Manganese species during flow procedure over 40 mmol



Graphic data for off-line analysis in continuous flow synthesis of 6a



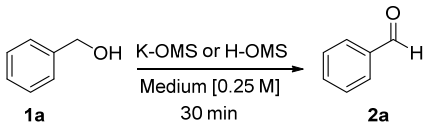
E-factor calculation for literature protocols for the synthesis of 2-arylbenzoxazoles

Reference	Procedure	E-factor
Pan *et al.* *Tetrahedron Lett.* 2002, **43**, 951–954	To a solution of 2-aminophenol (0.109 g, 1.0 mmol) in MeOH (5 mL) was added benzaldehyde (0.106 g, 1.0 mmol). The resulting mixture was heated at 45°C for 12 h. After concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (10 mL) and DDQ (0.250 g, 1.1 mmol) was then added. After stirring at room temperature for 30 min, the resulting mixture was diluted with additional CH_2Cl_2 (10 mL) and washed sequentially with saturated Na_2CO_3 (10 mL×2) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4. After evaporation, the crude was purified by flash column chromatography. Yield 93 %	{0.109 g [aminophenol] + 3.9 g [MeOH] + 0.106 g [benzaldehyde] + 26.6 g [DCM] + 0.250 g [DDQ] + 22.0 g [sodium carbonate] + 11.5 g [brine] – 0.181 g [product]} / 0.181 g [product] = **355**
P. H. Tran *et al.* *RSC Adv.*, 2018, **8**, 11834–11842	2-Aminophenol (109 mg, 1.0 mmol) was treated with benzaldehyde (106 mg, 1.0 mmol) in the presence of triphenyl(butyl-3-sulphonyl)phosphonium toluenesulfonate (20.5 mg, 7 mol%) in a 10 mL glass tube at 100 C under solvent-free magnetic stirring. Upon completion of the reaction as indicated by TLC after 30 min, the mixture was diluted and extracted with diethyl ether (10 x 5 mL). Then the ethereal solution was washed with water (2 x 20 mL) and dried over Na_2SO_4. The final	{0.109 g [aminophenol] + 0.106 g [benzaldehyde] + 0.02 g [catalyst] + 35.6 g [Diethyl Ether] + 40.0 g [water] – 0.177 g [product] – 0.02 g [catalyst]} / 0.177 g [product] = **427**

	product was obtained after solvent removal by a rotary evaporator followed by the purifcation on a silica gel column chromatography using acetone/petroleum ether (1/19) as an eluent solvent. Yield 91 %	
Panahi *et al.* *ACS Catal*. 2014, **4**, 1686−1692	To a mixture of primary alcohol (1 mmol) and 2-aminophenol (1 mmol) in toluene (2 mL), DABCO (0.5 mmol), PFMN (50 mg), and $Ru_2Cl_4(CO)_6$ (10 mg) were added, and the resulting mixture was heated to the refluxing temperature of toluene for 24 h under N2 gas. After completion of the reaction, the mixture was cooled to room temperature, and the PFMN ligand was magnetically separated from the reaction mixture. The reaction mixture was quenched with water and extracted with diethyl ether (10 mL, 3 times), and the organic phase was dried over Na2SO4. The benzoxazole product was purified by column chromatography and obtained in 77 % yield.	{0.112 g $_{[benzyl\ alcohol]}$ + 0.109 g $_{[aminophenol]}$ + 2.6 g $_{[Toluene]}$ + 0.06 g $_{[DABCO]}$ + 0.05 g $_{[PFMN]}$ + 0.01 g $_{[catalyst]}$ + 21.4 g $_{[diethyl\ ether]}$ – 0.05 g $_{[PFMN]}$ – 0.152 g $_{[product]}$} / 0.152 g $_{[product]}$ = **158**

Table of Manganese leaching in different reaction medium

Table S1. Leaching of Mn in different reaction medium for the oxidation of **1a**.[a]



1a **2a**

Entry	Medium	T (°C)	C (%)[b] H-OMS	Leaching of Mn (ppm)[c]
1	Toluene	110	>99	7.32
2	CH_3CN	82	47	2.63
3	Toluene/EtOH (1:1)	110	29	5.70
4	Toluene/EtOH (3:7)	110	9	-
5	EtOH	78	3	-
6	EtOAc	77	38	4.76
7	BuOH	82	30	3.28
8	^{t}BuOH	82	41	3.56
9	Solvent-free	-	2	-
10	2-MeTHF	80	55	0.83
11	TAME	86	> 99	1.04
12	CPME	106	> 99	0.06

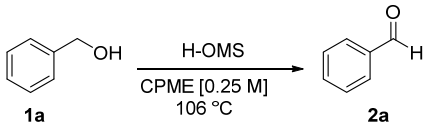
[a] Reaction condition: **1a** (1 mmol), medium 4 mL [0.25M], reaction time 30 min, K- or H-OMS: 1 eq. [b] Conversion to **2a**, measured by GLC analyses using samples of pure compounds as reference. [c] Leaching measurement has been determined with MP-AES.

Catalyst regeneration screening

General procedures for catalyst regeneration and reuse:

In a 5 mL schlenk pressure tube equipped with a magnetic stirring bar, benzyl alcohol **1a** (1 mmol, 103 µL), CPME (0.25 M, 4 mL), and H-OMS were consecutively added, and the resulting mixture was left under stirring at reflux temperature for the desired time. The reaction mixture was then removed from the heating plate and cooled to room temperature. An aliquot of the reaction mixture was filtered through a short pad of celite and analyzed by GLC to determine the conversion, using samples of pure compounds as reference. The reaction mixture was filtered over a Büchner funnel to recover the catalyst and washed with CPME (2x5 mL). The recovered catalyst has been placed in a schlenk pressure tube and heated at 100 °C under the desired gas pressure during 1h.

Table S2. Regeneration screening of the catalyst for the oxidation of **1a** with catalytic quantities of H-OMS.[a]

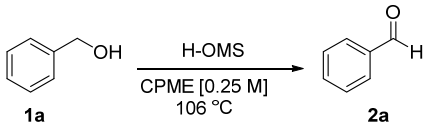


1a **2a**

Entry	C (%)[b] in Run 1	additive used for regeneration	Pressure (bar)	C (%)[c] over consecutive runs			
				Run 2	Run 3	Run 4	Run 5
1	> 99	O_2	1	> 99	96	90	88
2	> 99	N_2	1	26	-	-	-
3	> 99	Air	1	72	46	-	-
4	> 99	Argon	1	22	-	-	-
5	> 99	O_2	2	> 99	> 99	> 99	> 99
6	> 99	Air	2	92	85	83	77
7	> 99	-	-	32	-	-	-
8	> 99	O_2	3	> 99	> 99	> 99	> 99
9	> 99	H_2O_2 (1 eq)	-	58	43	-	-
10	> 99	H_2O_2 (10 eq)	-	72	57	37	-

[a] Reaction condition: **1a** (1 mmol), medium 4 mL [0.25M], reaction time 24 h, H-OMS: 20 mol %. [b] Conversion of **1a**, measured by GLC analyses using samples of pure compounds as reference, data refers to run 1 executed following optimized condition. [c] Conversion of **1a** over consecutive runs measured by GLC analyses using samples of pure

Table S3. Regeneration screening of the catalyst for the oxidation of **1a** with stoichiometric quantities of H-OMS.[a]

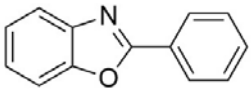


1a **2a**

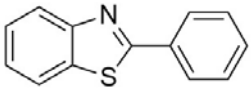
Entry	C (%)[b] in Run 1	additive used for regeneration	Pressure (bar)	C (%)[c] over consecutive runs			
				Run 2	Run 3	Run 4	Run 5
1	> 99	O_2	1	> 99	96	90	88
2	> 99	N_2	1	55	20	-	-
3	> 99	Air	1	89	44	-	-
4	> 99	Argon	1	44	21	-	-
5	> 99	O_2	2	> 99	> 99	> 99	> 99
6	> 99	Air	2	95	87	85	81
7	> 99	-	-	55	18	-	-
8	> 99	O_2	3	> 99	> 99	> 99	> 99
9	> 99	H_2O_2 (1 eq)	-	73	60	22	-
10	> 99	H_2O_2 (10 eq)	-	74	66	37	-

[a] Reaction condition: **1a** (1 mmol), medium 4 mL [0.25M], reaction time 30 min, H-OMS: 100 mol %. [b] Conversion of **1a**, measured by GLC analyses using samples of pure compounds as reference, data refers to run 1 executed following optimized condition. [c] Conversion of **1a** over consecutive runs measured by GLC analyses using samples of pure compounds as reference.

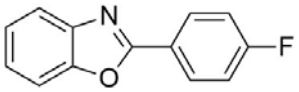
Characterization data for compound 6 a-s



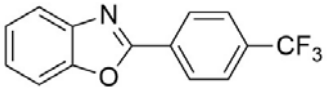
2-phenylbenzo[d]oxazole (6a)[1] has been synthesized following multi-gram scale flow procedure using benzyl alcohol (40 mmol) and *o*-aminophenol (37 mmol) in 98% Yield. White crystals. M.p. 102-105. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.26 (m, 2H), 7.81 – 7.79 (m, 1H), 7.62 – 7.50 (m, 4H), 7.37 – 7.35 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.1, 150.8, 142.1, 131.5, 128.9, 127.6, 127.2, 125.1, 124.6, 120.0, 110.6. GC-EIMS (m/z, %): 195 (100), 181 (68), 180 (54), 161 (62), 145 (22), 121 (16). Elemental Analysis calculated for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17; experimental: C, 79.91; H, 4.68; N, 7.02



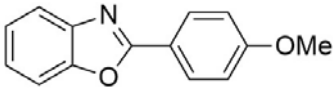
2-phenylbenzo[d]thiazole (6b)[2] has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminothiophenol (3.7 mmol) in 98% Yield. White crystals. M.p. 116-118. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 3H), 7.94 – 7.89 (m, 1H), 7.54 – 7.48 (m, 4H), 7.42 – 7.39 (m, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.09, 154.18, 135.10, 133.65, 131.00, 129.05, 127.59, 126.35, 125.22, 123.27, 121.65. GC-EIMS (m/z, %): 211 (100), 184 (25), 108 (75), 82 (34), 68 (54). Elemental Analysis calculated for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63; S, 15.17; experimental: C, 74.01; H, 3.98; N, 6.53; S, 15.12



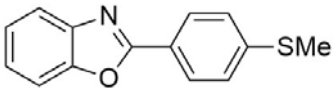
2-(4-fluorophenyl)benzo[d]oxazole (6c)[3] has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 95% Yield. Pale yellow crystals. M.p. 94-96. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.21 (m, 2H), 7.81 – 7.71 (m, 1H), 7.63 – 7.54 (m, 1H), 7.36 (dd, *J* = 6.0, 3.2 Hz, 2H), 7.22 (t, *J* = 8.6 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.9 (d, J_{CF}= 251.2 Hz), 162.2, 150.8, 142.0, 129.9 (d, J_{CF}= 8.9 Hz), 125.2, 124.7, 123.5 (d, J_{CF}= 3.0 Hz), 120.0, 116.2 (d, J_{CF}= 22.1 Hz), 110.6. ^{19}F-NMR (376 MHz, $CDCl_3$) δ - 107.4. GC-EIMS (m/z, %): 213 (100), 194 (63), 193 (17), 180 (57), 161 (30), 121 (18). Elemental Analysis calculated for $C_{13}H_8FNO$: C, 73.23; H, 3.78; N, 6.57; experimental: C, 73.18; H, 3.59; N, 6.40



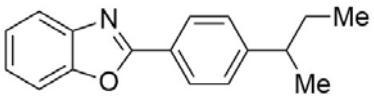
2-(4-(trifluoromethyl)phenyl)benzo[d]oxazole (6d)[3] has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 96% Yield. White crystals. M.p. 145-146. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.1 Hz, 2H), 7.80 (t, *J* = 8.3 Hz, 3H), 7.65 – 7.57 (m, 1H), 7.40 (td, *J* = 6.1, 5.0, 3.5 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.5, 150.9, 141.9, 133.0 (q, J_{CF}= 32.8 Hz), 130.4, 127.9, 125.9 (q, J_{CF}= 3.7 Hz), 125.8, 125.0, 122.4 (q, J_{CF}= 270.8 Hz), 120.4, 110.8. ^{19}F-NMR (376 MHz, $CDCl_3$) δ – 63.0. GC-EIMS (m/z, %): 263 (100), 244 (62), 243 (15), 181 (60), 121 (24). Elemental Analysis calculated for $C_{14}H_8F_3NO$: C, 63.88; H, 3.06; N, 5.32; experimental: C, 63.64; H, 2.98; N, 5.12



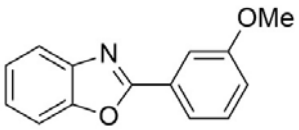
2-(4-methoxyphenyl)benzo[d]oxazole (6e)[1] has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 98% Yield. Pale yellow crystals. M.p. 99-101.^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.9 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.83 – 7.67 (m, 1H), 7.59 – 7.52 (m, 1H), 7.37 – 7.28 (m, 2H), 7.03 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 1H), 3.89 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.2, 162.4, 150.6, 142.1, 132.3, 129.5, 124.7, 124.5, 121.8, 119.6, 119.5, 114.4, 113.7, 110.4, 55.5. GC-EIMS (m/z, %): 225 (100), 195 (80), 181 (64), 160 (25), 121 (15), 107 (55). Elemental Analysis calculated for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22; experimental: C, 74.50; H, 4.84; N, 6.16



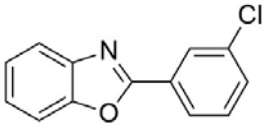
2-(4-(methylthio)phenyl)benzo[d]oxazole (6f)[1] has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 94% Yield. Pale yellow crystals. M.p. 105-107. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.82 – 7.68 (m, 1H), 7.62 – 7.51 (m, 1H), 7.41 – 7.30 (m, 4H), 2.55 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 162.9, 150.6, 143.8, 142.0, 127.9, 125.8, 125.0, 124.6, 123.2, 119.8, 110.5, 15.0. GC-EIMS (m/z, %): 241 (100), 196 (74), 195 (82), 181 (77), 121 (28), 106 (53). Elemental Analysis calculated for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29; experimental: C, 69.33; H, 4.12; N, 5.64; S, 13.25



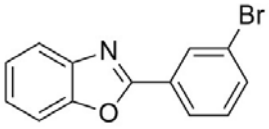
2-(4-(sec-butyl)phenyl)benzo[d]oxazole (6g) has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 99% Yield. White crystals. M.p. 98-101.^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 2H), 7.81 – 7.73 (m, 1H), 7.61 – 7.54 (m, 1H), 7.38 – 7.28 (m, 4H), 2.56 (d, *J* = 7.2 Hz, 2H), 1.94 (dt, *J* = 13.5, 6.8 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.4, 150.7, 145.9, 142.1, 129.7, 127.5, 124.9, 124.6, 124.5, 119.9, 110.5, 45.5, 30.2, 29.7, 22.4. GC-EIMS (m/z, %): 251 (100), 223 (43), 222 (32), 196 (77), 195 (63), 145 (20), 121 (33). Elemental Analysis calculated for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57; experimental: C, 81.09; H, 6.64; N, 5.32



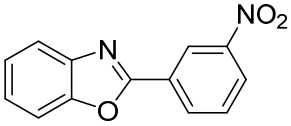
2-(3-methoxyphenyl)benzo[d]oxazole (6h) has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 98% Yield. White crystals. M.p. 70-72. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.79 (dd, *J* = 6.2, 2.9 Hz, 2H), 7.58 (dt, *J* = 7.4, 3.7 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 6.0, 3.3 Hz, 2H), 7.09 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.92 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.0, 160.0, 150.8, 142.0, 130.0, 128.3, 125.2, 124.6, 120.1, 120.0, 118.4, 111.9, 110.6, 55.5. GC-EIMS (m/z, %): 225 (100), 195 (82), 181 (60), 180 (17), 160 (28), 121 (18). Elemental Analysis calculated for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22; experimental: C, 74.54; H, 4.82; N, 6.20



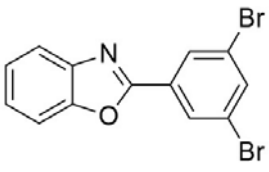
2-(3-chlorophenyl)benzo[d]oxazole (6k) has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 98% Yield. White crystals. M.p. 125-127. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 1.9 Hz, 1H), 8.14 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.62 – 7.56 (m, 1H), 7.53 – 7.42 (m, 2H), 7.42 – 7.33 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.7, 150.8, 141.9, 135.1, 131.5, 130.3, 128.9, 127.6, 125.7, 125.6, 124.8, 120.2, 110.7. GC-EIMS (m/z, %): 231 (33), 229 (100), 197 (52), 196 (44), 181 (29), 160 (37). Elemental Analysis calculated for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10; experimental: C, 67.83; H, 3.34; N, 6.01



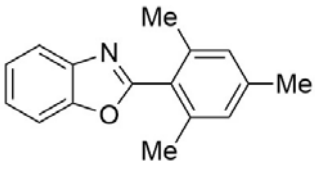
2-(3-bromophenyl)benzo[d]oxazole (6i) has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 96% Yield. Pale brown crystals. M.p. 128-129. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.41 (t, *J* = 1.8 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.65 (dt, *J* = 8.1, 1.4 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.42 – 7.33 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.5, 150.8, 141.9, 134.4, 130.5, 130.5, 129.1, 126.1, 125.6, 124.8, 123.0, 120.2, 110.7. GC-EIMS (m/z, %): 275 (100), 273 (100), 247 (32), 245 (31), 194 (51), 166 (23), 139 (17). Elemental Analysis calculated for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11; experimental: C, 56.93; H, 2.90; N, 5.03



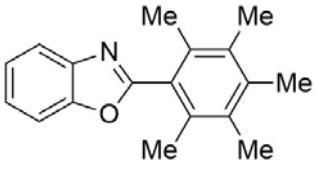
2-(3-nitrophenyl)benzo[d]oxazole (6j)[4] has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 92% Yield. Yellow crystals. M.p. 209-211. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.11 (t, *J* = 2.0 Hz, 1H), 8.59 (d, *J* = 7.8 Hz, 1H), 8.43 – 8.36 (m, 1H), 7.87 – 7.78 (m, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.49 – 7.35 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.6, 150.9, 148.7, 141.8, 133.0, 130.2, 129.0, 126.1, 125.8, 125.2, 122.5, 120.5, 110.9. GC-EIMS (m/z, %): 240 (100), 224 (17), 196 (22), 195 (47), 121 (22). Elemental Analysis calculated for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66; experimental: C, 65.10; H, 3.12; N, 11.43



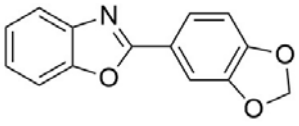
2-(3,5-dibromophenyl)benzo[d]oxazole (6l) has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 98% Yield. Pale brown crystals. M.p. 132-133. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 1.8 Hz, 2H), 7.88 – 7.72 (m, 2H), 7.65 – 7.54 (m, 1H), 7.45 – 7.36 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.1, 150.8, 141.7, 136.7, 130.4, 129.1, 126.0, 125.1, 123.5, 120.4, 110.8. GC-EIMS (m/z, %): 355 (49), 353 (100), 351 (50), 274 (22), 272 (22), 193 (17), 165 (18). Elemental Analysis calculated for $C_{13}H_7Br_2NO$: C, 44.23; H, 2.00; N, 3.97; experimental: C, 44.18; H, 2.01; N, 3.78



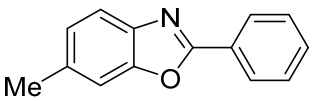
2-mesitylbenzo[d]oxazole (6m) has been synthesized following small scale flow procedure using the appropriate benzylalcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 98% Yield. White crystals. M.p. 112-115. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 2H), 7.64 – 7.55 (m, 1H), 7.40 – 7.37 (m, 1H), 6.98 (s, 2H), 2.36 – 2.30 (m, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.3, 150.6, 141.6, 140.3, 138.5, 130.5, 128.7, 125.0, 124.9, 124.2, 120.2, 110.6, 21.3, 20.4. GC-EIMS (m/z, %): 237 (100), 222 (48), 208 (43), 194 (20), 130 (26), 118 (52). Elemental Analysis calculated for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; experimental: C, 80.82; H, 6.17; N, 5.88



2-(2,3,4,5,6-pentamethylphenyl)benzo[d]oxazole (6n) has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 99% Yield. White crystals. M.p. 130-131. ^{1}H-NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.79 (m, 1H), 7.63 – 7.55 (m, 1H), 7.45 – 7.33 (m, 2H), 2.31 (s, 3H), 2.25 (s, 6H), 2.09 (s, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.8, 150.7, 141.5, 137.6, 133.4, 132.9, 126.3, 124.9, 124.2, 120.2, 110.7, 18.1, 17.0, 16.3. GC-EIMS (m/z, %): 265 (100), 250 (52), 235 (25), 157 (46), 132 (22), 114 (16). Elemental Analysis calculated for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28; experimental: C, 81.27; H, 7.14; N, 5.18

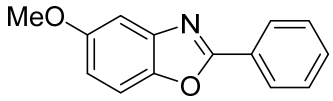


2-(benzo[d][1,3]dioxol-5-yl)benzo[d]oxazole (6o) has been synthesized following small scale flow procedure using the appropriate benzyl alcohol (4 mmol) and *o*-aminophenol (3.7 mmol) in 99% Yield. Pale yellow crystals. M.p 137-138. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.59 – 7.52 (m, 1H), 7.39 – 7.29 (m, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.08 (s, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 162.88, 150.68, 150.58, 148.24, 142.19, 124.79, 124.51, 122.81, 121.17, 119.73, 110.43, 108.75, 107.70, 101.77. GC-EIMS (m/z, %): 239 (100), 238 (82), 209 (25), 181 (32), 153 (44), 119 (51), 63 (55). Elemental Analysis calculated for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86; experimental: C, 70.01; H, 3.70; N, 5.78

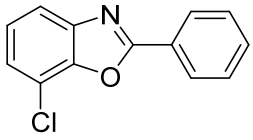


6-methyl-2-phenylbenzo[d]oxazole (6p) has been synthesized following small scale flow procedure using benzyl alcohol (4 mmol) and 3-methyl-2-aminophenol (3.7 mmol) in 98% Yield. White crystals. M.p. 143-145. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.23 (m, 2H), 7.54 – 7.52 (m, 3H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.81, 157.41, 145.42, 142.91, 131.42, 128.90, 127.50, 127.25, 113.74, 110.73, 102.87, 55.93. GC-EIMS (m/z, %): 209 (100), 208 (75), 195 (35), 194 (25), 130

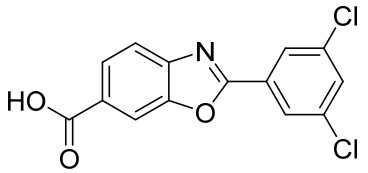
(55), 118 (32). Elemental Analysis calculated for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69; experimental: C, 80.34; H, 5.28; N, 6.68



5-methoxy-2-phenylbenzo[d]oxazole (6q) has been synthesized following small scale flow procedure using benzyl alcohol (4 mmol) and 4-methoxy-2-aminophenol (3.7 mmol) in 98% Yield. White crystals. M.p. 155-157. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.23 (m, 2H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.52 (m, 3H), 7.42 (s, 1H), 7.20 (dd, *J* = 8.2, 1.5 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.58, 155.68, 151.07, 139.92, 135.59, 131.30, 128.89, 127.47, 125.83, 119.35, 110.78, 21.83. GC-EIMS (m/z,%): 225 (100), 195 (75), 194 (35), 181 (45), 180 (37), 160 (25), 158 (55), 121 (40). Elemental Analysis calculated for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22; experimental: C, 74.61; H, 4.88; N, 6.20



7-chloro-2-phenylbenzo[d]oxazole (6r) has been synthesized following small scale flow procedure using benzyl alcohol (4 mmol) and 6-chloro-2-aminophenol (3.7 mmol) in 95% Yield. Pale yellow crystals. M.p. 118-121. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.7, 2.0 Hz, 2H), 7.69 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.59 – 7.55 (m, 3H), 7.39 – 7.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.45, 158.64, 147.40, 143.36, 131.99, 129.00, 127.88, 126.56, 125.43, 125.33, 118.48. GC-EIMS (m/z, %): 231 (35), 229 (100), 197 (22), 196 (64), 194 (44), 181 (32), 160 (57), 158 (25). Elemental Analysis calculated for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10; experimental: C, 67.93; H, 3.46; N, 6.11



2-(3,5-dichlorophenyl)benzo[d]oxazole-6-carboxylic acid (Tafamidis) has been synthesized following small scale flow procedure using 3,5-dichlorobenzyl alcohol (4 mmol) and 4-amino-3-hydroxybenzoic acid (3.7 mmol) in 92% Yield. Pale yellow crystals. M.p. 187-188. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.92 (s, 1H), 8.15 (d, *J* = 2.0 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.48 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 166.27, 157.95, 152.25, 139.57, 135.17, 130.80, 130.72, 127.54, 126.05, 121.41, 120.07, 112.44. GC-EIMS (m/z, %): 310 (63), 308 (100), 306 (50), 292 (22), 294 (27), 272 (47), 264 (44), 236 (38), 181 (25). Elemental Analysis calculated for $C_{14}H_7Cl_2NO_3$: C, 54.58; H, 2.29; N, 4.55; experimental: C, 54.57; H, 2.25; N, 4.58

E-factor = [24 g (CPME) + 0.708 g (3,5-dichlorobenzyl alcohol) + 0.566 g (o-aminophenol) + 3.9 g (EtOH)] – [23.5 (CPME recovered) + 1.05 g (product, 92 % yield)]/ 1.05 g (product, 92 % yield)] = **4.4**

References:

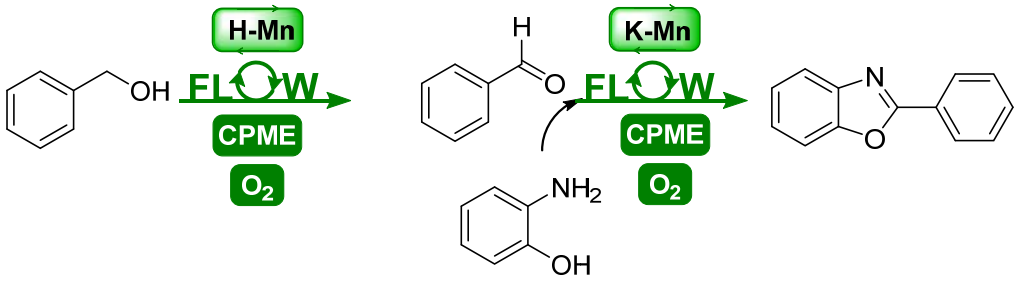
[1] N. Khatun, S. Guin, S. K. Routa, B. K. Patel *RSC Adv.*, 2014, **4**, 10770-10778

[2] K. Chakrabarti, M. Majia, S. Kundu *Green Chem.*, 2019, **21**, 1999-2004

[3] L. Tang, Z. Yang, T. Sun, D. Zhang, X. Ma, W. Rao, Y. Zhou *Adv. Synth. Catal*. 2018, **360**, 3055–3062

[4] P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul, T. Punniyamurthy *J. Org. Chem.*, 2009, **74**, 8719–8725

Chem. Name	*2-phenylbenzo[d]oxazole (6a)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 1M CPME solution of benzyl alcohol (43.2 mmol, 4.7 g, 4.5 mL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (40 mmol, 4.3 g in 43 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 25 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 15 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6a** (39.2 mmol, 7.7 g) in 98% yield with a productivity of 2.3 g/h after steady state was reached.

Mol Formula	$C_{13}H_9NO$	**m.p.**	102-105 °C

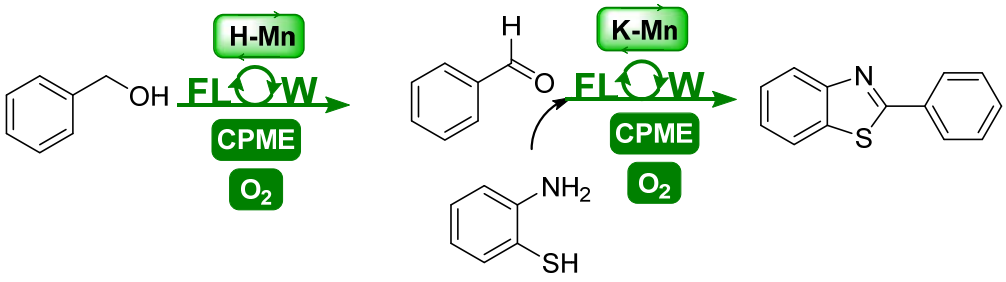
Elemental Analysis: Calc.: C, 79.98; H, 4.65; N, 7.17; found: C, 79.91; H, 4.68; N, 7.02

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	7.37 – 7.35	2	*m*	
	7.62 – 7.50	4	*m*	
	7.81 – 7.79	1	*m*	
	8.29 – 8.26	2	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 163.1, 150.8, 142.1, 131.5, 128.9, 127.6, 127.2, 125.1, 124.6, 120.0, 110.6.

GC-EIMS (m/z, %): 195 (100), 181 (68), 180 (54), 161 (62), 145 (22), 121 (16).

Chem. Name	*2-phenylbenzo[d]thiazole (6b)*
Lit. Ref.	K. Chakrabarti, M. Majia, S. Kundu *Green Chem*., 2019, **21**, 1999-2004



METHOD:
Reservoir 1 was charged with 4 mL of CPME and benzyl alcohol (4 mmol, 0.432 g, 414 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminothiophenol solution (3.7 mmol, 0.463 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6b** (3.6 mmol, 0.766 g) in 98% yield

Mol Formula	$C_{13}H_9NS$	**m.p.**	116-118 °C

Elemental Analysis: Calc.: C, 73.90; H, 4.29; N, 6.63; S, 15.17; found: C, 74.01; H, 3.98; N, 6.53; S, 15.12

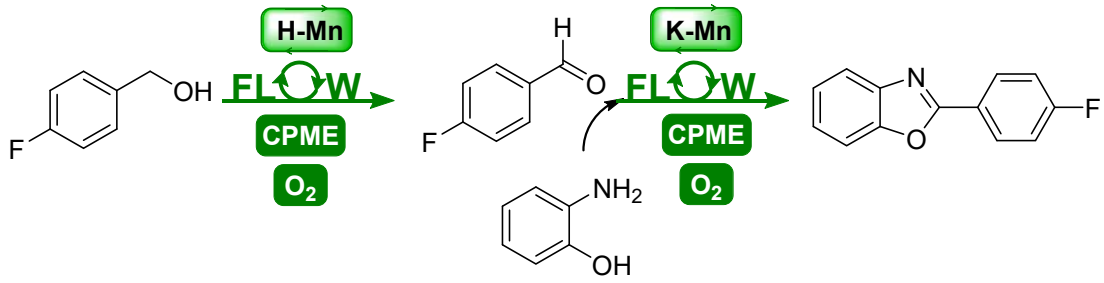
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
7.42 – 7.39	1	*m*	
7.54 – 7.48	4	*m*	
7.94 – 7.89	1	*m*	
8.15 – 8.08	3	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 168.09, 154.18, 135.10, 133.65, 131.00, 129.05, 127.59, 126.35, 125.22, 123.27, 121.65

GC-EIMS (m/z, %): 211 (100), 184 (25), 108 (75), 82 (34), 68 (54)

Chem. Name	*2-(4-fluorophenyl)benzo[d]oxazole (6c)*
Lit. Ref.	L. Tang, Z. Yang, T. Sun, D. Zhang, X. Ma, W. Rao, Y. Zhou *Adv. Synth. Catal*. 2018, **360**, 3055–3062



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 4-fluoro benzyl alcohol (4 mmol, 436 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6c** (3.5 mmol, 0.749 g) in 95% yield

Mol Formula	$C_{13}H_8FNO$	**m.p.**	94-96 °C

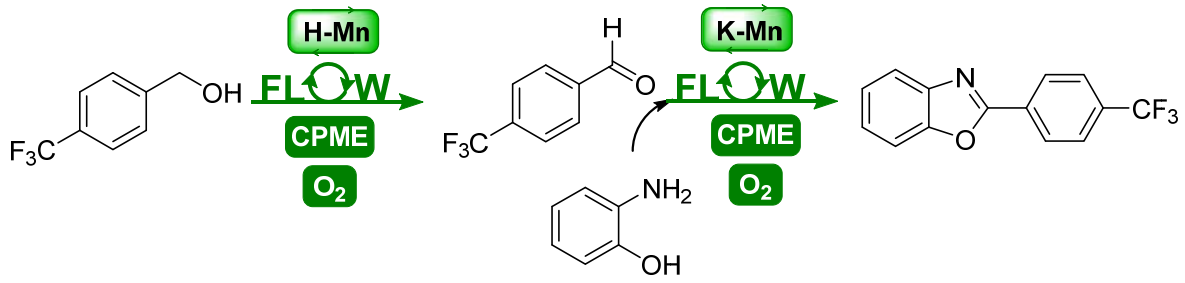
Elemental Analysis: Calc.: C, 73.23; H, 3.78; N, 6.57; found: C, 73.18; H, 3.59; N, 6.40

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.32 – 8.21	2	*m*	
	7.81 – 7.71	1	*m*	
	7.63 – 7.54	1	*m*	
	7.36	2	*dd*	6.0, 3.2
	7.22	2	*t*	8.6

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 164.9 (d, J_{CF}= 251.2 Hz), 162.2, 150.8, 142.0, 129.9 (d, J_{CF}= 8.9 Hz), 125.2, 124.7, 123.5 (d, J_{CF}= 3.0 Hz), 120.0, 116.2 (d, J_{CF}= 22.1 Hz), 110.6

GC-EIMS (m/z, %): 213 (100), 194 (63), 193 (17), 180 (57), 161 (30), 121 (18)

Chem. Name	*2-(4-(trifluoromethyl)phenyl)benzo[d]oxazole (6d)*
Lit. Ref.	L. Tang, Z. Yang, T. Sun, D. Zhang, X. Ma, W. Rao, Y. Zhou *Adv. Synth. Catal*. 2018, **360**, 3055–3062



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 4-trifluoromethyl benzyl alcohol (4 mmol, 548 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6d** (3.6 mmol, 0.935 g) in 96% yield

Mol Formula	$C_{14}H_8F_3NO$	**m.p.**	145-146 °C

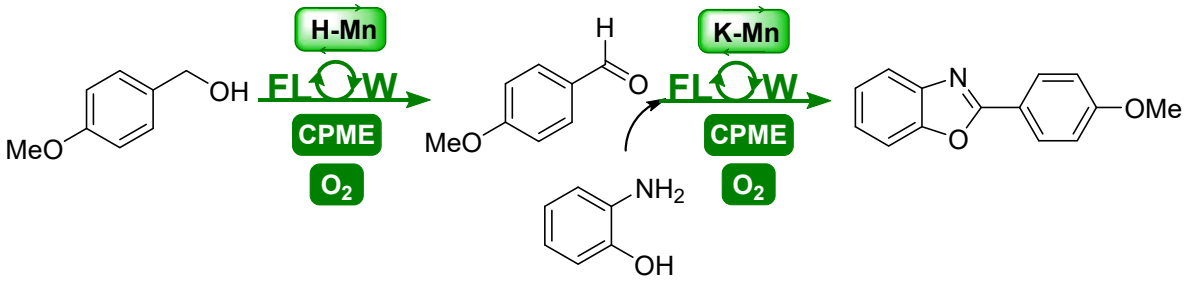
Elemental Analysis: Calc.: C, 63.88; H, 3.06; N, 5.32; found: C, 63.64; H, 2.98; N, 5.12

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.37	2	*d*	8.1
	7.80	3	*t*	8.3
	7.65 – 7.57	1	*m*	
	7.40	2	*td*	6.1, 5.0, 3.5

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 161.5, 150.9, 141.9, 133.0 (q, J_{CF}= 32.8 Hz), 130.4, 127.9, 125.9 (q, J_{CF}= 3.7 Hz), 125.8, 125.0, 122.4 (q, J_{CF}= 270.8 Hz), 120.4, 110.8

GC-EIMS (m/z, %): 263 (100), 244 (62), 243 (15), 181 (60), 121 (24)

Chem. Name	*2-(4-methoxyphenyl)benzo[d]oxazole (6e)*
Lit. Ref.	N. Khatun, S. Guin, S. K. Routa, B. K. Patel *RSC Adv*., 2014, **4**, 10770-10778



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 4-methoxy benzyl alcohol (4 mmol, 497 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6e** (3.6 mmol, 0.817 g) in 98% yield

Mol Formula	$C_{14}H_{11}NO_2$	**m.p.**	99-101 °C

Elemental Analysis: Calc.: C, 74.65; H, 4.92; N, 6.22; found: C, 74.50; H, 4.84; N, 6.16

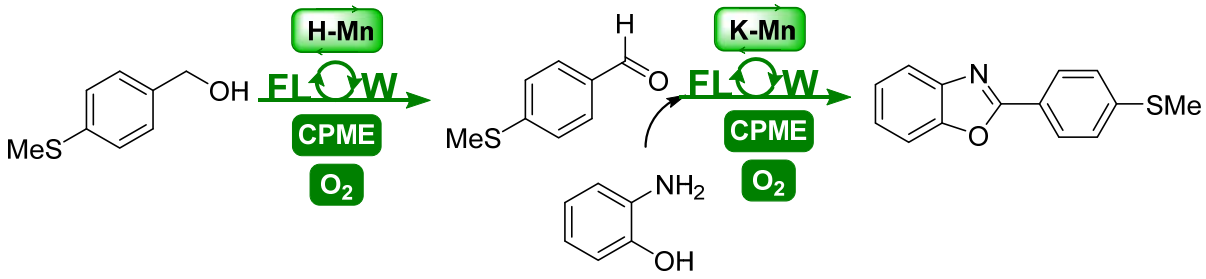
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
8.21	2	*d*	8.9
8.08	1	*d*	8.8
7.83 – 7.67	1	*m*	
7.59 – 7.52	1	*m*	
7.37 – 7.28	2	*m*	8.1
7.03	2	*d*	8.9
6.95	1	*d*	8.9
3.89	3	*s*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 163.2, 162.4, 150.6, 142.1, 132.3, 129.5, 124.7, 124.5, 121.8, 119.6, 119.5, 114.4, 113.7, 110.4, 55.5

GC-EIMS (m/z, %): 225 (100), 195 (80), 181 (64), 160 (25), 121 (15), 107 (55)

Chem. Name	*2-(4-(methylthio)phenyl)benzo[d]oxazole (6f)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 4-methylthio benzyl alcohol (4 mmol, 617 mg), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6f** (3.4 mmol, 0.820 g) in 94% yield

Mol Formula	$C_{14}H_{11}NOS$	**m.p.**	105-107 °C

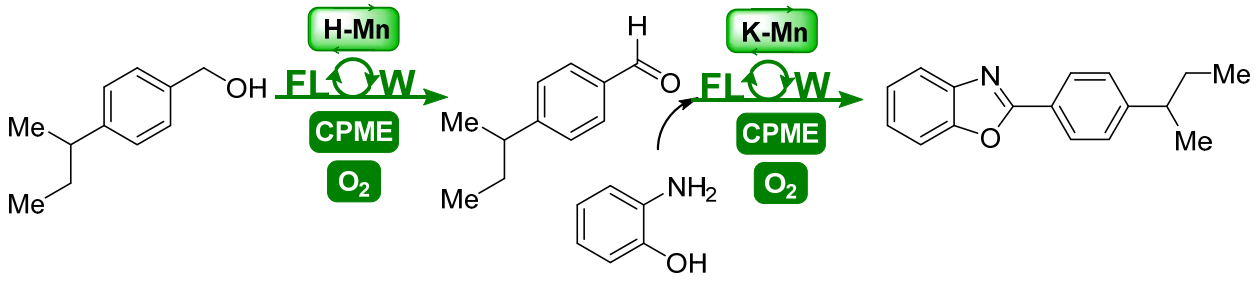
Elemental Analysis: Calc.: C, 69.68; H, 4.59; N, 5.80; S, 13.29; found: 69.33; H, 4.12; N, 5.64; S, 13.25

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.17	2	*d*	8.6
	7.82 – 7.68	1	*m*	8.1
	7.62 – 7.51	1	*m*	8.9
	7.41 – 7.30	4	*m*	8.9
	2.55	3	*s*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 162.9, 150.6, 143.8, 142.0, 127.9, 125.8, 125.0, 124.6, 123.2, 119.8, 110.5, 15.0

GC-EIMS (m/z, %): 241 (100), 196 (74), 195 (82), 181 (77), 121 (28), 106 (53)

Chem. Name	*2-(4-(sec-butyl)phenyl)benzo[d]oxazole (6g)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 4-secbutyl benzyl alcohol (4 mmol, 672 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6g** (3.6 mmol, 0.919 g) in 99% yield

Mol Formula	$C_{17}H_{17}NO$	**m.p.**	98-101 °C

Elemental Analysis: Calc.: C, 81.24; H, 6.82; N, 5.57; found: C, 81.09; H, 6.64; N, 5.32

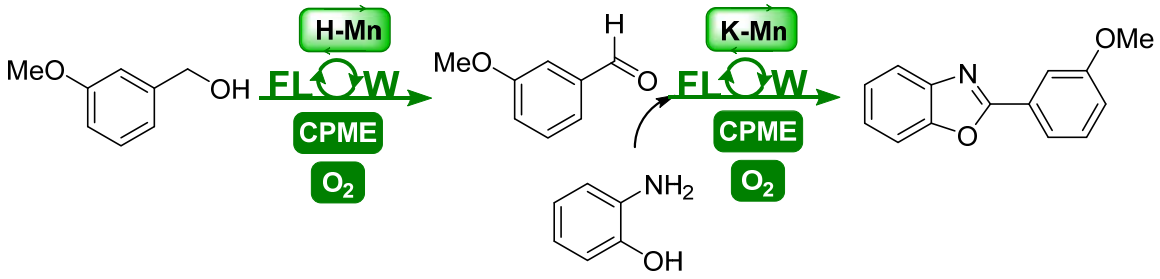
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
8.17	2	*d*	8.0
7.81 – 7.73	1	*m*	
7.61 – 7.54	1	*m*	
7.38 – 7.28	4	*m*	
2.56	2	*d*	7.2
1.94	1	*dt*	13.5, 6.8
0.94	6	*d*	6.6

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 163.4, 150.7, 145.9, 142.1, 129.7, 127.5, 124.9, 124.6, 124.5, 119.9, 110.5, 45.5, 30.2, 29.7, 22.4

GC-EIMS (m/z, %): 251 (100), 223 (43), 222 (32), 196 (77), 195 (63), 145 (20), 121 (33).

Chem. Name	*2-(3-methoxyphenyl)benzo[d]oxazole (6h)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 3-methoxy benzyl alcohol (4 mmol, 497 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6h** (3.6 mmol, 0.816 g) in 98% yield

Mol Formula	$C_{14}H_{11}NO_2$	**m.p.**	70-72 °C

Elemental Analysis: Calc.: C, 74.65; H, 4.92; N, 6.22; found: C, 74.54; H, 4.82; N, 6.20

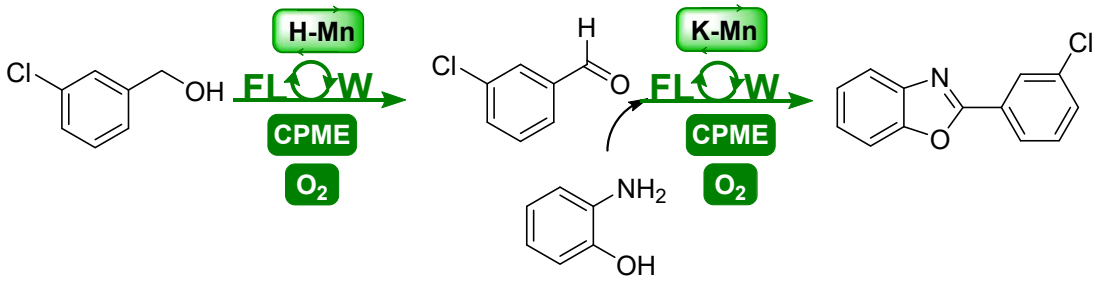
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
7.86	1	*d*	7.7
7.79	2	*dd*	6.2, 2.9
7.58	1	*dt*	7.4, 3.7
7.43	1	*t*	8.0
7.36	2	*dd*	6.0, 3.3
7.09	1	*dd*	8.2, 2.6
3.92	3	*s*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 163.0, 160.0, 150.8, 142.0, 130.0, 128.3, 125.2, 124.6, 120.1, 120.0, 118.4, 111.9, 110.6, 55.5

GC-EIMS (m/z, %): 225 (100), 195 (82), 181 (60), 180 (17), 160 (28), 121 (18)

Chem. Name	*2-(3-chlorophenyl)benzo[d]oxazole (6k)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 3-chloro benzyl alcohol (4 mmol, 471 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6k** (3.6 mmol, 0.827 g) in 98% yield

Mol Formula	$C_{13}H_8ClNO$	**m.p.**	125-127 °C

Elemental Analysis: Calc.: C, 67.99; H, 3.51; N, 6.10; found: C, 67.83; H, 3.34; N, 6.01

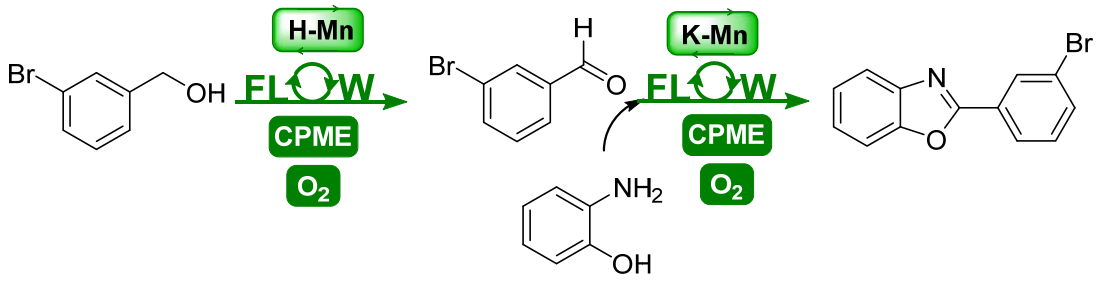
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
8.26	1	*d*	1.9
8.14	1	*dd*	7.5, 1.1
7.81 – 7.75	1	*m*	
7.62 – 7.56	1	*m*	
7.53 – 7.42	2	*m*	
7.42 – 7.33	2	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 161.7, 150.8, 141.9, 135.1, 131.5, 130.3, 128.9, 127.6, 125.7, 125.6, 124.8, 120.2, 110.7

GC-EIMS (m/z, %): 231 (33), 229 (100), 197 (52), 196 (44), 181 (29), 160 (37)

Chem. Name	*2-(3-bromophenyl)benzo[d]oxazole (6i)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 3-bromo benzyl alcohol (4 mmol, 354 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6i** (3.5 mmol, 0.973 g) in 96% yield

Mol Formula	$C_{13}H_8BrNO$	**m.p.**	128-129 °C

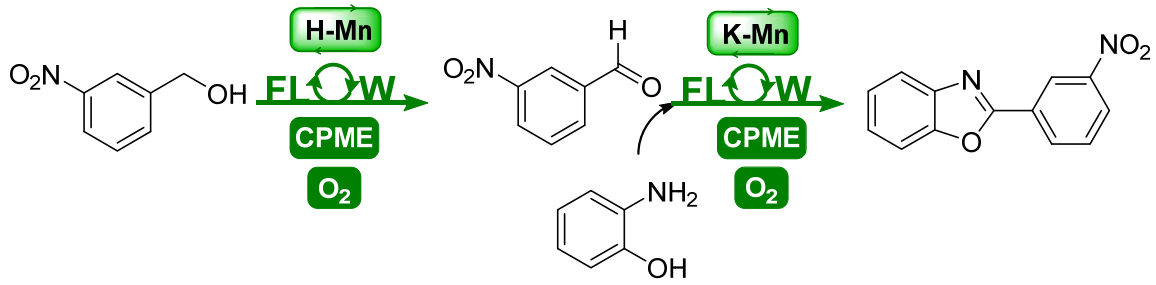
Elemental Analysis: Calc.: C, 56.96; H, 2.94; N, 5.11; found: C, 56.93; H, 2.90; N, 5.03

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.41	1	*t*	1.8
	8.18	1	*d*	7.8
	7.81 – 7.75	1	*m*	
	7.65	1	*dt*	8.1, 1.4
	7.61 – 7.55	1	*m*	
	7.42 – 7.33	3	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 161.5, 150.8, 141.9, 134.4, 130.5, 130.5, 129.1, 126.1, 125.6, 124.8, 123.0, 120.2, 110.7

GC-EIMS (m/z, %): 275 (100), 273 (100), 247 (32), 245 (31), 194 (51), 166 (23), 139 (17)

Chem. Name	*2-(3-nitrophenyl)benzo[d]oxazole (6j)*
Lit. Ref.	P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul, T. Punniyamurthy *J. Org. Chem.*, 2009, **74**, 8719–8725



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 3-nitro benzyl alcohol (4 mmol, 475 µL), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6j** (3.4 mmol, 0.818 g) in 92% yield

Mol Formula	$C_{13}H_8N_2O_3$	**m.p.**	209-211 °C

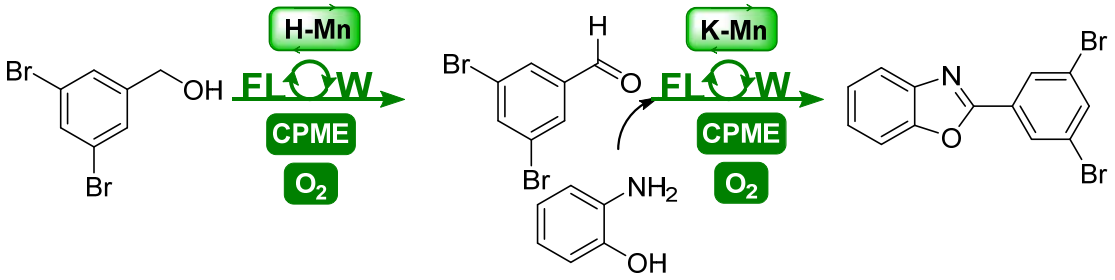
Elemental Analysis: Calc.: C, 65.00; H, 3.36; N, 11.66; found: C, 65.10; H, 3.12; N, 11.43

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	9.11	1	*t*	2.0
	8.59	1	*d*	7.8
	8.43 – 8.36	1	*m*	7.8
	7.87 – 7.78	1	*m*	
	7.74	1	*t*	8.0
	7.69 – 7.60	1	*m*	
	7.49 – 7.35	2	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 160.6, 150.9, 148.7, 141.8, 133.0, 130.2, 129.0, 126.1, 125.8, 125.2, 122.5, 120.5, 110.9.

GC-EIMS (m/z, %): 240 (100), 224 (17), 196 (22), 195 (47), 121 (22).

Chem. Name	*2-(3,5-dibromophenyl)benzo[d]oxazole (6l)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 3,5-dinitro benzyl alcohol (4 mmol, 1.06 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6l** (3.6 mmol, 1.3 g) in 98% yield

Mol Formula	$C_{13}H_7Br_2NO$	**m.p.**	132-133 °C

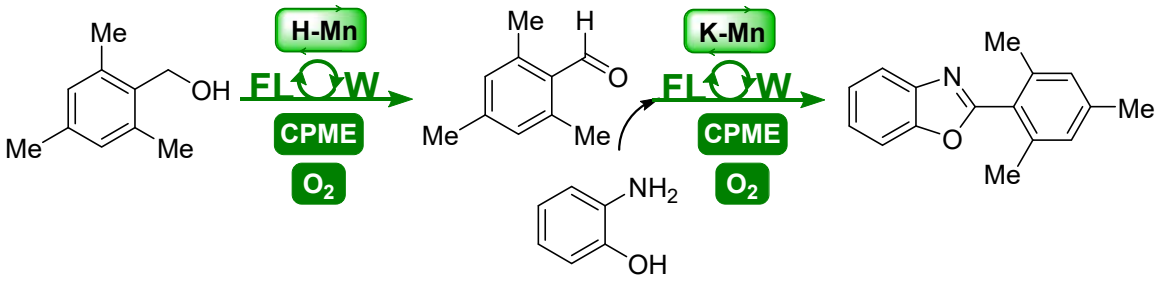
Elemental Analysis: Calc.: C, 44.23; H, 2.00; N, 3.97; found: C, 44.18; H, 2.01; N, 3.78

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.34	2	*d*	1.8
	7.87 – 7.78	1	*m*	
	7.88 – 7.72	1	*m*	8.0
	7.65 – 7.54	1	*m*	
	7.45 – 7.36	2	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 160.1, 150.8, 141.7, 136.7, 130.4, 129.1, 126.0, 125.1, 123.5, 120.4, 110.8

GC-EIMS (m/z, %): 355 (49), 353 (100), 351 (50), 274 (22), 272 (22), 193 (17), 165 (18)

Chem. Name	*2-mesitylbenzo[d]oxazole (6m)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 2,4,6-trimethyl benzyl alcohol (4 mmol, 0.600 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6m** (3.6 mmol, 0.854 g) in 98% yield

Mol Formula	$C_{16}H_{15}NO$	**m.p.**	112-115 °C

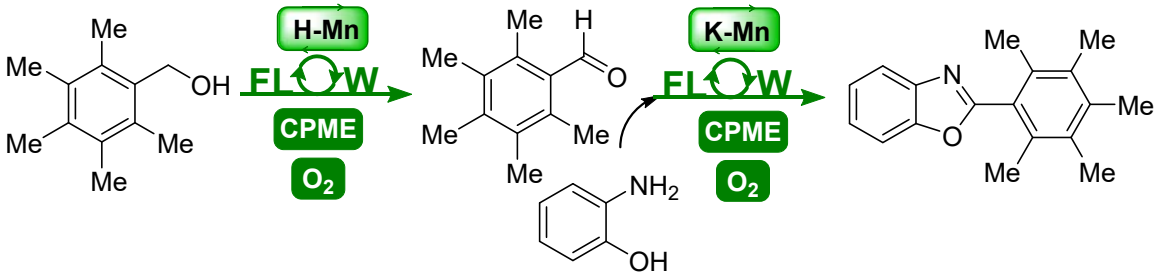
Elemental Analysis: Calc.: C, 80.98; H, 6.37; N, 5.90; found: C, 80.82; H, 6.17; N, 5.88

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	7.87 – 7.80	2	*m*	
	7.64 – 7.55	1	*m*	
	7.40 – 7.37	1	*m*	
	6.98	2	*s*	
	2.36 – 2.30	9	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 163.3, 150.6, 141.6, 140.3, 138.5, 130.5, 128.7, 125.0, 124.9, 124.2, 120.2, 110.6, 21.3, 20.4

GC-EIMS (m/z, %): 237 (100), 222 (48), 208 (43), 194 (20), 130 (26), 118 (52)

Chem. Name	*2-(2,3,4,5,6-pentamethylphenyl)benzo[d]oxazole (6n)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 2,3,4,5,6-pentamethyl benzyl alcohol (4 mmol, 0.713 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6n** (3.7 mmol, 0.972 g) in 99% yield

Mol Formula	$C_{18}H_{19}NO$	**m.p.**	130-131 °C

Elemental Analysis: Calc.: C, 81.47; H, 7.22; N, 5.28; found: C, 81.27; H, 7.14; N, 5.18

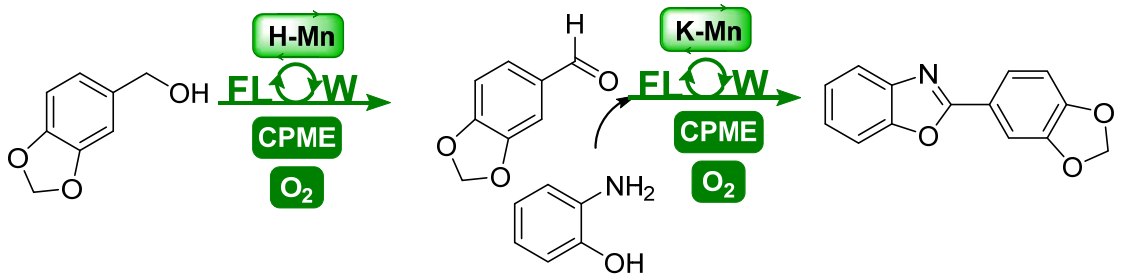
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
7.93 – 7.79	1	*m*	
7.63 – 7.55	1	*m*	1.8
7.45 – 7.33	2	*m*	
2.31	3	*s*	8.0
2.25	6	*s*	
2.09	6	*s*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 164.8, 150.7, 141.5, 137.6, 133.4, 132.9, 126.3, 124.9, 124.2, 120.2, 110.7, 18.1, 17.0, 16.3

GC-EIMS (m/z, %): 265 (100), 250 (52), 235 (25), 157 (46), 132 (22), 114 (16)

Chem. Name	*2-(benzo[d][1,3]dioxol-5-yl)benzo[d]oxazole (6o)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 4-piperyl benzyl alcohol (4 mmol, 0.609 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.404 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6o** (3.7 mmol, 0.876 g) in 99% yield

Mol Formula	$C_{14}H_9NO_3$	**m.p.**	137-138 °C

Elemental Analysis: Calc.: C, 70.29; H, 3.79; N, 5.86; found: C, 70.01; H, 3.70; N, 5.78

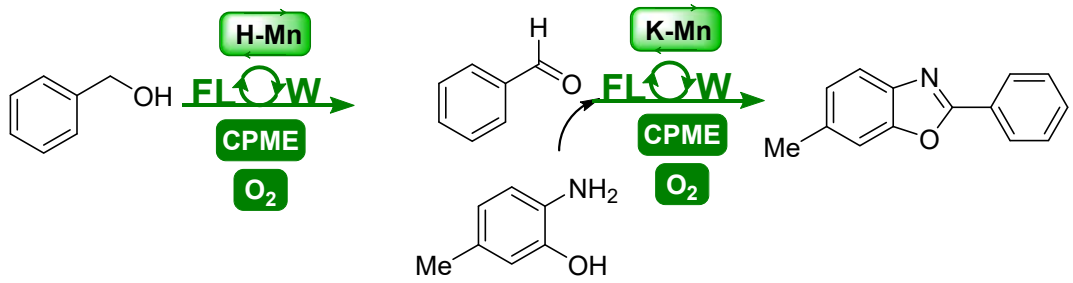
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
7.84	1	*dd*	8.2, 1.7
7.78 – 7.69	2	*m*	1.8
7.59 – 7.52	1	*m*	
7.39 – 7.29	2	*m*	
6.95	1	*d*	8.2
6.08	2	*s*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 162.88, 150.68, 150.58, 148.24, 142.19, 124.79, 124.51, 122.81, 121.17, 119.73, 110.43, 108.75, 107.70, 101.77

GC-EIMS (m/z, %): 239 (100), 238 (82), 209 (25), 181 (32), 153 (44), 119 (51), 63 (55)

Chem. Name	*6-methyl-2-phenylbenzo[d]oxazole (6p)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and benzyl alcohol (4 mmol, 0.432 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the 3-methyl-2-aminophenol solution (3.7 mmol, 0.455 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6p** (3.6 mmol, 0.757 g) in 98% yield

Mol Formula	$C_{14}H_{11}NO$	**m.p.**	143-145 °C

Elemental Analysis: Calc.: C, 80.36; H, 5.30; N, 6.69; found: C, 80.34; H, 5.28; N, 6.68

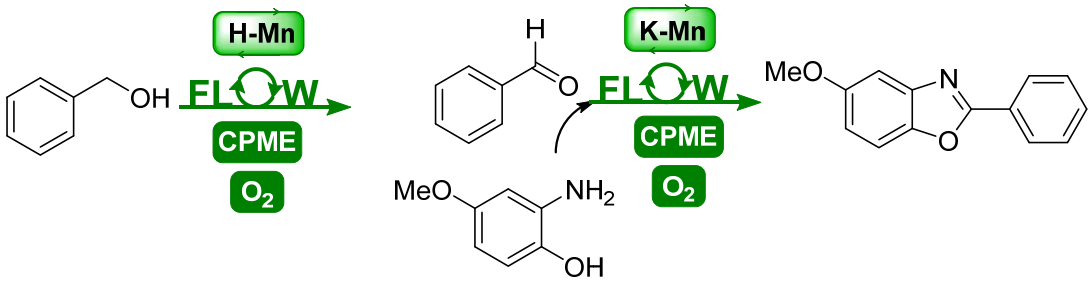
^{1}H NMR 400 MHz $CDCl_3$

□ value	No. H	Mult.	j value/Hz
8.26 – 8.23	2	*m*	
7.54 – 7.52	3	*m*	
7.47	1	*d*	8.8
7.29	1	*d*	2.4
6.97	1	*dd*	8.9, 2.6
3.89	3	*s*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 163.81, 157.41, 145.42, 142.91, 131.42, 128.90, 127.50, 127.25, 113.74, 110.73, 102.87, 55.93

GC-EIMS (m/z, %): 209 (100), 208 (75), 195 (35), 194 (25), 130 (55), 118 (32)

Chem. Name	*5-methoxy-2-phenylbenzo[d]oxazole (6q)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and benzyl alcohol (4 mmol, 0.432 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the 4-methoxy-2-aminophenol solution (3.7 mmol, 0.514 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6q** (3.6 mmol, 0.810 g) in 98% yield

Mol Formula	$C_{14}H_{11}NO_2$	**m.p.**	155-157 °C

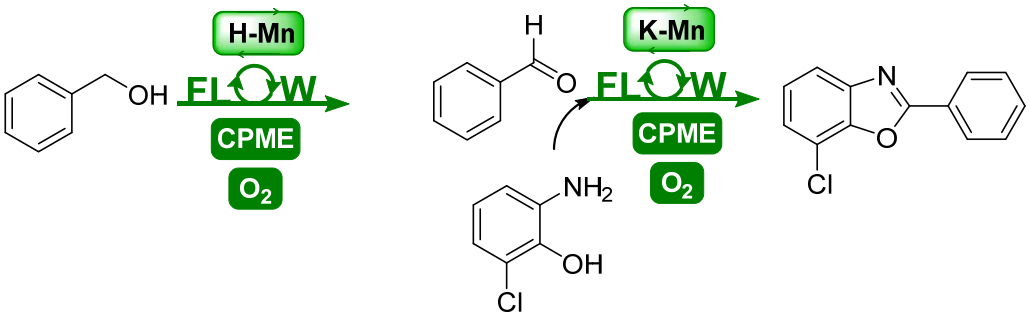
Elemental Analysis: Calc.: C, 74.65; H, 4.92; N, 6.22; found: C, 74.61; H, 4.88; N, 6.20

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.29 – 8.23	2	*m*	
	7.67	1	*d*	8.1
	7.58 – 7.52	3	*m*	
	7.42	1	*s*	
	7.20	1	*dd*	8.2, 1.5
	2.54	3	*s*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 162.58, 155.68, 151.07, 139.92, 135.59, 131.30, 128.89, 127.47, 125.83, 119.35, 110.78, 21.83

GC-EIMS (m/z, %): 225 (100), 195 (75), 194 (35), 181 (45), 180 (37), 160 (25), 158 (55), 121 (40)

Chem. Name	*7-chloro-2-phenylbenzo[d]oxazole (6r)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and benzyl alcohol (4 mmol, 0.432 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (3.7 mmol, 0.531 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6r** (3.5 mmol, 0.804 g) in 95% yield

Mol Formula	$C_{13}H_8ClNO$	**m.p.**	118-121 °C

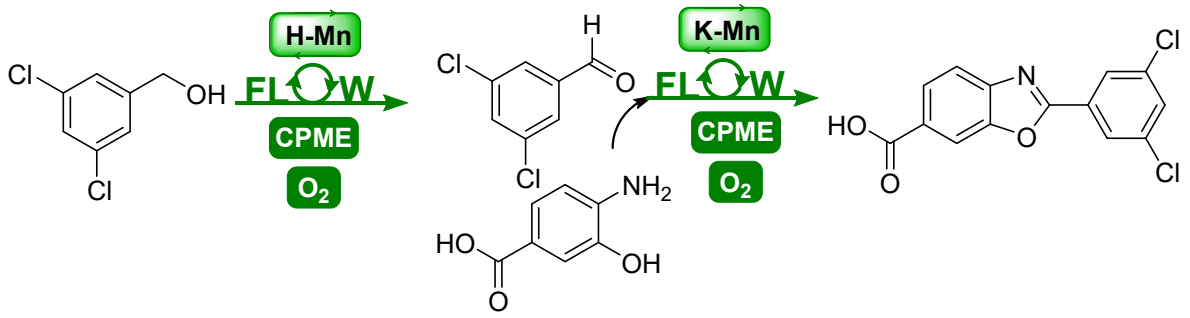
Elemental Analysis: Calc.: C, 67.99; H, 3.51; N, 6.10; found: C, 67.93; H, 3.46; N, 6.11

^{1}H NMR 400 MHz $CDCl_3$	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.32	2	*dd*	7.7, 2.0
	7.69	1	*dd*	7.7, 1.2
	7.59 – 7.55	3	*m*	
	7.39 – 7.28	2	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 163.45, 158.64, 147.40, 143.36, 131.99, 129.00, 127.88, 126.56, 125.43, 125.33, 118.48

GC-EIMS (m/z, %): 231 (35), 229 (100), 197 (22), 196 (64), 194 (44), 181 (32), 160 (57), 158 (25)

Chem. Name	*2-(3,5-dichlorophenyl)benzo[d]oxazole-6-carboxylic acid (Tafamidis)*
Lit. Ref.	



METHOD:
Reservoir 1 was charged with 4 mL of CPME and 3,5-dichlorobenzyl alcohol (4 mmol, 0.708 g), then the oxygen line has been set to 5 bar of pressure and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL/min with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the 4-Amino-3-hydroxybenzoic acid solution (3.7 mmol, 0.566 g in 4 mL of CPME 0.9M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL/min with a residence time of 40 min. At the end of the process the system has been completely flushed, both line with 10 mL of CPME in order to wash the catalyst columns. The product has been collected into the product reservoir. Then CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR) and the residue was washed with 5 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **Tafamidis** (3.4 mmol, 1.05 g) in 92% yield

Mol Formula	$C_{14}H_7Cl_2NO_3$	**m.p.**	187-188 °C

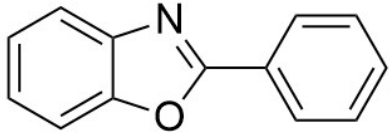
Elemental Analysis: Calc.: C, 54.58; H, 2.29; N, 4.55; found: C, 54.57; H, 2.25; N, 4.58

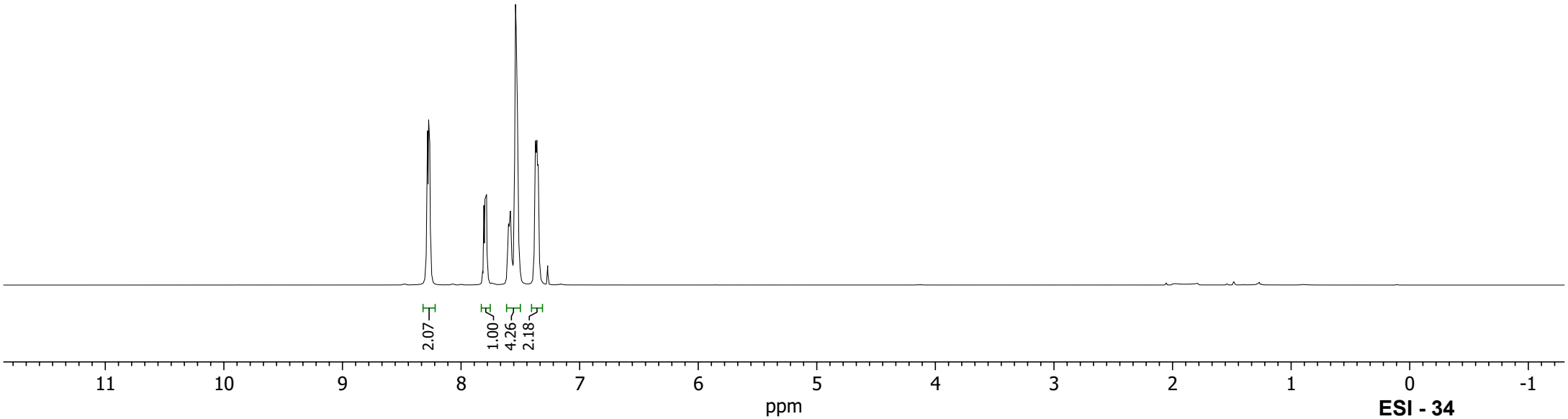
^{1}H NMR 400 MHz Acetone-d_6	**□ value**	**No. H**	**Mult.**	**j value/Hz**
	8.92	1	*s*	
	8.15	2	*d*	2
	7.63 – 7.58	2	*m*	
	7.48	1	*d*	8.7

^{13}C NMR (100.6 MHz, Acetone-d_6) δ : 166.27, 157.95, 152.25, 139.57, 135.17, 130.80, 130.72, 127.54, 126.05, 121.41, 120.07, 112.44.

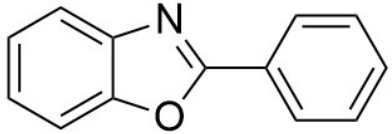
GC-EIMS (m/z, %): 310 (63), 308 (100), 306 (50), 292 (22), 294 (27), 272 (47), 264 (44), 236 (38), 181 (25).

2-phenylbenzo[d]oxazole (6a)

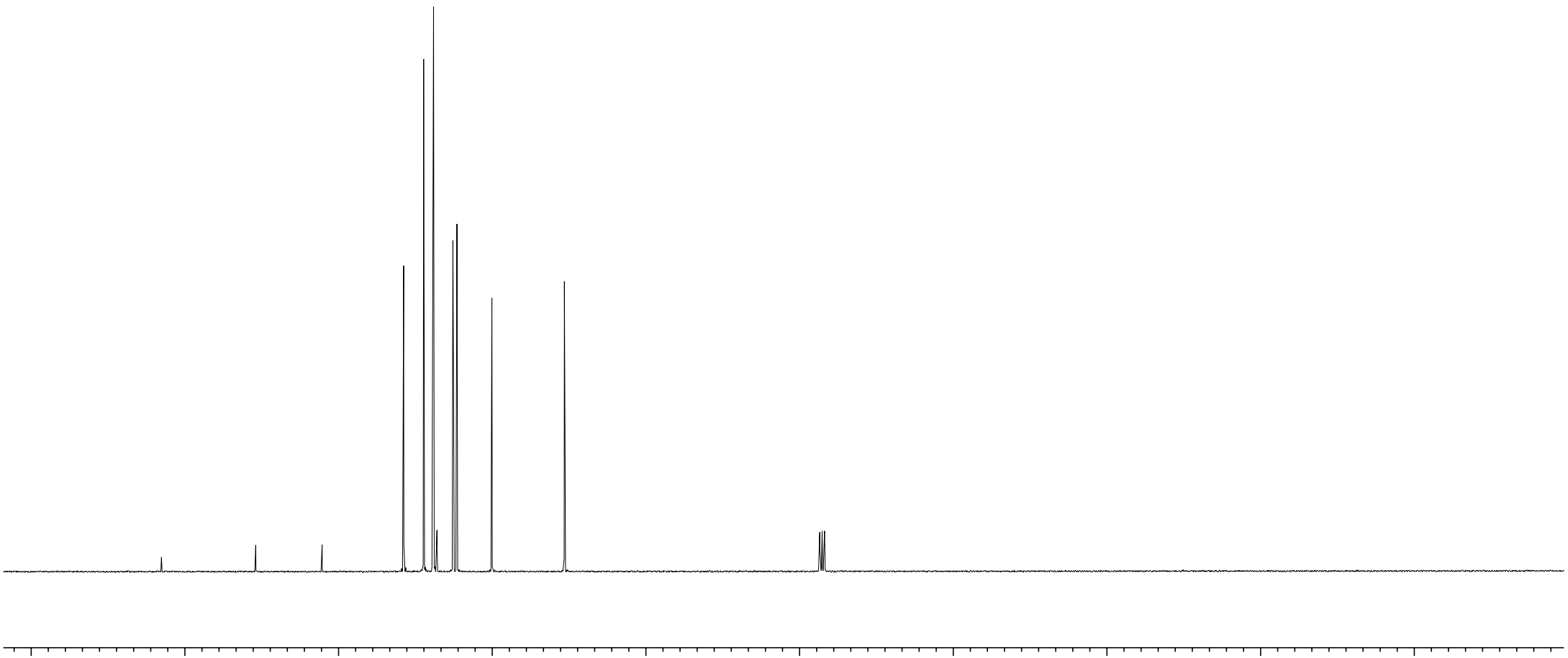




2-phenylbenzo[d]oxazole (6a)

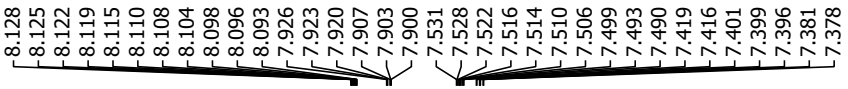


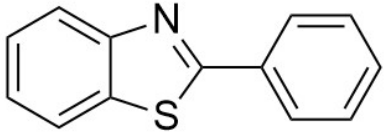
163.052
150.779
142.140
131.527
128.923
127.639
127.193
125.119
124.591
120.042
110.610

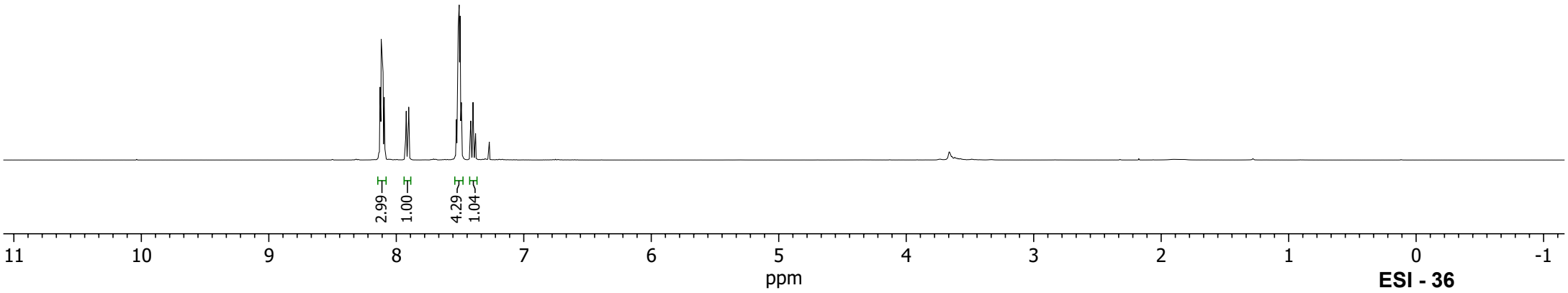


ESI - 35

2-phenylbenzo[d]thiazole (6b)

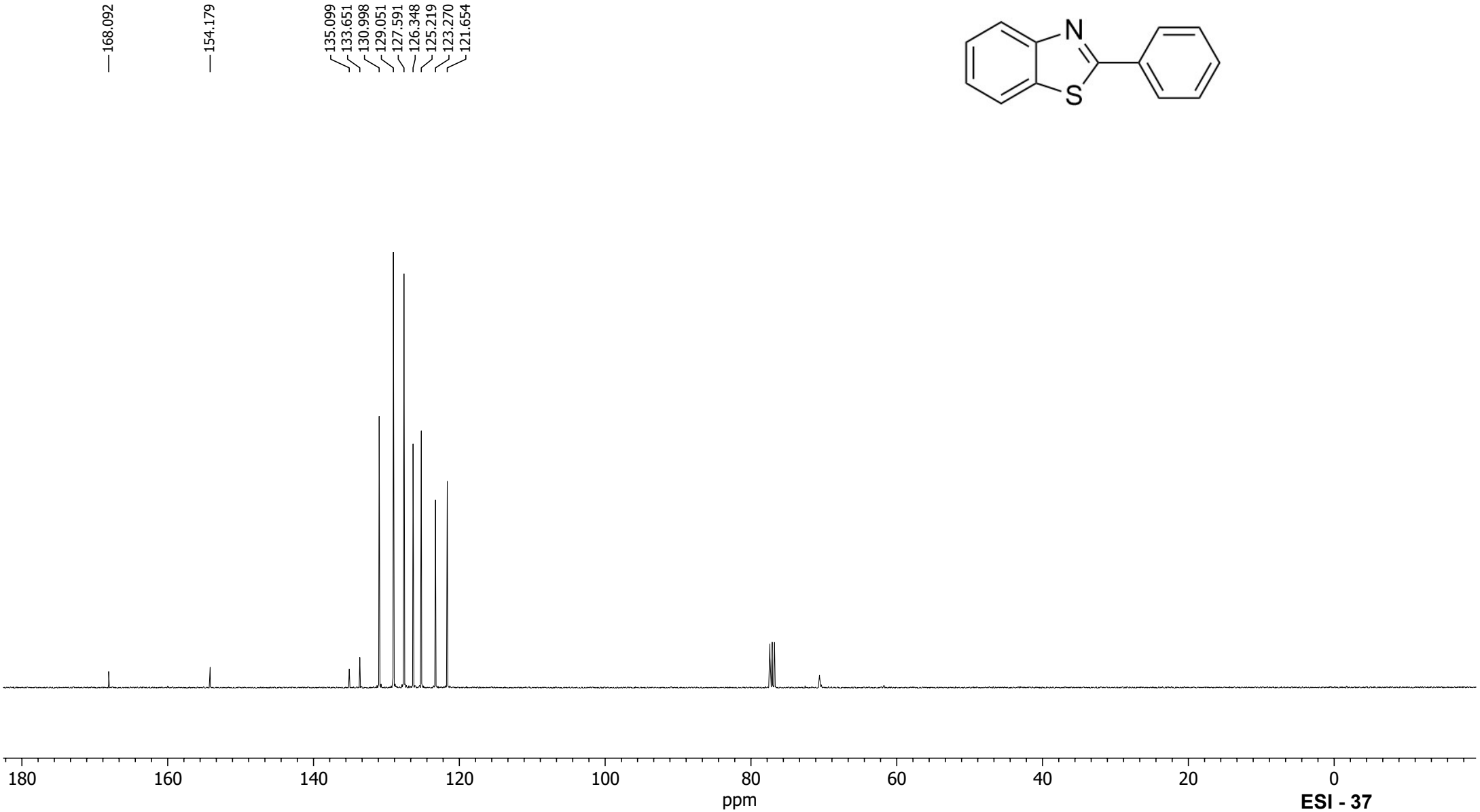






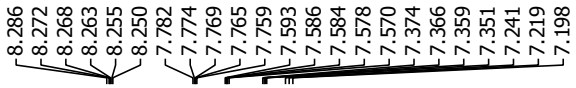
ESI - 36

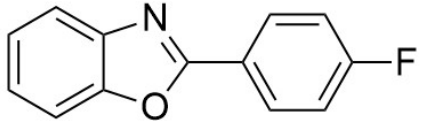
2-phenylbenzo[d]thiazole (6b)

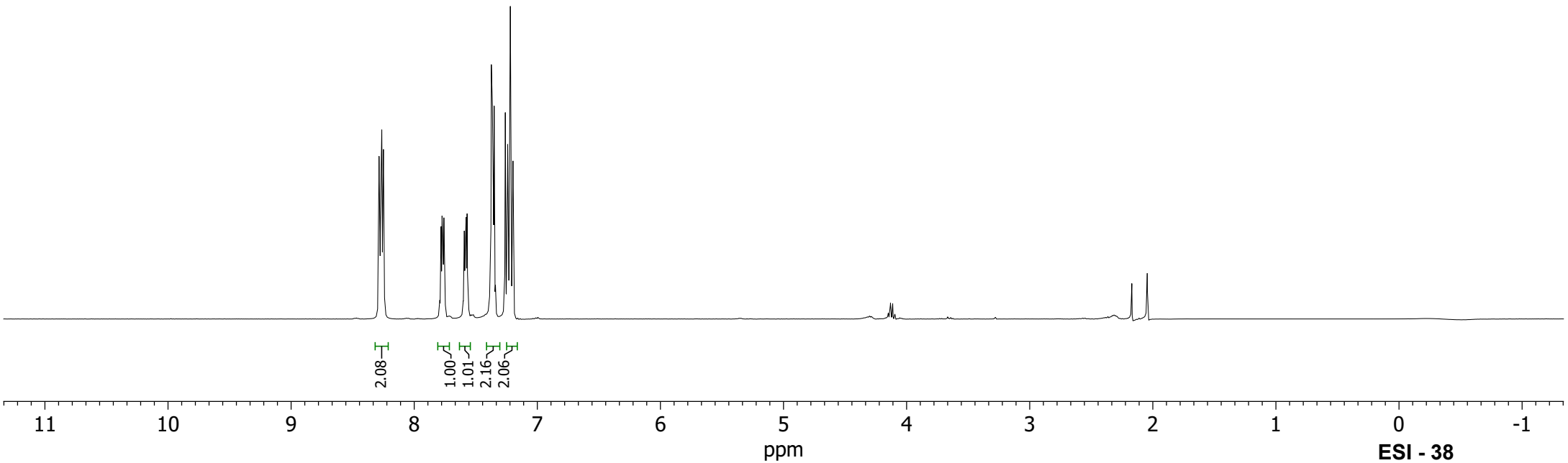


ESI - 37

2-(4-fluorophenyl)benzo[d]oxazole (6c)

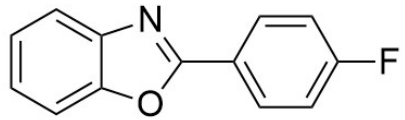




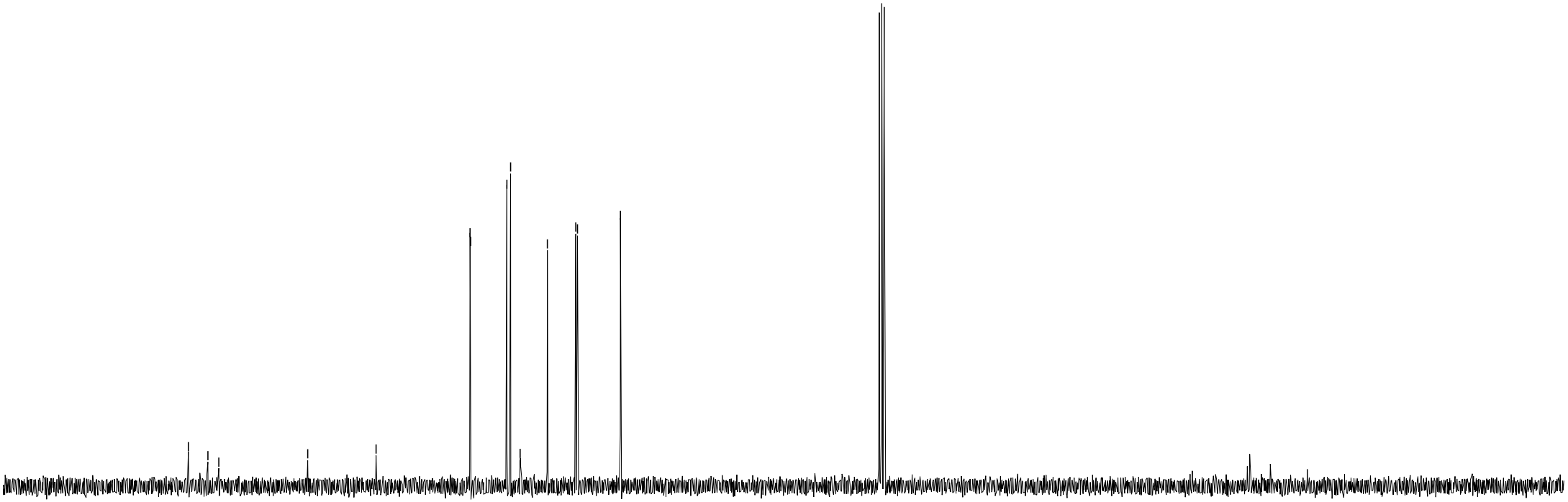


ESI - 38

2-(4-fluorophenyl)benzo[d]oxazole (6c)



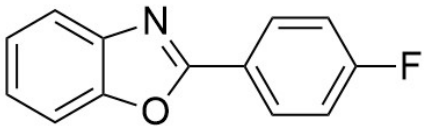
166.107
163.595
162.194
150.772
141.989
129.918
129.829
125.183
124.707
123.483
123.453
119.984
116.335
116.114
110.596



180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

ppm

2-(4-fluorophenyl)benzo[d]oxazole (6c)



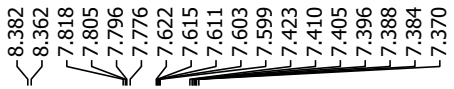
-107.438
-107.452
-107.460
-107.466
-107.474
-107.483
-107.489
-107.497
-107.511

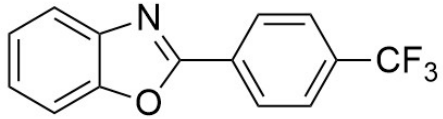
-85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135

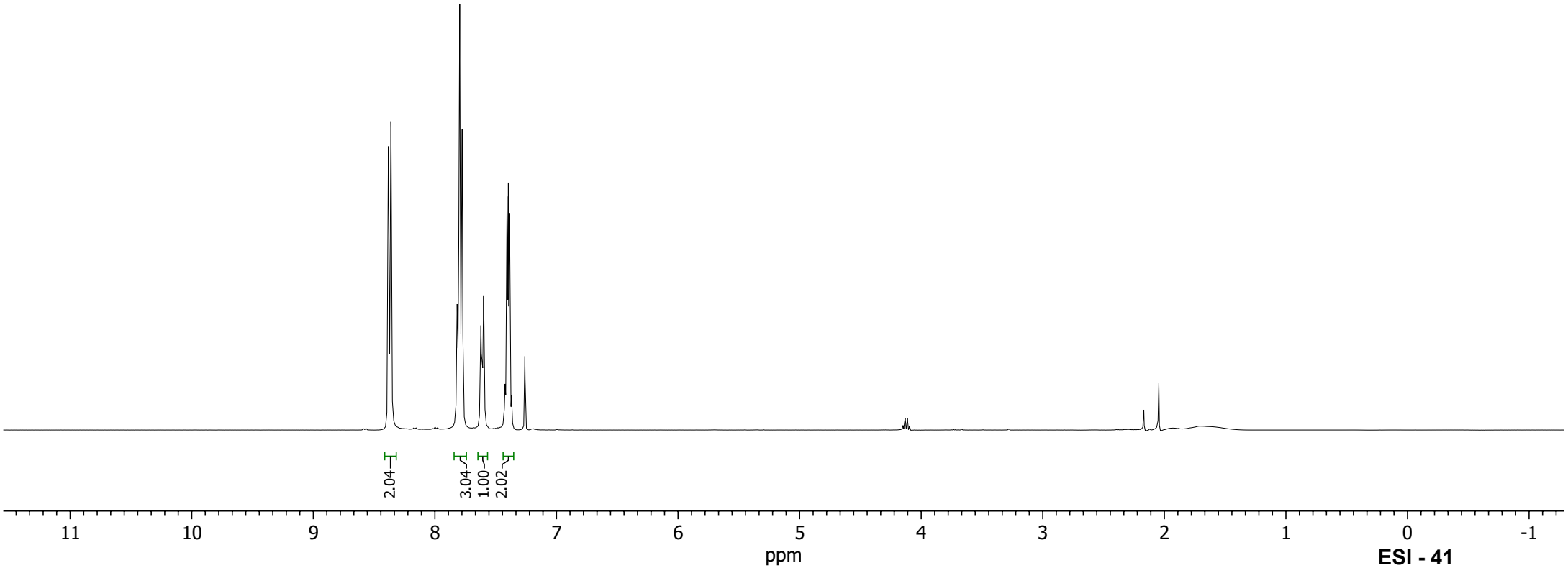
ppm

ESI - 40

2-(4-(trifluoromethyl)phenyl)benzo[d]oxazole (6d)

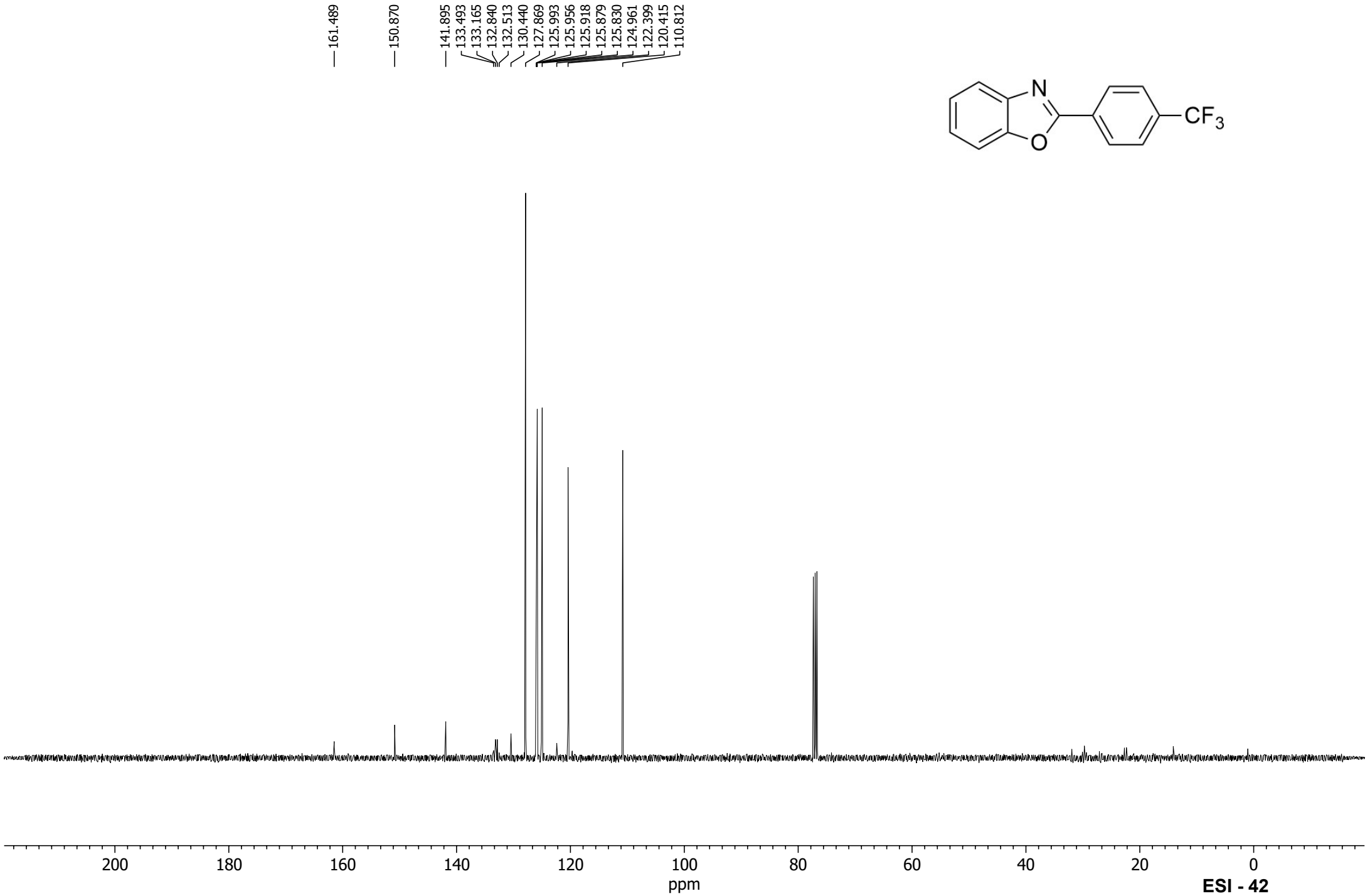




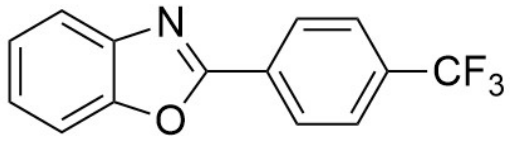


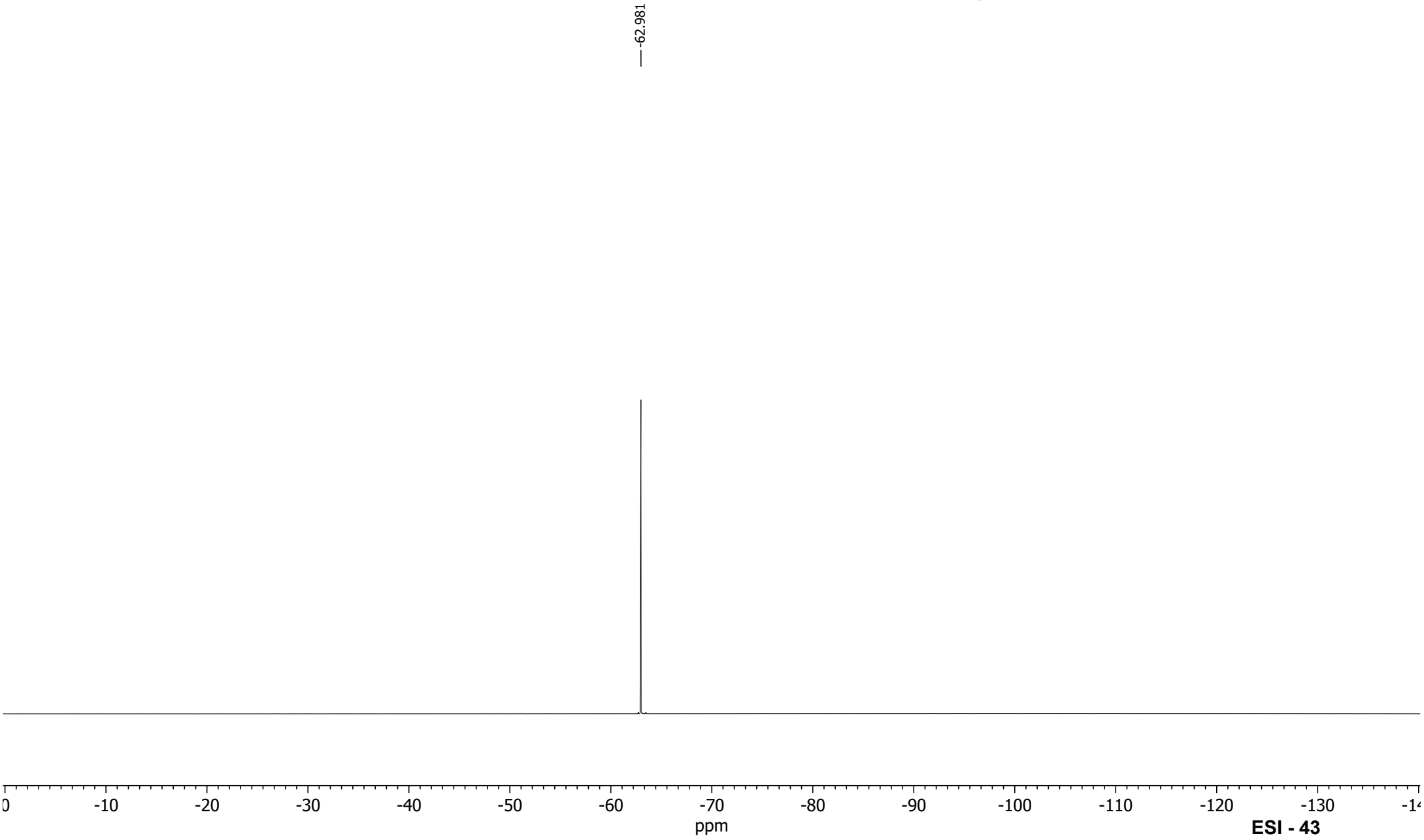
ESI - 41

2-(4-(trifluoromethyl)phenyl)benzo[d]oxazole (6d)

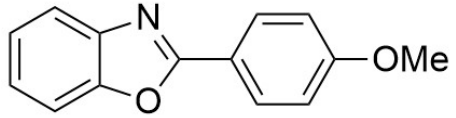


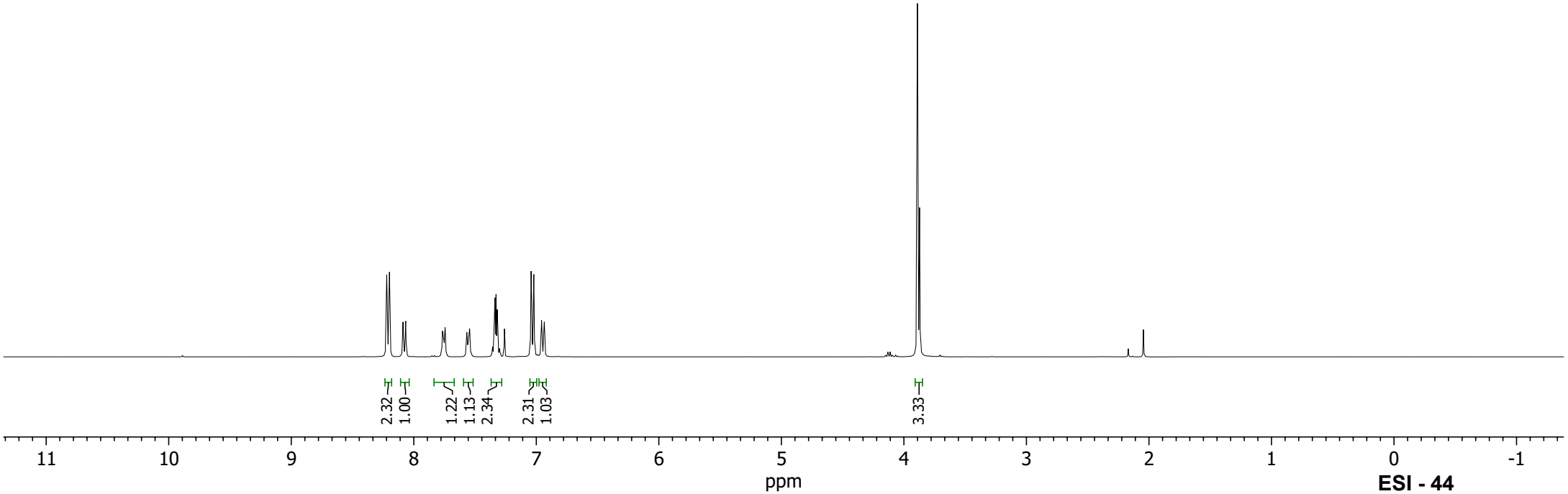
2-(4-(trifluoromethyl)phenyl)benzo[d]oxazole (6d)





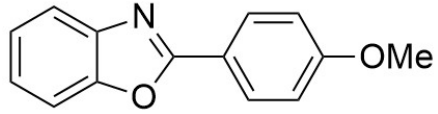
2-(4-methoxyphenyl)benzo[d]oxazole (6e)

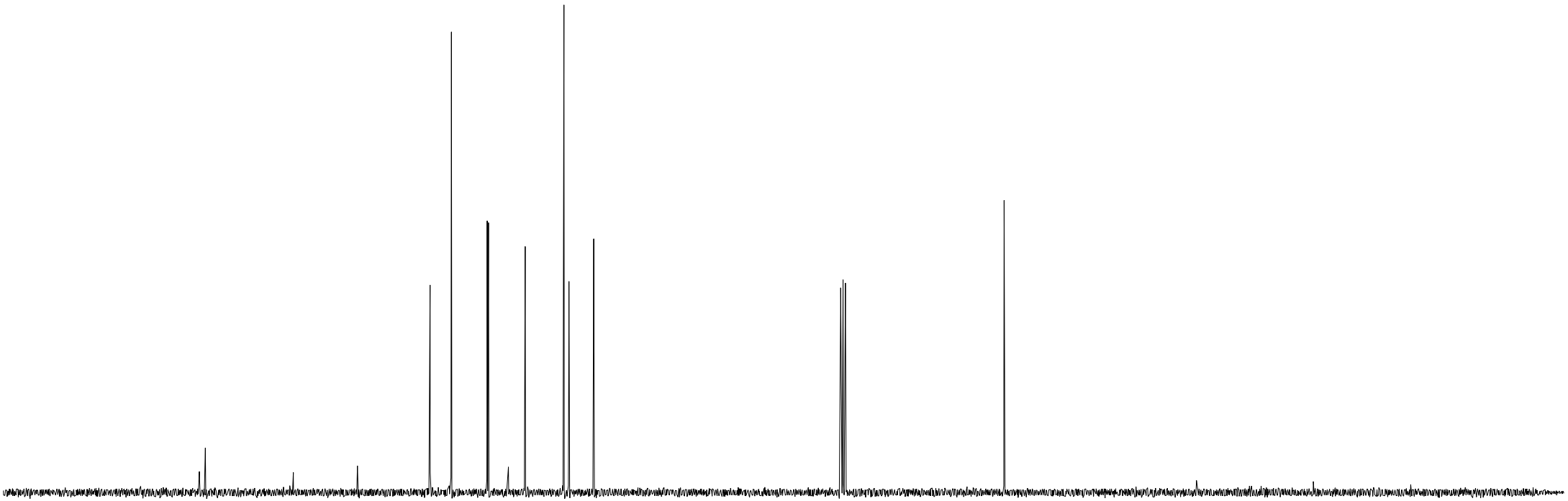


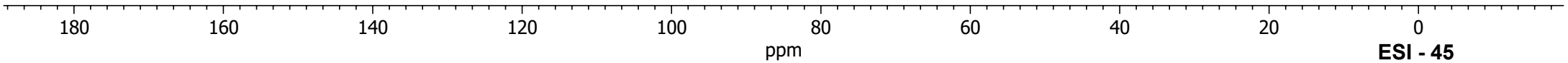


ESI - 44

2-(4-methoxyphenyl)benzo[d]oxazole (6e)

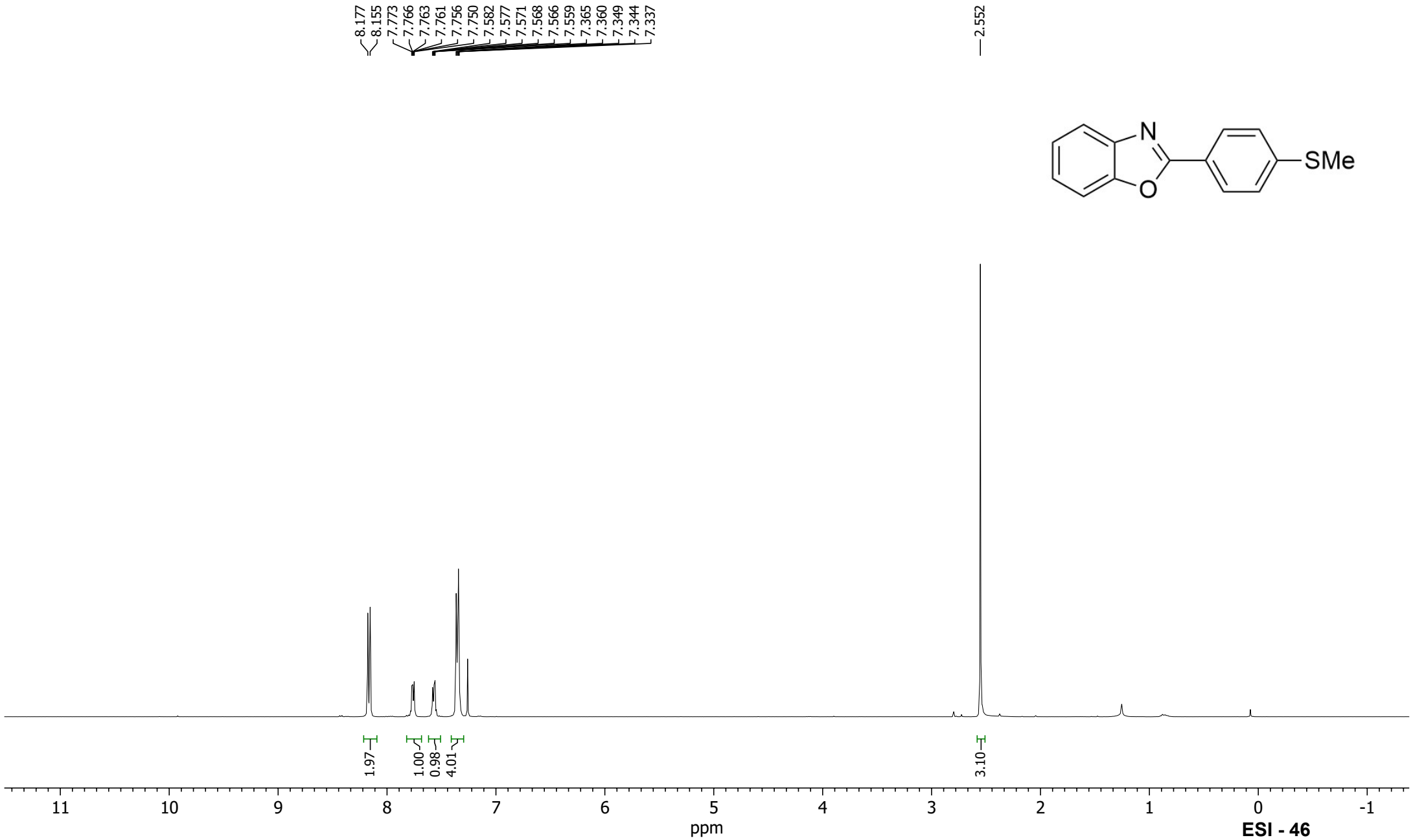




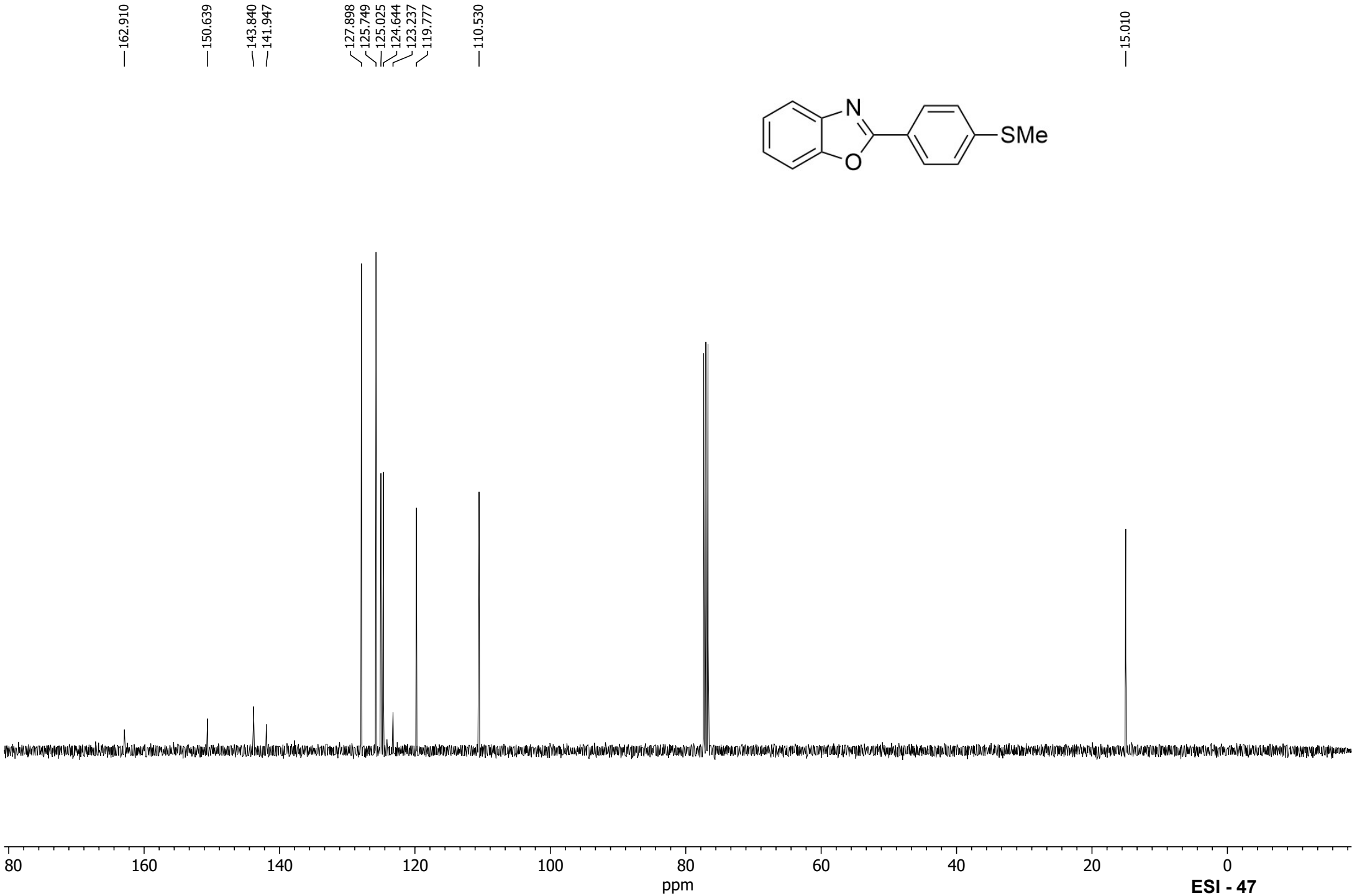


ESI - 45

2-(4-(methylthio)phenyl)benzo[d]oxazole (6f)

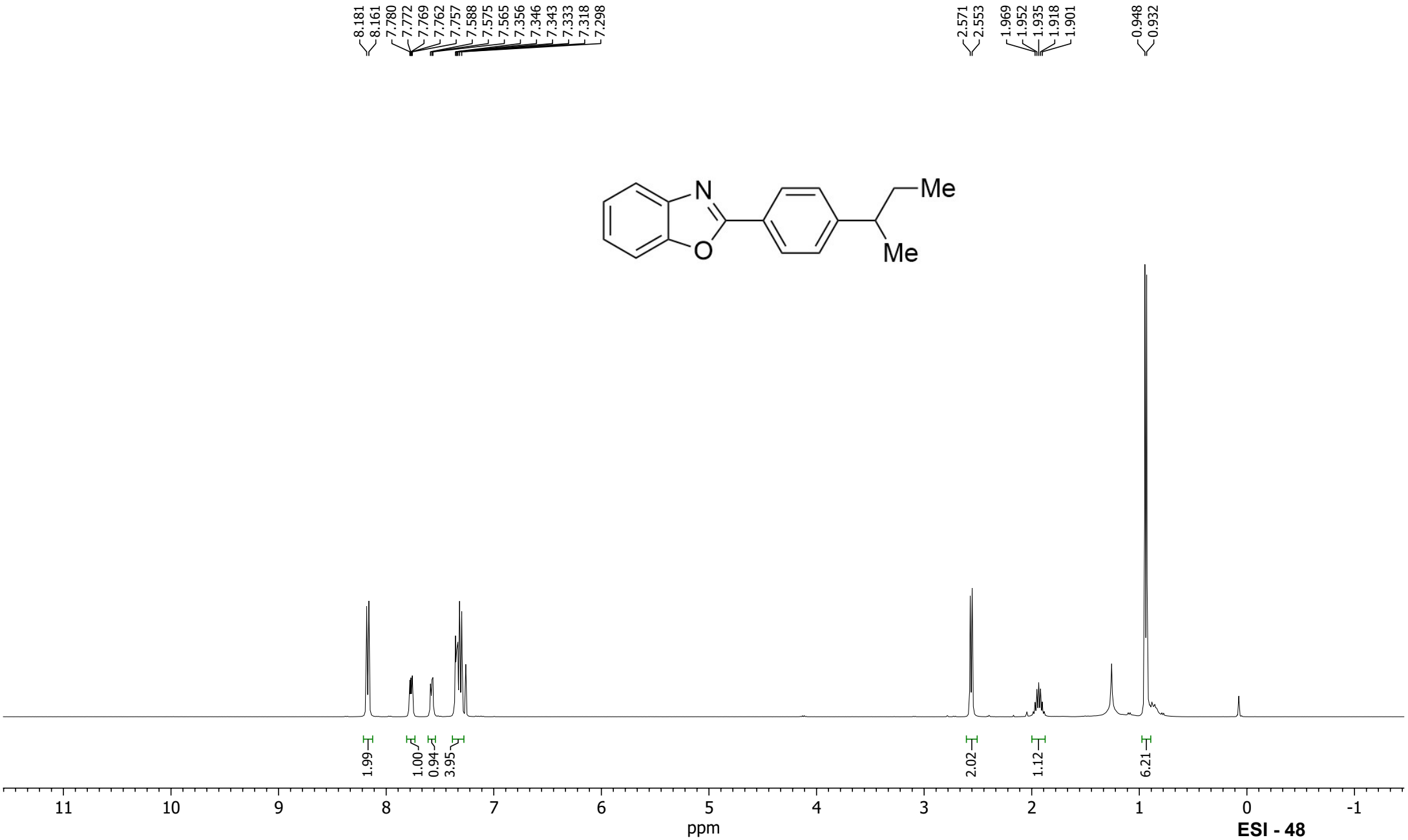


2-(4-(methylthio)phenyl)benzo[d]oxazole (6f)

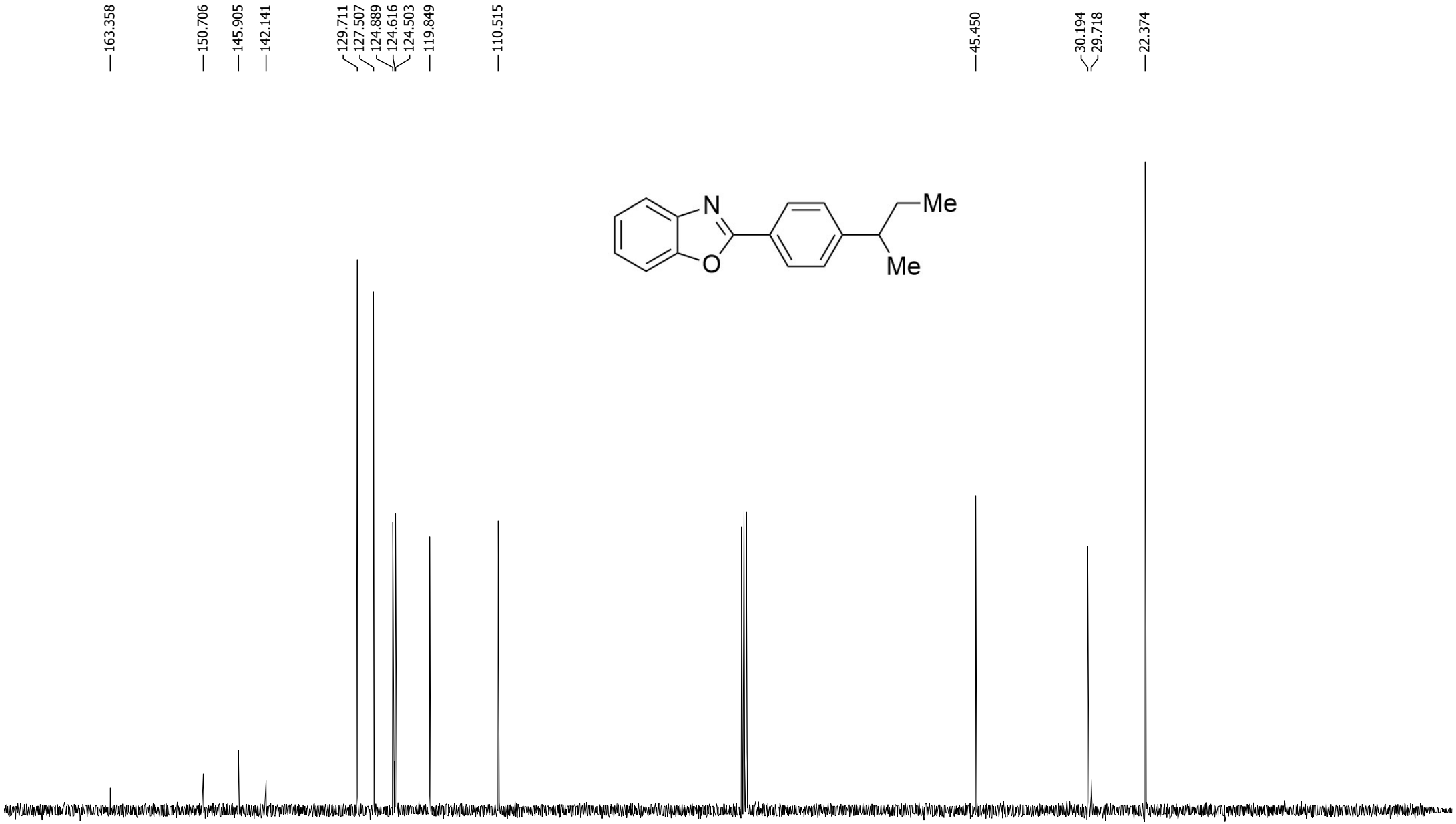


ESI - 47

2-(4-(sec-butyl)phenyl)benzo[d]oxazole (6g)

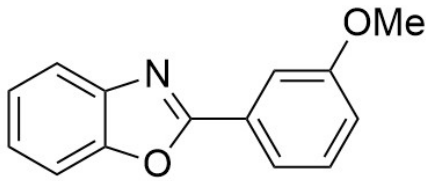


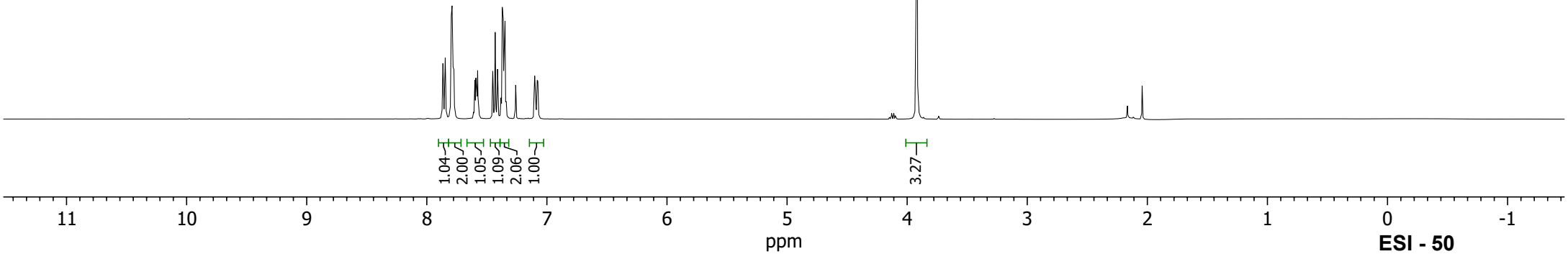
2-(4-(sec-butyl)phenyl)benzo[d]oxazole (6g)



ESI - 49

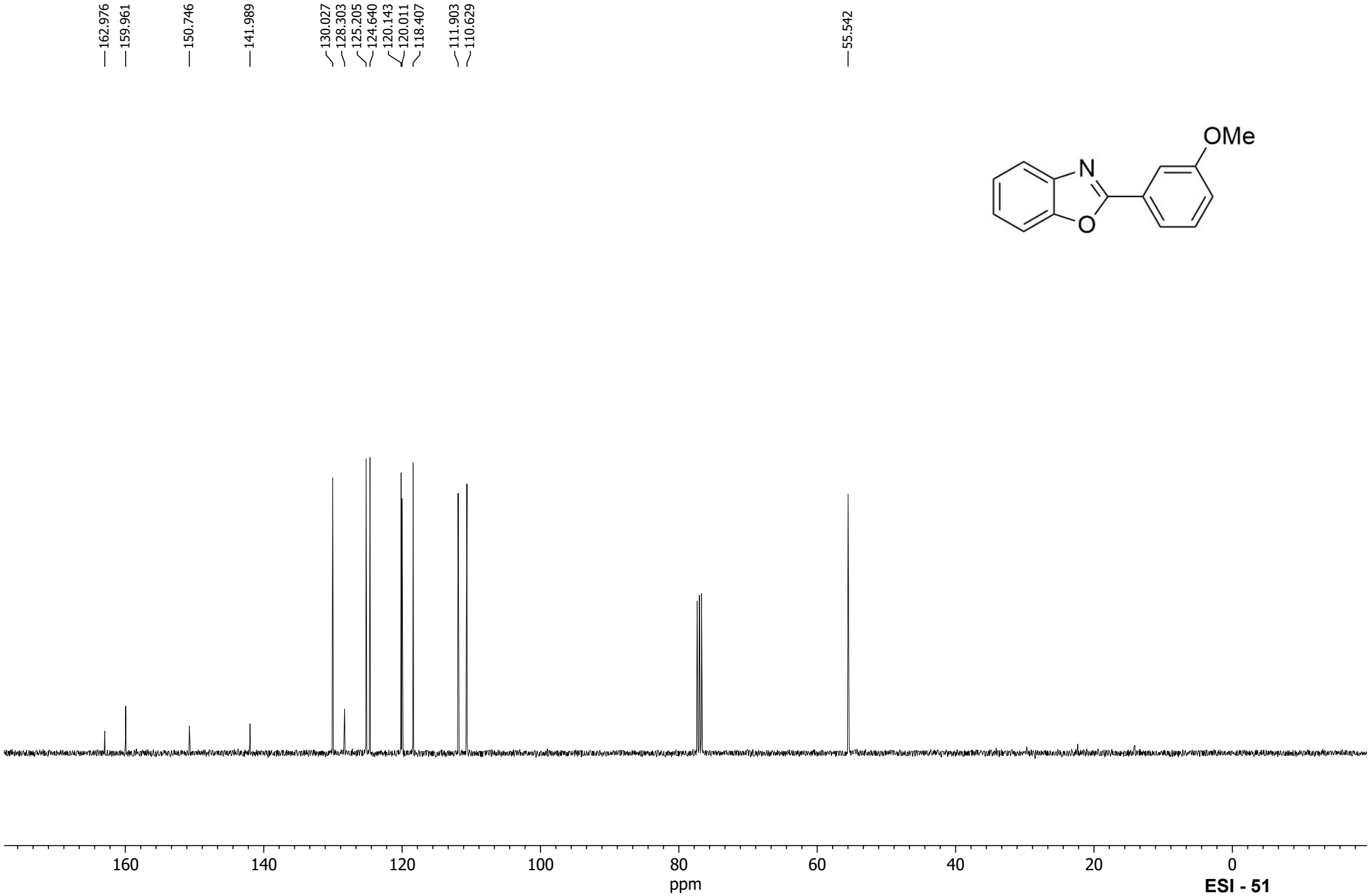
2-(3-methoxyphenyl)benzo[d]oxazole (6h)



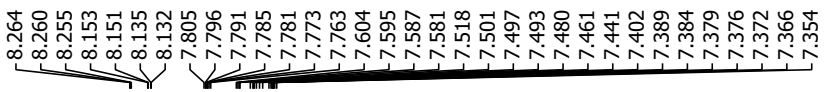


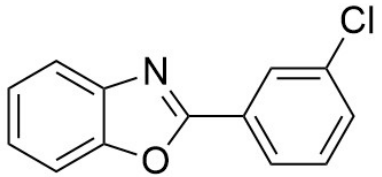
ESI - 50

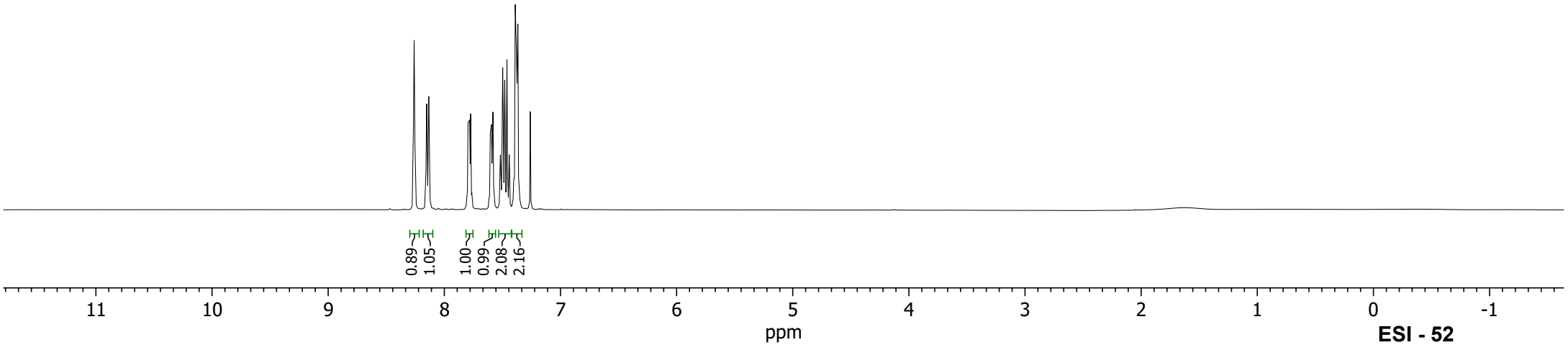
2-(3-methoxyphenyl)benzo[d]oxazole (6h)



2-(3-chlorophenyl)benzo[d]oxazole (6k)

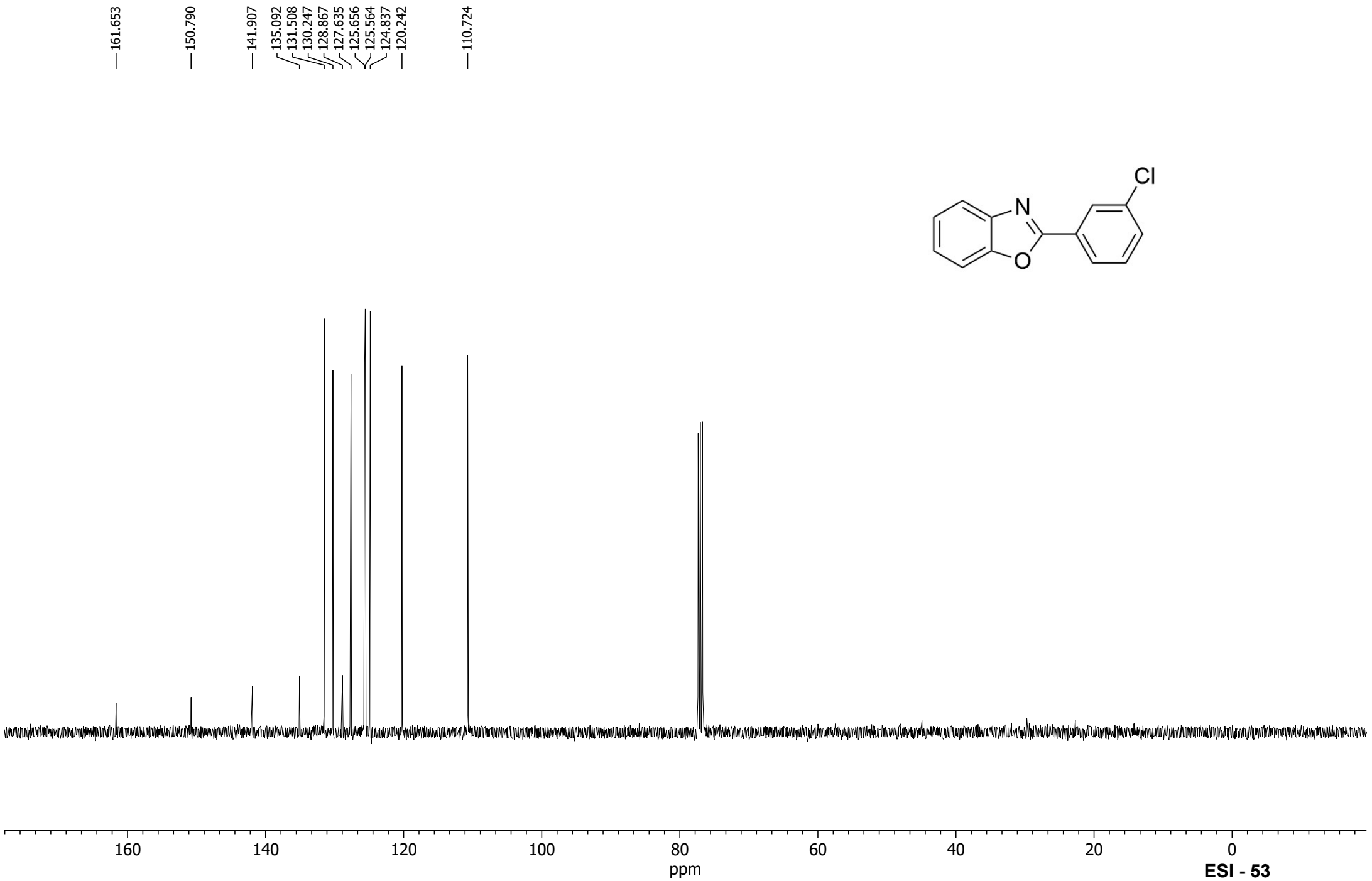






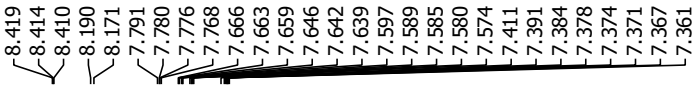
ESI - 52

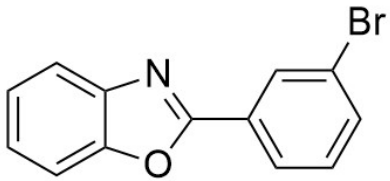
2-(3-chlorophenyl)benzo[d]oxazole (6k)

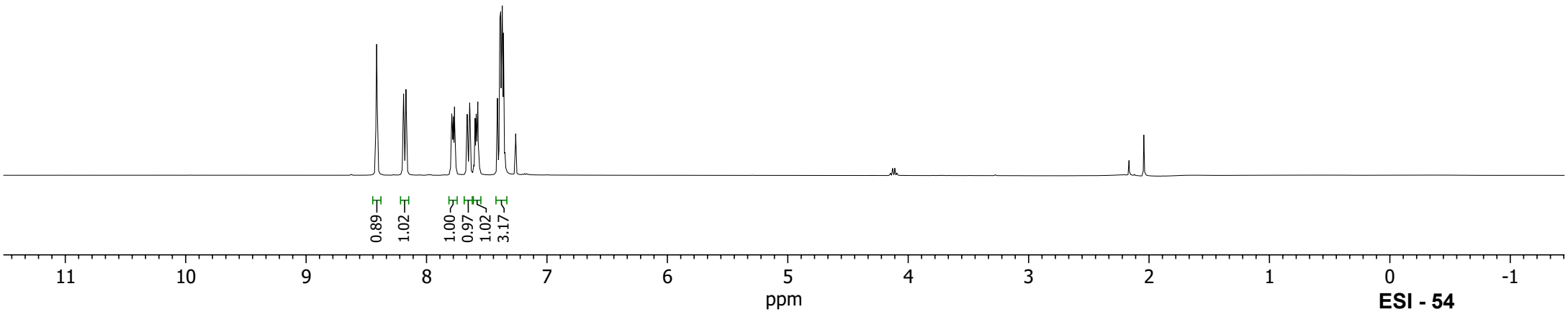


ESI - 53

2-(3-bromophenyl)benzo[d]oxazole (6i)

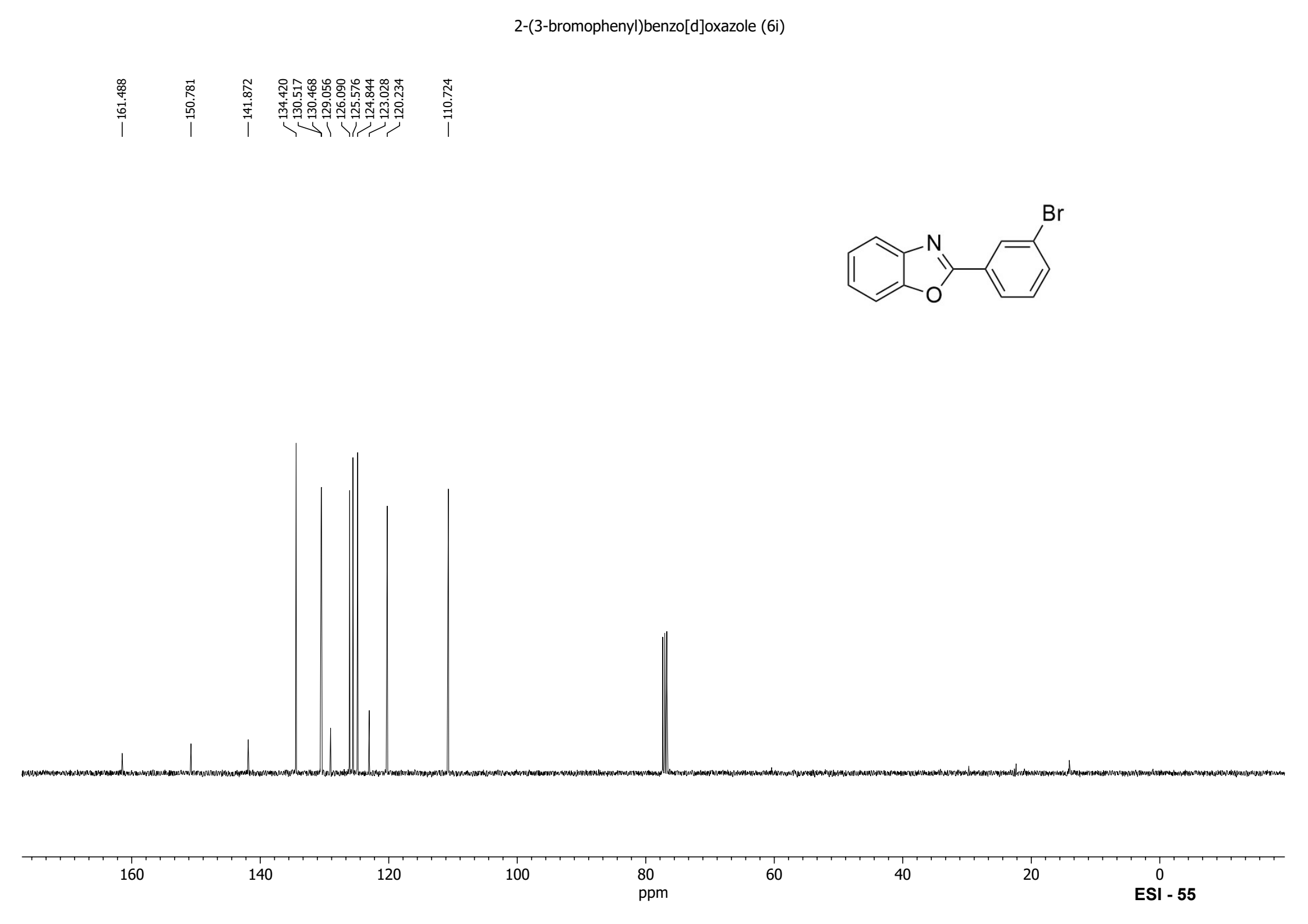




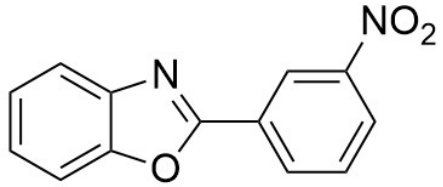


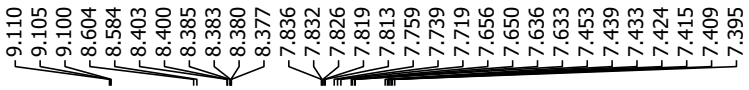
ESI - 54

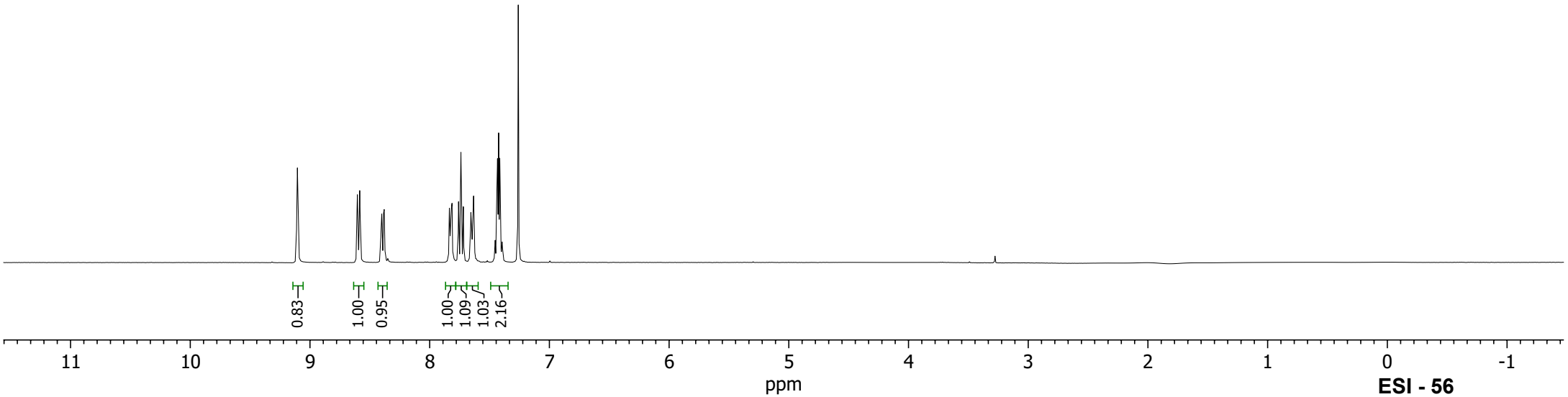
2-(3-bromophenyl)benzo[d]oxazole (6i)



2-(3-nitrophenyl)benzo[d]oxazole (6j)

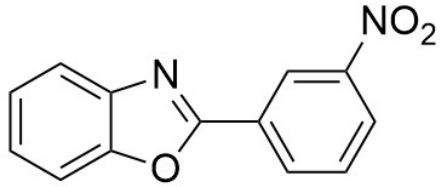






ESI - 56

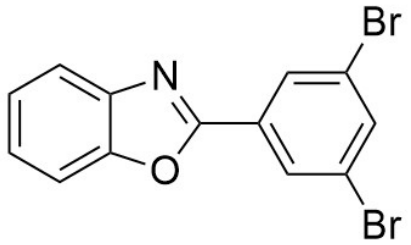
2-(3-nitrophenyl)benzo[d]oxazole (6j)

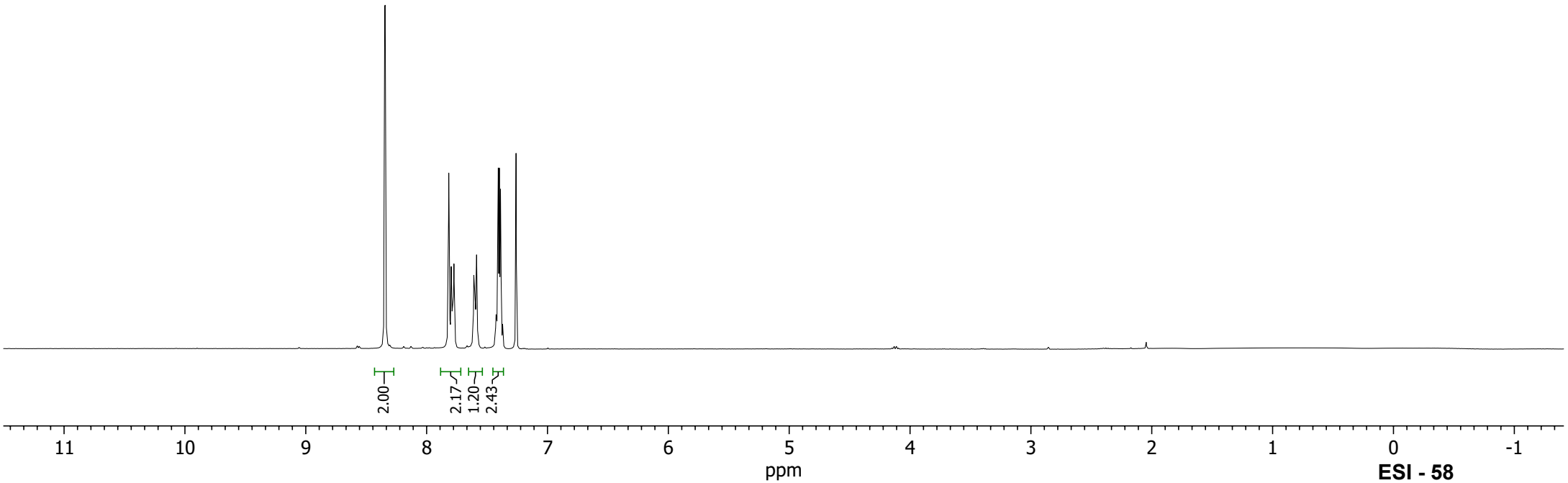


160.597
150.901
148.731
141.811
133.044
130.153
128.984
126.098
125.812
125.148
122.519
120.531
110.917

200 180 160 140 120 100 80 60 40 20 0
ppm

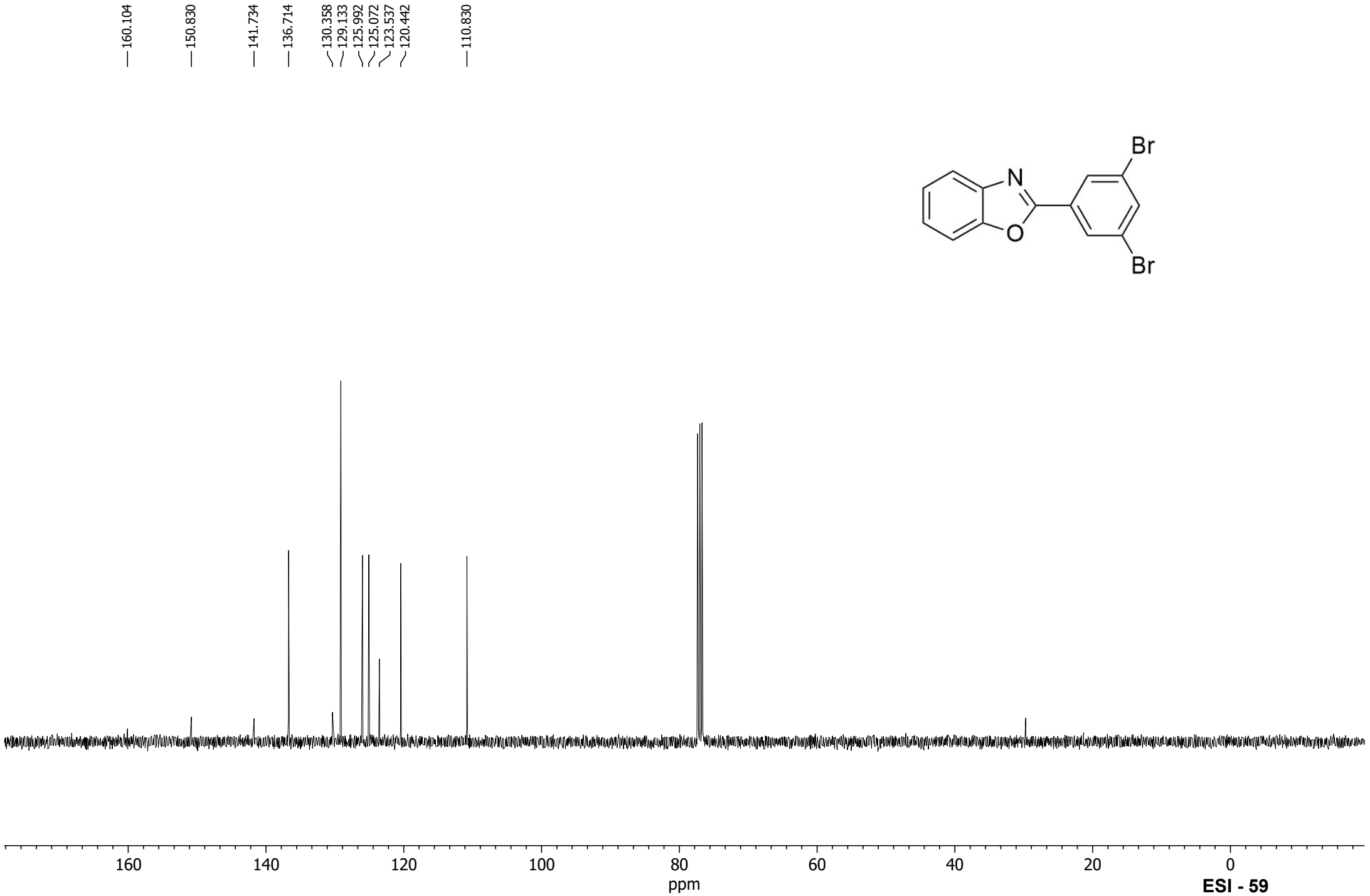
2-(3,5-dibromophenyl)benzo[d]oxazole (6l)



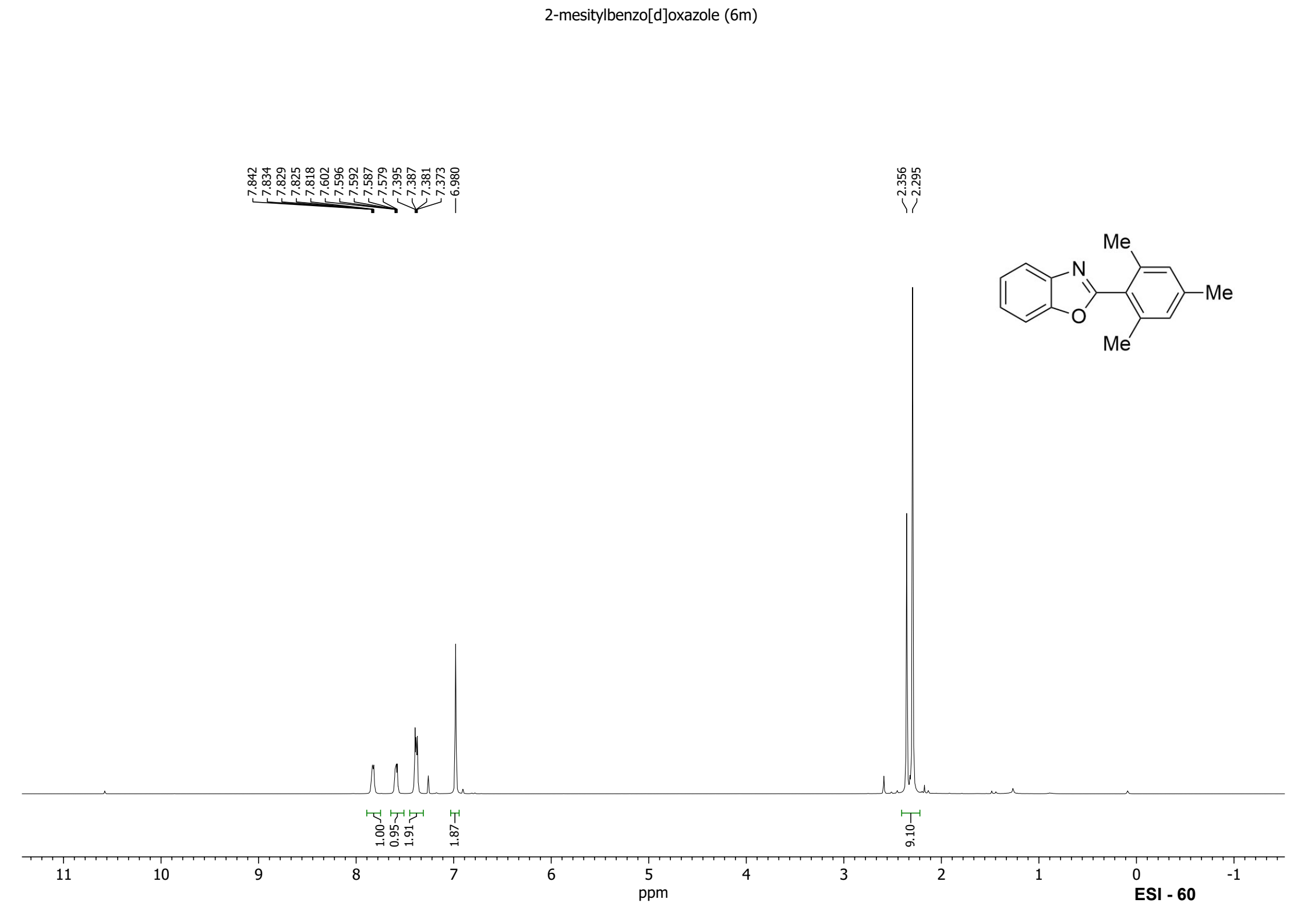


ESI - 58

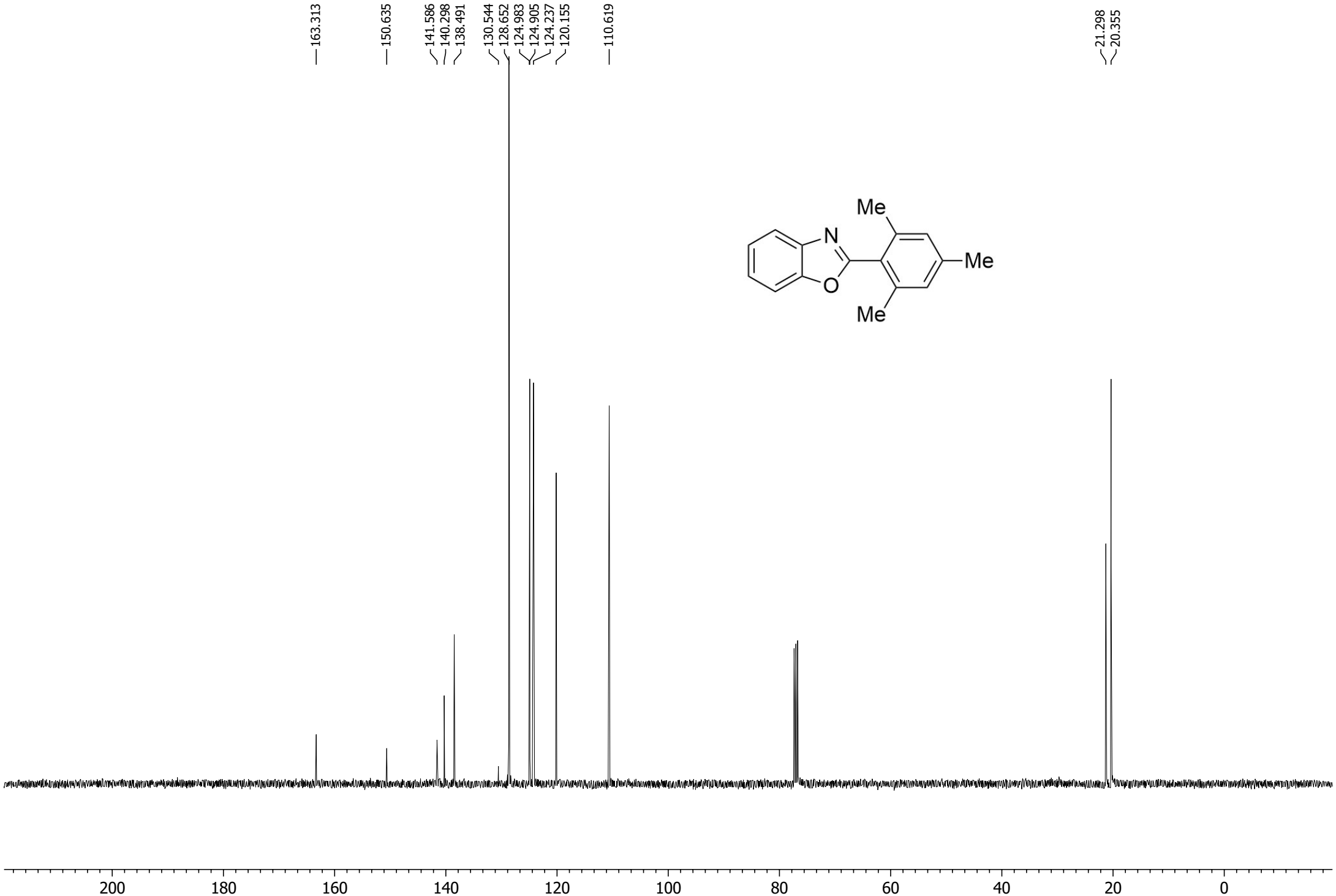
2-(3,5-dibromophenyl)benzo[d]oxazole (6l)



2-mesitylbenzo[d]oxazole (6m)

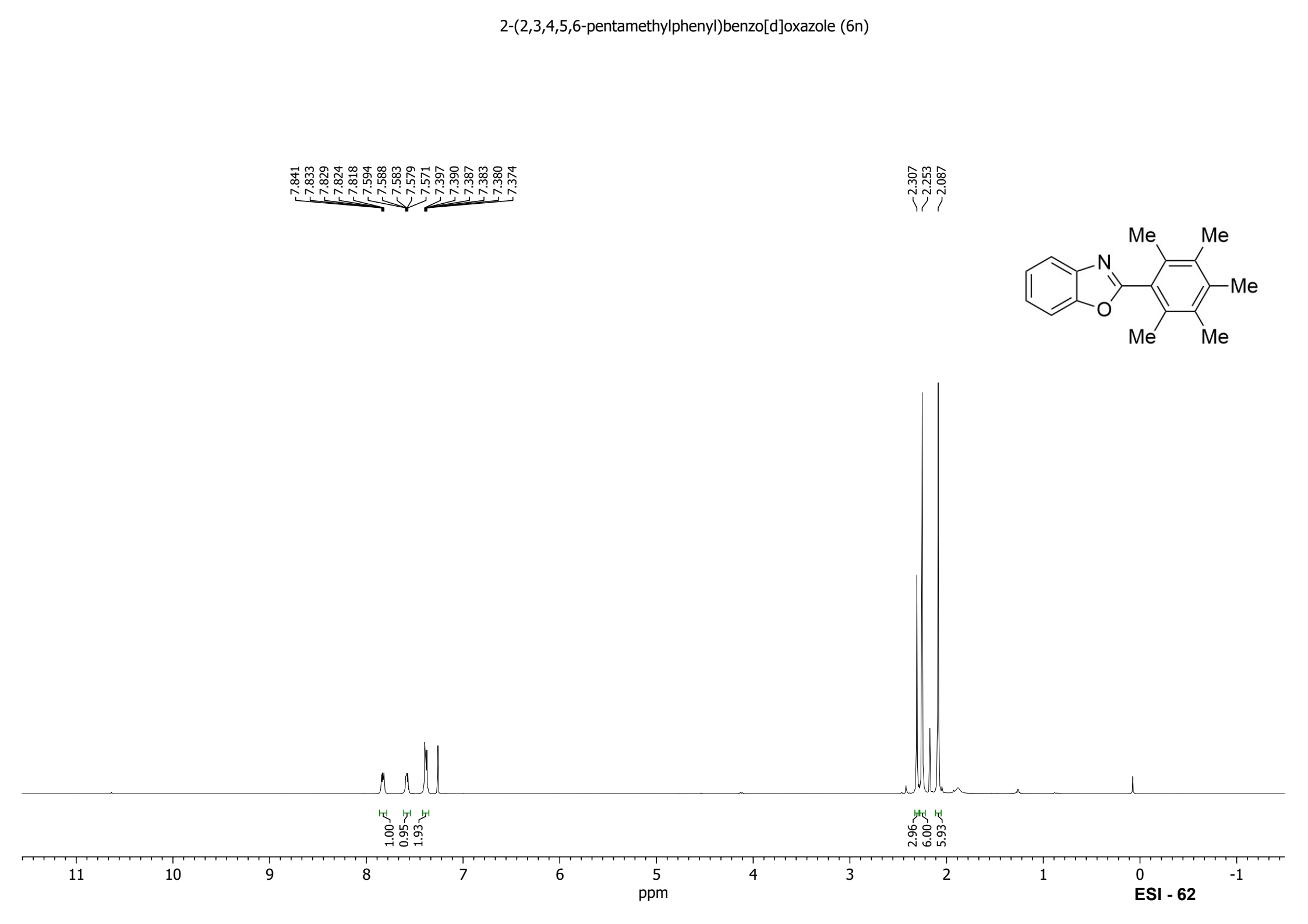


2-mesitylbenzo[d]oxazole (6m)

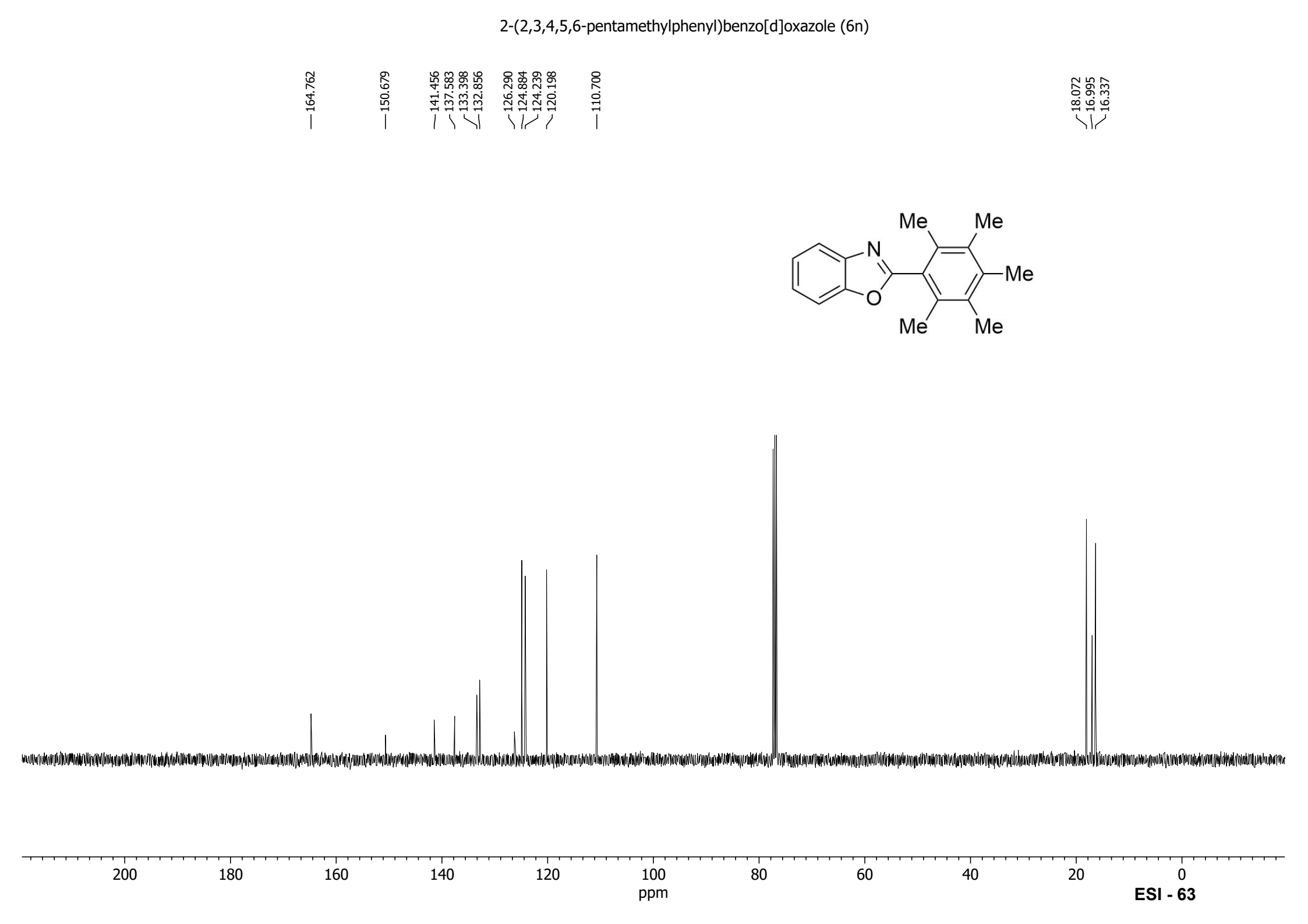


ESI - 61

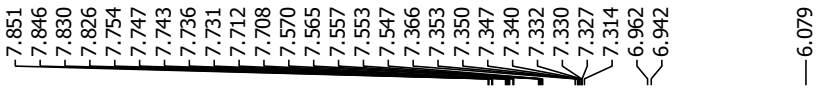
2-(2,3,4,5,6-pentamethylphenyl)benzo[d]oxazole (6n)

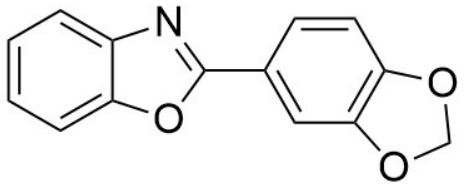


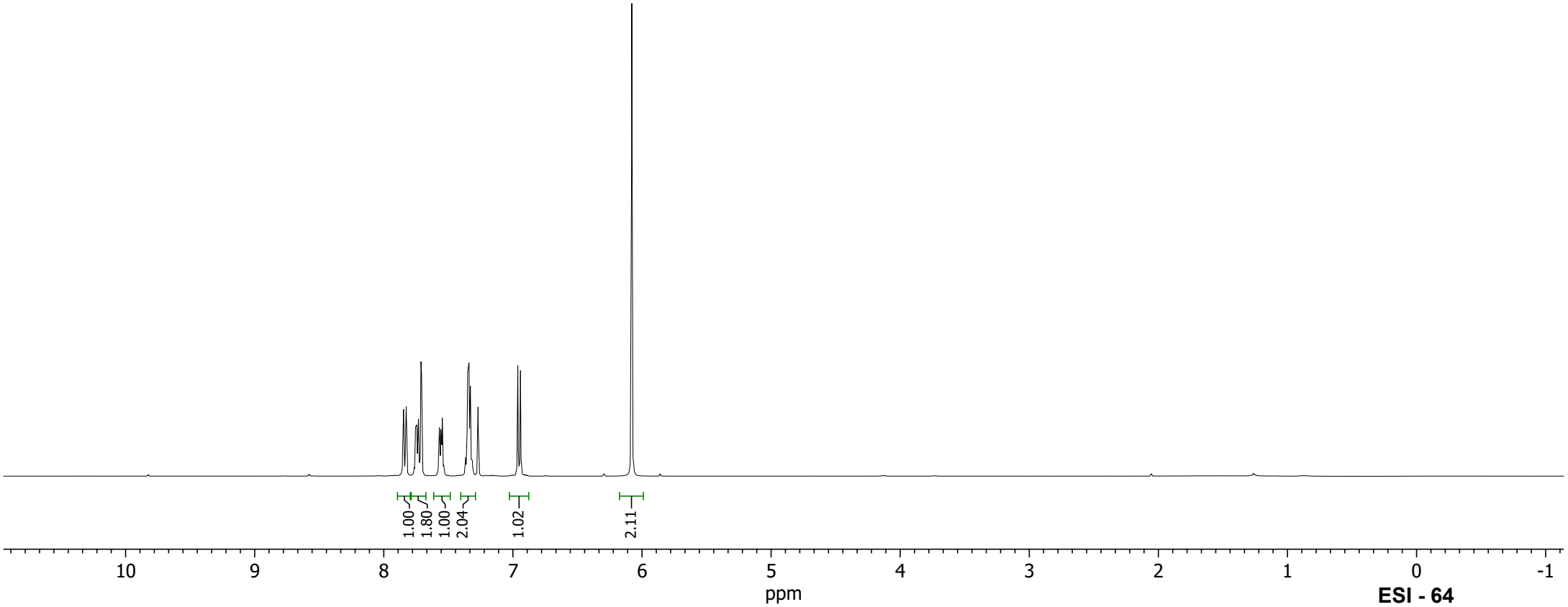
2-(2,3,4,5,6-pentamethylphenyl)benzo[d]oxazole (6n)



2-(benzo[d][1,3]dioxol-5-yl)benzo[d]oxazole (6o)

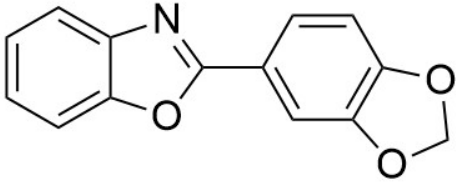




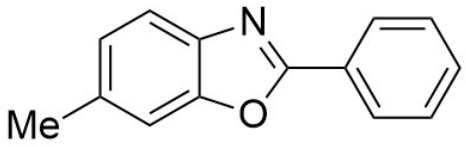


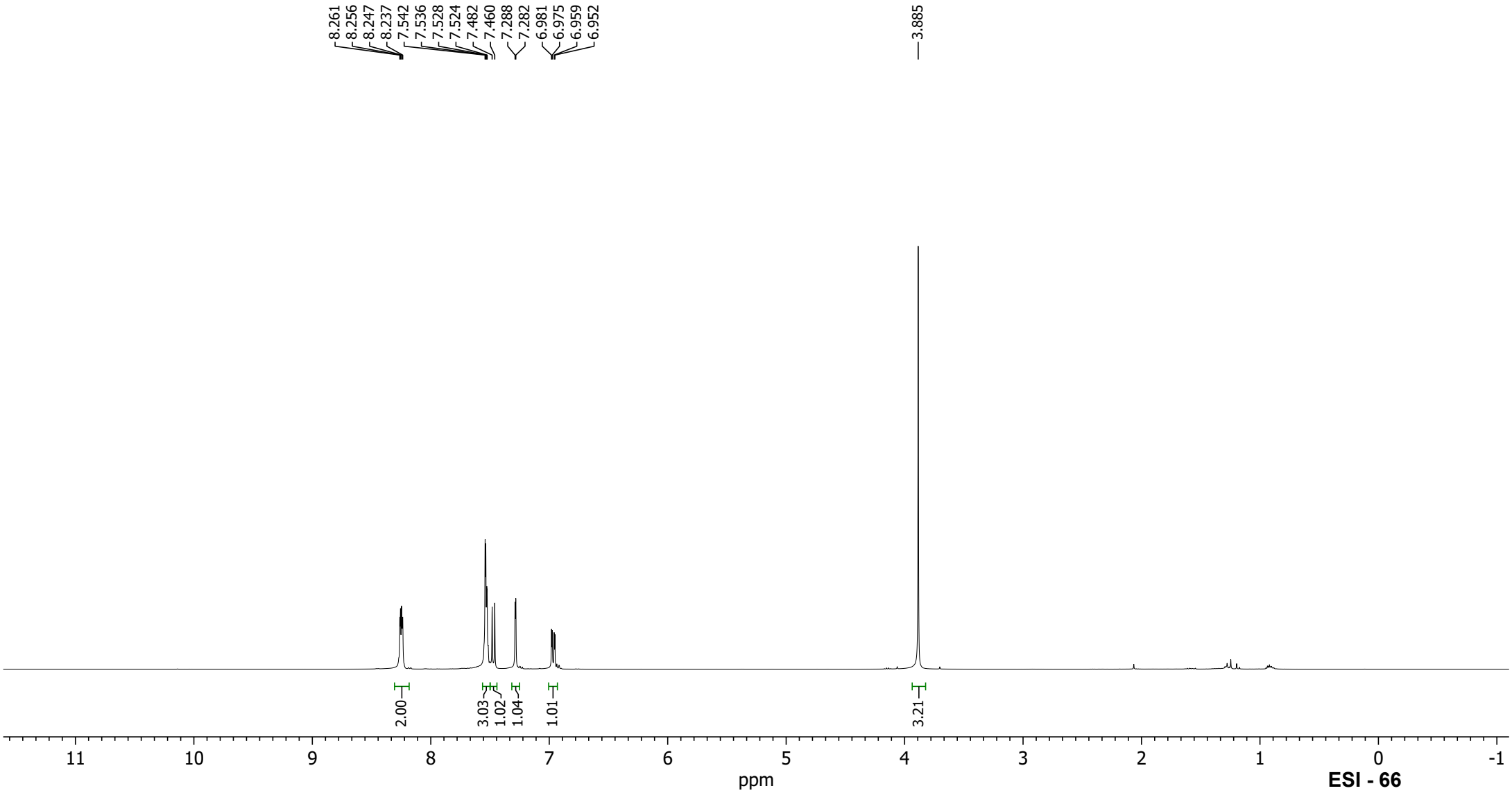
ESI - 64

2-(benzo[d][1,3]dioxol-5-yl)benzo[d]oxazole (6o)



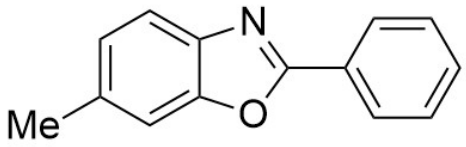
6-methyl-2-phenylbenzo[d]oxazole (6p)

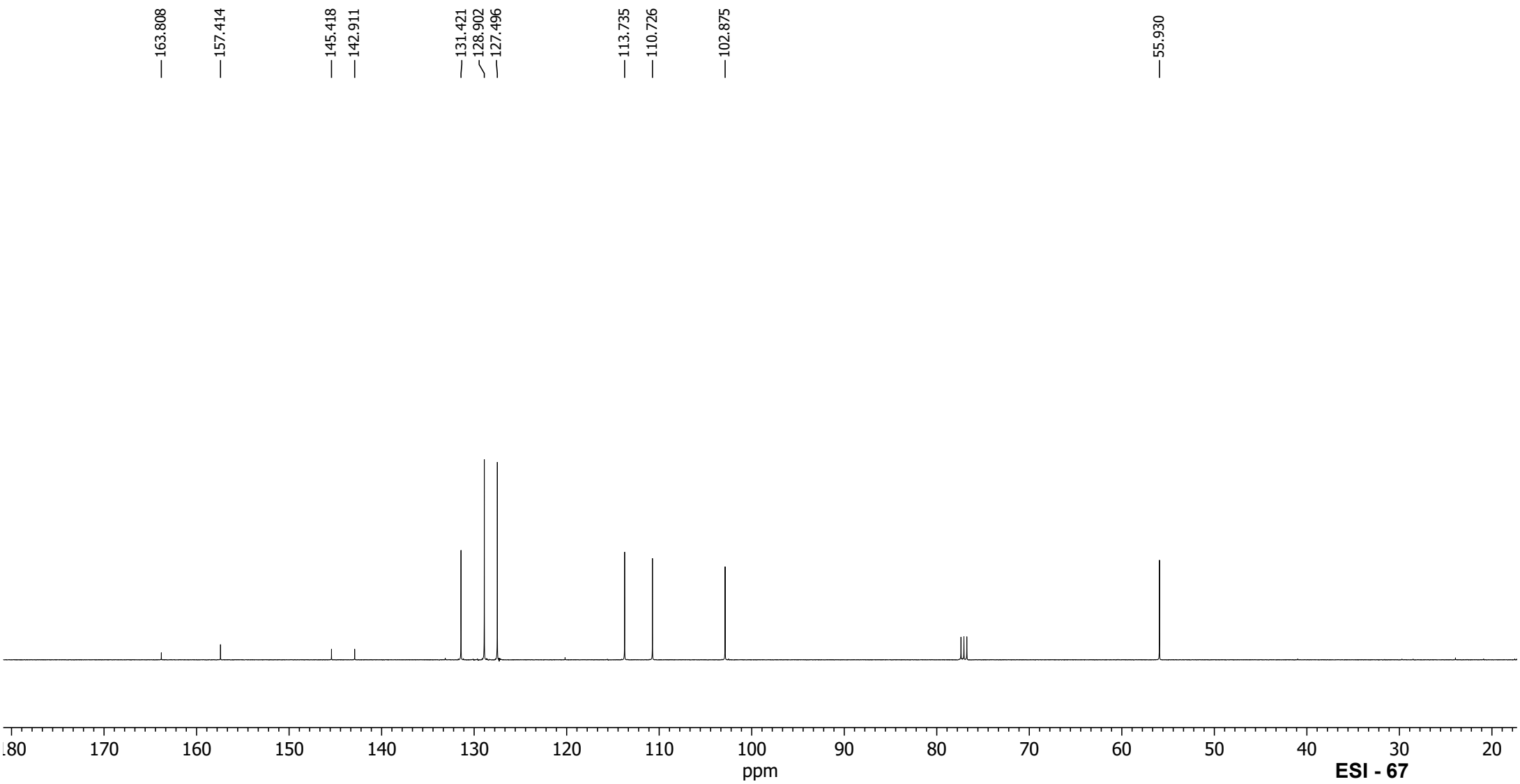




ESI - 66

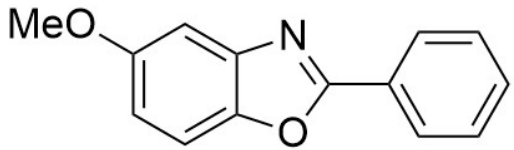
6-methyl-2-phenylbenzo[d]oxazole (6p)

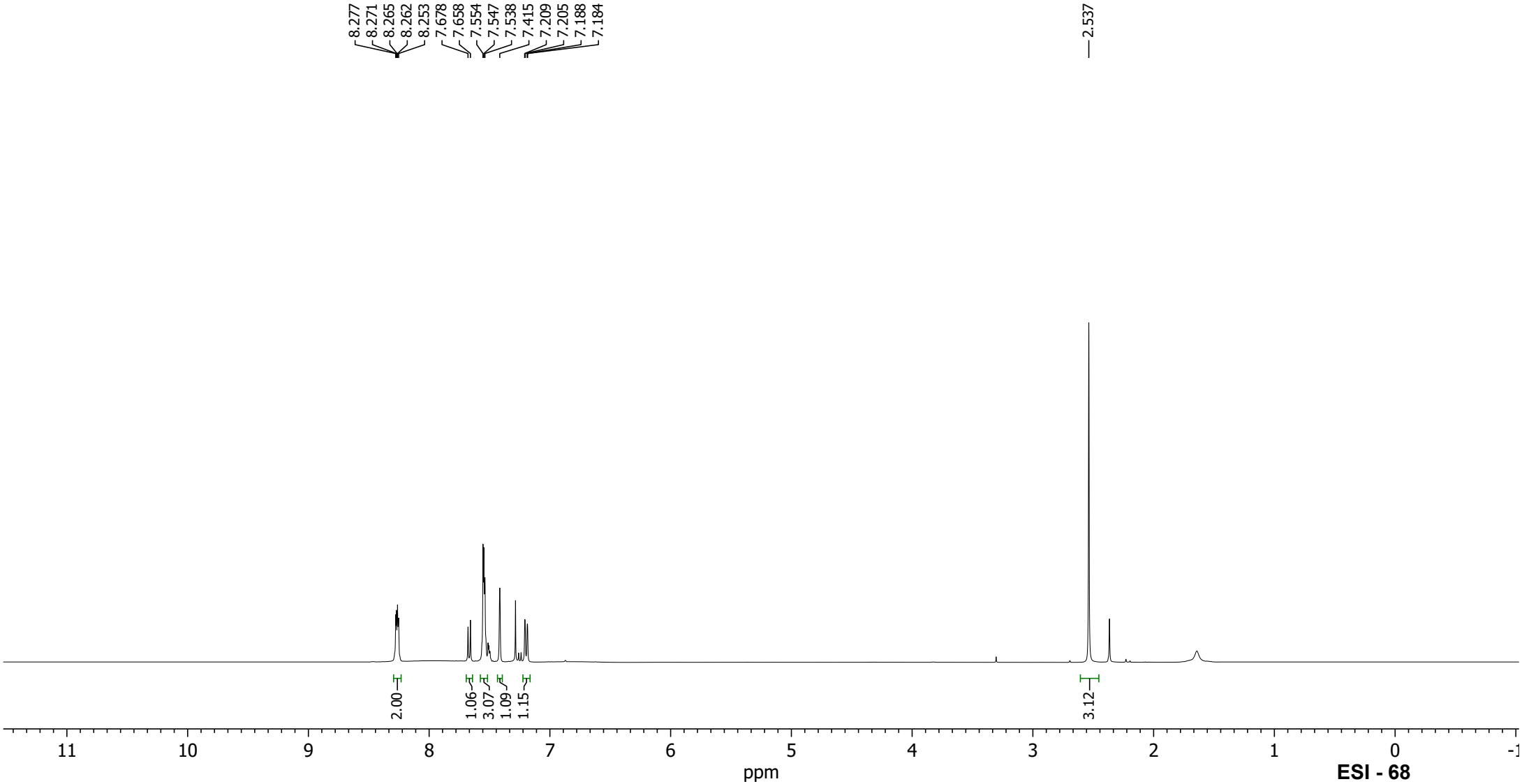




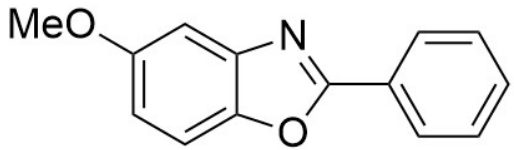
ESI - 67

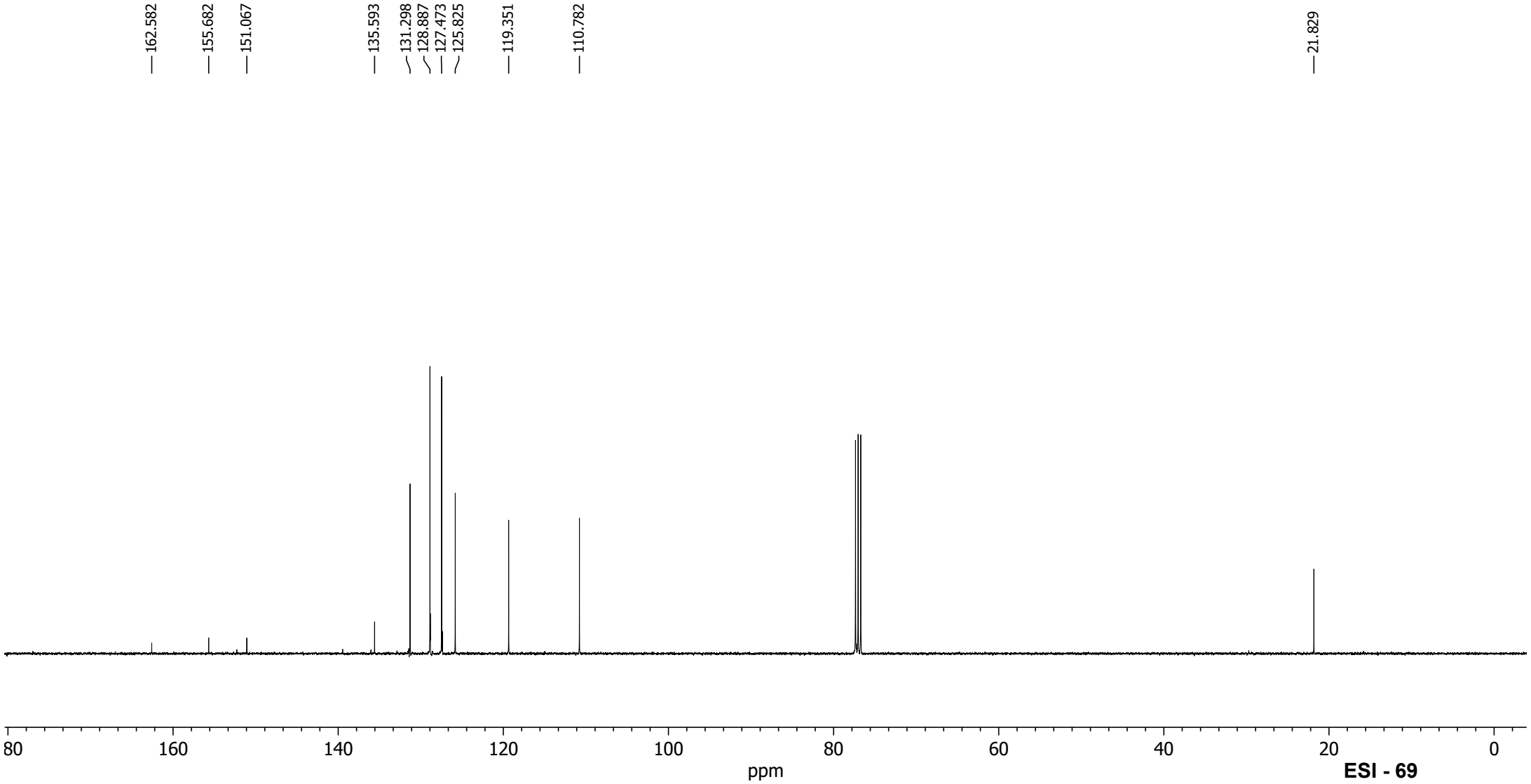
5-methoxy-2-phenylbenzo[d]oxazole (6q)





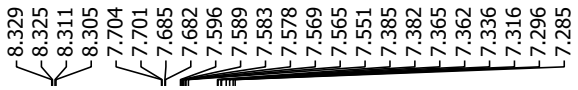
5-methoxy-2-phenylbenzo[d]oxazole (6q)

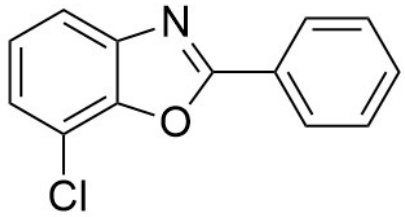


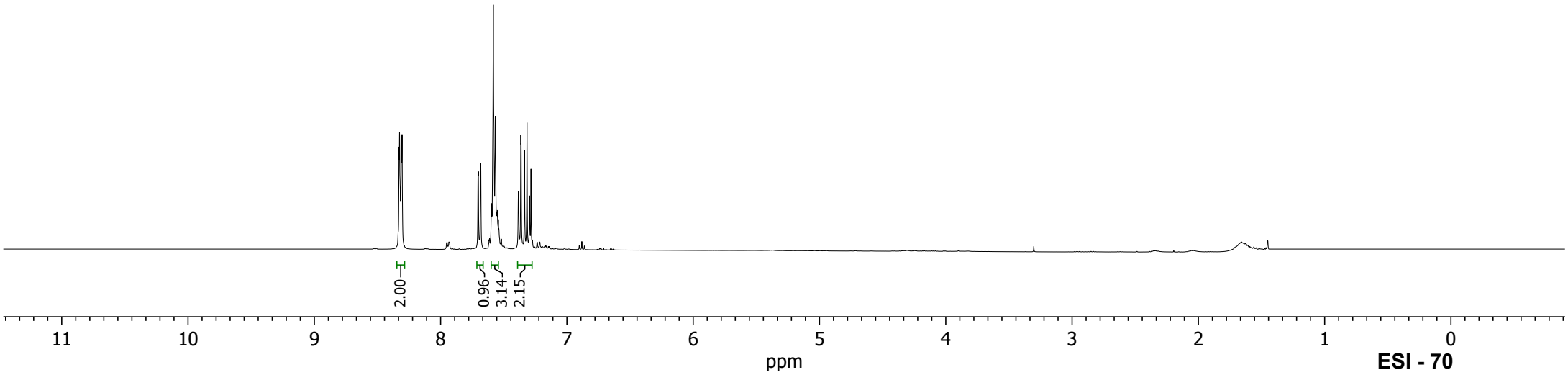


ESI - 69

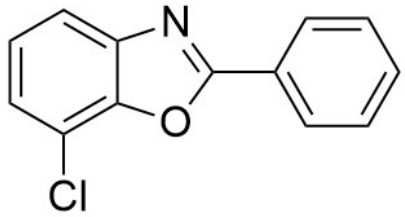
7-chloro-2-phenylbenzo[d]oxazole (6r)



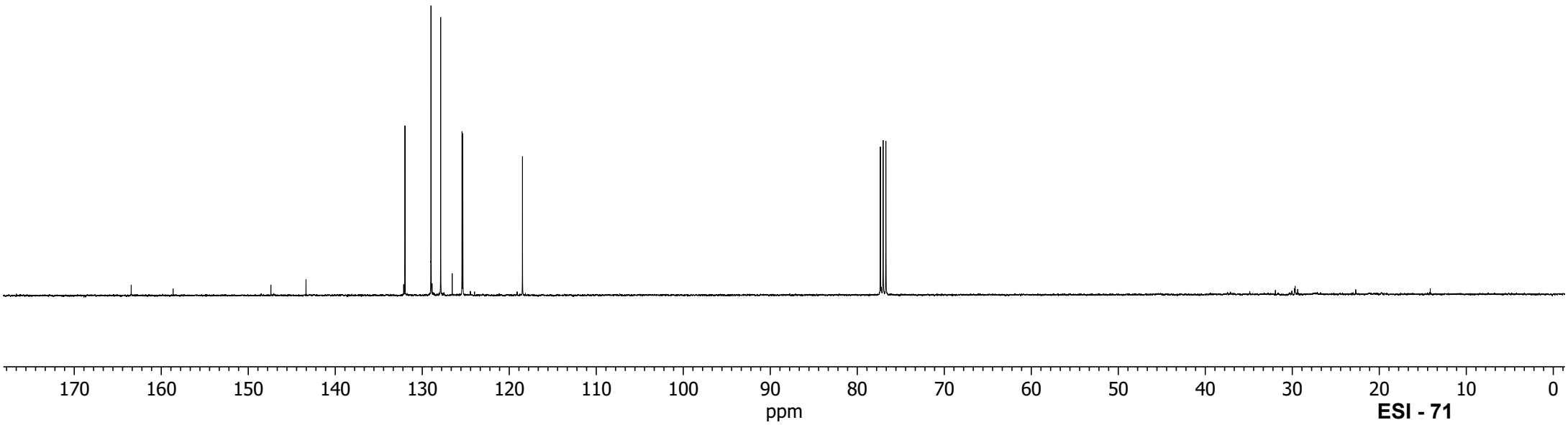




7-chloro-2-phenylbenzo[d]oxazole (6r)

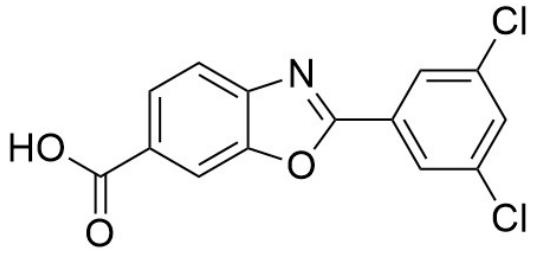


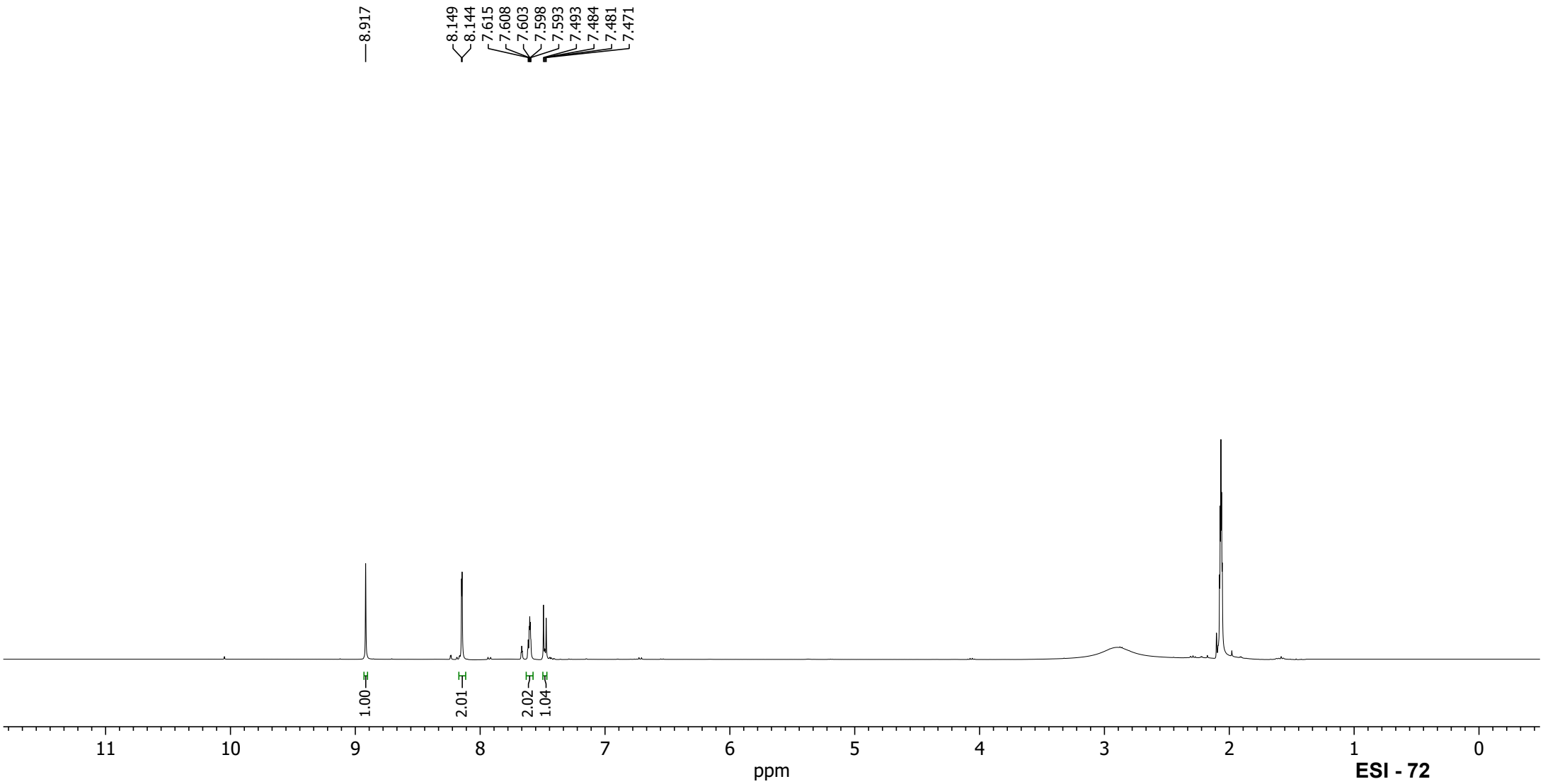
163.454
158.637
147.396
143.362
131.986
128.997
127.882
126.559
125.429
125.333
118.483



ESI - 71

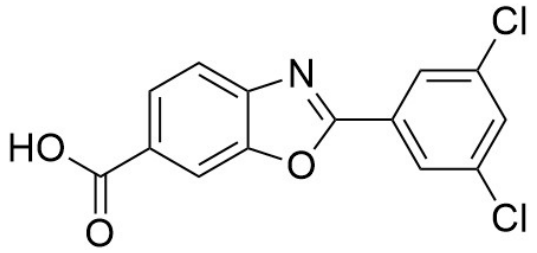
2-(3,5-dichlorophenyl)benzo[d]oxazole-6-carboxylic acid (Tafamidis)

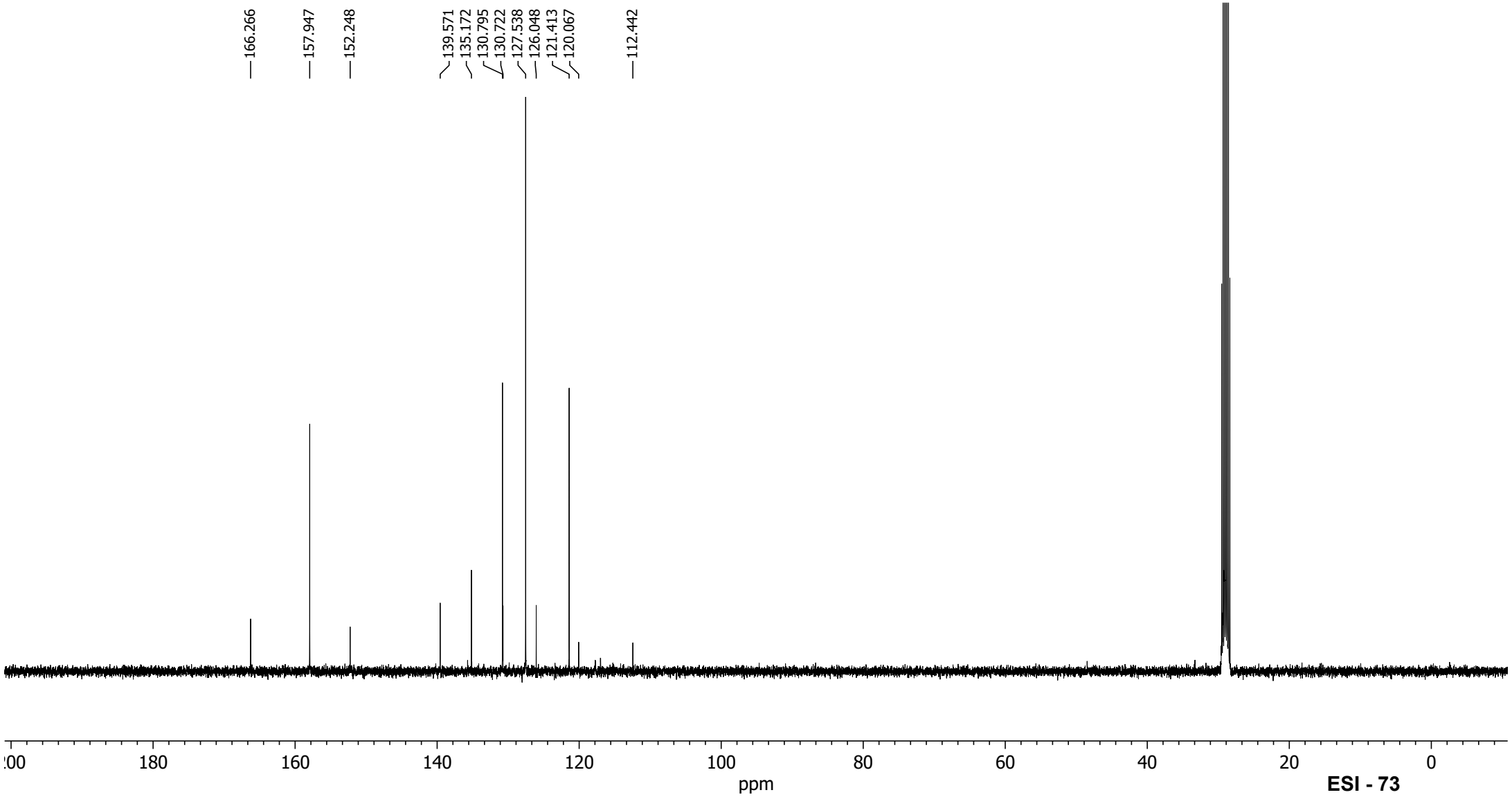




ESI - 72

2-(3,5-dichlorophenyl)benzo[d]oxazole-6-carboxylic acid (Tafamidis)





ESI - 73