Supplementary Material

Table 1: Metalation/methylation with N-phenylated Pyridones **4a** and **4b - Most Successful Results**

Entry*	Exchange conditions	Solvent	MeI	Time	% Distribution of Products^			
					SM	4d	5	6
1 [d]	**4a** + TG + CuCN•2LiCl (10% mol)	THF 20 V	4 eq.	20h	8.6	**40.8**	27.6	11.8
2 [a]	**4b** + TG + CuCN•2LiCl (10% mol)	"	"	3h	0	43.2	26.5	14.1
3 [a]	**4b** + TG + CuCN•2LiCl (5% mol)	"	"	20h	0	12.6	47.7	39.6
4 [a]	**4a** + TG + CuCN•2LiCl (10% mol)	"	**10 eq.**	4h [b]	0	**83.1**	14.7	2.2
5 [d]	**4b** + TG + CuCN•2LiCl (10% mol)	"	"	1h	0	**69.1**	24.4	6.4
6 [a]	**4a** + Ate Complex (3 eq.) [c]	Me-THF	4 eq.	1h	0	66	32.8	1.2
				2h	0	**74.4**	14.1	11.5

[*] Under N_2, analysis is based on HPLC: 98% of H Product (**5**) after end of addition of TG (besides in entry 1."Turbo Grignard", 1.5 eq.) or "Ate Complexes" and quenching a rx. sample with water and sampling the rx again after addition of MeI; ^ main products, the rest are side products such as **7**-**9**; [a] (-10°C) ->RT; [b] isolated yield after flash chromatography is: ~ 50% with 80% **4d** (in HPLC), ^{1}NMR clearly showed 84% **4d** & 15% **5**, only 1% of D-**5** (quenching of rx. was done with D_2O); [c] BuLi+^{i}PrMgCl-2:1. **Eq. means total metalating agent vs. SM**; [d] @rt

Table 2: Metalation/methylation with N-phenylated Pyridones **4a** and **4b**

Entry	Exchange conditions	Solvent	Methylation reagent	Time	Products			
					SM	5	4d	6
1*	**4a** + Turbo Grignard (1.15 eq.)	THF (20V)	MeI (2 eq.)	2h [a]	10-20%	60-70%		10%
			+ MeI (2 eq.)	24h	0	80.6%	5%	13%
2 [b]	**4a** + Turbo Grignard (1. 5 eq.)		MeI (2 eq.)	4h		75%	4.2%	20%
				24h		73%	4.5%	22%
3 [b]			methyltriflate (2 eq.)	5h		82%	0.3%	2.6%
				5d.		83%	0.3%	3%
4 [b]			dimethyl sulfate (2 eq.)	5h		70.3%	4.1%	2.8%
				5d.		72.5%	4.0%	3%
5 [c]	**4a** + Bu-Li (1 eq.) + MeMgCl (0.5 eq.)	THF (10V)	MeI (4 eq.)	5h	47.4%	38.8%	0	0
				20h	49%	40%	2%	0
6 [d]	**4a** + Turbo Grignard (1.5 eq.) + CuCN•2LiCl (0.1 eq., 10 mol %)	THF (20V)		3h	8.9%	27.5%	40.5%	12%
				20h	8.6%	27.6%	40.8%	11.8%
7 [d]	**4a** + Turbo Grignard (1.5 eq.) + CuCN•2LiCl (1 eq.)			3h	0	24%	33%	42%
				20h		28.5%	30.5%	41%
8 [d]	**4a** + Turbo Grignard (1.5 eq.) + CuCN•2LiCl (0.025 eq., 2.5 mol %)			0.5h	0	83.3%	3.59%	13.11%
				1h		66%	7.42%	26.55%
				3h		25.92%	21.43%	52.65%
9 [d]	**4b** + Turbo Grignard (1.5 eq.) + 10 mol% CuCN•2LiCl			3h	0	26.51%	43.24%	14.16%
				20h		24.22%	39.41%	13.51%

10 [d]	**4b** + Turbo Grignard (1.5 eq.) + 5 mol% CuCN•2LiCl			3h	0	49.72%	9.48%	40.81%
				20h		47.77%	12.61%	39.62%
11 [d]	**4a** + Turbo Grignard (1.5 eq.) with 10 mol% CuCN•2LiCl	THF (20V)	MeI (10 eq.)	0.5h	0	16.99%	81.87%	1.14%
				1h		17.89%	80.62%	1.49%
				2h		16.04%	82.01%	1.94%
				3h		14.99%	83.36%	1.66%
				4h [e]		14.77%	83.07%	2.16%
12 [f]	**4a** + "Ate Complex" (BuLi+iPrMgCl-2:1)	THF (10V)	MeI (4 eq.)	3h		64.19%	35.22%	0.59%
				3d.		50.19%	37.81%	11.27%
13 [d]	**4a** + Turbo Grignard (1.5 eq.) with 10 mol% CuCN•2LiCl	THF (20V)	dimethyl sulfate (10 eq.)	1h	0	62.3%	9.7%	27.9%
				20h		32.4%	12.9%	54.7%
14	**4a** + "Ate Complex" (BuLi+iPrMgCl-2:1)	THF (10V)	MeI (10 eq.)	2h	0	77.9%	11.5%	10.6%
				4h		72.1%	20.44%	7.4%
15 [g]	**4b** + "Ate Complex" (BuLi+iPrMgCl-2:1) + 10 mol% CuCN•2LiCl		MeI (4 eq.)	1h	0	46.1%	26.3%	27.6%
				2h		10.5%	36.9%	52.6%
16 (@rt)	**4a** + Turbo Grignard (1.5 eq.) with 10 mol% CuCN•2LiCl	THF (20V)	MeI (10 eq.)	1h	0	24.4%	69.1%	6.4%
17 [d]	**4a** + "Ate Complex" (BuLi+iPrMgCl-2:1)	Me-THF (10V)	MeI (4 eq.)	1h	0	32.8%	66%	1.18%
				2h		14.1%	74.4%	11.5%
18 (-5°C ->0->rt)	**4a** + Turbo Grignard (1.6 eq)	THF (20V)	MeI (5 eq.)	1h	0	87.2%	12.8%	0
19 [h]	**4a** + Hexyl Li (1.1eq)	THF (10V)	MeI (1.1 eq.)	2h	0	0	0	0

*@-30°C, under N_2, after 2 h (based on TLC & HPLC: 96% of H Product after end of addition of Turbo Grignard and quenching with water) [a]additional MeI (2 eq.) was added reaction monitored by TLC; [b]@-2°C-0°C; [c] (-10°C) ->0°C->RT; [d] (-10°C) ->RT; [e] isolated yield after flash chromatography is: ~ 50% with 80% **4d** (in HPLC), ^{1}H-NMR clearly showed 84% **4d** & 15% **5**, only 1% of D-5 (quenching of rx. was done with D_2O); [f] "Ate complex" prepared @-5°C and was added into a solution of **4a** @-10°C, under N_2; [g]@0°C; [h]reaction @-55°C-50°C, **4a** decomposition. Entries marked in yellow are on table 1 which shows our most successful result with TG and Ate complexes; **Eq. means total metalating agent vs. SM.**

Table 3: Optimization of the SMC of Scheme 13

Entry*	Substrate	Catalyst	RuPhos (% mol)	Conversion to 4d in HPLC	Isolated Yield
1	**4a** (Br)	5% mol $Pd(OAc)_2$	5	100%	88%
2	"	2.5% mol $Pd(OAc)_2$	"	93%	55%
3[a]	"	1% mol $Pd(OAc)_2$	"	94.2%	n/a
4	"	5% mol **$Pd_2(dba)_3$**	10	100%	90%
5[b]	"	5% mol **$PdCl_2(dppf)$•DCM**	5	73.3%	n/a
6[c]	**4b** (I)	5% mol $Pd(OAc)_2$	10	66%	50%
7[d]	**4c** (Cl)	"	"	7.8%	n/a
8[e]	**4b** (I)	"	"	67%	n/a

*reactions performed under the conditions of Scheme 13; [a]4.9% **4a** still remained with 0.82% **5** and 0.08% **6**; [b]3.6% **4a**, 5% of **5** and 18.1% of **6**; [c]with 1.3 eq. $MeBF_3K$ for 24 h, followed by addition of 0.35 eq. of each of the salt, catalyst and Ligand, and stirring for additional 5 h; [d]with 1.3 eq. $MeBF_3K$, 88.5% **4c** and 3.7% **5** after 24 h; [e]with **$MeB(OH)_2$** under the conditions of Scheme 13 **BUT** after 24 h, 30.5% **4b**, 2.3% **5** and 0.20% **6**.

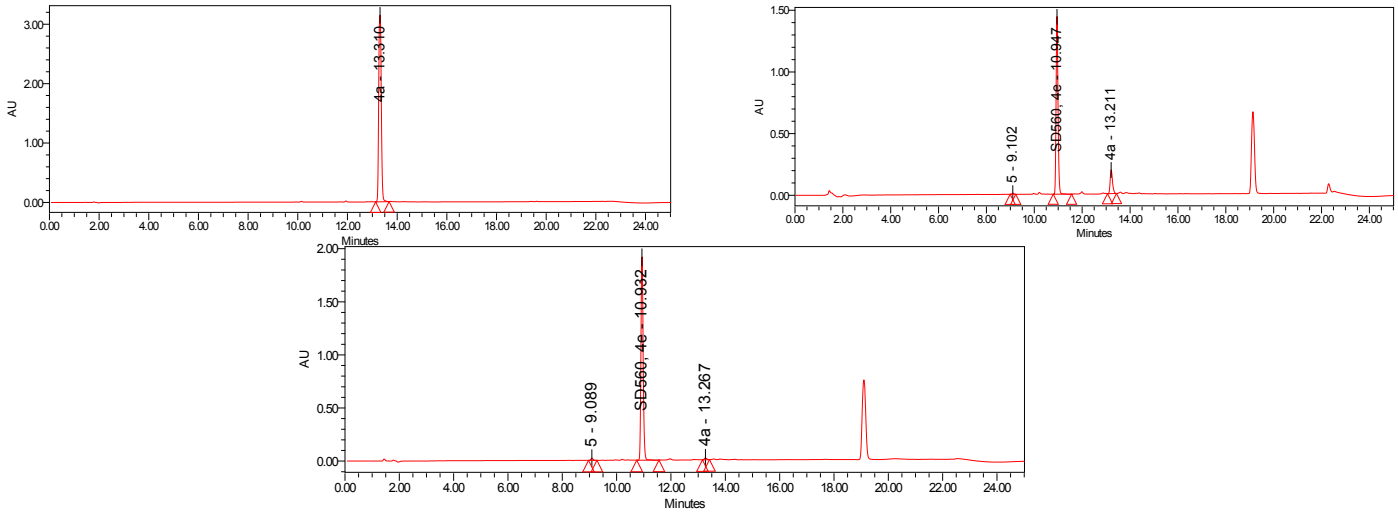
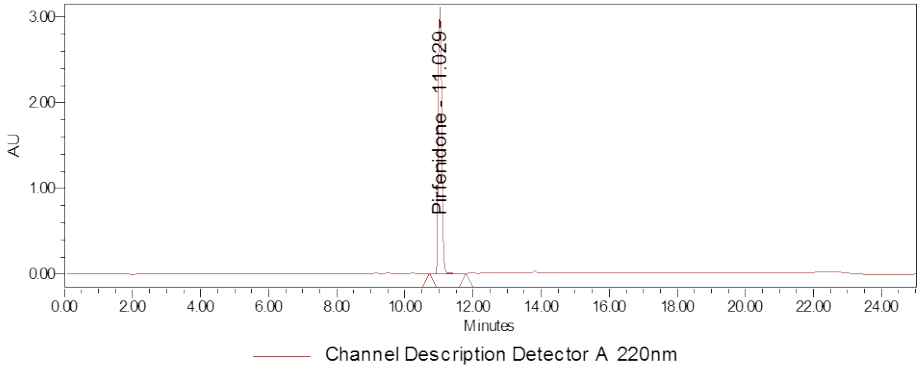


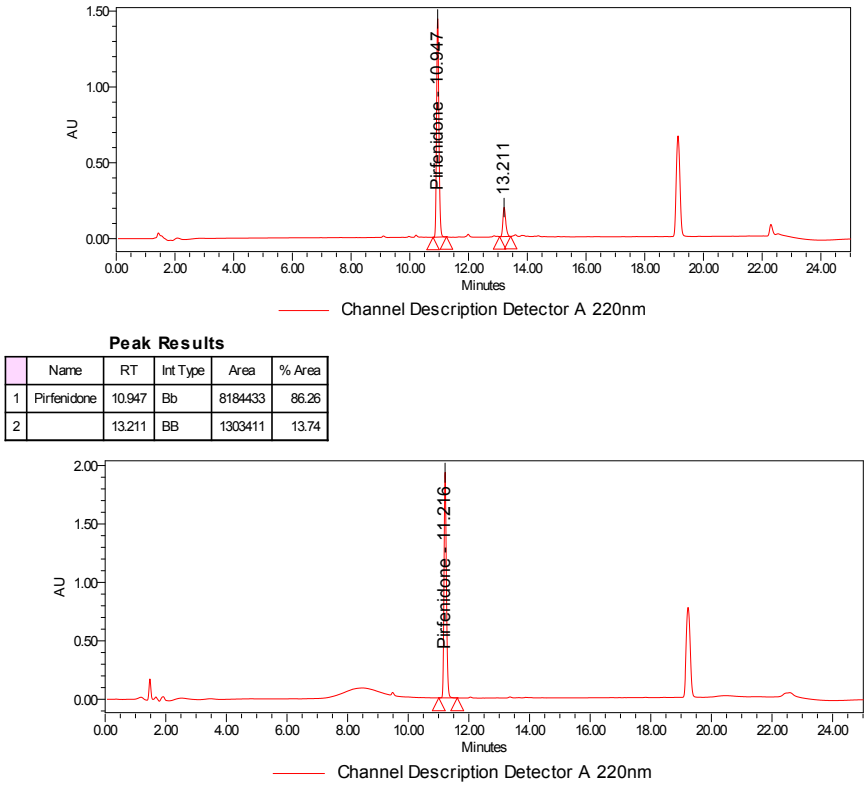
Fig. 1: Progress of methylation of **4a** *via* SMC with $CD_3B(OH)_2$: the left panel, at start (only **4a is** present), the right panel after 30 min and the last (lower) panel after 2h (end of reaction, **4a** fully consumed, 98% **SD-560** (**4e**) with only a negligible amount of **5** are present, (at ~19 min toluene (rx. solvent) can be detected).



Peak Results

	Name	RT	Area	% Area
1	Pirfenidone	11.029	22812771	100.00

Reference Standard for Pirfenidone **4d** in HPLC (above)



Peak Results

	Name	RT	Int Type	Area	% Area
1	Pirfenidone	10.947	Bb	8184433	86.26
2		13.211	BB	1303411	13.74

Peak Results

	Name	RT	Int Type	Area	% Area
1	Pirfenidone	11.216	Bb	10800206	100.00

Fig 2.: Below the reference standard for **pirfenidone**, **4d** (the most upper chromatogram), is the HPLC monitoring for **4a** (13.21 min.)->**4d, pirfenidone** (10.94 min.), after ½ h of reaction with $MeB(OH)_2$/$Pd(OAc)_2$ (5 mol%)/RuPhos (10%) (mid chromatogram) and after 2 h (lower chromatogram. At ~19.5 min, toluene (rx. solvent) can be detected)

Experimental Part

NMR spectra were recorded, in Bruker instruments: Avance-III-700 (^1H and ^{13}C at 700.5 and 176.1 MHz, respectively), DMX-600 (600.1 and 150.9 MHz, respectively) and Avance-400 (400.1 and 100.6 MHz, respectively). Series of 2D spectra were also obtained (COSY – $^1H \times ^1H$ correlation; HMQC – one-bond $^{13}C \times ^1H$ correlation; and HMBC – long-range $^{13}C \times ^1H$ correlation), which allowed the full attribution of all carbon and proton signals and confirms the chemical structure. UPLC (Agilent 1260) integrated with high-resolution mass spectra (HRMS) were obtained on a 6545 QTOF (ESI) instrument (Agilent). Mass spectra were obtained on SQ 6120 (Agilent) spectrometer (ESI). Progress of the reactions was monitored by thin-layer chromatography (TLC) on silica gel (60F, Merck Art. 5554), with visualization of the TLC plates using ultraviolet light, and by high pressure/performance liquid chromatography (HPLC) using an Agilent column (eclipse XDB-C18, 5 micron, 4.6x150 mm) attached to Shimadzu instrument where solution A was 0.02% TFA/water and solution B was 0.02% TFA/AcCN, in a gradient of 95% A and 5% B (T=0) to 30% A and 70% B (T=20 min), the flow rate was 1mL/min, run time was 25 min with UV detector at 220 nm. Column temperature was 35°C. Injection volume was 10 µl. Flash chromatography was carried out using Combi-Flash.

Scheme 3: Methylation 1st *via* lithiation (1a->(70%)2a->(65%)3a->(70%)4d; Overall Yield: 32%)

*2-Methoxy-5-methylpyridine HCl salt (**2a**).* Methylation of 5-Bromo-2-methoxypyridine, **1a**, ***via lithiation***: 5-Bromo-2-methoxy pyridine (**1a**, 5 g, 26.6 mmol) dissolved in MTBE (extra dry, 37.5 mL) at 25°C under N_2 and the solution was cooled to -50°C. n-BuLi (1.6 M in hexane, 18.13 mL, 29 mmol, 1.1 eq.) was added slowly into the mixture with stirring at -50°C for 2 h under N_2, after which time methyl iodide (MeI, 2.15 mL, 35 mmol, 1.3 eq.) in MTBE (2.5 mL) was added at -50°C and the mixture was stirred at -50°C for 0.5 h after which time it was allowed to reach rt and stirred at rt for 12 h TLC (2% EtOAc/hexane) indicated full consumption of **1a** and formation of **2a**. The mixture was then cooled to 5°C and water was added (10 mL) with stirring for 0.5 h The organic phase was separated, the water phase extracted with MTBE and the organic phases combined and

washed again with water (15 mL), the organic layer separated and washed with brine (15 mL) and dried over Na_2SO_4, filtered and cooled to 5°C. n-BuOH (1.97 g, 2.43 mL, 26.5 mmol, 1 eq.) was added followed by addition of acetyl chloride (2.08 g, 1.89 mL, 26.6 mmol, 1 eq.) to result in immediate precipitation of a grayish solid. The suspension was stirred at 5°C for 8 h, then filtered, the solid washed with MTBE and dried on the funnel (~ 3 g, 70%) and then dried under vacuum to leave **2a** (1.6 g, 37%) as a grayish solid (hygroscopic and volatile). ^{1}H-NMR ($DMSOd_6$) δ 8.10 (d, J = 2 Hz, 1 H), 7.88 (dd, J = 8, 2 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 3.95 (s, 3H, OMe), 2.27 (s, 3H, Me); ^{13}C-NMR ($DMSOd_6$) δ 160.52, 143.86, 142.51, 126.80, 110.27, 55.11, 16.73; ^{1}H-NMR ($CDCl_3$) δ 8.2 (br s, 1H), 8.06 (d, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 4.30 (s, 3H, OMe), 2.42 (s, 3H, Me); ^{13}C-NMR ($CDCl_3$) δ 158.76, 147.93, 137.93, 128.34, 111.98, 58.69, 17.26; HRMS (m/z): [M+H]+ calcd. for C_7H_9NO, 124.0756; found, 124.0757.

*5-Methylpyridin-2(1H)-one, (**3a**).* **2a** (1.48 g, 9.27 mmol) was dissolved in 1,4 dioxane/Con. HCl (7.4 mL: 7.4 mL, 5V/5V) and the solution was heated to 100°C for 48 h after which time TLC indicated disappearance of **2a** and formation of **3a**. Reaction was cooled to rt and the mixture was evaporated to dryness and toluene (3 mL) was charged to chase residual acidic water. Then the residue was dissolved in water (7.4 mL, 5V) and the solution was stirred at rt for ½ h and cooled to 15°C. NaOH (10% solution) was added until pH = 6.5-7.5 and the solution was stirred at rt for additional ½ h and extracted with DCM (3 x 3V, 13 mL). Organic phase was separated and evaporated and hexane was added (3V, 4.5 mL) resulting in **3a** as an off-white solid which was dried in vacuum overnight (0.66 g, 65%). ^{1}H-NMR ($CDCl_3$) δ 7.32 (dd, J = 9, 2.5 Hz, 1H), 7.16 (s, 1H), 6.52 (d, J = 9 Hz, 1H), 2.08 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 164.48, 144.29, 132.34, 119.51, 116.22, 16.93; HRMS (m/z): [M+H]+ calcd. for C_6H_7NO, 110.0600; found, 110.0599.

*5-Methyl-1-phenylpyridin-2(1H)-one, (**4d, Pirfenidone**).* **3a** (2.56 g, 23.46 mmol), phenylboronic acid (4.29 g, 35.19 mmol, 1.5 eq.), $Cu(OAc)_2 \bullet H_2O$ (0.47 g, 2.35 mmol, 10%mol) and pyridine (3.71 g, 3.8 mL, 43.9 mmol, 1.87 eq.) stirred in DCM (44 mL, 17V) for 24 h with air bubbling into the mixture. After HPLC indicated disappearance of **3a** and formation of **4d**, Reaction mixture was filtered through a celite pad and the filtrate washed with HCl (2N, 2 x 13 mL, 10V) the organic phase was separated and washed with NaOH (1N, 13 mL, 5V) and brine (8 mL, 3V) and then evaporated to leave a reside which was co-distilled with MTBE (2 x 5 mL, ~4 V), and finally precipitated from MTBE (5 mL, 2V) at 5°C. The suspension maintained at 5-10°C for 2 h and then filtered, solid was washed with MTBE (2.5 mL, 1V) and dried under vacuum at 50-55°C for 8 h to give crude **4d** which was purified by chromatography (3.03 g, 70%). ^{1}H-NMR (DMSO d_6) δ 7.51-7.48 (t, J = 8.0 Hz, 2H), 7.44-7.40 (m, 2H), 7.39-7.36 (m, 3H), 6.42 (d, J = 9 Hz, 1H), 2.04 (s, 3H, Me). ^{13}C-NMR ($DMSOd_6$) δ 160.36, 142.98, 140.98, 136.03, 128.93, 127.90, 126.69, 120.15, 113.95, 16.25; HRMS (m/z): $[M+H]^+$ calcd. for $C_{12}H_{11}NO$, 186.0913; found, 186.0914.

<u>Scheme 10: Methylation 1st *via* SMC and Molander's reagent (1a->(90%)2a (*via* SMC instead of lithiation) ->(97%)3a->(66%)4d; Overall Yield: 58%)</u>

*2-Methoxy-5-methylpyridine hydrochloride, **2a**, via Suzuki-Miyaura Cross-Coupling (SMC) using potassium methyltrifluoroborate ($MeBF_3K$).* 5-Bromo-2-methoxy pyridine (**1a**, 5 g, 26.87 mmol), 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos, 10% mol, 1.26 g), palladium(II) acetate ($Pd(OAc)_2$, 5% mol, 0.31 g), potassium methyltrifluoroborate ($MeBF_3K$, 1.3 eq., 4.26 g, 34.94 mmol) and potassium carbonate (K_2CO_3, 3 eq., 11.14 g) were added under N_2 atmosphere into a mixture of toluene/water (50 : 5 mL, (11V) respectively) heated at 87°C for 6 h to give **2-methoxy-5-methylpyridine, 2a** (free base, 100% conversion in HPLC) after which time the mixture was filtered, the solid was washed with extra 10 mL of toluene and the combined organic layer was dried with Na_2SO_4. **2-Methoxy-5-methylpyridine** was isolated as its **HCl salt 2a** by adding acetyl chloride (2.1 g, 1.91 mL, 26.87 mmol) and n-butanol (1.99 g, 2.45 mL, 26.87 mmol) into the dried toluene solution (~60 mL) and stirring at 0-5°C for 2 h resulting in precipitation of a greyish solid which was dried on the funnel under N_2 (3.87 g, 90%). ^{1}H-and ^{13}C-NMR and MS data are identical to **2a** (•HCl) prepared *via* lithiation (by scheme 3).

*2-Methoxy-5-(methyl-d_3)pyridine (**2b**).* **1a** (1 g, 5.32 mmol), CD_3BF_3K (0.86 g, 6.91 mmol, 1.3 eq.), $Pd(OAc)_2$ (0.06 g, 0.27 mmol, 5%mol) and RuPhos (0.25 g, 0.53 mmol, 10% mol) and K_2CO_3 (2.21 g, 15.96 mmol, 3 eq.) were mixed in toluene/water (4 mL : 1 mL, (5V)) at 87°C for 6 h HPLC showed full conversion of **1a** into **2b** which was isolated as HCl salt (0.71 g, 82%). ^{1}H-NMR ($CDCl_3$) δ 8.21 (d, J = 9 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 7.17 (d, J = 9 Hz, 1H), 4.32 (s, 3H, OMe); ^{13}C-NMR ($CDCl_3$) δ 158.68, 148.11, 137.75, 128.28, 112.08, 58.87, 16.50 (hardly seen); HRMS (m/z): [M+H]+ calcd. for $C_7H_6D_3NO$, 127.0945; found, 127.0946.

*5-Methylpyridin-2(1H)-one, (**3a**)*. **2a** (prepared from **1a** *via* SMC with $MeBF_3K$, 2.87 g, 17.98 mmol) was dissolved in 37% HCl solution/water (15 mL/15 mL), KI (14.95 g, 90 mmol, 5 eq.) was added and the solution was heated to 130°C for 3 h after which time the mixture was cooled to rt and NaOH solution (25%) was added until pH ≈ 7. Water was evaporated to dryness and the residue extracted with DCM (20 mL x 3). The organic phase, separated, dried ($MgSO_4$) and evaporated to leave **3a** as a grayish solid (1.91 g, 97%). ^{1}H-NMR and ^{13}C-NMR and MS were found identical to **3a** prepared *via* scheme 3.

*5-(Methyl-d_3)pyridin-2(1H)-one, (**3b**)*. **2b** (prepared from **1a** *via* SMC with CD_3BFK and $CD_3B(OH)_2$, 1.15 g, 7.07 mmol) underwent OMe cleavage as described for **3a** in 37% HCl (5.75 mL) and KI (5.9 g). After work up and evaporation of the DCM **3b** was obtained as a slightly brown solid (0.71 g, 90%). ^{1}H-NMR ($CDCl_3$) δ 7.35 (d, J = 9Hz, 1H), 7.18 (s, 1H), 6.55 (d, J = 9 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 164.71, 144.37, 132.45, 119.72, 116.11, 16.26 (hardly seen); HRMS (m/z): [M+H]+ calcd. for $C_6H_4D_3NO$, 113.0788; found, 113.0789.

*5-methyl-1-phenylpyridin-2(1H)-one, (**4d, Pirfenidone**).* **3a** (prepared from **2a** which was prepared from **1a** *via* SMC with $MeBF_3K$, 1.91 g, 17.5 mmol), phenylboronic acid (3.2 g, 26.25 mmol), $Cu(OAc)_2$ (0.32 g, 1.75 mmol, 10%mol) and pyridine (2.77 g, 2.82 mL, 35 mmol, 2 eq.) stirred in DCM (33 mL, 17V) for 24 h with air bubbling into the mixture. Reaction mixture was filtered through a celite pad, which was washed with DCM the organic phase was then washed with HCl (1N), water, NaOH (1N) and brine. Organic phase evaporated and the residue chromatographed to give **4d** (2.15 g, 66%). ^{1}H and ^{13}C NMR and MS were identical to **4d** obtained from the lithiation process.

Scheme 13: Methylation last *via* SMC with $CD_3B(OH)_2$ (1a->(96%)3c->(95%)4a->(92%)4e; Overall Yield: 84%)

*5-Bromopyridin-2(1H)-one, (**3c**).* 5-Bromo-2-methoxypyridine (**1a**, 18.8 g, 0.1 mol) was dissolved in HCl (6N (100 mL 37% water solution and 100 mL water)) and the solution was refluxed for 7 h, after which time it was cooled to 0-5°C and 50% NaOH (~ 70 mL) were added until pH ≈ 4. Then 1N NaOH was added until pH ≈ 6-7 to result in white suspension which was cooled to 0-5°C and stirred for 1½ h The precipitate was filtered, washed with cold water (20 mL) and the solid was dried in vacuum oven at 50°C to give 16.8 g (96%) of **3c**. ^{1}H-NMR (DMSO d_6) δ 11.75 (br s, OH); 7.69 (d, J = 3 Hz, 1H); 7.55 (dd, J = 9, 3 Hz, 1H); 6.37 (d, J = 9 Hz, 1H); ^{13}C-NMR (DMSO d_6) δ 161.23, 143.09, 137.64, 120.06, 98.40; MS *m/z* 174.0 and 176.0 $[M+H]^+$ (1:1 boublet).

*5-Bromo-1-phenylpyridin-2(1H)-one, (**4a**)*. **3c** (5.12 g, 29.43 mmol), phenyl boronic acid (5.38 g, 44.14 mmol, 1.5 eq.), $Cu(OAc)_2$ (0.54 g, 2.94 mmol, 10% mol) and pyridine (4.66 g, 58.86 mmol, 2 eq.) were stirred in DCM (87 mL, 17V) with constant bubbling of air through the mixture, at rt for 17 h after which time TLC indicated complete disappearance of **3c** and clean formation of **4a**. Then the mixture was washed with 1N HCl, organic phase was separated, washed with water, dried (Na_2SO_4), filtered and solvent evaporated and the residue was purified by chromatography to yield **4a** (7 g, 95%) as an off-white solid. This solid was crystallized from DIPE to give pure **4a** as a white solid, mp = 76-78°C. ^{1}H-NMR ($CDCl_3$) δ 7.51-7.45 (m, 3H), 7.44-7.39 (m, 2H), 7.36-7.34 (m, 2H), 6.56 (d, J = 9.5 Hz, 1H); ^{13}C-NMR (CDCl3) δ 160.74, 142.83, 140.14, 137.70, 129.47, 128.86, 126.37, 123.00, 98.02; Element analysis calculated for $C_{11}H_8BrNO$, C, 52.83%; H, 3.22%; Br, 31.95%; N, 5.60%; found C, 52.90%, H, 3.14%, Br, 31.45%, N, 5.47.

*5-(Methyl-d_3)-1-phenylpyridin-2(1H)-one (**4e, deuterated Pirfenidone, SD-560**)*. Preparation of **4e** *via* SMC using (methyl-d_3)boronic acid. **4a** (1 g, 4 mmol), $CD_3B(OH)_2$ (0.33 g, 5 mmol, 1.3 eq.), $Pd(OAc)_2$ (0.045 g, 0.2 mmol, 5% mol), RuPhos (0.09 g, 0.4 mmol, 10% mol) and K_2CO_3 (1.65 g, 11.9 mmol, 3 eq.) in toluene/water (4 mL/1 mL, 5V) were stirred under N_2 at 87°C for 2 h (see Fig. 2) After which time the reaction mixture worked up, crude **4e** purified by chromatography to give 0.69 g (92%) of yellowish solid. ^{1}H-NMR (DMSO d_6) δ 7.52-7.48 (t, J = 8.0 Hz, 2H), 7.46-7.42 (m, 2H), 7.40-7.36 (m, 3H), 6.42 (d, J = 9 Hz, 1H); ^{13}C-NMR (DMSO d_6) δ 160.40, 143.01, 141.01, 136.09, 128.96, 127.93, 126.73, 120.17, 113.85, 15.49 (hardly seen); HRMS (m/z): $[M+H]^+$ calcd. for $C_{12}H_8D_3NO$, 189.1101; found, 189.11049.

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Scheme 13 leading to 4d :

*Preparation of **4d** via SMC using methylboronic acid*. **4a** (1 g, 4 mmol) was dissolved in toluene (4 mL, 4V) at rt under N_2 and $MeB(OH)_2$ (0.31 g, 5.16 mmol, 1.3 eq.), $Pd(OAc)_2$ (0.045 g, 0.2 mmol, 5% mol), RuPhos (0.09 g, 0.4 mmol, 10% mol) and K_2CO_3 (1.65 g, 11.91 mmol, 3 eq.) were added followed by addition of water (1 mL, 1V) and

the mixture was stirred under N_2 at 87°C for 2 hr after which HPLC indicated full consumption of **4a** and formation of **4d** (see Fig. 3). The mixture was filtered through celite and the filtrate was evaporated to leave a residue which was purified by Combi-Flash chromatography to yield **4d** (0.64 g, 87%) as an off-white solid. ^{1}H & ^{13}C-NMR (DMSO d_6) & HRMS were identical to the spectra reported for **4d** obtained from lithiation process as well as from SMC with $MeBF_3K$.

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Scheme 9:

*Preparation of **4d** via SMC using potassium methyltrifluoroborate ($MeBF_3K$)*. 5-Bromo-1-phenylpyridin-2(1H)-one (**4a**, 3.9 g, 15.59 mmol) was dissolved in toluene (39 mL, 10V) and RuPhos, (10% mol, 0.76 g), palladium(II) acetate ($Pd(OAc)_2$, 5% mol, 0.184 g), potassium methyltrifluoroborate ($MeBF_3K$, 1.3 eq., 2.47 g, 20.26 mmol) and potassium carbonate (K_2CO_3, 3 eq., 6.41 g) were added under N_2 atmosphere followed by addition of water (3.9 mL, 1V) and the heterogeneous reaction mixture was heated for 6-7 h at 87°C under N_2 atmosphere, after which time the mixture was filtered through celite and the filtrate was evaporated to leave a reside which was purified by Combi-Flash chromatography to yield **5-methyl-1-phenylpyridin-2(1H)-one, 4d** (2.82 g, 97%) as an off-white solid. ^{1}H & ^{13}C-NMR & MS were identical to the spectra reported for **4d** obtained from lithiation process as well as from SMC with $MeB(OH)_2$.

Preparation of 4d in tens gram scale. **4a** (10 g, 40 mmol), $MeBF_3K$ (6.34 g, 51.98 mmol, 1.3 eq.), $Pd(OAc)_2$ (0.45 g, 2 mmol, 5% mol), RuPhos (1.87 g, 4 mmol, 10% mol) and K_2CO_3 (16.58 g, 120 mmol) in mixture of toluene/water (40 mL/10 mL, 5V), were mixed in 100 mL reactor, under N_2 at 87°C for 7 h after which time HPLC indicated almost quantitative conversion to **4d** which was isolated after work-up and chromatography in 88% yield (6.5 g). ^{1}H and ^{13}C-NMR and MS data confirmed the structure as described above for **4d**.

*Preparation of trifluoro(methyl-d_3)- borane, potassium salt (**CD_3BF_3K**)*. **(**Methyl-d_3)boronic acid (2.52 g, 0.04 mol) was dissolved in methanol (12 mL) at rt and a water (20 mL) solution of KHF_2 (9.4 g, 0.12 mol, 3eq.) was added dropwise, within 10 min., into the methanolic solution resulting in an exothermic reaction (internal temperature was raised to 40°C). The mixture was stirred at rt for 6 h after which it was evaporated to dryness (at 45°C) to leave a white solid which was dried in vacuum oven overnight to leave 13 g of white solid. This solid was treated with AcCN (125 mL) at 45°C, and the solvent evaporated to furnish 4.4 g (88%) of **CD_3BF_3K** as a white solid, after drying. ^{13}C-NMR (D_2O) δ 0.568 (very broad and hardly seen signal); ^{11}B-NMR (D_2O) δ 5.91 (q, J = 65 Hz); ^{19}F-NMR (D_2O) δ -132.39 (q, J = 65 Hz); HRMS (m/z): $[M]^-$ calcd. for $CD_3BF_3^-$, 85.0510 and 86.0474; found, 85.0512 and 86.0475.

*5-(Methyl-d_3)-1-phenylpyridin-2(1H)-one (**4e**, **deuterated Pirfenidone**)*. **4a** (1 g, 4 mmol), CD_3BF_3K (0.65 g, 5.2 mmol, 1.3 eq.), $Pd(OAc)_2$ (0.045 g, 0.2 mmol, 5% mol), RuPhos (0.19 g, 0.4 mmol, 10% mol) and K_2CO_3 (1.66 g, 12 mmol, 3 eq.) in a mixture of toluene/water (4 mL/1 mL, 5V), were stirred under N_2 at 87°C for 7 h after which time HPLC indicated quantitative conversion to **4e** which was isolated after work-up and chromatography as a slightly yellowish solid (0.68 g, 90%). ^{1}H-NMR ($CDCl_3$) δ 7.48 (t of multiplets, J = 7.5 Hz, 2H), 7.39 (m, 3H), 7.26 (dd, J = 9, 2.5 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 6.61 (dd, J = 9, 0.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 161.65, 142.52, 141.08, 135.30, 129.22, 128.26, 126.51, 121.38; 114.68, 16.25 (*C*D_3 is hardly seen).

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Scheme 12:

*Preparation of **2a** via SMC using methylboronic acid*. **1a** (2 g, 10.64 mmol), $MeB(OH)_2$ (0.84 g, 13.84 mmol, 1.3 eq.), $Pd(OAc)_2$ (0.12 g, 0.54 mmol, 5% mol), RuPhos (0.26 g, 0.54 mmol, 5% mol) and K_2CO_3 (4.42 g, 31.9 mmol, 3 eq.) were mixed in toluene/water (8:2 mL, (5V)) at 87°C for 3 h after which HPLC showed complete consumption of **1a** and full conversion into **2a**. The reaction was worked-up and product isolated as HCl salt to give 0.8 g (47%) of **2a** with analytical data identical to **2a** obtained by lithiation and by cross-coupling with $MeBF_3K$.

*Preparation of **2b** via SMC using (methyl-d_3)boronic acid*. **1a** (1 g, 5.32 mmol), $CD_3B(OH)_2$ (0.44 g, 6.92 mmol, 1.3 eq.), $Pd(OAc)_2$ (0.06 g, 0.27 mmol, 5% mol), RuPhos (0.25 g, 0.53 mmol, 10% mol) and K_2CO_3 (2.21 g, 15.96 mmol, 3 eq.) were mixed in toluene/water (4:1 mL (5V)) at 87°C for 3 h, after which the mixture filtered, the residue washed with minimum amount of toluene, the organic phase was dried (Na_2SO_4) and IPA/HCl was added

to result precipitation, the mixture was cooled to 0°C, stirred for few min. and then filtered under N_2 to yield 0.62 g (72%) of **2a** (HCl salt) with NMR and MS data identical to **2b** prepared *via* lithiation and by cross-coupling with CD_3BF_3K.

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*6,6'-Dimethoxy-3,3'-bipyridine, (**2d**)*. (6-methoxypyridin-3-yl)boronic acid (0.5 g, 3.27 mmol), $Pd(OAc)_2$ (0.02 g, 0.1 mmol, 3% mol), 1,1'-Ferrocenediyl-bis(diphenylphosphine) (DPPF, 0.17 g, 0.3 mmol, 9% mol), K_2CO_3 (0.9 g, 6.54 mmol) were mixed in a mixture of THF and water (13 mL : 0.12 mL) under N_2 atmosphere at rt and MeI (0.7 g, 0.31 mL, 4.9 mmol, 1.5 eq) was added and the reaction was monitored by TLC (75% EtOAc/Hexane, for monitoring the boronic acid disappearance and 10% EtOAc/Hexane for monitoring **2a** and **2d** accumulation). After 43 h TLC indicated that starting boronic acid is still present and that **2d** is formed with only minor amount of **2a**. Therefore, the mixture was filtered through celite bed which was washed with EtOAc. The organic layer was evaporated and the residue was chromatographed to give **2d** as a white powder (60 mg, 8.5%). ^{1}H-NMR ($DMSOd_6$) δ 8.47 (d, J = 2 Hz, 2H), 8.00 (dd, J = 8.5, 2Hz, 2H), 6.91 (d, J = 8.5Hz, 2H), 3.89 (s, 6H, OMe); ^{13}C-NMR ($DMSOd_6$) δ 162.91, 144.22, 137.18, 126.21, 110.56, 53.15; MS (ESI) *m/z* 217.2 $[M+H]^+$.

***General Procedure I** for SMC Cross-Coupling of 5-Bromo-2-methoxypyridine (**1a**) with alkyl and alkenyl trifluoroborates.* **1a** (1 eq.) was dissolved in toluene (5 volumes) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos, 5% - 10% mol), palladium(II) acetate ($Pd(OAc)_2$, 5% mol), potassium alkyl/alkenyl-trifluoroborate (RBF_3K, 1.3 eq.), and potassium carbonate (K_2CO_3, 3 eq.) were added under N_2 atmosphere followed by addition of water (1 volume) and the heterogeneous reaction mixture was stirred and heated at 87°C and reaction was monitored by HPLC for a few h after which time the mixture was filtered through celite and the filtrate was evaporated to leave a reside which was purified by Combi-Flash chromatography (Hexane/EtOAc) to yield the **5-alkyl/alkenyl-2-methoxypyridine 2e**-**2h**.

*5-Isobutyl-2-methoxypyridine, (**2e**)*. Prepared according to the general procedure I from 1 g of **1a** and ^{i}Bu-BF_3K (1.13 g) to give 0.7 g **2e** (•HCl) (65%) which was basified and underwent chromatography to **2e**. ^{1}H-NMR ($CDCl_3$) δ 7.93 (br s, 1H), 7.35 (dd, J = 8, 2 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 3.92 (s, 3H, OMe), 2.39 (d, J = 7 Hz, 2H), 1.80 (sept, J = 7 Hz, 1H), 0.89 (d, J = 7 Hz, 6H, 2xMe); ^{13}C-NMR ($CDCl_3$) δ 162.66, 146.62, 139.51, 129.36, 110.21, 53.26, 41.41, 30.09, 22.15; HRMS (m/z): $[M+H]^+$ calcd. for $C_{10}H_{15}NO$, 166.1226; found, 166.1228.

*5-Cyclopropyl-2-methoxypyridine, (**2f**)*. According to general procedure I from **1a** (1 g) and cyclopropyl-BF_3K (1 g), to give **2f** (•HCl) (0.59 g, 60%). ^{1}H-NMR ($CDCl_3$) δ 8.11 (br s, 1H), 7.93 (d, J = 8 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 4.30 (s, 3H, OMe), 1.95 (m, 1H), 1.13 (d, J = 7.5 Hz, 2H), 0.77 (d, J = 4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 158.49, 145.11, 135.93, 135.01, 112.12, 58.93, 12.10, 9.01; HRMS (m/z): $[M+H]^+$ calcd. for $C_9H_{11}NO$, 150.0913; found, 150.0917

*2-Methoxy-5-vinylpyridine, (**2g**)*. According to general procedure I from **1a** (1 g) and vinyl-BF_3K (0.93 g), HPLC showed quantitative conversion into **2g** which was isolated as **2g** (•HCl) (0.35 g, 38%). ^{1}H-NMR ($DMSOd_6$) δ 8.22 (d, J = 2.5 Hz, 1H), 7.98 (dd, J = 9, 2.5 Hz, 1H), 6.87 (dt, J = 9, 0.5 Hz, 1H), 6.71 (ddd, J = 17, 11, 0.5 Hz, 1H), 5.81 (dd, J = 17, 1 Hz, 1H), 5.25 (d, J = 10.5 Hz, 1H), 3.88 (s, 3H, OMe); ^{13}C-NMR ($DMSOd_6$) δ 162.89, 144.78, 136.20, 132.61, 126.65, 113.90, 110.58, 53.47; MS *m/z* 135.2 $[M+H]^+$.

*(E)-2-Methoxy-5-(prop-1-en-1-yl)pyridine, (**2h**)*. According to general procedure I from **1a** (1 g) and trans-1-propenyl-BF_3K (0.5 g), HPLC indicated on 95.5% conversion after 3 h **2h** (•HCl) was isolated (0.21 g, 44%). ^{1}H-NMR ($DMSOd_6$) δ 8.13 (d, J = 2.5 Hz, 1H), 7.88 (dd, J = 8.5, 2.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H); 6.38 (d, J = 15 Hz, 1H), 6.26 (dq, J = 15, 6.5 Hz, 1H), 3.87 (s, 3H, OMe), 1.83 (dd, J = 6.5, 1.5 Hz, 3H, Me); ^{13}C-NMR ($DMSOd_6$) δ 162.07, 143.44, 136.40, 126.97, 126.50, 125.44, 110.48, 53.56, 18.19; HRMS (m/z): $[M+H]^+$ calcd. for $C_9H_{11}NO$, 150.0913; found, 150.0905.

*5-Iodo-1-phenylpyridin-2(1H)-one, (**4b**)*. 5-Iodo-2-methoxypyridine (**1c**, 3 g, 0.013 mol) was dissolved in HCl (6N, 30 mL) and the solution was refluxed for 8 h after which time it was cooled to 0-5°C and 50% NaOH (~ 7 mL) was added until pH ≈ 3-4. 1N NaOH was added to correct the pH to 6-7 and cooled to 0-5°C and stirred for ½ h and filtered. Then the water phase extracted with EtOAc (40 mL x 2) and the organic phase dried (Na_2SO_4), filtered and evaporated and the residue was dried at 50°C under vacuum to furnish crude **5-iodopyridin-2(1H)-one 3d** (2.65 g, 92%) which was used in the next Chan-Lam phenylation without further purification. **3d** (2.65 g, 0.012 mol), phenyl boronic acid (3.7 g, 0.03 mol , 2.5 eq.), $Cu(OAc)_2$•H_2O (2.4 g, 0.012 mol 1 eq.), pyridine (3.8 g,

0.048 mol 4 eq.) and molecular sieves (4Å, 4.3 g) were stirred in DCM (85 mL) with constant bubbling of air through the mixture, at rt for 24 h, after which time TLC indicated complete disappearance of **3d**. Then the mixture was filtered and washed with 1N HCl, followed by wash with water, 1N NaOH and brine. Organic phase was separated, washed with water dried (Na_2SO_4), filtered and solvent evaporated to leave an oily residue (3.1 g) which was crystallized twice from DIPE and dried in vacuum oven to give **4b** (1.85 g, 51%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ 7.56 (d, J = 3 Hz, 1H), 7.50-7.40 (m, 4H), 7.34 (d, J = 8 Hz, 2H), 6.47 (d, J = 10 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 160.75, 147.17, 142.64, 140.00, 129.46, 128.86, 126.36, 123.57, 64.39; HRMS (m/z): $[M+H]^+$ calcd. for C_9H_8NOI, 297.9723; found, 297.9725.

*5-Chloro-1-phenylpyridin-2(1H)-one, (**4c**)*. 5-Chloropyridin-2(1H)-one (**3e**, 9 g, 0.07 mol), phenyl boronic acid (21.3 g, 0.175 mol , 2.5 eq.), $Cu(OAc)_2 \bullet H_2O$ (13.9 g, 0.07 mol 1 eq.) and pyridine (22 g, 0.28 mol 4 eq.) were stirred in DCM (500 mL) with constant bubbling of air through the mixture, at rt for 24 h, after which time TLC indicated complete consumption of **3e**. Then the mixture was filtered and washed with 1N HCl (300 mL), water (300 mL), 1N NaOH (300 mL) and with water again followed by wash with brine. The organic phase was separated, dried (Na_2SO_4) and activated charcoal (5 g) was added and the mixture was stirred for ½ h then filtered (Na_2SO_4 and activated C) solvent evaporated to leave an oil which upon further drying under vacuum (2 bar) solidified (14.5 g). This solid was dissolve in DIPE (87 mL) at reflux and then the green solution was slowly cooled to 17°C resulting in precipitation of a solid which was filtered, washed with cold ether and dried under vacuum to furnish **4c** (10.8 g, 75%) as an off-white solid. ^{1}H-NMR ($CDCl_3$) δ 7.53-7.50 (m, 1H), 7.49-7.48 (m, 1H), 7.46-7.42 (m, 1H), 7.40 (dd, J = 2.75, 0.5 Hz, 1H), 7.38 (m, 1H), 7.36 (m, 1H), 7.35 (dd, J = 9, 2.75 Hz, 1H), 6.63 (d, J = 9 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 160.74, 140.81, 140.18, 135.42, 129.48, 128.86, 126.36, 122.65, 112.44; MS *m/z* 206.0 $[M+H]^+$.

***General Procedure II** for SMC Cross-Coupling of 5-bromo-1-phenylpyridin-2(1H)-one (**4a**) with alkyl and alkenyl trifluoroborates.* **4a** (1 eq.) was dissolved in toluene (5 volumes) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos, 5% - 10% mol), palladium(II) acetate ($Pd(OAc)_2$, 5% mol), potassium alkyl/alkenyl-trifluoroborate (RBF3K, 1.3 eq.), and potassium carbonate (K_2CO_3, 3 eq.) were added under N_2 atmosphere followed by addition of water (1 volume) and the heterogeneous reaction mixture was stirred and heated at 87°C and reaction was monitored by HPLC for a few h after which time the mixture was filtered through celite and the filtrate was evaporated to leave a reside which was purified by Combi-Flash chromatography (Hexane/EtOAc) to yield the 5-alkyl/alkenyl-1-phenylpyridin-2(1H)-ones (5-substituted pirfenidone analogs) **4f-4i**.

*5-Isobutyl-1-phenylpyridin-2(1H)-one, (**4f**)*. As in the general procedure II: 5-bromo-1-phenylpyridin-2(1H)-one (**4a**, 1 g, 4 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos, 10% mol, 0.2 g), palladium(II) acetate ($Pd(OAc)_2$, 5% mol, 0.045 g), potassium *iso*-butyl-trifluoroborate (^{i}Bu-BF_3K, 1.3 eq., 0.85 g, 5.2 mmol) and potassium carbonate (K_2CO_3, 3 eq., 1.7 g) in a mixture of toluene/water (5:1.2 mL, respectively. Total of 6.2V) heated at 87°C for 24 h under N_2 atmosphere, work-up and flash chromatography gave **4f** (0.6 g, 66%) as a transparent oil. ^{1}H-NMR ($CDCl_3$) δ 7.49-7.47 (m, 2H), 7.41-7.37 (m, 3H), 7.26 (dd, J = 9, 2.5 Hz, 1H), 7.07 (d, J = 2.5 Hz, 1H), 6.61 (d, J = 9 Hz, 1H) 2.22 (d, J = 7 Hz, 2H), 1.77 (m, 1H), 0.92 (d, J = 7 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 161.87, 142.17, 141.17, 135.79, 129.29, 128.32, 126.59, 121.35, 118.67, 40.87, 29.24, 22.06; HRMS (m/z): $[M+H]^+$ calcd. for $C_{15}H_{17}NO$, 228.1383; found, 228.1395.

*5-Cyclopropyl-1-phenylpyridin-2(1H)-one, (**4g**)*. As described in the general procedure II: 5-bromo-1-phenylpyridin-2(1H)-one (**4a**, 2 g, 6.73 mmol), 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos, 10% mol, 0.31 g), palladium(II) acetate ($Pd(OAc)_2$, 5% mol, 0.076 g), potassium cyclopropyltrifluoroborate (cyclopropyl-BF_3K, 1.3 eq., 1.3 g, 8.75 mmol) and potassium carbonate (K_2CO_3, 3 eq., 2.79 g) in a mixture of toluene/water (8:2 mL, respectively. 5V) heated at 87°C for 6.5 h under N_2 atmosphere, work-up and flash chromatography furnish **4g** (1.39 g, 98%) as an off-white solid. ^{1}H-NMR ($DMSOd_6$) δ 7.52-7.48 (m, 2H), 7.45-7.37 (m, 4H), 7.24 (dd, J = 9.5, 2.5 Hz, 1H), 6.42 (d, J = 9.5 Hz, 1H), 1.76 (m, 1H), 0.77 (m, 2H), 0.59 (m, 2H); ^{13}C-NMR ($DMSOd_6$) δ 160.37, 140.94, 139.30, 134.68, 128.86, 127.86, 126.70, 120. 38, 119.89, 11.27, 6.53; HRMS (m/z): $[M+H]^+$ calcd. for $C_{14}H_{13}NO$, 212.1070; found, 212.1075.

*1-Phenyl-5-vinylpyridin-2(1H)-one, (**4h**)*. As in the general procedure: 5-bromo-1-phenylpyridin-2(1H)-one (**4a**, 2 g, 6.73 mmol), 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos, 10% mol, 0.31 g), palladium(II) acetate ($Pd(OAc)_2$, 5% mol, 0.076 g), potassium vinyltrifluoroborate (Vinyl-BF_3K, 1.3 eq., 1.2 g, 8.75 mmol) and potassium carbonate (K_2CO_3, 3 eq., 2.79 g) in a mixture of toluene/water (8: 2 mL, respectively, 5V) heated at 87°C for 3.5 h

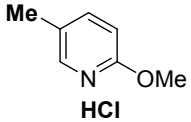
under N_2 atmosphere, work-up and flash chromatography gave **4h** (1.29 g, 98%) as a yellowish solid. ^{1}H-NMR ($DMSOd_6$) δ 7.86 (dd, J = 9.5, 2.5 Hz, 1H), 7.73 (d, J = 2.5 Hz, 1H), 7.54-7.50 (m, 2H), 7.47-7.41 (m, 3H), 6.54 (dd, J = 16.5, 10.5 Hz, 1H), 6.52 (d, J = 9 Hz, 1H), 5.62 (d, J = 16.5 Hz, 1H), 5.11 (d, J = 10.5 Hz, 1H); ^{13}C-NMR ($DMSOd_6$) δ 160.60, 140.54, 137.53, 136.80, 131.65, 128.95, 128.11, 126.70, 120.64, 116.22, 111.41; HRMS (m/z): $[M+H]^+$ calcd. for $C_{13}H_{11}NO$, 198.0913; found, 198.0922.

*(E)-1-Phenyl-5-(prop-1-en-1-yl)pyridin-2(1H)-one, (**4i**)*. As in the general procedure: 5-bromo-1-phenylpyridin-2(1H)-one (**4a**, 1.25 g, 5 mmol), 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos, 10% mol, 0.23 g), palladium(II) acetate ($Pd(OAc)_2$, 5% mol, 0.056 g), potassium *trans*-1-propenyltrifluoroborate (*trans*-1-propenyl-BF_3K, 1.3 eq., 0.96 g, 6.5 mmol) and potassium carbonate (K_2CO_3, 3 eq., 2 g) in a mixture of toluene/water (5: 1.25 mL, respectively, 5V) heated at 87°C for 1 h under N_2 atmosphere, work-up and flash chromatography gave **4i** (0.9 g, 85%) as a yellowish solid. ^{1}H-NMR ($CDCl_3$) δ 7.58 (dd, J = 8.5, 2.5 Hz, 1H), 7.5 (m, 2H), 7.45-7.35 (m, 3H), 7.2 (d, J = 2.5 Hz, 1H), 6.65 (d, J = 9.5 Hz, 1H), 6.13 (dq, J = 16, 0.5 Hz, 1H), 5.97 (dq, J = 16, 6.5 Hz, 1H), 1.86 (dd, J = 6.5, 1.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 161.87, 141.03, 137.36, 134.83, 129.43, 128.55, 126.65, 125.47, 124.27, 121.89, 117.60, 18.41; HRMS (m/z): $[M+H]^+$ calcd. for $C_{14}H_{13}NO$, 212.1070; found, 212.1072.

*1-Phenylpyridin-2(1H)-one, (**5**)*. **4a** (2 g, 8 mmol), methylboronic acid (1.92 g, 32 mmol, 4 eq.), Na_2CO_3 (2.5 g, 24 mmol, 3 eq.) and $Pd(PPh_3)_4$ (0.92 g, 0.79 mmol, 10%mol) were mixed in DME/water (160 mL/32 mL, 96 V) under argon atmosphere in reflux for 24 h after which time the mixture was filtered through a celite pad and evaporated to dryness to leave a residue which was partitioned between EtOAc (100 mL) and water (30 mL). Then the organic phase separated, dried (Na_2SO_4), filtered and evaporated to leave a residue which was a mixture of **4d** (48%), **5** (6.32%), **6** (15%) and **10** (5%) and triphenylphosphine oxide and which was separated by chromatography to give: **5** ^{1}H-NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.41 (m, 1H), 7.38 (m, 1H), 7.36 (m, 2H), 7.32 (ddd, J = 7, 2, 1 Hz, 1H), 6.65 (dq, J = 9, 1 Hz, 1H), 6.23 (td, J = 6.75, 1.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 162.39, 140.97, 139.85, 138.00, 129.33, 128.47, 126. 53, 121.90, 105.87; HRMS (m/z): [M+H]+ calcd. for $C_{11}H_9NO$, 172.0757; found, 172.0759. **5** was synthesized also *via* Chan-Lam reaction between **pyridin-2-ol** (4.75 g, 0.05 mol) and phenyl boronic acid (15.1 g, 0.125 mol) in the presence of $Cu(OAc)_2 \bullet H_2O$ (9.9 g, 0.05 mol) in DCM (350 mL), pyridine (15. 8 g, 0.2 mol) and molecular sieves (4Å, 23 g) as described for **4a**-**4c**. After work-up and crystallization (10. 6 g of crude product in a mixture of 170 mL DIPE and 50 mL EtOAc in reflux followed by cooling to 0-5°C) a solid was filtered and dried to yield 6.5 g (76%) of **5** as a white solid, mp = 127.5-128.2°C, which its ^{1}H and ^{13}C NMR were identical to the spectra of **5** obtained from chromatography of the mixture **4d**, **5, 6** and **10**.

*1,1'-Diphenyl-[3,3'-bipyridine]-6,6'(1H,1'H)-dione, (**6**)*. 0.4 g (14.7%) of this compound was isolated by chromatography of the mixture described for **5** after SMC with $Pd(PPh_3)_4$ in DME/water. ^{1}H-NMR (DMSO d_6) δ 7.97 (d, J = 2.5 Hz, 2H), 7.86 (dd, J = 9.5, 2.5 Hz, 2H), 7.53-7.42 (m, 10H), 6.54 (d, J = 9.5 Hz, 2H); ^{13}C-NMR (DMSO d_6) δ 160.20, 140.66, 139.20, 135.09, 128.84, 128.04, 126.87, 120.42, 114.26; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{16}N_2O_2$, 341.1284; found, 341.1286.

*1,5-Diphenylpyridin-2(1H)-one, **(10)***. This compound was isolated by chromatography of the mixture described for **5** after SMC with $Pd(PPh_3)_4$ in DME/water. ^{1}H-NMR ($CDCl_3$) δ 7.69 (dd, J = 9.5, 2.5 Hz, 1H), 7.55 (dd, J = 2.5, 0.7 Hz, 1H), 7.50 (m, 2H), 7.43-7.40 (m, 7H), 7.32 (m, 1H), 6.74 (dd, J = 9.5, 0.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 161.64, 141.03, 139.75, 136.21, 135.24, 129.40, 129.08, 128.59, 127.42, 126.61, 125.76, 121.83, 120.02; HRMS (m/z): $[M+H]^+$ calcd. for $C_{17}H_{13}NO$, 248.1067; found, 248.1072.



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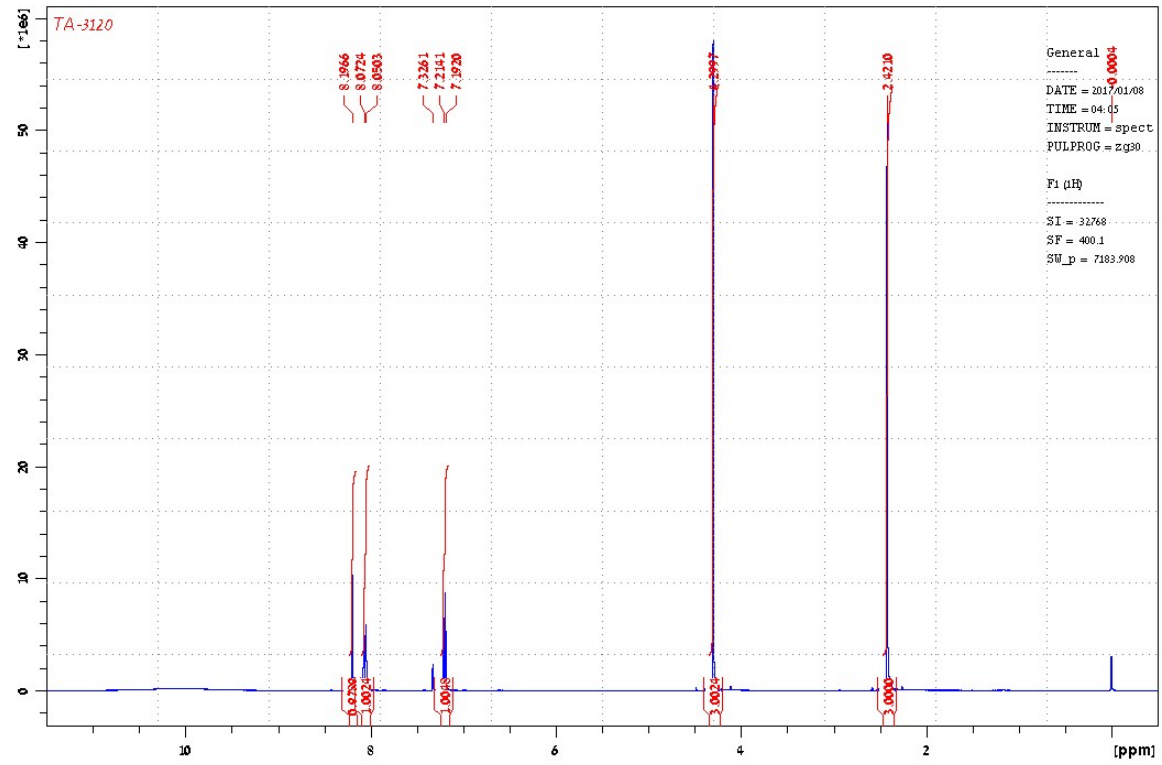
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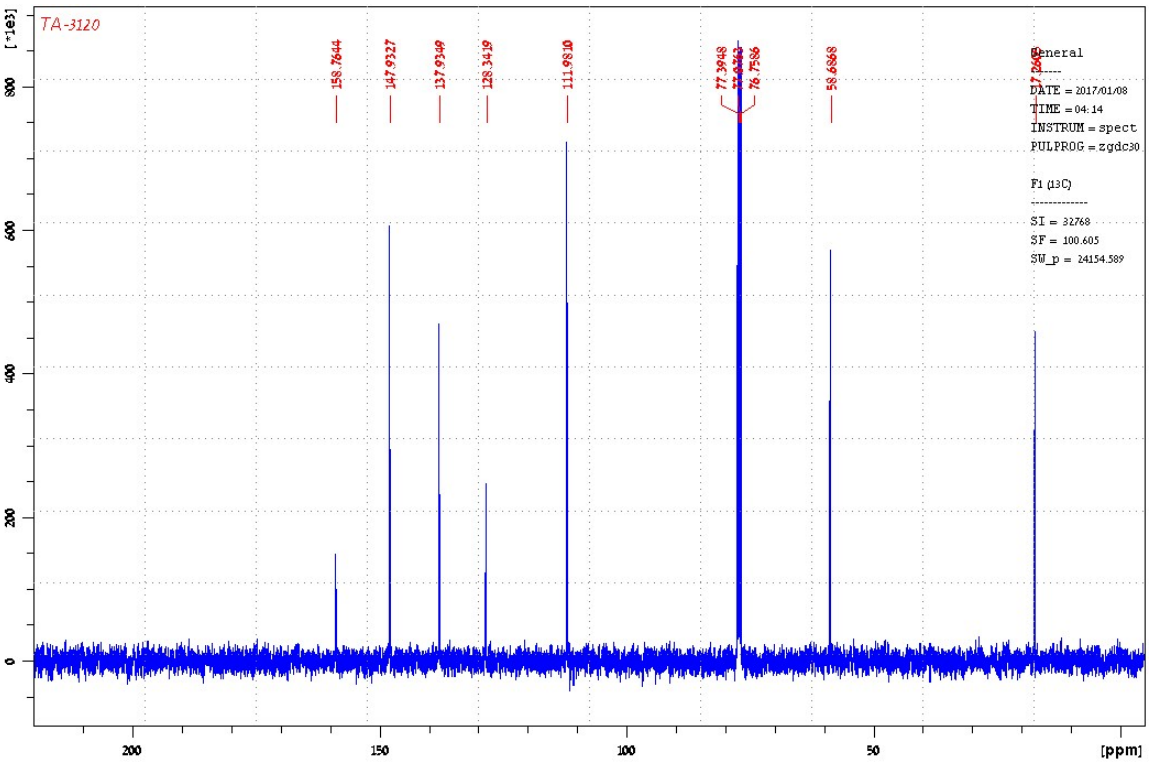
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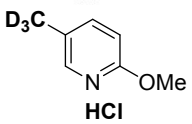
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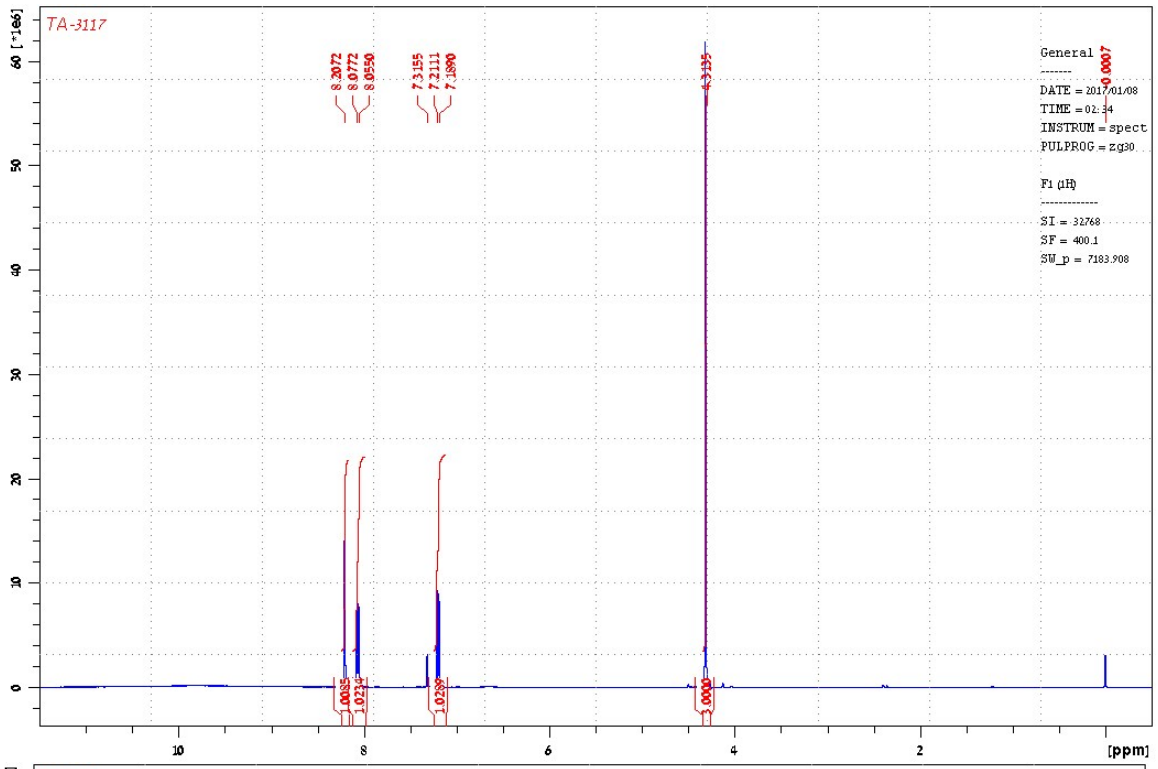
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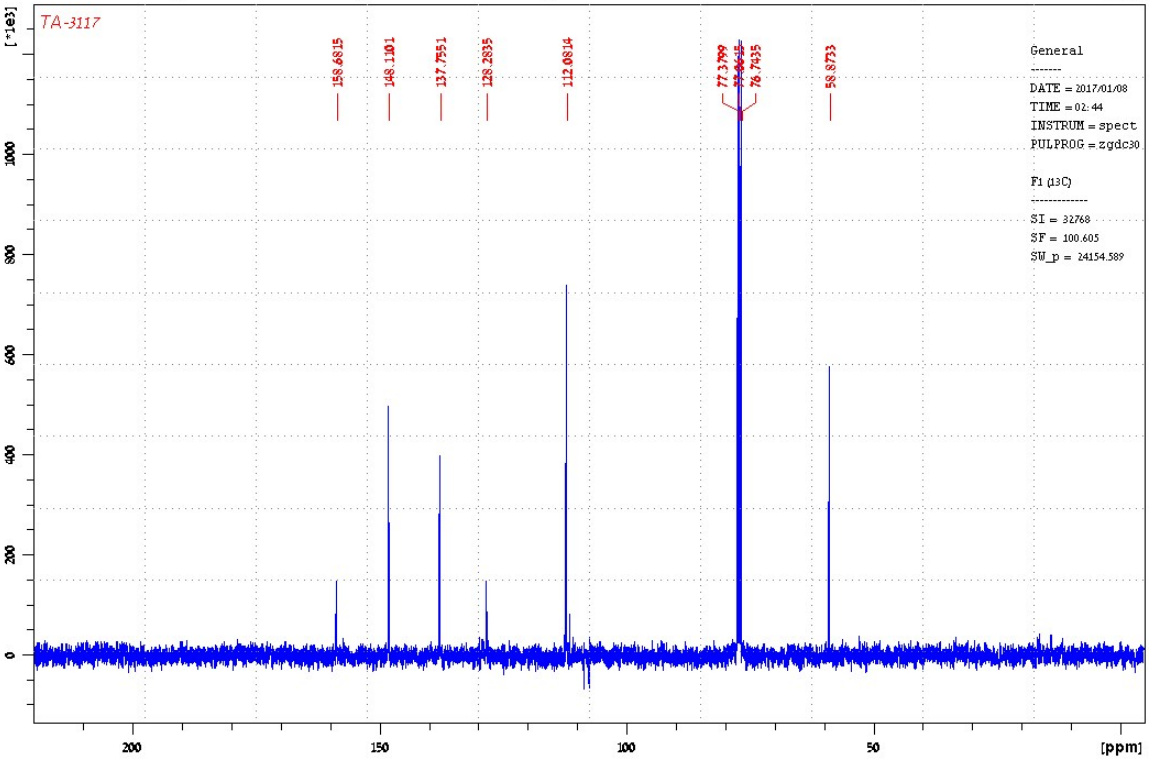
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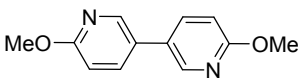
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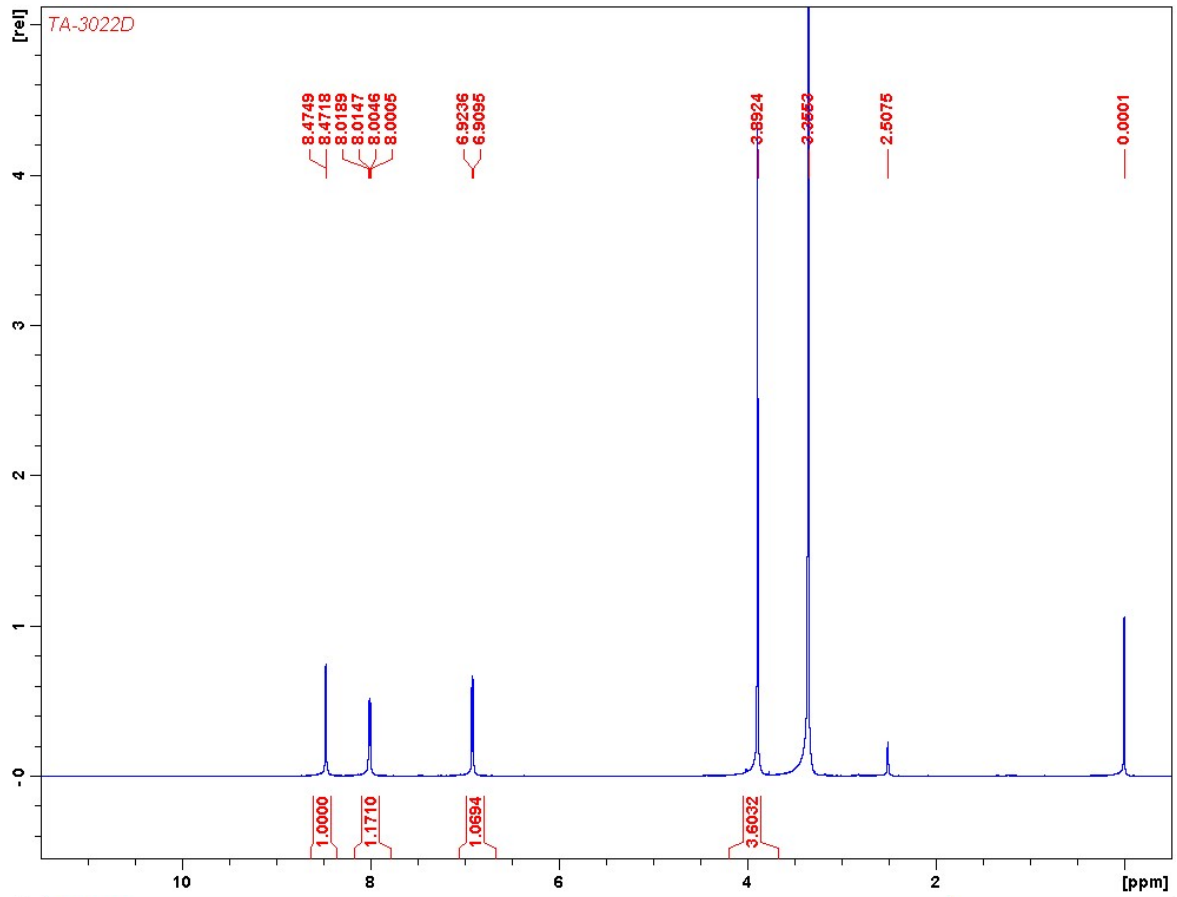
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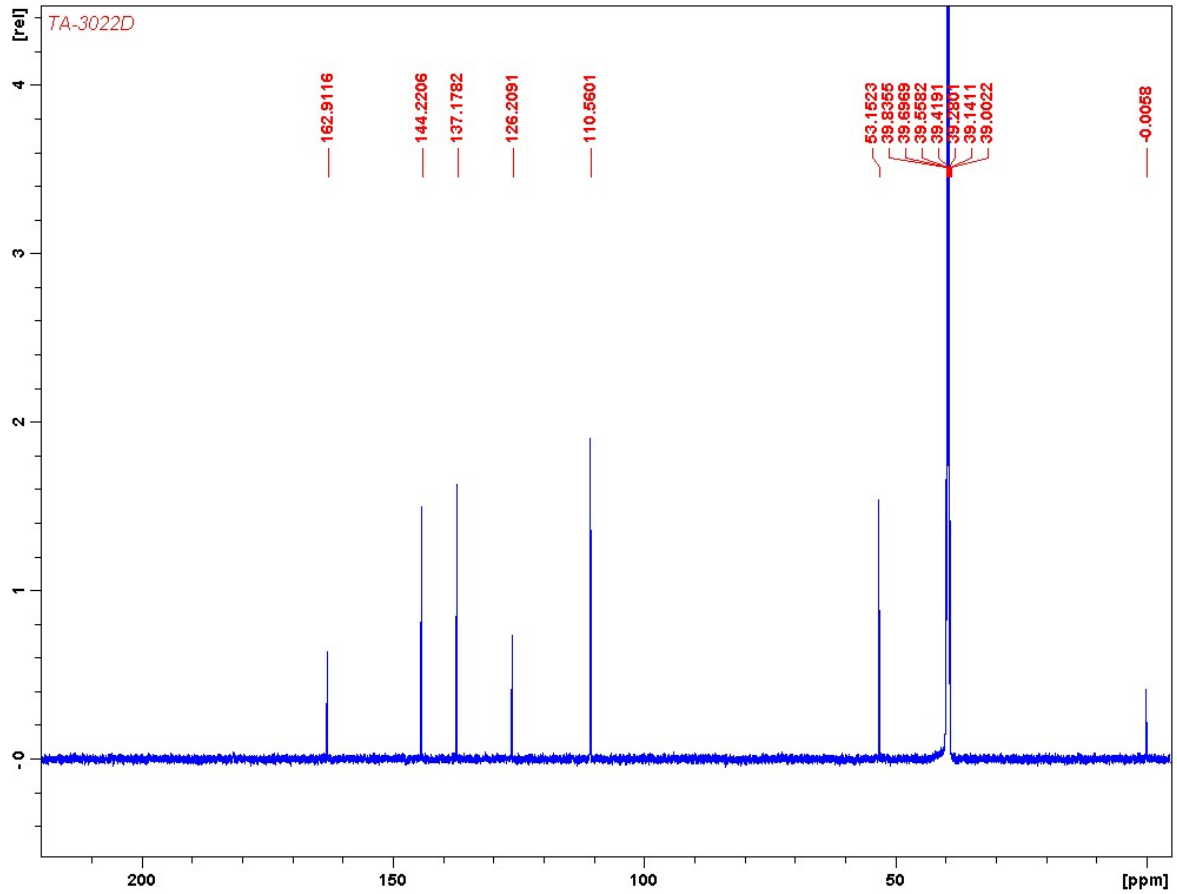
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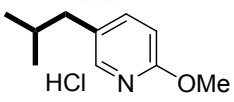
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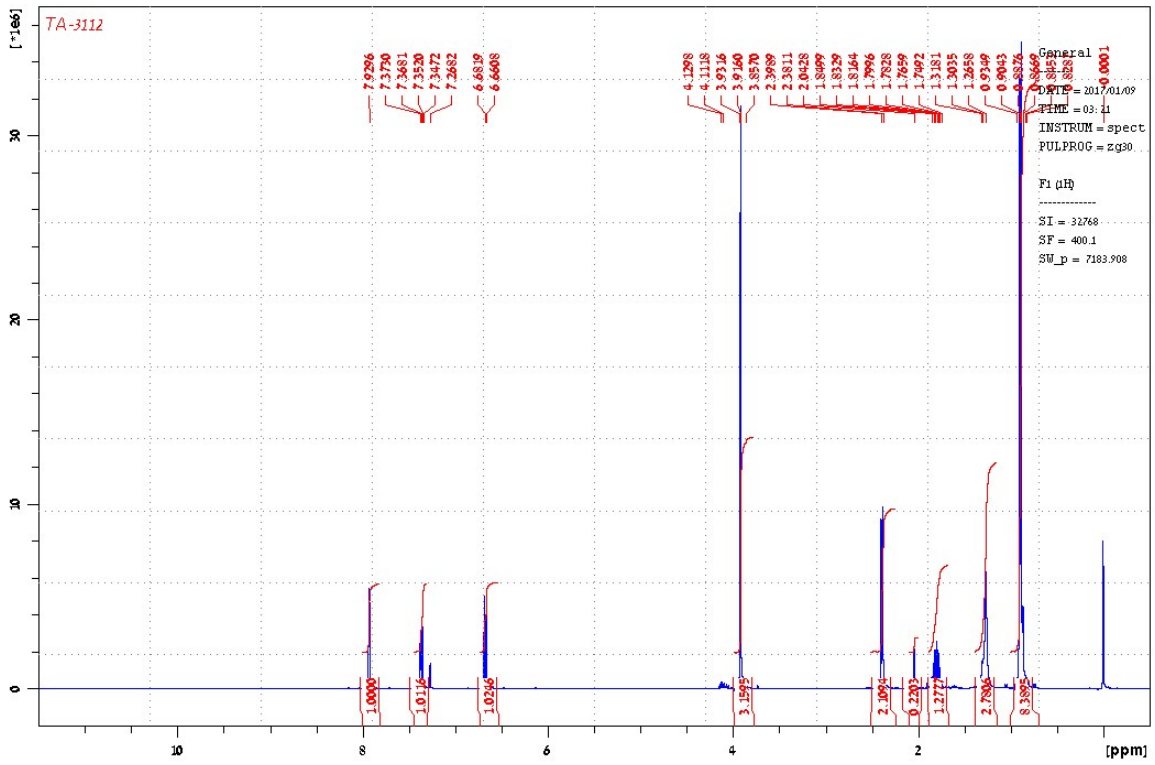
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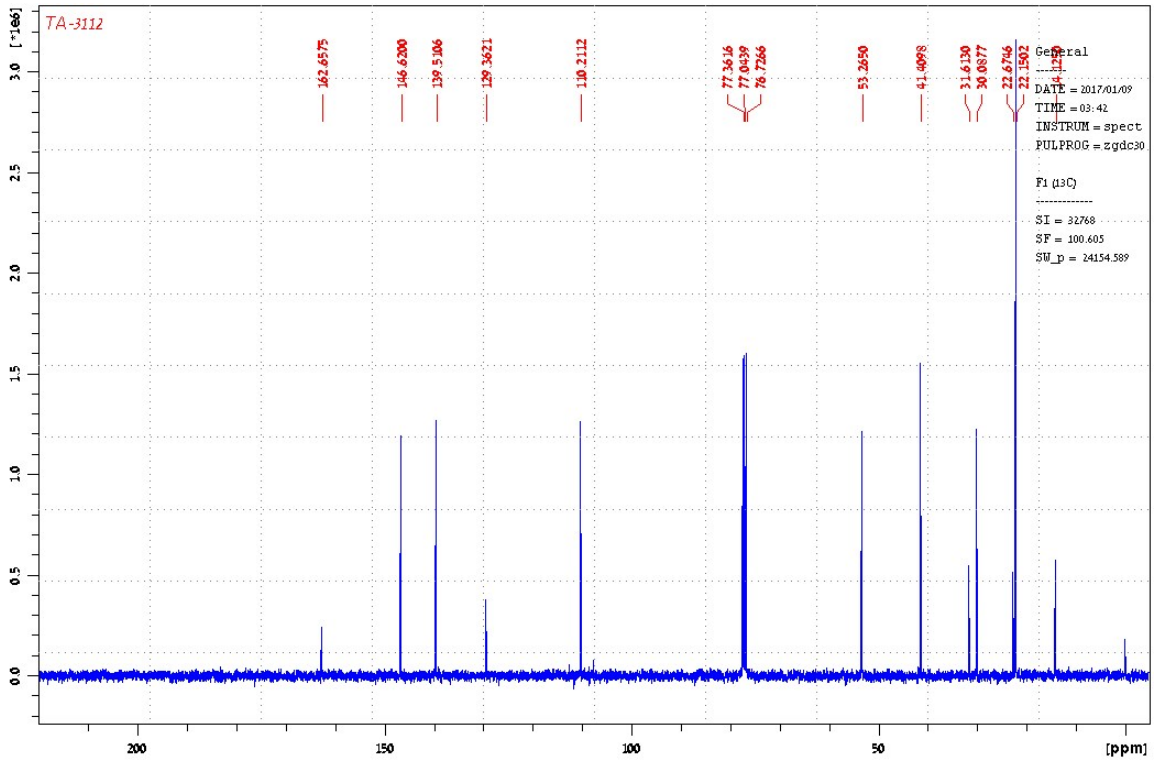
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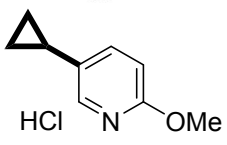
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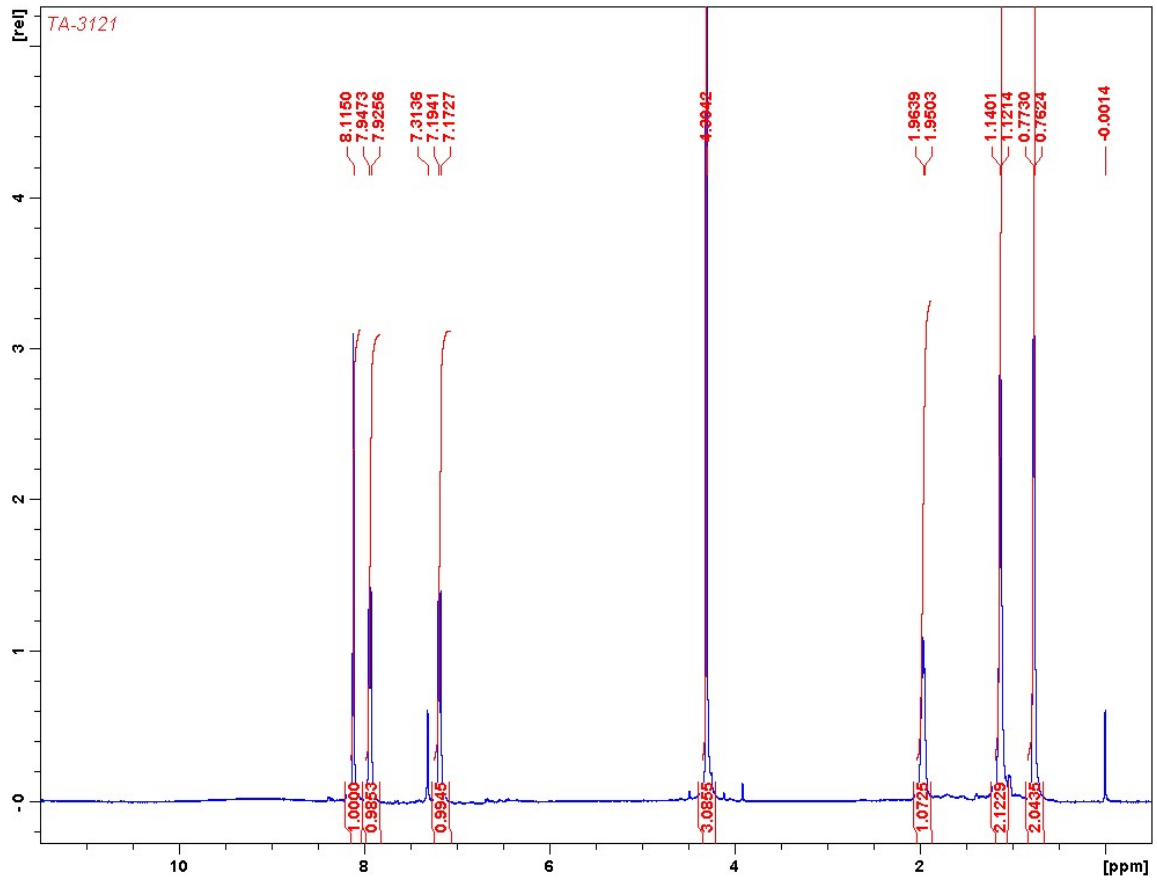
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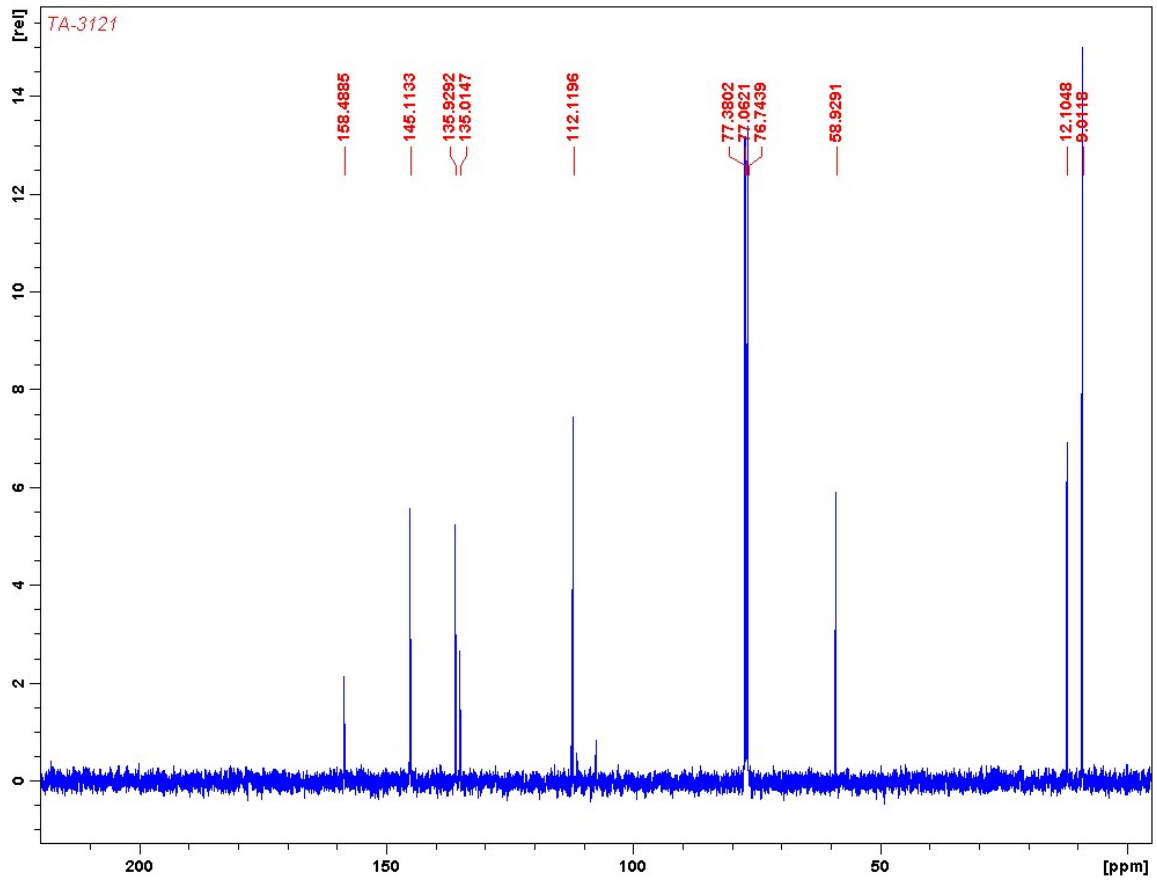
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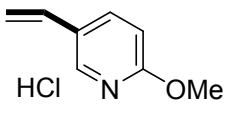
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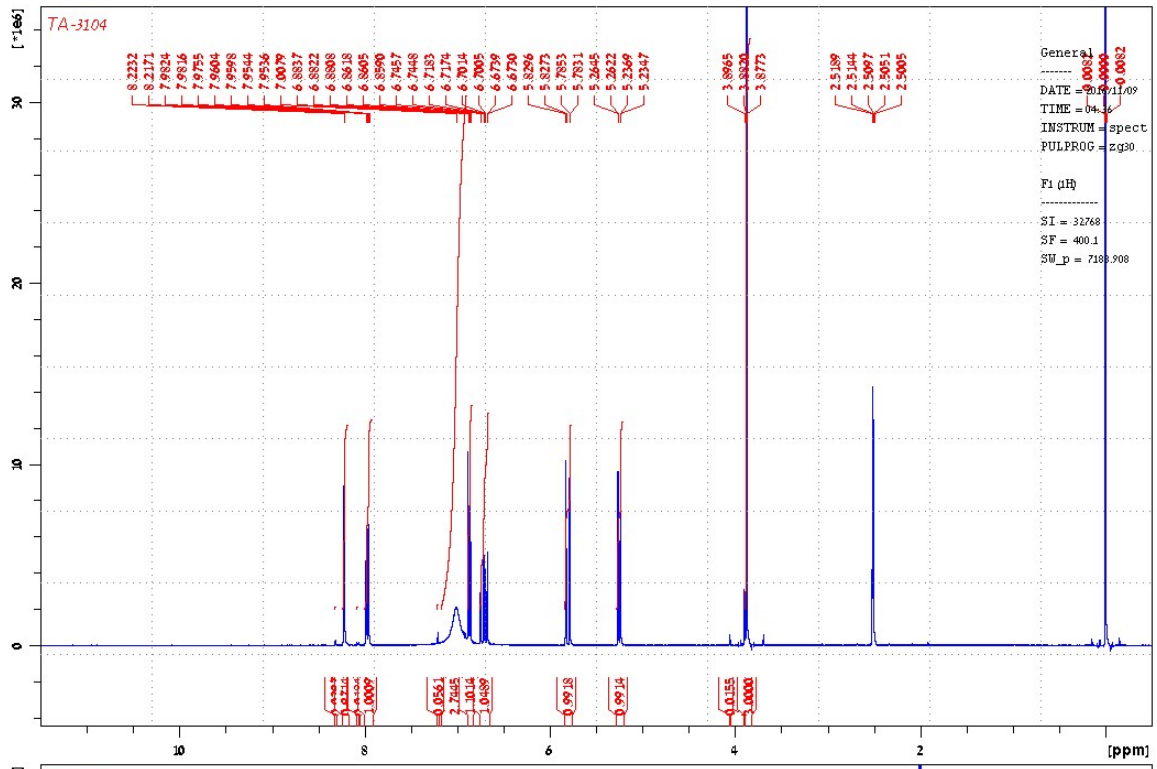
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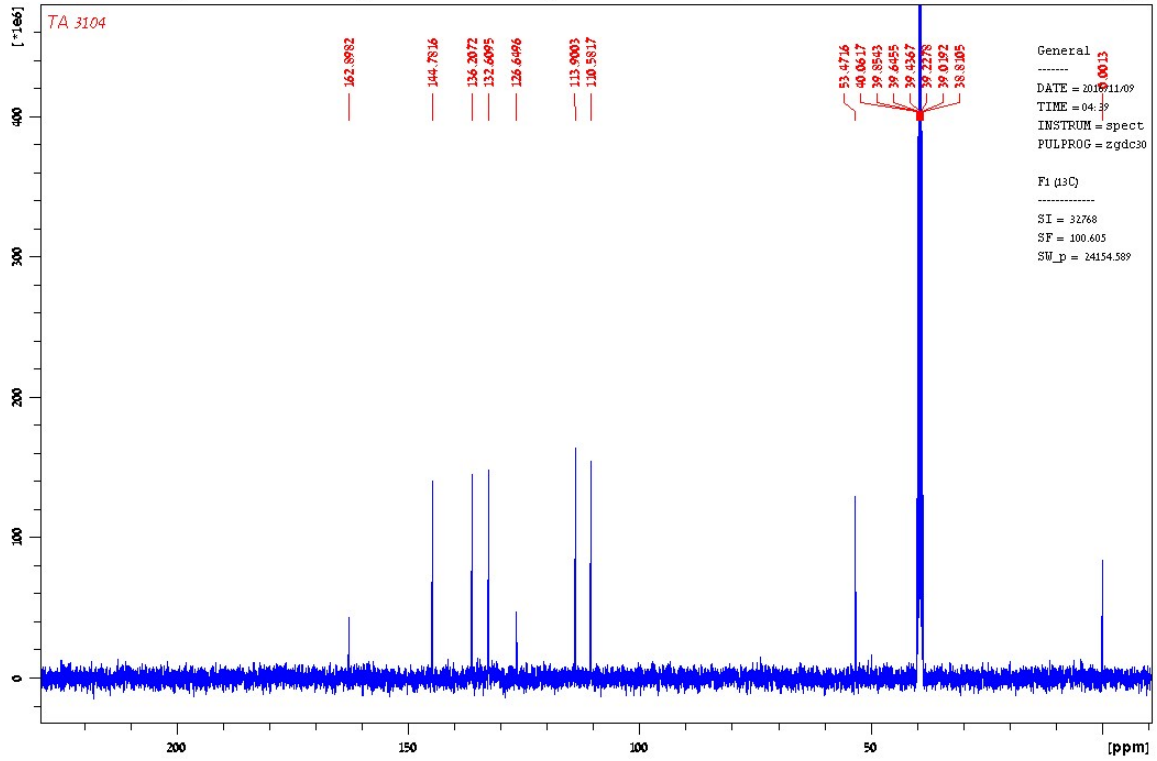
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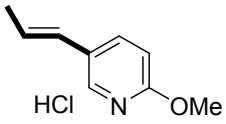
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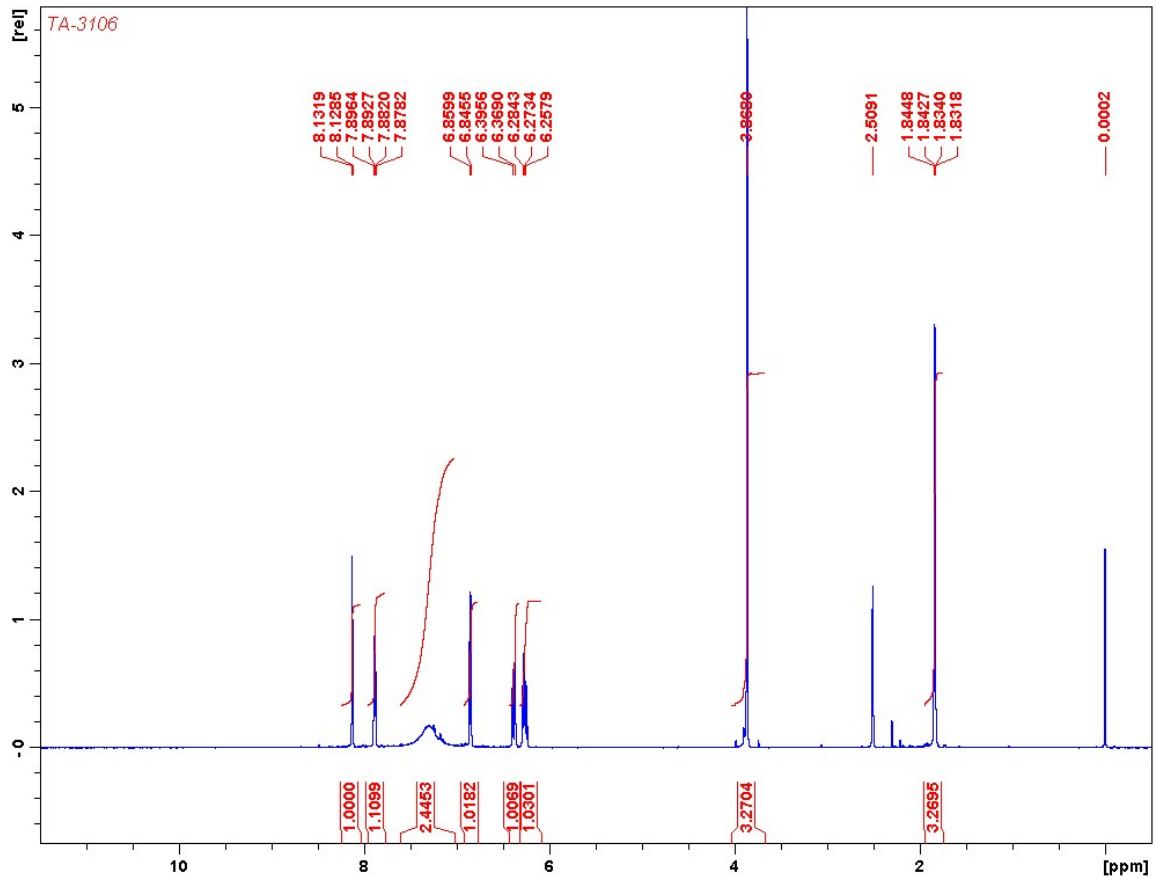
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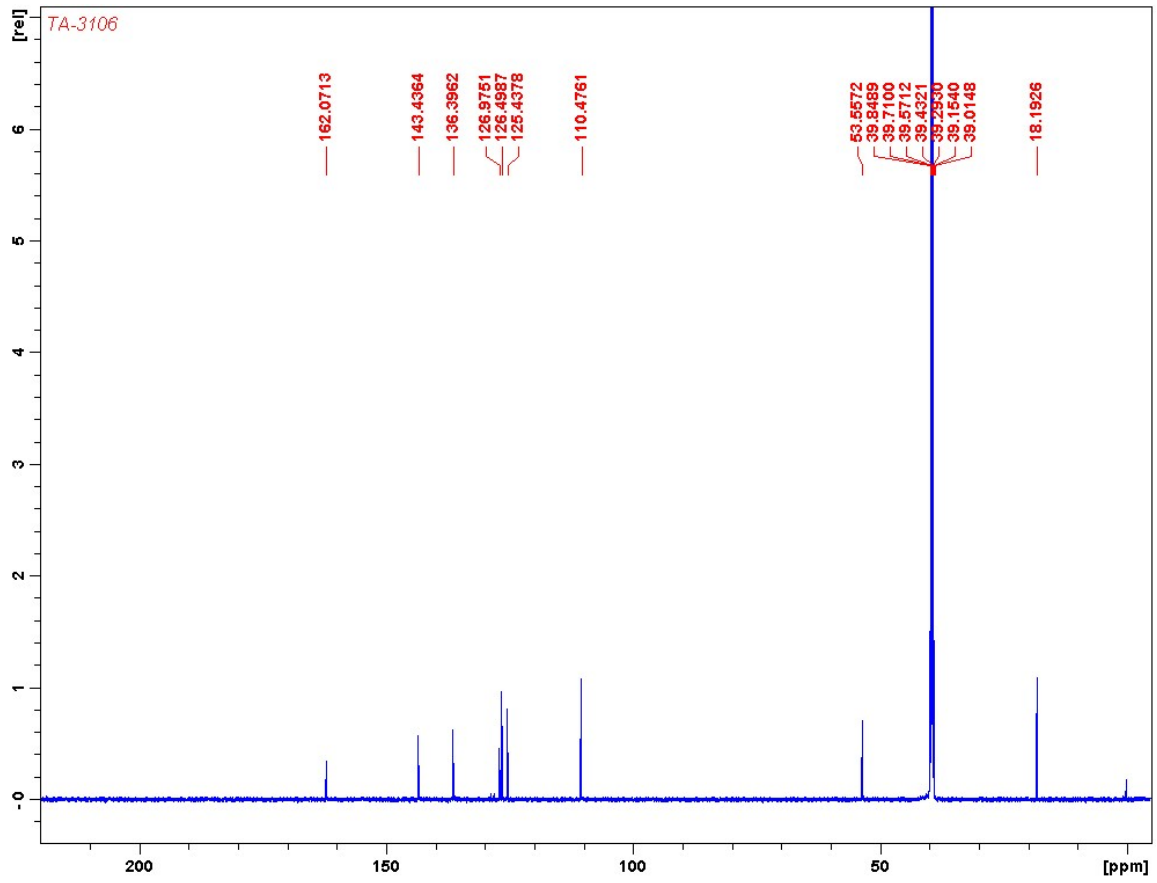
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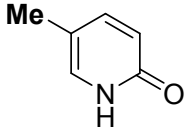
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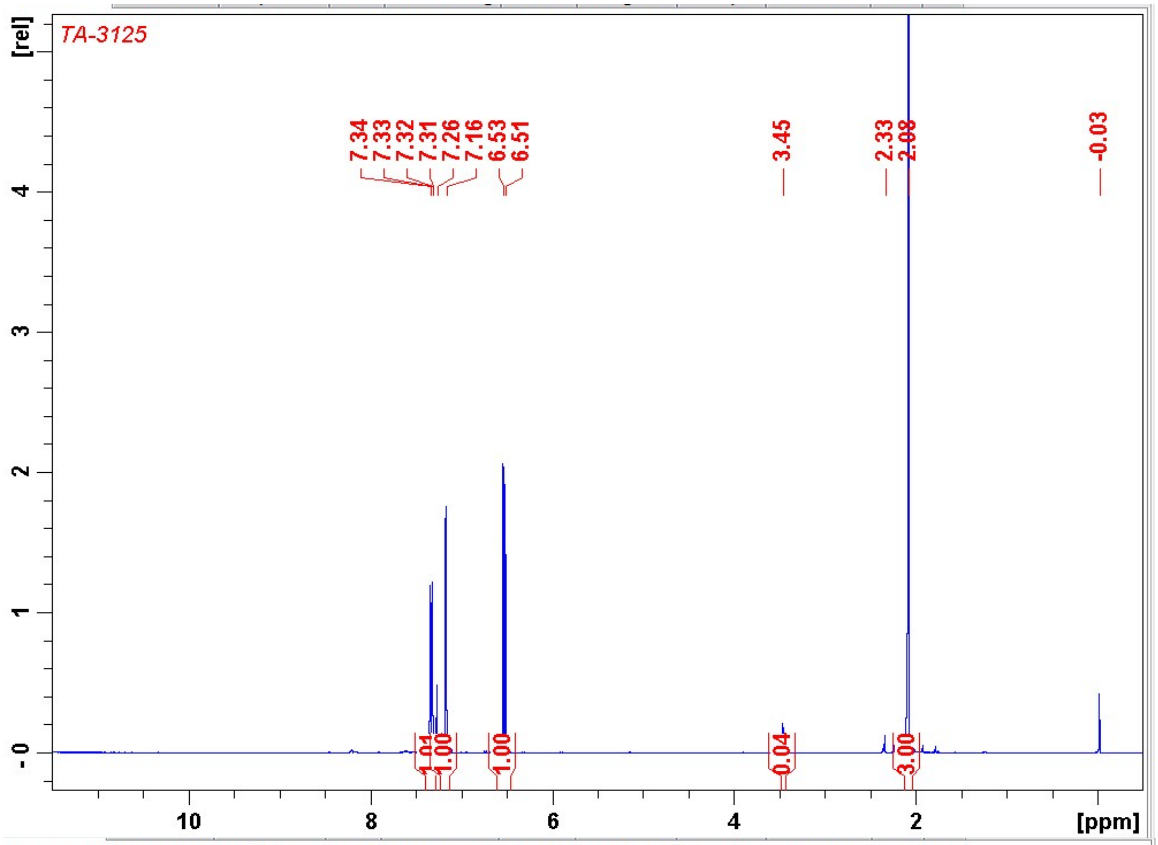
3a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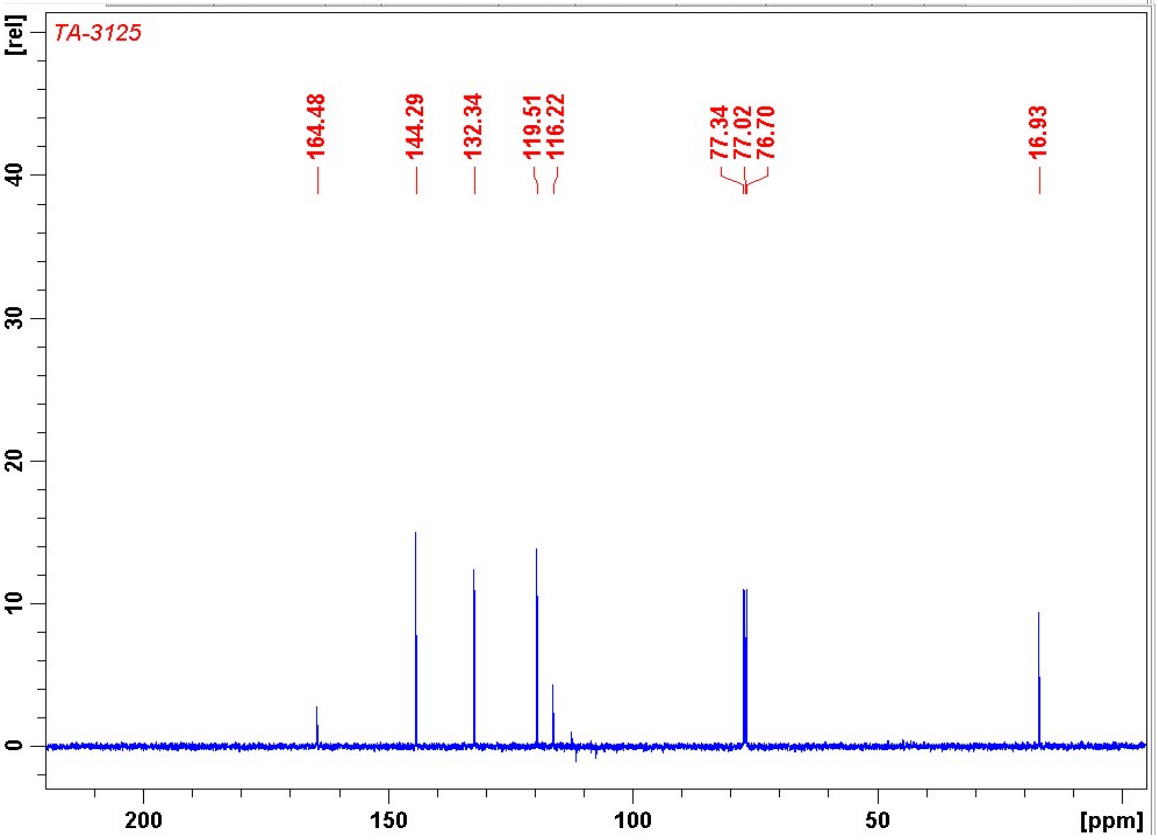
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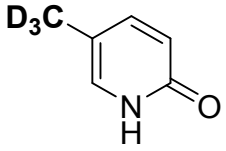
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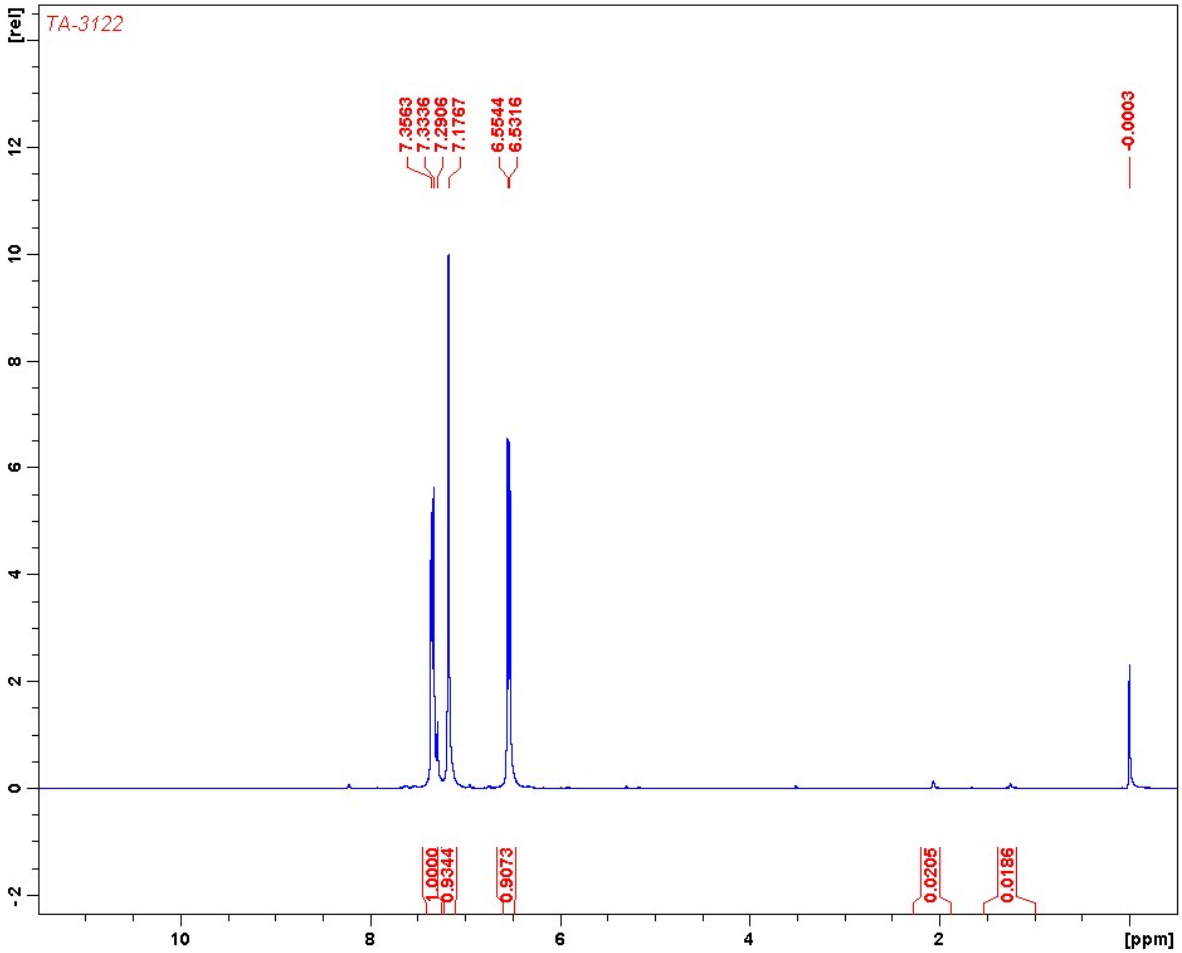
3b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6.5316
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1.0000
0.9344
0.9073
0.0205
0.0186
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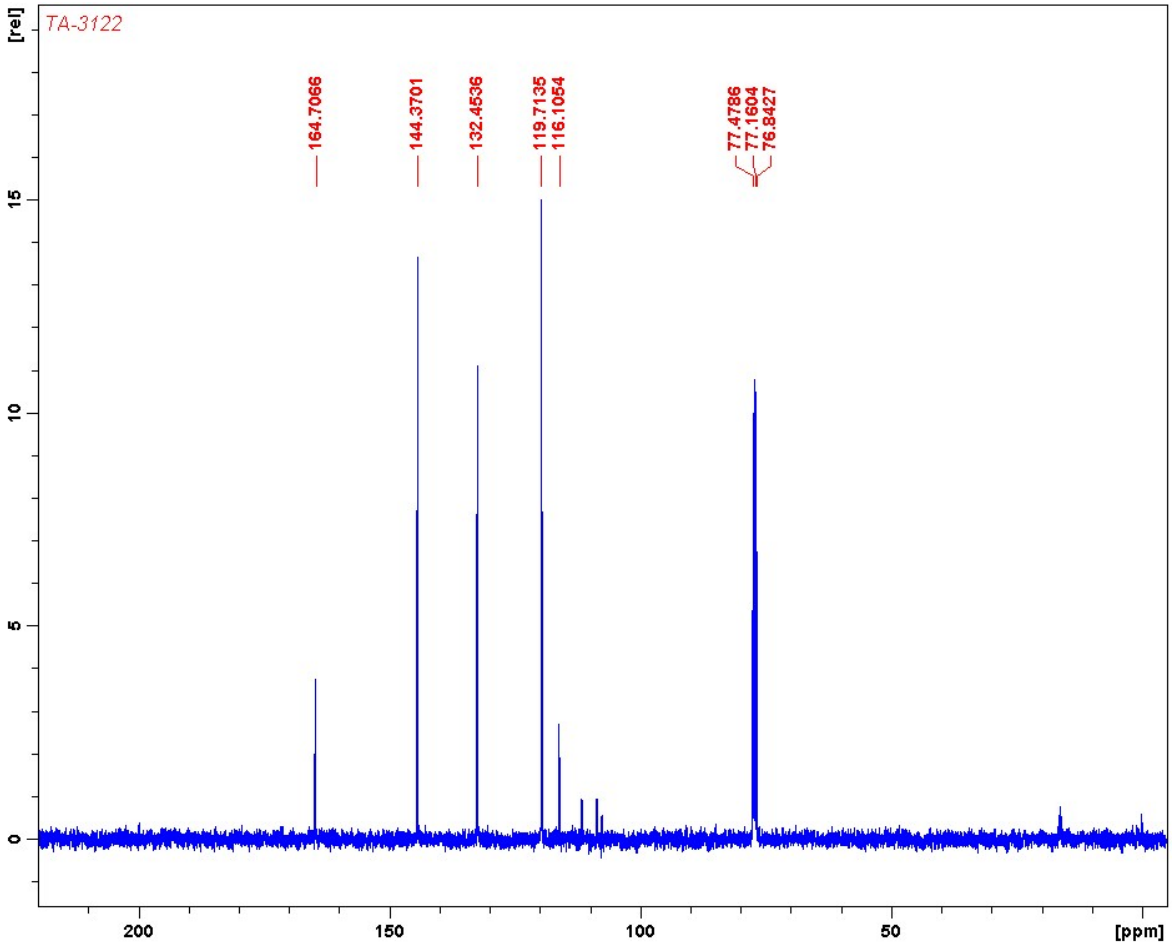
TA-3122
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116.1054
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77.1604
76.8427
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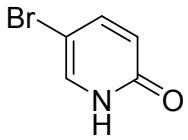
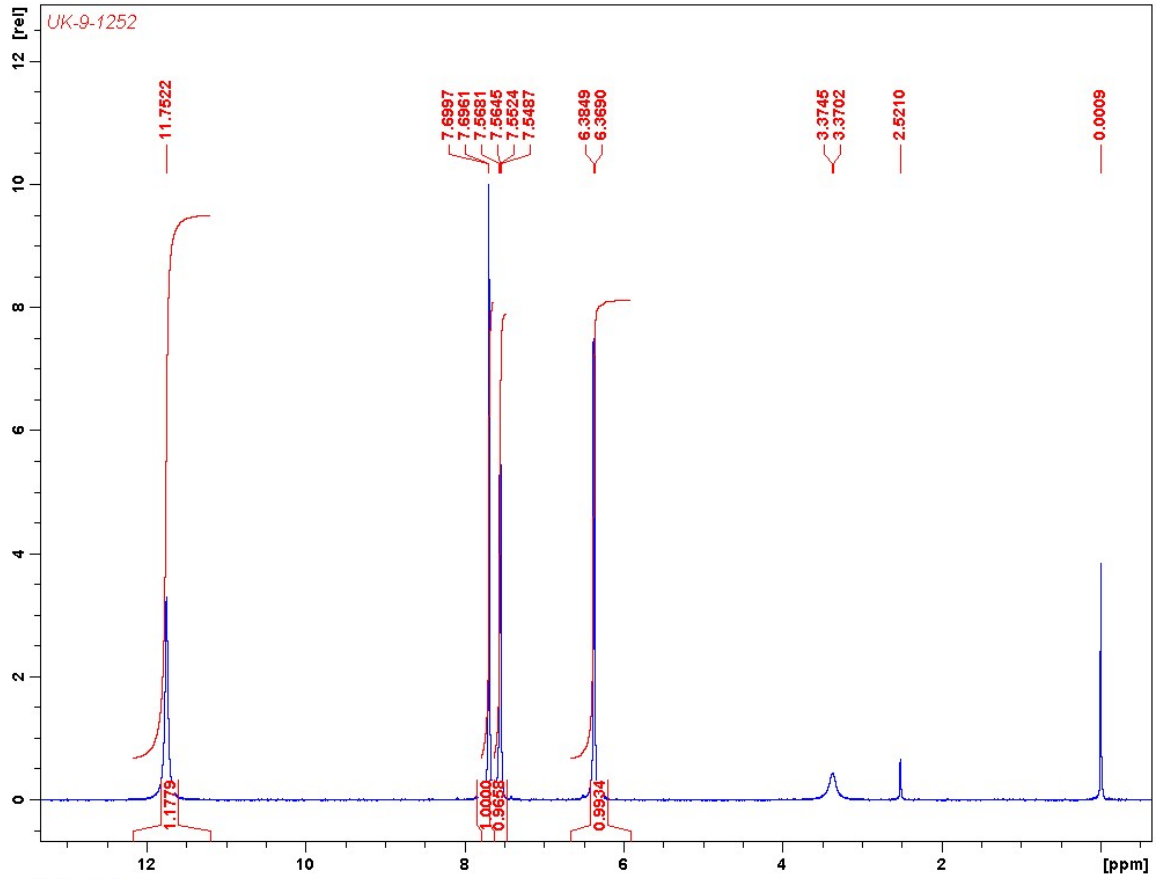

Br
N
H
O

3c


UK-9-1252
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7.6961
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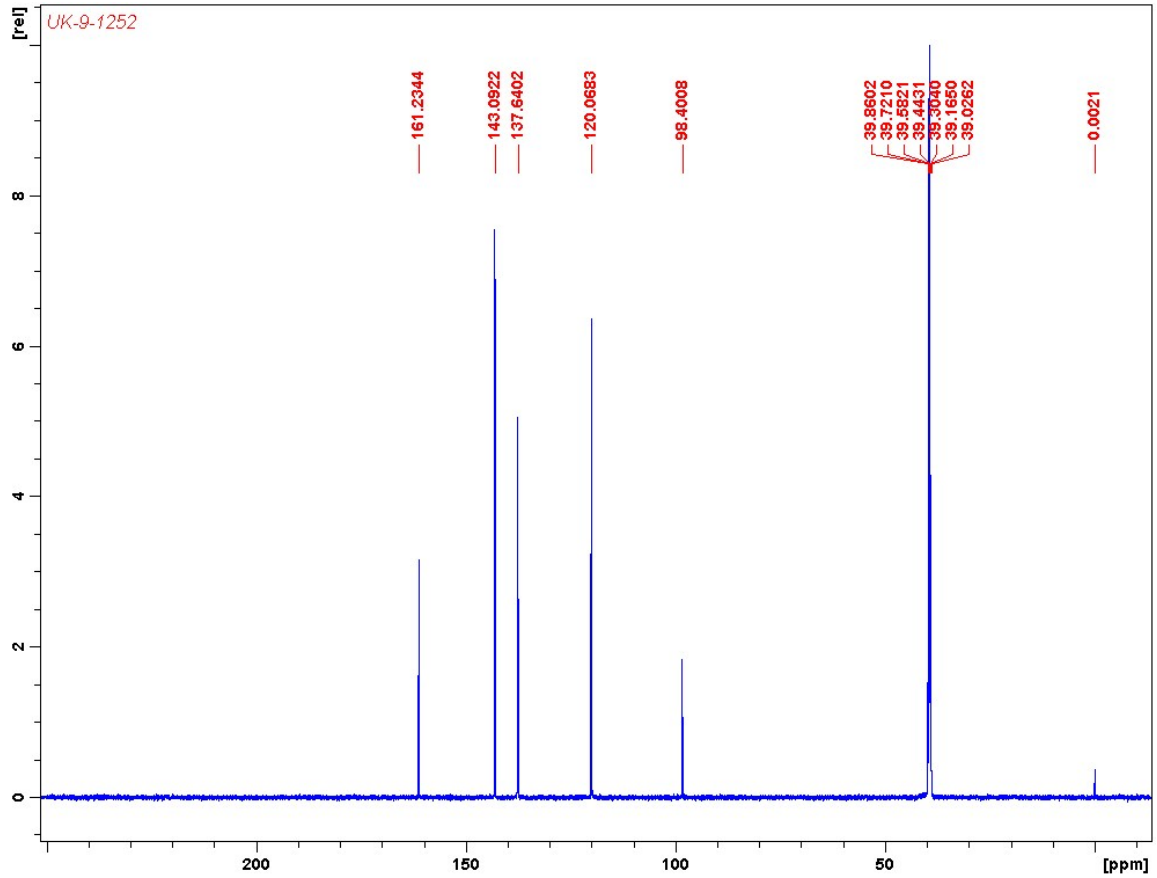
7.5645
7.5524
7.5487
6.3849
6.3690
3.3745
3.3702
2.5210
0.0009
1.1779
1.0000
0.9658
0.9934
[ppm]


UK-9-1252
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39.3040
39.1650
39.0262
0.0021
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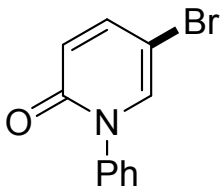
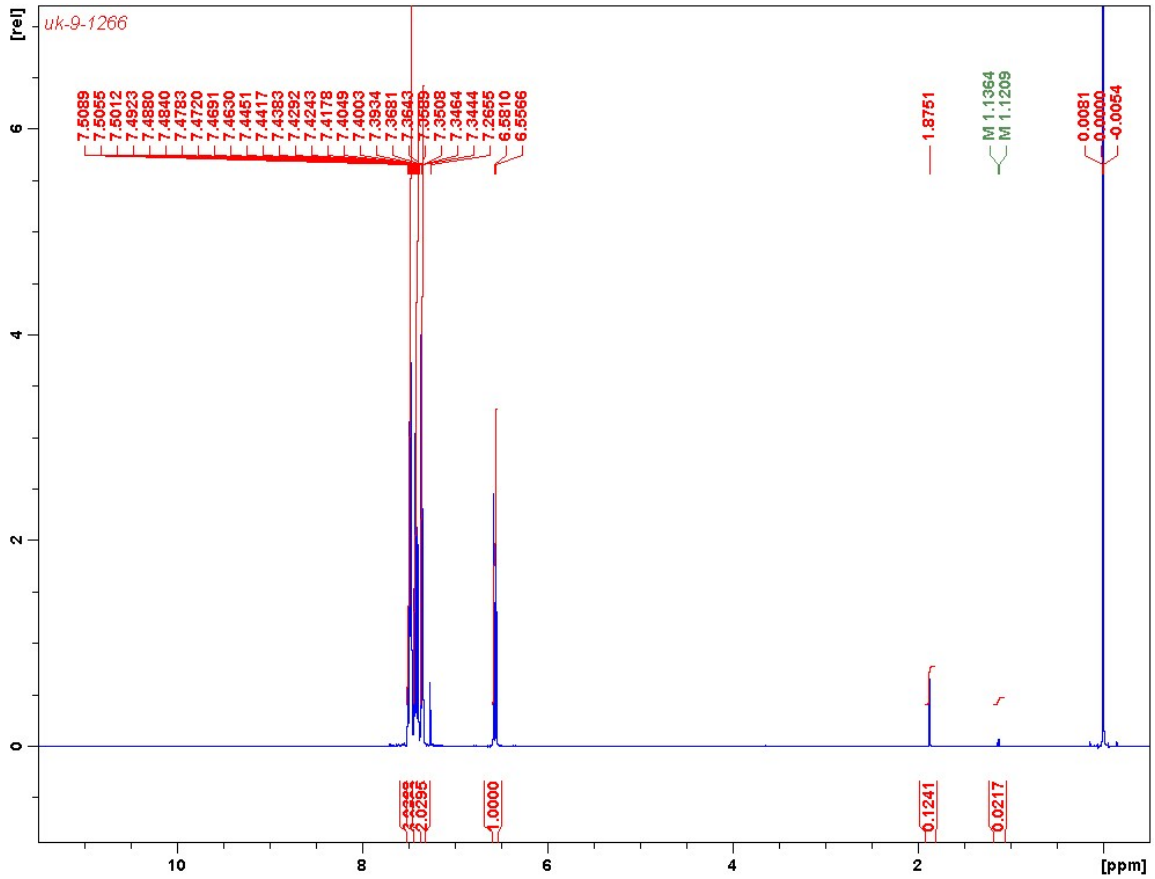

Br
O
N
Ph

4a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7.4880
7.4840
7.4783
7.4720
7.4691
7.4630
7.4451
7.4417
7.4383
7.4292
7.4243
7.4178
7.4049
7.4003
7.3934
7.3681
7.3643
7.3589
7.3508
7.3464
7.3444
7.2655
6.5810
6.5566
1.8751
M 1.1364
M 1.1209
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0.0000
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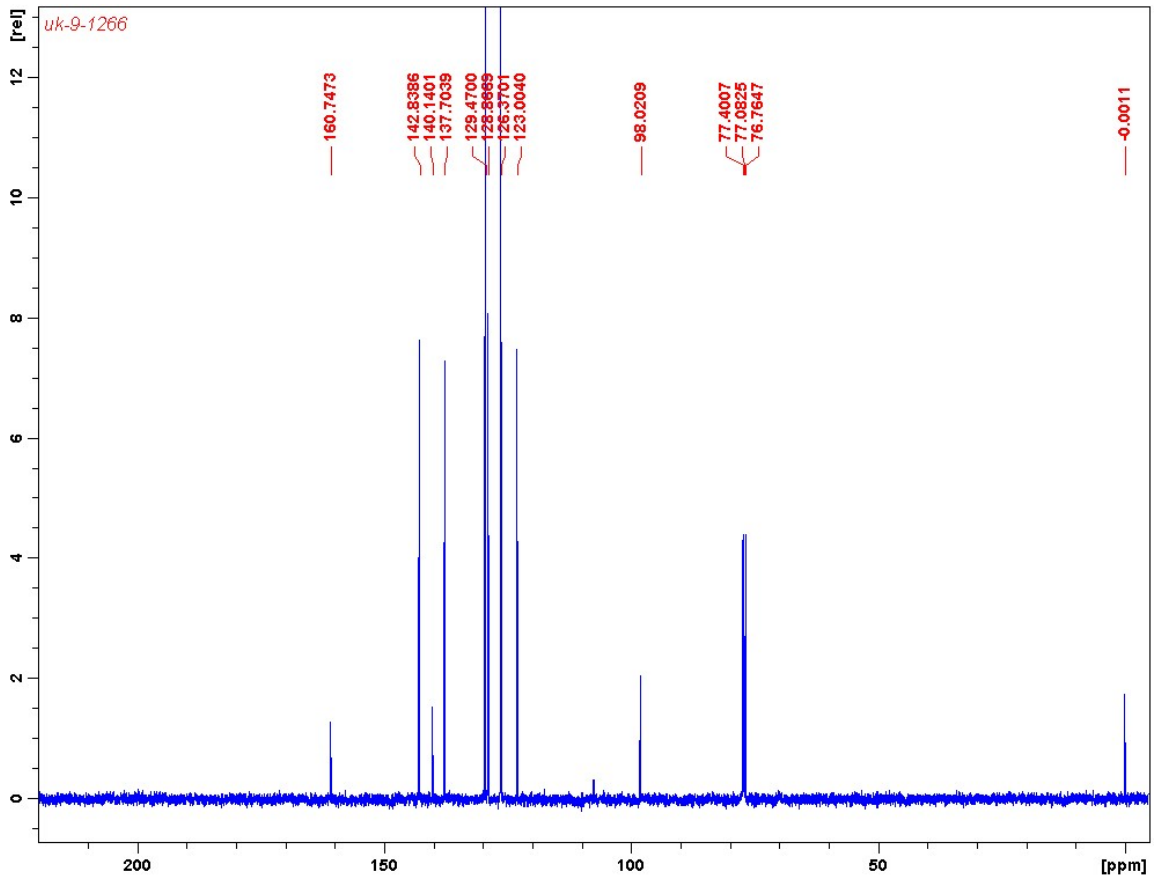
1.0000
0.1241
0.0217
[ppm]


uk-9-1266
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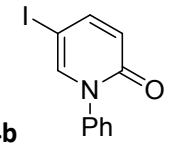
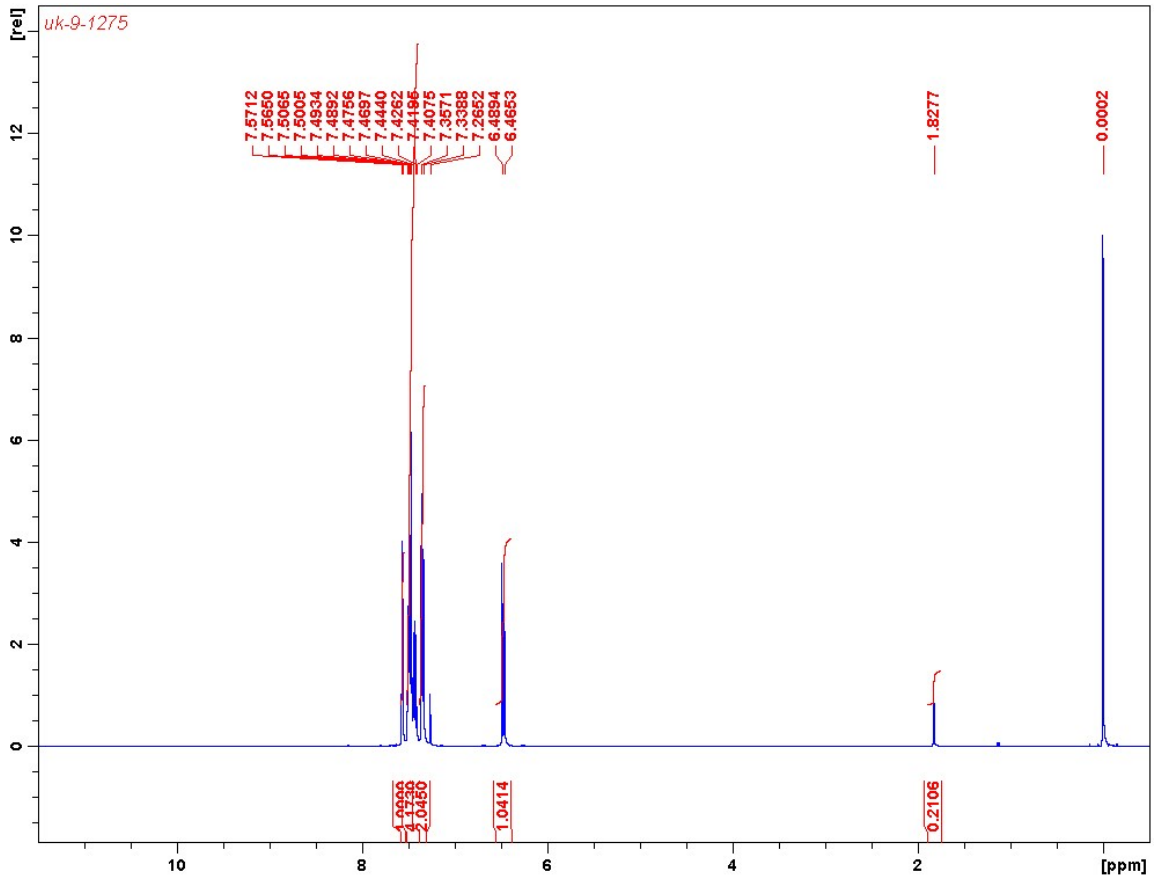
126.3701
123.0040
98.0209
77.4007
77.0825
76.7647
-0.0011
[ppm]


I
N
O
Ph

4b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7.5005
7.4934
7.4892
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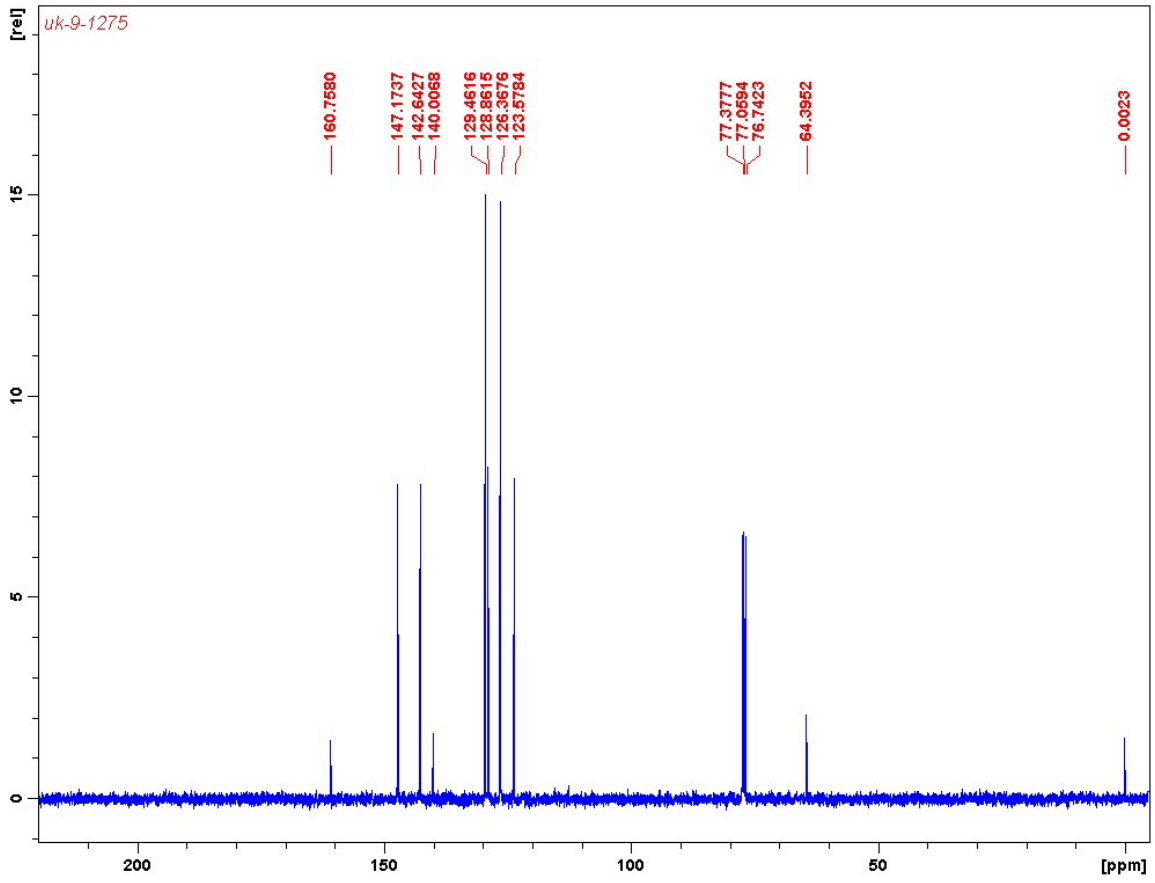
7.4697
7.4440
7.4262
7.4196
7.4075
7.3571
7.3388
7.2652
6.4894
6.4653
1.8277
0.0002
1.0414
0.2106
[ppm]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123.5784
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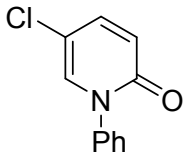
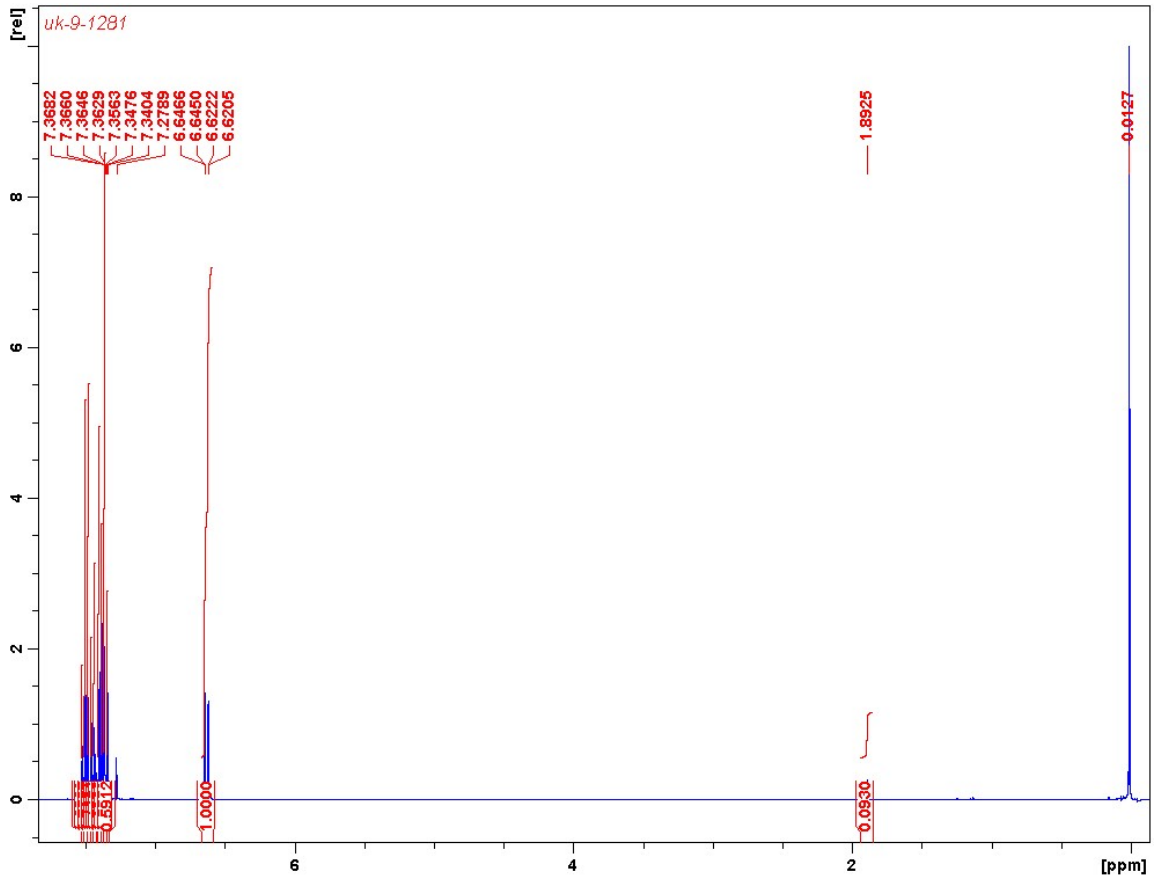
77.0594
76.7423
64.3952
0.0023
[ppm]


Cl
N
O
Ph

4c


uk-9-1281
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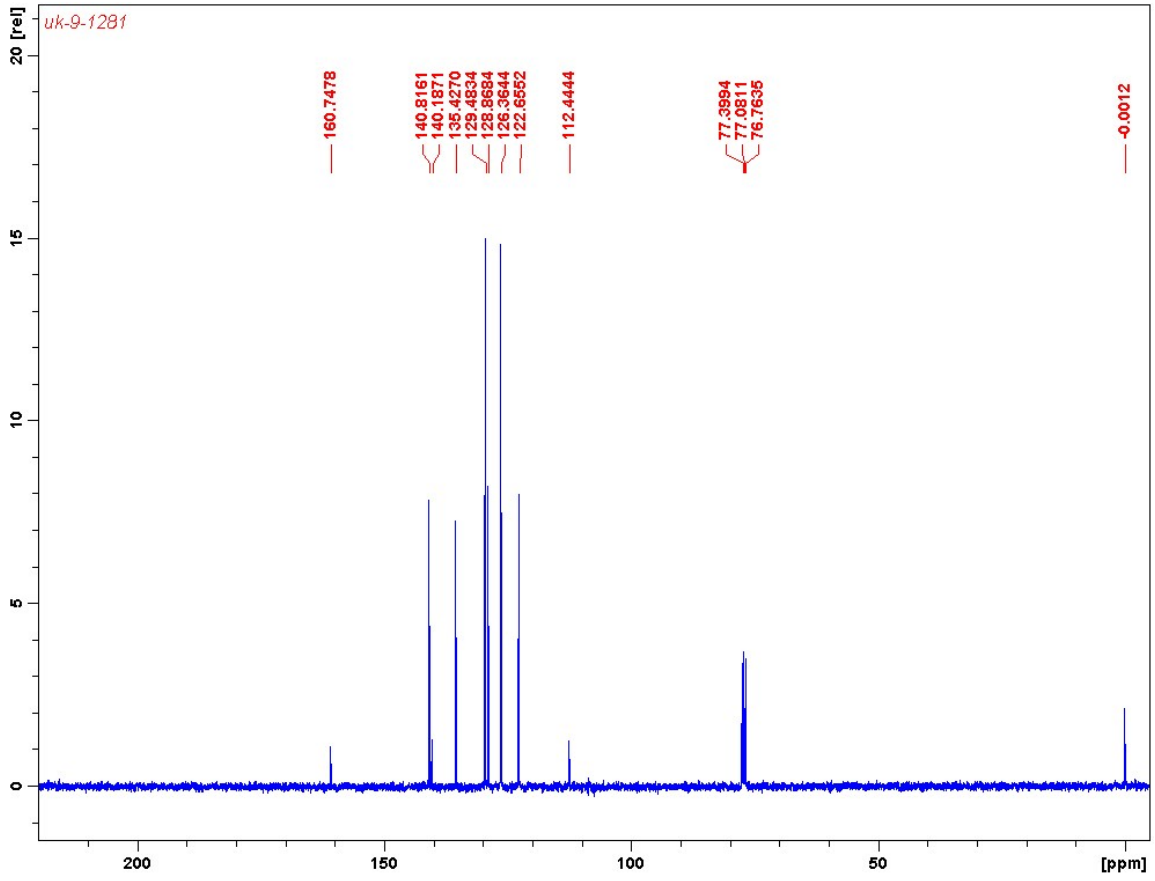
7.3660
7.3646
7.3629
7.3563
7.3476
7.3404
7.2789
6.6466
6.6450
6.6222
6.6205
1.8925
0.0127
1.0000
0.0930
[ppm]


uk-9-1281
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112.4444
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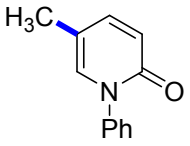
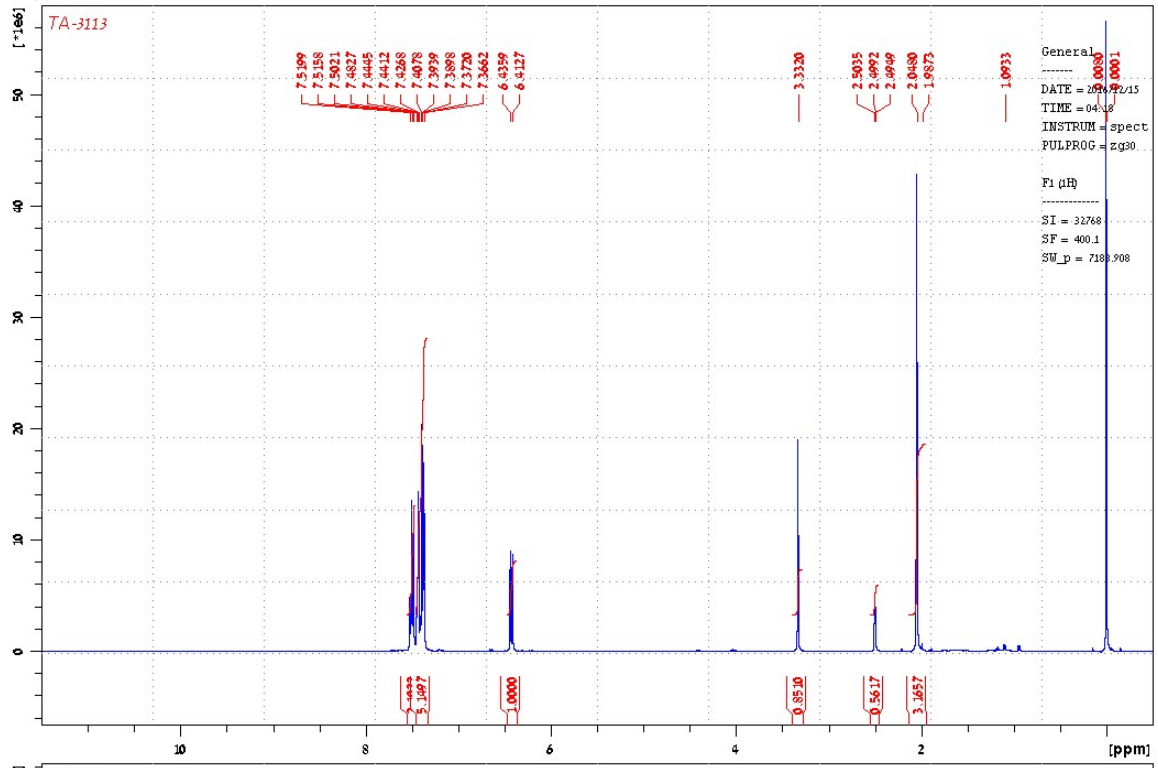
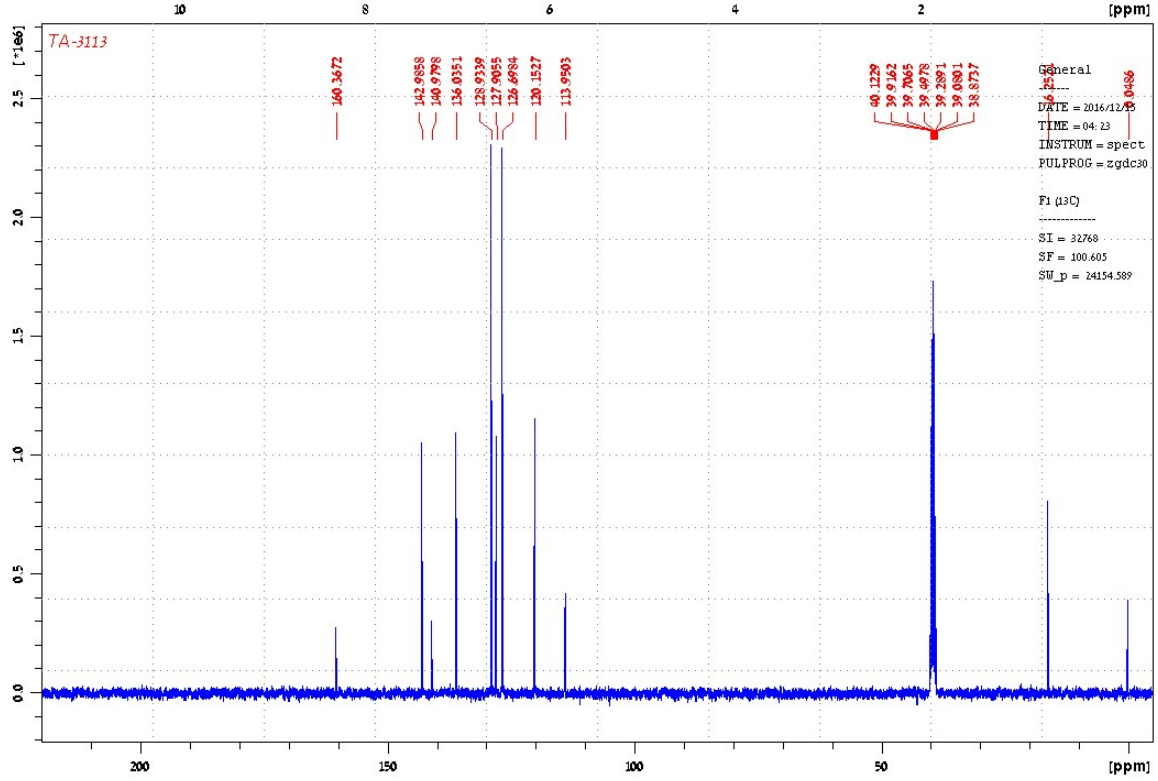
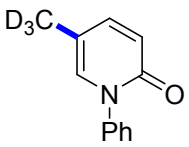
77.0811
76.7635
-0.0012
[ppm]



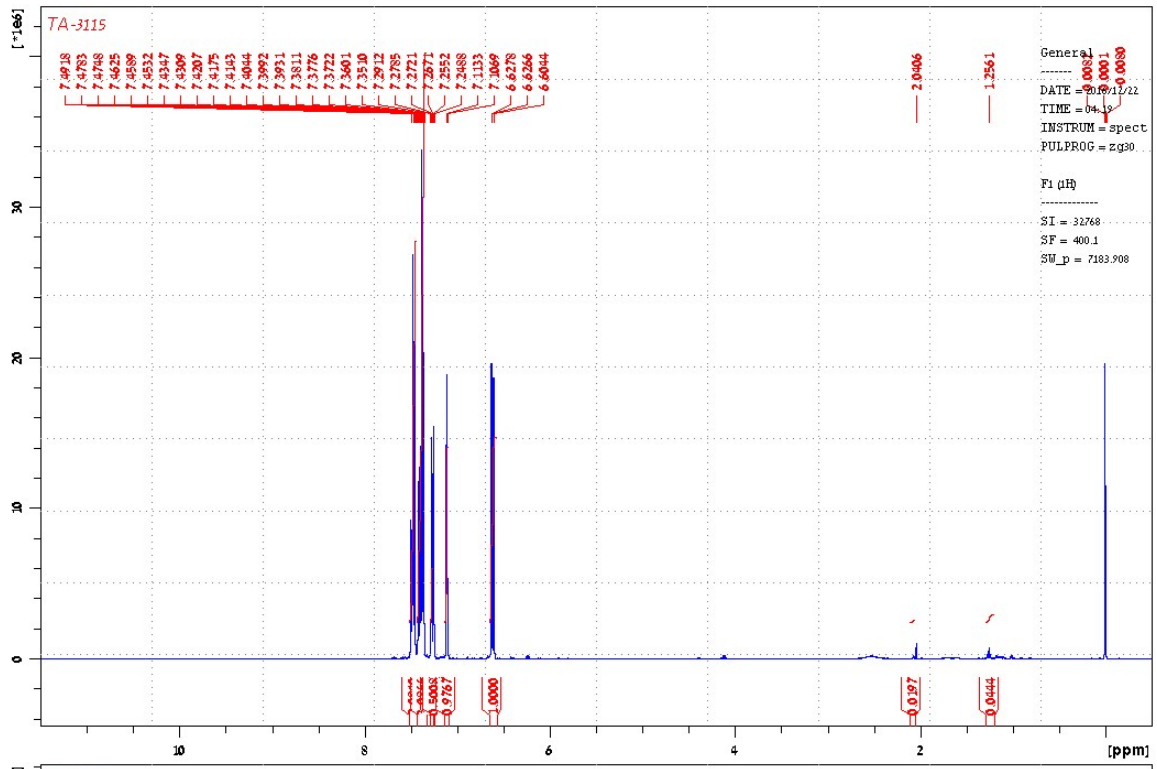
4d, Pirfenidone







4e, SD-560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7.4625
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7.4532
7.4347
7.4309
7.4207
7.4175
7.4143
7.4044
7.3992
7.3931
7.3811
7.3776
7.3722
7.3601
7.3510
7.2912
7.2785
7.2721
7.2671
7.2552
7.2488
7.1133
7.1069
6.6278
6.6266
6.6044
2.0406
1.2561
0.0082
0.0001
0.0000
General
DATE = 2016/12/22
TIME = 04:19
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 32768
SF = 400.1
SW_p = 7183.908
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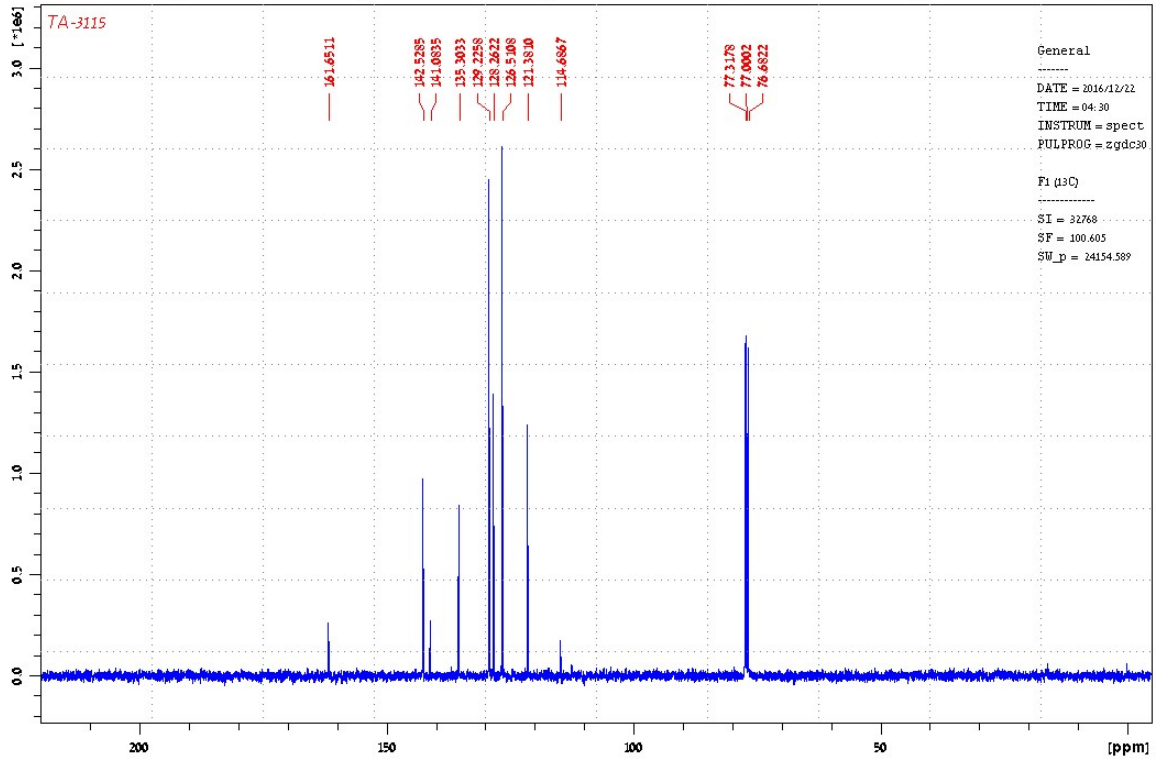
1.0000
0.0197
0.0444
[ppm]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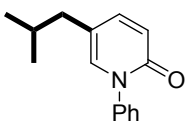
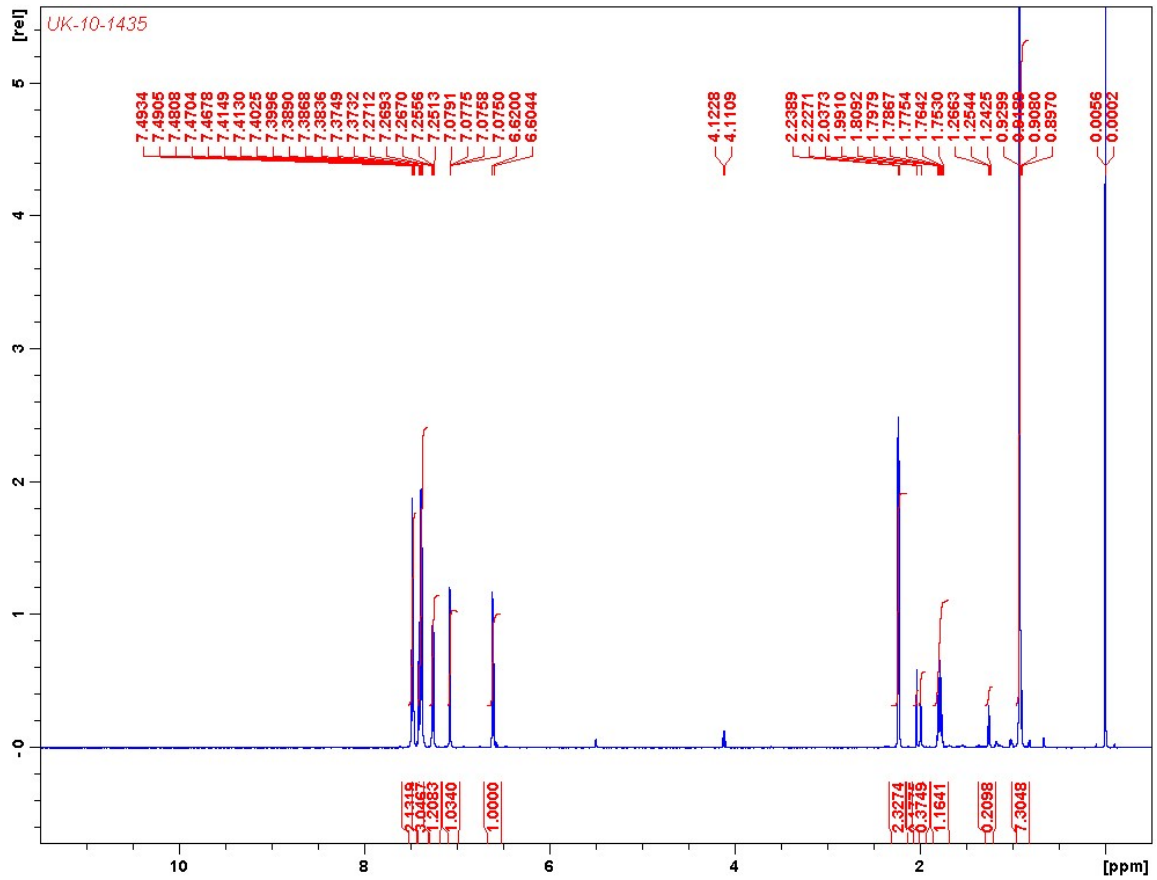
142.5285
141.0835
135.3033
129.2258
128.2622
126.5308
121.3810
114.6867
77.3178
77.0002
76.6822
General
DATE = 2016/12/22
TIME = 04:30
INSTRUM = spect
PULPROG = zgdc30
F1 (13C)
SI = 32768
SF = 100.605
SW_p = 24154.589
[ppm]


N
O
Ph

4f


UK-10-1435
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7.4130
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7.3996
7.3890
7.3868
7.3836
7.3749
7.3732
7.2712
7.2693
7.2670
7.2556
7.2513
7.0791
7.0775
7.0758
7.0750
6.6200
6.6044
4.1228
4.1109
2.2389
2.2271
2.0373
1.9910
1.8092
1.7979
1.7867
1.7754
1.7642
1.7530
1.2663
1.2544
1.2425
0.9299
0.9080
0.8970
0.0056
0.0002
2.1319
3.0467
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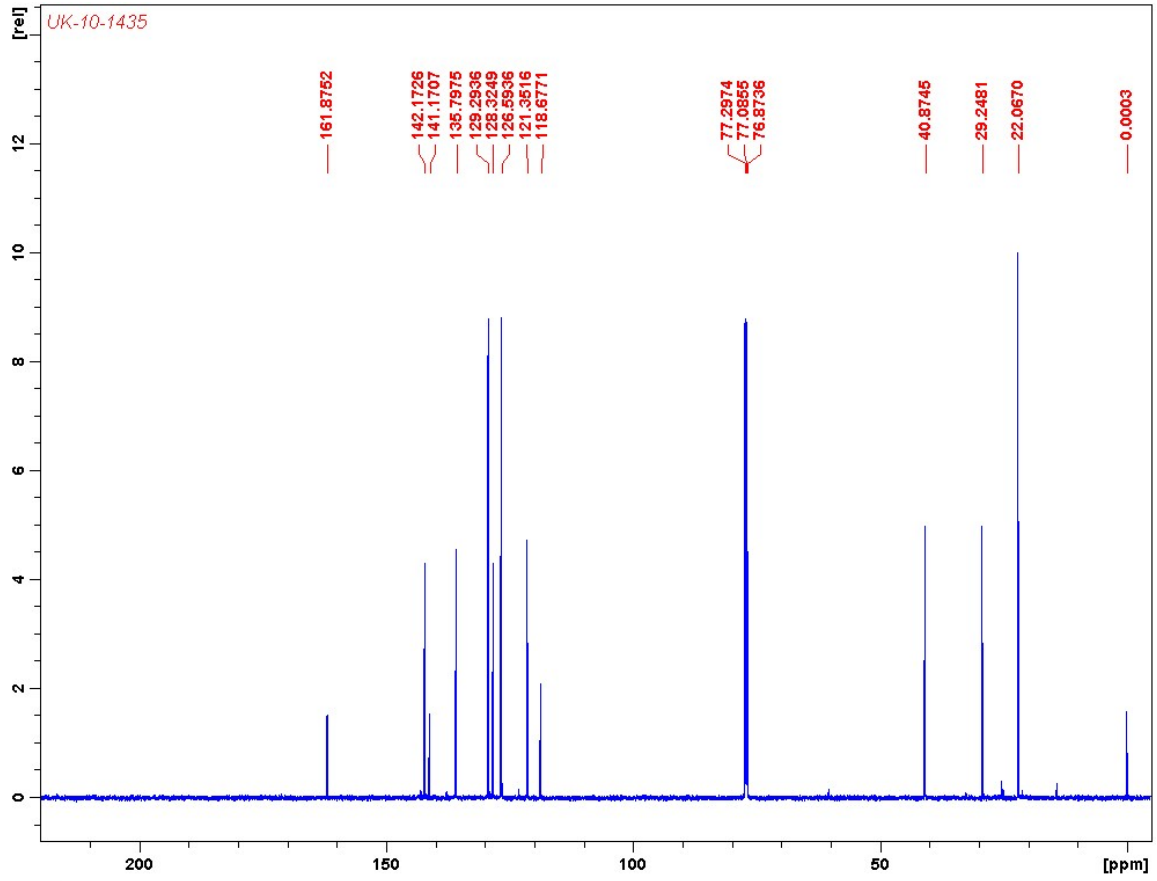
1.0340
1.0000
2.3274
0.3749
1.1641
0.2098
7.3048
[ppm]


UK-10-1435
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128.3249
126.5936
121.3516
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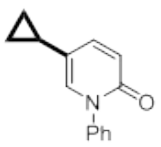
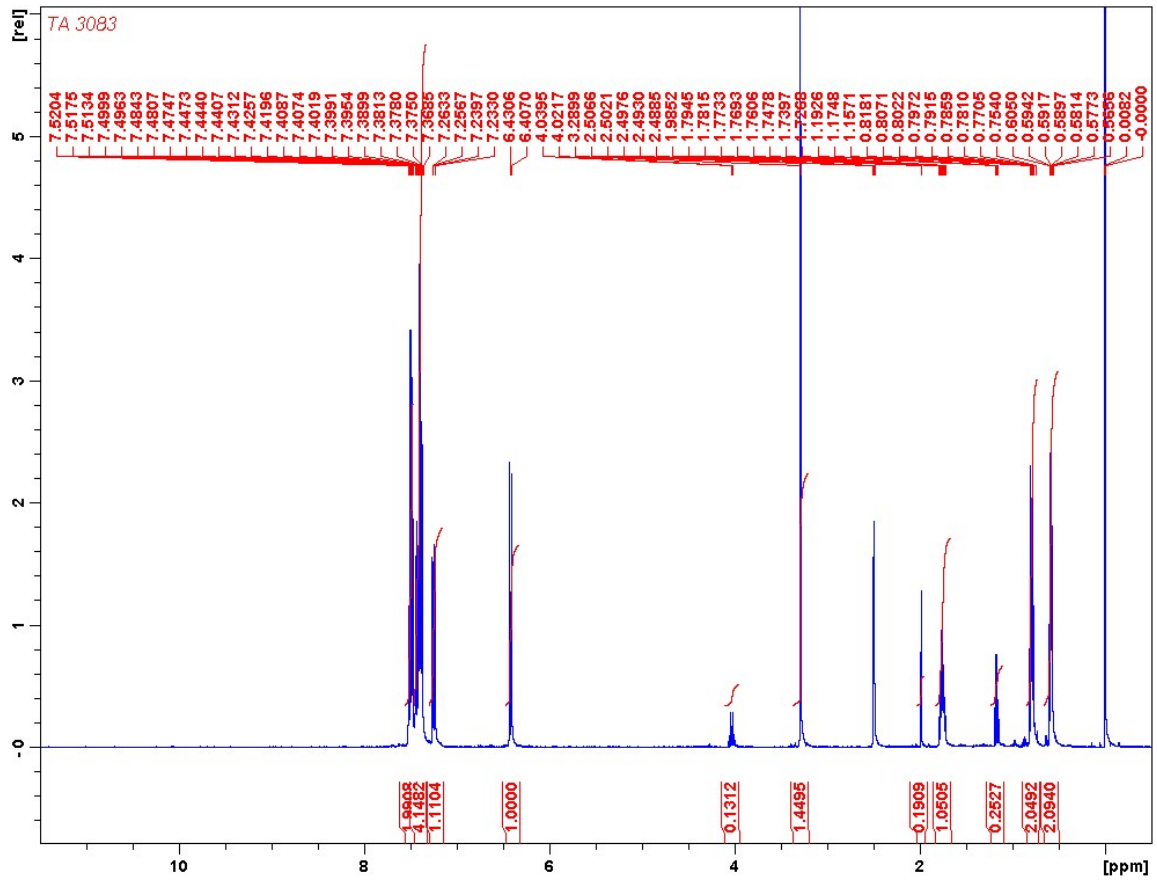
76.8736
40.8745
29.2481
22.0670
0.0003
[ppm]


N
O
Ph

4g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7.4843
7.4807
7.4747
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7.4440
7.4407
7.4312
7.4257
7.4196
7.4087
7.4074
7.4019
7.3991
7.3954
7.3899
7.3813
7.3780
7.3750
7.3685
7.2633
7.2567
7.2397
7.2330
6.4306
6.4070
4.0395
4.0217
3.2899
2.5066
2.5021
2.4976
2.4930
2.4885
1.9852
1.7945
1.7815
1.7733
1.7693
1.7606
1.7478
1.7397
1.1926
1.1748
1.1571
0.8181
0.8071
0.8022
0.7972
0.7915
0.7859
0.7810
0.7705
0.7540
0.6050
0.5942
0.5917
0.5897
0.5814
0.5773
0.0082
-0.0000
1.9608
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1.0000
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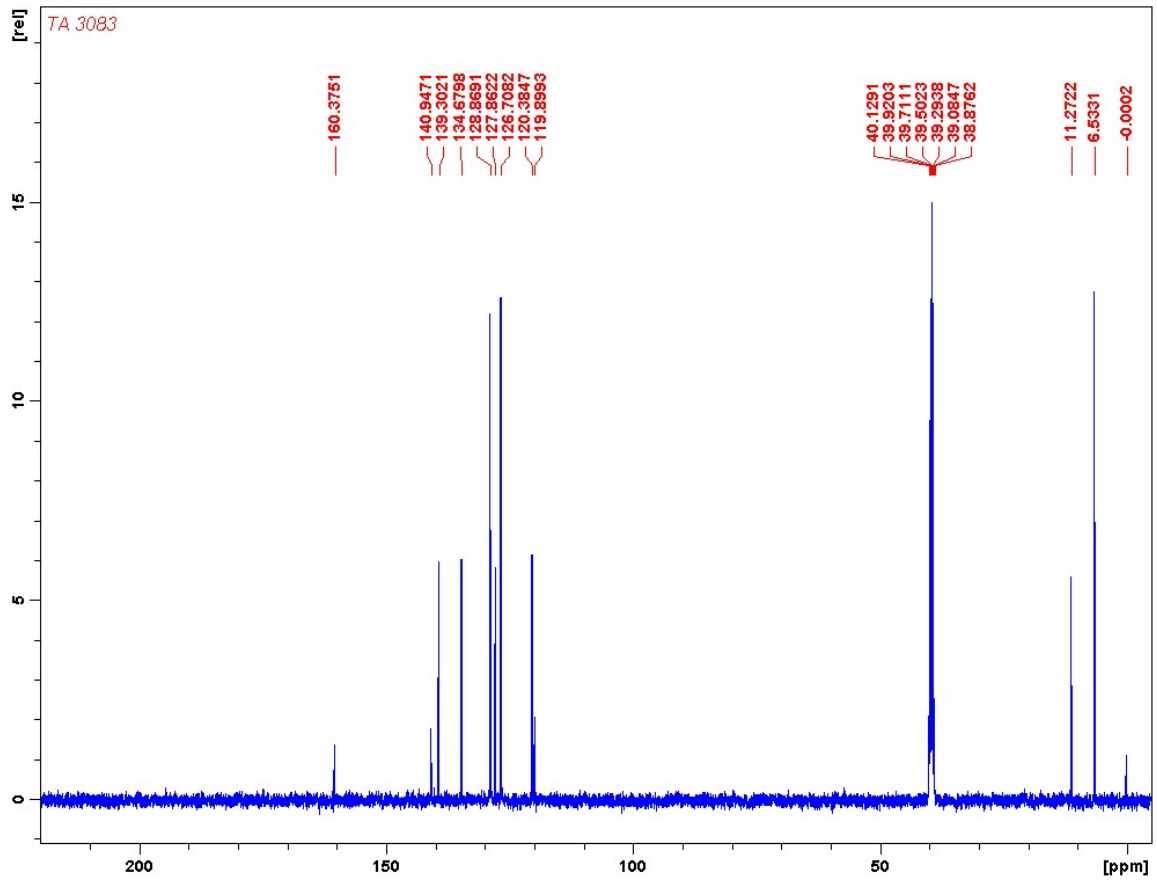
1.4495
0.1909
1.0505
0.2527
2.0492
2.0940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120.3847
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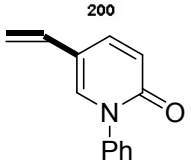
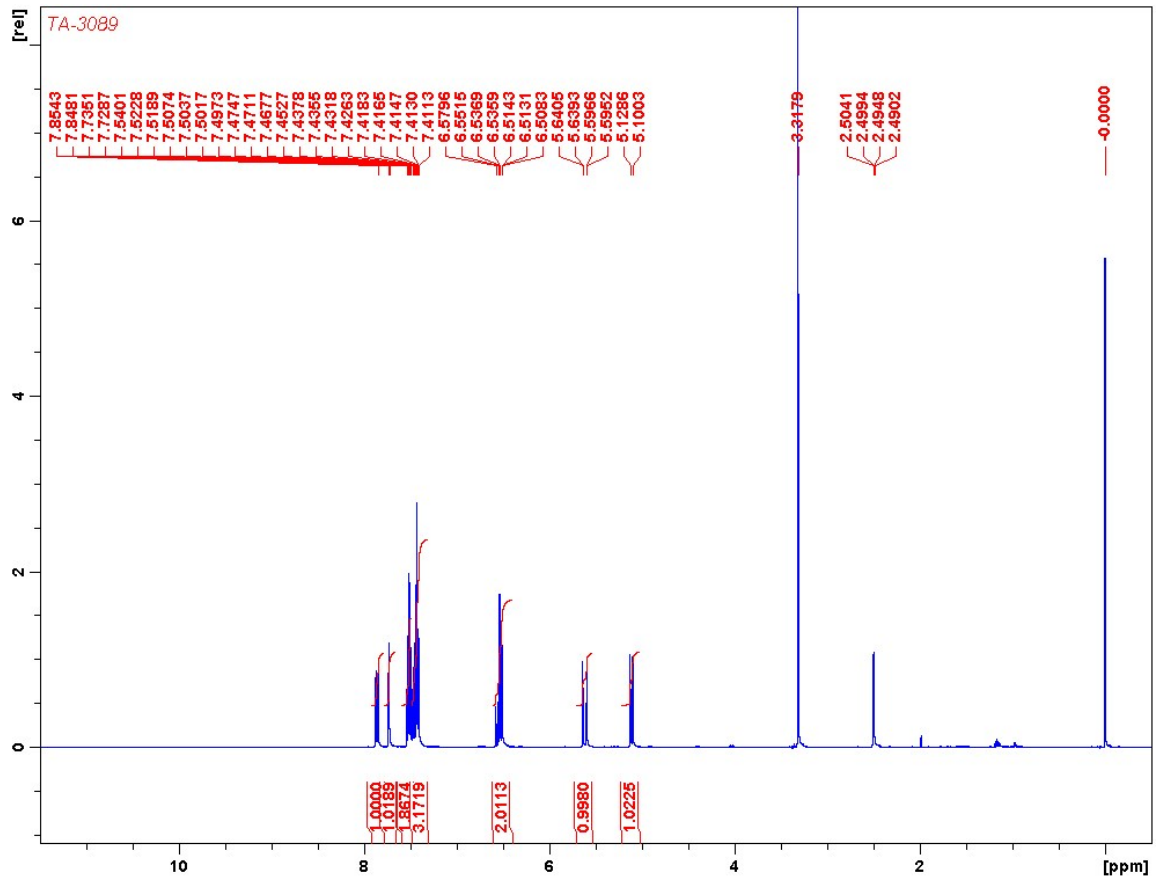
38.8762
11.2722
6.5331
-0.0002


N
O
Ph

4h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7.5037
7.5017
7.4973
7.4747
7.4711
7.4677
7.4527
7.4378
7.4355
7.4318
7.4263
7.4183
7.4165
7.4147
7.4130
7.4113
6.5796
6.5515
6.5369
6.5359
6.5143
6.5131
6.5083
5.6405
5.6393
5.5966
5.5952
5.1286
5.1003
3.3179
2.5041
2.4994
2.4948
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1.0000
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3.1719
2.0113
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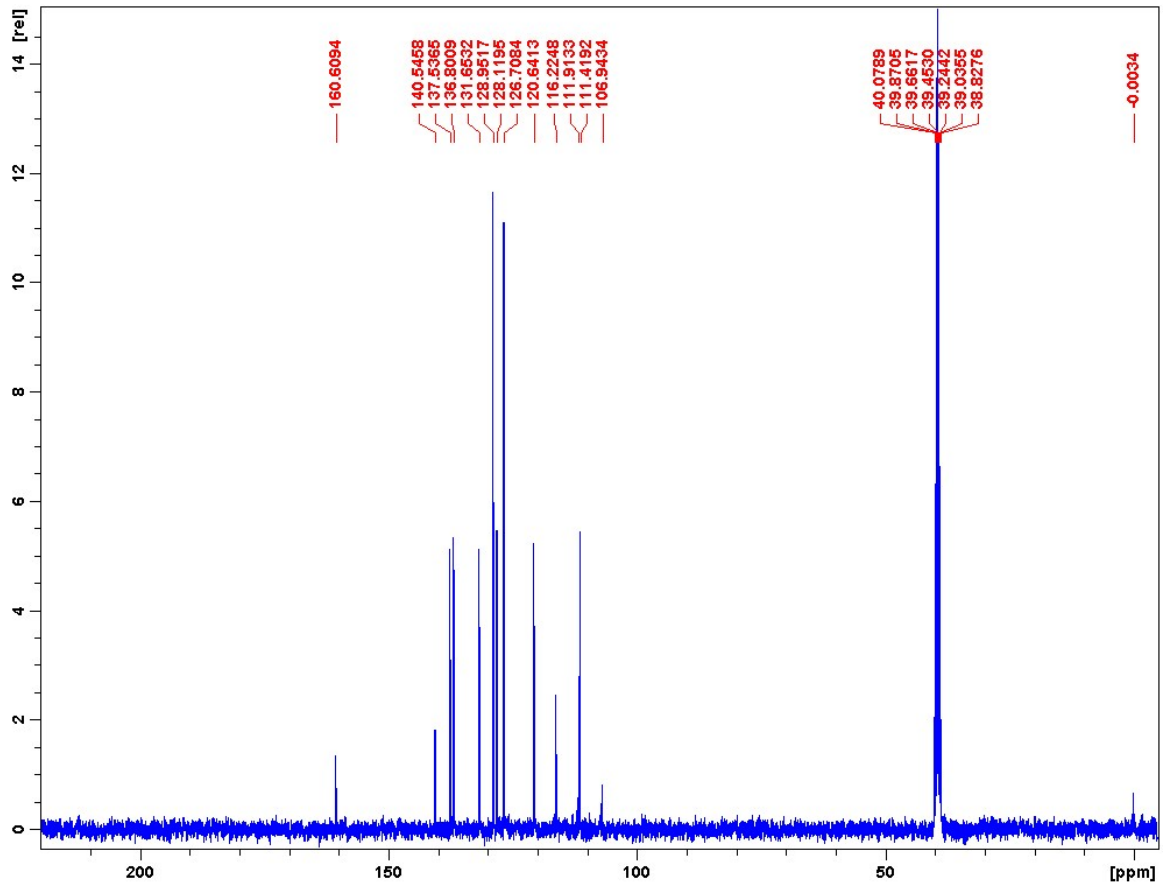
1.0225
[ppm]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126.7084
120.6413
116.2248
111.9133
111.4192
106.9434
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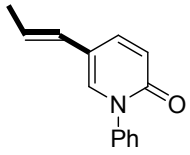
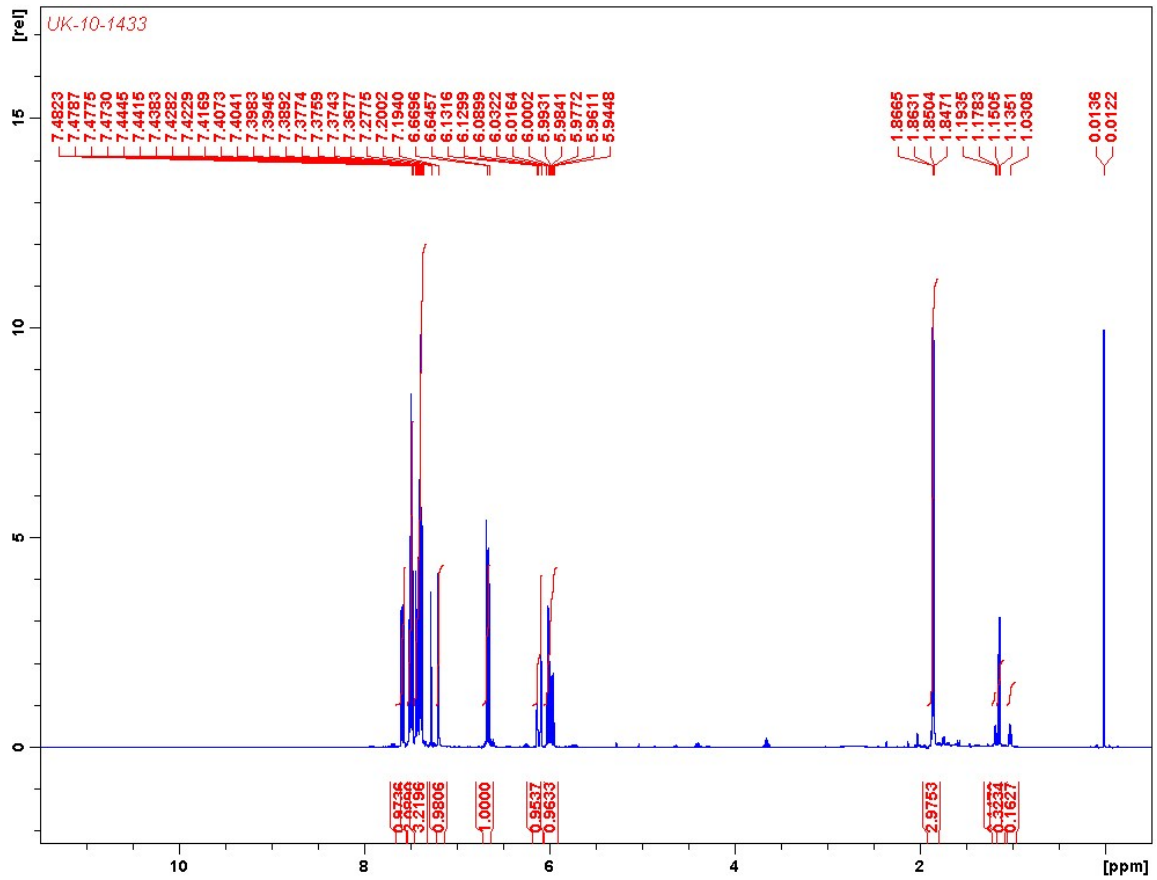
39.8705
39.6617
39.4530
39.2442
39.0355
38.8276
-0.0034
[ppm]


N
O
Ph

4i


UK-10-1433
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7.4775
7.4730
7.4445
7.4415
7.4383
7.4282
7.4229
7.4169
7.4073
7.4041
7.3983
7.3945
7.3892
7.3774
7.3759
7.3743
7.3677
7.2775
7.2002
7.1940
6.6696
6.6457
6.1316
6.1299
6.0899
6.0322
6.0164
6.0002
5.9931
5.9841
5.9772
5.9611
5.9448
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1.8631
1.8504
1.8471
1.1935
1.1783
1.1505
1.1351
1.0308
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0.0122
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1.0000
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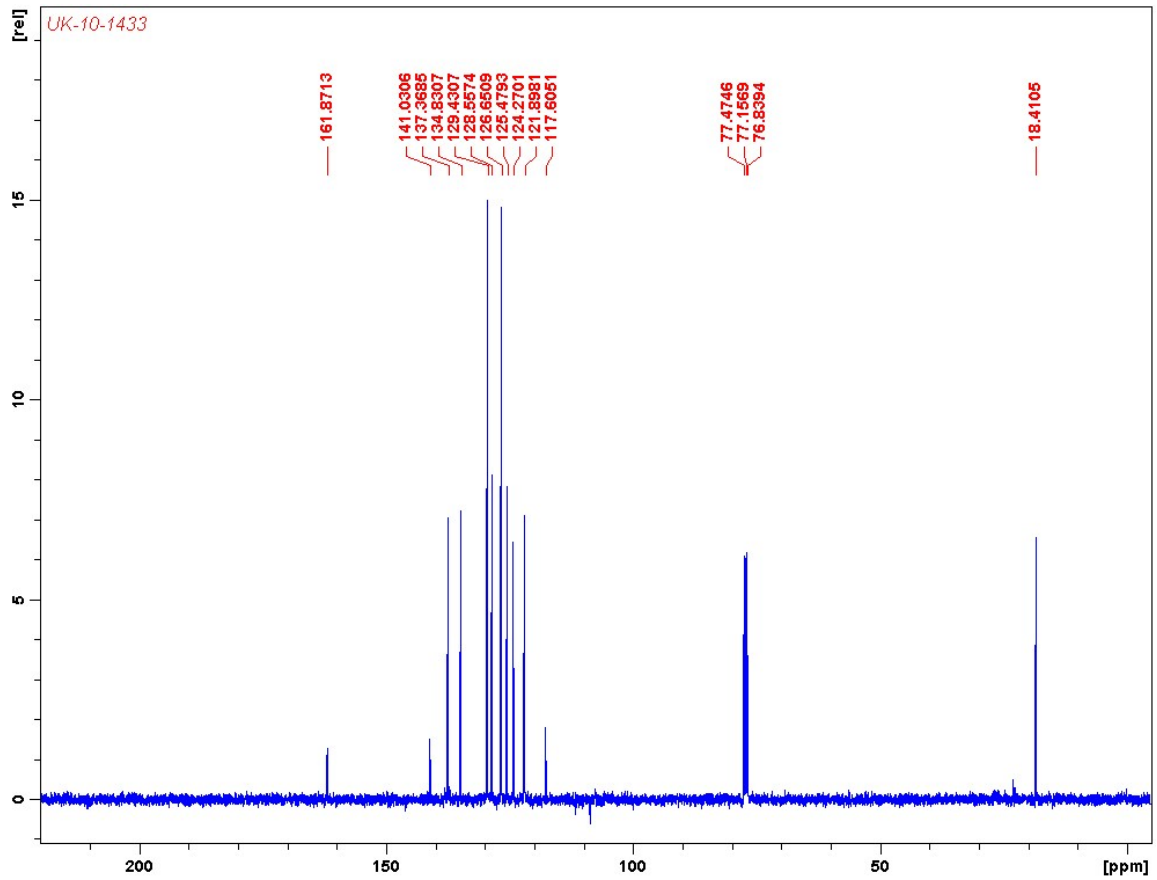
0.9633
2.9753
0.1627
[ppm]


UK-10-1433
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129.4307
128.5574
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124.2701
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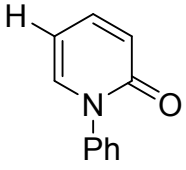
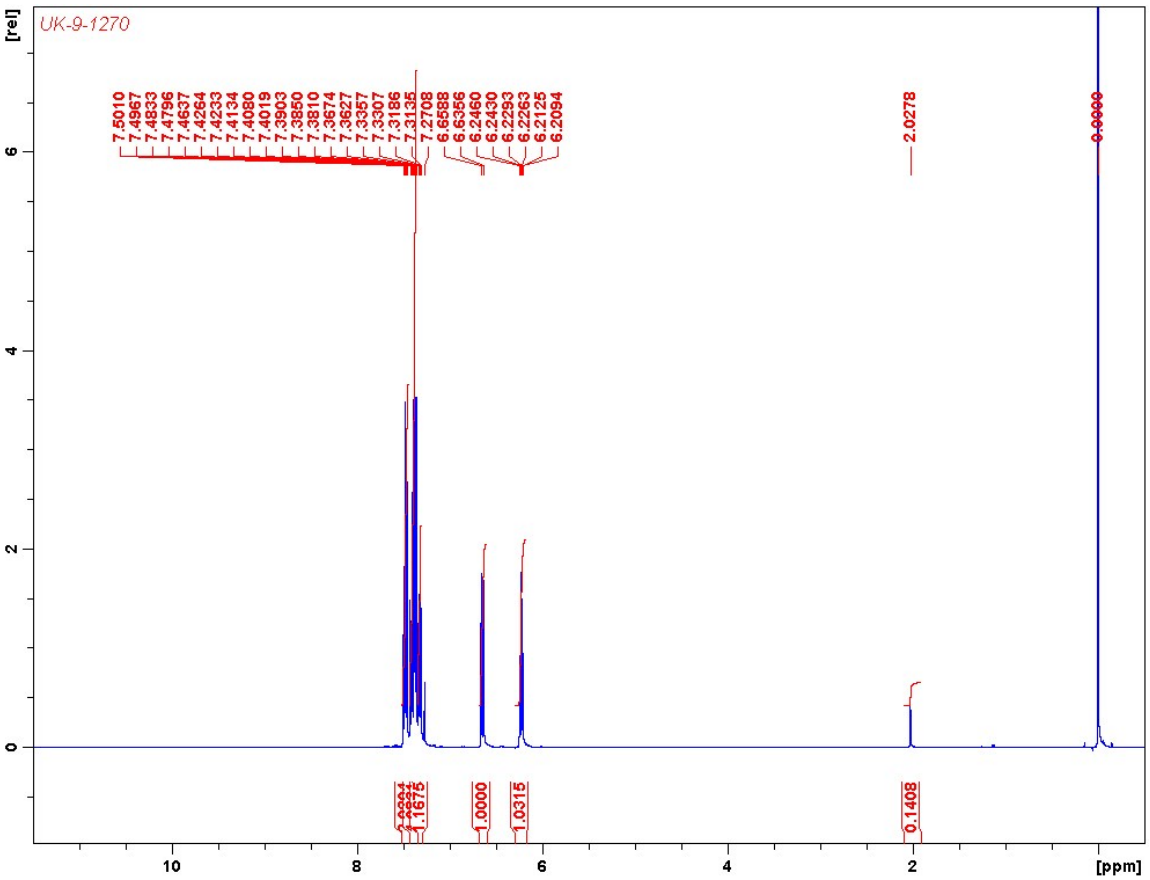
117.6051
77.4746
77.1569
76.8394
18.4105
[ppm]


H
N
O
Ph

5


UK-9-1270
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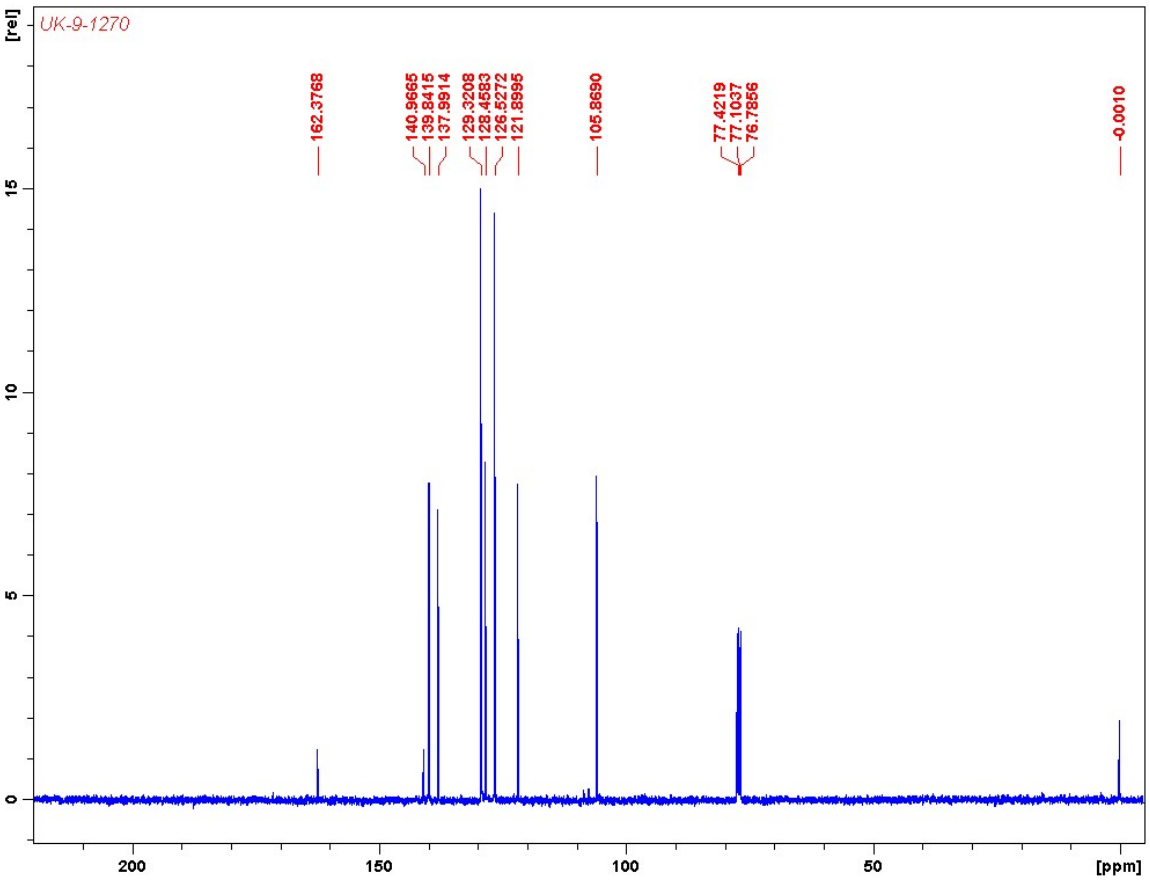
7.4264
7.4233
7.4134
7.4080
7.4019
7.3903
7.3850
7.3810
7.3674
7.3627
7.3357
7.3307
7.3186
7.3135
7.2708
6.6588
6.6356
6.2460
6.2430
6.2293
6.2263
6.2125
6.2094
2.0278
0.0000
1.0000
1.0315
0.1408
[ppm]


UK-9-1270
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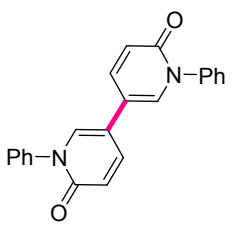
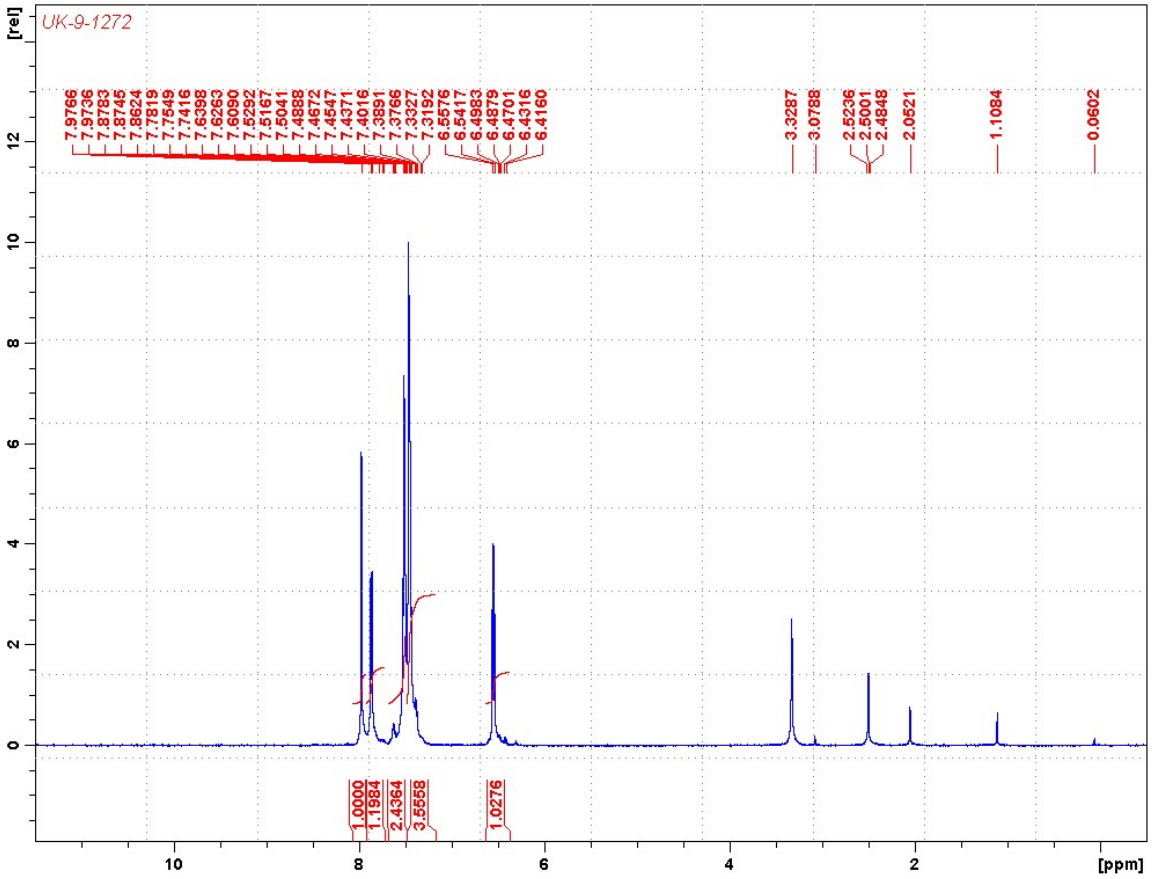
162.3768
140.9665
139.8415
137.9914
129.3208
128.4583
126.5272
121.8995
105.8690
77.4219
77.1037
76.7856
-0.0010
[ppm]


O
N–Ph
Ph–N
O

6


UK-9-1272
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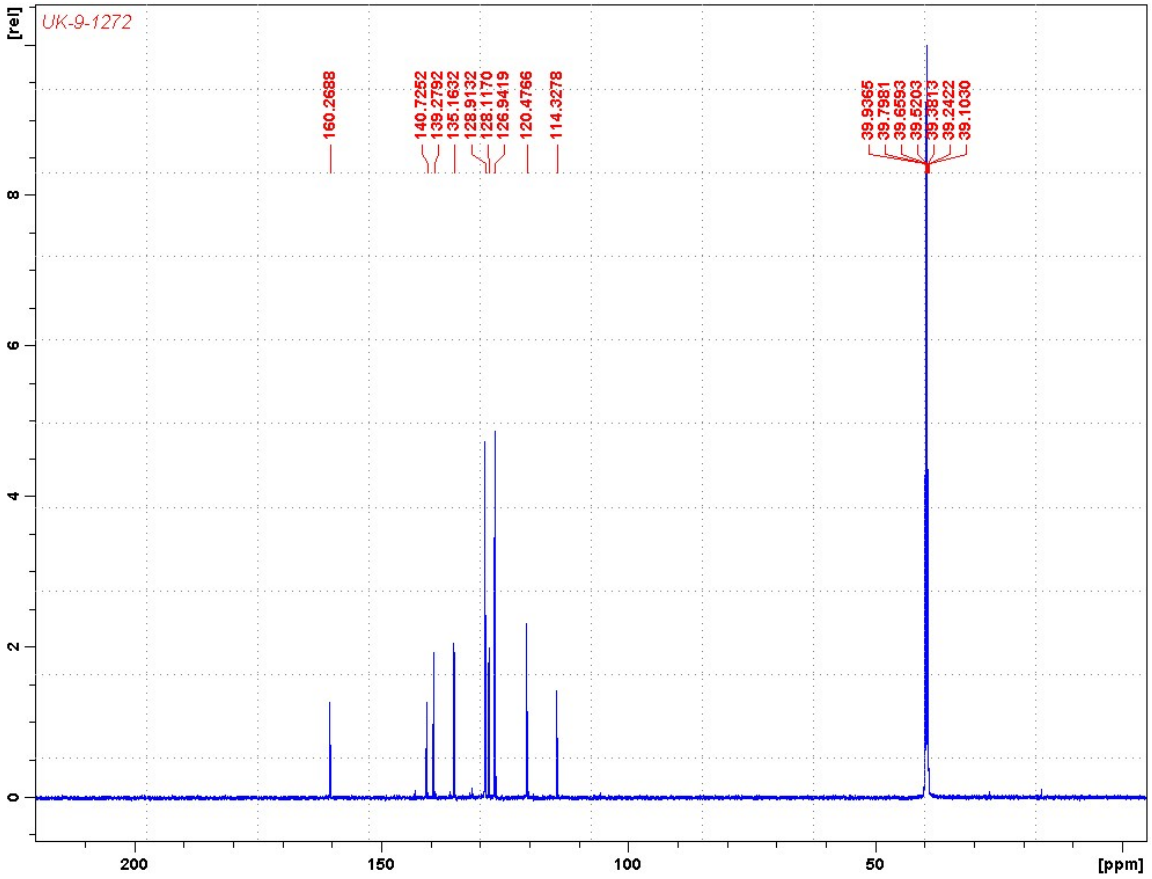
7.9736
7.8783
7.8745
7.8624
7.7819
7.7549
7.7416
7.6398
7.6263
7.6090
7.5292
7.5167
7.5041
7.4888
7.4672
7.4547
7.4371
7.4016
7.3891
7.3766
7.3327
7.3192
6.5576
6.5417
6.4883
6.4879
6.4701
6.4316
6.4160
3.3287
3.0788
2.5236
2.5001
2.4848
2.0521
1.1084
0.0602
1.0000
1.1984
2.4364
3.5558
1.0276
[ppm]


UK-9-1272
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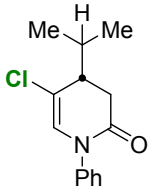
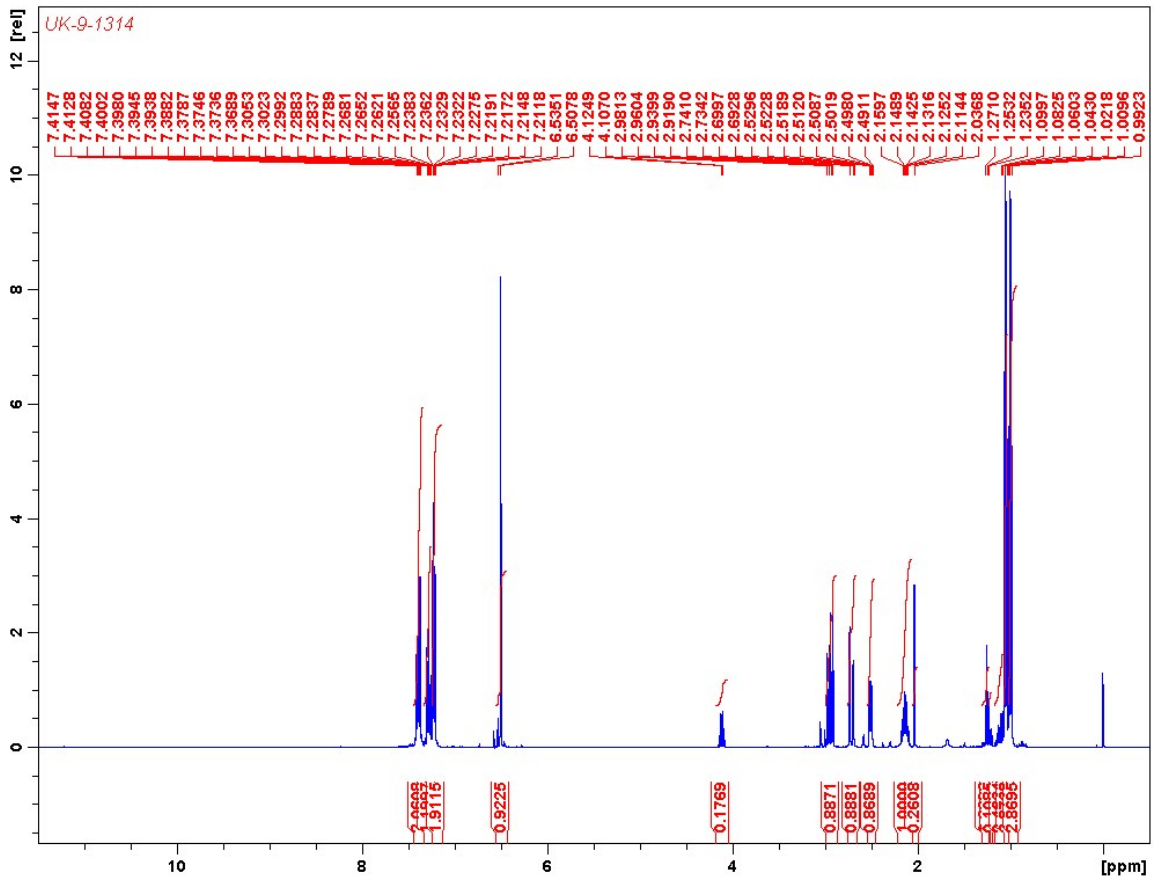
140.7252
139.2792
135.1632
128.9132
128.1170
126.9419
120.4766
114.3278
39.9365
39.7981
39.6593
39.5203
39.3813
39.2422
39.1030
[ppm]


Me
H
Me
Cl
N
O
Ph

7


UK-9-1314
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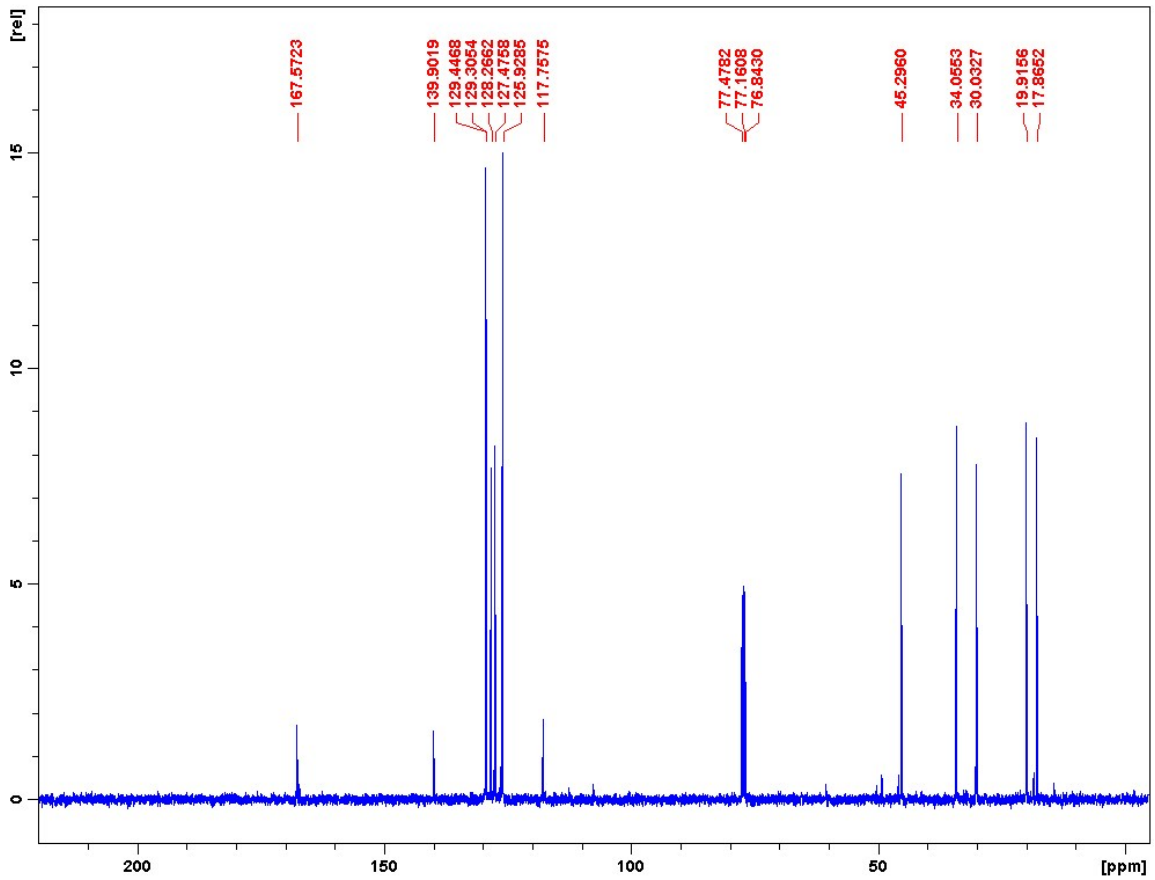
7.3945
7.3938
7.3882
7.3787
7.3746
7.3736
7.3689
7.3053
7.3023
7.2992
7.2883
7.2837
7.2789
7.2681
7.2652
7.2621
7.2565
7.2383
7.2362
7.2329
7.2322
7.2275
7.2191
7.2172
7.2148
7.2118
6.5351
6.5078
4.1249
4.1070
2.9813
2.9604
2.9399
2.9190
2.7410
2.7342
2.6997
2.6928
2.5296
2.5228
2.5189
2.5120
2.5087
2.5019
2.4980
2.4911
2.1597
2.1489
2.1425
2.1316
2.1252
2.1144
2.0368
1.2710
1.2532
1.2352
1.0997
1.0825
1.0603
1.0430
1.0218
1.0096
0.9923
2.0668
1.9115
0.9225
0.1769
0.8871
0.8881
0.8689
1.0000
0.2608
2.8695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[ppm]
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129.4468
129.3054
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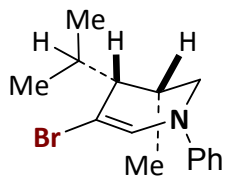
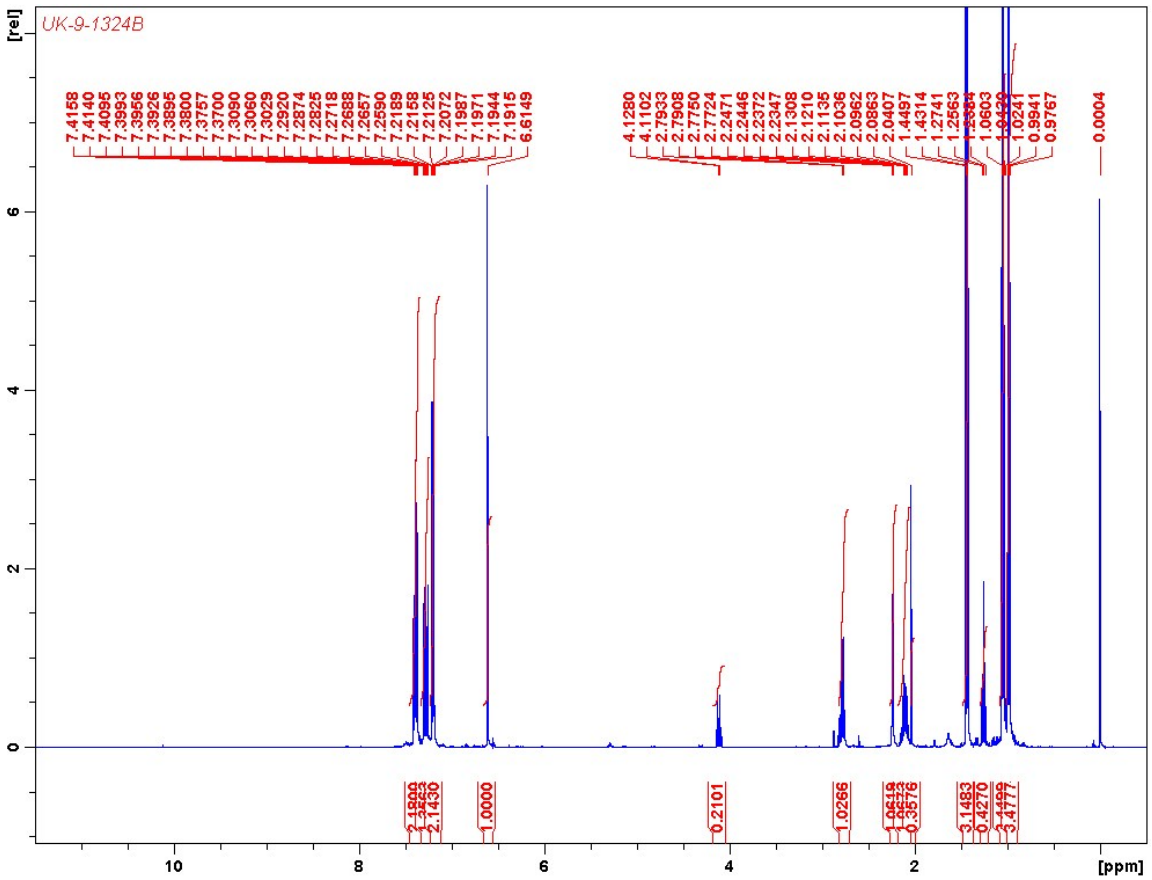
127.4758
125.9285
117.7575
77.4782
77.1608
76.8430
45.2960
34.0553
30.0327
19.9156
17.8652


Me
H
H
H
Me
N
Br
Me
Ph

8


UK-9-1324B
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[ppm]
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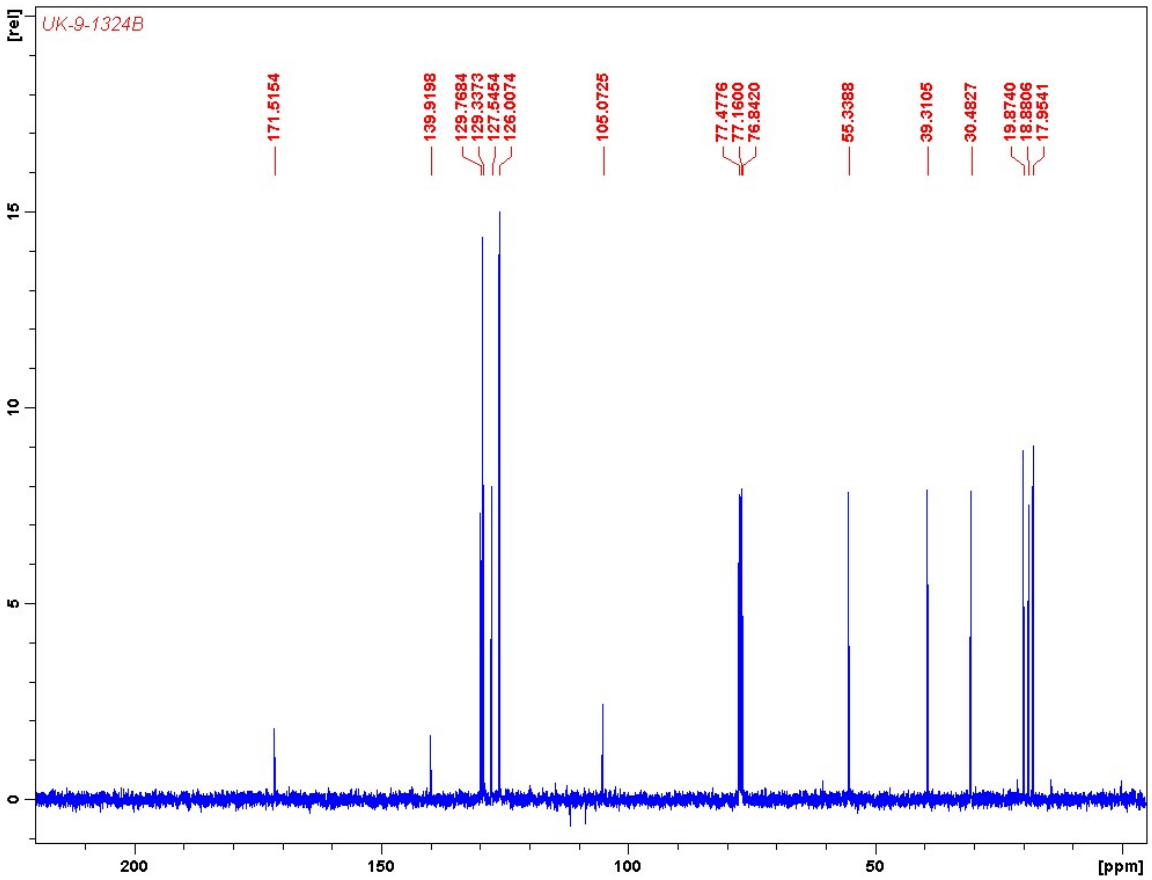
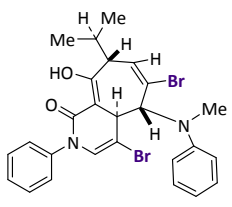
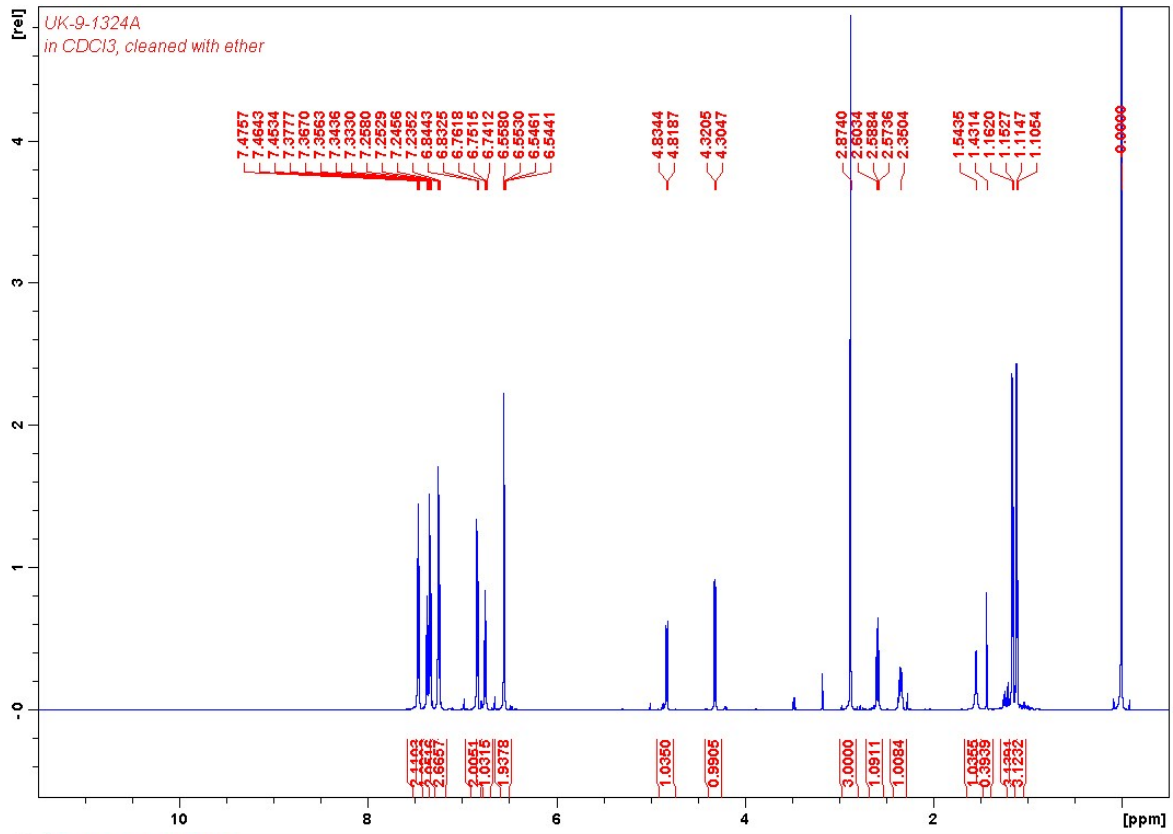
7.4140
7.4095
7.3993
7.3956
7.3926
7.3895
7.3800
7.3757
7.3700
7.3090
7.3060
7.3029
7.2920
7.2874
7.2825
7.2718
7.2688
7.2657
7.2590
7.2189
7.2158
7.2125
7.2072
7.1987
7.1971
7.1944
7.1915
6.6149
4.1280
4.1102
2.7933
2.7908
2.7750
2.7724
2.2471
2.2446
2.2372
2.2347
2.1308
2.1210
2.1135
2.1036
2.0962
2.0863
2.0407
1.4497
1.4314
1.2741
1.2563
1.0603
1.0241
0.9941
0.9767
0.0004
2.1800
2.1463
2.1430
1.0000
0.2101
1.0266
1.0619
1.0533
1.0376
3.1483
0.4270
3.1499
3.4777


UK-9-1324B
[rel]
[ppm]
171.5154
139.9198
129.7684
129.3373
127.5454
126.0074
105.0725
77.4776
77.1600
76.8420
55.3388
39.3105
30.4827
19.8740
18.8806
17.9541


H
Me
Me
H
H
HO
Br
O
H
N
Me
H
N
Br

9


UK-9-1324A
in CDCl3, cleaned with ether
[rel]
[ppm]
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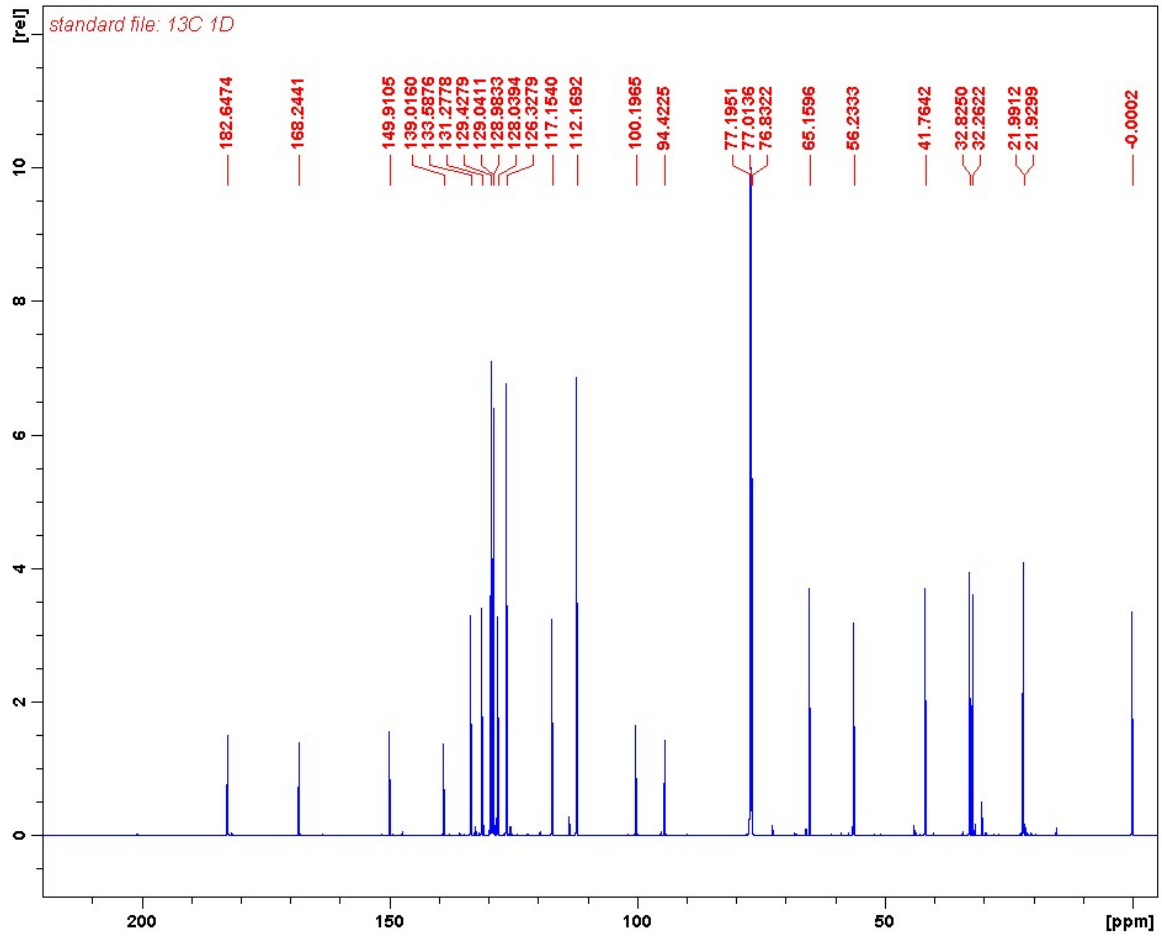
7.4643
7.4534
7.3777
7.3670
7.3563
7.3436
7.3330
7.2580
7.2529
7.2456
7.2352
6.8443
6.8325
6.7618
6.7515
6.7412
6.5580
6.5530
6.5461
6.5441
4.8344
4.8187
4.3205
4.3047
2.8740
2.6034
2.5884
2.5736
2.3504
1.5435
1.4314
1.1620
1.1527
1.1147
1.1054
0.0000
1.0350
0.9905
3.0000
1.0911
1.0084
1.0355
0.3939
3.1384
3.1232


standard file: 13C 1D
[rel]
[ppm]
182.6474
168.2441
149.9105
139.0160
133.5876
131.2778
129.4279
129.0411
128.9833
128.0394
126.3279
117.1540
112.1692
100.1965
94.4225
77.1951
77.0136
76.8322
65.1596
56.2333
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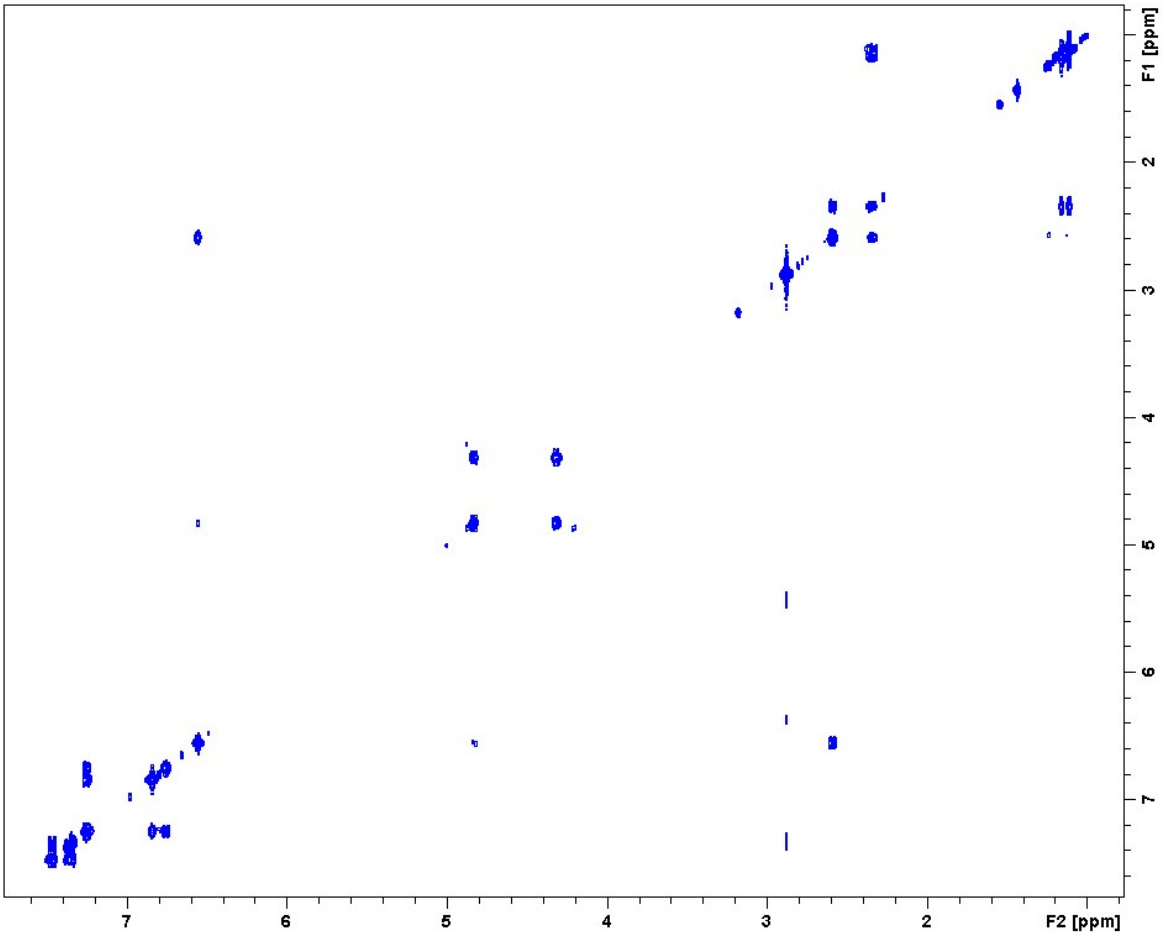
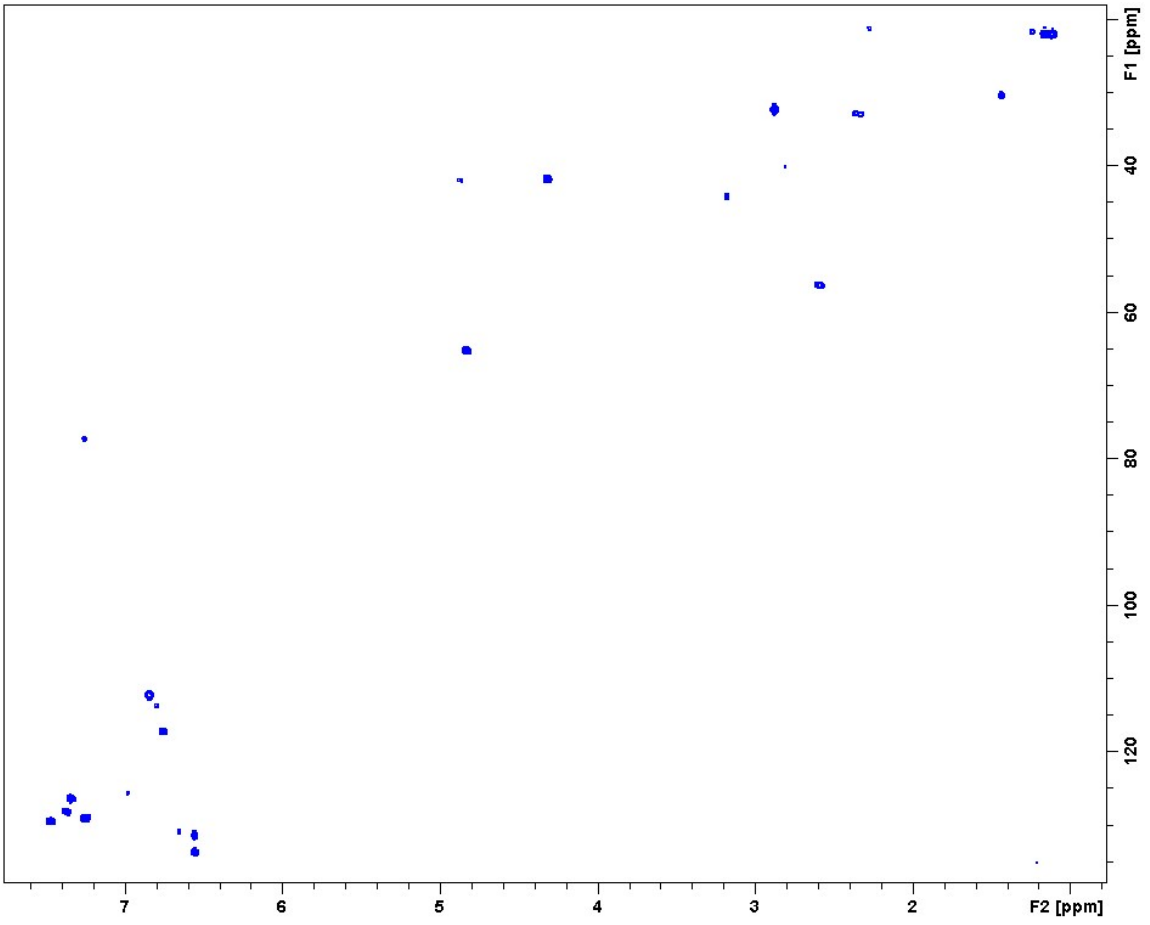
32.2622
21.9912
21.9299
-0.0002

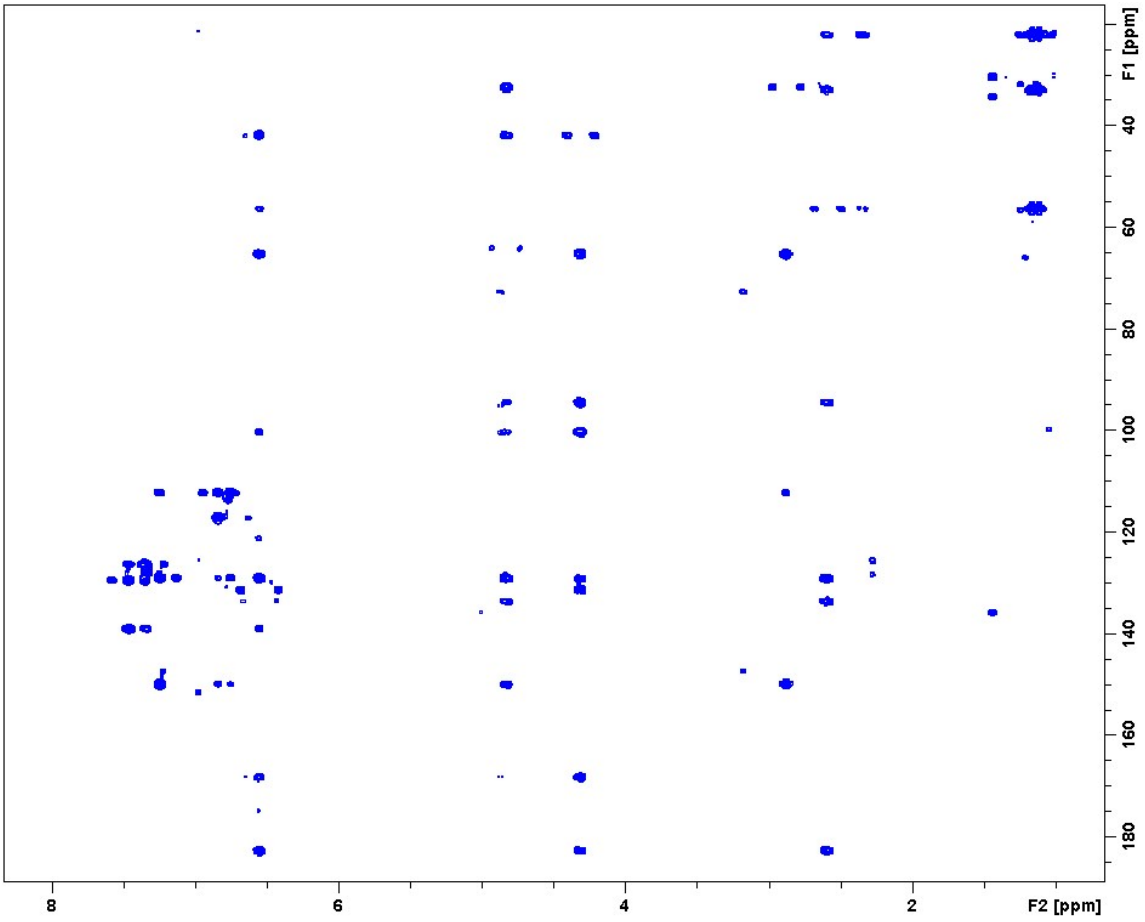
COSY

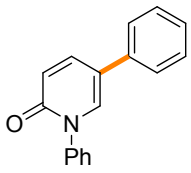

F1 [ppm]
2
3
4
5
6
7
7
6
5
4
3
2
F2 [ppm]

HMQC

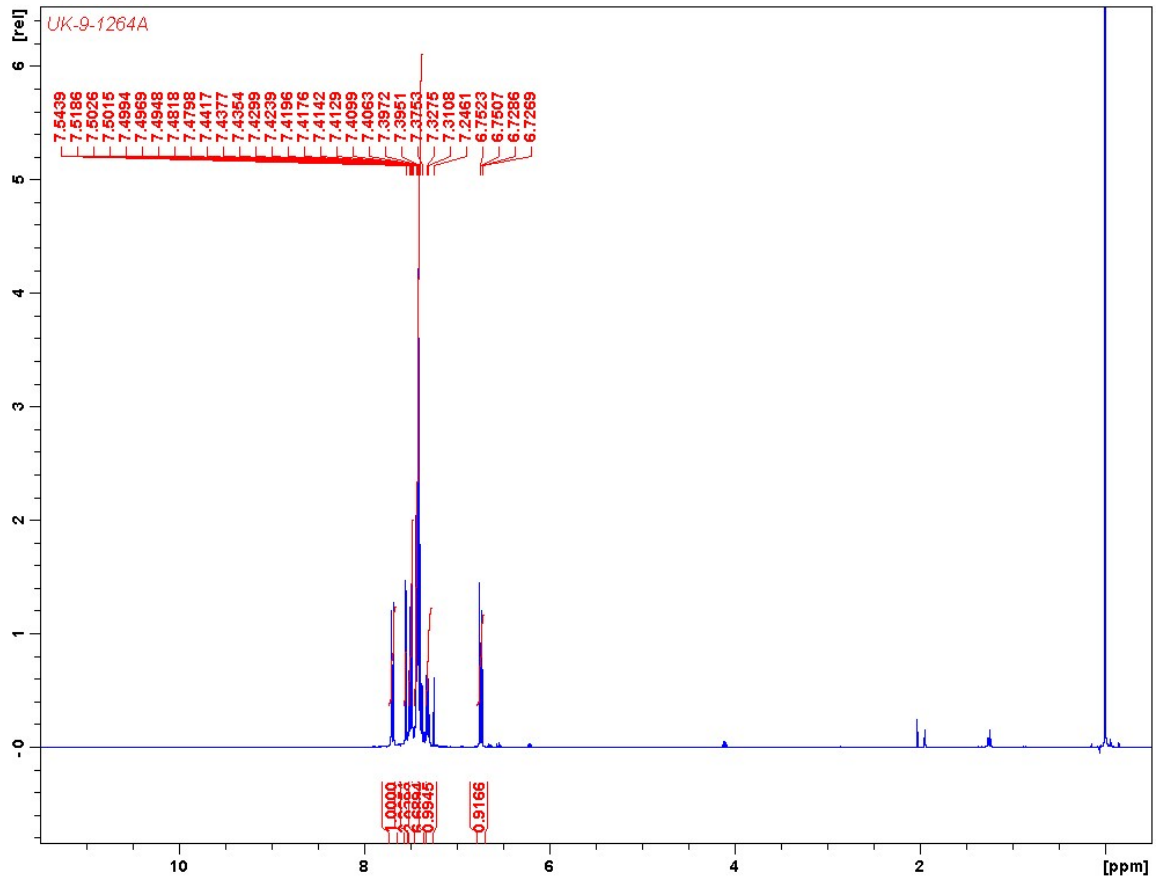

F1 [ppm]
40
60
80
100
120
7
6
5
4
3
2
F2 [ppm]

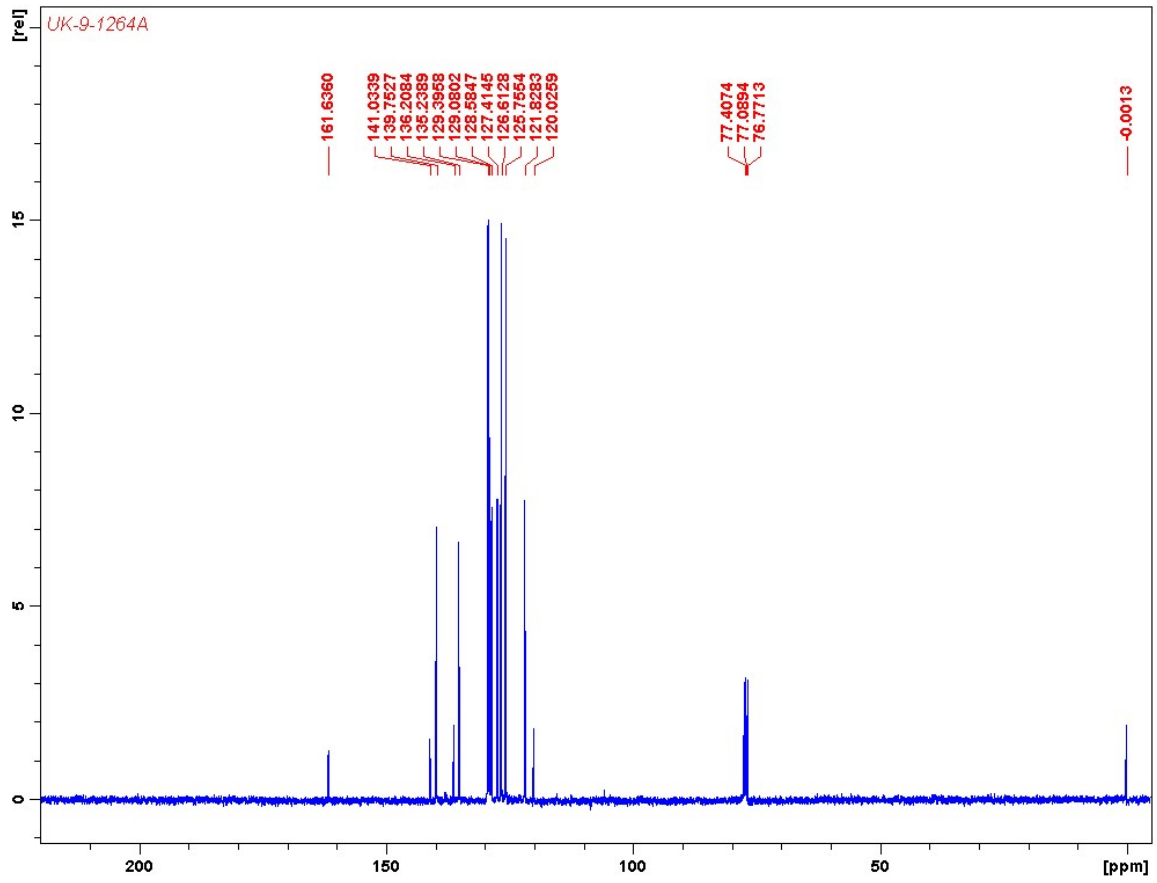
HMBC



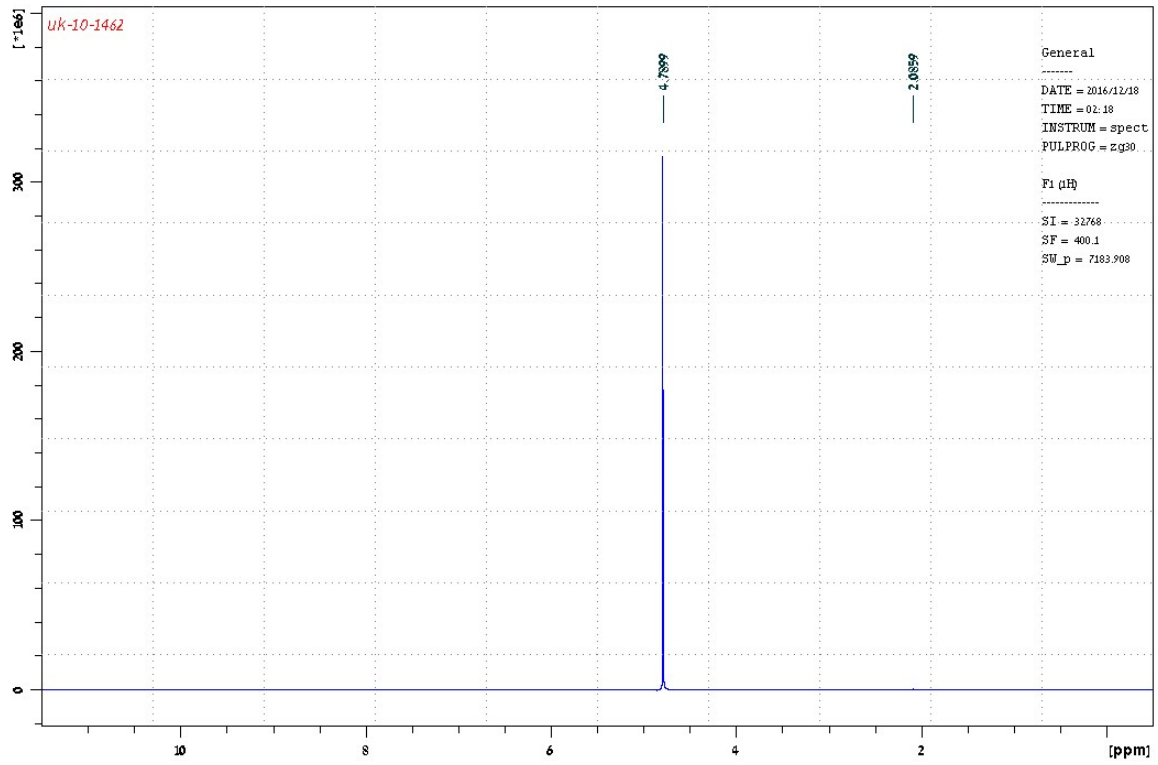


10





CD_3BF3K (^1H NMR in D_2O)


uk-10-1462
4.7899
2.0359
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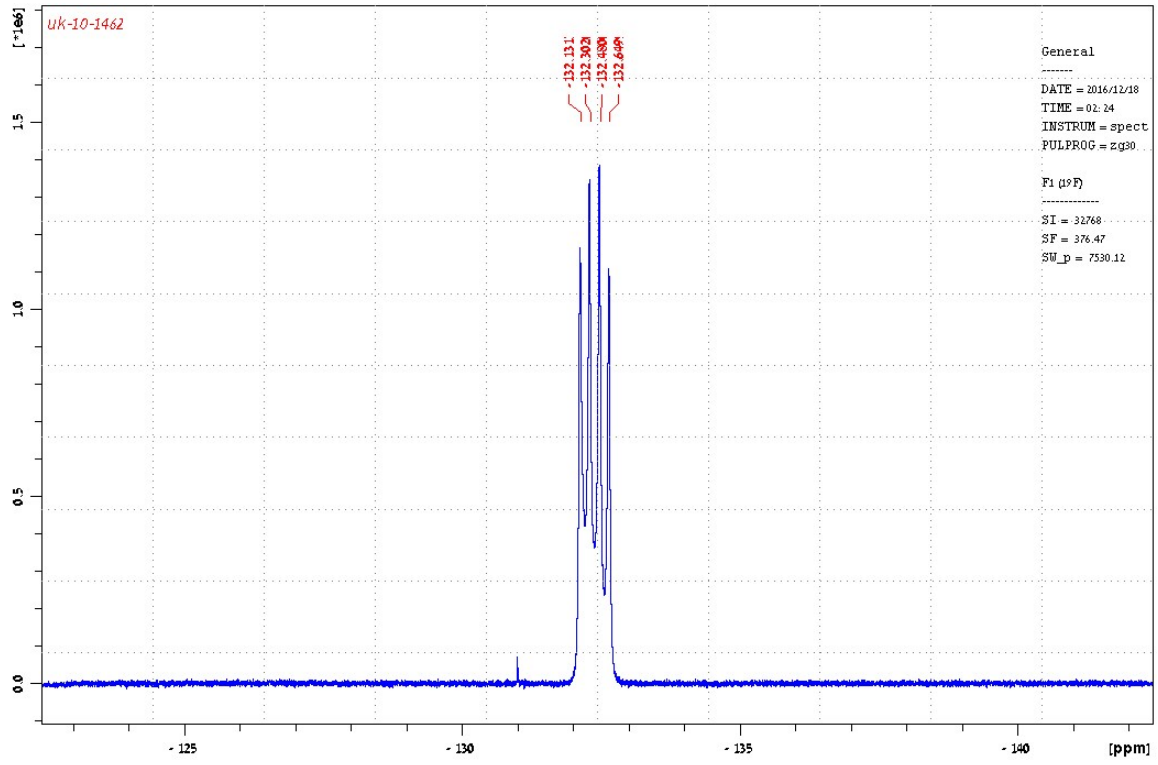
DATE = 2016/12/18
TIME = 02:18
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 32768
SF = 400.1
SW_p = 7183.908
[*1e6]
300
200
100
0
10
8
6
4
2
[ppm]

^{19}F


uk-10-1462
-132.131
-132.302
-132.480
-132.649
General
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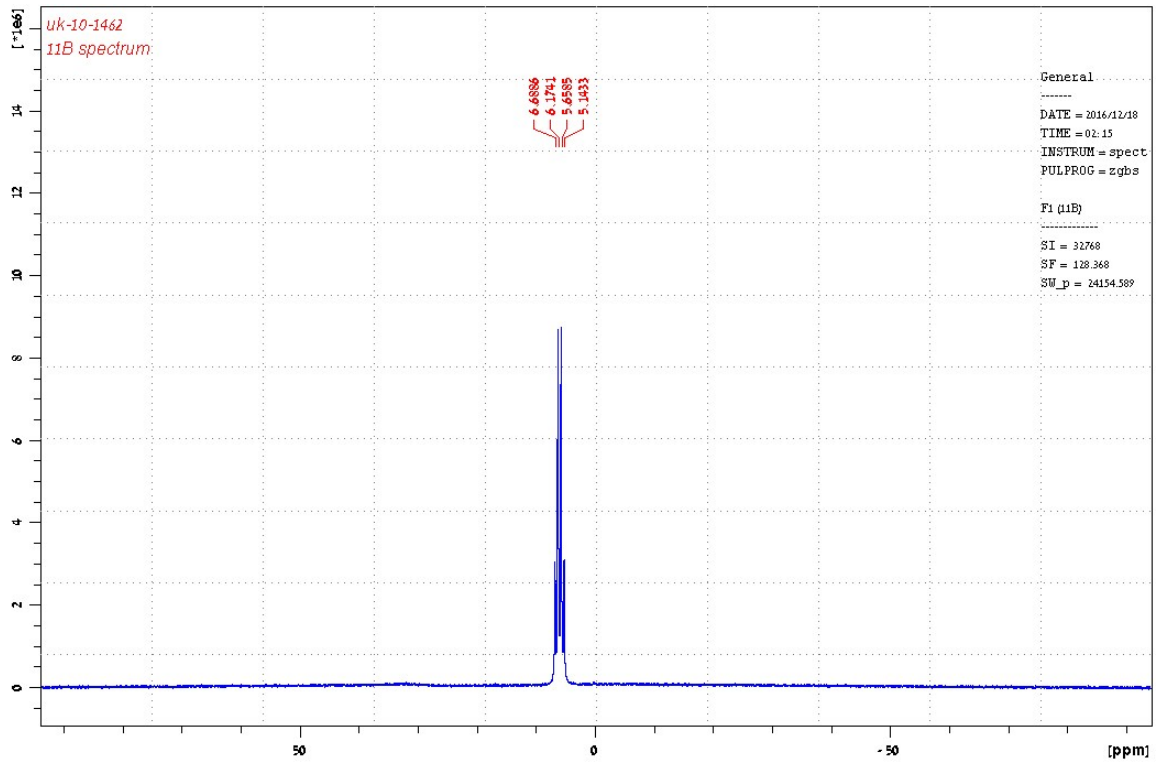
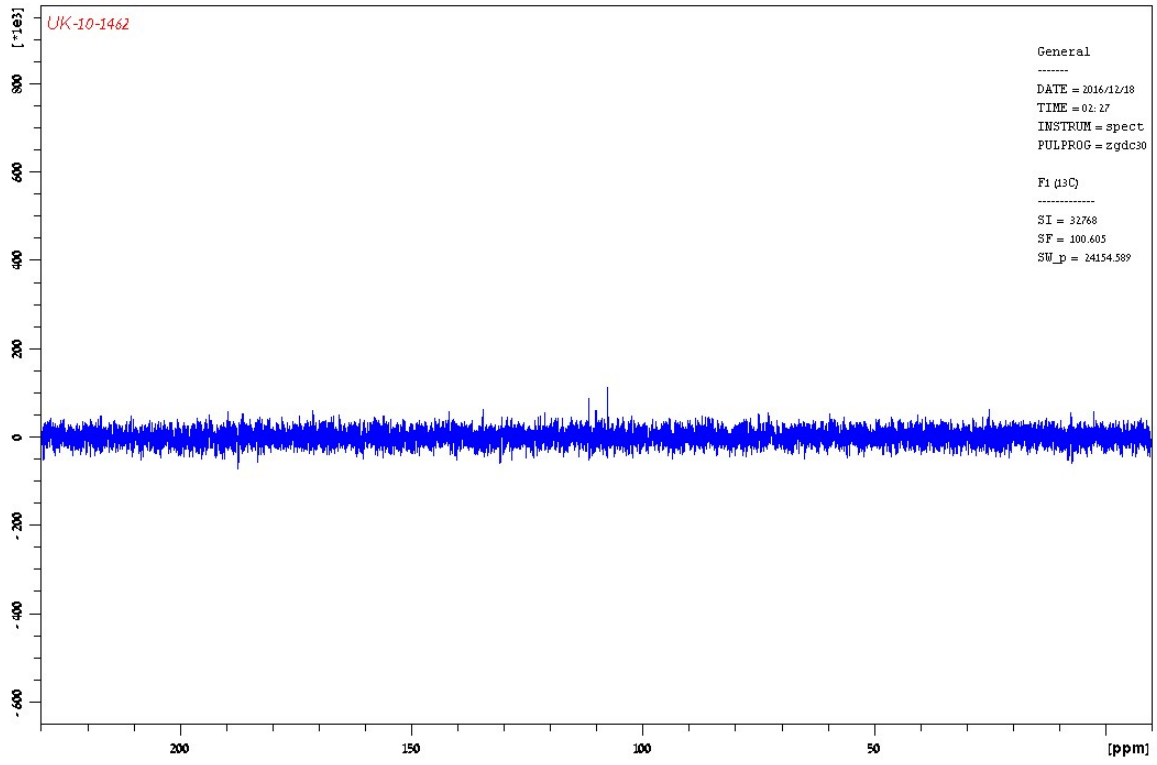
TIME = 02:24
INSTRUM = spect
PULPROG = zg30
F1 (19F)
SI = 32768
SF = 376.47
SW_p = 7530.12
[*1e6]
1.5
1.0
0.5
0.0
-125
-130
-135
-140
[ppm]


uk-10-1462
11B spectrum
6.6886
6.1741
5.6585
5.1433
General
DATE = 2016/12/18
TIME = 02:15
INSTRUM = spect
PULPROG = zgbs
F1 (11B)
SI = 32768
SF = 128.368
SW_p = 24154.589
[*1e6]
14
12
10
8
6
4
2
0
50
0
-50
[ppm]

^{13}C


UK-10-1462
General
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TIME = 02:27
INSTRUM = spect
PULPROG = zgdc30
F1 (13C)
SI = 32768
SF = 100.605
SW_p = 24154.589
[*1e3]
800
600
400
200
0
-200
-400
-600
200
150
100
50
[ppm]