Supporting Information:
Optimization of 3,5-Dimethylisoxazole Derivatives as Potent Bromodomain Ligands

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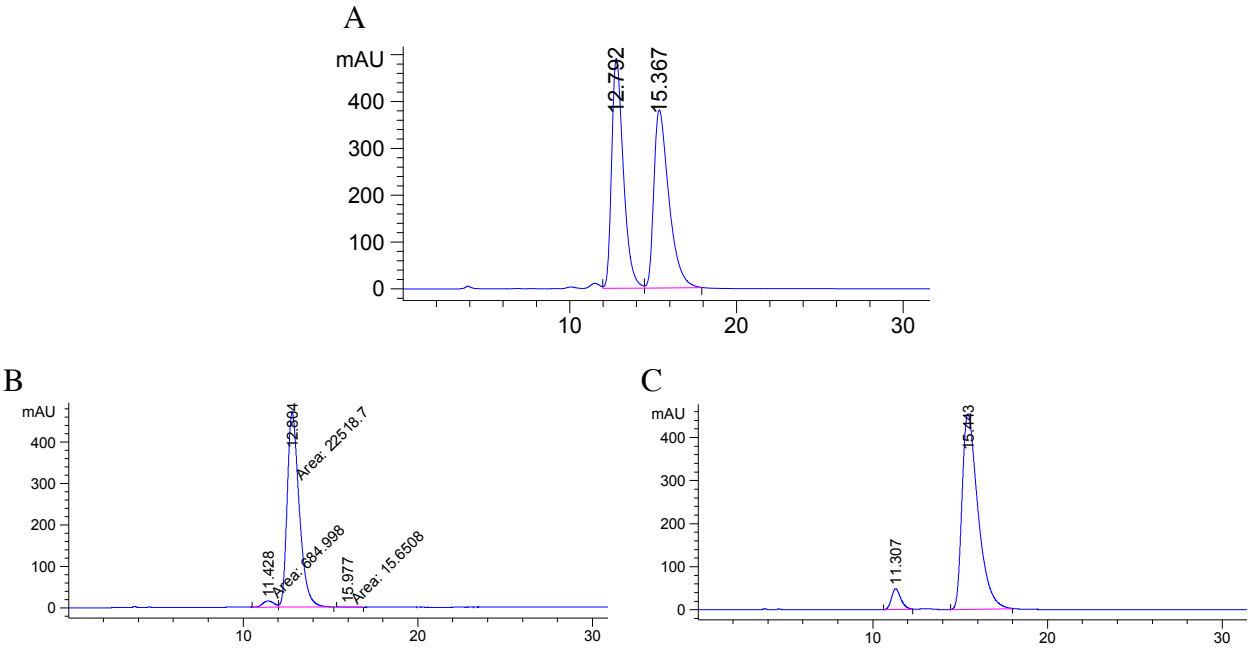
Abbreviations used in Supporting Information:

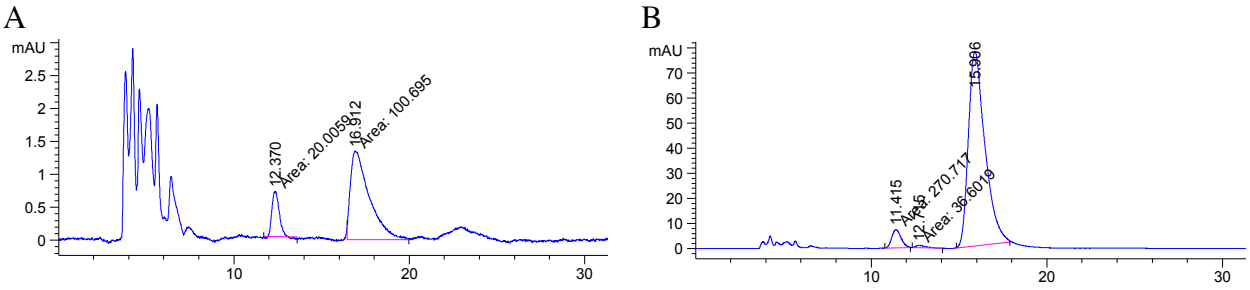
DMEM: Dulbecco's modified Eagle's medium; MTS: (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium); RuPhos: 2-dicyclohexylphosphino-2′,6′; -diisopropoxybiphenyl; WST-1: water-soluble tetrazolium 1.

Supporting Figure S1. Enantiomeric purity determination of **8** by chiral HPLC.



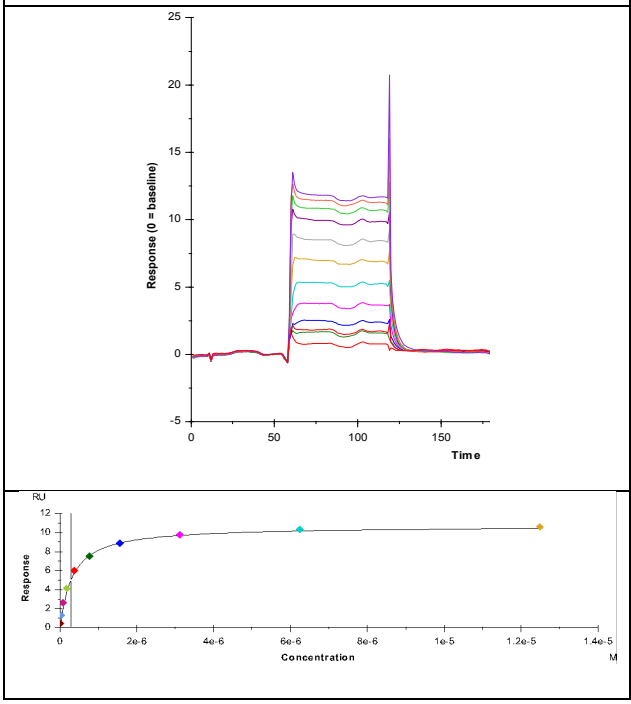
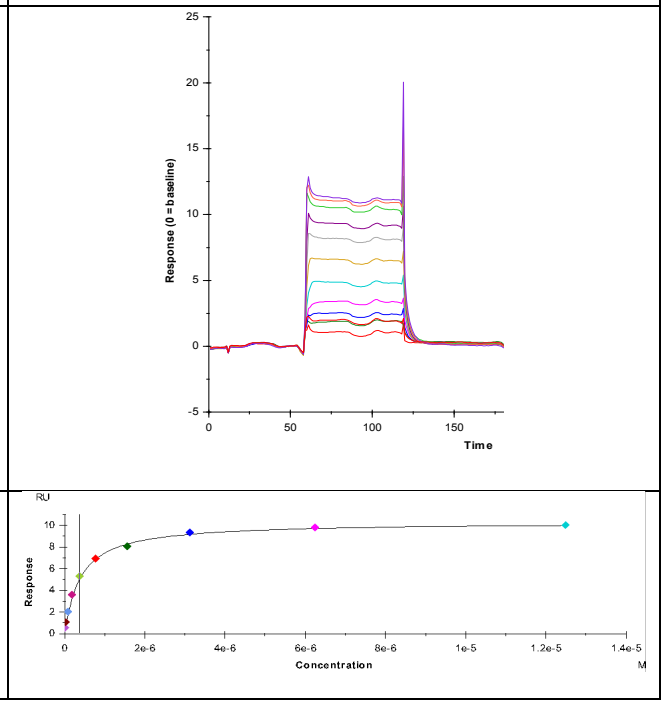
A: Racemic **8**; **B**: (–)-**8**; **C**: (+)-**8**. UV absorbance monitored at 230 nM. Analytical chiral HPLC indicates >99% ee in both cases.

Supporting Figure S2. Stability of (+)-**8** in aqueous buffer.



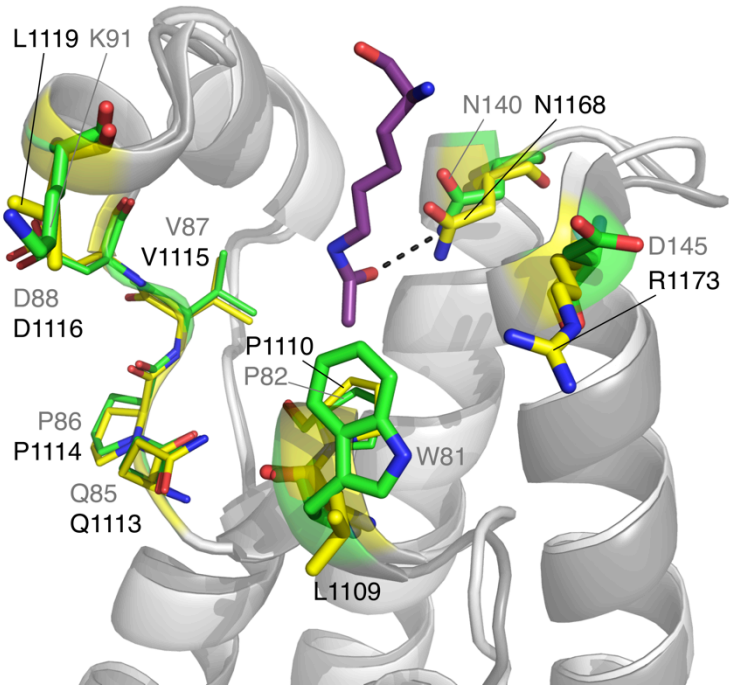
A: Blank (buffer only); **B**: (+)-**8** after 2 h in AlphaScreen buffer. Analytical chiral HPLC indicates >98% ee and 95% purity.

Supporting Figure S3. SPR steady state affinity analysis of *R*- and *S*-**8** binding to BRD4(1)

R-**8**	*S*-**8**
	

Response analyzed over a concentration range of 0.024 µM to 12.5 µM.

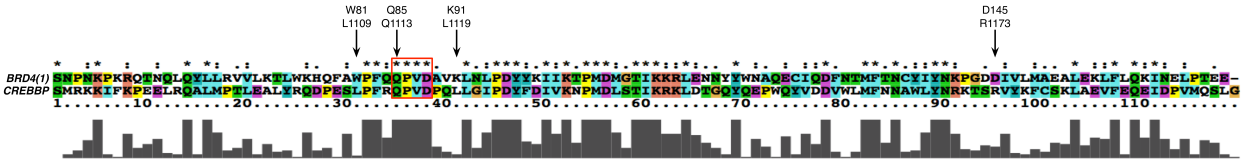
Supporting Figure S4. An overlay of X-ray crystal structures of BRD4(1) (PDB ID, 3UVW, key residues carbon = green) bound to $H4_{1-11}$KAc5,8 (KAc carbon = purple) and the CREBBP bromodomain (PDB ID, 3P1F key residues carbon = yellow). Residue numbers for BRD4(1) are shown in gray; residue numbers for CREBBP are shown in black.



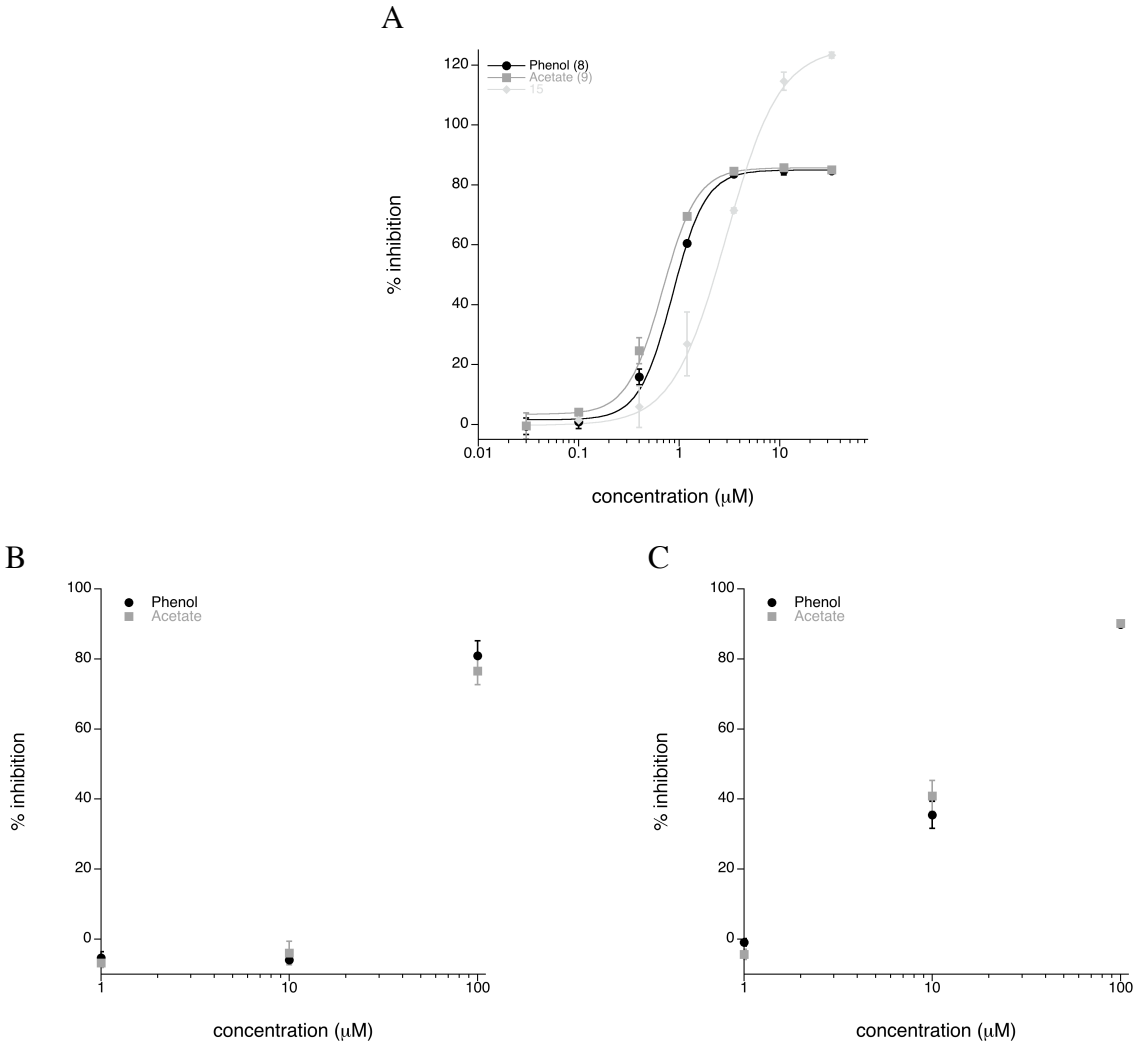
Although the BRD4(1) and CREBBP bromodomains adopt similar protein folds, there are a number of differences between key residues. The sequence alignment of BRD4(1) (3SVG) and CREBBP (3SVH) bromodomains performed in clustalX is shown in Figure S5. Three important residues that differ are W81, K91 and D145 in BRD4(1), which correspond to L1109, L1119 and R1173 in CREBBP, respectively (Figure S4). These residues alter the nature of the two ZA loop regions to which the acetylated peptides bind. In particular, CREBBP does not have a WFP shelf region in the same way as BRD4(1) and the other BET bromodomains. However, the loop region that forms the ZA channel and binds to two waters molecules, which comprises P82, Q85, P86, V87 and D88, is conserved in CREBBP (P1110, Q1113, P1114, V1115 and D1116) (Figure S5).

Consequently, the ZA channel water molecules are bound in a very similar manner by both bromodomains and therefore comparison between them is valid.

Supporting Figure S5. The sequence alignment of BRD4(1) (3SVG) and CREBBP (3SVH) bromodomains performed in clustalX. The residues that bind to the ZA channel water molecules are highlighted by the red box.

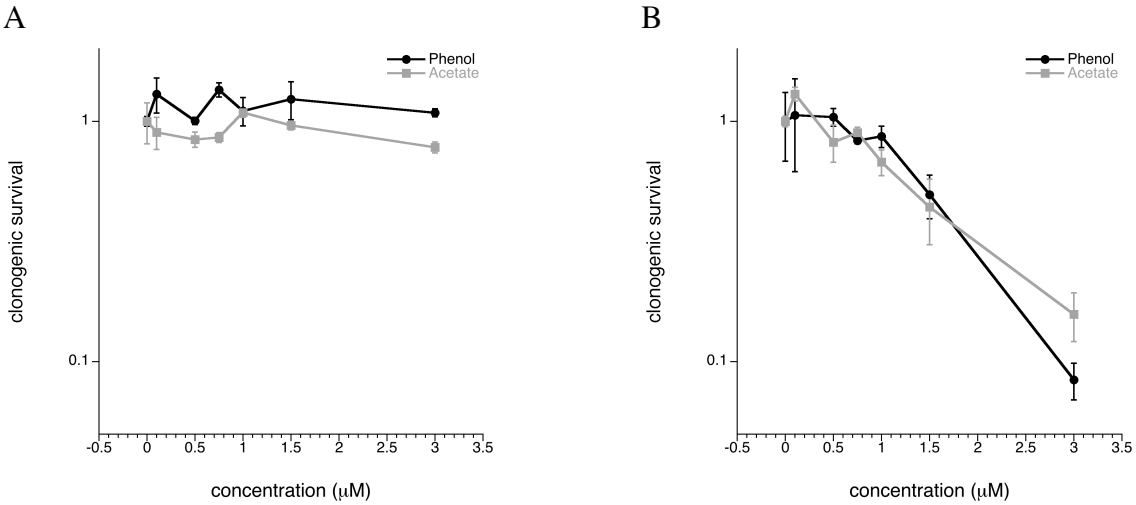


Supporting Figure S6. MTS viability assays for MV4;11, A549 and H1975 cells.



Viability as determined by MTS assay after 72 h of treatment with **8** (phenol), **9** (acetate) or **15**. **A:** IC_{50} determination for compounds **8** and **9** in MV4;11 AML cell line; 3-point viability assays for A549 (**B**) and H1975 (**C**).

Supporting Figure S7. Clonogenic assay for A549 and H1975 cells.



Clonogenic (colony formation) assay for lung adenocarcinoma cell lines A549 (**A**) and H1975 (**B**) after treatment with **8** (phenol) or **9** (acetate).

Supporting Table S1. Steady state analysis parameters for *R*- and *S*- **8** binding to BRD4(1)

	K_D Steady State Analysis (μM)	R_{max} (RU)	$\%TR_{max}$	Chi^2(RU)
R (n=1)	0.30	11.1	34.6	0.014
R (n=2)	0.41	9.0	28.0	0.052
S (n=1)	0.37	10.5	32.8	0.013
S (n=2)	0.40	8.7	27.1	0.021

Supporting Table S2. Effect of **8** and (+)-JQ1 in cancer cells after 72 h.

Cell line	IC_{50} (μM)	
	8	**(+)-JQ1**
U2OS (osteosarcoma)	19	2.9
HeLa (cervical adenocarcinoma)	24	2.1

Viability was assessed after 72 h incubation using MTS.

Cloning, Protein Expression and Purification: cDNA encoding human BRD4 (NCBI accession numbers NP 055114.1) was obtained from FivePrime and was used as template to amplify the N-terminal bromodomain region of the protein. Protein expression and purification was carried out as previously described.[1]

Protein Crystallization: Aliquots of the purified proteins were set up for crystallization using a mosquito® crystallization robot (TTP Labtech, Royston UK). Coarse screens were typically setup onto Greiner 3-well plates using three different drop ratios of precipitant to protein per condition (100+50 nL, 75+75 nL and 50+100 nL). Initial hits were optimized further using Greiner 1-well plates and scaling up the drop sizes in steps. All crystallizations were carried out using the sitting drop vapor diffusion method at 4 °C. BRD4(1) crystals with *(R)*-(–)-**8** (5 mM final concentration) were grown by mixing 200 nL of the protein (9.8 mg/mL) with 100 nL of reservoir solution containing 0.2 M NaI, 20 % PEG3350 and 10 % ethylene glycol. BRD4(1) crystals with *(S)*-(+)-**8** (5 mM final concentration) were grown by mixing 200 nL of the protein (14 mg/mL) with an 100 nL of reservoir solution containing 0.2 M Na/KPO_4, 20 % PEG3350 and 10 % EtGly.

Data Collection and Structure Solution: Crystals were cryo-protected using the well solution supplemented with additional ethylene glycol and were flash frozen in liquid nitrogen. Data were collected at a Rigaku FRE Superbright using an RAXIS-VI detector at 1.52 Å. Indexing and integration was carried out using XDS[2,3] and scaling was performed with SCALA.[4] Initial phases were calculated by molecular replacement with PHASER[5] using an ensemble of known bromodomain models (PDB IDs 2OSS, 2OUO, 2GRC, 2OO1, 3DAI, 3D7C, 3DWY). Initial models were built by ARP/wARP[6] and building was completed manually with COOT.[7] Refinement was carried out in REFMAC5.[8] Thermal motions were analyzed using TLSMD[9] and

hydrogen atoms were included in late refinement cycles. Data collection and refinement statistics can be found in Supporting Table S1. The models and structure factors have been deposited with PDB accession codes: 4J0R (BRD4(1)/ *(R)*-(–)-**8** complex) and 4J0S (BRD4(1)/ *(S)*-(+)-**8** complex).

Data collection and refinement statistics

Data Collection		
Protein	BRD4(1)	BRD4(1)
Ligand	*(R)*-(−)-**8**	*(S)*-(+)-**8**
PDB ID	4J0R	4J0S
Space group	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions: a, b, c (Å)	38.60 42.86 79.43	38.65 42.98 79.55
α, β, γ (deg)	90.00 90.00 90.00	90.00 90.00 90.00
Resolution* (Å)	1.72 (1.81-1.72)	1.84 (1.94-1.84)
Unique observations*	14500 (2056)	11949 (1676)
Completeness* (%)	99.5 (99.0)	99.2 (98.1)
Redundancy*	4.6 (4.5)	4.6 (4.6)
Rmerge*	0.119 (0.766)	0.160 (0.767)
I/ σI*	10.3 (2.0)	8.4 (2.0)
Refinement Statistics		
Resolution (Å)	1.72	1.84
R_{work} / R_{free} (%)	15.64/22.01	15.94/22.58
Number of atoms (protein/other/water)	1057/39/188	1059/38/156
B-factors (Å^2) (protein/other/water)	15.46/15.19/25.54	16.04/14.53/24.56
r.m.s.d bonds (Å)	0.015	0.016
r.m.s.d angles (^{o})	1.561	1.571
Ramachadran Favoured (%)	98.31	98.31
Allowed (%)	1.61	1.61
Disallowed (%)	0.00	0.00

* Values in parentheses correspond to the highest resolution shell.

Further General Experimental

Preparative chiral HPLC for the separation of (–)-**8** and (+)-**8** was carried out on a CHIRALCEL OG column (2 × 25 cm) using an Agilent 1260 Infinity Series instrument, eluent hexane:2-propanol 85:15, flow rate 18 mL/min. UV absorbance was monitored at 230 nM. Retention times for (–) and (+) enantiomers were 18.7 and 24.4 min respectively.

Analytical chiral HPLC was carried out on a CHIRALCEL OG column (4.6 × 250 mm) using an Agilent 1200 Series instrument, eluent hexane:2-propanol 80:20, flow rate 0.80 mL/min. UV absorbance was monitored at 230 nM. Retention times for (–)-**8** and (+)-**8** enantiomers were 12.8 and 15.4 min respectively. [Enantiomeric excess of both enantiomers was >99%.]

Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} aluminum-supported thin layer chromatography sheets. Visualization was by absorption of UV light (λ_{max} 254 nm), or thermal development after dipping in an aqueous solution of potassium permanganate, potassium carbonate and sodium hydroxide.

Flash column chromatography was performed on a Biotage SP1 or SP4 system using KP-Sil™ cartridges.

Anhydrous solvents were obtained under the following conditions: dry 1,4-dioxane, dry DMF and dry MeOH were purchased from Sigma-Aldrich UK in SureSeal™ bottles and used without further purification; THF and Et_2O were dried over activated basic alumina and stored over activated 3 Å molecular sieves under an argon or nitrogen atmosphere prior to use.

Chemicals were purchased from Acros UK, Sigma-Aldrich UK, Alfa Aesar UK, Fisher UK or Fluka UK. Where appropriate and if not stated otherwise, all non-aqueous reactions were performed in a flame-dried flask under an inert atmosphere of nitrogen or argon, using a double

vacuum manifold with the inert gas passing through a bed of activated 4 Å molecular sieves and self-indicating silica gel. Cs_2CO_3, K_2CO_3 and activated MnO_2 were dried in an oven prior to use. PhMgBr (in THF) was titrated against salicaldehyde phenylhydrazone prior to use, according to the procedure of Love and Jones.[9]

Reactions with microwave irradiation were carried out in a Biotage Initiator microwave synthesizer.

In vacuo refers to the use of a rotary evaporator attached to a diaphragm pump. Brine refers to a saturated aqueous solution of sodium chloride. Petroleum ether refers to the fraction boiling between 30–40 °C unless otherwise stated.

Stability of 8 in buffer: 0.5 mg of (+)-**8** in 10 μL DMSO was suspended in buffer (50 mM HEPES, 0.01% TWEEN, 0.1% BSA). After 2 h, the suspension was lyophilised then extracted with EtOH. A sample of buffer without DMSO or compound was similarly lyophilised and extracted. Analytical chiral HPLC was carried out as described above, indicating >98% ee and 95% purity.

Cytotoxcity of **8** in HeLa and U2OS cells: HeLa cells were grown and maintained in DMEM supplemented with L-glutamine and 10% fetal calf serum; U2OS cells were grown and maintained in McCoy's medium supplemented with 10% fetal calf serum. Cells were seeded in a 96-well plate at a density of 5×10^3 cells per well in 100 μL of media. After 24 h, cells were inoculated with DMSO (negative control), staurosporine (positive control) or **8**. After 24 h or 72 h, 10 μL of WST-1 (Roche Diagnostics) was added to the culture medium and cell viability was determined by colorimetric WST-1 conversion assay. Formazan dye formation was measured at 450 nm using a Molecular devices Spectramax Plus^{384} microplate reader. Relative WST-1 conversion in treated cells compared with untreated control cells was calculated after

subtraction of a WST-1 conversion in the absence of cells. Dose response graphs of staurosporine or **8** treatment were analyzed using the GraphPad Prism 5 program (GraphPad Software, Inc.).

Cytotoxicity of **8**, **9** and **15** in MV4;11 cells: MV4;11 cells were grown and maintained in RPMI-1640 medium with L-glutamine supplemented with 10% fetal calf serum and 1% (v/v) penicillin/streptomycin antibiotics. MV4;11 cells were seeded in a 96-well plate at a density of 1 × 10^4 cells per well in 100 μL of media. Cells were treated with **8**, **9**, **15**, DMSO (negative control), (+)-JQ1 or SGI-1776 (SuperGen) (positive controls) in 100 μL of media. After 72 h at 37 ˚C, 25 μL of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) coupled with phenazine methosulfate was added to each well, according to the manufacturers' instructions. Plates were incubated for 2 h at 37 ˚C, 5% CO_2 and the absorbance read at 490 nm. Positive and negative controls behaved as expected (IC_{50} SGI-1176: 53 nM, (+)-JQ1: 242 nM).

Clonogenic survival assay: H1975 or A549 cells were plated in a 6-well plate at a density of 300 cells/well, and allowed to adhere for 5 h before treatment. The cells were treated with either **8**, **9** or DMSO (as a control). Colonies (of at least 50 cells) were allowed to form for 10-14 days. The media was removed, and colonies were stained with crystal violet and counted.

Surface plasmon resonance methods and analysis of compound binding to BRD4(1): Duplicate SPR data for compound binding to immobilized BRD4(1) was generated on a Biacore T200 instrument at 25 °C. In all cases, a series S NTA chip was used to immobilize N-His tagged BRD4(1) via Ni^{2+} capture of the affinity tag followed by amine coupling at neutral pH 7.4. Flow cells of a NTA chip were primed using 350 mM EDTA injected for 60 seconds at 20 μL/min and then 500 μM Ni^{2+} for 120 seconds at 15 μL/min, this was repeated twice. The

surface was activated with 0.2 M *N*-ethyl-*N*'-(diethylaminopropyl)-carbodiimide (EDC) and 0.05 M *N*-hydroxysuccimide (NHS). Typically 6.25 μg/mL of BRD4(1) protected with I-BET at pH 7.4 in 50 mM HEPES pH7.4, 150 mM NaCl was injected at 5 μL/min for 45 seconds resulting in 1.2K RU – 4K RU of protein immobilized on the surface. The surface was neutralized with ethanolamine and extensively washed in the running buffer 50 mM HEPES pH7.4, 150 mM NaCl. A control surface of carbonic anhydrase was immobilized using the same methodology with a 600 s injection time at 5 μL/min resulting in >5K RU protein immobilized on the surface. Binding of test compounds was determined in 50 mM HEPES pH7.4, 150 mM NaCl, 0.05% Tween and 1% Ethanol.

Sensorgrams and binding curves were analyzed with BIAevaluation (GE Healthcare) software using a 1: 1 binding model. All compounds tested were selective for binding to BRD4(1) over carbonic anhydrase.

Good agreement was observed in the K_D values derived from kinetic and equilibrium analysis (within 2- fold). The kinetic parameters Ka and Kd could not be accurately determined in this experiment due to the rapid rates of association and dissociation observed under these conditions. Reported data were generated using steady state analysis with a 1:1 binding model.

Synthesis and Characterization of 10, 11, 18-20

3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde **10**

To a solution of 3-bromo-5-hydroxybenzoic acid (434 mg, 2.00 mmol) in MeOH (6 mL) was added conc. H_2SO_4 (5 mL), and the mixture was heated under reflux for 5 h. After cooling to rt, H_2O (20 mL) was added, and the resultant precipitate was filtered and washed with cold H_2O.

The solid was dried by azeotropic distillation with toluene, giving methyl 3-bromo-5-hydroxybenzoate as a colorless solid (354 mg, 77%).

To a suspension of $LiAlH_4$ (144 mg, 3.79 mmol, 2.5 eq) in dry THF (7 mL) was added methyl 3-bromo-5-hydroxybenzoate (354 mg, 1.53 mmol, 1.0 eq), and the mixture was heated under reflux for 5 h. After cooling to rt, the mixture was poured onto ice, then acidified with HCl (aq. 10%) and extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 3-bromo-5-hydroxybenzyl alcohol as a colorless solid (255 mg, 84%).

To a suspension of freshly-prepared pyridinium chlorochromate (515 mg, 2.39 mmol, 1.5 eq) in CH_2Cl_2 was added 3-bromo-5-hydroxybenzyl alcohol (322 mg, 1.59 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) slowly at 0 °C. The mixture was stirred at rt for 3.5 h, then concentrated *in vacuo*. The residue was washed with Et_2O (4 × 10 mL), then filtered. The filtrate was washed with $NaHCO_3$ (sat. aq. 30 mL) and the aqueous later was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 3-bromo-5-hydroxybenzaldehyde as a colorless solid (192 mg, 60%); mp 137-140 °C; ^{1}H NMR (DMSO-D_6) 7.27-7.26 (2H, m); 7.52 (1H, m), 9.88 (1H, s); *m/z* (ES$^+$) 201 ([^{79}M+H]$^+$), 203 ([^{81}M+H]$^+$).

Following the procedure of Molander *et al*.,[10] to a round-bottomed flask containing 3-bromo-5-hydroxybenzaldehyde (5.0 g, 25.0 mmol, 1.0 eq), potassium 3,5-dimethylisoxazol-4-yl trifluoroborate (5.6 g, 27.5 mmol, 1.1 eq), $Pd(OAc)_2$ (340 mg, 1.5 mmol, 0.06 eq), RuPhos (1.4 g, 3.0 mmol, 0.12 eq) and Na_2CO_3 (5.3 g, 50 mmol, 2.0 eq) under N_2 was added degassed EtOH (70 mL), and the mixture heated under reflux for 2 h. The mixture was cooled to rt and filtered through a plug of silica gel (eluent 25% MeOH/EtOAc). The filtrate was concentrated *in vacuo*, and the residue was dissolved in THF (15 mL) at 70 °C then filtered. The filtrate was

concentrated *in vacuo* to a volume of approximately 4 mL and then cooled. Filtration gave **10** as a colorless solid (3.55 g). The filtrate was concentrated *in vacuo* and the residue purified by silica gel column chromatography (gradient elution, 9 → 33% EtOAc/petroleum ether) to give **10** as a colorless solid (0.42 g, combined yield 73%); mp 184-187 °C; ^{1}H NMR (500 MHz, DMSO-D_6) 2.24 (3H, s), 2.42 (3H, s), 7.09 (1H, dd, *J* = 2.4, 1.6 Hz), 7.26 (1H, dd, *J* = 2.4, 1.3 Hz), 7.36 (1H, dd, *J* = 1.6, 1.3 Hz), 9.96 (1H, s); ^{13}C NMR (126 MHz, DMSO-D_6) 10.5, 11.4, 113.6, 115.1, 121.6, 121.9, 132.1, 138.1, 158.0, 158.5, 165.5, 193.0; HRMS *m/z* (ES^+) found $[M–H]^-$ 216.0671; $C_{12}H_{10}NO_3$ requires M^- 216.0666; *m/z* (ES^-) 216 ($[M–H]^-$, 100), 433 ($[2M–H]^-$, 10). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.1; N, 6.5. Found: C, 66.4; H, 4.9; N, 6.5.

3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxybenzaldehyde **11**

Following the procedure of Sarju *et al*.,[11] anhydrous K_2CO_3 (1.91 g, 13.8 mmol, 1.0 eq) and **10** (3.00 g, 13.8 mmol, 1.0 eq) were added to a dry 10-20 mL microwave vial. The vial was sealed and purged with nitrogen (3 × evacuate/fill). EtBr (3.00 g, 2.06 mL, 27.6 mmol) and anhydrous MeOH (15 mL) were added, and the mixture was stirred at 120 °C for 30 min with microwave irradiation, then concentrated *in vacuo*. The residues were extracted with EtOAc (5 × 50 mL), and the combined organic extracts washed with H_2O (2 × 250 mL) and brine (250 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient elution, 20 → 40% Et_2O/petroleum ether) gave **11** as a colorless solid (2.32 g, 69 %); mp 99-100 °C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) 1.48 (3H, q, *J* = 7.0 Hz), 2.30 (3H, s), 2.44 (3H, s), 7.05 (1H, dd, *J* = 2.5, 1.5 Hz), 7.33 (1H, dd, *J* = 1.5, 1.3 Hz), 7.38 (1H, dd, *J* = 2.5, 1.3 Hz), 10.01 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 14.7, 64.0, 111.9, 115.5, 122.4, 123.5, 132.8, 138.2, 158.4, 159.8, 165.7, 191.7; HMRS *m/z* (ES^+) found $[M+Na]^+$ 268.0940; $C_{14}H_{15}NNaO_3$ M^+ requires 268.0944; *m/z* (ES^+) 246 ($[M+H]^+$, 4), 268 ($[M+Na]^+$, 10), 300

([M+MeOH+Na]$^+$, 40), 513 ([2M+Na]$^+$, 9), 577 ([2M+2MeOH+Na]$^+$, 100). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.6; H, 6.2; N, 5.6.

3-(3,5-Dimethylisoxazol-4-yl)-5-methoxybenzaldehyde **18**

Following the procedure of Parrish *et al*.,[12] anhydrous Cs_2CO_3 (225 mg, 690 μmol, 1.5 eq) was added to a dry 2-5 mL microwave vial containing **10** (100 mg, 460 μmol, 1.0 eq) and anhydrous DMF (2.3 mL) under a nitrogen atmosphere. The vial was sealed and MeI (131 mg, 57 μL, 920 μmol, 2.0 eq) was added. The suspension was stirred at rt for 2.5 h, then quenched with aq. HCl (1 M, 10 mL). The resultant precipitate was collected by filtration, washed with H_2O (20 mL) and dried under vacuum to give **18** as a brown solid (68 mg). The filtrate was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with H_2O (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **18** as a yellow solid (30 mg, combined yield 92%); mp 90-92 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 2.30 (3H, s), 2.44 (3H, s), 3.92 (3H, s), 7.06 (1H, dd, J = 2.3, 1.4 Hz), 7.35 (1H, dd, J = 1.4, 1.1 Hz), 7.40 (1H, dd, J = 2.3, 1.1 Hz), 10.02 (1H, s); ^{13}C (126 MHz, $CDCl_3$) 10.8, 11.6, 55.7, 111.2, 115.5, 122.1, 123.8, 132.8, 138.2, 158.4, 160.5, 165.8, 191.6; HRMS *m/z* (ES$^+$) found [M+Na]$^+$ 254.0789; $C_{13}H_{13}NNaO_3$, M$^+$ requires 254.0788; *m/z* (ES$^+$) 232 ([M+H]$^+$, 14), 254 ([M+Na]$^+$, 15), 286 ([M+Na+MeOH]$^+$, 83), 318 ([M+Na+2MeOH]$^+$, 33), 517 ([2M+Na+MeOH]$^+$, 9), 549 ([2M+Na+2MeOH]$^+$, 100). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.4; H, 5.6; N, 6.0.

3-(3,5-Dimethylisoxazol-4-yl)-5-(2-methoxyethoxy)benzaldehyde **19**

Following the procedure of Sarju *et al*.,[11] **10** (250 mg, 1.15 mmol, 1.0 eq) and anhydrous K_2CO_3 (159 mg, 1.15 mmol, 1.0 eq) were added to a dry 2–5 mL microwave vial. The vial was sealed, and MeOH (0.5 mL) and 2-bromoethyl methyl ether (192 mg, 130 μL, 1.38 mmol, 1.2

eq) were added under a nitrogen atmosphere. The mixture was stirred at 110 °C for 30 min with microwave irradiation, then concentrated *in vacuo*. The residues were extracted with EtOAc (40 mL), and the organic extracts were washed with H_2O (2 × 40 mL), aq. HCl (1 M, 40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient elution, 15 → 60% EtOAc/petroleum ether) gave **19** as pale yellow oil (221 mg, 70%); ^{1}H NMR (500 MHz, $CDCl_3$) 2.29 (3H, s), 2.43 (3H, s), 3.47 (3H, s), 3.80 (2H, d, J = 4.5 Hz), 4.23 (2H, d, J = 4.5 Hz), 7.12 (1H, dd, J = 2.5, 1.5 Hz), 7.35 (1H, dd, J = 1.5, 1.3 Hz), 7.41 (1H, dd, J = 2.5, 1.3 Hz), 10.00 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 59.3, 67.8, 70.8, 112.0, 115.5, 122.7, 123.9, 132.8, 138.2, 158.4, 159.7, 165.8, 191.5; HRMS *m/z* (ES^+) found $[M+Na]^+$ 298.1055; $C_{15}H_{17}NNaO_4$ requires M^+ 298.1050; *m/z* (ES^+) 298 ($[M+Na]^+$, 11), 330 ($[M+Na+MeOH]^+$, 70), 573 ($[2M+Na]^+$, 14), 605 ($[2M+Na+MeOH]^+$, 32), 637 ($[2M+Na+2MeOH]^+$, 100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.5; H, 6.1; N, 5.0.

3-(3,5-Dimethylisoxazol-4-yl)-5-(2-hydroxyethoxy)benzaldehyde **20**

To a dry 10–20 mL microwave vial under a nitrogen atmosphere were added **10** (200 mg, 921 μmol, 1.0 eq) and anhydrous DMF (5 mL). Anhydrous Cs_2CO_3 (450 mg, 1.38 mmol, 1.5 eq) was then added and the vial was sealed. 2-Bromoethyl acetate (230 mg, 150 μL, 1.38 mmol, 1.5 eq) was added by syringe, and the mixture was stirred at 80 °C for 16 h, then concentrated *in vacuo*. The residues were resuspended in MeOH (10 mL) and stirred at rt for 90 min, then concentrated *in vacuo*. HCl (aq. 1 M, 10 mL) was added, and the solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient elution, 30 → 70% EtOAc/petroleum ether) gave **20** as a colorless

solid (98 mg, 41%); mp 96–98 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 2.12 (1H, t, *J* = 3.5 Hz), 2.30 (3H, s), 2.44 (3H, s), 4.04 (2H, td, *J* = 4.5, 3.0 Hz), 4.20 (2H, t, *J* = 4.5 Hz), 7.10 (1H, dd, *J* = 2.5, 1.5 Hz), 7.37 (1H, dd, *J* = 1.5, 1.3 Hz), 7.41 (1H, dd, *J* = 2.5, 1.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 61.2, 69.7, 111.9, 115.4, 122.4, 124.1, 133.0, 138.2, 158.4, 159.6, 165.8, 191.5; HRMS *m/z* (ES^+) found $[M+Na]^+$ 284.0893; $C_{14}H_{15}NNaO_4$ requires M^+ 284.0893; *m/z* (ES^+) 284 ($[M+Na]^+$, 7), 316 ($[M+Na+MeOH]^+$, 56), 545 ($[2M+Na]^+$, 9), 577 ($[2M+Na+MeOH]^+$, 11), 609 ($[2M+Na+2MeOH]^+$, 100), 902 ($[3M+Na+3MeOH]^+$, 18). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8; N, 5.4. Found: C, 64.5; H, 5.7; N, 5.2.

Further Characterization for Compounds 8, 9, 12-17, 21-23

(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(phenyl)methanol **12**

^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 14.8, 63.6, 76.1, 111.4, 114.4, 116.5, 119.5, 126.5, 127.8, 128.6, 131.7, 143.5, 145.9, 158.6, 159.3, 165.2; Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.3; H, 6.6; N, 4.3. Found: C, 74.2; H, 6.7; N, 4.4.

(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(4-fluorophenyl)methanol **13**

^{13}C NMR (126 MHz, $CDCl_3$) 10.7, 11.5, 14.7, 63.6, 75.2, 111.4, 114.4, 115.3 (d, *J* = 21 Hz), 116.5, 119.4, 128.2 (d, *J* = 8.1 Hz), 131.7, 139.5 (d, *J* = 3.5 Hz), 145.9, 158.6, 159.3, 162.2 (d, *J* = 246 Hz), 165.3; ^{19}F NMR (470 MHz, $CDCl_3$) –114.7; Anal. Calcd for $C_{20}H_{20}FNO_3$: C, 70.4; H, 5.9; N, 4.1. Found: C, 70.2; H, 6.0; N, 4.0.

(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(3-fluorophenyl)methanol **14**

^{13}C NMR (126 MHz, $CDCl_3$) 10.7, 11.6, 14.7, 63.6, 75.3, 111.5, 113.3 (d, *J* = 23 Hz), 114.4, 114.6, 116.4, 119.4, 122.0 (d, *J* = 2.8 Hz), 130.0 (d, *J* = 8.1 Hz), 131.8, 145.5, 146.2 (d, *J* =

6.8 Hz), 158.6, 159.4, 162.9 (d, J = 246 Hz), 165.3; ^{19}F NMR (470 MHz, $CDCl_3$) –112.5; Anal. Calcd for $C_{20}H_{20}FNO_3$: C, 70.4; H, 5.9; N, 4.1. Found: C, 70.2; H, 5.8; N, 4.1.

(4-Chlorophenyl)(3-(3,5-dimethylisoxazol-4-yl)-5-ethoxyphenyl)methanol **15**

^{13}C NMR (126 MHz, $CDCl_3$) 10.9, 11.7, 14.8, 63.7, 75.4, 111.5, 114.6, 116.5, 119.4, 127.9, 128.7, 131.9, 133.5, 142.1, 145.7, 158.6, 159.5, 165.3; Anal. Calcd for $C_{20}H_{20}ClNO_3$: C, 67.1; H, 5.6; N, 3.9. Found: C, 67.1; H, 5.5; N, 3.8.

(3-Chlorophenyl)(3-(3,5-dimethylisoxazol-4-yl)-5-ethoxyphenyl)methanol **16**

^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 14.8, 63.7, 75.2, 111.6, 114.6, 116.5, 119.5, 124.7, 126.7, 127.8, 129.8, 131.9, 134.5, 145.5, 145.8, 158.6, 159.5, 165.4; Anal. Calcd for $C_{20}H_{20}ClNO_3$: C, 67.1; H, 5.6; N, 3.9. Found: C, 67.2; H, 5.6; N, 3.9.

3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenol **8**

^{13}C NMR (126 MHz, acetone-D_6) 10.9, 11.6, 75.9, 113.5, 115.2, 117.2, 119.3, 127.3, 127.8, 129.0, 132.3, 146.3, 148.8, 158.5, 158.9, 165.8; Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.1; H, 5.8; N, 4.8.

3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenyl acetate **9**

^{13}C NMR (126 MHz, $CDCl_3$) 10.7, 11.6, 21.3, 75.5, 115.8, 118.7, 121.1, 124.4, 126.6, 128.0, 128.7, 131.7, 143.2, 146.1, 150.9, 158.4, 165.6, 169.3; Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.2; H, 5.7; N, 4.2. Found: C, 71.1; H, 5.6; N, 4.1.

(3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxyphenyl)(phenyl)methanone **17**

^{13}C NMR (126 MHz, D_6-acetone) 10.9, 11.6, 116.2, 116.5, 120.6, 122.6, 129.3, 130.6, 133.0, 133.4, 138.5, 140.5, 158.7, 158.9, 166.3, 196.1.

(3-(3,5-Dimethylisoxazol-4-yl)-5-methoxyphenyl)(phenyl)methanol **21**

^{13}C NMR (126 MHz, $CDCl_3$) 10.7, 11.6, 55.3, 75.9, 110.8, 114.0, 116.5, 119.7, 126.5, 127.8, 128.6, 131.7, 143.6, 146.0, 158.6, 159.9, 165.3; Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5. Found: C, 74.0; H, 6.0; N, 4.4.

(3-(3,5-Dimethylisoxazol-4-yl)-5-(2-methoxyethoxy)phenyl)(phenyl)methanol **22**

^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 59.2, 67.3, 71.0, 75.9, 111.6, 114.5, 116.5, 119.9, 126.5, 127.8, 128.5, 131.6, 143.6, 146.0, 158.6, 159.2, 165.3; Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.4; H, 6.6; N, 4.0. Found: C, 71.5; H, 6.3; N, 3.8.

2-(3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenoxy)ethanol **23**

^{13}C NMR (126 MHz, DMSO-D_6) 10.5, 11.3, 59.5, 69.6, 73.9, 111.5, 112.9, 115.9, 119.0, 126.1, 126.8, 128.1, 130.7, 145.5, 148.0, 158.0, 158.9, 165.1; Anal. Calcd for $C_{20}H_{21}NO_4$: C: 70.8; H, 6.2; N, 4.1. Found: C, 70.7; H, 6.4; N, 4.1.

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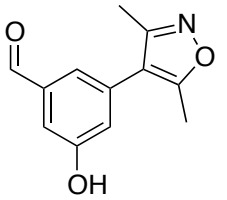
3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde **10** ^{1}H NMR

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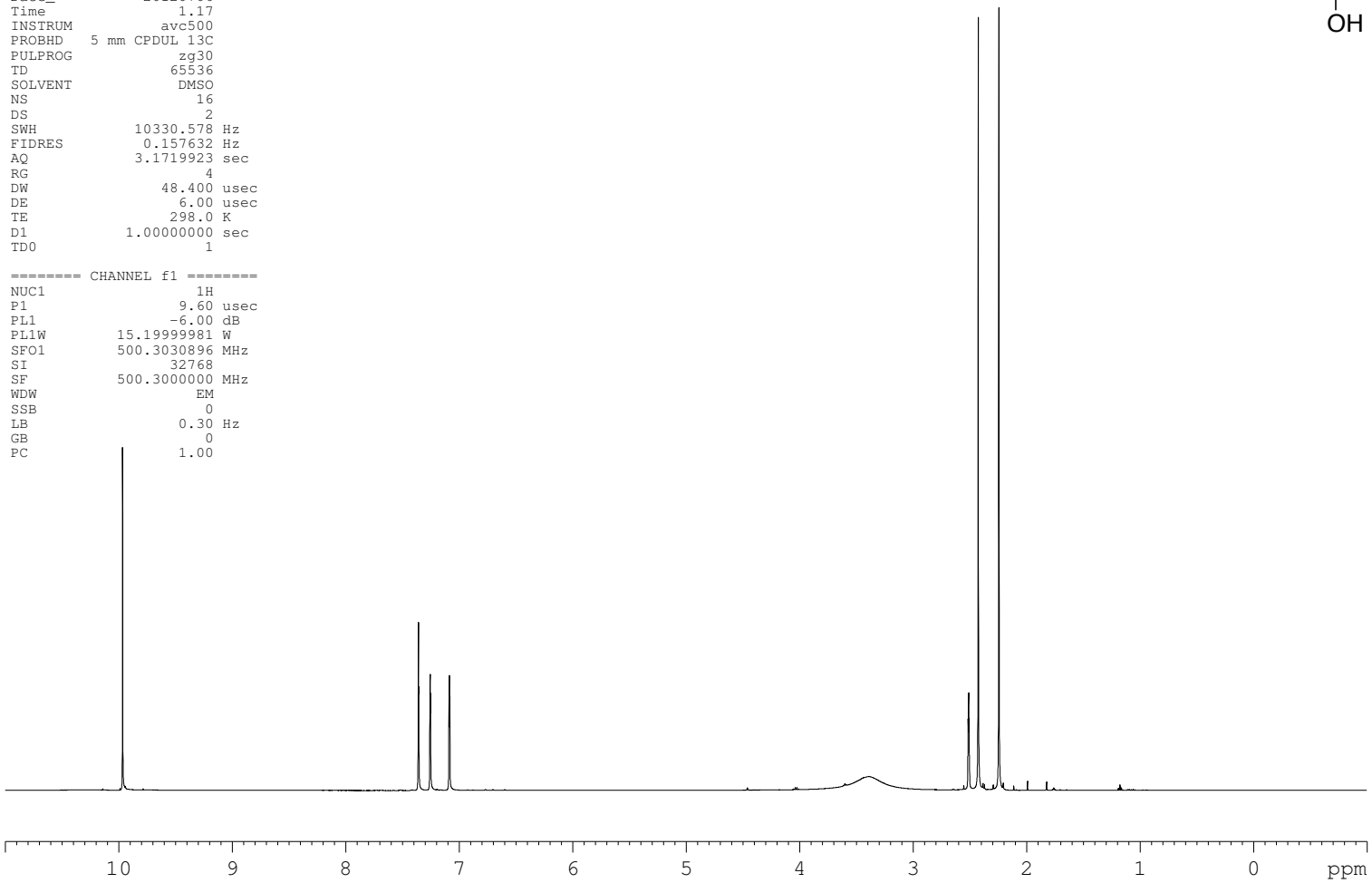

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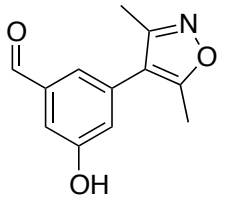


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PL12W        0.21869738 W
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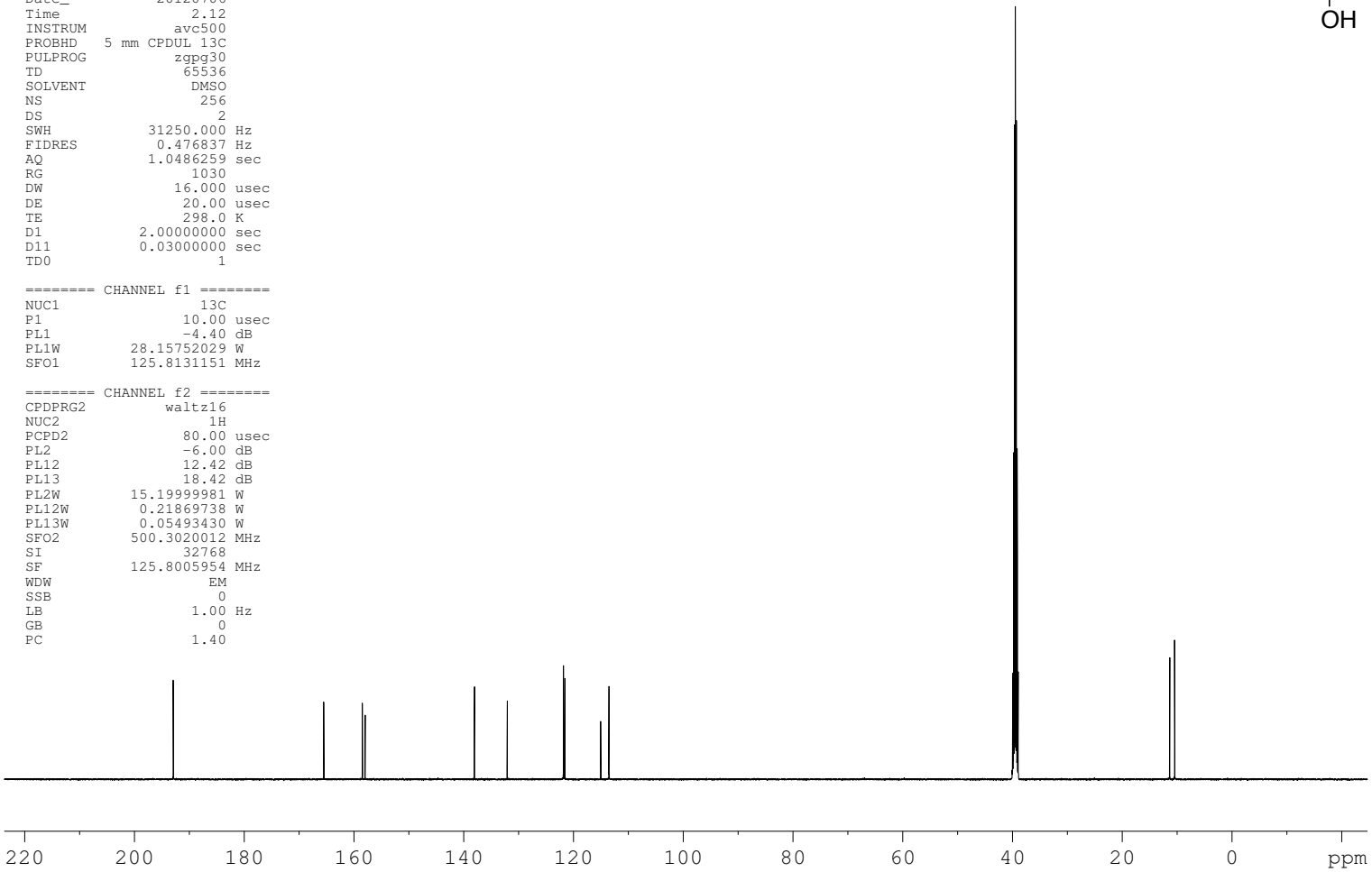
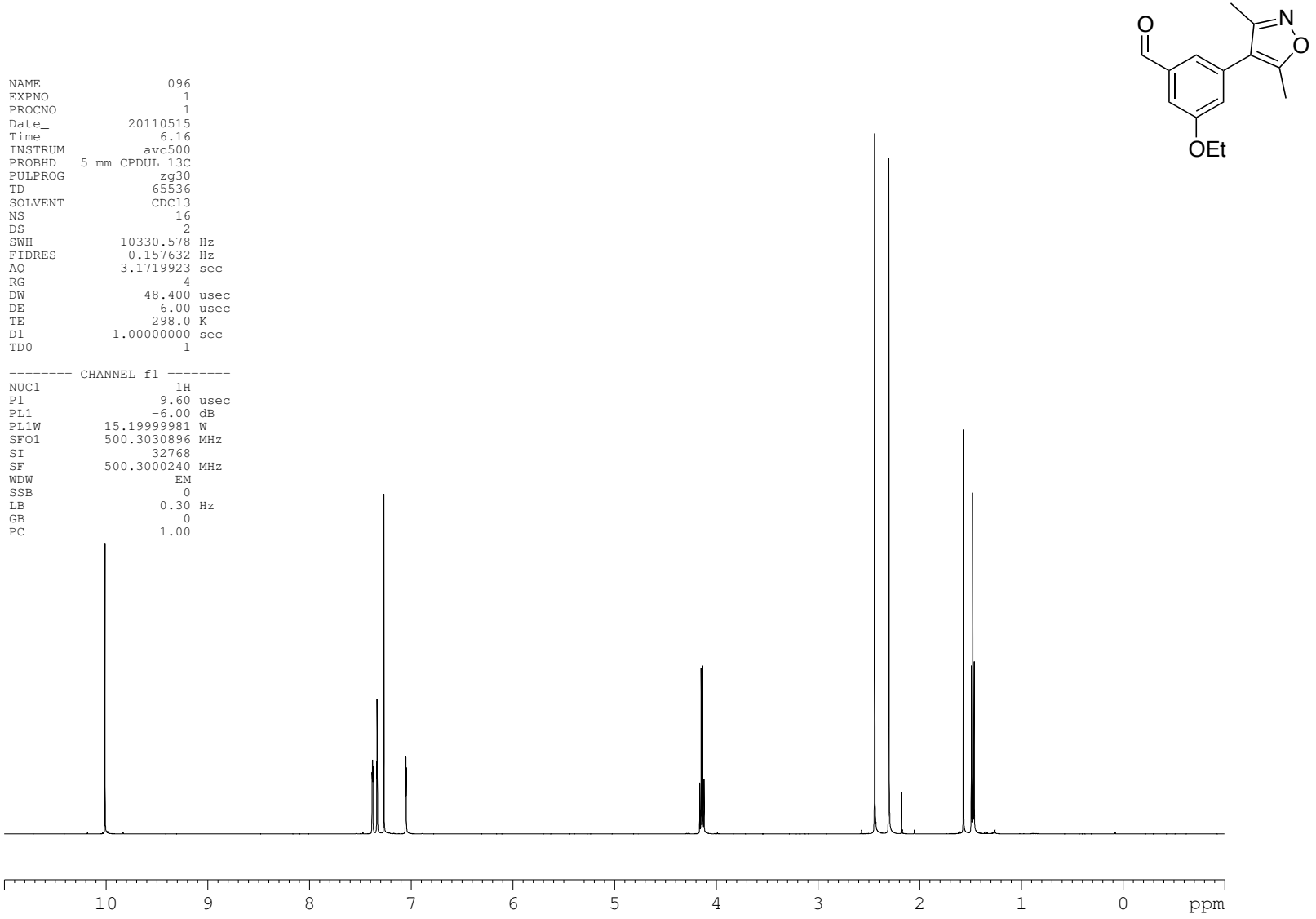
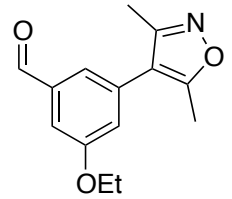
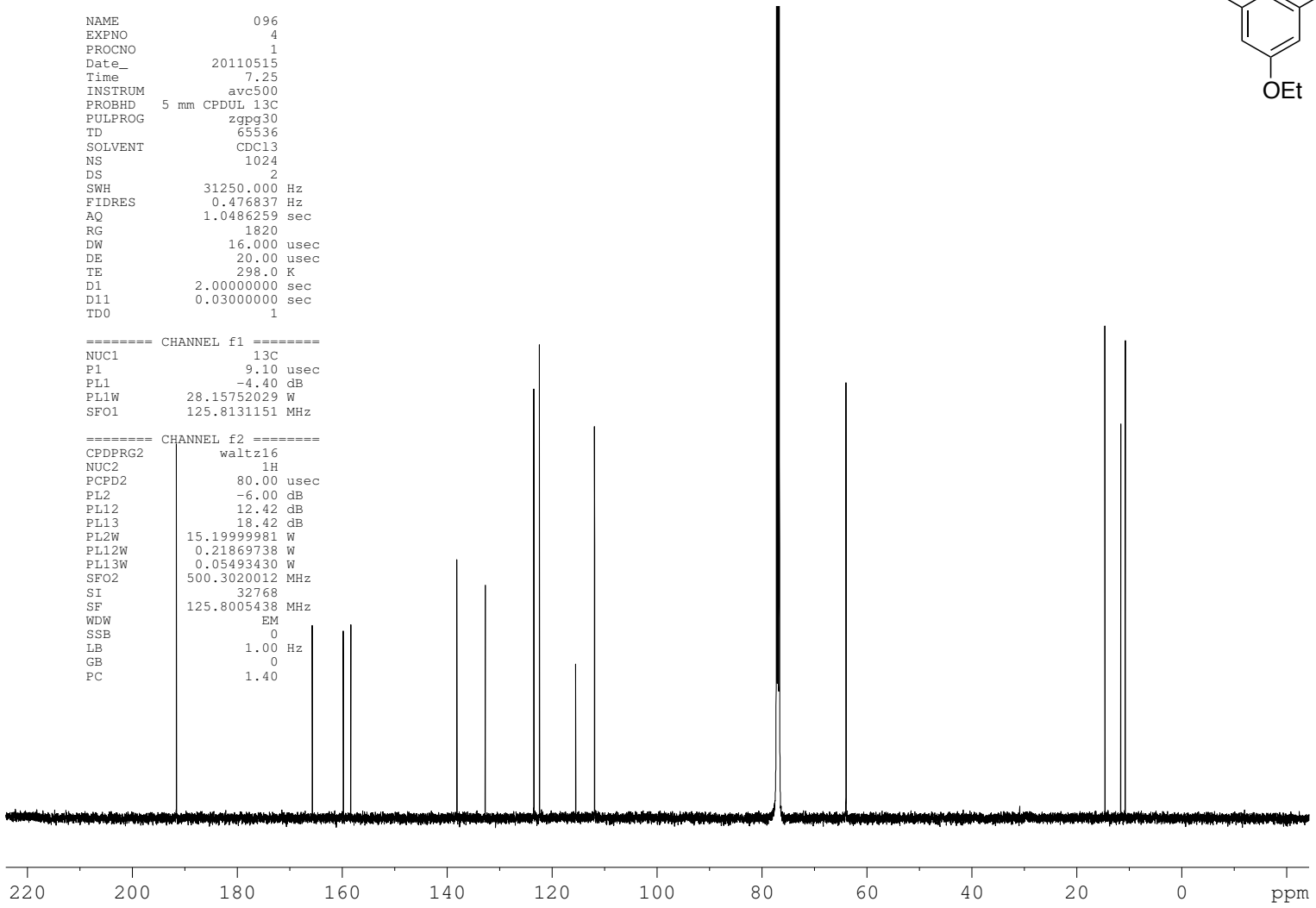


3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxybenzaldehyde **11** ^{1}H NMR

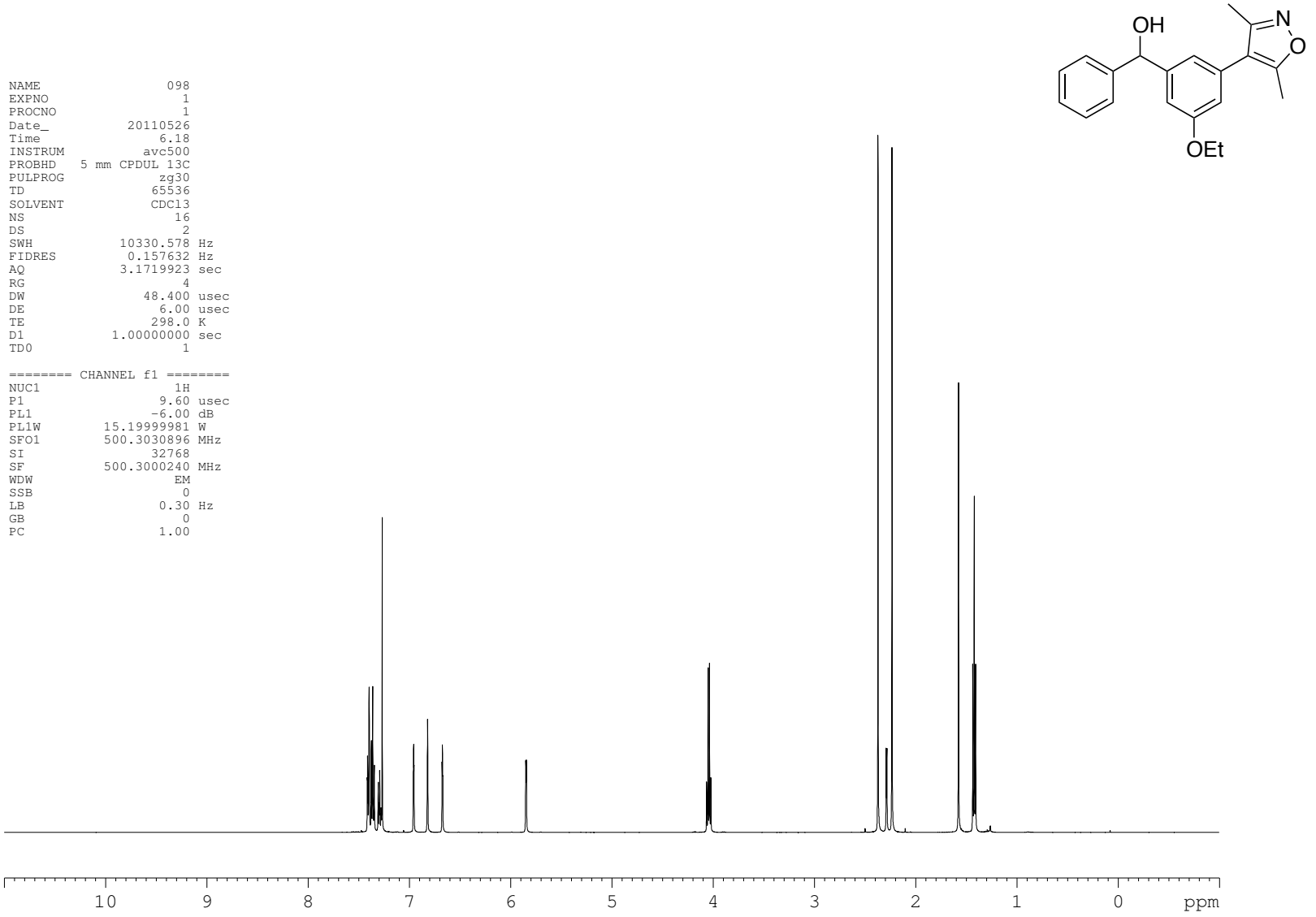


3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxybenzaldehyde **11** ^{13}C NMR

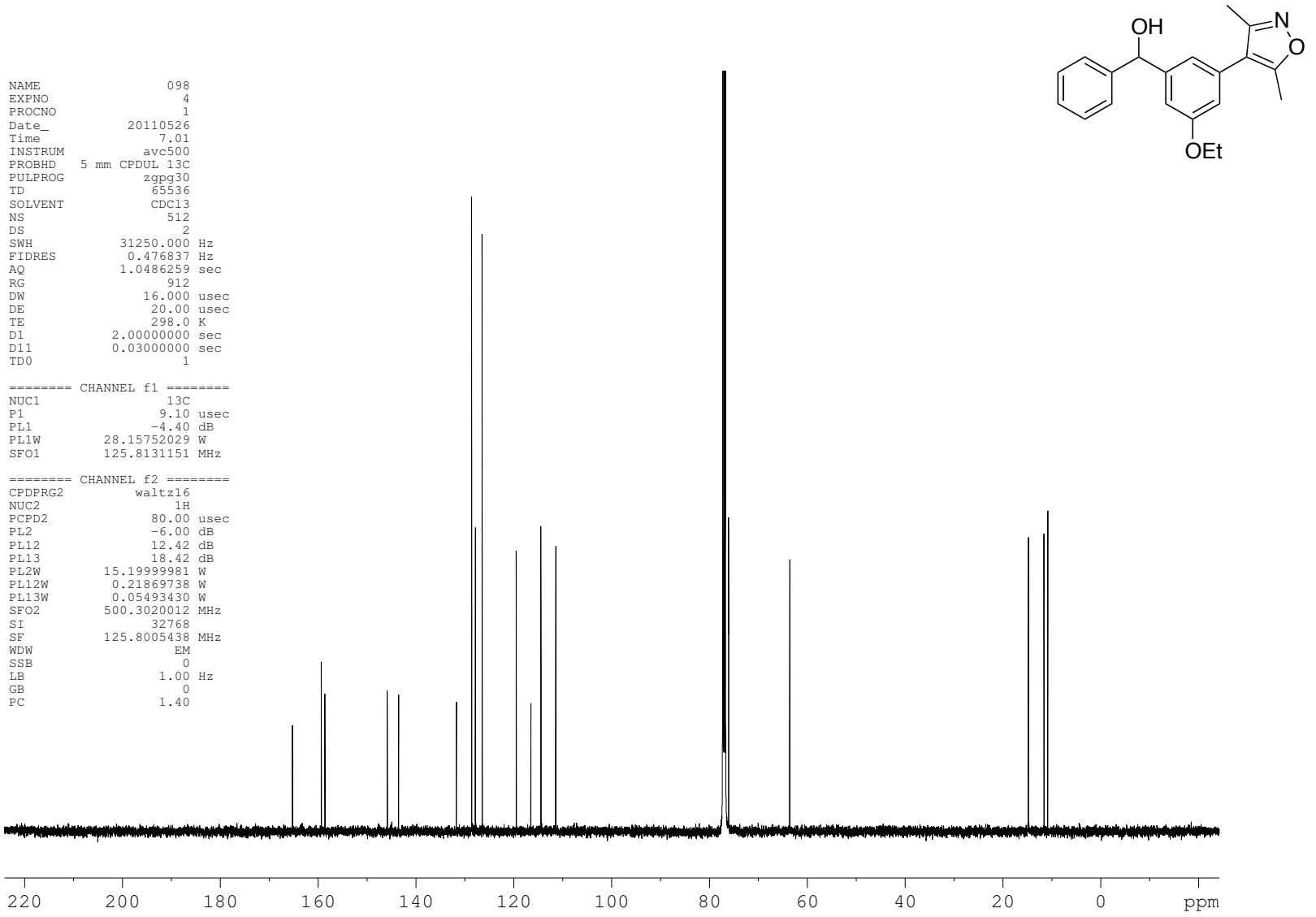




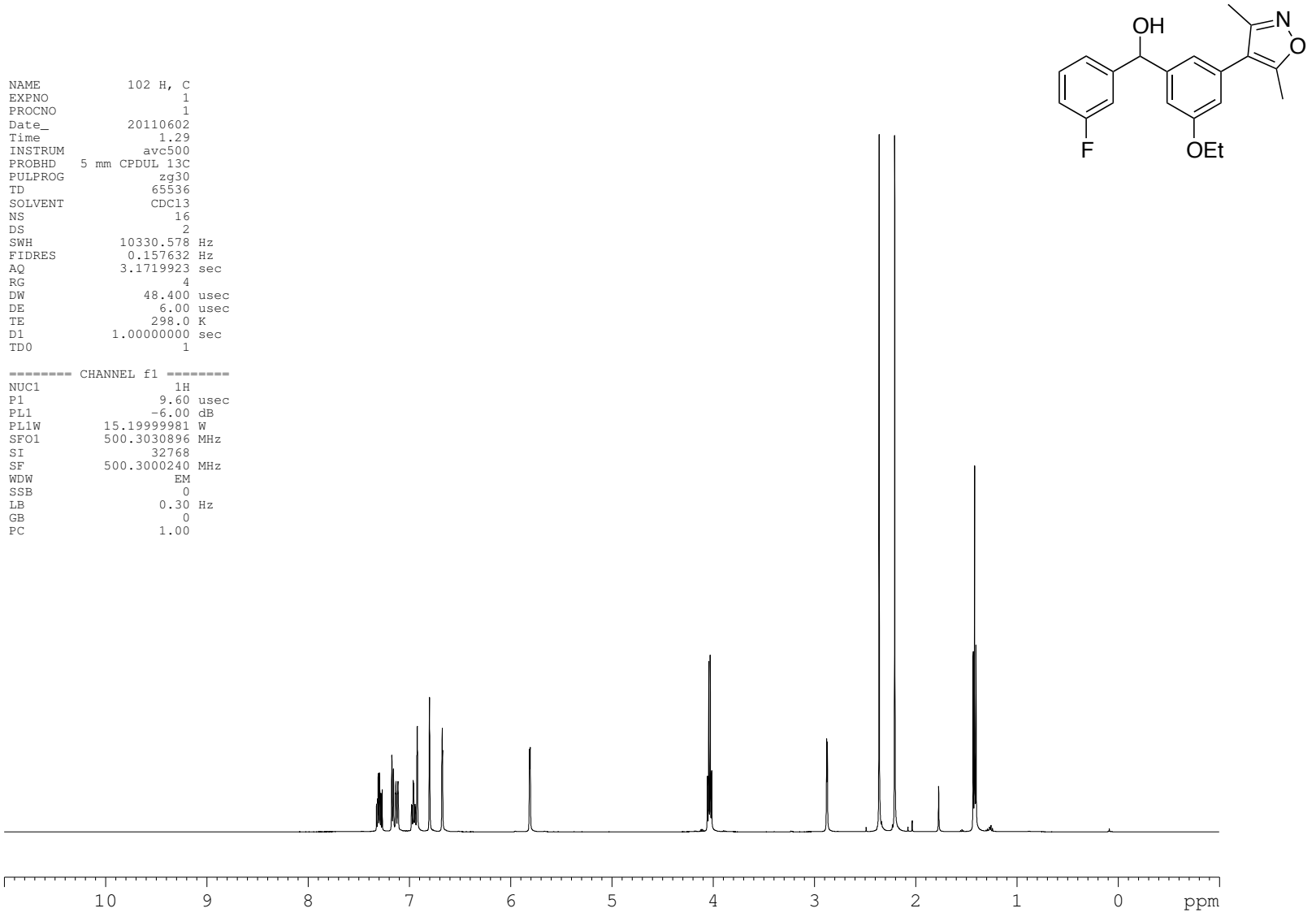
(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(phenyl)methanol **12** ^{1}H NMR



(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(phenyl)methanol **12** ^{13}C NMR



(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(3-fluorophenyl)methanol **13** ^{1}H NMR

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SSB                  0
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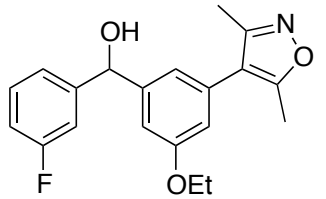
(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(3-fluorophenyl)methanol **13** ^{13}C NMR

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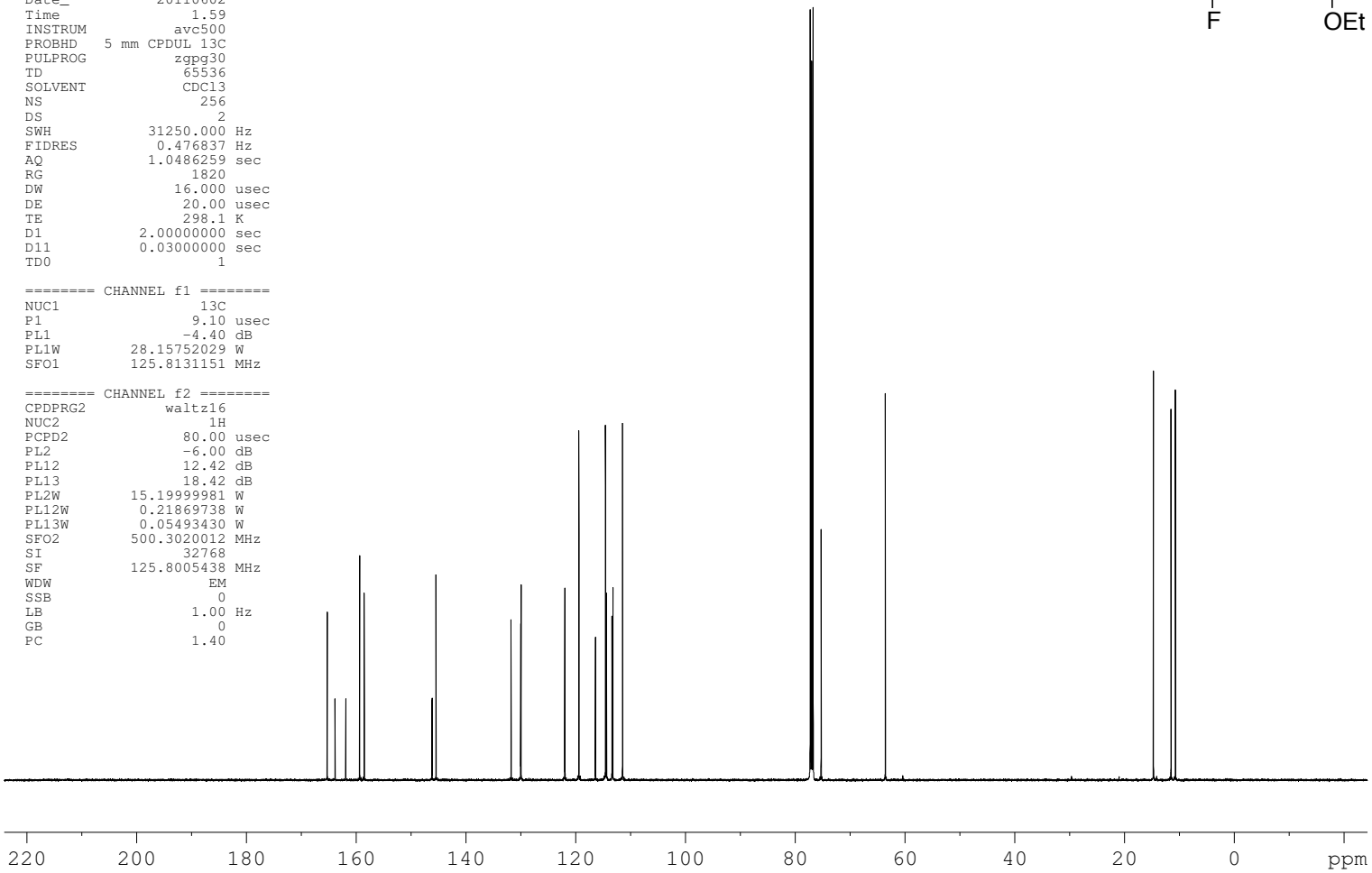
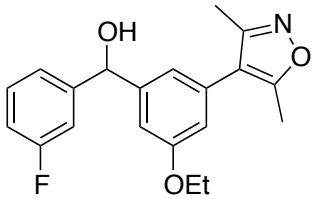


(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(3-fluorophenyl)methanol **13** ^{19}F NMR

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PC                 10.00
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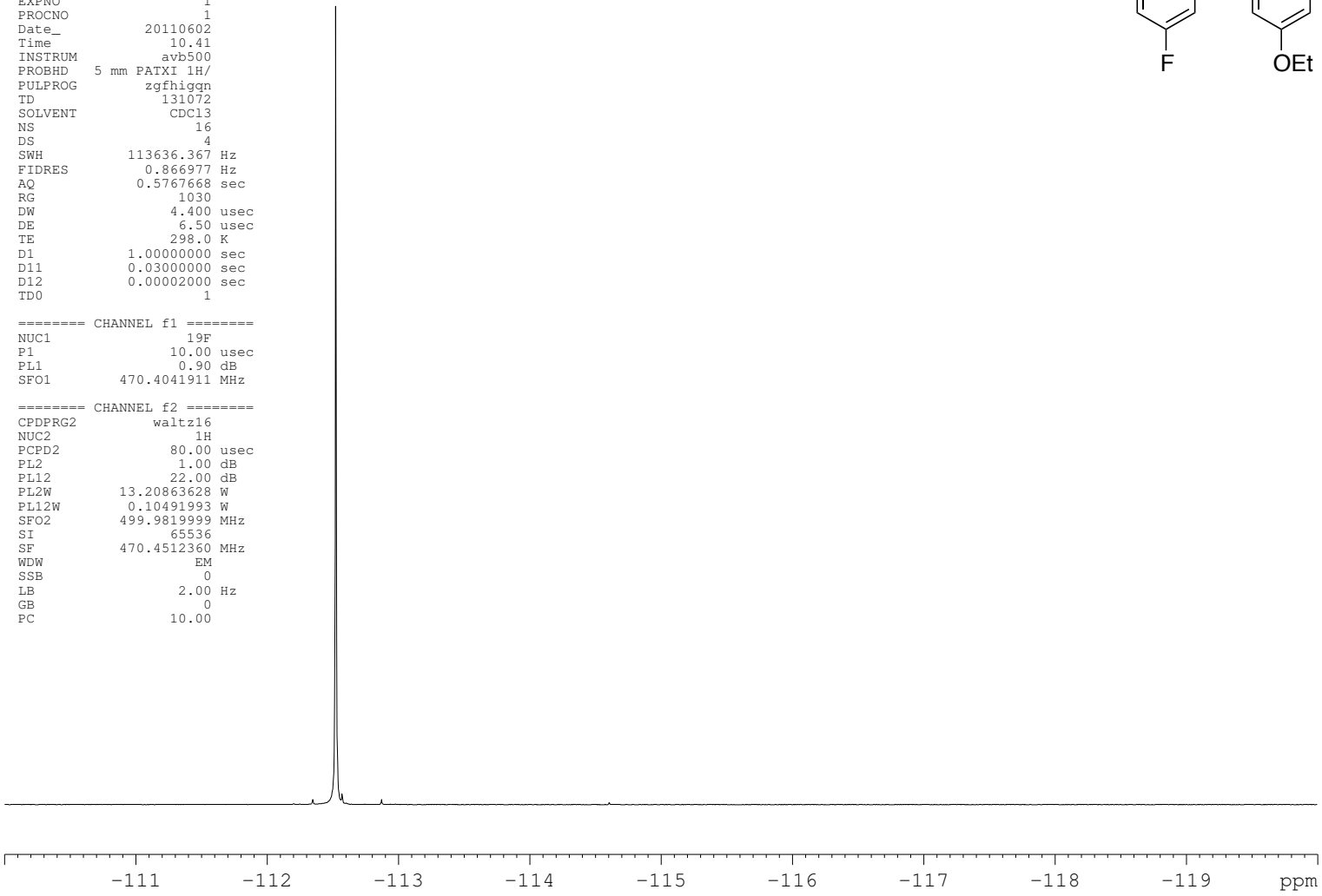
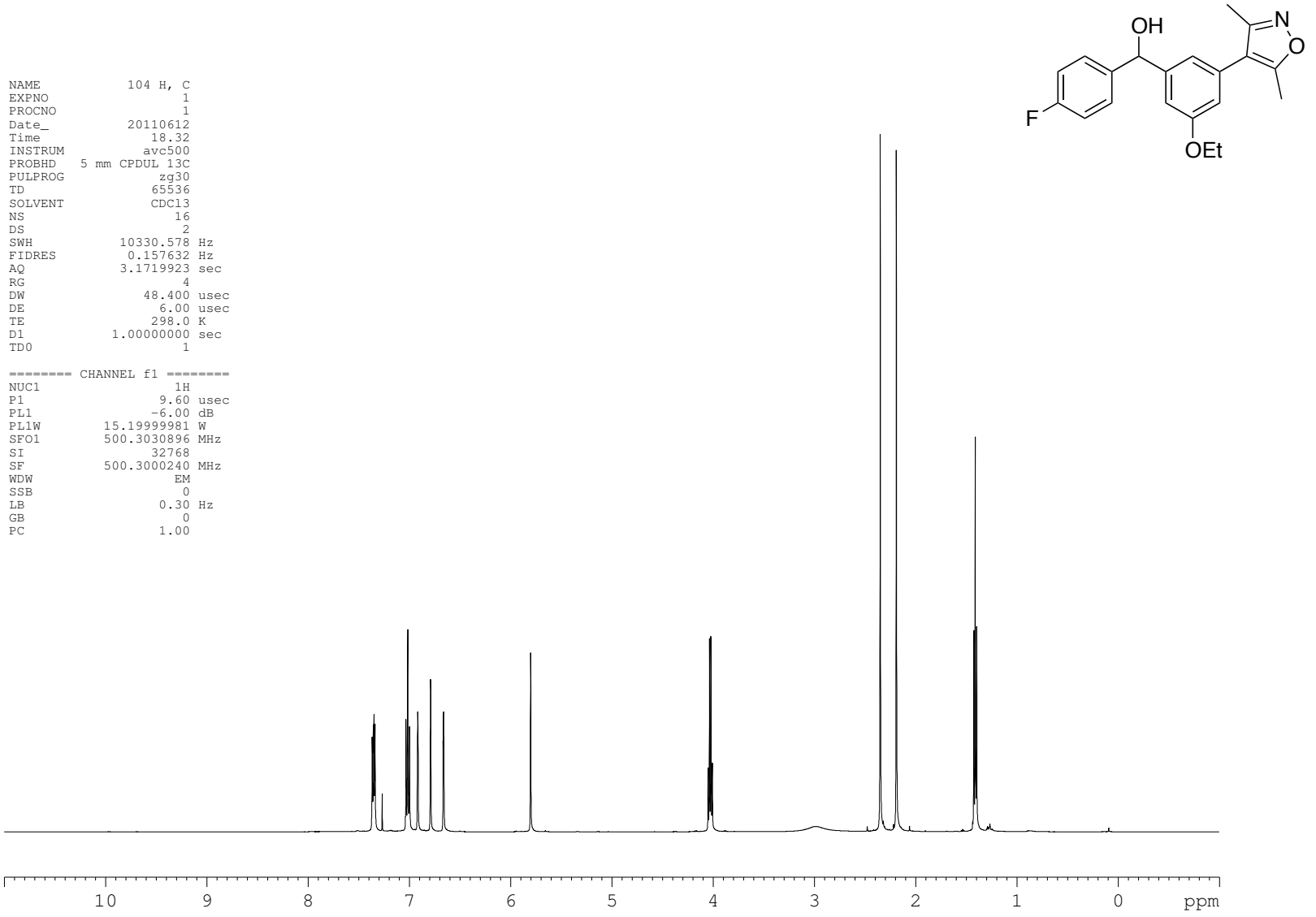
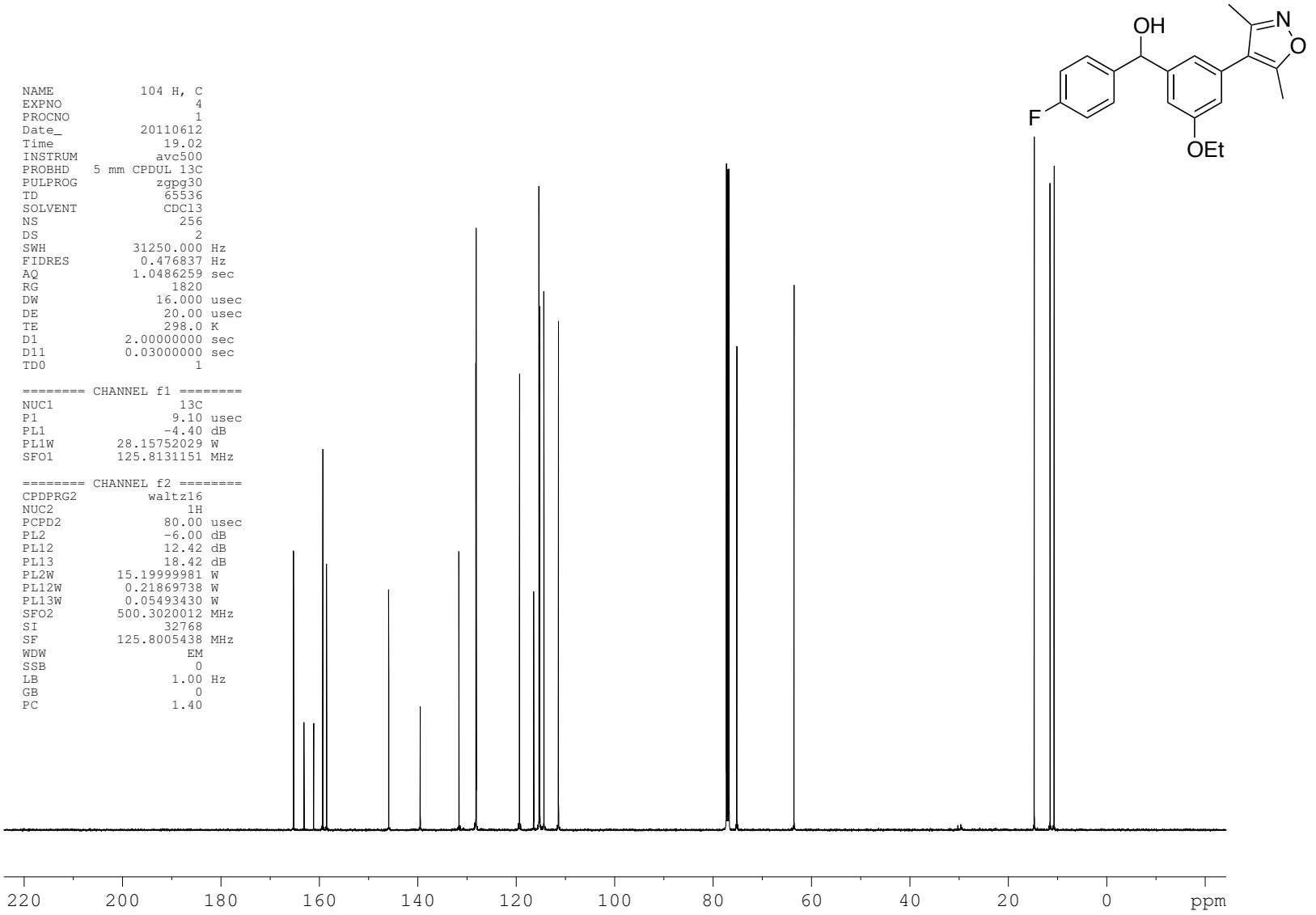


(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(4-fluorophenyl)methanol **14** ^{1}H NMR



(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(4-fluorophenyl)methanol **14** ^{13}C NMR

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EXPNO                  4
PROCNO                 1
Date_           20110612
Time               19.02
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ             1.0486259 sec
RG                 1820
DW                16.000 usec
DE                20.00 usec
TE                298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.10 usec
PL1                -4.40 dB
PL1W        28.15752029 W
SFO1        125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              80.00 usec
PL2                -6.00 dB
PL12               12.42 dB
PL13               18.42 dB
PL2W        15.19999981 W
PL12W        0.21869738 W
PL13W        0.05493430 W
SFO2        500.3020012 MHz
SI                 32768
SF          125.8005438 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
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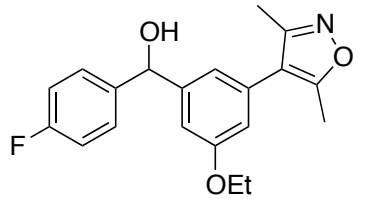
(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)(4-fluorophenyl)methanol **14** ^{19}F NMR

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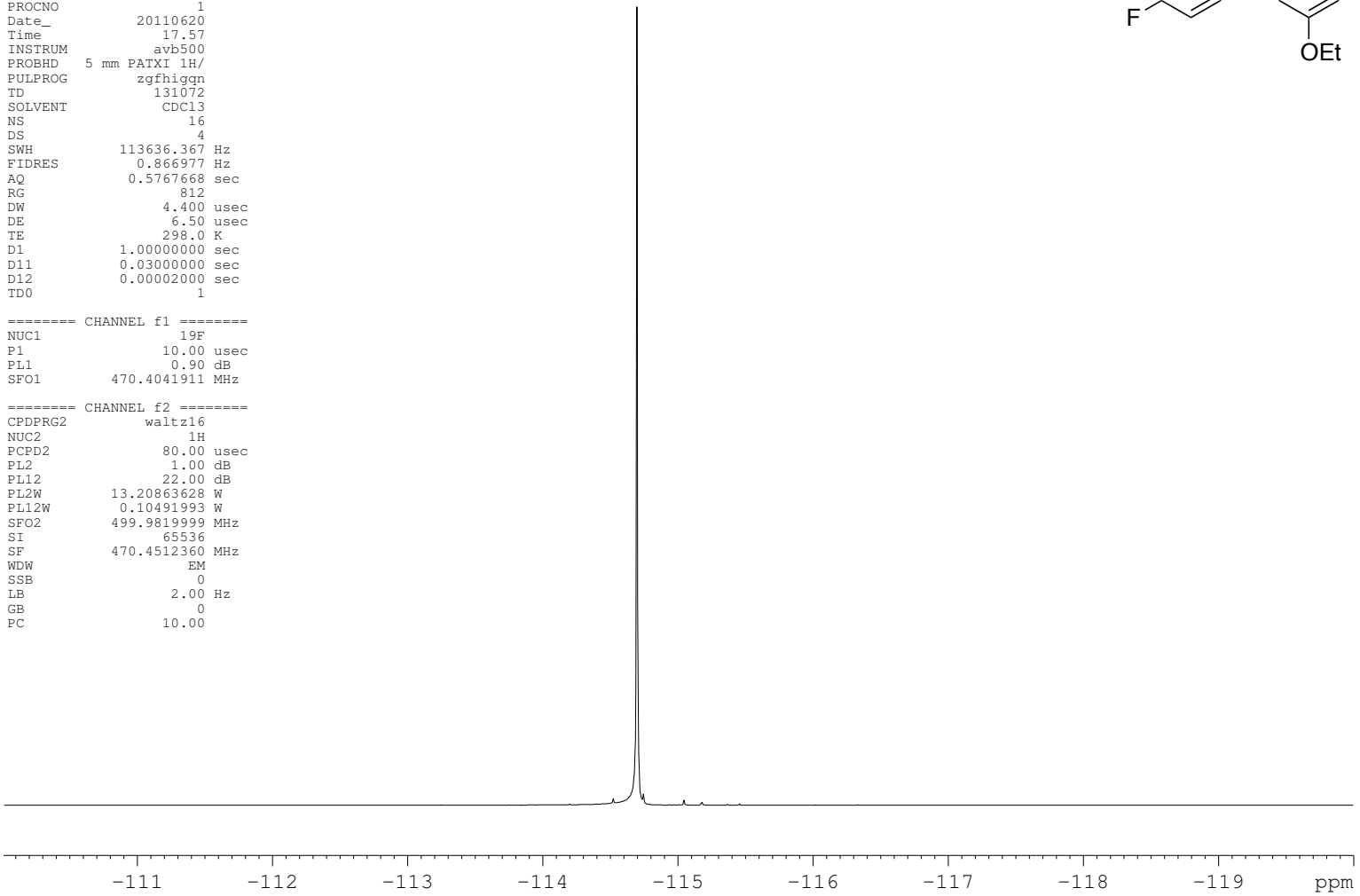
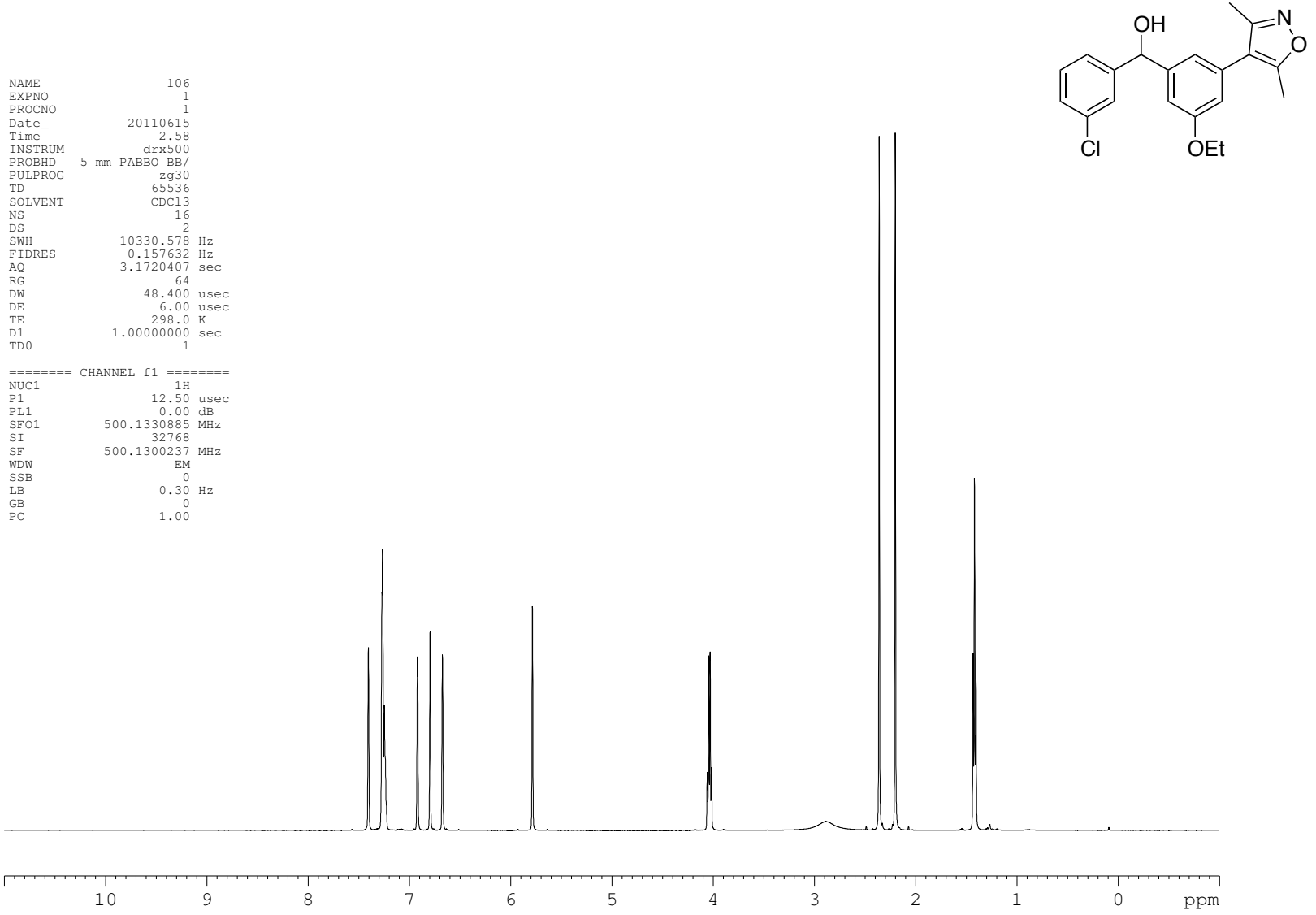
PROCNO               1
Date_         20110620
Time             17.57
INSTRUM         avb500
PROBHD   5 mm PATXI 1H/
PULPROG       zgfhigqn
TD             131072
SOLVENT          CDCl3
NS                  16
DS                   4
SWH         113636.367 Hz
FIDRES        0.866977 Hz
AQ            0.5767668 sec
RG                 812
DW                4.400 usec
DE                6.50 usec
TE                298.0 K
D1           1.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                19F
P1                10.00 usec
PL1                0.90 dB
SFO1        470.4041911 MHz

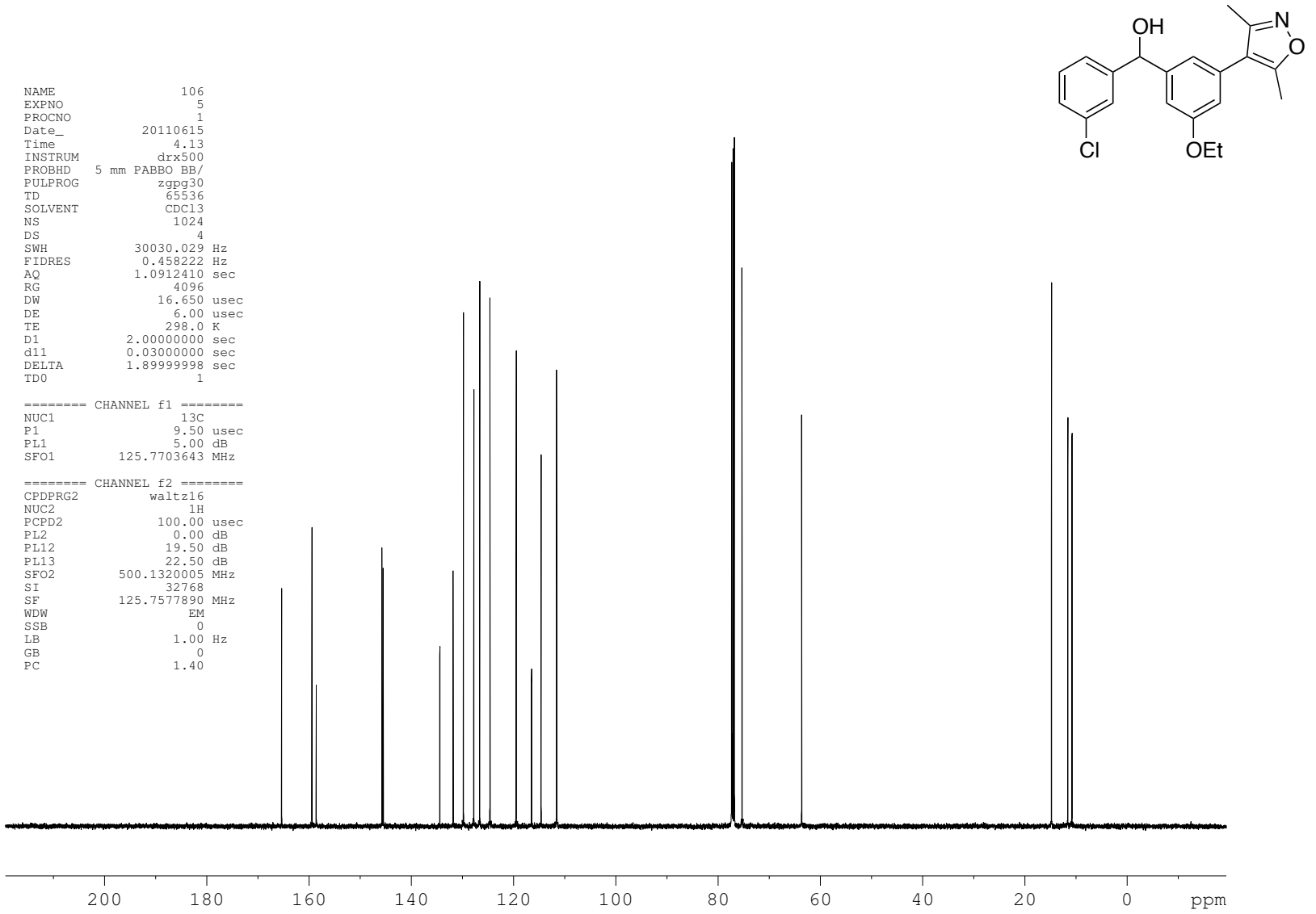
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             80.00 usec
PL2                1.00 dB
PL12              22.00 dB
PL2W        13.20863628 W
PL12W        0.10491993 W
SFO2        499.9819999 MHz
SI                65536
SF          470.4512360 MHz
WDW                  EM
SSB                  0
LB                2.00 Hz
GB                   0
PC                10.00
```



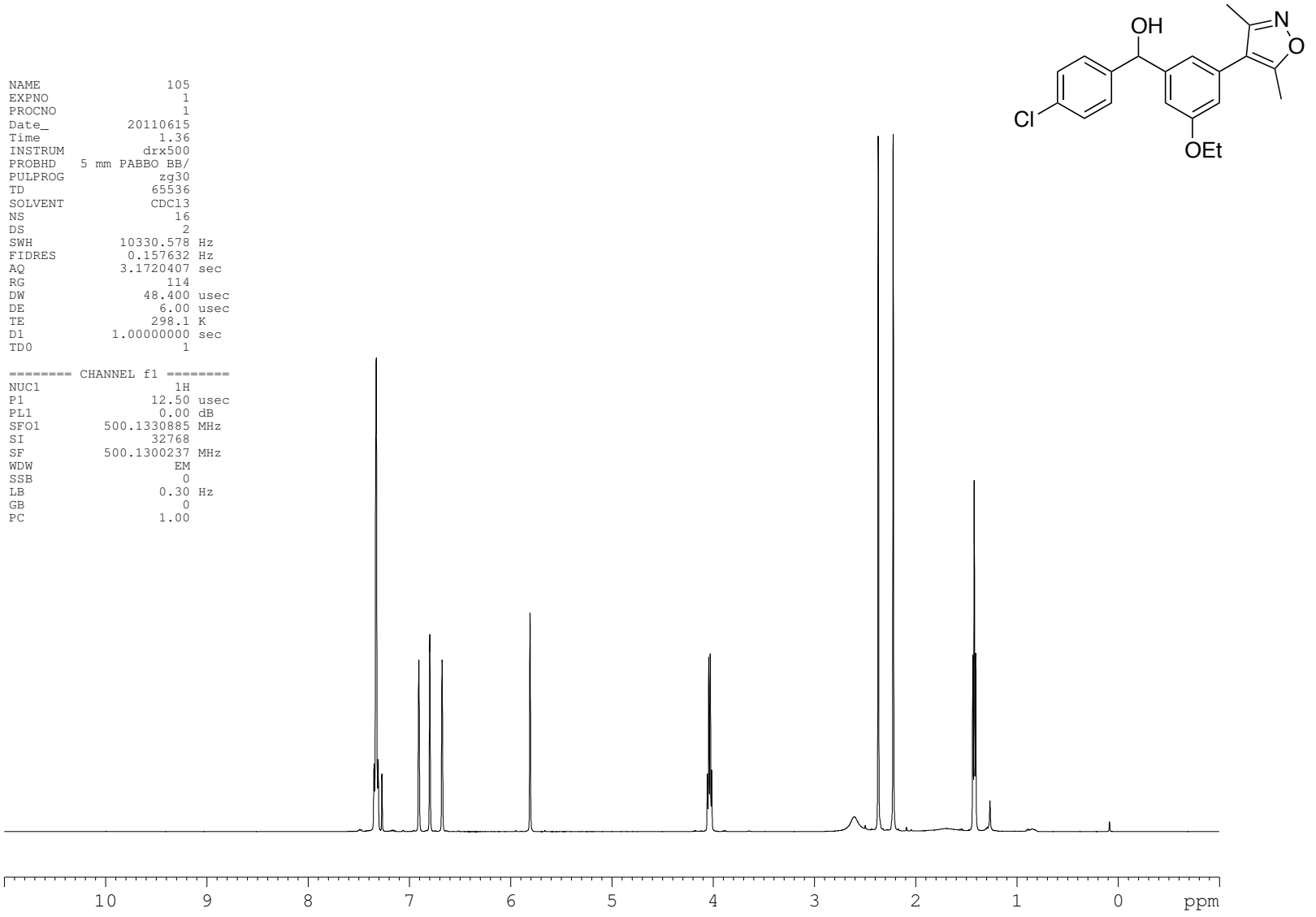
(3-Chlorophenyl)(3-(3,5-dimethylisoxazol-4-yl)-5-ethoxyphenyl)methanol **15** ^{1}H NMR



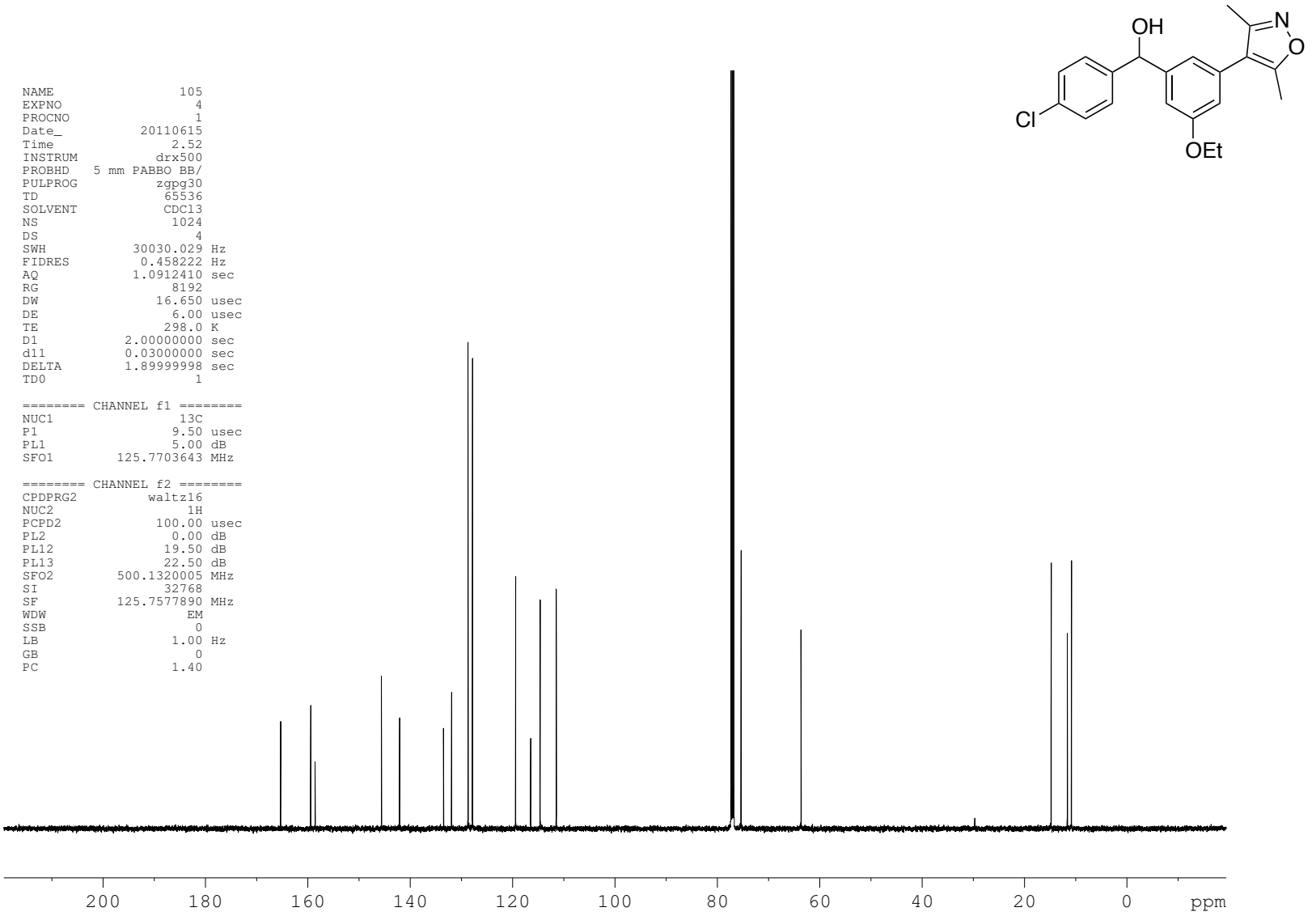
(3-Chlorophenyl)(3-(3,5-dimethylisoxazol-4-yl)-5-ethoxyphenyl)methanol **15** ^{13}C NMR



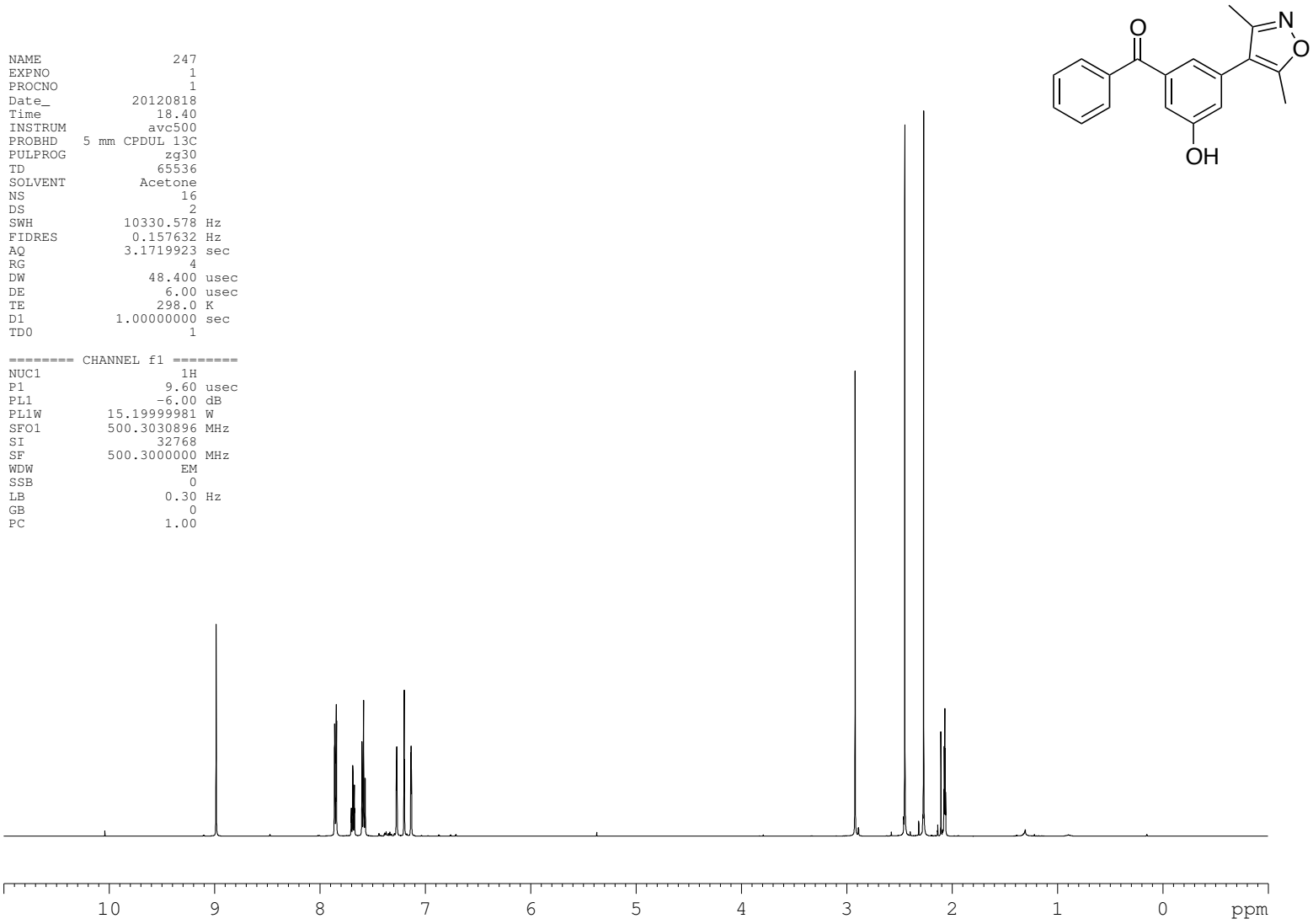
(4-Chlorophenyl)(3-(3,5-dimethylisoxazol-4-yl)-5-ethoxyphenyl)methanol **16** ^{1}H NMR



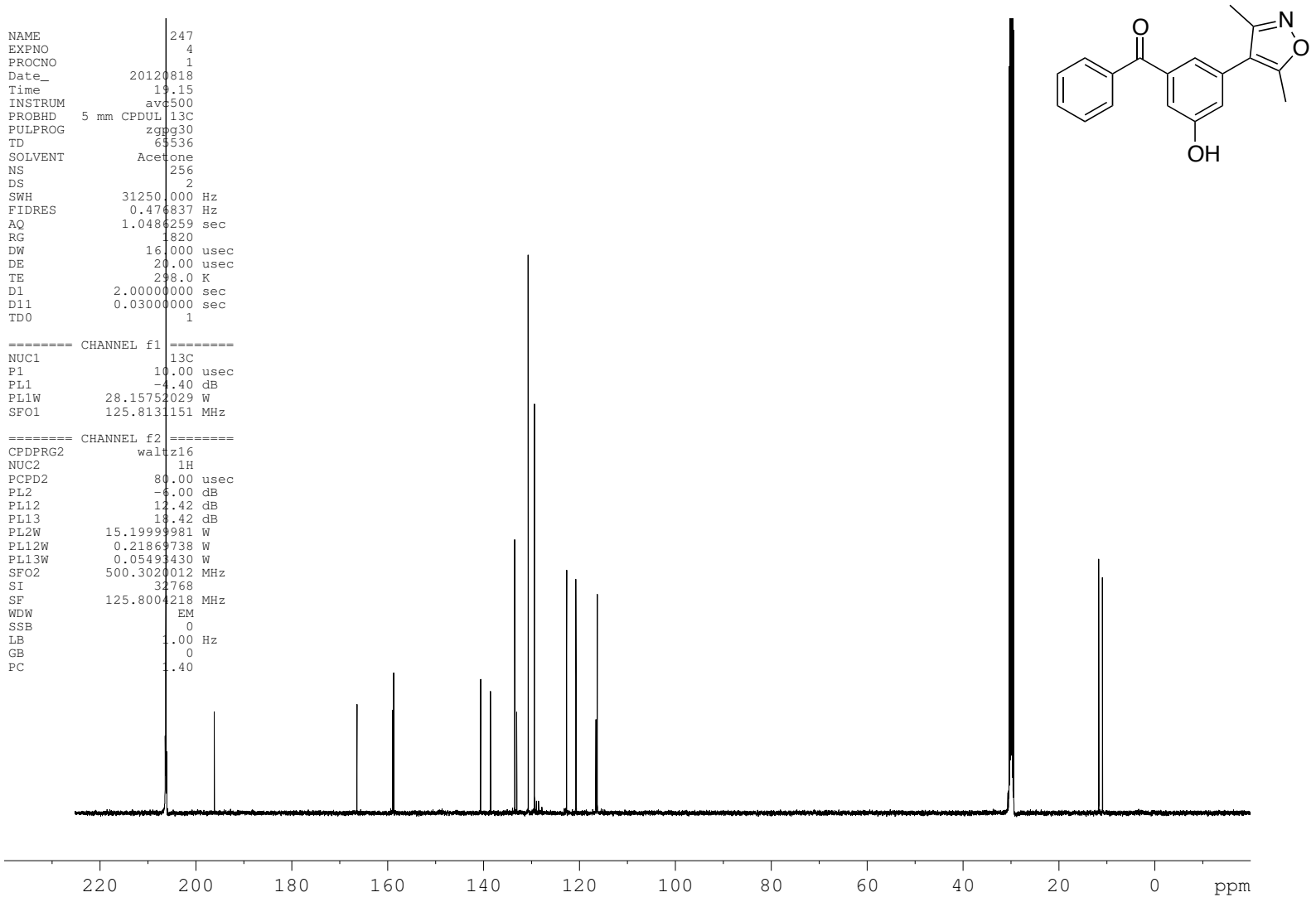
(4-Chlorophenyl)(3-(3,5-dimethylisoxazol-4-yl)-5-ethoxyphenyl)methanol **16** ^{13}C NMR



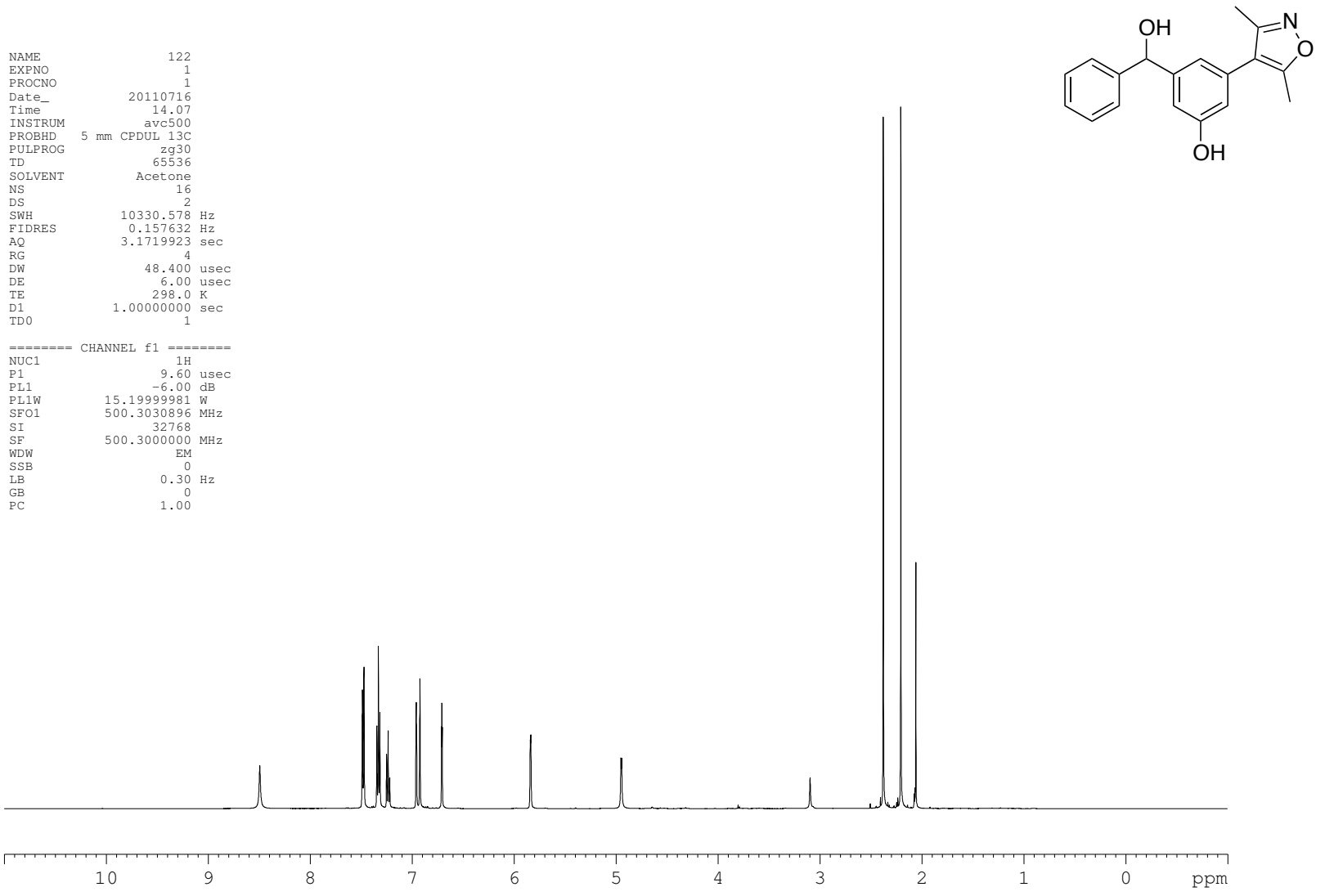
(3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxyphenyl)(phenyl)methanone **17** ^{1}H NMR



(3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxyphenyl)(phenyl)methanone **17** ^{13}C NMR



3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenol **8** ^{1}H NMR

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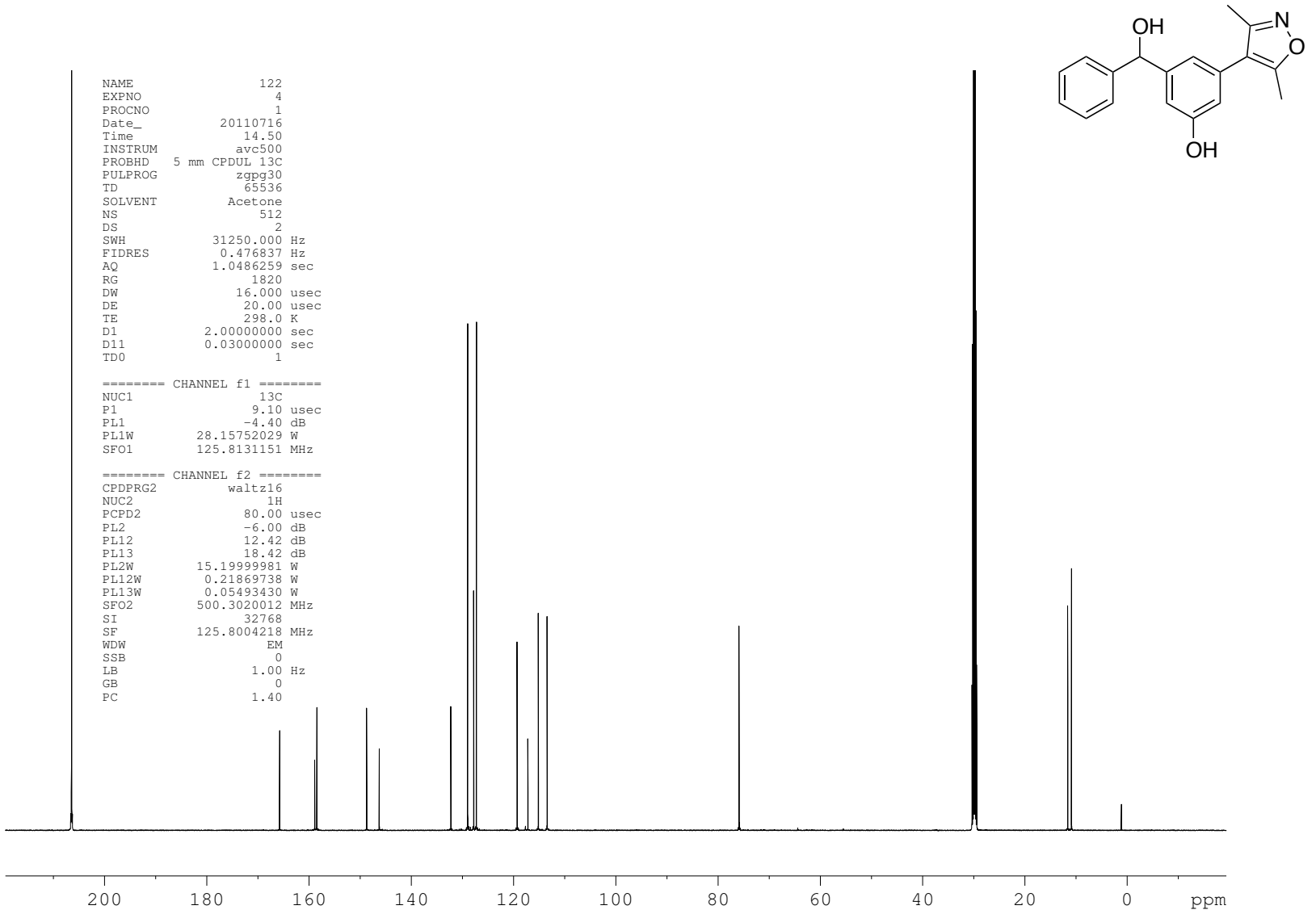
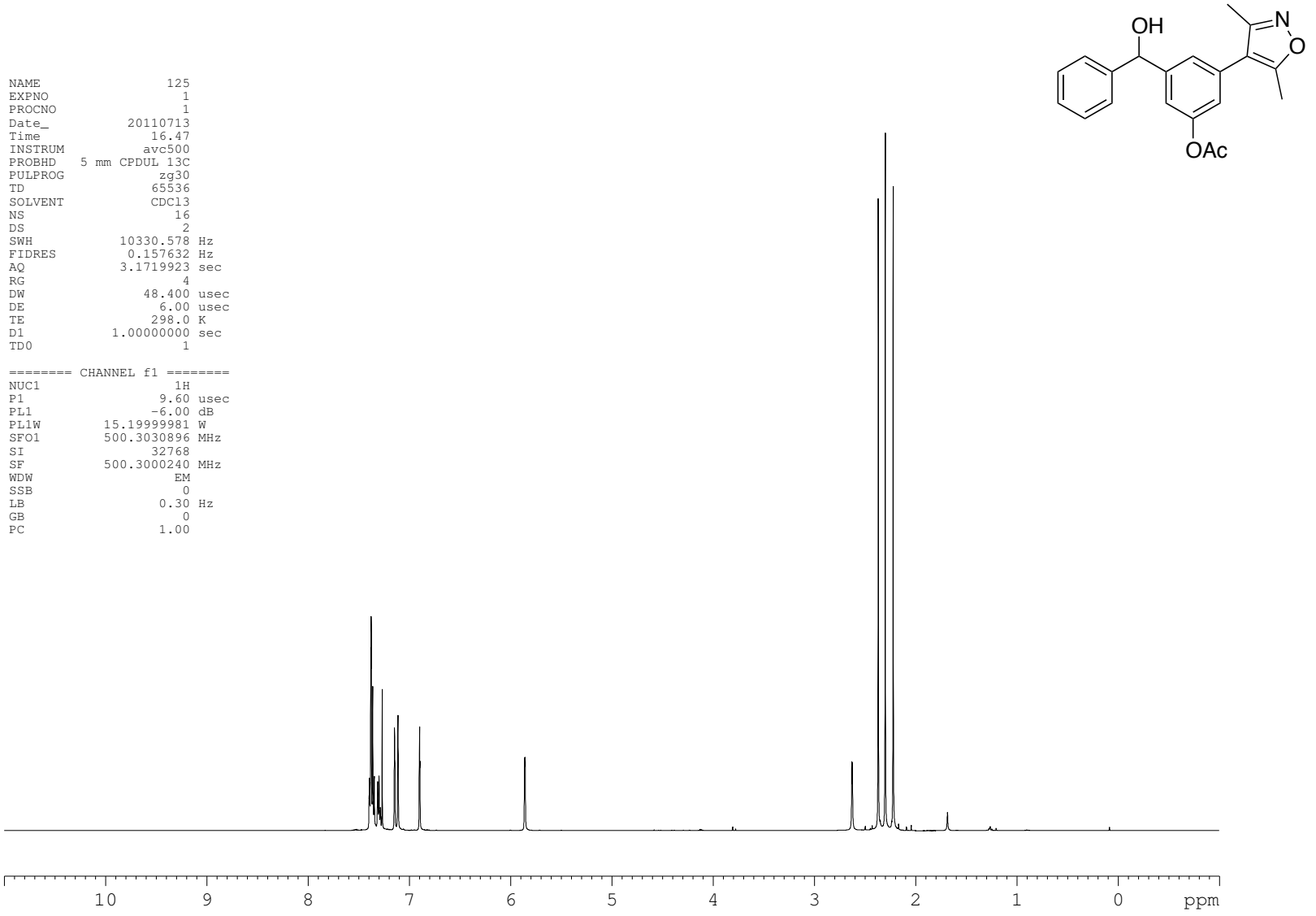
NAME                 122
EXPNO                  1
PROCNO                 1
Date_           20110716
Time               14.07
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT          Acetone
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                     4
DW                48.400 usec
DE                 6.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenol **8** ^{13}C NMR



3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenyl acetate **9** ^{1}H NMR




```
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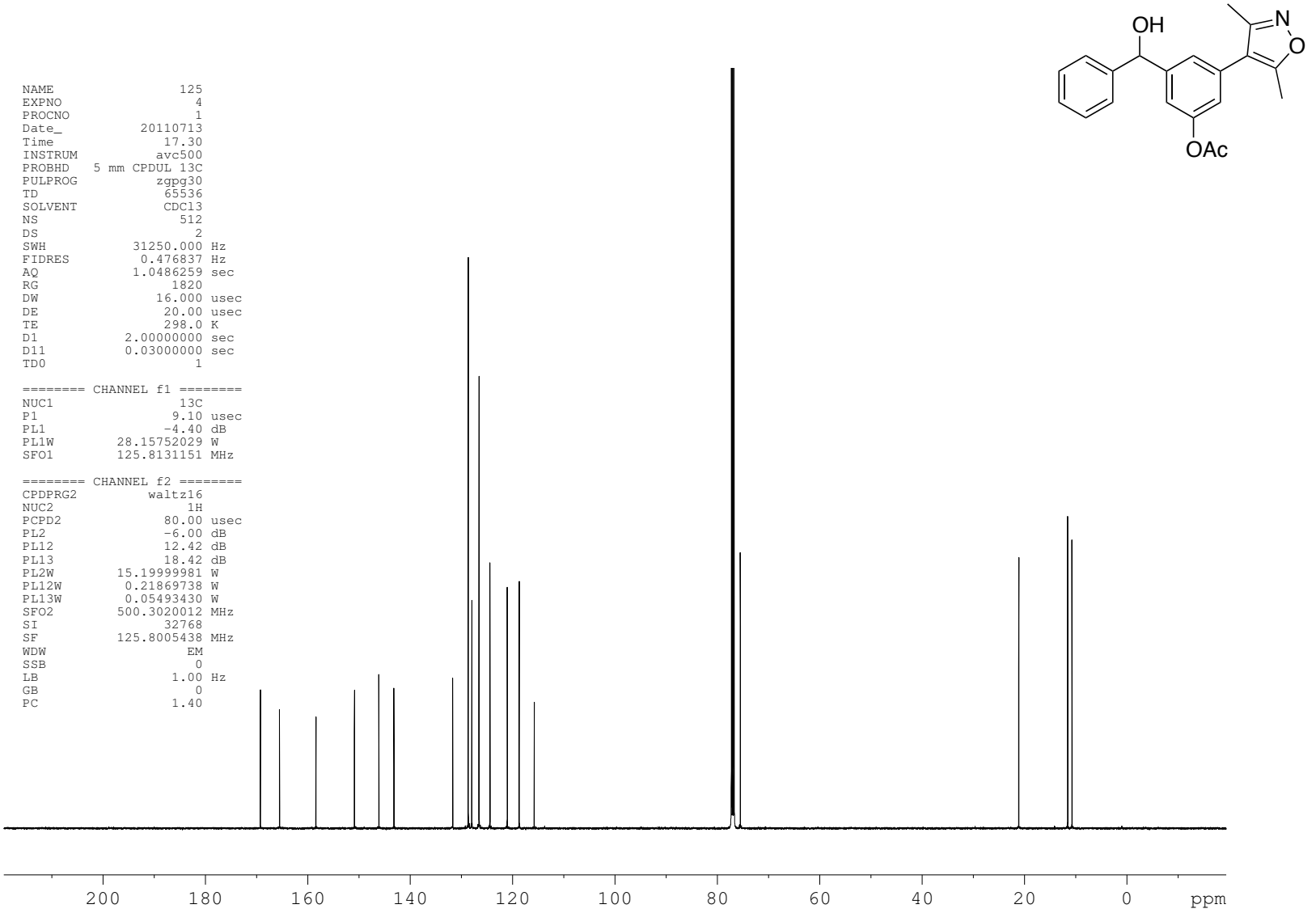
EXPNO                  1
PROCNO                 1
Date_           20110713
Time               16.47
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                     4
DW                48.400 usec
DE                 6.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenyl acetate **9** ^{13}C NMR

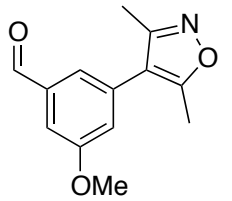



```
NAME                125
EXPNO                 4
PROCNO                1
Date_          20110713
Time              17.30
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ            1.0486259 sec
RG                 1820
DW               16.000 usec
DE               20.00 usec
TE               298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.10 usec
PL1               -4.40 dB
PL1W        28.15752029 W
SFO1        125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2              80.00 usec
PL2                -6.00 dB
PL12               12.42 dB
PL13               18.42 dB
PL2W        15.19999981 W
PL12W        0.21869738 W
PL13W        0.05493430 W
SFO2        500.3020012 MHz
SI                32768
SF          125.8005438 MHz
WDW                 EM
SSB                 0
LB                1.00 Hz
GB                  0
PC                1.40
```

3-(3,5-Dimethylisoxazol-4-yl)-5-methoxybenzaldehyde **18** ^{1}H NMR

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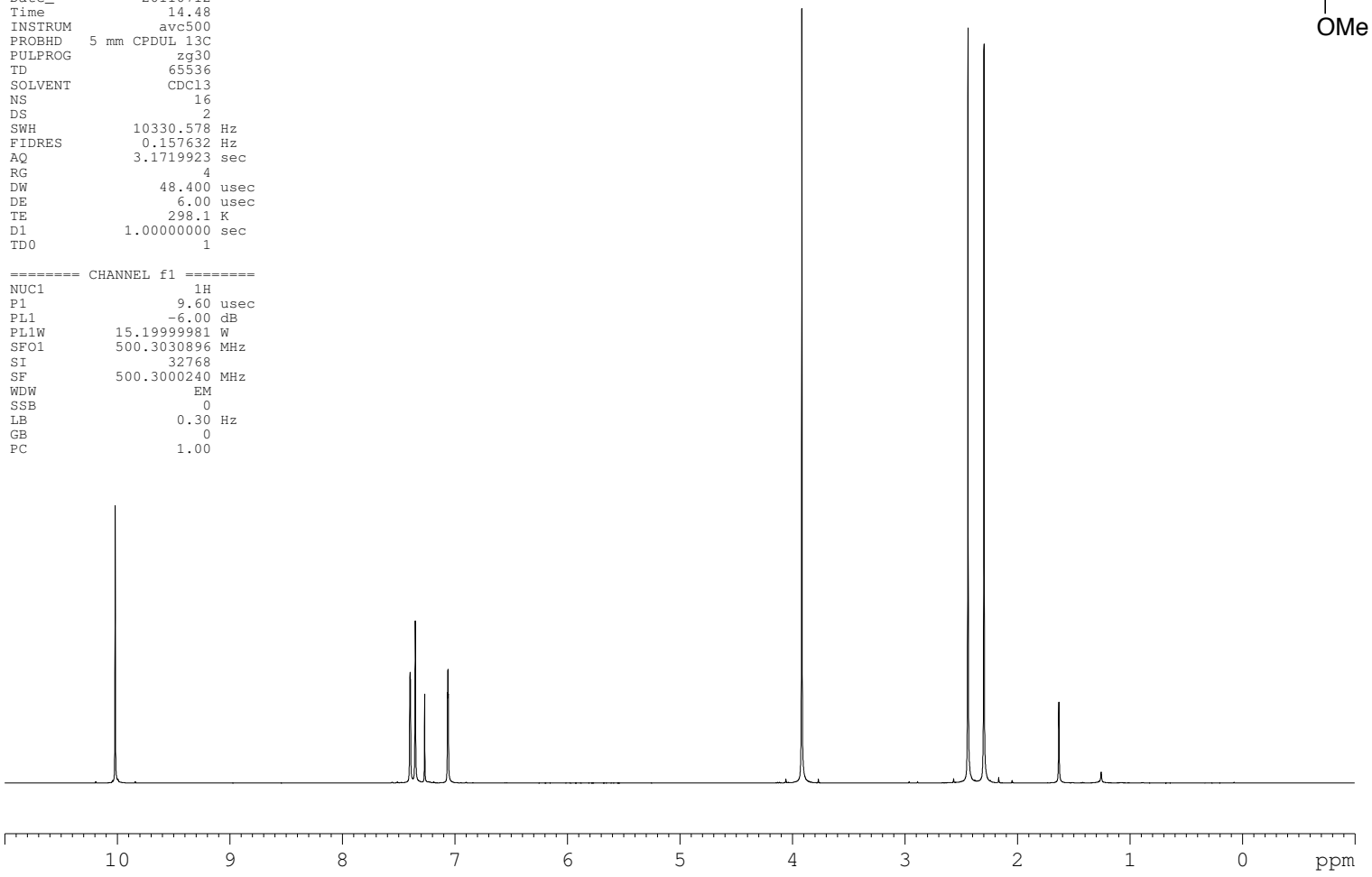
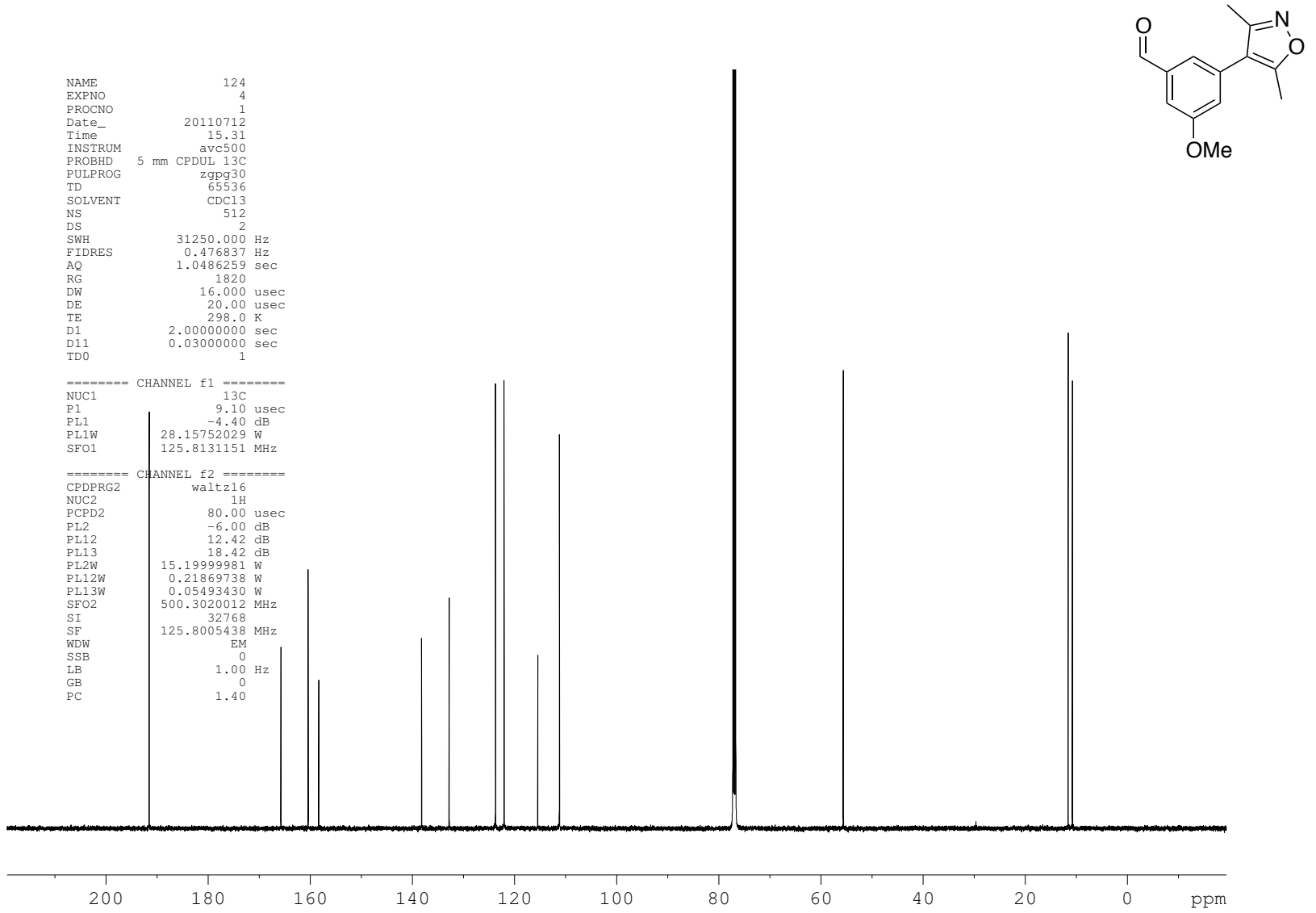
NAME                 124
EXPNO                  1
PROCNO                 1
Date_           20110712
Time               14.48
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                     4
DW                48.400 usec
DE                 6.00 usec
TE                298.1 K
D1           1.00000000 sec
TD0                    1

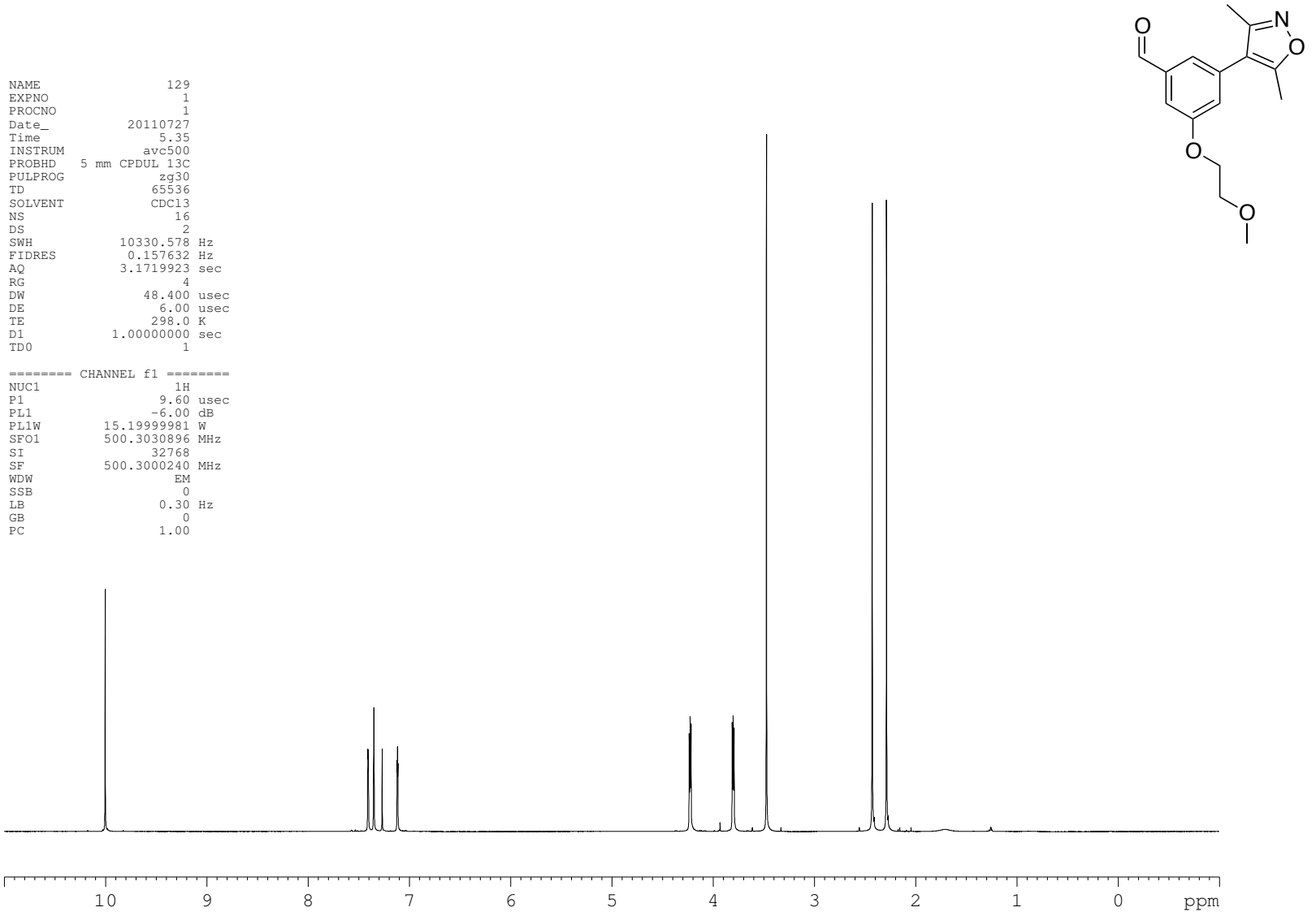
======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



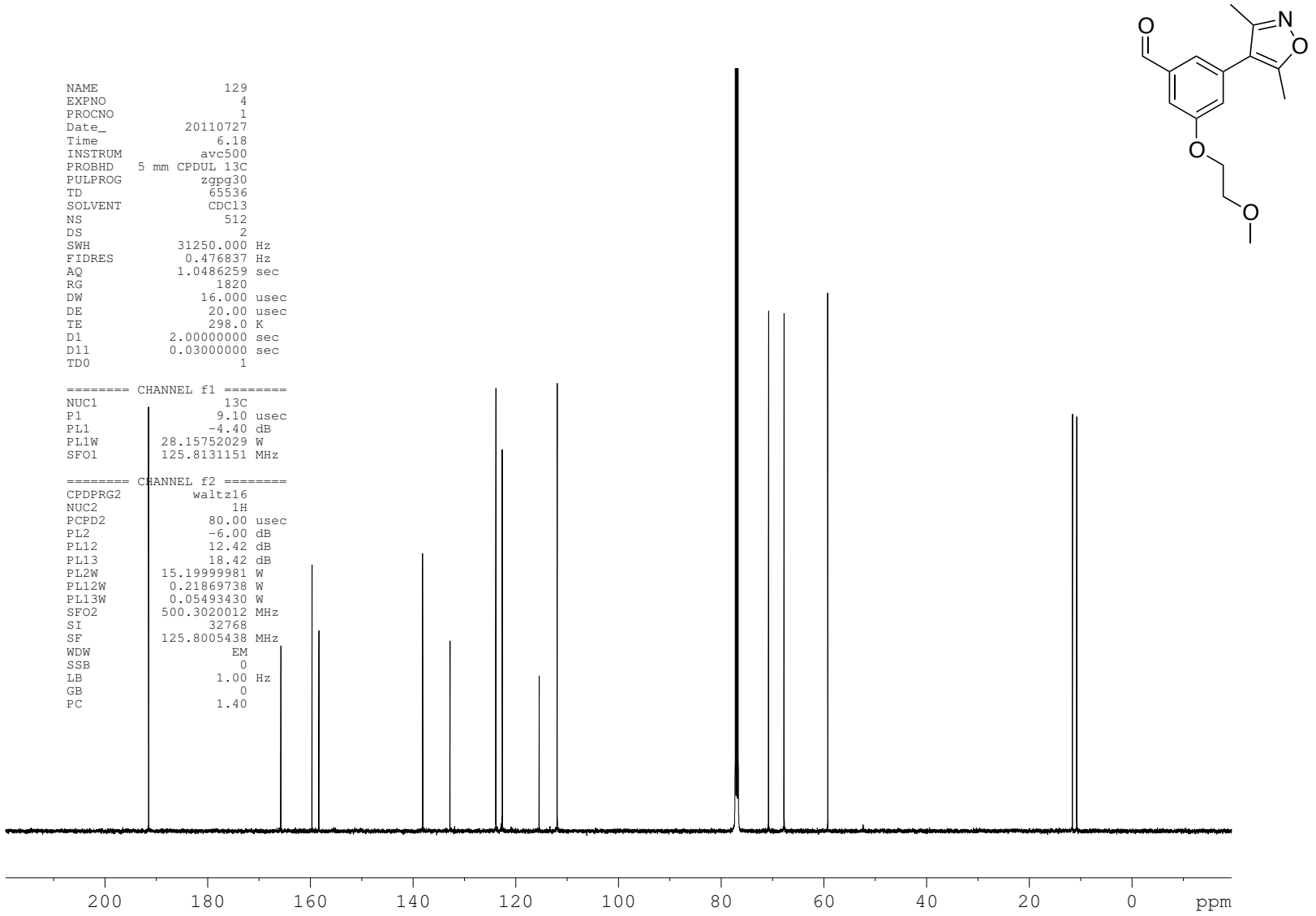
3-(3,5-Dimethylisoxazol-4-yl)-5-methoxybenzaldehyde **18** ^{13}C NMR



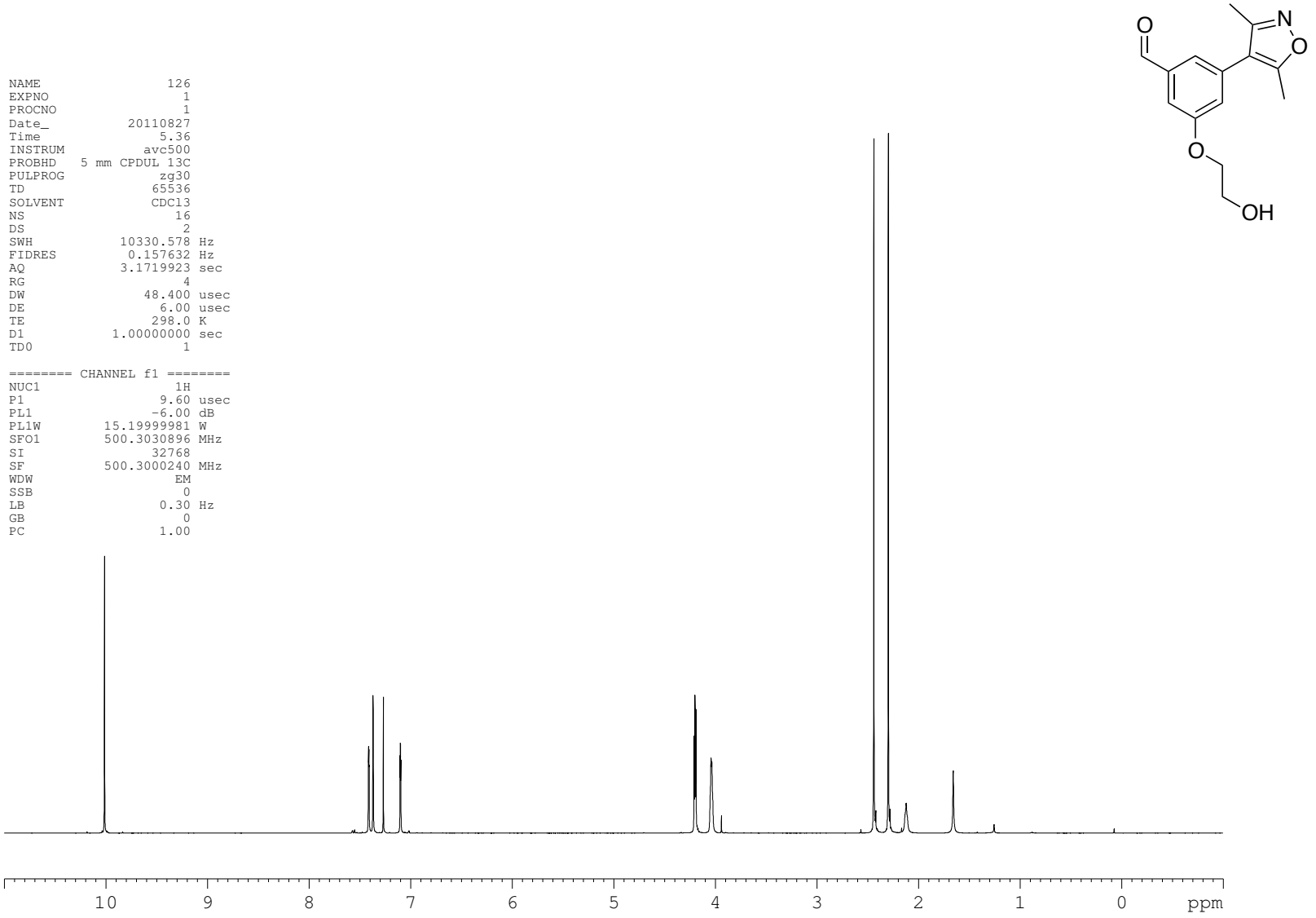
3-(3,5-Dimethylisoxazol-4-yl)-5-(2-methoxyethoxy)benzaldehyde **19** ^{1}H NMR



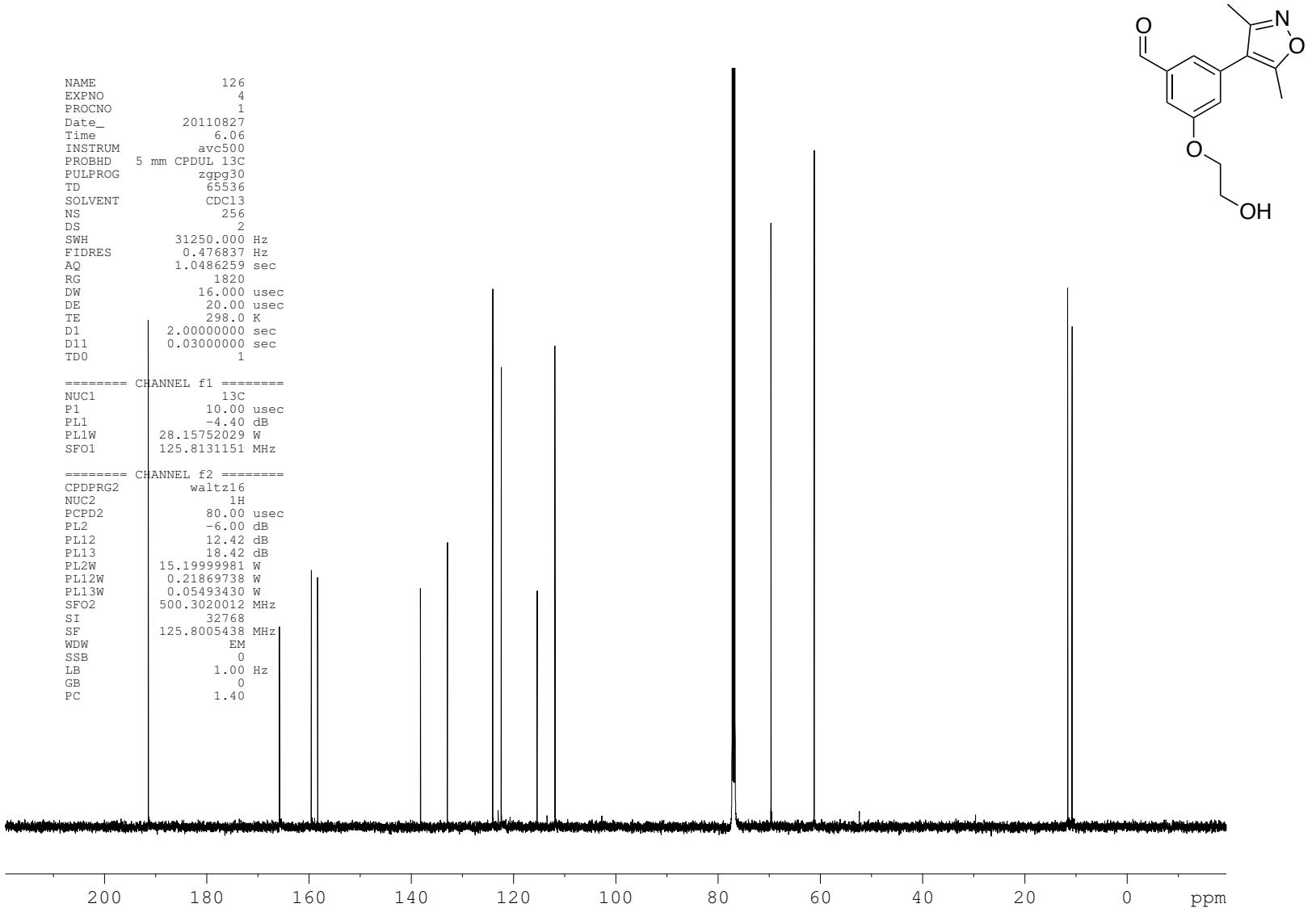
3-(3,5-Dimethylisoxazol-4-yl)-5-(2-methoxyethoxy)benzaldehyde **19** ^{13}C NMR



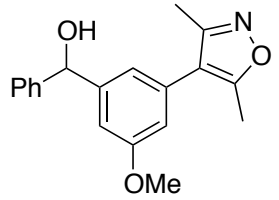
3-(3,5-Dimethylisoxazol-4-yl)-5-(2-hydroxyethoxy)benzaldehyde **20** ^{1}H NMR



3-(3,5-Dimethylisoxazol-4-yl)-5-(2-hydroxyethoxy)benzaldehyde **20** ^{13}C NMR



(3-(3,5-Dimethylisoxazol-4-yl)-5-methoxyphenyl)(phenyl)methanol **21** ^{1}H NMR

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EXPNO                  1
PROCNO                 1
Date_           20110803
Time               18.17
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PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH            10330.578 Hz
FIDRES          0.157632 Hz
AQ              3.1719923 sec
RG                     4
DW                48.400 usec
DE                 6.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W         15.19999981 W
SFO1         500.3030896 MHz
SI                 32768
SF           500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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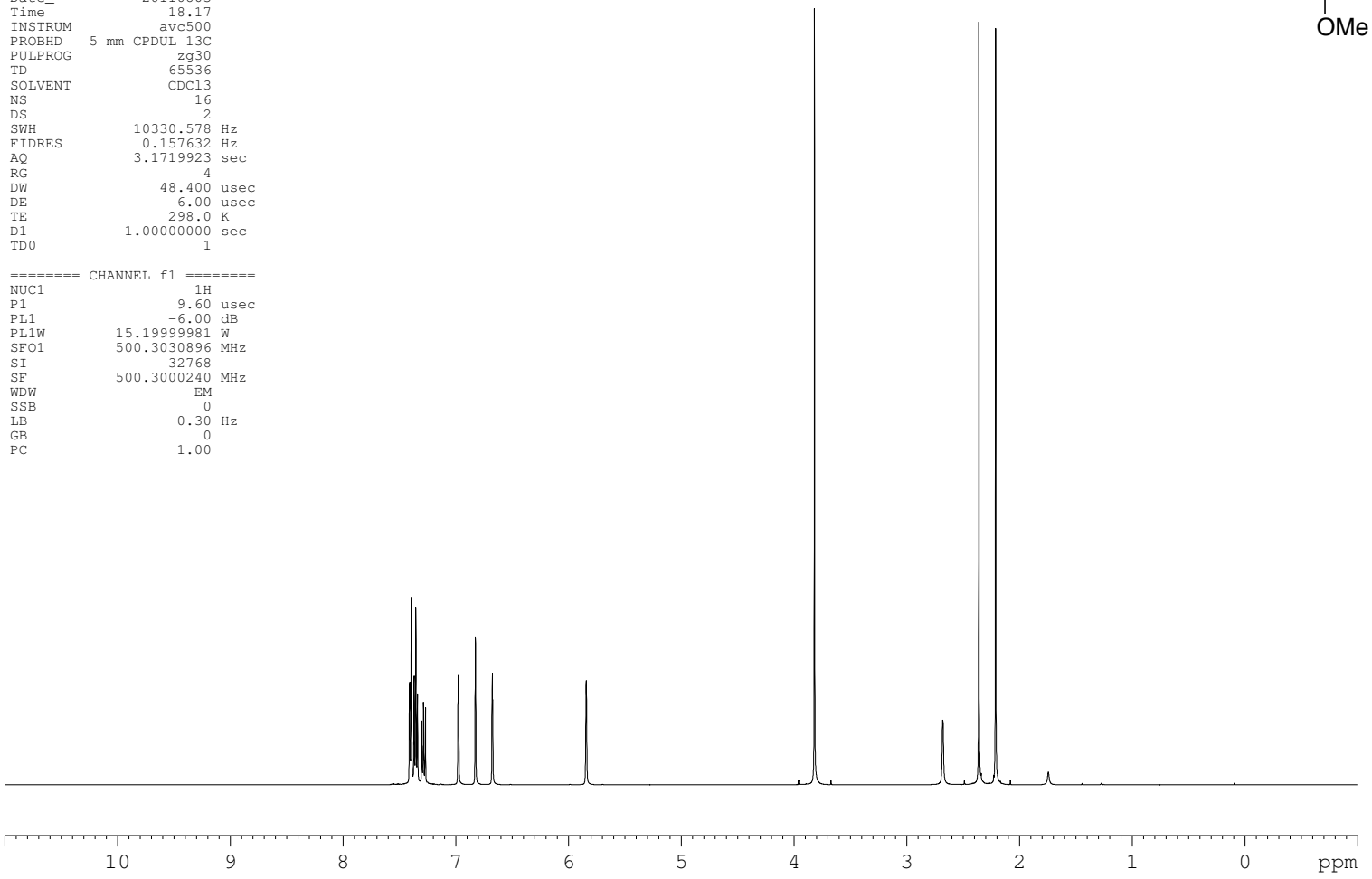
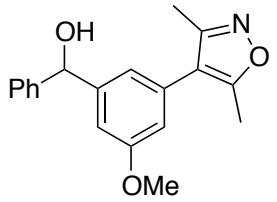


(3-(3,5-Dimethylisoxazol-4-yl)-5-methoxyphenyl)(phenyl)methanol **21** ^{13}C NMR

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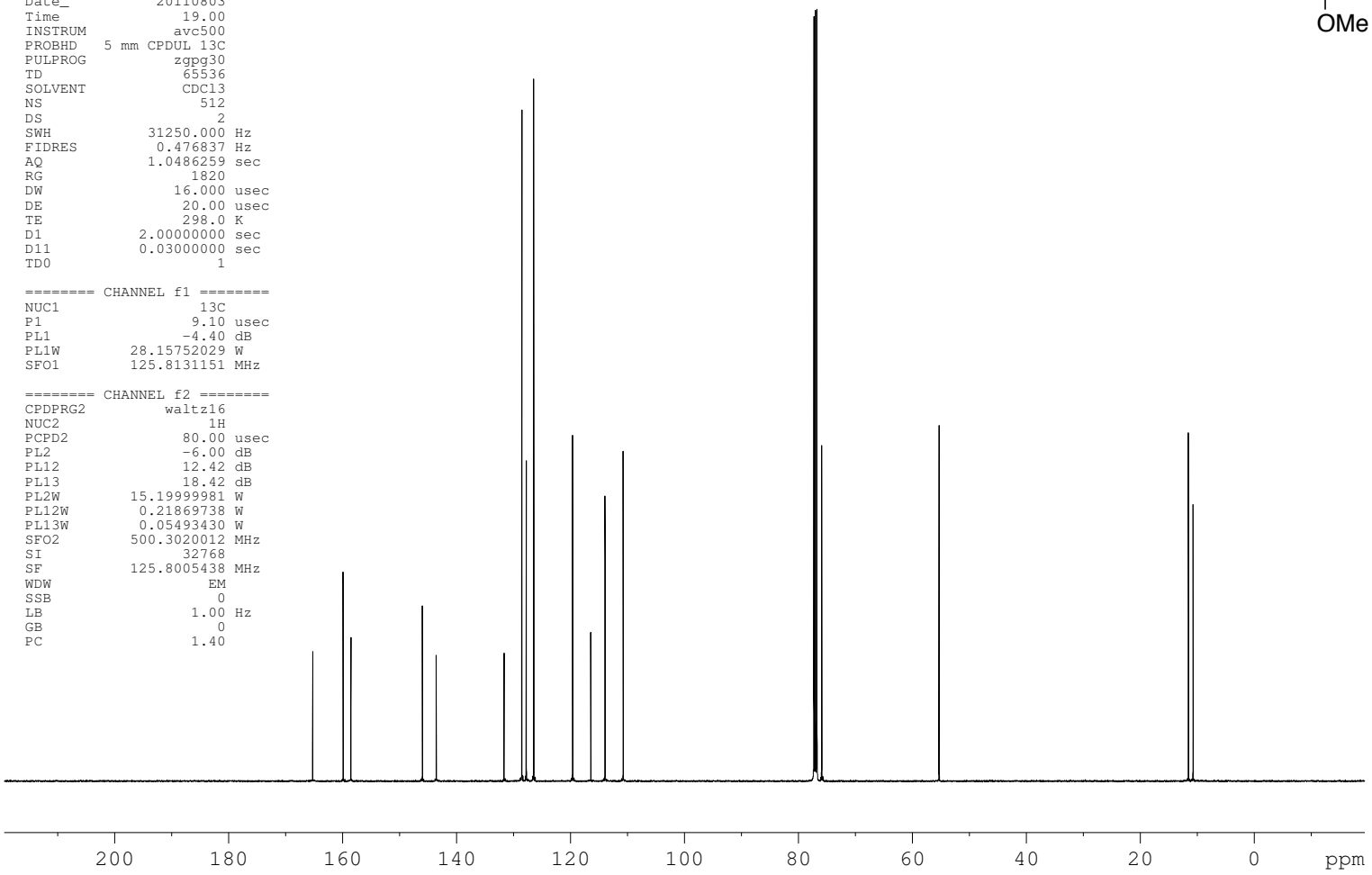
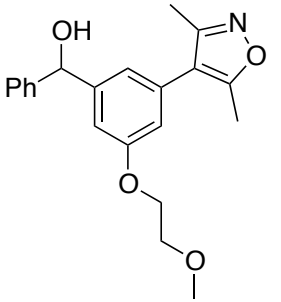
NAME                128
EXPNO                 4
PROCNO                1
Date_          20110803
Time              19.00
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ            1.0486259 sec
RG                 1820
DW               16.000 usec
DE               20.00 usec
TE               298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.10 usec
PL1               -4.40 dB
PL1W        28.15752029 W
SFO1        125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2              80.00 usec
PL2                -6.00 dB
PL12               12.42 dB
PL13               18.42 dB
PL2W        15.19999981 W
PL12W        0.21869738 W
PL13W        0.05493430 W
SFO2        500.3020012 MHz
SI                32768
SF          125.8005438 MHz
WDW                 EM
SSB                 0
LB                1.00 Hz
GB                  0
PC                1.40
```



(3-(3,5-Dimethylisoxazol-4-yl)-5-(2-methoxyethoxy)phenyl)(phenyl)methanol **22** ^{1}H NMR

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NAME                 133
EXPNO                  1
PROCNO                 1
Date_           20110803
Time               19.38
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ             3.1719923 sec
RG                     4
DW                48.400 usec
DE                 6.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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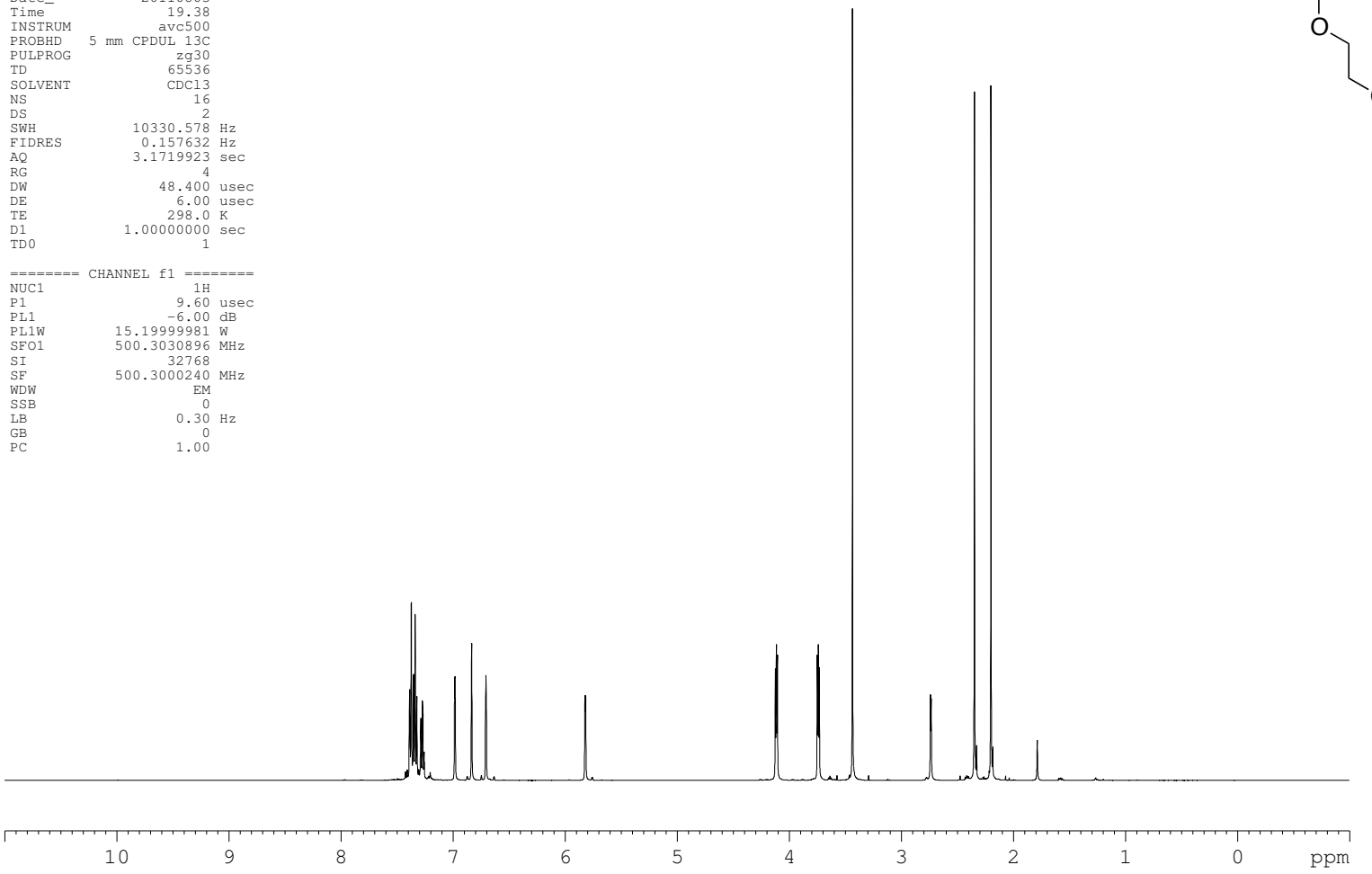
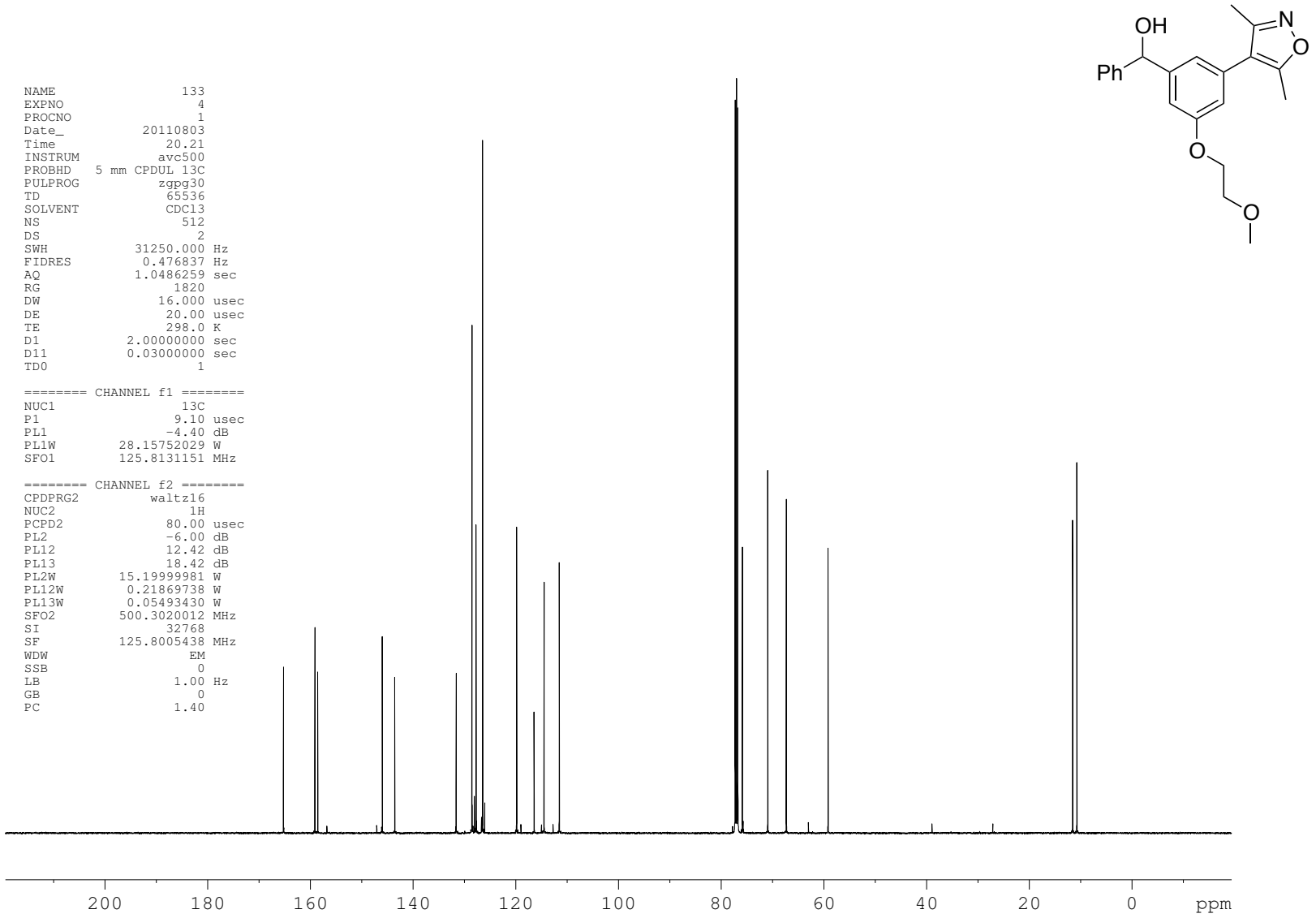
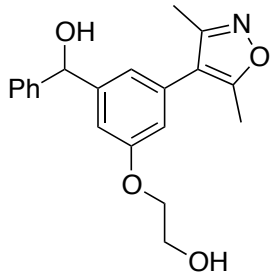


(3-(3,5-Dimethylisoxazol-4-yl)-5-(2-methoxyethoxy)phenyl)(phenyl)methanol **22** ^{13}C NMR



2-(3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenoxy)ethanol **23** ^{1}H NMR

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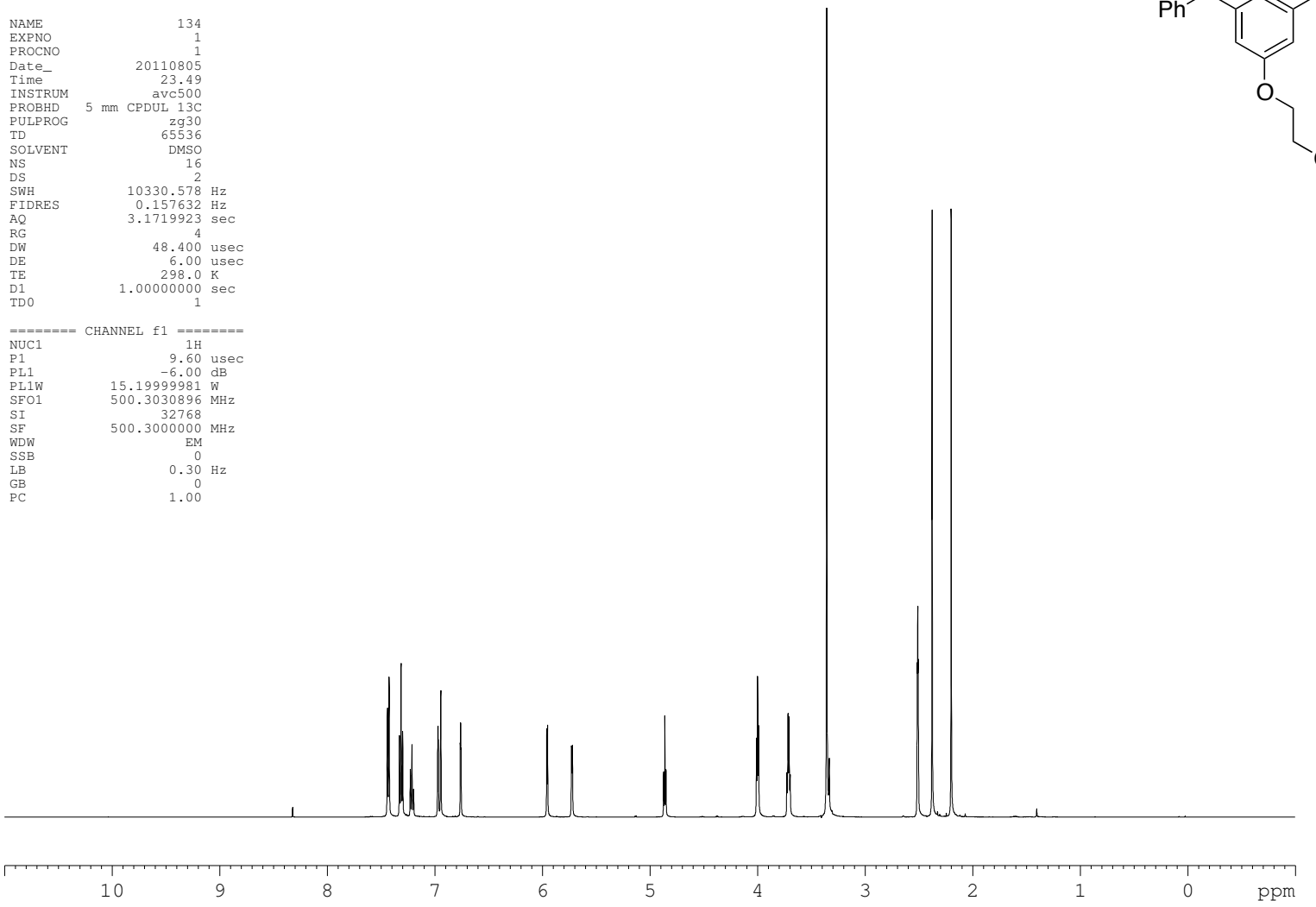
NAME                 134
EXPNO                  1
PROCNO                 1
Date_           20110805
Time               23.49
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                     4
DW                48.400 usec
DE                 6.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



2-(3-(3,5-Dimethylisoxazol-4-yl)-5-(hydroxy(phenyl)methyl)phenoxy)ethanol **23** ^{13}C NMR