Supporting Information:

3,5-Dimethylisoxazoles act as acetyl-lysine mimetic bromodomain ligands

David S. Hewings,[†,‡] Minghua Wang,[†] Martin Philpott,[†] Oleg Fedorov,[†] Sagar Uttarkar,[†] Panagis Filippakopoulos,[†] Sarah Picaud,[†] Chaitanya Vuppusetty,[†] Brian Marsden,[†] Stefan Knapp,[†] Stuart J. Conway[‡,] and Tom D. Heightman[†,§,]**

[†]Nuffield Department of Clinical Medicine, Structural Genomics Consortium, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford, OX3 7DQ, UK; [‡]Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK; [§]Current address: Astex Therapeutics, 436 Cambridge Science Park, Cambridge, CB4 0QA, UK.

*To whom correspondence should be addressed: stuart.conway@chem.ox.ac.uk, telephone: +44 (0)1865 285 109, fax: +44 (0)1865 285 002; t.heightman@astex-therapeutics.com, telephone: +44 (0)1223 226270.

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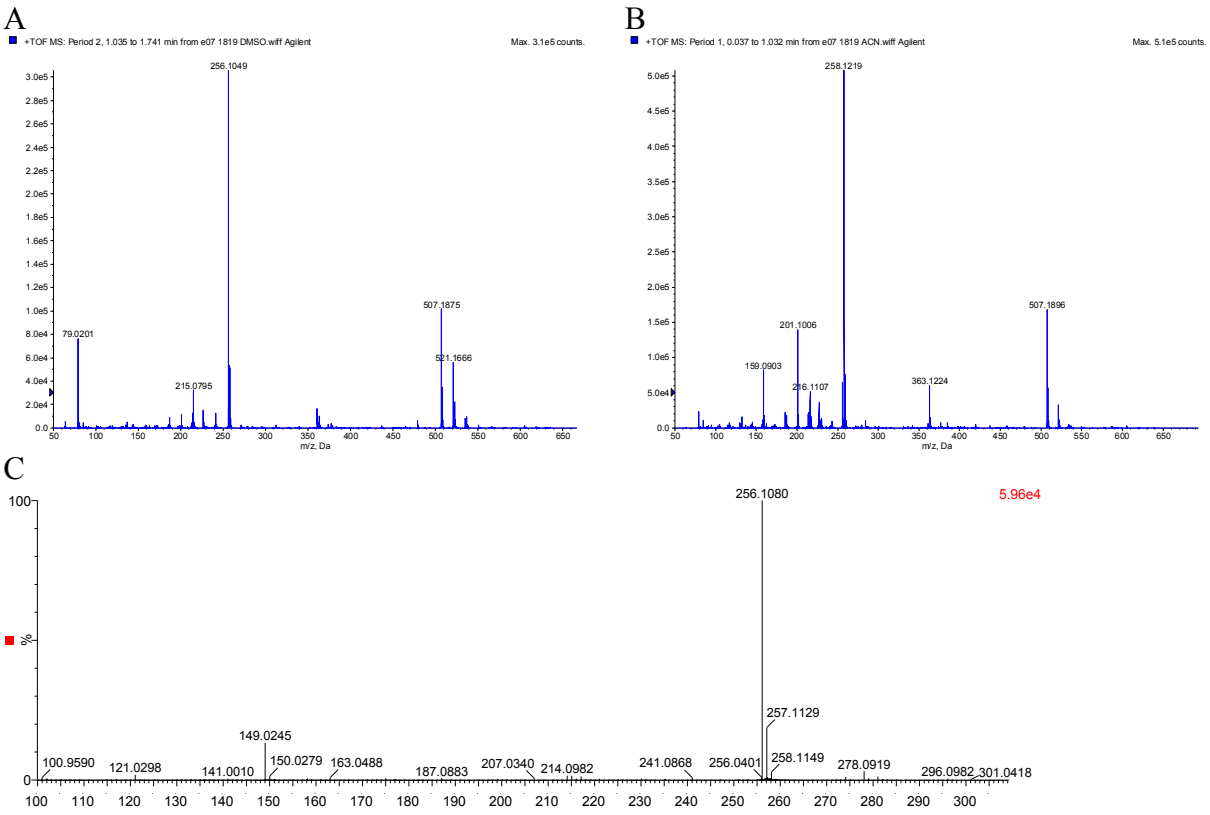
Abbreviations used in Supporting Information:

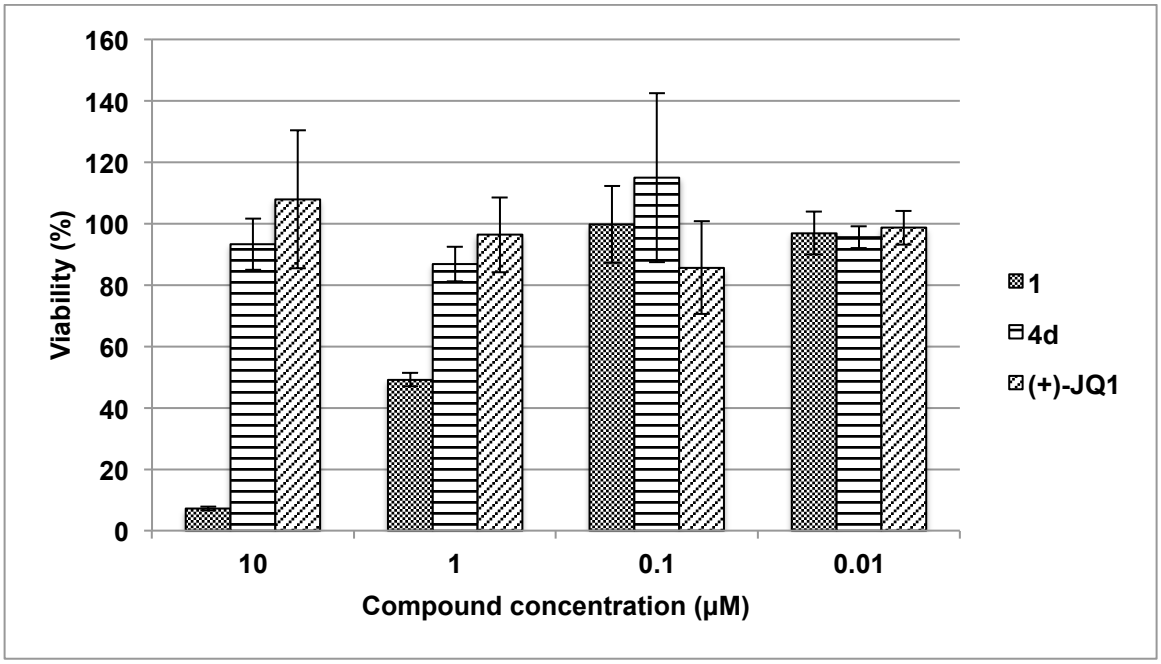
BRD(1): First bromodomain of bromodomain-containing protein 4; CREBBP: c-AMP response element binding protein binding protein; DMAc: *N*,*N*-dimethylacetamide; DMEM: Dulbecco's modified Eagle's medium; LE: Ligand efficiency; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylltetrazolium bromide; RuPhos: 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

Supporting Figure S1. Mass spectra of **1**



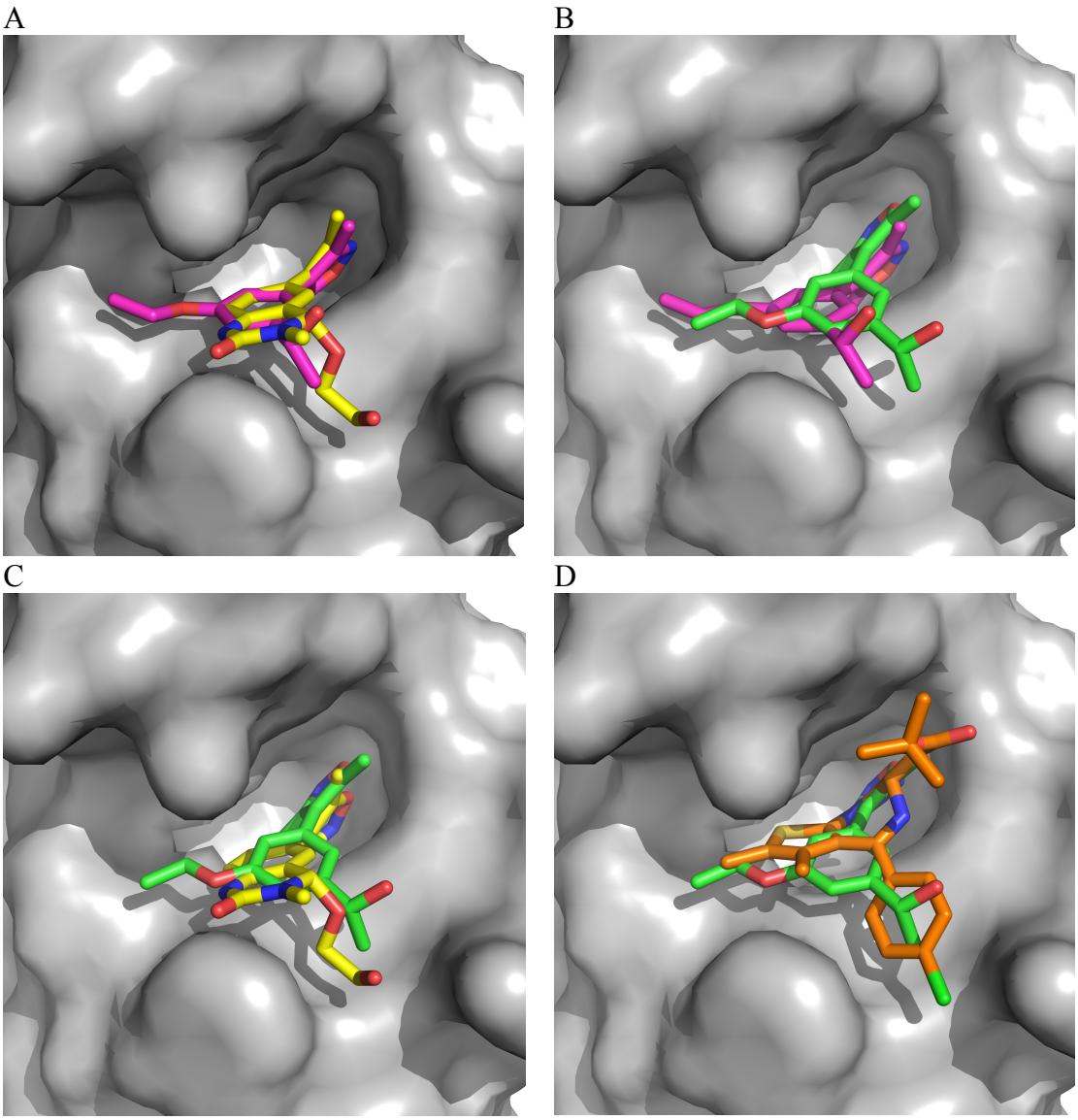
1 is liable to oxidation under laboratory conditions. **A**: Mass spectrum of purchased **1** after storage in DMSO for one month; $[M\text{-}H]^+$ is likely to arise from oxidation at the benzylic position; **B**: Mass spectrum of freshly-prepared MeCN suspension of purchased **1**; $[M+H]^+$ is observed, but $[M\text{-}H]^+$ is not; **C**: High-resolution LCMS of resynthesized **1** after stirring in DMSO for 5 days; $[M\text{-}H]^+$ present. For **1**, calculated $[M+H]^+$: 258.1237, $[M\text{-}H]^+$: 256.1081. Details of MS experiments are given below (S11).

Supporting Figure S2. Cytotoxicity assay.



Cytotoxicity of lead compound **1**, **4d** and (+)-JQ1 in HeLa cells, as determined by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylltetrazolium bromide) assay, indicating mitochondrial reductase activity. A reduction in viability indicates cytotoxicity in this cell line. Experiments were performed in triplicate. Error bars indicate standard deviation.

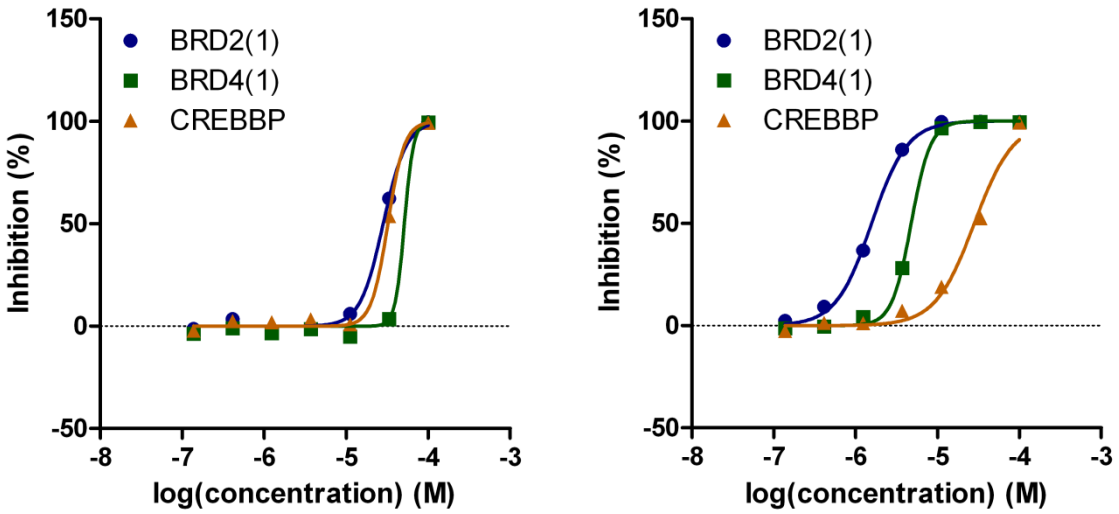
Supporting Figure S3. Overlays of crystal structure of **2**, JQ1, and comparison with predicted binding mode of **4d**.



A: Overlay of the crystal structure of lead **2** (yellow, PDB ID: 3SVF) and predicted binding mode of compound **4d** (magenta) bound to BRD4(1); **B**: Comparison of the crystal structure of compound **4d** (green, PDB ID: 3SVG) and its predicted binding mode; **C**: Comparison of the crystal structure of lead compound **2** (yellow) and the crystal structure of final compound **4d** (green); **D**: Overlay of the crystal structures of compound **4d** and JQ1 bound to BRD4(1) (PDB ID: 3MXF).

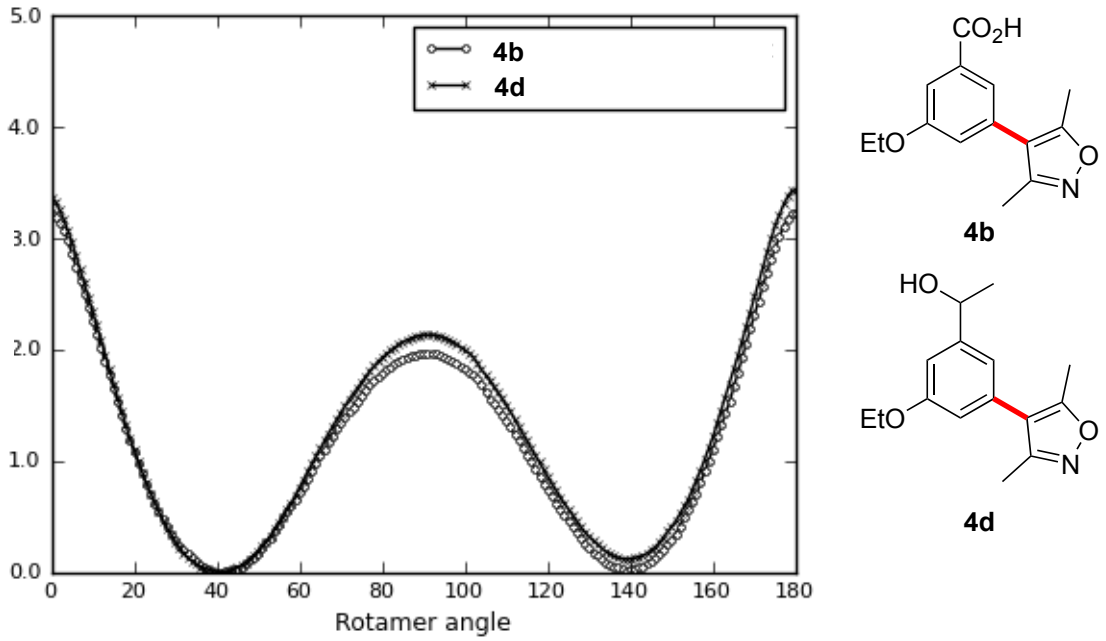
Supporting Figure S4. Selected dose-response curves

A B



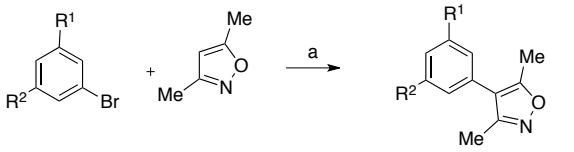
Dose-response curves for A: **4b** and B: **4d** in three bromodomains. Curves were constrained to 0% and 100% inhibition. Experiments were carried out in duplicate on the same plate; intra-experimental variation was too small to be visualized with error bars. Curves plotted in GraphPad Prism (GraphPad Software).

Supporting Figure S5. Calculation of minimum energy torsion angle.



Calculated energy as a function of torsion angle around C–C bond (indicated). 0˚ corresponds to planarity. Energy is in kcal/mol relative to the energy minimum. Calculations were performed in Macromodel (Schrödinger) using OPLS2005 force field.

Supporting Scheme S1. Synthesis of 4-aryl-3,5-dimethylisoxazoles **3a-b, 4a** by direct arylation of 3,5-dimethylisoxazole.[a]

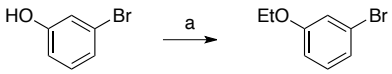


5 R^1 = H, R^2 = H
6 R^1 = Ac, R^2 = H
10 R^1 = CO_2Et, R^2 = OEt

3a R^1 = H, R^2 = H
3b R^1 = Ac, R^2 = H
4a R^1 = CO_2Et, R^2 = OEt

[a]Conditions: (a) R_1 = H, R_2 = H: $PdCl_2$, KOAc, DMAc, 130 °C, 27 h, 69%; R_1 = Ac, R_2 = H: $PdCl_2$, KOAc, DMAc, 130 °C, 20 h, 51%; R_1 = CO_2Et, R_2 = OEt: $PdCl_2$, KOAc, DMAc, 130 °C, 44 h, 44%.[1]

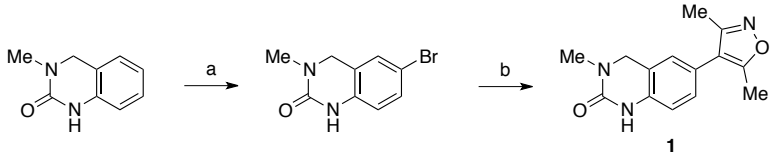
Supporting Scheme S2. Synthesis of 3-bromoethoxybenzene **7**.[a]



7

[a]Conditions: (a) EtBr, K_2CO_3 MeOH, 120 °C (microwave), 20 min, 95%.[2]

Supporting Scheme S3. Synthesis of 6-(3,5-dimethylisoxazol-4-yl)-3-methyl-3,4-dihydroquinazolin-2(1*H*)-one **1**.[a]



1

[a]Conditions: (a) *N*-Bromosuccinimide, DMF, rt, 2 h, 12%; (b) **8**, Na_2CO_3, $Pd(OAc)_2$, RuPhos, EtOH, 110 ˚C (microwave), 3 h, 70%.

Supporting Table S1. Ligand efficiency.[a]

	1		**4d**		**(+)-JQ1**	**NMP**	
	BRD4(1)	CREBBP	BRD4(1)	BRD2(1)	BRD4(1)	BAZ2B	CREBBP
IC_{50} (M)	4.8×10^{-6}	3.4×10^{-6}	4.8×10^{-6}	1.6×10^{-6}	77×10^{-9}	34×10^{-3}	2.4×10^{-3}
pIC_{50}	5.32	5.47	5.32	5.8	7.11	1.47	2.64
Heavy atom count	19	19	19	19	31	7	7
LE	0.39	0.40	0.39	0.43	0.32	0.30	0.53

[a] $\mathrm{pIC_{50}} = -\log_{10} \mathrm{IC_{50}}$

$$\mathrm{LE} = \frac{\mathrm{pIC_{50}} \times 1.4\ (\mathrm{kcal/mol})}{\text{Heavy atom count}}$$

Supporting Table S2. Data collection and refinement statistics.[a]

Data Collection

PDB ID	3SVF	3SVG	3SVH
Protein/Ligand	BRD4(1)/**2**	BRD4(1)/**4d**	CREBBP/**4b**
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Cell dimensions: a, b, c (Å) α, β, γ (deg)	43.56 48.98 60.28 90.00 90.00 90.00	37.66 44.19 77.85 90.00 90.00 90.00	42.36 61.92 58.42 90.00 111.38 90.00
Resolution (Å)	1.98 (2.08-1.98)	1.68 (1.77-1.68)	1.80 (1.90-1.80)
Unique observations	9376 (1302)	15429 (2207)	24992 (3517)
Completeness (%)	98.8 (96.4)	99.8 (99.0)	95.4 (92.4)
Redundancy	6.5 (5.2)	4.4 (3.8)	2.7 (2.7)
Rmerge	0.185 (0.745)	0.067 (0.580)	0.095 (0.265)
I/ σ I	7.5 (2.0)	13.5 (2.0)	8.1 (3.4)
Refinement			
Resolution (Å)	1.98	1.68	1.80
R_{work} / R_{free} (%)	17.7/22.6	17.6/21.5	18.8/22.9
Number of atoms (protein/other/water)	1054/23/86	1082/31/125	1986/80/232
B-factors (Å^2) (protein/other/water)	23.46/24.36/26.29	18.77/22.88/26.26	12.49/15.21/17.80
r.m.s.d bonds (Å) r.m.s.d angles (^{o})	0.016 1.526	0.015 1.552	0.015 1.611
Ramachadran Favoured (%) Allowed (%) Disallowed (%)	98.40 1.60 0.00	98.33 1.67 0.00	100.00 0.00 0.00

[a] Values in parentheses correspond to the highest resolution shell.

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 scaling up the drop sizes. All crystallizations were carried out using the sitting drop vapor diffusion method at 4 ˚C. CREBBP crystals with **4b** were grown by mixing 150 nL of the protein (10.6 mg/mL and 10 mM final ligand

concentration) with an equal volume of reservoir solution containing 0.25 M potassium thiocyanate, 10% PEG3350 and 5% ethylene glycol. BRD4(1) crystals with **2** were grown by mixing 50 nL of protein (10.3 mg/mL and 5 mM final ligand concentration) with 100 nL of reservoir solution containing 0.2 M sodium acetate, 0.1 M Bis-Tris pH 8.5, 20% PEG3350 and 10% ethylene glycol. BRD4(1) crystals with **4d** were grown by mixing 75 nL of protein (9.9 mg/mL and 5 mM final ligand concentration) with an equal volume of reservoir solution containing 0.2 M sodium sulfate, 0.1 M BT-propane pH 8.5, 20% PEG3350 and 10% ethylene glycol. In all cases diffraction quality crystals grew within a few days.

Data Collection and Structure Solution: All crystals were cryo-protected using the well solution supplemented with additional ethylene glycol and were flash frozen in liquid nitrogen. Data were collected in-house on a Rigaku FRE rotating anode system equipped with a RAXIS-IV detector at 1.52 Å. Indexing and integration was carried out using MOSFLM[3] and scaling was performed with SCALA.[4] Initial phases were calculated by molecular replacement with PHASER[5] using the known models of BRD4(1) (PDB ID: 2OSS) and CREBBP (PDB ID: 3DWY). Initial models were built by ARP/wARP[6] followed by manual building in COOT.[7] Refinement was carried out in REFMAC5.[8] In all cases 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 S2. The models and structure factors have been deposited with PDB accession codes: 3SVF (BRD4(1)/**2**), 3SVG (BRD4(1)/**4d**), 3SVH (CREBBP/**4b**).

Further General Experimental

Mass spectra of purchased **1** (Supporting Figure S1A, B) were obtained using an Agilent MSD-ToF electrospray ionisation orthogonal time-of-flight mass spectrometer. The sample was diluted 1:100 (v/v) in LC-MS grade acetonitrile and infused directly into the ion source at a flow rate of 3 μL per minute using a syringe pump. The instrument was configured with the standard ESI source and operated in positive ion mode. Data analysis was performed using Quantitative Analysis software (Agilent Technologies Inc). LCMS of resynthesized **1** (Supporting Figure S1C) was obtained using a Waters Nano Acquity nano-LC system interfaced to a Waters Synapt mass spectrometer *via* an electrospray source. LC conditions were: Waters 1.7 μM BEH C18 75 μM × 150 mm column with a binary solvent system using water + 0.1% formic acid and MeCN. Data analysis was performed with using Synapt software (Waters Corporation).

Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} aluminum-supported thin layer chromatography sheets. Visualisation 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 DMF and dry MeOH were purchased from Sigma-Aldrich UK in SureSeal™ bottles and used without further purification; anhydrous THF was distilled from sodium and benzophenone in a recycling still and stored over activated 3 Å molecular sieves under an argon atmosphere;

Dry DMAc (Sigma) was degassed by repeated freeze-thaw cycles and stored over activated 3 Å molecular sieves under an argon atmosphere. EtOH was degassed by repeated freeze-thaw cycles and stored under an argon atmosphere, but was not dried.

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. K_2CO_3 and Na_2CO_3 were dried in an oven prior to use. *N*,*O*-Dimethylhydroxylamine hydrochloride was dried in a vacuum desiccator prior to use.

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.

Synthesis and characterization of compounds 1, 7, 8, 10-13

6-(3,5-Dimethylisoxazol-4-yl)-3-methyl-3,4-dihydroquinazolin-2(1*H*)-one **1**

To a solution of 3-methyl-3,4-dihydroquinazolin-2(1*H*)-one (5.00 g, 31.0 mmol) in DMF (120 mL) was added *N*-bromosuccinimide (6.61 g, 37.1 mmol). The reaction was stirred at rt for 2 h then concentrated *in vacuo*. The resulting residue was resuspended in EtOAc, washed with H_2O (3 × 100 mL), dried and concentrated *in vacuo*. Purification by silica gel column chromatography (5:1 CH_2Cl_2:EtOAc) gave 6-bromo-3-methyl-3,4-dihydroquinazolin-2(1*H*)-one as a colorless solid (916 mg, 12%); mp 195–197 °C (EtOH); ^{1}H NMR (500 MHz, DMSO-D_6) 2.85 (s, 3H) 4.39 (s, 2H), 6.70-6.74 (m, 1H), 7.28–7.32 (m, 2H), 9.33 (s, 1H); ^{13}C NMR (125 MHz, DMSO-D_6) 33.8, 49.2, 112.0,

115.2, 120.3, 128.1, 130.4, 137.3, 153.3; HRMS *m/z* (ES^+) found $[M+H]^+$ 240.9969, $C_9H_{10}{}^{79}BrN_2O^+$ requires 240.9971; *m/z* (ES^+) 263 ($[^{79}M+Na]^+$, 56), 265 ($[^{81}M+Na]^+$, 55), 295 ($[^{79}M+MeOH+Na]^+$, 12), 297 ($[^{81}M+MeOH+Na]^+$, 12), 503 ($[2^{79}M+Na]^+$, 53), 505 ($[^{79}M+^{81}M+Na]^+$, 100), 507 ($[2^{81}M+Na]^+$, 52). Anal. Calcd for $C_9H_9BrN_2O$: C, 44.8; H, 3.8; N, 11.6. Found: C, 44.8; H, 3.7; N, 11.6.

To a dry 2-5 mL microwave vial were added **8** (93 mg, 456 μmol), 6-bromo-3-methyl-3,4-dihydroquinazolin-2(1*H*)-one (100 mg, 415 μmol), $Pd(OAc)_2$ (1 mg, 4 μmol), RuPhos (6 mg, 13 μmol) and anhydrous Na_2CO_3 (88 mg, 830 μmmol). The vial was sealed and purged with argon (3 × evacuate/fill). Degassed EtOH (2.3 mL) was added by syringe, and the mixture was heated at 110 ˚C for 3 h with microwave irradiation. Purification of the crude reaction mixture by silica gel column chromatography (gradient elution, gradient 60 → 100% EtOAc/petroleum ether) gave **1** as a colorless solid (68 mg, 64%); mp 224-226 ˚C (MeOH); ^1H NMR ($CDCl_3$) 2.24 (s, 3H), 2.38 (s, 3H), 3.07 (s, 3H), 4.50 (s, 2H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.91 (s, 1H), 7.05 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR ($CDCl_3$) 10.8, 11.5, 34.6, 50.8, 114.2, 116.1, 117.8, 123.8, 126.0, 129.1, 136.6, 154.5, 158.7, 165.0; HRMS *m/z* (ES^+) found 280.1055; $C_{14}H_{15}N_3NaO_2$ requires M^+ 280.1056. *m/z* (ES^+) 258 ($[M+H]^+$, 28), 280 ($[M+Na]^+$, 86), 312 ($[M+Na+MeOH]^+$, 85), 537 ($[2M+Na]^+$, 100). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.4; H, 5.9; N, 16.3. Found: C, 65.2; H, 5.9; N, 16.2.

1-Bromo-3-ethoxybenzene **7**

To a dry 2-5 mL microwave vial were added anhydrous K_2CO_3 (829 mg, 6.00 mmol), 3-bromophenol (1.04 g, 637 μL, 6.00 mmol), EtBr (981 mg 672 μL, 9.00 mmol) and anhydrous MeOH (1.8 mL) under a nitrogen atmosphere. The vial was sealed, and the

mixture stirred at 120 ˚C for 20 min with microwave irradiation, then concentrated *in vacuo*. The residues were extracted with 40-60 ˚C petroleum ether (3 × 15 mL) and concentrated *in vacuo* to give **7** as a pale yellow oil (1.14 g, 95%); ^{1}H NMR (500 MHz, $CDCl_3$) 1.42 (t, J = 7.0 Hz, 3H), 4.02 (q, J = 7.0 Hz, 2H), 6.83 (ddd, J = 8.1, 2.3, 1.0 Hz, 1H), 7.05-7.08 (m, 2H), 7.14 (dd, J = 8.1, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.7, 63.7, 113.6, 117.7, 122.8, 123.6, 130.5, 159.7; HRMS *m*/*z* (FI^+) found M^+ 199.9838, 201.9817; $C_8H_9{}^{79}BrO$ requires M^+ 199.9837, $C_8H_9{}^{81}BrO$ requires M^+ 201.9811. Anal. Calcd for C_8H_9BrO: C, 47.8; H, 4.5. Found: C, 47.7; H, 4.4.

Potassium (3,5-dimethylisoxazol-4-yl)trifluoroborate **8**[10]

To a suspension of 3,5-dimethylisoxazol-4-ylboronic acid (254 mg, 1.80 mmol) in MeOH (1.0 mL) at 0 ˚C was added KHF_2 (420 mg, 5.38 mmol). H_2O (1.20 mL) was then added dropwise. The solution was warmed to rt and stirred for 10 min, then concentrated and dried overnight *in vacuo*. The crude solid was purified by Soxhlet extraction (16 h) with acetone (15 mL). The collected solvent was concentrated *in vacuo*, and the residues redissolved the minimum amount of acetone (40 mL). The product was precipitated by the addition of Et_2O (60 mL) and collected by filtration. The filtrate was concentrated *in vacuo*, redissolved in acetone (5 mL) and further product was precipitated by the addition of Et_2O (20 mL) and collected by filtration. The combined solids were dried *in vacuo* to give **8** as a powdery colorless solid (312 mg, 85%); mp >275 ˚C (lit. >200 ˚C)[10]; ^{1}H NMR (400 MHz, DMSO-D_6) 2.05 (s, 3H), 2.20 (s, 3H); ^{11}B NMR (160 MHz, DMSO-D_6) 2.33 (q, J = 49 Hz); ^{19}F NMR (470 MHz, DMSO-D_6) −134.8-−134.2; *m*/*z* (ES^-) 164 ($[M\text{-}K]^-$, 100), 351 ($[2M-2K+Na]^-$, 43), 367 ($[2M-K]^-$, 22). Anal. Calcd for $C_5H_6BF_3KNO$: C,

29.6; H, 3.0; N, 6.9. Found: C, 29.7; H, 2.9; N, 6.8. These data are in good agreement with the literature values.[10]

Ethyl 3-bromo-5-ethoxybenzoate **10**

To a dry 10-20 mL microwave vial were added 3-bromo-5-hydroxybenzoic acid **9** (1.30 g, 5.99 mmol), anhydrous K_2CO_3, anhydrous DMF (5 mL) and EtBr (1.96 g, 1.34 mL, 18.0 mmol) under a nitrogen atmosphere. The vial was sealed, and the mixture stirred at 100 ˚C for 15 min, then concentrated *in vacuo*. The mixture was diluted with H_2O (40 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with H_2O (2 × 120 mL) and brine (120 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **10** as an orange solid (1.57 g, 96%); mp 43-44 ˚C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) 1.39 (t, J = 7.2 Hz, 3H), 1.42 (t, J = 7.0 Hz, 3H), 4.06 (q, J = 7.0 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 7.22 (dd, J = 2.4, 1.8 Hz, 1H), 7.49 (dd, J = 2.4, 1.5 Hz, 1H), 7.73 (dd, J = 1.8, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 14.6, 61.4, 64.1, 114.1, 122.4, 122.6, 124.7, 133.0, 159.6, 165.3; HRMS m/z (ES^+) found $[M+Na]^+$ 294.9931, 296.9925, $C_{11}H_{13}{}^{79}BrNaNO_3$ requires M^+ 294.9940, $C_{11}H_{13}{}^{81}BrNaNO_3$ requires M^+ 296.9920; m/z (ES^+) 295 ($[^{79}M+Na]^+$, 100), 297 ($[^{81}M+Na]^+$, 97), 567 ($[2^{79}M+Na]^+$, 42), 569 ($[^{79}M+^{81}M+Na]^+$, 78), 571 ($[2^{81}M+Na]^+$, 37). Anal. Calcd for $C_{11}H_{13}BrNO_3$: C, 48.4; H, 4.8. Found: C, 48.3; H, 4.8.

3-Bromo-5-ethoxybenzoic acid **11**

To a solution of **10** (500 mg, 1.83 mmol) in THF (2 mL) were added H_2O (1 mL) and LiOH (66 mg, 2.75 mmol), and the mixture was stirred for 23 h at rt. Aqueous HCl (1 M, 10 mL) was then added, and the mixture extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and

concentrated *in vacuo* to give **11** as a pale yellow solid (425 mg, 95%); mp 139-143 ˚C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 1.44 (t, J = 7.0 Hz, 3H), 4.09 (q, J = 7.0 Hz, 2H), 7.30 (dd, J = 2.5, 1.8 Hz, 1H), 7.55 (dd, J = 2.5, 1.4 Hz, 1H), 7.83 (dd, J = 1.8, 1.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) 14.6, 64.2, 114.5, 122.8, 123.5, 125.3, 131.6, 159.7, 170.3; HRMS *m*/*z* (ES^-) found $[M-H]^-$ 242.9962, 244.9642; $C_9H_9{}^{79}BrO_3$ requires M^- 242.9962, $C_9H_9{}^{81}BrO_3$ requires M^- 244.9642; *m*/*z* (ES^-) 243 ($[^{79}M]^-$, 96), 245 ($[^{81}M]^-$, 100), 487 ($[2^{79}M]^-$, 6) 489 ($[^{79}M+^{81}M]^-$, 13), 491 ($[2^{81}M]^-$, 6), 509 ($[2^{79}M–2H+Na]^-$, 45), 511 ($[^{79}M+^{81}M-2H+Na]^-$, 80), 513 ($[2^{81}M–2H+Na]^-$, 37). Anal. Calcd for $C_9H_9BrO_3$: C, 44.1; H, 3.7. Found: C, 44.0; H, 3.6.

3-Bromo-5-ethoxy-*N*-methoxy-*N*-methylbenzamide **12**

To a dry flask containing **11** (353 mg, 1.44 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (285 mg, 2.92 mmol) and HBTU (576 mg, 1.52 mmol) were added anhydrous DMF (3.5 mL) and diisopropylethylamine (1.0 g, 1.3 mL, 7.46 mmol) at 0 ˚C under a nitrogen atmosphere. The mixture was warmed to rt and stirred for 14 h, then concentrated *in vacuo*. The residues were redissolved in EtOAc (50 mL), washed with citric acid (10% w/v, 2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), H_2O (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient elution, gradient 6 → 40% EtOAc/petroleum ether) gave **12** as a colorless oil (331 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 (t, J = 7.0 Hz, 3H), 3.34 (s, 3H), 3.57 (s, 3H), 4.03 (q, J = 7.0 Hz, 2H), 7.10-7.14 (m, 2H), 7.35-7.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.6, 33.7, 61.2, 64.0, 113.2, 119.9, 122.3, 123.1, 136.6, 159.3, 168.1; HRMS *m*/*z* (ES^+) found $[M+Na]^+$ 310.0055, 312.0034; $C_{11}H_{14}{}^{79}BrNNaO_3$ requires M^+ 310.0049, $C_{11}H_{14}{}^{81}BrNNaO_3$

requires M^+ 312.0029; *m*/*z* (ES^+) 288 ($[^{79}M+H]^+$, 25), 290 ($[^{81}M+H]^+$, 24), 310 ($[^{79}M+Na]^+$, 57), 312 ($[^{81}M+Na]^+$, 55), 597 ($[2^{79}M+Na]^+$, 96), 599 ($[^{79}M+^{81}M+Na]^+$, 100), 601 ($[2^{81}M+Na]^+$, 95). Anal. Calcd for $C_{11}H_{14}BrNO_3$: C, 45.9; H, 4.9; N, 4.9. Found: C, 46.0; H, 4.8; N, 4.7.

1-(3-Bromo-5-ethoxyphenyl)ethanone **13**

To a solution of **12** (250 mg, 868 μmol) in anhydrous THF (8 mL) under an argon atmosphere was added MeMgBr solution (1.0 M in dibutyl ether, 2.6 mL, 2.6 mmol) dropwise at 0 ˚C. The solution was warmed to rt and stirred for 15 h, then quenched with aqueous HCl (1 M, 15 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient elution, gradient 3 → 30% Et_2O/petroleum ether) gave **13** as a colorless solid (181 mg, 86%); mp 40-41 ˚C (15% Et_2O:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) 1.43 (t, *J* = 7.0 Hz, 3H), 2.57 (s, 3H), 4.07 (q, *J* = 7.0 Hz, 2H), 7.23-7.25 (m, 1H), 7.38-7.41 (m, 1H), 7.63-7.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.6, 26.7, 64.2, 112.7, 122.5, 123.0, 123.8, 139.4, 159.8, 196.5; HRMS *m*/*z* (ES^+) found $[M+Na]^+$ 264.9833, 266.9814; $C_{10}H_{11}{}^{79}BrNaO_2$ requires M^+ 264.9835, $C_{10}H_{11}{}^{81}BrNaO_2$ requires M^+ 266.9814; *m*/*z* (ES^+) 265 ($[^{79}M+Na]^+$, 100), 267 ($[^{81}M+Na]^+$, 97). Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.4; H, 4.6. Found: C, 49.6; H, 4.4.

Further characterization for compounds 3a-d, 4a-d

3,5-Dimethyl-4-phenylisoxazole **3a**

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N; 8.1. Found: C, 76.4; H, 6.5; N, 8.0.

1-3-(3,5-Dimethylisoxazol-4-yl)phenyl)ethanone **3b**

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.1; N, 6.5. Found: C, 72.6; H, 6.2; N, 6.4.

4-(3-Ethoxyphenyl)-3,5-dimethylisoxazole **3c**

^{13}C NMR (100 MHz, $CDCl_3$) 10.8, 11.6, 14.8, 63.5, 113.2, 115.6, 116.6, 121.3, 129.8, 131.7, 158.6, 159.2, 165.2. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.5. Found: C, 72.0; H, 7.1; N, 6.4.

(*RS*)-1-(3-(3,5-Dimethylisoxazol-4-yl)phenyl)ethanol **3d**

^{13}C NMR (100 MHz, $CDCl_3$) 10.8, 11.6, 25.4, 70.1, 116.6, 124.6, 126.1, 128.0, 128.9, 130.6, 146.6, 158.7, 165.2. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.5. Found: C, 72.0; H, 7.0; N; 6.3.

Ethyl 3-(3,5-dimethylisoxazol-4-yl)-5-ethoxybenzoate **4a**

^{13}C NMR (100 MHz, $CDCl_3$) 10.8, 11.6, 14.3, 14.7, 61.3, 63.9, 113.5, 115.9, 120.5, 122.5, 131.9, 132.3, 158.5, 159.2, 165.6, 166.1. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.6; H, 66.5; N, 4.7.

3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxybenzoic acid **4b**

^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 14.7, 64.0, 113.8, 115.7, 121.6, 123.1, 131.0, 132.1, 158.5, 159.3, 165.7, 171.1. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8; N, 5.4. Found: C, 64.2; H, 5.9; N, 5.3.

1-(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)ethanone **4c**

^{13}C NMR (126 MHz, $CDCl_3$) 10.8, 11.6, 14.7, 26.7, 63.9, 112.3, 115.9, 120.5, 121.5, 132.2, 138.9, 158.5, 159.5, 165.6, 197.5. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.6; N, 5.4. Found: C, 69.6; H, 6.7; N, 5.3.

(*RS*)-1-(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)ethanol **4d**

^{13}C NMR (100 MHz, $CDCl_3$) 10.8, 11.6, 14.8, 25.4, 63.6, 70.1, 110.3, 114.4, 116.6, 118.3, 131.8, 148.1, 158.6, 159.4, 165.2. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.3; N, 5.3. Found: C, 69.1; H, 71; N, 5.5.

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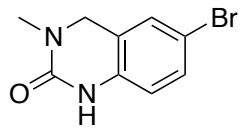
6-bromo-3-methyl-3,4-dihydroquinazolin-2(1*H*)-one

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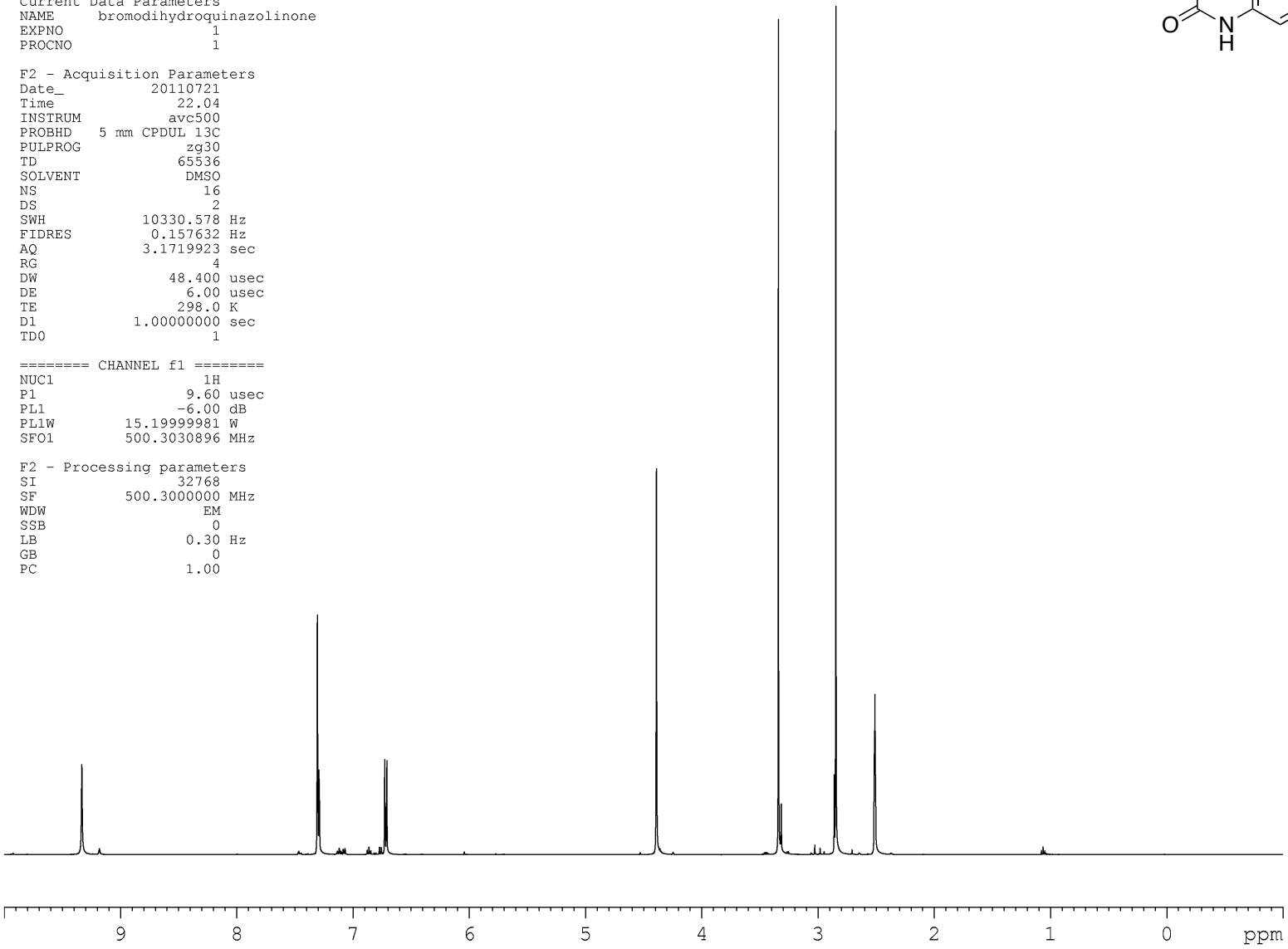

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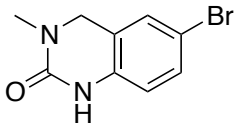


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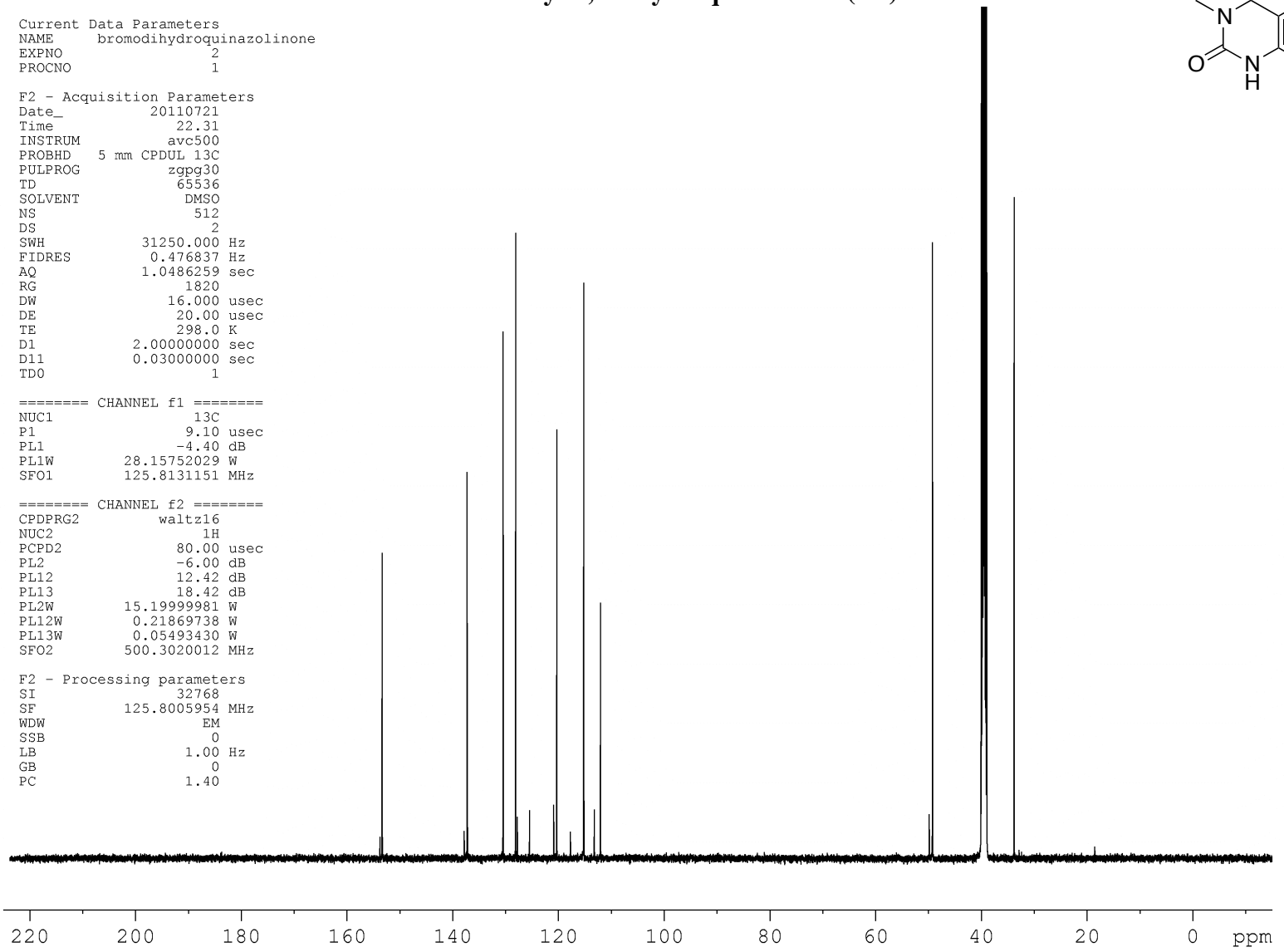

6-(3,5-dimethylisoxazol-4-yl)-3-methyl-3,4-dihydroquinazolin-2(1*H*)-one 1

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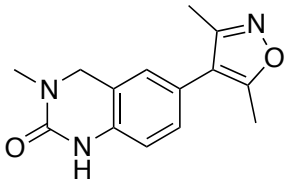
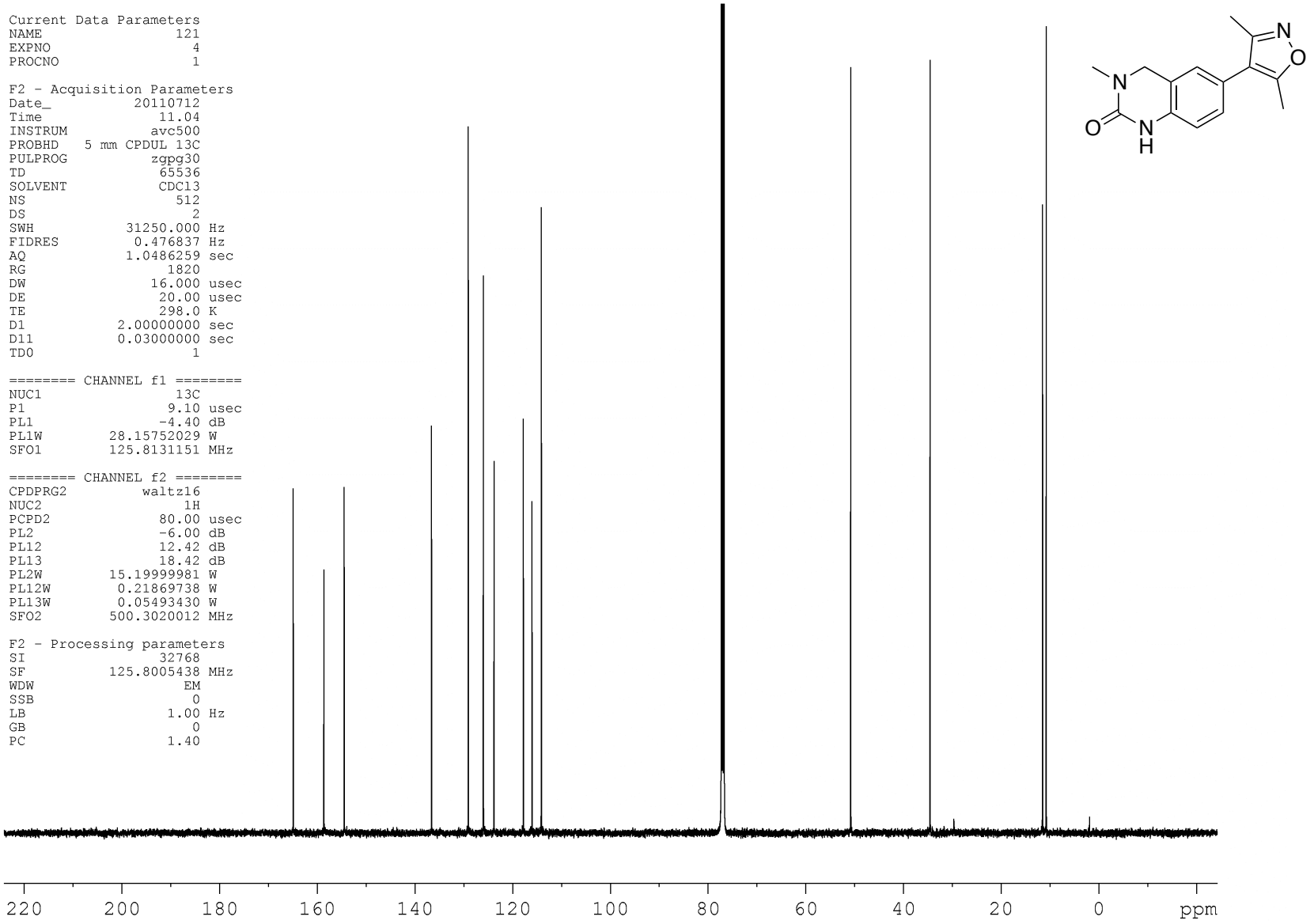
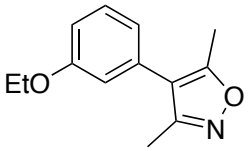


6-(3,5-dimethylisoxazol-4-yl)-3-methyl-3,4-dihydroquinazolin-2(1*H*)-one 1



4-(3-Ethoxyphenyl)-3,5-dimethylisoxazole 3c

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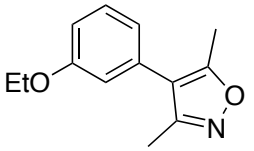
4-(3-Ethoxyphenyl)-3,5-dimethylisoxazole 3c

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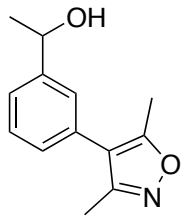
(*RS*)-1-(3-(3,5-Dimethylisoxazol-4-yl)phenyl)ethanol 3d

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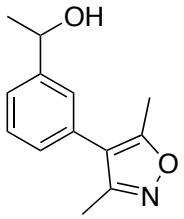
(*RS*)-1-(3-(3,5-Dimethylisoxazol-4-yl)phenyl)ethanol 3d

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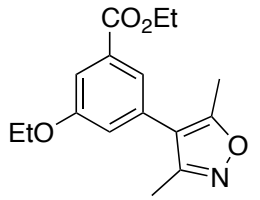
Ethyl 3-(3,5-dimethylisoxazol-4-yl)-5-ethoxybenzoate 4a

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TE                300.0 K
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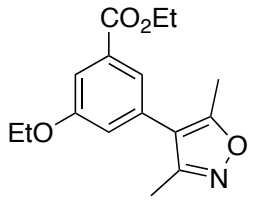
Ethyl 3-(3,5-dimethylisoxazol-4-yl)-5-ethoxybenzoate 4a

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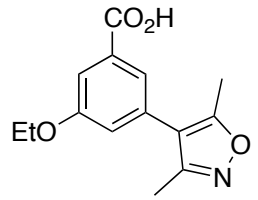
```

3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxybenzoic acid 4b

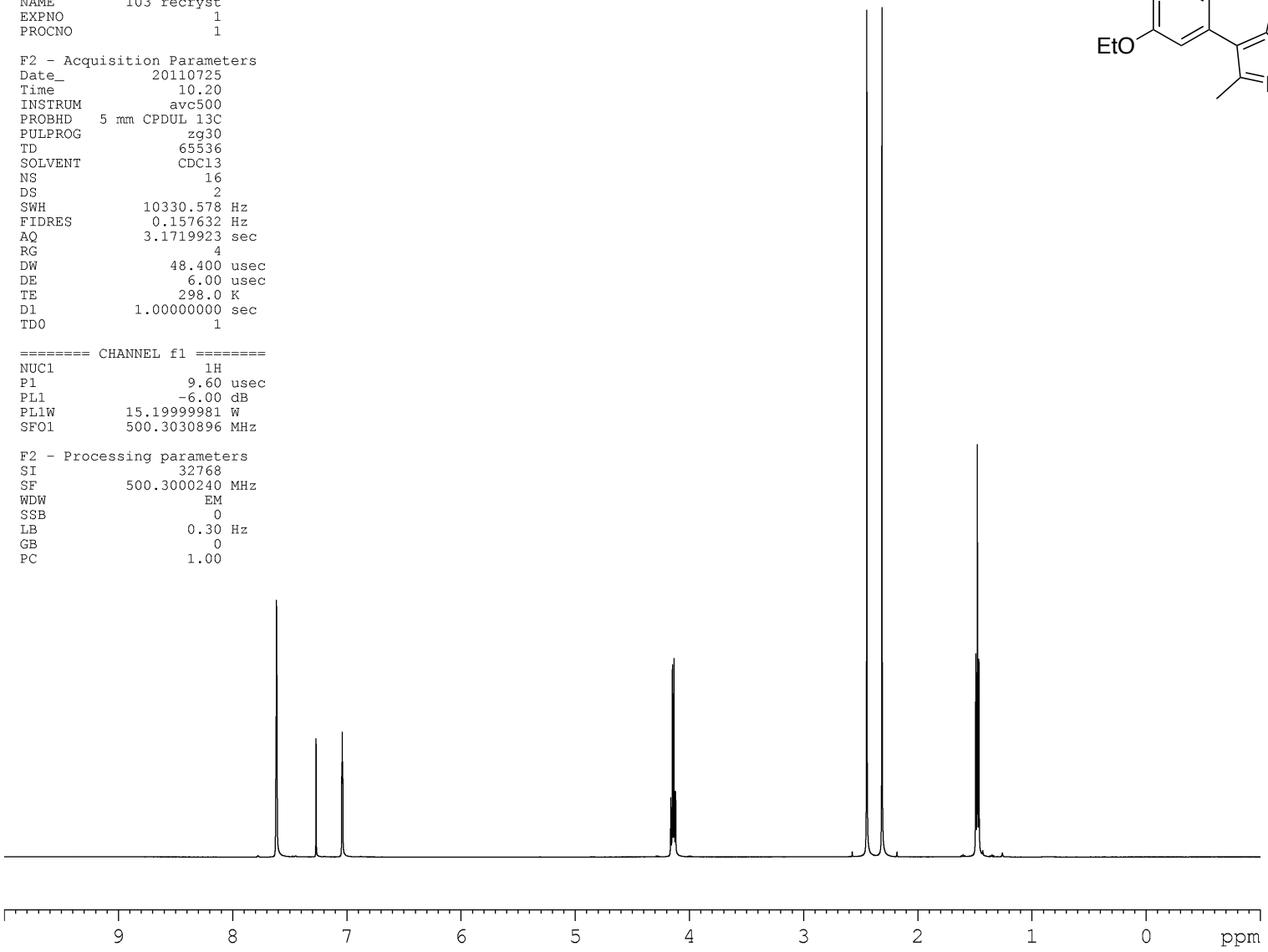



```
Current Data Parameters
NAME         103 recryst
EXPNO                  1
PROCNO                 1

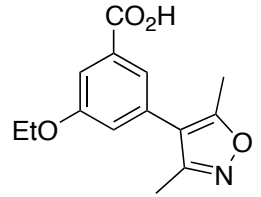
F2 - Acquisition Parameters
Date_           20110725
Time               10.20
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10330.578 Hz
FIDRES          0.157632 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

F2 - Processing parameters
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-ethoxybenzoic acid 4b




```
Current Data Parameters
NAME        103 recryst
EXPNO                 2
PROCNO                1

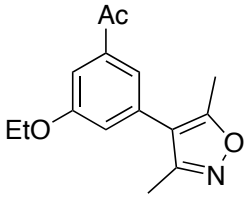
F2 - Acquisition Parameters
Date_          20110725
Time              10.47
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ            1.0486259 sec
RG                  645
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

F2 - Processing parameters
SI                32768
SF          125.8005438 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

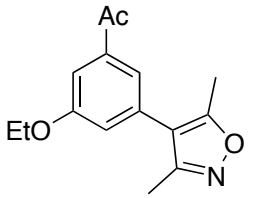
1-(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)ethanone 4c




```
NAME                  042
EXPNO                   1
PROCNO                  1
Date_            20101217
Time                12.12
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
```

1-(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)ethanone 4c




```
NAME                 042
EXPNO                  4
PROCNO                 1
Date_           20101217
Time               12.42
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                  9.50 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
```

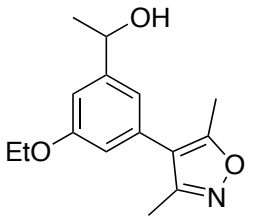
(*RS*)-1-(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)ethanol 4d

```
Current Data Parameters
NAME           046 wash
EXPNO                 1
PROCNO                1

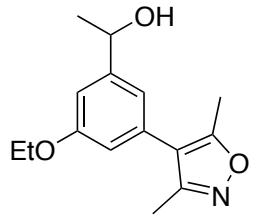
F2 - Acquisition Parameters
Date_          20110505
Time              10.41
INSTRUM          dpx400
PROBHD   5 mm Dual 1H/1
PULPROG             zg60
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             5592.841 Hz
FIDRES          0.170680 Hz
AQ              2.9295092 sec
RG                143.7
DW                89.400 usec
DE                17.00 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  7.30 usec
PL1                 0.00 dB
SFO1        400.1320007 MHz

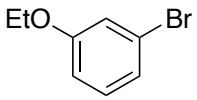
F2 - Processing parameters
SI                 32768
SF          400.1300182 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  0.60
```



(*RS*)-1-(3-(3,5-Dimethylisoxazol-4-yl)-5-ethoxyphenyl)ethanol 4d

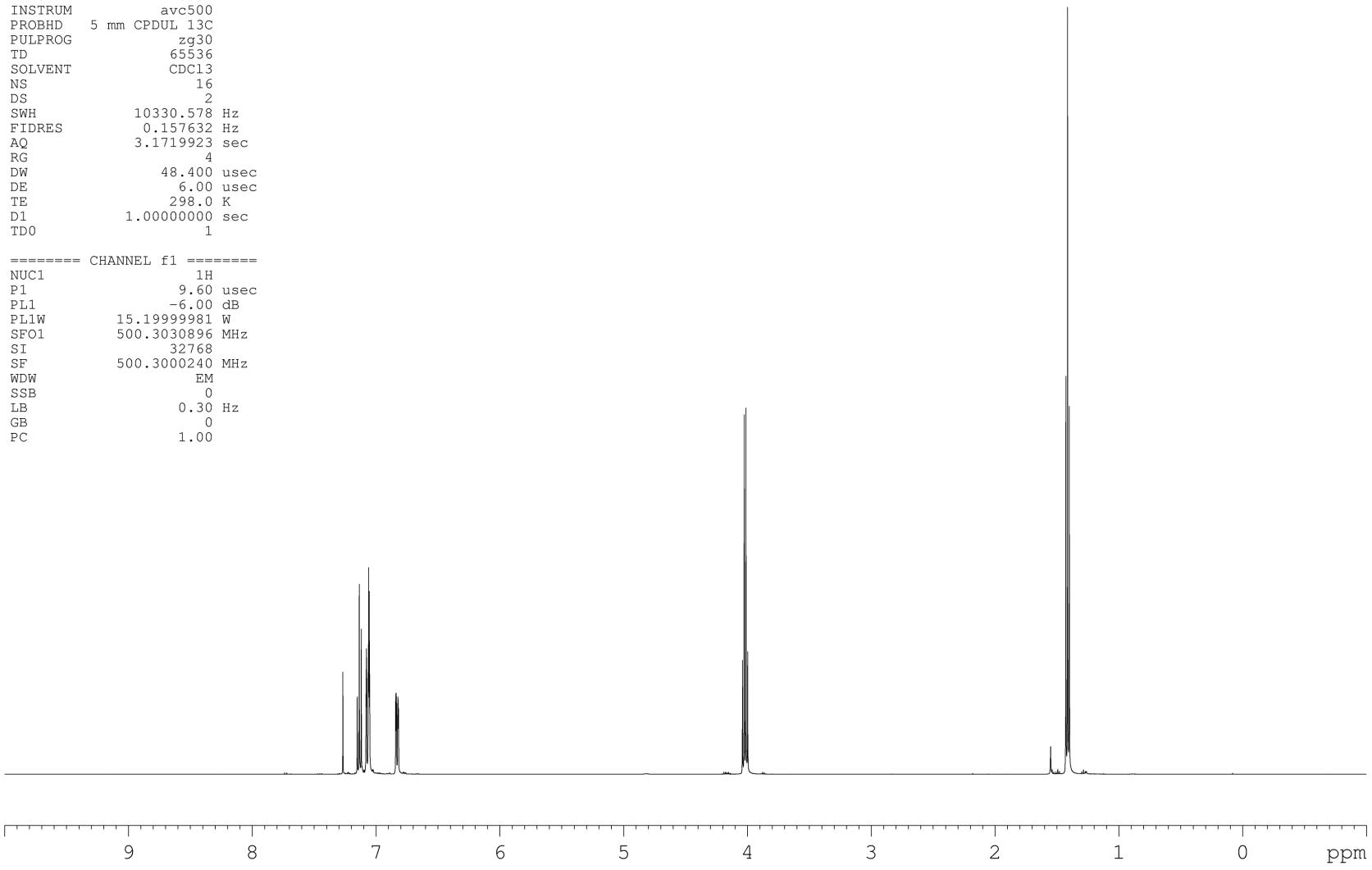


1-Bromo-3-ethoxybenzene 7

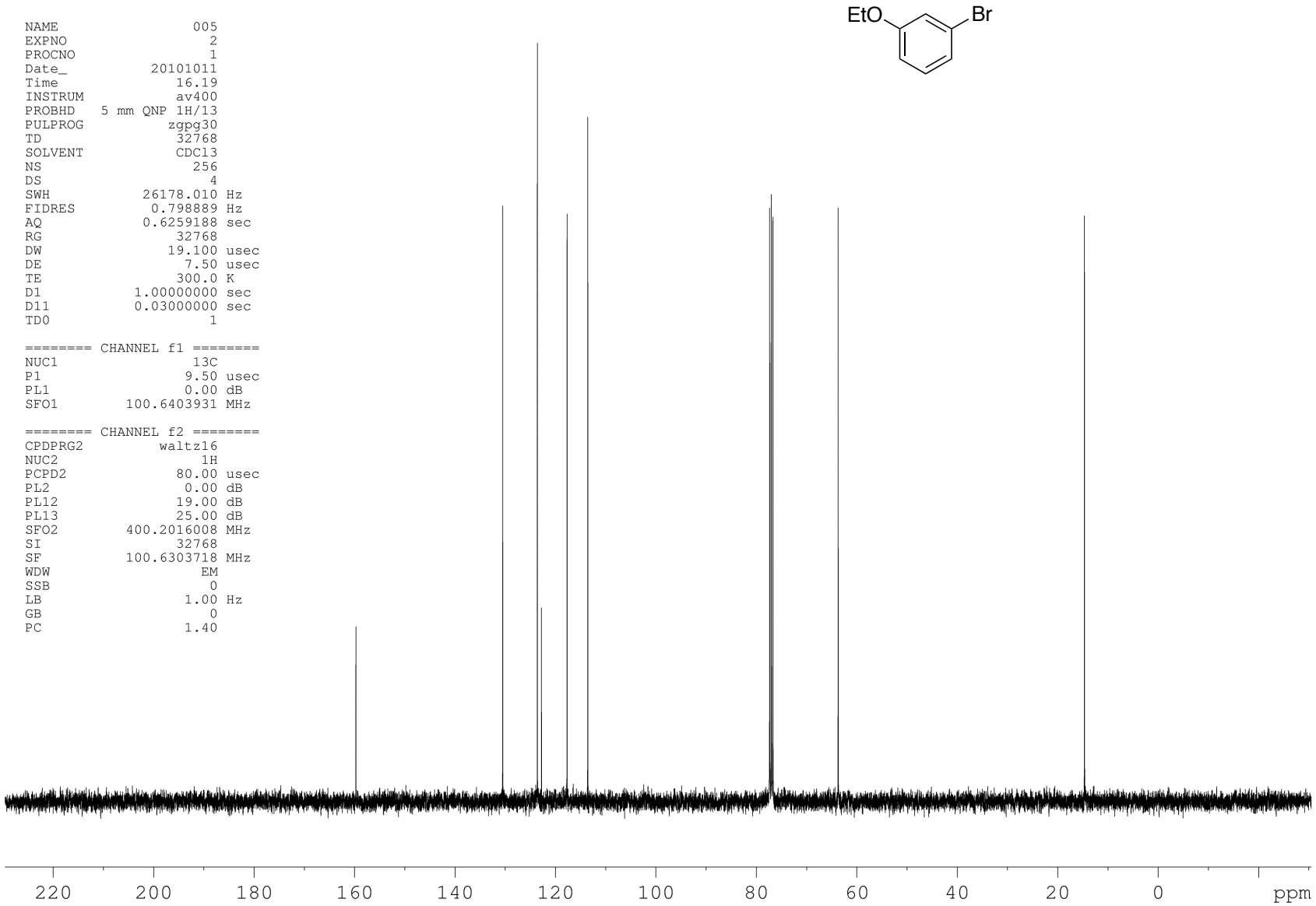



```
NAME      005 H and HMBC
EXPNO                  1
PROCNO                 1
Date_           20101208
Time                3.54
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
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

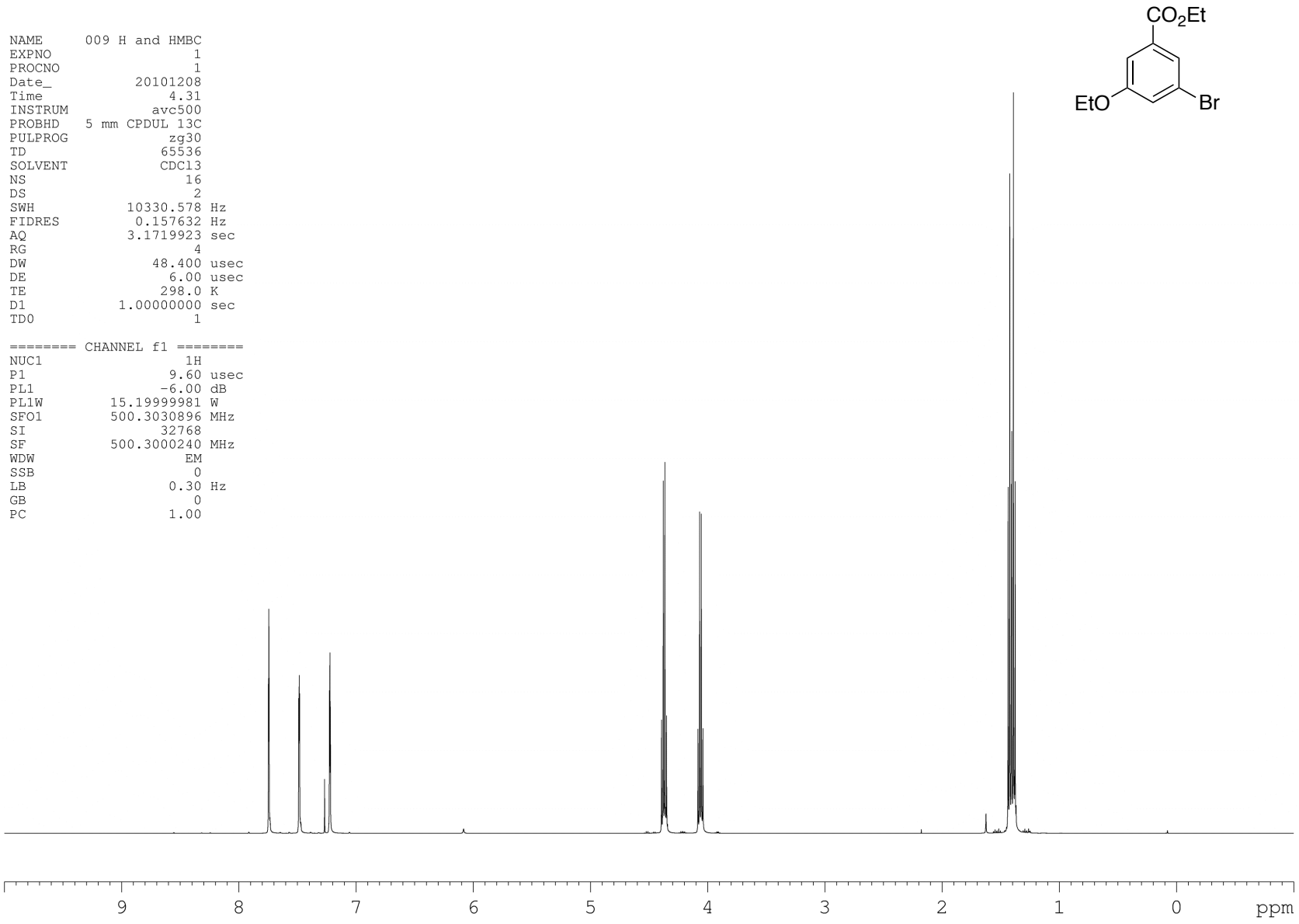
======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB 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



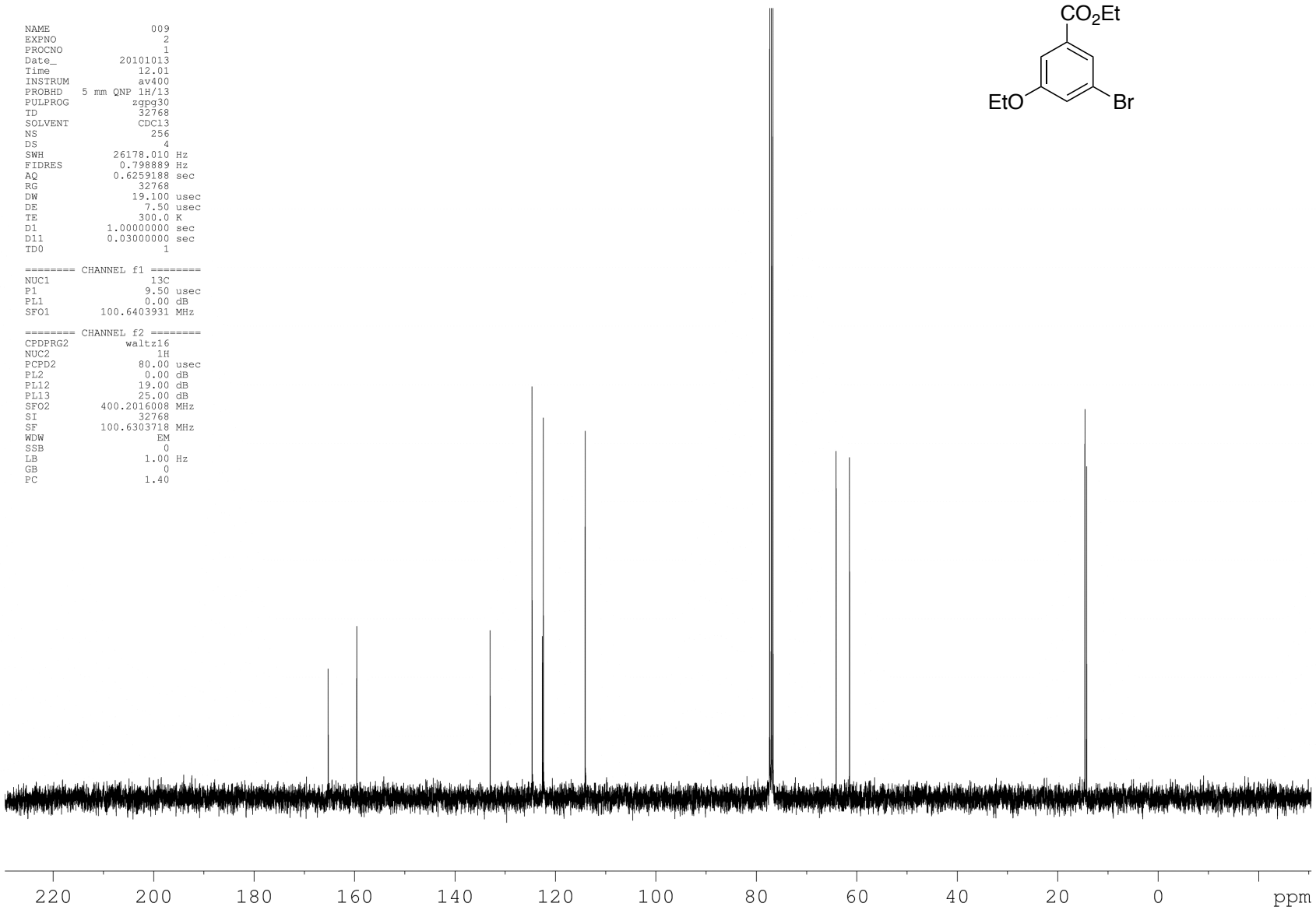
1-Bromo-3-ethoxybenzene 7



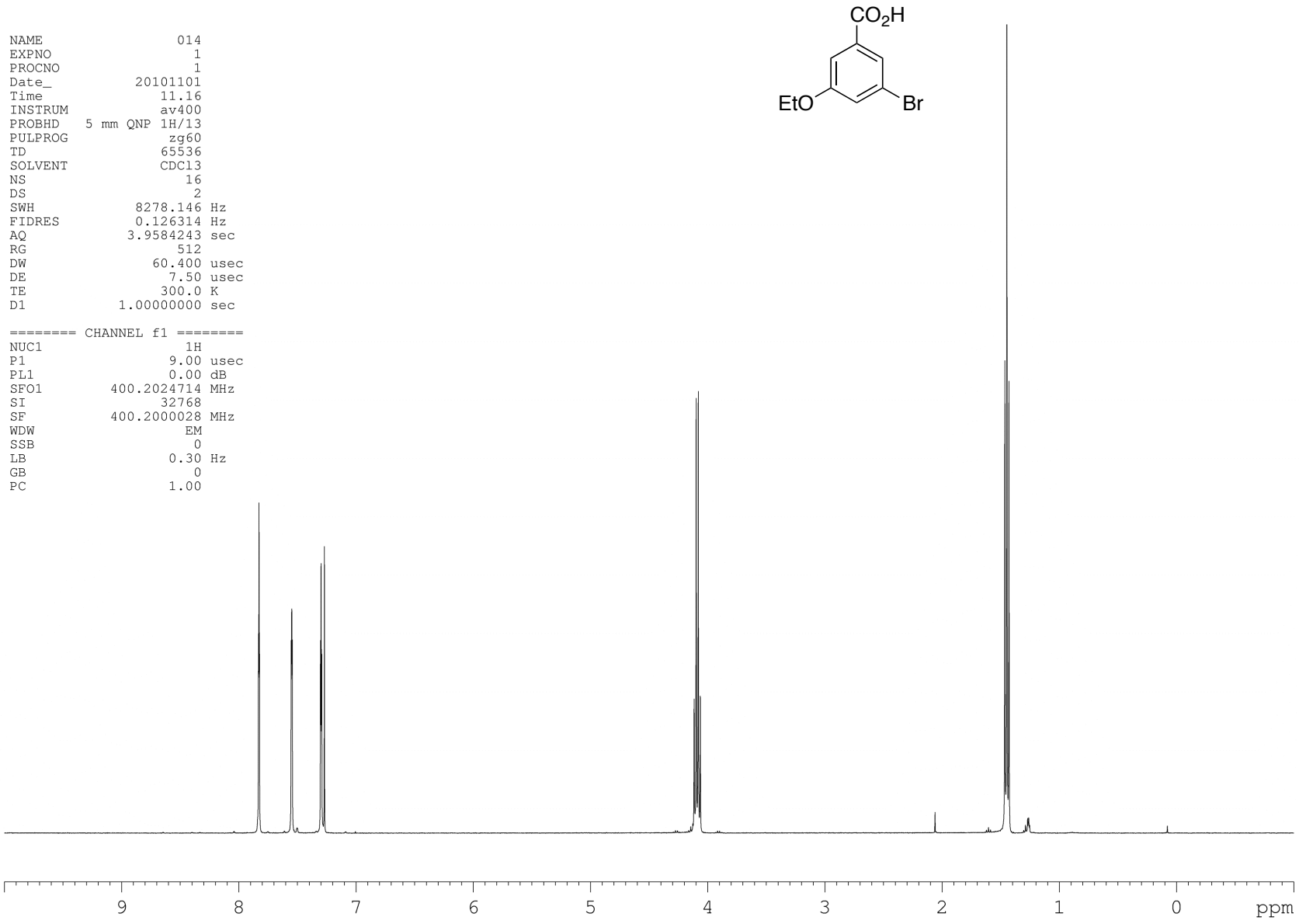
Ethyl 3-bromo-5-ethoxybenzoate 10



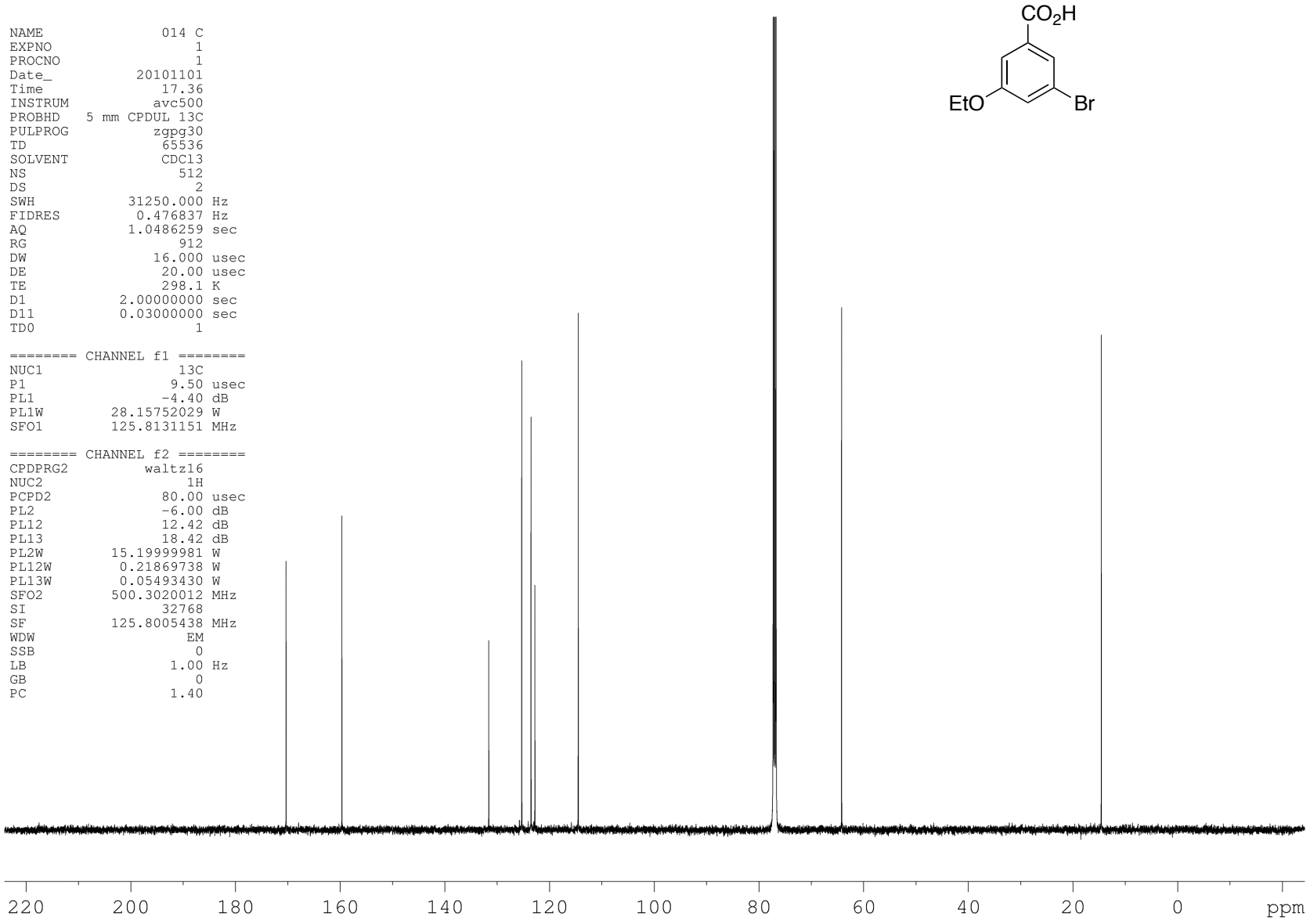
Ethyl 3-bromo-5-ethoxybenzoate 10



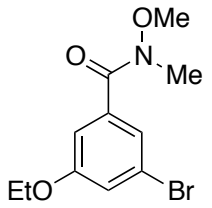
3-Bromo-5-ethoxybenzoic acid 11



3-Bromo-5-ethoxybenzoic acid 11

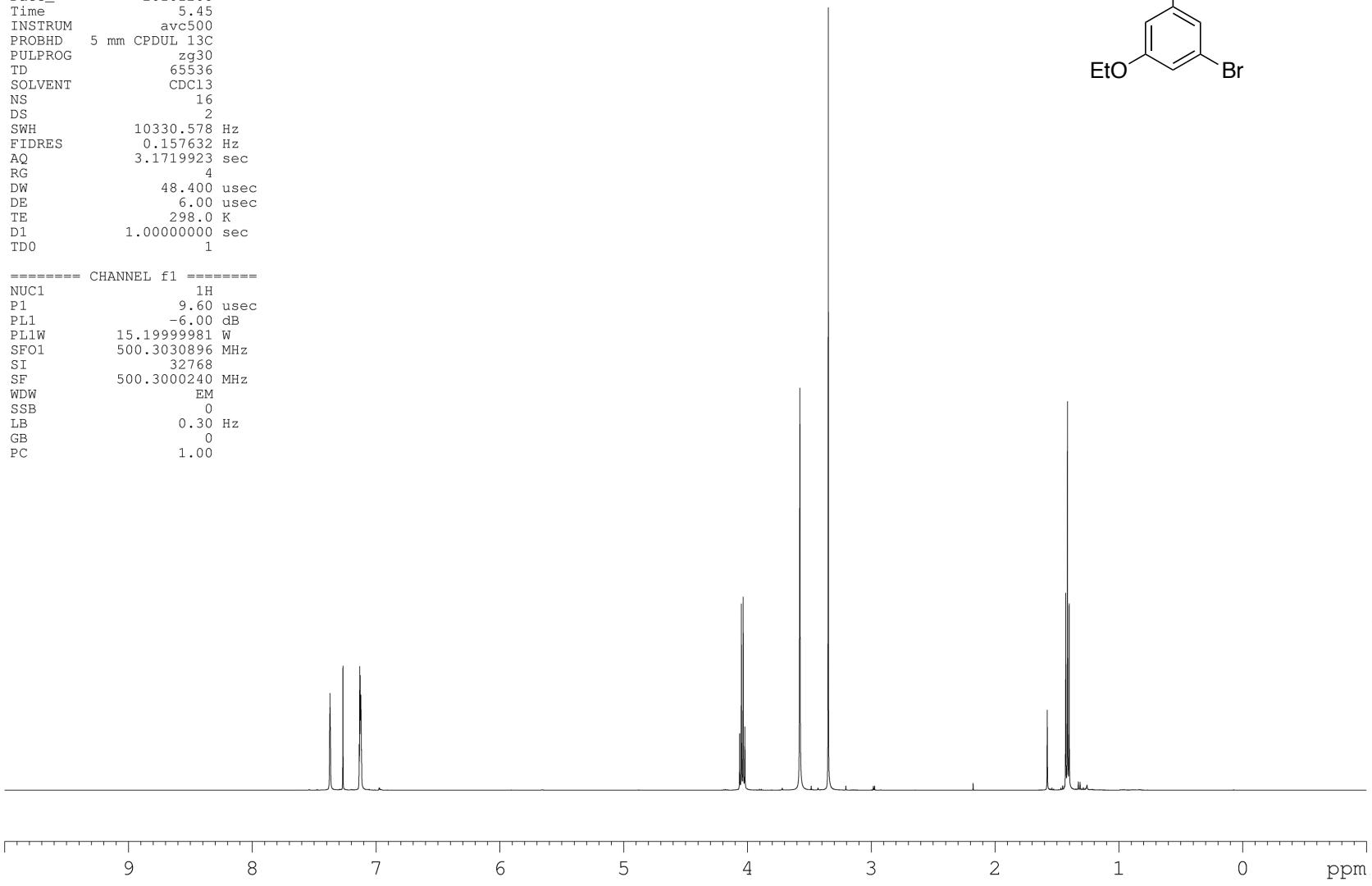


3-Bromo-5-ethoxy-*N*-methoxy-*N*-methylbenzamide 12

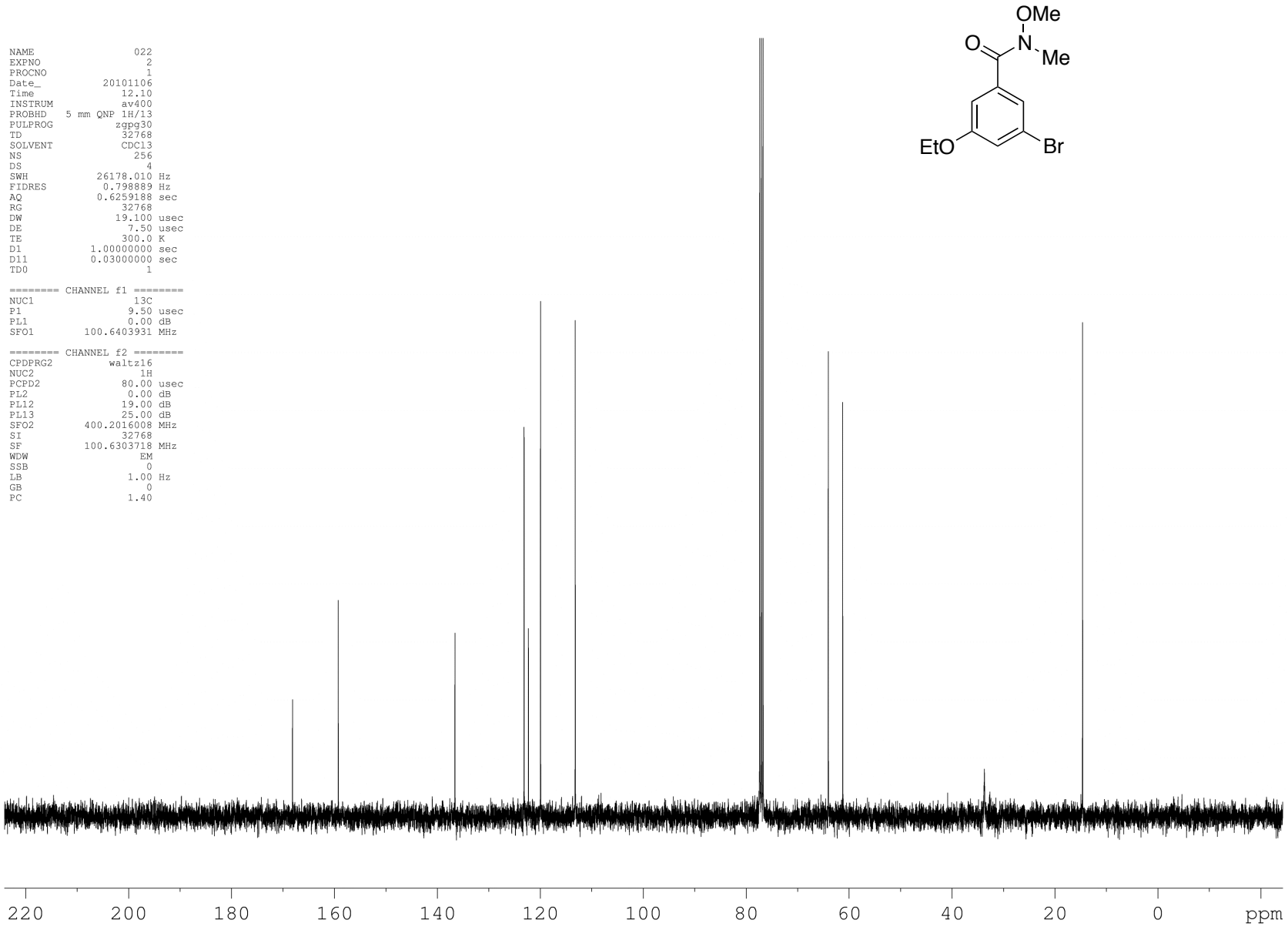



```
NAME      022 H and HMBC
EXPNO                  1
PROCNO                 1
Date_           20101208
Time                5.45
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
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

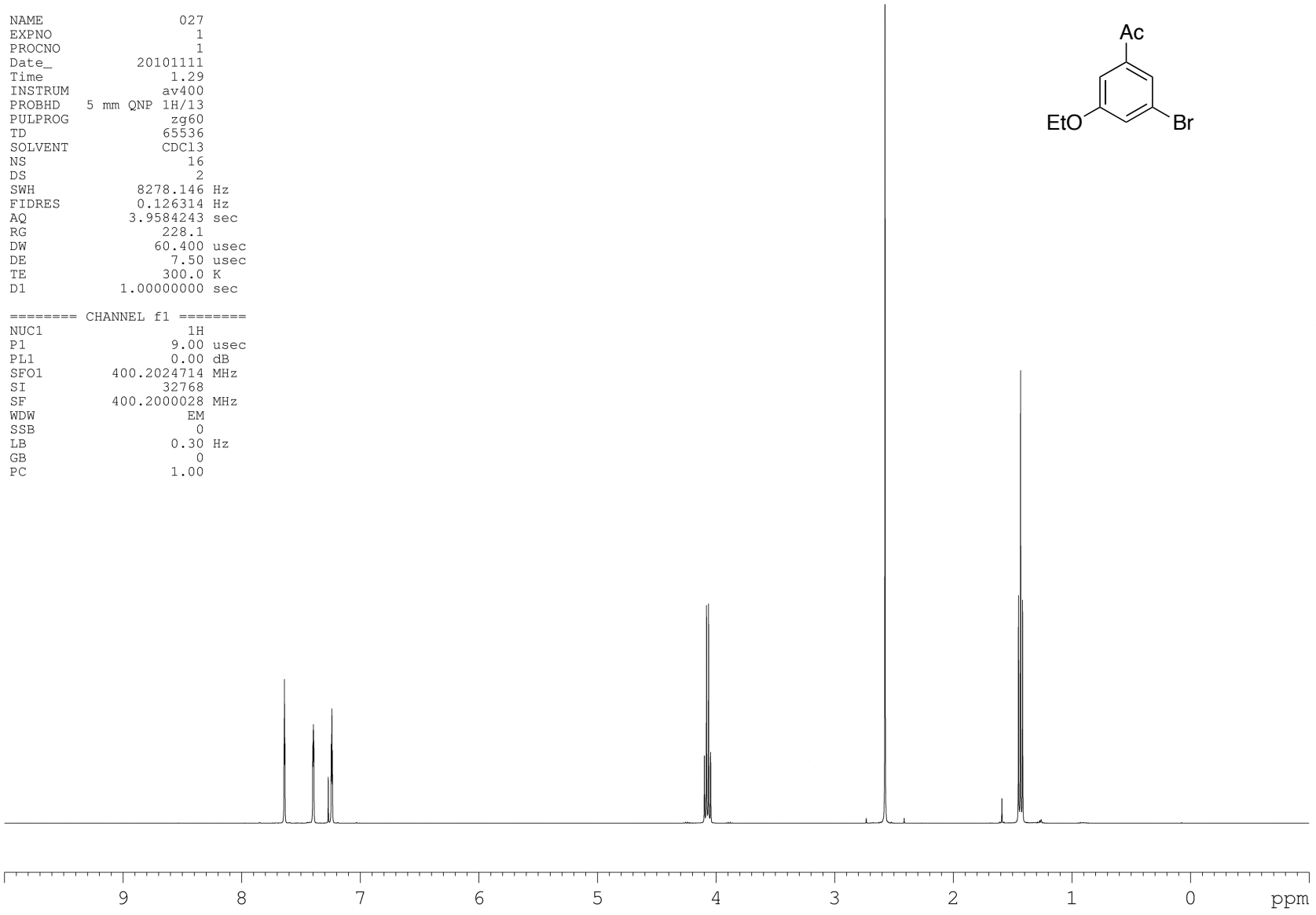
======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB 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



3-Bromo-5-ethoxy-*N*-methoxy-*N*-methylbenzamide 12



1-(3-Bromo-5-ethoxyphenyl)ethanone 13



1-(3-Bromo-5-ethoxyphenyl)ethanone 13