Treating tuberculosis: New InhA inhibitors based on expanded triclosan and *di*-triclosan analogues

Supplementary Information

Author information:

Sarentha Chetty[1], Tom Armstrong[1], Shalu Sharma Kharkwal[1], William C. Drewe[1], Cristina de Matteis[2], Dimitris Evangelopoulos,[3] Sanjib Bhakta,[3] Neil R. Thomas[1*]

[1]Biodiscovery Institute, School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK

[2]School of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD, UK

[3]Department of Biological Sciences, Birkbeck, University of London, London, WC1E 7HX, UK

Contents

Docking of designed ligands

A list of the docking results for all compounds including intermediates (Figure S1) is found in table S1.

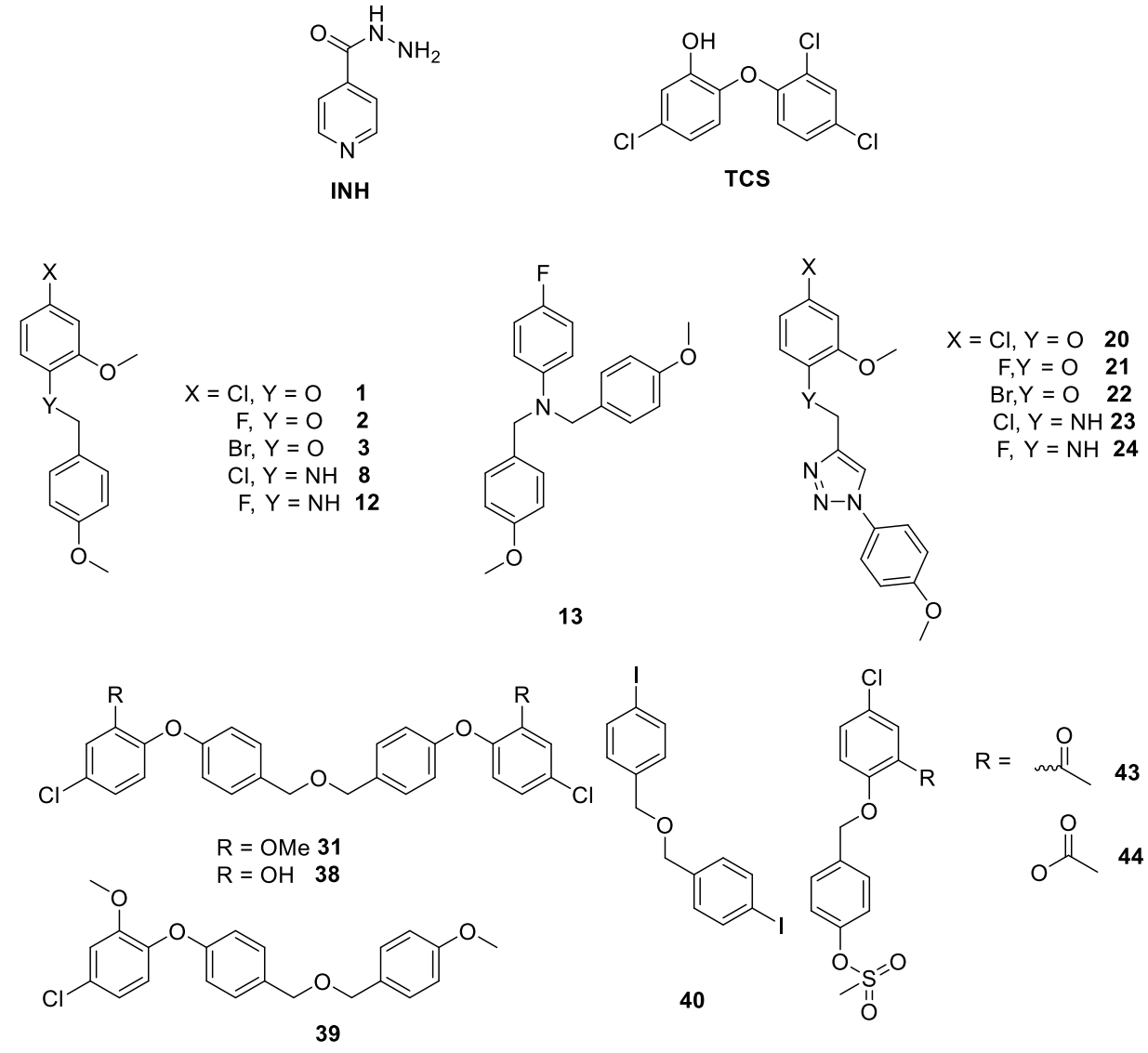

Figure S1 Compounds tested.

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Table S1 Fitness scores and rank list (high to low) for designed compounds and intermediates

Mol	Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)
31	90.79	0.85	70.20	0.00	-7.97
38	86.50	0.27	65.31	0.00	-3.57
23	76.22	0.83	56.00	0.00	-1.61
22	75.80	2.74	56.47	0.00	-4.59
20	75.59	3.18	55.00	0.00	-3.21
39	72.92	0.77	58.14	0.00	-7.79
24	72.63	4.72	52.89	0.00	-4.81
21	71.55	4.07	51.52	0.00	-3.36
43	68.54	1.21	52.99	0.00	-5.53
44	62.44	1.59	47.91	0.00	-5.03
8	60.28	2.18	43.18	0.00	-1.28
40	59.03	0.00	40.14	0.00	59.03
3	58.66	0.00	44.99	0.00	-3.20
1	57.22	0.00	44.89	0.00	-2.59
12	55.62	0.00	43.42	0.00	-3.09
2	53.86	0.04	40.62	0.00	-2.04

Interaction with the active site residues

For the benzylphenyl ether/aniline target molecules, all the compounds displayed the correct orientation within the active site with the exception of **2** which had an inverted orientation. Compound **2** made an H-bond, in this case the lone pairs on the oxygen act as a HBA (Figure S2). This compound had an inverse orientation to what was expected.

Please note that the docked structures below include the lone-pairs on the hetero atoms of ligands.

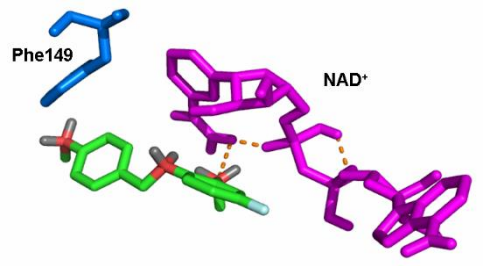


Figure S2 Interactions with the active site with benzylphenyl derivative 2.

The active site residues (blue), NAD^+ (magenta) and ligand (Atoms, C-green, O-red, H-white). Hydrogen bonds (orange).

Compound **8** had the best docking and inhibition data from the benzyl phenyl ether and benzyl phenyl aniline analogue series. It displayed 63 % inhibition in the isolated enzyme assay. Inspection of the docked structures, revealed that compound **8** (Figure 5) had an orientation similar to TCS, with a hydrogen bond occurring between the amine linker and the 2'-OH of the cofactor, where the amine acts as an H-bond donor. Beside H-bond interactions, a л-stacking interaction with NAD^+ and a van der Waals interaction with Phe149 (cation-л interaction) was also observed.

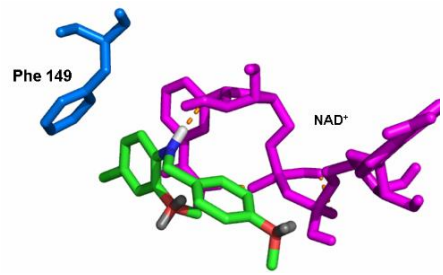


Figure S3. A view of the docking of **8** into the InhA active site. The active site residues (blue), NAD^+ (magenta) and ligand (green).

Mol	Fitness score	Tyr158[a]	Phe149[b]	NAD^{+}[a]	NAD^{+}[c]	Additional interactions
12	55.21	N	Y	Y	Y	N
1	57.22	N	Y	N	Y	N
2[e]	53.86	N	Y	Y	N	N
3	58.66	N	Y	N	Y	Leu218[d]
8	60.28	N	Y	Y	Y	N

Table S2 Summary of the interactions of the benzylphenyl analogues with the InhA active site.

[a] Hydrogen bond, [b] van der Waals interaction, [c] л-interaction, [d] hydrophobic interactions,

[e] Inverted orientation

Overall similar fitness scores were displayed for the triazole linked series of compounds. The compound that had the best docking results was **23** (Figure S3).

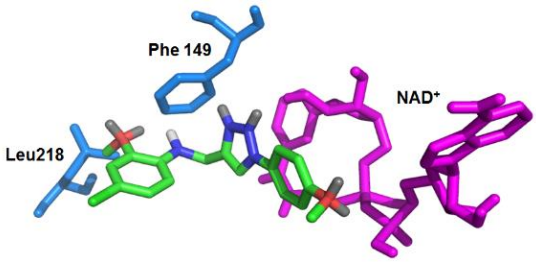


Figure S4 Docking of 23 into the InhA active site.
The active site residues (blue), NAD^{+} (magenta) and ligand.

A summary of the docking results is shown in Table S3.

Mol	**Fitness score**	**Tyr158[a]**	**Phe149[b]**	**NAD[a]**	**NAD[c]**	**Additional interactions**
20	75.59	N	Y	N	Y	Leu218[d]
21	71.55	N	Y	N	Y	Leu218[d]
22	75.80	N	Y	N	Y	Leu218[d]
23	76.22	N	Y	N	Y	Leu 218[d]
24	72.63	N	Y	Y	Y	Leu 218[d]

Table S3 Summary of the interactions of the triazole linked analogues with the InhA active site.

[a] Hydrogen bond, [b] van der Waals interaction, [c] л-interaction, [d] hydrophobic interactions.

Overall similar fitness scores were displayed for the bi-triclosan series of compounds. Compound **31** had the best fitness score (Figure S4).

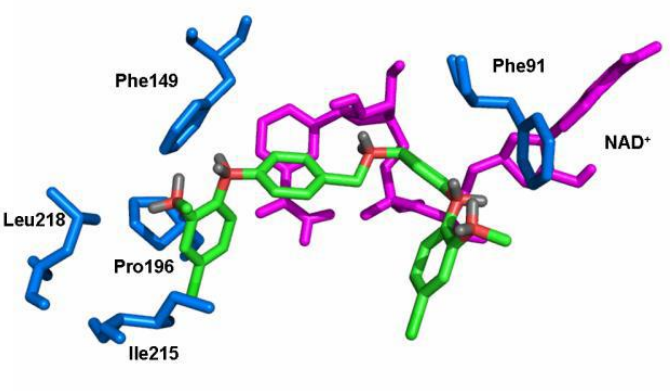


Figure S5. A view of the docking of **31** into the InhA active site. The active site residues (blue), NAD^+ (magenta) and ligand (green).

A summary of the docking results is shown in Table S4

Mol	Fitness score	Tyr158[a]	Phe149[b]	NAD[a]	NAD[c]	Additional interactions
31	90.79	N	Y	N	Y	Phe91[b], Leu218[d], Glu219[d], Pro196[b],
38	86.50	N	Y	Y	Y	Leu218[d], Ile215[d]
39	72.92	N	Y	N	Y	Phe91[b]

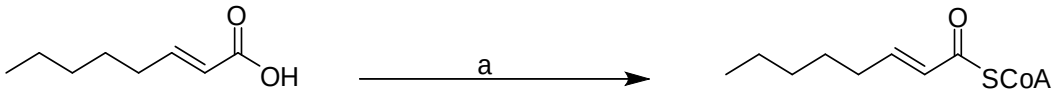
Table S4 Summary of the interactions of the di-triclosan analogues with the InhA active site.

[a] Hydrogen bond, [b] van der Waals interaction, [c] л-interaction, [d] hydrophobic interactions

Synthesis

2-*trans*-Octenyl CoA

The substrate octenyl CoA (Scheme S1) was synthesized using a one pot synthesis using the peptide coupling agent PyBOP. This substrate was used in the isolated enzyme assays.



Scheme S1 Synthesis of Octenyl CoA

a) K_2CO_3, H_2O, CoA, THF, PyBOP, rt, 5hr, 38 %

Experimental Section

4-Chloro-2-methoxy-1-[(4-methoxybenzyl)oxy]benzene (1)

Following general procedure A (1), compound **1** was synthesised from 4-chloro-2-methoxybenzyl alcohol (1.00 g, 6.31 mmol) and *p*-methoxybenzyl chloride (2.96 g, 18.92 mmol). The cream crude product was purified by flash column chromatography EtOAc/Petrol (1:19 v/v), followed by further purification by precipitation using general method E, to give white crystals (0.52 g, 29 %); M.p. 92-94°C; IR ($CHCl_3$): V_{max} = 1250, 1515, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (2 H, d, *J* = 8.7 Hz, H-Ar), 6.89 (2 H, d, *J* = 8.7 Hz, H-AR), 6.86 (1 H, d, *J* = 1.8 Hz, H-Ar), 6.81 (2 H, m, H-Ar), 5.04 (2 H, s, CH_2), 3.86, 3.81 (2 x 3 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C–Ar), 150.4 (C-Ar), 146.9 (C-Ar), 129.1 (C-Ar), 128.1 (C-Ar), 126.2 (C-Ar), 120.3 (C-Ar), 115.1 (C-Ar), 113.98 (C-Ar), 112.5 (C-Ar), 71.2 (CH_2), 56.1, 55.3 (2 x CH_3), HRMS

(ESI) required for $C_{15}H_{15}{}^{35}ClO_3{}^+$ ([MNa]$^+$) m/z = 301.0607 found 301.0613; $C_{15}H_{15}ClO_3$, requires C, 64.64; H, 5.42 % found C, 64.39; H,5.39 %.

4-Fluoro-2-methoxy-1-[(4-methoxybenzyl)oxy]benzene (2)

Following general procedure A, (1) compound **2** was synthesized from 4-fluoro-2-methoxyphenol (0.30 g, 2.11 mmol) and *p*-methoxybenzylchloride (0.99 g, 6.34 mmol). Purification was achieved by flash column chromatography EtOAC/Petrol (1:19 v/v), followed by further purification by precipitation using general method E, to give white crystals (0.26 g, 47 %); M.p. 84-85 °C; IR ($CHCl_3$): V_{max} = 3007, 1514, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (2 H, d, *J* =8.7 Hz, H-Ar), 6.89 (2 H, d, *J* = 8.7 Hz, H-Ar), 6.80 (1 H, dd, *J* = 8.6 Hz, 6.4 Hz, H-Ar), 6.64 (1 H, dd, *J* = 6.4 Hz, 3.0 Hz), 6.52 (1 H, ddd, *J* = 8.6 Hz, 3.0 Hz, 1Hz), 5.01 (2 H, s, CH_2), 3.85, 3.81 (2 x 3 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C-Ar), 157.8 (d, *J* = 239.3 Hz, C-Ar), 150.8 (d, *J* = 9.9 Hz, C-Ar), 144.3 (C-Ar), 144.3 (d, *J* = 2.9 Hz, C-Ar), 129.2, 129.1, 115.3 (d, *J* = 22.5 Hz, C-Ar), 113.9 (C-Ar), 100.4 (d, *J* = 27.3 Hz, C-Ar), 71.8 (CH_2), 56.05, 55.29 (2 x CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = 120.1 (m, 1 F); HRMS (ESI) required for $C_{15}H_{15}FO_3{}^+$ ([M+Na]$^+$) *m/z* = 285.0903, found 285.0897; $C_{15}H_{15}FO_3$ requires C, 68.69; H, 5.76 % found C, 68.52; H, 5.75 %.

4-Bromo-2-methoxy-1-[(4-methoxybenzyl)oxy]benzene (3)

Following general procedure A, (1) compound **3** was synthesized from 4-bromo-2-methoxyphenol (0.30 g, 1.50 mmol) and *p*-methoxybenzylalcohol (0.69 g, 4.50 mmol). Purification was done by flash column chromatography EtOAc/Petrol (1:19 v/v), followed by further purification by precipitation using general method E to give white crystals (0.11 g, 23 %); M.p. 110-112 °C; IR

($CHCl_3$): V_{max} = 3008, 1615, 1586, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (2 H, d, *J* = 8.6 Hz), 6.99 (1 H, d, *J* = 2.5 Hz, H-Ar), 6.96 (1 H, dd, *J* = 8.5 Hz, 2.5 Hz, H-Ar), 6.89 (2 H, d, *J* = 8.6 Hz, H-Ar), 6.74 (1 H, d, *J* = 8.5 Hz, H-Ar), 5.04 (2 H, s, CH_2), 3.86, 3.81 (2 x 3 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C-Ar), 150.6 (C-Ar), 147.4 (C-Ar), 129,1 (C-Ar), 128.8 (C-Ar), 123.3 (C-Ar), 115.6 (C-Ar), 115.3 (C-Ar), 113.9 (C-Ar), 113.3 (C-Ar), 71.1 (CH_2), 56.1, 55.3 (CH_3); HRMS (ESI) required for $C_{15}H_{15}{}^{79}BrO_3{}^+$ ($[MNa]^+$) *m/z* = 345.0102, found 345.0103.

***tert*-Butyl(4-chloro-2-hydroxyphenyl)carbamate (5)**

A literature procedure (2) was modified to synthesise compound **5**. To a suspension of 2-amino-5-chlorophenol (1.50 g, 10.50 mmol) in dioxane (30 mL), Boc anhydride (2.41 g, 11.00 mmol) was added. The solution was cooled to 0 °C, followed by the dropwise addition of a solution of $NaHCO_3$ (3.5 g, 41.7 mmol) in H_2O (30 mL). The brown solution was allowed to warm to room temperature and stirred overnight. Water (30 mL) was added and the solution was extracted with DCM (3 x 30 mL). The combined organic layers were washed with 1M $HCl_{(aq)}$ (100 mL), brine (100 mL), and dried over $MgSO_4$, before the solvent was removed *in vacuo*. The dark orange crude product was purified by flash column chromatography with EtOAc/Petrol (1:19-1:9 v/v) to give a pale orange solid (1.44 g, 56 %); M.p. 136-138 °C; IR ($CHCl_3$): V_{max} = 3630, 1691, 1515, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (1 H, s, NH), 6.96 (2 H, m, H- Ar H-Ar), 6.82 (1 H, dd, 8.4 Hz, 2.3 Hz, H- Ar), 6.59 (1 H, s, OH), 1.53 (9 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (C-Ar), 148.4 (C-Ar), 130.52 (C-Ar), 124.3 (C-Ar), 122.13 (C-Ar), 120.67 (C-Ar), 119.23 (C-Ar), 82.59, 28.19 (CH_3); HRMS (ESI) required for $C_{11}H_{14}{}^{35}ClNO_4{}^+$ ($[MNa]^+$) *m/z* =266.0560, found 266.0547.

***tert*-Butyl (4-chloro-2-methoxyphenyl)carbamate (6)**

A literature procedure (3, 4) was modified to synthesise compound **6**. Under a nitrogen atmosphere K_2CO_3 (4.08 g, 29.60 mol) and iodomethane (7.37 g, 51.10 mmol) were added to a solution of the Boc protected aniline **5** (1.44 g, 5.90 mmol) in anhydrous acetone (25 mL). The suspension was heated to reflux for 6.5 h then allowed to cool to room temperature, followed by the addition of saturated $NH_4Cl_{(aq)}$ (20 mL). The solvent was removed by evaporation and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (100 mL) and dried over $MgSO_4$, and the solvent was removed *in vacuo*. Purification of a portion of the crude (100 mg) by flash column chromatography EtOAc/Petrol (1:9 v/v) gave a yellow oil (0.88 g, 82 %); IR ($CHCl_3$): V_{max} = 3432, 3010, 1722, 1517, 1247, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (1 H, d, *J* = 8.5 Hz, H-Ar), 6.99 (1 H, s, NH), 6.91 (1 H, dd, *J* = 8.5 Hz, 2.2 Hz, H- Ar), 6.82 (1 H, d, *J* = 2.2 Hz, H-Ar), 3.858 (3H, s, CH_3), 1.517 (9 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6 (C=O), 147.9 (C-Ar), 127.1 (C-Ar), 126.8 (C-Ar), 120.8 (C-Ar), 118.7 (C-Ar), 110.7 (C-Ar), 80.60 (C-8), 55.89 (C-10), 28.34 (CH_3); HRMS (ESI) required for $C_{12}H_{16}{}^{35}ClNO_3{}^+$ ($[MNa]^+$) *m/z* =280.0716, found 280.0703.

4-Chloro-2-methoxyaniline (7)

A literature procedure(5, 6) was modified to synthesise compound **7**. To a solution of **6** (1.38 g, 5.40 mmol) in DCM (0.8 mL) cooled to 0 °C, TFA (1.19 g, 10.7 mmol) was added slowly dropwise *via* a syringe. The brown solution was allowed to warm to room temperature and left stirring for 2 h. The solvent and TFA were removed by evaporation. Purification by flash column chromatography EtOAc/Petrol (1:9-3:7 v/v) gave a brown oil (0.71 g, 85 %); IR ($CHCl_3$): V_{max} = 3459, 1504, 1614, 1584, 1278, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (2 H, m,

H-Ar, H-Ar), 6.60 (1 H, d, J = 8.8 Hz, H-Ar), 3.84 (3 H, s, CH_3) which is consistent with the literature(7); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0 (C-Ar), 133.8 (C-Ar), 123.6 (C-Ar), 115.8 (C-Ar), 111.15 (C-Ar), 55.7 (CH_3); HRMS (ESI) required for $C_7H_8{}^{35}ClNO^+$ ($[MH]^+$) m/z = 158.0373, found 158.0367.

4-Chloro-2-methoxy-*N*-(4-methoxybenzyl) aniline (8)

To a solution of aniline **7** (0.20 g, 1.3 mmol) in anhydrous DCM (13 mL) cooled to 0 °C, triethylamine (0.26 g, 2.5 mmol) was added dropwise *via* a syringe. The solution was stirred at 0 °C for 10 min followed by dropwise addition of *p*-methoxybenzyl chloride (0.27 g, 1.3 mmol). The solution was allowed to warm to room temperature and was stirred for 5.5 h, followed by the addition of saturated $NH_4Cl_{(aq)}$ solution (15 mL). The phases were separated and the organic phase was then washed with water (15 mL) and brine (15 mL). The combined aqueous phases were extracted with DCM (2 x 30 mL). The combined organic phases were dried over $MgSO_4$, before the solvent was removed *in vacuo*. Purification by flash column chromatography EtOAc/Petrol (1:19 v/v), gave a waxy cream solid (43.2 mg, 12 %); M.p. 97-98 °C, IR ($CHCl_3$): V_{max} = 3062, 1512, 1246; ^1H NMR (400 MHz,$CDCl_3$): δ = 7.31 (2 H, d, J = 8.7 Hz, H-Ar), 6.92 (2 H, d, J = 8.7 Hz, H-Ar), 6.82 (1 H, dd, J = 8.6 z, 2.2 Hz, H-Ar), 6.77 (1 H, d, J = 2.2 Hz, H-Ar), 6.51 (1 H, d, J = 8.6 Hz, H-Ar), 4.53 (1 H, s, NH), 4.28 (2 H, s), 3.86, 3.84 (2 x 3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C-Ar), 147.1 (C-Ar), 136.8 (C-Ar), 131.11 (C-Ar), 128.8 (C-Ar), 121.1 (C-Ar), 120.8 (C-Ar), 114.1 (C-Ar), 110.33 (C-Ar), 110.13 (C-Ar), 55.7, 55.3 (2 x CH_3); 47.5 (CH_2); HRMS (EI) required for $C_{15}H_{16}{}^{35}ClNO_2{}^+$ m/z = 277.0870 found 277.0864.

4-Fluoro-2-methoxy-1-nitrobenzene (10)

A literature procedure (3, 4) was modified to synthesise compound **10**. Under a nitrogen atmosphere, K_2CO_3 (13.20 g, 95.5. mol) and iodomethane (27.11 g, 190.9 mmol) were added to a solution of compound **9** (3 g, 19.0 mmol) in anhydrous acetone (81 mL). The mixture was heated to reflux for 5 h. The yellow solution was allowed to cool to room temperature, followed by the addition of saturated $NH_4Cl_{(aq)}$ solution (100 mL). The solution was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (100 mL) and dried over $MgSO_4$, before the solvent was removed *in vacuo*. Purification by flash column chromatography EtOAc/Petrol (1:4 v/v) gave a bright yellow powder (2.64 g, 81 %); M.p. 97-98 °C; IR ($CHCl_3$): V_{max} = 1623, 1527, 1352, 1291 cm^{-1} which is consistent with literature values(8); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (1 H, app. dd, *J* = 9.0, 5.9 Hz, H-Ar), 6.79 (1 H, app. dd, *J* = 10.2, 2.5, H-Ar), 6.73 (1 H, m, H-Ar), 3.97 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8 (d, *J* = 256.1 Hz, C-Ar), 155.3 (d, *J* = 11.3 Hz, C-Ar), 135.9 (C-Ar), 128.2 (d, *J* = 11.3 Hz, C-Ar), 107.3 (d, *J* = 23.6 Hz, C-Ar), 56.8 (CH_3); ^{13}C and ^{1}H NMR data is consistent with literature values considering difference in chemical shifts due to the usage of a different solvent (acetone).(8) ^{19}F NMR (376 MHz): δ = -100.4 (1 F); HRMS (ESI) required for $C_7H_6FNO_3^+$ ($[MNa]^+$) *m/z* = 194.0229, found *m/z* = 194.0209.

4-Fluoro-2-methoxyaniline (11)

A literature procedure (9) was modified to synthesise compound **11**. To a solution of **10** (2.30 g, 13.44 mmol) in MeOH (230 mL), ammonium formate (8.48 g, 13.4 mmol) was added followed by the addition of 10 % Pd/C catalyst (0.23 g, 0.1 w/w equiv) (added very slowly with **CAUTION**). The solution was allowed to stir overnight at room temperature then filtered through a bed of celite.

The solvent was removed by evaporation and the residue was dissolved in chloroform (10 mL) and washed with 5 % aqueous ammonia (3 x 10 mL) and brine (3 x 10 mL). The organic layer was dried over $MgSO_4$, before the solvent was removed *in vacuo* to give an orange oil (1.90 g, 13.4 mmol, 100 %); IR ($CHCl_3$): V_{max} = 3452, 3369, 1614, 1591, 1034, 946.29, 834 cm^{-1} which is consistent with literature values(10); ^1H NMR (400 MHz,$CDCl_3$): δ = 6.21 (1 H, dd, *J* = 8.5 , 5.7 Hz, H-Ar), 6.56 (1H, dd, *J* = 2.6 Hz, 10.3 Hz, H-Ar), 6.49 (1 H, m, H-Ar), 3.84 (3 H, s, CH_3), 3.62 (2 H, s, NH_2) which is consistent with literature values(7); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (d, *J* = 236.2 Hz, C-Ar), 147.8 (d, *J* = 9.5 Hz, C-Ar), 131.9 (C-Ar), 114.7 (d, *J* = 9.5 Hz, C-Ar), 106.4 (d, *J* = 21.9 Hz, C-Ar), 98.6 (d, *J* = 26.7 Hz, C-Ar), 55.7 (CH_3) which is consistent with literature values(11); ^{19}F NMR (376 MHz): δ = -124.2 (1 F); HRMS (ESI) required for $C_7H_7FNO^+$ ($[MH]^+$) *m/z* = 142.0668, found *m/z* = 142.0654.

4-Fluoro-2-methoxy-*N*-(4-methoxybenzyl) aniline (12)

Following general procedure B,(12) compound **12** was synthesised from aniline **11** (0.30 g, 2.03 mmol) and *p*-methoxybenzylchloride (0.33 g, 2.1 mmol). Purification was performed in two steps with initial purification by flash column chromatography EtOAc/Petrol (1:9 to 3:7 v/v) to give a waxy cream solid which was further purified by precipitation using general method E to give white crystals (0.08 g, 14 %); M.p. 96-97 °C; IR ($CHCl_3$): V_{max} = 3007, 1515, 1249, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (2 H, d, *J* = 8.7 Hz, H-Ar), 6.88 (2 H, d, *J* = 8.7 Hz, H-Ar), 6.52 (3 H, m,3 x H-Ar), 4.33 (1 H, s, NH), 4.24 (2 H, s, CH_2), 3.82, 3.81 (2 x 3 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7 (d, *J* = 226.6 Hz, C-Ar), 154.26 (C-Ar), 147.3 (d, 9.5 Hz, C-Ar), 134.4 (C-Ar), 131.4 (C-Ar), 128.8 (C-Ar), 113.9 (C-Ar), 109.7 (d, *J* = 9.0 Hz, C-Ar), 106.1 (d, *J* = 21.5 Hz, C-Ar), 98.5 (d, *J* = 27.2 Hz, C-Ar), 55.6, 55.30 (2 x CH_3), 47.9 (CH_2); ^{19}F NMR

(376 MHz): δ = 126.4 (1 F) HRMS (ESI) required for $C_{15}H_{16}FNO^+$ ($[MH]^+$) *m/z* = 262.1243, found *m/z* = 262.1231.

4-Fluoro-2-methoxy-*N*-(4-*bis*-methoxybenzyl) aniline (13)

Following general method B, (12) compound **13** was synthesised from aniline **11** (0.30 g, 2.03 mmol) and *p*-methoxybenzylchloride (0.99 g, 6.38 mmol). Purification was done in two steps with initial purification by flash column chromatography EtOAc/Petrol (1:9 to 3:7 /vv) gave a yellow oil, followed by a second purification by flash column chromatography EtOAc/Petrol (1:9 v/v) gave a colourless oil (0.29 g, 36 %); IR ($CHCl_3$): V_{max} = 3009, 1611, 1511, 1247, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (4 H, d, *J* = 8.8 Hz, H-Ar), 6.79 (4 H, d, *J* = 8.8 Hz, H-Ar), 6.63 (2 H, m, 2 x H-Ar), 6.42 (1 H, m, H-Ar), 4.08, (4 H, s, CH_2), 3.90 (3 H, s, CH_3), 3.77 (6 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (d, *J* = 240.0 Hz, C-Ar), 154.5 (d, *J* = 9.9 Hz, C-Ar), 135.6 (d, *J* = 3.1 Hz, C-Ar), 130.8 (C-Ar), 129.7 (C-Ar), 122.9 (d, *J* = 9.9 Hz, C-Ar), 113.4, 105.9 (d, *J* = 21.5 Hz), 99.9 (d, *J* = 26.3 Hz), 55.7 (2 x CH_2, 2 x CH_3), 55.2 (CH_3); ^{19}F NMR (376 MHz): δ = -118.9 (m, 1 F); HRMS (ESI) required for $C_{23}H_{24}FNO_3^+$ ($[MH]^+$) *m/z* = 382.1818, found *m/z* = 382.1816.

4-Chloro-2-methoxy-1-(prop-2-yn-1-yloxy) benzene (14)

Following general method B, (12) compound **14** was synthesised from 4-chloro-2-methoxyphenol (1.0 g, 7.20 mmol) and propargyl bromide (1.06 g, 8.70 mmol) Purification was by flash column chromatography EtOAc/Petrol (1:9 v/v), to give white crystals (1.07 g, 75 %); M.p. 43-44°C; IR ($CHCl_3$): V_{max} = 3307, 3011, 1594, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.95 (1 H, m, H-Ar), 6.88 (2 H, m, H-Ar), 4.73 (2 H, d, 2.4 Hz, CH_2), 3.86 (s, 3 H, H-10), 2.51 (t, 2.4 Hz, 1 H,

CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4 (C-Ar), 145.5 (CH), 127.2 (C-Ar), 120.2 (C-Ar), 115.5 (C-Ar), 112.5 (C-Ar), 78.2 (C-Ar), 76.1 (CH), 57.1 (CH_2), 56.1 (CH_3); HRMS (EI) required for $C_{10}H_9{}^{35}ClO_2{}^+$ *m/z* = 196.0291, found 196.0279.

4-Fluoro-2-methoxy-1-(prop-2-yn-1-yloxy) benzene (15)

Following general method B, (12) compound **15** was synthesised from 4-fluoro-2-methoxyphenol (0.50 g, 3.5 mmol) and propargyl bromide (0.50 g, 4.2 mmol). Purification by flash column chromatography EtOAc/Petrol (1:9 v/v), gave a white solid (0.38 g, 75 %); M.p. 36-37 °C; IR ($CHCl_3$): V_{max} = 3308, 3010, 1612, 1506, 1467, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (1 H, dd, *J* = 8.8 Hz, H-Ar), 6.65 (1 H, dd, *J* = 2.8 Hz, 10.1 Hz, H-Ar), 6.59 (1 H, m, H-Ar), 4.71 (2 H, d, *J* = 2.4 Hz, CH_2), 3.85 (3 H, s, CH_3), 2.49 (1 H, t, *J* = 2.4 Hz, CH) which are consistent with literature values(15); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (d, *J* = 240.0 Hz , C-Ar), 150.9 (d, *J* = 9.9 Hz, C-Ar), 142.9 (d, *J* = 2.6 Hz, C-Ar), 116.0 (d, *J* = 9.9 Hz, C-Ar), 105.9 (d, *J* = 22.7 Hz, C-Ar), 100.4 (d, 24.5 Hz, C-Ar), 78.6 (CH), 75.8, 57.6 (CH_2), 56.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): -118.79 (m, 1 F); HRMS (EI) required for $C_{10}H_9FO_2{}^+$ *m/z* = 180.0587, found *m/z* = 180.0587; $C_{10}H_9FO_2$ requires C, 66.66, H, 5.03 %, found C, 66.71 %; H, 5.03 %.

4-Bromo-2-methoxy-1-(prop-2-yn-1-yloxy) benzene (16)

Following general method B, (12) compound **16** was synthesised from 4-bromo-2-methoxyphenol (0.50 g, 2.50 mmol) and propargyl bromide (0.35 g, 2.90 mmol). Purification by column chromatography EtOAc/Petrol (1:9 v/v), gave a cream solid (0.43 g, 71 %); M.p. 43-44 °C, IR ($CHCl_3$): V_{max} = 3307, 3011, 1592, 1501, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (2 H, m, H-Ar, H-Ar), 6.91 (1 H, d, *J* = 8.4 Hz, H-Ar), 4.74 (2 H, d, *J* = 2.4 Hz, CH_2), 3.86 (3 H, s, CH_3),

2.51 (1 H, t, *J* = 2.4 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5 (C-Ar), 145.9 (C-Ar), 123.3 (C-Ar), 123.3 (C-Ar), 115.9 (C-Ar), 115.3 (C-Ar), 114.4 (C-Ar), 78.1, 76.1 (CH), 56.9 (CH_2), 56.1 (CH_3); HRMS (EI) required for $C_{10}H_9{}^{79}BrO_2{}^+$ *m/z* = 239.9786, found $[C_{10}H_9O_2]^+$ $[M^+\text{-}Br^-]$, *m/z* = 161.0587; $C_{10}H_9BrO_2$ requires C, 49.82; H, 3.76 % found C, 49.99, H, 3.77 %.

4-Chloro-2-methoxy-*N*-(prop-2-yn-1-yl) aniline (17)

Following general method B, (12) compound **17** was synthesised from 4-chloro-2-methoxyaniline (0.30 g, 1.9 mmol) and propargyl bromide (0.27 g, 2.3 mmol). Purification by flash column chromatography EtOAc/Petrol (1:9 v/v) gave a yellow oil (0.09 g, 71 %); IR ($CHCl_3$): V_{max} = 3461, 3377, 3008, 1613, 1505, 1278, 879 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ =6.87 (1 H, dd, *J* = 8.4 Hz, 2.2 Hz, H-Ar), 6.76 (1 H, d, *J* = 2.2 Hz, H-Ar), 6.59 (1 H, d, *J* = 8.4 Hz, H-Ar), 4.42 (1 H, bs, NH), 3.94 (2 H, s, CH_2), 3.84 (3 H, s, CH_3), 2.21 (1 H, t, *J* = 2.5 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7 (C-Ar), 135.4 (C-Ar), 120.7 (C-Ar), 111.1 (C-Ar), 110.4 (C-Ar), 80.7, 71.3 (CH), 55.7 (CH_3), 33.2 (CH_2); HRMS (EI) required for $C_{10}H_{10}{}^{35}ClNO^+$ *m/z* = 195.0451, found 195.0441.

4-Fluoro-2-methoxy-*N*-(prop-2-yn-1-yl) aniline (18)

Following general procedure B, (12) compound **18** was synthesised from 4-fluoro-2-methoxyaniline (0.30 g, 2.10 mmol) and propargyl bromide (0.31 g, 2.50 mmol). Purification was by flash column chromatography EtOAc/Petrol (1:9 v/v), followed by a second purification of a portion (0.072 g) of the crude by column chromatography DCM/Petrol (2:8 v/v) to give a yellow oil (0.06 g, 30 %); IR ($CHCl_3$): V_{max} = 3425, 3307, 3011, 1610, 1518, 1454, 1252, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (3 H, m, H-Ar), 4.25 (1 H, bs, NH), 3.94 (2 H, d, *J* = 2.4 Hz,

CH_2), 3.83 (3 H, s, H-10), 2.20 (1 H, t, *J* = 2.4 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1 (d, *J* = 235 Hz, C-Ar), 147.9 (d, *J* = 9.5 Hz, C-Ar), 132.9 (C-Ar), 110.7 (d, *J* = 9.3 Hz, C-Ar), 106.2 (d, *J* = 21.5 Hz, C-Ar), 98.7 (d, *J* = 27.2 Hz, C-Ar), 81.0, (C), 81.2 (CH_3), 55.7 (CH), 33.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$): -124.9 (m, 1 F); HRMS (EI) required for $C_{10}H_{10}FNO^+$ *m/z* = 179.0746, found 179.0739.

1-Azido-4-methoxybenzene (19)

Following general procedure C, (13) compound **19** was synthesised from *p*-methoxyaniline, $NaNO_2$ (2.52 g, 36.6 mmol) and NaN_3 (2.38 g, 36.60 mmol). Purification by column chromatography EtOAc/Petrol (1:9 v/v) gave a brown solid (2.99 g, 82 %); M.p. 40-42 °C; IR (KBr): V_{max} = 2106, 1505, 1245 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$): δ = 6.94 (2 H, d, *J* = 9.0 Hz, 2 x H-Ar), 6.89 (2 H, d, *J* =9.0 Hz, H-Ar), 3.79 (3 H, s, CH_3), which is consistant with literature values(14); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 (C-Ar), 132.3 (C-Ar), 119.9 (C-Ar), 115.1 (C-Ar), 55.5 (CH_3).

4-[(4-Chloro-2-methoxyphenoxy) methyl]-1-(4-methoxyphenyl)-1-*H*-1,2,3 triazole (20)

Following general method D, (9) compound **20** was synthesised from the propargyl analogue **14** (0.10 g, 0.6 mmol) and azide **19** (0.25 g, 1.7 mmol). Purification was done by flash column chromatography EtOAc/Petrol [1:9 v/v to EtOAc/MeOH (one drop)] to give an orange powder (0.14 g, 74 %); M.p. 144-145 °C; IR ($CHCl_3$): V_{max} = 3009, 1519, 1503, 1254, 1037, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (1 H, s, CH), 7.61 (2 H, d, *J* = 9.0 Hz, H-Ar), 7.0 (2 H, m, 2 x H-Ar), 6.87 (2 H, m, 2 x H-Ar), 5.32 (2 H, s, CH_2), 3.86 (2 x 3H, s, 2 x CH_3), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (C-Ar), 150.2 (C-Ar), 146.3 (C-Ar), 130.4 (C-Ar), 126.8 (C-Ar), 122.28 (C-

Ar), 121.4 (CH), 120.4 (C-Ar), 115.1 (C-Ar), 114.8 (C-Ar), 112.5 (C-Ar), 63.3 (CH_2), 56.1, 55.6 (2 x CH_3); HRMS (ESI) required for $C_{17}H_{16}{}^{35}ClN_3O_3{}^+$ ($[MNa]^+$) *m/z* = 368.0778, found *m/z* = 368.0768.

4-[(4-Fluoro-2-methoxyphenoxy) methyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (21)

Following general method D, (9) compound **21** was synthesised from propargyl analogue **15** (0.20 g, 1.2 mmol) and azide **19** (0.54 g, 3.6 mmol) Purification by flash column chromatography EtOAc/Petrol [(1:9 v/v) to EtOAc/MeOH (one drop)] gave an orange powder (0.14 g, 77 %); M.p. 127-128 °C; IR ($CHCl_3$): V_{max} = 3087, 1612, 1466, 1519, 1035, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (1 H, s, CH), 7.64 (2 H, d, *J* = 9.0 Hz, H-Ar), 7.03 (3 H, m, H-Ar), 6.68 (1 H, dd, *J* = 10.1 Hz, 2.9 Hz, H-Ar), 6.61 (1 H, m, H-Ar), 5.33 (2 H, s, CH_2), 3.89, 3.86 (2 x 3 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (C-Ar), 158.1 (d, *J* = 240.0 Hz, C-Ar), 150.7 (d, *J* = 9.9 Hz, C-Ar), 143.8 (d, *J* = 3.0 Hz, C-Ar), 130.6 (C-Ar), 122.3 (CH), 115.4 (d, *J* = 9.9 Hz, C-Ar), 106.0 (d, *J* = 22.7 Hz, C-Ar), 100.7 (d, *J* = 27.4 Hz, C-Ar), 63.9 (CH_2), 56.1, 55.6 (2 x CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): -119.3 (m, 1 F); HRMS (ESI) required for $C_{17}H_{16}FN_3O_3{}^+$ ($[MNa]^+$) *m/z* = 352.1073, found *m/z* = 352.1058.

4-[(4-Bromo-2-methoxyphenoxy) methyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (22)

Following general method D, (9) compound **22** was synthesised from propargyl analogue **16** (0.20 g, 0.9 mmol) and azide **19** (0.39 g, 2.6 mmol). Purification by flash column chromatography EtOAc/Petrol (1:9v/v) to EtOAc, gave an orange powder (0.29 g, 83 %); M.p. 145-146 °C; IR ($CHCl_3$): V_{max} = 3012, 1680, 1465, 1519, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (1 H, s, CH), 7.61 (2 H, d, *J* = 6.9 Hz, H-Ar), 6.99 (4 H, m, H-Ar), 5.33 (2 H, s, CH_2), 3.86 (6 H, s, 2 x

CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (C-Ar), 150.33 (C-Ar), 146.8 (C-Ar), 144.4 (C-Ar), 130.4 (C-Ar), 123.5 (C-Ar), 122.3 (C-Ar), 121.4 (C-9), 115.5 (C-Ar), 115.2 (C-Ar), 114.8 (C-Ar), 113.9 (C-Ar), 63.3 (CH_2), 56.1, 55.6 (2 x CH_3); HRMS (ESI) required for $C_{17}H_{16}{}^{79}BrN_3O_3{}^+$ ($[MNa]^+$) *m/z* = 412.0273, found *m/z* = 412.0257.

4-Chloro-2-methoxy-*N*-[(1-4-methoxyphenyl)-1*H*-1,2,3 triazol-4-yl]methyl aniline (23)

Following general method D, (9) compound **23** was synthesised from propargyl analogue **17** (0.08 g, 0.4 mmol) and azide **19** (0.09 g, 0.6 mmol). Purification by flash column chromatography EtOAc/Petrol [(1:9 v/v) to EtOAc/ MeOH (one drop)] gave an orange powder (0.12 g, 84 %); M.p. 130-131°C; IR ($CHCl_3$): V_{max} = 3011, 1679, 1519, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (1 H, s, CH), 7.59 (2 H, d, *J* = 9.1 Hz, H-Ar), 6.99 (2 H, d, *J* = 9.1 Hz, H-Ar), 6.82 (1 H, dd, *J* = 2.2 Hz, 8.4 Hz, H-Ar), 6.75 (1 H, d, *J* = 2.2 Hz, H-Ar), 6.58 (1 H, d, *J* = 8.4 Hz, H-Ar), 4.75 (1 H, s, NH), 4.53 (2 H, s, CH_2), 3.85, 3.84 (2 x 3 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8 (C-Ar), 147.5 (C-ar), 146.7 (C-Ar), 136.2 (C-Ar), 130.5 (C-Ar), 122.2 (C-Ar), 121.9 (CH), 120.8 (C-Ar), 119.9 (C-Ar), 114.8 (C-Ar), 110.6 (C-Ar), 110.3 (C-Ar), 55.7, 55.6 (2 x CH_3), 39.7 (CH_2); HRMS (EI) required for $C_{17}H_{17}{}^{35}ClN_4O_2{}^+$ *m/z* = 344.1040, found 344.1023.

4-Fluoro-2-methoxy-*N*-[(1-4-methoxyphenyl)-1*H*-1,2,3 triazol-4-yl]methyl aniline (24)

Following general method D, (9) compound **24** was synthesised from propargyl analogue **18** (0.14 g, 0.9 mmol) and azide **19** (0.2 g, 1.31 mmol). Purification by flash column chromatography EtOAc/Petrol [(1:9 v/v) to (1:1 v/v)] gave a cream solid (0.22 g, 77 %); M.p. 138-139 °C; IR ($CHCl_3$): V_{max} = 1609, 1519, 1287, 1036, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (1 H, s, CH), 7.59 (2 H, d, *J* = 9.1 Hz, H-Ar), 6.99 (2 H, d, *J* = 9.1 Hz, H-Ar), 6.57 (3 H, m, H-Ar), 4.68

(1 H, s, NH), 4.52 (2 H, s, CH_2), 3.86, 3.84 (2 x 3 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8 (C-Ar), 155.8 (d, *J* = 236.6 Hz, C-Ar), 147.7 (d, *J* = 9.3 Hz, C-Ar), 146.9 (C-Ar), 133.8 (C-Ar), 130.6 (C-Ar), 122.2 (CH), 120.0 (C-Ar), 114.7 (C-Ar), 110.1 (d, *J* = 9.0 Hz, C-Ar), 106.2 (*J* = 21.8 Hz, C-Ar), 98.7 (d, *J* = 27.2 Hz, C-Ar), 40.21 (CH_2), 55.7-55.6 (2 x CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): -125.4 (m, 1 F); HRMS (ESI) required for $C_{17}H_{17}FN_4O_2^+$ ($[MNa]^+$) *m/z* = 351.1233, found *m/z* = 351.1222.

4-Iodo-phenyl-methanol (26)

Compound **26** was prepared following literature procedure.(16) Under a nitrogen atmosphere, 4-iodobenzoic acid (**25**) (2.00 g, 8.10 mmol, 1.0 eq.) was dissolved in anhydrous THF (16 mL). To this reaction mixture a 1 M solution of BH_3.THF (16 mL, 1.37 g, 0.016 mmol) was added slowly dropwise *via* a cannula over 15 minutes. The solution was left stirring at room temperature overnight followed by quenching by the dropwise addition of 2 M HCL (10 mL). The product was extracted with DCM (2 x 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 x 16 mL) and brine (2 x 16 mL) and then dried over $MgSO_4$ before removal of the solvent *in vacuo*. The crude product was purified by flash column chromatography EtOAc/Petrol (1:9 v/v) to yield a white powder (1.72 g, 91 %); M.p. 74-77˚C; IR ($CHCl_3$): V_{max} = 3610, 3010, 1485, 1006 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.68 (2 H, d, *J* = 8.0 Hz, H-Ar), 7.11 (2 H, d, *J* = 8.0 Hz, H-Ar), 4.65 (2 H, d, *J* = 5.8 Hz, CH_2), 1.66 (1 H, t, *J* = 5.8 Hz, OH) which is consistent with literature values(16); ^{13}C NMR (100MHz, $CDCl_3$): δ = 140.4 (C-Ar), 137.6 (C-Ar), 128.8 (C-Ar), 93.0 (C-Ar), 64.6 (CH_2) which is consistent with literature values(16); HRMS (ESI) required for $C_7H_6IONa^+$($[M+Na]^+$) *m/z* = 256.9439, found 256.9436.

***tert*-Butyl-[4-iodo-benzyloxy)dimethylsilane (27)**

A solution of (4-iodophenyl)methanol (**26**) (3.00 g, 12.82 mmol) in DCM (128 mL) was cooled to 0 °C followed by the addition of TBDMSCl (2.02 g, 15.38 mmol) and imidazole (1.92 g, 28.00 mmol). The solution was brought to room temperature and left stirring overnight. Saturated $NH_4Cl_{(aq)}$ solution (100 mL) was added and the phases were separated. The organic phase was washed with brine (2 x 100 mL). The combined aqueous phases were extracted with DCM (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, before the solvent was removed *in vacuo*. The product was purified by flash column chromatography EtOAc/Petrol (1:10 v/v) and concentrated *in vacuo* to give white crystals (4.20 g, 12.04 mmol, 94 %); M.p. 36-38 °C; IR ($CHCl_3$): V_{max} ($CHCl_3$): 3010, 2456, 2859, 1483, 1084, 1472, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (2 H, d, *J* = 8.5 Hz, H-Ar), 7.07 (2 H, d, *J* = 8.5 Hz, H-Ar), 4.67 (2 H, s, CH_2), 0.93 (9 H, s, 3 x CH_3), 0.09 (6 H, s, 2 x CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ = 141.1 (C-Ar), 137.2 (C-Ar), 128.0 (C-Ar); 91.9 (C-Ar), 64.3 (C-Ar), 25.9 (CH_3), 18.3 (CH_3), -5.3; HRMS (EI) required for $C_{13}H_{21}IOSi$ is 348.0406 found $[M\text{-}Bu]^+$, 290.9689; $C_{13}H_{21}IOSi$ required C,44.83; H,6.08 %, found C,44.69; H,6.04 %.

***tert*-Butyl-[4-(4-chloro-2-methoxy-phenoxy)-benzyloxy-dimethylsilane (28)**

A literature procedure (18) was modified to synthesise compound **28**. Under a nitrogen atmosphere, the silane **27** (3 g, 8.61 mmol), 4-chloro-2-methoxyphenol (2.73 g, 17.20 mmol), Cs_2CO_3 (5.61 g, 17.22 mmol), CuI (0.082 g, 0.40 mmol), ethyl acetate (0.03 μL, 0.29 mmol), 1-naphthoic acid (2.08 g, 12.10 mmol), powdered molecular sieves (4 Å) (0.04g) and dry toluene (6 mL) were added to an oven dried sealed tube and heated to 107 °C for 3 days until almost complete consumption of the halide had occurred. The dark purple suspension was allowed to cool

to room temperature followed by the addition of DCM (10 mL). The product was filtered and DCM (2 x 20 mL) was added with stirring to remove any residue. The combined organic phases were washed with 5 % $NaOH_{(aq)}$ (100 mL). Purification by flash chromatography EtOAc/Petrol (1:20 v/v) gave a yellow oil (1.80 g, 41 %); IR ($CHCl_3$):V_{max} = 3080, 1497, 1260, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (2 H, d, *J* = 8.6 Hz, H-Ar), 6.97 (1 H, s, H-Ar), 6.89 (2 H, d, *J* = 8.6 Hz, H-Ar), 6.87-6.86 (2 H, m, H-Ar), 4.69 (2 H, s, CH_2), 3.82 (3 H, s, CH_3), 0.93 (9 H, s3 x CH_3), 0.09 (6 H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (C-Ar), 151.8 (C-Ar), 144.2 (C-Ar), 135.9 (C-Ar), 129.3 (C-Ar), 127.5 (C-Ar), 121.3 (C-Ar), 120.8 (C-Ar), 117.1 (C-Ar), 113.3 (C-Ar), 64.5 (CH_2), 56.1 (CH_3), 25.9 (CH_3), 25.6 (CH_2), 18.4 (CH_3); HRMS (ESI) required for $C_{20}H_{27}{}^{35}ClO_3Si^+$ [$(MNa)^+$] *m/z* = 401.1316, found 401.1090.

[4-(4-Chloro-2-methoxyphenoxy)phenyl] methanol (29)

A solution of silyl ether **28** (0.48 g, 1.30 mmol) in THF (6 mL) was cooled to 0 °C followed by the addition of TBAF (0.40 g, 1.51 mmol). The brown solution was allowed to warm to room temperature and left stirring for 4.5 hr. The solvent was removed *in vacuo*. Purification by flash chromatography EtOAc/Petrol (1:3 v/v) gave a colourless powder (0.26 g, 79 %); M.p. 65-68 °C; IR ($CHCl_3$) V_{max} = 3692, 3692, 3059, 1422, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (1 H, d, J = 8.6 Hz, H-Ar), 6.91 (2 H, d, 8.6 Hz, H-Ar), 6.92 (1 H, s, H-Ar), 6.90 (2 H, m, H-Ar), 4.65 (2 H, s, CH_2), 3.83 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2 (C-Ar), 151.9 (C-Ar), 143.7 (C-Ar), 135.3 (C-Ar), 129.7 (C-Ar), 128.6 (C-Ar), 121.7 (C-Ar), 120.9 (C-Ar), 117.2 (C-Ar), 113.4 (C-Ar), 64.9 (CH_2), 56.2 (CH_3); HRMS (EI) required for $C_{14}H_{13}{}^{35}ClO_3$: *m/z* = 264.0548, found 264.0560.

4-Chloro-1-[4-(chloromethyl)phenoxy]-2-methoxybenzene (30)

A solution of alcohol **29** (0.14 g, 0.53 mmol) in DCM (5.3 mL) was cooled to 0 °C, followed by the addition of triethylamine (0.13 g, 1.27 mmol). The reaction mixture was left stirring for 5 minutes followed by the dropwise addition of methanesulfonylchloride (0.10 g, 0.64 mmol). The reaction mixture was allowed to warm to room temperature followed by stirring for 4 h. Saturated $NH_4Cl_{(aq)}$ solution (5 mL) was added and the phases were separated. The organic layer was washed with brine (2 x 10 mL) and the combined organic layers were extracted with DCM (2 x 10 mL) and dried over $MgSO_4$, before the solvent was removed *in vacuo*. The crude product was purified by flash chromatography EtOAc/Petrol (1:9 v/v) to give a sticky colourless solid (0.23 g, 0.74 mmol, 65 %); M.p. 83-86 °C; IR ($CHCl_3$): V_{max} = 3043, 2666, 1497, 1266, 854 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.31 (2 H, d, *J* = 8.7 Hz, H-Ar), 6.99 (1 H, s, H-Ar), 6.92 (2 H, m, H-Ar), 6.87 (2 H, d, *J* = 8.7Hz, H-Ar), 4.57 (2 H, s, CH_2), 3.81 (3 H, s, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8 (C-Ar), 154.9 (C-Ar), 152.1 (C-Ar), 143.2 (C-Ar), 131.7 (C-Ar), 130.1 (C-Ar), 122.2 (C-Ar), 121.0 (C-Ar), 116.9 (C-Ar), 113.5 (C-Ar), 56.2 (CH_3), 45.9 (CH_2); HRMS (EI) calculated for $C_{14}H_{14}{}^{35}Cl_2O_2$ m/z = 282.0214, found 282.0214.

***Di*-[(4'-chloro-2'-methoxy-)4-phenoxy] dibenzylether (31)**

A literature procedure(19) was modified to synthesise compound **31**. To a suspension of NaH (60 % dispersion in mineral oil, 0.018 g, 0.44 mmol) in DMF (1 mL), a solution of alcohol **29** (0.08 g, 0.29 mmol) in DMF (2 ml) was added, and left stirring for 30 min at room temperature. The solution was cooled to 0 °C, followed by the addition of a solution of compound **30** (0.10 g, 0.29 mmol) in DMF (2 mL). The solution was left stirring at room temperature for 4.5 h followed by the addition of water (5 mL). The solution was extracted with DCM (3 x 10 mL). The combined

organic extracts were dried over $MgSO_4$, before the solvent was removed *in vacuo*. Purification by flash column chromatography EtOAc/Petrol (1:4 v/v) gave a yellow oil (0.12 g, 79 %), IR ($CHCl_3$): V_{max} = 3009, 1491, 1271, 912, 858 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.28 (4 H, d, *J* = 8.7 Hz, H-Ar), 6.98 (2 H, m, H-Ar), 6.90 (8 H, m, H-Ar), 6.89, 4.49 (4 H, s, CH_2), 3.82 (6 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1 (C-Ar), 151.9 (C-Ar), 143.7 (C-Ar), 132.6 (C-Ar), 129.6 (C-Ar), 129.3 (C-Ar), 121.6 (C-Ar), 120.8 (C-Ar), 117.0 (C-Ar), 113.4 (C-Ar), 71.6 (CH_2), 56.1 (CH_3); HRMS (ESI) calculated for $C_{28}H_{24}{}^{35}Cl_2O_5N$ $([M+NH_4])^+$: *m/z* = 528.1339, found 528.1349.

4-(4-Chloro-2-methoxyphenoxy)benzaldehyde (32)

4-Chloro-2-methoxyphenol (5.00 g, 31.50 mmol) was dissolved in anhydrous DMF (40 mL), 4-fluorobenzaldehyde (4.30 g, 34.60 mmol) and K_2CO_3 (4.79 g, 34.60 mmol) were sequentially added and the reaction mixture was heated to 130 °C and stirred for 18 h. The reaction mixture was then allowed to cool to room temperature before being diluted with H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed sequentially with saturated $NaHCO_3$ (aq) solution, H_2O and Brine (100 mL). The organic layer was then dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by flash column chromatography Hexane/EtOAc (3:1) gave a dense orange oil (7.31 g, 89 %) ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H, CHO), 7.80 – 7.64 (m, 2H, H-Ar), 6.96 – 6.93 (m, 2H, H-Ar), 6.91 – 6.86 (m, 3H, H-Ar), 3.69 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7 (CHO), 163.2 (C-Ar), 152.4 (C-Ar), 141.6 (C-Ar), 131.9 (C-Ar), 131.4 (C-Ar), 131.2 (C-Ar), 123.3 (C-Ar), 121.2 (C-Ar), 116.2 (C-Ar), 113.7 (C-Ar), 56.1 (CH_3). HRMS (ESI) *m/z* calcd for $C_{14}H_{12}{}^{35}ClO_3$ $[M + H]^+$, 263.0469, found 263.0469

4-(4-Chloro-2-hydroxyphenoxy)benzaldehyde (33)

Compound **33** (8.00 g. 30.50 mmol) was suspended in AcOH (30 ml, 0.52 mol) followed by the addition of 47 % HBr (aq) (12 mL, 0.10 mol). The reaction mixture was then heated to 110 °C and stirred for 18 h. The reaction mixture was allowed to cool to room temperature before being concentrated *in vacuo*, the mixture was then neutralised by careful addition of $NaHCO_3$ before being diluted in H_2O (200 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were then dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by flash column chromatography Hexane/EtOAc (0 -> 21 %) gave a light yellow solid (2.20 g, 29 %). ^{1}H NMR (400 MHz, MeOD) δ 9.81 (s, 1H, CHO), 7.85 – 7.78 (m, 2H, H-Ar), 7.03 – 6.94 (m, 4H, H-Ar), 6.85 (dd, J = 8.6, 2.5 Hz, 1H, H-Ar). ^{13}C NMR (101 MHz, MeOD) δ 191.5 (CHO), 163.4 (C-Ar), 150.3 (C-Ar), 140.7 (C-Ar), 131.7 (C-Ar), 131.1 (C-Ar), 130.8 (C-Ar), 123.2 (C-Ar), 119.9 (C-Ar), 117.3 (C-Ar), 116.0 (C-Ar). HRMS (ESI) *m*/*z* calcd for $C_{13}H_8O_3{}^{35}Cl$ $[M - H]^-$, 247.0167, found 247.0175

4-(4-(4-Chloro-2-(methoxymethoxy)phenoxy)benzaldehyde (34)

Compound **33** (2.20 g, 8.90 mmol) was dissolved in CH_2Cl_2 (40 mL) under a nitrogen atmosphere. DIPEA (3.43 g, 26.54 mmol) and MOMCl (1.07 g, 13.29 mmol) were added sequentially and the reaction mixture was allowed to stir for 18 h. The reaction mixture was then diluted with saturated NH_4Cl (aq) solution (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by flash column chromatography Hexane/EtOAc (3:1) gave a light yellow oil (2.41 g, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 7.75 – 7.63 (m, 2H, H-Ar), 7.17 (dd, J = 2.1, 0.5 Hz, 1H, H-

Ar), 6.94 – 6.81 (m, 4H, H-Ar), 4.98 (s, 2H, CH_2), 3.22 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1 (CHO), 163.1 (C-Ar), 149.8 (C-Ar), 142.4 (C-Ar), 131.8 (C-Ar), 131.3 (C-Ar), 131.2 (C-Ar), 123.5 (C-Ar), 122.7 (C-Ar), 117.6 (C-Ar), 116.2 (C-Ar), 95.0 (CH_2), 56.3 (CH_3). HRMS (ESI) *m*/*z* calcd for $C_{15}H_{13}O_4{}^{35}ClNa$ $[M + Na]^+$, 315.0395, found 315.0398.

(4-(4-Chloro-2-(methoxymethoxy)phenoxy)phenyl)methanol (35)

Compound **34** (2.41 g, 8.25 mmol) was dissolved in MeOH (50 mL) and cooled to 0 °C. $NaBH_4$ (0.47 g, 12.38 mmol) was added portion-wise and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the addition of H_20 (40 mL) and was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were then dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by flash column chromatography Hexane/EtOAc (3:1) gave a light yellow oil (2.09 g, 86 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.07 (m, 3H, H-Ar), 6.88 (dd, J = 8.6, 2.4 Hz, 1H, H-Ar), 6.85 – 6.80 (m, 3H, H-Ar), 5.05 (s, 2H, CH_2), 4.52 (s, 2H, C*H*$_2$OH), 3.32 (s, 3H, CH_3), 2.47 (bs, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (C-Ar), 149.4 (C-Ar), 144.6 (C-Ar), 135.6 (C-Ar), 129.6 (C-Ar), 128.5 (C-Ar), 122.6 (C-Ar), 122.0 (C-Ar), 117.9 (C-Ar), 117.1 (C-Ar), 95.3 (CH_2), 64.6 (CH_2OH), 56.3 (CH_3). HRMS (ESI) *m*/*z* calcd for $C_{15}H_5O_4{}^{35}ClNa$ $[M + Na]^+$, 317.0551, found 317.0558

4-Chloro-1-(4-(chloromethyl)phenoxy)-2-(methoxymethoxy)benzene (36)

Compound **35** (0.35 g, 1.17 mmol) and Et_3N (0.24 g, 2.34 mmol) were dissolved in CH_2Cl_2 (7 mL) and cooled to 0 °C. Methanesulfonyl chloride (0.20 g, 1.75 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction

mixture was diluted with saturated NH_4Cl (aq) solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by flash column chromatography Hexane/EtOAc (4:1) gave a light yellow oil (0.20 g, 56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H, H-Ar), 7.30 – 7.26 (m, 1H, H-Ar), 7.03 – 6.95 (m, 2H, H-Ar), 6.94 – 6.89 (m, 2H, H-Ar), 5.16 (s, 2H, CH_2), 4.59 (s, 2H, CH_2Cl), 3.42 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (C-Ar), 149.6 (C-Ar), 144.0 (C-Ar), 131.8 (C-Ar), 130.1 (C-Ar), 122.6 (C-Ar), 122.6 (C-Ar)-, 117.8 (C-Ar), 117.0 (C-Ar), 95.3 (CH_2), 56.4 (45CH_3), 45.9 (CH_2Cl). HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}O_3{}^{35}Cl_2Na$ $[M + Na]^+$, 335.0212, found 335.0213

4,4'-(((Oxy*bis*(methylene))*bis*(4,1-phenylene))*bis*(oxy))*bis*(1-chloro-3-(methoxymethoxy)benzene) (37)

Compound **36** (0.13 g, 0.43 mmol) was dissolved in anhydrous DMF (5 mL) and cooled to 0 °C. NaH (60 % dispersion in mineral oil, 33 mg, 0.83 mmol) was added in a single portion and the reaction mixture was allowed to stir for 1 h. Compound **35** (0.20 g, 0.65 mmol) in DMF (2 mL) was then added dropwise and the reaction mixture was allowed to warm to room temperature before being stirred for a further 18 h. The reaction mixture was quenched by the addition of H_2O (5 mL) before being extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed sequentially with saturated $NaHCO_3$ (aq) solution, H_2O and Brine (20 mL). The organic layer was then dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by flash column chromatography Hexane/EtOAc (3:1) gave a light yellow oil (0.11 g, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 4H, H-Ar), 7.29 – 7.27 (m, 2H, H-Ar), 7.01 – 6.97 (m, 2H, H-Ar), 6.96 – 6.91 (m, 6H, H-Ar), 5.17 (s, 4H, OCH_2O), 4.52 (s, 4H, $ArCH_2$), 3.44 (s, 6H, CH_3). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 157.3 (C-Ar), 149.4 (C-Ar), 144.7 (C-Ar), 132.7 (C-Ar), 129.6 (C-Ar), 129.4 (C-Ar), 122.6 (C-Ar), 122.1 (C-Ar), 117.9 (C-Ar), 117.1 (C-Ar), 95.4 (OCH_2O), 71.6 ($ArCH_2$), 56.4 (CH_3). HRMS (ESI) *m*/*z* calcd for $C_{30}H_{28}O_7{}^{35}Cl_2Na$ $[M + Na]^+$, 593.1104, found 593.1088

***Di*-[(4'-chloro-2'-hydroxy-)4-phenoxy] dibenzylether (38)**

Compound **37** (0.11 g, 0.19 mmol) was dissolved in MeOH (7 mL) followed by the addition of 6 M HCl (0.2 mL, 1.2 mmol). The reaction mixture was heated to reflux and stirred for 2 h. The reaction mixture was then allowed to cool to room temperature before being concentrated *in vacuo*, the reaction mixture was then diluted with saturated $NaHCO_3$ (aq) solution (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were then dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by reverse-phase high performance liquid chromatography (Method B) gave an off-white solid (0.04 g, 44 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 4H, H-Ar), 7.07 (d, J = 2.2 Hz, 2H, H-Ar), 7.04 – 6.98 (m, 4H, H-Ar), 6.86 – 6.78 (m, 4H, H-Ar), 5.80 (s, 2H, OH), 4.56 (s, 4H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C-Ar), 148.1 (C-Ar), 142.4 (C-Ar), 133.8 (C-Ar), 129.7 (C-Ar), 129.5 (C-Ar), 120.6 (C-Ar), 119.5 (C-Ar), 118.0 (C-Ar), 116.7 (C-Ar), 71.6 (CH_2). HPLC r.t. ~ 17 min (Method B) HRMS (ESI) *m*/*z* calcd for $C_{26}H_{20}O_5{}^{35}Cl_2Na$ $[M + Na]^+$, 505.0580, found 505.0594. LC-MS Purity = 92 %

4-Chloro-2-methoxy-1-(4-[4-methoxybenzyl] oxy] methyl phenoxy) benzene (39)

A literature procedure (19) was modified to synthesise compound **39**. To a suspension of NaH (60 % dispersion in mineral oil, 0.02 g, 0.4 mmol) in DMF (1 mL), a solution of (4-methoxyphenyl)methanol (0.04 g, 0.3 mmol) in DMF (2 ml) was added and left stirring for 30 min

at room temperature. The solution was cooled to 0 °C, followed by the addition of a solution of compound **31** (0.10 g, 0.3 mmol) in DMF (2 mL). The solution was left stirring at room temperature for 4.5 h followed by the addition of water (5 mL). The reaction mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography EtOAc/Petrol (1:19 v/v) to give a colourless oil (0.08 g, 67 %), IR ($CHCl_3$): V_{max} = 3011, 1612-1597, 1464, 1251, 1118, 1032, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (4 H, d, *J* = 8.6 Hz, H-9, H-14), 7.00 (1 H, m, H-Ar), 6.92 (6 H, m, H-Ar), 4.51, 4.49 (2 x2 H, s, 2 x CH_2), 3.84, 3.83 (s, 2 x3 H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C-Ar), 157.1 (C-Ar), 151.9 (C-Ar), 143.9 (C-Ar), 132.8 (C-Ar), 130.3 (C-Ar), 129.6 (C-Ar), 129.4 (C-Ar), 121.6 (C-Ar), 120.9 (C-Ar), 117.1 (C-Ar), 113.8 (C-Ar), 113.4 (C-Ar), 71.78, 71.35 (C-Ar), 56.2 (2 x CH_2), 55.3 (2 x CH3); HRMS (ESI) required for $C_{22}H_{21}{}^{35}ClO_4$ $([M+Na])^+$: *m/z* = 407.1026, found 407.1024.

***Di*-1,1'(4-Iodo-phenyl)-dimethylether (40)**

A literature procedure was modified to synthesise compound **40** (17). Under a nitrogen atmosphere, to a suspension of NaH (60 % dispersion in mineral oil, 0.31 g, 17.67 mmol) in anhydrous THF (13 mL), a solution of (4-iodophenyl)methanol (0.20 g, 0.86 mmol) in anhydrous THF (16 mL) was added at 0 °C and stirred for 30 min at room temperature. A solution of 4-iodo-benzylbromide (0.50 g, 1.71 mmol) in dry THF (4 mL) was added to the solution at 0 °C. The solution was heated to reflux overnight and cooled to room temperature, followed by dropwise addition of water (13 mL), and extraction with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, before the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography EtOAc/Petrol (1:9 v/v) to give a white powder (0.28 g, 71 %);

M.p. 103 – 105 ˚C; IR ($CHCl_3$): V_{max} = 2860, 1083, 1488 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.68 (4 H, m, H-Ar), 7.09 (4 H, m, H-Ar), 4.48 (4 H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7 (C-Ar), 137.5 (C-Ar), 129.5 (C-Ar), 93.2 (C-Ar), 71.5 (CH_2); HRMS (EI) required for $C_{14}H_{12}I_2O^+$ is 449.8970. No parent ion was observed found $[M\text{-}C_7H_7IO]^+$, 217.9595 and $[M–C_7H_6I]^+$, 232.9468

4-(Chloromethyl)benzylmethanesulfonate (42)

To a solution of (4-methoxyphenyl)methanol (5.00 g, 40.3 mmol) in DCM (400 mL) at 0 °C, triethylamine (19.53 g, 193.00 mmol) was added, and the solution was left stirring for 5 min, followed by the addition of methanesulfonyl chloride (18.5 g, 161.00 mmol). The solution was allowed to warm to room temperature and stirred for 4 h, followed by the addition of saturated $NH_4Cl_{(aq)}$ solution (400 mL). The phases were separated and the organic phase was washed with brine (3 x 200 mL). The combined aqueous phases were extracted with DCM (3 x 200 mL). The combined organic phases were dried over $MgSO_4$, before the solvent was removed *in vacuo*. Purification by flash column chromatography EtOAc/Petrol (1/9 v/v) gave yellow crystals (4.92 g, 44 %); M.p. 40-42 °C; IR ($CHCl_3$): V_{max} = 1505, 1375, 1150, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (2 H, d, *J* = 8.7 Hz, H-Ar), 7.30 (2 H, d, *J* = 8.7 Hz, H-Ar); 4.61 (2 H, s, H-Ar), 3.18 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9 (C-Ar), 130.3 (C-Ar), 122.3 (C-Ar), 45.1 (CH_3), 37.5 (CH_2); HRMS (EI) required for $C_8H_9{}^{35}ClO_3S$ is 219.9961 found 219.9955.

4-[(2-Acetyl-4-chlorophenoxy)methyl]phenylmethanesulfonate (43)

Following general procedure B,(12) compound **43** was synthesised from ketone **41** (0.30 g, 1.80 mmol) and mesylate **42** (0.43 g, 2.10 mmol). Purification by flash column chromatography

EtOAc/Petrol (1:9 to 3:7 v/v) gave cream flakes (0.28 g, 51 %); M.p. 97-98°C, IR ($CHCl_3$): V_{max} = 1679, 1375, 1151, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (1 H, d, *J* = 2.8 Hz, H-Ar), 7.48 (2 H, d, *J* = 8.7 Hz, H-Ar), 7.39 (1 H, dd, *J* = 2.8 Hz, 8.9 Hz, H-Ar), 7.33 (2 H, d, *J* = 8.7 Hz, H-Ar), 6.94 (1 H, d, *J* = 8.9 Hz, H-Ar), 5.15 (2 H, s, CH_2), 2.98 (3 H, s, CH_3), 2.58 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2 (C-14), 156.1 (C-Ar), 148.9 (C-Ar), 135.1 (C-Ar), 133.1 (C-Ar), 130.3 (C-Ar), 129.9 (C-Ar), 129.1 (C-Ar), 126.7 (C-Ar), 122.5 (C-Ar), 114.3 (C-Ar), 70.2 (CH_2), 37.6 (CH_3), 31.9 (CH_3). HRMS (micOTOF) required for $C_{16}H_{15}{}^{35}ClO_5S^+$ ($[MNa]^+$) *m/z* = 377.0226, found *m/z* =377.0222.

4-[(2-Acetyl-4-chlorophenoxy) methyl] phenylmethanesulfonate (44)

A literature procedure (20) was adapted to synthesise compound **44**. To a solution of ketone **43** (0.28 g, 1.01 mmol) in chloroform (2 mL) *m*-CPBA (70-75 % purity) (0.87 g, 5.10 mmol), was added. The white suspension was left stirring at room temperature overnight. The reaction was quenched by the addition of saturated $NaS_2SO_{4(aq)}$ solution (5 mL). The aqueous layer was extracted with DCM (3 x 10mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed *in vacuo*. Purification by flash column chromatography EtOAc/Petrol (1:9 to 3:7 v/v) gave a white solid (0.25 g, 68 %); M.p. 132-133 °C; V_{max}: ($CHCl_3$): 1764, 1498, 1373, 1150, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (2 H, d, *J* = 8.7 Hz, H-Ar), 7.30 (2 H, d, *J* = 8.7 Hz, H-Ar), 7.14 (1 H, dd, *J* = 2.5 Hz, 8.7 Hz, H-Ar), 7.09 (1 H, d, *J* = 2.5 Hz, H-Ar), 6.89 (1 H, d, *J* = 8.7 Hz, H-Ar), 5.07 (2 H, s, CH_2), 3.16 (3 H, s, CH_3), 2.28 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8 (C-13), 140.6 (C-Ar), 135.7 (C-Ar), 128.7 (C-Ar), 126.7 (C-Ar), 126.0 (C-Ar), 123.5 (C-Ar), 122.3 (C-Ar), 114.7 (C-Ar), 70.1 (CH_2), 37.5 (CH_3), 20.6 (CH_3);

HRMS (ESI) required for $C_{16}H_{15}{}^{35}ClO_6S^+$ ($[MNa]^+$) *m/z* = 393.0176, found *m/z* = 393.0164; $C_{16}H_{15}ClO_6S$ requires C, 51.83; H, 4.08 % found C, 51.91; H, 4.15 %.

2-*trans*-Octenyl CoA

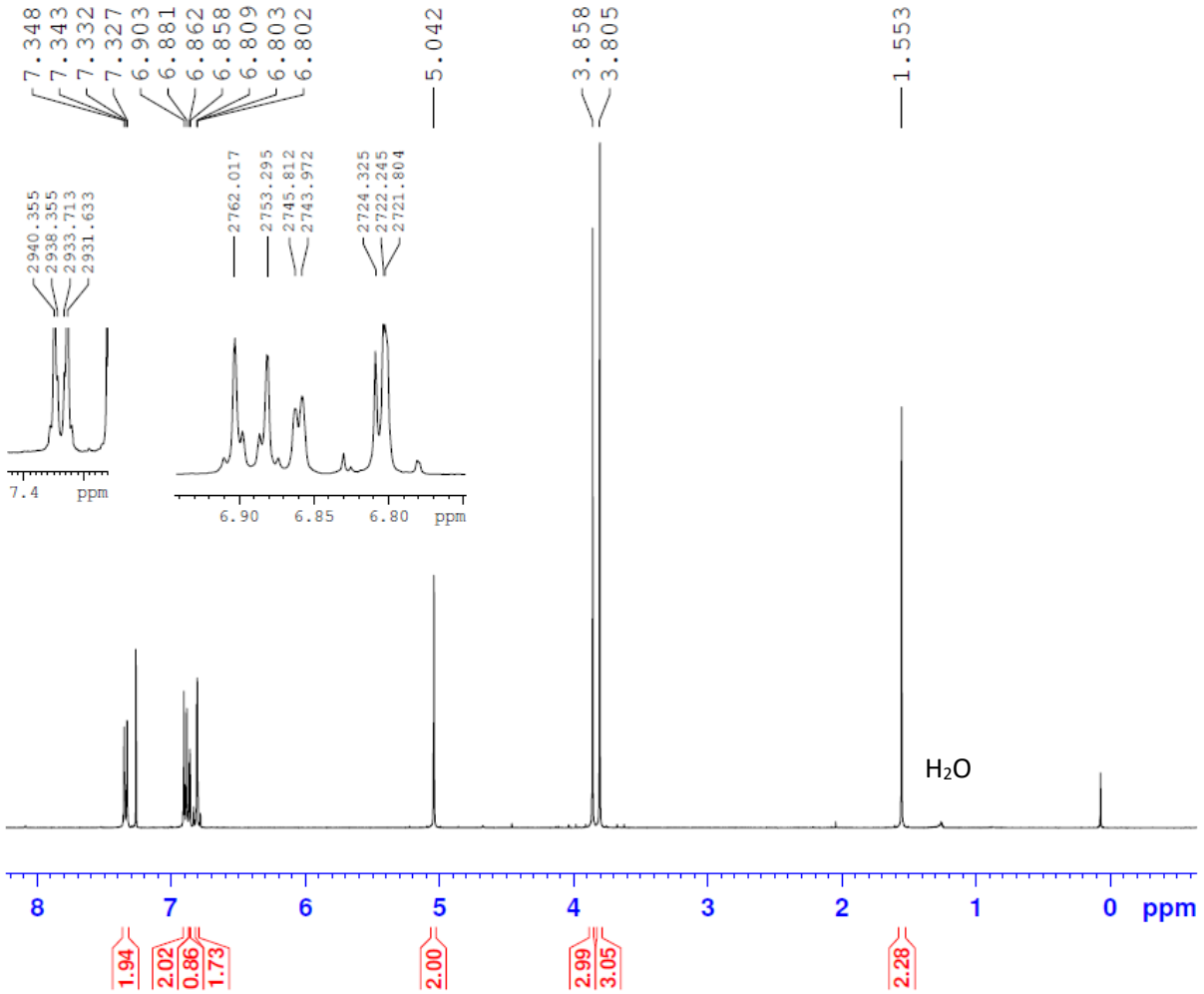
Using an method adapted from the literature(21), The reaction vessel was covered with foil. The addition of the starting materials was done in the dark: potassium carbonate (35 mg, 63.6 µmol) was dissolved in water (2.5 mL), followed by the addition of coenzyme A (50 mg, 63.6 µmol) and 2-*trans*-octenoic acid (Alfa Aesar, 94%) (16 µl, 110 µmol). THF (2.5 mL) was added followed by the addition of PyBOP (0.053 g, 102 µmol). The solution was left stirring at room temperature for 5 h and completion of the reaction was monitored with DTNB (to determine free CoA thiol). The organic layer was removed by evaporation and the water was removed by lyophilisation to give a crude cream solid. The crude product was dissolved in distilled water and purified by HPLC using 20 mM ammonium acetate (pH 5.8) (A) and acetonitrile (B). Gradient elution over 25 minutes 100 % A (0-1 min), 0-10 % B (1.01-2min), 10 % B (1.01-2 min), 10-20 % B (2-2.01 min), 20 % (2.01-5 min), 20-25 % B (5-5.01 min) 25-30 % B (5.01-15 min), 30-95 % B (15.01 min), 95 % (15.01-17 min),95-0 % B (17-20 min), 100 % A (20-25 min) at a flow rate of 2 mL/min gave an eluted product which was lyophilised thrice to give a white powder (27.7 mg, 24.3 µmol, 38 %); V_{max} (KBr): 3412, 2359, 2927, 1652, 1239, 1078, 951 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (1 H, s, H-Ar), 8.14 (1 H, s, H-Ar), 6.84 (1 H, m, CH), 6.04 (2 H, m, 2 x CH), 4.7 (2 H, m, 2 x CH), 4.47 (1 H, s, CH), 4.14 (bs, 2 H, CH_2), 3.91 (s, 1 H, CH), 3.72 (1 H, m, CH_B), 3.46 (1 H, m, CH_A), 3.32 (2 H, m, CH_2), 3.24 (2 H, m, CH_2), 2.92 (2 H, m, CH_2), 2.3 (2 H, m, CH_2), 2.06 (2 H, m, CH_2), 1.29 (2 H, m, CH_2), 1.13 (4 H, m, 2 x CH_2), 0.78 (3 H, s, CH_3), 0.73 (3 H, m, CH_3), 0.65 (3 H, s, CH_3); ^{31}P-NMR (162 MHz, D_2O): -0.6, -11.3 (2 P); ^{13}C NMR (100 MHz, D_2O): δ = 193.7, 174.7,

173.91, 152.3, 148.9, 148.2, 141.2, 127.6, 118.5, 86.8, 83.4, 74.0, 73.9, 71.8, 65.1, 38.6, 38.3, 38.2, 35.4, 35.3, 31.6, 30.5, 30.4, 27.7, 26.7, 21.7, 20.8, 18.1, 13.2; HRMS (ESI) required for $C_{29}H_{47}N_7O_{17}P_3S^-$: *m/z* = 890.2040, found 890.1869.

NMR Data

(see below)

4-chloro-22-methoxy-1-[(4-methoxybenzyl)oxy]benzene



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FIDRES	0.126314 Hz
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RG	2896.3
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DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
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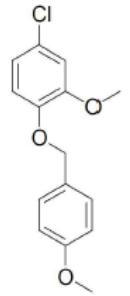
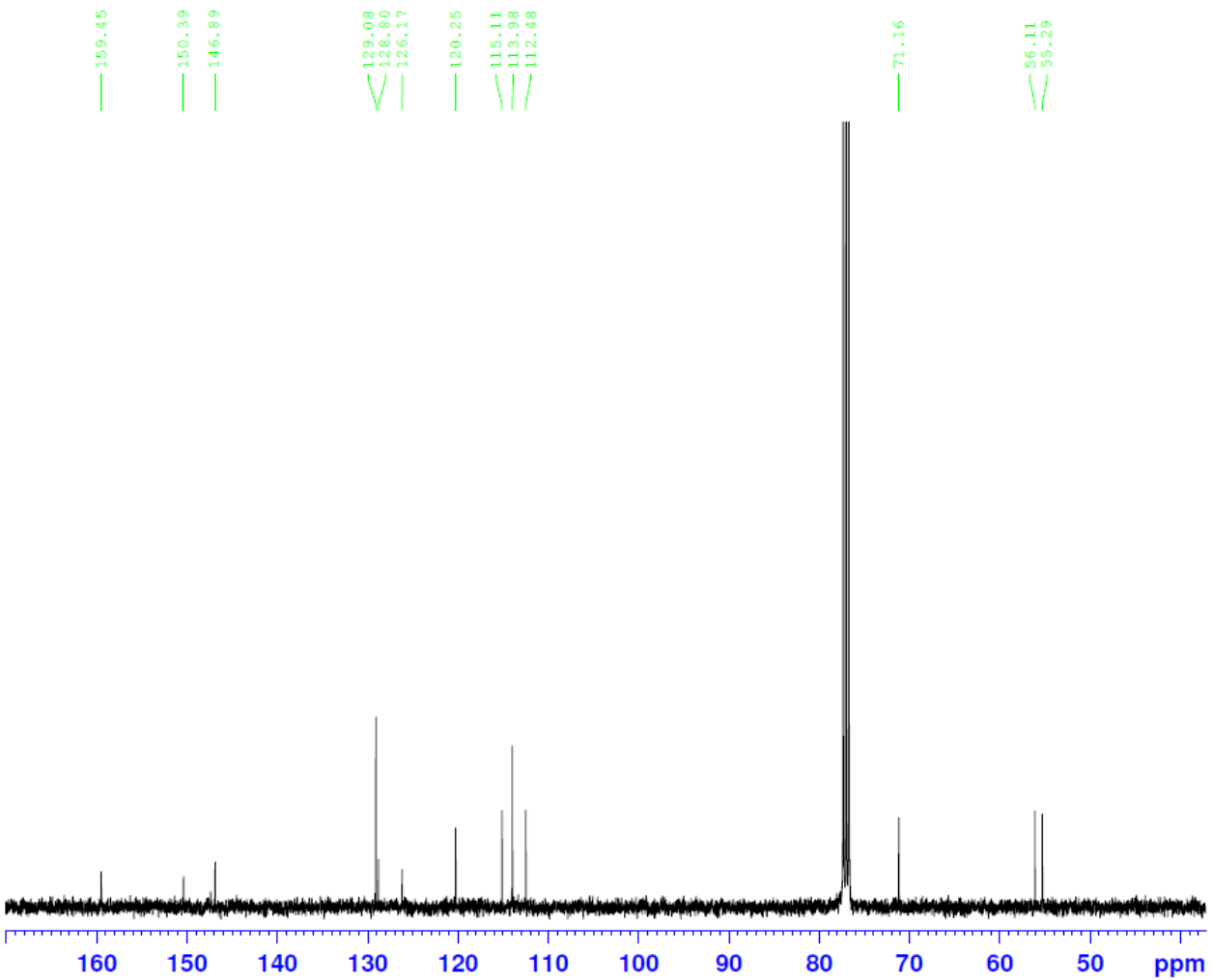


1

4-chloro-22-methoxy-1-[(4-methoxybenzyl)oxy]benzene

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SOLVENT                     CDCl3
NS                           1024
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SWH                    23980.814 Hz
FIDRES                  0.365918 Hz
AQ                      1.3664756 sec
RG                           2048
DW                         20.850 usec
DE                          6.50 usec
TE                         298.3 K
D1                     2.00000000 sec
D11                    0.03000000 sec
TD0                             1

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PL1                          0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
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PCPD2                       80.00 usec
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PL12                        16.06 dB
PL13                        21.00 dB
SFO2                400.1316005 MHz
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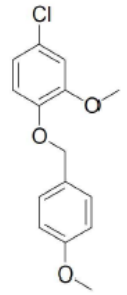

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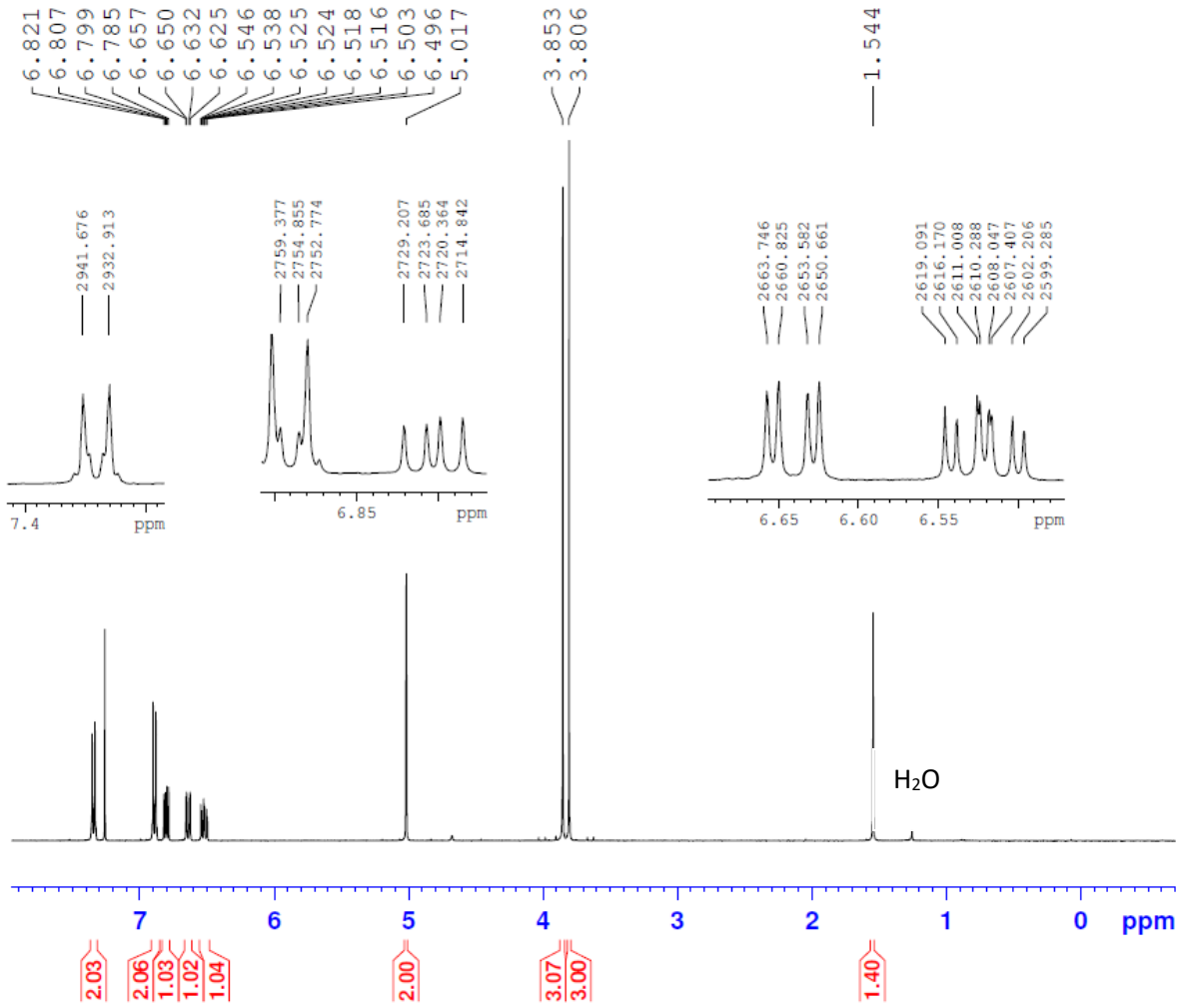
4-fluoro-2-methoxy-1-[(4-methoxybenzyl)oxy]benzene



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FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	2896.3
DW	60.400 use
DE	6.50 use
TE	298.2 K
D1	1.00000000 sec
TD0	1
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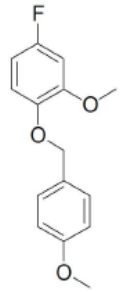
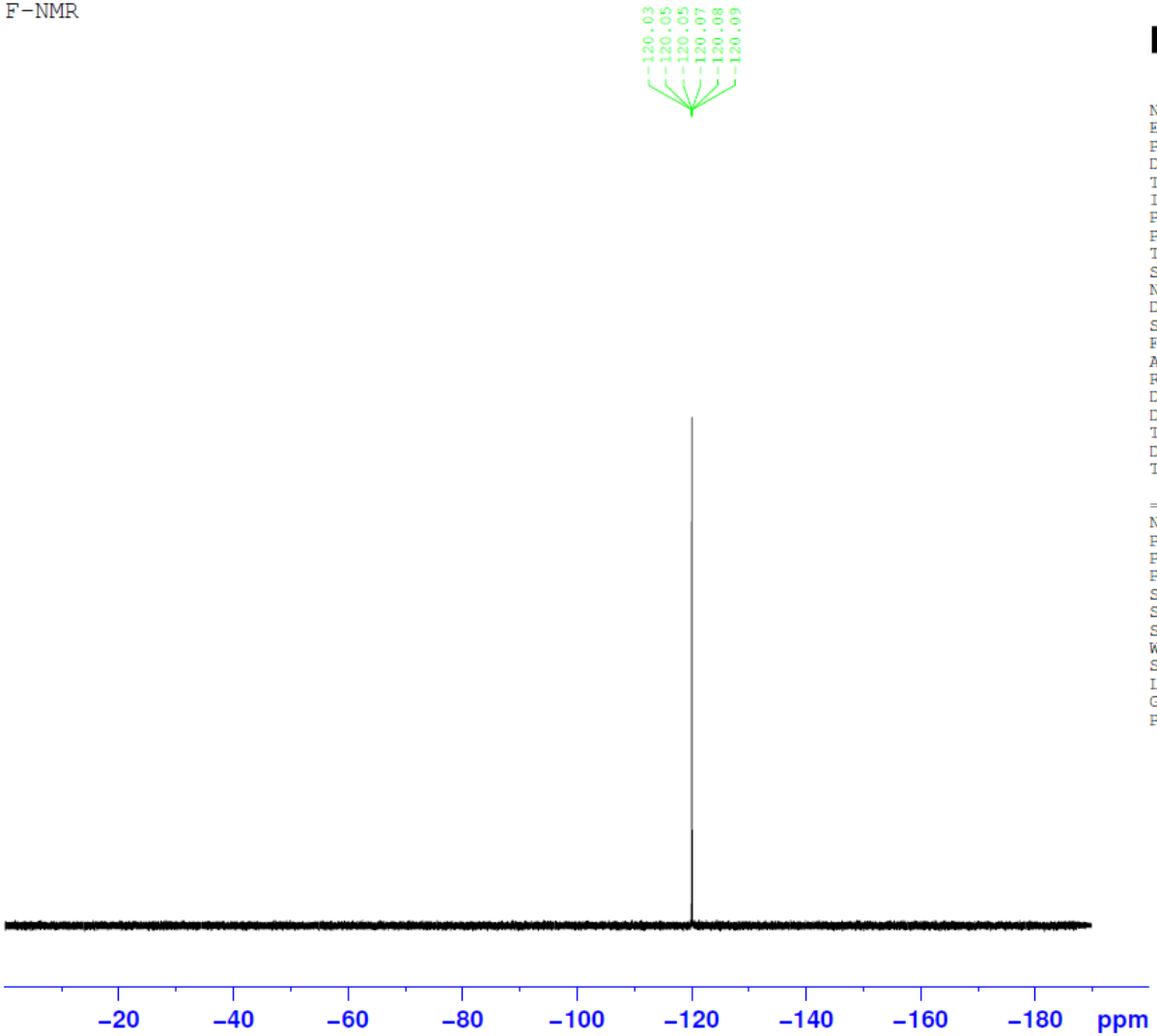


2

UserID s_che SampleID 147pure SupervisorID thoma Lab Phone No. 67990 S
F-NMR



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PROCNO	1
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PULPROG	zg
TD	262144
SOLVENT	CDCl3
NS	64
DS	2
SWH	75187.969 Hz
FIDRES	0.286819 Hz
AQ	1.7433076 sec
RG	2048
DW	6.650 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	19F
P1	10.00 usec
PL1	3.00 dB
PL1W	4.67061329 W
SFO1	376.4644798 MHz
SI	262144
SF	376.4983670 MHz
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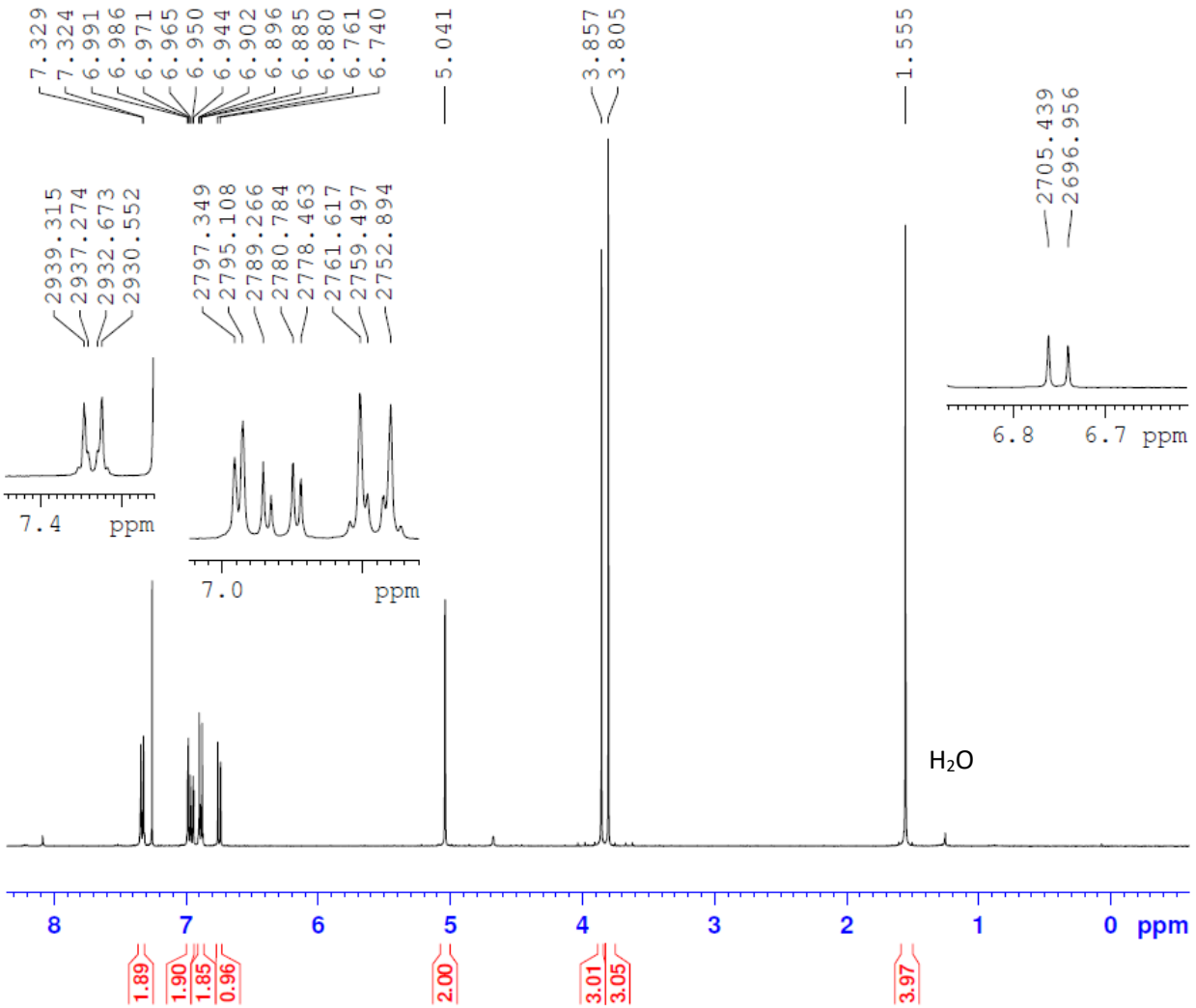
LB	0.80 Hz
GB	0
PC	1.00

4-bromo-2-methoxy-1-[(4-methoxybenzyl)oxy]benzene



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FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	4096
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DE	6.50 usec
TE	298.3 K
D1	1.00000000 sec
TD0	1
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NUC1	1H
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PL1	-1.10 dB
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SI	32768
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GB	0
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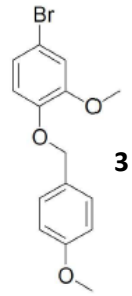
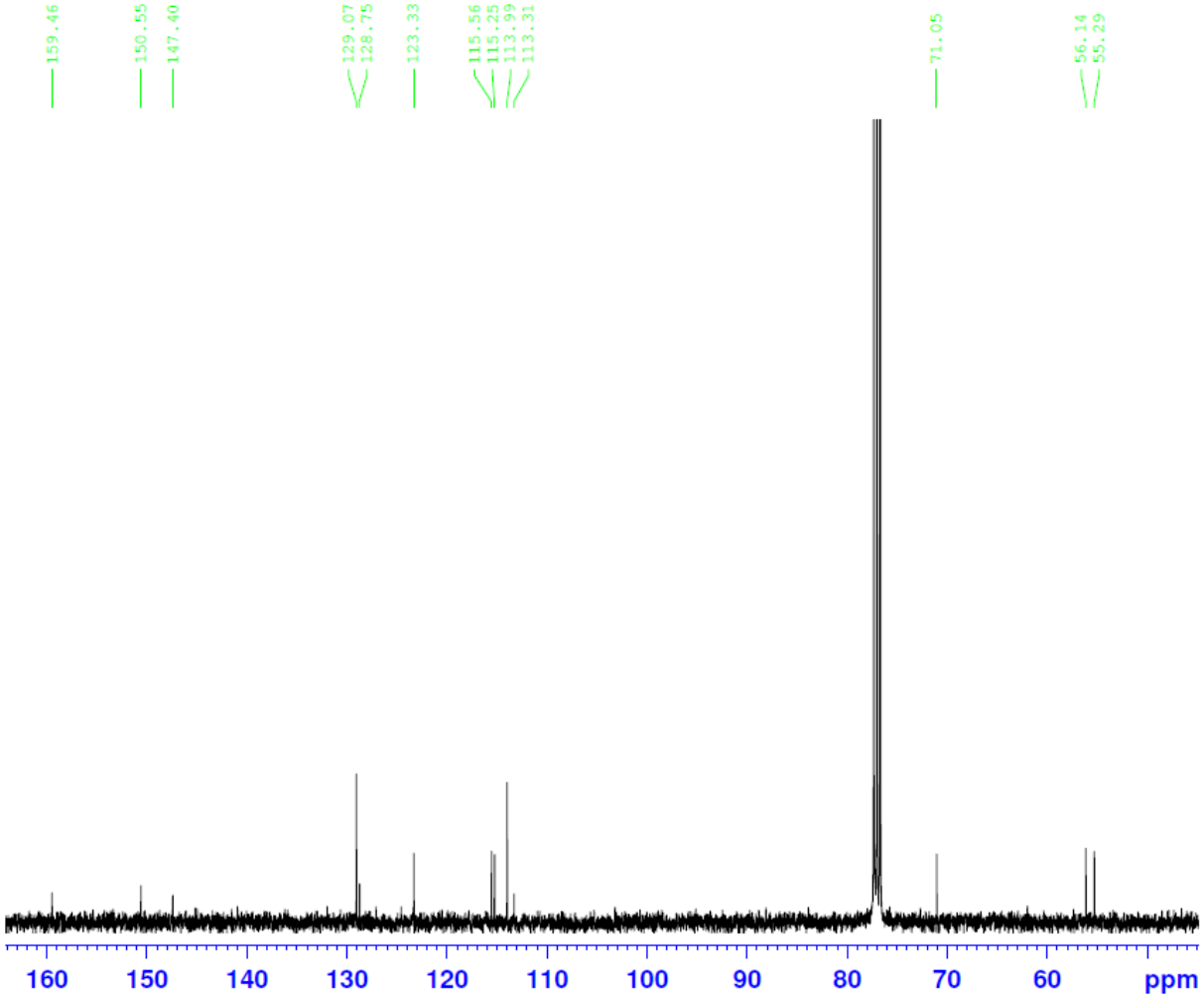


3

4-bromo-2-methoxy-1-[(4-methoxybenzyl)oxy]benzene



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FIDRES	0.365918 Hz
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RG	16384
DW	20.850 usec
DE	6.50 usec
TE	298.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
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PL1	0.00 dB
SFO1	100.6228298 MHz
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CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
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PL12	16.06 dB
PL13	21.00 dB
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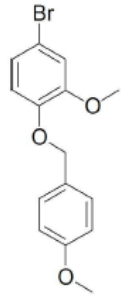
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



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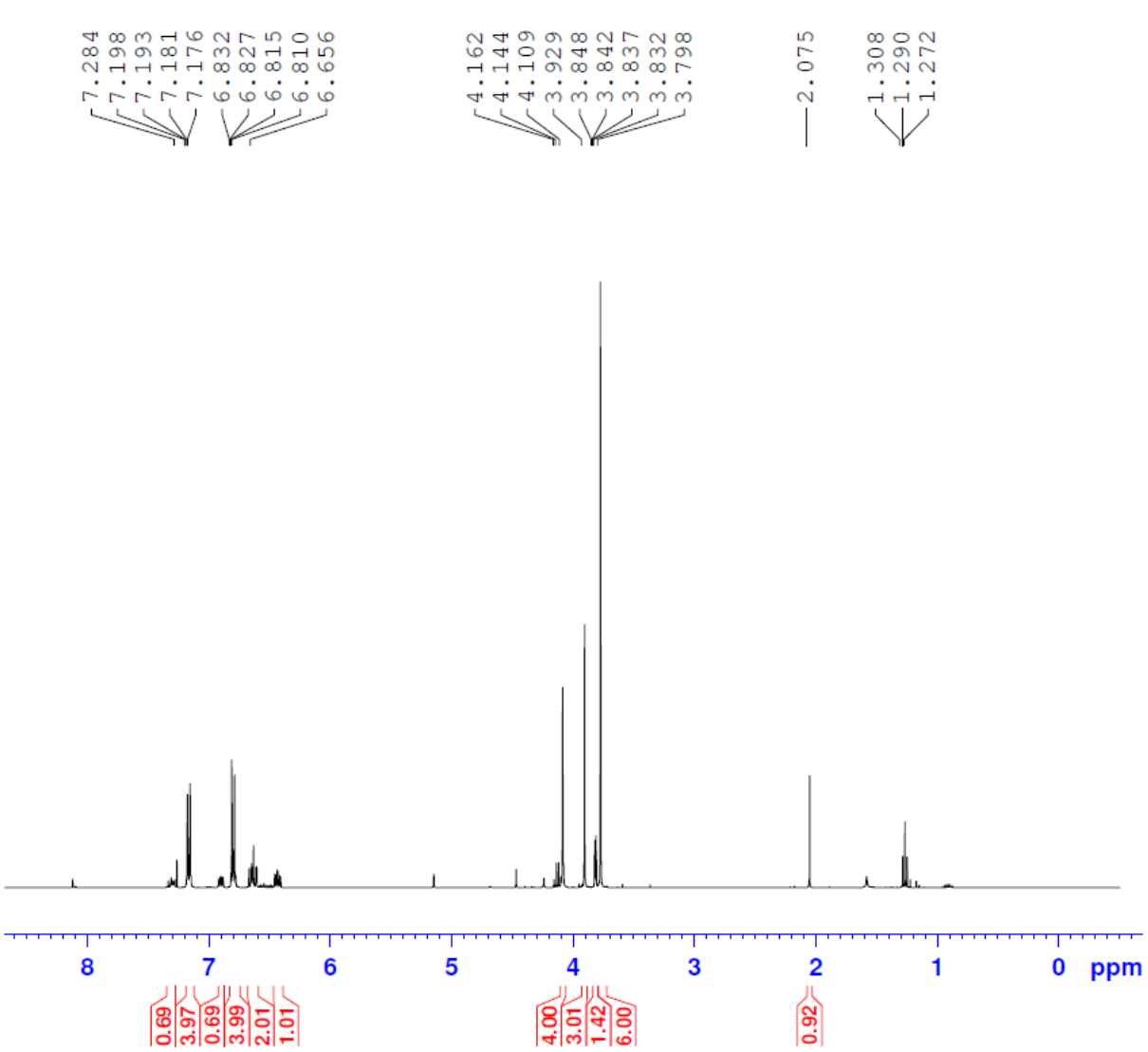

BRUKER

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PULPROG                      zg30
TD                          32768
SOLVENT                     CDCl3
NS                             16
DS                              2
SWH                      4789.272 Hz
FIDRES                   0.146157 Hz
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DE                           6.00 usec
TE                          298.2 K
D1                    1.00000000 sec
TD0                             1

======== CHANNEL f1 ========
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PL1W                 16.00390816 W
SFO1                400.1322007 MHz
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GB                              0
PC                           1.00
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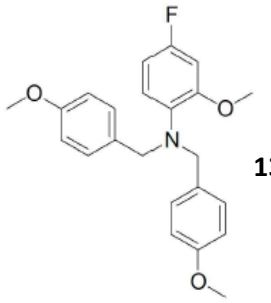
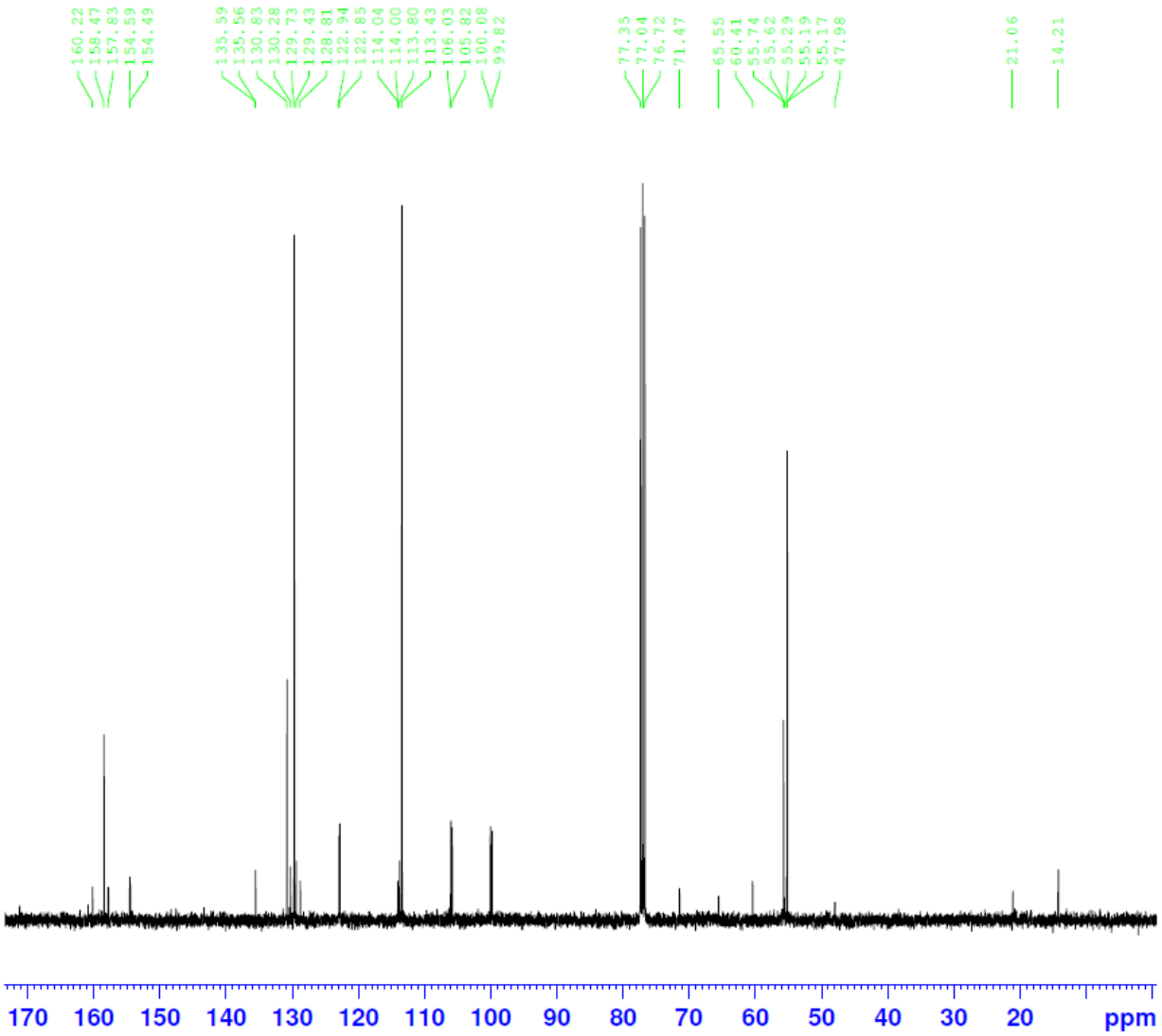


13

4-fluoro-2-methoxy-N-(4-bismethoxybenzyl) aniline



BRUKER

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PROCNO	
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FIDRES	0.766773 Hz
AQ	0.6521332 sec
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DW	19.900 usec
DE	10.00 usec
TE	298.2 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
-------- CHANNEL f1 --------	
NUC1	13C
P1	7.50 usec
PL1	-3.00 dB
PL1W	73.67452240 W
SFO1	100.6238350 MHz
-------- CHANNEL f2 --------	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	-2.00 dB
PL12	17.00 dB
PL13	19.30 dB
PL2W	16.00390816 W
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PL13W	0.11863863 W
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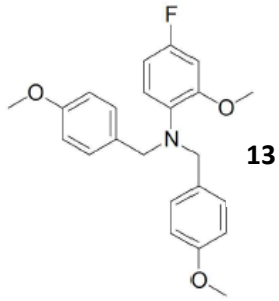
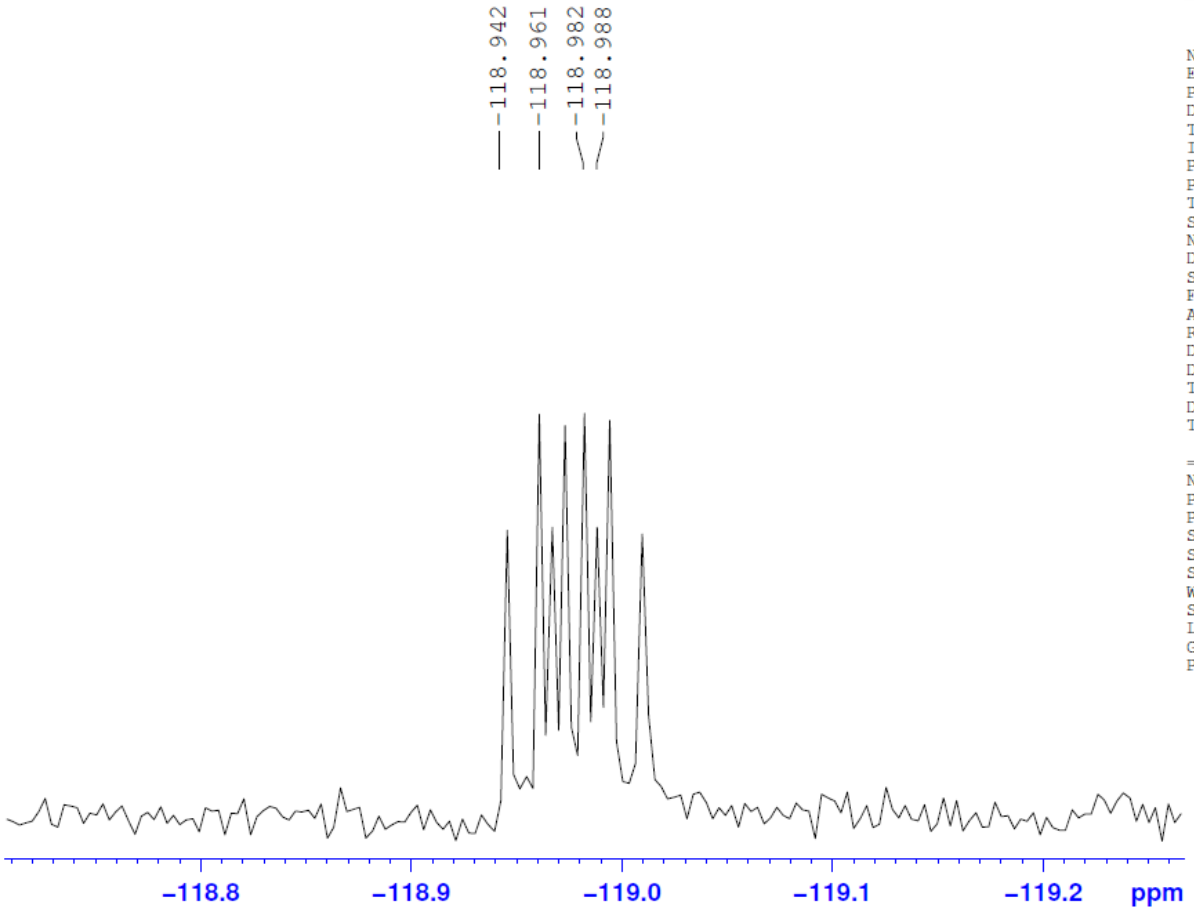


13

4-fluoro-2-methoxy-N-(4-bismethoxybenzyl) aniline

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TD                 131072
SOLVENT              CDCl3
NS                      16
DS                       4
SWH              75187.969 Hz
FIDRES           0.573639 Hz
AQ               0.8716788 sec
RG                   32768
DW                   6.650 usec
DE                    6.50 usec
TE                  298.2 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
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SI                   65536
SF            376.4983660 MHz
WDW                     no
SSB                      0
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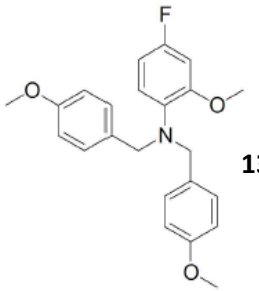
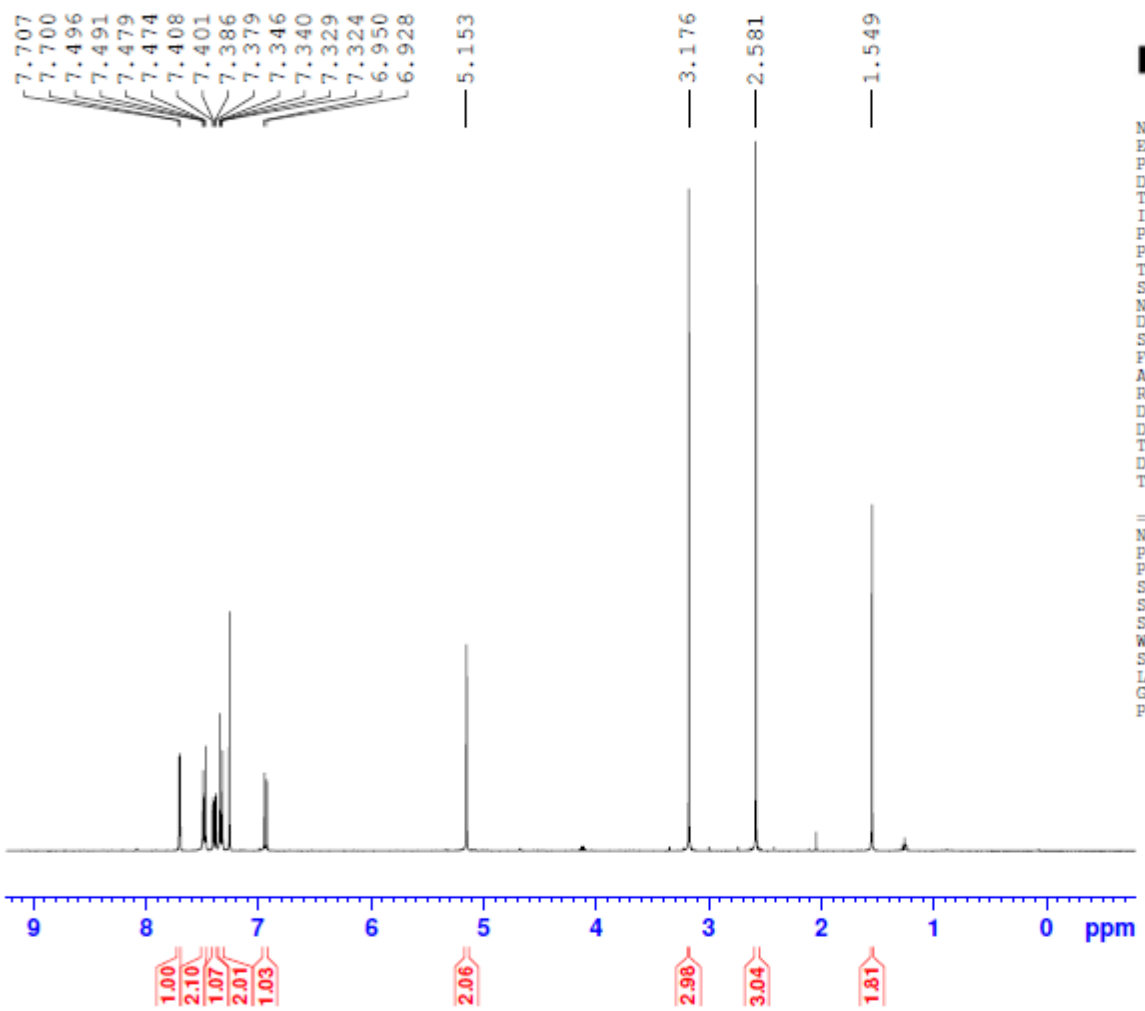
PC                    1.00
```



13

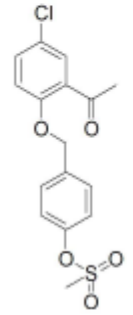


BRUKER

NAME	sc269p
EXPNO	1
PROCNO	1
Date_	20110218
Time	16.15
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	5792
DW	60.400 usec
DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1

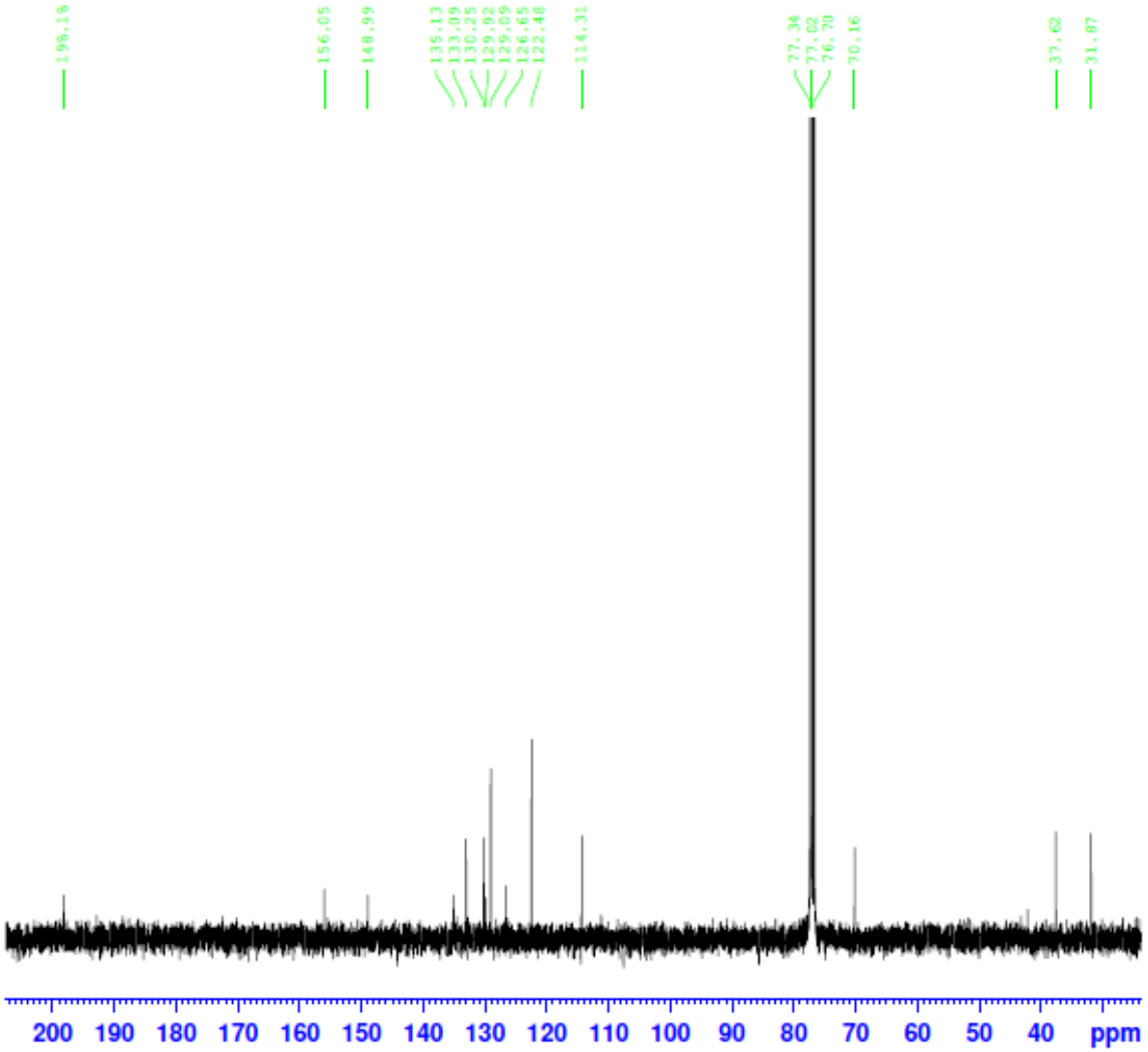
======== CHANNEL f1 ========

NUC1	1H
P1	11.10 usec
PL1	-1.10 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300097 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

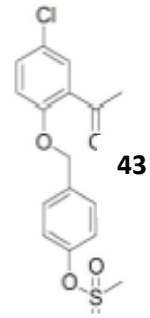


43

4-[(2-acetyl-4-chlorophenoxy) methyl] phenylmethanesulfonate

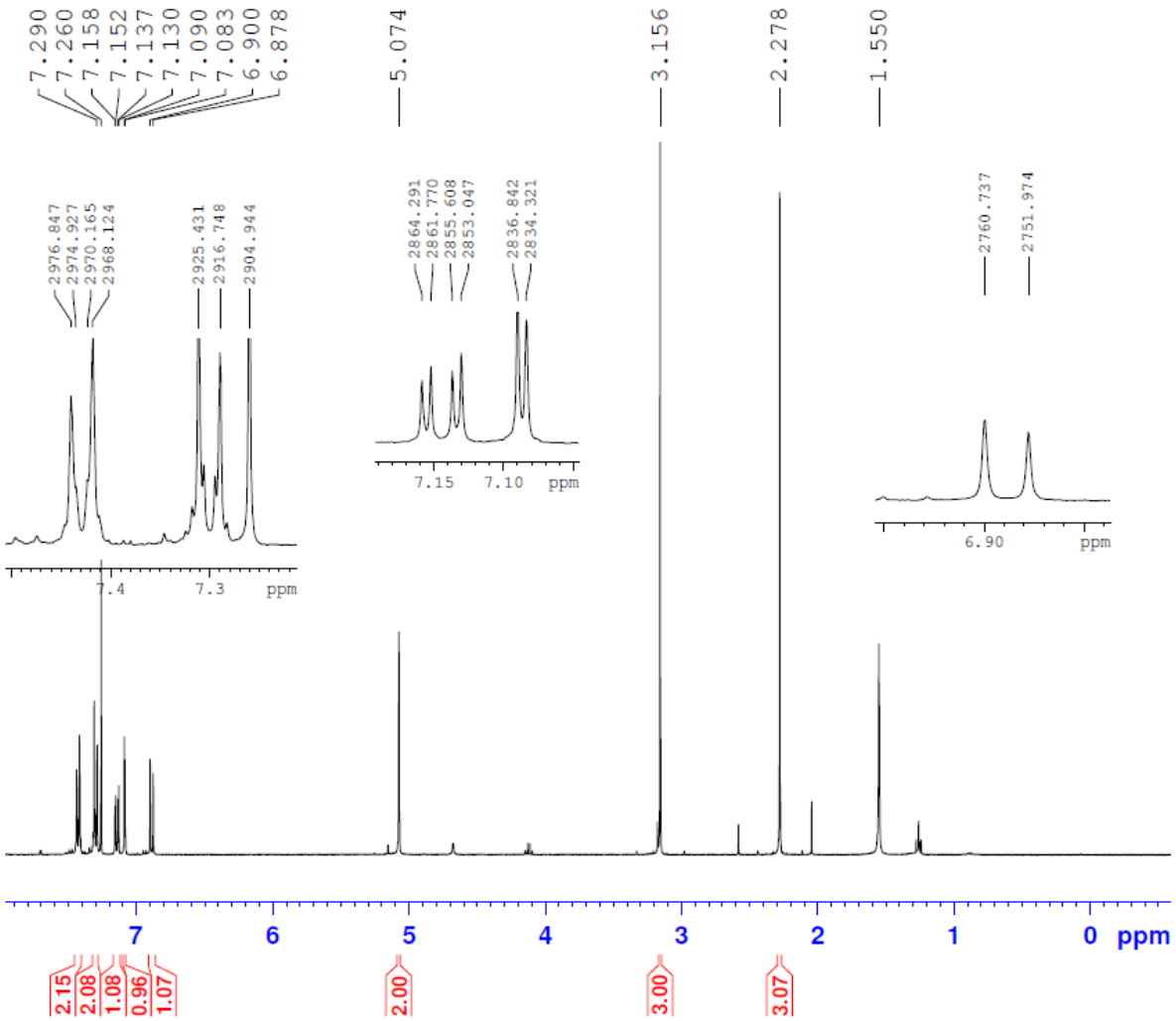


	69p
	2
	1
Date_	20110219
Time	2.19
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	5792
DW	20.850 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.38 usec
PL1	0.00 dB
SFO1	100.6228298 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-1.10 dB
PL12	16.06 dB
PL13	21.00 dB
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	0.50



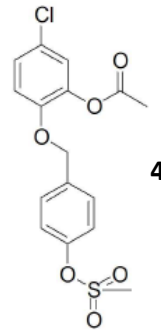
43

5-chloro-2-({4-[(methyl sulfonyl)oxy]benzyl}oxy)phenyl acetate



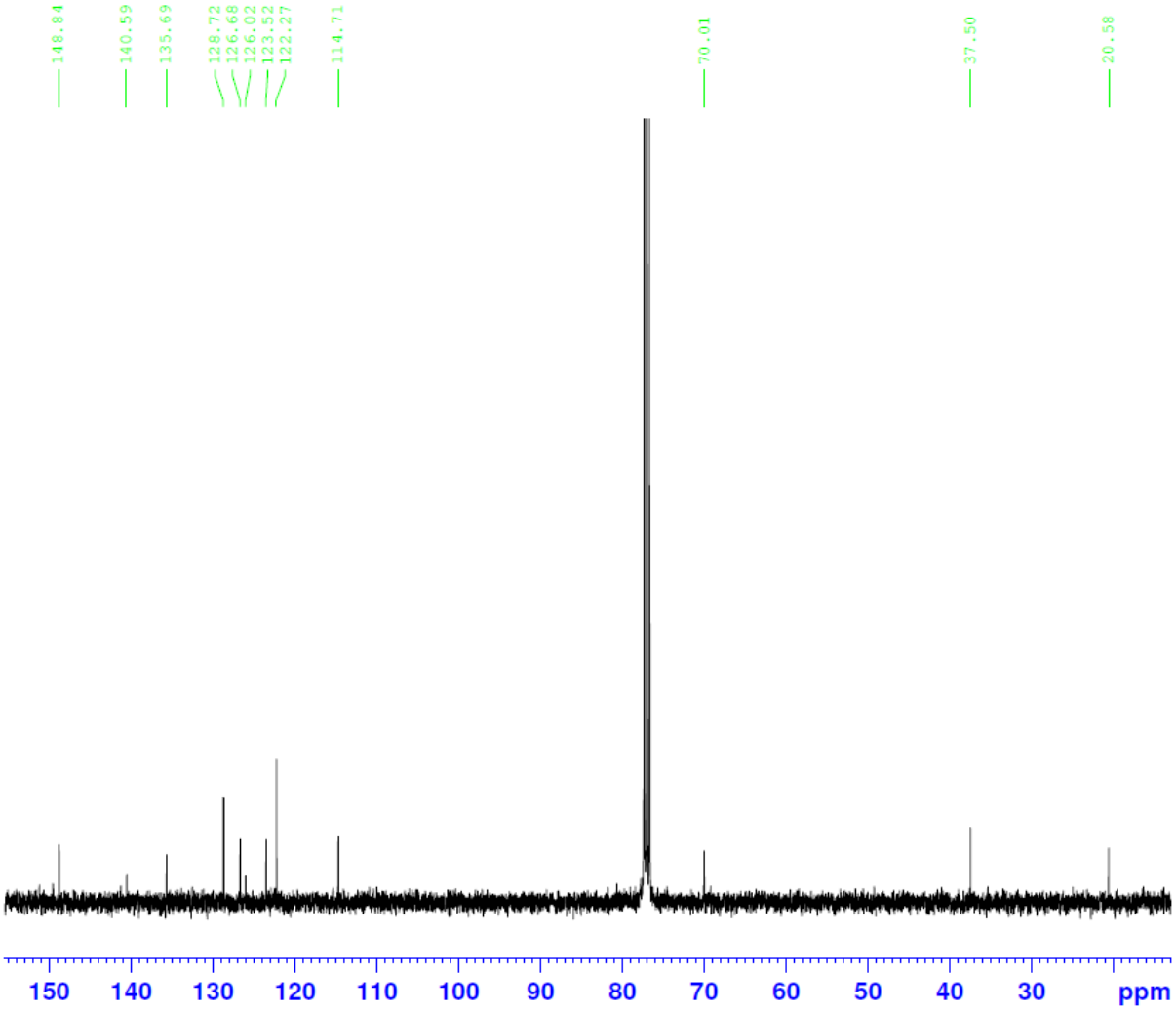
BRUKER

NAME	sc271p spot2
EXPNO	1
PROCNO	1
Date_	20110224
Time	17.02
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	5792
DW	60.400 usec
DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	11.10 usec
PL1	-1.10 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300095 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



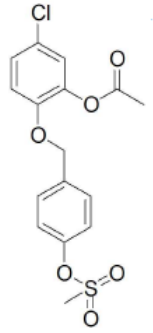
44

5-chloro-2-({4-[(methyl sulfonyl)oxy]benzyl}oxy)phenyl acetate



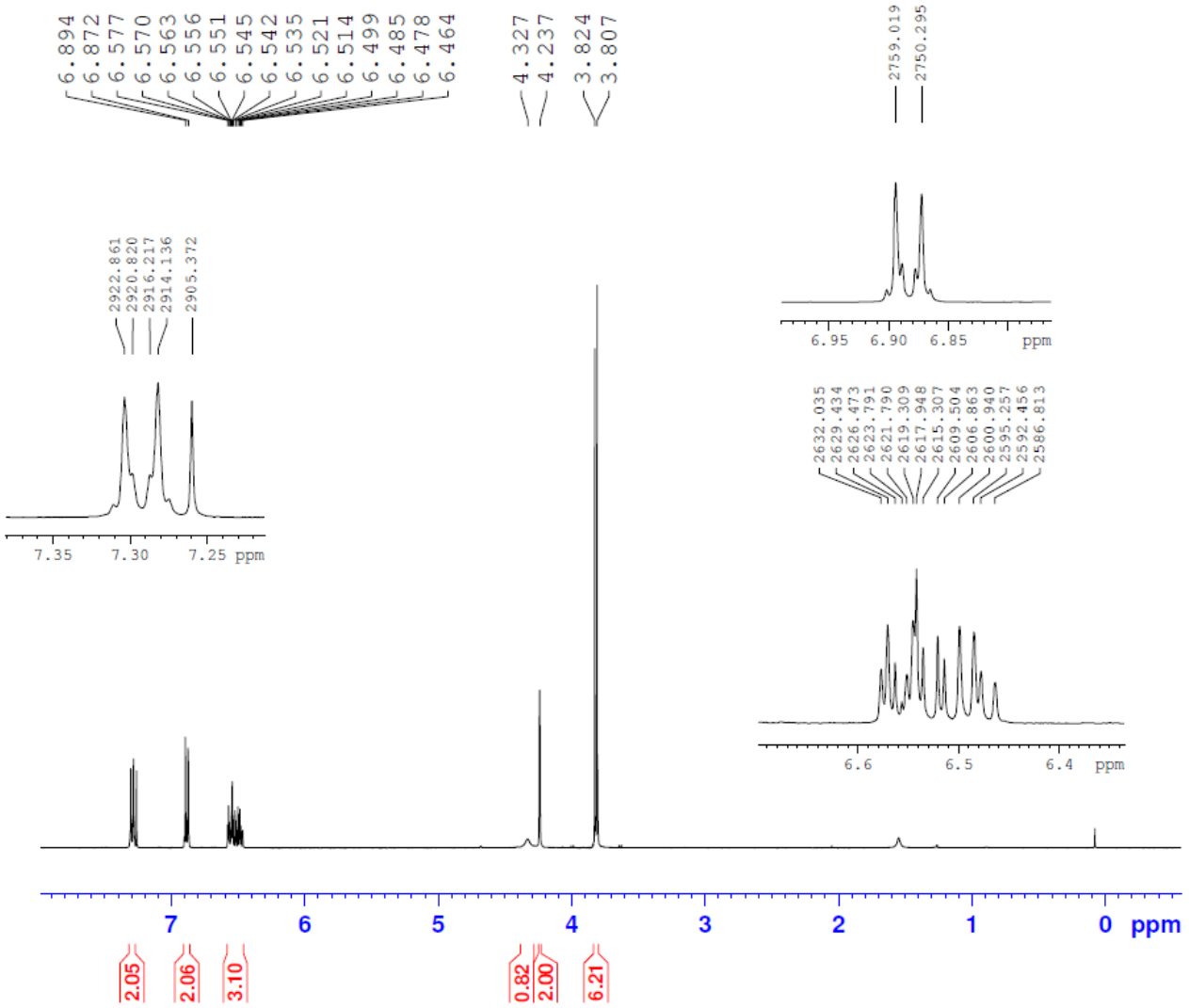
BRUKER

PROCNO	1
Date_	20110225
Time	3.10
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	5792
DW	20.850 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.38 usec
PL1	0.00 dB
SFO1	100.6228298 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-1.10 dB
PL12	16.06 dB
PL13	21.00 dB
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	.40

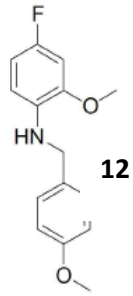


44

4-fluoro-2-methoxy-N-(4-methoxybenzyl)aniline

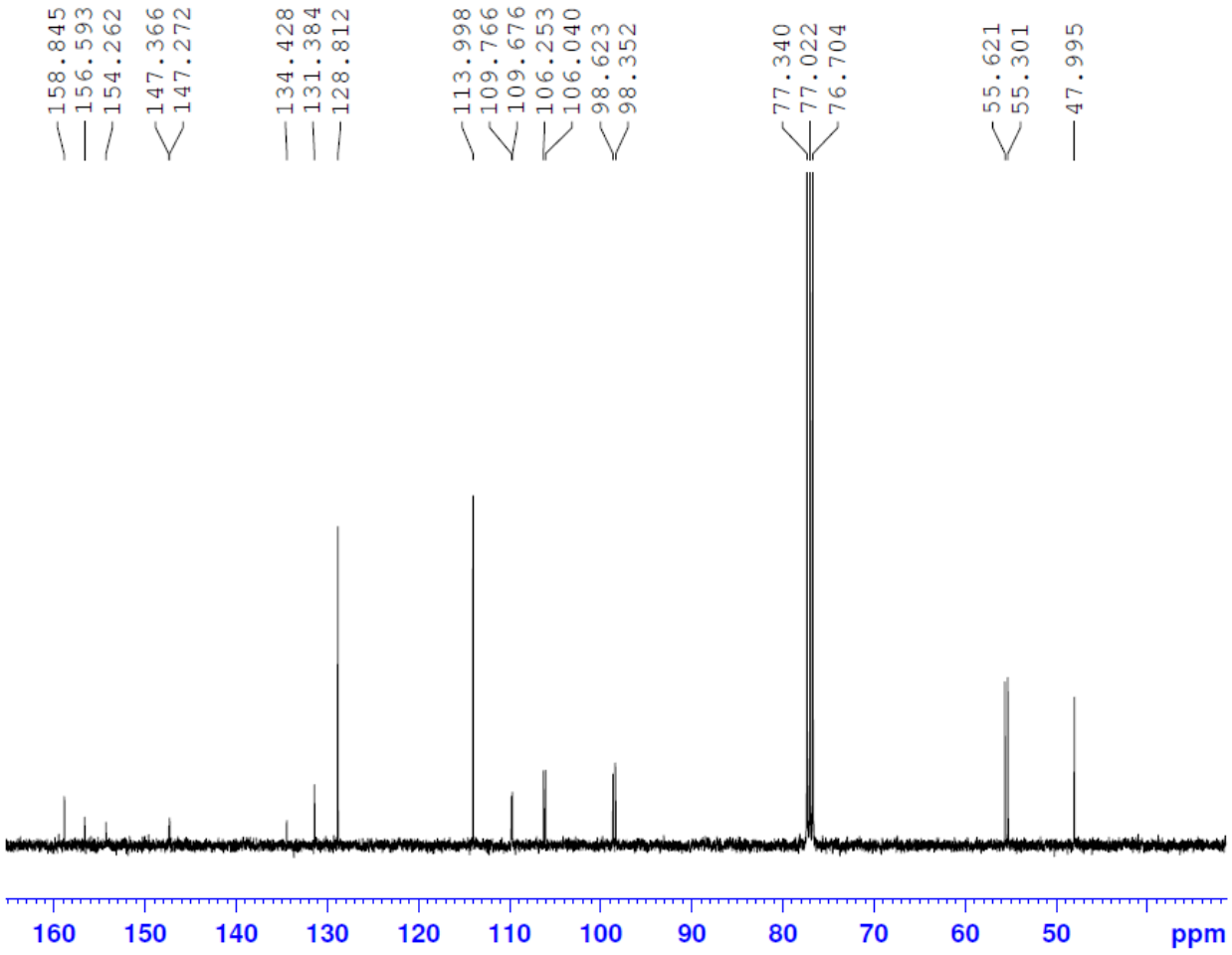


NAME	s_che.272recolumn
EXPNO	1
PROCNO	1
Date_	20110304
Time	11.31
INSTRUM	dpx400
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	645.1
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	13.40 usec
PL1	-6.00 dB
SFO1	400.2024712 MHz
SI	65536
SF	400.2000130 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



12

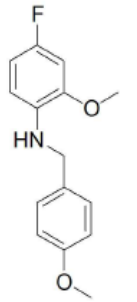
4-fluoro-2-methoxy-N-(4-methoxybenzyl)aniline




```
NAME          s_che.272spot2ppt
EXPNO                        1
PROCNO                       1
Date_                 20110306
Time                      7.29
INSTRUM                 av400
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                       32768
SOLVENT                  CDCl3
NS                        1024
DS                           2
SWH                25125.629 Hz
FIDRES              0.766773 Hz
AQ                  0.6521332 sec
RG                    20642.5
DW                     19.900 usec
DE                     10.00 usec
TE                     298.2 K
D1                1.00000000 sec
D11               0.03000000 sec
TD0                          1

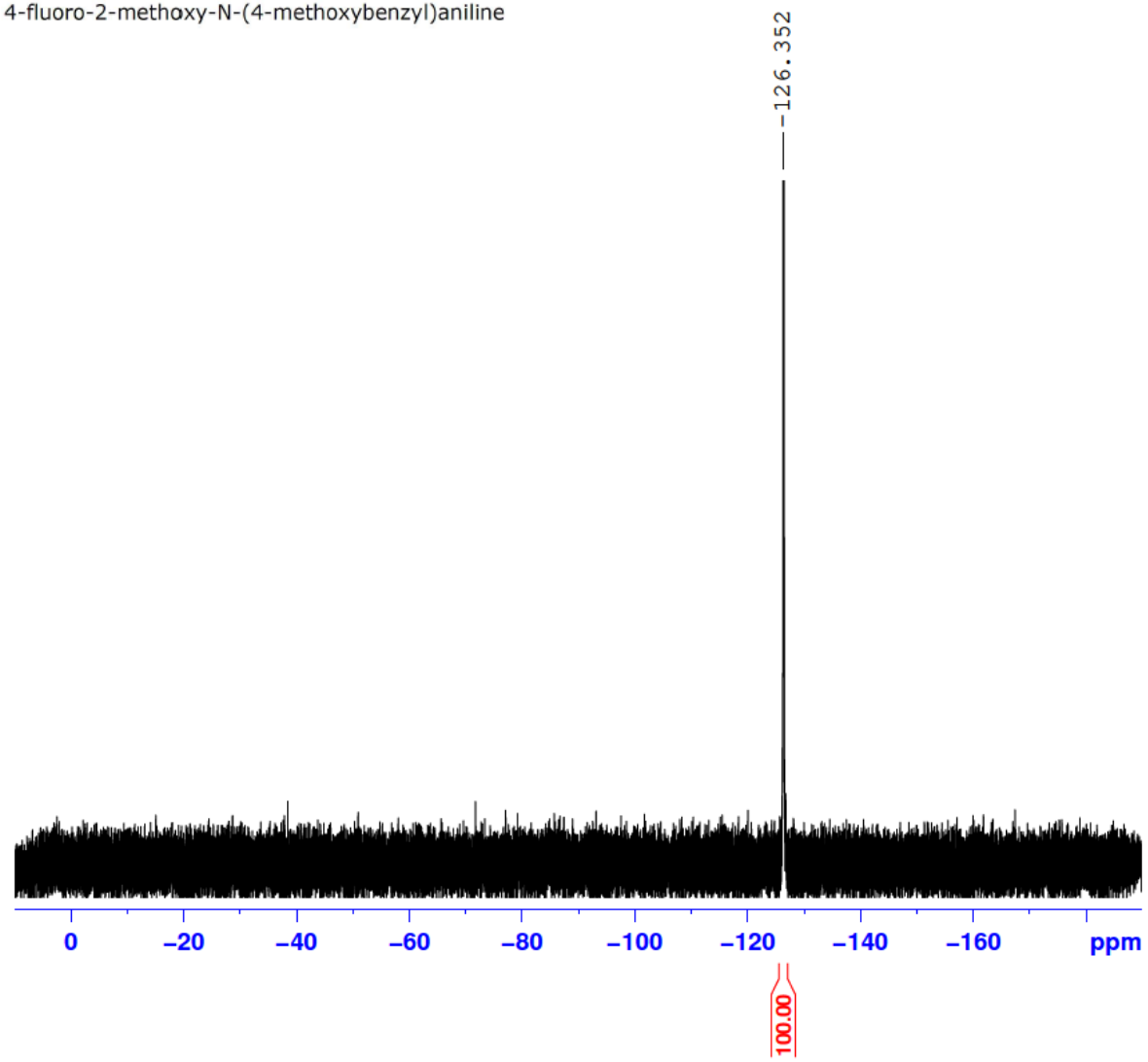
======== CHANNEL f1 ========
NUC1                       13C
P1                        7.50 usec
PL1                      -3.00 dB
PL1W              73.67452240 W
SFO1             100.6238350 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   100.00 usec
PL2                      -2.00 dB
PL12                     17.00 dB
PL13                     19.30 dB
PL2W              16.00390816 W
PL12W              0.20147727 W
PL13W              0.11863863 W
SFO2             400.1316005 MHz
SI                       32768
SF               100.6127690 MHz
WDW                        EM
SSB                         0
LB                       1.00 Hz
GB                          0
PC                       1.40
```



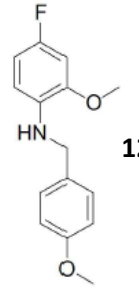
12

4-fluoro-2-methoxy-N-(4-methoxybenzyl)aniline



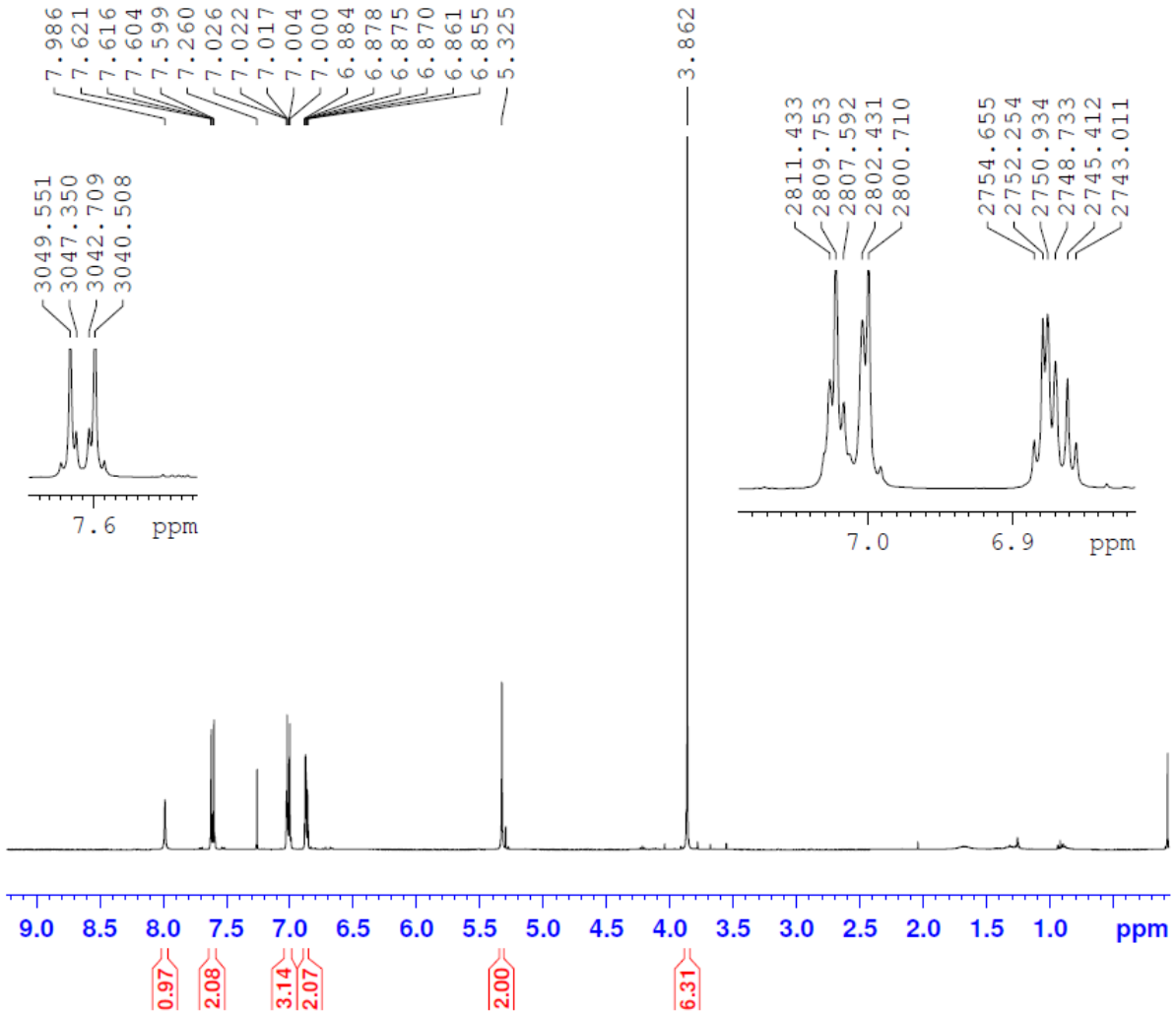

```
NAME        s_che.272spot2ppt
EXPNO                       2
PROCNO                      1
Date_                20110305
Time                     8.14
INSTRUM                av400
PROBHD    5 mm PABBO BB-
PULPROG                    zg
TD                     262144
SOLVENT                CDCl3
NS                         64
DS                          2
SWH                 75187.969 Hz
FIDRES                0.286819 Hz
AQ                    1.7433076 sec
RG                         2048
DW                        6.650 usec
DE                         6.50 usec
TE                       298.2 K
D1                   2.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       19F
P1                       10.00 usec
PL1                       3.00 dB
PL1W                4.67061329 W
SFO1               376.4644798 MHz
SI                     262144
SF                 376.4983670 MHz
WDW                        EM
SSB                         0
LB                       0.80 Hz
GB                          0
PC                       1.00
```



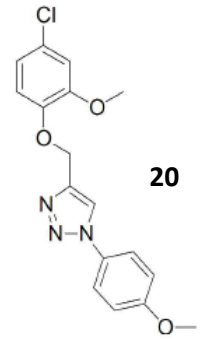
12

4-[(4-chloro-2-methoxyphenoxy)methyl]-1-(4-methoxyphenyl)-1-H-1,2,3 triazole



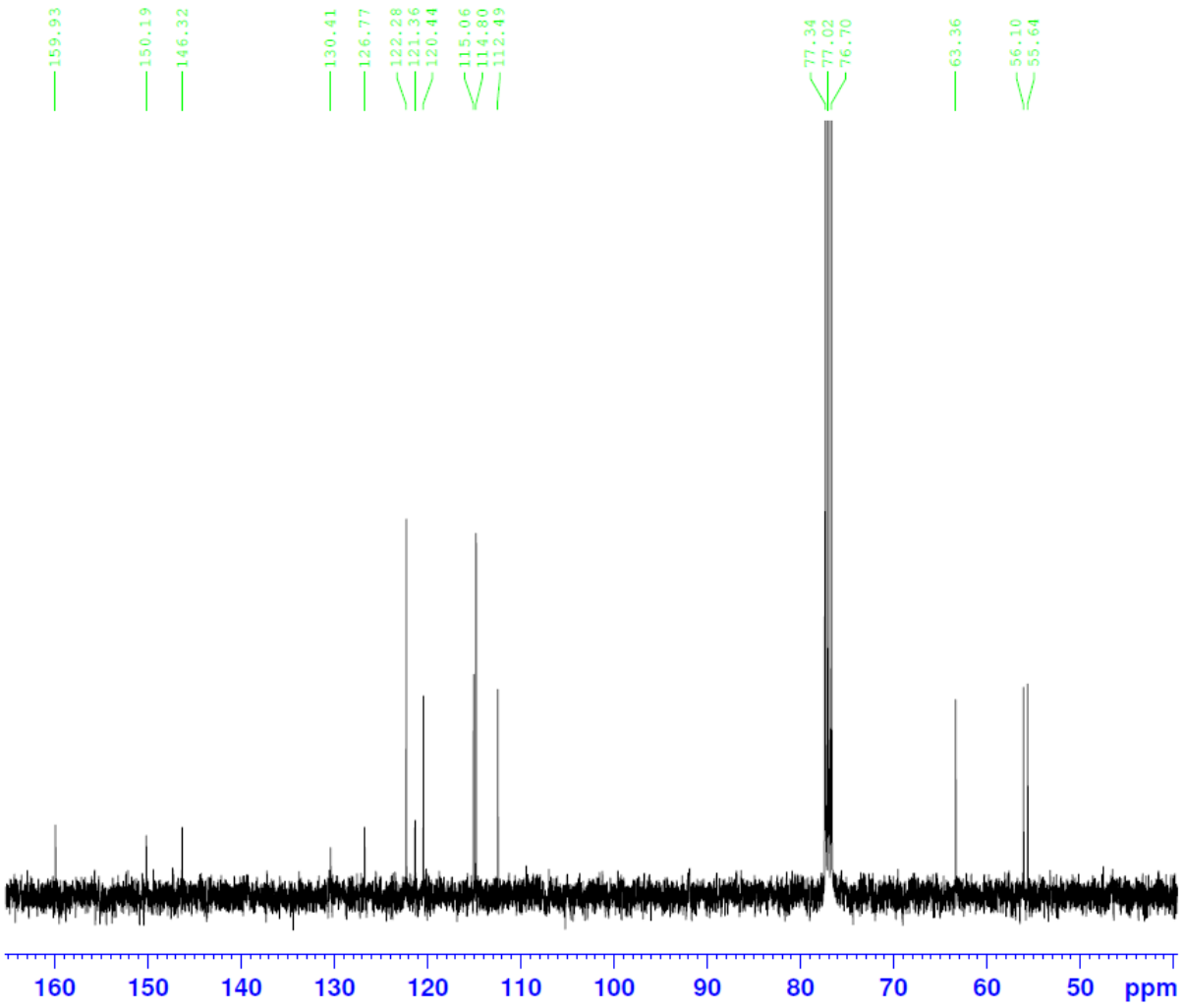
BRUKER

NAME	s_che.sample120p
EXPNO	1
PROCNO	1
Date_	20100209
Time	12.54
INSTRUM	av400
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	181
DW	104.400 usec
DE	6.00 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1
========	CHANNEL f1 ========
NUC1	1H
P1	9.60 usec
PL1	-3.00 dB
PL1W	20.14772606 W
SFO1	400.1322007 MHz
SI	32768
SF	400.1300094 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

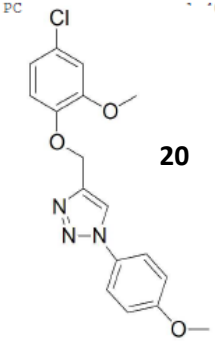


20

4-[(4-chloro-2-methoxyphenoxy)methyl]-1-(4-methoxyphenyl)-1-H-1,2,3 triazole

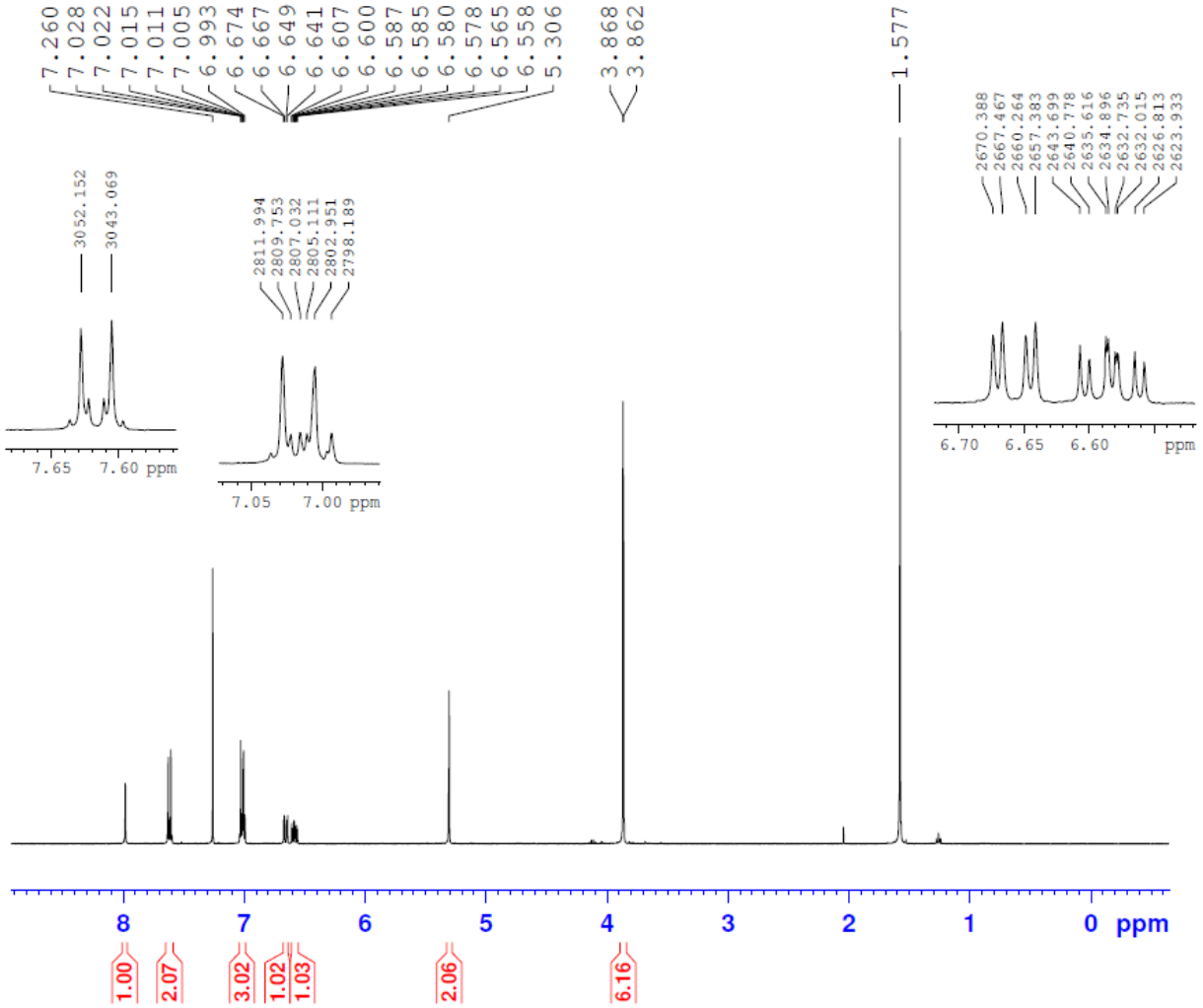


EXPNO	1
PROCNO	1
Date_	20110309
Time	18.47
INSTRUM	av400
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDC13
NS	1024
DS	2
SWH	25125.629 Hz
FIDRES	0.766773 Hz
AQ	0.6521332 sec
RG	14596.5
DW	19.900 usec
DE	10.00 usec
TE	298.2 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	7.50 usec
PL1	-3.00 dB
PL1W	73.67452240 W
SFO1	100.6238350 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	-2.00 dB
PL12	17.00 dB
PL13	19.30 dB
PL2W	16.00390816 W
PL12W	0.20147727 W
PL13W	0.11863863 W
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



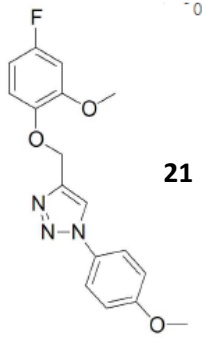
20

4-[(4-fluoro-2-methoxyphenoxy)methyl-1-(4methoxyphenyl)-1H-1,2,3-triazole



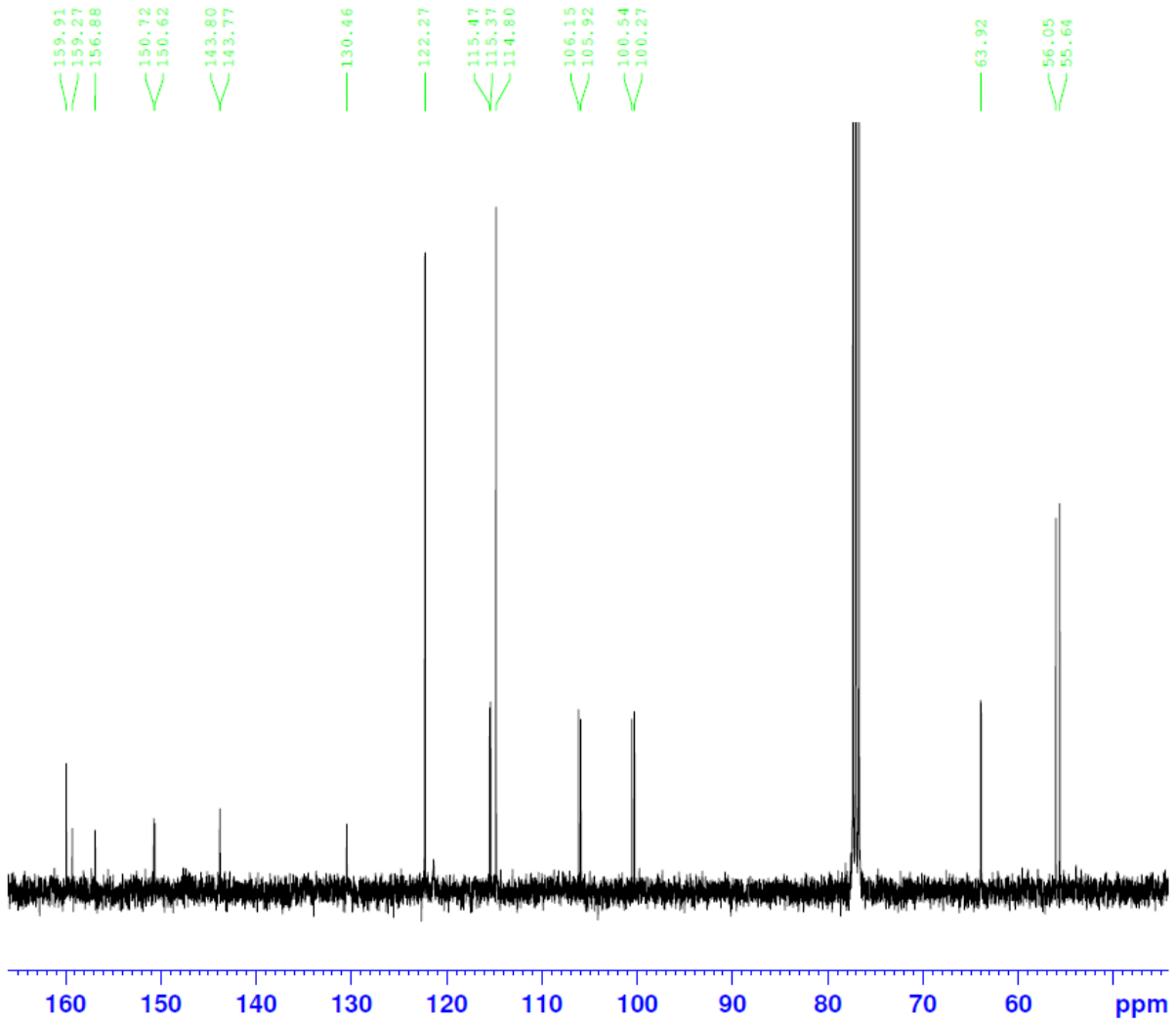
BRUKER

NAME	sc162pure
EXPNO	1
PROCNO	1
Date_	20100610
Time	16.15
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 se
RG	1448
DW	60.400 us
DE	6.50 us
TE	298.0 K
D1	1.00000000 se
TD0	1
======== CHANNEL f1 =======	
NUC1	1H
P1	11.10 us
PL1	-1.10 dB
SFO1	400.1324710 MH
SI	32768
SF	400.1300095 MH
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	0



21

4-[(4-fluoro-2-methoxyphenoxy)methyl-1-(4methoxyphenyl)-1H-1,2,3-triazole

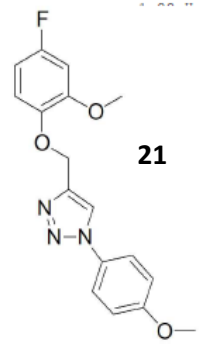


BRUKER

```
NAME          s_che.162p_2
EXPNO                    1
PROCNO                   1
Date_             20110309
Time                 19.22
INSTRUM              av400
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 32768
SOLVENT             CDCl3
NS                   1024
DS                      2
SWH           25125.629 Hz
FIDRES         0.766773 Hz
AQ             0.6521332 sec
RG               20642.5
DW                19.900 usec
DE                10.00 usec
TE                298.2 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

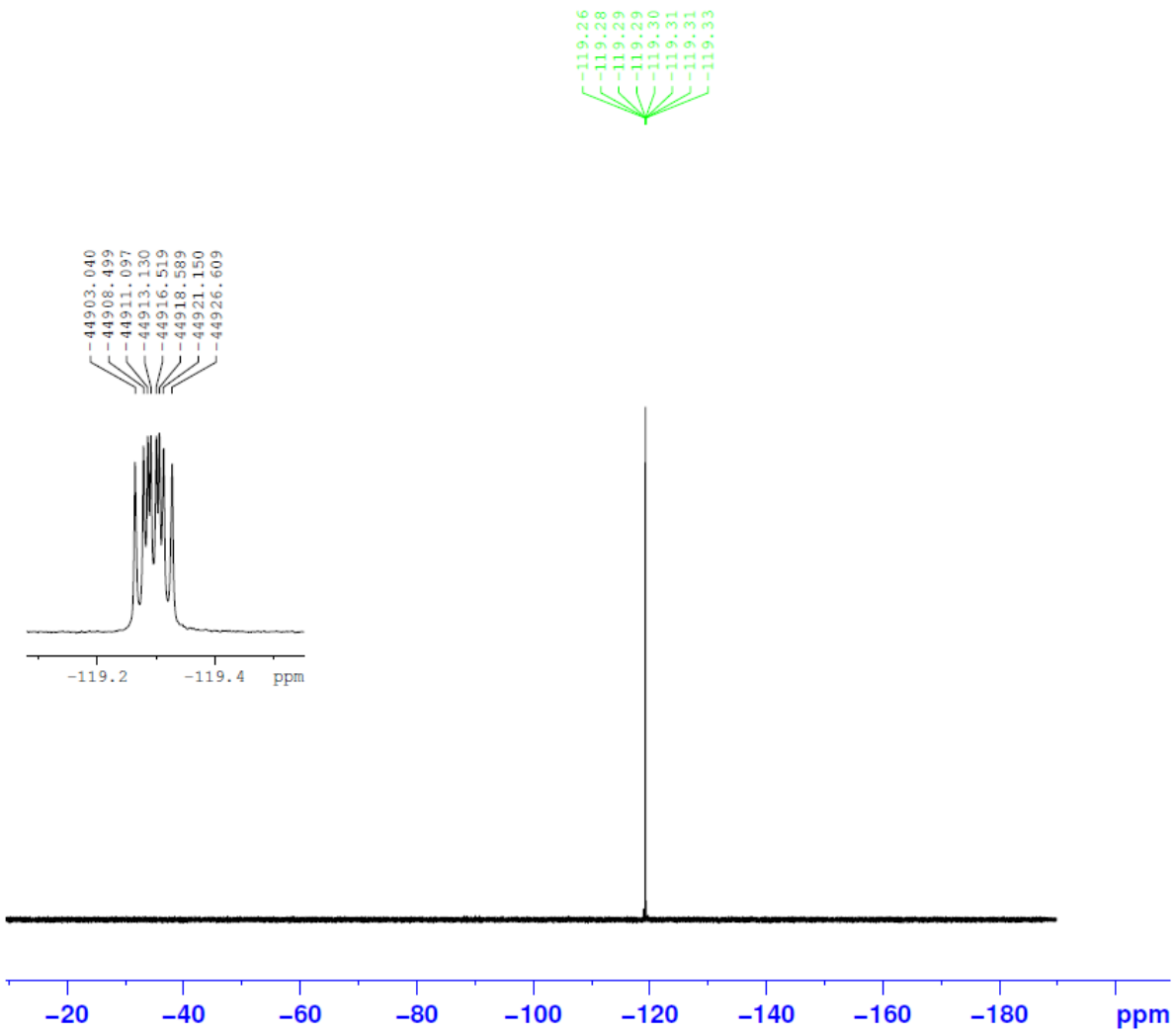
======== CHANNEL f1 ========
NUC1                  13C
P1                   7.50 usec
PL1                 -3.00 dB
PL1W         73.67452240 W
SFO1        100.6238350 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                 -2.00 dB
PL12                17.00 dB
PL13                19.30 dB
PL2W         16.00390816 W
PL12W         0.20147727 W
PL13W         0.11863863 W
SFO2        400.1316005 MHz
SI                 32768
SF          100.6127690 MHz
WDW                   EM
SSB                    0
LB
GB
PC
```



21

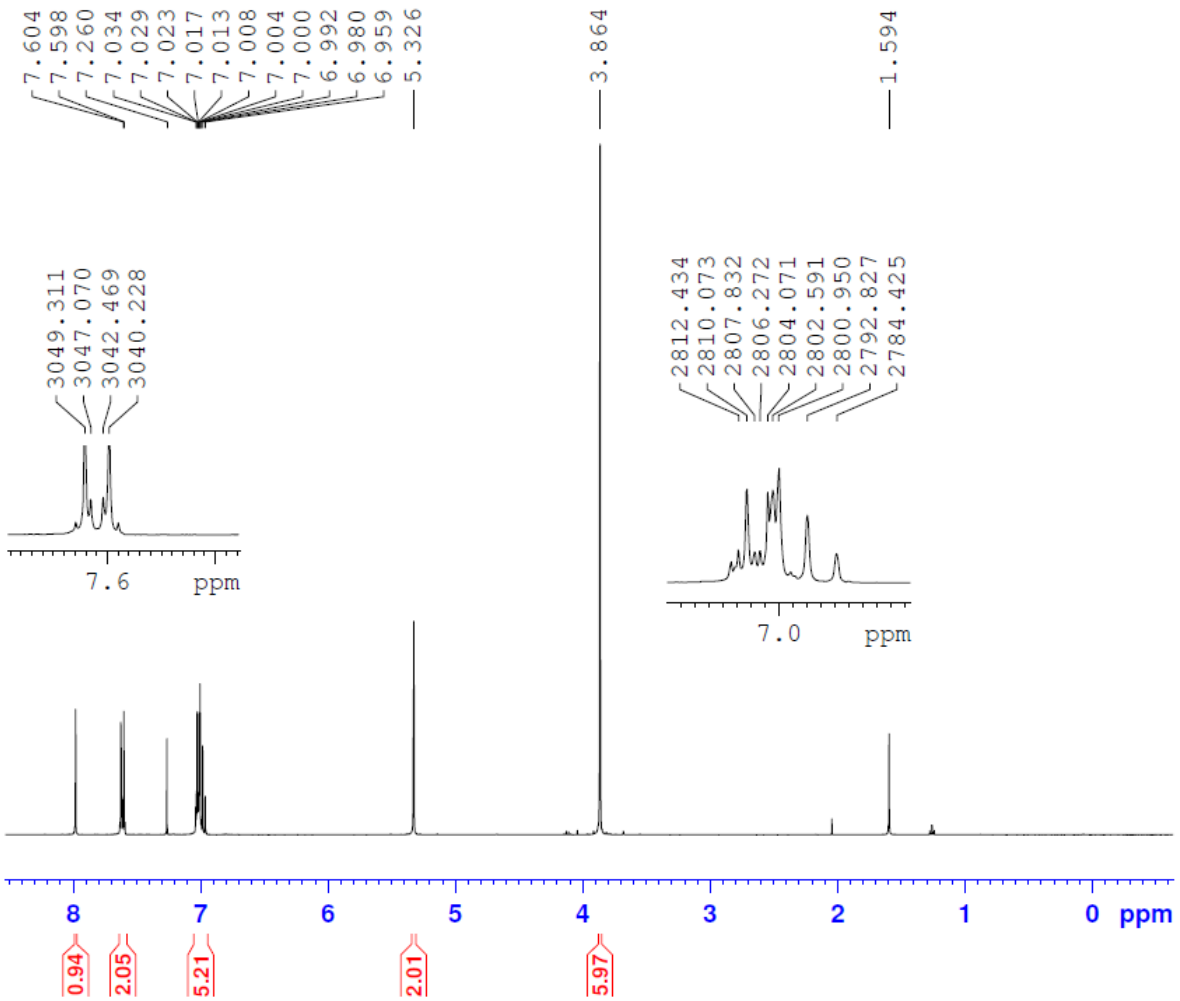
4-[(4-fluoro-2-methoxyphenoxy)methyl-1-(4methoxyphenyl)-1H-1,2,3-triazole



NAME	s_cne.16zp_4
EXPNO	2
PROCNO	1
Date_	20110309
Time	8.21
INSTRUM	av400
PROBHD	5 mm PABBO BB-
PULPROG	zg
TD	262144
SOLVENT	CDCl3
NS	16
DS	2
SWH	75187.969 Hz
FIDRES	0.286819 Hz
AQ	1.7433076 se
RG	2298.8
DW	6.650 us
DE	6.50 us
TE	298.2 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 ======	
NUC1	19F
P1	10.00 us
PL1	3.00 dB
PL1W	4.67061329 W
SFO1	376.4644798 MH
SI	262144
SF	376.4983670 MH
WDW	EM
SSB	0
LB	0.80 Hz
GB	0
PC	1.00

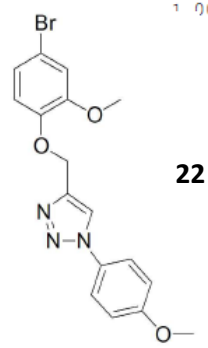
21

4-[(4-bromo-2-methoxyphenoxy)methyl-1-(4methoxyphenyl)-1H-1,2,3-triazole



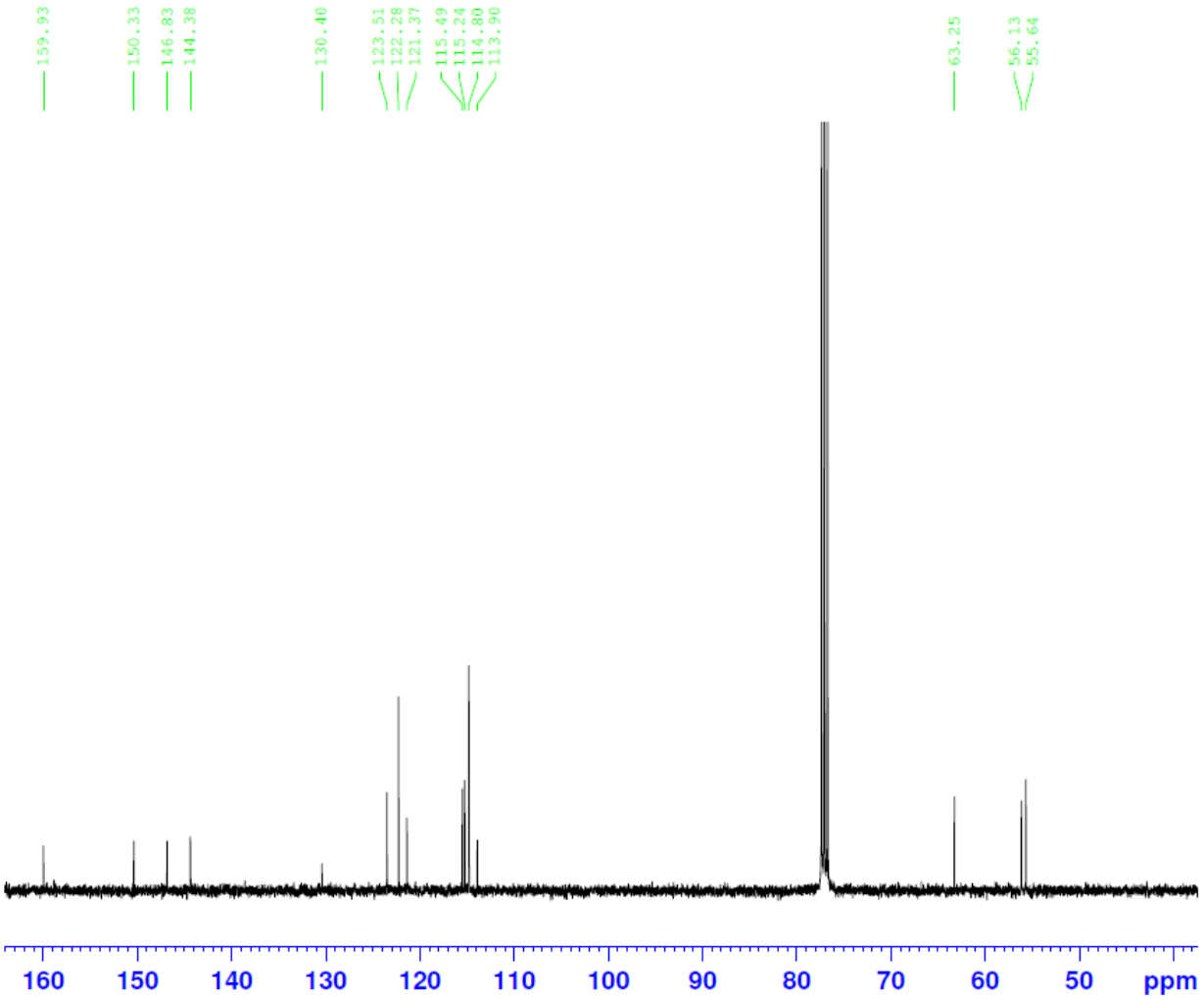
BRUKER

NAME	sc163p_2
EXPNO	1
PROCNO	1
Date_	20110310
Time	10.03
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	4096
DW	60.400 usec
DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	11.10 usec
PL1	-1.10 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300095 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



22

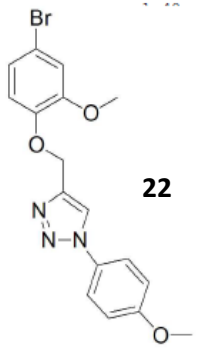
4-[(4-bromo-2-methoxyphenoxy)methyl-1-(4methoxyphenyl)-1H-1,2,3-triazole




```
NAME                sc163p_2
EXPNO                      2
PROCNO                     1
Date_               20110310
Time                   23.08
INSTRUM                spect
PROBHD    5 mm QNP 1H/13
PULPROG             zgpg30
TD                      65536
SOLVENT                CDC13
NS                      1024
DS                         4
SWH               23980.814 Hz
FIDRES             0.365918 Hz
AQ                 1.3664756 sec
RG                      8192
DW                    20.850 usec
DE                     6.50 usec
TE                    298.2 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                        1

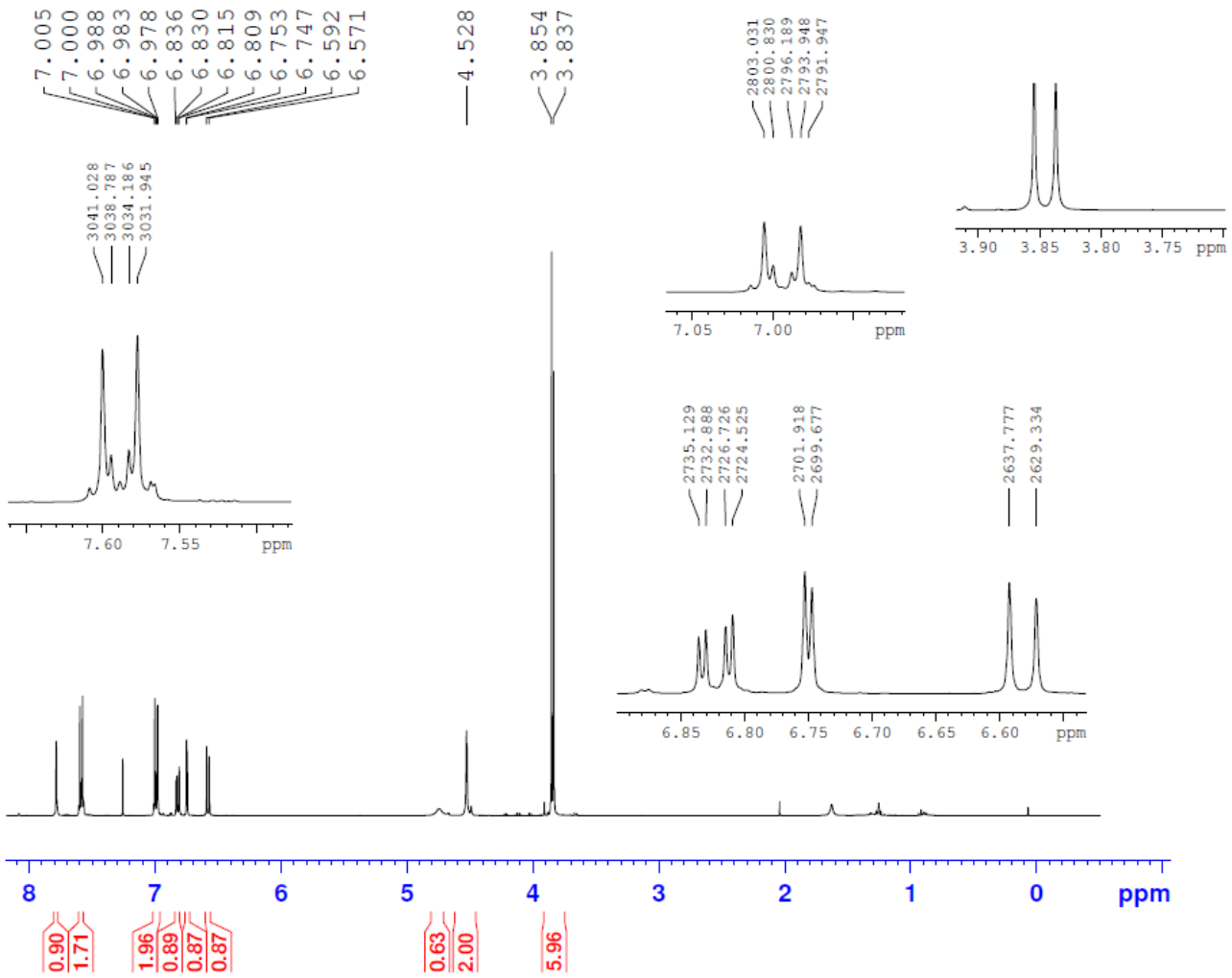
======== CHANNEL f1 ========
NUC1                     13C
P1                      9.38 usec
PL1                     0.00 dB
SFO1            100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -1.10 dB
PL12                  16.06 dB
PL13                  21.00 dB
SFO2            400.1316005 MHz
SI                     32768
SF              100.6127690 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC
```



22

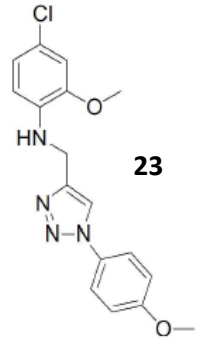
4-chloro-2-methoxy-N-{[1-4-methoxyphenyl)-1H-1,2,3 triazol-4-yl]methyl} aniline



BRUKER

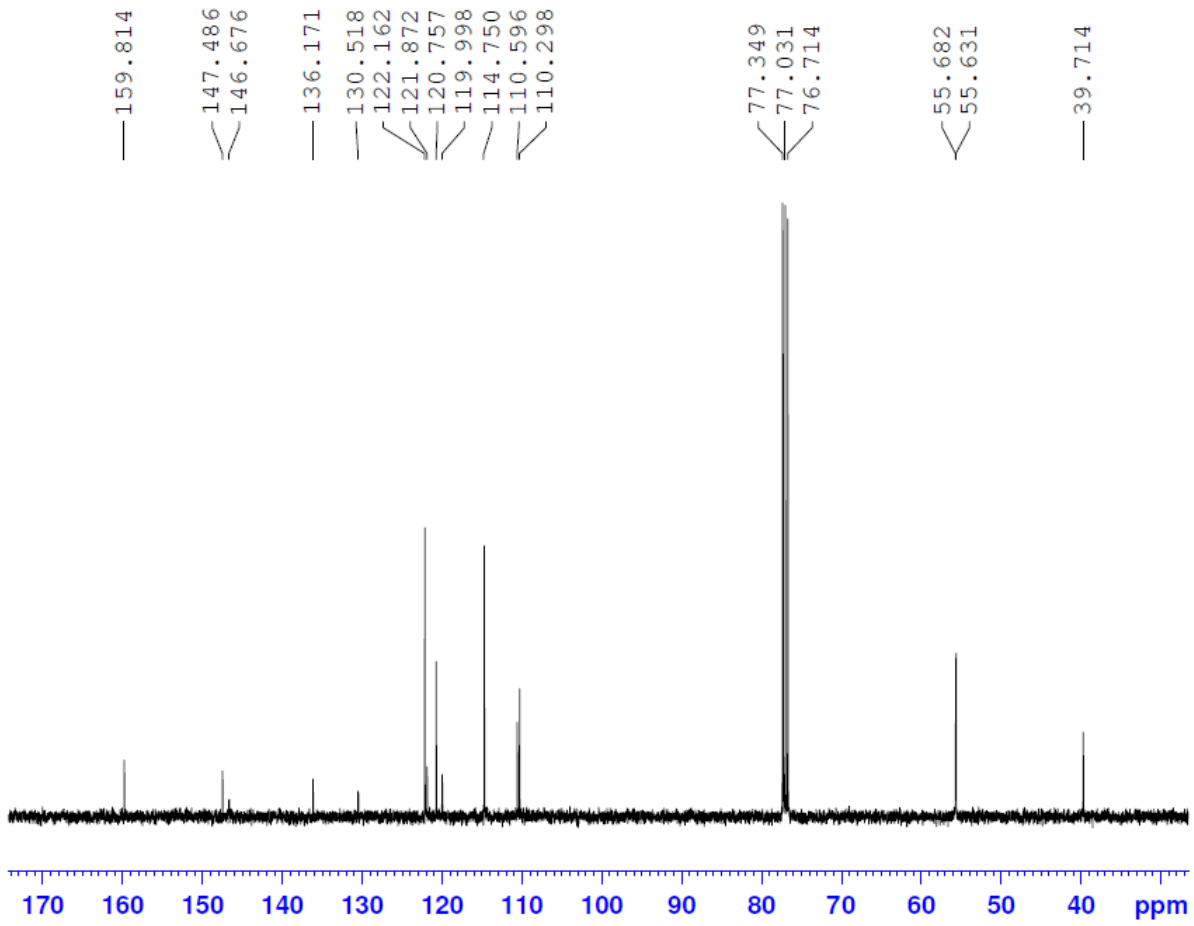
NAME	s_che.202pure
EXPNO	1
PROCNO	1
Date_	20101114
Time	12.32
INSTRUM	av400
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	161.3
DW	104.400 use
DE	6.00 use
TE	298.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	11.75 use
PL1	-2.00 dB
PL1W	16.00390816 W
SFO1	400.1322007 MHz
SI	32768
SF	400.1300098 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



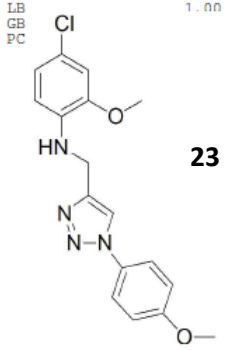
23

4-chloro-2-methoxy-N-{[1-4-methoxyphenyl)-1H-1,2,3 triazol-4-yl]methyl} aniline



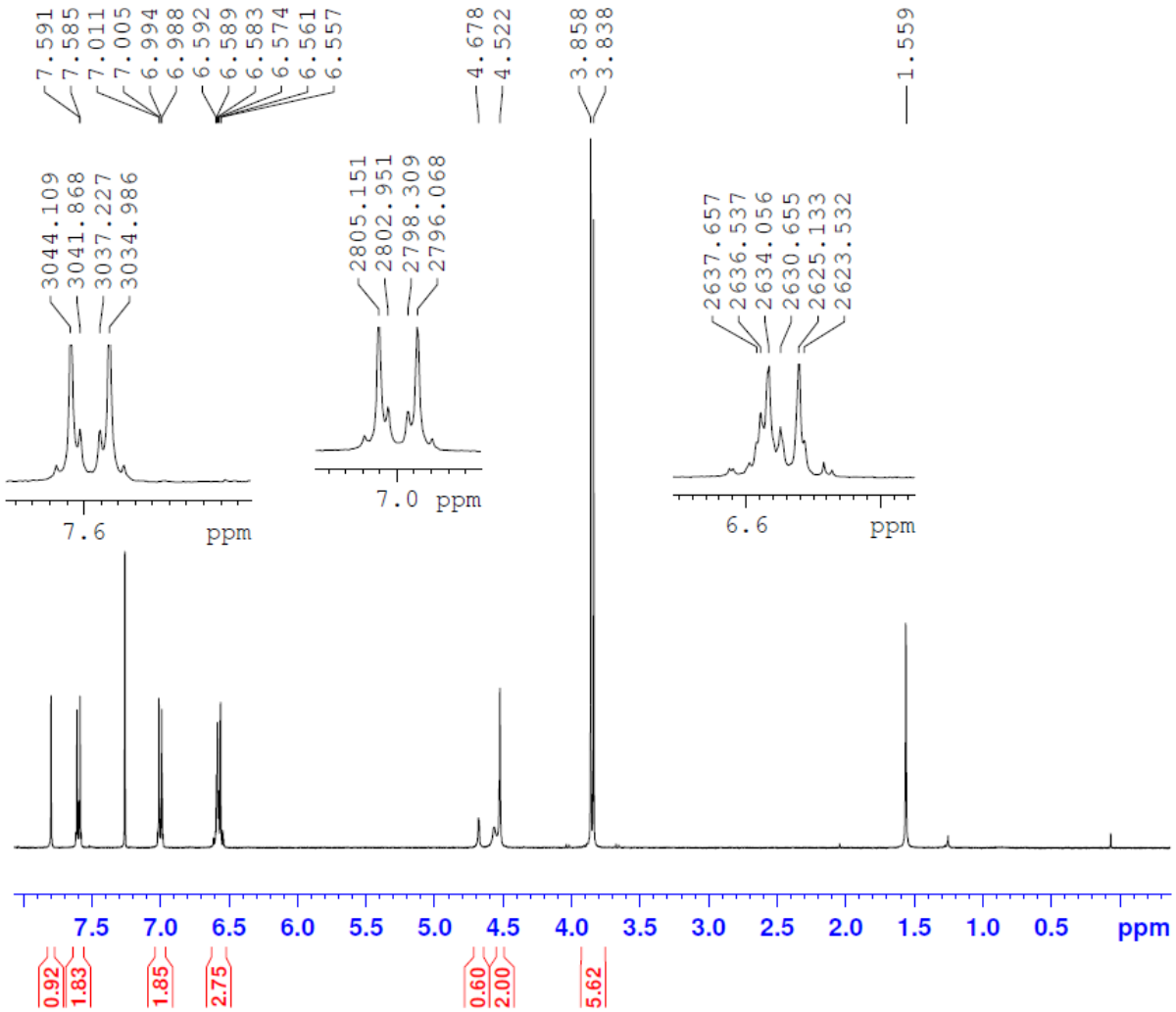
BRUKER

NAME	s_che.202pure
EXPNO	2
PROCNO	1
Date_	20101114
Time	12.55
INSTRUM	av400
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	512
DS	2
SWH	25125.629 Hz
FIDRES	0.766773 Hz
AQ	0.6521332 sec
RG	20642.5
DW	19.900 usec
DE	10.00 usec
TE	298.2 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
------- CHANNEL f1 -------	
NUC1	13C
P1	7.50 usec
PL1	-3.00 dB
PL1W	73.67452240 W
SFO1	100.6238350 MHz
------- CHANNEL f2 -------	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	-2.00 dB
PL12	17.00 dB
PL13	19.30 dB
PL2W	16.00390816 W
PL12W	0.20147727 W
PL13W	0.11863863 W
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	
PC	

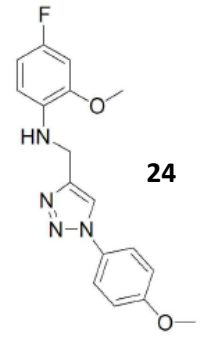


23

4-fluoro-2-methoxy-N-{[1-4-methoxyphenyl)-1H-1,2,3 triazol-4-yl]methyl} aniline

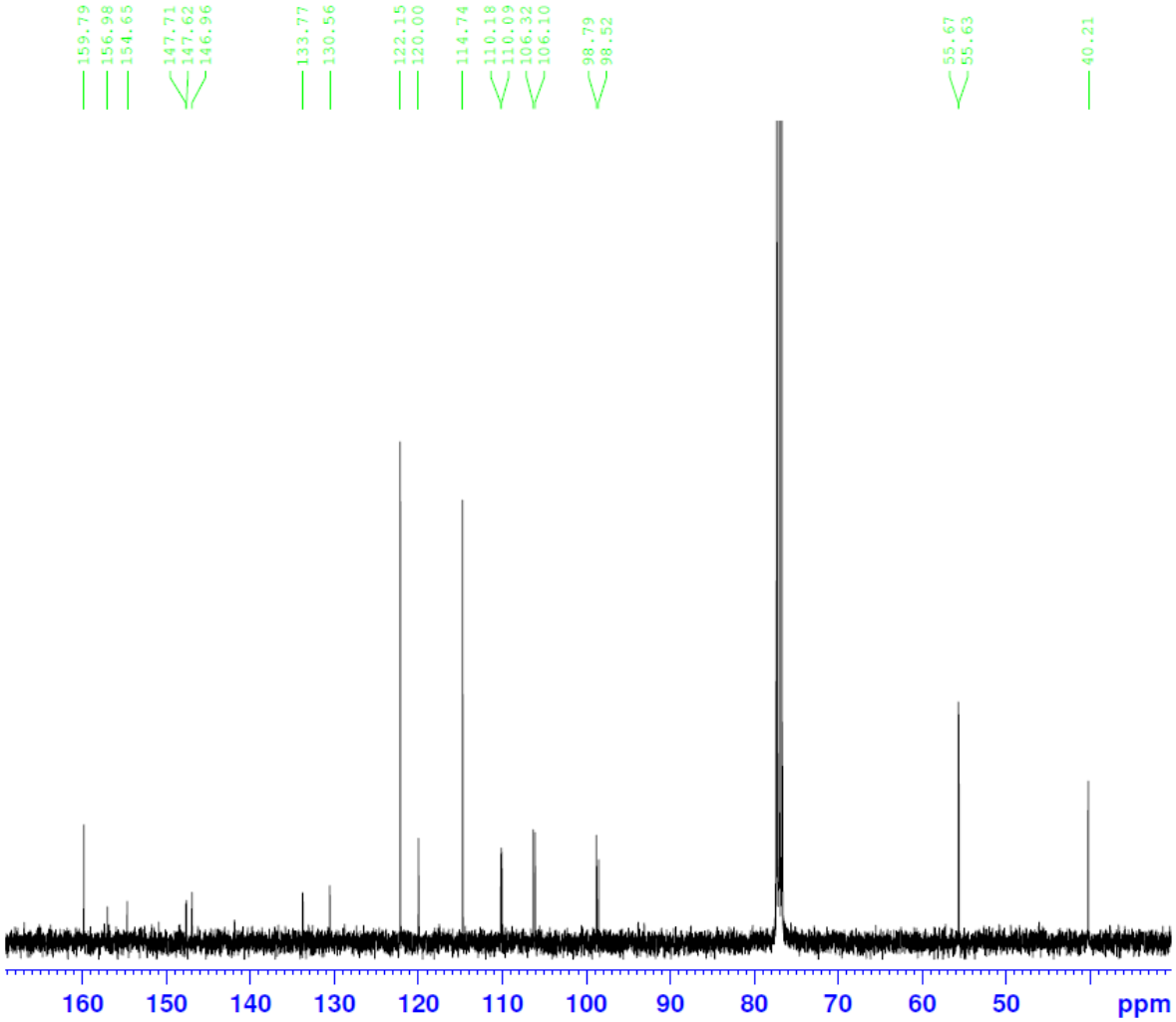


NAME	sc263spot3
EXPNO	1
PROCNO	1
Date_	20110202
Time	12.55
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	5792
DW	60.400 usec
DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	11.10 usec
PL1	-1.10 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300102 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



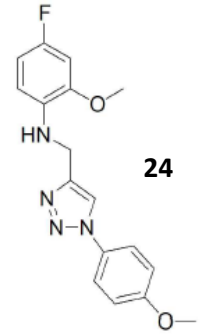
24

4-fluoro-2-methoxy-N-{[1-4-methoxyphenyl)-1H-1,2,3 triazol-4-yl]methyl} aniline



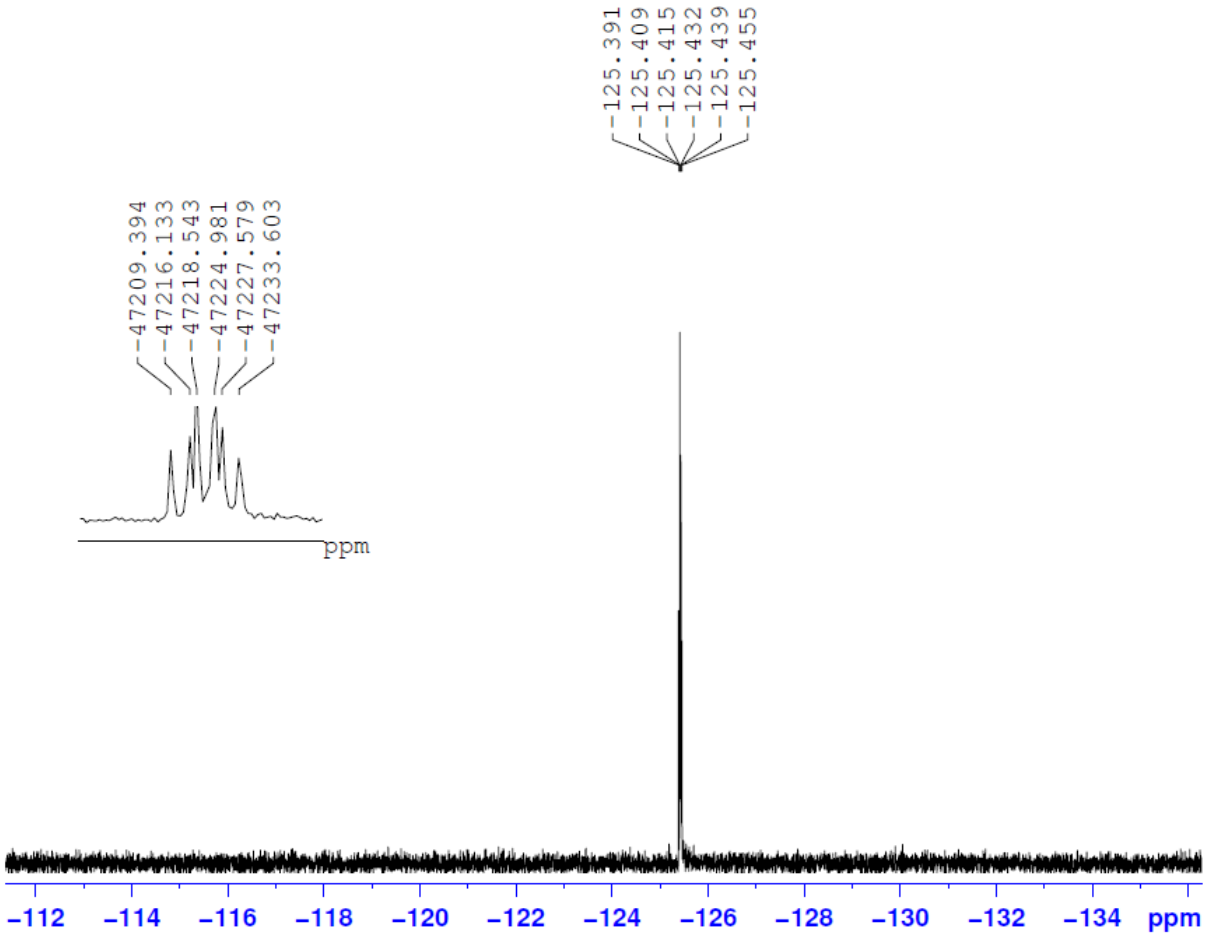
BRUKER

EXPNO	2
PROCNO	1
Date_	20110315
Time	2.23
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	4096
DW	20.850 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
-------- CHANNEL f1 --------	
NUC1	13C
P1	9.38 usec
PL1	0.00 dB
SFO1	100.6228298 MHz
-------- CHANNEL f2 --------	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-1.10 dB
PL12	16.06 dB
PL13	21.00 dB
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



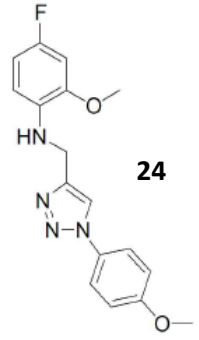
24

4-fluoro-2-methoxy-N-{[1-4-methoxyphenyl)-1H-1,2,3 triazol-4-yl]methyl} aniline

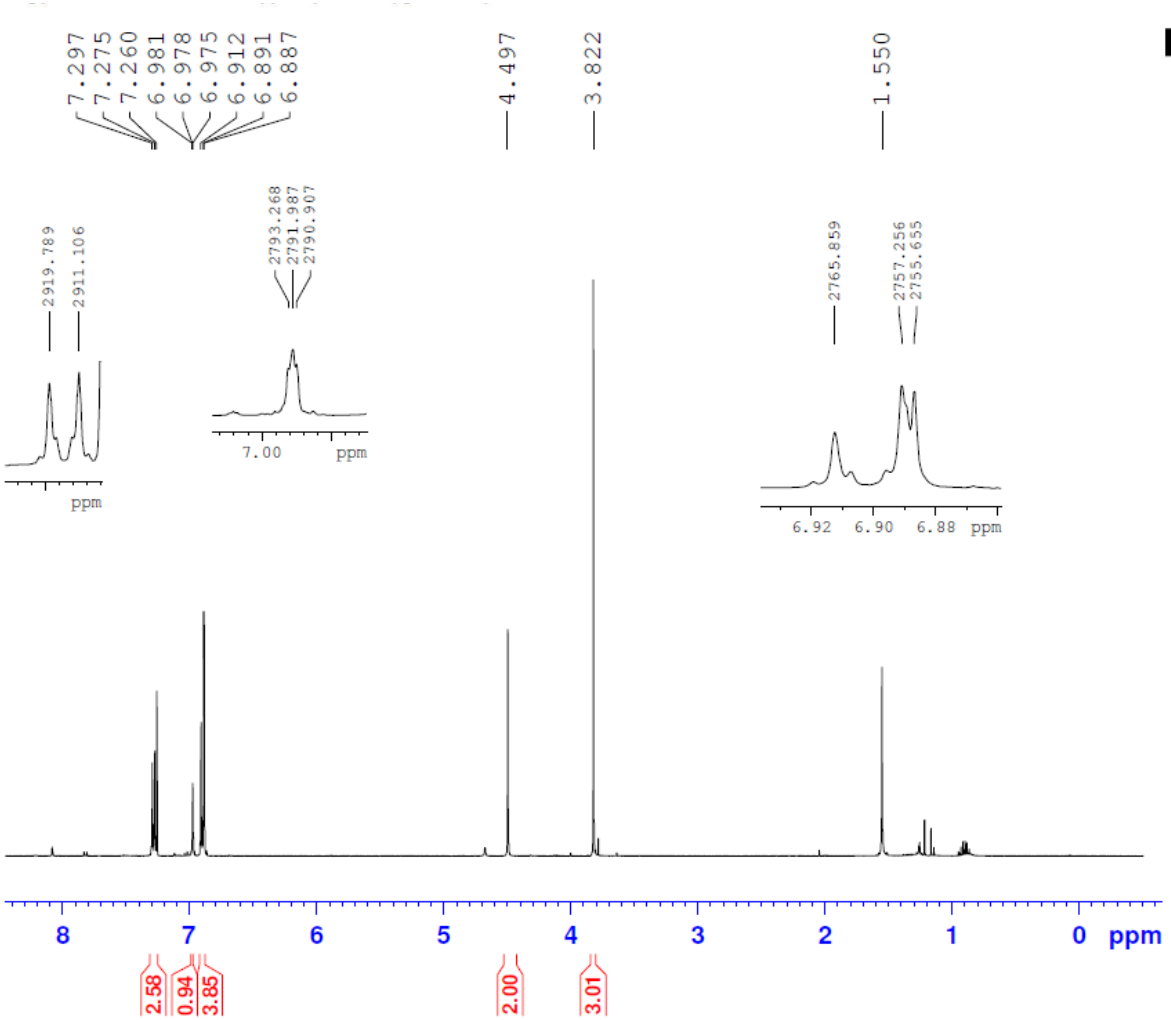


BRUKER

NAME	sc263_NMR2
EXPNO	3
PROCNO	1
Date_	20110315
Time	2.24
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgflqn
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	75187.969 Hz
FIDRES	0.573639 Hz
AQ	0.8716788 sec
RG	32768
DW	6.650 usec
DE	6.50 usec
TE	298.3 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	19F
P1	13.00 usec
PL1	0.00 dB
SFO1	376.4607164 MHz
SI	65536
SF	376.4983660 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

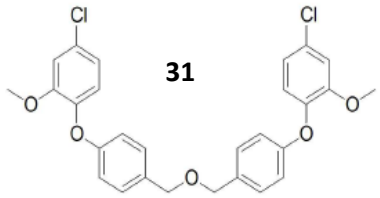


24



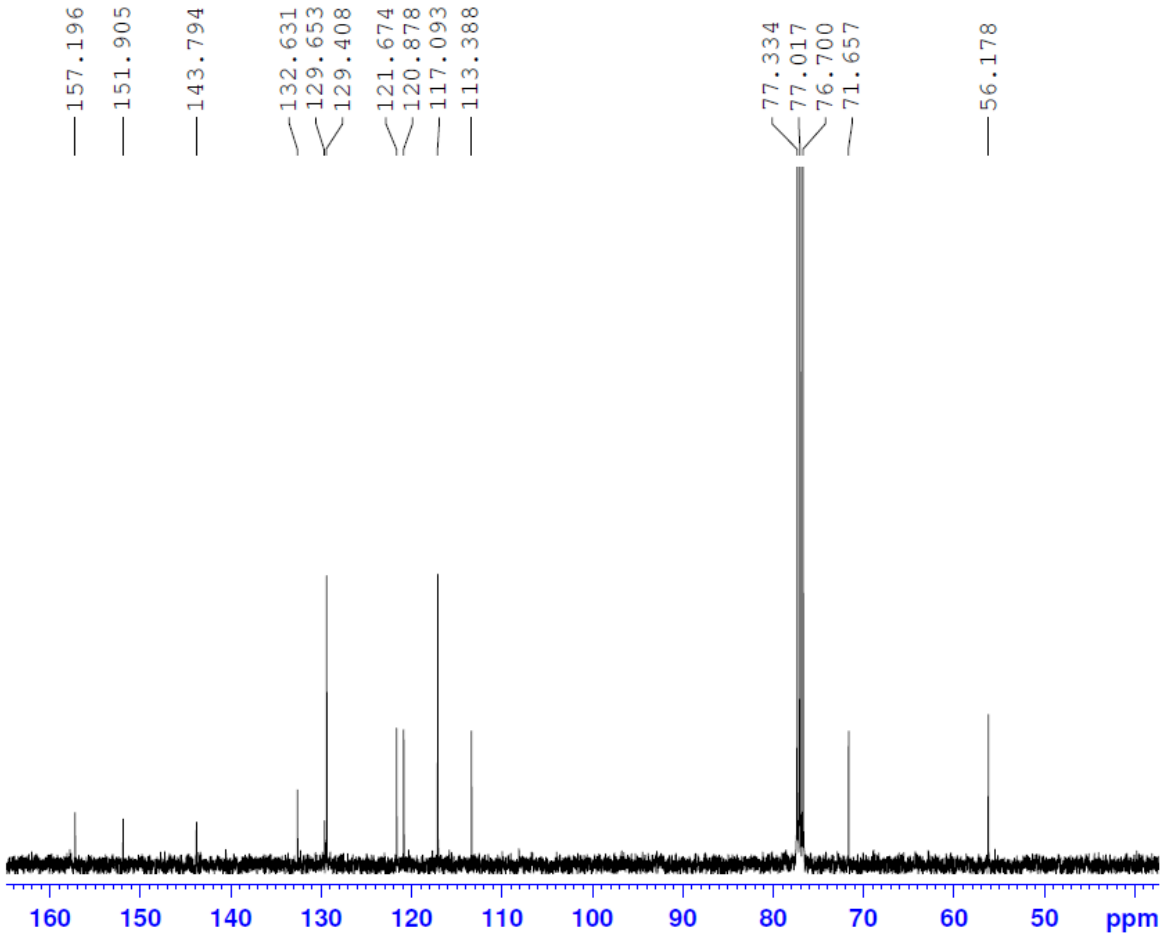
BRUKER

NAME	s_che.228pure
EXPNO	5
PROCNO	1
Date_	20101119
Time	8.13
INSTRUM	av400
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	456.1
DW	104.400 usec
DE	6.00 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	11.75 usec
PL1	-2.00 dB
PL1W	16.00390816 W
SFO1	400.1322007 MHz
SI	32768
SF	400.1300098 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



31

Bis [(4'-chloro-2'-methoxy)-4-phenoxy]dibenzyl ether

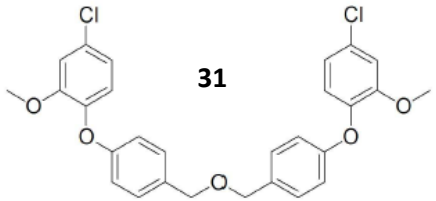


BRUKER

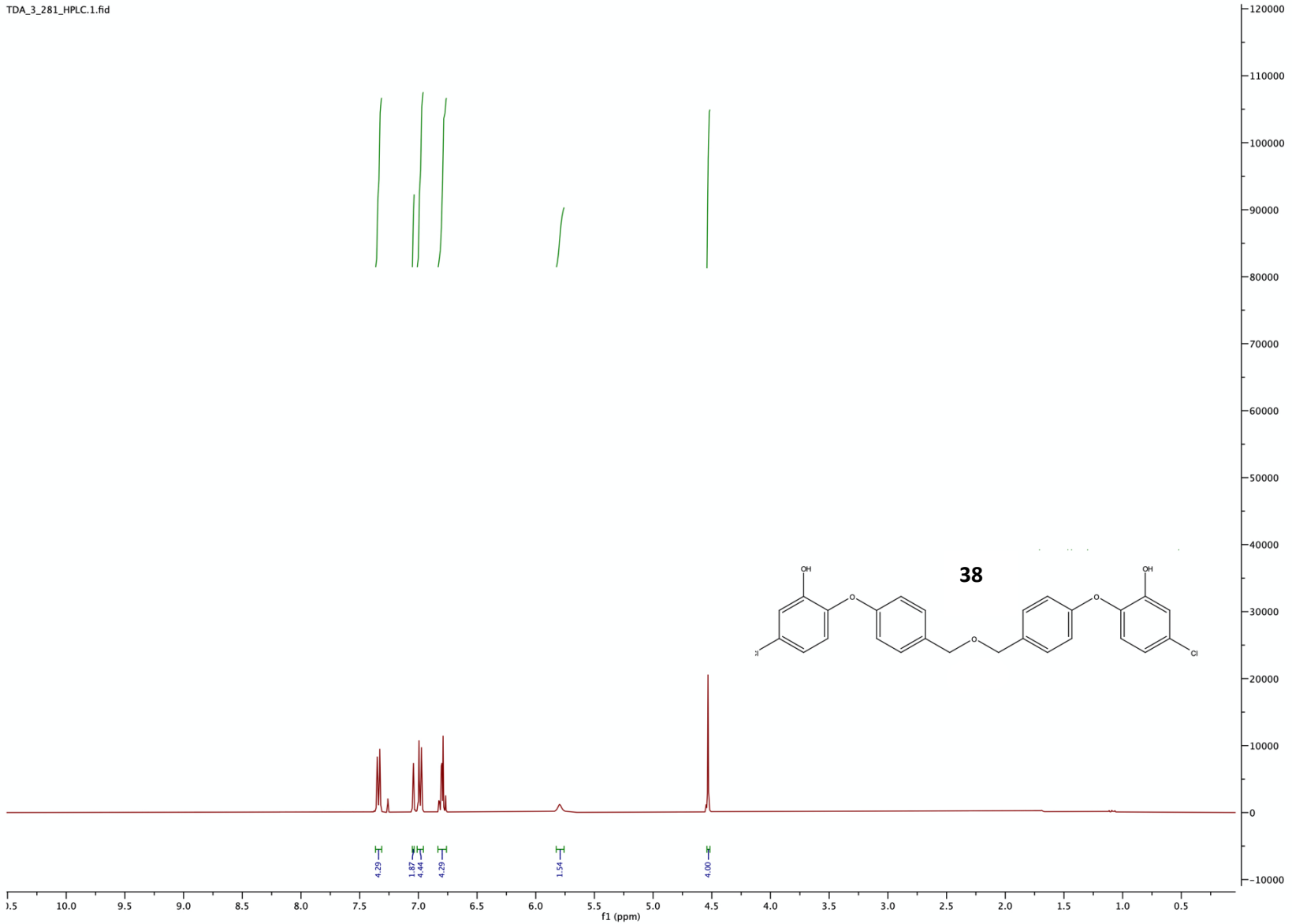
```
NAME          s_che.228pure
EXPNO                     1
PROCNO                    1
Date_              20101119
Time                   8.10
INSTRUM               av400
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    32768
SOLVENT               CDCl3
NS                     1024
DS                        2
SWH               25125.629 Hz
FIDRES            0.766773 Hz
AQ                0.6521332 sec
RG                  20642.5
DW                   19.900 usec
DE                   10.00 usec
TE                   298.2 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                       1

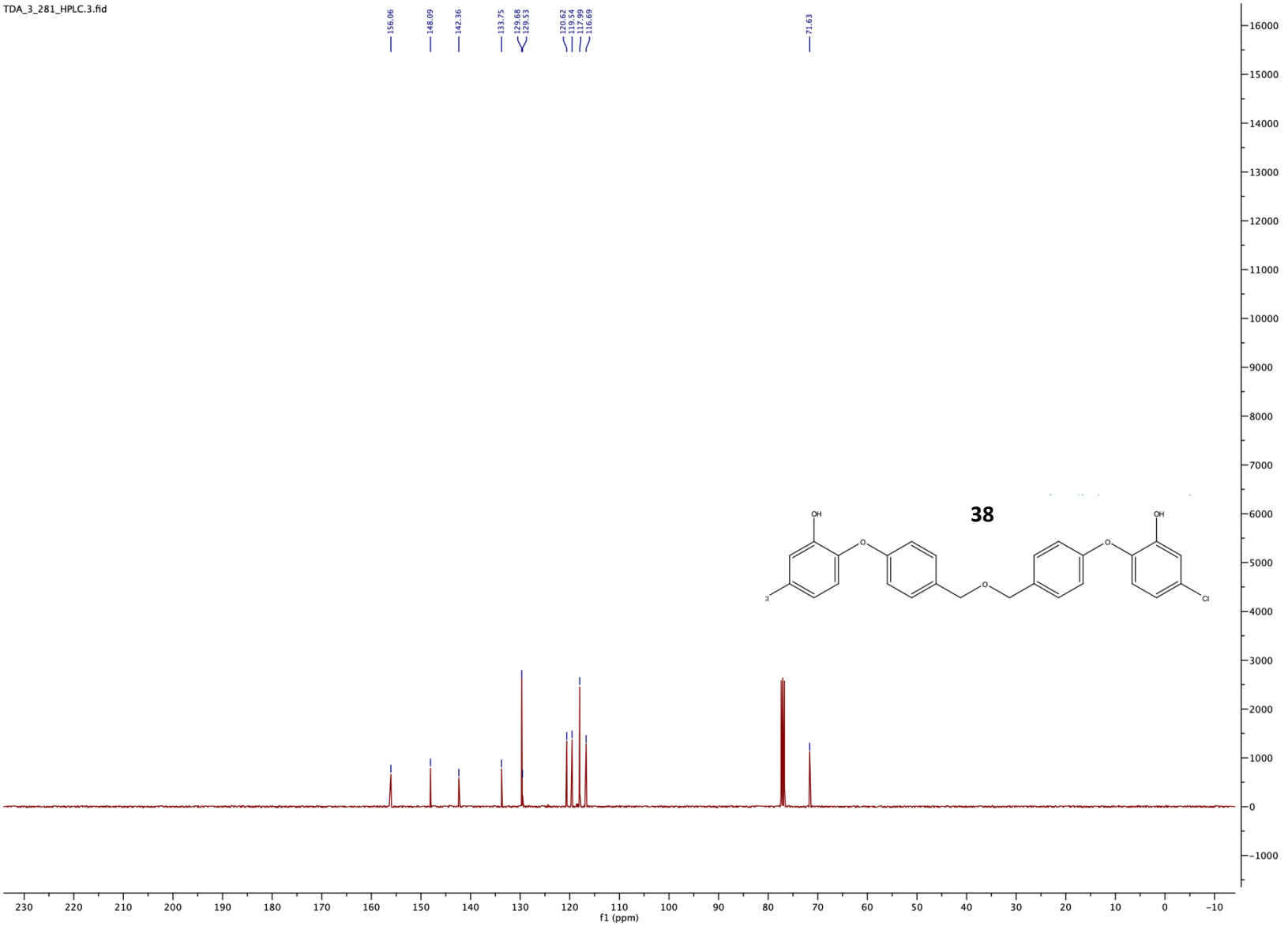
======== CHANNEL f1 ========
NUC1                    13C
P1                     7.50 usec
PL1                   -3.00 dB
PL1W          73.67452240 W
SFO1         100.6238350 MHz

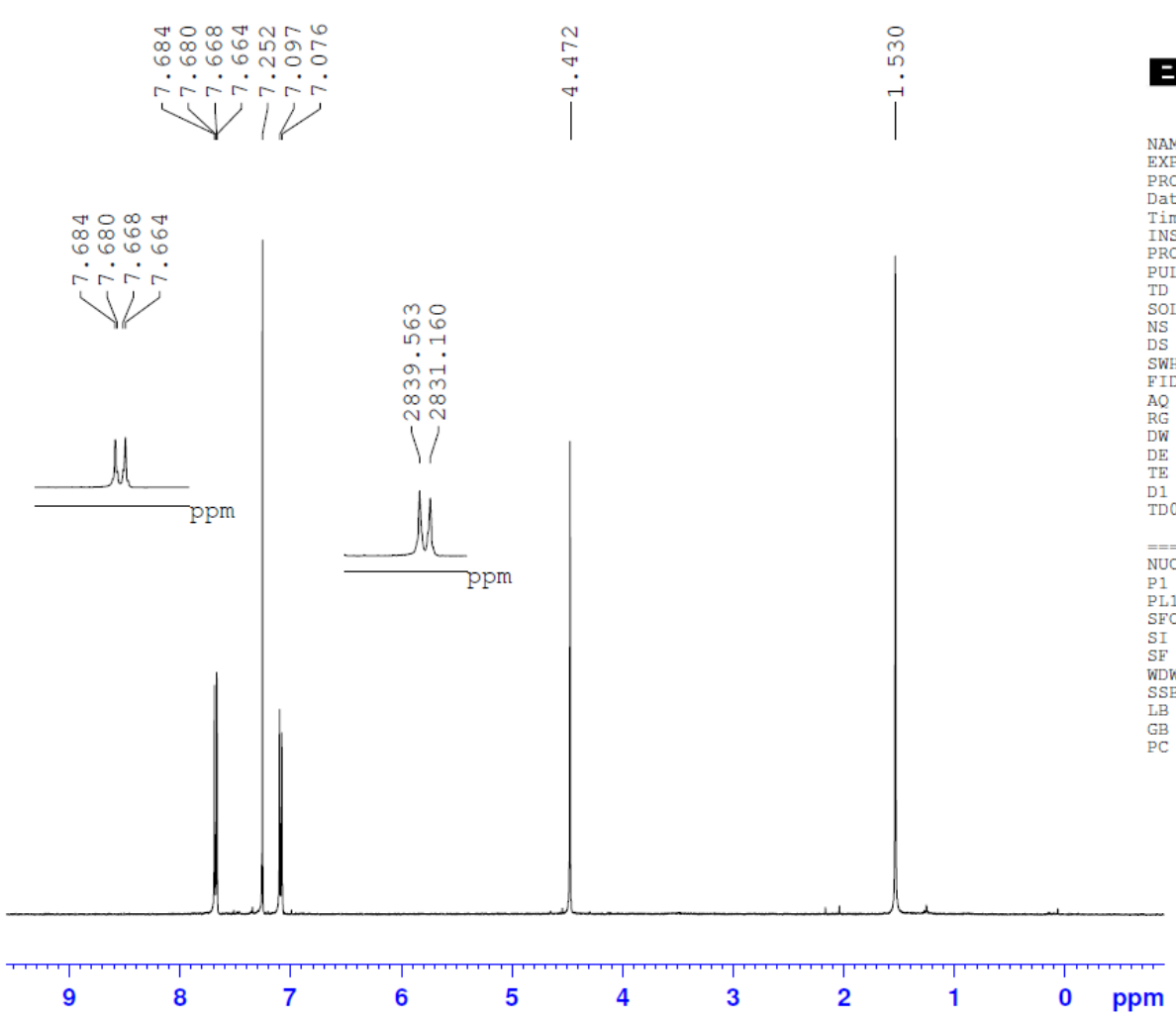
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                100.00 usec
PL2                   -2.00 dB
PL12                  17.00 dB
PL13                  19.30 dB
PL2W          16.00390816 W
PL12W          0.20147727 W
PL13W          0.11863863 W
SFO2         400.1316005 MHz
SI                    32768
SF           100.6127690 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```



31


TDA_3_281_HPLC.1.fid
38
OH
O
O
O
OH
Cl
4.29
1.87
4.44
4.29
1.54
4.00
f1 (ppm)


TDA_3_281_HPLC.3.fid
156.06
148.09
142.36
133.75
129.68
129.53
120.62
119.54
117.98
116.69
71.63
38
OH
OH
Cl
Cl
f1 (ppm)

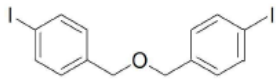


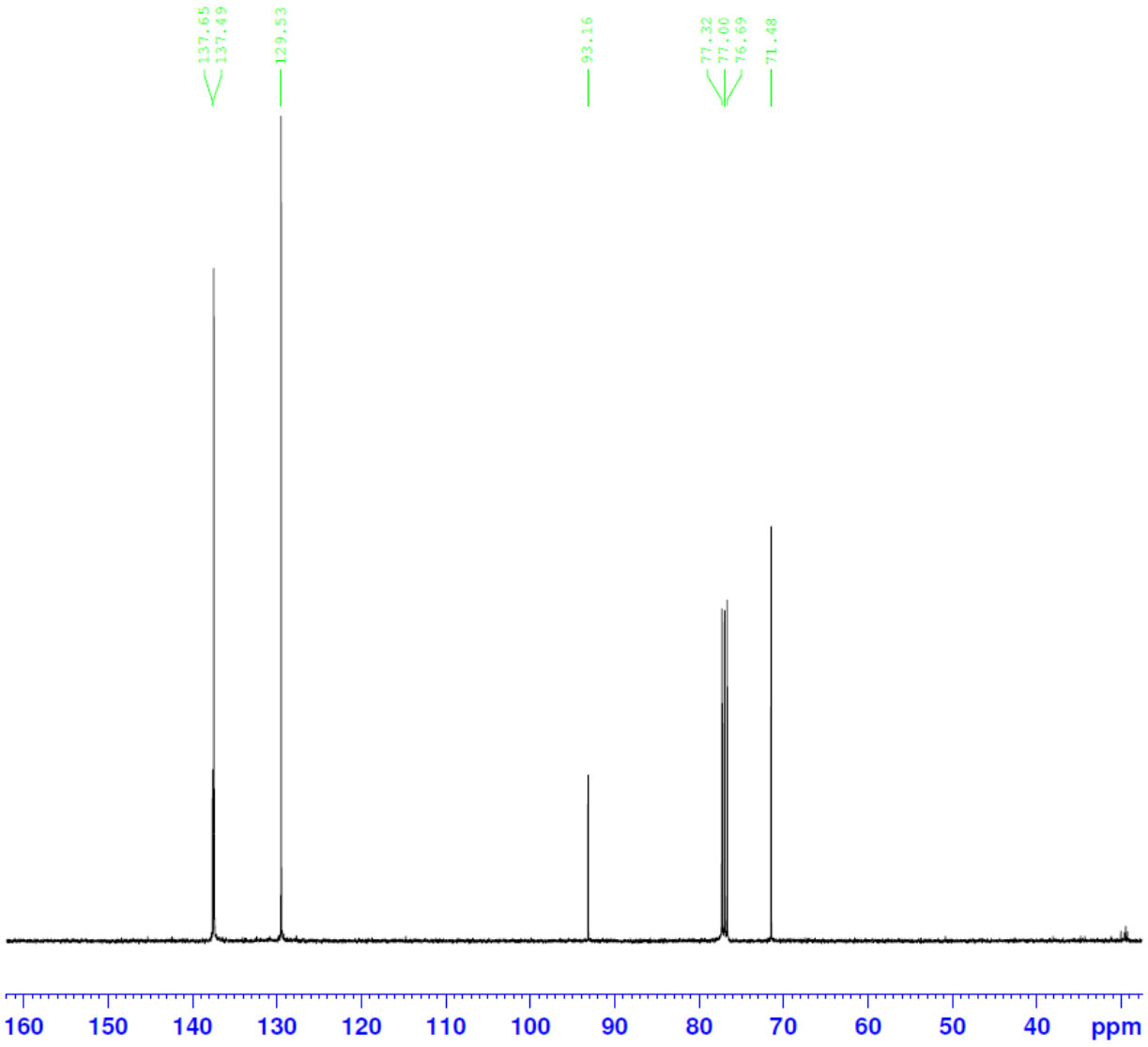
BRUKER

```
NAME                 sc022
EXPNO                    1
PROCNO                   1
Date_             20080819
Time                 13.16
INSTRUM              spect
PROBHD    5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                    1024
DW                  60.400 usec
DE                   6.50 usec
TE                  298.2 K
D1                1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   11.75 usec
PL1                   0.00 dB
SFO1          400.1324710 MHz
SI                   32768
SF            400.1300124 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

40

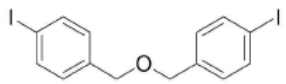





```
NAME                sc016b
EXPNO                    1
PROCNO                   1
Date_             20080701
Time                 20.03
INSTRUM               spect
PROBHD    5 mm QNP 1H/13
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH              23980.814 Hz
FIDRES           0.365918 Hz
AQ               1.3664756 sec
RG                     1024
DW                 20.850 usec
DE                  6.50 usec
TE                  298.2 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                       1

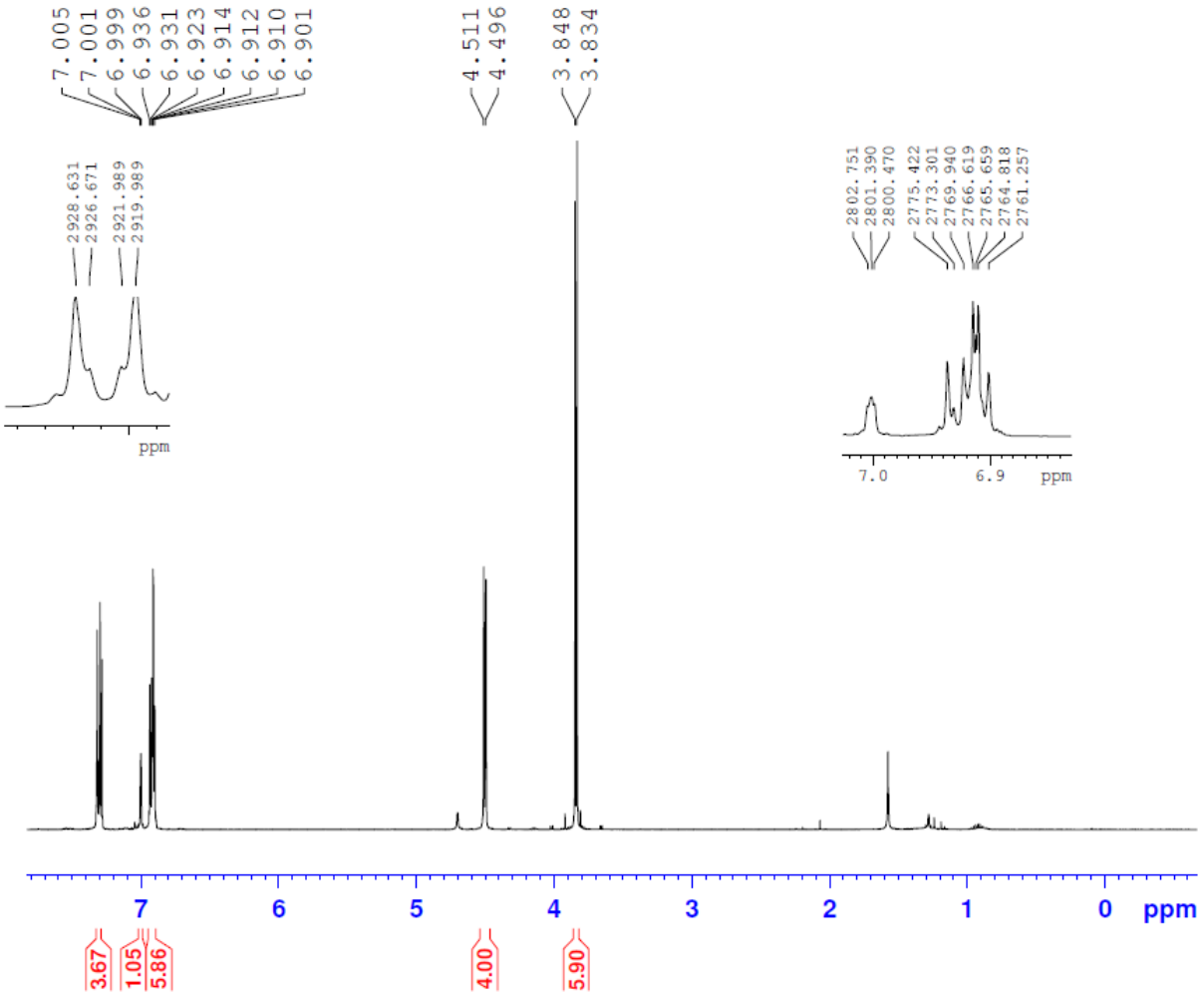
======== CHANNEL f1 ========
NUC1                    13C
P1                   8.12 usec
PL1                  0.00 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                18.00 dB
PL13                21.00 dB
SFO2          400.1316005 MHz
SI                   32768
SF            100.6127757 MHz
WDW                     EM
SSB                      0
LB                   1.00 Hz
GB                       0
PC                    1.40
```



40

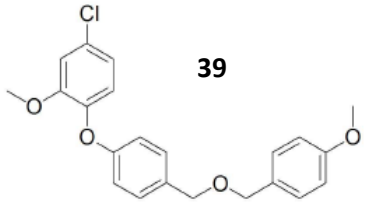
4-chloro-2-methoxy-1-(4-{[4-methoxybenzyl)oxy]methyl}phenoxy)benzene



BRUKER

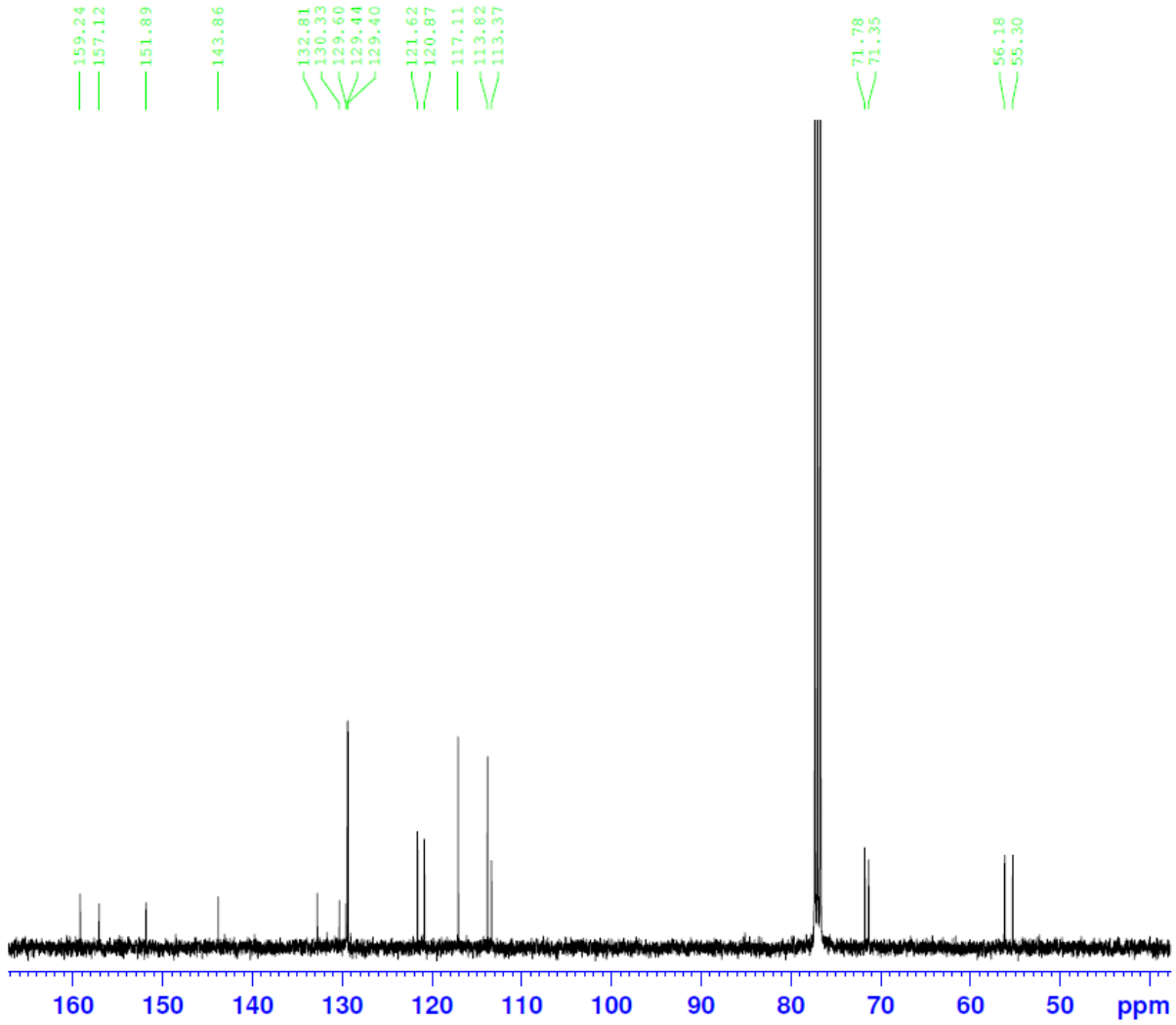
NAME	sc227pure
EXPNO	1
PROCNO	1
Date_	20101129
Time	4.00
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	1448
DW	60.400 usec
DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	11.10 usec
PL1	-1.10 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



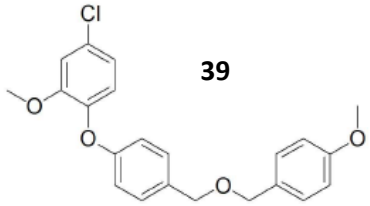
39

4-chloro-2-methoxy-1-(4-{[4-methoxybenzyl)oxy]methyl}phenoxy)benzene



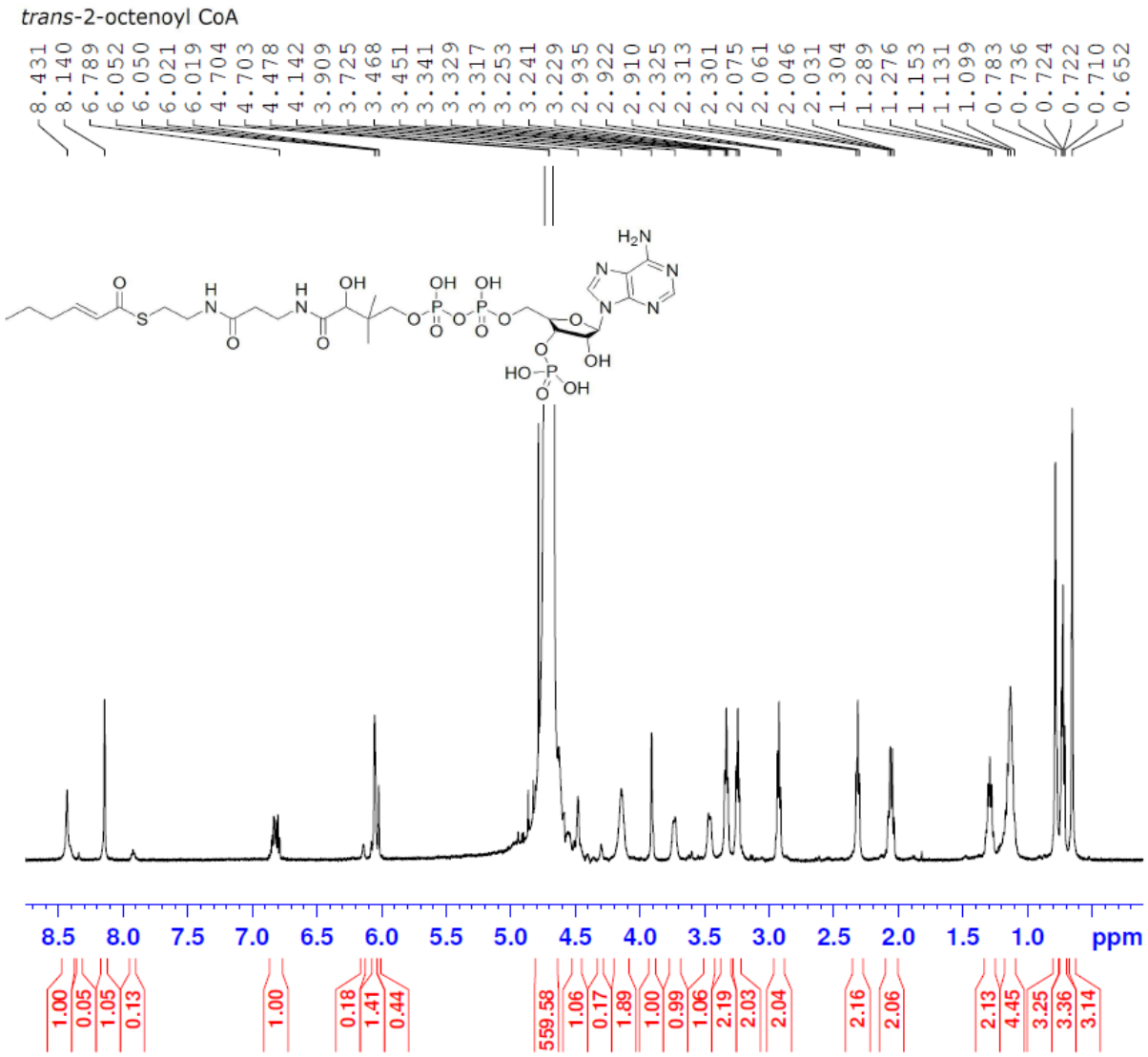
BRUKER

NAME	sc227pure_2
EXPNO	2
PROCNO	1
Date_	20101129
Time	5.00
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	5792
DW	20.850 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
------- CHANNEL f1 -------	
NUC1	13C
P1	9.38 usec
PL1	0.00 dB
SFO1	100.6228298 MHz
------- CHANNEL f2 -------	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-1.10 dB
PL12	16.06 dB
PL13	21.00 dB
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



39

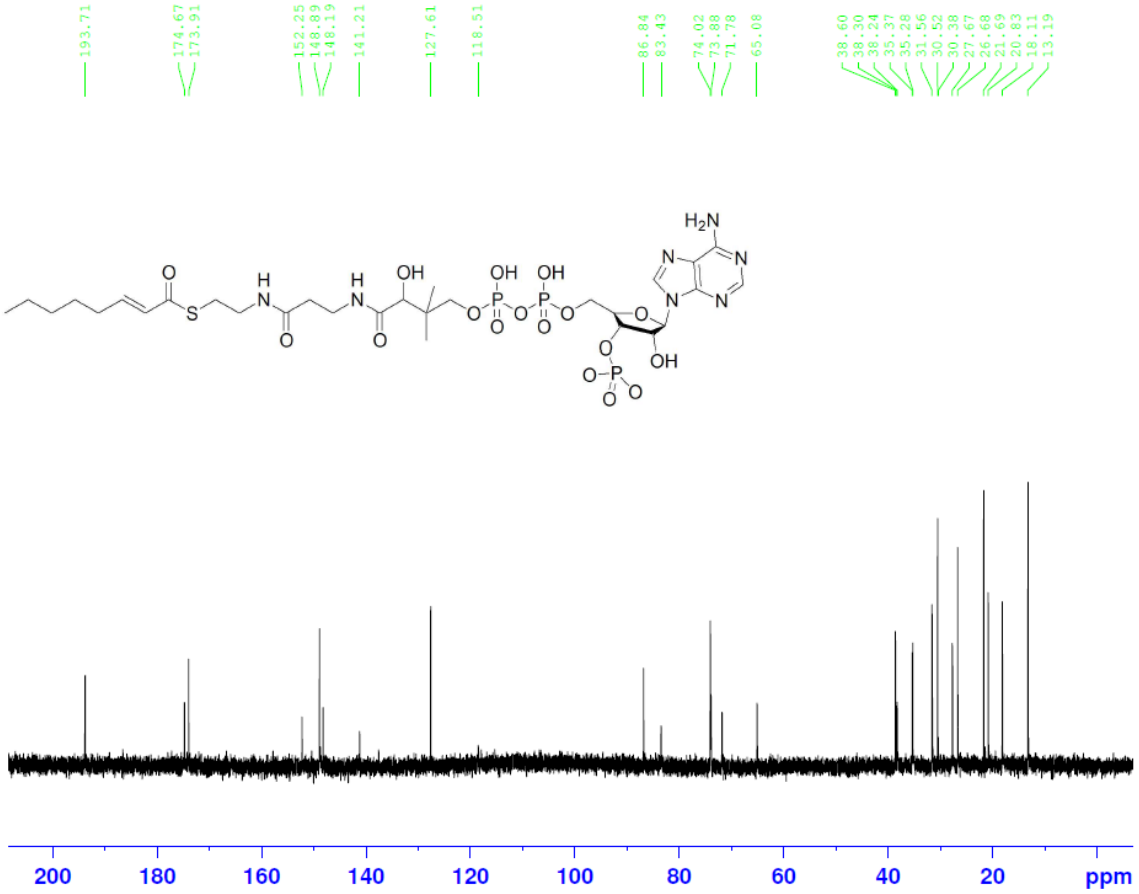
trans-2-octenoyl CoA



BRUKER

NAME	s_che.191
EXPNO	1
PROCNO	1
Date_	20100902
Time	14.08
INSTRUM	av3500
PROBHD	5 mm CPDCH 13C
PULPROG	zg30
TD	65536
SOLVENT	D2O
NS	16
DS	8
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 se
RG	101
DW	48.400 us
DE	82.19 us
TE	295.0 K
D1	1.00000000 se
TD0	1
======== CHANNEL f1 ======	
NUC1	1H
P1	7.90 us
PL1	1.60 dB
PL1W	20.50605011 W
SFO1	500.1330885 MH
SI	65536
SF	500.1300000 MH
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

trans-2-octenoyl CoA

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NAME              s_che.sc270
EXPNO                       2
PROCNO                      1
Date_              20110316
Time                  13.53
INSTRUM             av3500
PROBHD    5 mm CPDCH 13C
PULPROG             zgpg30
TD                   65536
SOLVENT                D2O
NS                     515
DS                      16
SWH              29761.904 Hz
FIDRES            0.454131 Hz
AQ                1.1010548 sec
RG                     512
DW                  16.800 use
DE                  31.09 use
TE                  298.0 K
D1              1.50000000 sec
D11             0.03000000 sec
TD0                     1

======== CHANNEL f1 =======
NUC1                   13C
P1                    7.30 use
PL1                   1.40 dB
PL1W          66.60105133 W
SFO1         125.7716224 MHz

======== CHANNEL f2 =======
CPDPRG2            waltz16
NUC2                   1H
PCPD2                82.00 use
PL2                   1.60 dB
PL12                 21.39 dB
PL13                 22.60 dB
PL2W          20.50605011 W
PL12W          0.21521972 W
PL13W          0.16288532 W
SFO2         500.1320005 MHz
SI                   65536
SF           125.7577890 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
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