Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Continuous Synthesis and Purification by Coupling a Multistep Flow Reaction with Centrifugal Partition Chromatography

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Author Contributions

R.Ö. Conceptualization: Equal; Data curation: Lead; Formal analysis: Equal; Investigation: Lead; Methodology: Lead; Project administration: Lead; Visualization: Lead; Writing—original draft: Lead
J.É. Resources: Equal; Supervision: Lead
F.F. Supervision: Equal
P.V. Methodology: Supporting; Resources: Supporting
A.P. Investigation: Supporting
Z.S. Validation: Supporting
J.K. Validation: Supporting
I.G. Conceptualization: Equal; Writing—review & editing: Lead.

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Acknowledgements

The authors thank Csaba Szántay Jr., Gyula Beke, György Tibor Balogh, Márta Meszlényiné Sipos, Judit Müller, Árpád Könczöl, Gábor Meszlényi, Eszter Riethmüller and Ildikó Balogh for their help, Tamás Patócs for his work on the literature background and members of our flow chemistry work team, especially Péter Bana and Klára Lövei.

1. General experimental details

All chemicals were purchased from commercial sources and were used without further purification.

Analytical thin-layer chromatography (TLC) was performed on aluminium foil-backed pre-coated silica and impregnated with a fluorescent indicator (Kieselgel 60 F_{254}; manufactured by Merck). The solvent front was allowed to ascend to 5-6 cm. The spots were visualized by exposure to ultraviolet light using a CAMAG type UV lamp (λ_1=254 nm, λ_2= 366 nm) and/or fumed with chlorine followed by submersion in the solution of 4-(4-amino-3-methylphenyl)-2-methylaniline (2.5 g/L) in water.

Column chromatography was performed using silica gel (0.040–0.063 mm, manufactured by Merck).

Organic solutions were concentrated by rotary evaporation (Büchi Rotavapor R-210, V-850 Vacuum Controller, B-491 Heating Bath) below 55 ºC.

Melting points were determined on Büchi B540 instrument and are reported as uncorrected values.

NMR measurements

NMR spectra were collected on either of the following Varian (now Agilent) instruments: VNMRS 500 spectrometer, equipped with a $^{1}H\{^{13}C/^{15}N\}$ pulsed field gradient (PFG) Triple Resonance ^{13}C Enhanced Cold Probe or a VNMRS 400 spectrometer, equipped with a OneNMR PFG Probe. Standard pulse sequences available in the VnmrJ 3.2A software were used. Besides the 1D ^{1}H and the phase-sensitive 2D $^{1}H,^{13}C$-HSQC (gHSQCAD) spectra, a 1D $^{13}C\{^{1}H\}$ and/or a band-selective 2D $^{1}H,^{13}C$-HMBC (bsgHMBC with $^{n}J_{C,H}$ = 8 Hz) spectrum was recorded for all compounds, while a 2D absolute-value COSY (gCOSY) and a 2D rotational-frame Overhauser effect ROESY (with a 3.2 kHz T-ROESY spinlock for a mixing time of 0.2 s) spectrum was acquired for compound **3c** and **5c**, respectively, to allow their unambiguous signal assignment. All experiments were run in standard 5-mm NMR tubes from Wilmad at 25 °C using either $CDCl_3$ (99.8% D), DMSO-d_6 (99.96% D) (both from Euriso-Top, France) or aceton-d_6 (99.95% D; from Merck, Germany) as solvent. ^{1}H and ^{13}C chemical shifts were referenced to internal TMS at 0.00 ppm (or in one case to the residual signal of acetone-d_6 solvent at 2.05 ppm), all coupling constants are reported in Hz units. The following abbreviations are used to indicate the signal multiplicities: br. s: broad singlet; d: doublet; m: multiplet. Spectral figures for the publication were produced by MestreNova (Mestrelab Research, Santiago de Compostela, Spain).

HRMS measurements

Electrospray high-resolution MS measurements (ESI-HRMS) were performed on a Thermo LTQ FT Ultra spectrometer (Thermo Fisher Scientific, Bremen, Germany). The ionization method was ESI, operated in positive ion mode. The ion transfer capillary temperature was set at 280˚C. Samples were infused into the ESI source MeOH solutions at a flow rate of 10 µL min^{-1}. The resolving power was 50,000 (FWHM) at *m/z* 400. Data acquisition and analysis were accomplished with the Xcalibur software version 2.1 (Thermo Fisher Scientific Inc.).

Electron impact high-resolution MS measurements (EI-HRMS) were performed on a Finnigan MAT 95XP mass spectrometer (Finnigan, Bremen, Germany). The ion source temperature was set at 220˚C, the applied ionization energy was 70 eV.

Data acquisition and analysis were accomplished with Xcalibur software version 2.0 (Thermo Fisher Scientific Inc.).

HPLC-DAD-QMS measurements

The HPLC-DAD-QMS experiments were performed on an Agilent 1100 HPLC system (G1379A degasser, G1311A quaternary gradient pump, G1367B autosampler, G1316A column thermostat and G1315B diode array detector) coupled with a 6120 quadrupole mass spectrometer equipped with an ESI ion source (Agilent Technologies, Waldbronn, Germany). The Masshunter B.03.01 software was used for qualitative analyses.

The solid samples were dissolved in acetonitrile (1 mg/mL), and separated on a Kinetex-XB C_{18} column (50×2.1 mm, 2.6 µm; Phenomenex, Torrance, CA, USA) maintained at 40°C. The injection volume was 1 µL. The following gradient elution program was applied at a flow rate of 0.75 mL min^{-1}; where eluent A was 0.1% (v/v) trifluoroacetic acid in water, eluent B was 0.1% (v/v) trifluoroacetic acid in acetonitrile: water = 95 : 5: 0 min: 0% (v/v) B; 4 min: 100% (v/v) B; 7 min: 100% (v/v) B; 7.01 min: 0% (v/v) B. Detection wavelength was 240±25 nm, UV spectra of the compounds were recorded

between 200 and 600 nm. Quadrupole mass spectrometric parameters were as follows: ion source: ESI, positive; drying gas (N_2) temperature: 350°C; drying gas (N_2) flow rate: 12 L min^{-1}; nebuliser gas (N_2) pressure: 60 psi; fragmentor voltage: 50 V; capillary voltage: 2500 V. Full-scan mass spectra were acquired over the *m/z* range 100-1150 (1 scan/sec).

GCMS measurements and instrumentation

Analyses were performed on a Shimadzu GCMS QP2010SE gas chromatograph mass spectrometer. Separations were carried out on a 30 m length, 0.32 mm internal diameter Zebron 5-HT inferno capillary column coated with 0.25 µm film thickness. The applied carrier gas was He maintained at a constant linear velocity of 51 cm/s. The developed GC oven temperature program starts at 100 °C ramped with 50 °C/min to 350 °C in 5 minutes. The solutions (0.3 µl) were injected in split mode (split ratio=10) at a temperature of 250 °C.

The temperatures of the ion source and interface were set to 250°C, the applied ionization energy was 15 eV.

Quantification of the analysis was achieved in selected ion monitoring (SIM mode) with GCMS Solution software.

Spectrophotometric p*K*a determination in aqueous medium

The proton-dissociation constants were determined by UV-spectrophotometric titrations using D-PAS technique (Sirius Analytical Instruments Ltd., Forest Row, UK) attached to a GLp*K*a[1,2]. The p*K*a values were calculated by the RefinementPro® software. Spectrophotometry can be applied for p*K*a measurement provided that the compound has a chromophore in proximity to the ionization centre, and the absorbance changes sufficiently as a function of pH. All measurements were performed in aqueous solutions of 0.15 M KCl under nitrogen atmosphere, at t = 25.0 ± 0.5 °C. Sample concentrations of 50 µM were used for UV/pH titration. The absorbances in the spectral region of 260–300 nm were used in the analysis. The results are given as a result of six independent determinations with standard deviation.

Centrifugal Partition Chromatography (CPC) instrumentation

The separations were performed on the combination of 'SCPC-100+1000-B' apparatus (Armen Instruments Sas, France) with a 'Spot Prep II' system (Armen Instruments Sas, France), using the 100 mL capacity column (Figure S1).

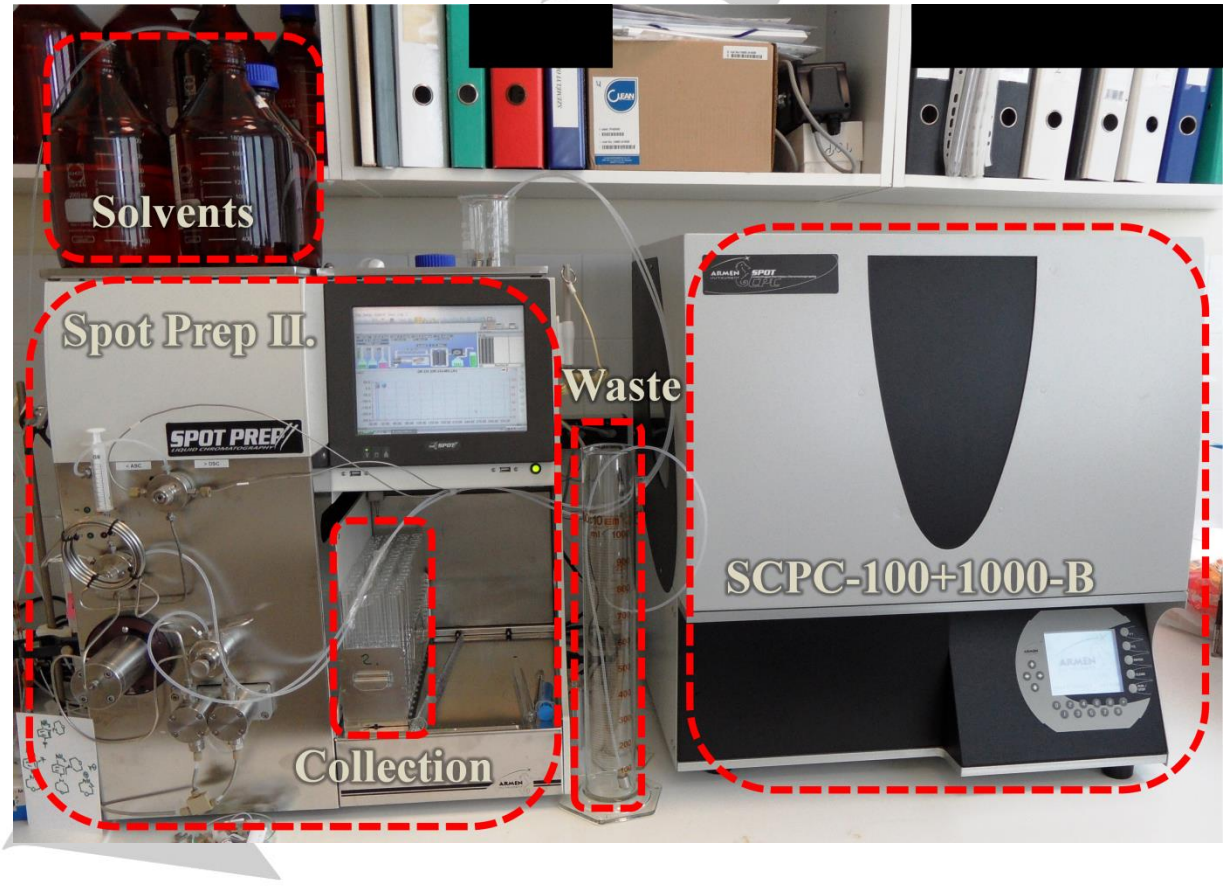


Figure S1. Detailed view of the used CPC instrumentation.

Rotation speed was adjusted at 2000 rpm for all separation. The solvents were pumped by "Spot Prep II" built-in pump. The samples were introduced into the CPC column through loop with manual injection or in case of automated sample intake mode through 'Spot Prep II' built-in pump's magnetic valves. The effluent was monitored with the 'Spot Prep II' built-in UV-Vis detector that was set on two wavelengths (240 and 300 nm) and continuous scan of the whole spectrum (from 200 to 600 nm) at the same time. The separations were controlled by an 'Armen Glider CPC' software installed on a 10.4" built-in panel PC with touch screen. Fractions were collected by 'Spot Prep II' built-in fraction collector. All experiments were conducted at room temperature.

GC-FID measurements

The *n*-hexane (*n*-Hex), methyl *tert*-butyl ether (MTBE) and ethanol (EtOH) content of solutions were quantified on an Agilent 6890 Gas Chromatography system (Agilent Technologies, Palo Alto, CA), equipped with a split/splitless inlet and a flame ionization detector (FID). Analytes were separated on a BP-20 (WAX) capillary column (30 m × 0.53 mm, 0.50 µm film thickness). Separation conditions: the oven temperature was held at 40 °C for 3 min then programmed linearly from 40 °C to 100 °C at a rate of 20 °C/min and held at 100 °C for 3.5 min; helium was used as carrier gas at 0.4 mL min^{-1}, an injection volume of 1 µL and a split (ratio 5:1) injection mode were adopted; the injection port temperature was 220°C and FID temperature was 250 °C with nitrogen as making up gas at 45 mL min^{-1}, and also hydrogen at 40 mL min^{-1}, and air at 450 mL min^{-1}. Retention times for *n*-hexane, methyl *tert*-butyl ether and ethanol, respectively: 2.73 min; 2.91 min and 5.03 min.

Water determination by coulometric Karl Kischer titration

Water contents of the lower phase were determined by TIM550 Coulumetric Karl Fischer Titrator according to Ph. Eur. (2.5.32.) and USP <921> (Method Ic).

2. Procedure for the continuous flow nucleophilic aromatic substitution (S_NAr) reaction.

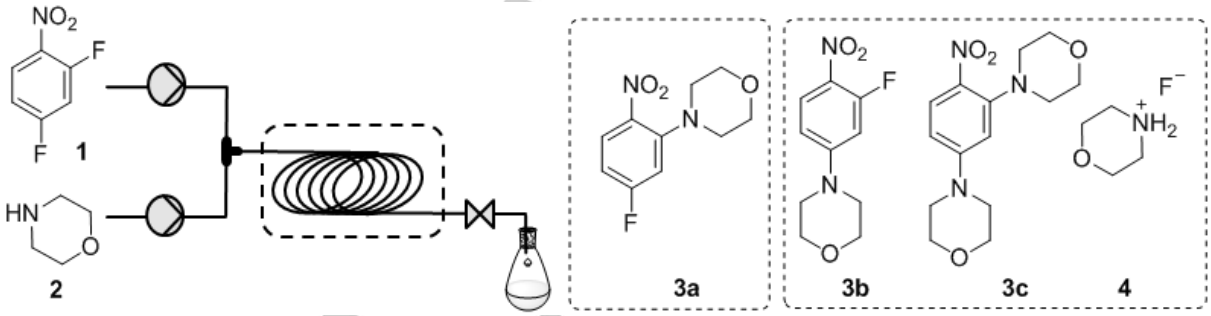


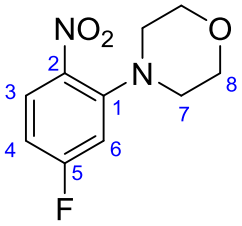
Figure S2. Schematic process of the continuous flow nucleophilic aromatic substitution (S_NAr) reaction.

2.a. The preparation and identification of compounds 3a-c.

Solutions of 2,4-difluoro-1-nitrobenzene **1** (3.50 g, 22.0 mmol, 159.09 g/mol; 1.451 g/mL; 1.0 ekv.) in ethanol (50.0 mL) and morpholine **2** (4.22 mL, 48.4 mmol, 87.12 g/mol; 1.007 g/mL; 2.2 ekv.) in ethanol (50.0 mL) were prepared and connected to individual pump channels of two Knauer *Azura* P2.1S pumps. The solution's streams were joined in a PEEK T-mixer unit, followed by a coil reactor (30 mL) made from 1/8" PTFE tubing. After that a Zaiput® BPR-10 back pressure regulator (10 bar) was connected. The temperature was adjusted to 100 ºC by oil bath that heated by IKA® RTC basic stirrer, equipped with IKA® ETS-D4 fuzzy temperature controller. The solutions were pumped at 1.5 mL min^{-1} each, so the reaction mixture flowed into the loop with a total flow rate 3.0 mL min^{-1} and residence time 10 minutes. After passing through a heat exchanger coil and a back pressure regulator, the thin layer chromatography showed no starting material **1** left (*n*-hexane:etil-acetate = 4:1; R_f (**1**) = 0.49; R_f (**3a**) = 0.36; R_f (**3b**) = 0.13; R_f (**3c**) = 0.07; R_f (**4**) = 0.0). The reaction mixture was collected and concentrated under reduced pressure. The residue was taken up in EtOAc (100 mL) washed with saturated aqueous ammonium chloride (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated

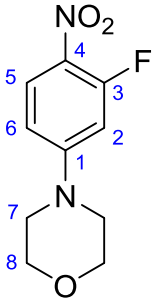
under reduced pressure to afford the crude mixture as an orange oil. This material was purified by column chromatography (ca. 250 g silica gel on a 30 x 5ø sized column) eluting with 20-80% gradient of EtOAc in *n*-hexane, then isocratic elution to obtain 3.95 g (79.5%) 4-(5-fluoro-2-nitrophenyl)morpholine **3a** as an orange oil; 0.33 g (6.5%) 4-(3-fluoro-4-nitrophenyl)morpholine **3b** as a yellow solid and 0.53 g (8.8%) 4-[2-nitro-5-(morpholyne-4-yl)phenyl]morpholine **3c** as an orange solid.

4-(5-Fluoro-2-nitrophenyl)morpholine (**3a**):



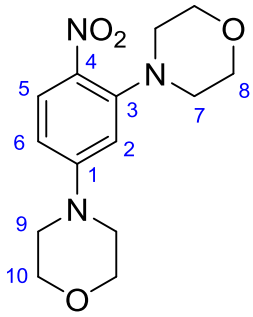
Appearance: orange oil; **LCMS purity:** >99.9%; **^{1}H NMR:** (399.8 MHz, $CDCl_3$, 25 °C) δ (ppm) 3.04 – 3.10 (m, 4H, 2 x 7-CH_2); 3.82 – 3.89 (m, 4H, 2 x 8-CH_2); 6.73 (ddd, 1H, *J* = 9.0; *J* = 7.1; *J* = 2.6; 4-CH); 6.78 (dd, 1H, *J* = 10.6; *J* = 2.6; 6-CH); 7.91 (dd, 1H, *J* = 9.0; *J* = 6.0; 3-CH). **^{13}C NMR:** (100.5 MHz, $CDCl_3$, 25 °C) δ (ppm) 51.7 (2 x 7-CH_2); 66.6 (2 x 8-CH_2); 107.2 (d, *J* = 24.9; 6-CH); 108.6 (d, *J* = 23.7; 4-CH); 129.0 (d, *J* = 11.2; 3-CH); 140.1 (2-C); 148.5 (d, *J* = 10.2; 1-C); 165.5 (d, *J* = 256.1; 5-C). **EI-HRMS:** calcd for $C_{10}H_{11}O_3N_2F$ $[M]^+$: 226.07482; found: 226.07496; delta=0.6 ppm.

4-(3-Fluoro-4-nitrophenyl)morpholine (**3b**):



Appearance: yellow solid; **LCMS purity:** > 97.9%; **Mp.:** 151 – 152 ºC, (Lit.: 146-148 ºC[3]); **^{1}H NMR:** (399.8 MHz, $CDCl_3$, 25 °C) δ (ppm) 3.34 – 3.40 (m, 4H, 2 x 7-CH_2); 3.83 – 3.89 (m, 4H, 2 x 8-CH_2); 6.54 (dd, 1H, *J* = 14.8; *J* = 2.7; 2-CH); 6.61 (dd, 1H, *J* = 9.4; *J* = 2.7; 6-CH); 8.03 (dd, 1H, *J* = 9.4, *J* = 9.0; 5-CH). **^{13}C NMR:** (100.5 MHz, $CDCl_3$, 25 °C) δ (ppm) 46.8 (2 x 7-CH_2); 66.2 (2 x 8-CH_2); 100.9 (d, *J* = 25.8; 2-CH); 108.2 (d, *J* = 2.3; 6-CH); 128.1 (d, *J* = 1.2; 5-CH); 128.5 (d, *J* = 19.3; 4-C); 155.9 (d, *J* = 10.9; 1-C); 158.0 (d, *J* = 262.2; 3-C). **EI-HRMS:** calcd for $C_{10}H_{11}O_3N_2F$ $[M]^+$: 226.07482; found: 226.07496; delta=0.6 ppm.

4-[3-(Morpholin-4-yl)-4-nitrophenyl]morpholine (**3c**):



Appearance: orange solid; **LCMS purity:** >99.9%; **Mp.:** 171 – 172 ºC, (Lit.: 164-166 ºC[3]); **^{1}H NMR:** (399.8 MHz, $CDCl_3$, 25 °C) δ (ppm) 3.04 – 3.09 (m, 4H, 2 x 7-CH_2); 3.31 – 3.36 (m, 4H, 2 x 9-CH_2); 3.83 – 3.87 (m, 4H; 2 x 10-CH_2); 3.87 – 3.91 (m, 4H; 2 x 8-CH_2); 6.33 (d, 1H, *J* = 2.6; 2-CH); 6.47 (dd, 1H, *J* = 9.3; *J* = 2.6; 6-CH); 8.03 (d, 1H, *J* = 9.3; 5-CH). **^{13}C NMR:** (100.5 MHz, $CDCl_3$, 25 °C) δ (ppm) 47.2 (2 x 9- CH_2); 52.2 (2 x 7-CH_2); 66.4 (2 x 10-CH_2); 66.8 (2 x 8-CH_2); 103.3 (2-CH); 107.0 (6-CH); 129.7 (5-CH); 133.0 (4-C); 149.4 (3-C); 155.1 (1-C). **EI-HRMS:** calcd for $C_{14}H_{19}O_4N_3$ $[M]^+$: 293.13701; found: 293.13706; delta=0.18 ppm.

2.b. Preparation of nitrobenzene derivatives (3a-c) by different flow rates.

(The reactions were carried out as described previously in section 2.a.)

For flow chemistry reactions, generally Knauer *Azura* P2.1S/P4.1S or Syrris Asia® syringe pumps (in case of chip reactor) were used. In the purpose-built reactor systems the reactant's streams were joined in PEEK T-mixers (purchased from Supelco; 576611). The reactors of the continuous flow nucleophile aromatic substitution were either 1/8" – 1/16" PTFE tubing (Supelco; 58696-U – 58699) that were rolled up into coil reactors, or 1.0 mL microchip reactor (Syrris). The latter one was used with Asia® Climat Controller and Asia® Pressure Regulator, while the coil reactor's temperature was adjusted using either oil bath (heated by IKA® RTC basic stirrer, equipped with IKA® ETS-D4 fuzzy temperature controller) or a GC column heater (Merck, LaChrome, L-7350). The pressure was controlled using Zaiput® BPR-10 adjustable back pressure regulator unit.

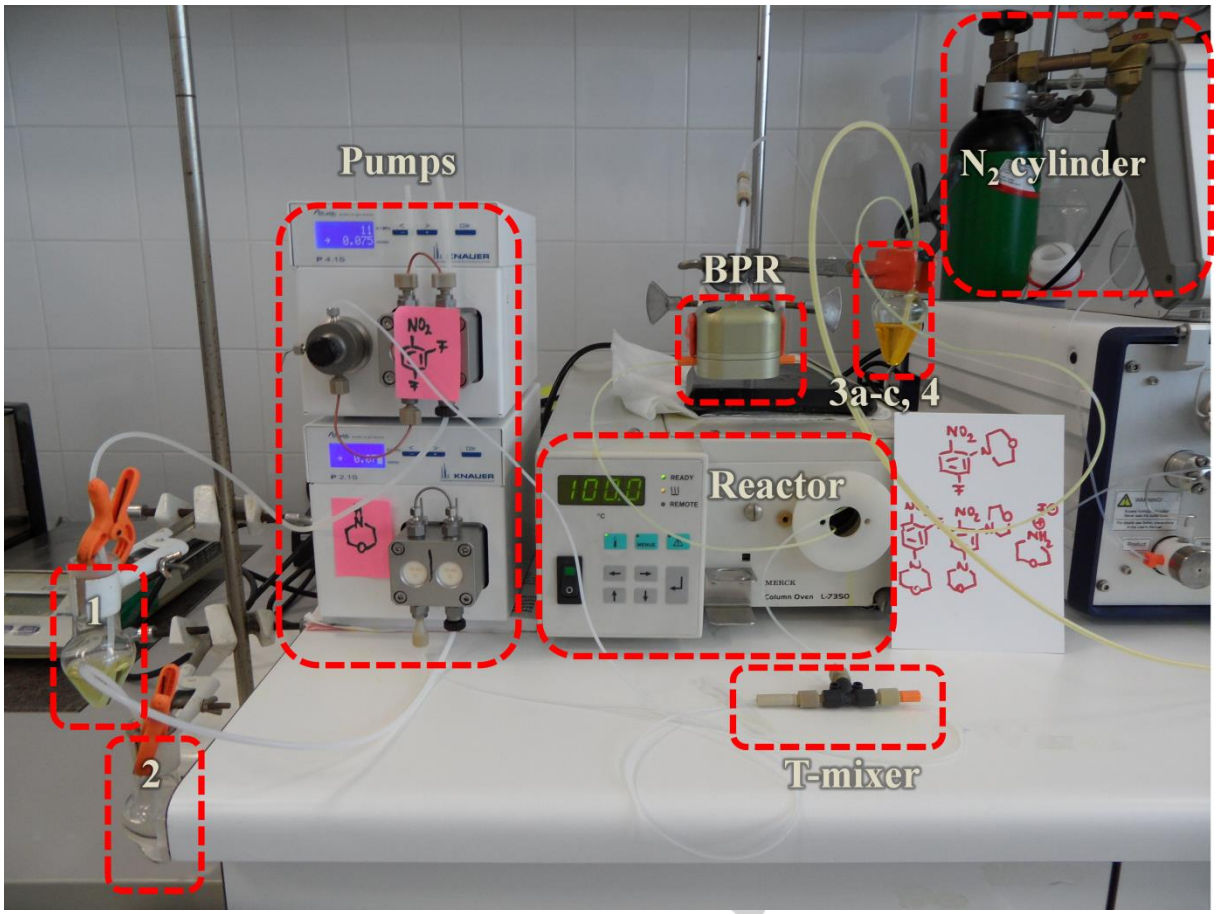


Figure S3. Detailed view of the applied system in the continuous flow S_NAr reaction.

Table S1. Regioselectivity dependence in various purpose-built reactors with different throughput.

Entry	Solv.	T (°C)	V_{react} (mL)	f_R[a] (mL min^{-1})	t_{res} (min)	p_{BPR} (bar)	Reactor's tubing Ø	Composition **3a**:**3b**:**3c** (%)	Yield (%)
1[3]	EtOH	100	10	1.0	10	8	-[b]	74:13:13[c]	96[c]
2[3]	THF	165	10	1.0	10	8	- [b]	92:5:3[c]	98[c]
3	EtOH	100	30	3.0	10	10	1/8"	84:7:9[d]	94[e]
4	EtOH	100	10	1.0	10	10	1/16"	91:6:3[f]	-
5	EtOH	100	10	0.8	12.5	10	1/16"	89:7:4[f]	-
6	EtOH	100	5	0.5	10	10	1/16"	90:7:3[f]	-
7	EtOH	100	1	0.1	10	10	1/16"	92:4:3[f]	-
8	EtOH	100	1	0.1	10	8	chip[g]	(89:6:5)[g]	-

[a] Toltal flow rate of 0.44 M solution of **1** and 0.968 M solution of **2** (2.2 ekv.) in a volumetric ratio of 1:1; [b] Vapourtec R2/R4 module. [c] Calculated from the crude product ^{1}H-NMR spectrum; [d] Calculated from the isolated yield; [e] Total isolated yield of the *orto*-, *para*- and di-substituted compounds (**3a-c**); [f] Determined by GCMS (%) measurements; [g] white precipitation (morpholine hydrofluoride) caused clogging.

3. Heterogeneous catalytic hydrogenation reactions.

The continuous heterogenic hydrogenation reactions were performed using H-Cube™ or H-Cube Pro™ (ThalesNano Inc.) devices operating with its original pumps.

3.a. The preparation and identification of 4-fluoro-2-(morpholin-4-yl)aniline (5a).

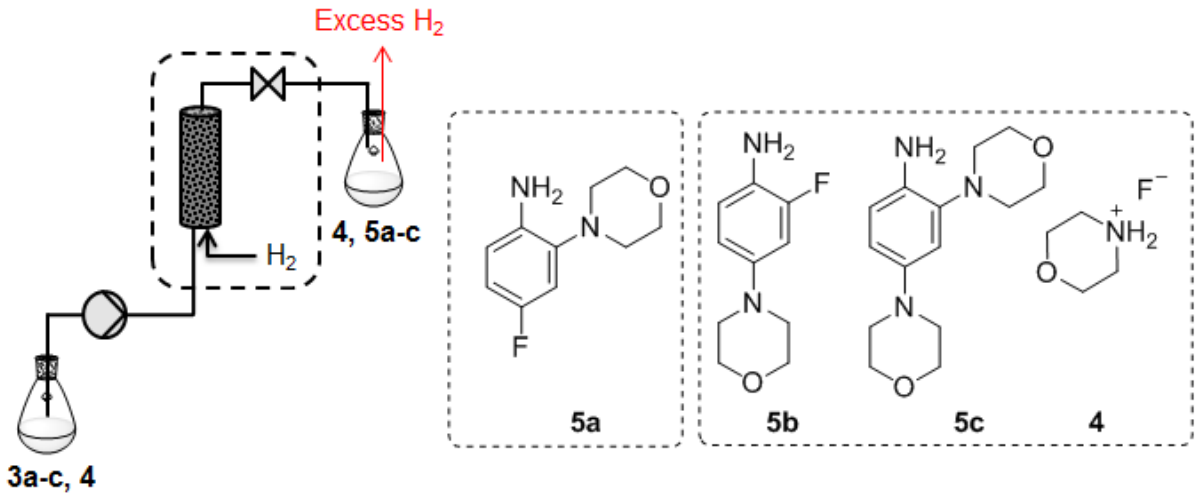
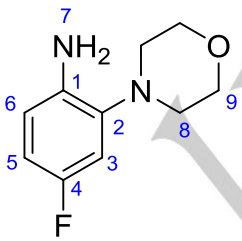


Figure 4. Schematic process for the continuous flow heterogeneous hydrogenation with H-Cube™ or H-Cube Pro™ devices.

The previously prepared (see section 2.a) reaction mixture (15 mL, 3.3 mmol **3a-c, 4**) was introduced to H-Cube™ continuous flow heterogeneous hydrogenation reactor operating in full H_2 mode (at atmospheric *in-situ* H_2 pressure) at the flow rate of 1.0 mL min^{-1} on the HPLC injector pump. The nitro group reductions were catalysed by 10% Pd/C (average particle size: 32-40 microns) catalyst bed (CatCart®), used as available from ThalesNano and were deactivated after use by introduction into sodium bisulfite solution. The reaction temperature was set to 50°C. The reaction mixture was collected after being exposed to the hydrogenation conditions in the H-Cube™ to afford quantitative conversions to the corresponding anilines (**5a-c**). It was checked by thin layer chromatography that showed no starting material **3a-c** left (*n*-hexane:etil-acetate = 2:1; R_f (**5a**) = 0.40; R_f (**5b**) = 0.31; R_f (**5c**) = 0.15; R_f (**4**) = 0.0). The reaction mixture was concentrated under reduced pressure. The residue was taken up in water (30 mL) washed with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude mixture as an off-white crystal (0.58 g). This material was purified by column chromatography (ca. 60 g silica gel) eluting with first 20% then 33% isocratic eluent of EtOAc in *n*-hexane to obtain 0.44 g (68%) 4-fluoro-2-(morpholin-4-yl)aniline **5a** as a beige solid. The by-product's (**5b**, **5c**) purity was inadequate therefore these compounds were prepared and identified from the previously purified corresponding nitro-derivatives (**3a**, **3c**), demonstrated in section 3.b. and 3.c.

4-Fluoro-2-(morpholin-4-yl)aniline (**5a**):



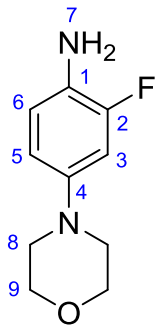
Appearance: beige solid; **GCMS purity:** >99%; **Mp.:** 109 – 111 ºC, **^{1}H NMR:** (499.9 MHz, DMSO-d_6, 25 °C) δ (ppm) 2.75 – 2.82 (m, 4H, 2 x 8-CH_2); 3.71 – 3.76 (m, 4H, 2 x 9-CH_2); 4.63 (br. s, 2H, 7-NH_2); 6.61 – 6.67 (m, 2H, 5,6-CH); 6.70 – 6.75 (m, 1H, 3-CH). **^{13}C NMR:** (125.7 MHz, DMSO-d_6, 25 °C) δ (ppm) 50.3 (2 x 8-CH_2); 66.4 (2 x 9-CH_2); 106.1 (d, *J* = 22.9; 3-CH); 109.6 (d, *J* = 21.6; 5-CH); 114.4 (d, *J* = 8.6; 6-CH); 138.5 (d, *J* = 2.0; 1-C); 138.6 (d, *J* = 7.3; 2-C); 154.5 (d, *J* = 232.1; 4-C). **ESI-HRMS:** calcd for $C_{10}H_{14}ON_2F$ $[M+H]^+$: 197.10847; found: 197.10850; delta=0.16 ppm. **p*Ka*** = 4.08 ± 0.015.

3.b. The preparation and identification of 2-fluoro-4-(morpholin-4-yl)aniline (5b)

The orange solution of **3b** (100 mg, 0.44 mmol, 226.204 g/mol) in ethanol (10 mL) was introduced to H-Cube™ continuous flow heterogeneous hydrogenation reactor operating in full H_2 mode (at atmospheric *in-situ* H_2 pressure) at the flow rate of 1.0 mL min^{-1} on the HPLC injector pump. The nitro group reductions were catalysed by 10% Pd/C (average particle size: 32-40 microns) catalyst bed (CatCart®), used as available from ThalesNano and were deactivated

after use by introduction into sodium bisulfite solution. The reaction temperature was set 50°C. The reaction mixture was collected after being exposed to the hydrogenation conditions in the H-Cube™ to afford quantitative conversions to the corresponding aniline (**5b**). The colorless reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (ca. 5 g silica gel) eluting with 20% isocratic eluent of EtOAc in *n*-hexane to obtain 39 mg (50%) of 2-fluoro-4-(morpholin-4-yl)aniline **5b** as a light brown solid.

2-Fluoro-4-(morpholin-4-yl)aniline (**5b**):

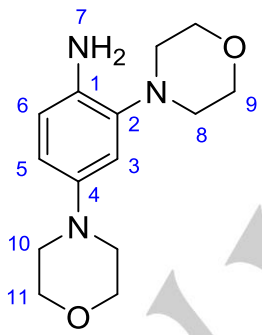


Appearance: light brown solid. **GCMS purity:** >95%; **Mp.:** 95 – 97 °C, **^{1}H NMR:** (499.9 MHz, DMSO-d_6, 25 °C) δ (ppm) 2.87 – 2.93 (m, 4H, 2 x 8-CH_2); 3.66 – 3.73 (m, 4H, 2 x 9-CH_2); 4.62 (br. s, 2H, 7-NH_2); 6.53 (dd, 1H, *J* = 8.6; *J* = 2.5; 5-CH); 6.66 (dd, 1H, *J* = 14.3; *J* = 2.5; 3-CH) 6.69 (dd, 1H, *J* = 9.9; *J* = 8.6; 6-CH). **^{13}C NMR:** (125.7 MHz, DMSO-d_6, 25 °C) δ (ppm) 49.8 (2 x 8-CH_2); 66.0 (2 x 9-CH_2); 103.8 (d, *J* = 21.7; 3-CH); 112.1 (d, *J* = 2.7; 5-CH); 116.9 (d, *J* = 5.7; 6-CH); 128.9 (d, *J* = 13.1; 1-C); 142.9 (d, *J* = 7.9; 4-C); 151.1 (d, *J* = 235.9; 2-C). **ESI-HRMS:** calcd for $C_{10}H_{14}ON_2F$ $[M+H]^+$: 197.10847; found: 197.10856; delta=0.47 ppm. **p*Ka* =** 4.06 ± 0.029.

3.c. The preparation and identification of 2,4-bis(morpholin-4-yl)aniline (5c).

The yellow solution of **3c** (120 mg, 0.41 mmol, 293.318 g/mol) in ethanol (12 mL) was introduced to H-Cube™ continuous flow heterogeneous hydrogenation reactor operating in full H_2 mode (at atmospheric *in-situ* H_2 pressure) at the flow rate of 1.0 mL min^{-1} on the HPLC injector pump. The nitro group reductions were catalysed by 10% Pd/C (average particle size: 32-40 microns) catalyst bed (CatCart®), used as available from ThalesNano and were deactivated after use by introduction into sodium bisulfite solution. The reaction temperature was set 50°C. The reaction mixture was collected after being exposed to the hydrogenation conditions in the H-Cube™ to afford quantitative conversions to the corresponding aniline (**5c**). The colourless reaction mixture was concentrated under reduced pressure to obtain 105.3 mg (98%) of **5b** as a light brown crystal without further purification.

2,4-Bis(morpholin-4-yl)aniline (**5c**):



Appearance: light brown crystal; **GCMS purity:** >98%; **Mp.:** 159 – 161 °C, **^{1}H NMR:** (499.9 MHz, DMSO-d_6, 25 °C) δ (ppm) 2.77 – 2.81 (m, 4H, 2 x 8-CH_2); 2.88 – 2.92 (m, 4H, 2 x 10-CH_2); 3.68 – 3.71 (m, 4H, 2 x 11-CH_2); 3.71 – 3.75 (m, 4H, 2 x 9-CH_2); 4.35 (br. s, 2H, 7-NH_2); 6.46 (dd, 1H, *J* = 8.5; *J* = 2.6; 5-CH); 6.55 (d, 1H, *J* = 2.6; 3-CH) 6.59 (d, 1H, *J* = 8.5; 6-CH). **^{13}C NMR:** (125.7 MHz, DMSO-d_6, 25 °C) δ (ppm) 50.4 (2 x 10-CH_2); 50.5 (2 x 8-CH_2); 66.1 (2 x 11-CH_2); 66.4 (2 x 9-CH_2); 108.5 (3-CH); 111.9 (5-CH); 114.8 (6-CH); 135.8 (1-C); 138.5 (2-C); 143.2 (4-C). **ESI-HRMS:** calcd for $C_{10}H_{22}O_2N_3$ $[M+H]^+$: 264.17065; found: 264.17074; delta=0.33 ppm. **p*Ka* =** 4.76 ± 0.023.

3.d. Measurement of 10% Pd/C cartridge activity over time.

Previously made mixture of nitro-compounds (**3a-c**) with the method: (Table S1, Entry 4) was introduced to H-Cube Pro™ reactor continuous flow heterogeneous hydrogenation reactor operating with 100% of hydrogen prepared *in-situ* (60 mL min^{-1}). The reduction was catalysed by a 30 mm 10% Pd/C cartridge (ThalesNano). The reaction temperature was set to 50°C and the flow rate was set to 0.1 mL min^{-1} on the HPLC pump. The sample collector flasks were exchanged the time specified in Table S2; and the collected reaction mixtures were analysed by GCMS.

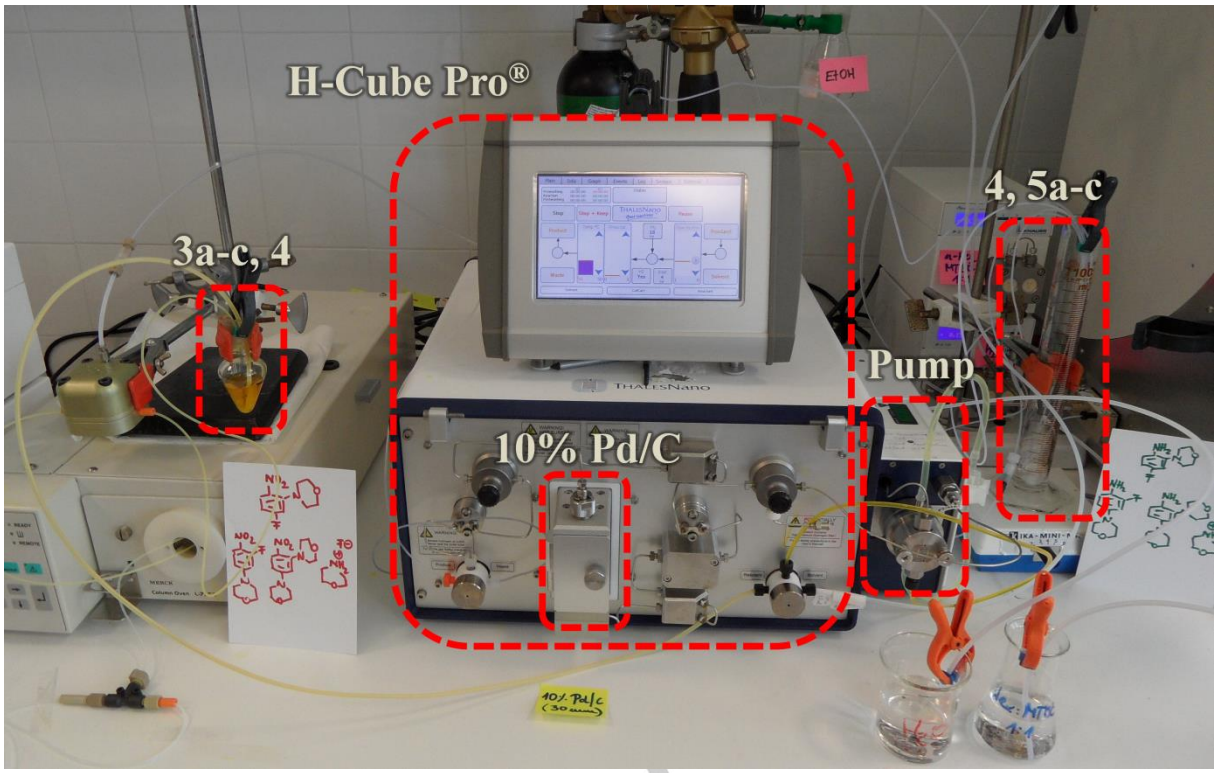


Figure S5. Detailed view of the applied continuous flow reactor system in the hydrogenation reaction.

Table S2. Measurement of the 10% Pd/C CatCart® (30 mm) activity and the selectivity in the reduction over time.

Entry	Time (h)	GCMS (%)[a]				
		Conversion	**5a**	**5b**	**5c**	by-products
1	0.5	100	88	4	5	3
2	1	100	82	5	12	2
3	2	100	80	5	14	1
4	3	100	81	5	13	1
5	4	100	83	5	12	1
6	5	100	83	5	11	1
7	6	100	83	5	12	0
8	7	100	83	6	11	1
9	23	100	83	5	12	0
10	24	100	79	6	15	0
11	25	100	79	6	15	0
12	30	100	80	5	12	3
13[b]	**-**	**100 (0)**	**81.5 (1.8)**	**5.4 (0.3)**	**12.3 (1.4)**	**0.8 (0.8)**

[a] Calculated by GCMS measurements; [b] average of 12 from entry 1 to 12, with deviation in parenthesis.

4. General procedure for determination of the partition coefficients and settling time

In separation techniques, the appropriate setting of the thermodynamic parameters is of great importance. In CPC as a rule of thumb the partition coefficients ($K_{u/l}=c_u/c_l$) should be around in the range $0.5 < K_{u/l} < 1.0$, and the settling time should be no more than 20 sec[4].

To approx. 8 mL vials, 5 - 5 mg of the crude anilines mixture (**4**, **5a-c**) was weighted in along with every solvents independently (to total volume of 5 mL) that contains the two-phase solvent systems were tested. The mixtures were homogenized by vortex shaker (IKA® *K* MS1 Minishaker) at 2200 rpm for 4 sec, after that the vials immediately placed in an up-right position to measure the time required for the two phases to form clear layers with a distinct interface by stopper watch. The two-phase were analysed by GCMS measurements. These experiments were performed in the linear range, thereof there is a directly proportional relationship between the method response and the analyte concentration. The partition coefficient can be determined by the ratio of the corresponding peak areas (*K* = peak area of the compound in the upper phase divided by the peak area of the compound in the lower phase).

The partition coefficients and the settling times in the corresponding biphasic liquid systems (BLSs) can be found in Table S3.

Table S3. Results of the settling times and partition coefficients for each BLS.

Entry	Volumetric Ratio of the BLSs[a]							$K_{U/L}$[b]			Settling time
	n-Hex	EtOH	EtOAc	*n*-BuOH	H_2O	MTBE	ACN	*K*(**5a**)	*K*(**5a**)	*K*(**5a**)	(s)
1			2.0	0.5	2.5[c]			74.74	20.16	26.01	20
2			1.5	1.0	2.5[c]			69.41	19.52	28.19	36
3			1.0	1.5	2.5[c]			55.33	14.61	22.62	27
4			0.5	2.0	2.5[c]			52.40	12.08	21.46	25
5				1.05	1.30[c]	1.60	1.05	23.17	9.14	11.00	>60
6				1.0	2.5[c]	1.0	0.5	31.50	11.76	16.14	27
7	9.5	5.0	0.5		5.0[d]			0.44	0.01	0.08	9
8	9.0	5.0	1.0		5.0[d]			0.52	0.09	0.07	2
9	8.5	5.0	1.5		5.0[d]			0.58	0.12	0.10	52
10	8.0	5.0	2.0		5.0[d]			0.75	0.17	0.12	>60
11	7.5	5.0	2.5		5.0[d]			1.01	0.25	0.19	>60
12	7.0	5.0	3.0		5.0[d]			0.96	0.26	0.19	19
13	9.0	2.5	1.0		7.5[d]			3.99	0.32	0.18	5
14	7.5	2.5	2.5		7.5[d]			6.69	0.75	0.43	>60
15	7.5	2.5	2.5		7.5			6.05	0.63	0.22	38
16	8.0	2.5	2.0		7.5[d]			5.46	0.58	0.24	20
17	8.0	2.5	2.0		7.5			5.48	0.58	0.23	2
18	9.0	5.0			5.0	1.0		0.51	0.09	0.08	2
19	**1.0**	**1.0**			**1.0**	**1.0**		**1.86**	**0.49**	**0.24**	**16**

[a] The BLS contains the following solvents in the described volumetric ratio: *n*-hexane (*n*-Hex), ethanol (EtOH), ethyl acetate (EtOAc), *n*-buthanol (*n*-BuOH), methyl tert-butyl ether (MTBE) and acetonitrile (ACN); [b] Calculated by GCMS measurements, [c] Phosphate buffer solution (pH=5.5) made from 278 mL of 0.2M Na_2HPO_4 solution, 222 mL of 0.1M citric acid solution and 500 mL water; [d] Acetate buffer solution (pH=5.4) made from 29 mL of 0.1M acetic acid solution and 171 mL of 0.1M sodium acetate solution.

5. Results for determination of the lower phase solvents contents

The lower phase solvents contents of the chosen solvent system (*n*-Hex:MTBE:EtOH:H_2O=1:1:1:1) was determined by GC-FID+KF titration or ^{1}H NMR+KF analyzes. Biphasic systems (1L) were prepared by mixing the selected solvents in a separatory funnel in suitable proportions (250 mL each). They were vigorously shaken and then allowed to settle until the phases became limpid and then the lower phase was separated from the upper phase and analyzed by the corresponding methods shown in Table S4.

Table S4. Results of the solvent content determination by different methods.

		v/v (%)[a]			
Entry	Method	H_2O	EtOH	MTBE	*n*-Hex
1	^{1}H NMR[b]+KF	54.4	40.6	5.0	~0.1
2	GC-FID+KF	52.7	39.0	8.3	0
3[c]	combined	53.0	40.0	7.0	0

[a] Calculated from m/m% of GC-FID and m/m% of KF measurement or n/n% of ^{1}H NMR and m/m% of KF measurement. [b] 10 µL of sample in 0.75 mL of acetone-d_6 at room temperature; [c] average of the two applied method's (Entry 1 and 2) results.

6. Procedures for purification with centrifugal partition chromatography

6.a. Simple CPC separation in ascending mode.

Biphasic systems (2L) were prepared by mixing the selected solvents (*n*-Hex:MTBE:EtOH: H_2O=1:1:1:1) in a separatory funnel in suitable proportions (500 mL each). They were vigorously shaken and then allowed to settle until the phases became limpid and then the lower phase (1950 mL) was separated from the upper phase (1870 mL). In ascending mode the lower phase, with a higher aqueous content, was used as stationary phase. The column was washed and filled with the stationary phase and equilibrated with the upper, mobile phase that flow rate was set at 5 mL min^{-1} while the rotational speed of the centrifuge was set at 2000 rpm and the back pressure regulator to max. 110 bar. These conditions were the same during the elution. The retention of the stationary phase in the centrifuge was 56% (44 mL of stationary phase was collected during the equilibration). The sample was made from 200 mg of crude anilines (**4**, **5a-c**; see section 3.d.) dissolved in 10 mL of lower phase. The samples were introduced into the CPC column through loop with manual injection. The effluent was monitored by UV-Vis detector that was set on two wavelengths (collection at 240 nm and 300 nm) and continuous scan of whole spectrum (from 200 to 600 nm) at the same time.

The fractions containing the desired product (**5a**) were collected and concentrated under reduced pressure to obtain 97.5 mg of **5a** as a light brown crystal. The GCMS purity of the product was 99.6%. The chromatogram of the separation is shown in Figure S6.

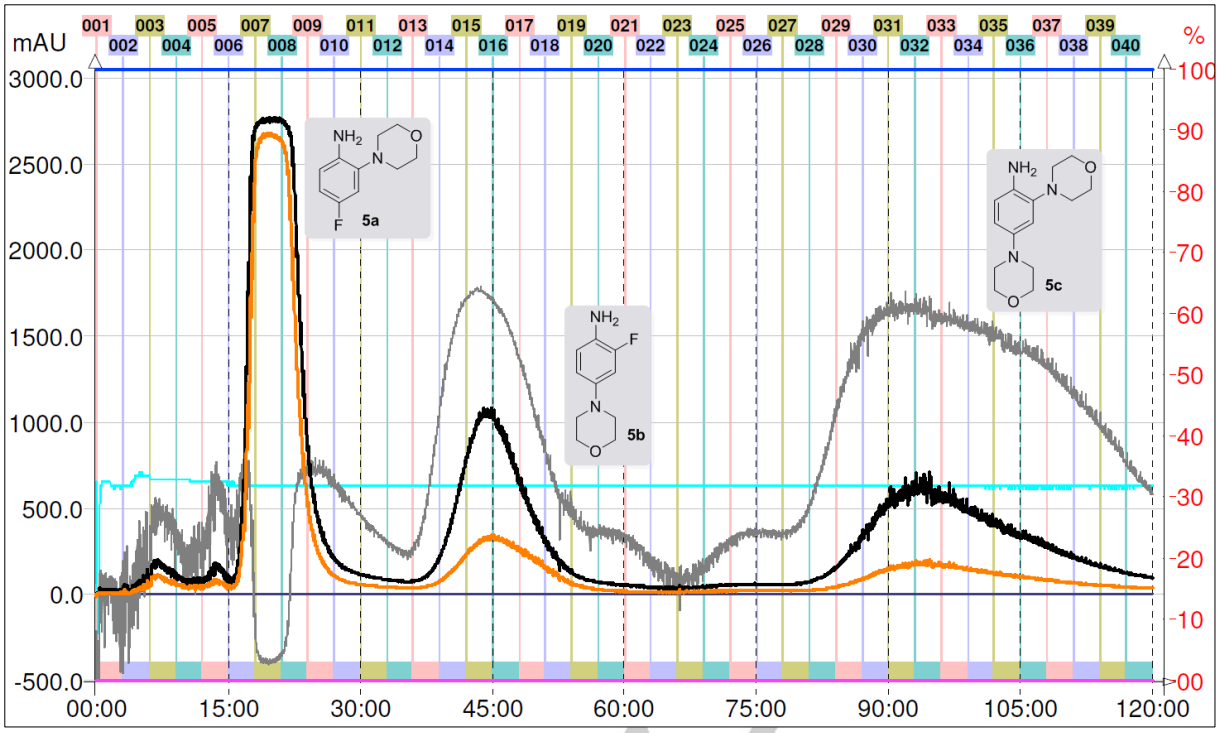


Figure S6. Chromatogram of the CPC separation in single ascending mode. Keys to the chromatograms are the following (applicable for all chromatogram): orange line: absorbance at 240 nm; black line: absorbance at 300 nm; grey line: differentiation of these two signal difference; light blue: back pressure; dark blue line: upper phase percentage as the mobile phase; green line: lower phase percentage as the mobile phase. The horizontal axis shows always the retention time in minutes.

6.b. Simple CPC separation in descending mode

Biphasic systems (*n*-Hex:MTBE:EtOH:H_2O=1:1:1:1) were made previously described (see section 6.a.). In descending mode the upper phase used as stationary phase. The column was washed and filled with the stationary phase and equilibrated with the lower, mobile phase that flow rate was set at 5 mL min^{-1} while the rotational speed of the centrifuge was set at 2000 rpm and the back pressure regulator to max. 110 bar. These conditions were the same during the elution. The retention of the stationary phase in the centrifuge was 47% (53 mL of stationary phase was collected during the equilibration). The sample was made from 200 mg of crude anilines (**4**, **5a-c**; see section 3.d.) dissolved in 10 mL of lower phase. The samples were introduced into the CPC column through loop with manual injection. The effluent was monitored by UV-Vis detector that was set on two wavelengths (collection at 240 nm and 300 nm) and continuous scan of whole spectrum (from 200 to 600 nm) at the same time. The fractions containing the desired product (**5a**) were collected and concentrated under reduced pressure to obtain 87.9 mg of **5a** as a light brown crystal. The GCMS purity of the product was over 99.99%. The chromatogram of the separation is shown in Figure S7.

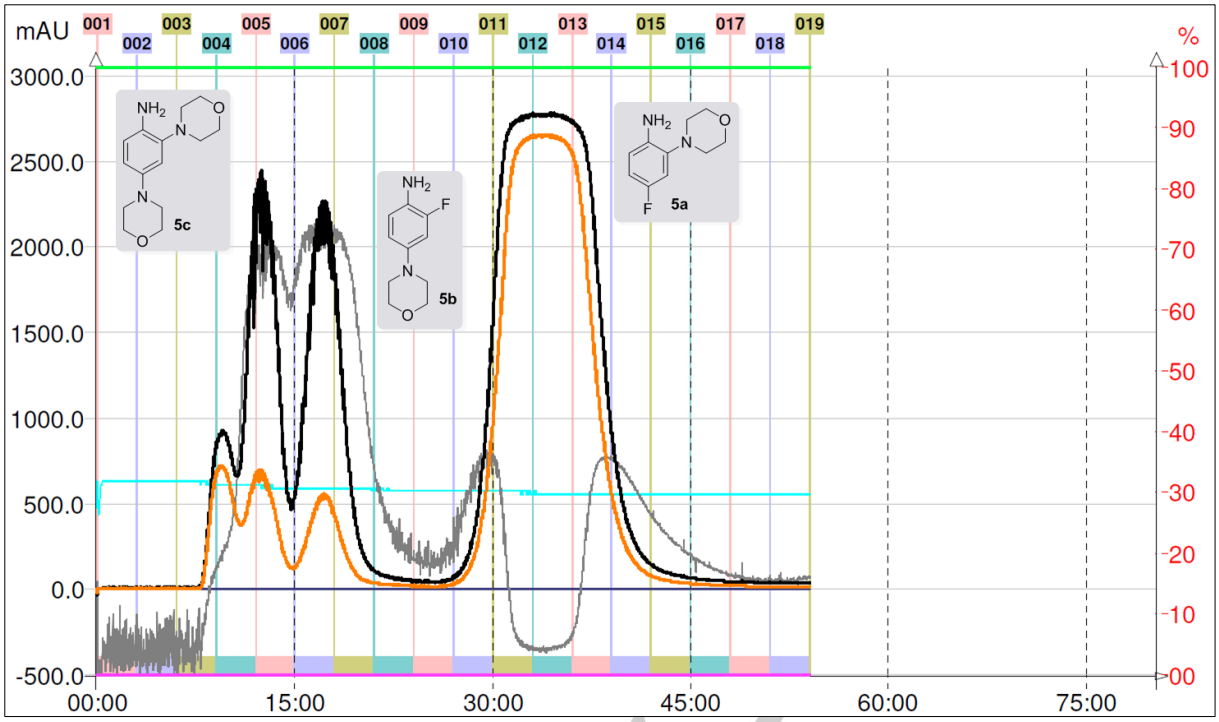


Figure S7. Chromatogram of the CPC separation in single descending mode.

6.c. CPC separation in multiple dual-mode (MDM) with sample injection through loop

Biphasic systems (*n*-Hex:MTBE:EtOH:H_2O=1:1:1:1) were made as previously described (section 6.a.). The sequence was started in descending mode; therefore the upper phase was used as stationary phase. The column was washed and filled with the stationary phase and equilibrated with the lower, mobile phase that flow rate was set at 5 mL min^{-1} while the rotational speed of the centrifuge was set at 2000 rpm and the back pressure regulator to max. 110 bar. These conditions were the same during the elution. The retention of the stationary phase in the centrifuge was 47% (53 mL of stationary phase was collected during the equilibration). The samples were made from 5 x 100 mg of crude anilines (**4**, **5a-c**; see section 3.d.) dissolved in 5 x 5 mL of lower phase. The samples were introduced into the CPC column through loop with manual injection demonstrated in Table S5. The effluent was monitored by UV-Vis detector that was set on two wavelengths (collection at 240 nm and 300 nm) and continuous scan of whole spectrum (from 200 to 600 nm) at the same time.

Table S5. CPC elution in MDM with 5 sample injections (through loop).

Entry[a]	Injection	Interval (min)[b]	Valve position		Mobile phase[c]		Mode	
1	1.[d]	0-5	Inj.	-	L	-	Desc.	-
2	-	5-25	-	Load	L	-	Desc.	-
3	2.[d]	25-30	Inj.	-	-	U	-	Asc.
4	-	30-50	-	Load	-	U	-	Asc.
5	3.[d]	50-55	Inj.	-	L	-	Desc.	-
6	-	55-75	-	Load	L	-	Desc.	-
7	4.[d]	75-80	Inj.	-	-	U	-	Asc.
8	-	80-100	-	Load	-	U	-	Asc.
9	5.[d]	100-105	Inj.	-	L	-	Desc.	-
10	-	105-125	-	Load	L	-	Desc.	-
11	-[e]	125-170	Inj	-	-	U	-	Asc.

[a] Mobile phases flow rate: 5 mL min^{-1}; rotational speed of the centrifuge: 2000 rpm; max back pressure: 110 bar. Detection at Chanel 1: 240 nm (collection); Chanel 2: 300 nm; Chanel 3: Scan (200-600 nm.); [b] After the equilibration elution starts with a descending mode (loop filled up with sample solution); [c] L = lower phase; U = upper phase; [d] 25 min elution; [e] 45 min elution.

The fractions containing the desired product (**5a**) were collected and concentrated to obtain 249 mg of **5a** as a light brown crystal. The GCMS purity of the product was over 99.99%. The chromatogram of the separation is shown in Figure S8.

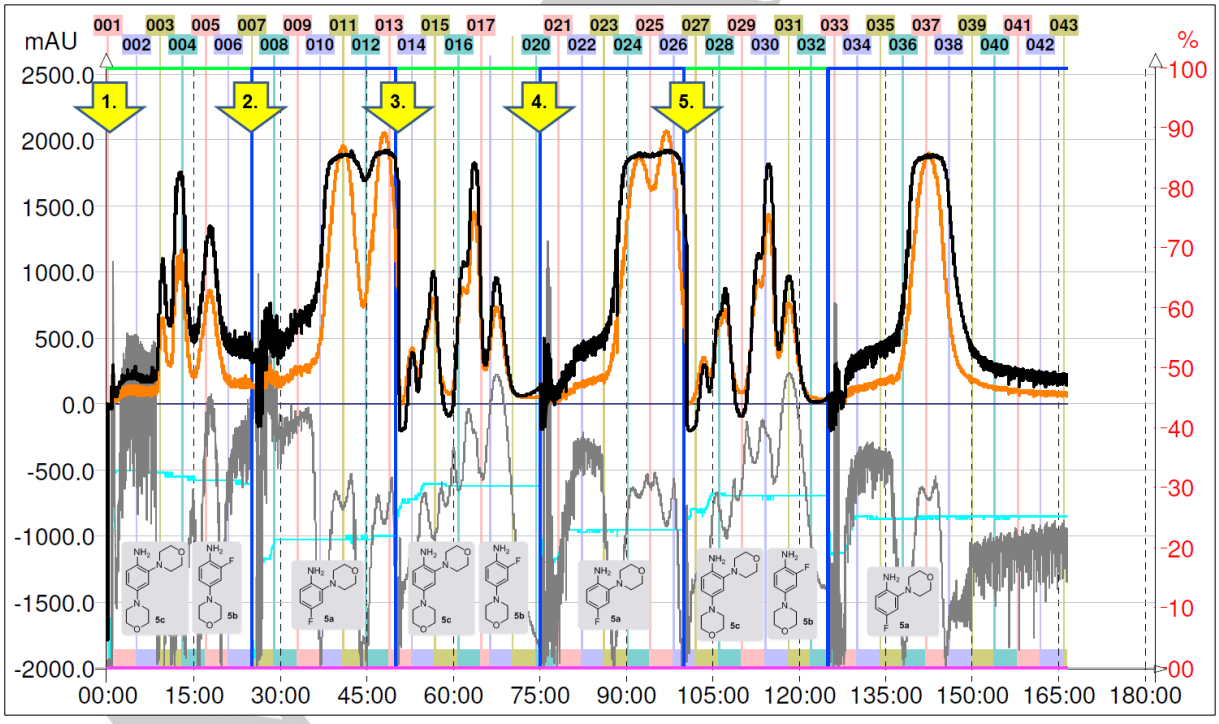


Figure S8. Chromatogram of the CPC separation in MDM with 5 injections. The yellow arrows show which sample injections take place and when.

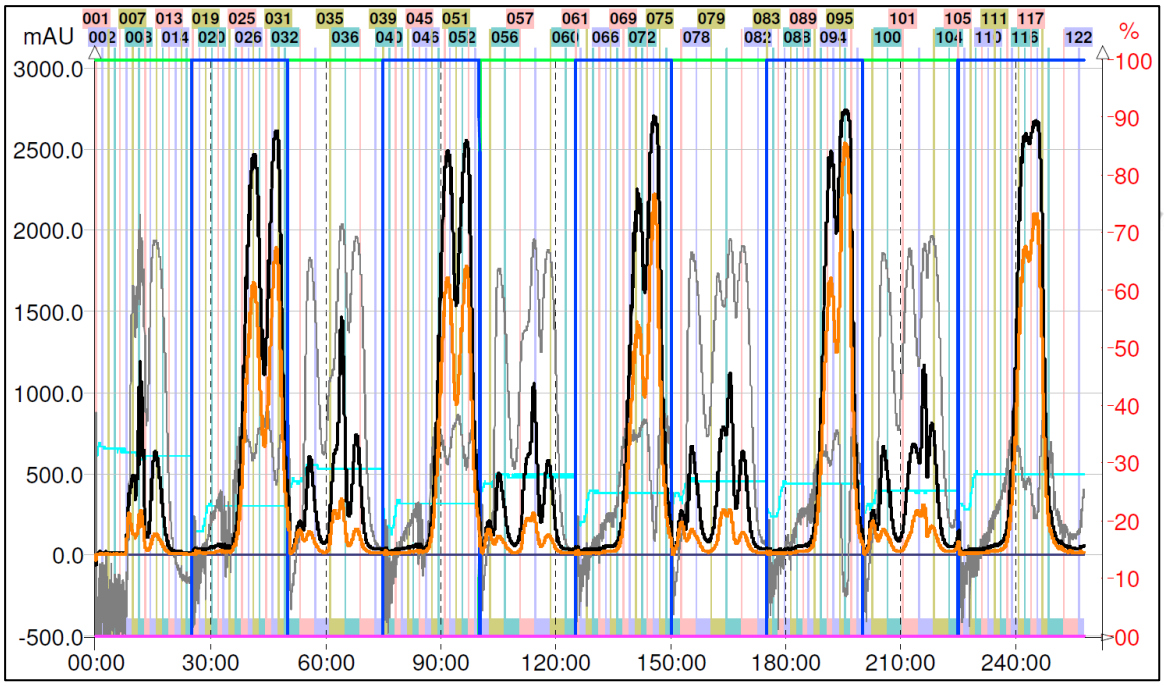


Figure S9. Chromatogram of the CPC separation in MDM with 10 injections.

Table S6. CPC elution in MDM with 10 sample injections (through loop).

Entry[a]	Injection	Interval (min)[b]	Loop valve position		Mobile phase[c]		Mode	
1	1.[d]	0-5	Inj.	-	L	-	Desc.	-
2	-	5-25	-	Load	L	-	Desc.	-
3	2.[d]	25-30	Inj.	-	-	U	-	Asc.
4	-	30-50	-	Load	-	U	-	Asc.
5	3.[d]	50-55	Inj.	-	L	-	Desc.	-
6	-	55-75	-	Load	L	-	Desc.	-
7	4.[d]	75-80	Inj.	-	-	U	-	Asc.
8	-	80-100	-	Load	-	U	-	Asc.
9	5.[d]	100-105	Inj.	-	L	-	Desc.	-
10	-	105-125	-	Load	L	-	Desc.	-
11	6.[d]	100-105	Inj.	-	-	U	-	Asc.
12	-	105-125	-	Load	-	U	-	Asc.
13	7.[d]	125-130	Inj.	-	L	-	Desc.	-
14	-	130-150	-	Load	L	-	Desc.	-
15	8.[d]	150-155	Inj.	-	-	U	-	Asc.
16	-	155-175	-	Load	-	U	-	Asc.
17	9.[d]	175-180	Inj.	-	L	-	Desc.	-
18	-	180-200	-	Load	L	-	Desc.	-
19	10.[e]	200-245	Inj.	-	-	U		Asc.

[a] Mobile phases flow rate: 5 mL min^{-1}; rotational speed of the centrifuge: 2000 rpm; max back pressure: 110 bar. Detection at Chanel 1: 240 nm (collection); Chanel 2: 300 nm; Chanel 3: Scan (200-600 nm.) [b] After the equilibration elution starts with a descending mode (loop filled up with sample solution); [c] L = lower phase; U = upper phase; [d] 25 min elution; [e] 45 min elution.

However, the purity of the desired compound was excellent we performed the same experiment for longer period of time to ensure stability of the system over time. The parameters of the purification were the same described above with a modification of the concentration and number of injected samples which were made from 10 x 50 mg of crude anilines (**4**, **5a-c**; see section 3.d.) dissolved in 10 x 5 mL of lower phase. The samples were introduced into the CPC column through loop with manual injection demonstrated in Table S6. The fractions containing the desired product (**5a**) were collected and concentrated to obtain 247 mg of **5a** as a light brown crystal. The GCMS purity of the product was over 99.99%. The recovery of **5a** was 91% calculated from the by-products mass and **5a** contents. The chromatogram of the separation is shown in Figure S9.

7. Automation and optimization multiple dual-mode purification

7.a. Automation and optimization of the sample intake in MDM-CPC separation (through built-in pumps).

In order to be able coupling of a flow reactor with CPC, we had to automated the intake of the sample mixture. The 'Spot Prep II' system, controlled by 'Armen Glider CPC' software made possible to connect the two eluting phases and the sample solution with the built-in pumps through a magnetically operated valves. MDM sequence is shown in Table S7

Table S7. MDM-CPC purification with automated sample intake (10 times).

Entry[a]	'Injection'	Interval (min)	Period (min)	Mobile phase (intake)[b]			Mode	
1	1.	0-1	1	S	-	-	Desc.	-
2	-	1-26	25	-	L	-	Desc.	-
3	2.	26-27	1	S	-	-	-	Asc.
4	-	27-52	25	-	-	U	-	Asc.
5	3.	52-53	1	S	-	-	Desc.	-
6	-	53-78	25	-	L	-	Desc.	-
7	4.	78-79	1	S	-	-	-	Asc.
8	-	79-104	25	-	-	U	-	Asc.
9	5.	104-105	1	S	-	-	Desc.	-
10	-	105-130	25	-	L	-	Desc.	-
11	6.	130-131	1	S	-	-	-	Asc.
12	-	131-156	25	-	-	U	-	Asc.
13	7.	156-157	1	S	-	-	Desc.	-
14	-	157-182	25	-	L	-	Desc.	-
15	8.	182-183	1	S	-	-	-	Asc.
16	-	183-208	25	-	-	U	-	Asc.
17	9.	208-209	1	S	-	-	Desc.	-
18	-	209-234	25	-	L	-	Desc.	-
19	10.	234-235	1	S	-	-	-	Asc.
20	-	235-280	45	-	-	U	-	Asc.

[a] Mobile phases (and sample solution's) flow rate: 5 mL min^{-1}; rotational speed of the centrifuge: 2000 rpm; max back pressure: 110 bar. Detection at Chanel 1: 240 nm (collection); Chanel 2: 300 nm; Chanel 3: Scan (200-600 nm.) [b] S = sample solution; L = lower phase; U = upper phase.

and its chromatogram of the separation is shown in Figure S10.The sample solution was made from 500 mg of crude anilines (**4**, **5a-c**; see section 3.d.).

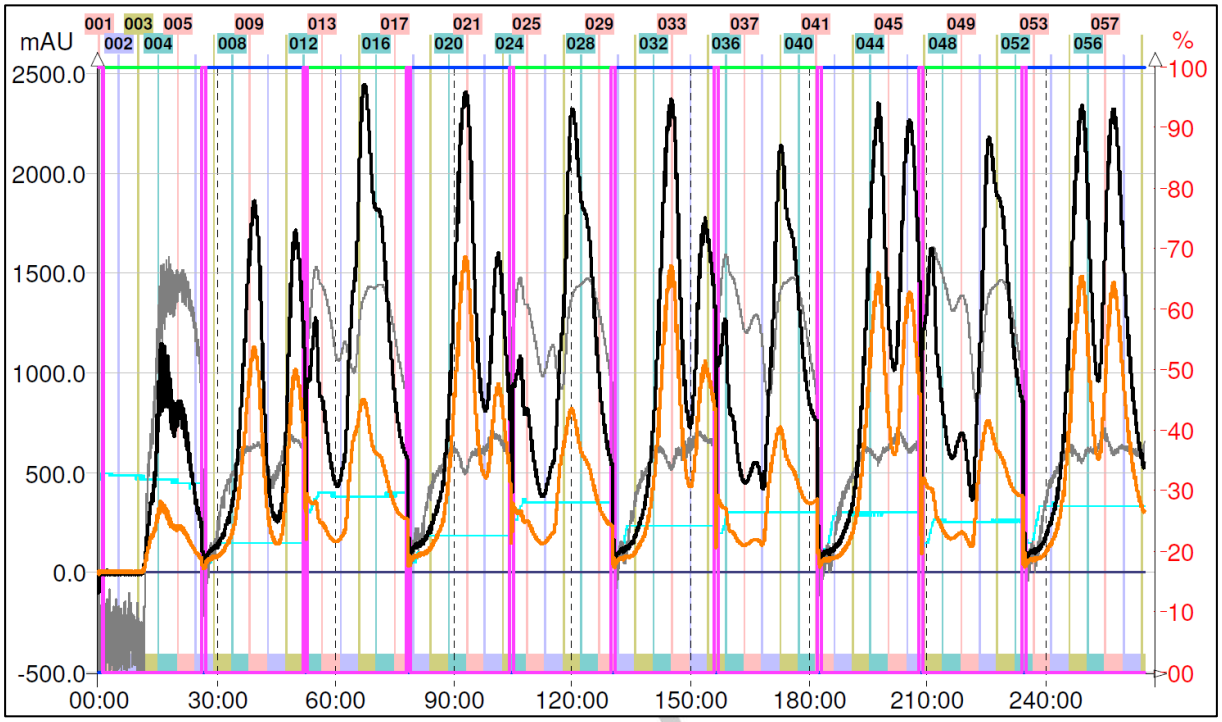


Figure S9. Chromatogram of the automated CPC separation in MDM with 10 injections.

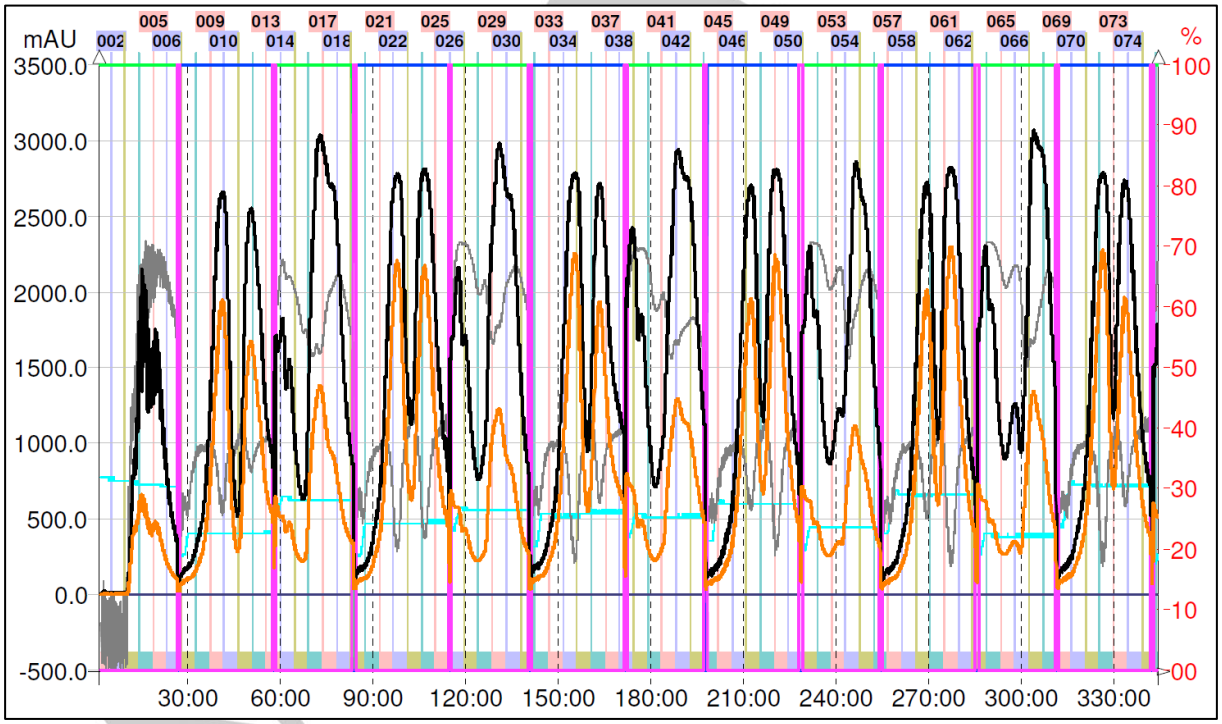


Figure S10. Chromatogram of the automated asymmetric elution MDM-CPC with 12 sample 'injections'.

Table S8. Automated MDM-CPC (intake 12 times) with asymmetric elution.

Entry[a]	'Injection'	Interval (min)	Period (min)	Mobile phase (intake)[b]			Mode	
1	1.	0-1	1	S	-	-	Desc.	-
2	-	1-26	25	-	L	-	Desc.	-
3	2.	26-27	1	S	-	-	-	Asc.
4	-	27-57	30	-	-	U	-	Asc.
5	3.	57-58	1	S	-	-	Desc.	-
6	-	58-83	25	-	L	-	Desc.	-
7	4.	83-84	1	S	-	-	-	Asc.
8	-	84-114	30	-	-	U	-	Asc.
9	5.	114-115	1	S	-	-	Desc.	-
10	-	115-140	25	-	L	-	Desc.	-
11	6.	140-141	1	S	-	-	-	Asc.
12	-	141-171	30	-	-	U	-	Asc.
13	7.	171-172	1	S	-	-	Desc.	-
14	-	172-197	25	-	L	-	Desc.	-
15	8.	197-198	1	S	-	-	-	Asc.
16	-	198-228	30	-	-	U	-	Asc.
17	9.	228-229	1	S	-	-	Desc.	-
18	-	229-254	25	-	L	-	Desc.	-
19	10.	254-255	1	S	-	-	-	Asc.
20	-	255-285	30	-	-	U	-	Asc.
21	11.	285-286	1	S	-	-	Desc.	-
22	-	286-311	25	-	L	-	Desc.	-
23	12.	311-312	1	S	-	-	-	Asc.
24	-	312-342	30	-	-	U	-	Asc.

[a] Mobile phases (and sample solution's) flow rate: 5 mL min^{-1}; rotational speed of the centrifuge: 2000 rpm; max back pressure: 110 bar. Detection at Chanel 1: 240 nm (collection); Chanel 2: 300 nm; Chanel 3: Scan (200-600 nm.)
[b] S = Sample solution; L = lower phase; U = upper phase.

dissolved in 50 mL of lower phase. The fractions containing the desired product (**5a**) were collected and concentrated to obtain 224 mg of **5a** as a light brown crystal. The GCMS purity of the product was 98.7%. The chromatogram of the separation is shown in Figure S10.

Nevertheless, the purity of **5a** was still high, due to the increased dead volume before the column, product's peaks drifted apart. To avoid loss of the product and keep the high purity, we investigated the possibility of increasing the elution time in ascending mode and create an asymmetric elution. The sample solution was made from 1.2 g of crude anilines (**4**, **5a-c**; see section 3.d.) dissolved in 60 mL of lower phase. The fractions containing the desired product (**5a**) were collected and concentrated to obtain 646 mg of **5a** as a light brown crystal. The GCMS purity of the product was 98.7%. The chromatogram of the separation is shown in Figure S10. MDM sequence of the experiment shown in Table S8.

In this constallation the purity of **5a** remained high although the amount of the product increased in comparison to the symmetric elution (see Table S7; Figure S9).

8. Coupling of the two-step synthesis and MDM CPC purification

8.a. Investigating the possibility of the sample intake in two-phase.

Biphasic system of the sample (*n*-Hex:MTBE:EtOH:H_2O=1:1:1:1) was made from 20 mL of previously synthetized anilines solution in ethanol (**4**, **5a-c**; see section 3.d.) mixed together with 20 mL of each corresponding solvents (MTBE, H_2O, *n*-Hex) in a separatory funnel. They were vigorously shaken and then allowed to settle until the phases became limpid and then the lower phase was separated from the upper phase. MDM sequence of the experiment shown in Table S9. The chromatogram of the separation is shown in Figure S11.

The fractions containing the desired product (**5a**) were collected and concentrated to obtain 606 mg of **5a** as a light brown crystal.

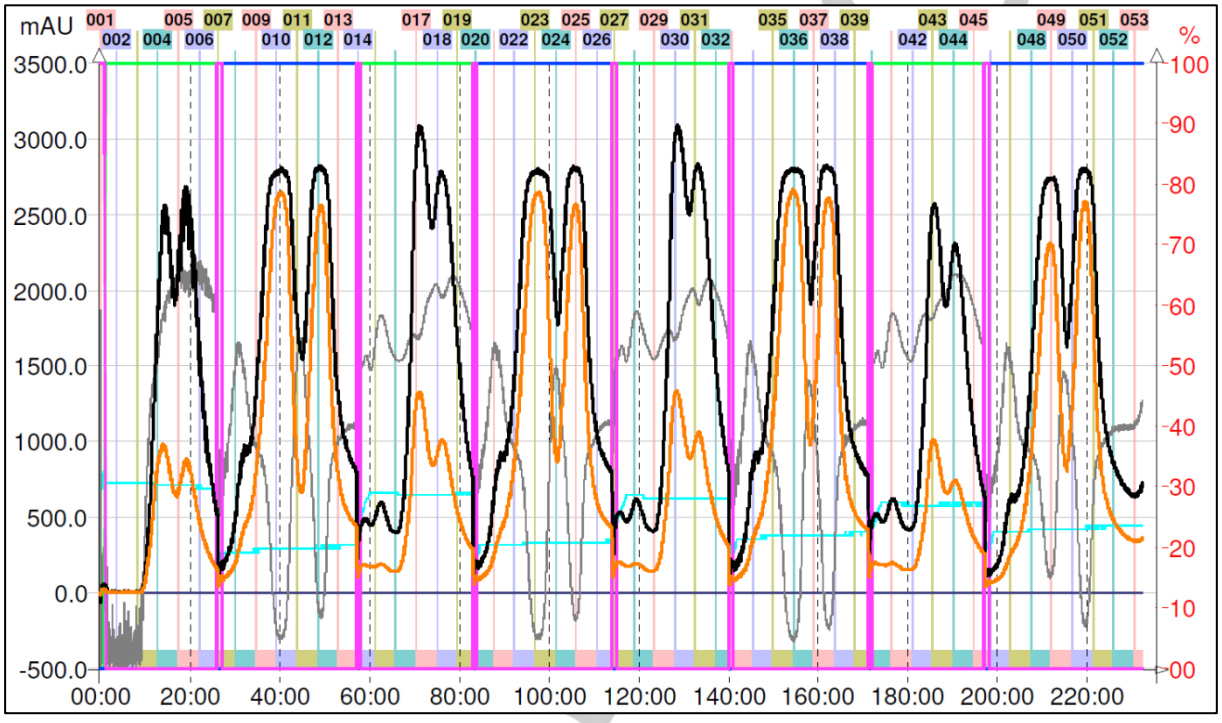


Figure S11. Chromatogram of the automated asymmetric elution MDM-CPC with 8 sample 'injections' in two-phases.

Although GCMS purity of the product was 98.1% it could be higher because 1.5% of the impurities (1.9%) was **3a** nitro-intermediate which means the catalytic hydrogenation reaction was not complete due to decreased catalyst activity. If 98.1% purity is acceptable the yield for the two steps is a bit over 70%, and the recovery of the main product is almost 87%.

8.b. Coupling the two-step synthesis and MDM CPC purification with two-phase intake method.

The keystone of the process is buffer flask between the flow reactors and the purification unit, which used as a gas-liquid separator simultaneously in this case. The inlet flow rate must be synchronized to the outlet flow rate in the time period of a descending and ascending elution and it's two sample intake (1+25+1+30 min) considering the sample solvent content (e.g. additional solvents flow rate) and dilatation or contraction of the solvent system. It means that 20 mL of the biphasic system's production needed in 57 minutes of time (two times sample intake for a minute at a flow rate of 10 mL min^{-1}), which gives us a flow rate of 87.8 µL min^{-1} of each additional solvents (MTBE, *n*-Hex, water) as well as the reaction mixture in EtOH. For the sake of simplicity it was rounded up to 100 µL min^{-1}. During almost an hour (57

Table S9. Automated MDM-CPC (intake 8 times in two phases) with asymmetric elution.

Entry [a]	'Injection'	Interval (min)	Period (min)	Mobile phase (intake)[b]			Flow rate (mL min^{-1})	Mode	
1	1.	0-1	1	$S_{(L)}$	-	-	10	Desc.	-
2	-	1-26	25	-	L	-	5	Desc.	-
3	2.	26-27	1	$S_{(U)}$	-	-	10	-	Asc.
4	-	27-57	30	-	-	U	5	-	Asc.
5	3.	57-58	1	$S_{(L)}$	-	-	10	Desc.	-
6	-	58-83	25	-	L	-	5	Desc.	-
7	4.	83-84	1	$S_{(U)}$	-	-	10	-	Asc.
8	-	84-114	30	-	-	U	5	-	Asc.
9	5.	114-115	1	$S_{(L)}$	-	-	10	Desc.	-
10	-	115-140	25	-	L	-	5	Desc.	-
11	6.	140-141	1	$S_{(U)}$	-	-	10	-	Asc.
12	-	141-171	30	-	-	U	5	-	Asc.
13	7.	171-172	1	$S_{(L)}$	-	-	10	Desc.	-
14	-	172-197	25	-	L	-	5	Desc.	-
15	8.	197-198	1	$S_{(U)}$	-	-	10	-	Asc.
15	-	198-148	50	-	-	U	5	-	Asc.

[a] Mobile phases (and sample solution's) flow rate: 5 mL min^{-1}; rotational speed of the centrifuge: 2000 rpm; max back pressure: 110 bar. Detection at Chanel 1: 240 nm (collection); Chanel 2: 300 nm; Chanel 3: Scan (200-600 nm.) [b] $S_{(L)}$ = Sample solution – lower phase; $S_{(U)}$ = Sample solution – upper phase; L = lower phase; U = upper phase.

minutes) four times 0.1 mL min^{-1} gives us 22.8 mL biphasic sample solution (without volume-contraction). The phases should be separated from each other, otherwise the equilibrium of the sample's solvent content would be upset. For that we used a simply separation funnel, but other continiuous liquid-liquid phase separator (e.g. Zaiput, Sep-10) can be applied, nevertheless a gas-liquid phase separator is required first, in order to get rid of the excess hydrogen used in the second step of the synthesis.The shematic flowchart of the whole process shown in Figure S12.

The elution pattern, used in the coupled process, is the same as in case of the automated MDM-CPC purification with asymmetric elution (Table S9). The chromatogram of the separation is shown in Figure S13.

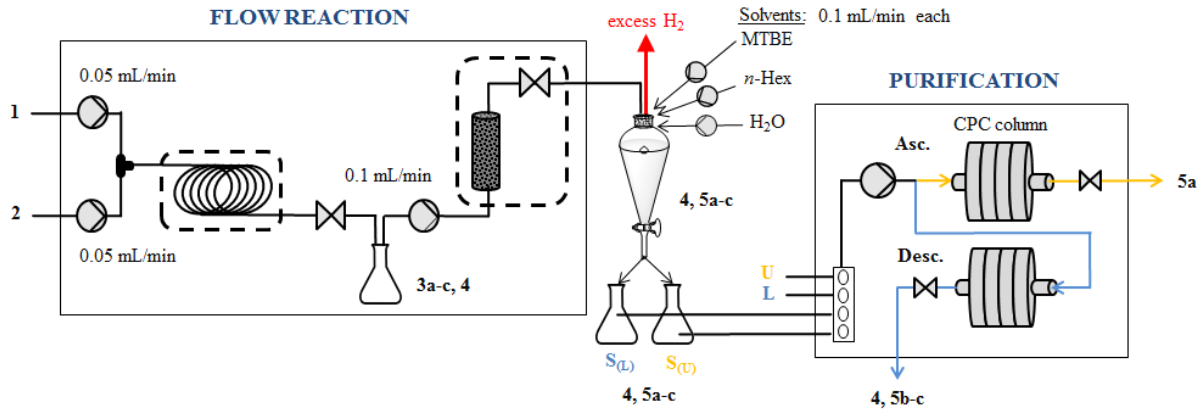


Figure S12. Schematic process of the coupled multistep continuous flow reaction with MDM-CPC with two-phase intake and asymmetric elution.

The fractions containing the desired product (**5a**) were collected and concentrated to obtain 1.105 g of **5a** as a light brown crystal which purity was over 99.9% (GCMS). It means that the overall yield is 57.2% and the productivity is

144 mg/h. The recovery of the purification is 86%, determined by collecting and evaporating the remaining fractions and analysing it (890 mg as black clammy syrup containing 22.3% **5a**, 56.1% **5b** and 21.6% **5c** by GCMS).

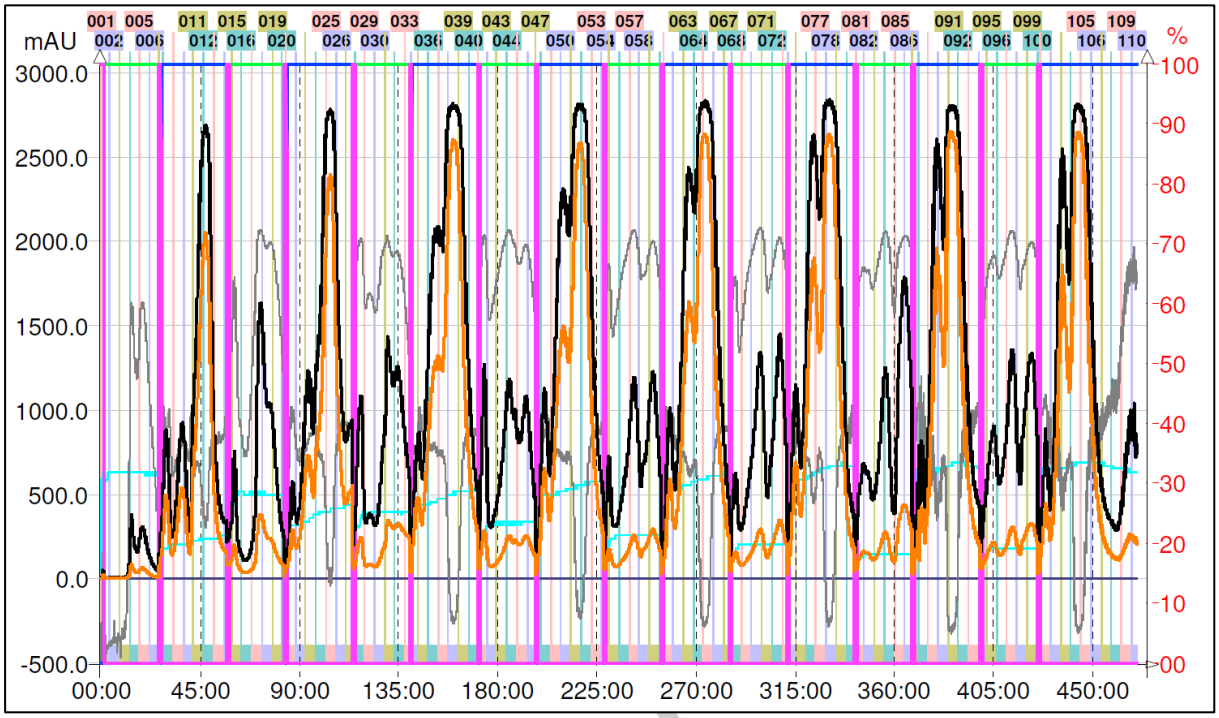


Figure S13. Chromatogram of the coupled flow reactor and MDM-CPC with two-phase intake.

8.c. Coupling the two-step synthesis and MDM CPC purification with one-phase intake method.

One-phase intake of the sample solution improves the productivity since the concentration of the reaction mixture is higher and higher throughput needed to synchronize to the inlet-outlet flow rate in the buffer flask between the flow reactors and the purification unit.

Based on the determination of the lower phase solvent content (see section 5), the flow rates were set at 150 µL min^{-1} (reaction mixture - EtOH), 25 µL min^{-1} (MTBE) and 195 µL min^{-1} (water) (Figure S14). The elution pattern, used in the coupled process, is the same as in case of the automated MDM-CPC purification with asymmetric elution (Table S9), the only exception is that every sample intake were implemented from the only phase is obtained. The shematic flowchart of the whole process shown in Figure S14, the assembled devices picture shown in Figure S15 and the chromatogram of the separation is shown in Figure S16.

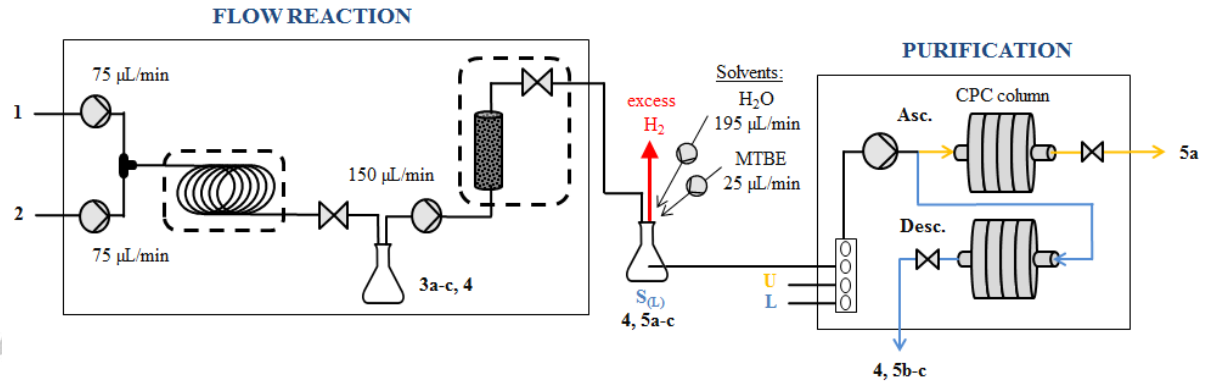


Figure S14. Schematic process of the coupled multistep continuous flow reaction with MDM-CPC with one-phase intake and asymmetric elution.

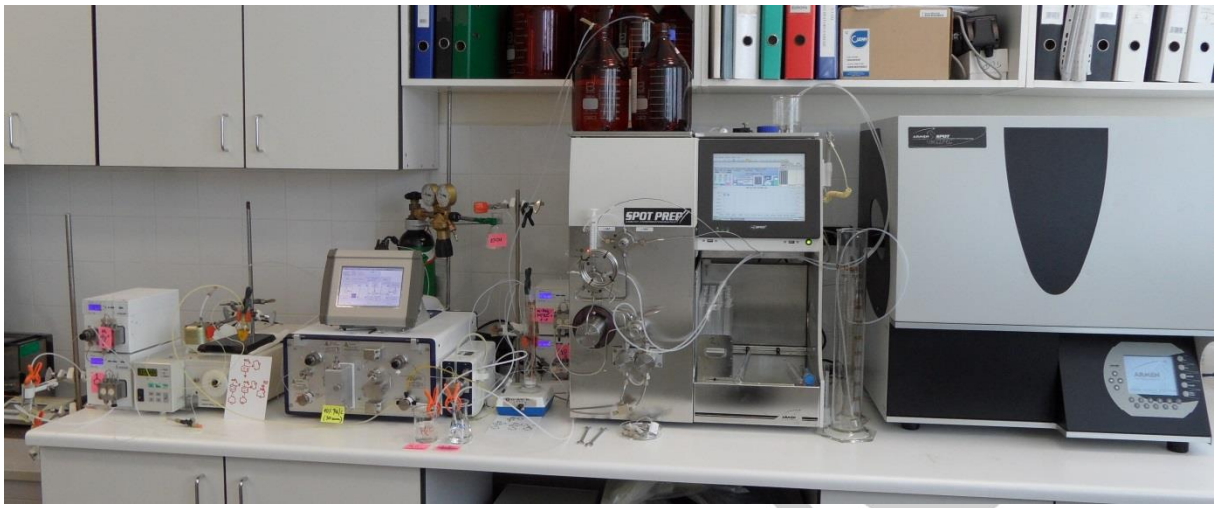


Figure S15. View of the coupled multistep continuous flow reaction with purification by MDM CPC with one-phase intake and asymmetric elution.

The fractions containing the desired product (**5a**) were collected and concentrated to obtain 870 mg of **5a** as a light brown crystal which purity was over 99.9% (GCMS). It means that the overall yield is 59% and productivity is 227 mg/h which is ~60% higher than in the two-phase intake method. The recovery of the purification is 77%, determined by collecting and evaporating the remaining fractions and analysing it (575 mg as black clammy syrup containing 35.6% **5a**, 27.3% **5b** and 36.1% **5c** by GCMS).

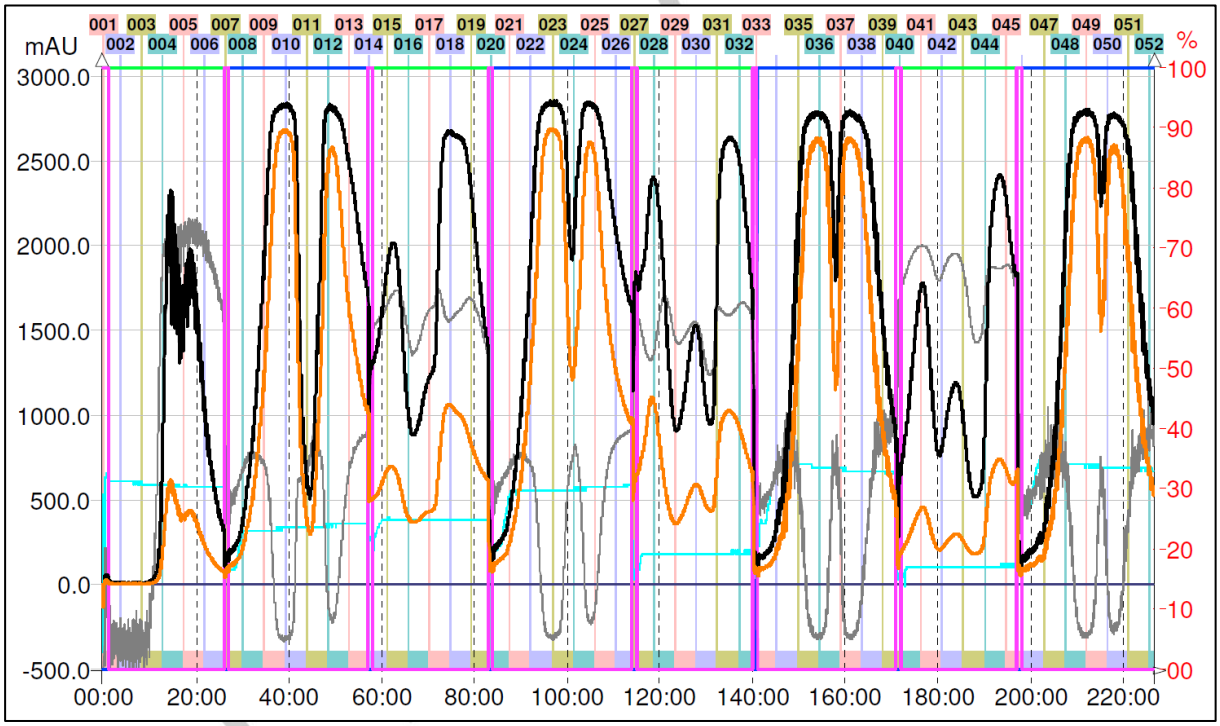


Figure 16. Chromatogram of the coupled flow reactor and MDM-CPC with one-phase intake.

The virtual-continuous purification can be operated in a truly continuous manner by synchronizing the flow reaction to the purification and by using buffer flasks and couple of pumps (Figure 17.).

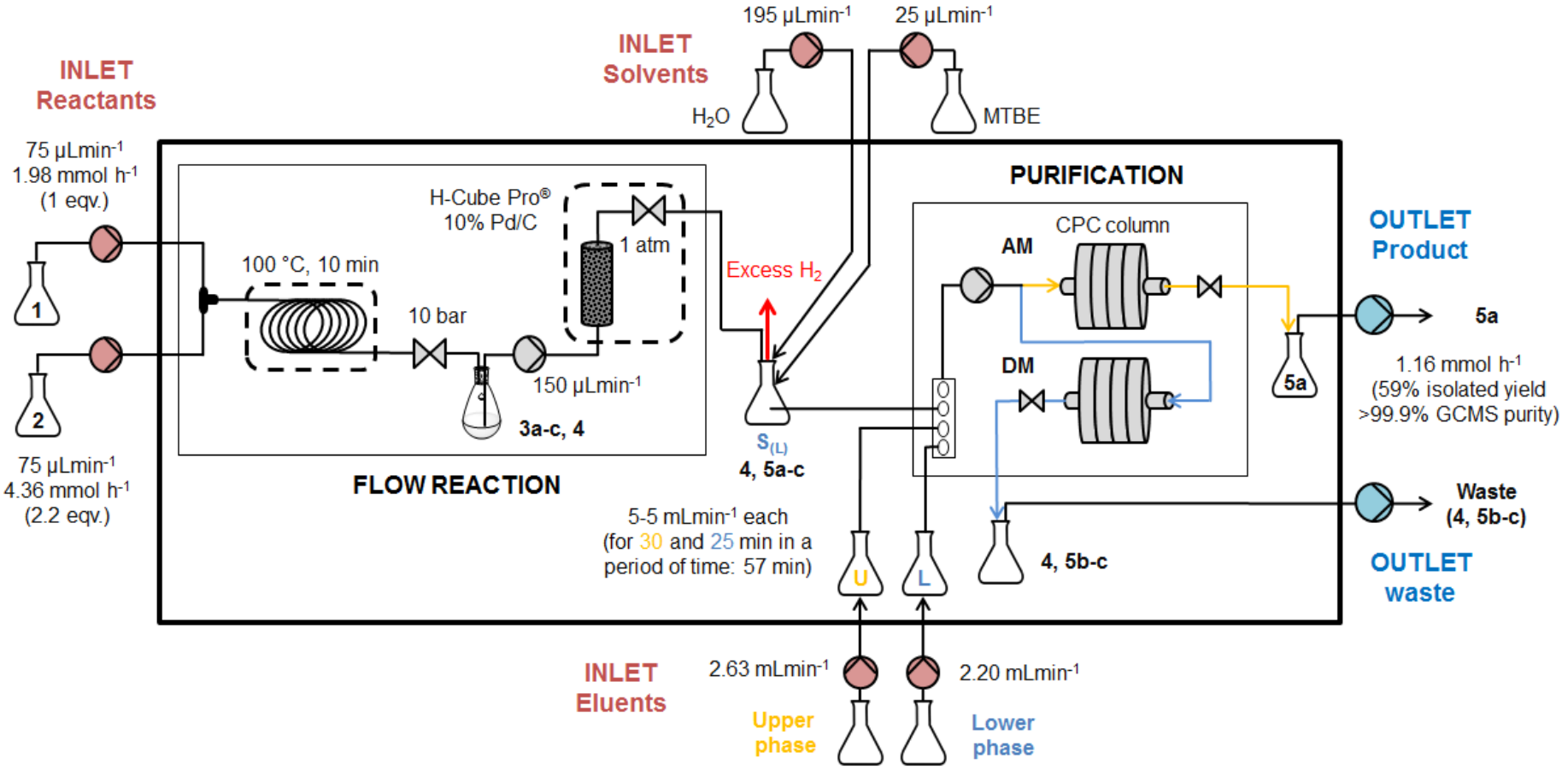
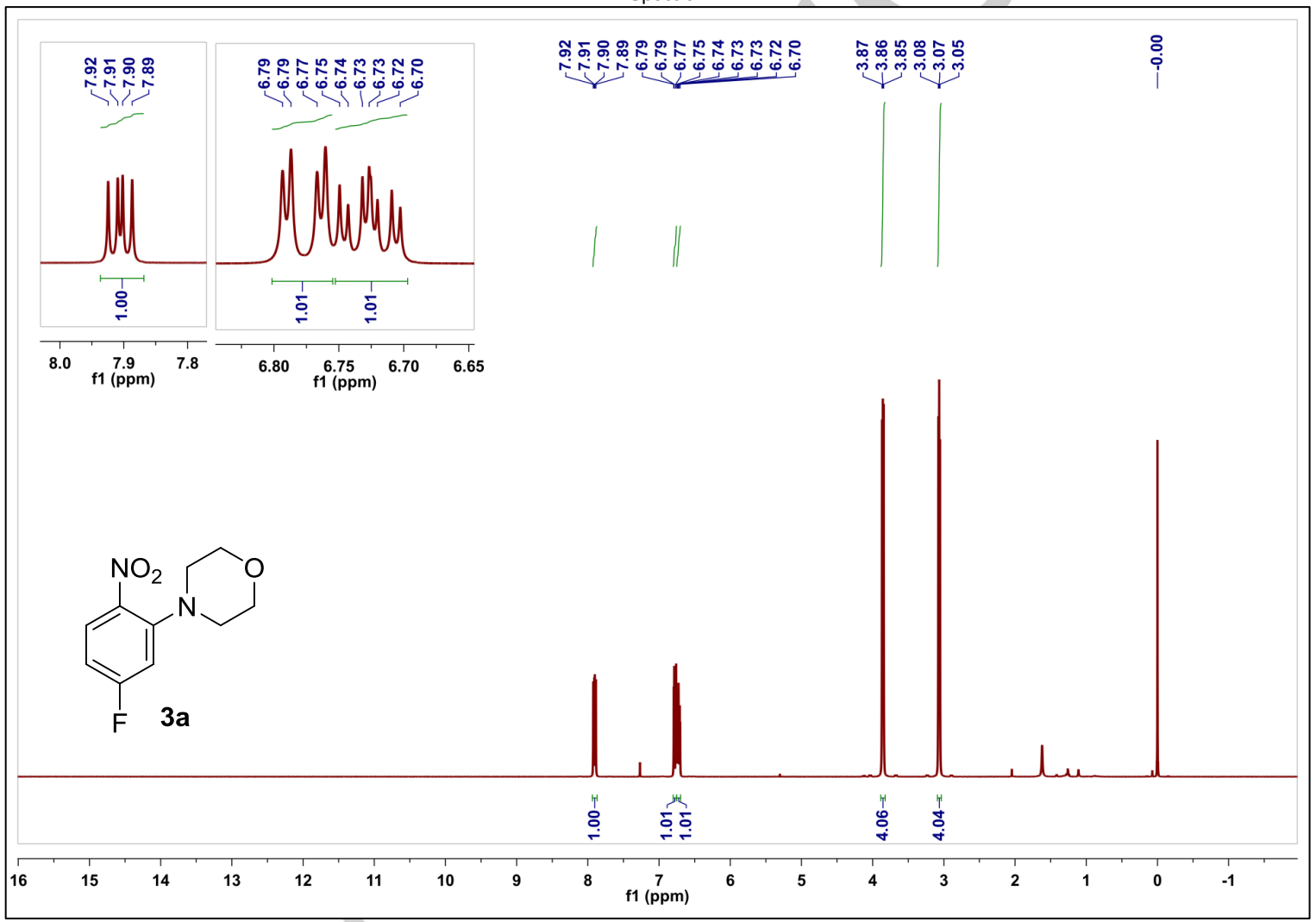


Figure 17. Schematic process of the coupled multistep continuous flow reaction with MDM-CPC in a truly continuous manner, using buffer additional buffer flasks and pumps.

9. NMR Spectra

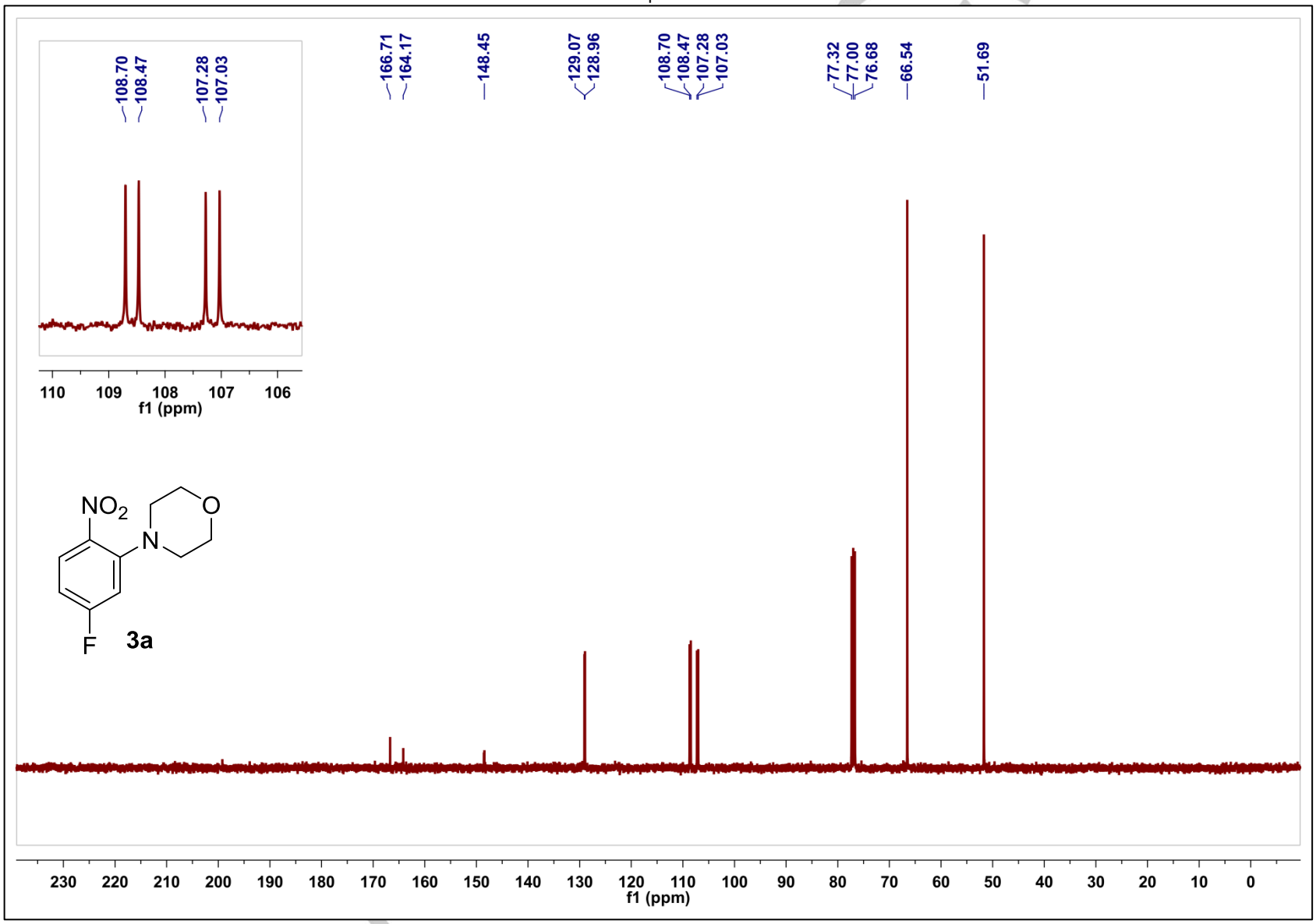
4-(5-fluoro-2-nitrophenyl)morpholine (**3a**)

^{1}H Spectrum

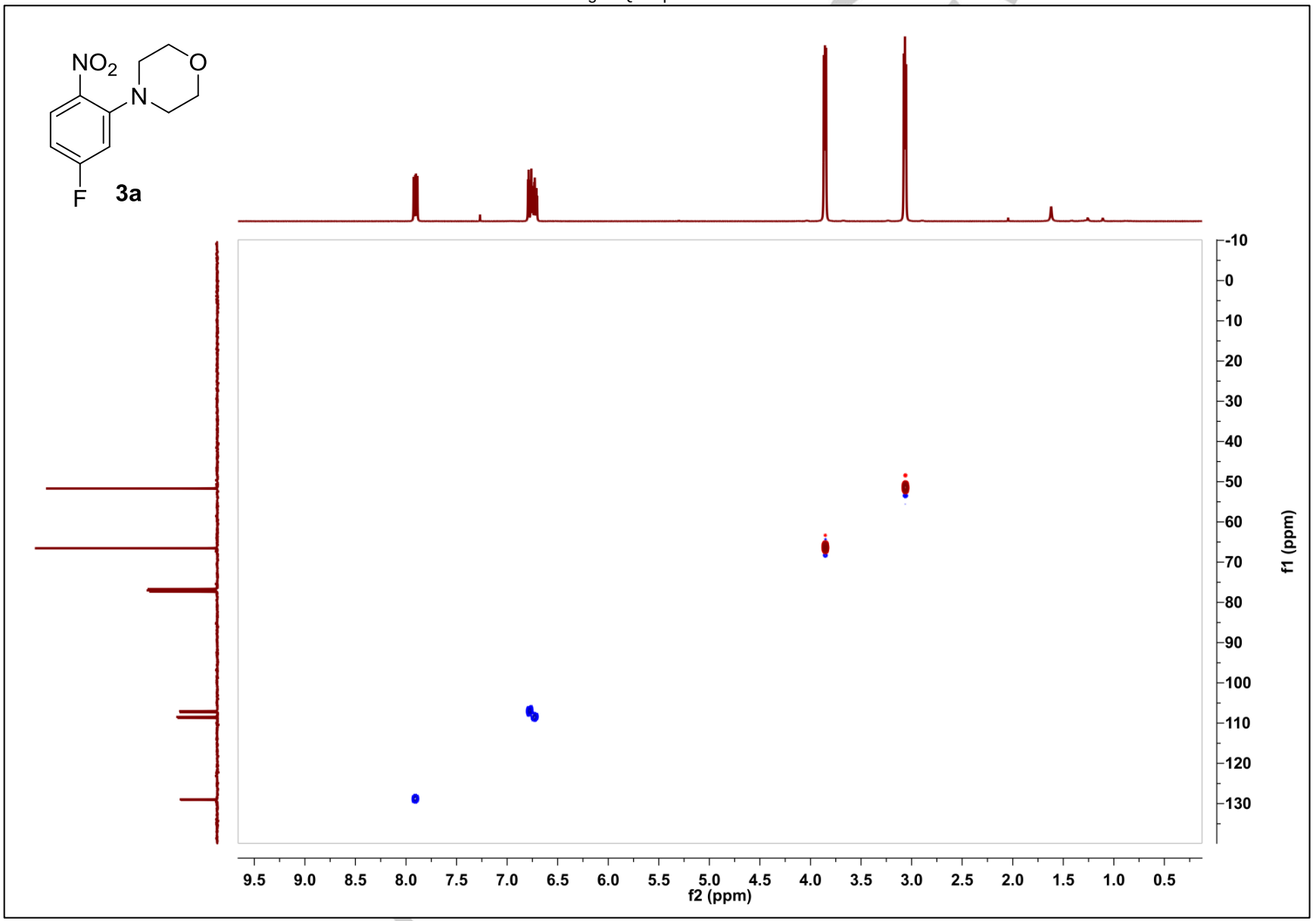


4-(5-fluoro-2-nitrophenyl)morpholine (**3a**)

^{13}C Spectrum

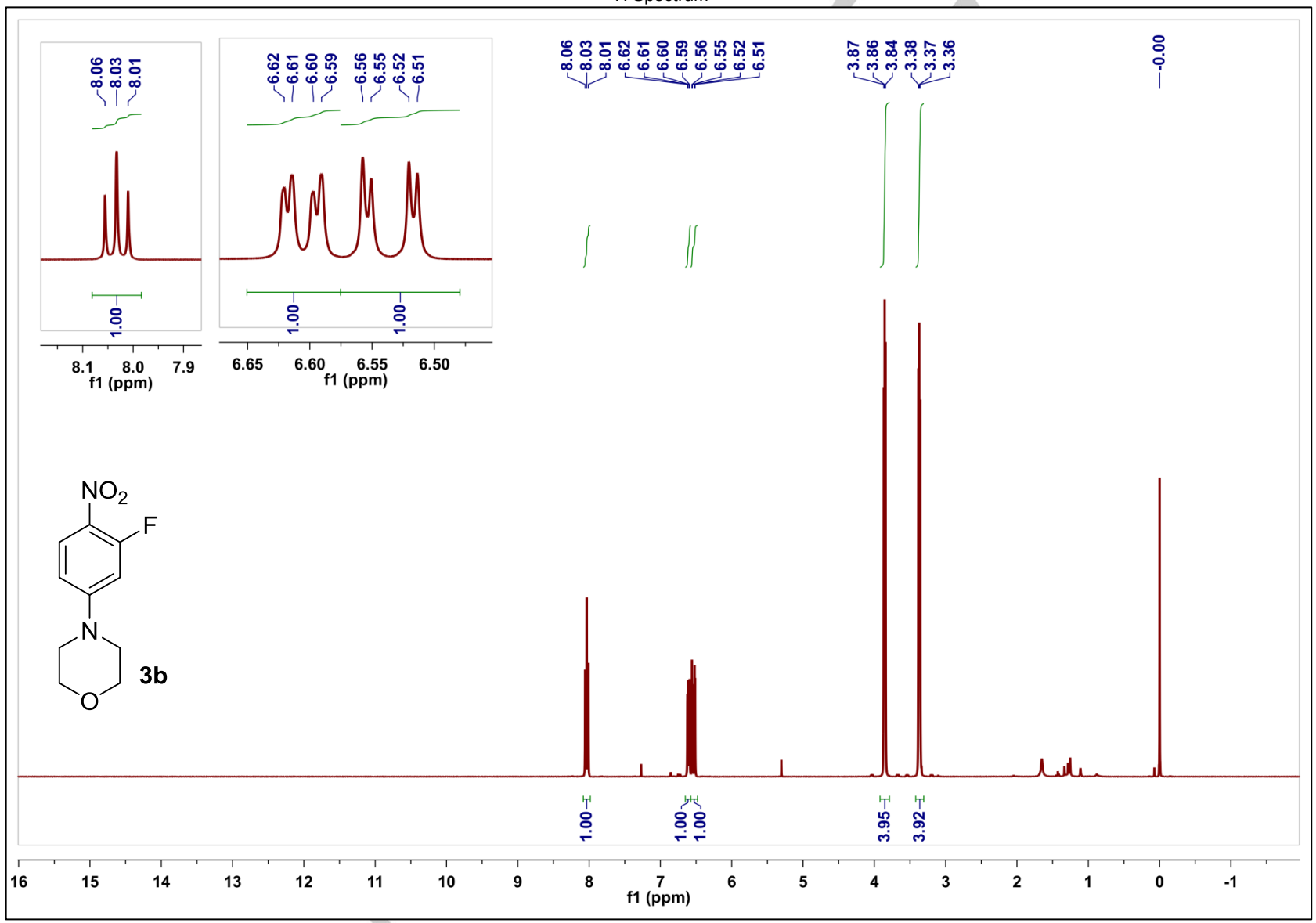


4-(5-fluoro-2-nitrophenyl)morpholine (**3a**)
gHSQC Spectrum



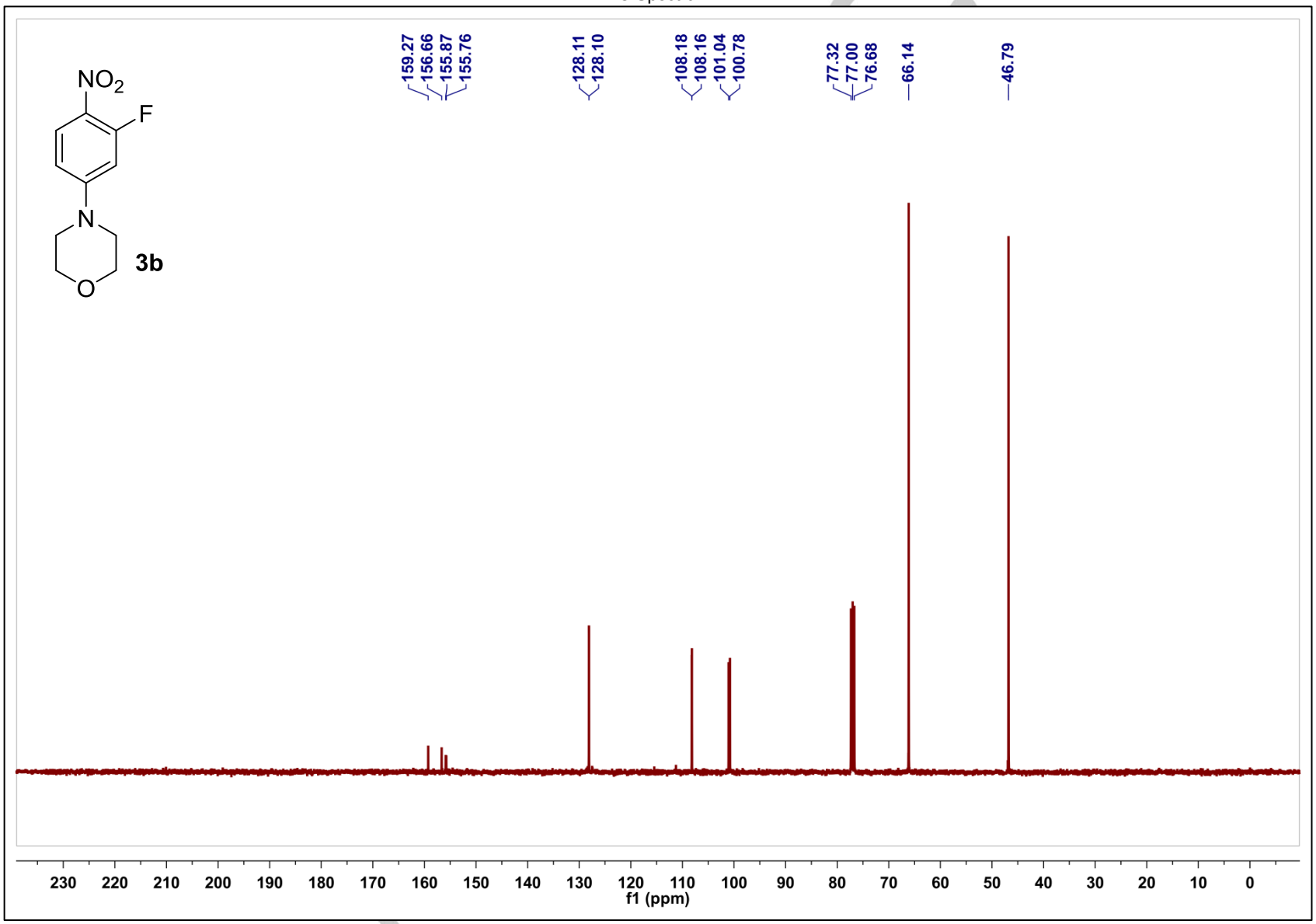
4-(3-fluoro-4-methylphenyl)morpholine (**3b**)

^{1}H Spectrum

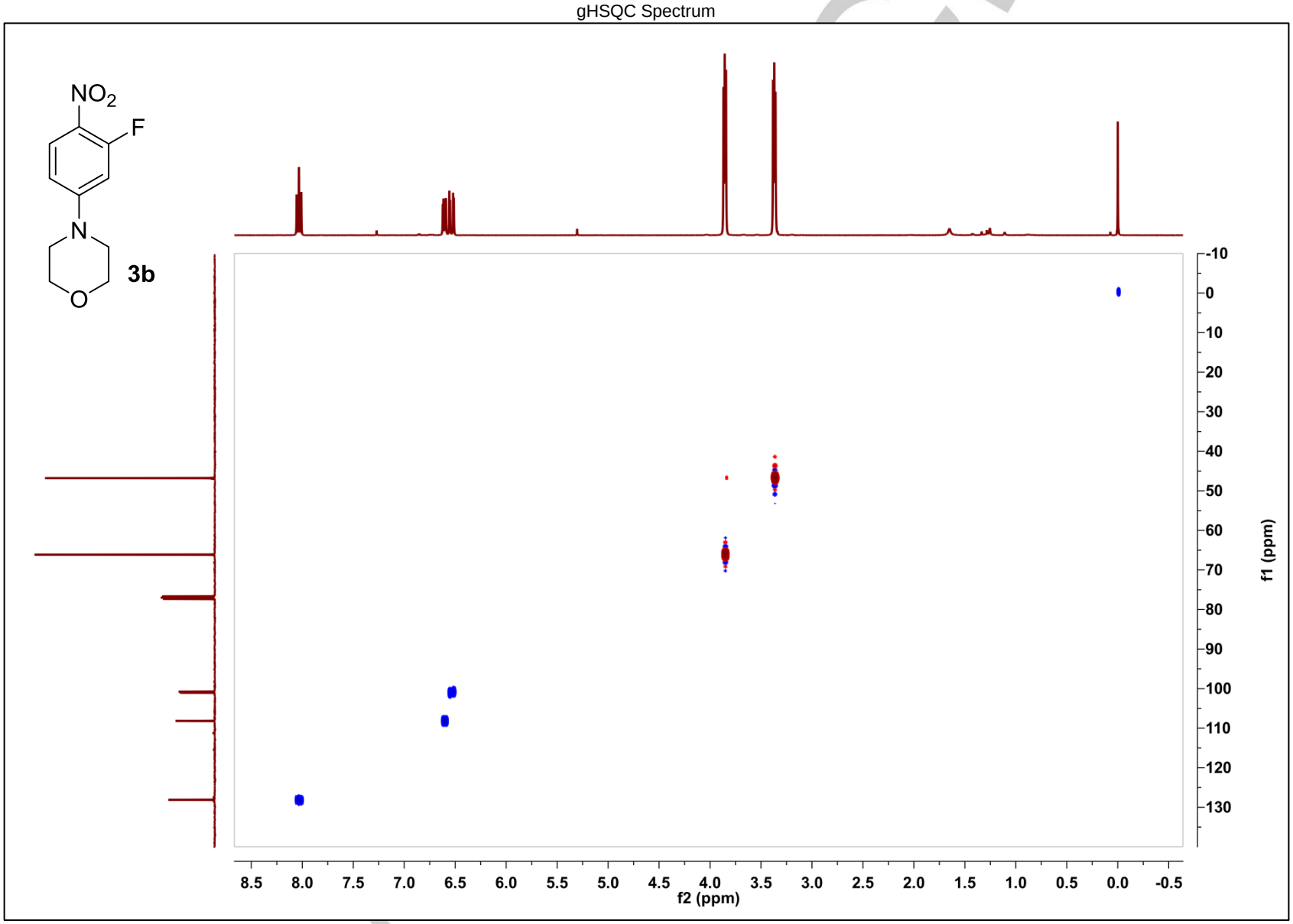


4-(3-fluoro-4-methylphenyl)morpholine (**3b**)

^{13}C Spectrum

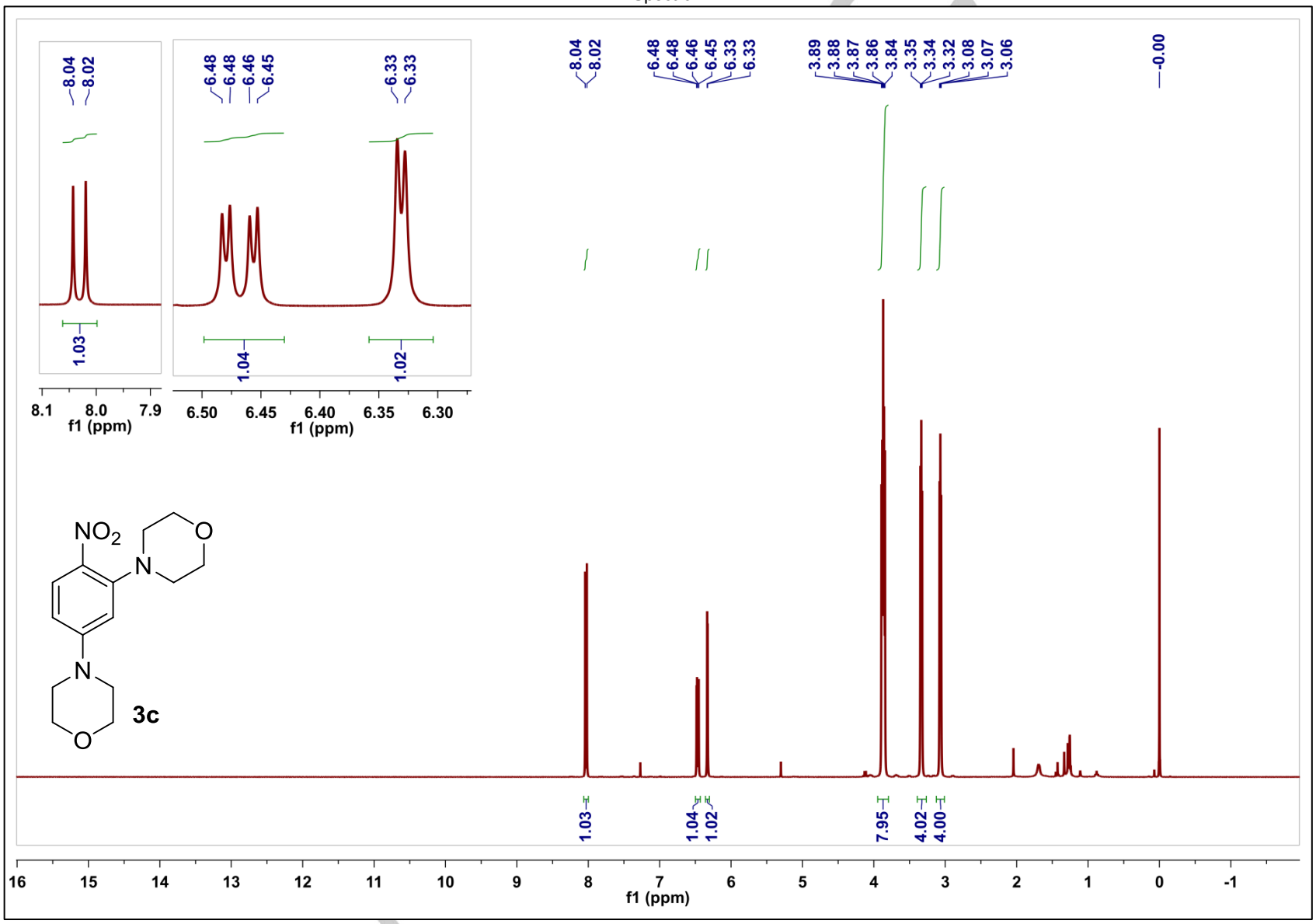


4-(3-fluoro-4-methylphenyl)morpholine (**3b**)



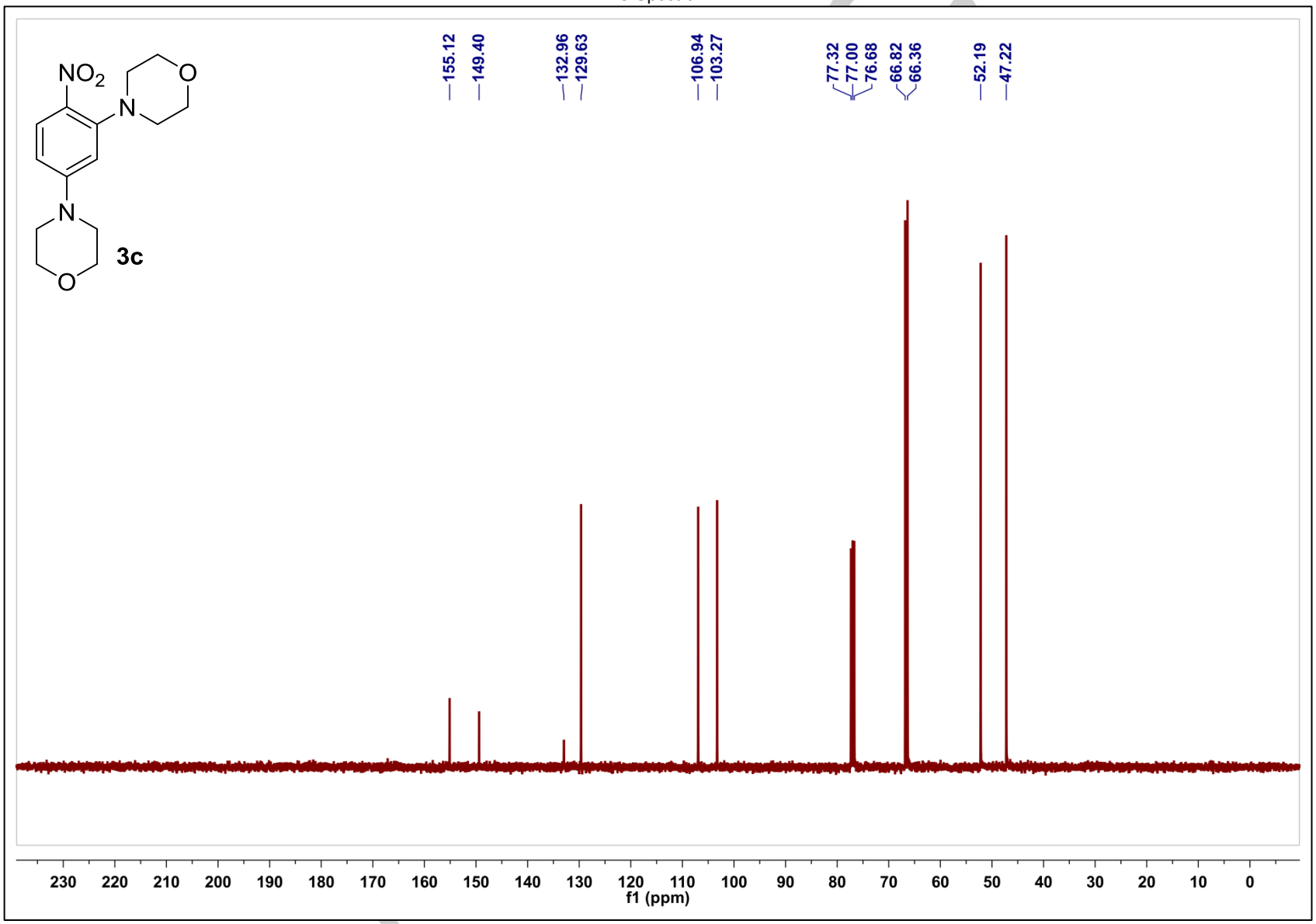
4-[2-methyl-5-(morpholine-4-yl)phenyl]morpholine (**3c**)

^{1}H Spectrum

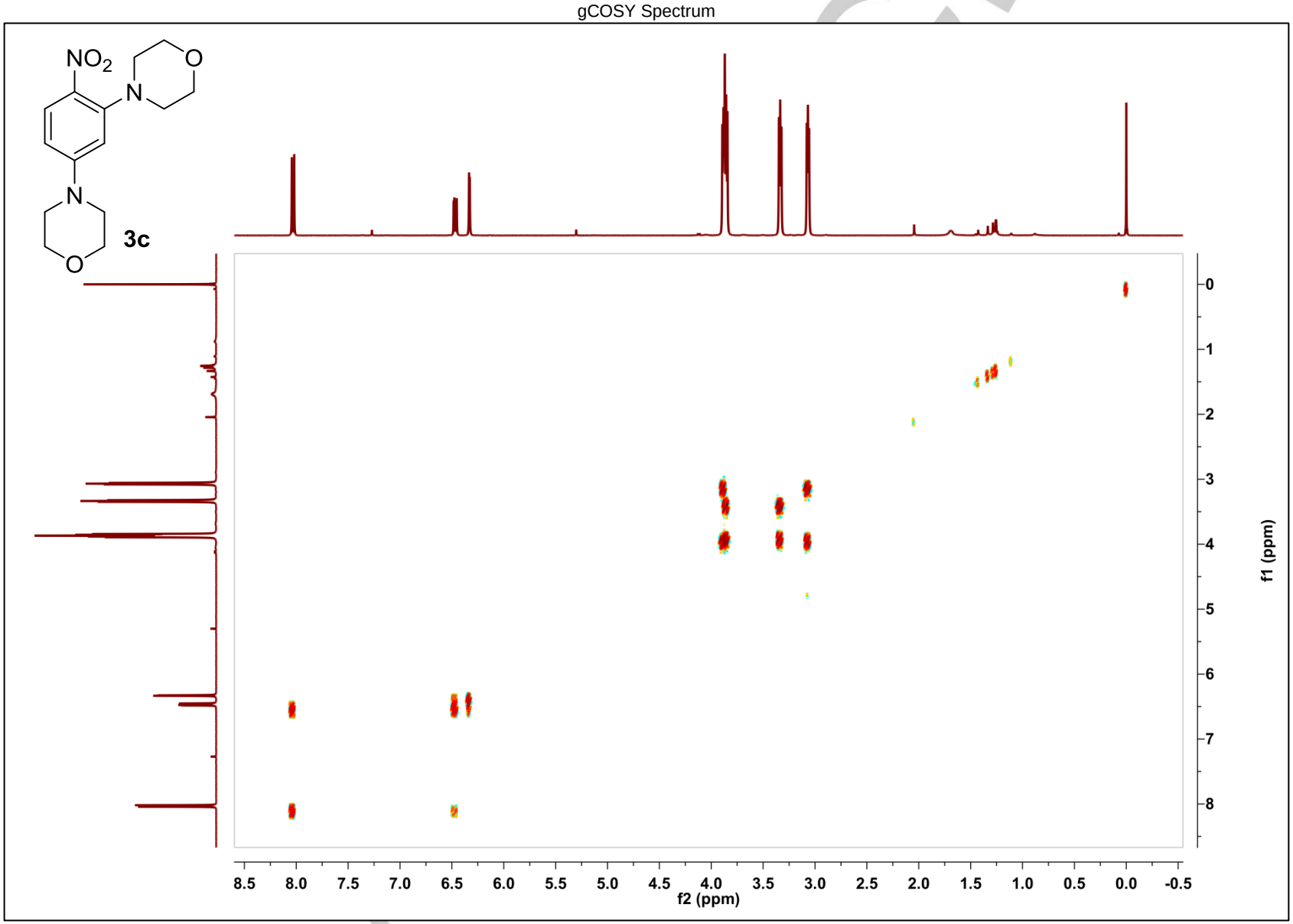


4-[2-methyl-5-(morpholine-4-yl)phenyl]morpholine (**3c**)

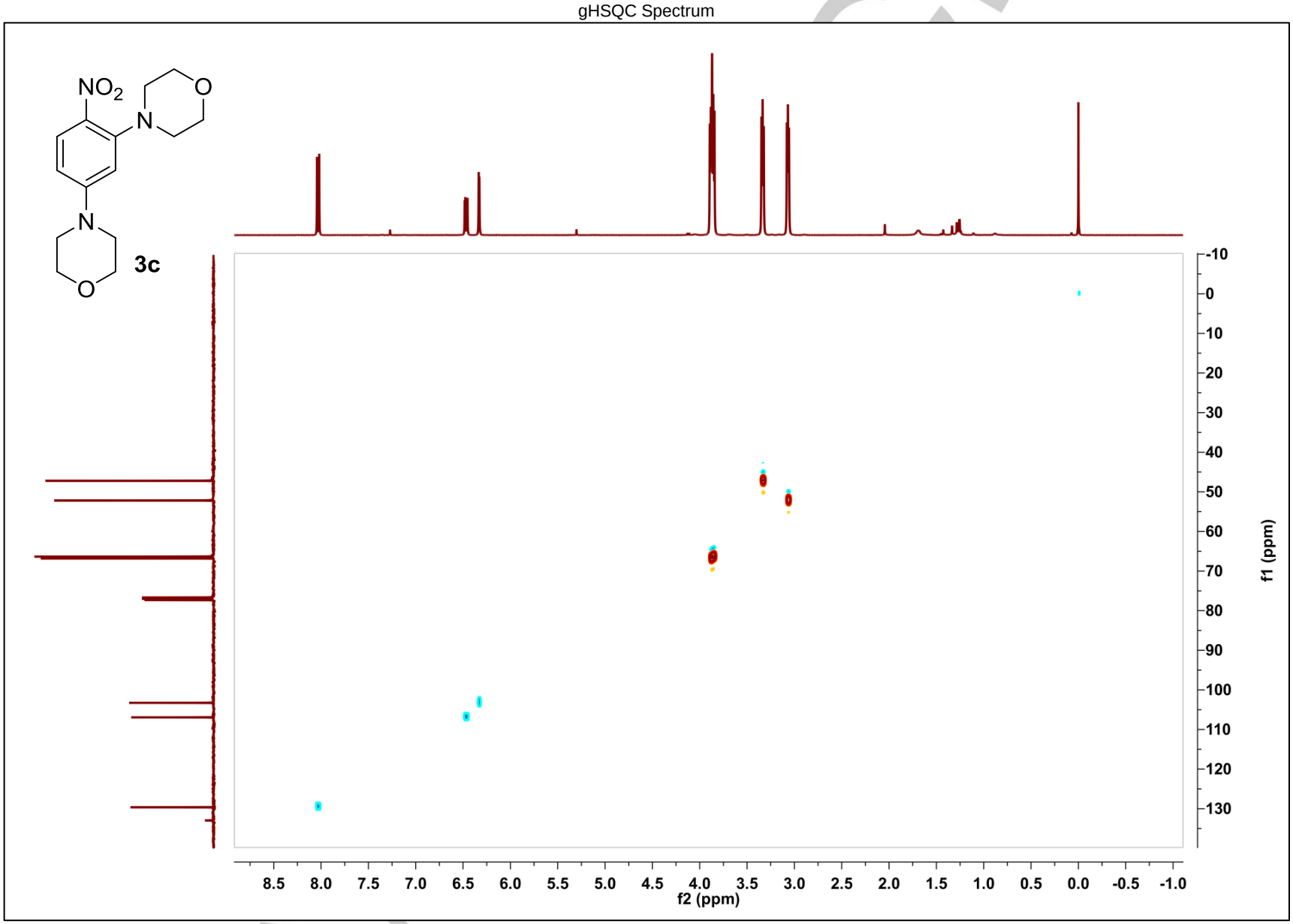
^{13}C Spectrum



4-[2-methyl-5-(morpholine-4-yl)phenyl]morpholine (**3c**)

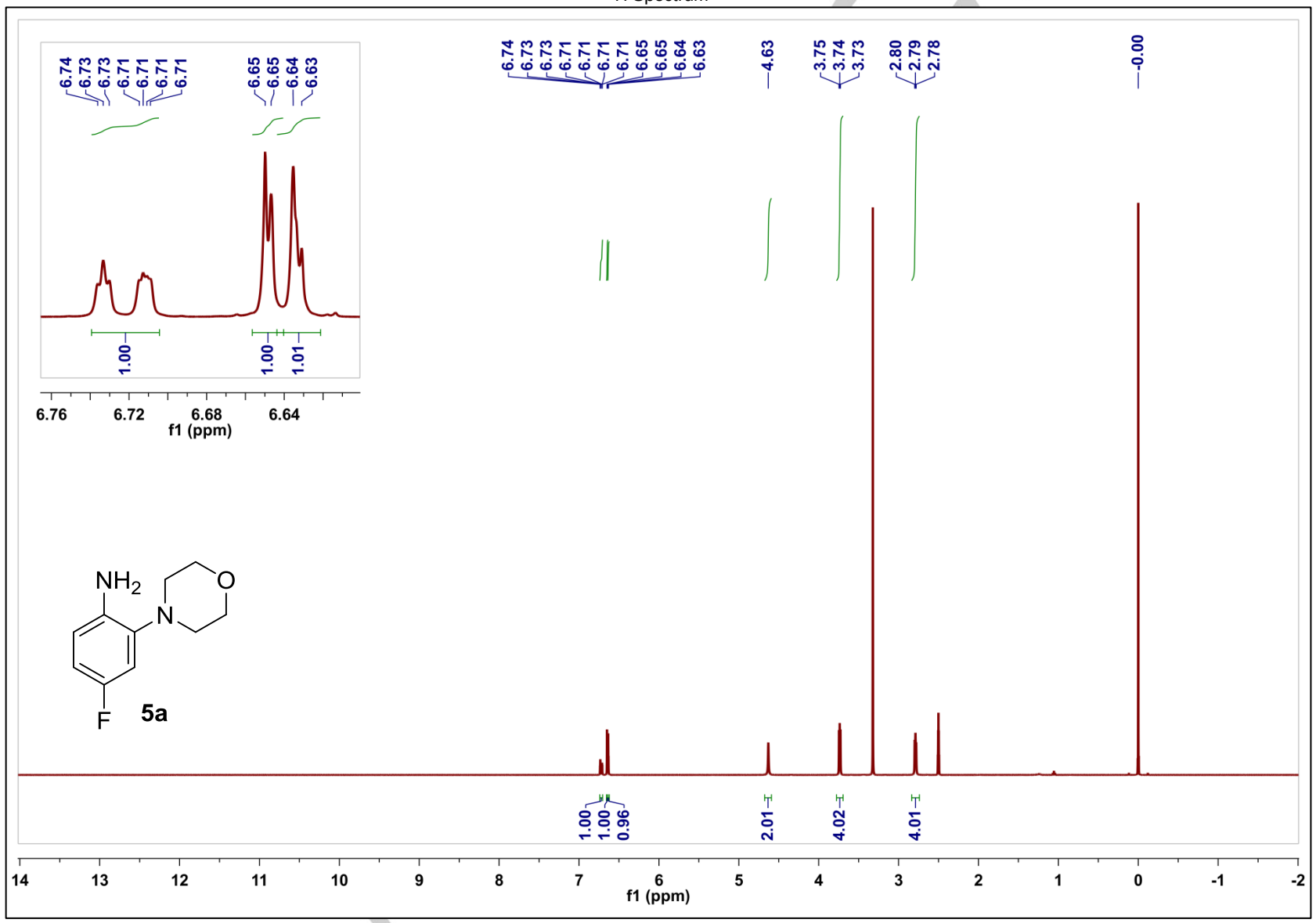


4-[2-methyl-5-(morpholine-4-yl)phenyl]morpholine (**3c**)



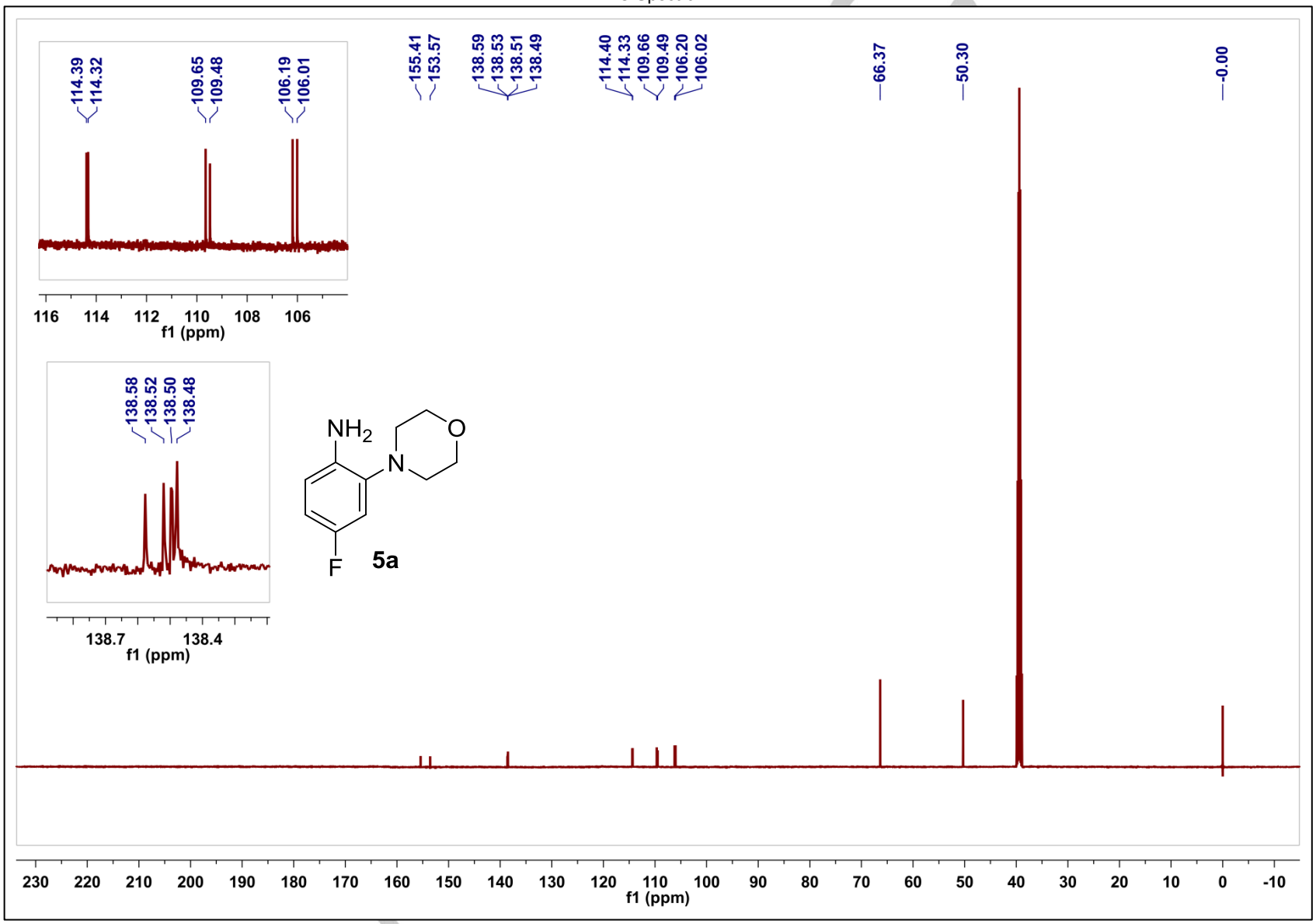
4-fluoro-2-(morpholin-4-yl)aniline (**5a**)

^{1}H Spectrum

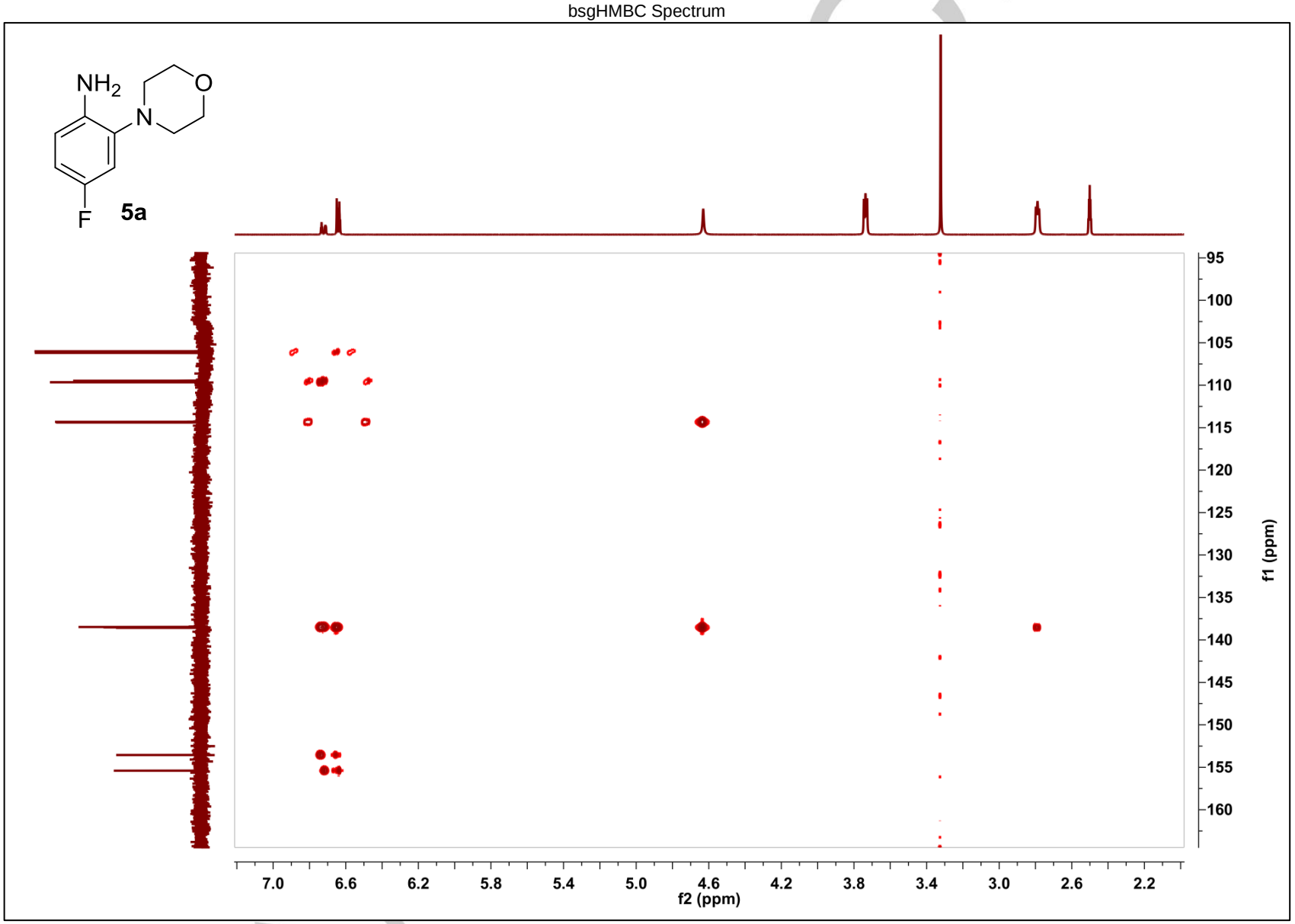


4-fluoro-2-(morpholin-4-yl)aniline (**5a**)

^{13}C Spectrum

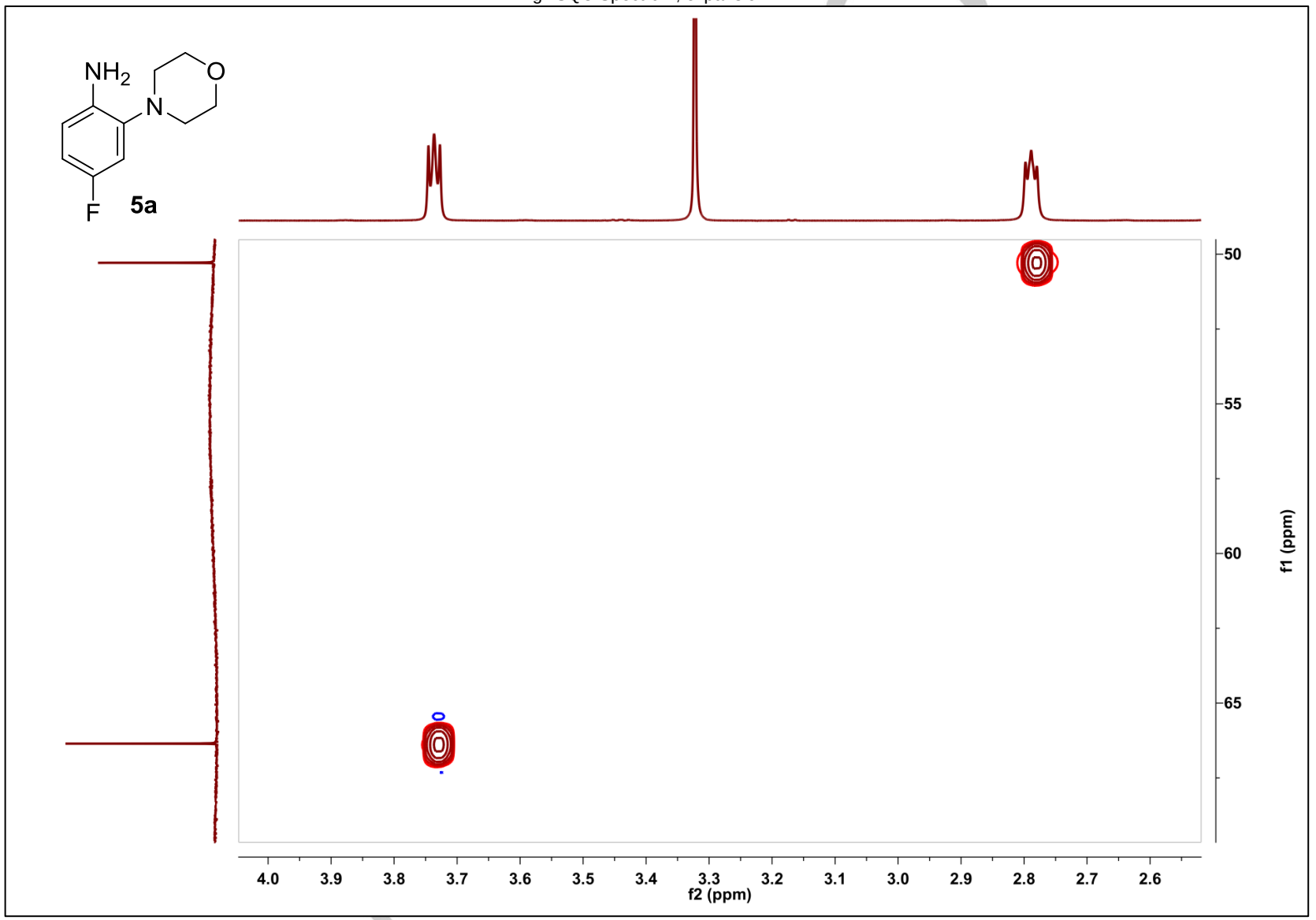


4-fluoro-2-(morpholin-4-yl)aniline (**5a**)



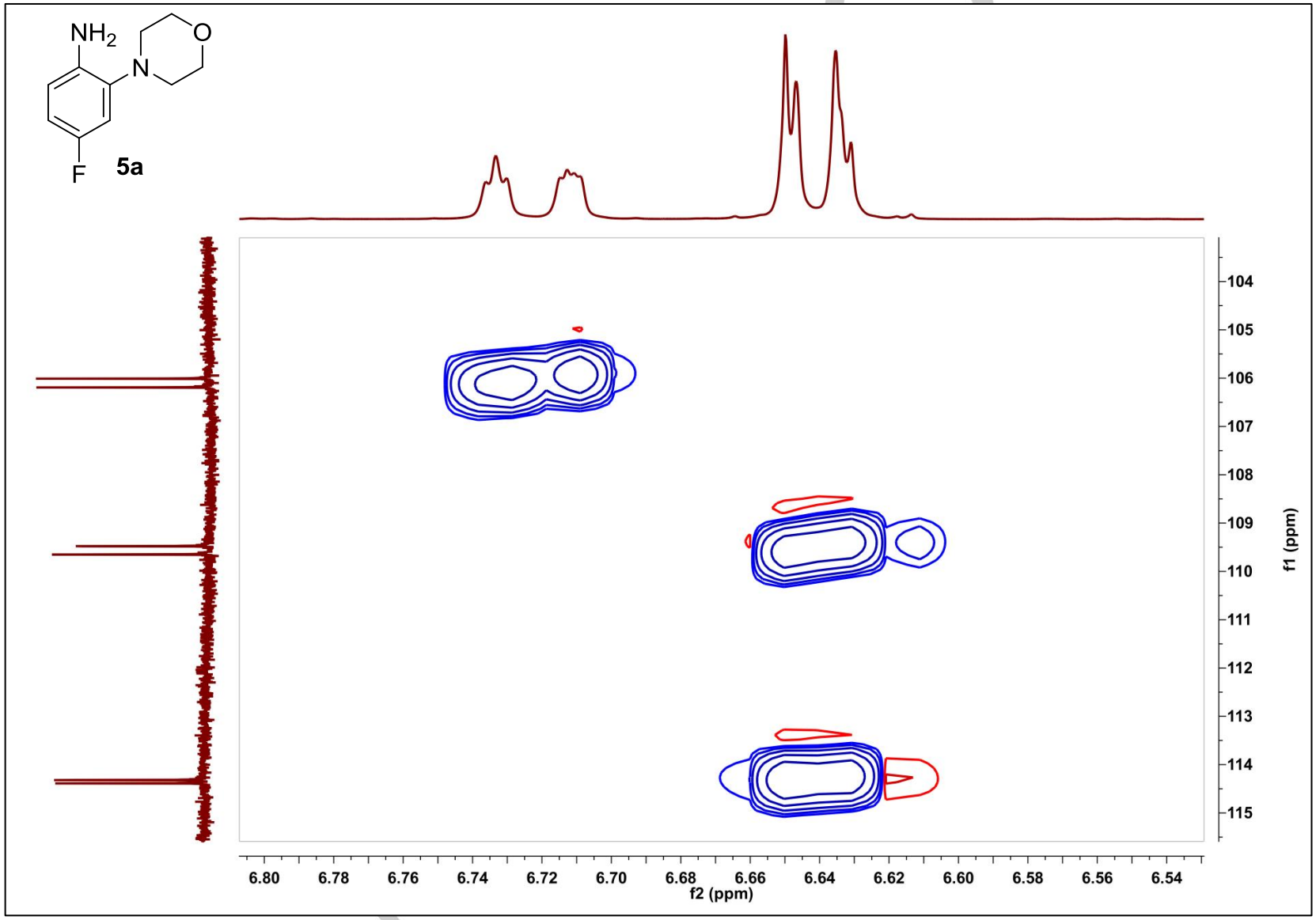
4-fluoro-2-(morpholin-4-yl)aniline (**5a**)

gHSQC Spectrum, expansion I.



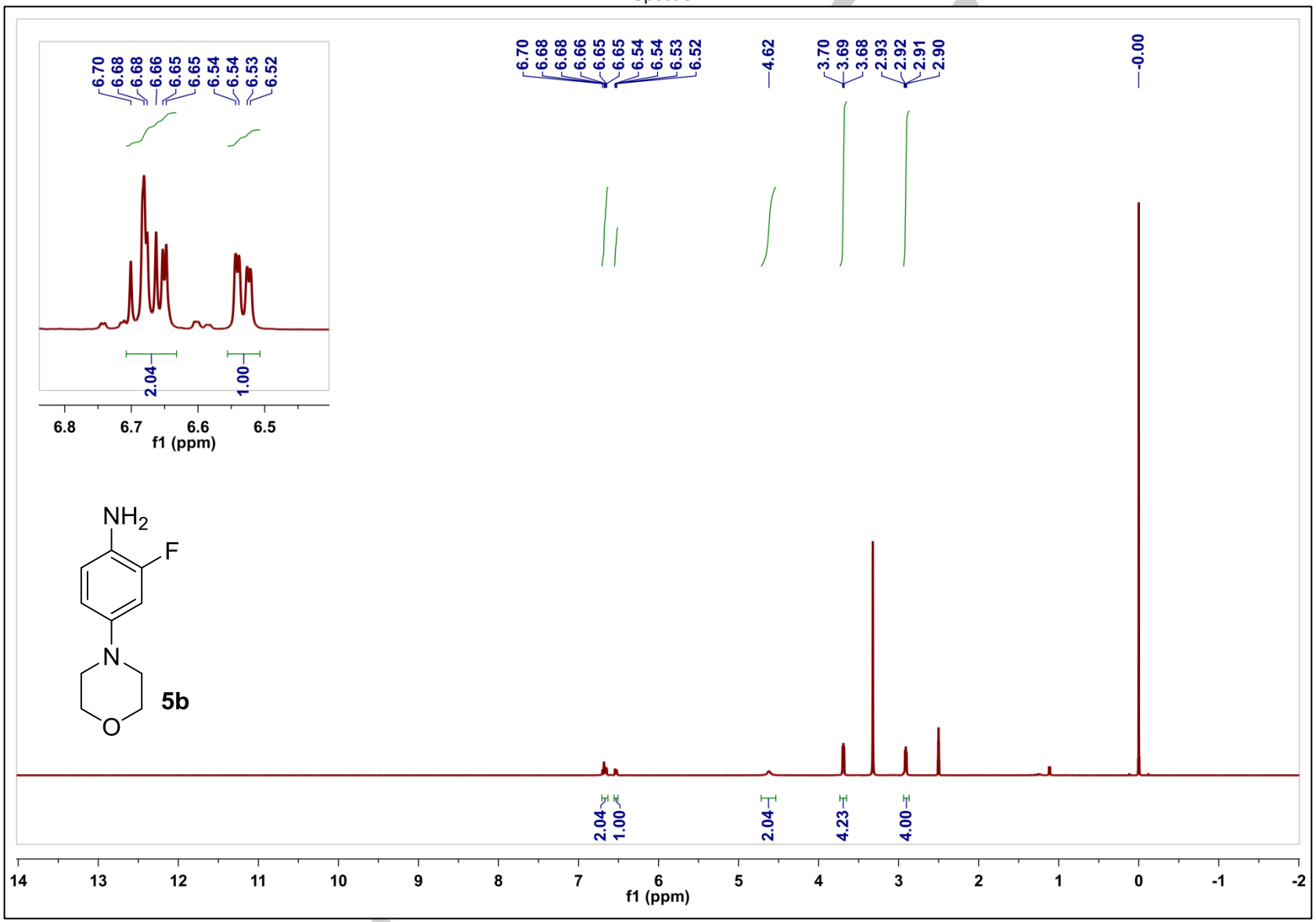
4-fluoro-2-(morpholin-4-yl)aniline (**5a**)

gHSQC Spectrum, expansion II.



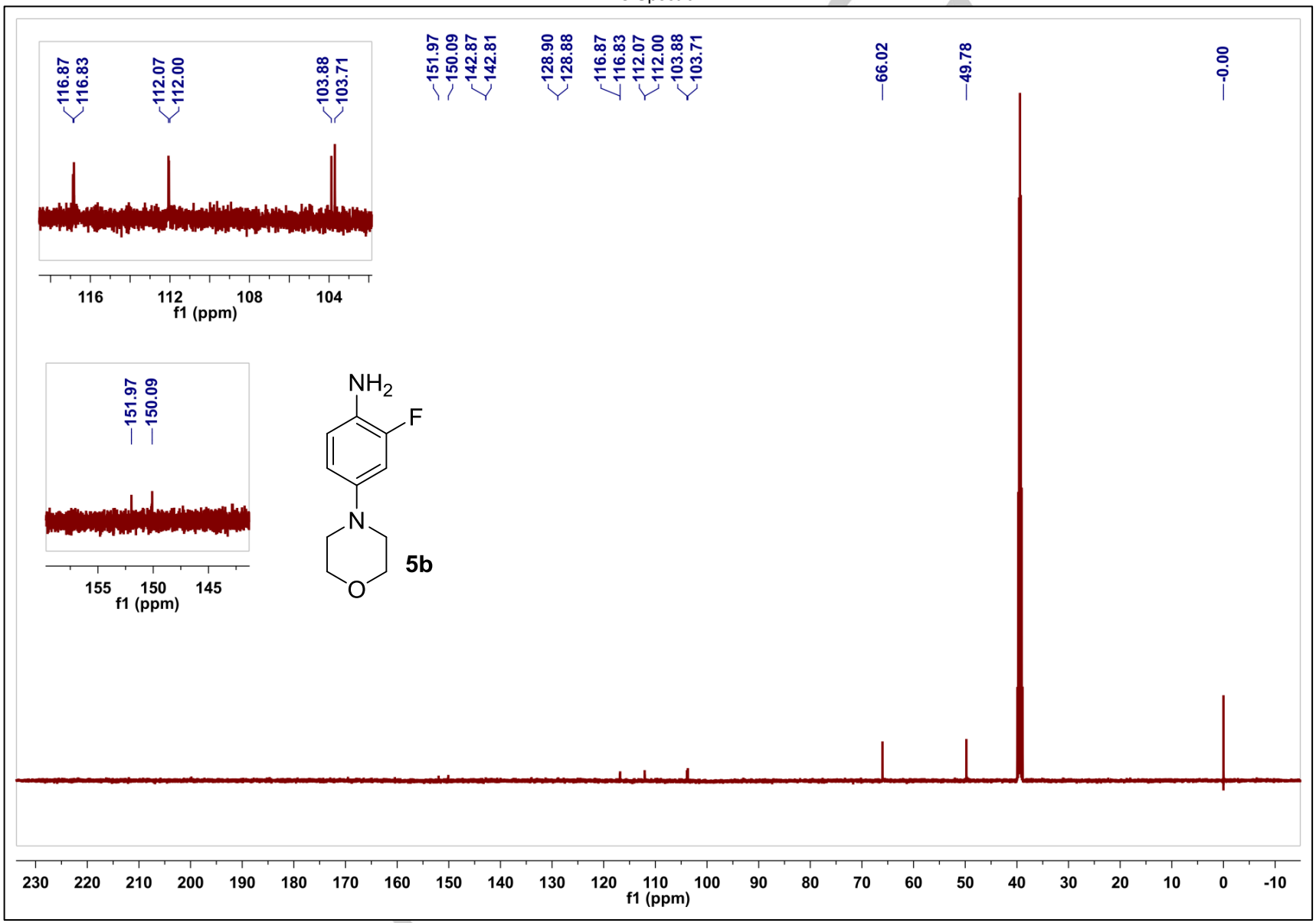
2-fluoro-4-(morpholin-4-yl)aniline (**5b**)

^{1}H Spectrum



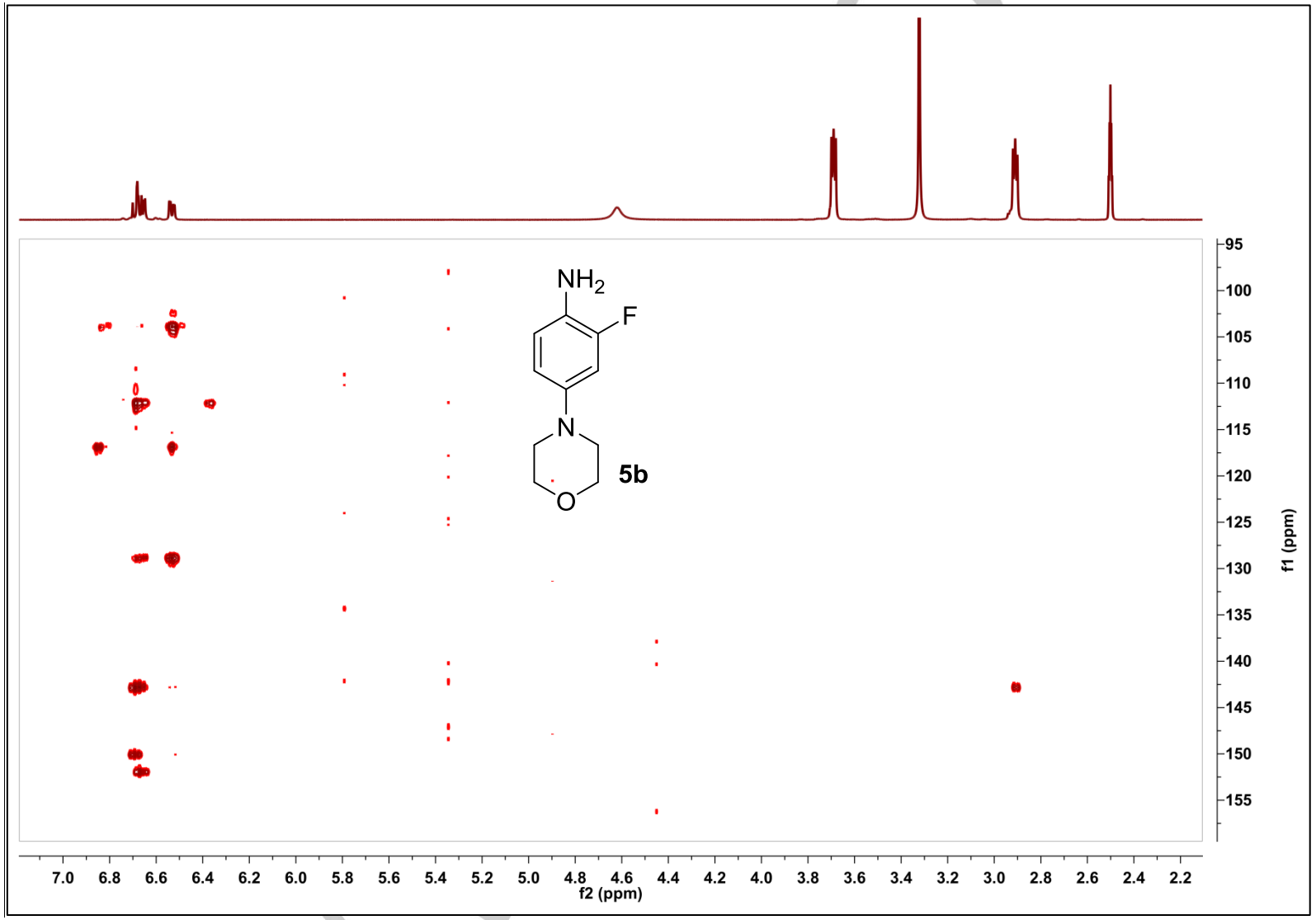
2-fluoro-4-(morpholin-4-yl)aniline (**5b**)

^{13}C Spectrum



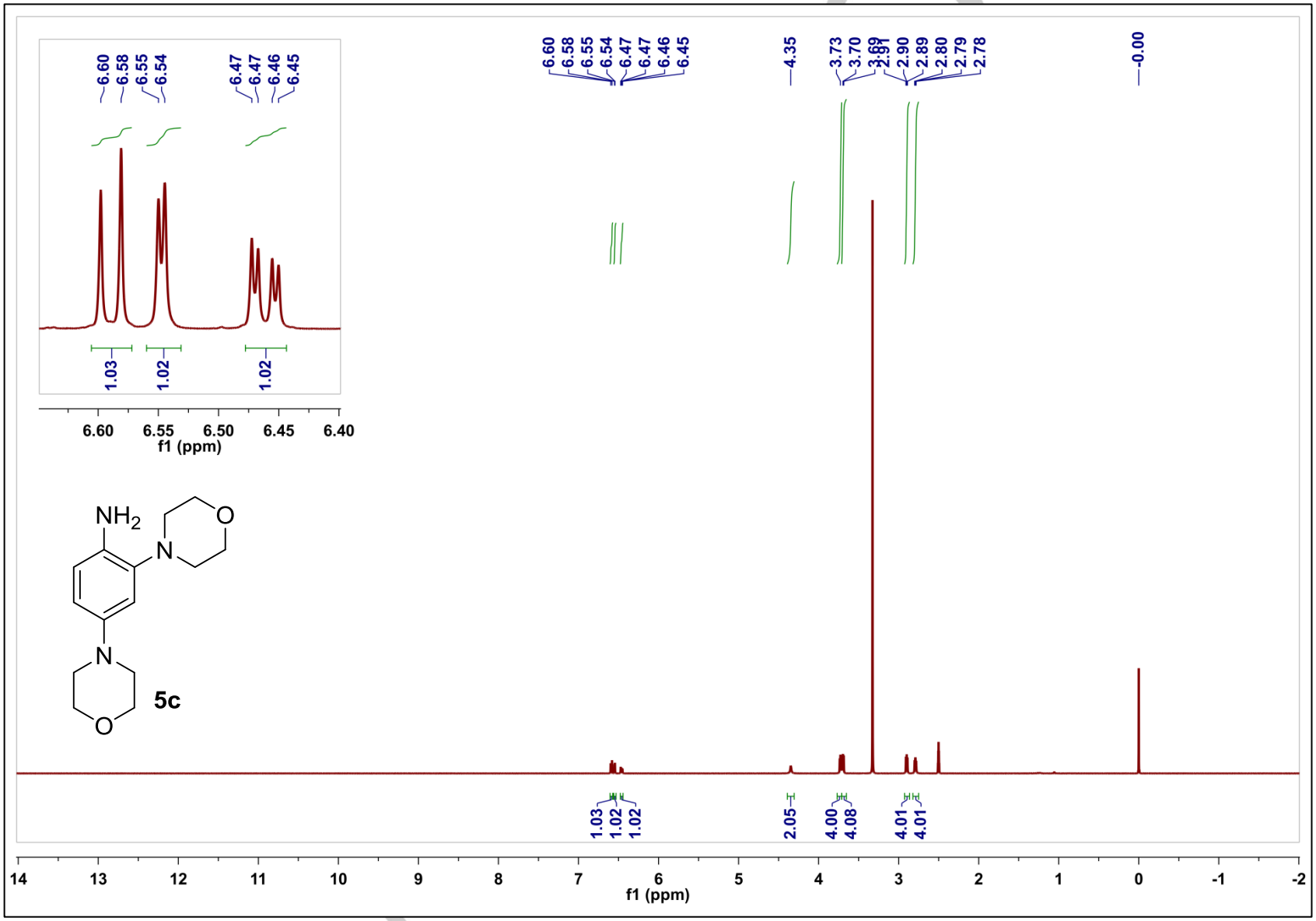
2-fluoro-4-(morpholin-4-yl)aniline (**5b**)

bsgHMBC Spectrum



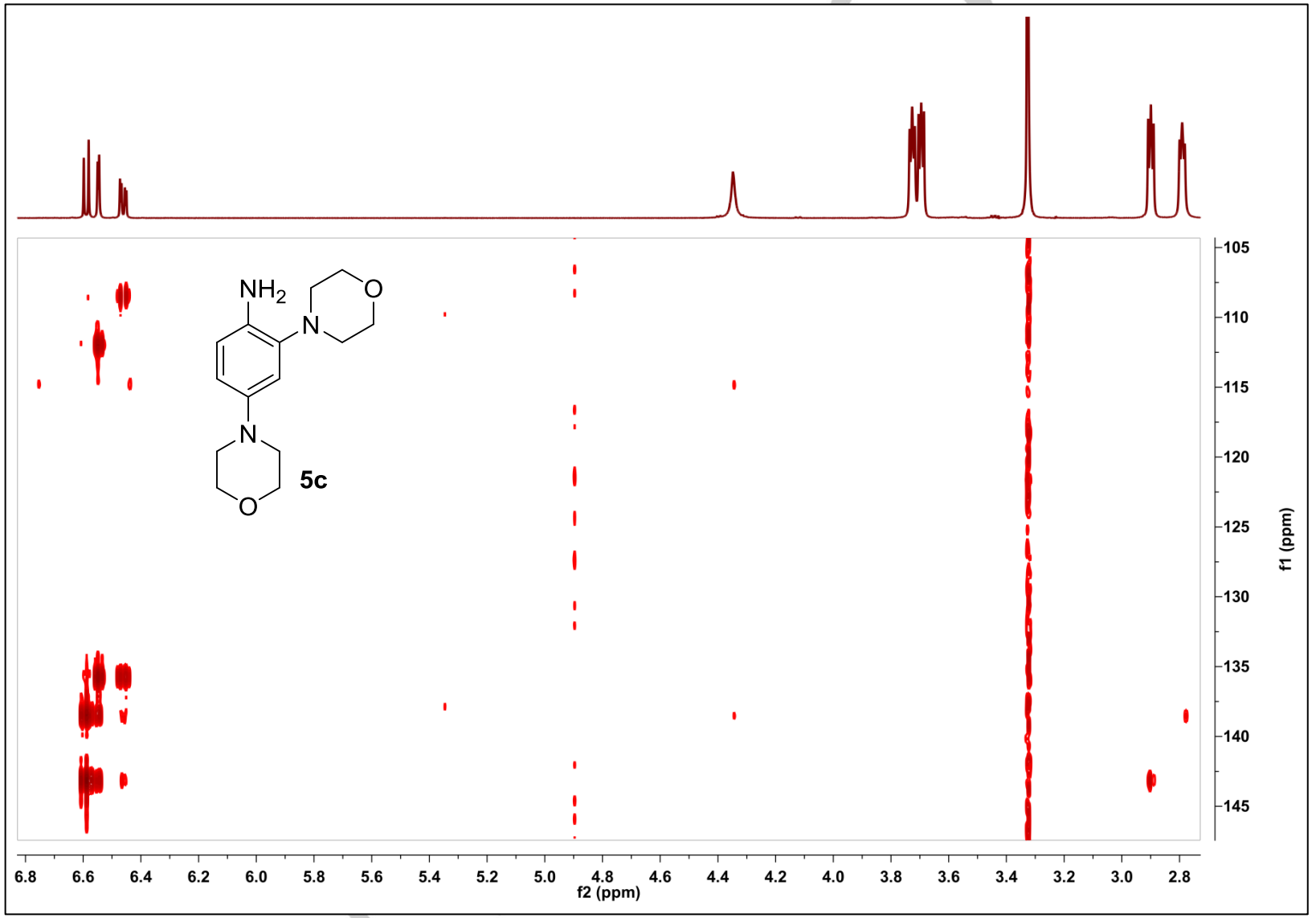
2,4-bis(morpholin-4-yl)aniline (**5c**)

^{1}H Spectrum



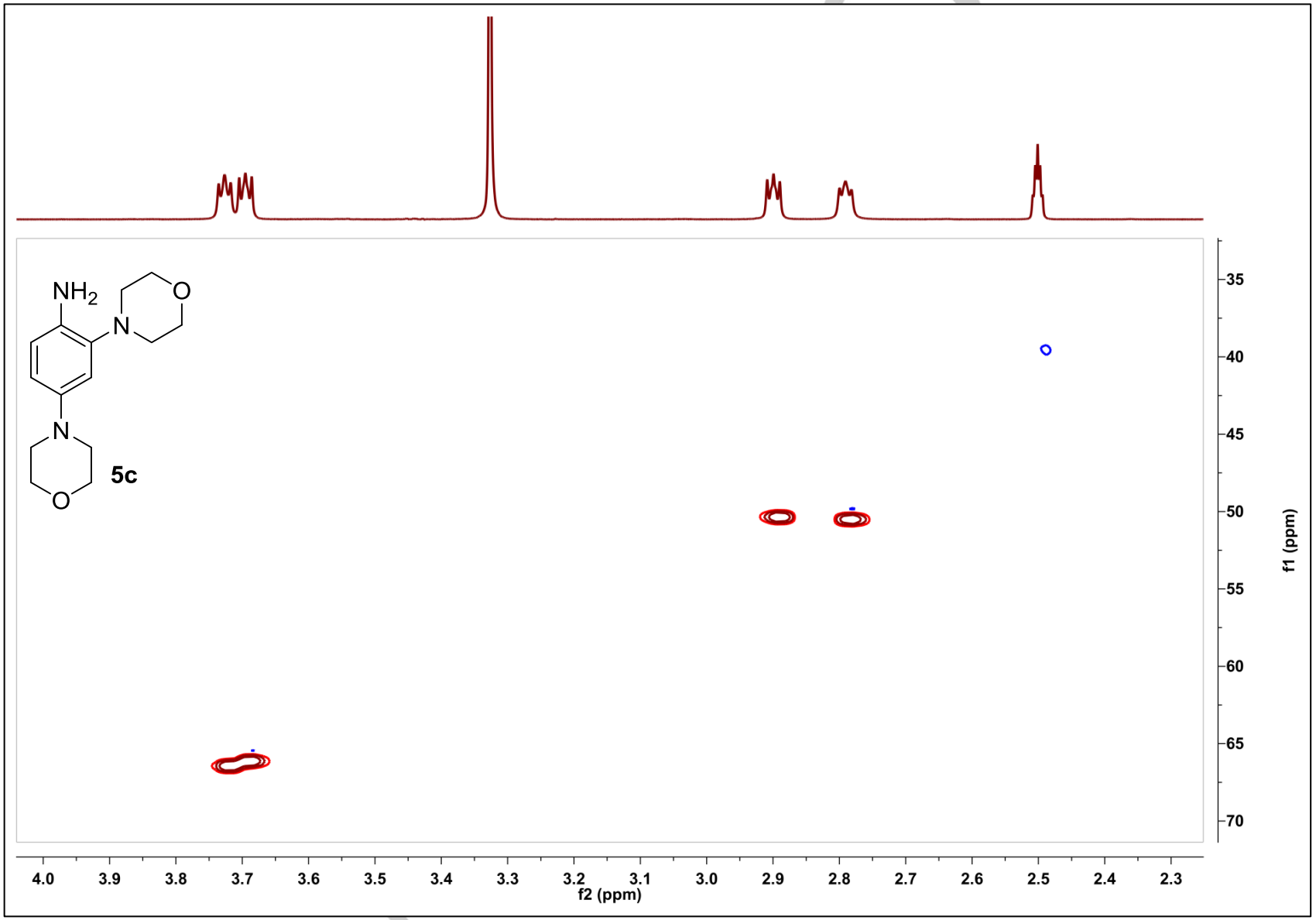
2,4-bis(morpholin-4-yl)aniline (**5c**)

bsgHMBC Spectrum



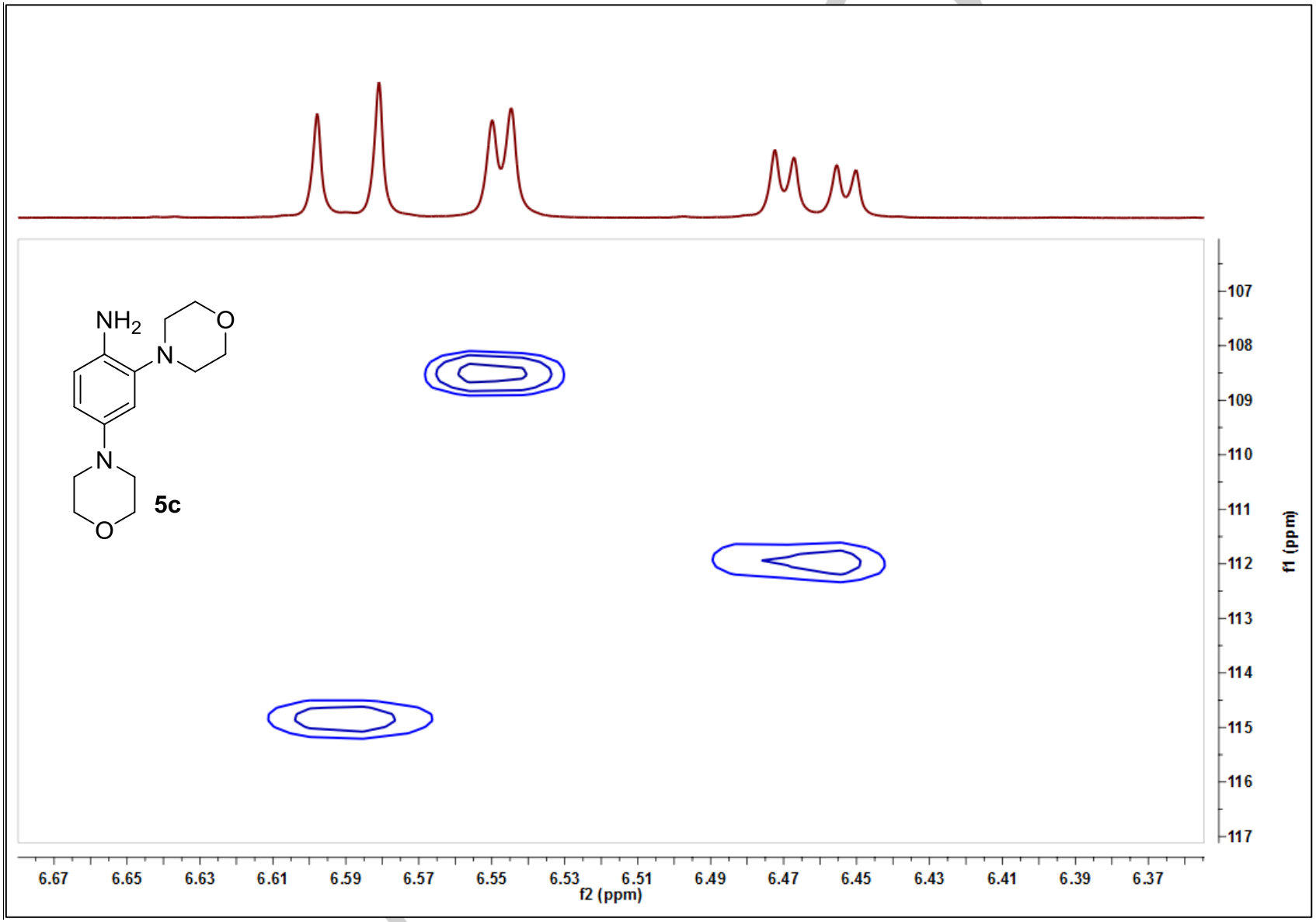
2,4-bis(morpholin-4-yl)aniline (**5c**)

gHSQC Spectrum, expansion I.



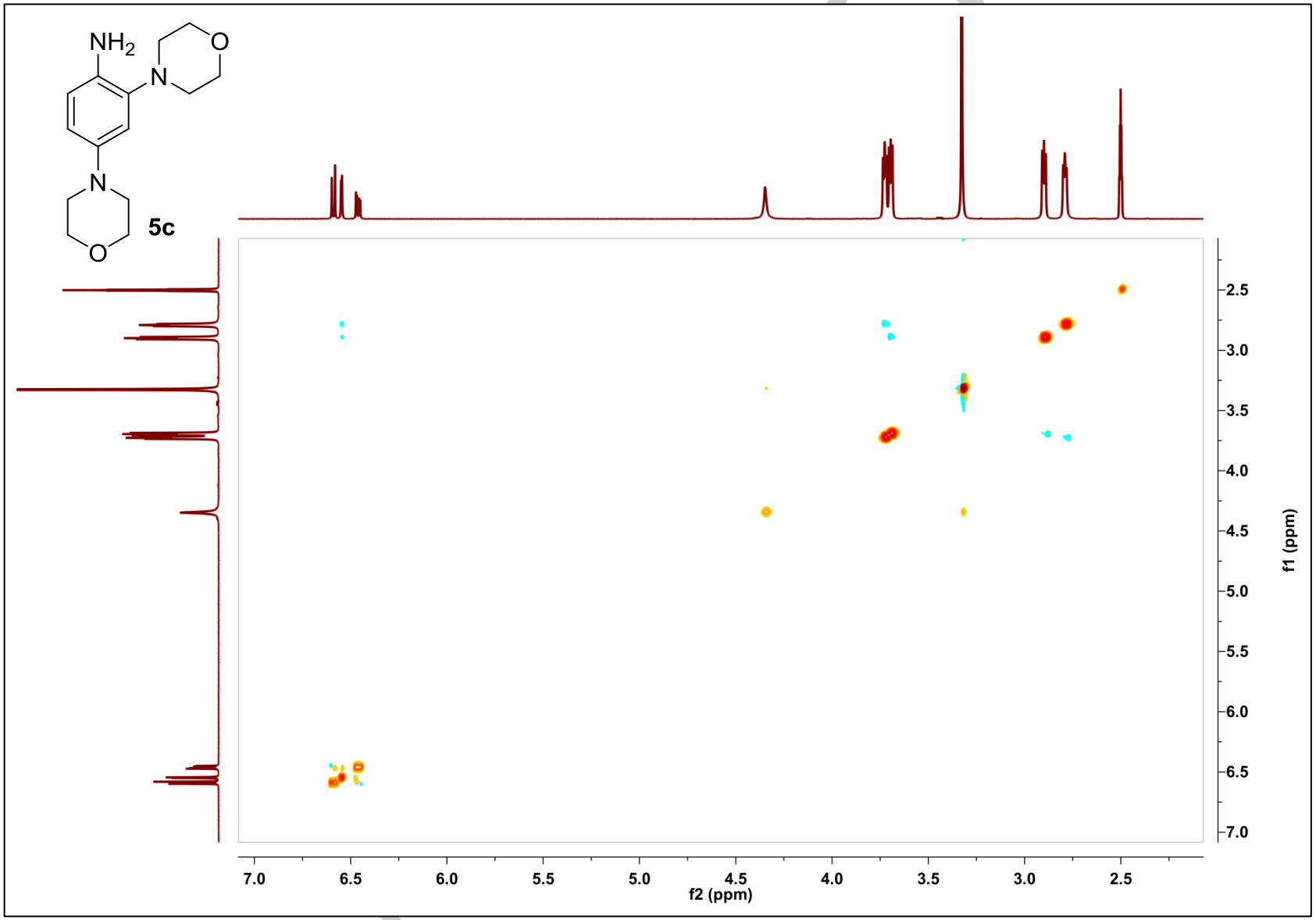
2,4-bis(morpholin-4-yl)aniline (**5c**)

gHSQC Spectrum, expansion II.

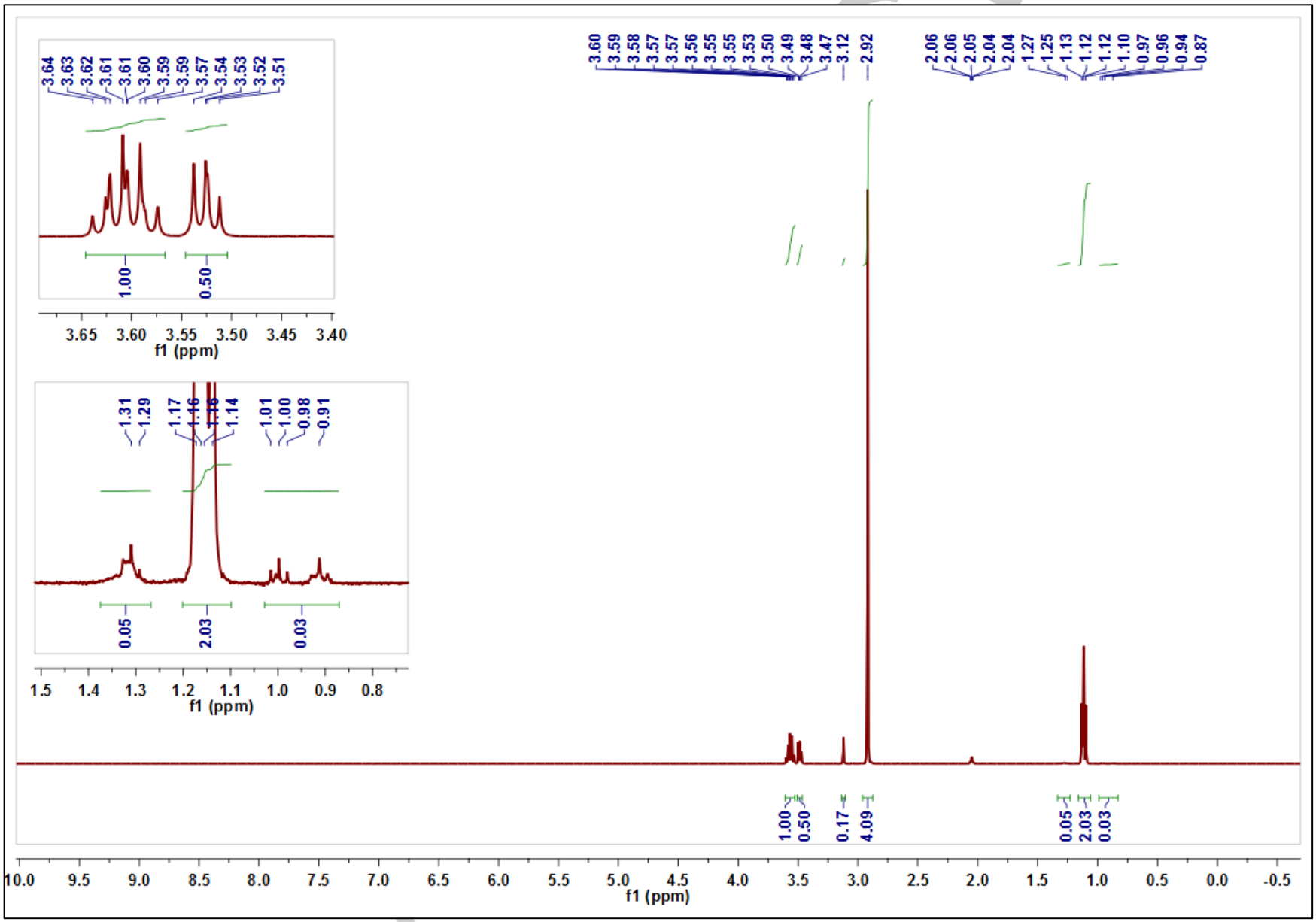


2,4-bis(morpholin-4-yl)aniline (**5c**)

ROESY Spectrum



^{1}H NMR spectrum of the lower phase of *n*-Hex:MTBE:EtOH:H_2O=1:1:1:1 solvent system (10 µL sample in 0.75 mL aceton-d_6).



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[2] M. Shalaeva, J. Kenseth, F. Lombardo, A. Bastin, *J. Pharm. Sci.* **2008**, *97*, 2581–2606.

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[4] Y. Ito, *J. Chromatogr. A* **2005**, *1065*, 145–168.