Electronic Supplementary Information

Two-Steps Continuous Flow-Driven Synthesis of 1,1-cyclopropane Aminoketones

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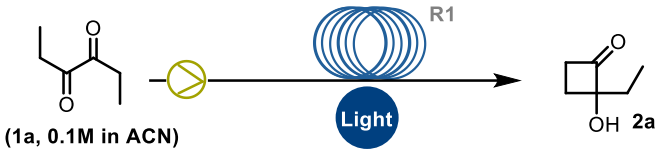
1. General remarks

Unless stated otherwise, respectively the synthesis of compounds **2** and **4** were performed at the reported temperatures using a continuous flow system as described in the corresponding procedures. The synthesis of the described compounds were also attempted in batch to compare the continuous flow process performances. Commercially available 1,2-diketones **1** and amines **3** were purchased from TCI, Fluorochem and Merck and were used as received unless otherwise noted. Enamine **3w** was synthetized following the literature procedure.[1] Al the organic solvents used in both batch and continuous flow processes have to be considered HPLC grade. ^{1}H NMR spectra were recorded on a Bruker Ascend 400 or 600, MHz spectrometer at 300.15 K ($CDCl_3$ ref. 7.26 ppm), ^{13}C NMR were recorded at 101 or 151 MHz ($CDCl_3$ ref. 77.00 ppm). Chemical shifts (δ) are given in ppm. Coupling constant values (*J*) are reported in Hz. Multiplicity is indicated as follows: s (*singlet*), d (*doublet*), t (*triplet*), q (*quartet*), m (*multiplet*), dd (*doublet of doublets*), tt (*triplet of triplets*). High Resolution Mass Spectra (HRMS) were obtained using a ThermoFisher Orbitrap Elite. Melting points were determined with a Büchi M-560. Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merk 70-200 mesh silica gel. For reactions carried out in batch or in continuous flow, yields refer to chromatographed/purified products. For continuous flow processes syringe pumps Harvard Apparatus Elite11 and HPLC pumps KNAUER, Azura P 4.1S were used. Vapourtec equipment R-series (R4), Photoreactor Vapourtec UV-150, (440 nm lamp). Column reactor manifold and thermocouple for 10mm bore column were also used.

2. Visible-light photocyclization of 1,2-diketones 1 to (HCBs) 2, under continuous flow conditions.

2.1. Custom-made coil reactor. Set-up



A freshly prepared stock solution of hexane-3,4-dione **1a** (0.1 M in acetonitrile) was pumped by syringe pump into a custom-made FEP - coil reactor (volume: 2 mL, internal diameter: 0.8 mm, length: 4 m). The coil reactor was placed in a cooling bath (Ethyl Acetate/submerged chiller piece to control the temperature 19-21 °C); the coil reactor was irradiated with a Kessil PR 160, 427 nm. Steady-state conditions were reached after 2 reactor volumes (4 mL). Reaction mixture was collected at the outlet of the flow reactor into a collection flask wrapped with a thin aluminium foil to avoid the formation of undesired side-products. Residual solvent was removed under vacuum to obtain the final product **2a**. NMR analysis were determined on the crude reactions using 1,3,5-trimetoxybenzene as internal standard (Table S1, Figure S2).

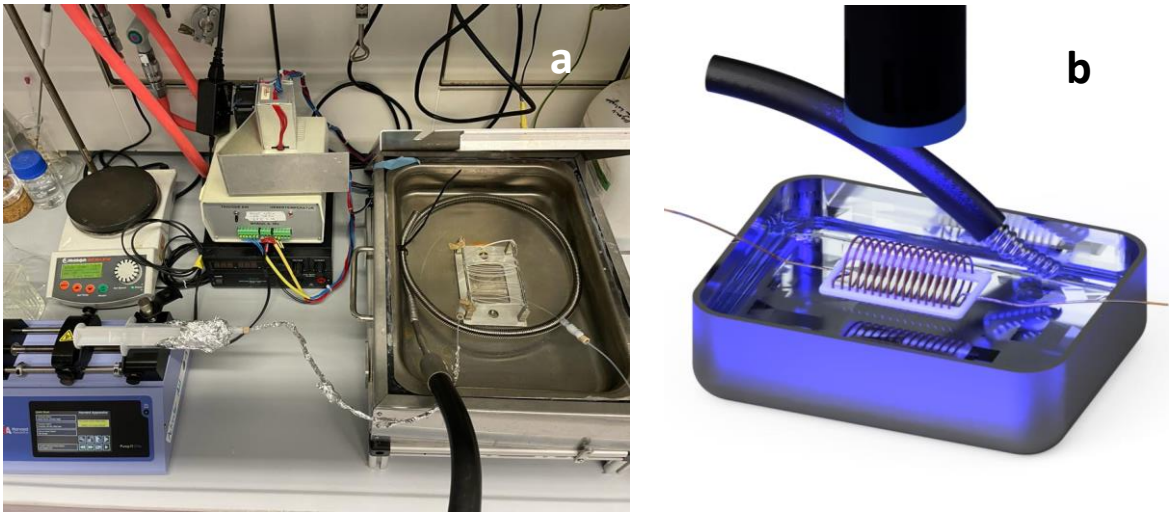


Figure S1 a) Continuous-flow set-up adapted for the photocyclization of **1a** to **2a;** b) 3D representation.

Table S1. Residence time screening.

Entry	Residence time [min]	Yield % of 2a[a]
1	30	90
2	20	87
3	15	81
4	10	69
5	5	51

[a]Yields calculated by NMR using 1,3,5-trimethoxybenzene as internal standard

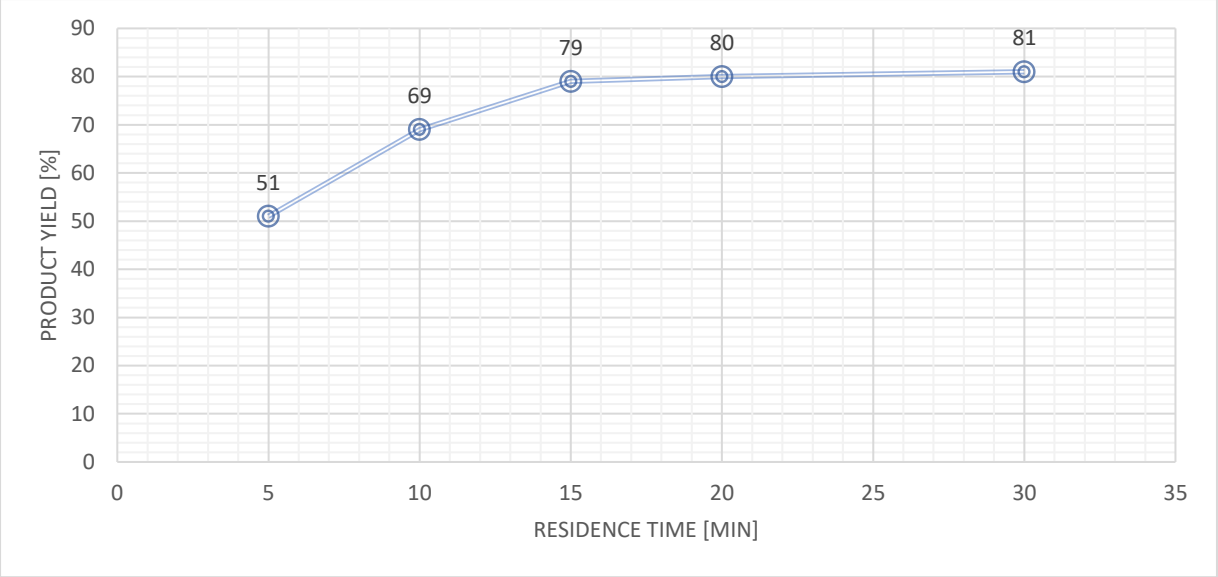


Figure S2. Residence time screening

2.2. Visible-light photocyclization of 1,2-diketones 1 to (HCBs) 2, under continuous flow conditions using Vapourtec UV-150 photoreactor.

Continuous flow Norrish-Yang II photocyclization was carried out in a commercially available Vapourtec photoreactor UV-150 (440 nm) connected to a R-series (R4) Vapourtec equipment. To precisely control the temperature, a dry ice heat exchanger was used to generate chilled nitrogen which is used to cool the reactor down to the low temperature required. The reactor temperature and light intensity were controlled directly from the Vapourtec R4 reactor, while the flow rate was set on syringe pump (Harvard Apparatus Elite 11) used for the infusion.

A freshly prepared tock solution of **1a** (0.1 M in acetonitrile) was pumped by syringe pump into a microcapillary FEP reactor (volume: 5 mL, internal diameter: 0.8 mm, length: 10 m) incorporated in Vapourtec UV-150 photoreactor. Steady-state conditions were reached after 2 reactor volumes (10 ml). The final product was collected on the outlet of the reactor into a collecting flask wrapped with thin aluminium foil to avoid the formation of undesired side-products. Residual solvent was concentrated under vacuum to obtain the product **2a**. NMR analysis were determined on the crude reactions using 1,3,5-trimetoxybenzene as internal standard (Table S2, Figure S4).

Figure S3. Equipment used for the photocyclization of hexane-3,4-dione **1a** to **2a**.

Table S2. Residence time screening using Vapourtec equipment.

Entry	Residence time [min]	Yield % of 2a[a]
1	15	90
2	10	87
3	5	85
4	4	84
5	3	84
6	2	82
7	1	79

[a]Yields calculated by NMR using 1,3,5-trimethoxybenzene as internal standard

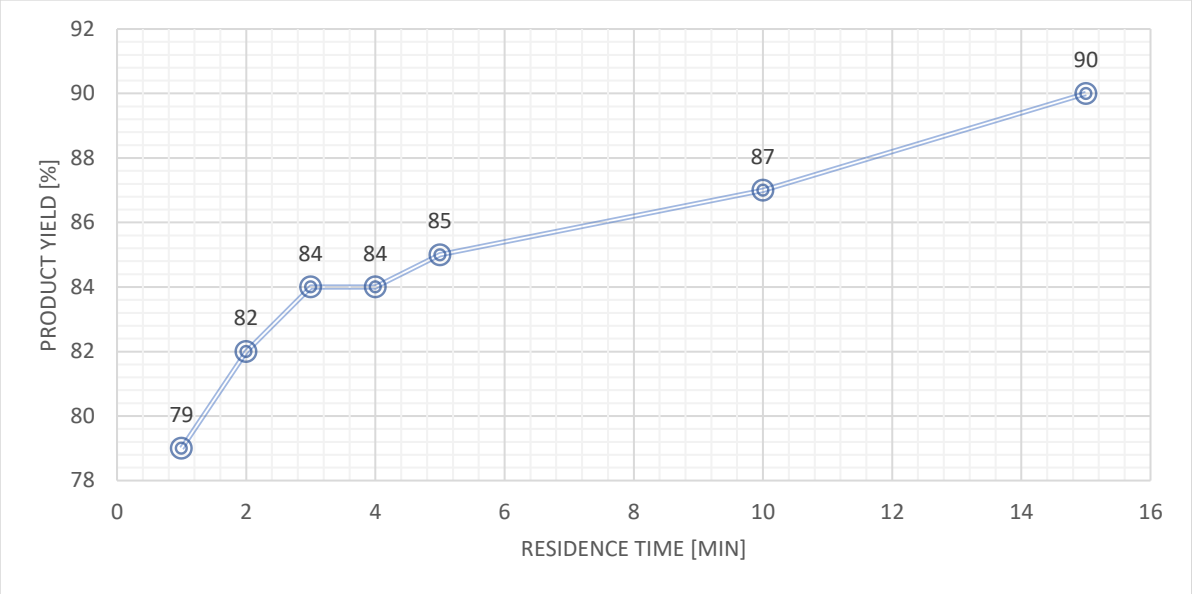
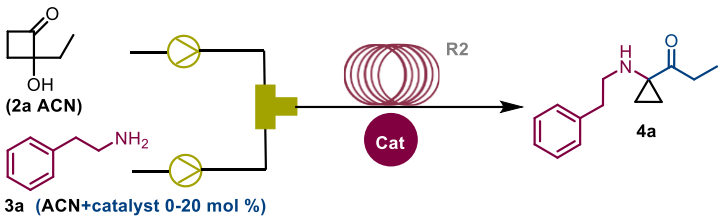


Figure S4. Residence time screening using Vapourtec equipment

3. Continuous flow synthesis of 1,1-cyclopropane aminoketones 4. Catalysts screening



A freshly prepared stock solution of **2a** (0.1 M in acetonitrile) and a solution of 2-phenylethylamine **3a** (1 eq, 0.1 M in acetonitrile) and a catalyst (see figure S7 and Table S3), were pumped by syringe pumps P1 (flow rate 0.133 mL/min) and P2 (flow rate 0.133 mL/min) into a custom-made PTFE coil reactor (volume: 2 mL, internal diameter: 0.8 mm, length: 4 m). The reactor was kept at ca. 22-24 °C using a coil bath (EtOAc-chiller). Steady-state conditions were reached after 2 reactor volumes (4 mL). The reaction mixture was collected at the outlet of the flow reactor into a collection flask. Residual solvent was concentrated under vacuum to obtain the final product **4a**. NMR analysis were determined on the crude reactions using 1,3,5-trimetoxybenzene as internal standard (Figure S5 and Table S3). Benchmark conditions for catalyst screening: 15 min residence time; 0.133 mL/min flow rate.

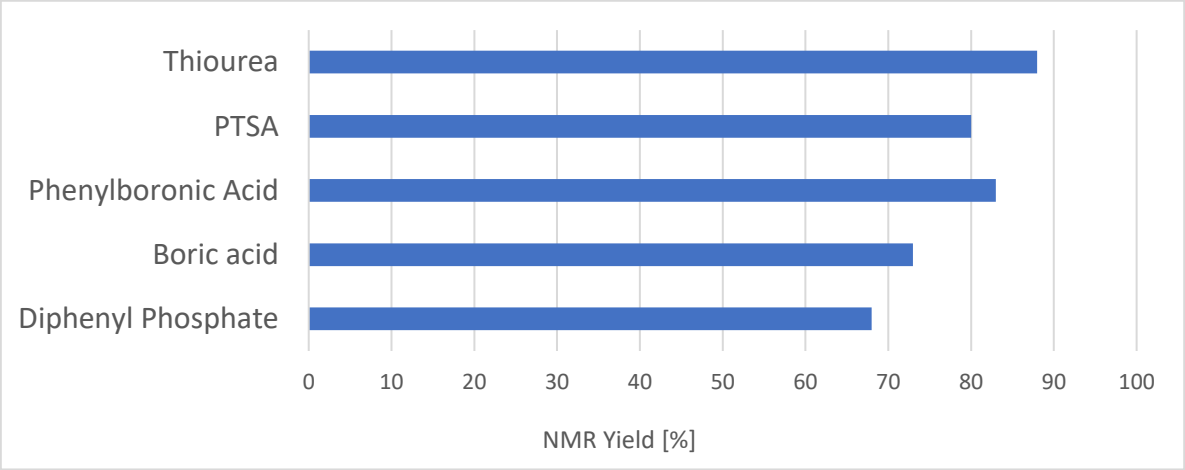


Figure S5. Catalyst screening

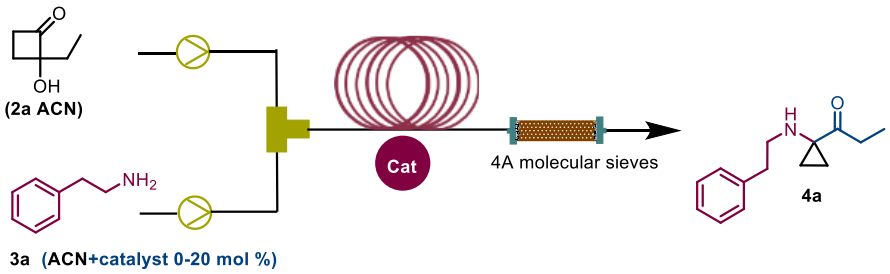
Table S3. Selected Catalysts Concentration Screening

Entry	n [mol]	qNMR Yield %[a]	
		Thiourea	Phenylboronic Acid
1	0.2	80	78
2	0.1	80	80
3	0.05	80	77
4	0.025	82	78

[a]Yields calculated by NMR using 1,3,5-trimethoxybenzene as internal standard.

3.1. Optimization of 1,1-cyclopropane aminoketones 4 synthesis under continuous flow conditions. Water removal using a 4Å molecular sieves packed bed.

This setup was investigated with the idea of evaluating a potential influence of water released into the reaction environment (1.0 equiv.) during the condensation process between HCB **1a** and the amine **3a**.



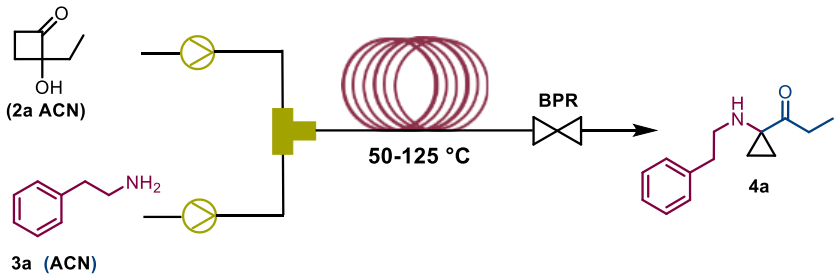
A freshly prepared stock solution of **2a** (0.1 M in acetonitrile) and **3a** (1 eq, 0.1 M in acetonitrile) were pumped by syringe pump into a custom-made PTFE coil reactor (volume: 2 mL, internal diameter: 0.8 mm, length: 4 m). Commercially available glass column Omnifit© (100 mm height, ID 6.6 mm, 2.4 mL volume) was packed with activated 4Å molecular sieves and placed at the outlet of the coil reactor.[2] Steady-state conditions were reached after 2 reactor volumes (4 mL+4.8mL for packed bed). The reaction mixture was collected into a collection flask. The residual solvent was concentrated under vacuum to obtain the final product **4a**. NMR analysis were determined on the crude reactions using 1,3,5-trimetoxybenzene as internal standard (Table S4). NMR analysis were determined on the crude reactions using 1,3,5-trimetoxybenzene as internal standard (Table S4).

Table S4. Residence time screening using a 4Å molecular sieves packed column.

Residence time [min]	qNMR Yield % of **4a**	qNMR Yield % of **4a**[a]
	4Å MS	**No MS**
15	79	41
30	79	57
60	75	70
180	90	78

[a]Yields calculated by NMR using 1,3,5-trimethoxybenzene as internal standard

3.2. Continuous flow synthesis of 1,1-cyclopropane aminoketones 4 using a Vapourtec reactor.



To study the temperature effect in the synthesis of **4a**, a freshly prepared stock solution of **1a** (0.1 M in acetonitrile) and 2-phenylethylamine **3a** (1 eq, 0.1 M in acetonitrile) were pumped into a Vapourtec tube reactor containing a PFA coil housed inside an insulated glass manifold (volume: 5 mL, internal diameter: 0.8 mm, length: 10 m) and fixed on an R-series (R4) Vapourtec equipment. The reactor temperature was controlled directly from the R4 reactor, while the flow rate was set on syringe pumps (Harvard Apparatus Elite 11) used for the infusion. At the outlet of the tube reactor a back pressure regulator (5.2 bar) was placed. Steady-state conditions were reached after 2 reactor volumes (10 mL). The reaction mixture was collected in a collection flask. The residual solvent was concentrated under vacuum to obtain the final product **4a**. NMR analysis were determined on the crude reactions using 1,3,5-trimetoxybenzene as internal standard (Table S5).

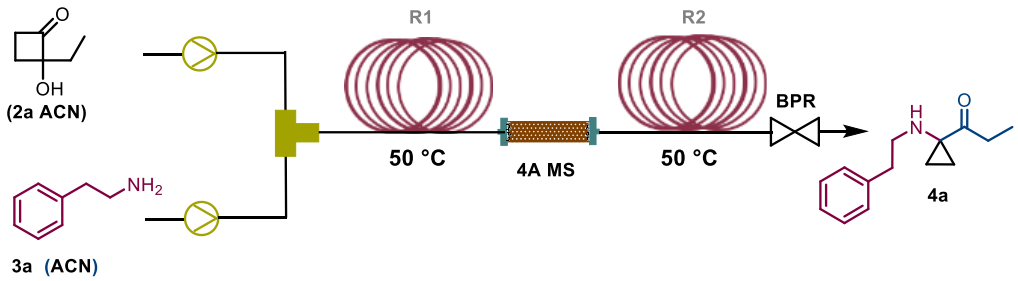
Table S5. Reaction temperature screening

Residence time [min]	Temperature/°C			
	50 °C	**75 °C**	**100 °C**	**125 °C**
5[a]	50%	78%	83%	88%
10[a]	59%	78%	87%	90%
15[a]	70%	75%	84%	85%

[a]Yields calculated by NMR using 1,3,5-trimethoxybenzene as internal standard

3.3. Continuous flow synthesis of 1,1-cyclopropane aminoketones 4 using in series Vapourtec reactors R1 and R2 and a 4Å molecular sieves packed bed.

This setup was investigated to evaluate the potential influence of water released into the reaction environment (1.0 equiv.) during the condensation process between HCB **1a** and the amine **3**.[2]



The immobilized reactor (R1) was connected to the bay 1 of a Vapourtec R4. An Omnifit© glass column within glass manifold (100 mm height, 6.6 mm, 2.4 ml volume) was fixed on the bay 2. The immobilised reactor (R2) (volume: 5 mL, internal diameter: 0.8 mm, length: 10 m) was connected to the bay 3. In both the reactors and the column, the temperature was controlled directly from the Vapourtec R4 reactor, while the flow rate was set on HPLC pumps (KNAUER) used for the infusion.

A freshly prepared stock solution of **1a** or **1b** (0.1 M in acetonitrile) and 2-phenylethylamine **3a** (1 eq, 0.1 M in acetonitrile) were pumped into an heated tube reactor R1 (50 °C), containing a PFA coil housed inside an insulated glass manifold (volume: 5 mL, internal diameter: 0.8 mm, length: 10 m) fixed on the 1st outlet of a R-series Vapourtec R4 equipment. On the second outlet an Omnifix© column within glass manifold (100 mm height, 6.6 mm, 2.4 mL volume) was fixed. The column was packed with activated 4Å MS and connected to both R1 and R2 tube reactors as described in the above reported general scheme. R2 reactor (volume: 5 mL, internal diameter: 0.8 mm, length: 10 m, 50 °C) was fixed on a third outlet. At the outlet of R2 tube reactor a back pressure regulator was placed. Steady-state conditions were reached after 2 reactors volumes (10mlx2+2.4mlx2). The reaction mixture was collected into a collection flask. The residual solvent was concentrated under vacuum to obtain the final product **2a**. NMR analysis were determined on the crude reactions using 1,3,5-trimetoxybenzene as internal standard (Table S6 and Table S7).

Table S6. Residence time screening at 125°C temperature and molecular sieves packed bed introduced

Entry	Residence time [min]	qNMR Yield %[a]
1	5,00	68
2	5,55	72
3	6,25	70
4	10,00	80
5	15,00	80

[a]Yields calculated by NMR using 1,3,5-trimethoxybenzene as internal standard

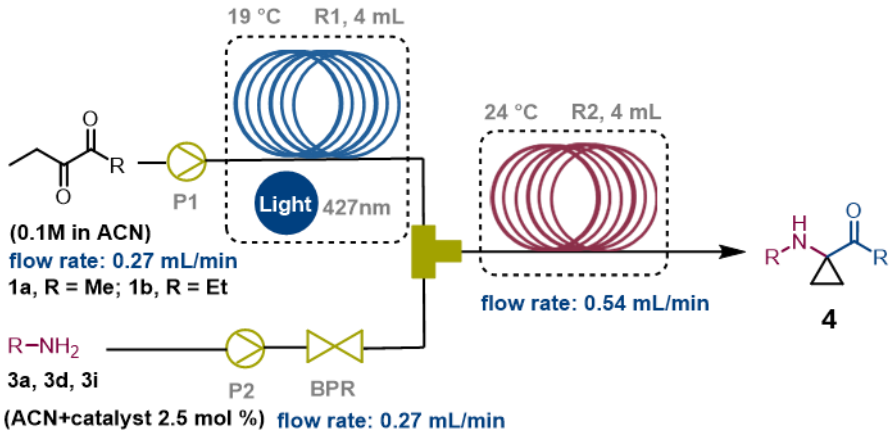
Figure S6. Representative Vapourtec equipment used in temperature-driven condensation reaction

Table S7. Optimization of the reaction using a Vapourtec apparatus[a]

Entry	Catalyst	Temp./°C	Final product conversion [4a/1a]	
			15 min	30 min
1	Thiourea 2.5 mol%	20	70/30	80/20
2	Thiourea 2.5 mol %	50	80/20	89/11
3	none	20	40/60	60/40
4	none	50	75/25	83/17

[a]Yields calculated by NMR using 1,3,5-trimethoxybenzene as internal standard

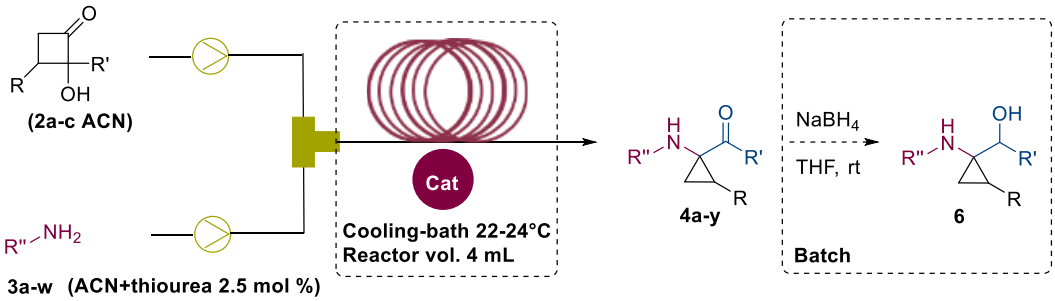
4. Telescoped 2-step synthesis of 1,1-cyclopropane aminoketones 4



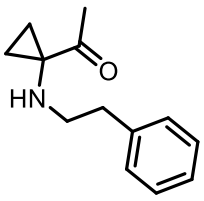
A freshly prepared stock solution of dione **1a** in acetonitrile (0.1 M) was streamed by the syringe pump P1 (0.27 mL/min flow rate). into a custom-made FEP flow reactor (4 mL, i.d. 0.8 mm) exposed to irradiation at 427 nm (Kessil lamp). Residence time: 15 min. At the outlet, the reaction mixture was mixed in a tee-piece mixer with an acetonitrile 0.1 M solution of phenylpropylamine **3a** and thiourea (2.5 mol%), pumped by a second syringe pump P2 at 0.27 mL/min flow rate. This second stream was equipped with BPR to balance overall system pressure. The resulting reaction solution was streamed into a 4 mL custom-made PTFA flow reactor (i.d. 0.8 mm) reaching the combined flow rate of 0.54 mL/min. Steady-state conditions were reached after 2 reactor volumes (4mL + 4mL). The reaction mixture was collected into a collection flask and the residual solvent was concentrated under vacuum.

The final products **4** were obtained after flash chromatography using hexanes-diethyl ether (5:1-1:1) as eluent.

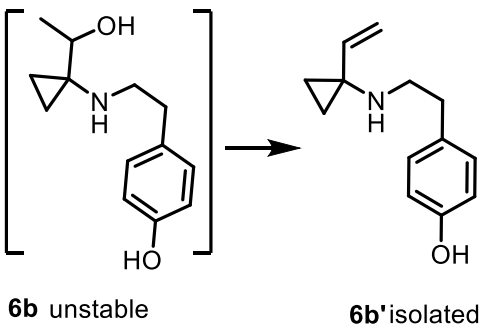
5. General procedure for the continuous flow synthesis of compounds 4 and 6



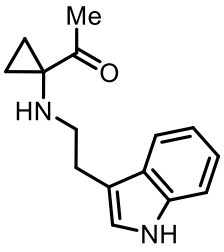
A stock solution of cyclobutanones **2** (0.1 M in acetonitrile) and a 0.1M solution of ammine **3** (1 eq, 0.1 M) and thiourea (2.5 mol%) in acetonitrile, were pumped into a custom-made PTFE coil reactor (volume: 4 mL, internal diameter: 0.8 mm) kept at ca. 22-24 °C using a coil bath by syringe pumps (combined flow rate 0.54 mL/min). Steady-state conditions were reached after 2 reactor volumes (8 mL). The reaction mixture was collected at the outlet of the flow reactor into a collection flask. Residual solvent was concentrated under vacuum and the reaction crude was purified by flash chromatography using hexanes-diethyl ether as eluents to isolate the corresponding 1,1-cyclopropane aminoketones **4**. For unstable compounds, the crude reactions were concentrated under vacuum to remove the acetonitrile, and analysed by NMR. Then the crude products were diluted with THF (3 mL THF/0.87 mmol of **4**) and cooled to 0 °C. $NaBH_4$ (2.0 equiv.) was added portion wise. The resulting mixtures were stirred for 2-8 hours. After quenching with methanol, the solvent was removed under reduced pressure and the crude products were purified by flash chromatography (eluents: hexanes-diethyl ether 5:1-1:1 to isolate the corresponding 1,1-cyclopropane amino alcohols **6**.



1-(1-(phenethylamino)cyclopropyl)ethan-1-one **4a**
Flash chromatography, silica gel (hexanes-Et_2O 5:1-1:1), yield 80%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32 – 7.27 (m, 2H), 7.22 (dd, *J* = 7.6, 3.1 Hz, 3H), 2.89 (t, *J* = 7.1 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 1.97 (s, 3H), 1.27 (q, *J* = 4.4 Hz, 2H), 1.05 (q, *J* = 4.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.8, 138.8, 128.7, 128.5, 126.4, 40.6, 38.5, 35.5, 29.8, 29.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ [M+H]: 204,1388; found: 204,1391.

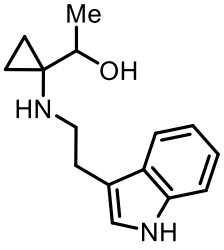


4-(2-((1-vinylcyclopropyl)amino)ethyl)phenol **6b'**
Obtained by reduction of **4b** (NMR yield 91%). Flash chromatography, silica gel (hexanes-Et_2O 5:1-1:1), overall yield 68%; pale yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.94 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.64 – 6.49 (m, 1H), 6.06 (t, *J* = 3.0 Hz, 1H), 5.86 (s, 1H), 4.04 – 3.86 (m, 1H), 2.91 (t, *J* = 7.4 Hz, 1H), 2.11 (s, 1H), 1.27 (dt, *J* = 15.0, 10.5 Hz, 2H), 0.98 – 0.81 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 154.3, 130.5, 129.8, 128.3, 119.6, 115.3, 106.7, 106.3, 48.3, 37.2, 11.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ [M+H]: 204,1388; found: 204,1393.



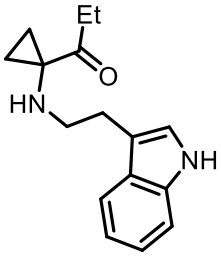
1-(1-((2-(1H-indol-3-yl)ethyl)amino)cyclopropyl)ethan-1-one **4c**

Yellow oil. The NMR data of the compound **4c** were obtained by analyzing the crude compound before the reduction step. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.00 (br. s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 3.03 – 2.95 (m, 2H), 2.95 – 2.88 (m, 2H), 2.01 (s, 3H), 1.28 (dd, *J* = 7.3, 4.4 Hz, 2H), 1.09 (dd, *J* = 7.0, 5.1 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 210.1, 136.3, 127.3, 121.9, 121.7, 119.1, 118.7, 111.1, 49.1, 47.6, 40.0, 29.8, 26.1, 17.9.



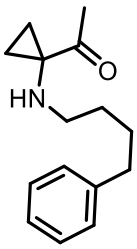
1-(1-((2-(1H-indol-3-yl)ethyl)amino)cyclopropyl)ethan-1-ol **6c**

Obtained by reduction of **4c** (NMR yield 88%). Flash chromatography, silica gel (hexanes-Et_2O 5:1-1:1). Yield 82%; pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.08 (br. s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 4.84 (dt, *J* = 8.7, 6.8 Hz, 1H), 3.80 – 3.72 (m, 2H), 3.03 – 2.96 (m, 2H), 2.66 – 2.58 (m, 2H), 2.48 - 2.45 (m, 2H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.62 br. (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 136.2, 127.4, 122.0, 121.8, 119.3, 118.6, 112.9, 111.1, 94.4, 40.4, 30.3, 28.9, 22.3, 21.3, 11.8; HRMS (ESI) *m/z* calcd for $C_{15}H_{21}N_2O$ [M+H]: 245,1654; found: 245,1655.



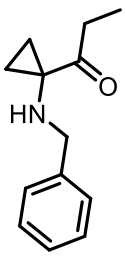
1-(1-((2-(1H-indol-3-yl)ethyl)amino)cyclopropyl)propan-1-one **4d**

Flash chromatography, sílica gel (hexanes-EtOAc 5:1-1:1), yield 84%; yellow deliquescente solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.17 (br s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 2.99 – 2.95 (m, 2H), 2.94 – 2.90 (m, 2H), 2.28 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 5.2 Hz, 2H), 1.03 (t, *J* = 6.3 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 212.6, 136.3, 127.5, 121.9, 121.7, 119.1, 118.8, 113.9, 111.0, 48.5, 47.7, 40.9, 30.0, 26.2, 17.8, 8.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}N_2O$ [M+H]: 257,1654; found: 257,1660.



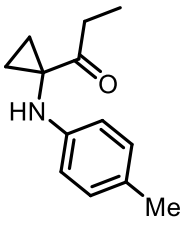
1-(1-((4-phenylbutyl)amino)cyclopropyl)ethan-1-one **4e**

Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 78%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 – 7.26 (m, 1H), 7.18 – 7.17 (m, 4H), 2.67 – 2.62 (m, 4H), 2.02 (s, 3H), 1.80-1.72 (m, 4H), 1.28 (dd, *J* = 7.4, 4.4 Hz, 2H), 1.07 (dd, *J* = 4.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 209.8, 142.1, 128.3, 128.2, 125.7, 77.2, 49.3, 47.1, 33.5, 32.1, 24.8, 17.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO$ [M+H]: 232,1701; found: 232,1710.

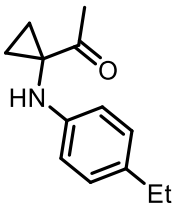


1-(1-(benzylamino)cyclopropyl)propan-1-one **4f**

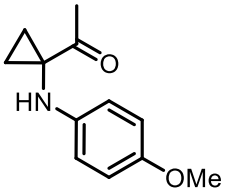
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 81%; pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35 – 7.28 (m, 4H), 7.26 – 7.22 (m, 1H), 3.78 (s, 2H), 2.36 (q, *J* = 7.3 Hz, 2H), 1.31 (q, *J* = 4.4 Hz, 2H), 1.13 (q, *J* = 4.4 Hz, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 212.2, 140.3, 128.3, 128.2, 126.9, 51.9, 48.8, 29.9, 17.9, 8.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ [M+H]: 204,1388; found: 204,1384. Spectral data are in accordance with the literature.[3]



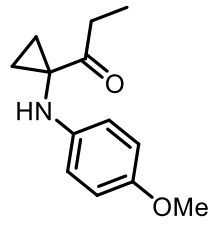
1-(1-(p-tolylamino)cyclopropyl)propan-1-one **4g**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 76%; yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.01 (d, *J* = 8.2 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 2H), 4.39 br (s, 1H), 2.73 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.63 (dd, *J* = 7.5, 3.8 Hz, 2H), 1.11 (dd, *J* = 7.5, 3.8 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 214.1, 144.2, 129.8, 127.1, 112.6, 43.1, 32.3, 21.4, 20.3, 7.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ [M+H]: 204,1388; found: 204,1393. Spectral data are in accordance with the literature.[3]



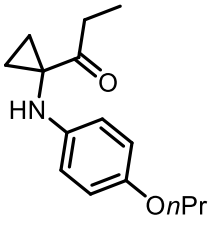
1-(1-((4-ethylphenyl)amino)cyclopropyl)ethan-1-one **4h**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 88%; yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.25 – 7.14 (m, 2H), 6.64 – 6.49 (m, 2H), 2.67 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.63 (dd, *J* = 7.5, 3.9 Hz, 2H), 1.14 – 1.05 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 213.4, 145.3, 131.1, 125.4, 113.3, 43.0, 32.3, 21.4, 18.7, 7.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ [M+H]: 204,1388; found: 204,1391.



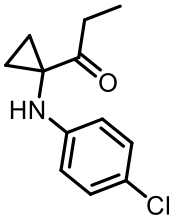
1-(1-((4-methoxyphenyl)amino)cyclopropyl)ethan-1-one **4i**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 88%; orange oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.83 – 6.73 (m, 2H), 6.65 – 6.49 (m, 2H), 3.75 (s, 3H), 2.25 (s, 3H), 1.65 – 1.58 (m, 2H), 1.59 (br. s, 1H), 1.12 (dd, *J* = 7.5, 3.9 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 211.9, 152.3, 140.4, 114.9, 113.5, 55.7, 43.9, 27.1, 21.3; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NNaO_2$ [M+Na]: 228,1000; found: 228,1004.



1-(1-((4-methoxyphenyl)amino)cyclopropyl)propan-1-one **4j**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 84%; orange oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.83 – 6.71 (m, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 3H), 2.65 (q, *J* = 7.2 Hz, 2H), 1.61 (q, *J* = 3.9 Hz, 2H), 1.15 (dd, *J* = 7.4, 4.0 Hz, 2H), 0.98 (t, *J* = 8.6, 5.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 214.13, 152.4, 140.6, 115.0, 113.5, 55.7, 43.5, 32.3, 21.3, 7.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO_2$ [M+H]: 220,1338; found: 220,1342. Spectral data are in accordance with the literature.[3]

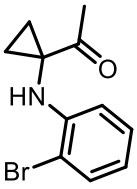


1-(1-((4-propoxyphenyl)amino)cyclopropyl)propan-1-one **4k**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 81%; orange oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.81 – 6.74 (m, 2H), 6.60 – 6.50 (m, 2H), 3.84 (t, *J* = 6.6 Hz, 2H), 2.67 (q, *J* = 7.2 Hz, 2H), 1.76 (dd, *J* = 14.0, 6.7 Hz, 2H), 1.60 (q, *J* = 3.9 Hz, 2H), 1.10 (q, *J* = 3.9 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 214.2, 151.8, 140.5, 115.8, 113.5, 70.2, 43.5, 32.3, 22.7, 21.3, 10.5, 7.7; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_2$ [M+H]: 248,1651; found: 248,1660. Spectral data are in accordance with the literature.[3]



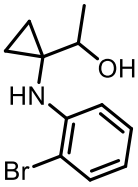
1-(1-((4-chlorophenyl)amino)cyclopropyl)propan-1-one **4l**

Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 80%; pale yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.20 – 7.04 (m, 2H), 6.63 – 6.42 (m, 2H), 2.64 (q, *J* = 7.2 Hz, 2H), 1.64 (q, *J* = 3.9 Hz, 2H), 1.11 (q, *J* = 3.9 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 213.1, 145.1, 129.2, 122.8, 113.7, 43.1, 32.3, 21.3, 7.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}ClNO$ [M+H]: 224,0842; found: 224,0844. Spectral data are in accordance with the literature.[3]



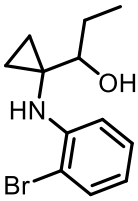
1-(1-((2-bromophenyl)amino)cyclopropyl)ethan-1-one **4m**

Flash chromatography, silica gel (hexanes-Et_2O 5:1-1:1), yield 83%; colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.46 (d, *J* = 1.4 Hz, 1H), 7.21 – 7.13 (m, 1H), 6.72 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.64 (td, *J* = 7.8, 1.4 Hz, 1H), 5.14 (br s, 1H), 2.23 (s, 3H), 1.70 (q, *J* = 3.9 Hz, 2H), 1.19 (q, *J* = 3.8 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 210.8, 143.5, 132.7, 128.5, 118.9, 112.2, 109.1, 43.4, 27.0, 21.5; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}BrNO$ [M+H]: 254,0181; found: 254,0189.



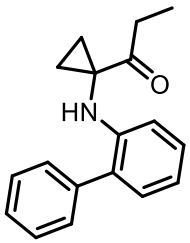
1-(1-((2-bromophenyl)amino)cyclopropyl)ethan-1-ol **6m**

Obtained by reduction of **4m**. Flash chromatography (hexanes-Et_2O 5:1-1:1), 74%; colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.39 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.15 (dd, *J* = 11.3, 4.1 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.61 – 6.49 (m, 1H), 4.86 (br s, 1H), 3.79 (q, *J* = 6.3 Hz, 1H), 2.07 (br s, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.03 – 0.90 (m, 2H), 0.88 – 0.75 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 143.8, 132.3, 127.9, 117.9, 113.3, 109.1, 69.8, 39.1, 19.8, 12.7, 11.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}BrNO$ [M+H]: 256,0337; found: 256,0341.



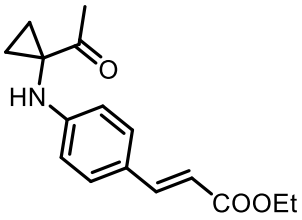
1-(1-((2-bromophenyl)amino)cyclopropyl)propan-1-ol **6n**

Obtained by reduction of **4n** (NMR yield 88%). Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), Yield after reduction 70%. White solid Mp: 86 °C; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.38 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.13 (dtd, *J* = 10.0, 8.2, 1.5 Hz, 2H), 6.56 (ddd, *J* = 7.9, 7.1, 1.8 Hz, 1H), 4.82 (br s, 1H), 3.41 (d, *J* = 6.9 Hz, 1H), 1.69 (dqd, *J* = 15.0, 7.5, 3.5 Hz, 1H), 1.59 (br s, 1H), 1.46 (ddq, *J* = 14.6, 9.6, 7.3 Hz, 1H), 0.99 – 0.94 (m, 2H), 0.88 – 0.78 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 144.0, 132.4, 128.0, 117.9, 113.4, 109.2, 38.5, 27.2, 12.6, 12.4, 10.6; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}BrNO$ [M+H]: 270,0494; found: 270,0499.



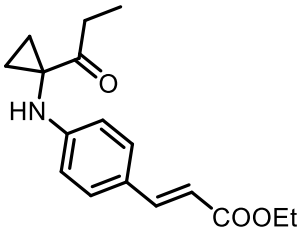
1-(1-([1,1'-biphenyl]-2-ylamino)cyclopropyl)propan-1-one **4o**

Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 82%; orange solid, Mp: 120-122 °C; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.48 (dd, *J* = 10.6, 4.5 Hz, 2H), 7.42 – 7.38 (m, 3H), 7.22 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.82 (td, *J* = 7.4, 1.0 Hz, 1H), 6.76 (dd, *J* = 8.2, 0.8 Hz, 1H), 2.68 (q, *J* = 7.2 Hz, 2H), 1.62 (dd, *J* = 7.4, 3.9 Hz, 2H), 1.06 (dd, *J* = 3.8 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 213.7, 143.4, 139.1, 130.4, 129.2, 129.0, 128.6, 127.4, 127.3, 117.7, 111.1, 42.9, 32.3, 21.5, 7.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}NO$ [M+H]: 266,1545; found: 266,1549. Spectral data are in accordance with the literature.[3]



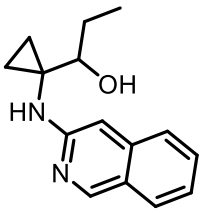
ethyl (E)-3-(4-((1-acetylcyclopropyl)amino)phenyl)acrylate **4p**

Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 61%; orange oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 15.9, 3.1 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.3 Hz, 1H), 6.63 (m, 2H), 6.23 (dd, *J* = 15.9, 3.6 Hz, 1H), 4.82 (br s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.00 (s, 3H), 1.68 (dd, *J* = 7.5, 4.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.16 (dd, *J* = 7.4, 3.9 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 210.6, 167.6, 148.4, 144.6, 129.8, 124.7, 114.8, 112.8, 60.1, 43.3, 39.5, 27.1, 21.4, 14.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_3$ [M+H]: 274,1443; found: 274,1445.



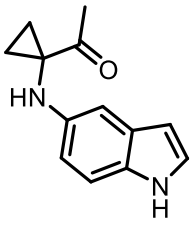
ethyl (E)-3-(4-((1-propionylcyclopropyl)amino)phenyl)acrylate **4q**

Flash chromatography, silica gel (hexanes-Et_2O 5:1-1:1), yield 66%; orange oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.57 (dd, *J* = 15.9, 4.1 Hz, 1H), 7.35 (m, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.61 (dd, *J* = 13.2, 8.5 Hz, 1H), 6.21 (dd, *J* = 15.9, 3.6 Hz, 1H), 4.99 (br s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.64 (q, *J* = 7.2 Hz, 2H), 1.64 (dd, *J* = 7.4, 4.0 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.12 (dd, *J* = 7.5, 3.8 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 212.9, 167.6, 144.7, 129.8, 114.7, 113.5, 112.7, 60.1, 42.8, 32.2, 21.3, 14.2, 7.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{22}NO_3$ [M+H]: 288,1600; found: 288,1611.



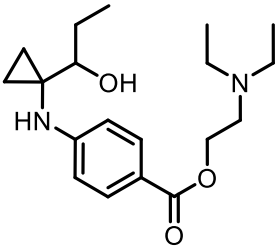
1-(1-(isoquinolin-3-ylamino)cyclopropyl)propan-1-ol **6r**

Obtained by reduction of **4r** (NMR yield 88%). Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1),. Yield after reduction 86%. White solid, Mp: 97°C; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.82 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.22 – 7.17 (m, 1H), 6.75 (s, 1H), 4.87 (br s, 1H), 3.13 (dd, *J* = 8.2, 5.1 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.66 – 1.59 (m, 1H), 1.08 (ddd, *J* = 9.8, 6.3, 4.8 Hz, 1H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.94 – 0.90 (m, 1H), 0.88 – 0.83 (m, 1H), 0.82 – 0.77 (m, 1H); m^{13}C NMR (151 MHz, $CDCl_3$) δ: 154.7, 150.9, 138.8, 130.5, 127.8, 124.6, 122.8, 99.1, 78.5, 38.5, 28.0, 14.8, 13.6, 10.6; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}N_2O$ [M+H]: 243,1497; found: 243,1501.

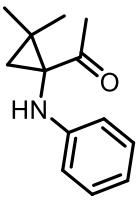


1-(1-((1H-indol-5-yl)amino)cyclopropyl)ethan-1-one **4s**

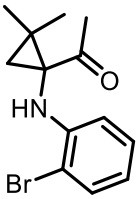
Flash chromatography, silica gel (hexanes-Et_2O 5:1-1:1), yield 63%; Orange yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.01 (br s, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.13 (s, 1H), 6.84 (s, 1H), 6.59 (d, *J* = 8.6 Hz, 1H), 6.39 (s, 1H), 2.29 (s, 3H), 1.66 (d, *J* = 3.5 Hz, 2H), 1.17 (d, *J* = 3.6 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 212.9, 140.4, 130.2, 128.7, 124.6, 111.8, 111.0, 102.0, 101.7, 44.1, 27.3, 21.5; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}N_2O$ [M+H]: 215,1184; found: 215,1185.



2-(diethylamino)ethyl 4-((1-(1-hydroxypropyl)cyclopropyl)amino)benzoate **6t**
Obtained by reduction of **4t** (NMR yield 90%). Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1). Yield 78%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.69 (br. s, 1H), 4.68 (t, *J* = 6.1 Hz, 2H), 3.06 (t, *J* = 6.1 Hz, 2H), 2.92 (qd, *J* = 13.2, 7.1 Hz, 4H), 1.68 (ddd, *J* = 13.9, 7.5, 3.5 Hz, 1H), 1.60 (br. s, 1H), 1.49 – 1.38 (m, 1H), 1.23 (t, *J* = 7.3 Hz, 6H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.97 (t, *J* = 3.2 Hz, 2H), 0.82 (q, *J* = 4.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 166.3, 151.6, 131.3, 117.9, 112.5, 76.5, 58.9, 56.4, 53.6, 38.5, 27.1, 12.9, 12.4, 10.6, 8.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}N_2O_3$ [M+H]: 335,2335; found: 335,2338.

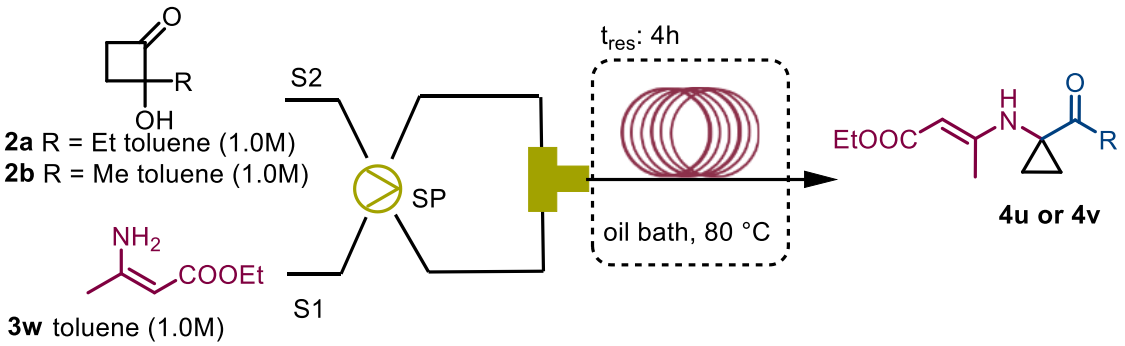


1-(2,2-dimethyl-1-(phenylamino)cyclopropyl)ethan-1-one **4w**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 90%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.18 (dd, *J* = 8.3, 7.5 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.69 – 6.50 (m, 2H), 4.52 (br. s, 1H), 2.21 (s, 3H), 1.92 (d, *J* = 3.5 Hz, 1H), 1.36 (s, 4H), 1.15 (s, 3H), 0.79 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 210.0, 146.7, 129.3, 117.9, 112.5, 51.8, 28.4, 21.7, 19.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ [M+H]: 204,1388; found: 204,1394. Spectral data are in accordance with the literature.[3]



1-(1-((2-bromophenyl)amino)-2,2-dimethylcyclopropyl)ethan-1-one **4x**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), pale yield 87%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.43 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.17 – 7.03 (m, 1H), 6.67 – 6.52 (m, 2H), 5.22 (br. s, 1H), 2.19 (s, 3H), 1.95 (s, 1H), 1.41 (s, 3H), 1.14 (s, 3H), 0.74 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 209.2, 143.5, 132.4, 128.5, 118.6, 111.8, 109.1, 51.8, 31.8, 28.1, 21.8, 19.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}BrNO$ [M+H]: 282,0494; found: 282,0500.

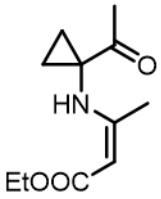
5.1. Synthesis of compounds 4u and 4v



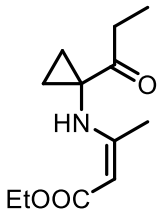
The enamine **3u** was synthesized following the literature[1] by reacting ethyl acetoacetate with ammonia. The desired compound **3u** was used without further purification in the following steps.

The continuous flow synthesis of compounds **4u** and **4v** were performed as follows. A stock solution of enamine **3u** (1.0 M in toluene) and a stock solution of HCB **2a** or **2b** (1.0 M in toluene) were

dispensed using two syringes mounted on the same syringe pump (SP). The two lines, converging at a T-mixer, were introduced into a stainless steel coil reactor with an internal volume of 1 mL (residence time: 4 hours), thermostated at 80 °C.



ethyl (Z)-3-((1-acetylcyclopropyl)amino)but-2-enoate **4u**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 25%; yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 9.03 (s, 1H), 4.64 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.25 (s, 3H), 1.91 (s, 3H), 1.59 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.20 (d, J = 3.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 209.05, 170.57, 162.14, 85.88, 58.88, 43.88, 31.06, 27.21, 21.18, 20.02, 14.66; HRMS (ESI) *m/z* calcd for $C_{11}H_{18}NO_3$ [M+H]: 212.1287; found: 212.2000.

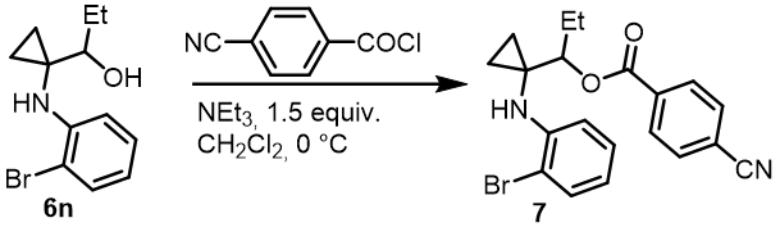


ethyl (Z)-3-((1-propionylcyclopropyl)amino)but-2-enoate **4v**
Flash chromatography, sílica gel (hexanes-Et_2O 5:1-1:1), yield 27%; yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 9.03 (s, 1H), 4.62 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.61 (q, J = 7.2 Hz, 2H), 1.89 (s, 3H), 1.26 (t, J = 7.1 Hz, 4H), 1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 211.53, 170.60, 162.23, 85.76, 58.88, 43.44, 32.79, 21.08, 20.04, 14.67, 7.97; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}NO_3$ [M+H]: 226.1443; found: 226,1443.

The same reactions were also carried out in Batch at 80 °C following the procedure reported in the literature[3] accessing the compounds **4u** and **4v** in 43 and 45% respectively.

6. Synthesis of compounds 7-9

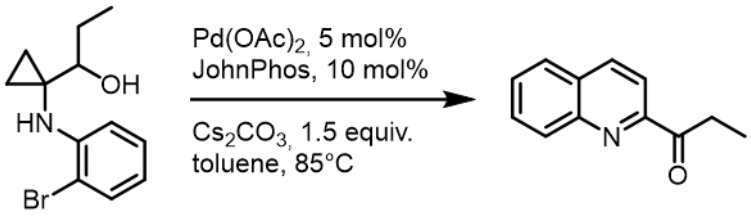
6.1. Synthesis of compound 7



To a stirred solution of compound 6n (50 mg, 0.12 mmol) and triethylamine (165 μL, 1.19 mmol) in dichloromethane at 0°C, 4-cyanobenzoyl chloride (162 μL, 0.12 mmol) was added dropwise. The reaction mixture was stirred for 12 hours. Afterward, a 10% aqueous HCl solution (10 mL) was added. The phases were separated, and the organic layer was dried over Na_2SO_4. The organic solution was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel (hexanes-Et_2O 10:1-5:1) affording the compound **7** in 75% yield as a pale yellow oil.
^1H NMR (600 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.41 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.06 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.59 – 6.52 (m, 1H), 4.91 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.88 (br. s, 1H), 1.99 – 1.83 (m, 2H), 1.14 (ddd, *J* = 9.1, 6.9, 4.7 Hz, 1H), 1.01 (dd, *J* = 9.9, 5.8 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.87 (dd, *J* = 13.6, 6.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$)

δ: 164.6, 143.8, 133.8, 132.4, 132.1, 130.3, 127.9, 118.3, 116.4, 113.7, 111.6, 109.1, 109.1, 81.0, 36.7, 25.0, 10.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}BrN_2NaO_2$ [M+Na]: 421,0528; found: 421,0533.

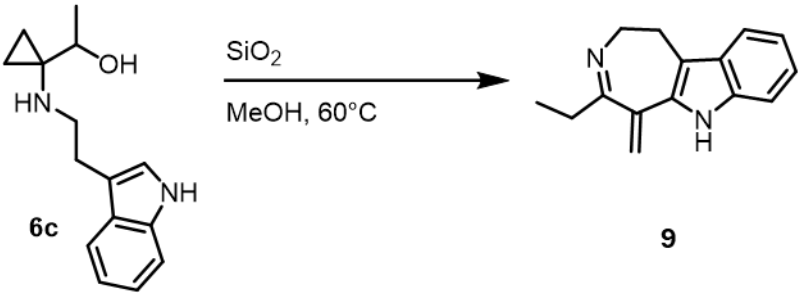
6.2. Synthesis of compound 8



6n **8**

$Pd(OAc)_2$ (2.2 mg, 5 mol %), JohnPhos (5.7 mg, 10 mol %) and Cs_2CO_3 (93 mg, 1.5 equiv.) were stirred under vacuum for 1h then degassed toluene (4mL) was added. The resulting suspension was stirred under argon atmosphere and **6n** (50 mg, 0.19 mmol) was added in 1 mL of toluene. and the reaction mixture was heated to 85°C for 16 hours. The solvent was removed under vacuum and the crude product was loaded on a silica gel column for purification (hexanes-Et_2O 10:1-3:1) to afford the compound **8** in 70% yield as a pale yellow solid, Mp: 81 °C.
^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 3.43 (q, *J* = 7.3 Hz, 2H), 1.28 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ: 203.3, 153.2, 147.3, 137.0, 130.7, 130.1, 129.7, 128.6, 127.8, 118.3, 31.0, 8.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}NNaO$ [M+Na]: 208,0738; found: 208,0741. Spectral data are in accordance with the literature.[9] The XRD analysis of compound **7** is reported in section 8.

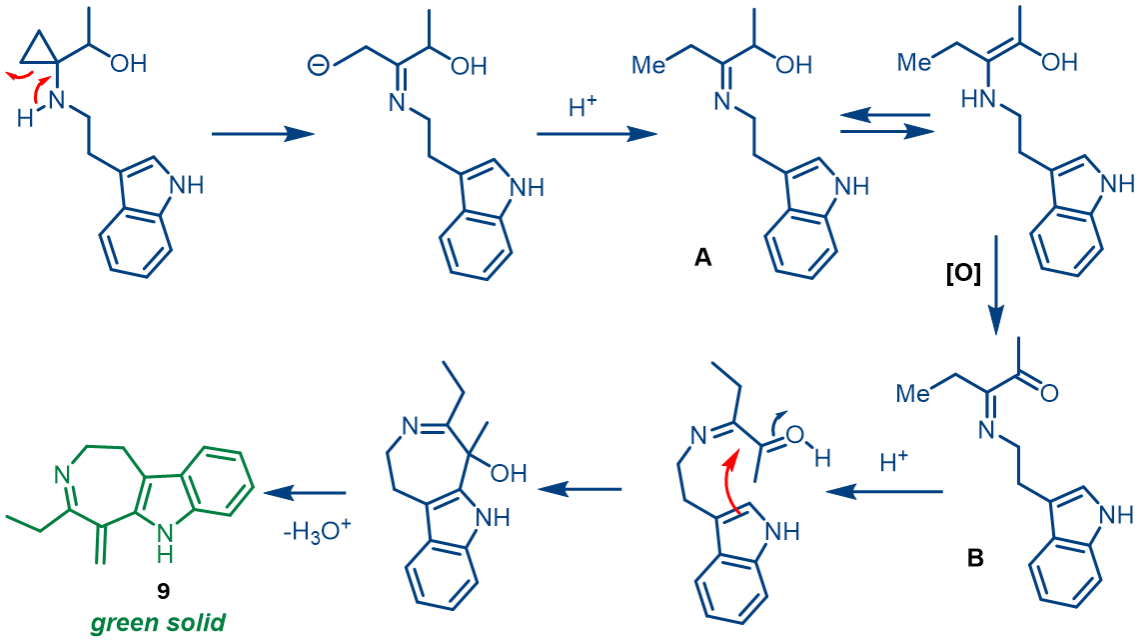
6.3. Synthesis of compound 9



6c **9**

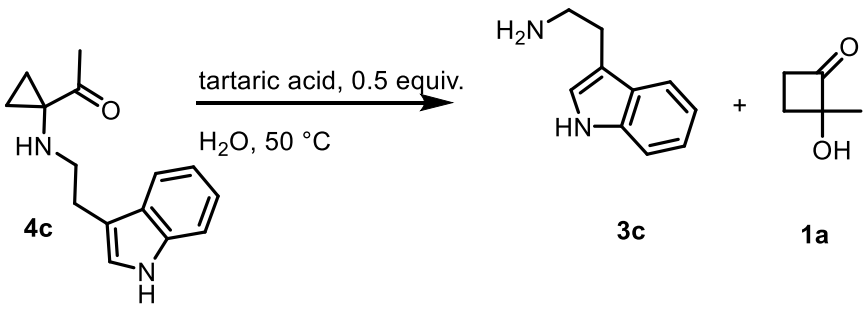
To a solution of **6c** (100 mg, 0.41 mmol) in MeOH (10 mL), SiO_2 was added (100 mg). The reaction was stirred at 60°C for 12h. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resulting crude oil was loaded on a silica gel column for purification (hexanes-Et_2O 10:1-1:1) to afford the compound **9** in 81% yield.
Green solid Mp: 215 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.96 (s, 1H), 7.40 (dd, *J* = 6.1, 2.3 Hz, 1H), 7.26 (dd, *J* = 6.2, 2.3 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.16 (d, *J* = 3.5 Hz, 1H), 5.89 (d, *J* = 3.5 Hz, 1H), 3.98 (t, *J* = 7.0 Hz, 2H), 3.05 (t, *J* = 7.0 Hz, 2H), 2.60 (dt, *J* = 15.0, 6.0 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 156.4, 136.4, 129.5, 127.1, 123.8, 121.1, 119.8, 117.6, 110.7, 105.0, 104.3, 101.0, 41.8, 21.0, 19.7, 12.8; HRMS (ESI) *m/z* calcd for $C_{15}H_{16}N_2Na$ [M+Na]: 247,1211; found: 247,1215.

The reaction outcome was rationalized as follows: the amino alcohol **6c** can undergo ring opening rearrangement accessing the corresponding imino-alcohol derivative A. Through an Heyns-type rearrangement, the iminol **A** can generate the imino-ketone **B** that in aerobic environment and in the presence of an acid, is involved in a intramolecular aromatic electrophilic substitution to yield the corresponding product **9** as reported in the Scheme S1.



Scheme S1. Proposed reaction mechanism for the formation of compound **9**

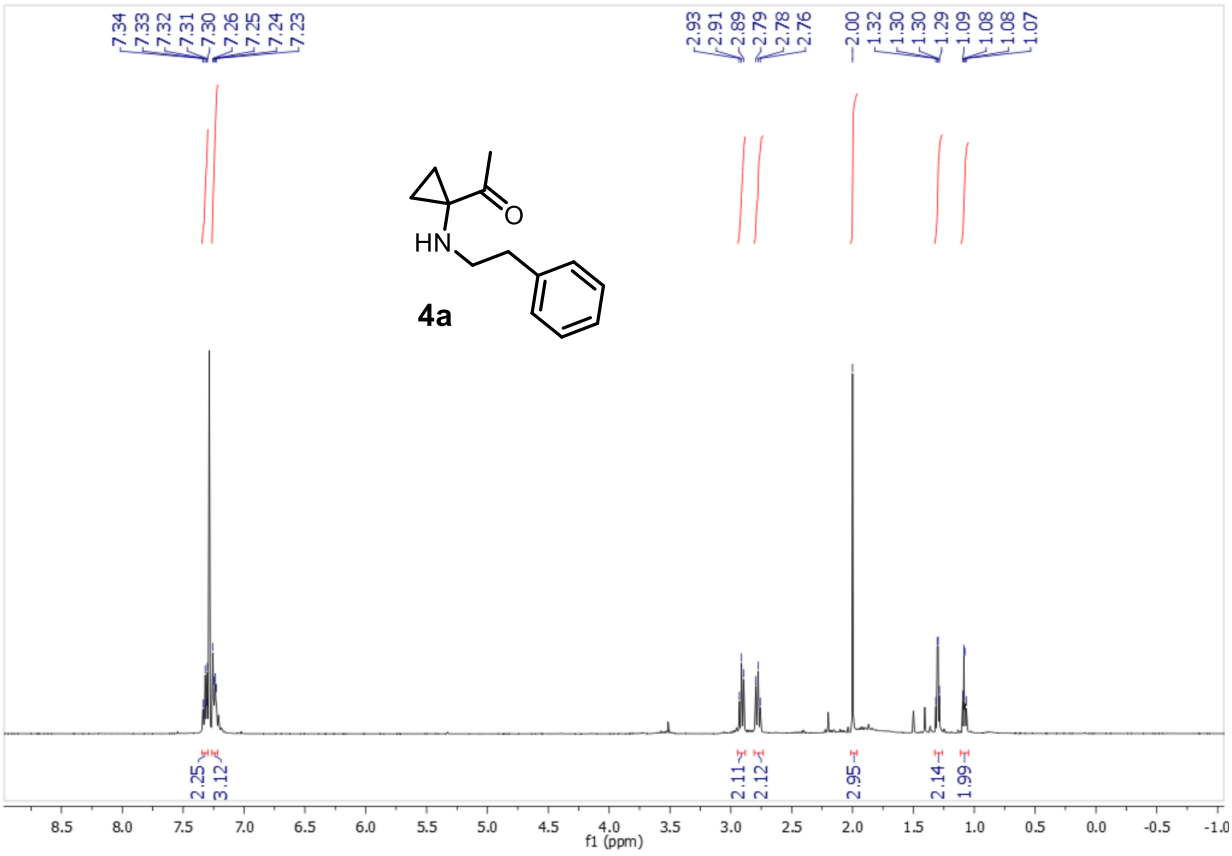
Hydrolysis of compound 4c

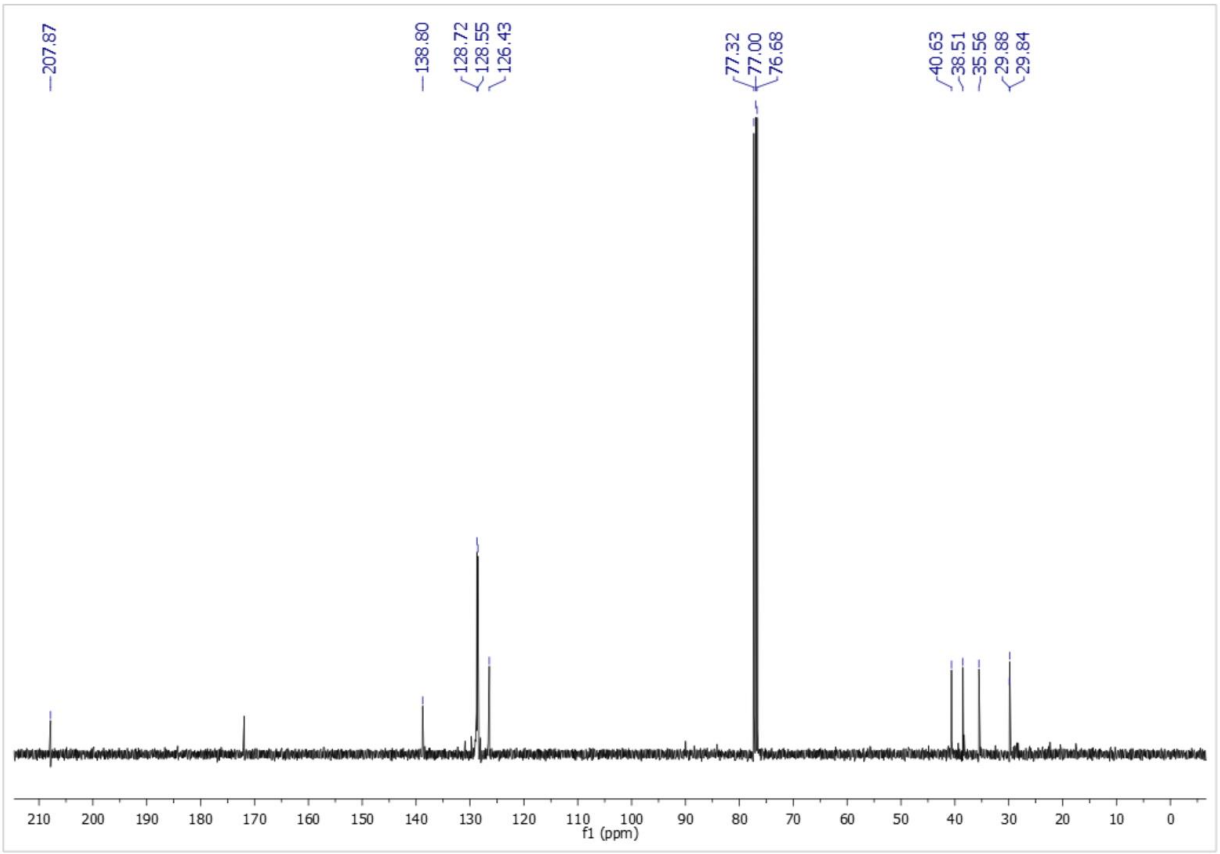


To a stirred solution of compound **4c** (100 mg, 0.41 mmol) and tartaric acid (30.7 mg, 0.5 equiv.) in distilled water (8 mL) at 50 °C. After 24 hours the reaction mixture was diluted with DCM (10 mL) and washed with a 10 % solution of K_2CO_3. The organic phase was dried with Na_2SO_4 and analyzed by ^1H NMR. After drying with Na_2SO_4 and filtration, the solvent was removed under reduced pressure to yield a brown oil. The crude product was loaded on a silica gel column for purification (hexanes-EtOAc 10:1-1:1) to afford the compounds **1a** and **3c**.

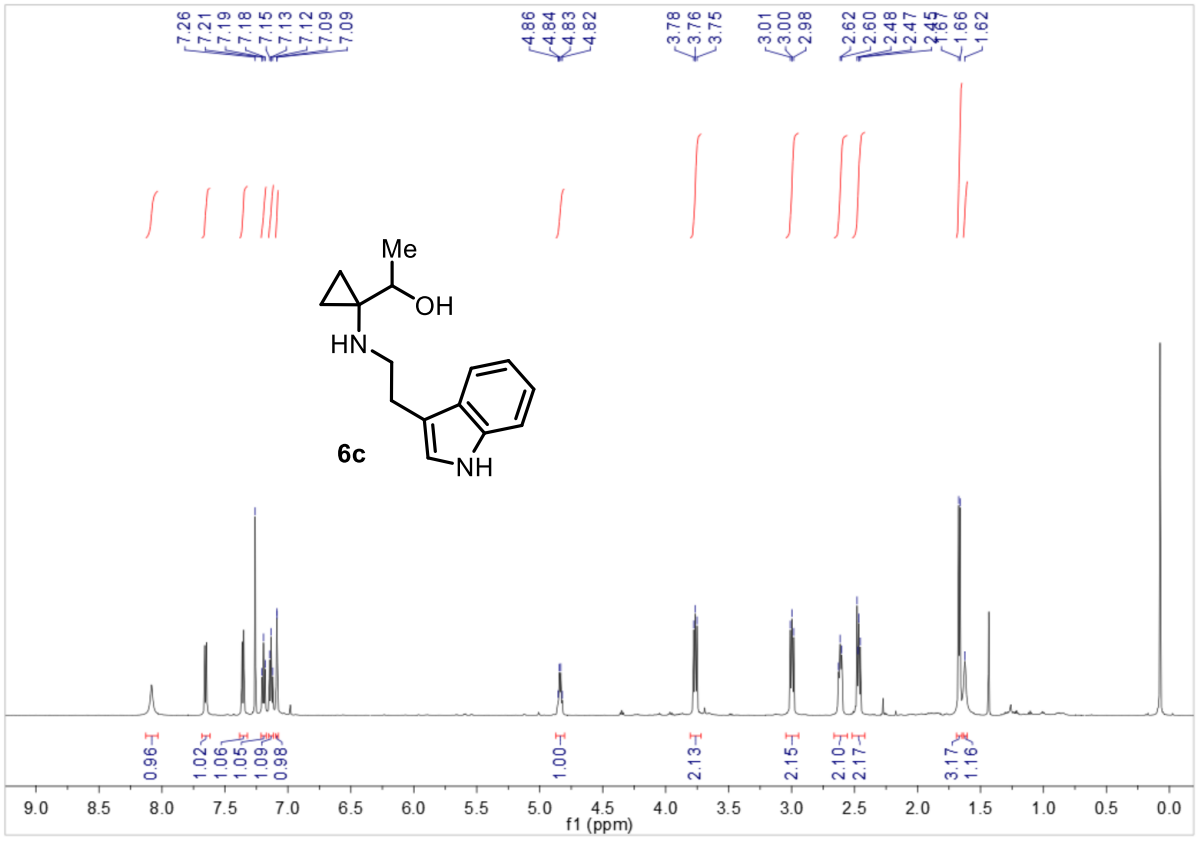
7. ^1H and ^{13}C NMR spectra of compounds 4-6, 7-9

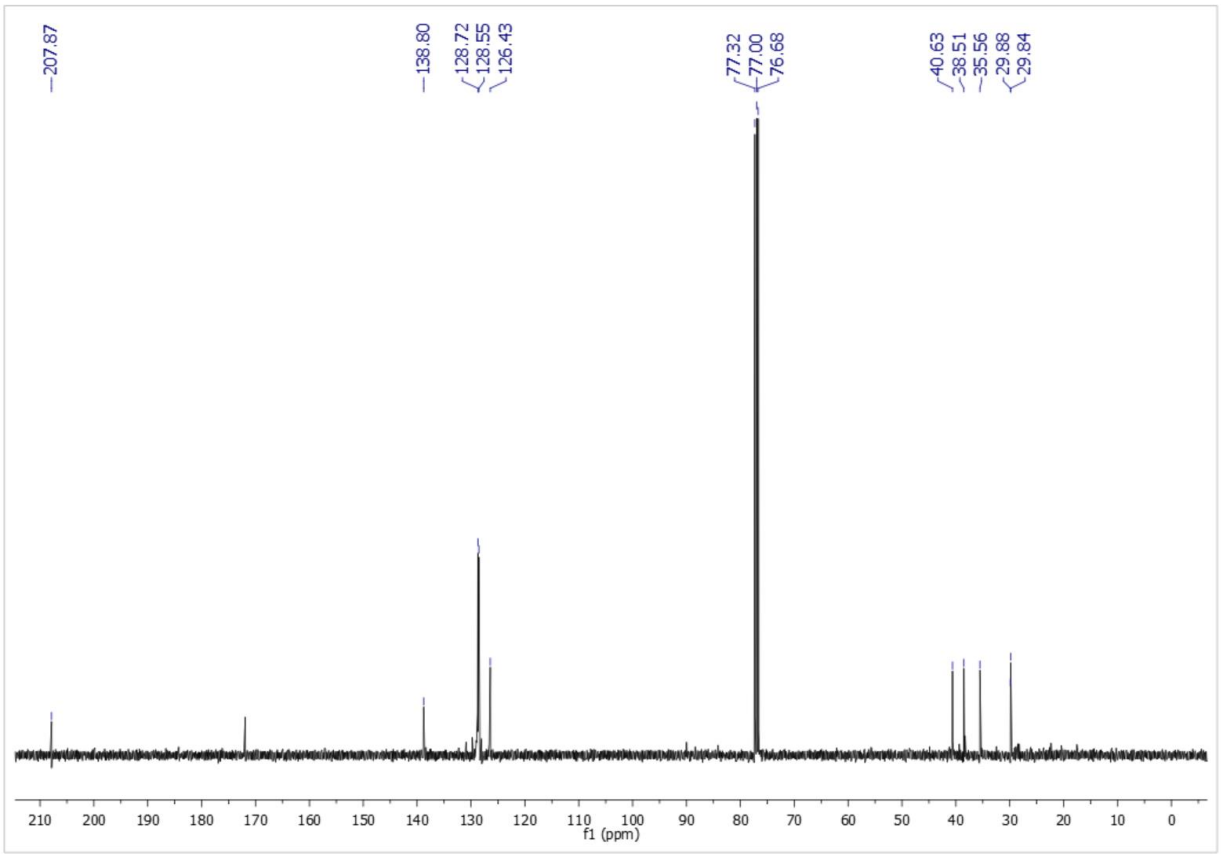
1-(1-(phenethylamino)cyclopropyl)ethan-1-one

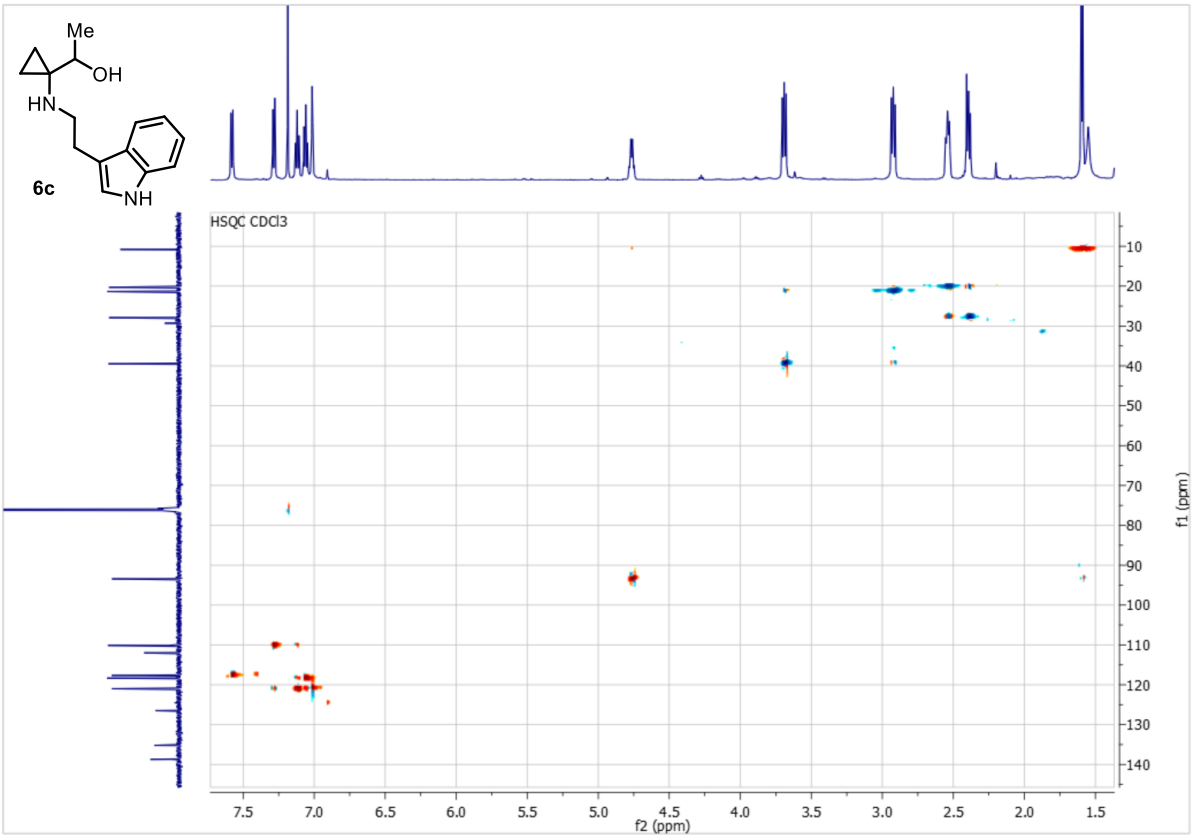




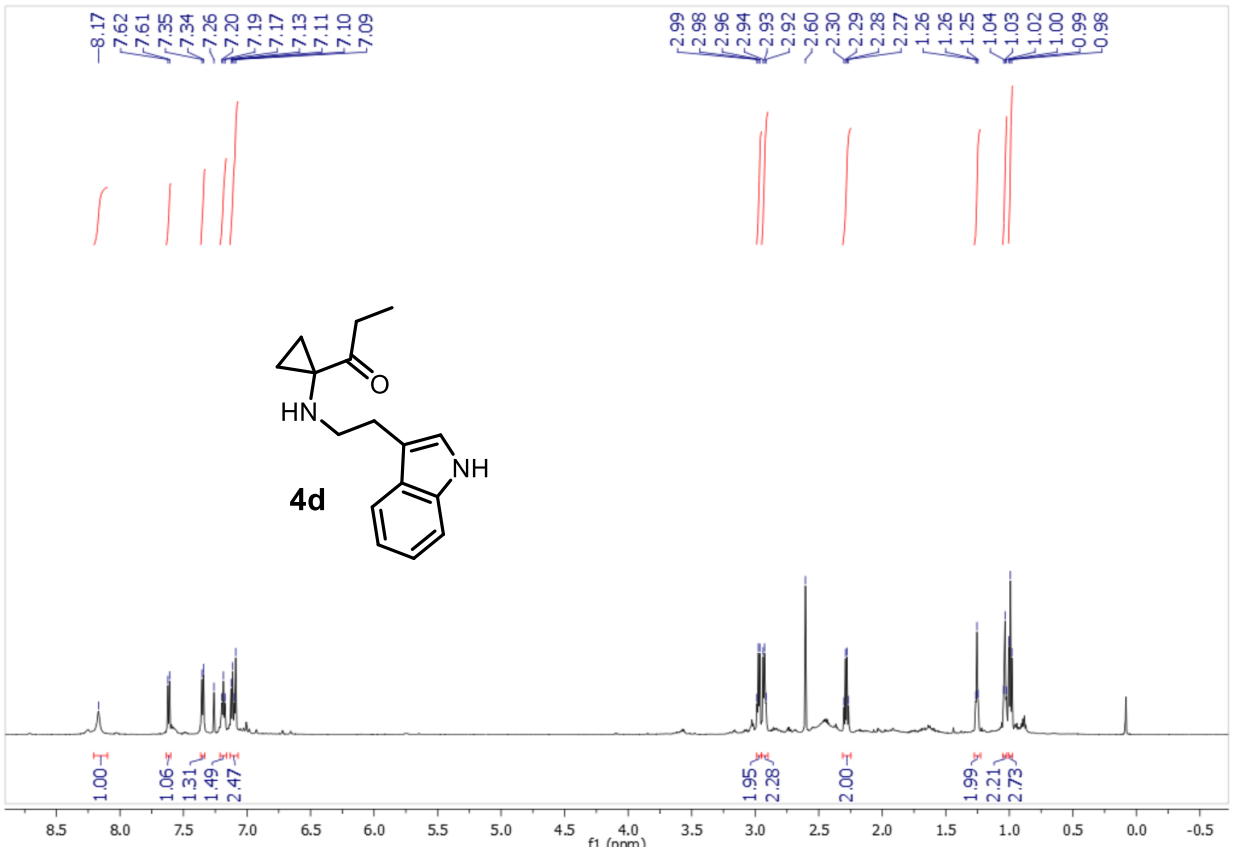
1-(1-((2-(1H-indol-3-yl)ethyl)amino)cyclopropyl)ethan-1-ol

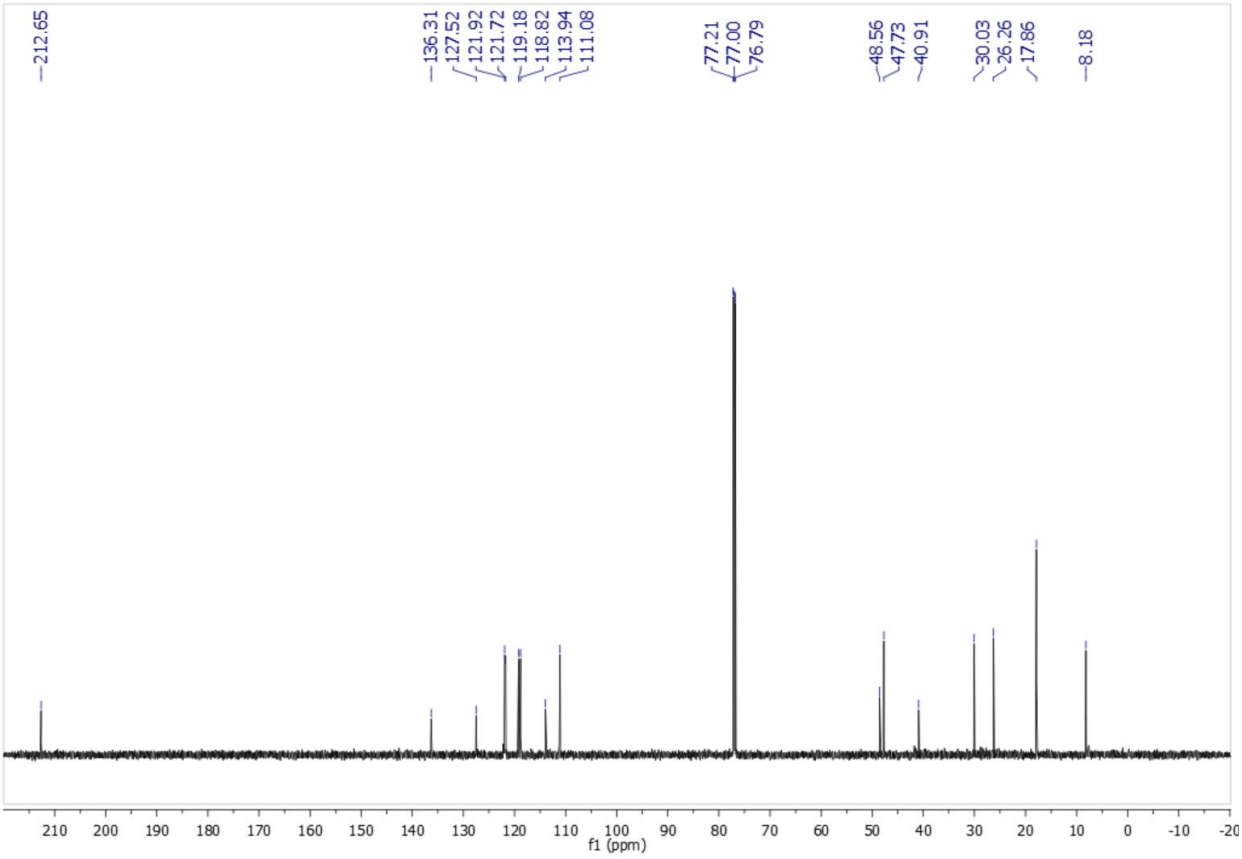




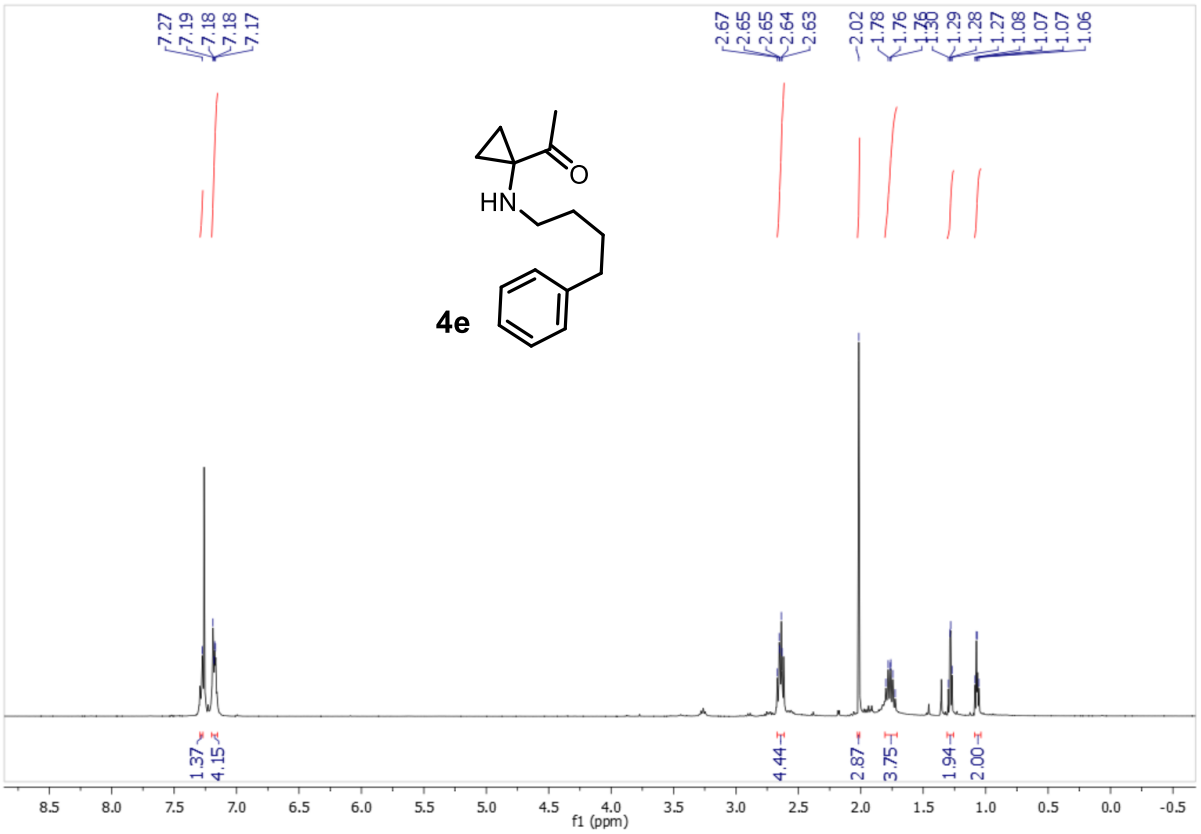

Me
OH
HN
NH
6c
HSQC CDCl3
f2 (ppm)
f1 (ppm)

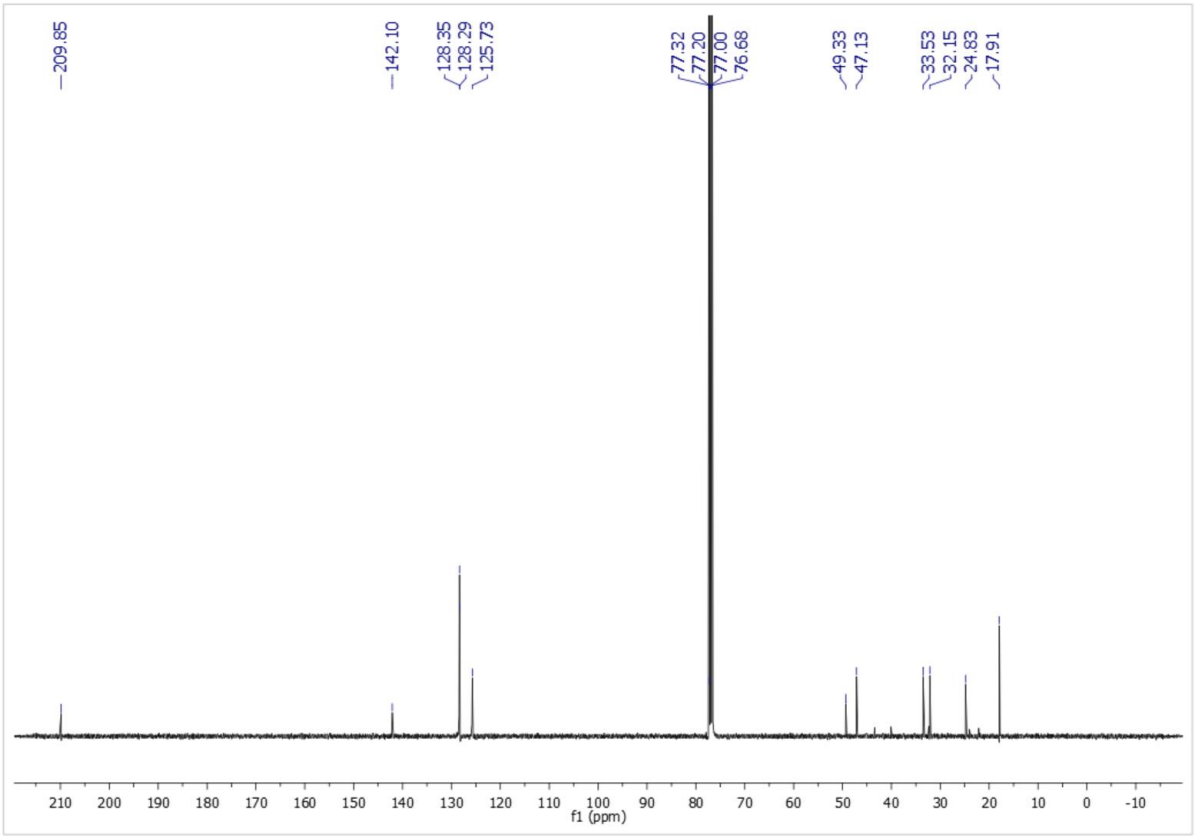
1-(1-((2-(1H-indol-3-yl)ethyl)amino)cyclopropyl)propan-1-one



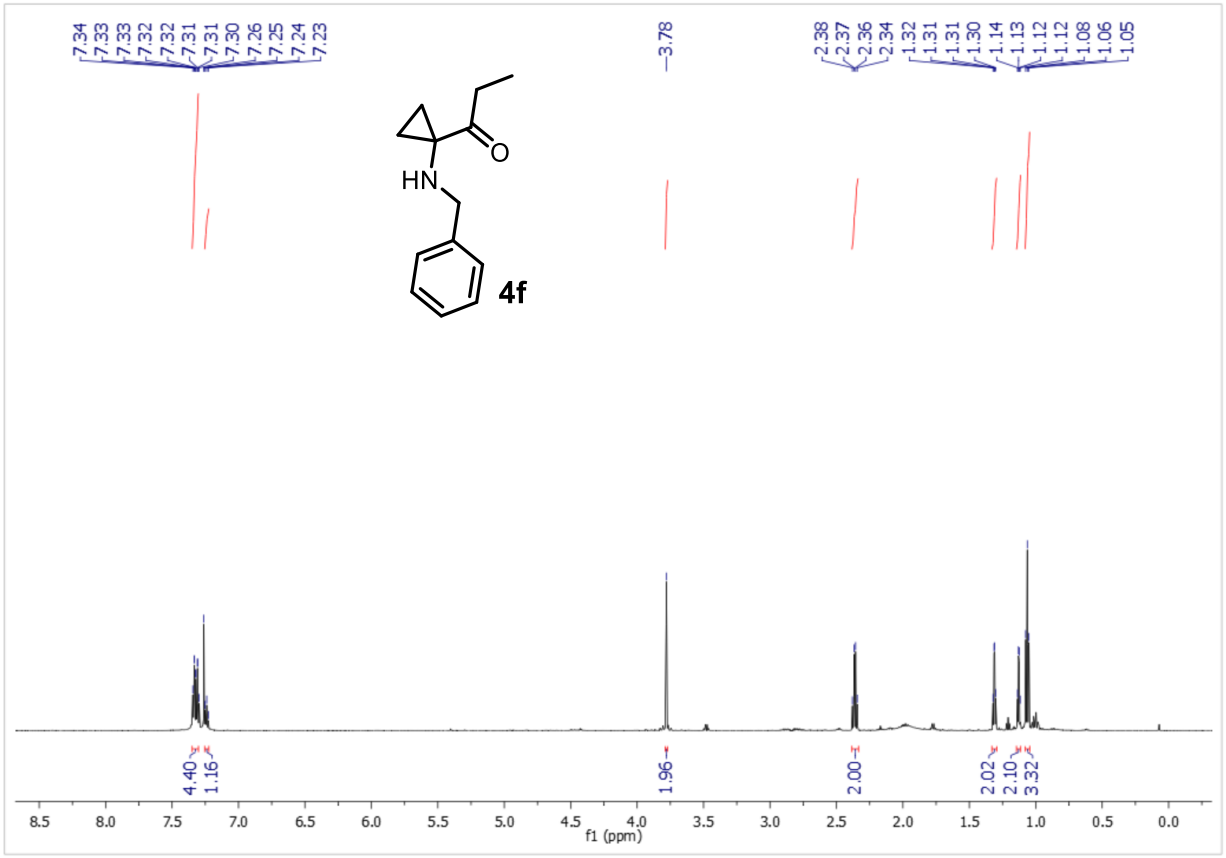


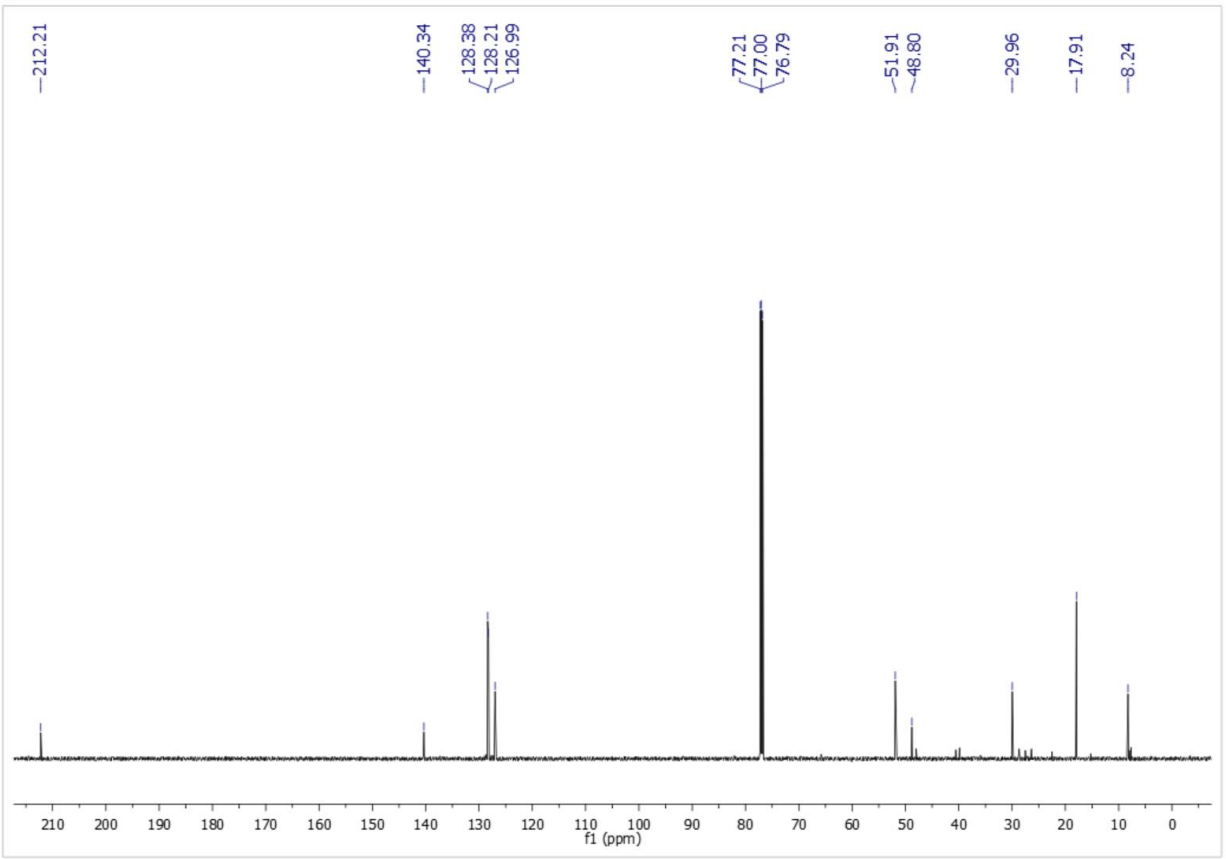
1-(1-((4-phenylbutyl)amino)cyclopropyl)ethan-1-one



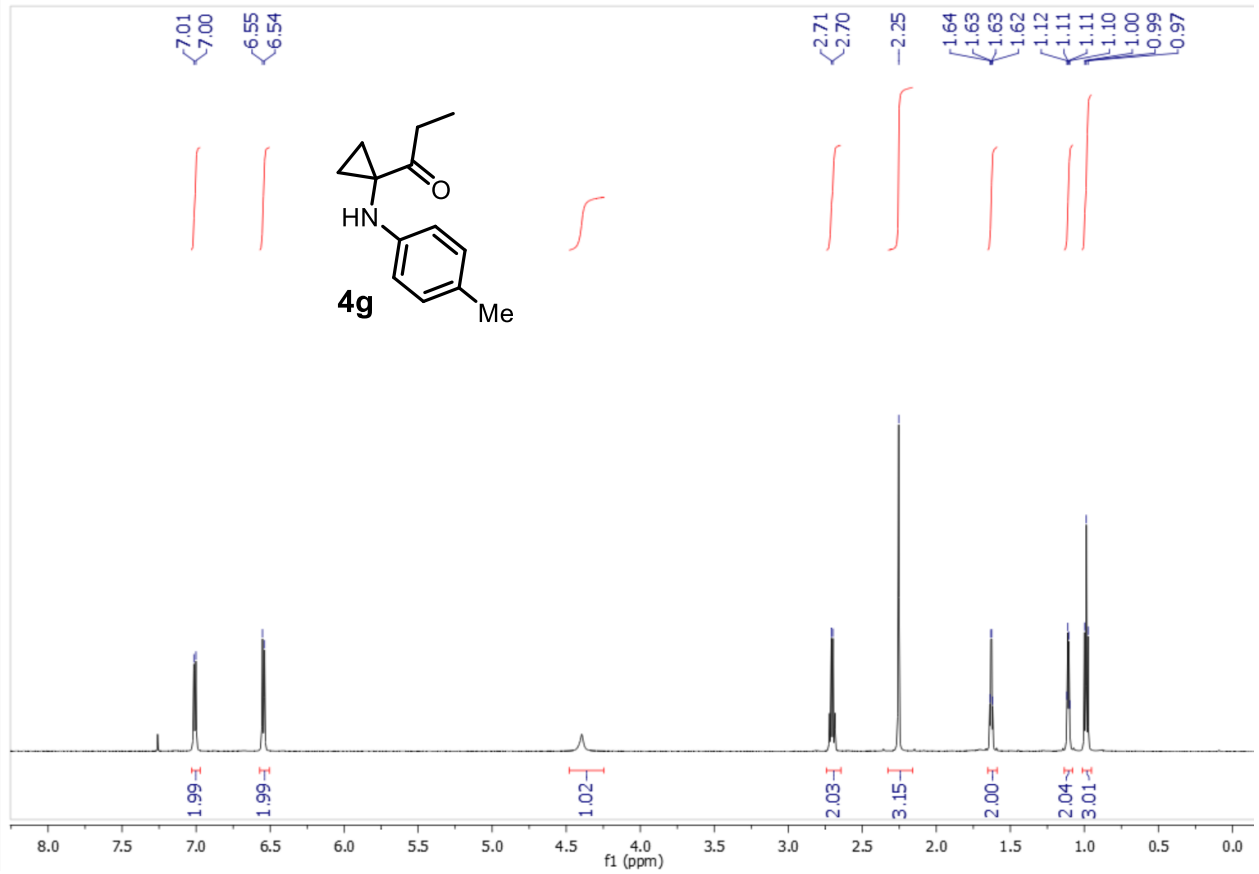


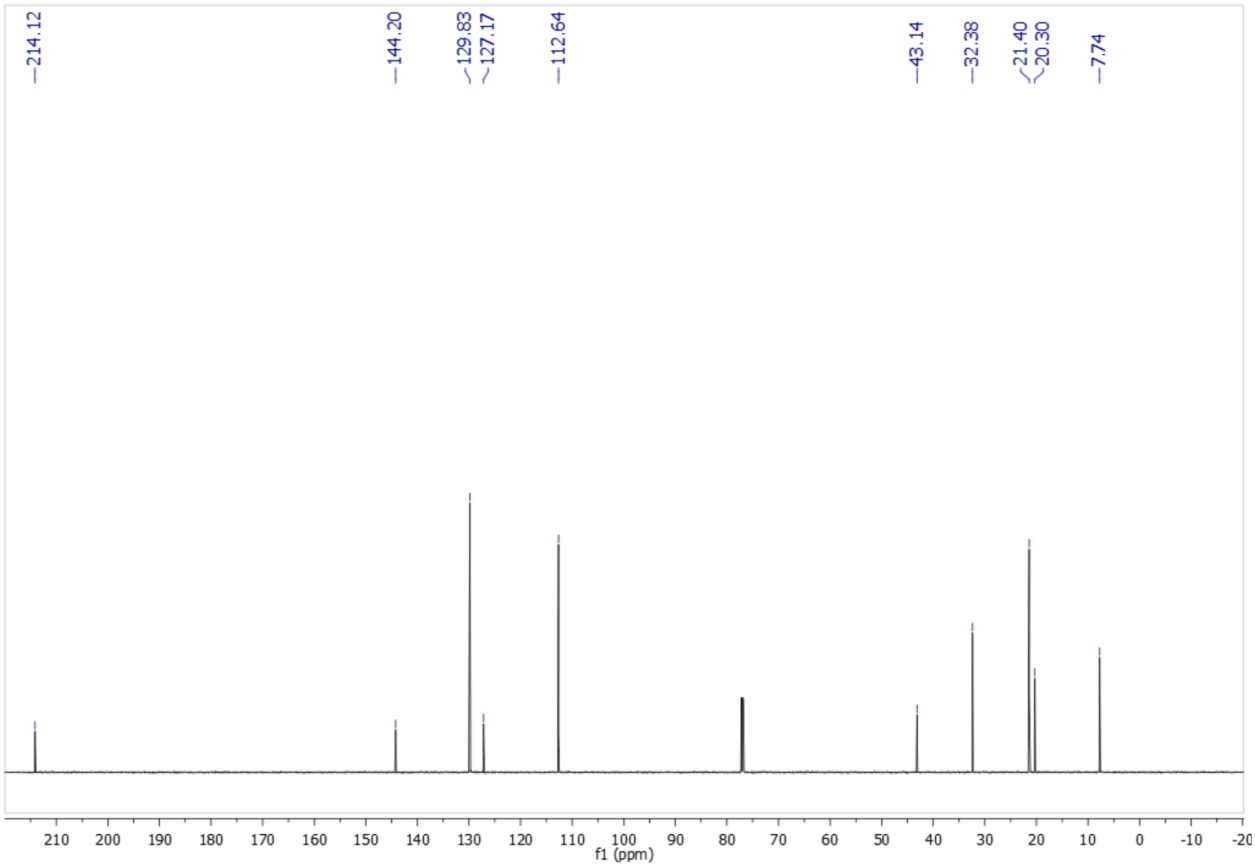
(benzylamino)cyclopropyl)propan-1-one



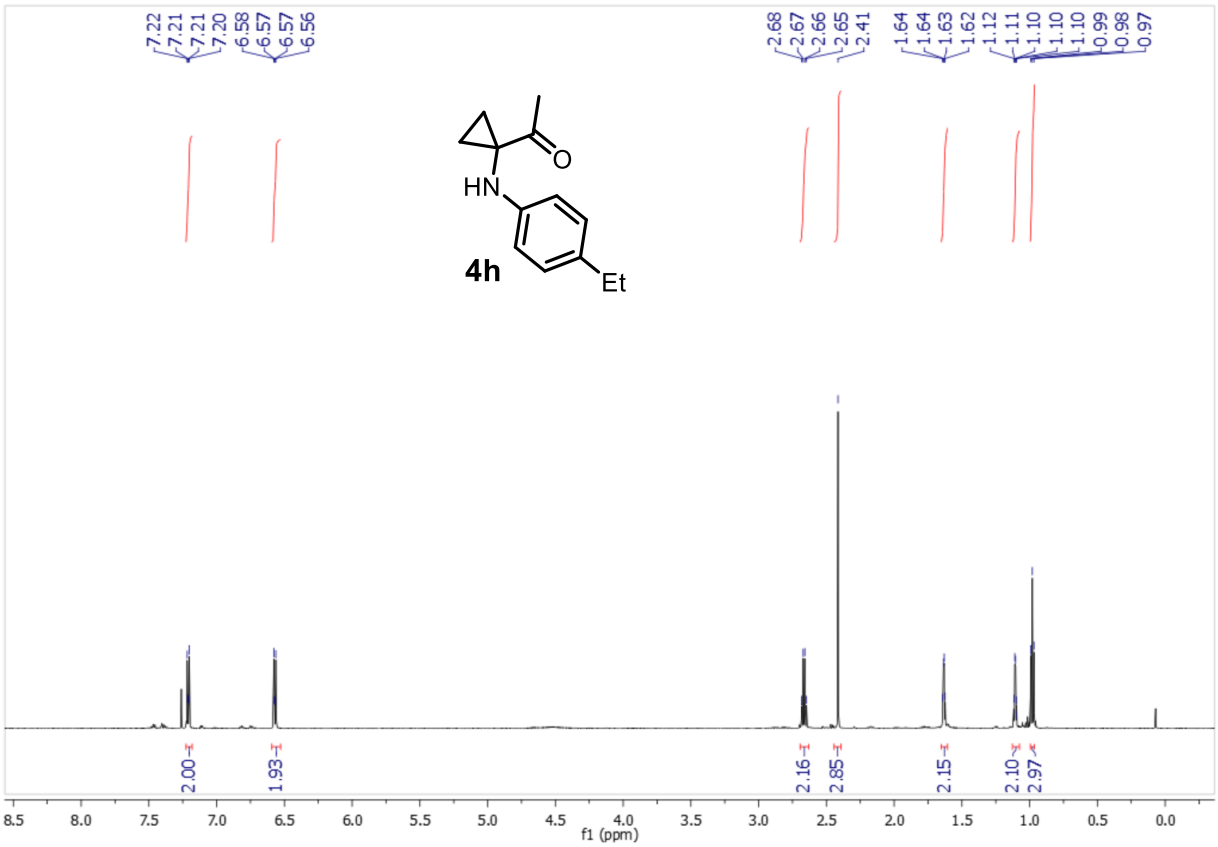


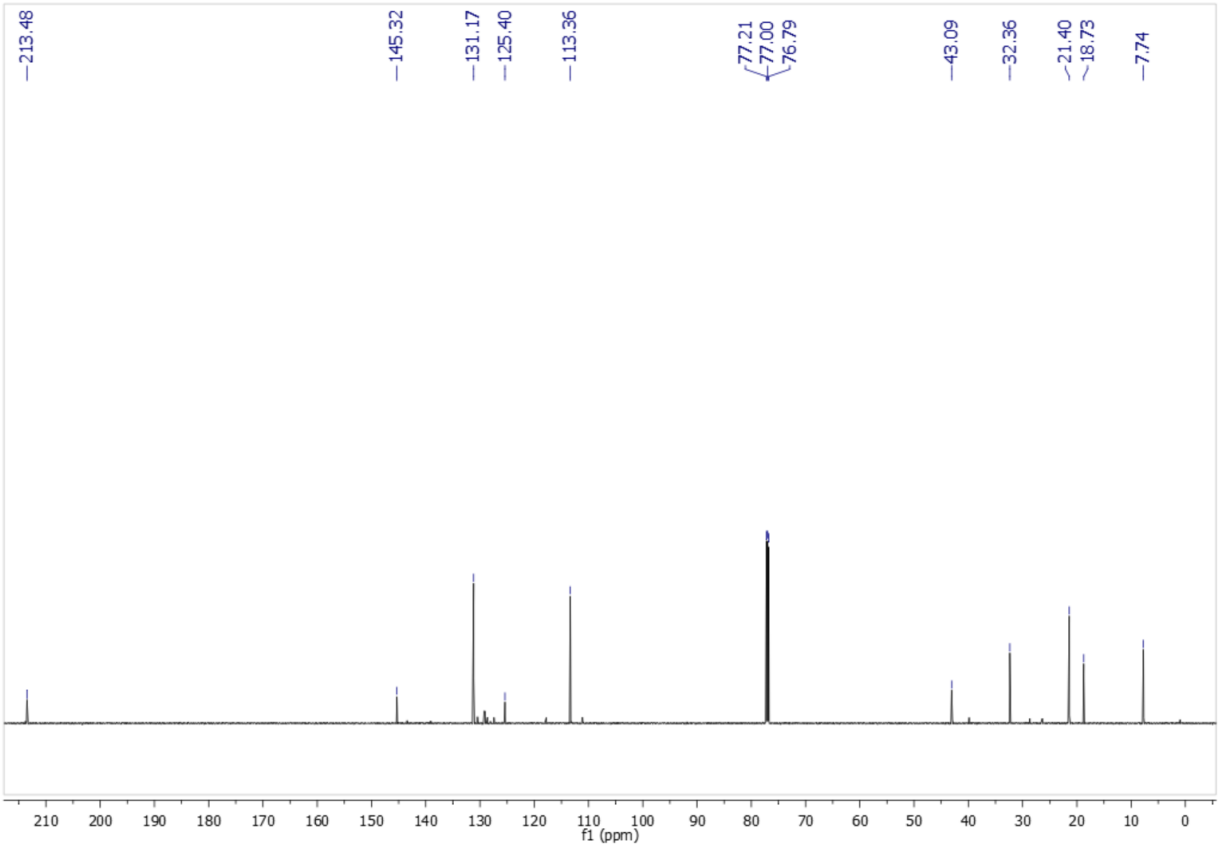
1-(1-(p-tolylamino)cyclopropyl)propan-1-one



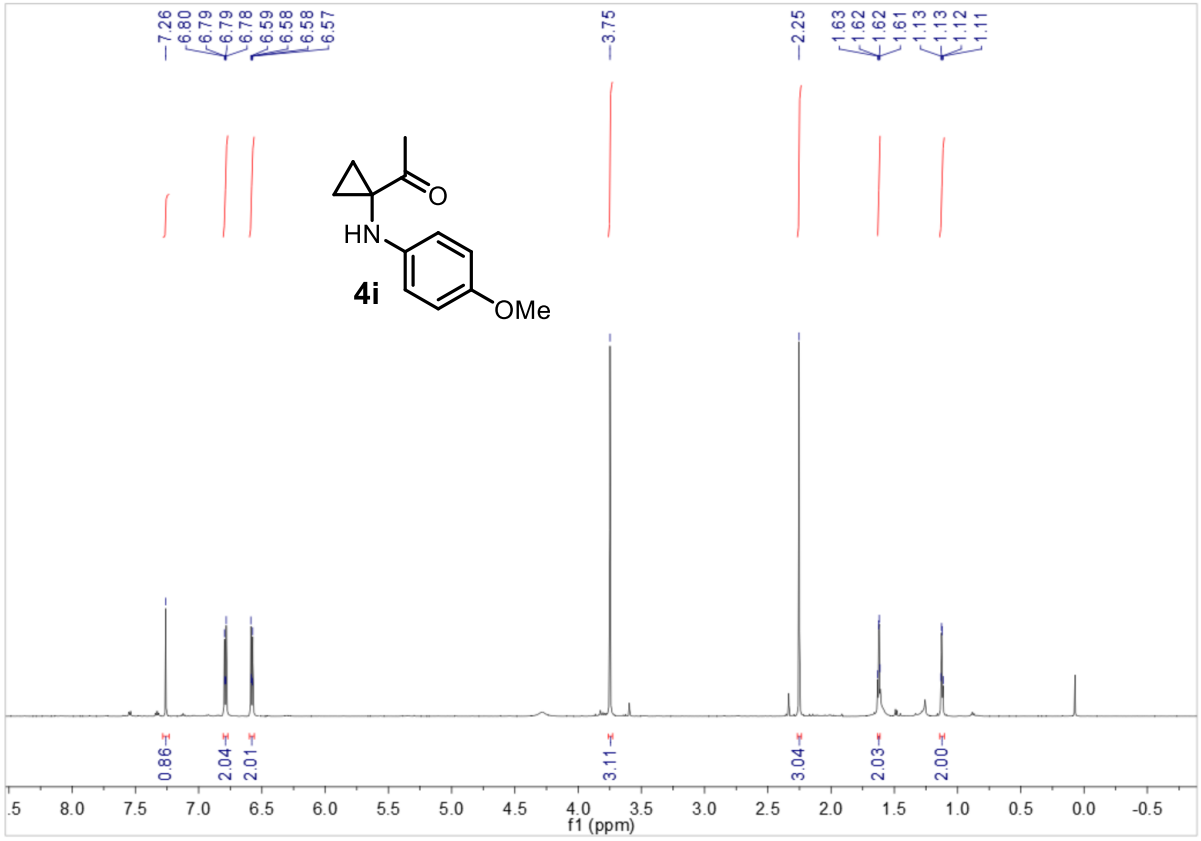


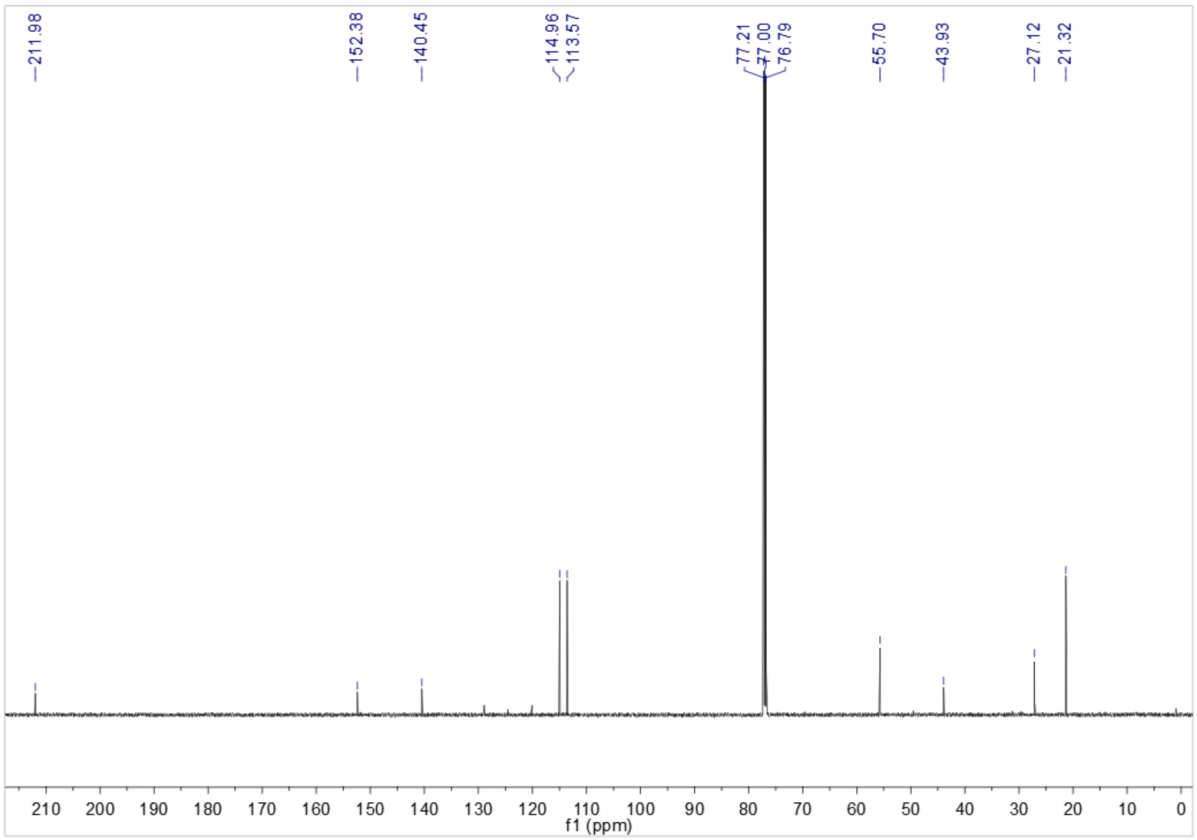
1-(1-((4-ethylphenyl)amino)cyclopropyl)ethan-1-one



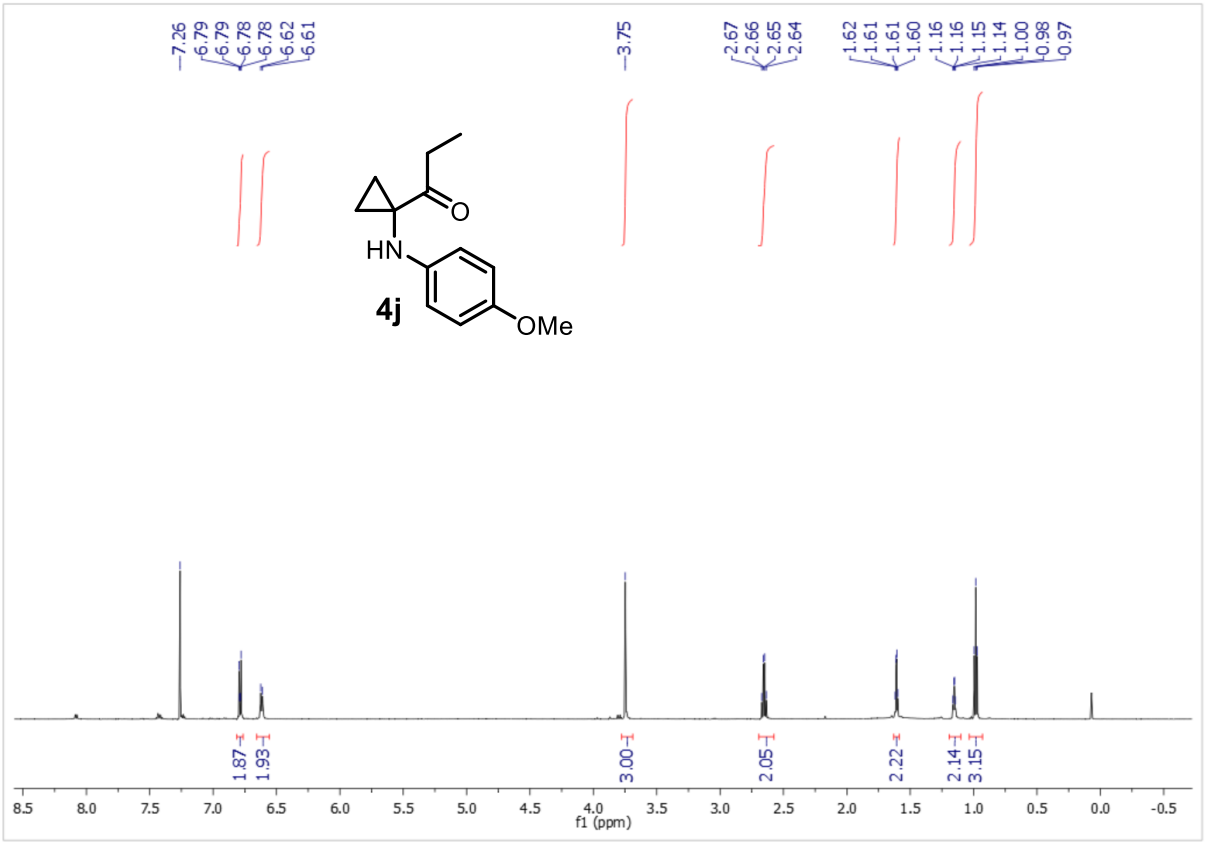


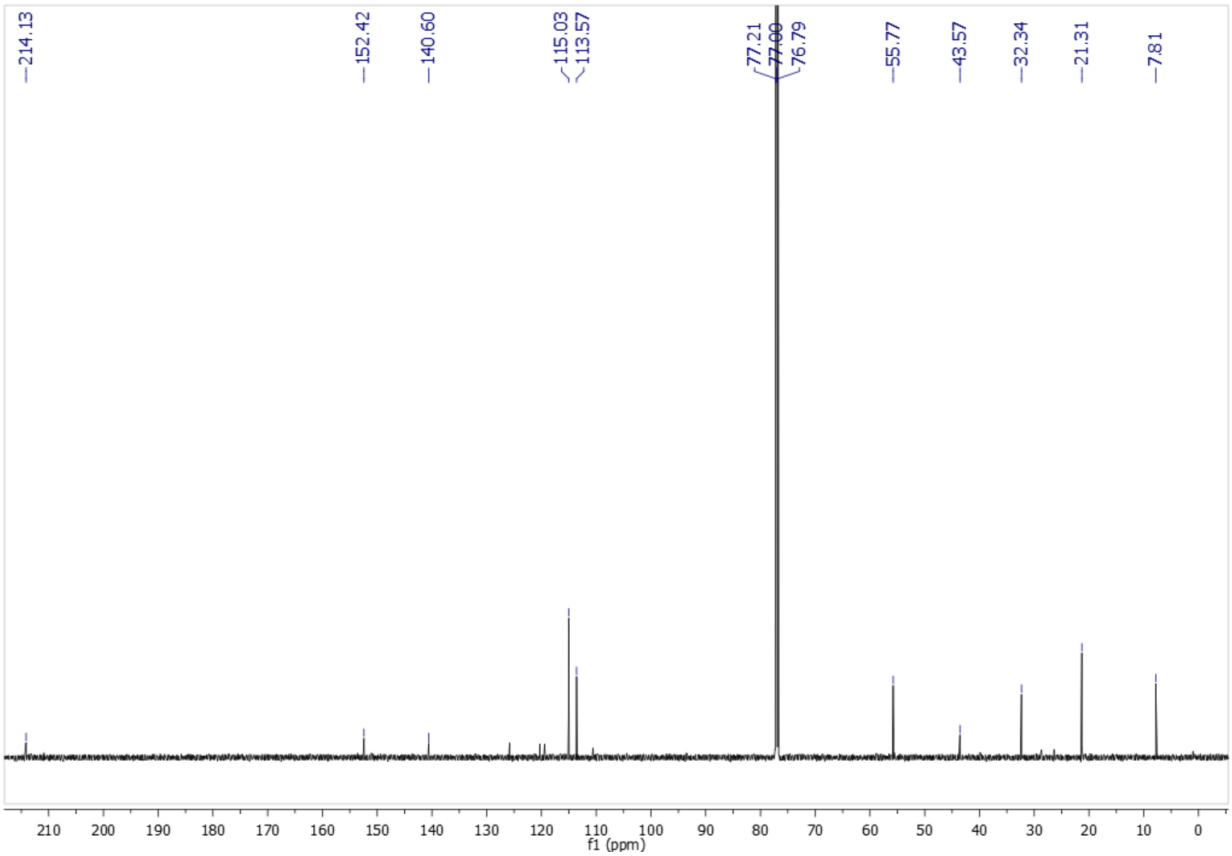
1-(1-((4-methoxyphenyl)amino)cyclopropyl)ethan-1-one



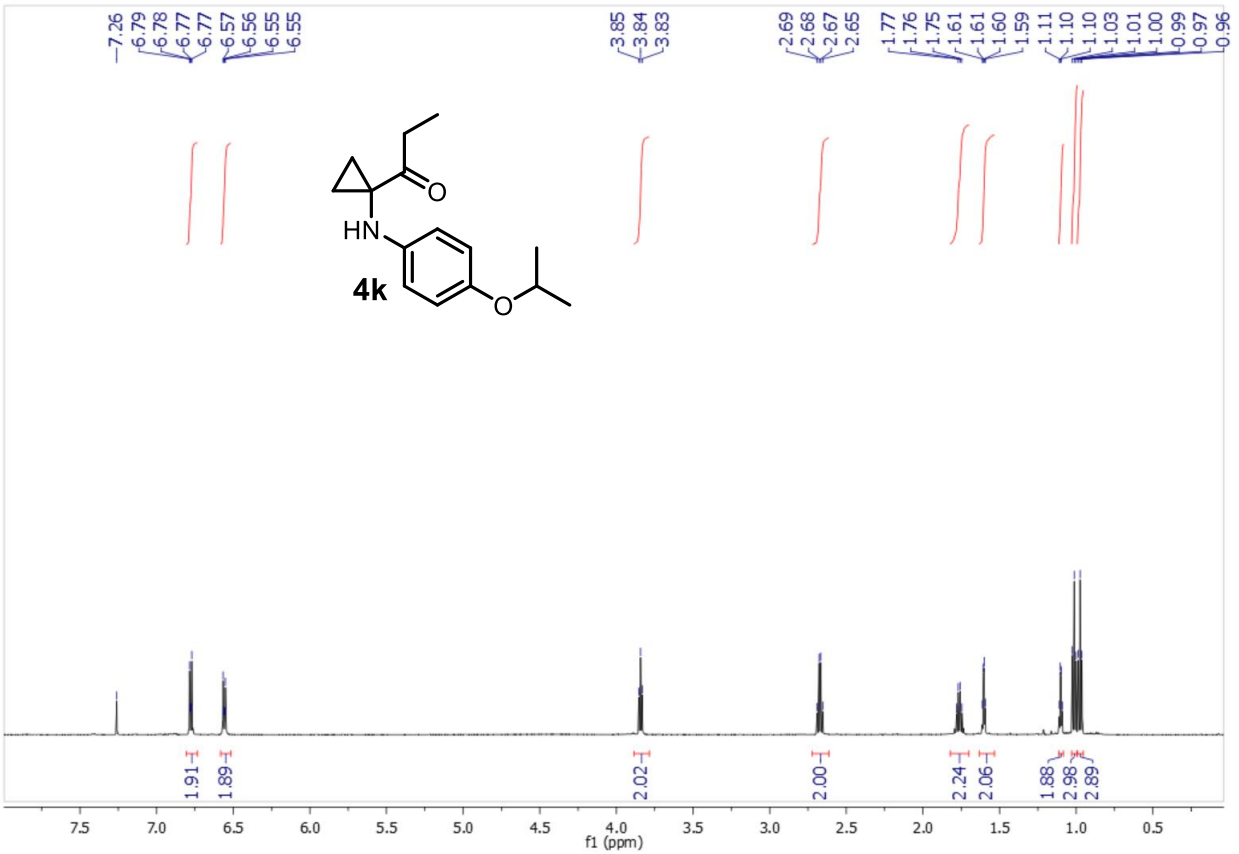


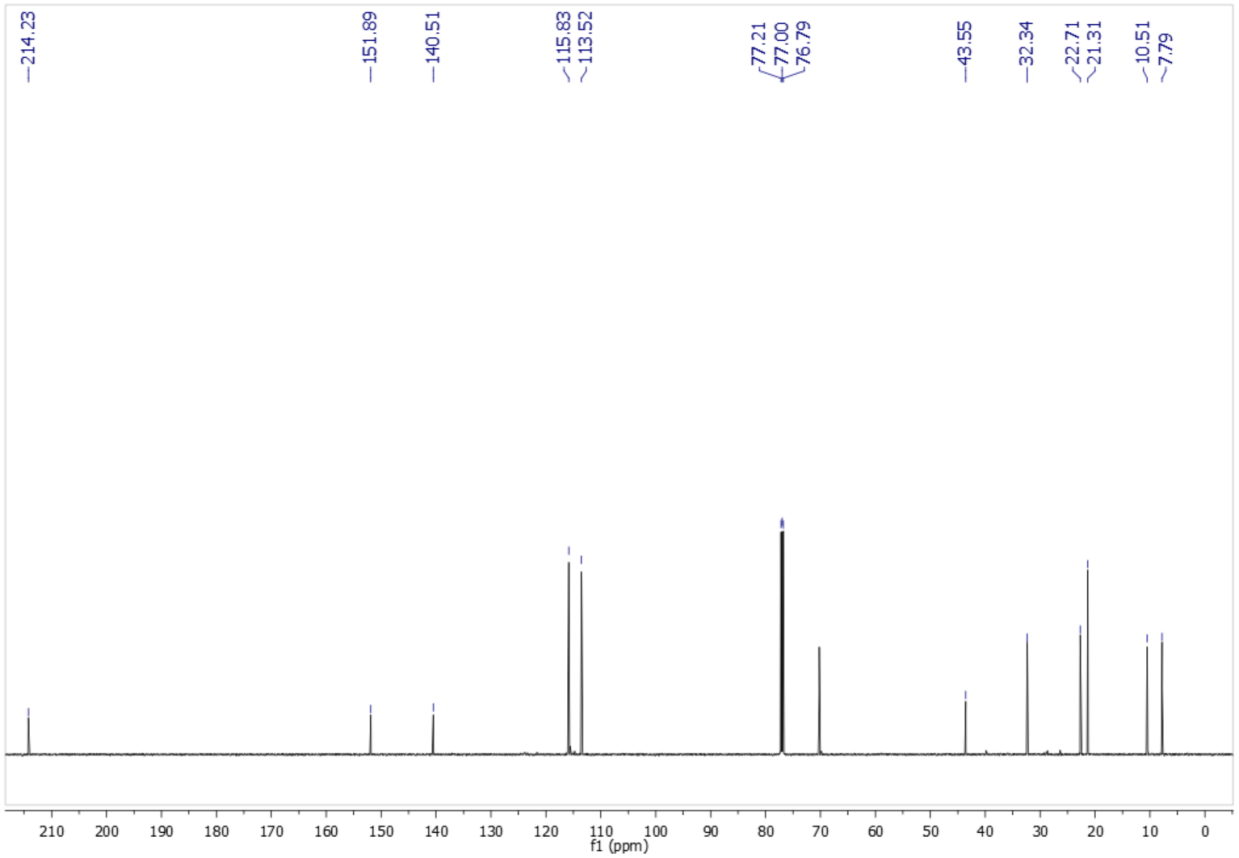
1-(1-((4-methoxyphenyl)amino)cyclopropyl)propan-1-one



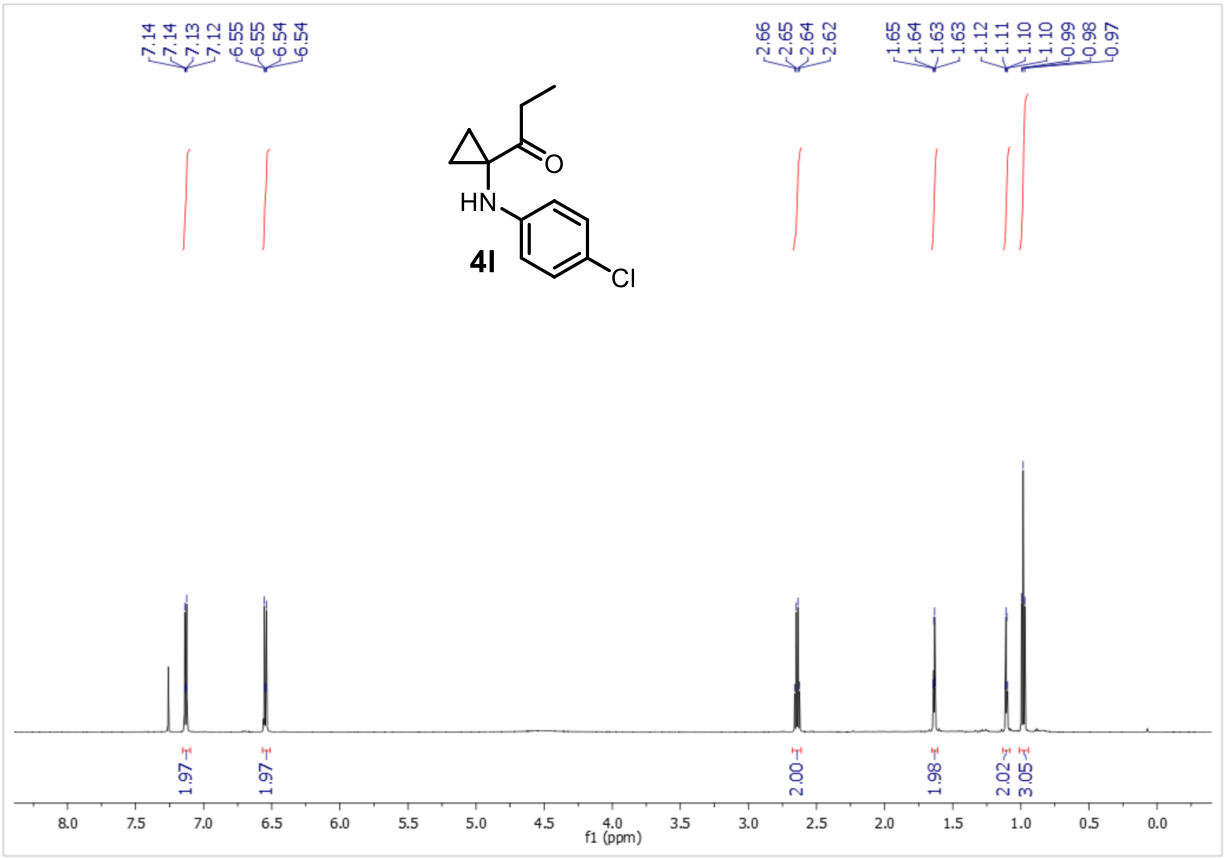


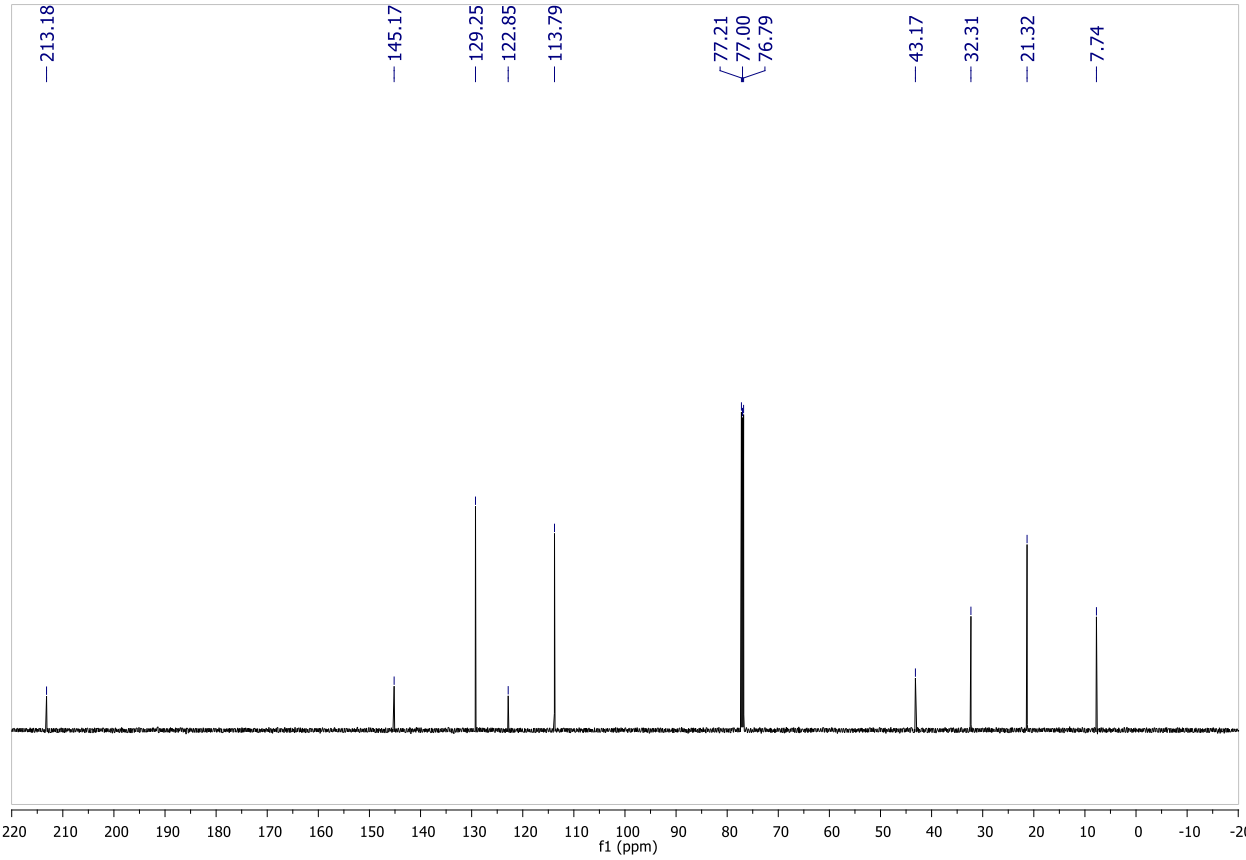
1-(1-((4-propoxyphenyl)amino)cyclopropyl)propan-1-one



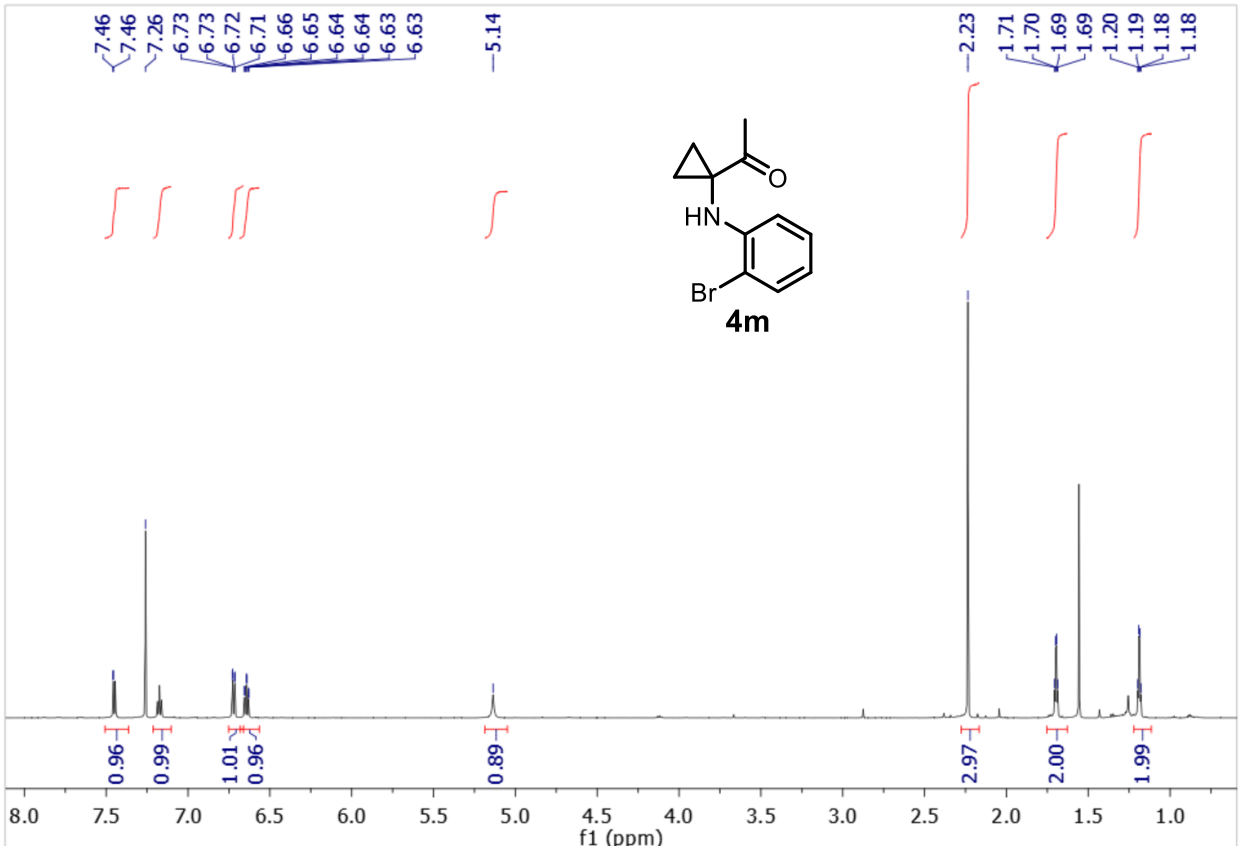


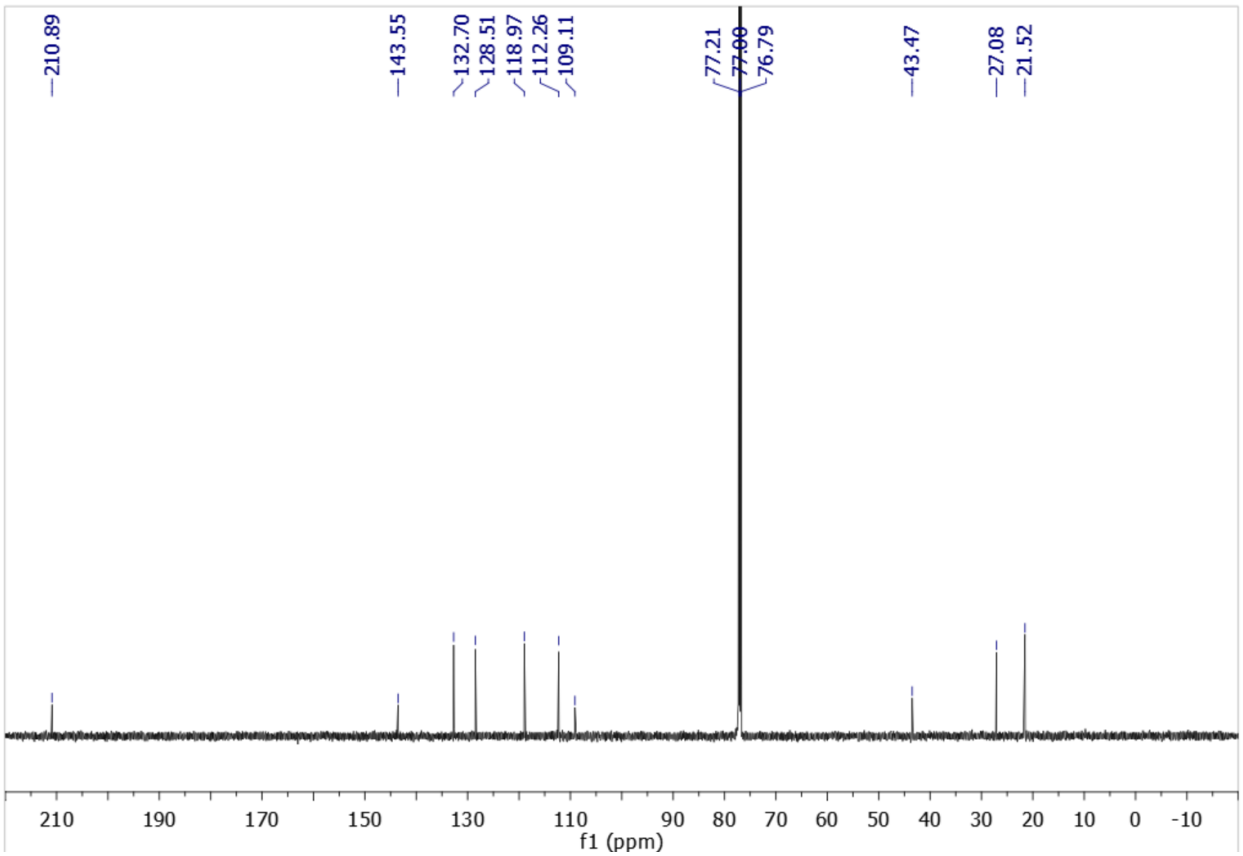
1-(1-((4-chlorophenyl)amino)cyclopropyl)propan-1-one



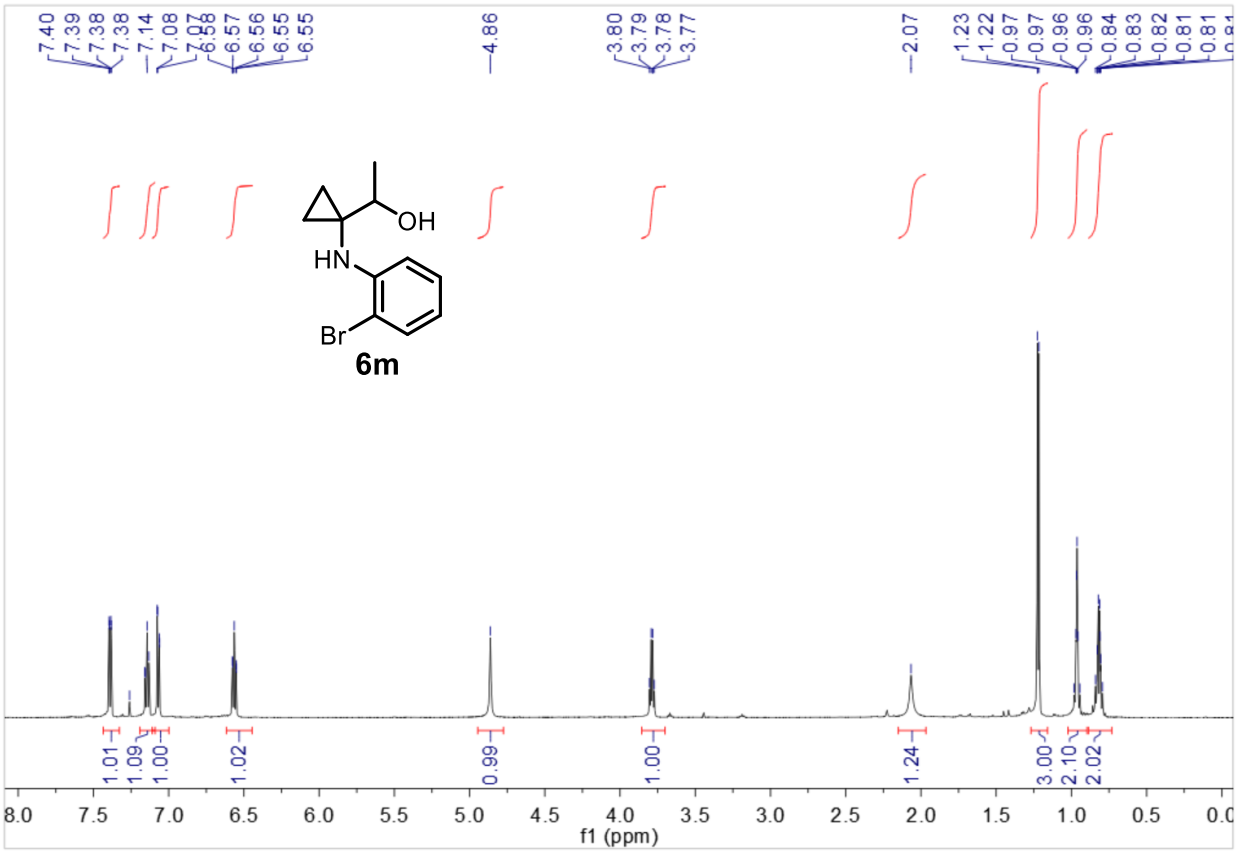


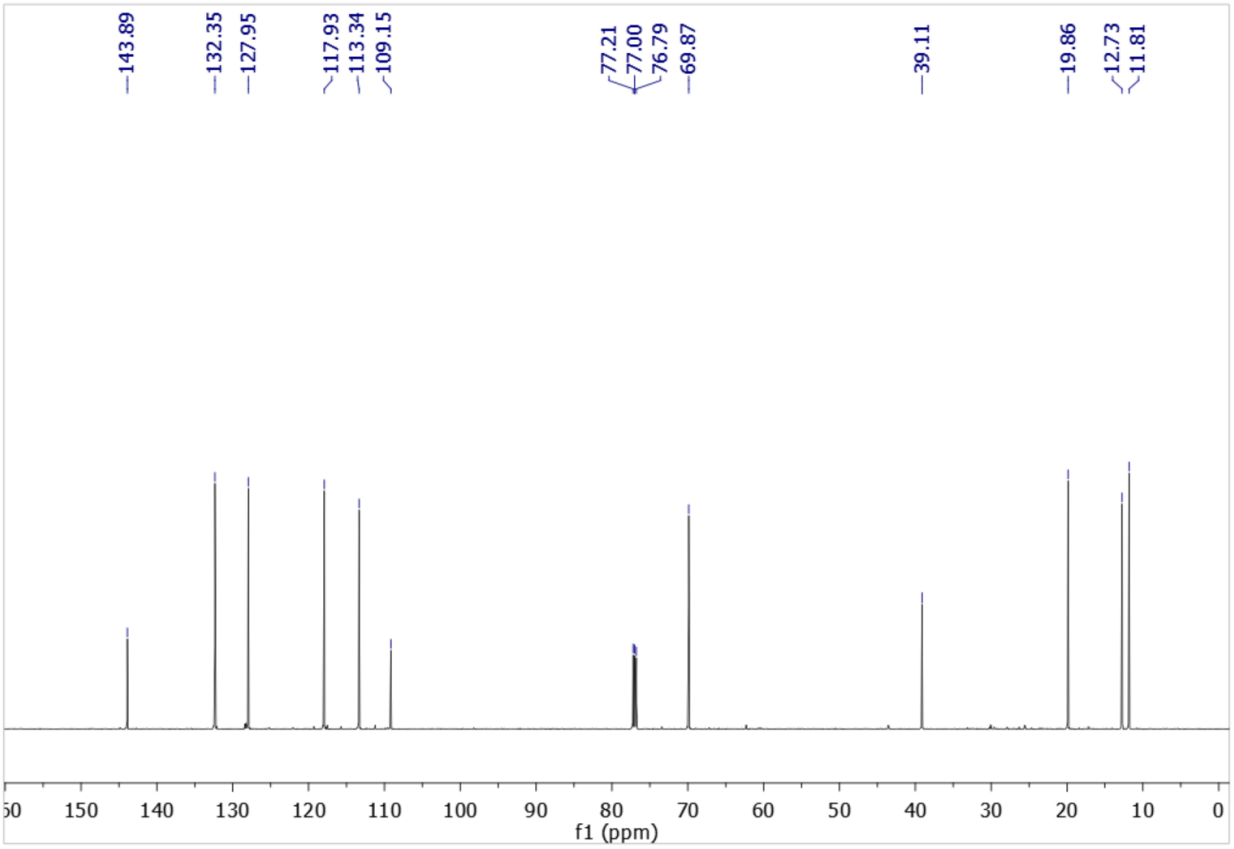
1-(1-((2-bromophenyl)amino)cyclopropyl)ethan-1-one



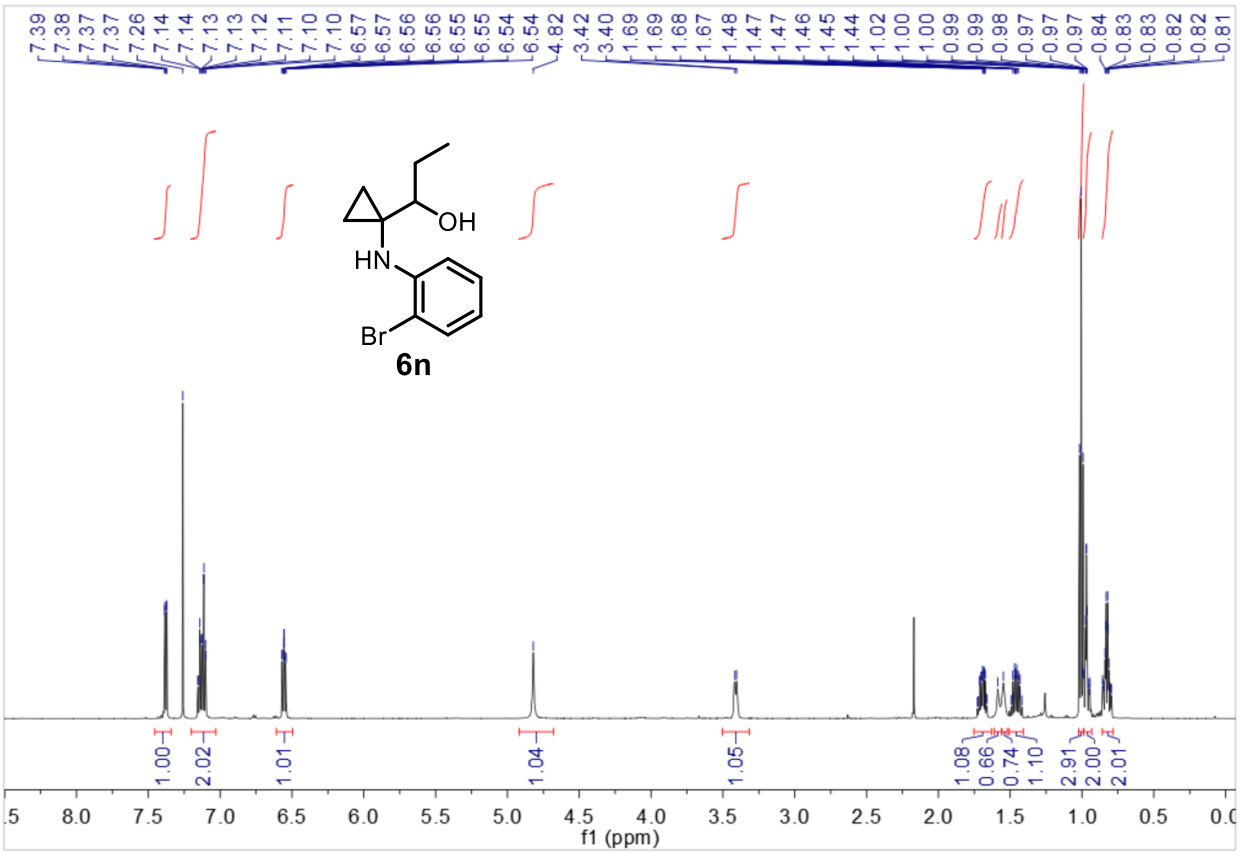


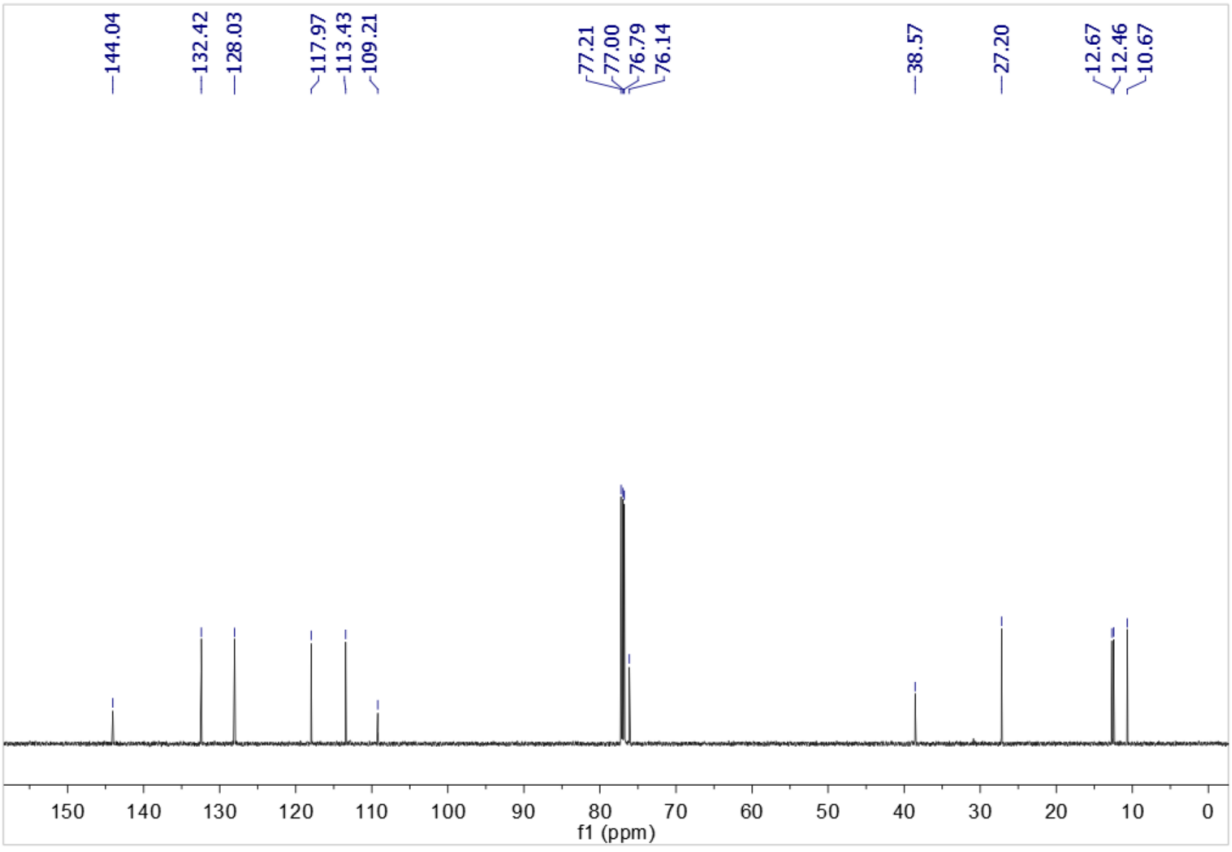
1-(1-((2-bromophenyl)amino)cyclopropyl)ethan-1-ol



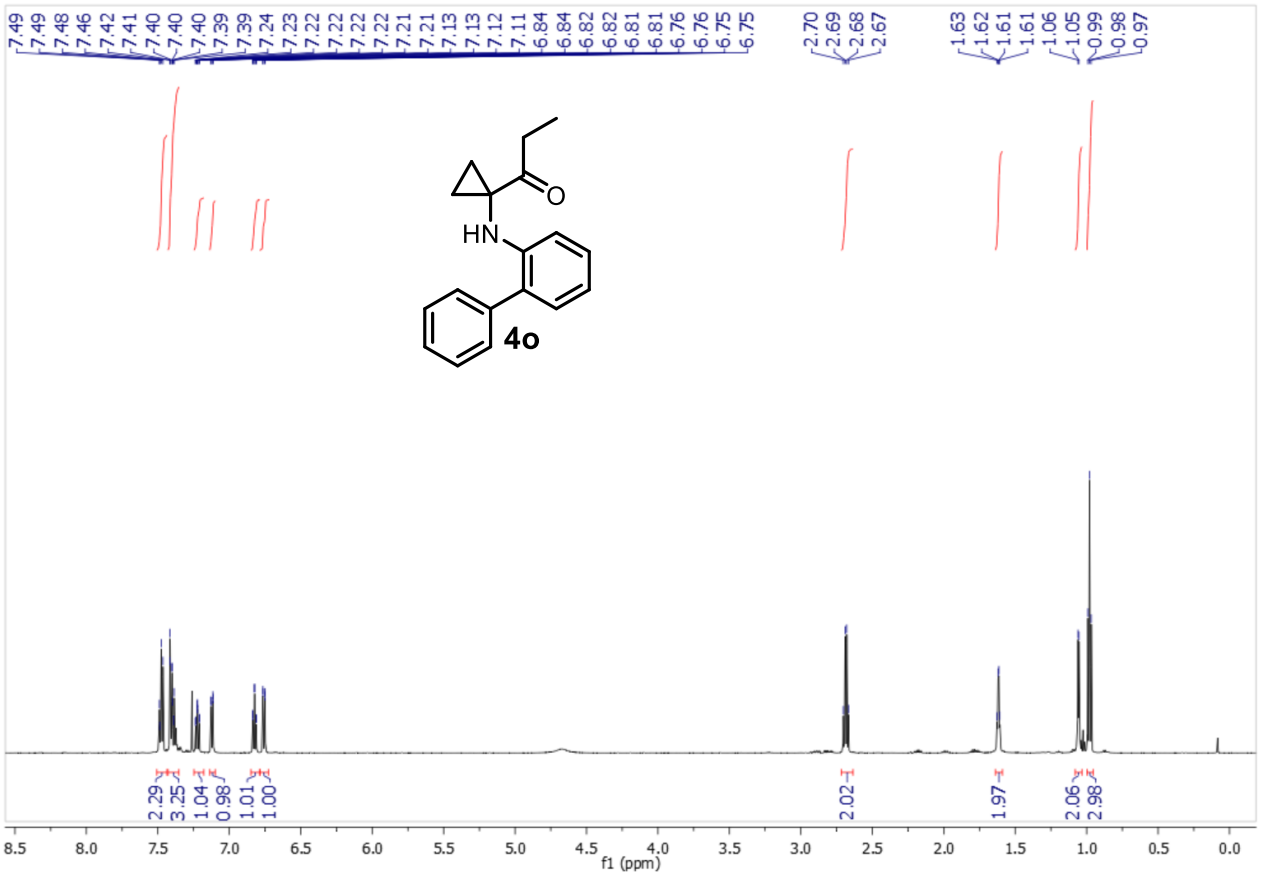


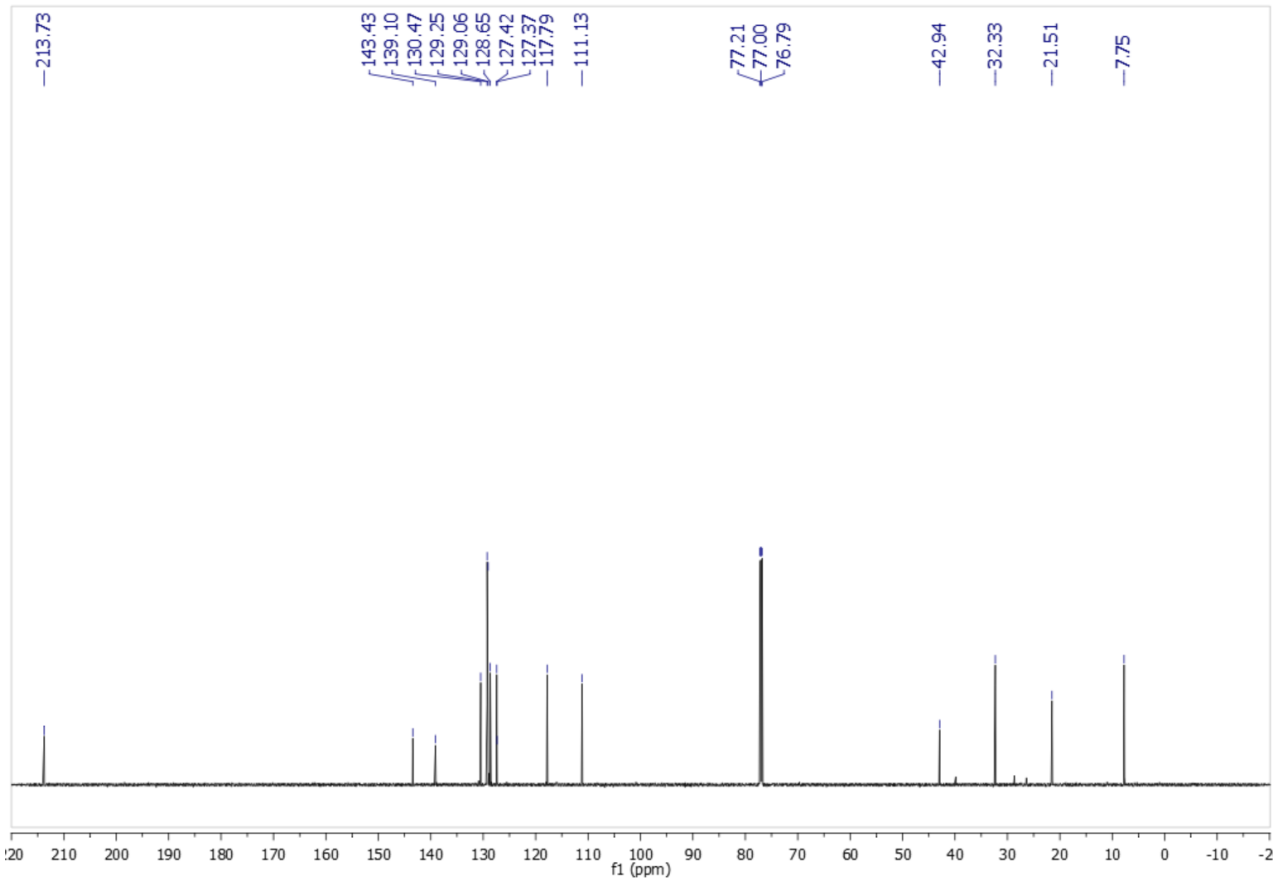
1-(1-((2-bromophenyl)amino)cyclopropyl)propan-1-ol



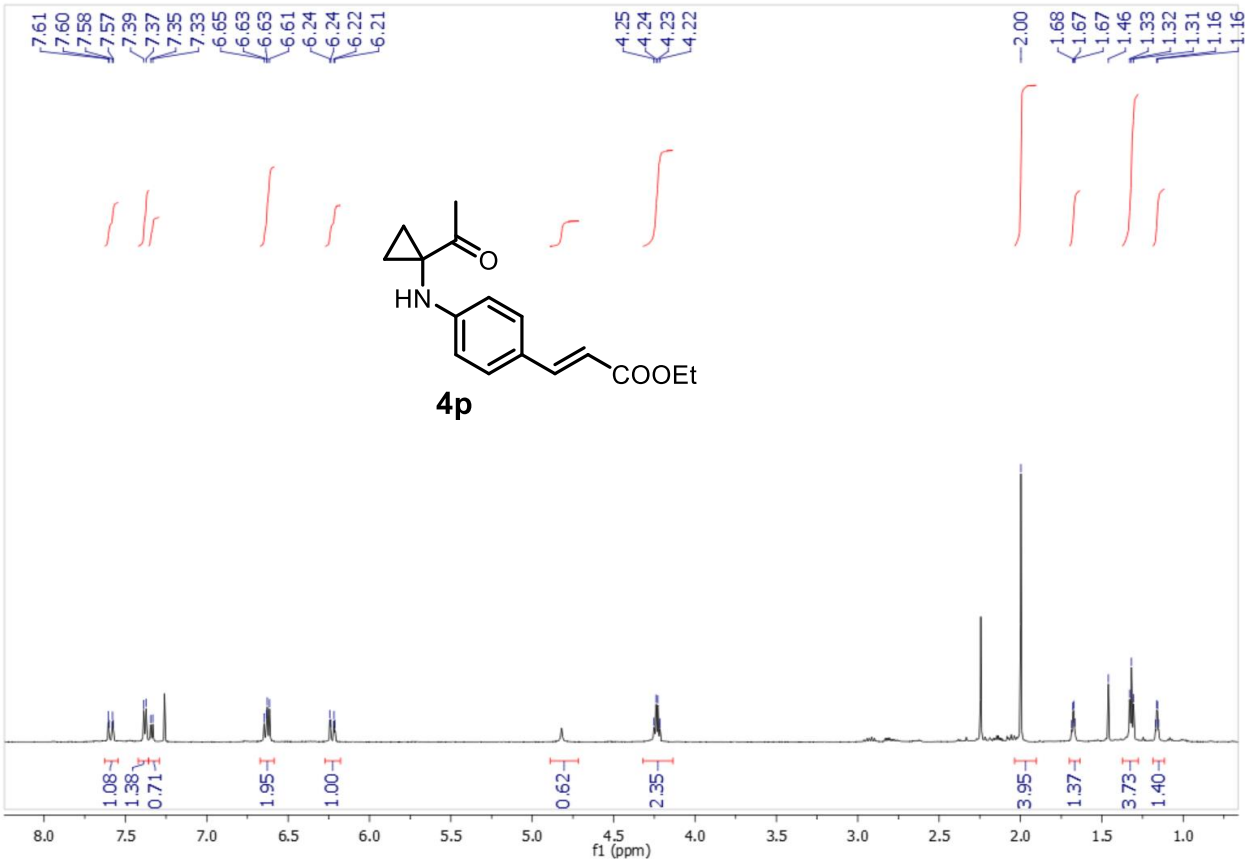


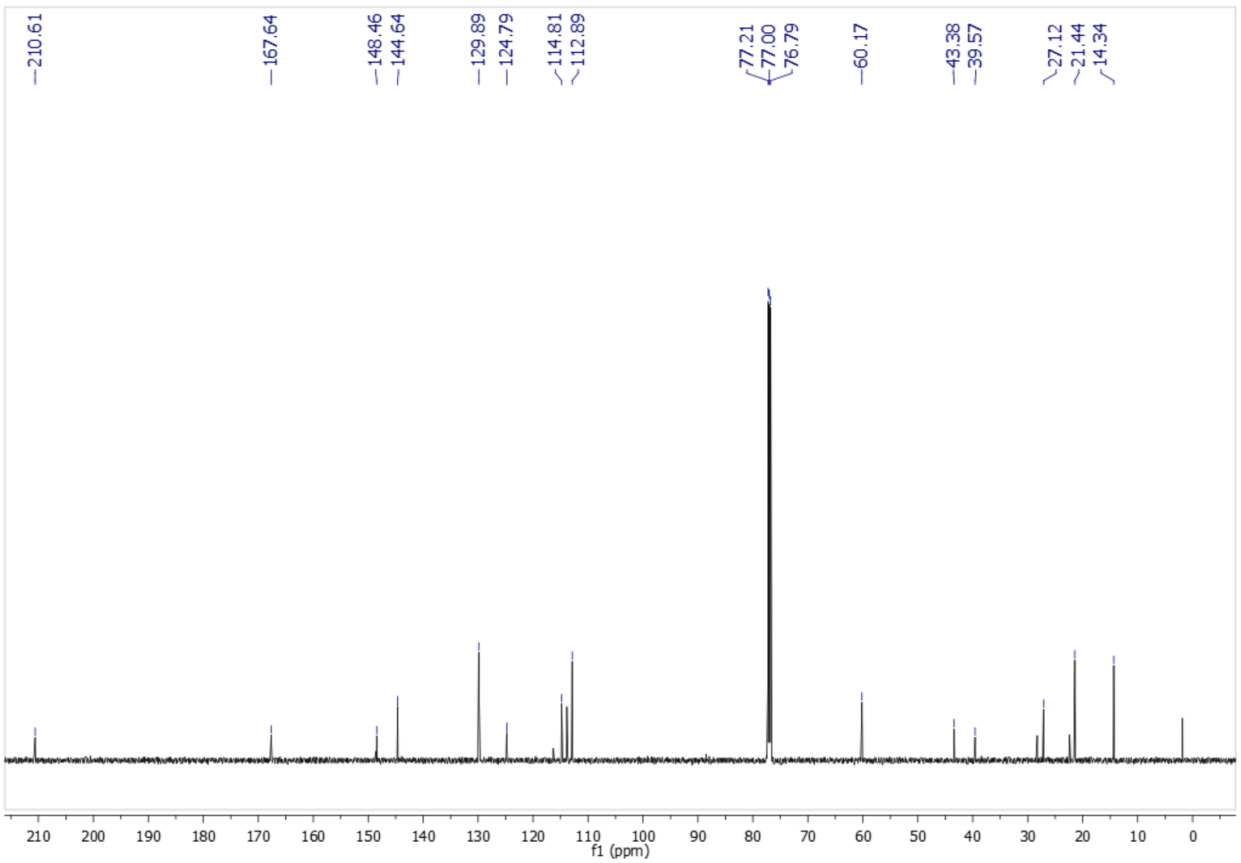
1-(1-([1,1'-biphenyl]-2-ylamino)cyclopropyl)propan-1-one





ethyl (E)-3-(4-((1-acetylcyclopropyl)amino)phenyl)acrylate





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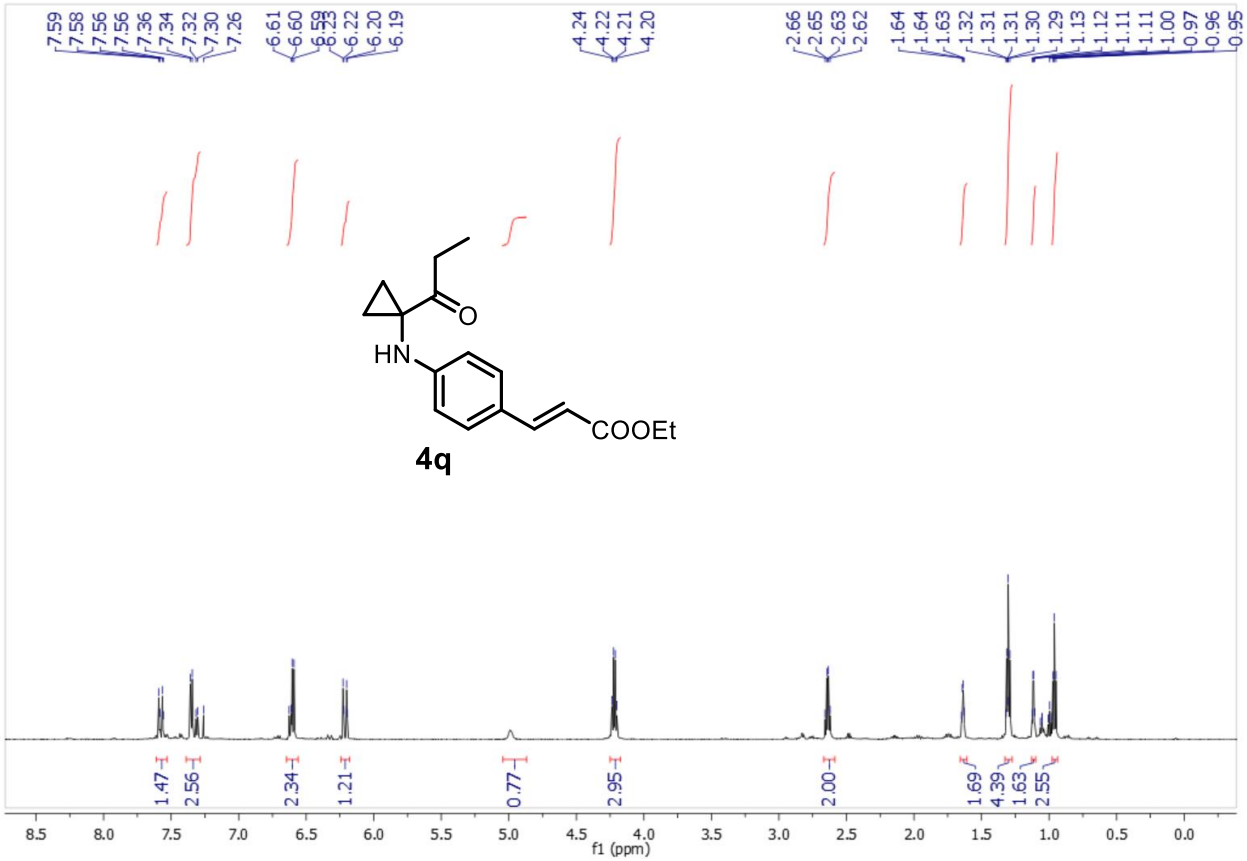
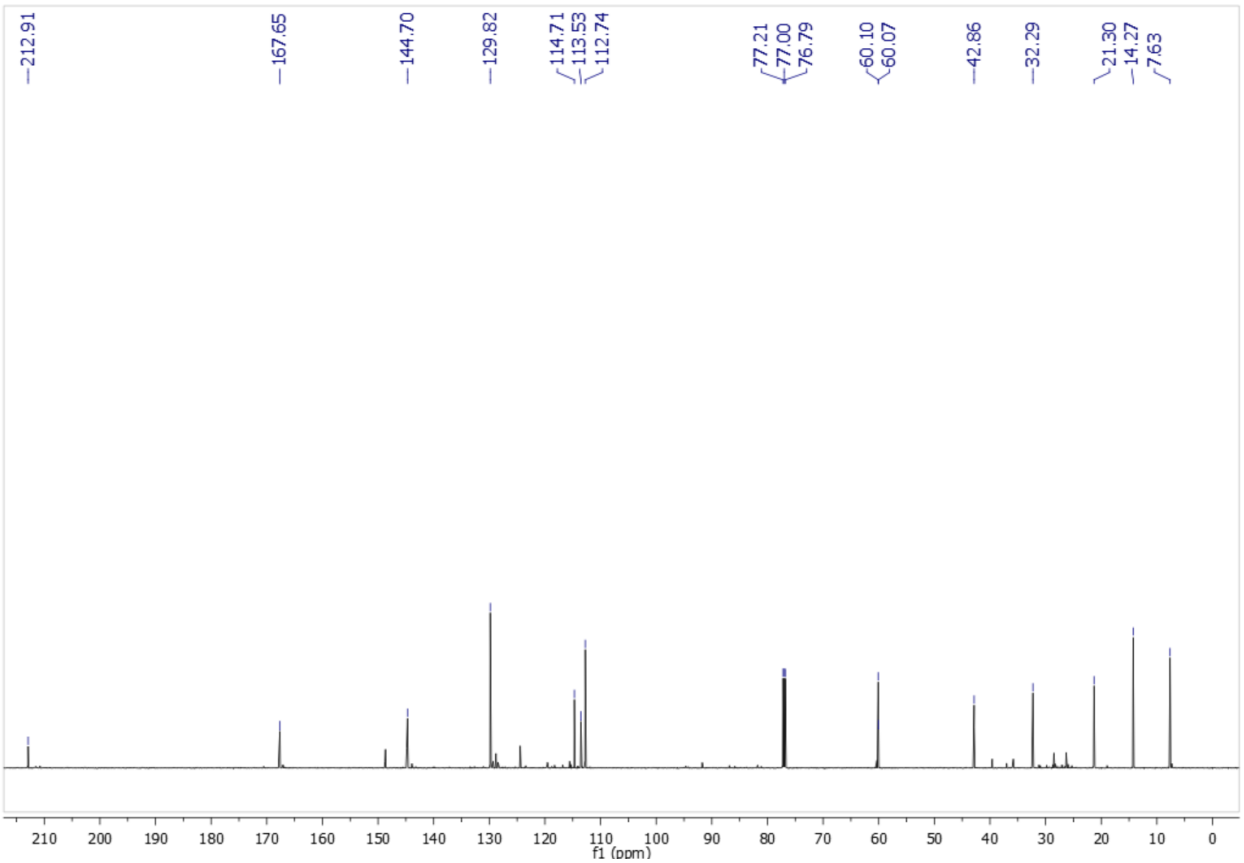
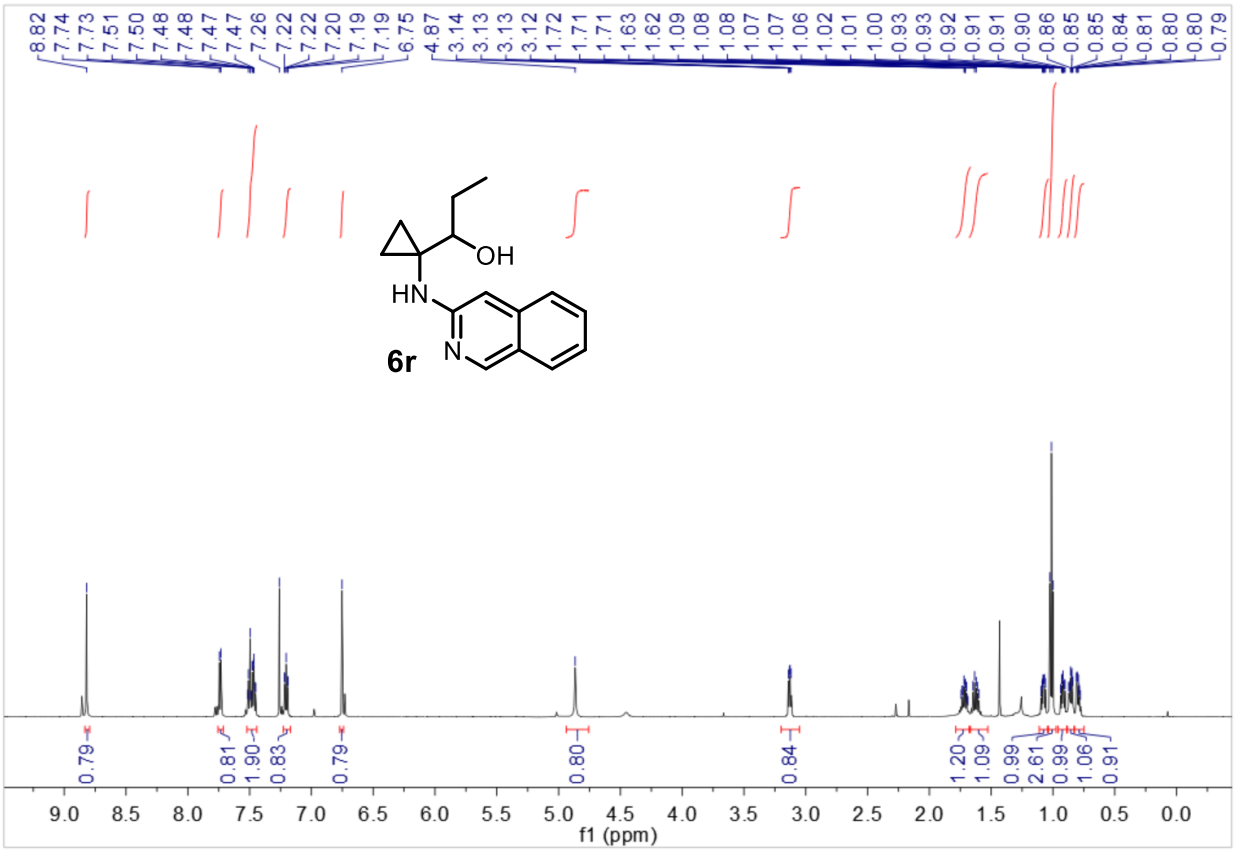
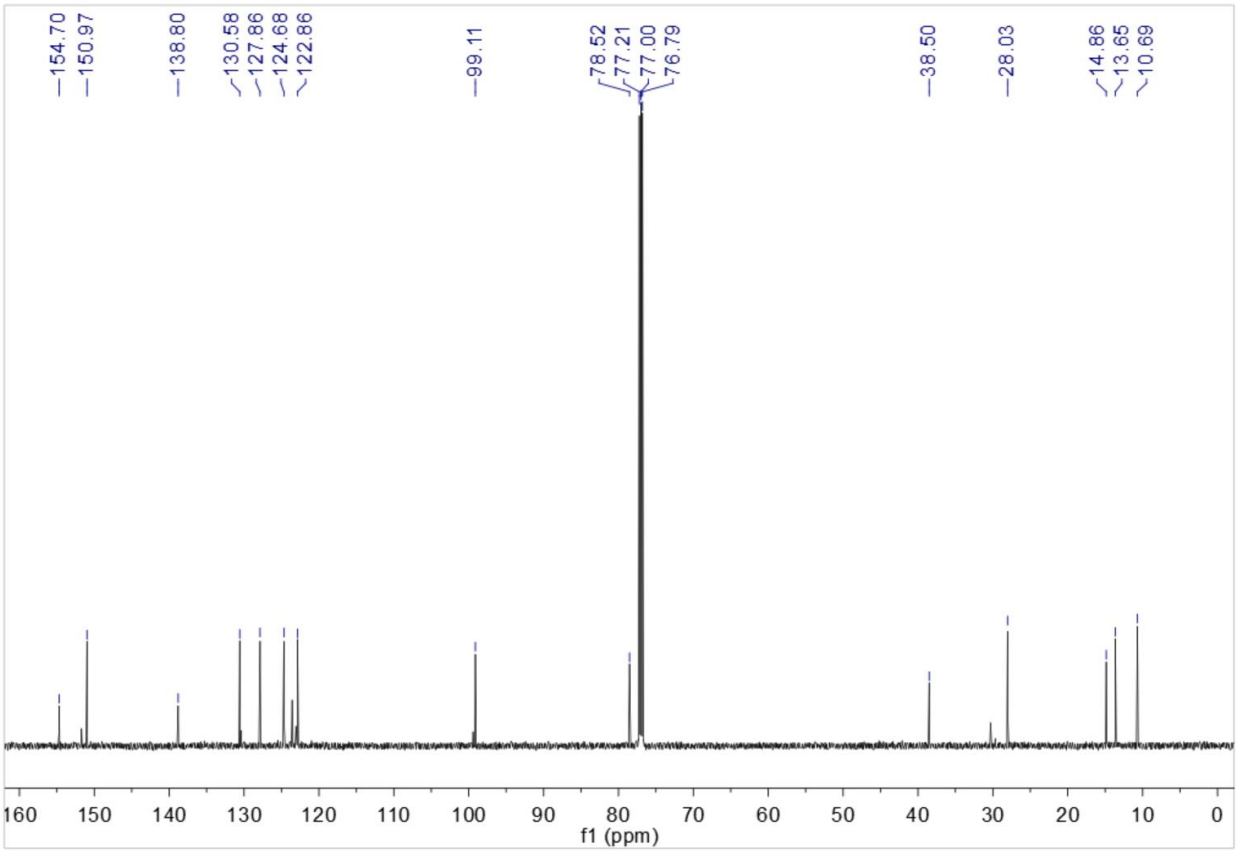


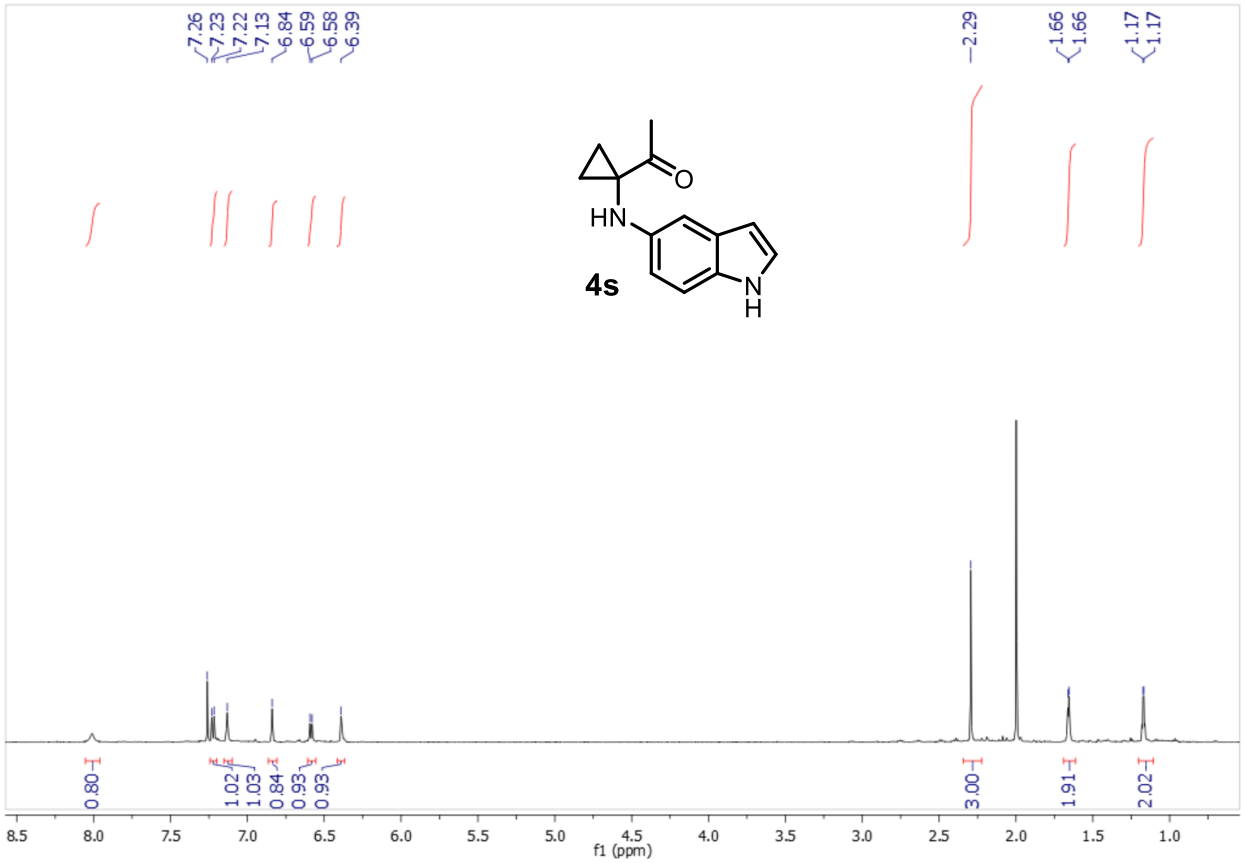


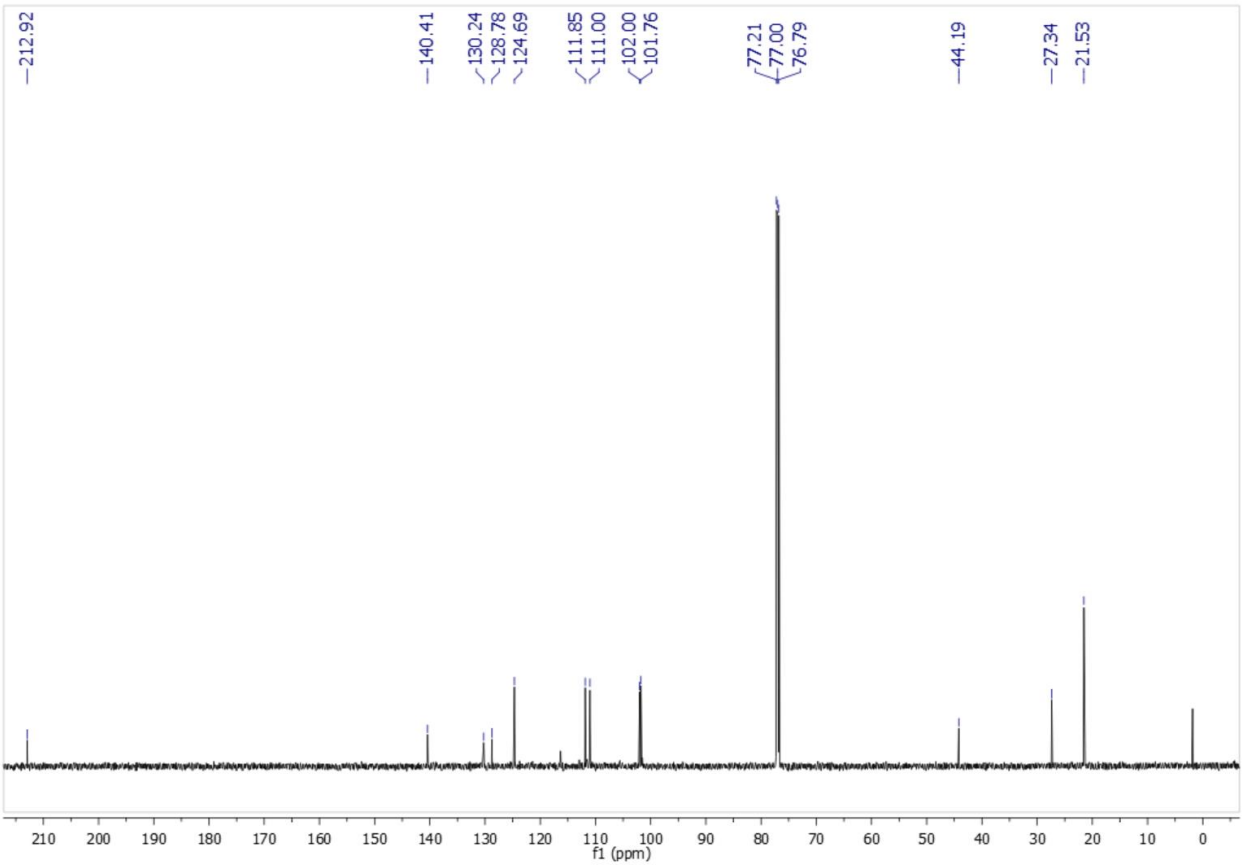
1-(1-(isoquinolin-3-ylamino)cyclopropyl)propan-1-ol



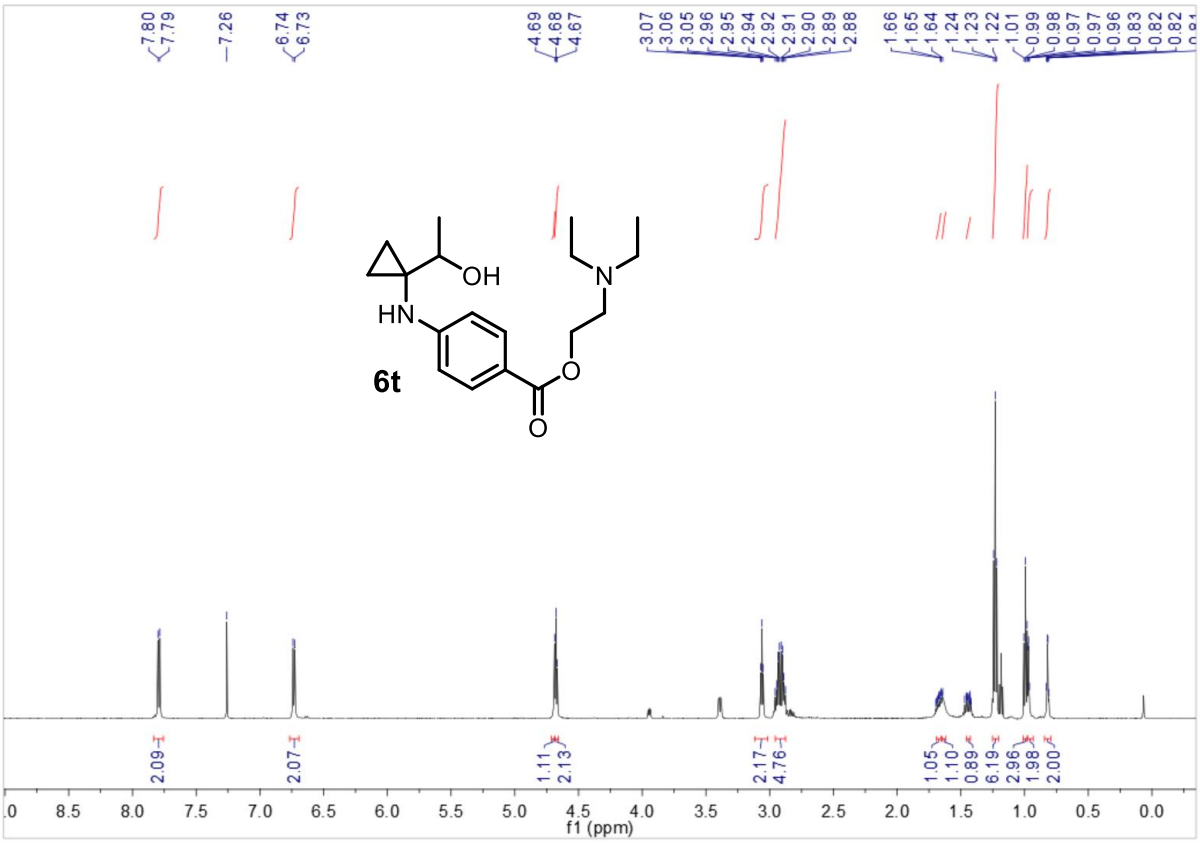


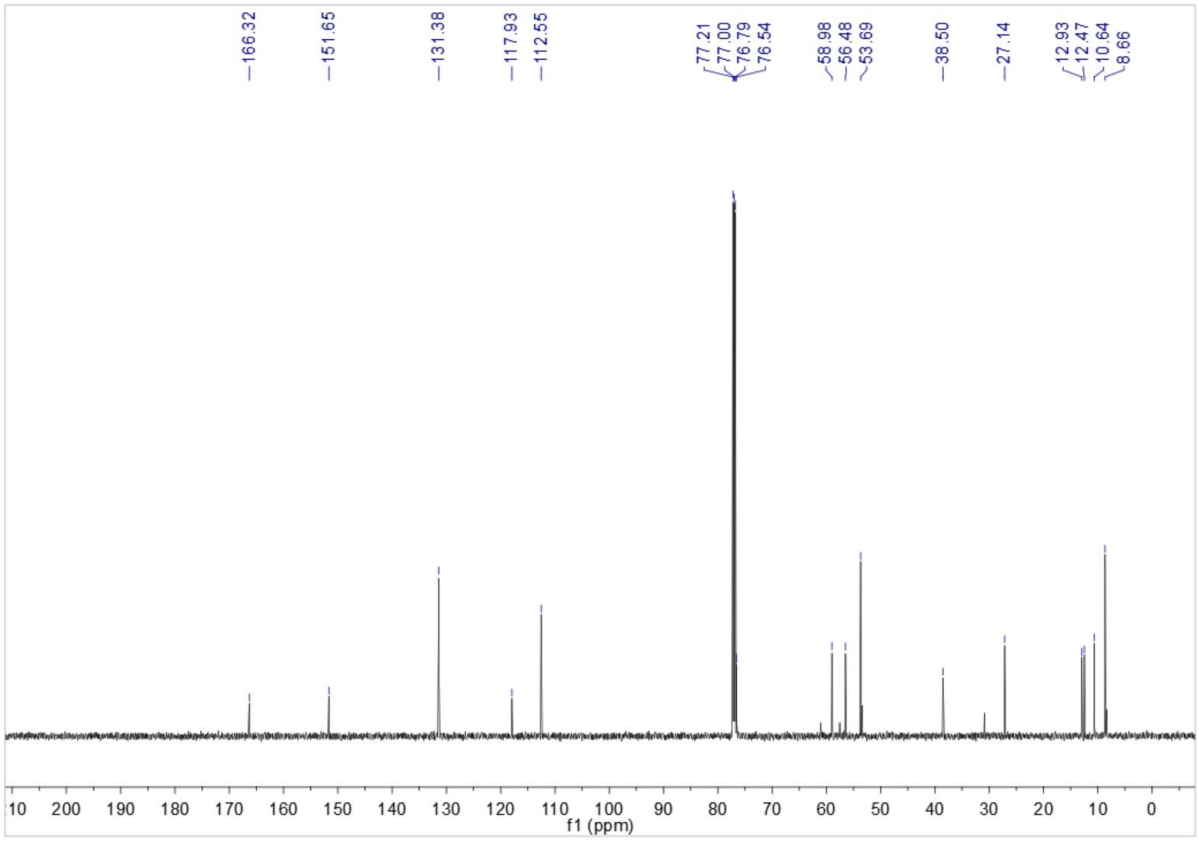
1-(1-((1H-indol-5-yl)amino)cyclopropyl)ethan-1-one





2-(diethylamino)ethyl 4-((1-(1-hydroxyethyl)cyclopropyl)amino)benzoate





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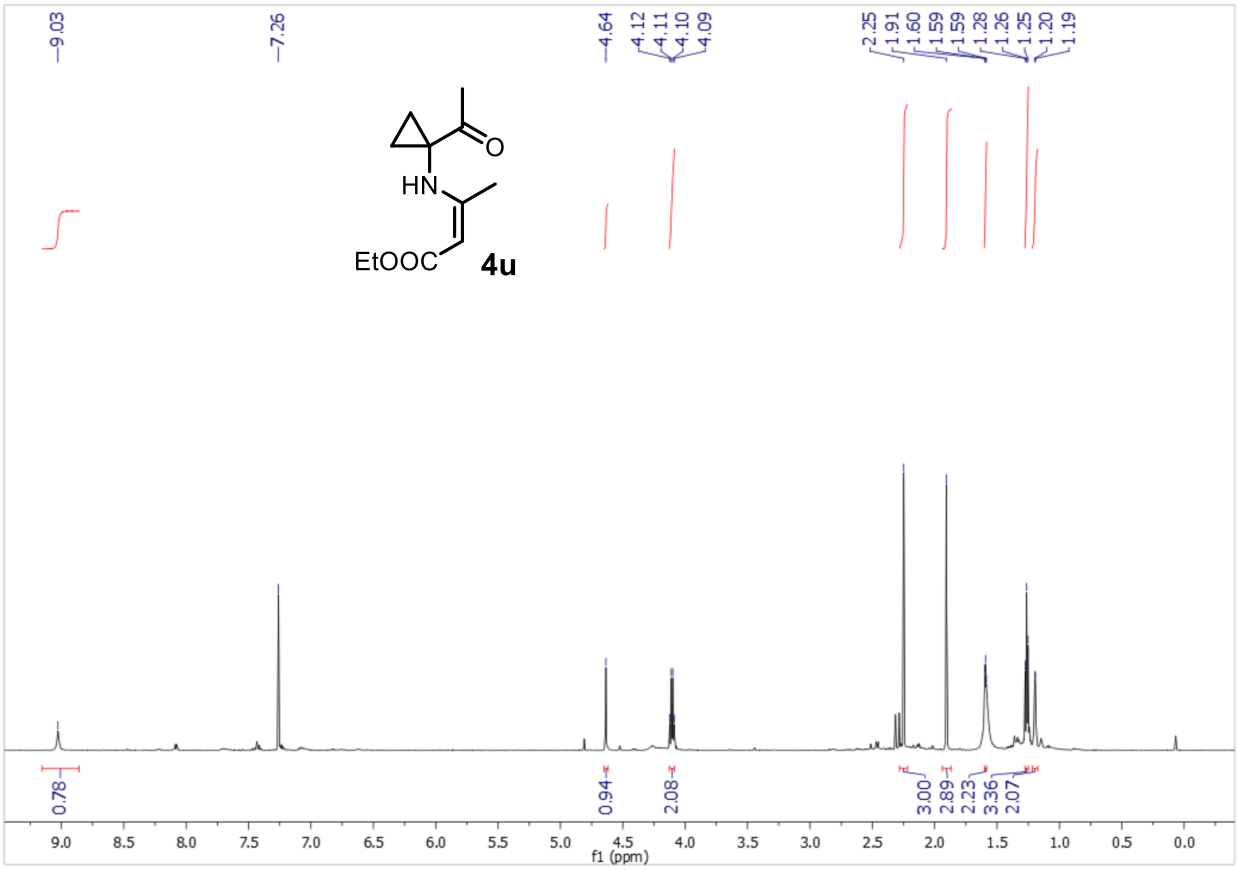
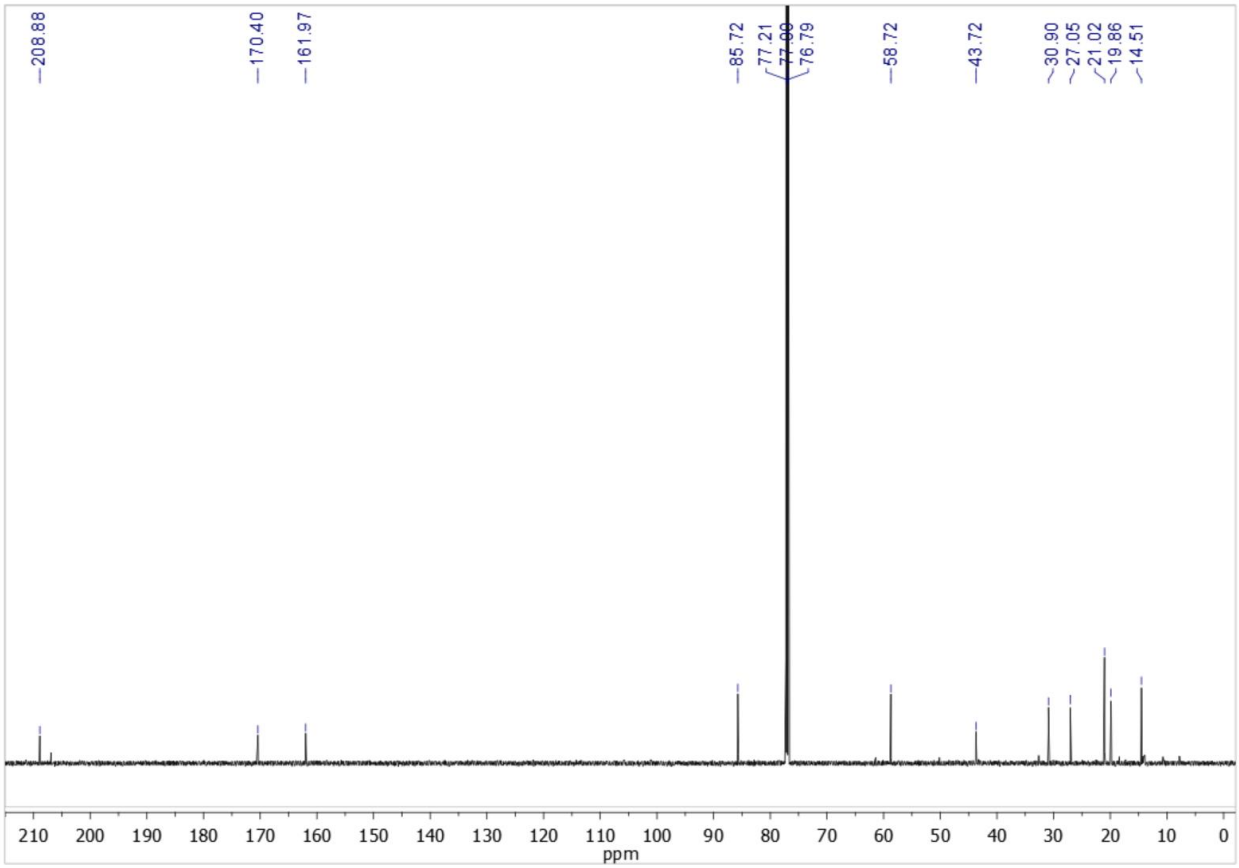
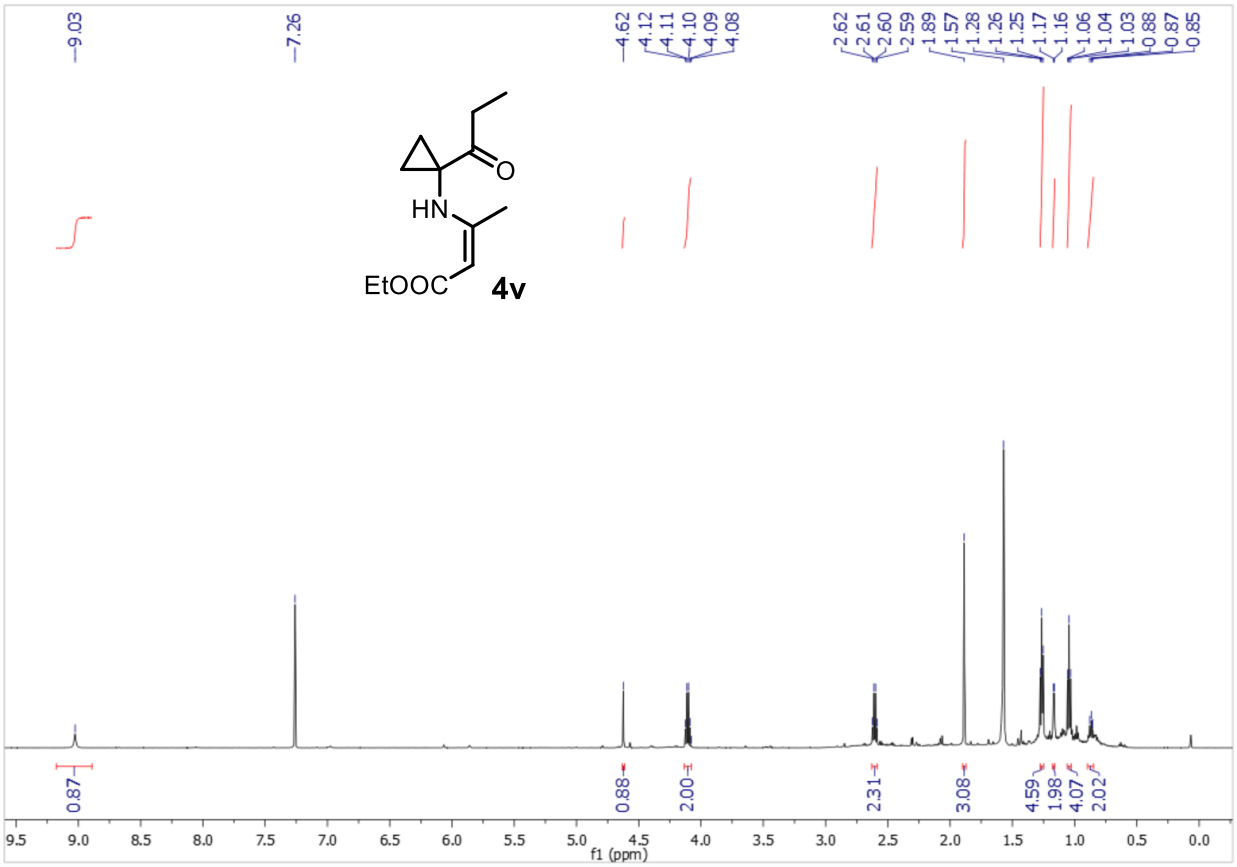
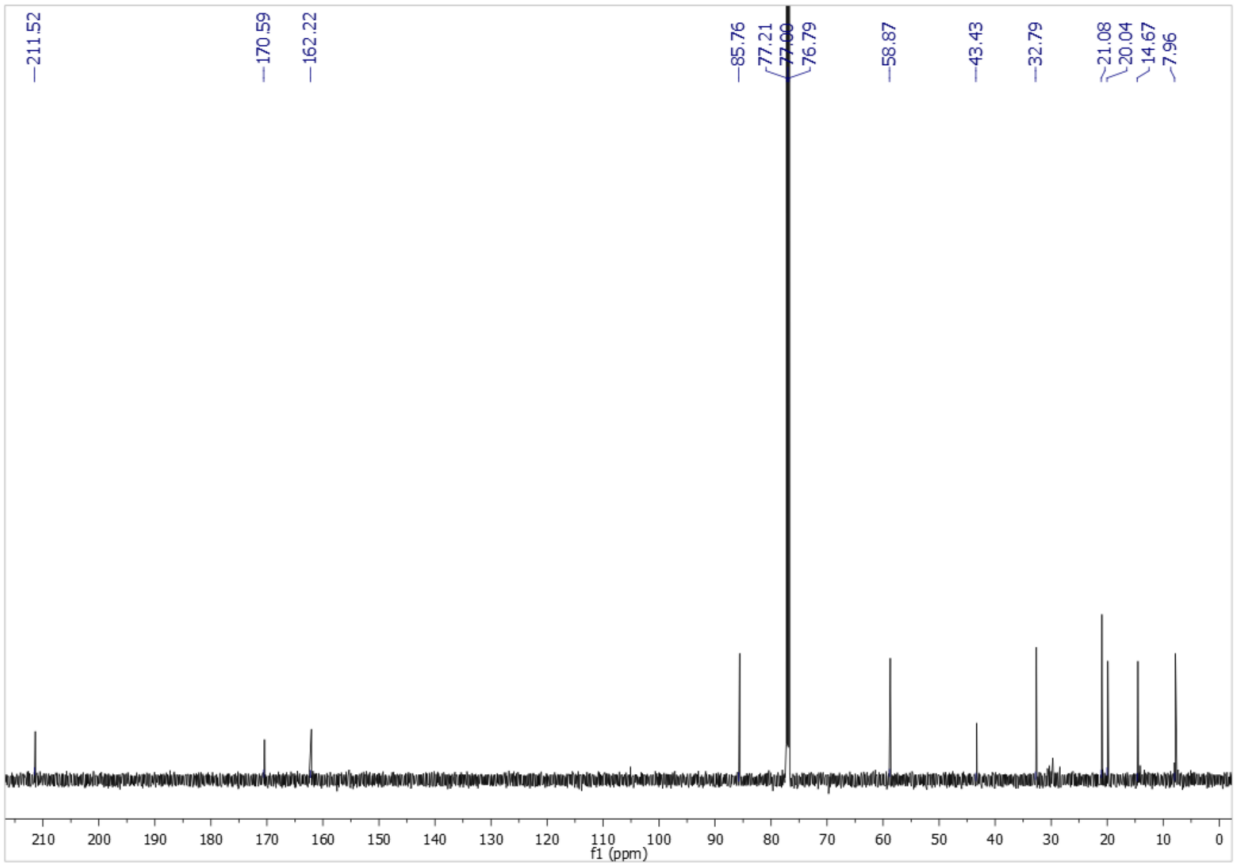


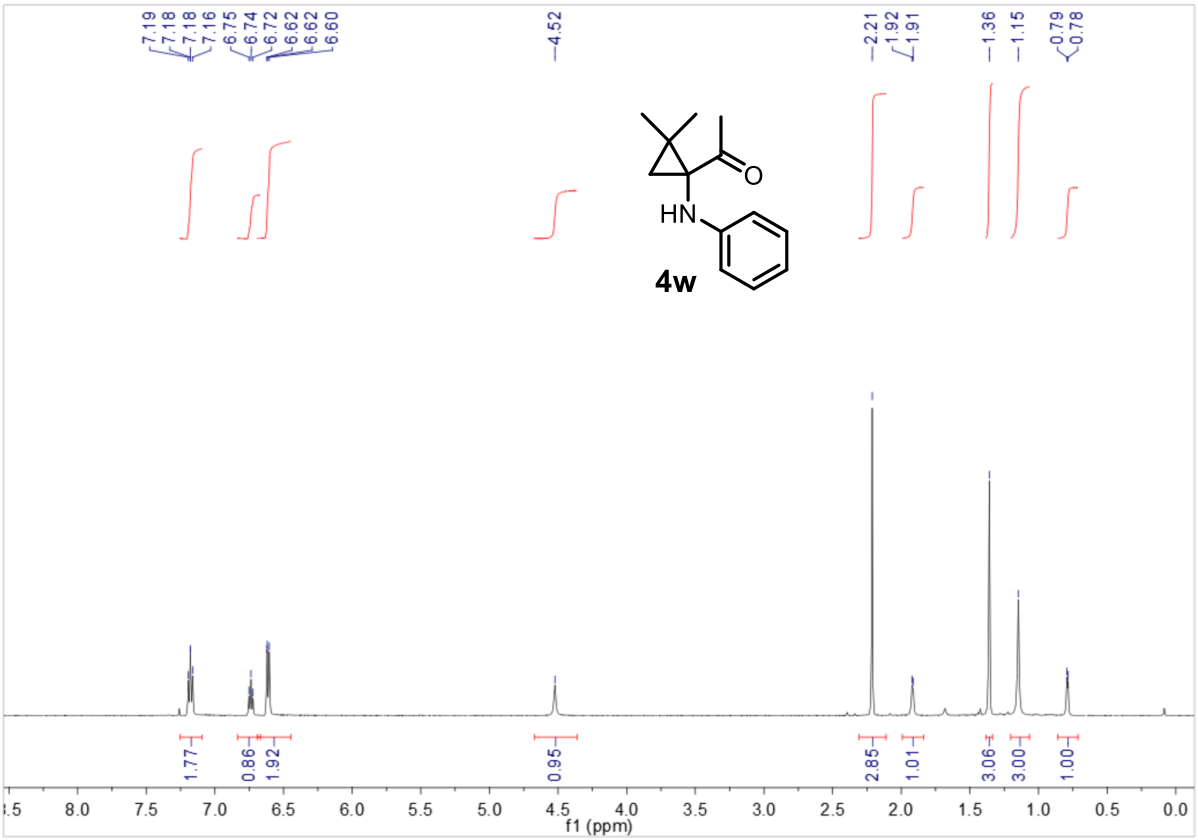


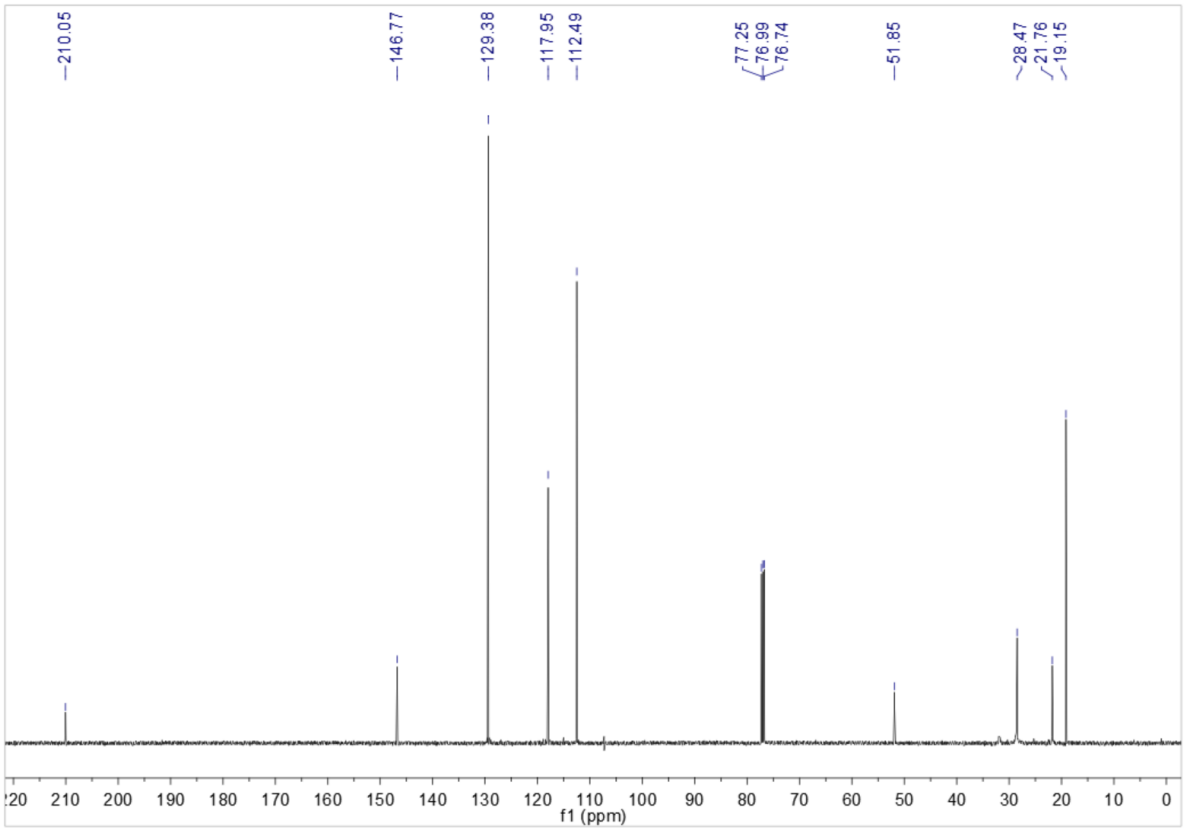
ethyl (*E*)-3-((1-propionylcyclopropyl)amino)but-2-enoate





1-(2,2-dimethyl-1-(phenylamino)cyclopropyl)ethan-1-one





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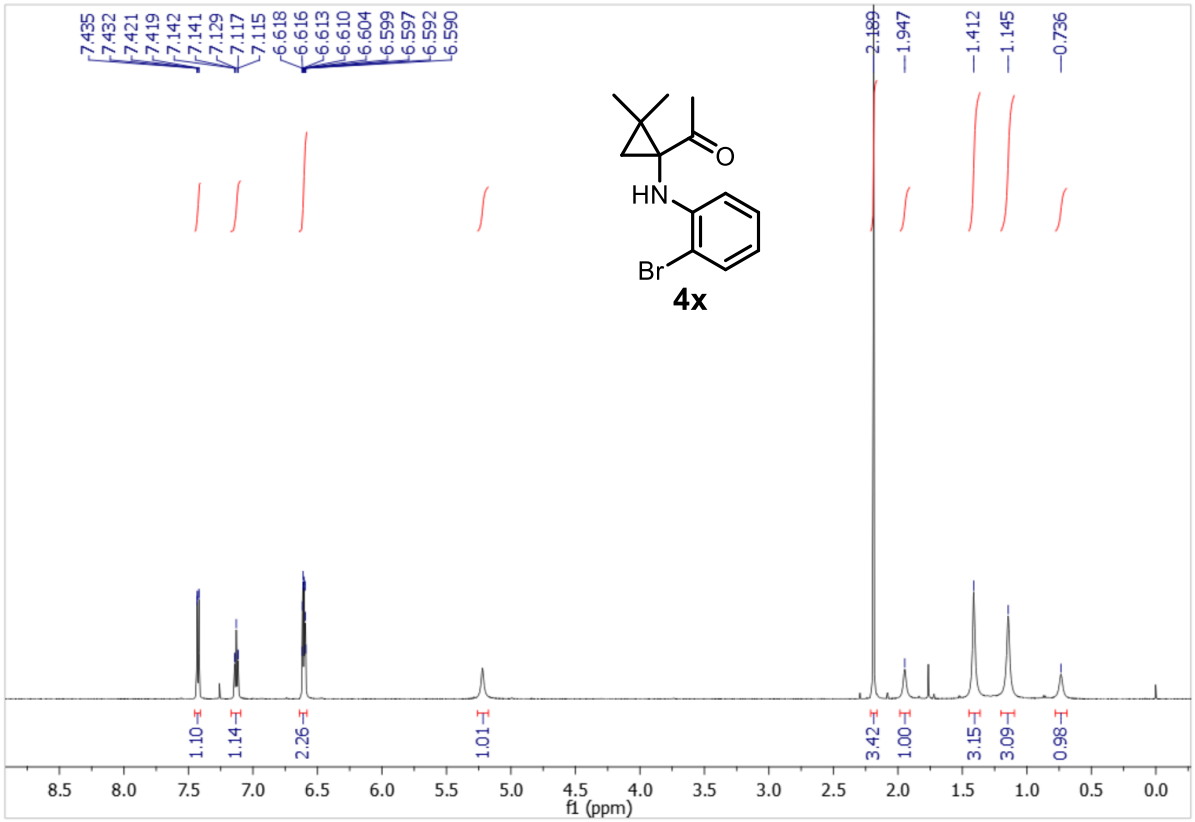

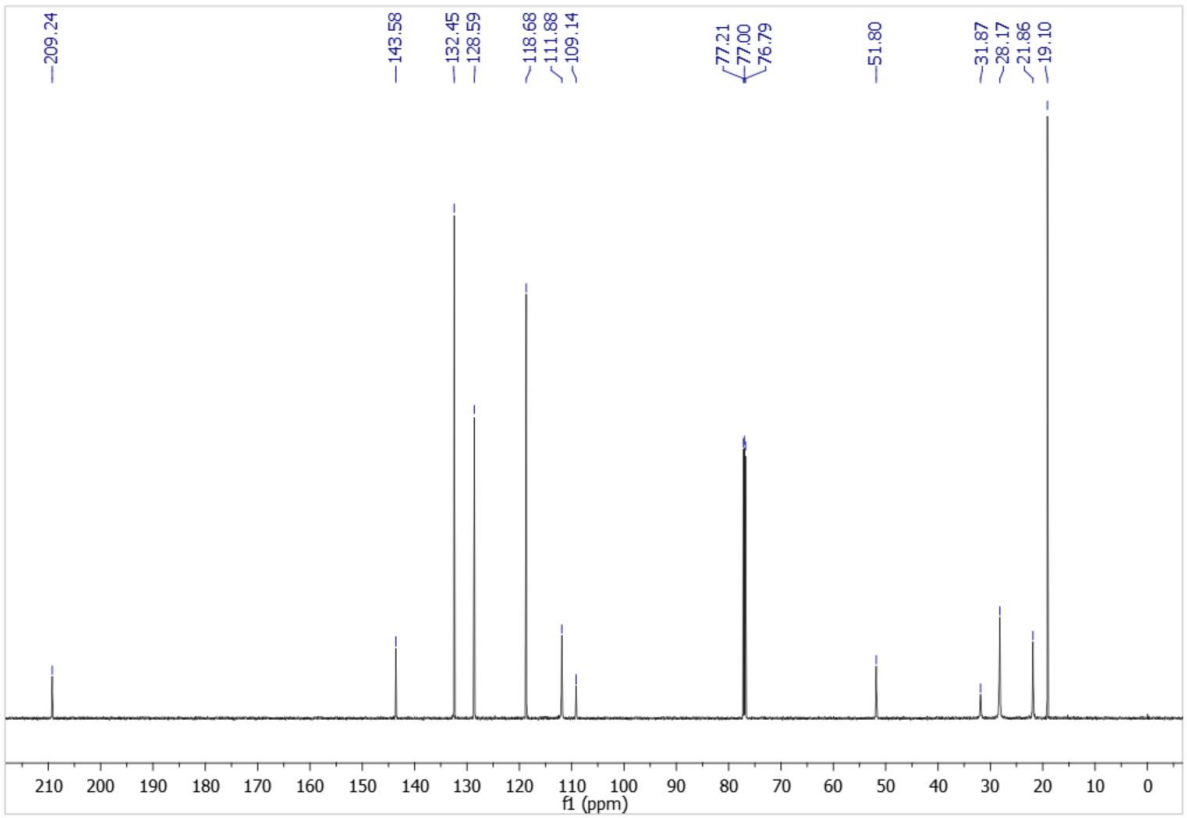

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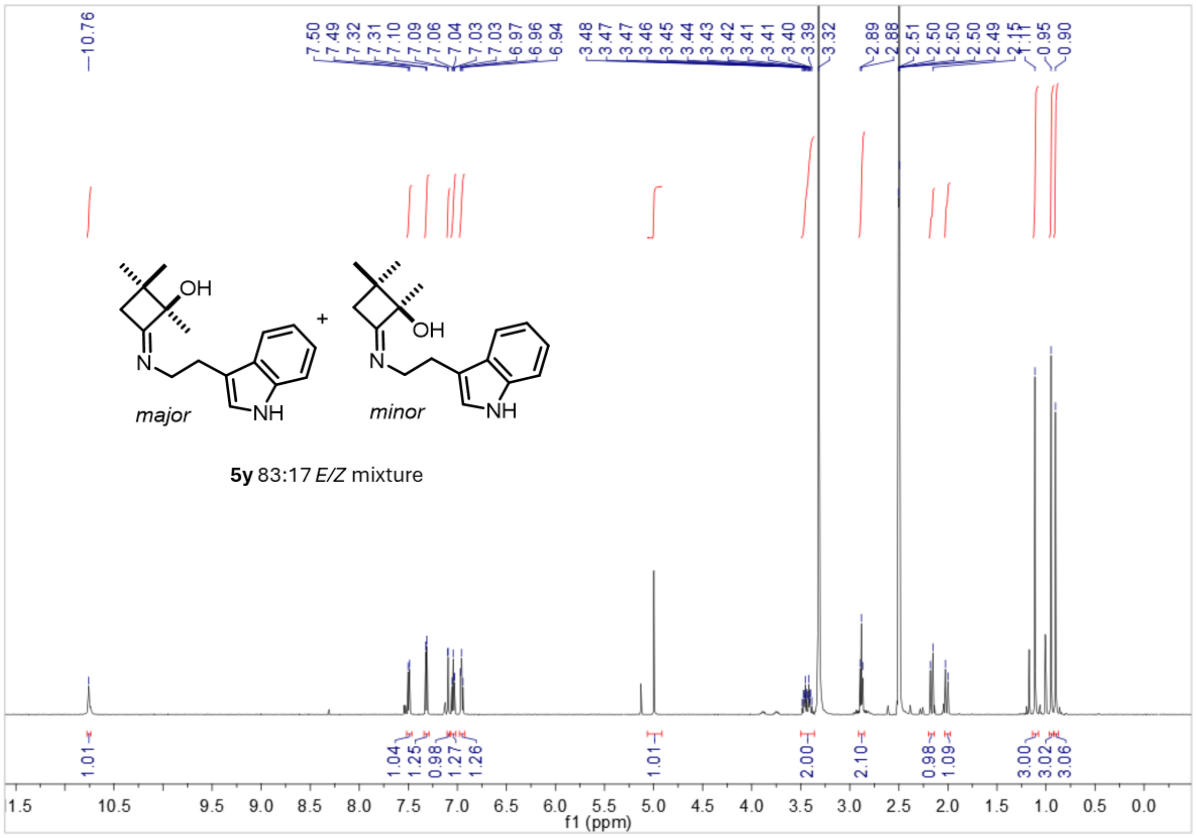
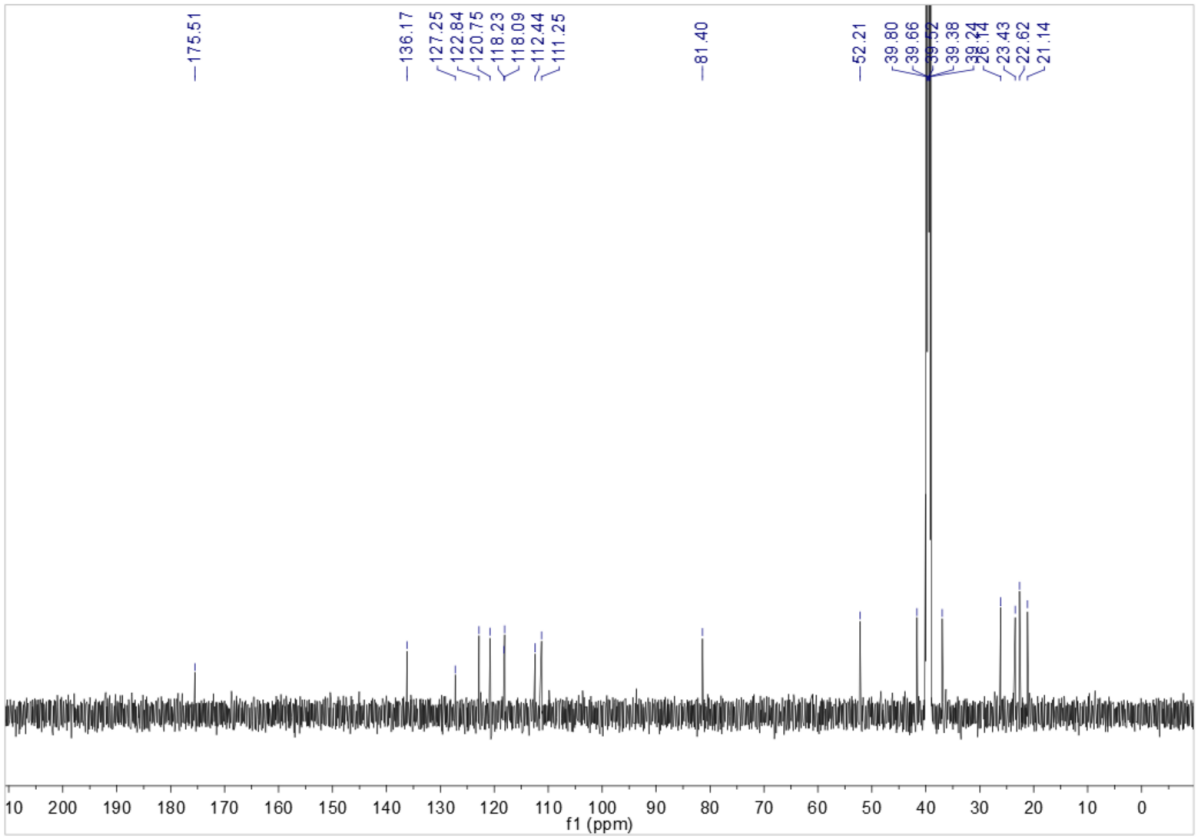
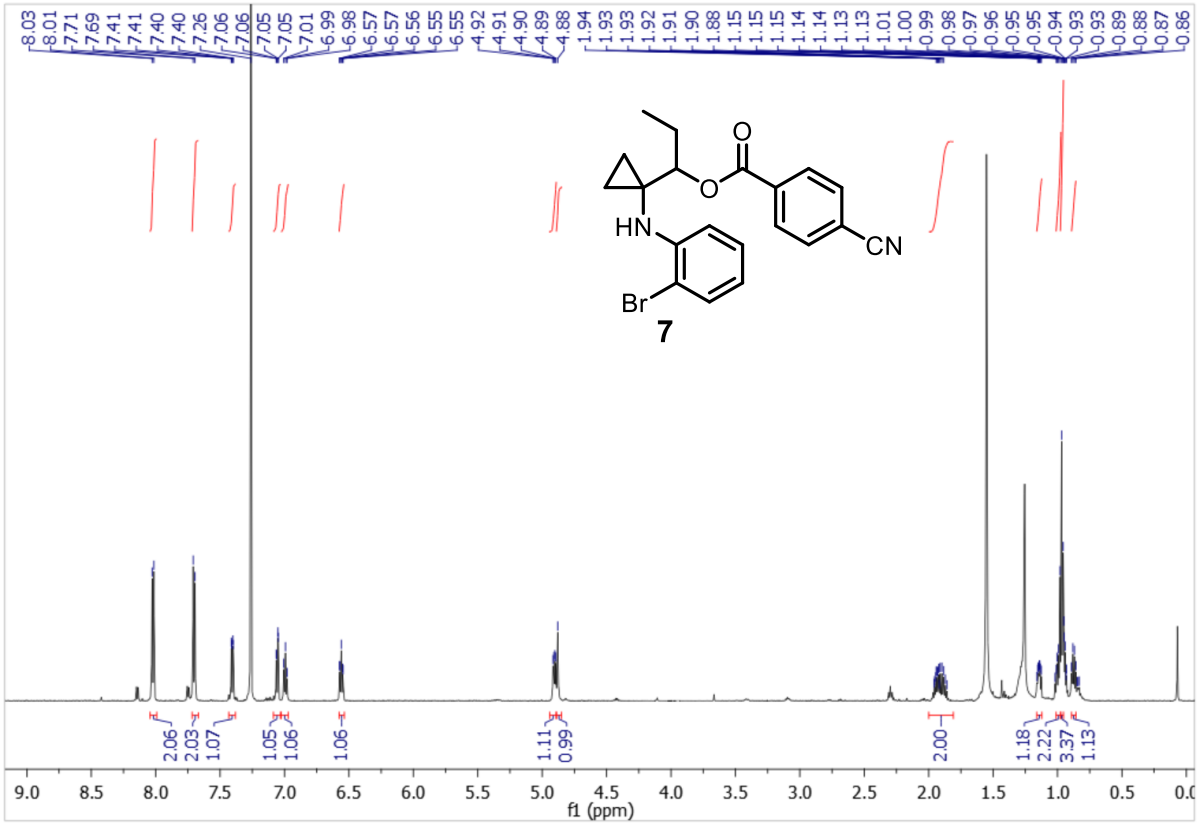
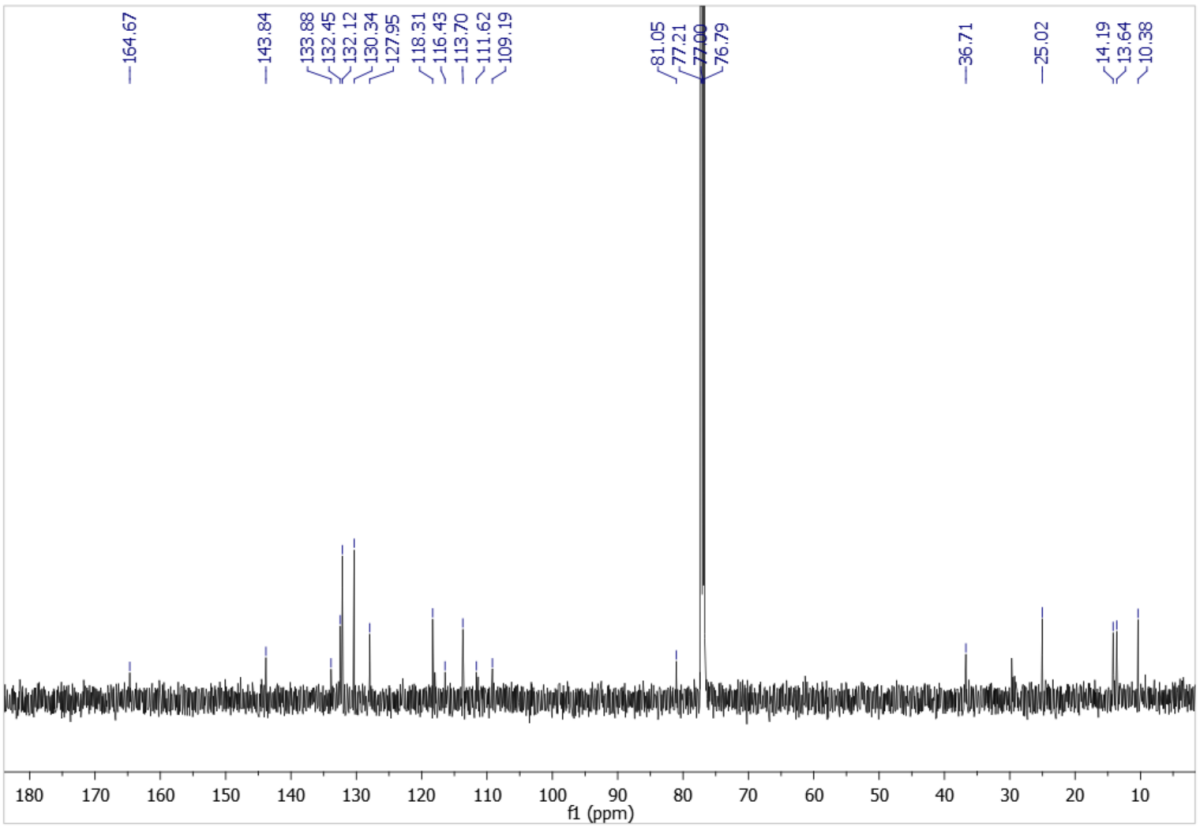


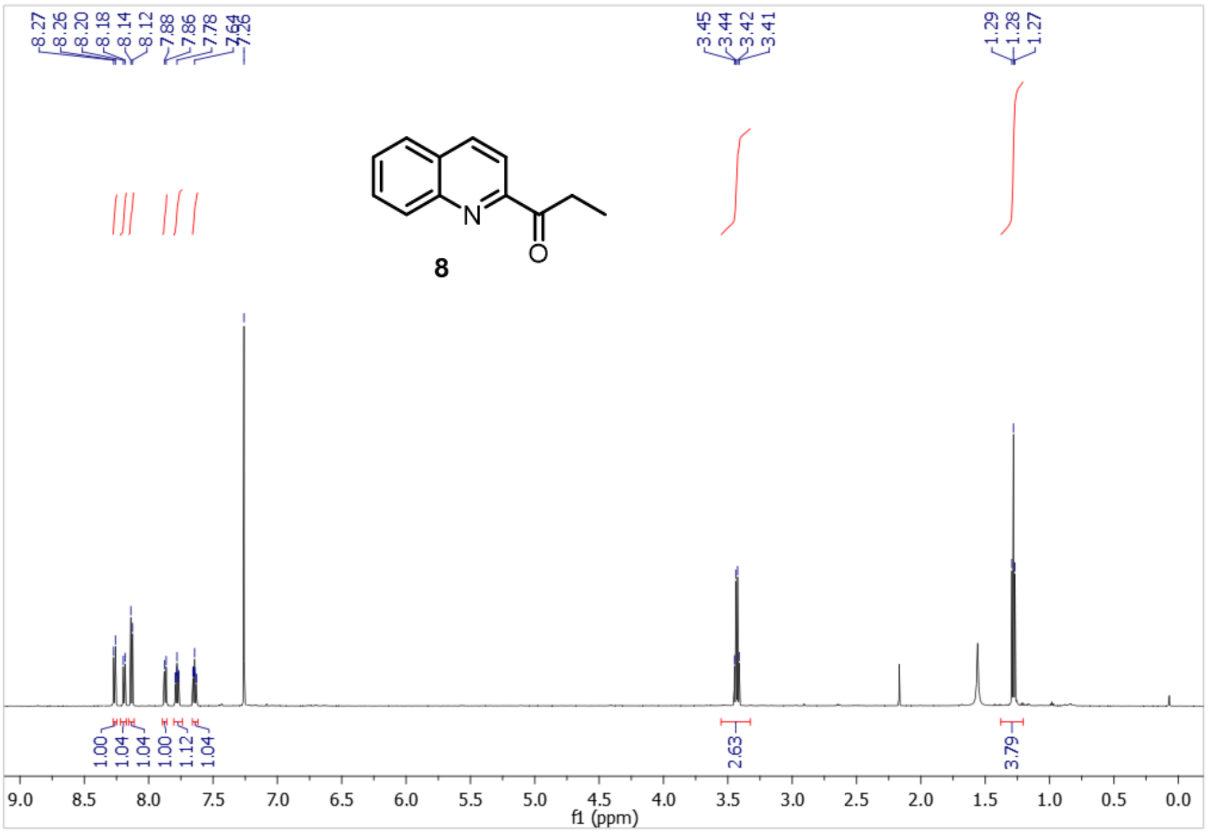


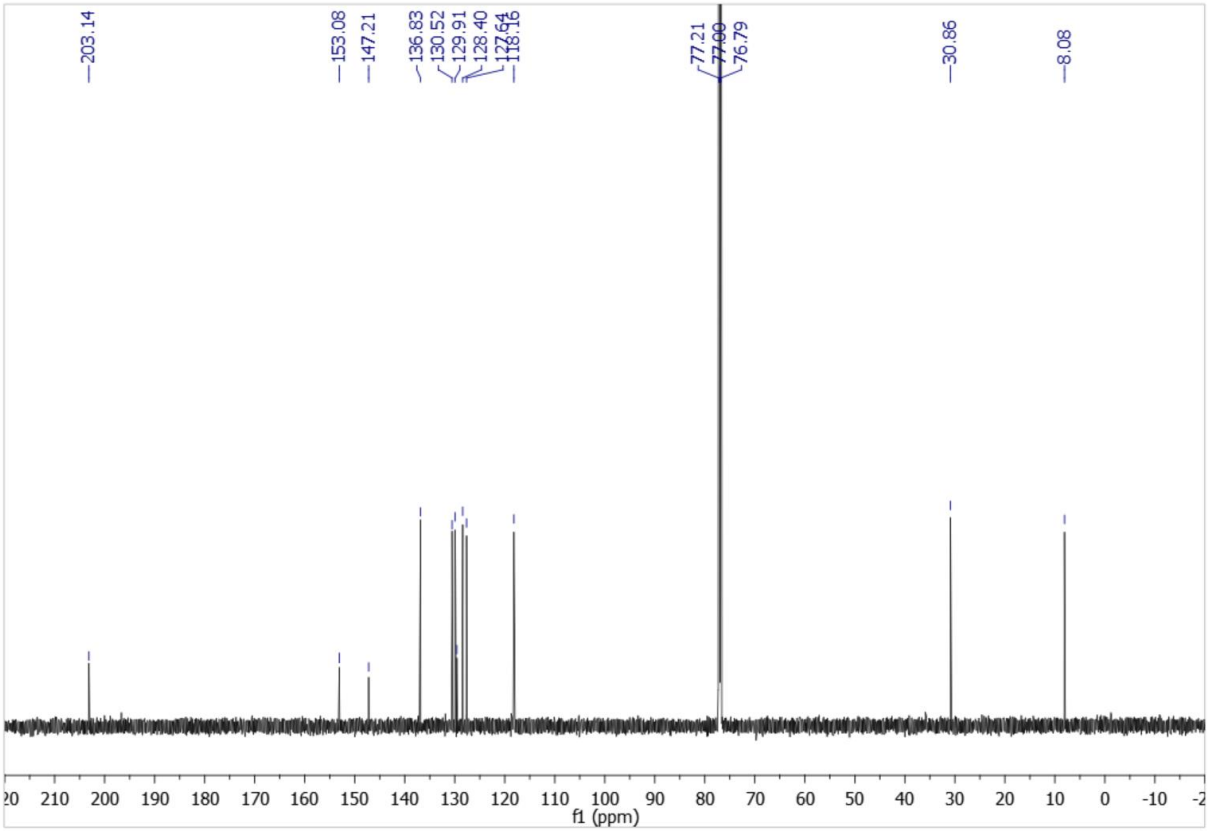
1-(1-((2-bromophenyl)amino)cyclopropyl)ethyl 4-cyanobenzoate



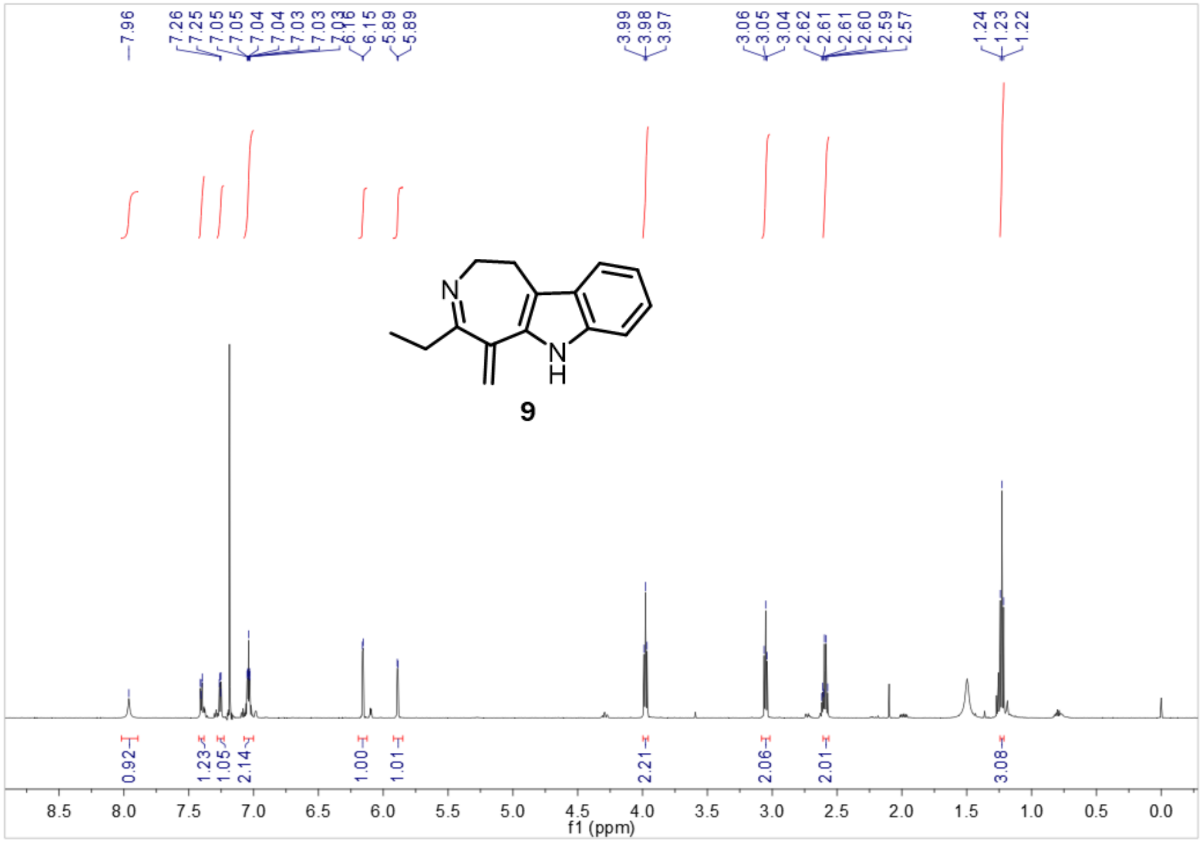


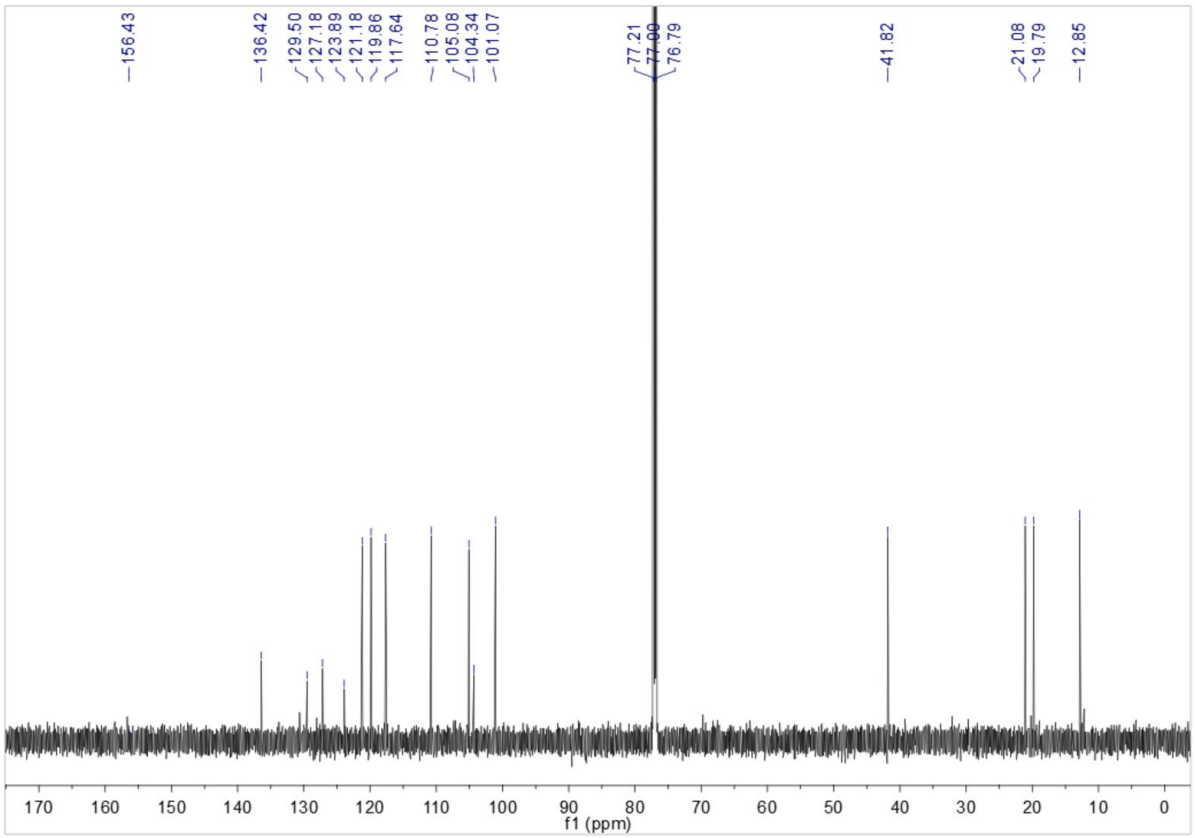
1-(quinolin-2-yl)propan-1-one



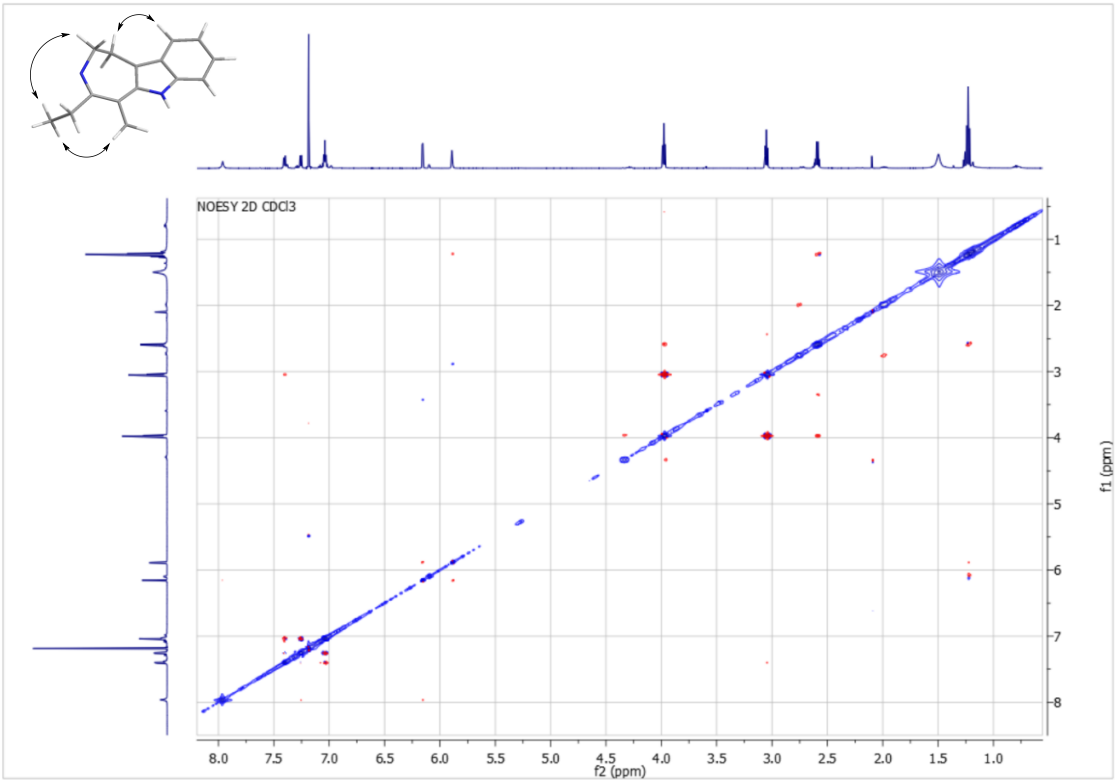


4-ethyl-5-methylene-1,2,5,6-tetrahydroazepino[4,5-b]indole

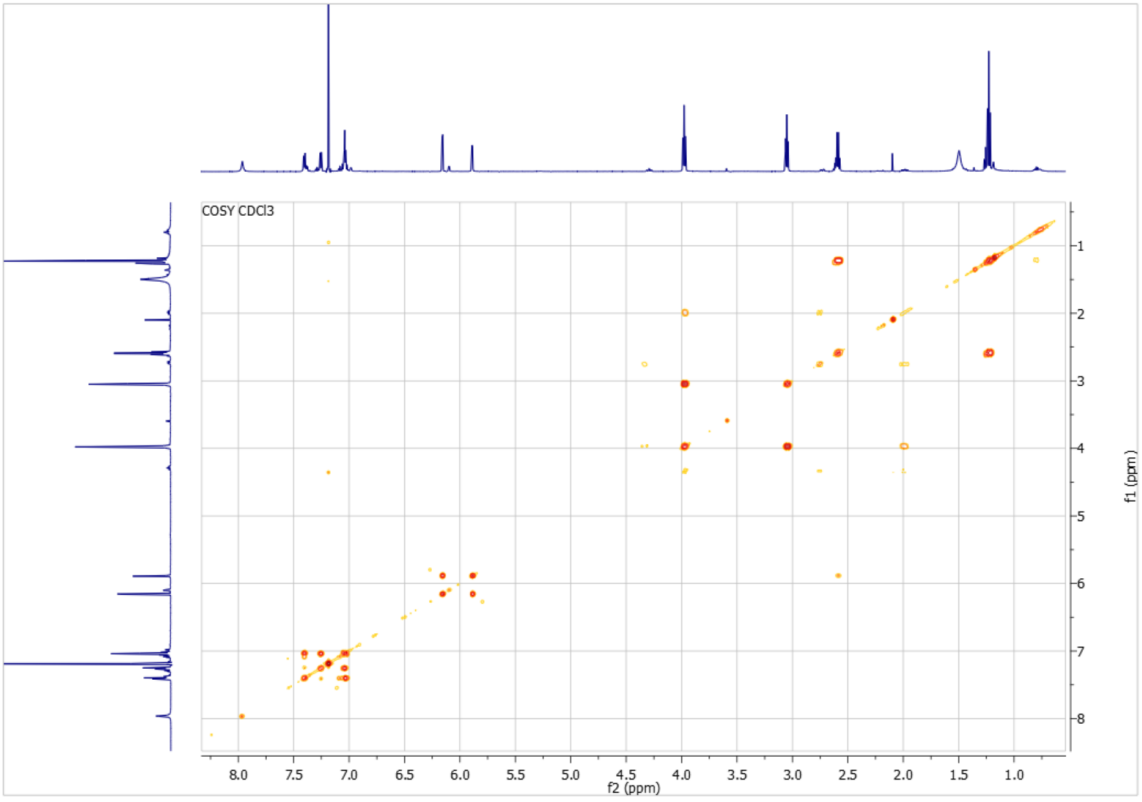




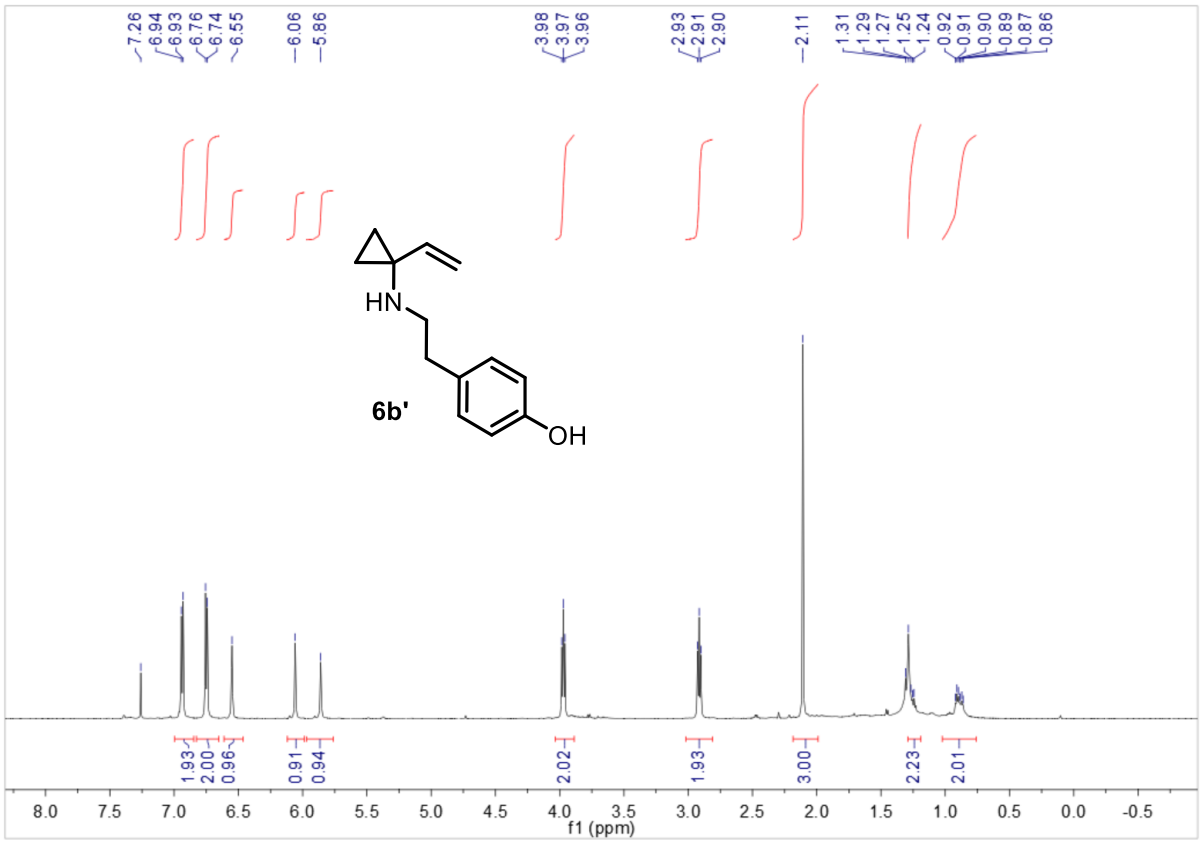
NOESY *4-ethyl-5-methylene-1,2,5,6-tetrahydroazepino[4,5-b]indole* **9**

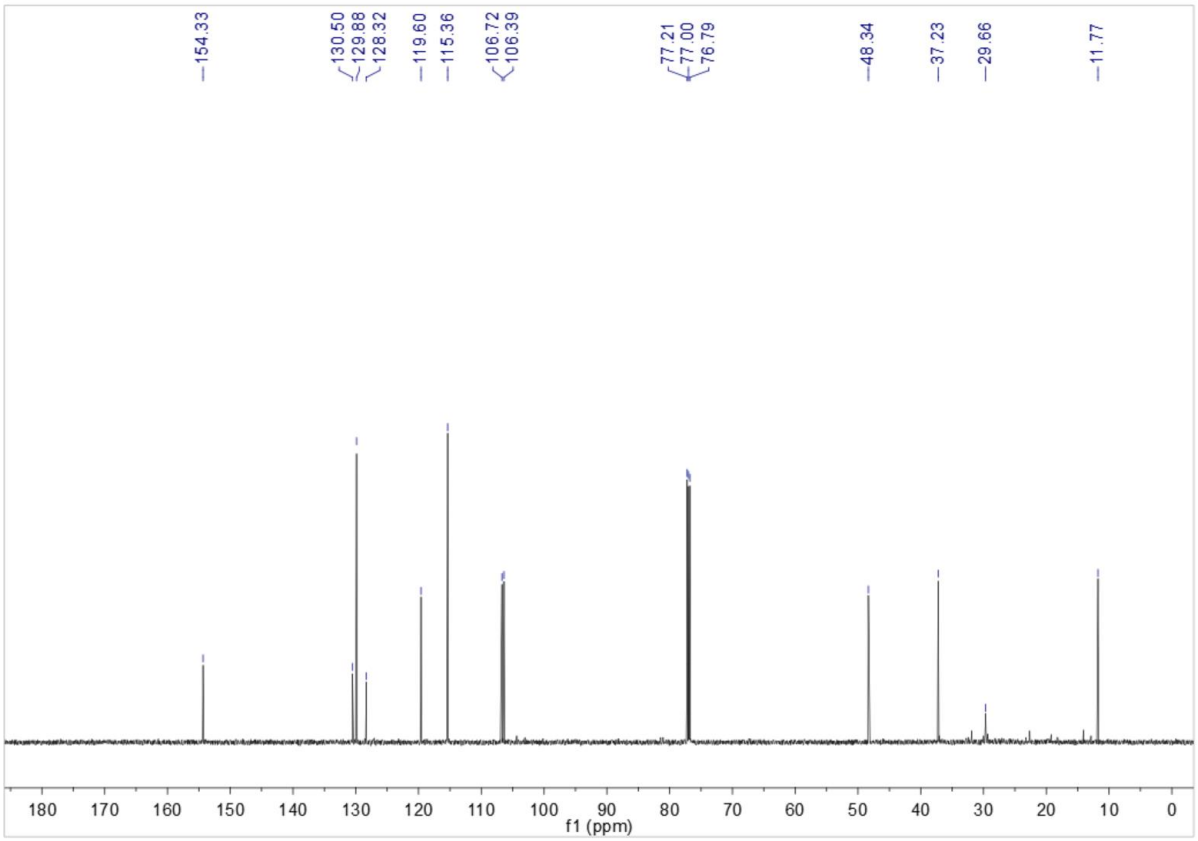


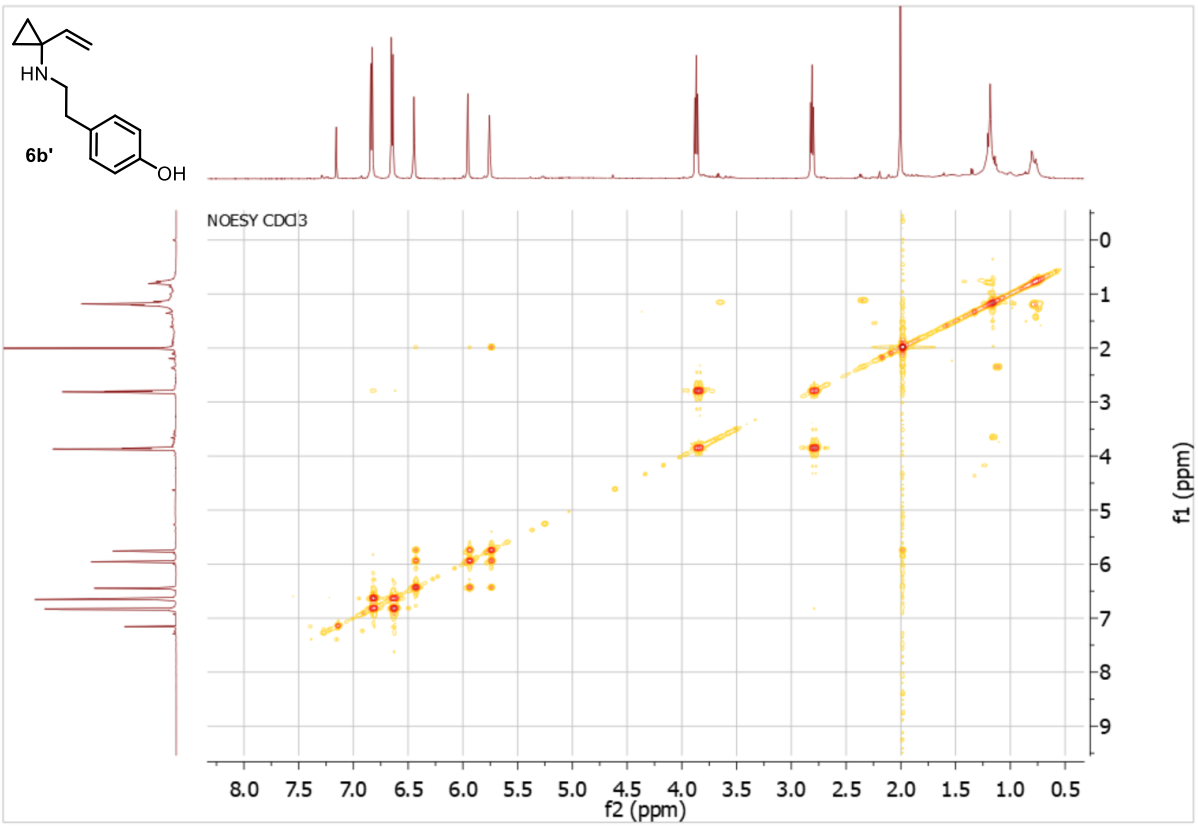
COSY *4-ethyl-5-methylene-1,2,5,6-tetrahydroazepino[4,5-b]indole* **9**

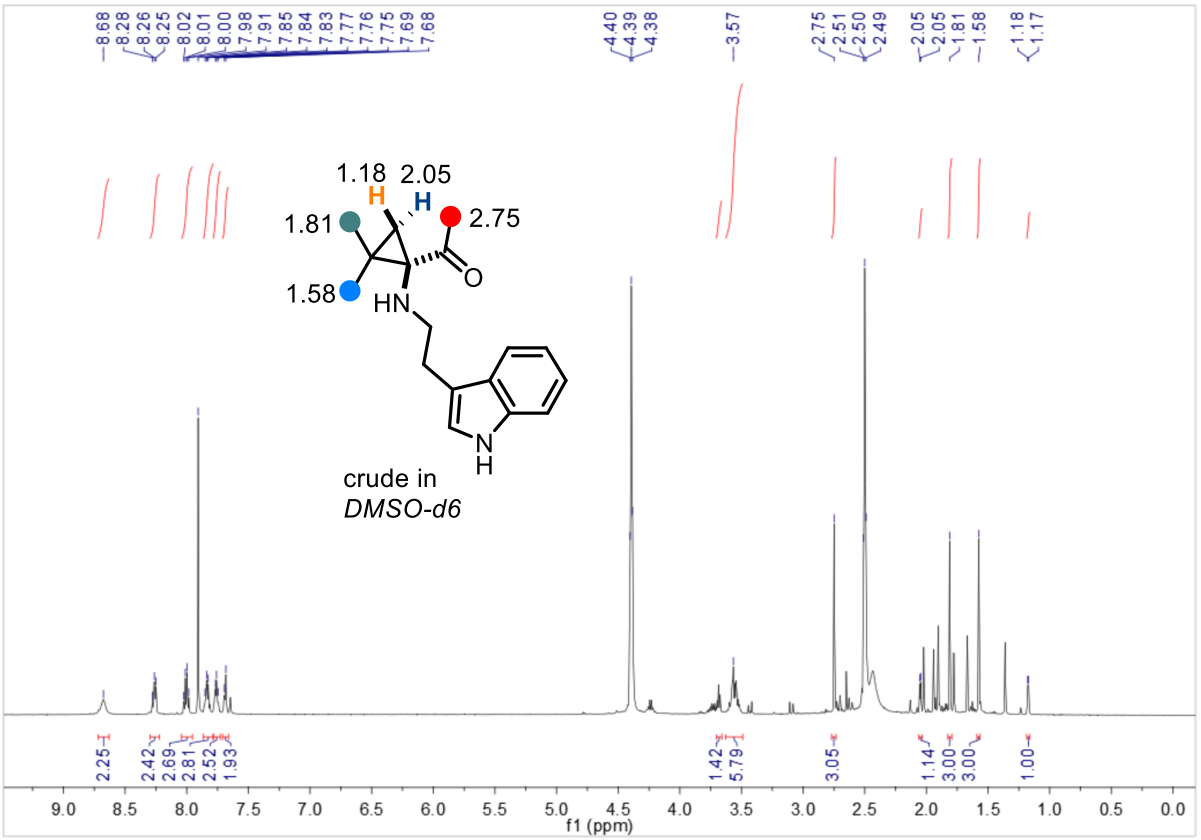


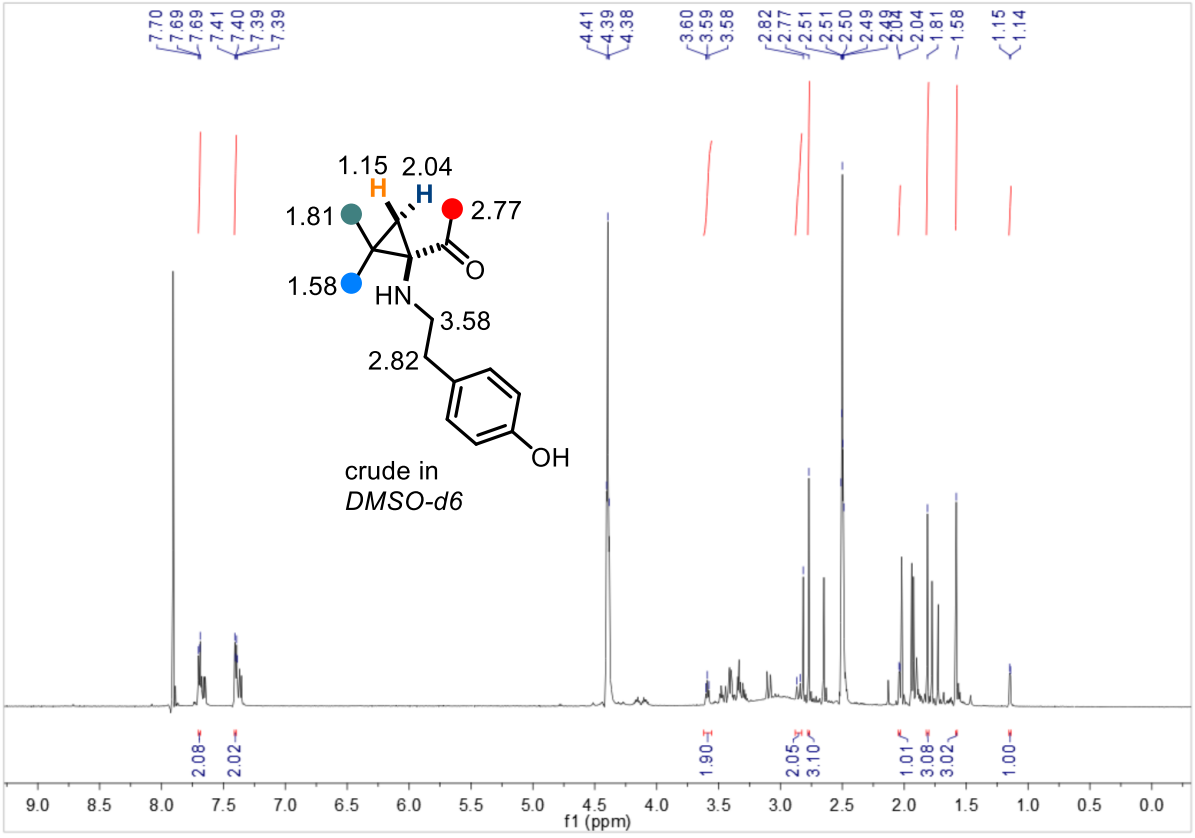
4-(2-((1-vinylcyclopropyl)amino)ethyl)phenol






HN
6b'
OH
NOESY CDCl3
f1 (ppm)
f2 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
0 1 2 3 4 5 6 7 8 9


1.18
2.05
H
H
1.81
2.75
1.58
HN
O
N
H
crude in
DMSO-d6
f1 (ppm)


1.15
2.04
H
H
1.81
2.77
1.58
HN
O
3.58
2.82
OH
crude in
DMSO-d6
f1 (ppm)

8. Single-Crystal X-ray diffraction analysis

8.1. Materials and methods

Single-crystal X-ray diffraction data of **4**r , **5**y and **5**z and 8 were collected at 100 K on a Bruker D8 Venture diffractometer equipped with a PHOTON II detector. The structures were solved with the ShelXT[5] solution program using dual methods and developed by iterative cycles of least-squares refinement on F^2 using ShelXL 2018/3.[6] Olex2 1.5[7] was used as the graphical interface and for the preparation of figures. Hydrogen atoms were placed geometrically and refined isotropically riding on their parent C atom with $U_{iso}(H) = 1.2U_{eq}(C)$. H atoms bonded to heteroatoms were located from the difference Fourier map and their position were refined freely.

*Compound **4**r CCDC deposition number: **2373554***

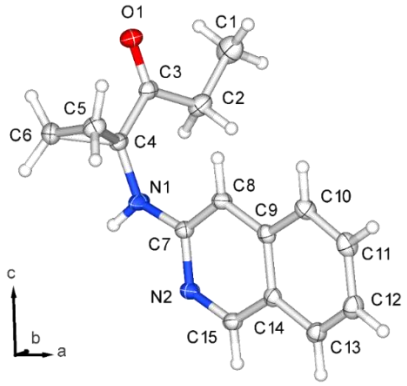


Figure S7 Ellipsoid plot and atomic labelling scheme of compound **4**r . Thermal ellipsoids are drawn at 50% probability level.

Compound **4**r crystallized in the orthorhombic space group *Pbca* with a single molecule in the asymmetric unit (Figure S7, TableS9). The hydrogen bonding of the type N–H···N between the amino and quinoline groups results in dimers as shown in Figure S8. The crystal packing is further decorated by slightly slipped π-π stacking interaction between adjacent quinoline moieties with intercentroid distance of about 3.79 Å (Figure S9).

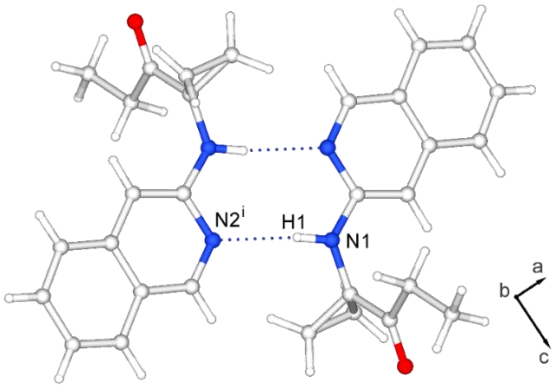


Figure S8 View along the *b*-axis of the hydrogen bonding interactions found in the crystal structure of **4**r **.** N1–H1 = 0.88(2); H1···N1^i = 2.13(2); N1···N1^i = 3.003(2) Å; N1–H1···N1^i = 172(2)°. Symmetry code: ^{i} = −*x*, 1−*y*, 1−*z*.

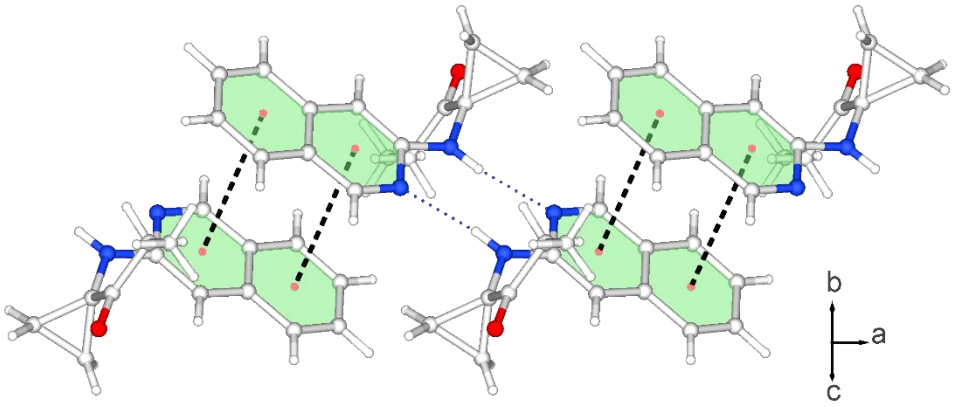


Figure S9 Partial view of the π-π stacking interaction between adjacent quinoline moieties in the crystal structure of **4**r .

Compound **5**y *CCDC deposition number:* ***2373554***

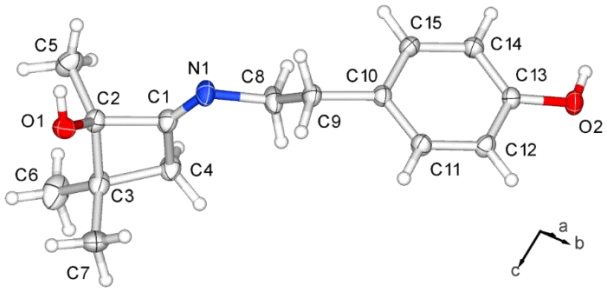


Figure S10. Ellipsoid plot and atomic labelling scheme of compound **5**y. Thermal ellipsoids are drawn at 50% probability level.

Single crystals of compound **5**y were grown by diffusion of hexane vapour on a chloroform solution of the title compound. An X-ray diffraction analysis established compound **5**y as racemate crystallized in the monoclinic centrosymmetric space group $P2_1/n$ featuring the two enantiomers related by symmetry (Figure S10, Table S11). Adjacent molecules interact via self-complementary O–H···N interactions between the hydroxyl group (O1–H1 and the iminic N-atom (interaction *a* in Figure S14) determining a $R_2^2(10)$ hydrogen-bonding motif.[4] The presence of an additional hydroxyl group at the *para*-substituted phenyl moiety further decorates the crystal packing with a strong hydrogen bond of the type O–H···O (interaction *b* in Figure S11).

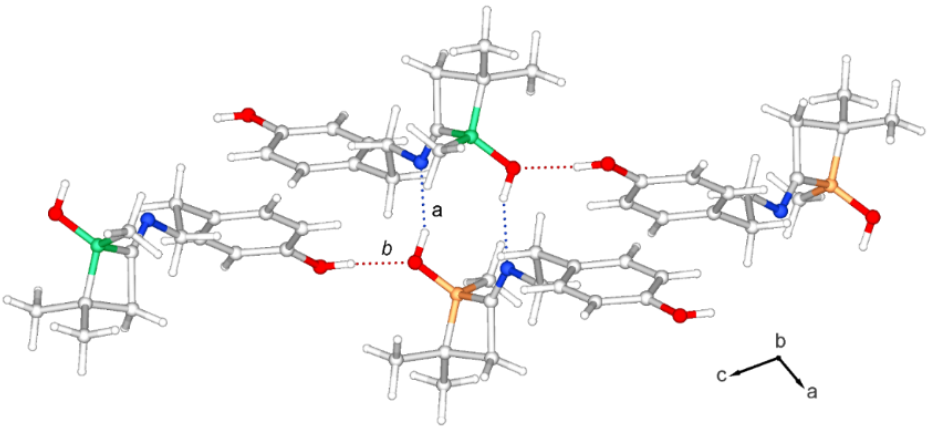


Figure S11. Intermolecular interactions found in the crystal structure of racemate **5**y showing the stereogenic centers in orange and green, respectively. Interactions: a) O1–H1 = 0.84(2); H1 · · ·N1^{i} = 1.90(2); O1 · · · N1^{i} = 2.700(2) Å; O1–H1 · · ·N1^{i} = 159(3)°; *b*) O2^{ii}–H2^{ii} = 0.85(3); H2^{ii} · · ·O1 = 1.87(3); O2^{ii} · · ·O1 = 2.718(2) Å; O2^{ii}–H2^{ii} · · ·O1 = 173(2)°. Symmetry codes: ^{i} = −*x*, 1−*y*, 1−*z*; ^{ii} = −1/2+*x*, 3/2−*y*, 1/2+*z*].

Compound **5**z *CCDC deposition number:* ***2373556***

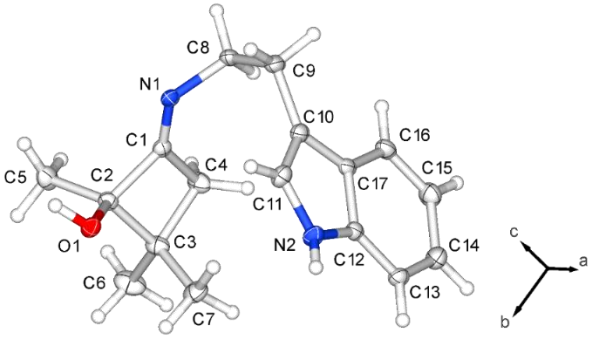


Figure S12. Ellipsoid plot and atomic labelling scheme of compound **5**z. Thermal ellipsoids are drawn at 50% probability level.

Single-crystal X-ray diffraction analysis of compound **5**z revealed that crystallized in the monoclinic space group $P2_1/c$ (Figure S12, Table S14). Similarly to what observed in the case of compound **5**y, compound **5**z is a racemate with the asymmetric unit consisting of a single enantiomer featuring a remarkable folded conformation (Figure S12). It is worth mention that both enantiomers are present in equal amounts in the crystals since they are related by symmetry. The same hydrogen-bonding motif $\mathrm{R}_2^2(10)$ observed for compound **5**y is found in the crystal structure of compound **5**z (interaction *a* in Figure S13) revealing its predominant role in the crystal packing for both compounds. Worthy of note, the presence of indole groups in the latter case extends the dimensionality of the hydrogen-bonded network through N–H···O interactions (interaction *b* in Figure S13) generating ribbons developing along the *c*-axis (Figure S8). It is noteworthy that the crystal structures of imine-cyclobutan-1-ol have never been reported in the literature, and compounds **5**y and **5**z are the first examples of such derivatives to be structurally characterized.

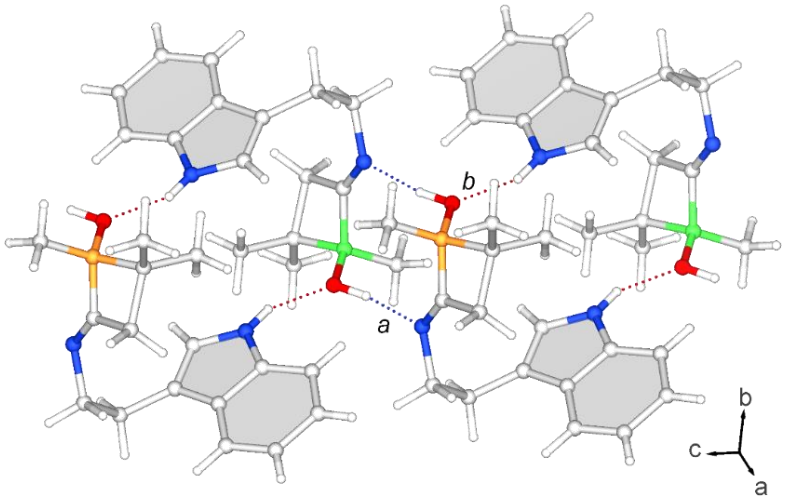


Figure S13 Intermolecular interactions found in the crystal structure of compound **5**z showing the stereogenic centers in orange and green, respectively. Interactions: *a*) O1–H1 = 0.90(2); H1 · · · N1^{i} = 1.87(2); O1 · · · N1^{i} = 2.757(2) Å; O1–H1 · · · N1^{i} = 167(2)°; *b*) N2^{ii}–H2^{ii} = 0.90(2); H2^{ii} · · · O1 = 2.07(2); N2^{ii} · · · O1 = 2.929(2) Å; N2^{ii}–H2^{ii} · · · O1 = 159(2)°. Symmetry codes: ^{ii} = −*x*, 1−*y*, 1−*z*; ^{i} = −*x*, 1−*y*, 2−*z*.

a) b)

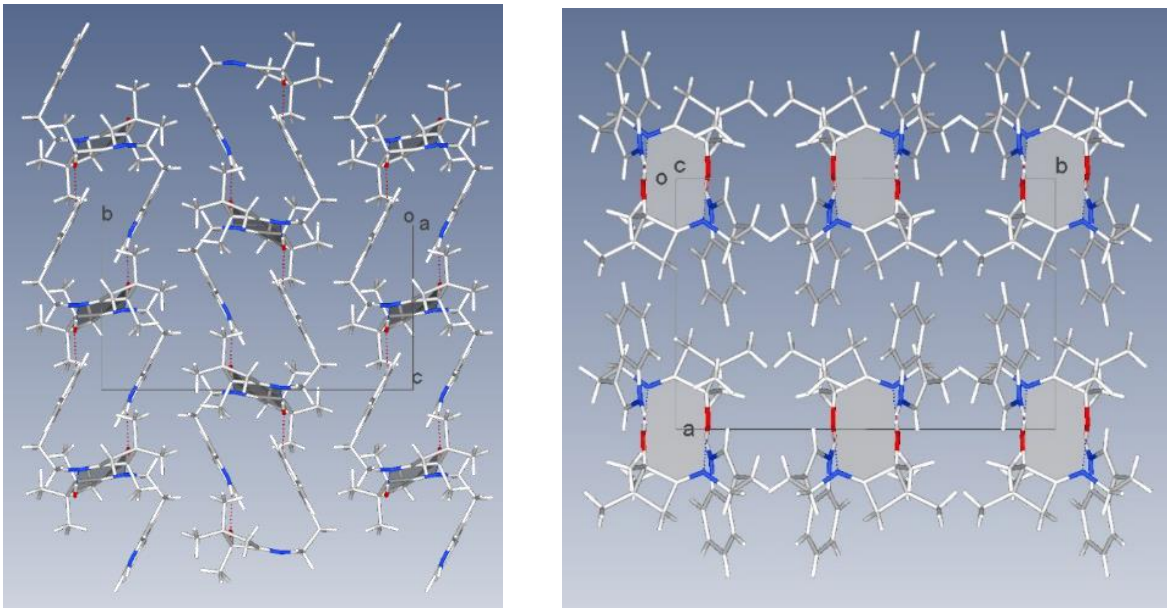


Figure S14 Partial view of the packing diagrams for **5**z showing the relative orientation of adjacent hydrogen-bonded ribbons along the *a*- (a) and the *c*-axis (b) with $R_2^2(10)$ motifs depicted in grey.

Table S9 Crystal data and structure refinement parameters for compounds **4**r , **5**y and **5**z.

Compound	**4**r	**5**y	**5**z
Empirical formula	$C_{15}H_{16}N_2O$	$C_{15}H_{21}NO_2$	$C_{17}H_{22}N_2O$
Formula weight	240.30	247.33	270.36
Temperature/K	100(2)	100(2)	100(2)
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	*Pbca*	$P2_1/n$	$P2_1/c$
a/Å	9.2850(3)	9.6259(3)	10.9369(3)
b/Å	14.3459(4)	11.2341(3)	16.1988(5)
c/Å	18.9431(5)	13.6882(4)	8.7551(2)
α/°	90	90	90
β/°	90	109.5000(10)	101.1140(10)
γ/°	90	90	90
Volume/Å^3	2523.25(13)	1395.32(7)	1522.00(7)
Z	8	4	4
ρ_{calc} g/cm^3	1.265	1.177	1.180
μ/mm^{-1}	0.081	0.077	0.074
Crystal size/mm^3	0.45 × 0.14 × 0.02	0.30 × 0.08 × 0.08	0.51 × 0.12 × 0.02
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	5.652 - 56.572	4.544 - 56.59	5.368 - 56.59
Reflections collected	30814	32973	37962
Independent reflections	3122	3460	3780
Data/restraints/parameters	3122/0/167	3460/0/172	3780/0/190
GooF on F^2	1.029	1.077	1.050
Final R indexes [I ≥ 2σ (I)]	R_1 = 0.0399, wR_2 = 0.0965	R_1 = 0.0590, wR_2 = 0.1455	R_1 = 0.0388, wR_2 = 0.0969
Final R indexes [all data]	R_1 = 0.0520, wR_2 = 0.1058	R_1 = 0.0672, wR_2 = 0.1509	R_1 = 0.0445, wR_2 = 0.1014
Largest diff. peak/hole / e Å^{-3}	0.29/−0.20	0.72/−0.28	0.37/−0.20

Table S10 Bond lengths (Å) for compound **4**r .

O1–C3	1.2149(14)	C4–C3	1.4989(17)
N2–C15	1.3163(15)	C4–C6	1.5186(17)
N2–C7	1.3725(14)	C4–C5	1.5222(17)
N1–C4	1.4236(15)	C3–C2	1.5045(17)
N1–C7	1.3745(15)	C9–C10	1.4188(16)
C8–C9	1.4092(16)	C6–C5	1.4856(18)
C8–C7	1.3793(16)	C13–C12	1.3670(18)
C14–C9	1.4180(16)	C10–C11	1.3656(17)
C14–C15	1.4113(16)	C2–C1	1.5203(19)
C14–C13	1.4165(16)	C11–C12	1.4129(18)

Table S11 Bond angles (°) for compound **4**r .

C15–N2–C7	118.03(10)	C8–C9–C14	118.19(10)
C7–N1–C4	123.09(10)	C8–C9–C10	123.93(11)
C7–C8–C9	119.53(10)	C14–C9–C10	117.87(11)
C15–C14–C9	117.33(10)	N2–C15–C14	124.41(11)
C15–C14–C13	122.15(11)	N2–C7–N1	113.04(10)
C13–C14–C9	120.52(11)	N2–C7–C8	122.46(10)
N1–C4–C3	118.33(10)	N1–C7–C8	124.49(10)
N1–C4–C6	116.82(10)	C5–C6–C4	60.88(8)
N1–C4–C5	118.58(10)	C12–C13–C14	119.98(11)
C3–C4–C6	115.02(10)	C6–C5–C4	60.64(8)
C3–C4–C5	115.76(10)	C11–C10–C9	120.55(12)
C6–C4–C5	58.49(8)	C3–C2–C1	113.50(11)
O1–C3–C4	120.66(11)	C10–C11–C12	121.26(12)
O1–C3–C2	122.05(11)	C13–C12–C11	119.79(11)
C4–C3–C2	117.30(10)		

Table S12 Bond lengths (Å) for compound **5**y.

O1–C2	1.406(2)	C3–C7	1.533(3)
O2–C13	1.3654(19)	C8–C9	1.523(3)
N1–C1	1.256(2)	C9–C10	1.510(2)
N1–C8	1.462(2)	C10–C11	1.390(2)
C1–C2	1.520(2)	C10–C15	1.392(2)
C1–C4	1.516(2)	C11–C12	1.389(2)
C2–C3	1.570(2)	C12–C13	1.386(2)
C2–C5	1.523(2)	C13–C14	1.391(2)
C3–C4	1.561(2)	C14–C15	1.388(2)
C3–C6	1.513(3)		

Table S13 Bond angles (°) for compound **5**y.

C1–N1–C8	118.27(15)	C7–C3–C4	109.80(16)
N1–C1–C2	130.10(16)	C1–C4–C3	87.28(13)
N1–C1–C4	137.50(16)	N1–C8–C9	111.40(14)
C4–C1–C2	92.33(13)	C10–C9–C8	111.44(14)
O1–C2–C1	117.34(14)	C11–C10–C9	121.91(15)
O1–C2–C3	114.32(14)	C11–C10–C15	117.67(15)
O1–C2–C5	110.66(15)	C15–C10–C9	120.39(15)
C1–C2–C3	86.84(13)	C12–C11–C10	121.37(15)
C1–C2–C5	111.20(15)	C13–C12–C11	120.10(15)
C5–C2–C3	114.77(15)	O2–C13–C12	117.81(15)
C4–C3–C2	88.74(13)	O2–C13–C14	122.75(15)
C6–C3–C2	119.34(16)	C12–C13–C14	119.44(15)
C6–C3–C4	117.36(17)	C15–C14–C13	119.72(15)
C6–C3–C7	109.85(18)	C14–C15–C10	121.63(16)
C7–C3–C2	110.08(15)		

Table S14 Bond lengths (Å) for compound **5**z.

O1–C2	1.4101(12)	C13–C14	1.3808(16)
N1–C1	1.2598(14)	C17–C10	1.4391(15)
N1–C8	1.4650(13)	C17–C16	1.4017(15)
N2–C12	1.3720(14)	C10–C9	1.4979(14)
N2–C11	1.3822(14)	C10–C11	1.3638(16)
C1–C2	1.5285(14)	C16–C15	1.3809(17)
C1–C4	1.5221(15)	C9–C8	1.5320(15)
C12–C13	1.3937(15)	C4–C3	1.5610(15)
C12–C17	1.4146(14)	C3–C7	1.5232(16)
C2–C3	1.5763(15)	C3–C6	1.5206(16)
C2–C5	1.5251(15)	C14–C15	1.4040(17)

Table S15 Bond angles (°) for compound **5**z.

C1–N1–C8	118.62(9)	C16–C17–C10	134.07(10)
C12–N2–C11	108.22(9)	C17–C10–C9	126.30(10)
N1–C1–C2	130.52(10)	C11–C10–C17	106.22(9)
N1–C1–C4	137.17(10)	C11–C10–C9	127.48(10)
C4–C1–C2	92.20(8)	C15–C16–C17	118.94(10)
N2–C12–C13	129.87(10)	C10–C9–C8	113.03(9)
N2–C12–C17	108.02(9)	C1–C4–C3	87.62(8)
C13–C12–C17	122.09(10)	C10–C11–N2	110.64(10)
O1–C2–C1	116.91(8)	N1–C8–C9	109.86(9)
O1–C2–C3	114.12(8)	C4–C3–C2	88.95(8)
O1–C2–C5	111.13(9)	C7–C3–C2	111.01(9)
C1–C2–C3	86.85(8)	C7–C3–C4	110.56(10)
C5–C2–C1	110.81(8)	C6–C3–C2	117.69(10)
C5–C2–C3	115.15(9)	C6–C3–C4	116.58(9)
C14–C13–C12	117.57(10)	C6–C3–C7	110.45(10)
C12–C17–C10	106.89(9)	C13–C14–C15	121.30(11)
C16–C17–C12	118.99(10)	C16–C15–C14	121.10(11)

Compound 8 *CCDC deposition number*: ***2387960***

Compound 8 crystallized in the orthorhombic space group $Pca2_1$ with two crystallographically independent molecules in the asymmetric unit (Figure S15). Both molecules adopt a planar conformation and participate in intermolecular π-π stacking interactions with neighbouring molecules (Figure S16a) resulting in an alternating double-row arrangement as shown in Figure S16b.

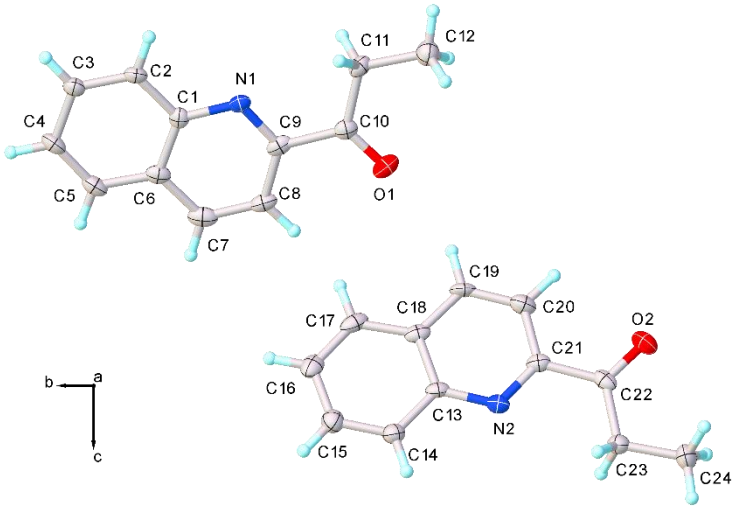


Figure S15. Ellipsoid plot and atomic labelling scheme of compound 8. Thermal ellipsoids are drawn at 50% probability level.

a) b)

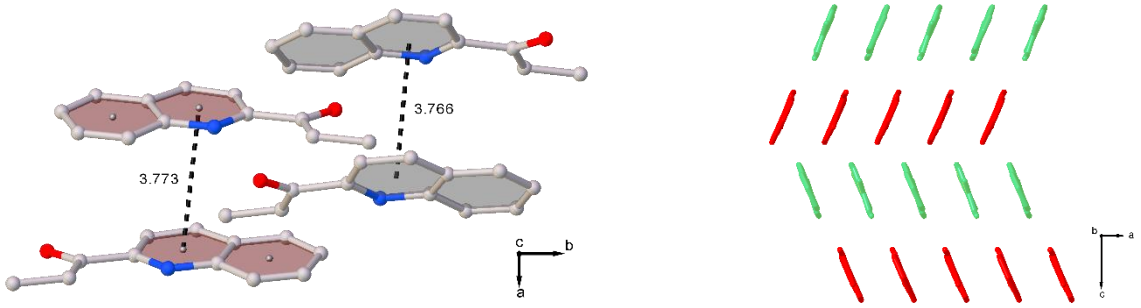


Figure S16. a) Intermolecular π-π stacking interactions observed in the crystal structure of compound 8, with intercentroid distances reported in Å; b) view of the crystal packing of 8 along the *b*-axis, with molecules coloured according to their symmetry equivalence.

Table S16. Crystal data and structure refinement parameters for compound 8.

Empirical formula	$C_{12}H_{11}NO$
Formula weight	185.22
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$Pca2_1$
a/Å	7.4979(5)
b/Å	11.2676(6)
c/Å	22.4890(12)
α, β, γ /°	90
Volume/Å^3	1899.95(19)
Z	8
Z'	2
ρ_{calc}g/cm^3	1.295
μ/mm^{-1}	0.083
Crystal size/mm^3	0.37 × 0.04 × 0.02
Radiation	Mo*K*α (λ = 0.71073)
2θ range for data collection/°	5.118 to 52.744
Reflections collected	19847
Independent reflections	3863 [R_{int} = 0.0970, R_{sigma} = 0.0653]
Data/restraints/parameters	3863/1/255
Goodness of Fit on F^2	1.033
Final R indexes [I ≥ 2σ (I)]	R_1 = 0.0503, wR_2 = 0.1142
Final R indexes [all data]	R_1 = 0.0740, wR_2 = 0.1285
Largest diff. peak/hole / e Å^{-3}	0.17/−0.25
Flack parameter	0.5(10)

Table S17. Bond lengths (Å) for 8.

O2–C22	1.224(5)	C1–C2	1.413(7)
O1–C10	1.212(6)	C18–C13	1.419(7)
N1–C1	1.369(8)	C18–C17	1.413(7)
N1–C9	1.328(6)	C13–C14	1.419(7)
N2–C21	1.309(6)	C5–C6	1.414(7)
N2–C13	1.367(8)	C5–C4	1.353(7)
C21–C20	1.409(6)	C6–C7	1.412(8)
C21–C22	1.510(7)	C2–C3	1.368(6)
C10–C11	1.502(7)	C8–C7	1.366(7)
C10–C9	1.510(7)	C8–C9	1.408(7)
C19–C18	1.417(7)	C4–C3	1.426(7)
C19–C20	1.364(6)	C14–C15	1.366(7)
C23–C22	1.499(6)	C15–C16	1.402(8)
C23–C24	1.516(6)	C16–C17	1.376(8)
C1–C6	1.417(7)	C11–C12	1.519(6)

Table S18. Bond angles (°) for 8.

C9–N1–C1	116.6(4)	C5–C6–C1	119.2(5)
C21–N2–C13	118.2(4)	C7–C6–C1	117.4(5)
N2–C21–C20	123.5(5)	C7–C6–C5	123.4(5)
N2–C21–C22	116.9(4)	C3–C2–C1	120.9(4)
C20–C21–C22	119.6(5)	C7–C8–C9	118.2(5)
O1–C10–C11	122.5(5)	C19–C20–C21	119.4(5)
O1–C10–C9	120.6(5)	C5–C4–C3	120.1(5)
C11–C10–C9	116.8(4)	C15–C14–C13	119.7(4)
C20–C19–C18	119.2(5)	C2–C3–C4	119.9(5)
C22–C23–C24	113.1(4)	C14–C15–C16	121.4(5)
N1–C1–C6	123.1(4)	C17–C16–C15	119.8(5)
N1–C1–C2	118.2(4)	C16–C17–C18	120.7(5)
C2–C1–C6	118.7(5)	C8–C7–C6	119.9(6)
C19–C18–C13	117.3(5)	C10–C11–C12	114.1(4)
C17–C18–C19	124.0(5)	O2–C22–C21	119.6(5)
C17–C18–C13	118.8(5)	O2–C22–C23	123.5(5)
N2–C13–C18	122.4(4)	C23–C22–C21	116.9(4)
N2–C13–C14	118.0(4)	N1–C9–C10	115.5(4)
C18–C13–C14	119.6(5)	N1–C9–C8	124.8(5)
C4–C5–C6	121.1(5)	C8–C9–C10	119.7(4)

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