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Multiphase Photochemistry in Flow Mode via an Integrated Continuous Stirred Tank Reactor (CSTR) Approach

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General materials and methods

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Also, unless otherwise stated, all substrates and reagents were purchased from Fluorochem or Sigma-Aldrich and used as received.

^{1}H NMR spectra were recorded on 400 and 500 MHz instruments and are reported relative to the residual solvent: $CHCl_3$ (δ 7.26 ppm). ^{13}C{1H} NMR spectra were recorded on the same instruments (100 and 125 MHz) and are reported relative to $CHCl_3$ (δ 77.0 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ/ ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br s = broad singlet, app = apparent. Data for ^{13}C{1H} NMR are reported in terms of chemical shift (δ/ppm) and multiplicity (C, CH, CH_2, or CH_3).

High-resolution mass spectrometry was performed using the indicated techniques on a micromass LCT orthogonal time-of-flight mass spectrometer with leucine-enkephalin (Tyr-Gly- Phe-Leu) as an internal lock mass.

Spectra were recorded on a Waters GCT Premier Mass Spectrometer calibrated using perfluorotributylamine (PFTBA / FC-43) purchased from Sigma Aldrich. Chromatography was carried out with an Agilent 7890A GC equipped with a Agilent DB-5MS capillary column (15m x 0.250mm). A gradient from 40 to 300 °C was used, with an inlet temperature of 160 °C and a split ratio of 1:10.

Continuous flow experiments were performed on a Vapourtec E-Series system equipped with peristaltic pumps. For photochemical experiments one or two CSTRs were used, equipped with a high-power LED (365 nm) regulated between 25-60 W and cooled to 25-40 °C by passing a stream of compressed air directly through the reactor unit or through the dewar containing dry ice.

TLC was performed on Merck pre-coated Silica gel 60 F254 aluminium plates with realisation by UV irradiation at 254 nm, $KMnO_4$ and vanillin stain. Flash chromatography was performed using Macherey-Nagel silica gel 60 M, with a particle range of 0.04 - 0.063 mm.

Synthesis of Starting Materials

The synthesis of *N*-tosylhydrazones was performed according to literature procedures.[1]

General experimental protocols

General procedure A:

A solution of *N*-tosylhydrazone (3 mmol, 1.5 equiv.) and methyl methacrylate (2 mmol, 1 equiv.) in 20 mL of DCM is prepared. Once total solubility is achieved, the solution is degassed with N_2 for 30 seconds. Then, the solution is pumped into the CSTR filled with Cs_2CO_3 (3 mmol, 1.5 eq.) using 1.0 mL/min as flow rate. Beforehand, all the system is stabilised with the corresponding conditions of light intensity (36.7 W), stirring (500 rpm), temperature (≈ 35 °C) and flow rate (1.0 mL/min) for 5 minutes. After 20 min of residence time, the second pump is turned on to withdraw the mixture from the CSTR using 0.7 mL/min as flow rate. The CSTR system is flushed with CH_2Cl_2 to recover all product. The mixture is collected under steady state conditions, quenched by addition of water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was then washed with brine, dried over sodium sulfate, concentrated under vacuum and the yield is calculated. The residue is purified by silica gel flash chromatography (pentane/ethyl acetate) to give the desired product.

General procedure B:

A solution of *N*-tosylhydrazone (2.4 mmol, 1.2 equiv.) and acrylate (2 mmol, 1 equiv.) in 20 mL of DCM is prepared. Once total solubility is achieved, the solution is degassed with N_2 for 30 seconds. Then, the solution is pumped into the CSTR filled with Cs_2CO_3 (2.4 mmol, 1.2 eq.) using 1.0 mL/min as flow rate. Beforehand, the system is stabilised with the corresponding conditions of light intensity (52.0 W), stirring (500 rpm), temperature (≈ 35 °C) and flow rate (1.0 mL/min) for 5 minutes. After 30 min of residence time, the second pump is turned on to withdraw the mixture from the CSTR using 0.7 mL/min as flow rate. The CSTR system is flushed with CH_2Cl_2 to recover all product. The mixture is quenched by addition of water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase is then washed brine, dried over sodium sulfate, concentrated under vacuum and the yield is calculated.

General procedure C (scale up with two CSTRs):

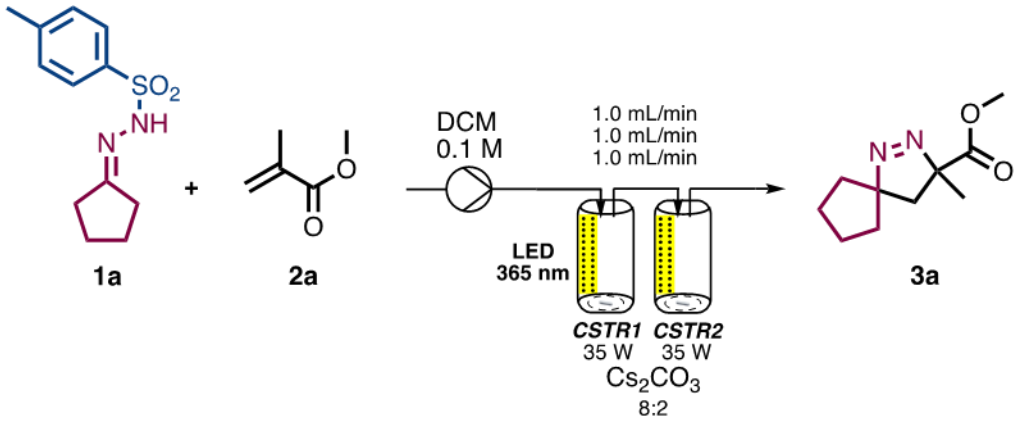
A solution of *N*-tosylhydrazone (15 mmol or 12 mmol, 1.5 or 1.2 equiv.) and acrylate (10 mmol, 1 equiv.) in 100 mL of DCM is prepared. Once total solubility is achieved, the solution is degassed with N_2 for 30 seconds. Then, the solution is pumped in the first CSTR filled with Cs_2CO_3 (12 mmol or 9.6 mmol, 1.2 or 0.96 equiv.) using 1.0 mL/min as flow rate. Beforehand, the system is stabilised with the corresponding conditions of light intensity (36.7 W or 52.0 W), stirring (0.5), temperature (≈ 35 °C) and flow rate (1.0 mL/min) for 5 minutes. After 15 min of residence time, the second pump is turned on to withdraw the mixture from the first CSTR to direct it into the second CSTR filled with Cs_2CO_3 (3 mmol or 2.4 mmol, 0.3 equiv. or 0.24 equiv.), using 1.0 mL/min as flow rate. After 5 min of residence time, the third pump is turned on to withdraw the mixture from the second CSTR to the collecting flask containing water. The CSTR system is flushed with CH_2Cl_2 to recover all product. The mixture is extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase is then washed with brine, dried over sodium sulfate, concentrated under vacuum and the yield is calculated.

General procedure D (with in-line work-up):

A solution of *N*-tosylhydrazone (15 mmol or 12 mmol, 1.5 or 1.2 equiv.) and acrylate (10 mmol, 1 equiv.) in 100 mL of DCM is prepared. Once total solubility is achieved, the solution is degassed with N_2 for 30 seconds. Then, the solution is pumped in the first CSTR filled with Cs_2CO_3 (12 mmol or 9.6 mmol, 1.2 or 0.96 equiv.) using 1.0 mL/min as flow rate. Beforehand, the system is stabilised with the corresponding conditions of light intensity (36.7 W or 52.0 W), stirring (0.5), temperature (≈ 35 °C) and flow rate (1.0 mL/min) for 5 minutes. After 15 min of residence time, the second pump is turned on to withdraw the mixture from the first CSTR to direct it into the second CSTR filled with Cs_2CO_3 (3 mmol or 2.4 mmol, 0.3 equiv. or 0.24 equiv.), using 1.0 mL/min as flow rate. After 5 min of residence time, the third pump is turned on to withdraw the mixture from the second CSTR to a T-piece, where it is mixed with water pumped by a syringe pump at 1.0 mL/min to quench the reaction. The output stream is directed into a Zaiput Flow Technologies Liquid-Liquid Separator (SEP-10) equipped with a hydrophobic PTFE *OB-900* membrane to achieve the in-line work up. The CSTR system is flushed with CH_2Cl_2 to recover all product. The organic phase is dried over sodium sulfate, concentrated under vacuum and the yield is calculated.

Optimisation tables

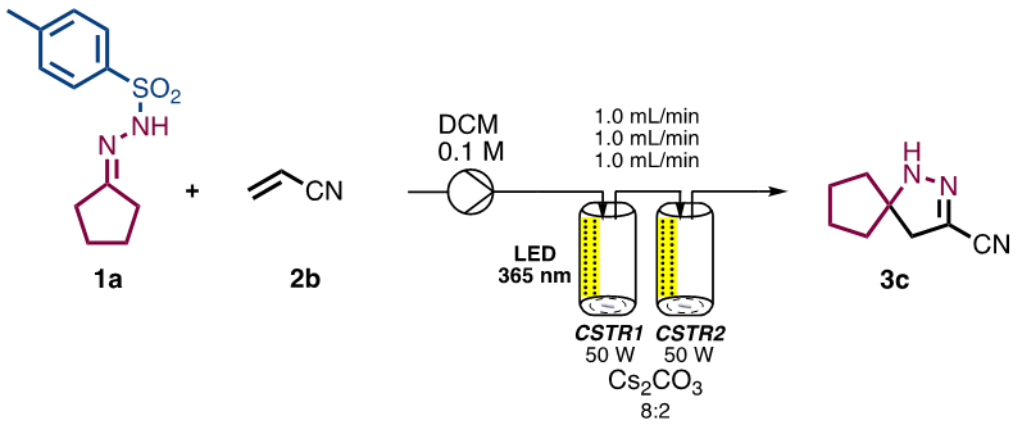
Screening conditions for the synthesis of compound **3a** with two CSTRs:



Entry	Deviations from above conditions	[a] Yield % 3a
1[b]	**none**	**96**
2[c]	17 W each, Cs_2CO_3 7:3	38
3[c]	25 W each, Cs_2CO_3 7:3	60
4[c]	35 W each, Cs_2CO_3 7:3	60
5[c]	25 W each, Cs_2CO_3 8:2	60
6[d]	25 W each, Cs_2CO_3 8:2	75
7[b]	35 W each, Cs_2CO_3 8:2	96

Table S1: All reactions were carried out using two CSTRs equipped with LED 365 nm on 2 mmol scale. [a]Yields of **3a** are calculated by ^{1}H NMR using trichloroethylene as internal standard. [b] Two different dry-ice cooling modules were used. [c] Air cooling was used. [d] One dry-ice cooling module was used.

Screening conditions for the synthesis of compound **3c** with two CSTRs**:**



Entry	Deviations from above conditions	[a] Yield % 3c
1[b]	**none**	**99**
2[b]	35 W each	58
3[b]	1 equiv.	73

Table S2: All reactions were carried out using two CSTRs equipped with LED 365 nm on 2 mmol scale. [a]Yields of **3c** are calculated by ^{1}H NMR using trichloroethylene as internal standard. [b] Two different dry-ice cooling modules were used.

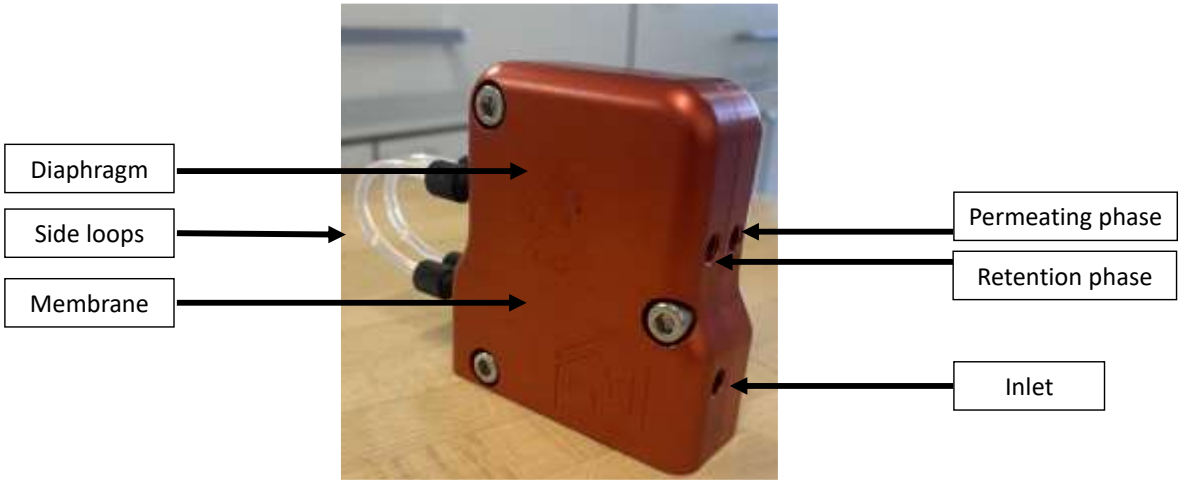
Technical information

CSTR

The Vapourtec E-Series system can operate with a cascade of 2 CSTRs with integrated LED light sources, suitable for flow reactions involving solids. Volume: 50 mL; pressure: up to 5.0 bar; temperature range: -10 °C to +150 °C; stirring: 100 rpm to 1200 rpm; LED sources: 365 nm to 650 nm. The wetted parts are made of glass, PTFE, PFA, Kalrez. Each LED module has an input power up of 70 W. All CSTRs are individually temperature controlled, to provide maximum versatility and the stirring speed can also be set independently for each CSTR.

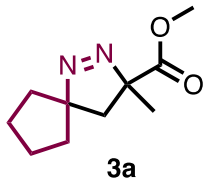
Zaiput Flow Technologies

The Zaiput Liquid-Liquid Separator Sep-10 is a small footprint device designed for separation of immiscible phases at the laboratory scale. This is based on a porous membrane and pressure controller to selectively allow the flow of one phase to permeate through the membrane while retaining the other. Height: 77 mm; width: 77 mm; depth 29 mm.



Characterisation data

3a: Methyl 3-methyl-1,2-diazaspiro[4.4]non-1-ene-3-carboxylate:



3a

Following the general procedure A, using 756.2 mg of *N'*-cyclopentylidene-4-methylbenzenesulfonohydrazide (3 mmol), 213 µL of methyl methacrylate (2 mmol), 370 mg of **3a** (95% yield) were obtained as yellowish oil, isolated after column chromatography using silica gel and pentane/ethyl acetate 8:2 as eluent. The same reaction was performed on 2.6 and 6.6 mmol scale, furnishing 95% and 77% yield, respectively.

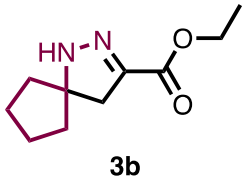
Following the general procedures C and D, the product was obtained on 10 and 15 mmol scale with 97% yield in both cases.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 2.20 – 2.12 (m, 2H), 2.09 (d, *J* = 13.1 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.83 – 1.74 (m, 2H), 1.69 – 1.61 (m, 2H), 1.59 (s, 3H), 1.45 (d, *J* = 13.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (C), 100.5 (C), 94.6 (C), 52.7 (CH_3), 41.4 (CH_2), 38.8 (CH_2), 38.4 (CH_2), 25.8 (CH_2), 25. 6 (CH_2), 23.0 (CH_3).

HRMS (TOF-ES+) calc for $C_{10}H_{17}N_2O_2$ 197.1285, found $(M+H)^+$ 197.1285.

3b: Ethyl 1,2-diazaspiro[4.4]non-2-ene-3-carboxylate:



3b

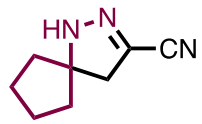
Following the general procedure B, using 605.0 mg of *N'*-cyclopentylidene-4-methylbenzenesulfonohydrazide (2.4 mmol), 213 µL of ethyl acrylate (2 mmol), 389 mg of **3b** (99% yield) were obtained as yellowish oil without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, broad, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.86 (s, 2H), 1.82 – 1.73 (m, 4H), 1.73 – 1.65 (m, 4H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (C), 141.9 (C), 75.2 (C), 61.1 (CH_2), 42.7 (CH_2), 38.9 (CH_2), 29.9 (C), 23.4 (2 CH_2), 14.5 (CH_3).

HRMS (TOF-ES+) calc for $C_{10}H_{17}N_2O_2$ 197.1285, found $(M+H)^+$ 197.1287.

3c: 1,2-Diazaspiro[4.4]non-2-ene-3-carbonitrile:



3c

Following the general procedure B, using 605.0 mg of *N'*-cyclopentylidene-4-methylbenzenesulfonohydrazide (2.4 mmol), 131 µL of acrylonitrile (2 mmol), 295 mg of **3c** (99% yield) were obtained as yellowish oil without further purification.

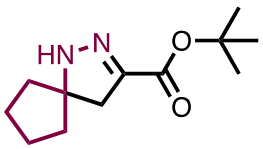
Following the general procedures C and D, the product was obtained on 10 mmol scale with 99% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, broad, 1H), 2.82 (s, 2H), 1.80 – 1.69 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 122.3 (C), 115.3 (C), 74.9 (C), 44.8 (CH_2), 38.8 (2 CH_2), 23.4 (2 CH_2).

HRMS (TOF-ES+) calc for $C_8H_{12}N_3$ 150.1026, found $(M+H)^+$ 150.1026.

3d: *tert*-Butyl 1,2-diazaspiro[4.4]non-2-ene-3-carboxylate:



3d

Following the general procedure B, using 605.0 mg of *N'*-cyclopentylidene-4-methylbenzenesulfonohydrazide (2.4 mmol), 292 µL of *tert*-butyl acrylate (2 mmol), 442 mg of **3d** (99% yield) were obtained as yellowish oil without further purification.

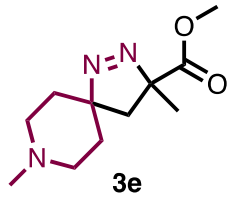
Following the general procedures C, the product was obtained on 10 mmol scale with 99% yield.

^{1}H NMR (400 MHz,$CDCl_3$) δ 5.95 (s, 1H), 2.81 (s, 2H), 1.77 – 1.66 (m, 8H), 1.54 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5 (C), 143.5 (C), 81.5 (C), 74.9 (C), 42.8 (CH_2), 38.9 (2 CH_2), 28.3 (3 CH_3), 23.4 (2 CH_2).

HRMS (TOF-ES+) calc for $C_{12}H_{21}N_2O_2$ 225.1598, found $(M+H)^+$ 225.1600.

3e: Methyl 3,8-dimethyl-1,2,8-triazaspiro[4.5]dec-1-ene-3-carboxylate:



3e

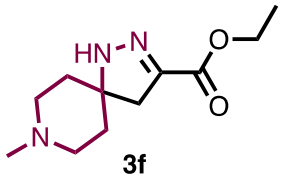
Following the general procedure A, using 844.1 mg of 4-methyl-*N'*-(1-methylpiperidin-4-ylidene)benzenesulfonohydrazide (3 mmol), 213 µL of methyl methacrylate (2 mmol), 382 mg of **3e** (85% yield) were obtained as orange oil, isolated after column chromatography using silica gel and pentane/ethyl acetate 1:1 as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 2.95 – 2.86 (m, 2H), 2.34 (s, 3H), 2.20 (d, *J* = 18.4 Hz, 4H), 2.02 (d, *J* = 13.1 Hz, 1H), 1.64 (s, 3H), 1.30 (d, *J* = 13.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (C), 95.3 (C), 93.9 (C), 53.1 (CH_3), 52.9 (CH_2), 52.9 (CH_2), 46.3 (CH_3), 39.5 (CH_2), 36.3 (CH_2), 35.3 (CH_2), 24.3 (CH_3).

HRMS (TOF-ES+) calc for $C_{11}H_{20}N_3O_2$ 226.1550, found $(M+H)^+$ 226.1552.

3f: Ethyl 8-methyl-1,2,8-triazaspiro[4.5]dec-2-ene-3-carboxylate:



3f

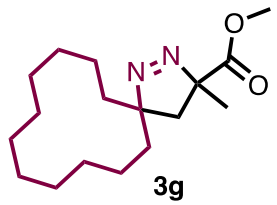
Following the general procedure B, using 674.0 mg of 4-methyl-*N*′-(1-methylpiperidin-4-ylidene)benzenesulfonohydrazide (2.4 mmol), 213 µL of ethyl acrylate (2 mmol), 445 mg of **3f** (99% yield) were obtained as orange oil without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, broad, 1H), 4.32 – 4.27 (m, 2H), 2.76 (s, 2H), 2.57 – 2.44 (m, 2H), 2.37 (d, *J* = 15.8 Hz, 2H), 2.29 (s, 3H), 1.77 (t, *J* = 5.7 Hz, 4H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (C), 141.8 (C), 61.2 (CH_2), 52.8 (2 CH_2), 46.2 (CH_3), 36.3 (2 CH_2), 29.8 (C), 14.5 (CH_3).

HRMS (TOF-ES+) calc for $C_{11}H_{20}N_3O_2$ 226.1550, found 226.1552.

3g: Methyl 3-methyl-1,2-diazaspiro[4.11]hexadec-1-ene-3-carboxylate:



3g

Following the general procedure A, using 1051.6 mg of *N*′-cyclododecylidene-4-methylbenzenesulfonohydrazide (3 mmol), 213 µL of methyl methacrylate (2 mmol), 399 mg of **3g**

(68% yield) were obtained as yellowish oil, isolated after column chromatography using silica gel and pentane/ethyl acetate 8:2 as eluent.

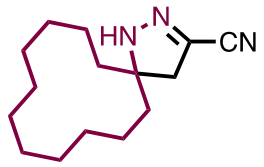
Following the general procedure C, the product was obtained on 10 mmol scale with 96% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 1.96 (d, *J* = 13.1 Hz, 1H), 1.92 – 1.78 (m, 2H), 1.73 – 1.64 (m, 2H), 1.62 (s, 3H), 1.49 – 1.32 (m, 18H), 1.24 (d, *J* = 13.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C), 99.2 (C), 95.2 (C), 52.9 (CH_3), 40.0 (CH_2), 34.2 (CH_2), 33.2 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.1 (2 CH_2), 24.3 (CH_2), 22.8 (2 CH_2), 22.3 (CH_3), 20.1 (CH_2), 19.9 (CH_2).

HRMS (TOF-ES+) calc for $C_{17}H_{31}N_2O_2$ 295.2380, found $(M+H)^+$ 295.2381.

3h: 1,2-Diazaspiro[4.11]hexadec-2-ene-3-carbonitrile:



3h

Following the general procedure B, using 1051.6 mg of *N*'-cyclododecylidene-4-methylbenzenesulfonohydrazide (3 mmol), 131 µL of acrylonitrile (2 mmol), 490 mg of **3h** (99% yield) were obtained as yellowish oil without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, broad, 1H), 2.64 (s, 2H), 1.37 (m, 22H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 122.7 (C), 115.4 (C), 71.2 (C), 44.3 (CH_2), 32.3 (2 CH_2) 26.3 (2 CH_2), 26.0 (CH_2), 22.6 (2 CH_2), 22.1 (2 CH_2), 19.5 (2 CH_2).

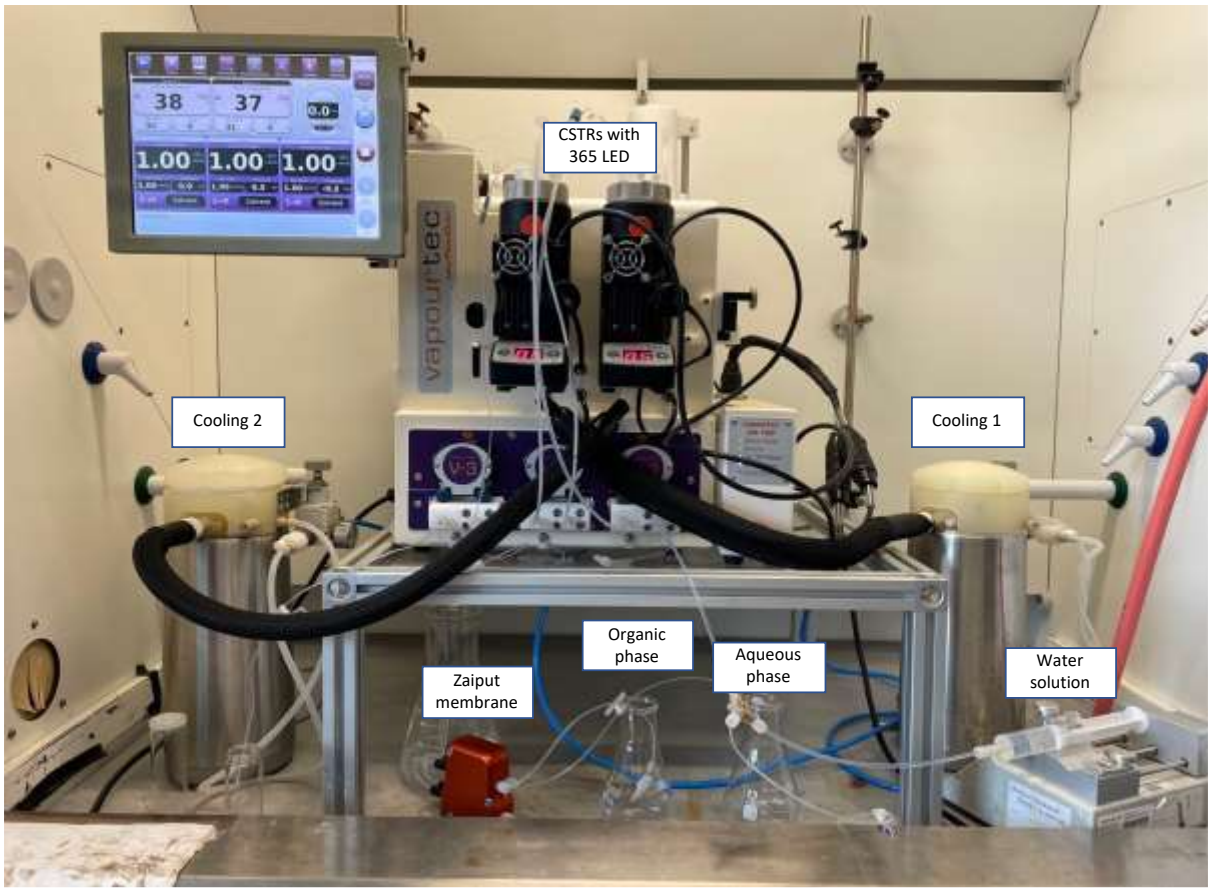
HRMS (TOF-ES+) calc for $C_{15}H_{26}N_3$ 248.2121, found $(M+H)^+$ 248.2123.

References

1) Allwood, D. M., Blakemore, D. C., Ley, S. V., *Org. Lett.* **2014**, *16*, 3064–3067.

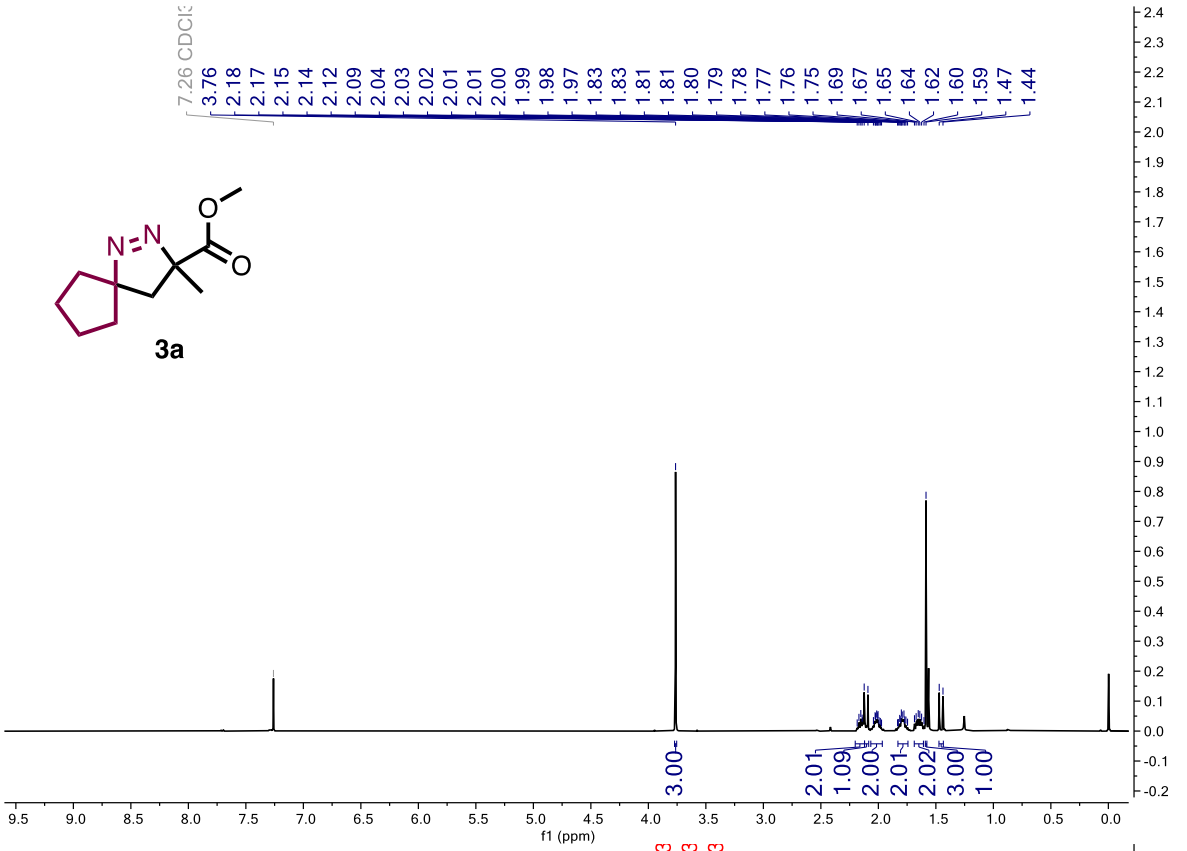
Picture of the flow experiment

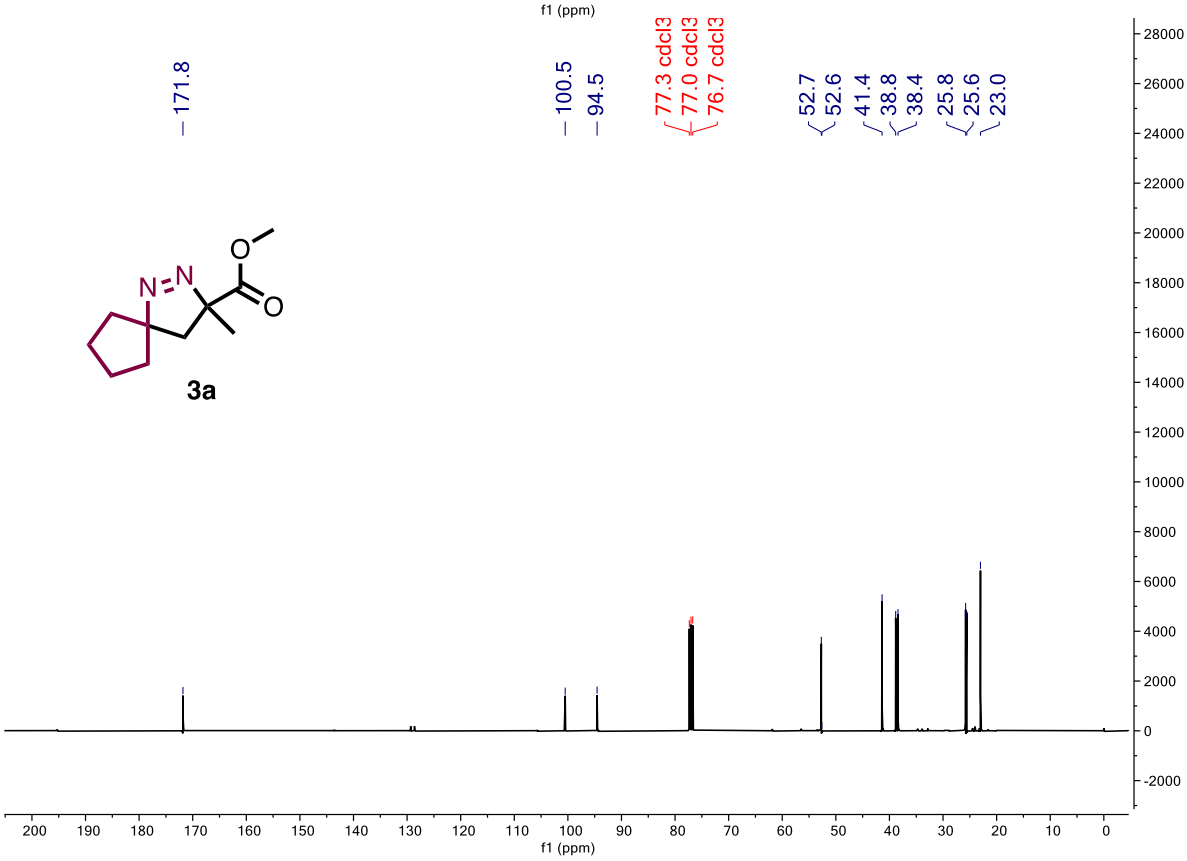
Photo-CSTR cascade with integrated in-line work up using Zaiput membrane technology.



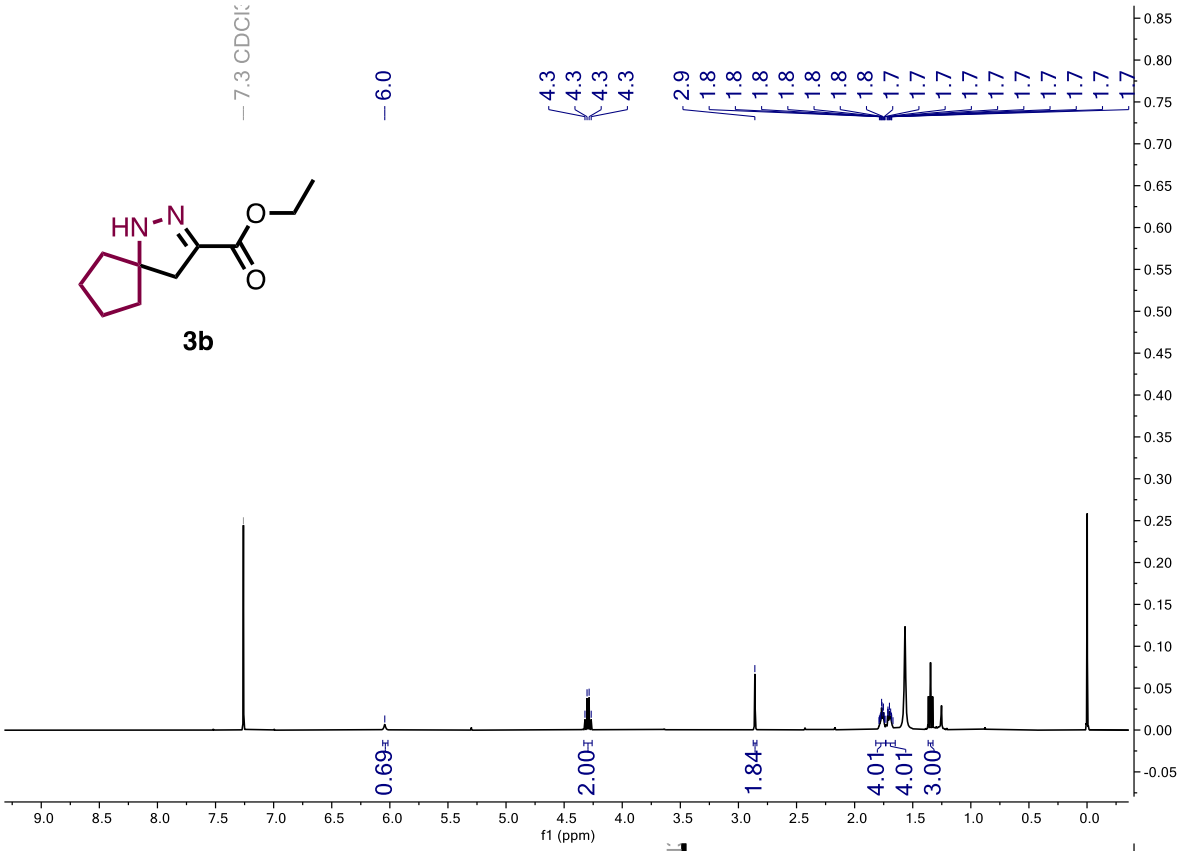
Copies of NMR Spectra of Products

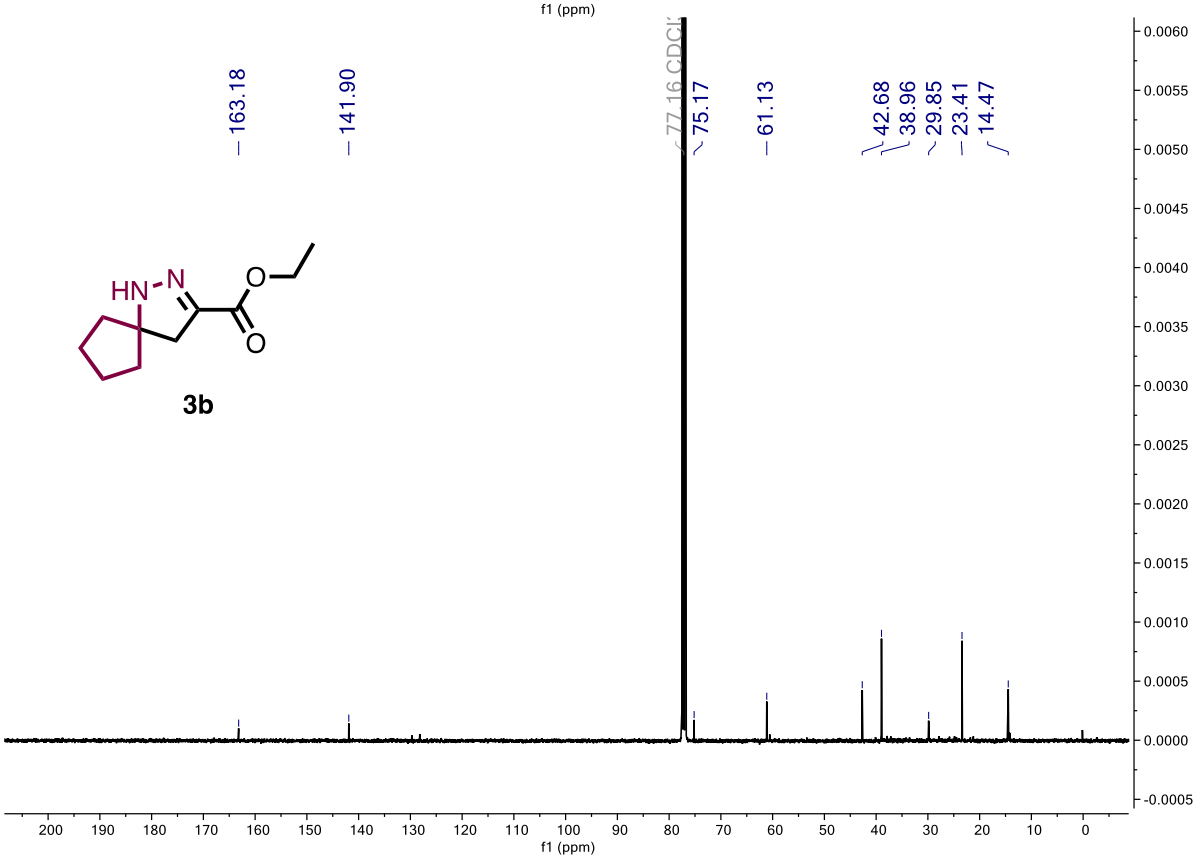
^{1}H and ^{13}C of compound **3a**



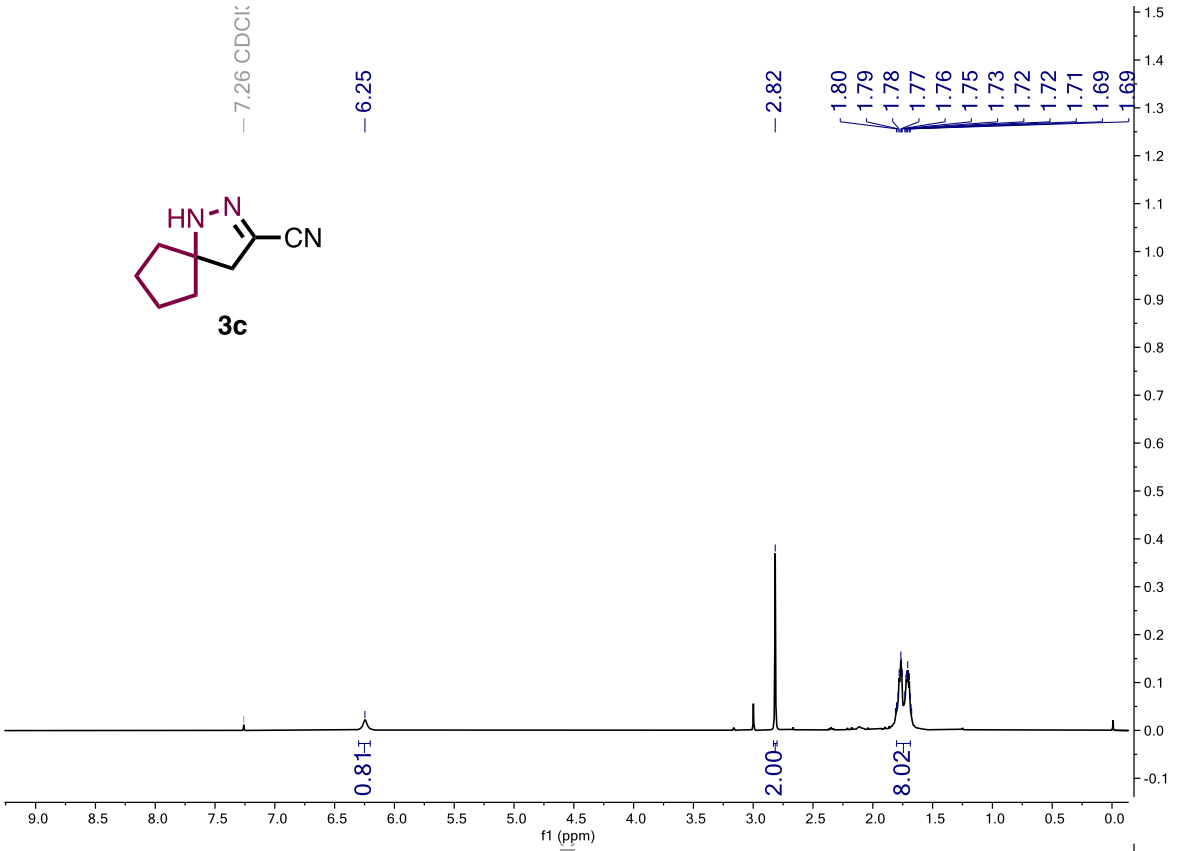


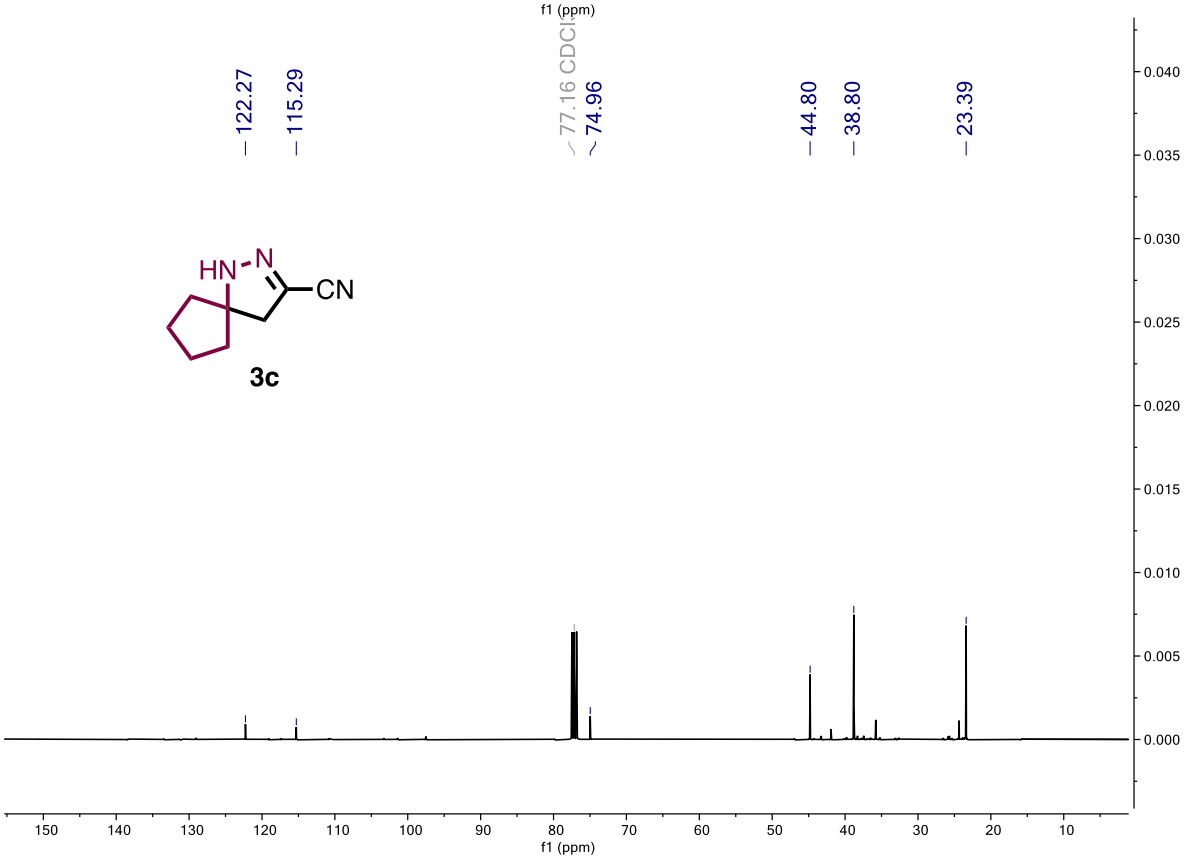
^{1}H and ^{13}C of compound **3b**



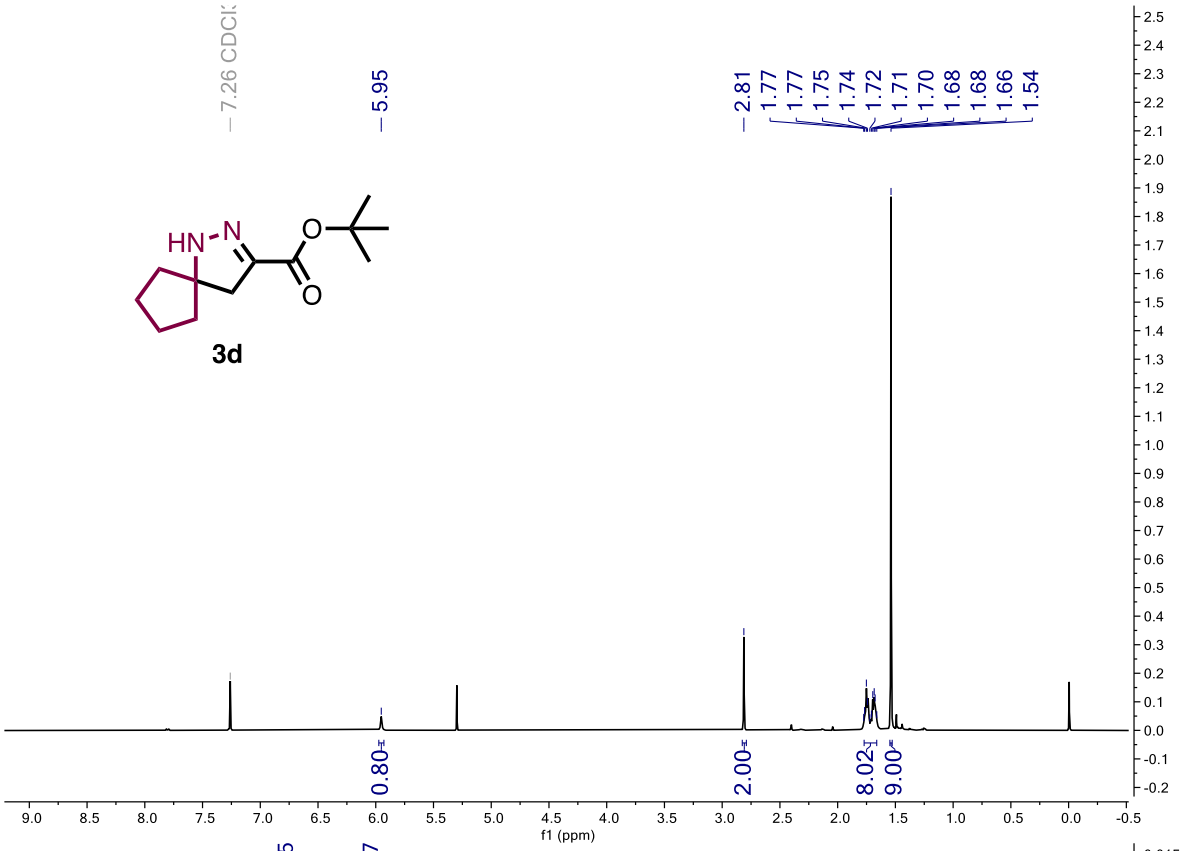


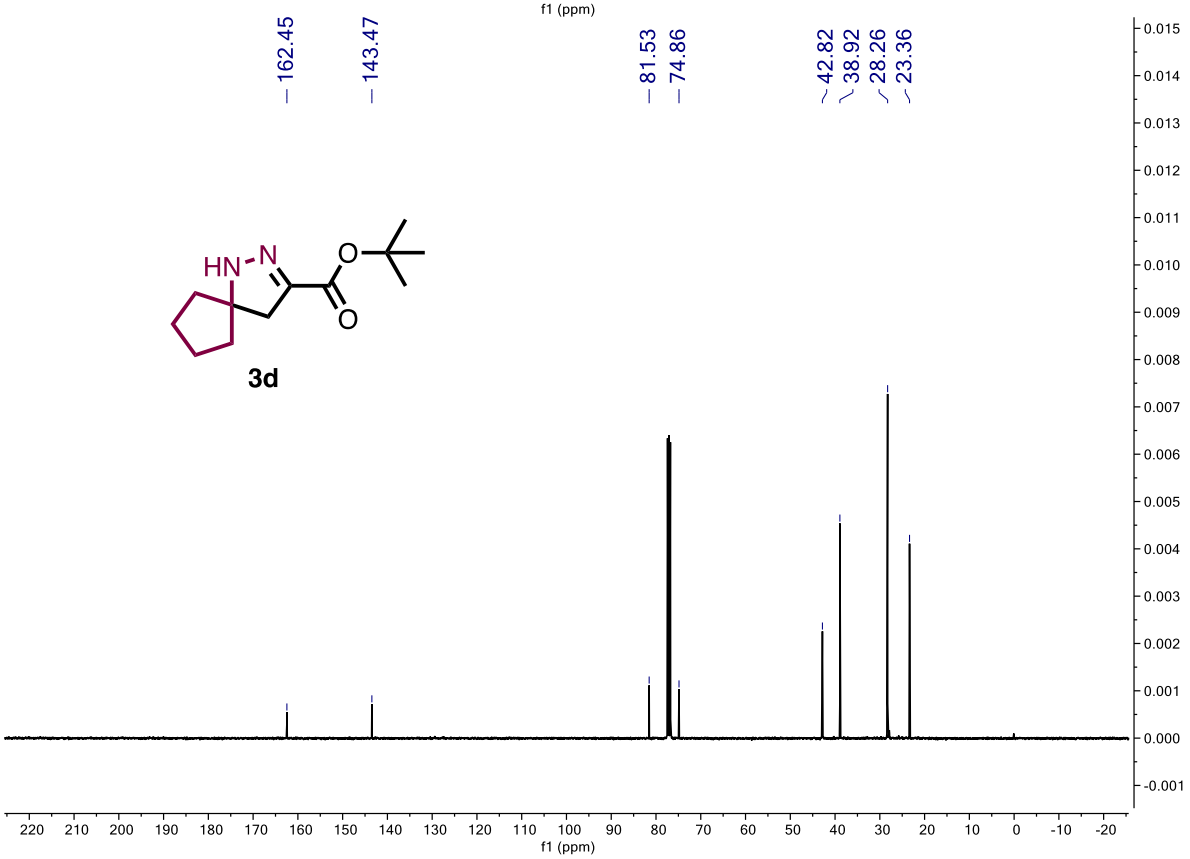
^{1}H and ^{13}C of compound **3c**



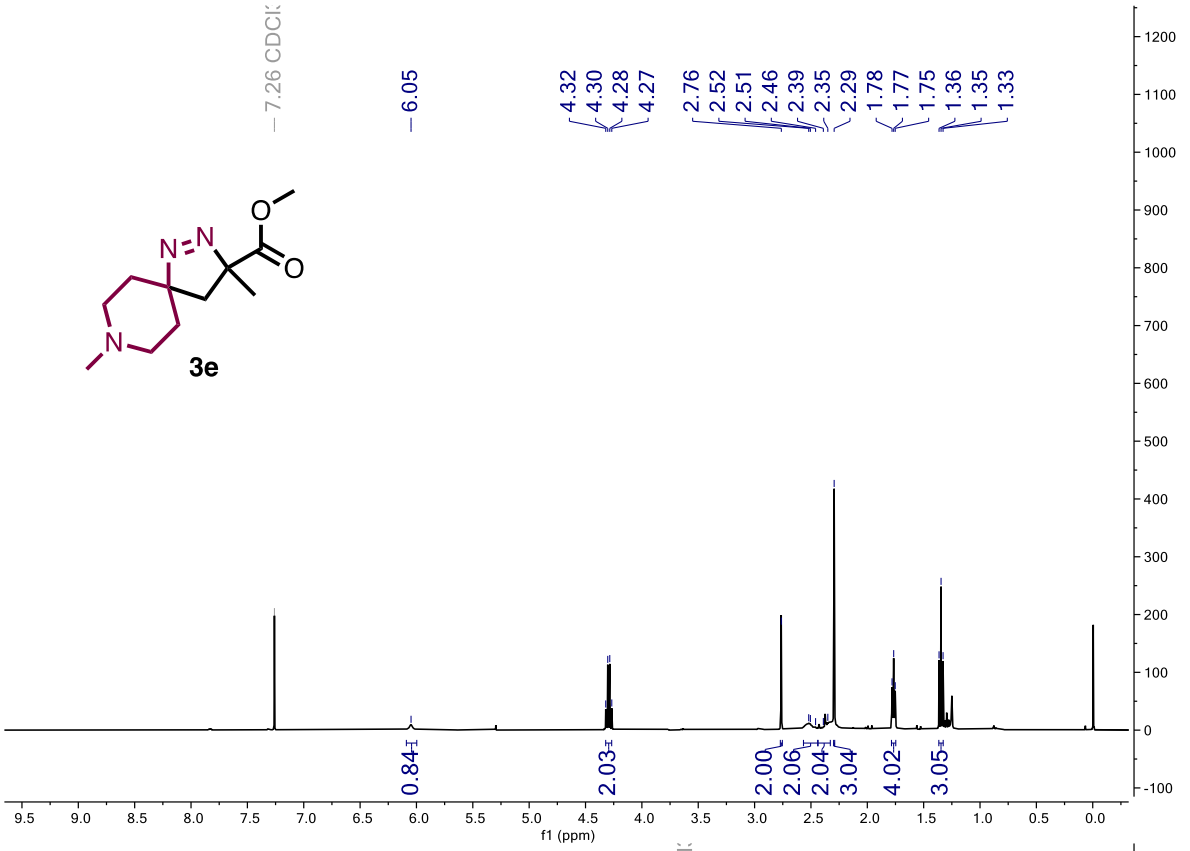


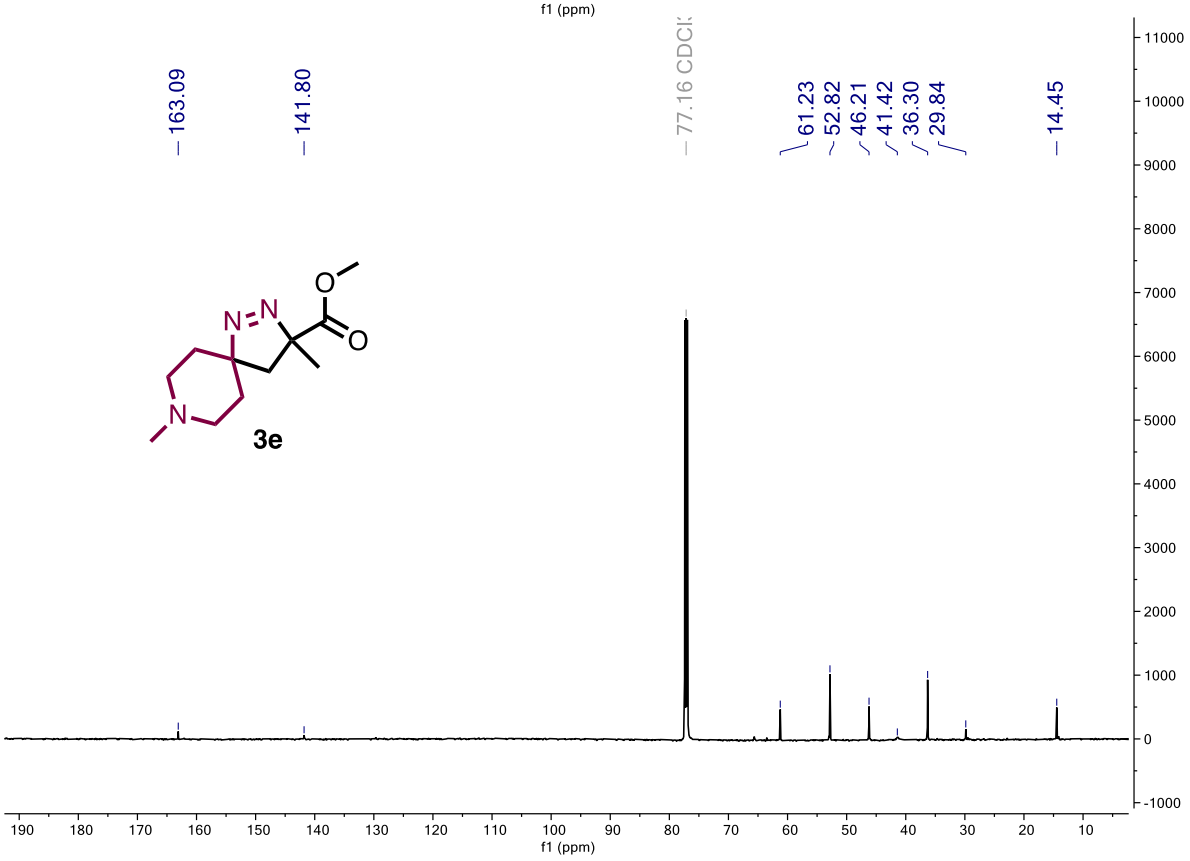
^{1}H and ^{13}C of compound **3d**



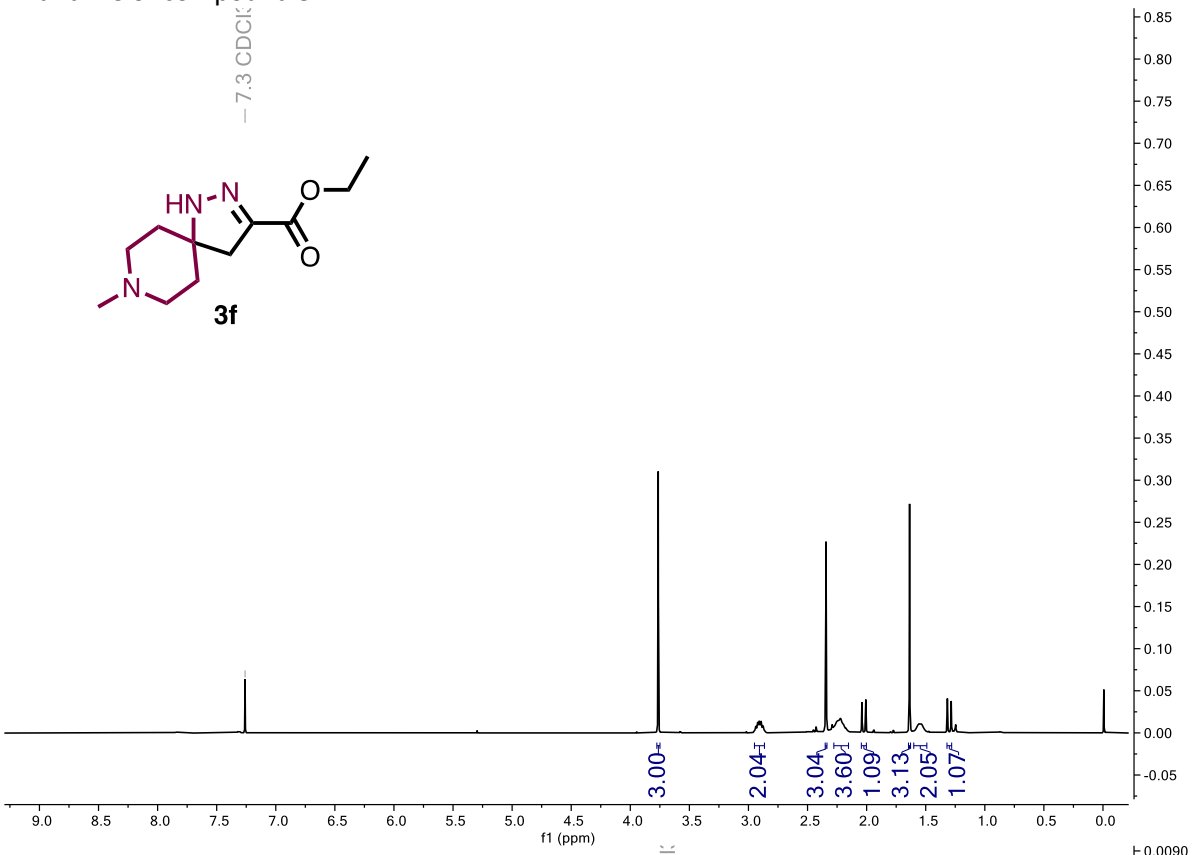


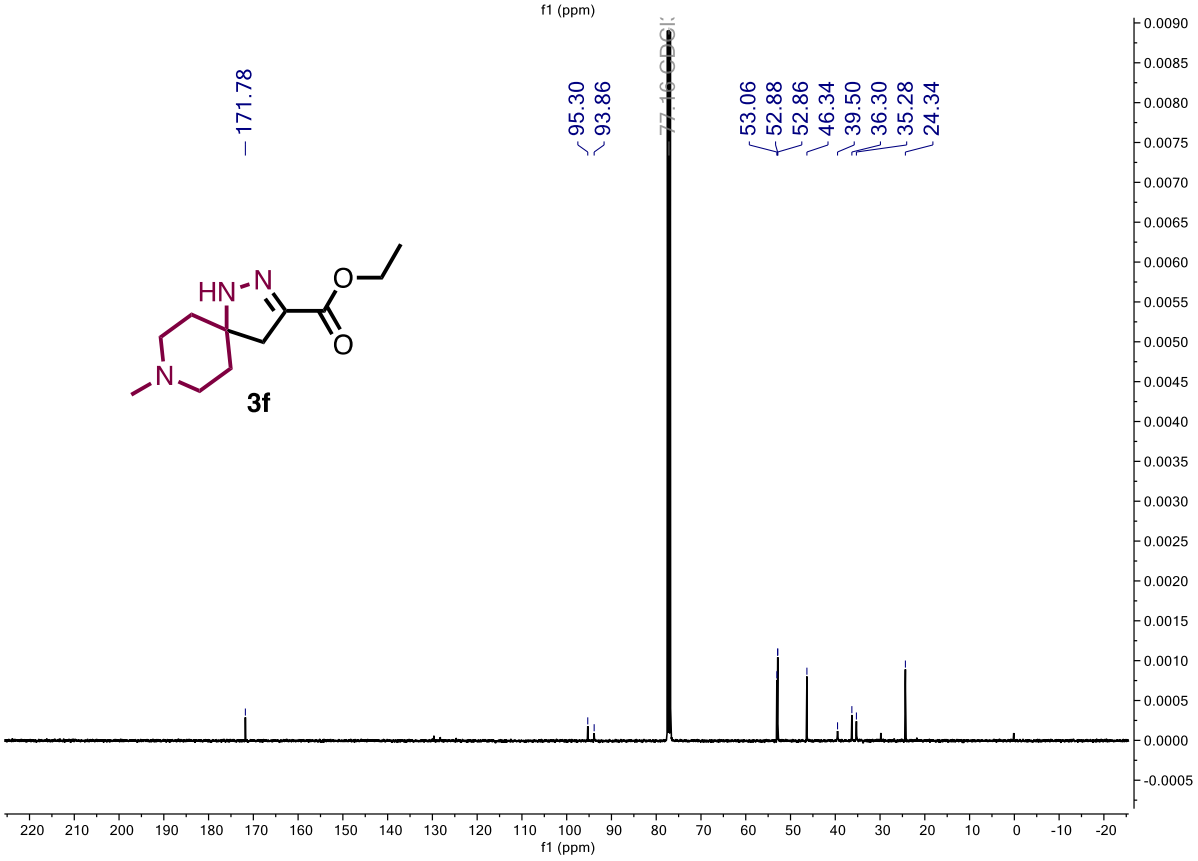
^{1}H and ^{13}C of compound **3e**



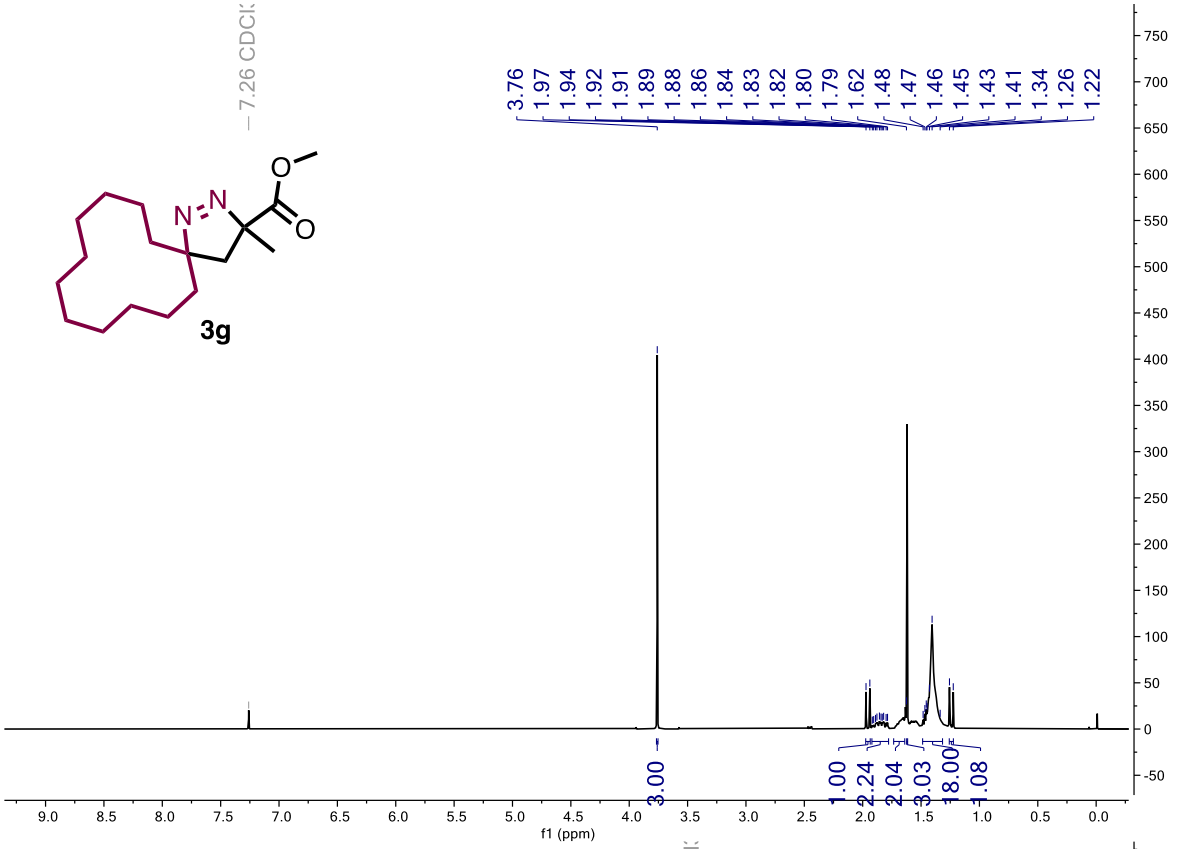


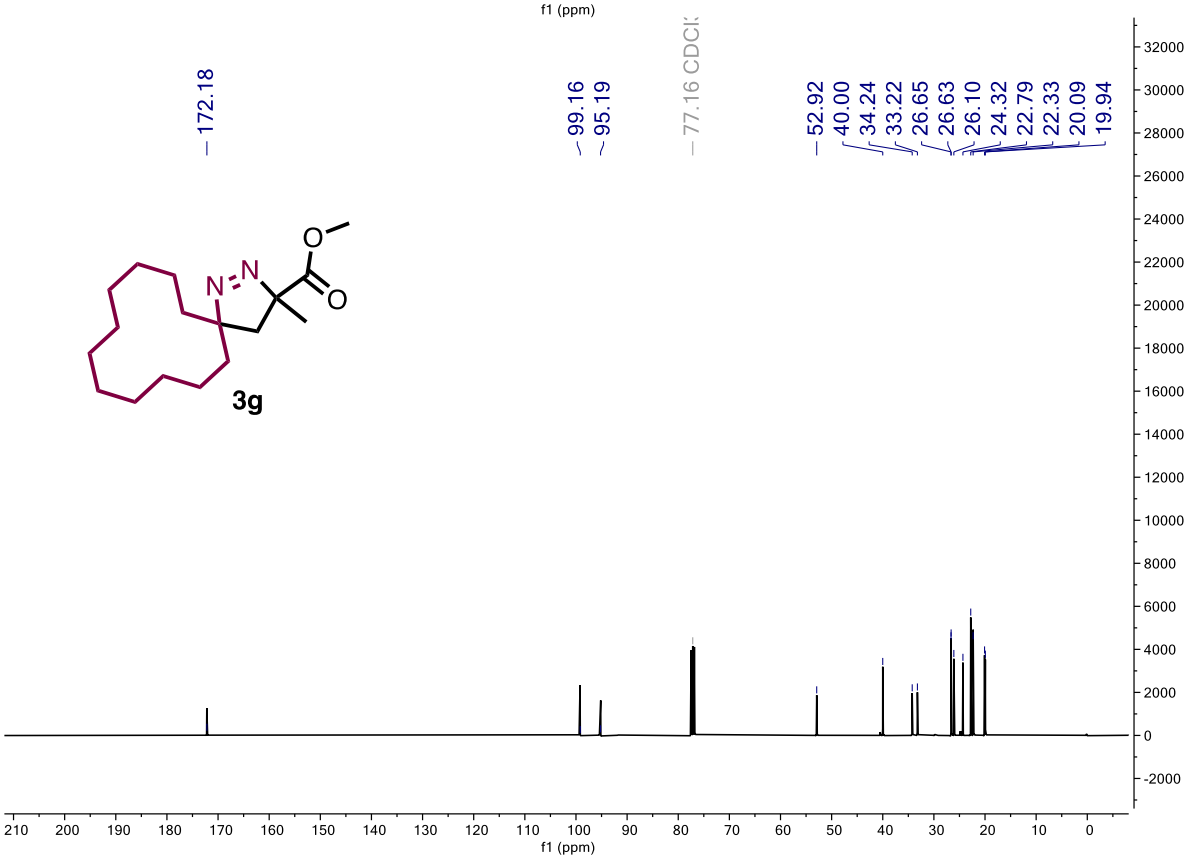
^{1}H and ^{13}C of compound **3f**





^{1}H and ^{13}C of compound **3g**





^{1}H and ^{13}C of compound **3h**