Supporting Information

for

Development of a flow photochemical aerobic oxidation of benzylic C-H bonds

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1. General information

All reactants purchased from commercial sources were used as received. Acetonitrile and distillated water were used as received. Cylinder of oxygen O_2 (UN1072) was provided by Air liquid and used as received.

All flow reactions were performed on $R2^+$ and R4 system from Vapourtec using FEP tubing. The Oxygen was measured with a mass flow controller SLA5800 from Brooks instrument or a mass flow controller SmartTrack 100 from Sierra Intruments. The UV-150 equipment, the UV lamp (106 W) and the LED lamp (450 nm, 24 W) were purchased from Vapourtec. The coil reactor of 10 mL with FEP tubing (length: 22 meters, diameter: 0.03 inch) was purchased from Vapourtec.

Flash chromatography was performed on silica gel 60 Å pore diameter and 40-63 µm particules size. ^1H, ^{13}C-{^1H} Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker ADVANCE 400 MHz spectrometer at ambient temperature (298K) using the residual solvent peak in $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm) and using TMS as internal standard. The multiplicity of ^1H NMR signals are indicated as s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, or combinations of thereof. Coupling constants *J* are quoted in Hz and are reported to the nearest 0.1 Hz. Where appropriate, averages of the signals that display multiplicity were used to calculate the value of the coupling constant.

GC-MS analysis was performed on a ThermoFisher scientific Trace GC ultra combined with a ITQ900 MS.

2. Synthesis of Riboflavine tetraacetate (1, RFT)

To a solution of riboflavin (1.0 g, 2.7 mmol) in acetic acid (30.0 mL) and acetic anhydride (30.0 mL) at room temperature, perchloric acid (0.8 mL, 70 %) was added dropwise. After complete dissolution of the solid, the reaction mixture was stirred 5 minutes at room temperature and water (200 mL) was added carefully. The mixture was stirred for another 5 minutes at room temperature and the product was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to 5.0 mL. After the addition of a cold solution of diethylether (50.0 mL), the orange precipitate was filtered and dried over the week-end in a desiccator protected from light. The desired product (76 %, 1.1 g) was obtained pure as an orange solid.

^1H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 8.35 (s, 1H), 8.04 (s, 1H), 7.56 (s, 1H), 5.67 (m, 1H), 5.43 (m, 2H), 4.91 (brd s, 1H), 4.44 (m, 1H), 4.24 (m, 1H), 2.57 (s, 3H), 2.45 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H), 2.08 (s, 3H), 1.76 (s, 3H).

NMR is in accordance with the literature.[1]

3. Photochemical aerobic oxidation procedure

3.1. Reaction optimization studies

A solution of riboflavin tetraacetate (10 mol %), iron catalyst (5 mol %) and 5-fluoroindane (0.1 mmol) in MeCN/H_2O (0.9 mL/0.3 mL) was prepared and injected in a loop of 1.0 mL. The solution was pumped with MeCN as a solvent at a flow rate of 0.1-0.3 mL.min^{-1} and mixed in an arrowhead T-mixing piece with oxygen at a flow rate of 1.0-3.0 mL.min^{-1}. The mixture was pumped through a coil reactor of 10 mL with FEP tubing (length: 7.5 meters, bore tubing: 0.03 mm) using the Vapourtec R4 and R2$^+$ series, irradiated by the Vapourtec UV lamp (106 W, 70 %) or LED lamp (450 nm, 24 W) and cooled down to 50°C. The crude material was collected in a round bottom flask and the conversion determined by GC-MS based on the 5-Fluoroindane. The reported yields are the averages of two reactions.

Entry[a]	[Fe]	MeCN (mL.min^{-1})	O_2 (mL.min^{-1})	**3a** conv (%)[b]
1	Chen-White	0.3	1	64
2	$Fe(ClO_4)_2$	0.3	1	62
3	$Fe(acac)_2$	0.3	1	56
4	$Fe(OAc)_2$	0.3	1	49
5	/	0.3	1	49
6	$Fe(ClO_4)_2$	0.3	2	64
7	$Fe(ClO_4)_2$	0.3	3	49
8	$Fe(ClO_4)_2$	0.5	1	41
9	$Fe(ClO_4)_2$	0.1	1	69(59)[f]
10[c]	$Fe(ClO_4)_2$	0.3	1	32
11[d]	$Fe(ClO_4)_2$	0.3	1	0
12[e]	$Fe(ClO_4)_2$	0.3	1	0
13	$Fe(ClO_4)_2$	0.1	2	64
14	Chen-White	0.1	2	58
15	$Fe(ClO_4)_2$	0.1	3	59
16	Chen-White	0.1	3	56
17[g]	$Fe(ClO_4)_2$	0.3	1	23
18[h]	$Fe(ClO_4)_2$	0.3	1	25
19[i]	$Fe(ClO_4)_2$	0.1	1	71
20[j]	$Fe(ClO_4)_2$	0.3	1	53

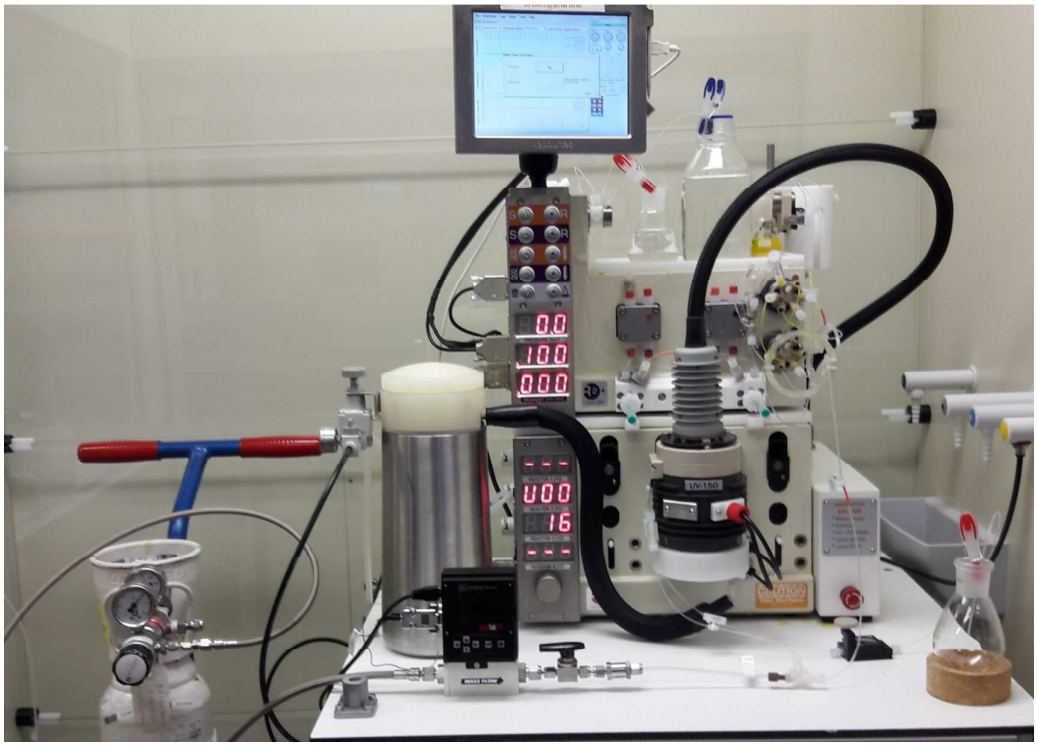
(a) 5-Fluoroindane (0.1 mmol), 1 (10 mol %), [Fe] (5 mol %), 50°C, UV lamp (106 W), MeCN (mL.min^{-1}), O_2 (mL.min^{-1}). (b) Conversion based on the 5-Fluoroindane. (c) Reaction irradiated with a 450 nm LED lamp (24 W). (d) Reaction without irradiation. (e) Reaction without photocatalyst. (f) Isolated yield. (g) Reaction using Vapourtec wavelength gold filter. (h) Reaction using Vapourtec wavelength red filter. (i) [Fe] (10 mol %). (j) 35 °C.

3.2. General procedure for continuous-flow oxidation

A solution of riboflavin tetraacetate (10 mol %), [$Fe(ClO_4)_2$] (5 mol %) and the substrate (0.5 mmol) in MeCN/H_2O (3.8 mL/1.3 mL) was prepared and injected in a loop of 5.0 mL. The solution was pumped with MeCN as a solvent at a flow rate of 0.1 mL.min^{-1} and mixed in an arrowhead T-mixing piece with

oxygen at a flow rate of 1.0 mL.min^{-1}. The mixture was pumped through a coil reactor of 10 mL with FEP tubing (length: 7.5 meters, bore tubing: 1.3 mm) using the vapourtec R4 and R2^{+} series, irradiated by the vapourtec UV lamp (106 W, 70 %) and cooled down to 50 °C. The crude material was collected in a round bottom flask and water (10 mL) was added. The aqueous layer was extracted with EtOAc (2 X 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated to dryness. The desired product was obtained after purification using flash chromatography. The reported yields are the averages of two reactions.

The equipment used is depicted in the following picture.



3.3. Scope

3.3.1. 5-fluoroindan-1-one (3a)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 50/50), 42.5 mg (59%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.76 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 3.14 (t, *J* = 8.0 Hz, 2H), 2.72 (t, *J* = 8.0 Hz, 2H).

NMR is in accordance with the literature (CAS number 700-84-5).

3.3.2. Indan-1-one (3b)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 50/50), 38.1 mg (60 %) of the title compound as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.76 (m, 1H), 7.59 (m, 1H), 7.48 (m, 1H), 7.37 (m, 1H), 3.14 (m, 2H), 2.70 (m, 2H).

NMR is in accordance with the literature (CAS number 83-33-0).

3.3.3. N,N-diethyl-1-oxo-indane-5-carboxamide (3c)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 9.5 mg (17 %) of the title compound as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.79 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 3.60-3.53 (m, 2H), 3.26-3.20 (m, 2H), 3.17 (t, *J* = 8.0 Hz, 2H), 2.73 (t, *J* = 8.0 Hz, 2H), 1.28-1.25 (m, 2H), 1.13-1.10 (m, 2H).

^{13}C-{^{1}H} HSQC NMR (101 MHz, $CDCl_3$, 298 K, TMS): δ (ppm) = 125.3, 124.6, 123.8, 43.3, 39.1, 36.3, 25.8, 14.1, 12.9

3.3.4. 5-methoxyindan-1-one (3d)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 80/20), 38.9 mg (50%) of the title compound as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.69 (d, *J* = 8.0 Hz, 1H), 6.90 (m, 2H), 3.89 (s, 3H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.67 (t, *J* = 8.0 Hz, 2H).

NMR is in accordance with the literature.[2]

3.3.5. 3-chloro-5-oxo-6,7-dihydrocyclopenta[c]pyridine-4-carbonitrile (3e)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 100/0), 27.7 mg (30%) of the title compound as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 8.90 (s, 1H), 3.39-3.36 (m, 2H), 2.89-2.86 (m, 2H).

^{13}C-{^{1}H} HSQC NMR (101 MHz, $CDCl_3$, 298 K, TMS): δ (ppm) = 148.7, 36.1, 26.0.

3.3.6. 2-chloro-5-oxo-6,7-dihydrocyclopenta[b]pyridine-3-carbonitrile (3f)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 80/20), 15.7 mg (18%) of the title compound as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 8.30 (s, 1H), 3.37 (t, *J* = 6.0 Hz, 2H), 2.89 (t, *J* = 6.0 Hz, 2H).

^{13}C-{^{1}H} HSQC NMR (101 MHz, $CDCl_3$, 298 K, TMS): δ (ppm) = 138.4, 36.0, 29.0.

3.3.7. 1-hydroxyindane-1-carboxylic acid (3g)

The general procedure yielded, after flash chromatography on silica gel (DCM/MeOH 70/30), 50.5 mg (59%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.75 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 3.13 (t, *J* = 8.0 Hz, 2H), 2.67 (t, *J* = 8.0 Hz, 2H).

^{13}C-{^{1}H} HSQC NMR (101 MHz, $CDCl_3$, 298 K, TMS): δ (ppm) = 134.3, 127.3, 126.9, 123.6, 36.4, 25.9.

3.3.8. Tetralin-1-one (3h)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 46.3 mg (66%) of the title compound as a colorless solid.

^{1}H NMR (400 MHz, DMSO, 298K) : δ (ppm) = 7.86 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.35 (m, 2H), 2.94 (t, *J* = 4.0 Hz, 2H), 2.60 (t, *J* = 4.0 Hz, 2H), 2.04 (q, *J* = 4.0 Hz, 2H).

NMR is in accordance with the literature (CAS number 529-34-0).

3.3.9. Anthracene-9,10-dione (3i)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 50/50), 72.0 mg (72%) of the title compound as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 8.33 (m, 4H), 7.81 (m, 4H)

NMR is in accordance with the literature (CAS number 84-65-1).

3.3.10. 5,6-dihydro-4H-benzothiophen-7-one (3j)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 57.7 mg (79%) of the title compound as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.61 (d, *J* = 4.0 Hz, 1H), 6.98 (d, *J* = 4.0 Hz, 1H), 2.88 (t, *J* = 8.0 Hz, 2H), 2.61 (t, *J* = 8.0 Hz, 2H), 2.18 (p, *J* = 8.0 Hz, 2H).

NMR is in accordance with the literature.[3]

3.3.11. 1-(4-acetylphenyl)ethanone (3k)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 12.5 mg (16%) of the title compound as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 8.03 (s, 4H), 2.65 (s, 6H)

NMR is in accordance with the literature (CAS number 1009-61-6).

3.3.12. 1-(4-chlorophenyl)ethanone (3l)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 51.2 mg (69%) of the title compound as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.90 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 2.59 (s, 3H).

NMR is in accordance with the literature (CAS number 99-91-2).

3.3.13. 4-oxo-4-phenyl-butanenitrile (3m)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 23.5 mg (29%) of the title compound as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.96 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 3.39 (t, *J* = 8.0 Hz, 2H), 2.79 (t, *J* = 8.0 Hz, 2H).

NMR is in accordance with the literature.[4]

3.3.14. 6,7-dihydrocyclopenta[b]pyridine-5-one (3n)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane/triethylamine 0/99/1 – 80/19/1), 38 mg (57%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 8.82-8.81 (m, 1H), 8.04-8.02 (m, 1H), 7.35-7.32 (m, 1H), 3.30 (t, *J* = 4Hz, 2H), 2.80 (t, *J* = 4 Hz, 2H).

NMR is in accordance with the literature.[5]

3.3.15. 2-methyl-[4-(2-methylpropanoyl)phenyl]propanoate (3o)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 22.8 mg (19%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.92 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 3.79 (q, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.53 (septet, *J* = 7.0 Hz, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 6H).

NMR is in accordance with the literature.[6]

3.3.16. 2-hydroxy-2-(4-isobutylphenyl)propanoic acid (5)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 58.7 mg (55%) of the title compound as an colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.88 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.58 (s, 3H), 2.54 (d, *J* = 4.0 Hz, 2H), 1.90 (septet, *J* = 4.0 Hz, 1H), 0.91 (d, *J* = 4.0 Hz, 6H).

^{13}C-{^{1}H} HSQC NMR (101 MHz, $CDCl_3$, 298 K, TMS): δ(ppm) = 128.9, 128.0, 45.3, 30.5, 26.7, 22.2.

3.3.17. 2-(9H-fluoren-3-yl)-2-hydroxy-propanoic acid (10)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 68.4 mg (56%) of the title compound as an colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 8.14 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.85 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 2.19 (m, 2 H), 3.96 (s, 2H), 2.66 (s, 3H).

^{13}C-{^{1}H} HSQC NMR (101 MHz, $CDCl_3$, 298 K, TMS): δ (ppm) = 127.9, 127.7, 127.5, 125.5, 125.2, 120.9, 119.9, 37.1, 26.9.

3.3.18. 7-acetyl-5-tert-butyl-3,3-dimethyl-indan-1-one (13)

The general procedure yielded, after flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 8.7 mg (7%) of the title compound as an colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS) : δ (ppm) = 7.54 (s, 1H), 7.33 (s, 1H), 2.64 (s, 3 H), 2.61 (s, 2H), 1.43 (s, 6 H), 1.36 (s, 9H).

^{13}C-{^{1}H} HSQC NMR (101 MHz, $CDCl_3$, 298 K, TMS): δ (ppm) = 123.4, 121.8, 53.3, 31.2, 31.0, 30.0.

3.4. General procedure for 2 mmol scale of 3j

A solution of riboflavin tetraacetate (108.9 mg, 10 mol %), $[Fe(ClO_4)_2]$ (37.0 mg, 5 mol %) and (285 mg, 2 mmol) in $MeCN/H_2O$ (18.0 mL/2.0 mL) was prepared in a 100 mL round bottom flask. The solution was pumped with MeCN as a solvent at a flow rate of 0.1 $mL.min^{-1}$ and mixed in an arrowhead T-mixing piece with oxygen at a flow rate of 1.0 $mL.min^{-1}$. The mixture was pumped through a coil reactor of 10 mL with FEP tubing (length: 7.5 meters, bore tubing: 1.3 mm) using the vapourtec R4 and $R2^+$ series, irradiated by the vapourtec UV lamp (106 W, 70 %) and cooled down to 50°C. The crude material was collected in a round bottom flask and water (20 mL) was added. The aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated to dryness. The desired product was obtained after purification using flash chromatography on silica gel (EtOAc/Hexane 0/100 – 70/30), 233.0 mg (77 %) of the title compound as a yellowish oil.

4. References

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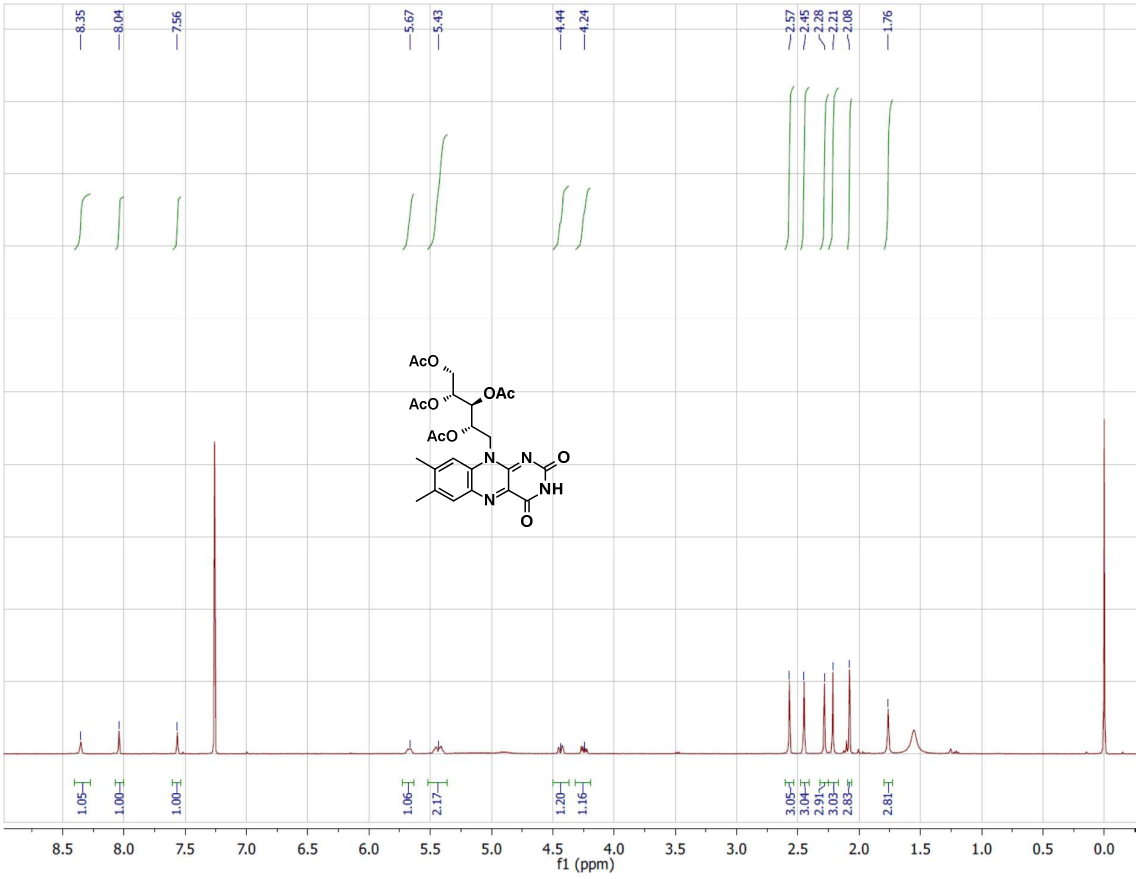
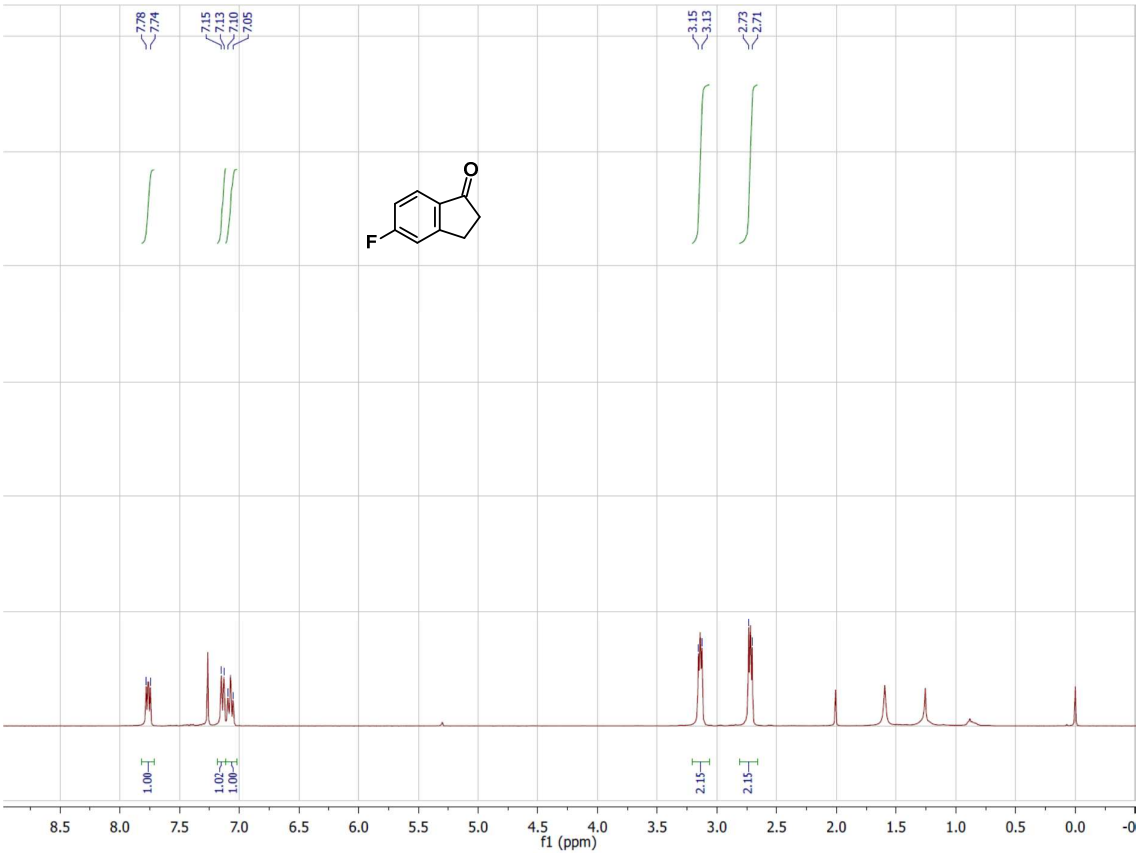
5. NMR spectra

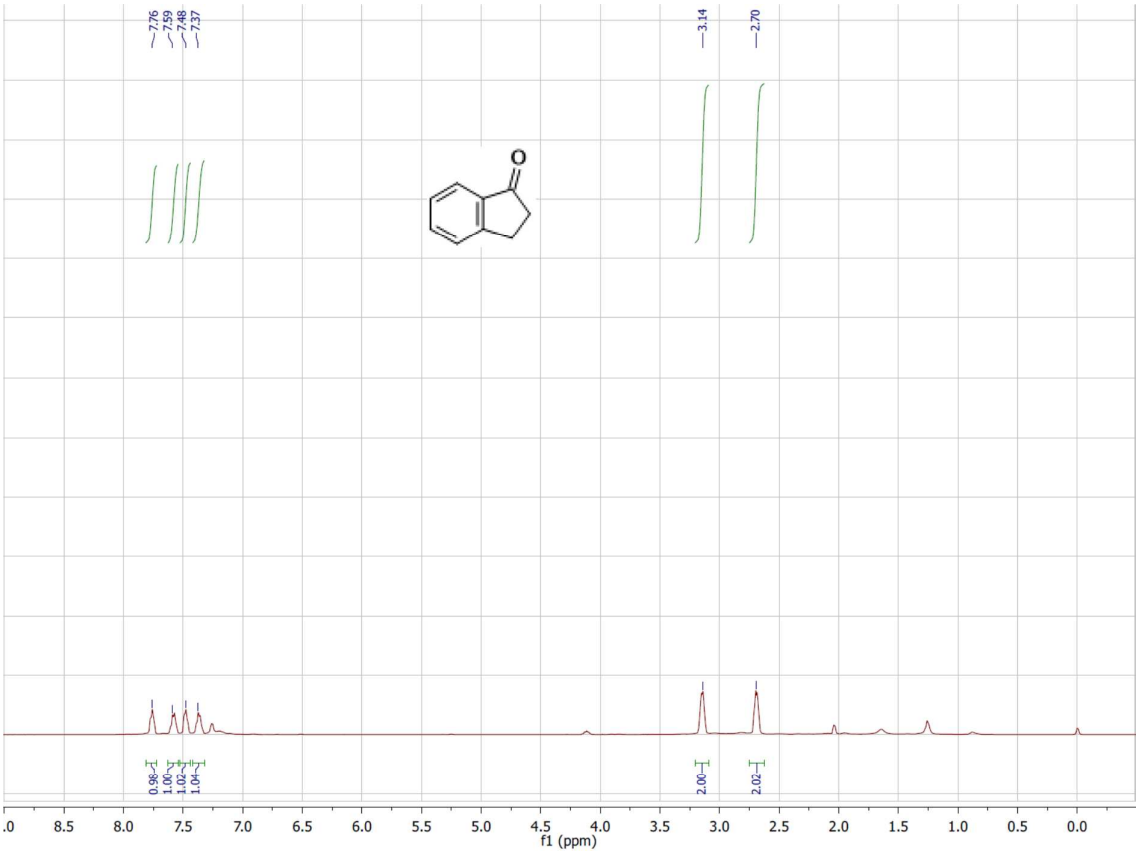
5.1. ^{1}H NMR spectra of compound 1



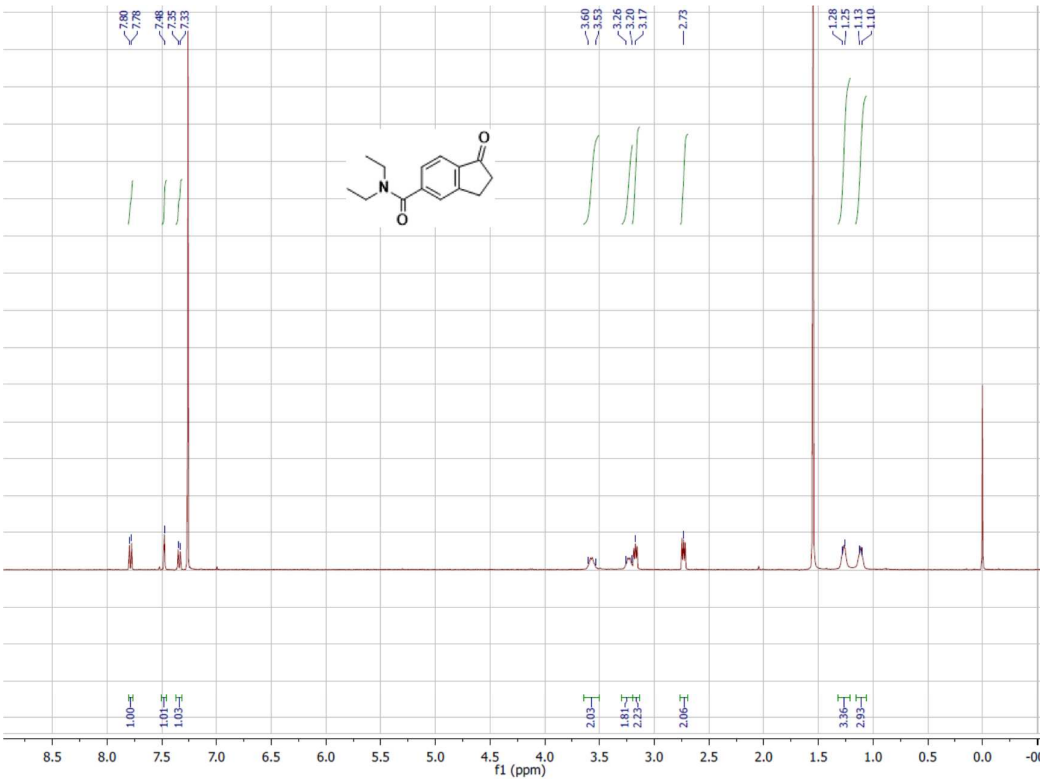
5.2. ^{1}H NMR spectra of compound 3a

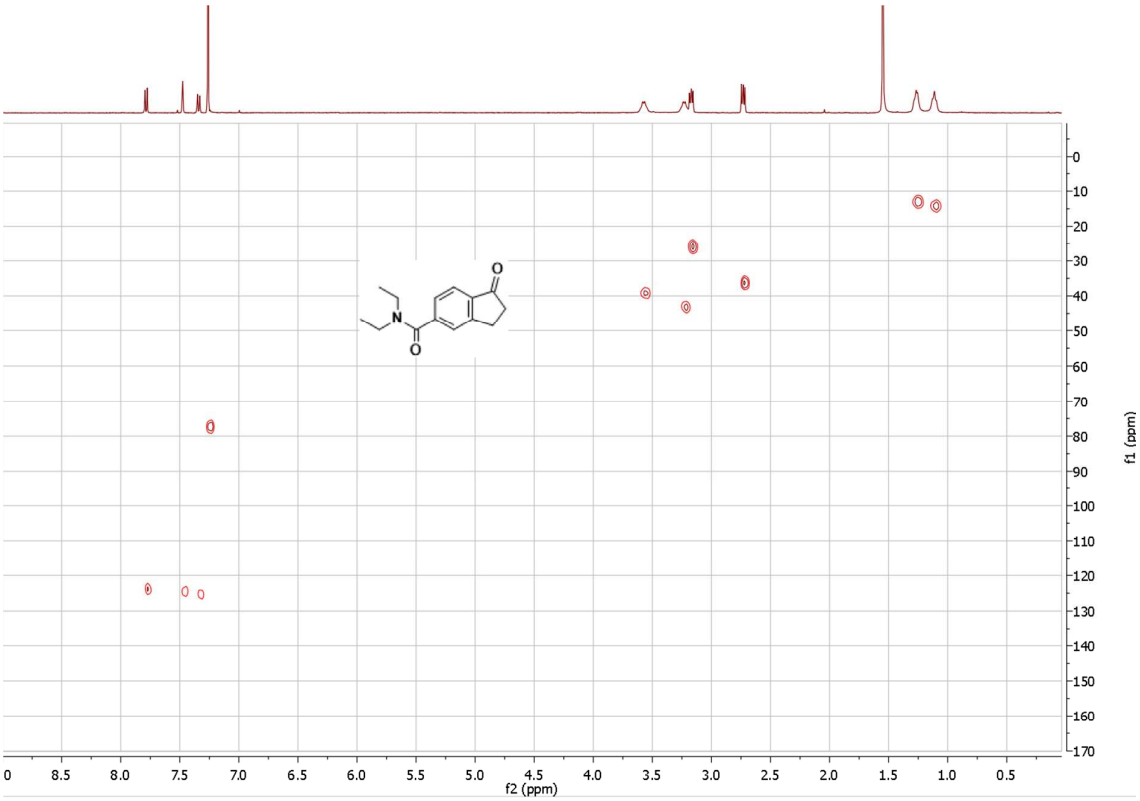


5.3. ^{1}H NMR spectra of compound 3b

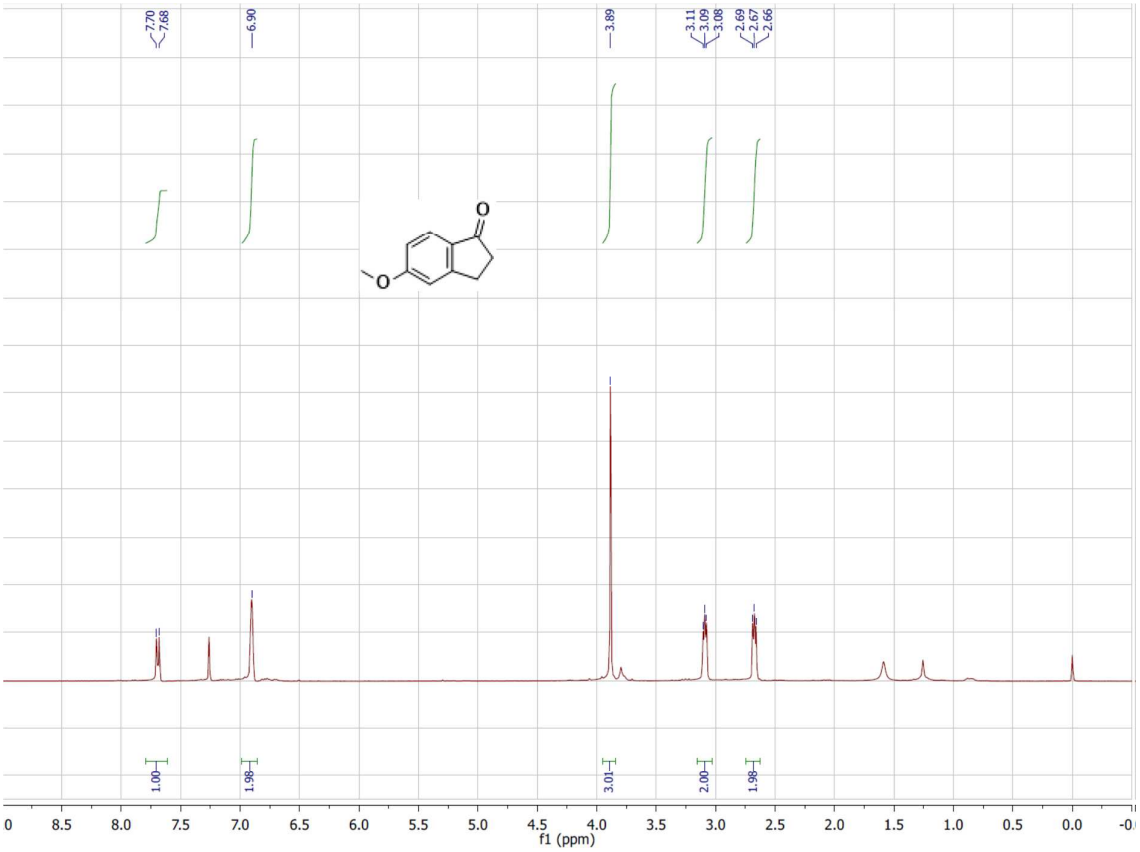


5.4. ^{1}H and ^{13}C NMR spectra of compound 3c

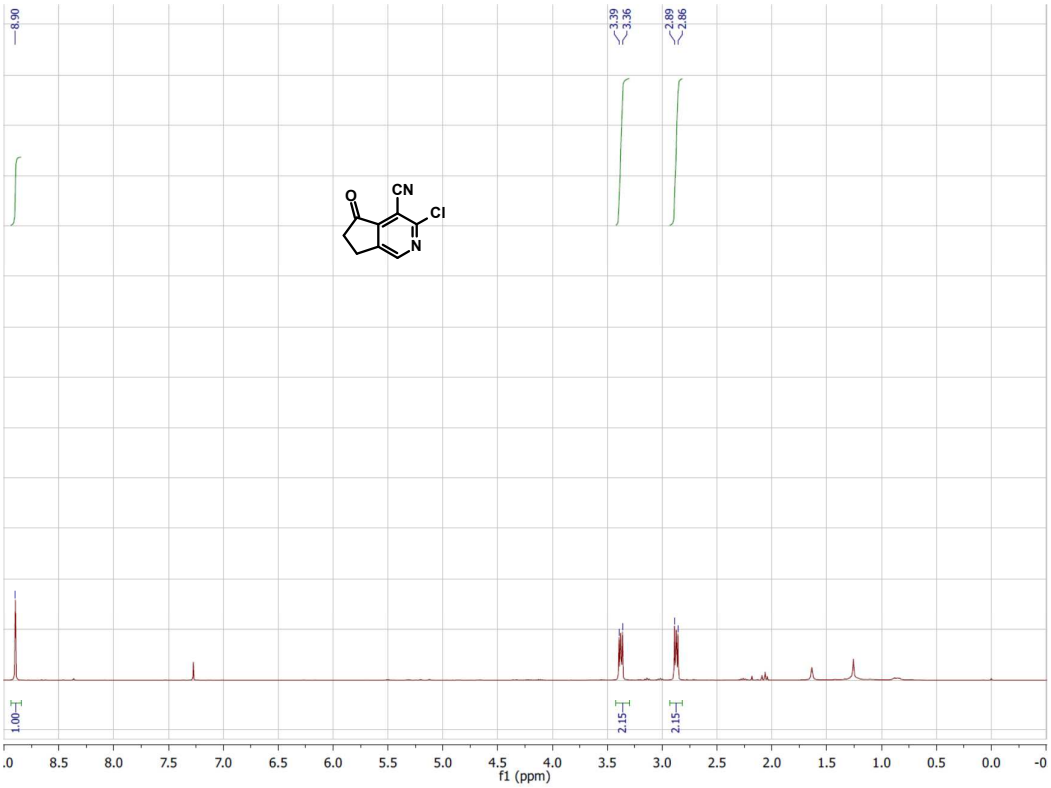


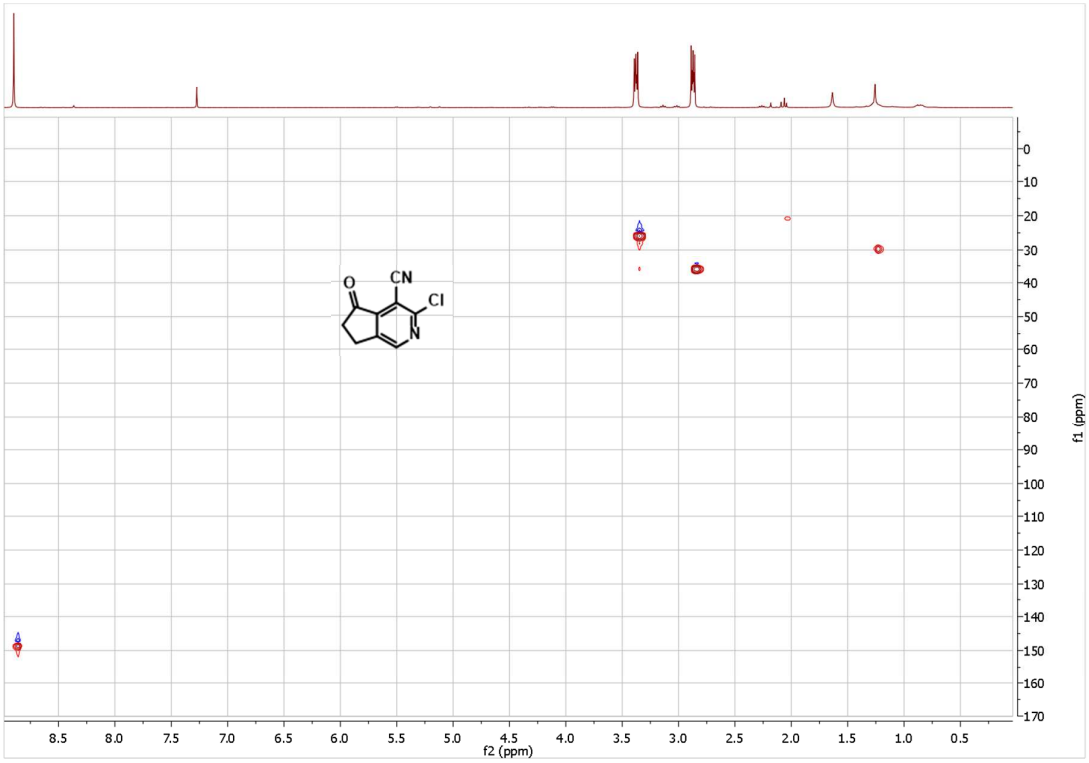


5.5. ^{1}H NMR spectra of compound 3d

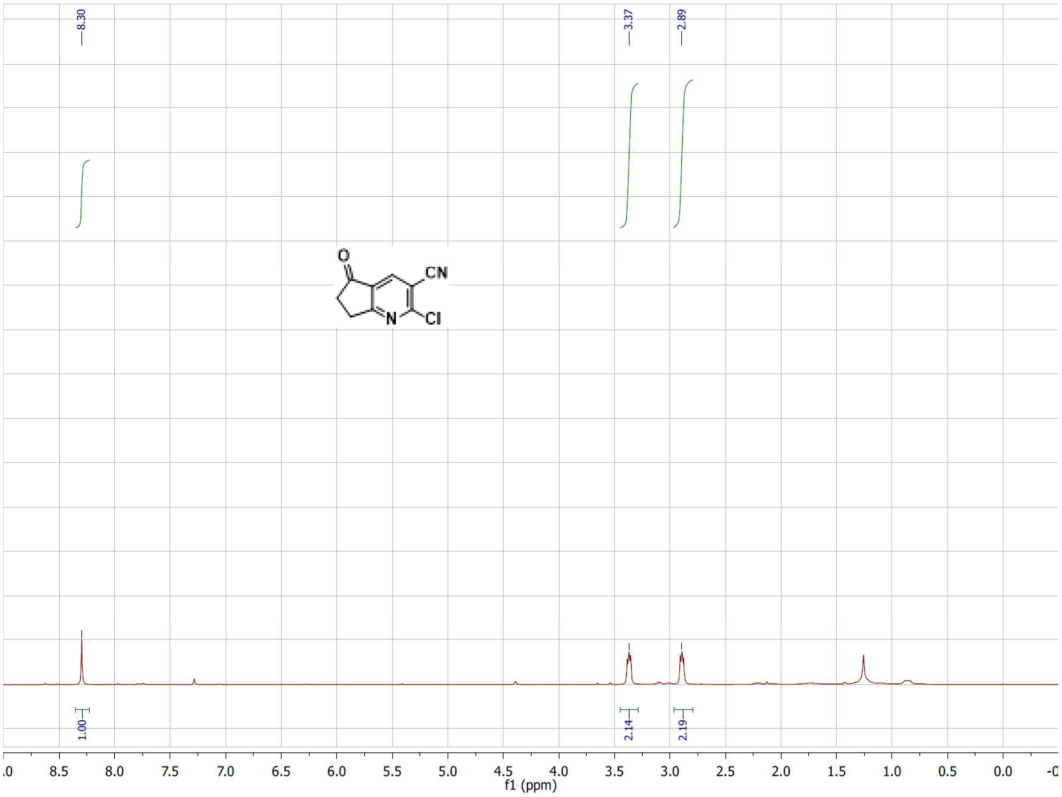


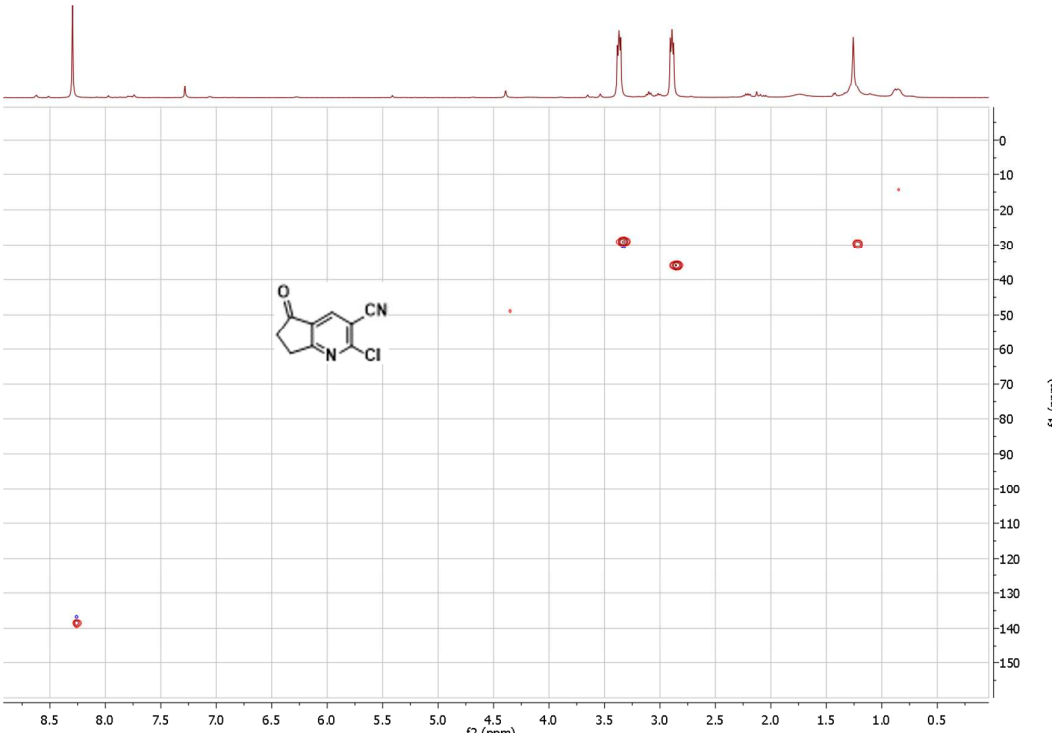
5.6. ^{1}H and ^{13}C NMR spectra of compound 3e



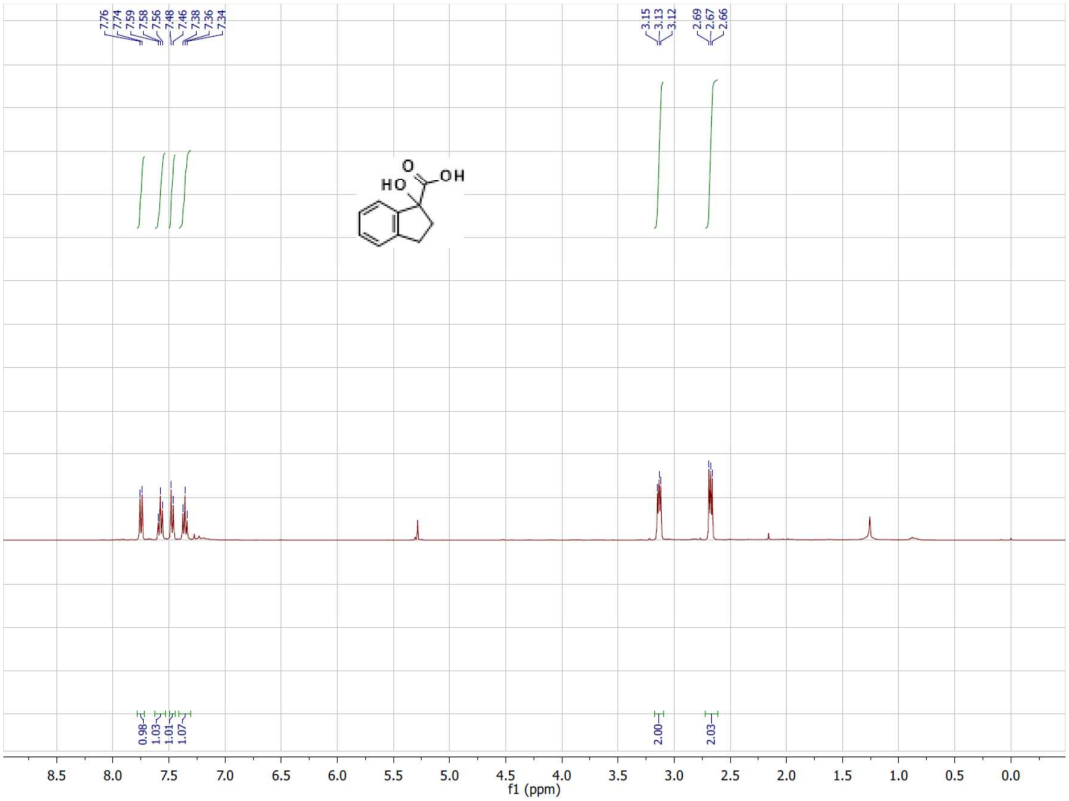


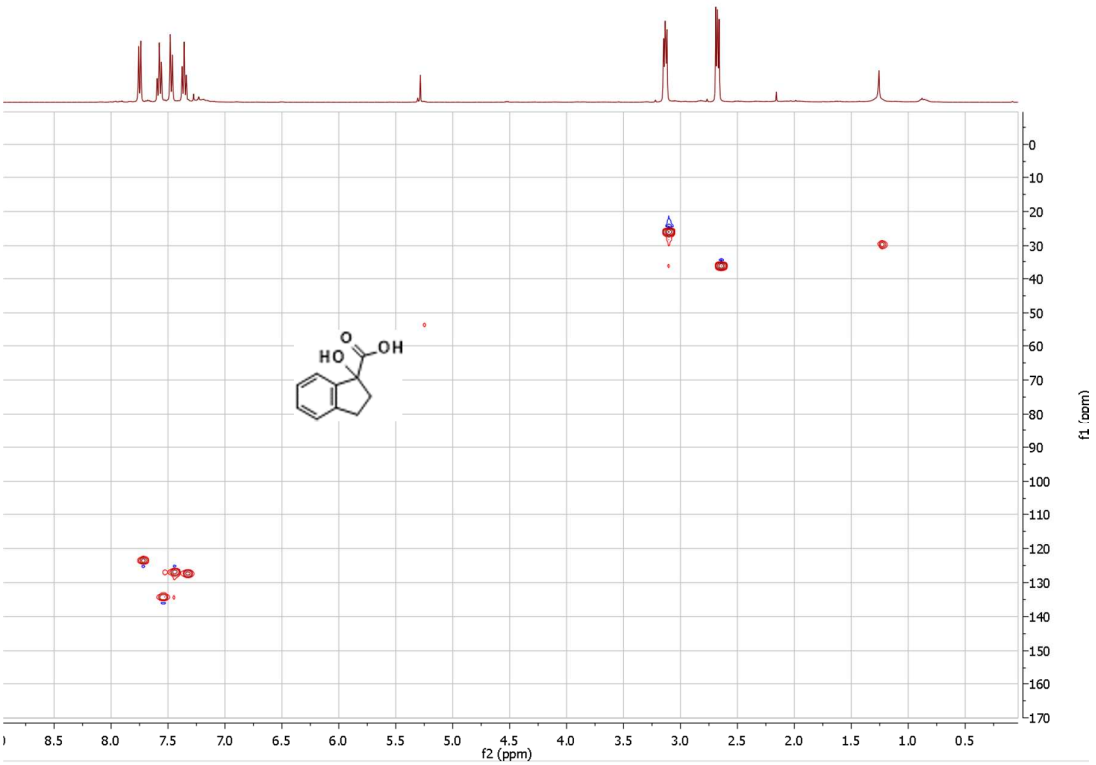
5.7. ^{1}H and ^{13}C NMR spectra of compound 3f



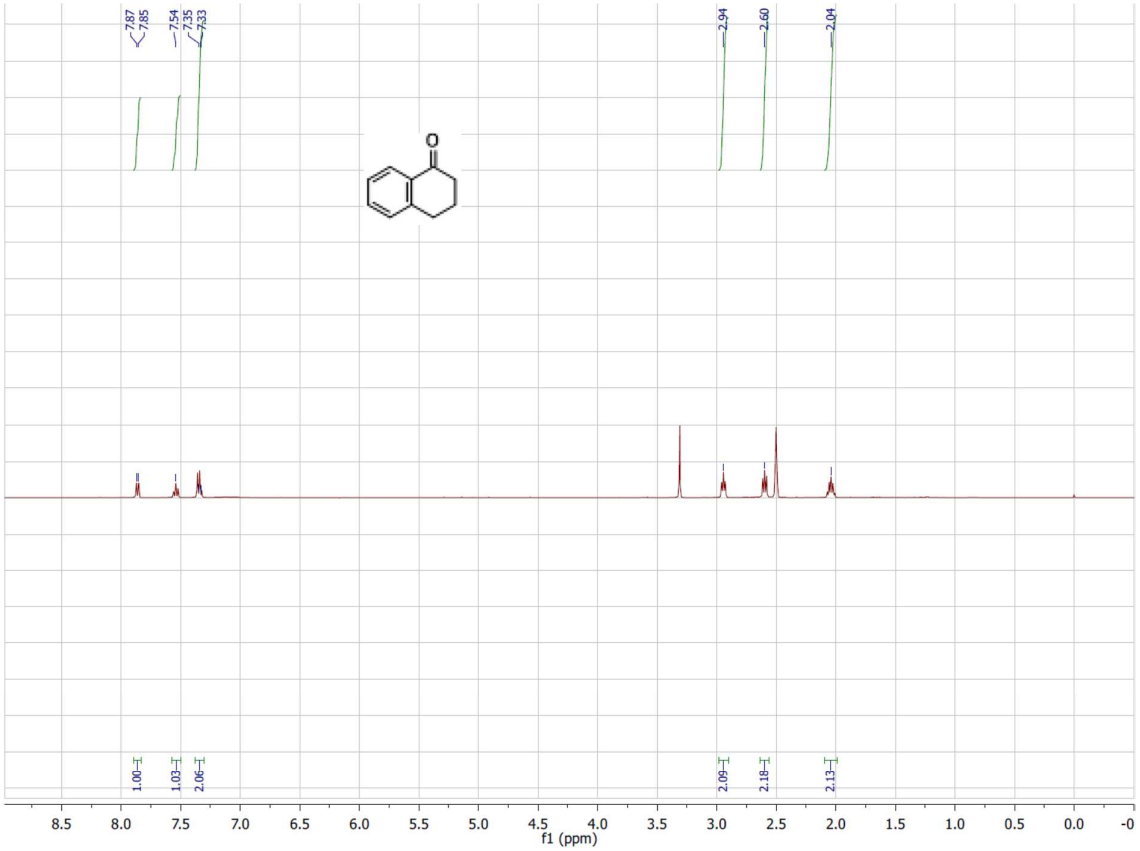


5.8. ^{1}H and ^{13}C NMR spectra of compound 3g

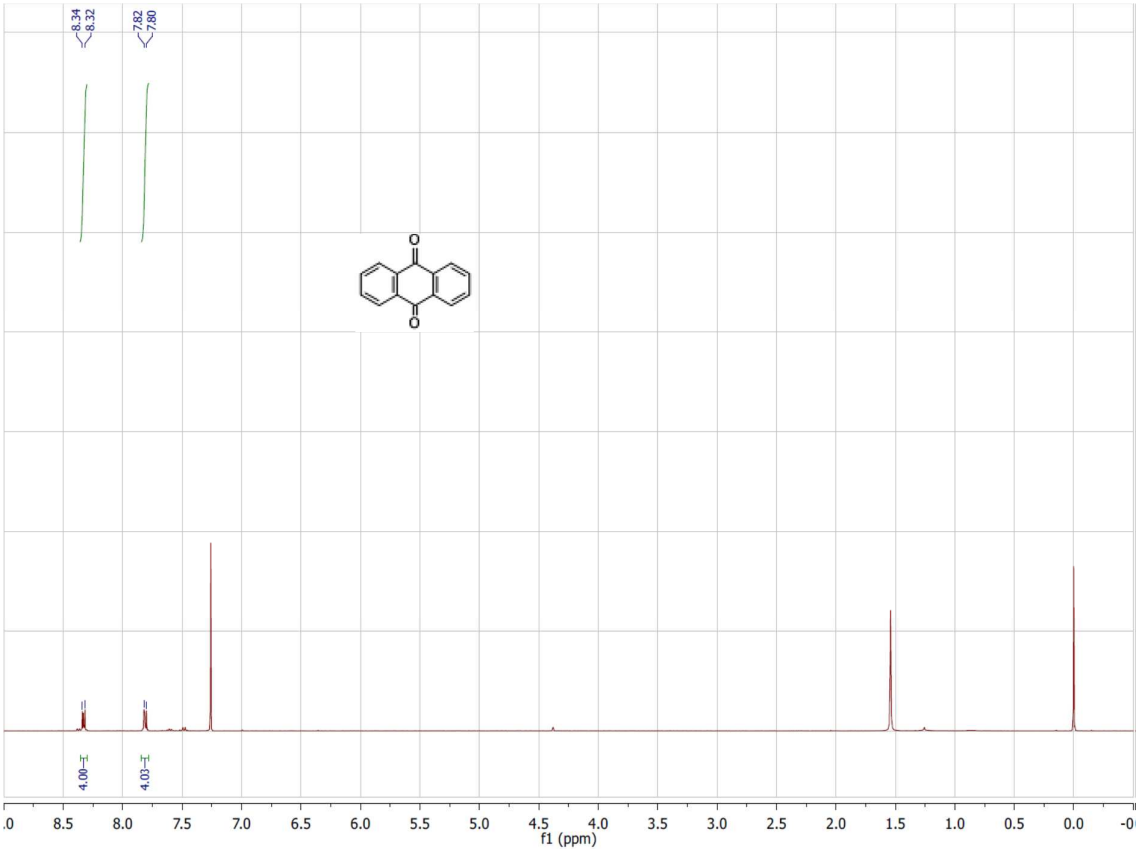




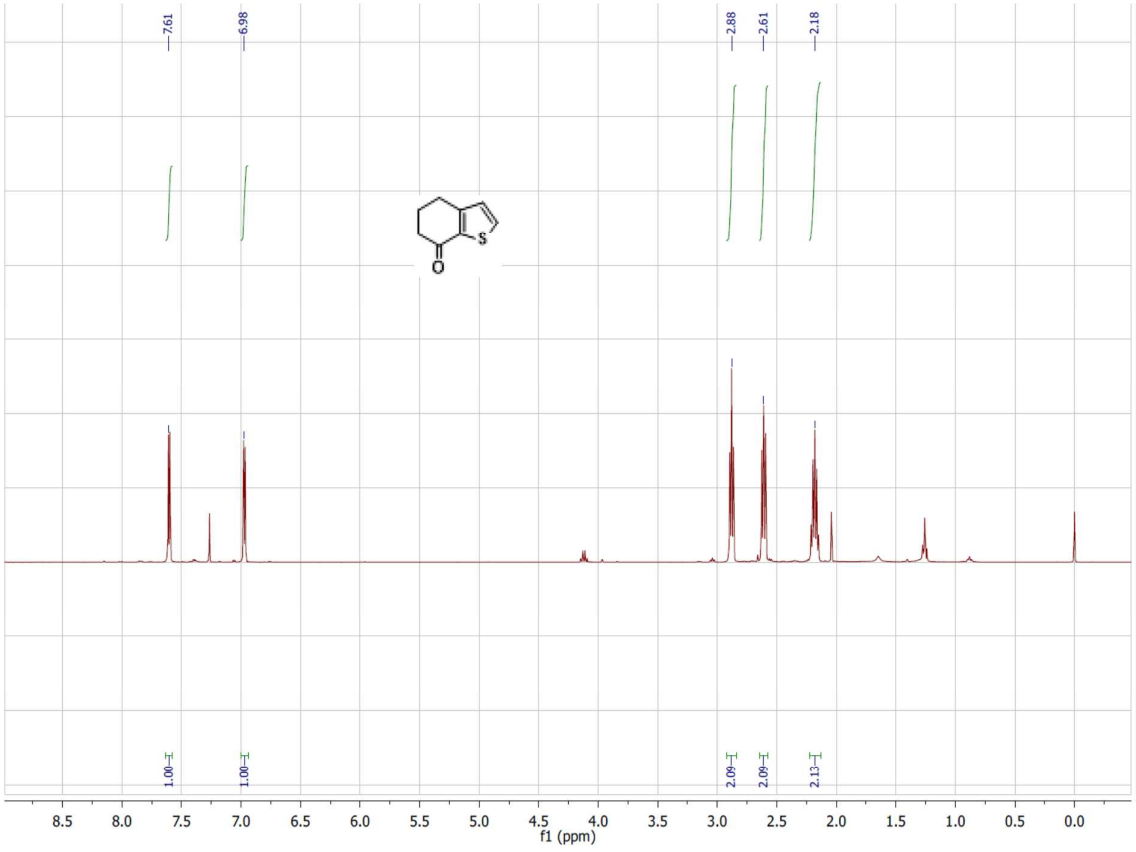
5.9. ^{1}H NMR spectra of compound 3h



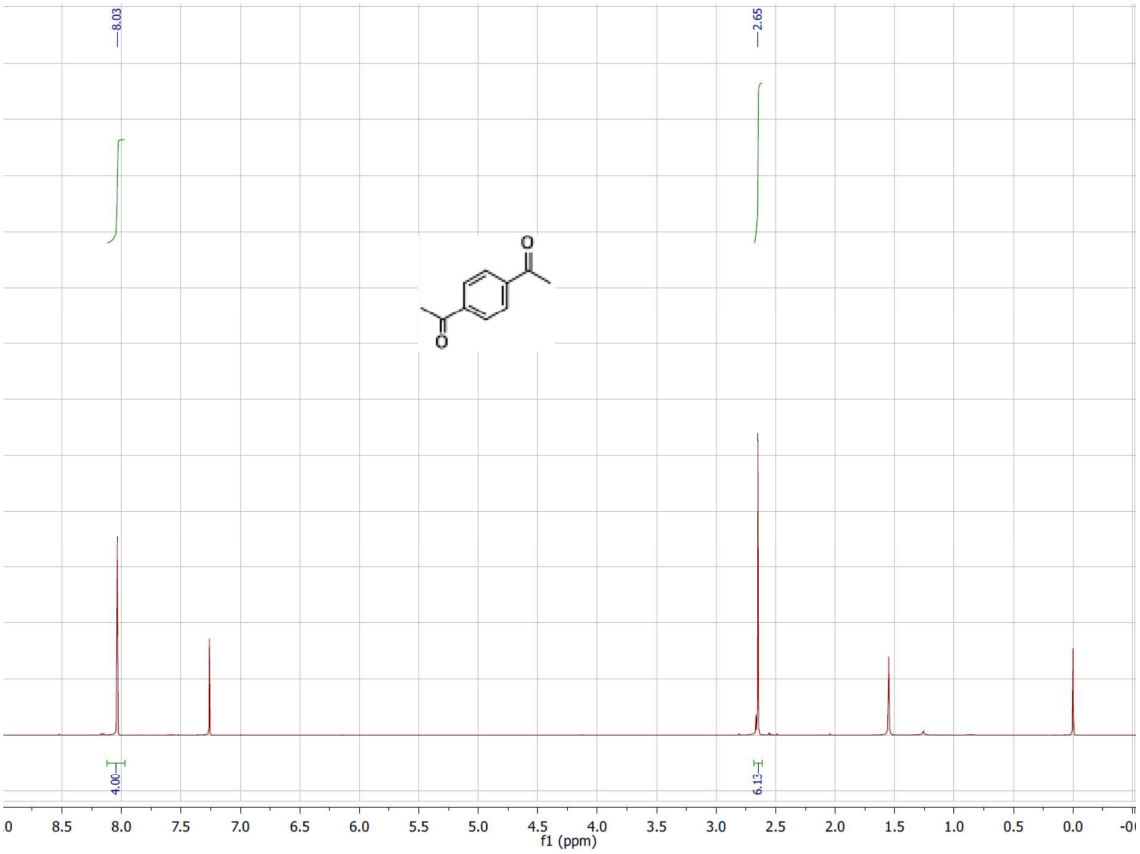
5.10. ^{1}H NMR spectra of compound 3i



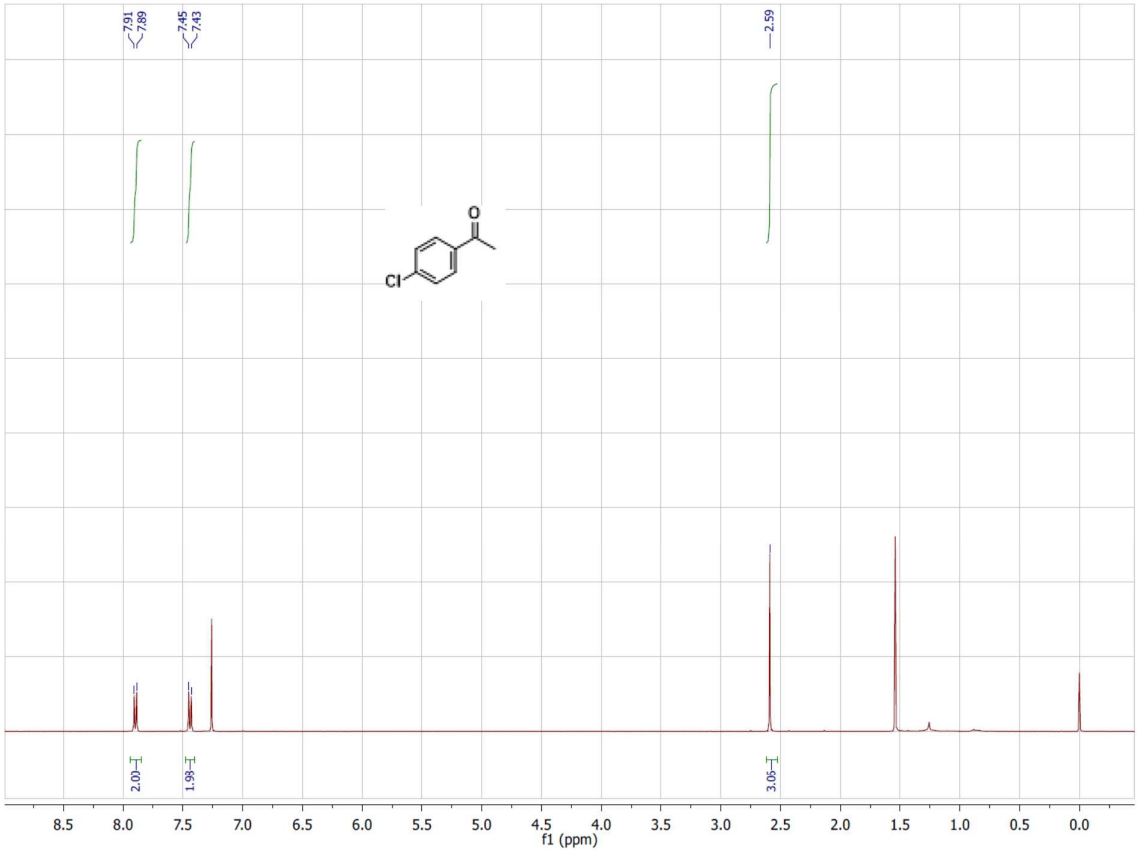
5.11. ^{1}H NMR spectra of compound 3j



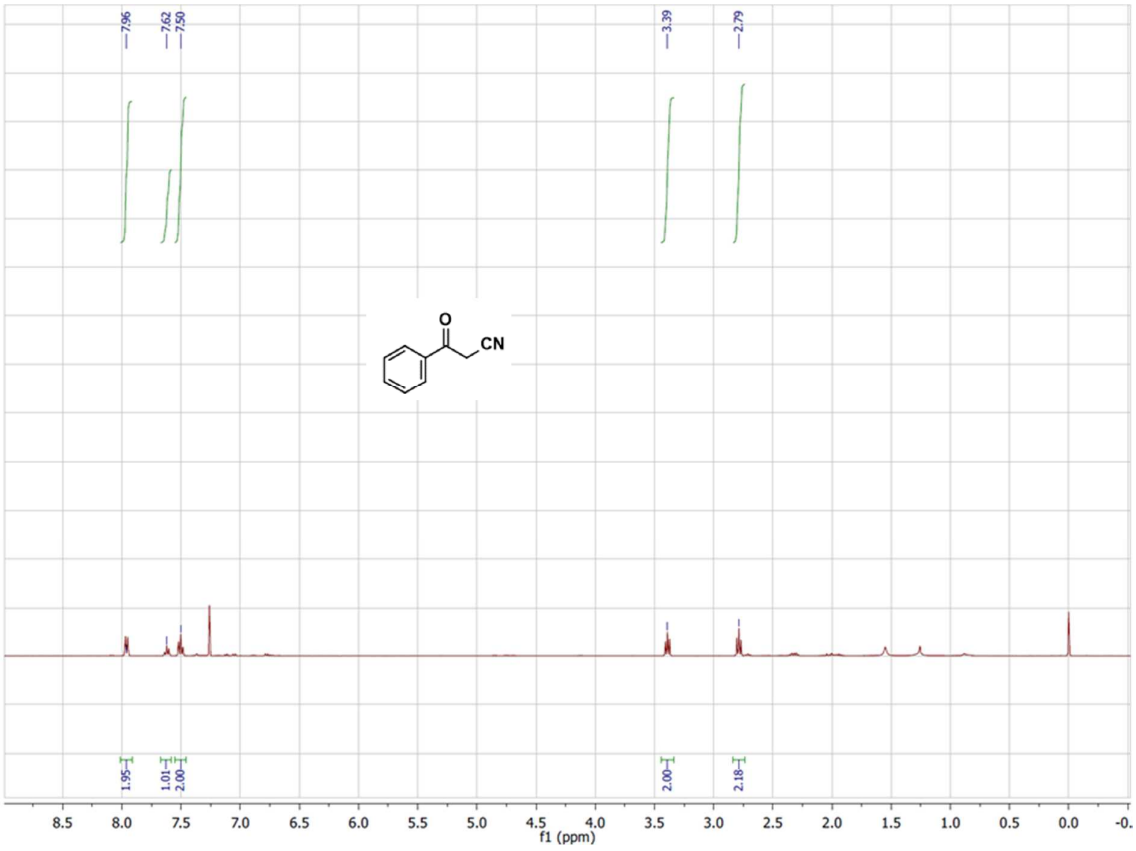
5.12. ^{1}H NMR spectra of compound 3k



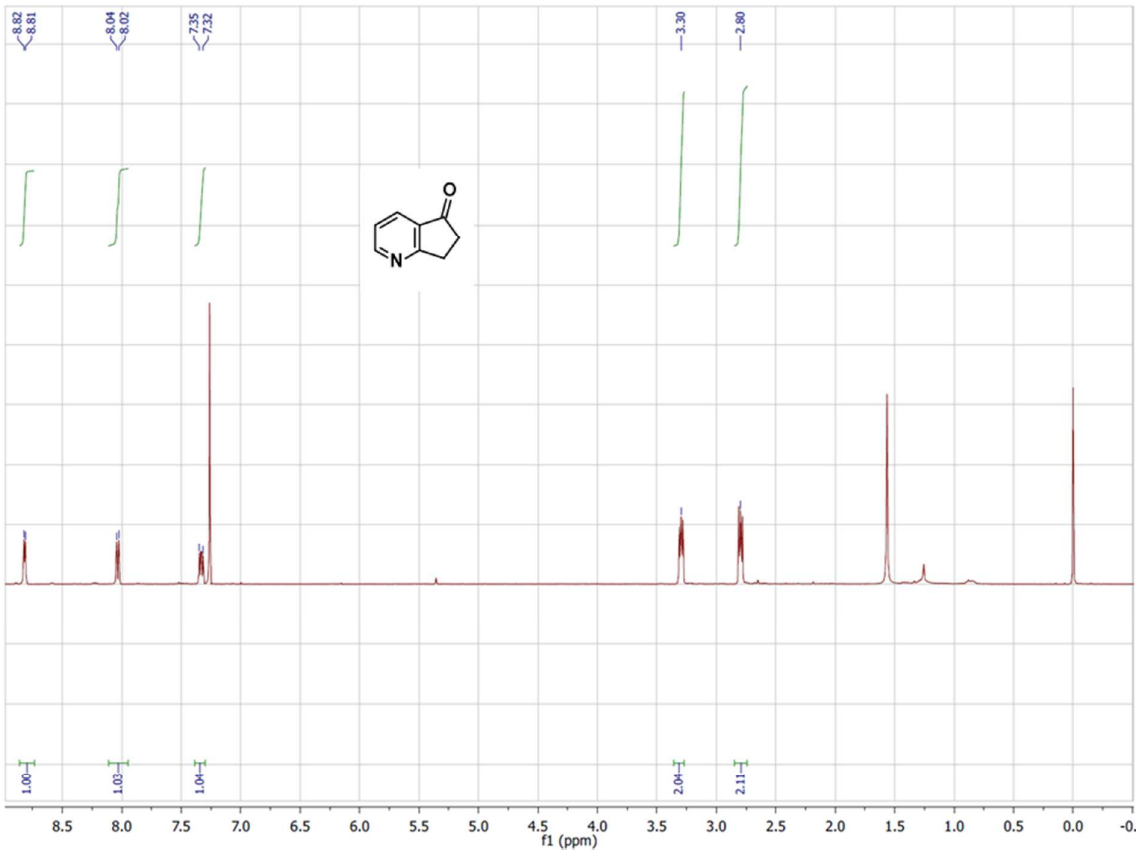
5.13. ^{1}H NMR spectra of compound 3l



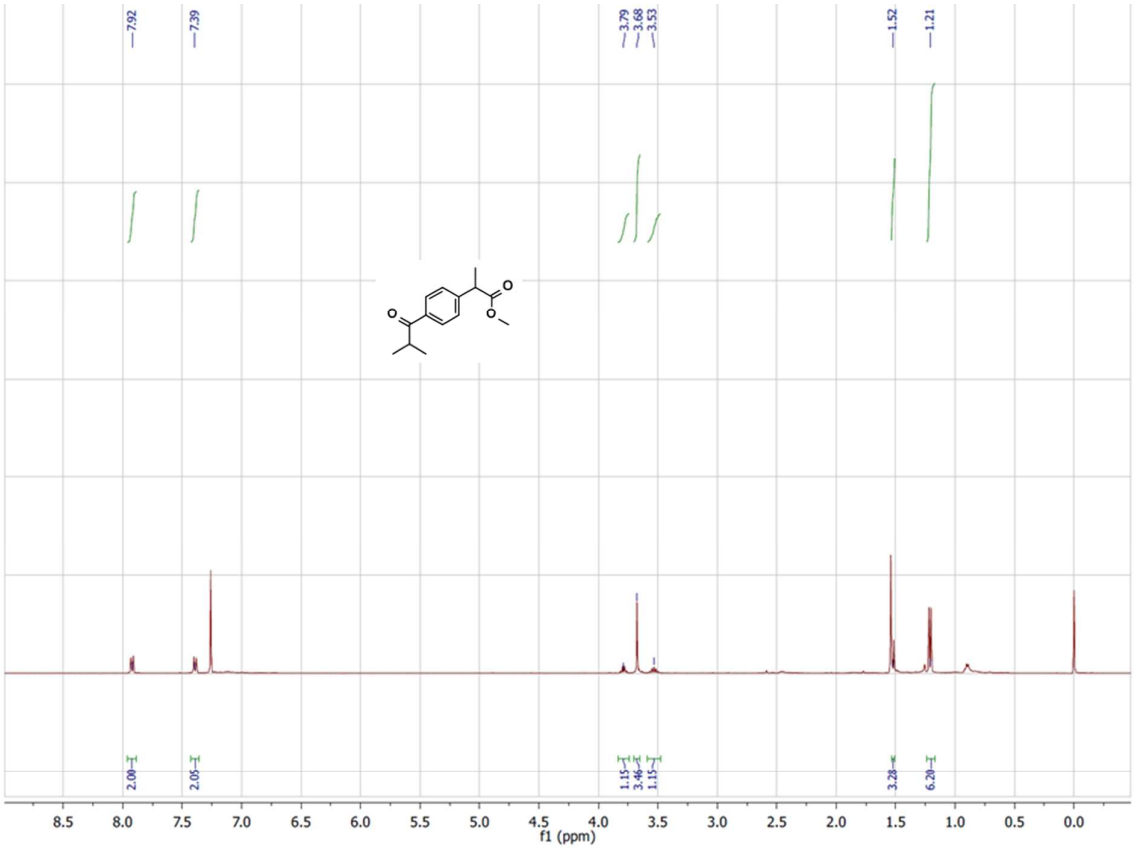
5.14. ^{1}H NMR spectra of compound 3m



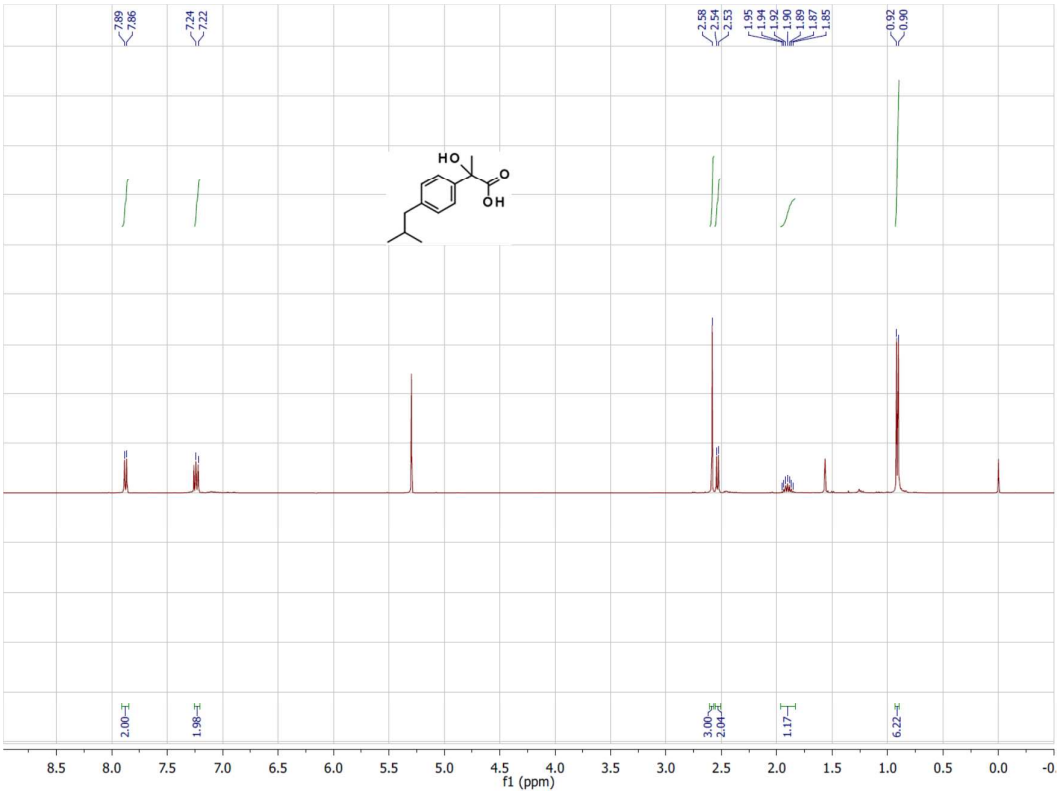
5.15. ^{1}H NMR spectra of compound 3n

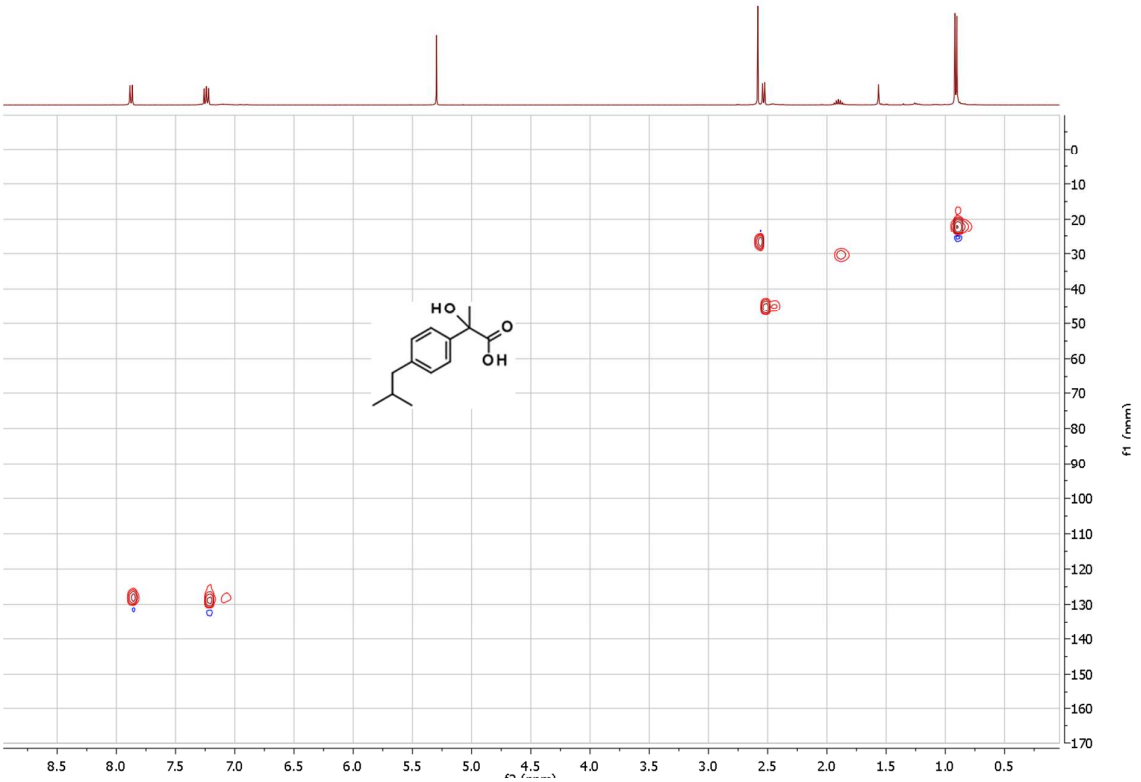


5.16. ^{1}H NMR spectra of compound 3o

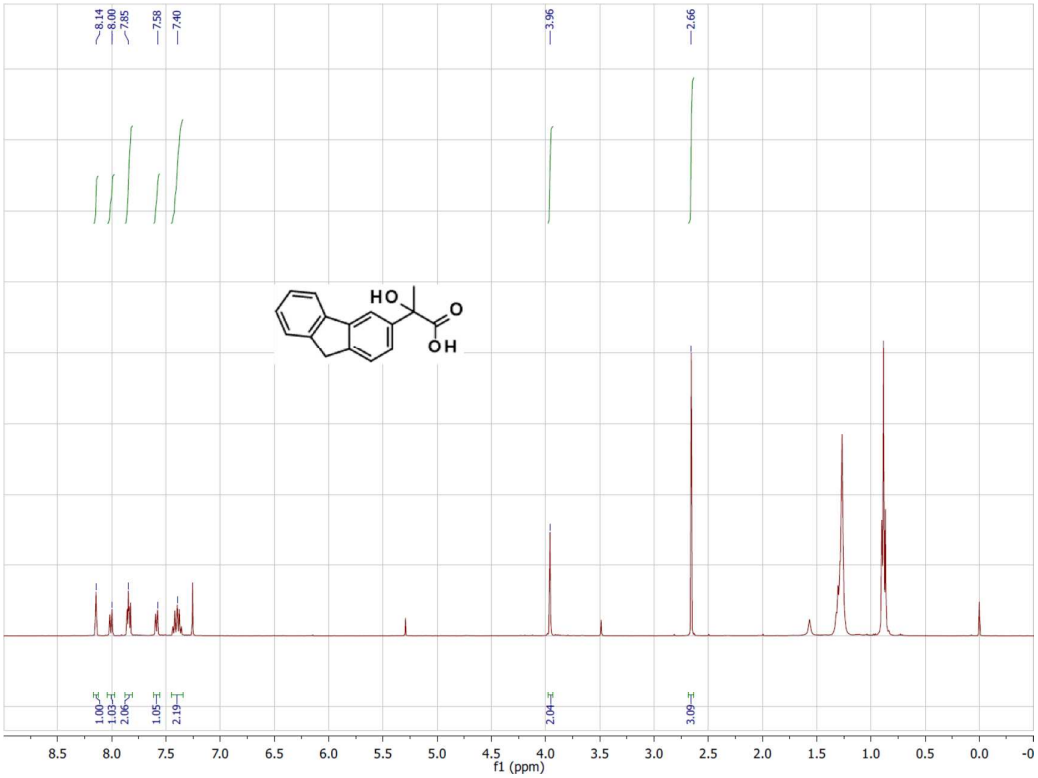


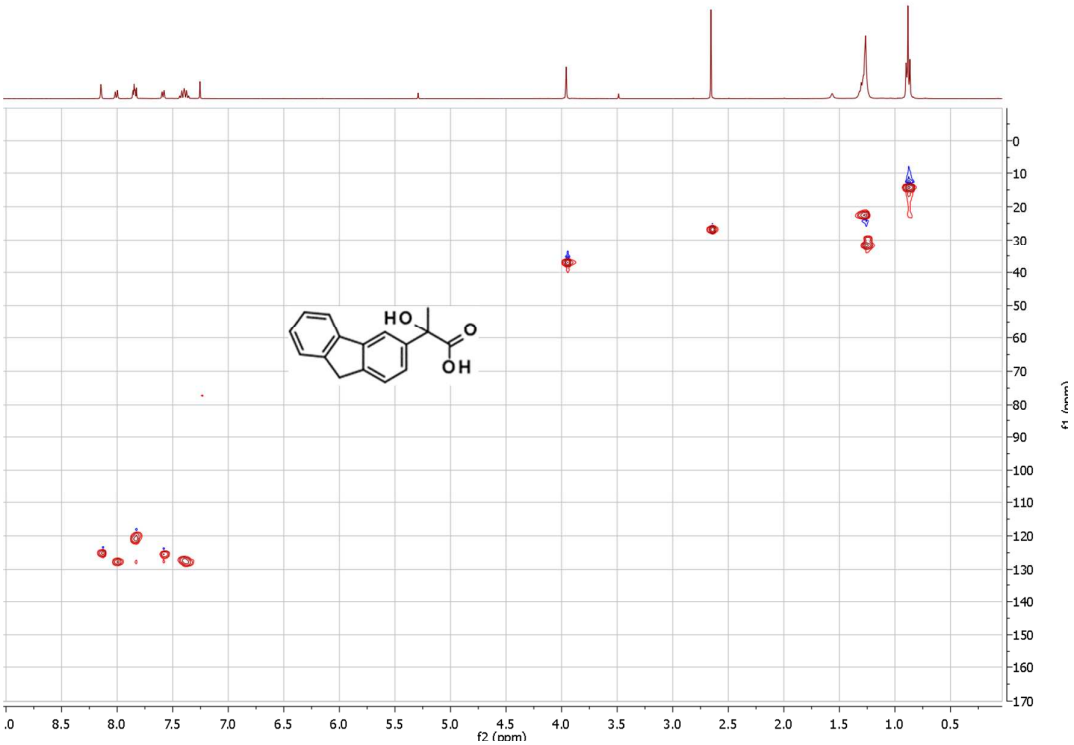
5.17. ^{1}H and ^{13}C NMR spectra of compound 5





5.18. ^{1}H and ^{13}C NMR spectra of compound 10





5.19. ^{1}H NMR spectra of compound 13