Revisiting the Minisci reaction: a new mild amidoalkylation of benzo-fused *N*-heteroaromatic bases under metal-free conditions

Supporting Information

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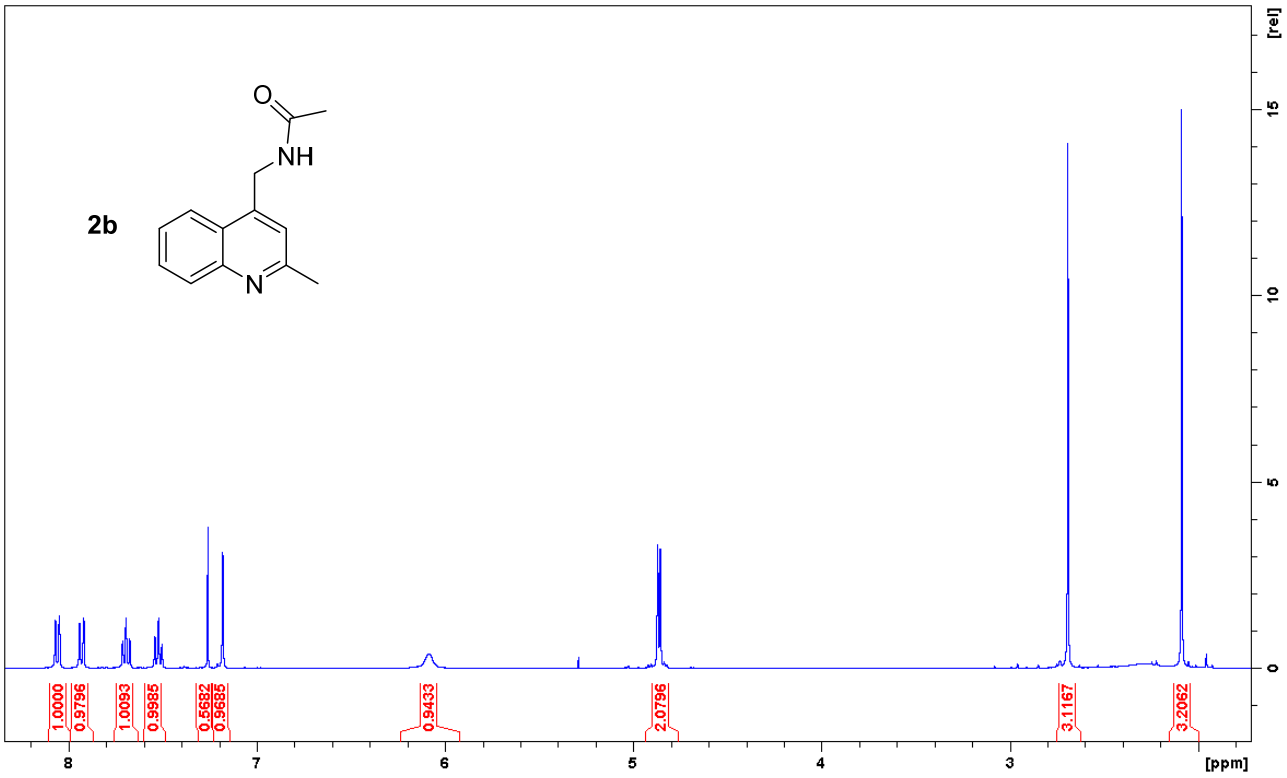
General Information

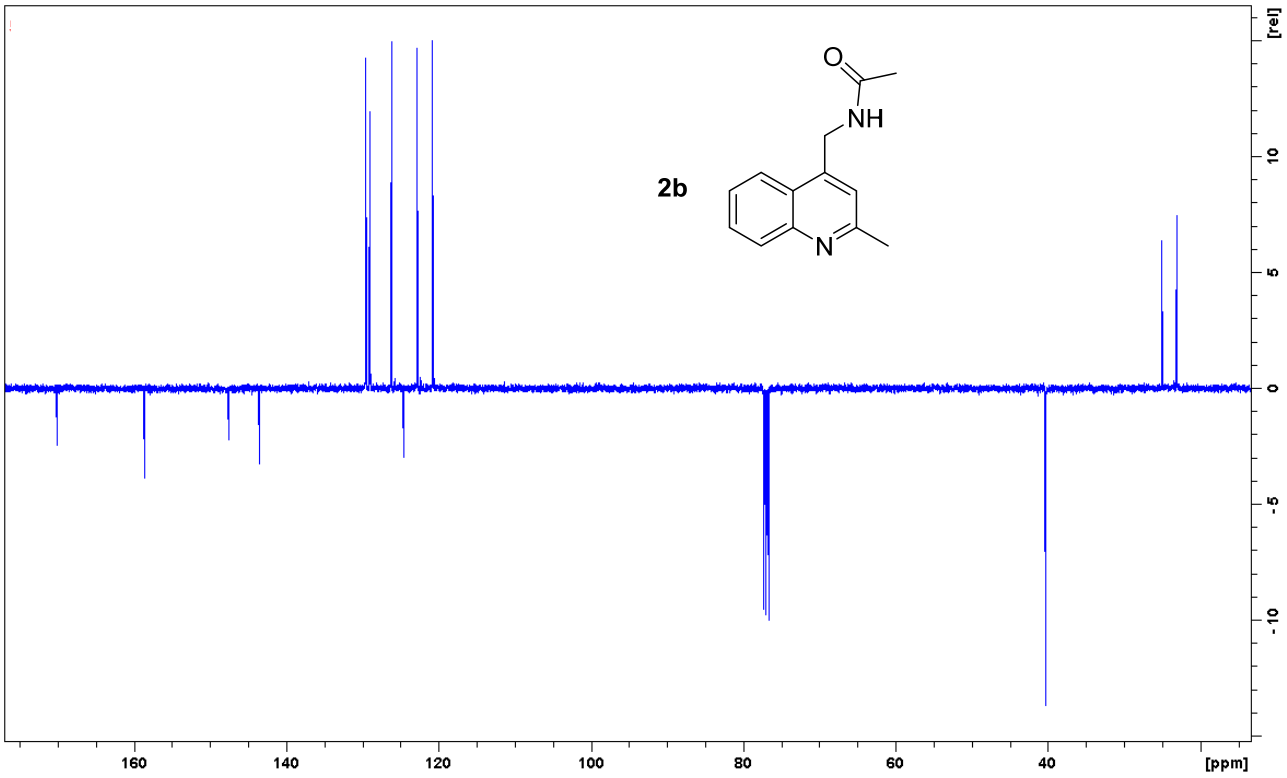
Reagents and solvents (reagent grade) were purchased from Aldrich and used without any further purification. GC-MS analyses were performed on a Agilent 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP5MS column (length 30 m, cross section 0.25 mm); the following temperature program was employed: 50°C (1 min) // 20°C/min // 280°C (20 min). Bruker AV 400 MHz and DRX 500 MHz instruments equipped with a 5 mm multinuclear probe with reverse detection were used to record ^{1}H NMR spectra and ^{13}C NMR; 32 scans were acquired with an acquiring time of 5 seconds for ^{1}H and 512 scans were acquired for ^{13}C with an acquiring time of 5 seconds. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual protonated chloroform or acetonitrile peak. ESI-MS spectrum was recorded with an Esquire 3000 plus ion trap mass spectrometer equipped with an ESI source. Melting point was measured with a Bibby Stuart Scientific SMP1 instrument and is uncorrected.

Part 1: ^{1}H and ^{13}C list of following spectra of isolated new compounds:

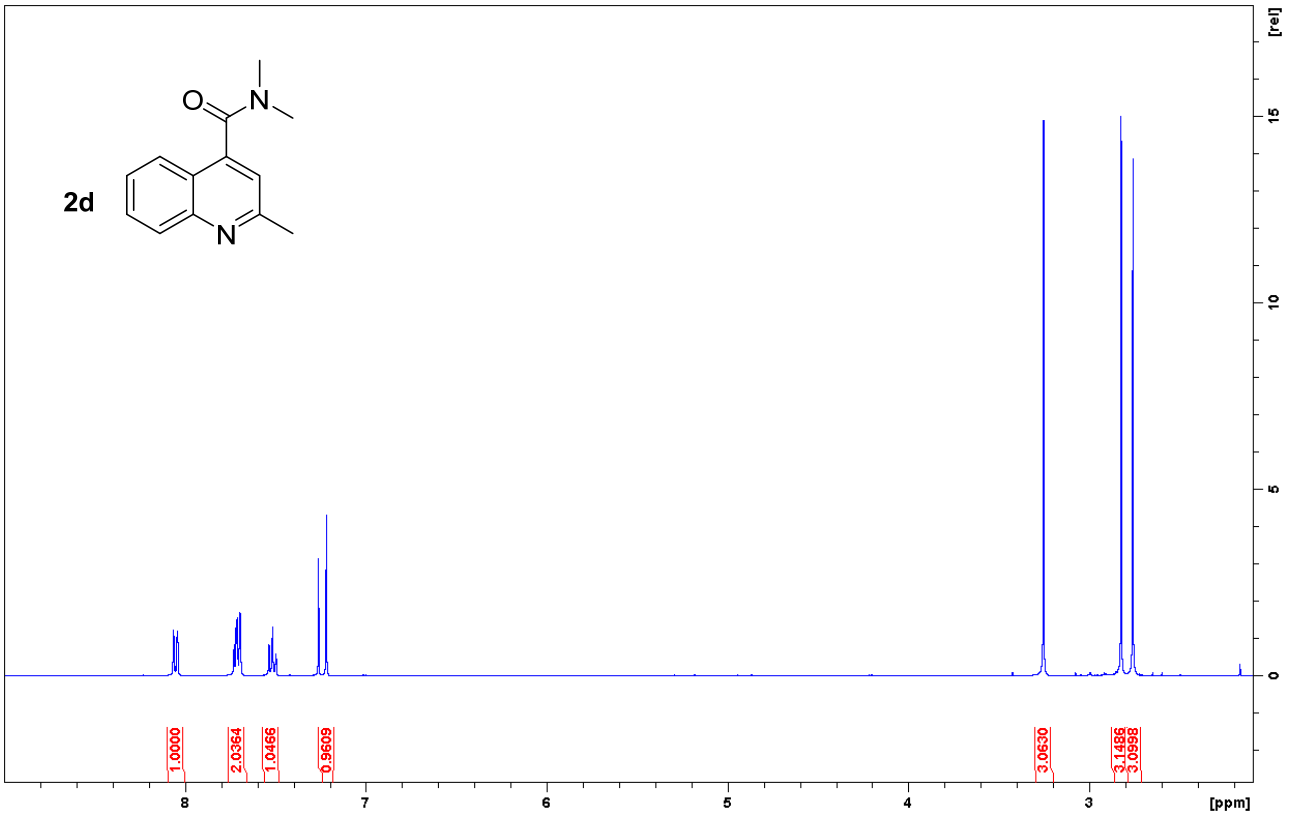
- *N*-((2-methylquinolin-4-yl)methyl)acetamide (**2b**)
- *N*,*N*,2-trimethylquinoline-4-carboxamide (**2d**)
- *N*-((6-methoxyquinolin-4-yl)methyl)-*N*-methylacetamide (**6a**)
- *N*,*N*'-((6-methoxyquinoline-2,4-diyl)bis(methylene))bis(*N*-methylacetamide) (**6b**)
- *N*-((6-methoxyquinolin-2-yl)methyl)-*N*-methylacetamide (**6c**) (^{1}H NMR only)
- *N*,*N*'-(quinoxaline-2,3-diylbis(methylene))bis(*N*-methylacetamide) (**8b**)
- *N*-((4-cyanopyridin-2-yl)methyl)-*N*-methylacetamide (**10a**)
- *N*- ((4-cyanopyridin-2-yl)methyl)acetamide (**10b**)
- *N*-((4-hydroxyquinazolin-2-yl)methyl)-*N*-methylacetamide (**11a**)



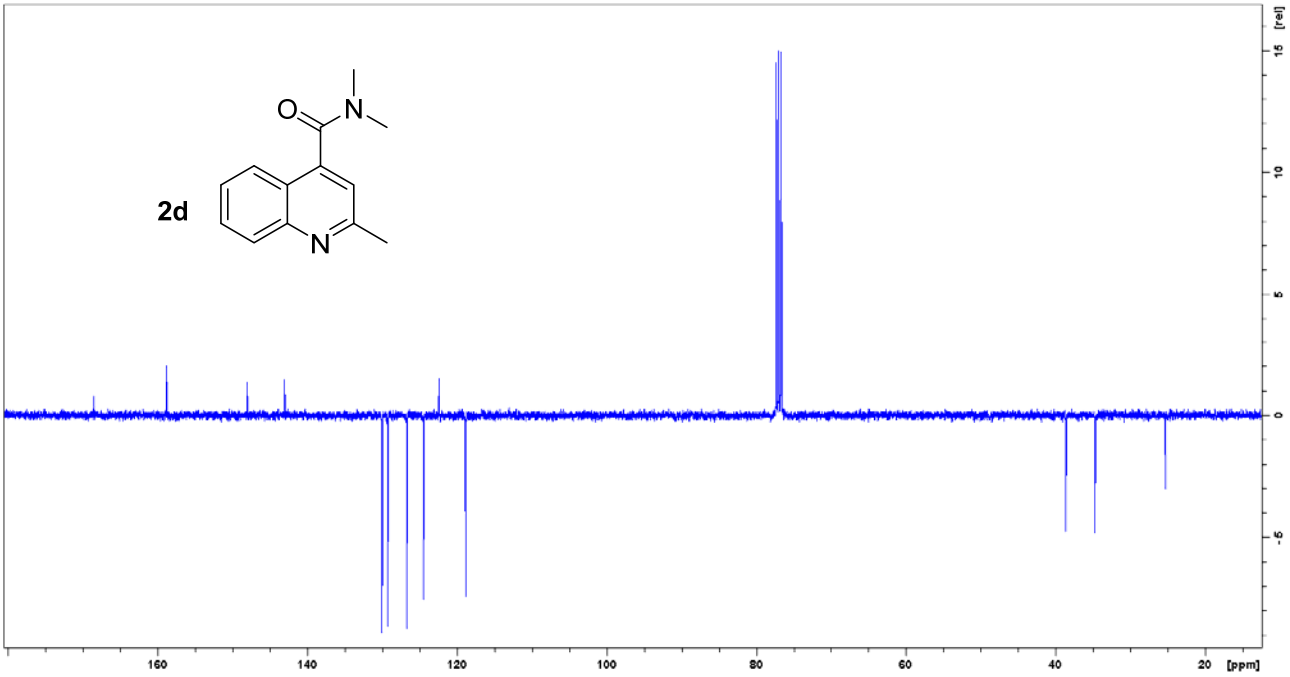
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3H), 2.69 (s, 3H), 4.86 (d, J = 5.8 Hz, 2H), 6.09 (bs, 1H), 7.18 (s, 1H), 7.52 (m, 1H), 7.69 (m, 1H), 7.93 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H) ppm



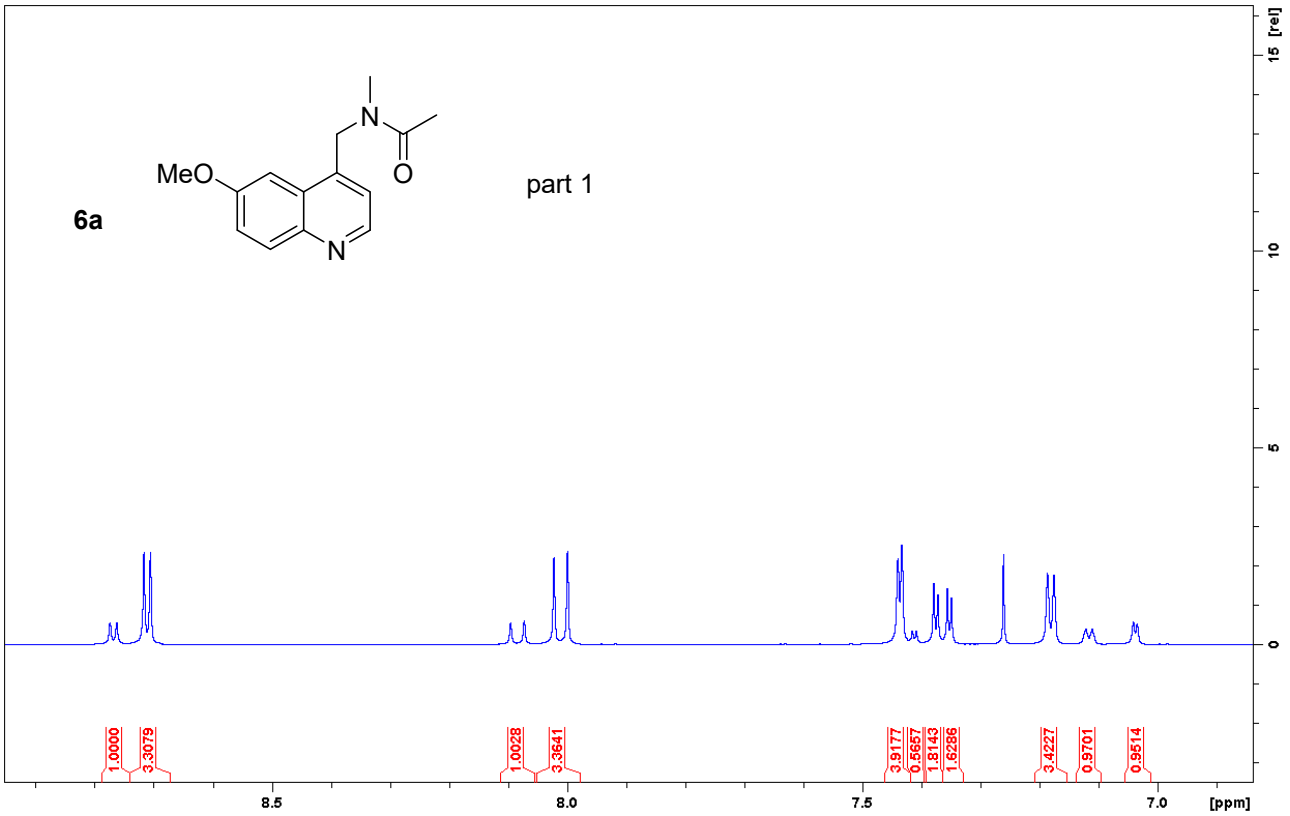
^{13}C NMR APT (100.6 MHz, $CDCl_3$) δ = 23.2, 25.1, 40.4, 120.8, 122.8, 124.6, 126.2, 129.0, 129.6, 143.5, 147.6, 158.7, 170.1 ppm



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (s, 3H), 2.82 (s, 3H), 3.25 (s, 3H), 7.22 (s, 1H), 7.52 (m, 1H), 7.68-7.74 (m, 2H), 8.05 (m, 1H) ppm.



^{13}C APT NMR (100.6 MHz, $CDCl_3$) δ. 25.3, 34.7, 38.6, 118.8, 122.4, 124.5, 126.7, 129.3, 130.0, 143.0, 148.0, 158.8, 168.6 ppm.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O
N
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8.0
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10
5
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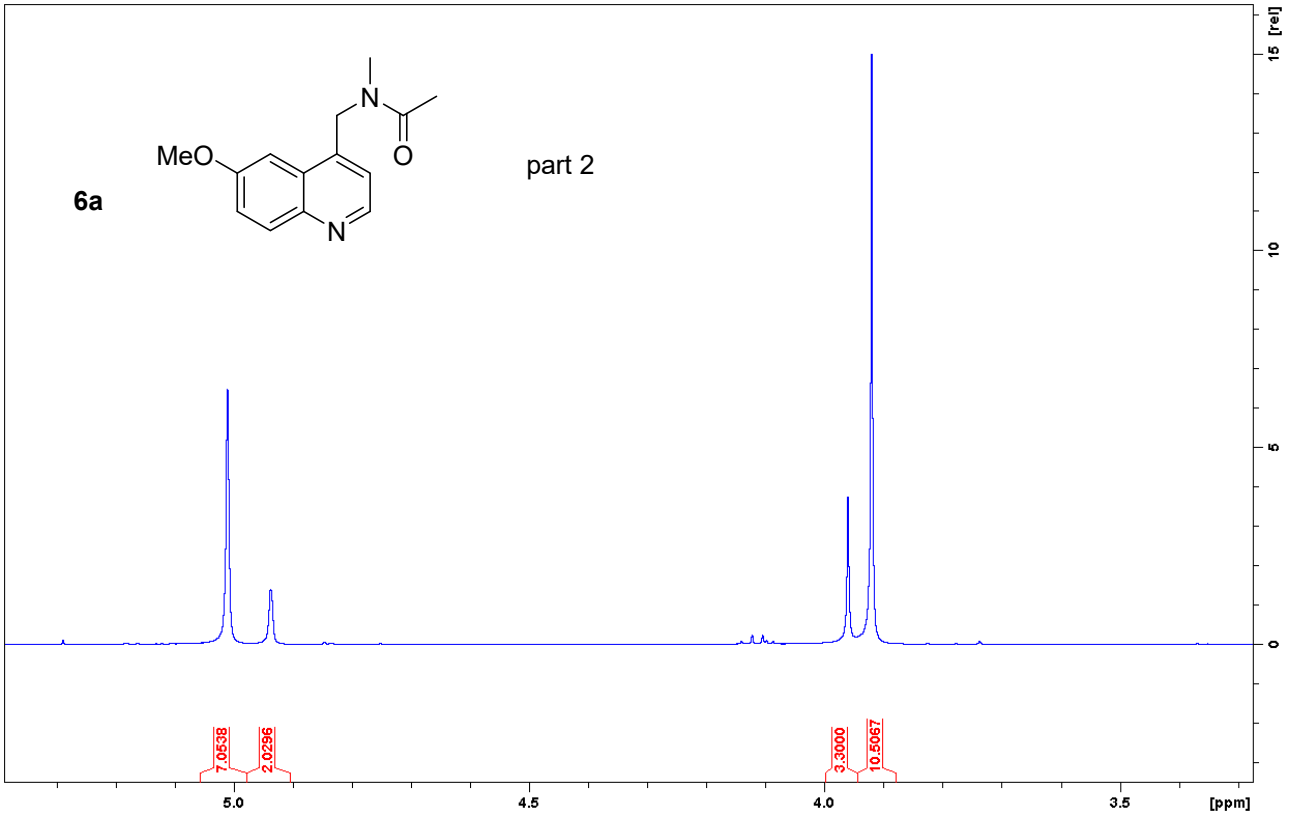
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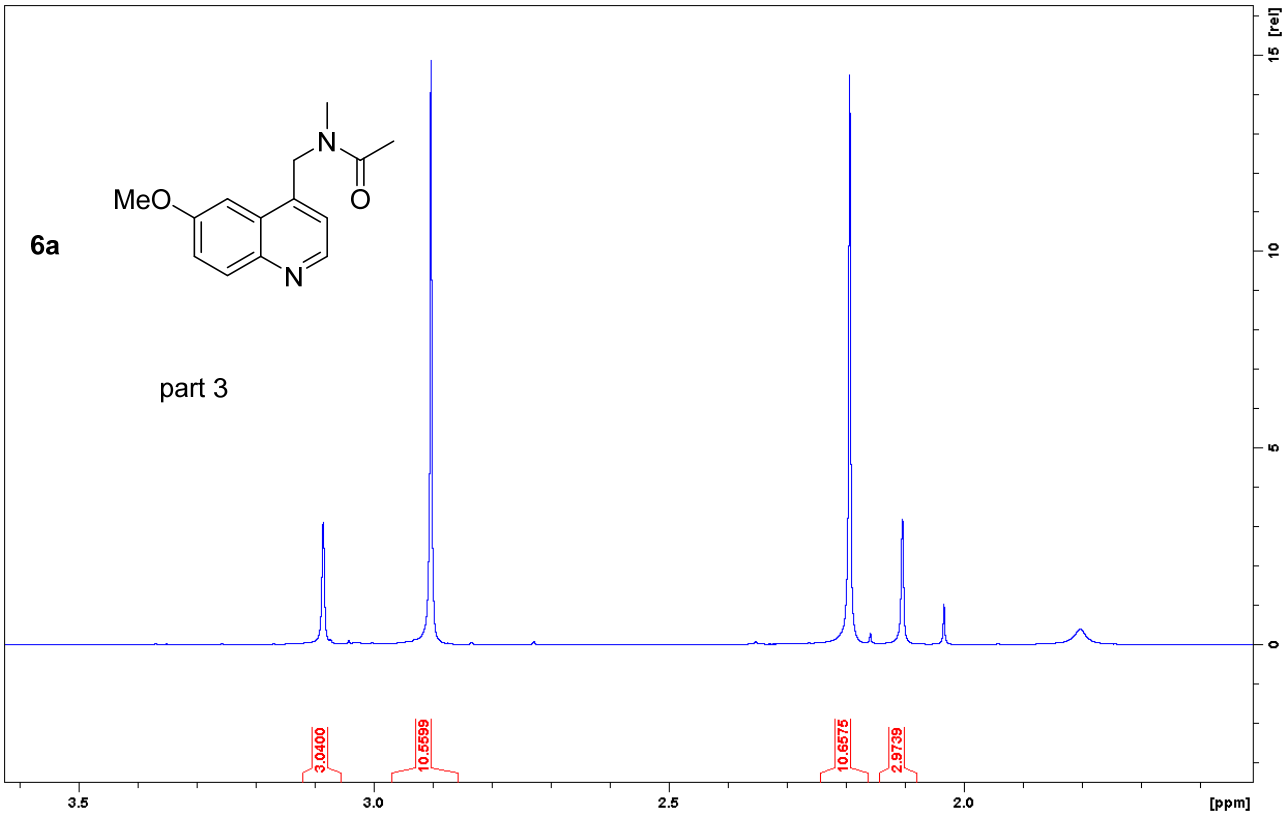
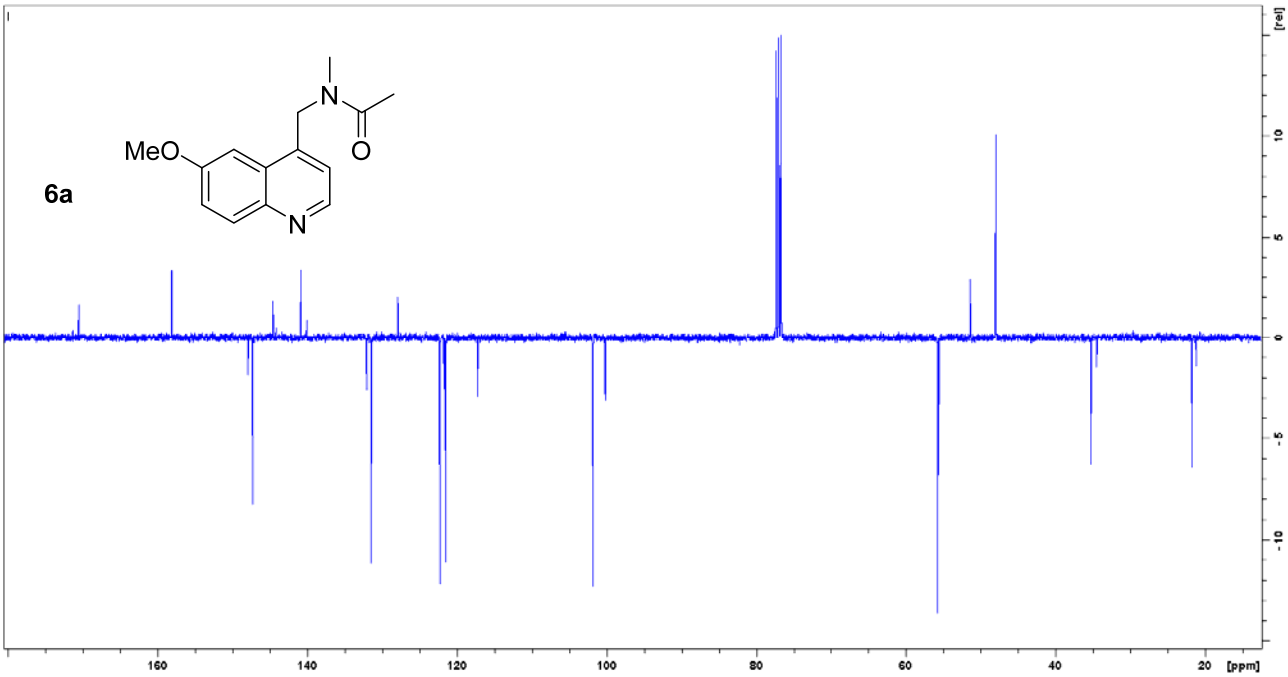
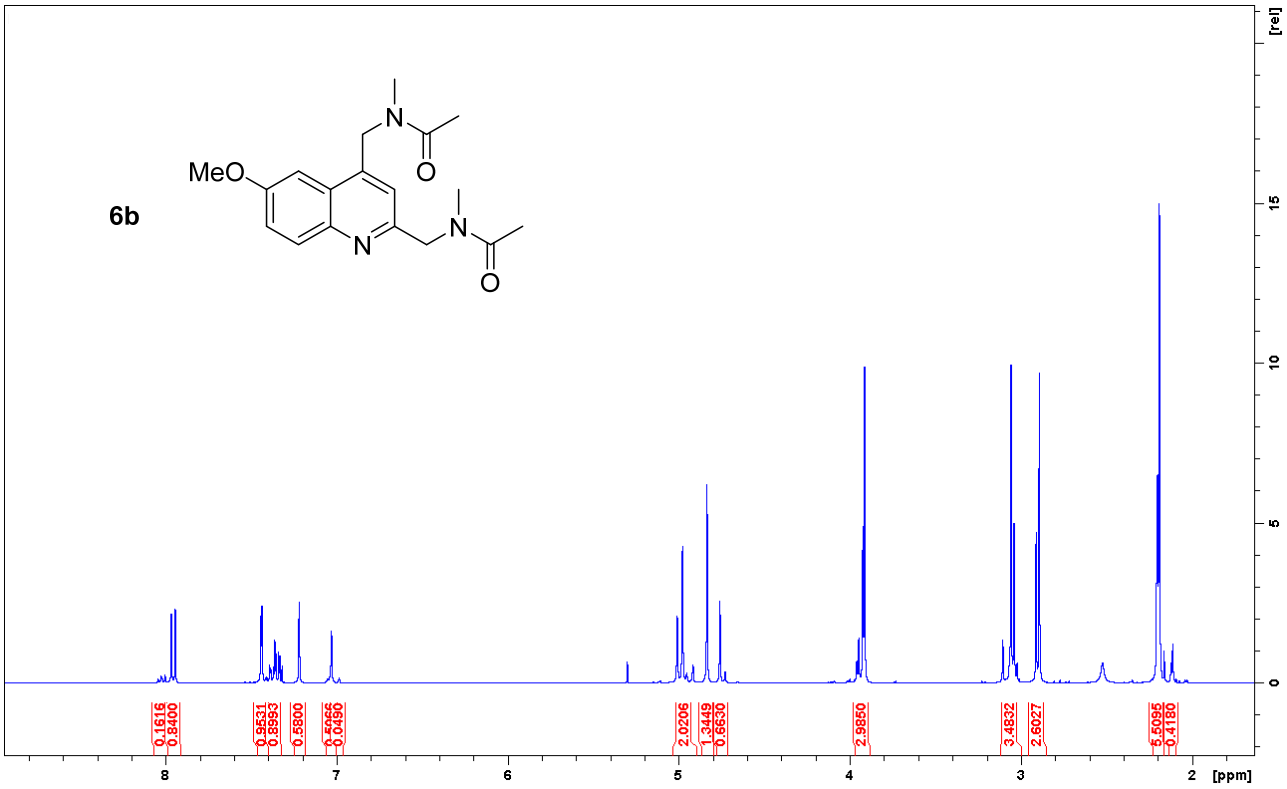


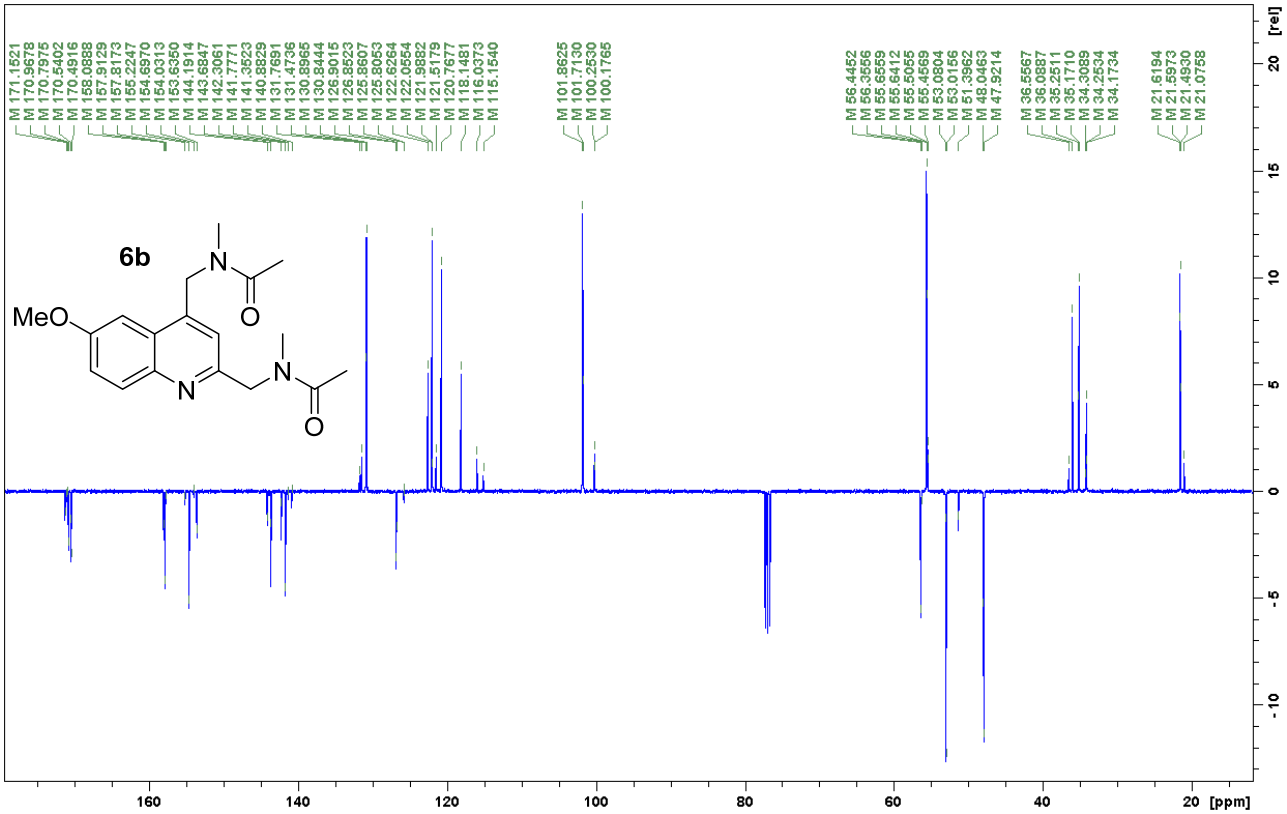
^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.10 (s, 3H, rotamer B), 2.19 (s, 3H, rotamer A), 2.90 (s, 3H, rotamer A), 3.08 (s, 3H, rotamer B), 3.92 (s, 3H, rotamer A), 3.96 (s, 2H, rotamer B), 4.94 (s, 2H, rotamer B), 5.01 (s, 2H, rotamer A), 7.04 (d, J = 2.7 Hz, 1H, rotamer B), 7.12 (bd, J = 4.5 Hz, 1H, rotamer B), 7.18 (d, J = 4.4 Hz, 1H, rotamer A), 7.36 (dd, 1H, J = 9.2 Hz and 2.7 Hz, rotamer A), 7.40-7.45 (m, 1H, rotamer A + 1H, rotamer B), 8.01 (d, J = 9.2 Hz, 1H, rotamer A), 8.08 (d, J = 9.2 Hz, 1H, rotamer B), 8.71 (d, J = 4.4 Hz, 1H, rotamer A), 8.77 (d, J = 4.5 Hz, 1H, rotamer B) ppm.



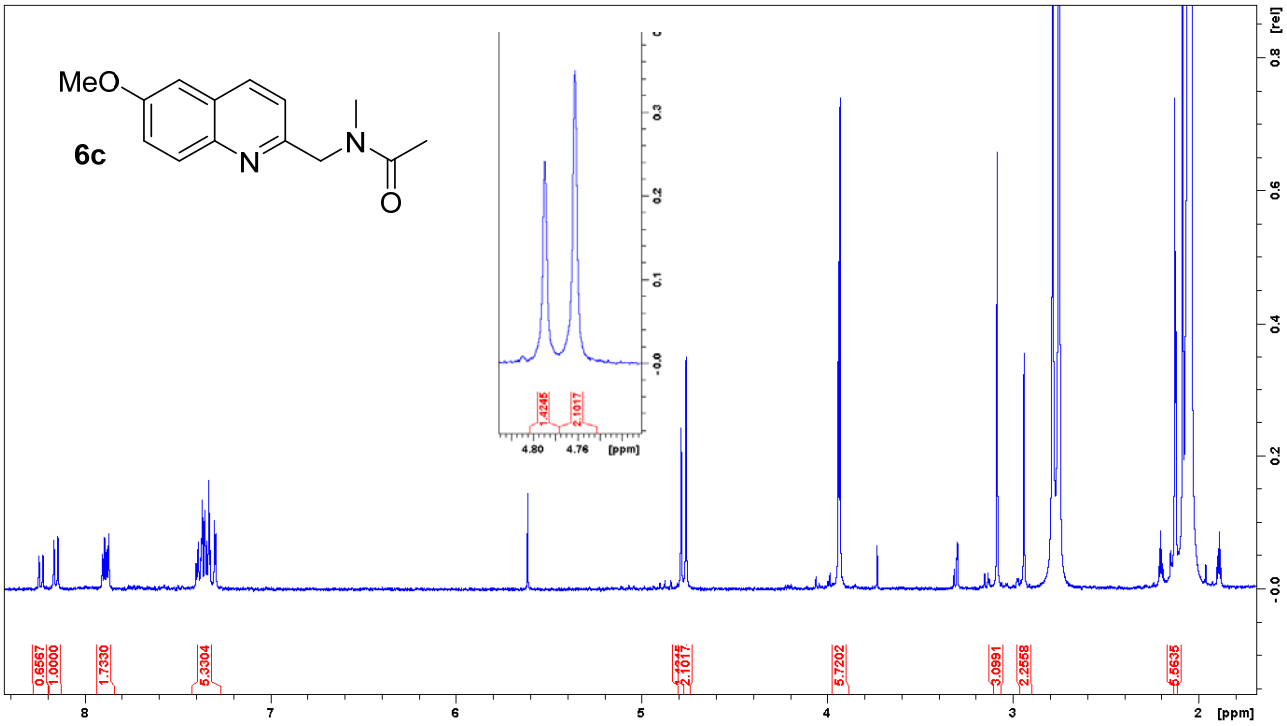
^{13}C APT NMR (100.6 MHz, $CDCl_3$) δ = 21.2, 21.7, 34.5, 35.3, 48.0, 51.4, 55.6, 55.8, 100.2, 101.8, 117.3, 121.5, 121.7, 122.3, 127.9, 131.5, 132.1, 140.1, 140.9, 144.2, 144.6, 147.3, 147.9, 158.1, 170.6, 171.4 ppm.



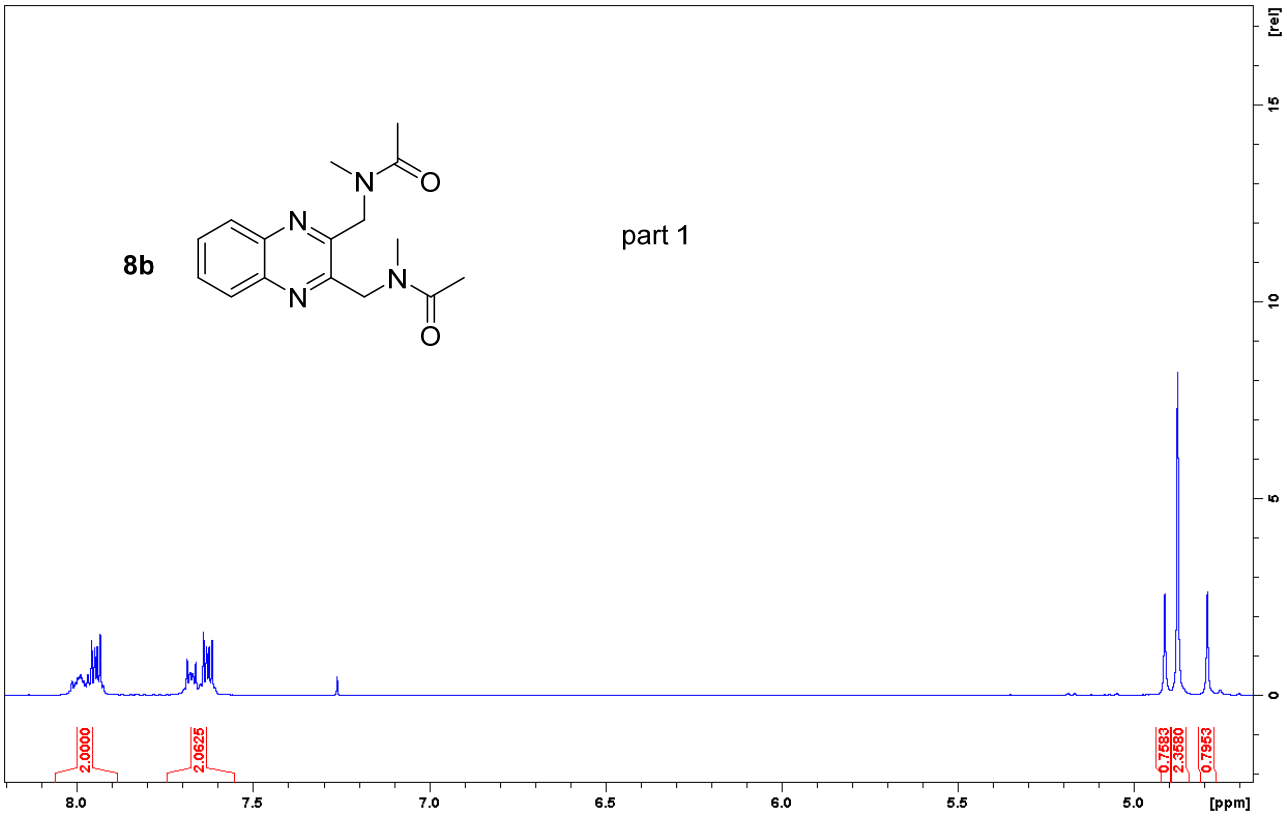
^{1}H NMR (400 MHz, $CDCl_3$), mixture of all rotamers

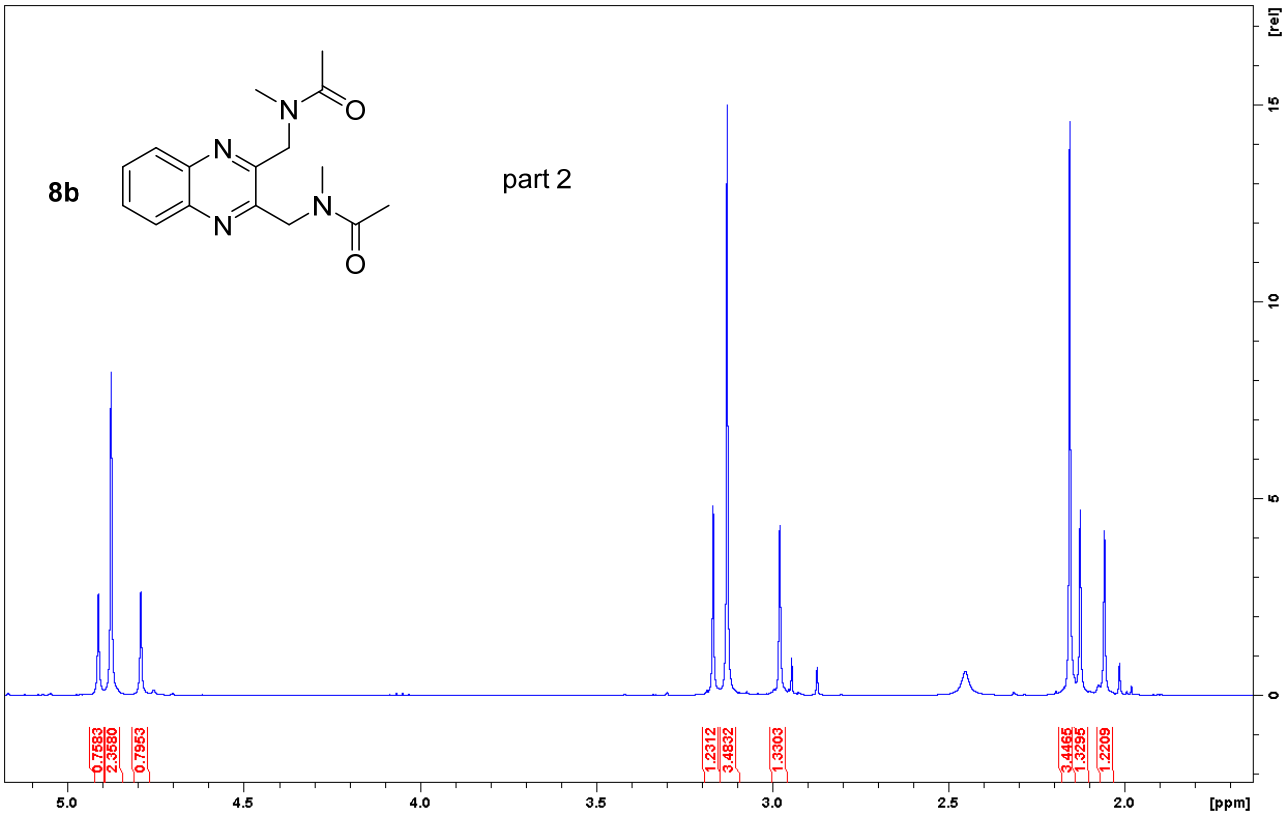


^{13}C APT NMR (100.6 MHz, $CDCl_3$), mixture of all rotamers

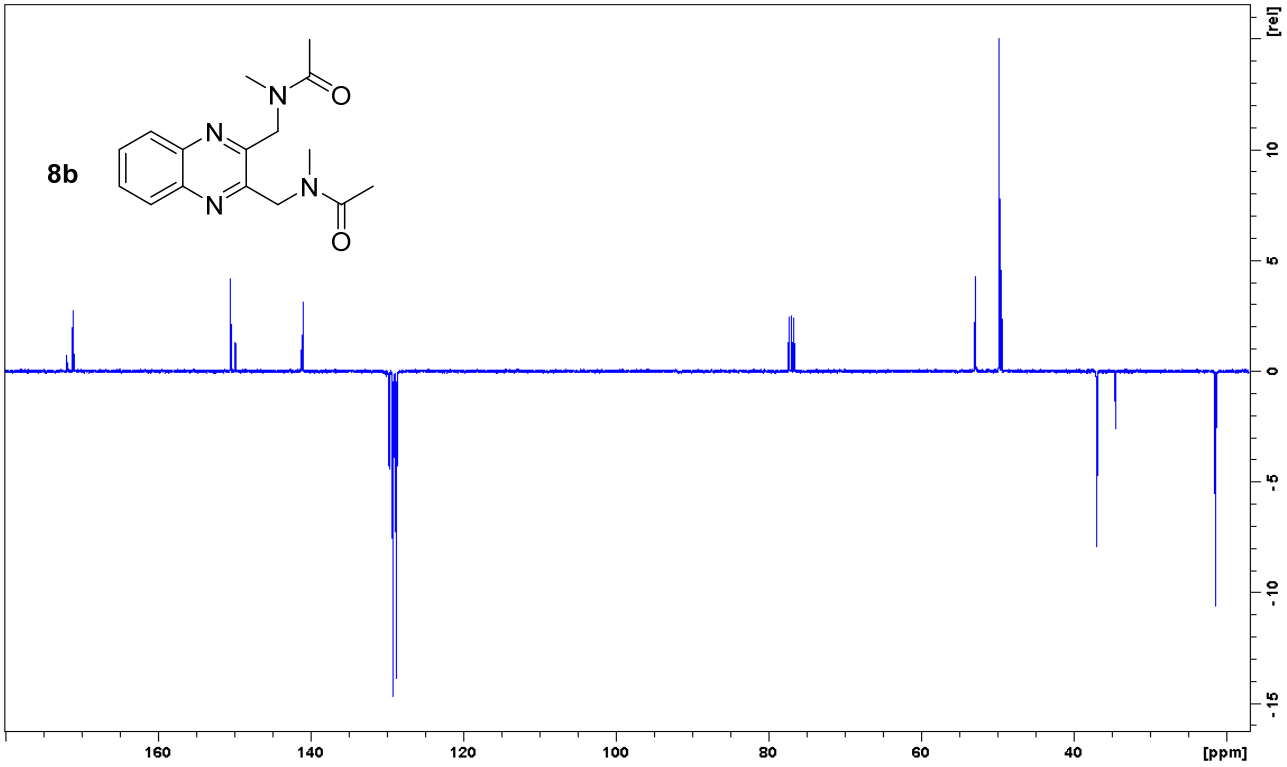


^{1}H NMR (400 MHz, acetone,d6) δ = 2.13 (2×s, 3H, rotamer A, 3H, rotamer B), 2.94 (s, 3H, rotamer B), 3.09 (s, 3H, rotamer A), 3.94 (2×s, 3H, rotamer A, 3H, rotamer B), 4.76 (s, 2H, rotamer A), 4.79 (s, 2H, rotamer B), 7.28-7.41 (m, 3H, rotamer A, 3H, rotamer B), 7.86-7.91 (m, 1H, rotamer A, 1H, rotamer B), 8.16 (d, J = 8.5 Hz, 1H, rotamer A), 8.24 (d, J = 8.5 Hz, 1H, rotamer B) ppm.

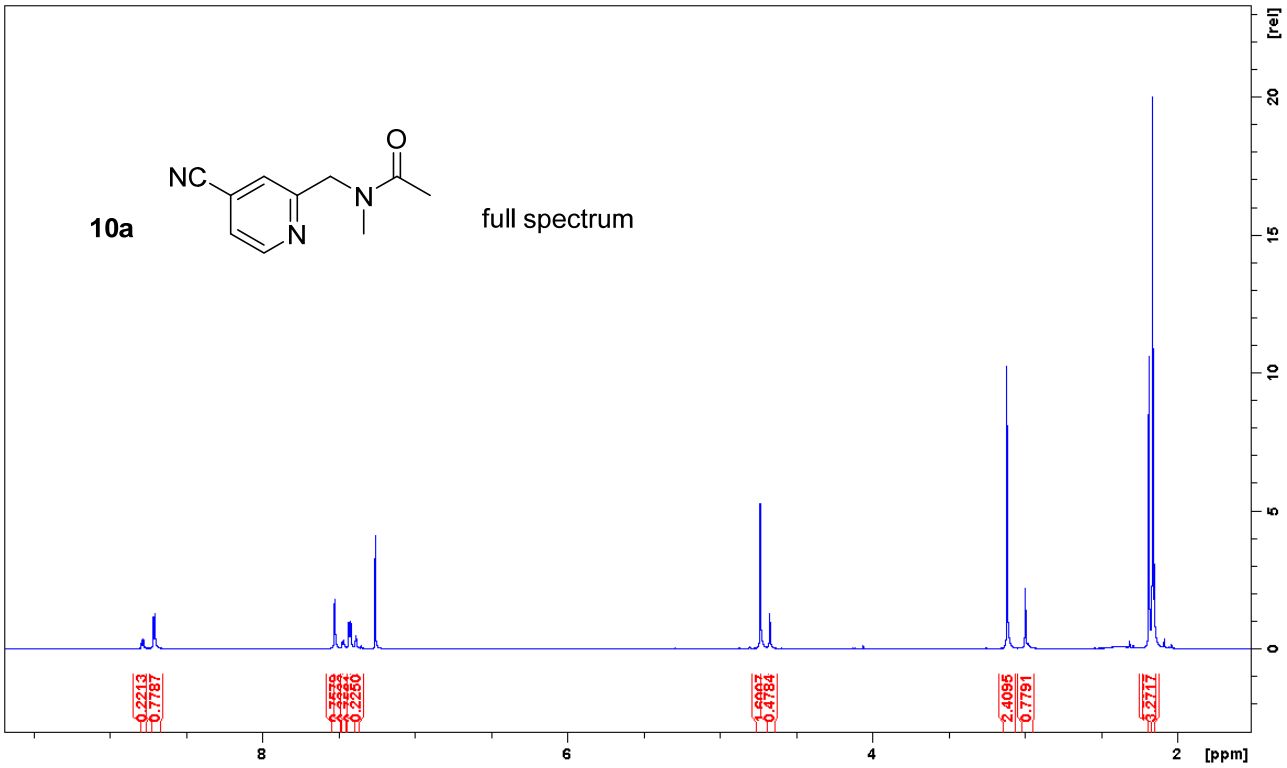




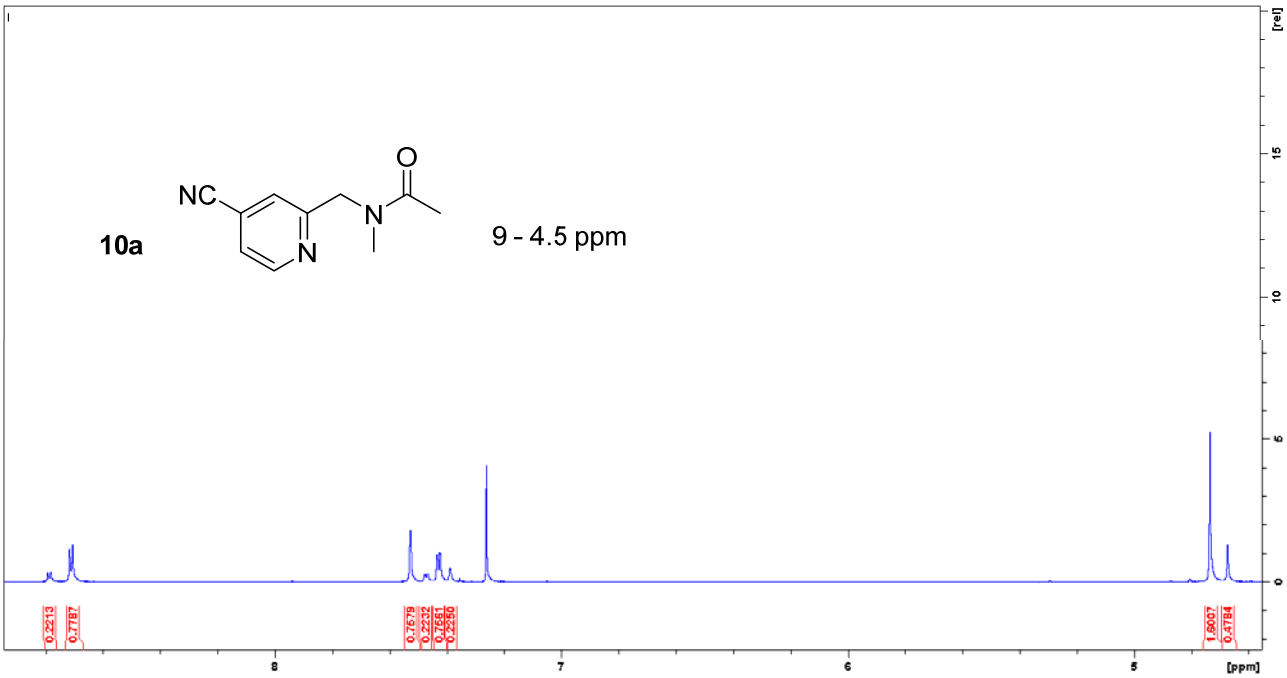
^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.06 (s, 6H, rotamer C), 2.12 (s, 6H, rotamer B), 2.15 (s, 6H, rotamer A), 2.98 (s, 6H, rotamer B), 3.13 (s, 6H, rotamer A), 3.17 (s, 6H, rotamer C), 4.79 (s, 4H, rotamer B), 4.87 (s, 4H, rotamer A), 4.91 (s, 4H, rotamer C), 7.60-7.70 (m, 2H, mix of rotamers), 7.90, 8.05 (m, 2H, mix of rotamers) ppm.

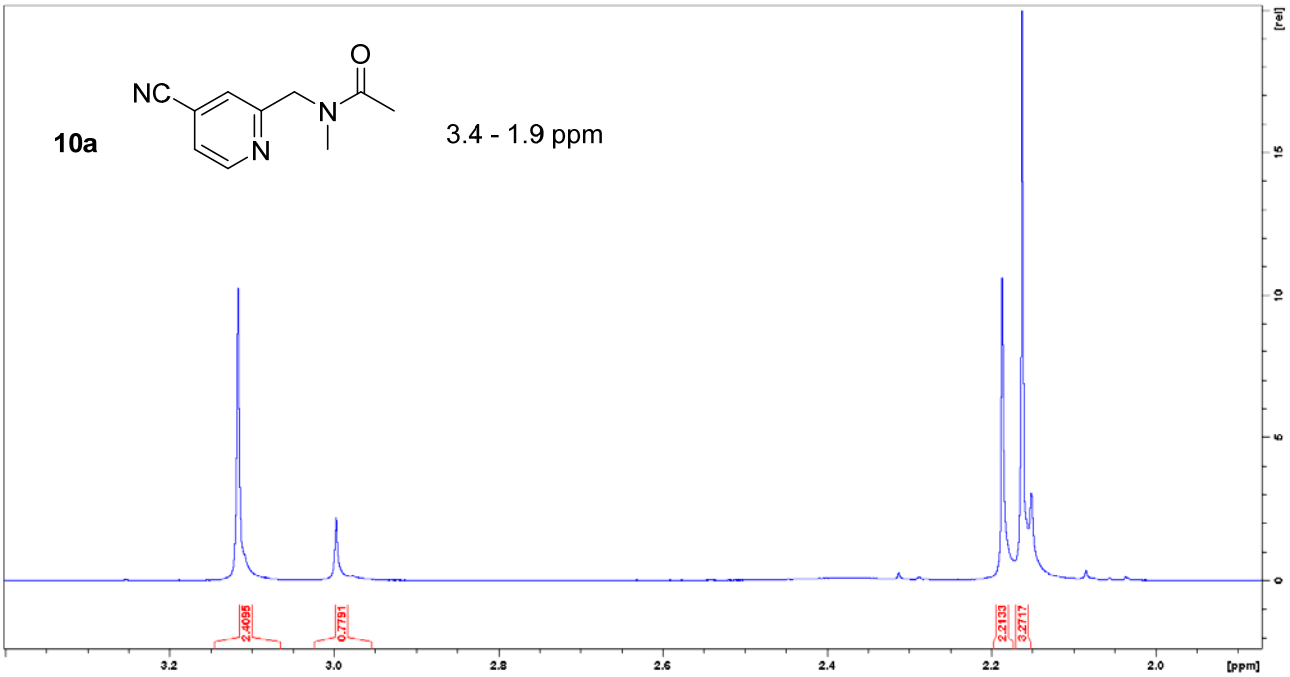


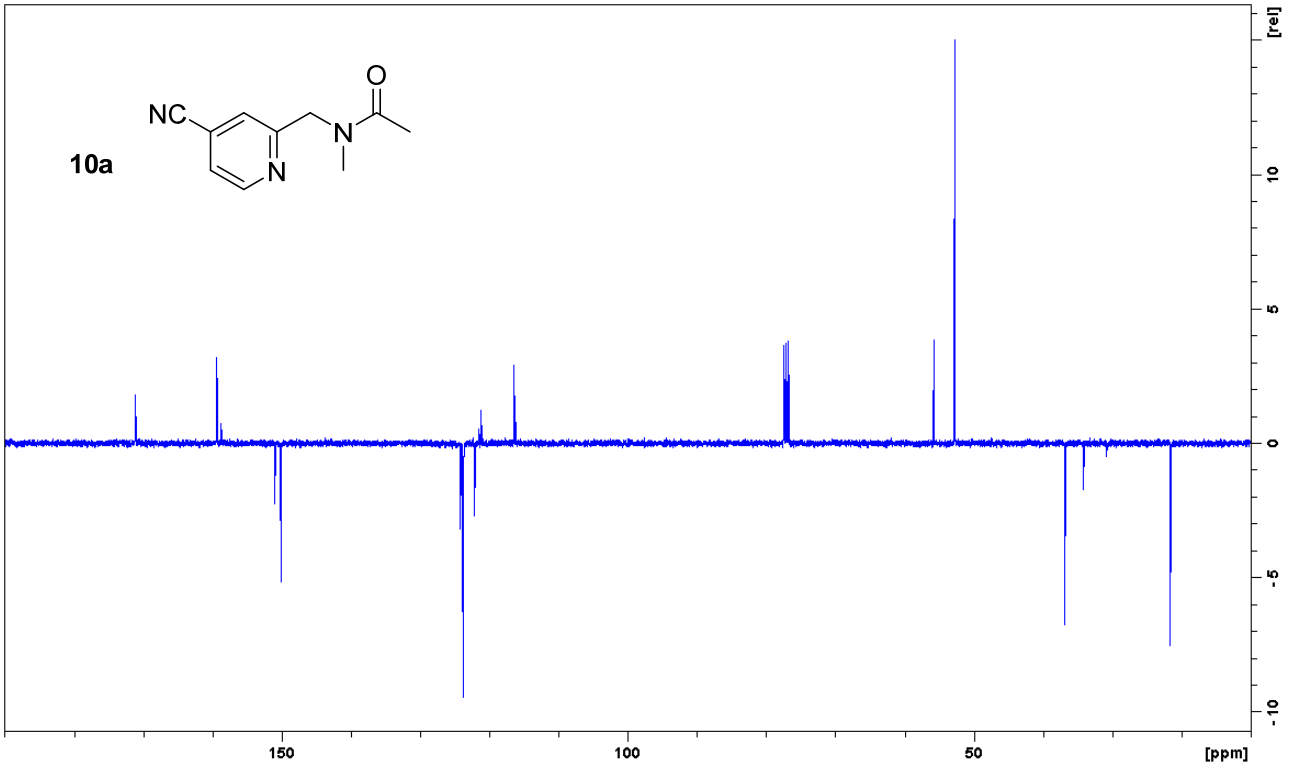
^{13}C APT NMR (100.6 MHz, $CDCl_3$) δ = 21.2, 21.5, 34.5, 36.9, 37.0, 49.5, 49.8, 52.9, 128.7, 128.8, 129.1, 129.2, 129.7, 129.8, 140.9, 141.0, 141.3, 149.8, 149.9, 150.5, 171.0, 171.1, 171.9 ppm.



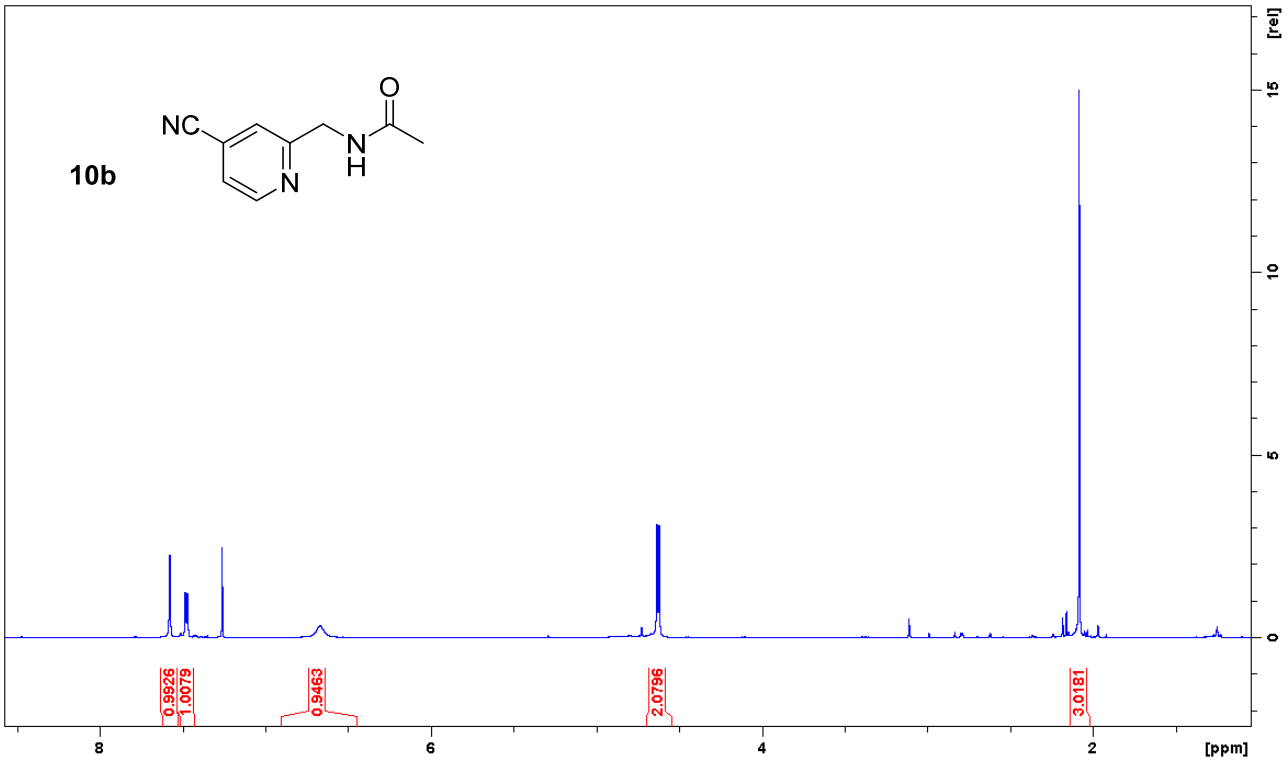
^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.16 (s, 3H, rotamer A), 2.19 (s, 3H, rotamer B), 3.00 (s, 3H, b), 3.12 (s, 3H, rotamer A), 4.67 (s, 2H, rotamer B), 4.73 (s, 2H, rotamer A), 7.39 (s, 2H, rotamer B), 7.43 (dd, J = 4.9 Hz and 1.4 Hz, 1H, rotamer A), 7.47 (d, J = 4.9 Hz, 1H, rotamer B), 7.53 (bs, 1H, rotamer A), 8.71 (d, J = 4.9 Hz, 1H, rotamer A), 8.79 (d, J = 4.9 Hz, 1H, rotamer B) ppm.



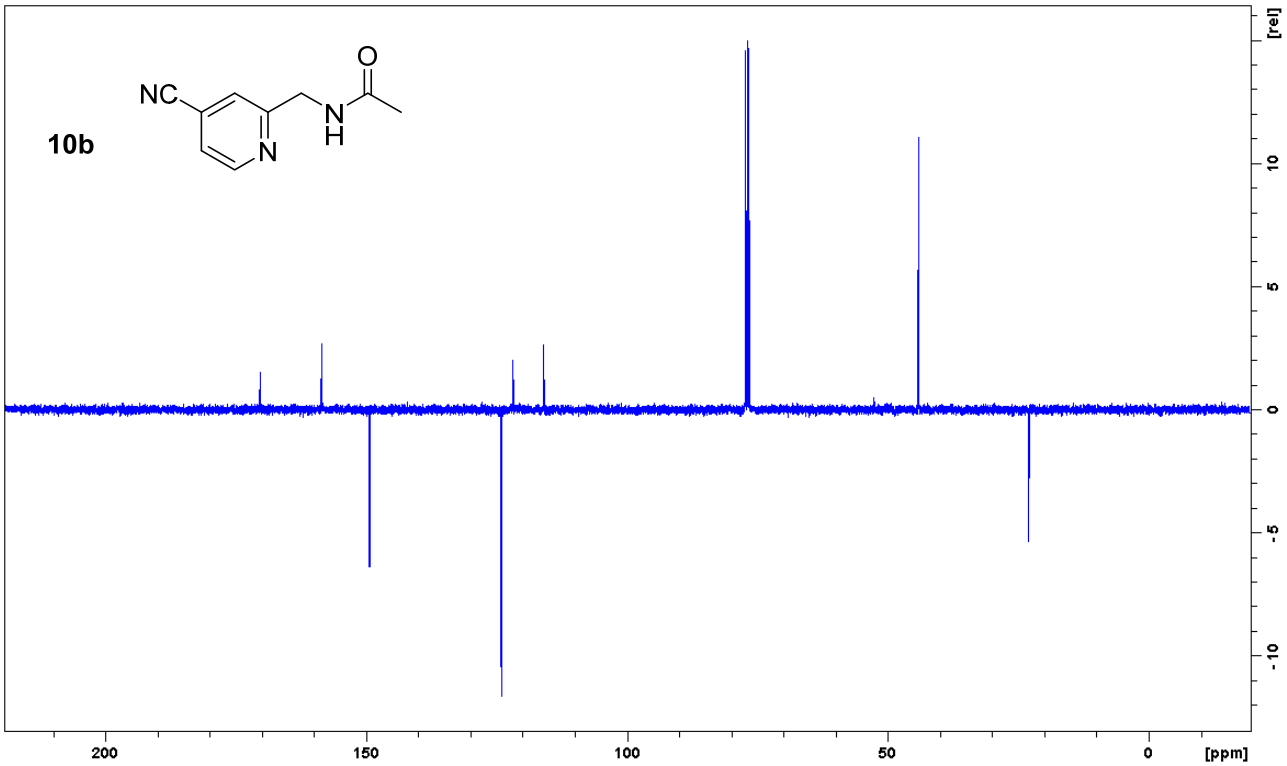




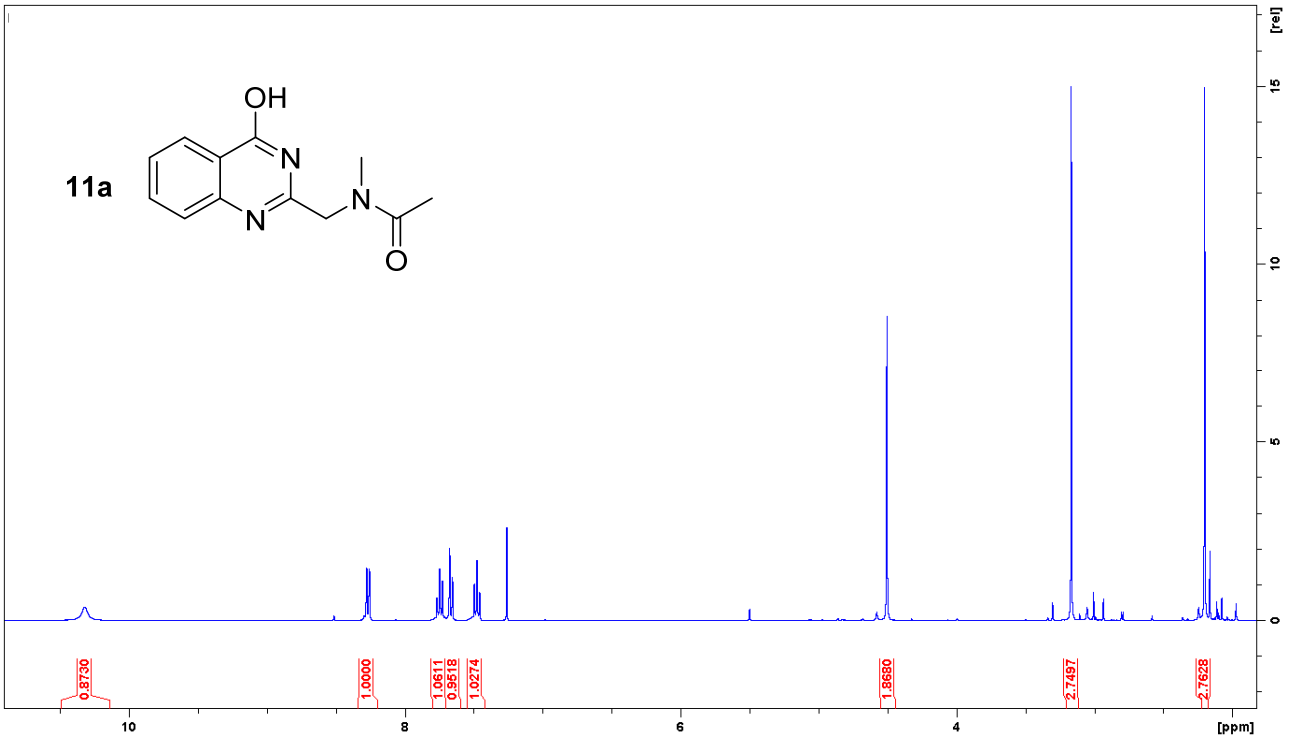
^{13}C APT NMR (100.6 MHz, $CDCl_3$) δ = 21.4, 21.5, 34.1, 36.8, 52.7, 55.7, 116.1, 116.3, 121.1, 121.4, 122.0, 44.1, 123.6, 123.7, 124.1, 150.0, 150.9, 158.6, 159.3, 171.0, 171.1 ppm.



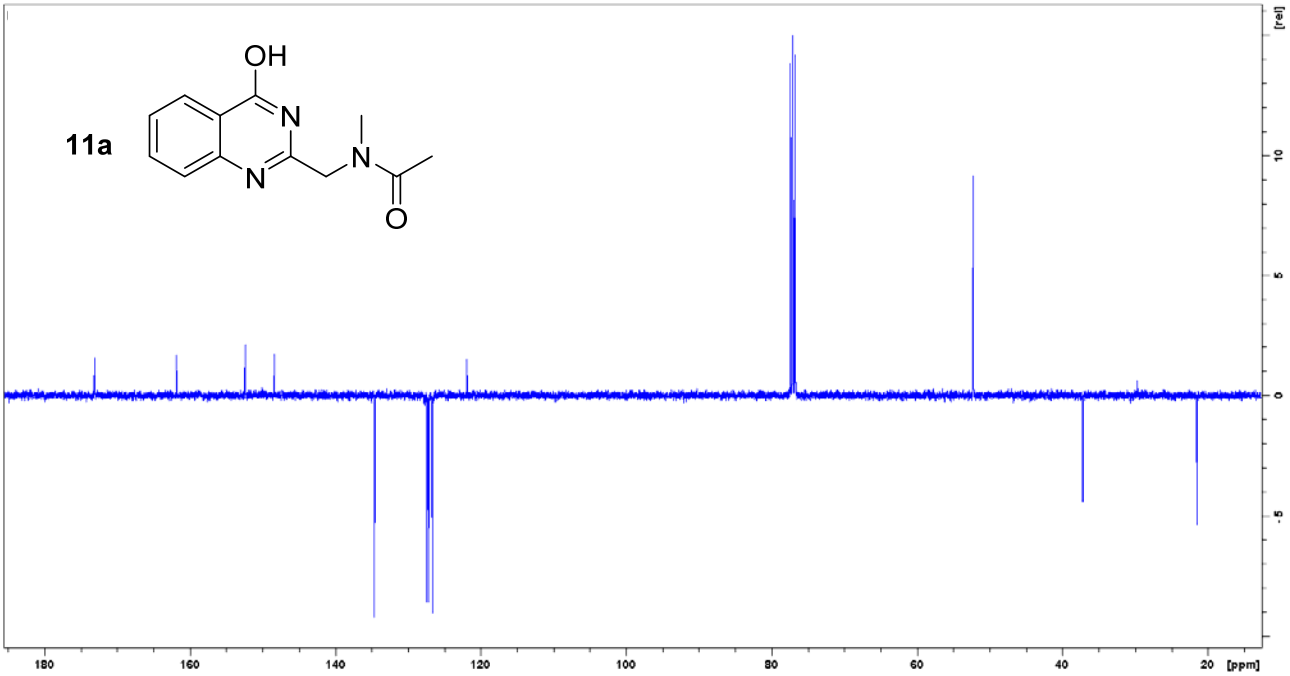
^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.08 (s, 3H), 4.63 (d, J = 5.4 Hz, 2H), 6.67 (bs, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.58 (s, 1H), 8.72 (d, J = 5.0 Hz, 1H) ppm.



^{13}C APT NMR (100.6 MHz, $CDCl_3$) δ = 23.1, 44.1, 116.0, 121.9, 124.1, 124.2, 149.4, 158.5, 170.4 ppm.



^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.20 (s, 3H), 3.17 (s, 3H), 4.51 (s, 2H), 7.48 (m, 1H), 7.67 (bd, J = 8.0 Hz, 1H), 7.75 (m, 1H), 8.27 (m, J = 1.0, 1H), 10.32 (bs, 1H) ppm.



^{13}C APT NMR (100.6 MHz, $CDCl_3$) δ = 21.4, 37.1, 52.2, 121.9, 126.6, 127.1, 127.3, 134.5, 148.3, 152.3, 161.8, 173.1 ppm.

Part 2: Identification and comparison procedure of known compounds

All the experiments were analysed as follow: a known amount of internal standard (1,4-dimethoxybenzene or benzophenone, >99% by Aldrich) was added to the reaction mixture, then a sample of the resulting mixture was diluted in CD_3CN (D_2O for experiment with 4-hydroxyquinazoline) and analysed by ^1H NMR. Due to the presence of amide and the use of a different deuterated solvent, the chemical shifts of the signals were generally shifted with respect to the spectra of the corresponding products reported in literature (typically acquired in $CDCl_3$). For these reasons, another sample of the same reaction mixture was diluted in aqueous saturated $NaHCO_3$ solution, extracted with dichloromethane and the solvent evaporated. A sample of the obtained residue was dissolved in $CDCl_3$ and re-analysed by ^1H NMR and another sample was analysed by GC-MS. The ^1H NMR spectra generally showed chemical shifts closer to those reported in literature, however the presence of residual amide, even in very low quantities, again showed small shifts in the signals. Notice that the yields evaluated after these simple extractions were very close to those calculated on the reaction mixture except in the case of 4-cyanopyridine because of partial solubility in water of both reagent and corresponding product. The ^1H NMR analysis in $CDCl_3$ of another reaction mixture sample, washed many times with water/brine after the extraction in order to eliminate the residual amide, showed chemical shifts very close to those reported in literature (see #1).

Notice that the crude of reaction of 6-fluoro-2-methylquinoline with DMA (resulting product **4a**) was analyzed immediately after the dilution in CD_3CN because in about 1 hour the product began to precipitate.

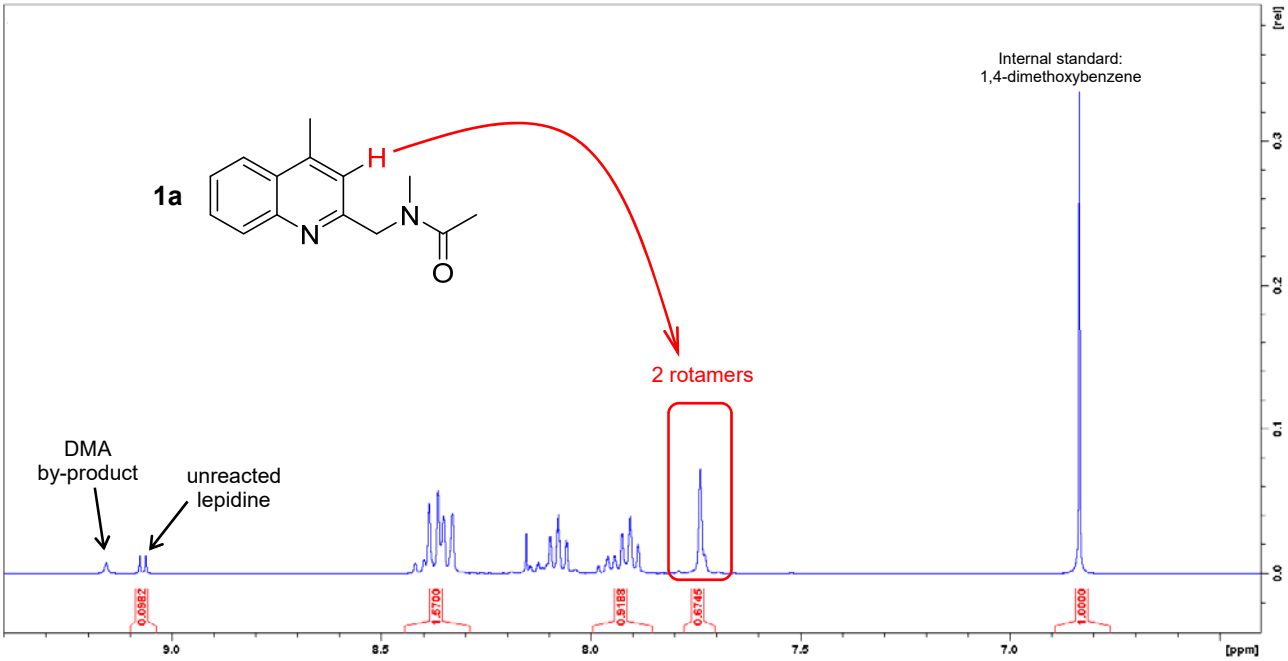
In the reaction of quinaldine with DMF (#6) the yields were determined by GC-MS. The main product (**2c**) was purified by flash chromatography and utilized to calculate the GC-MS correction factor vs the internal standard.

Identification and quantification by spectral data.

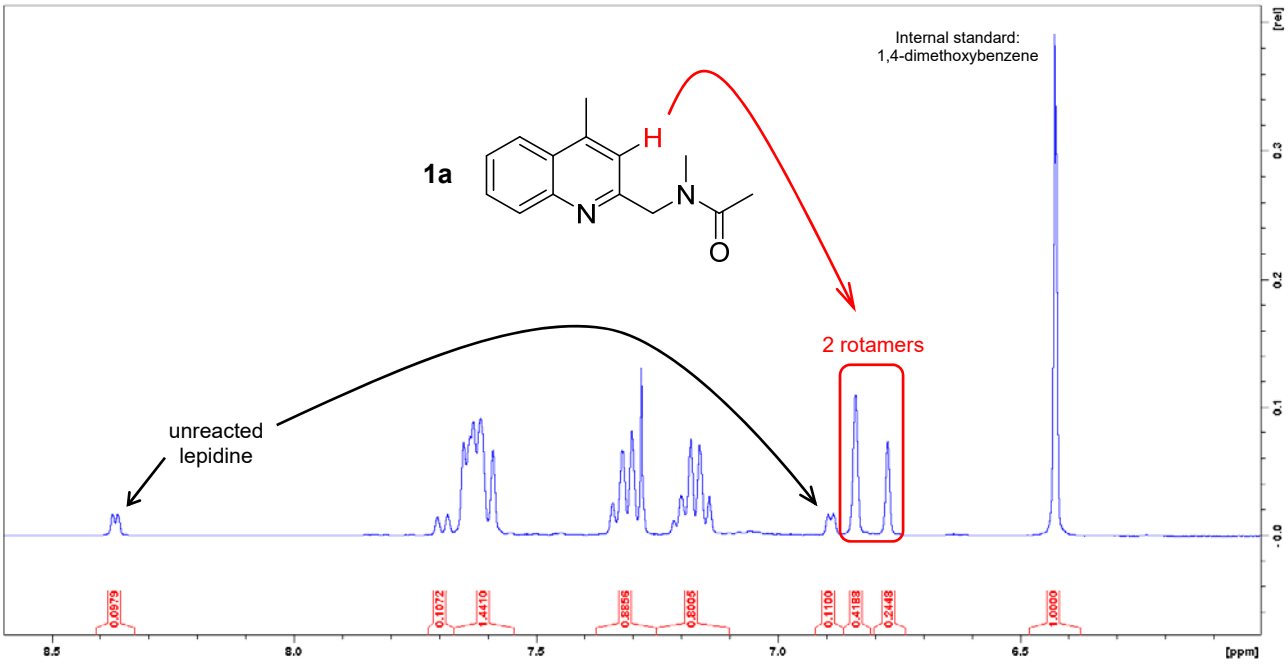
- **#1** ^1H NMR and GC-MS of product **1a**
- **#2** ^1H NMR and GC-MS of product **1b**
- **#3** ^1H NMR and GC-MS of product **1c**
- **#4** ^1H NMR and GC-MS of products **1d** and **1e**
- **#5** ^1H NMR and GC-MS of product **2a**

- **#6** GC-MS of product **2c**
- **#7** ^{1}H NMR and GC-MS of product **3a**
- **#8** ^{1}H NMR and GC-MS of product **4a**
- **#9** ^{1}H NMR and GC-MS of product **5a**
- **#10** ^{1}H NMR and GC-MS of product **7a**
- **#11** ^{1}H NMR and GC-MS of product **8a**
- **#12** ^{1}H NMR and GC-MS of product **9a**

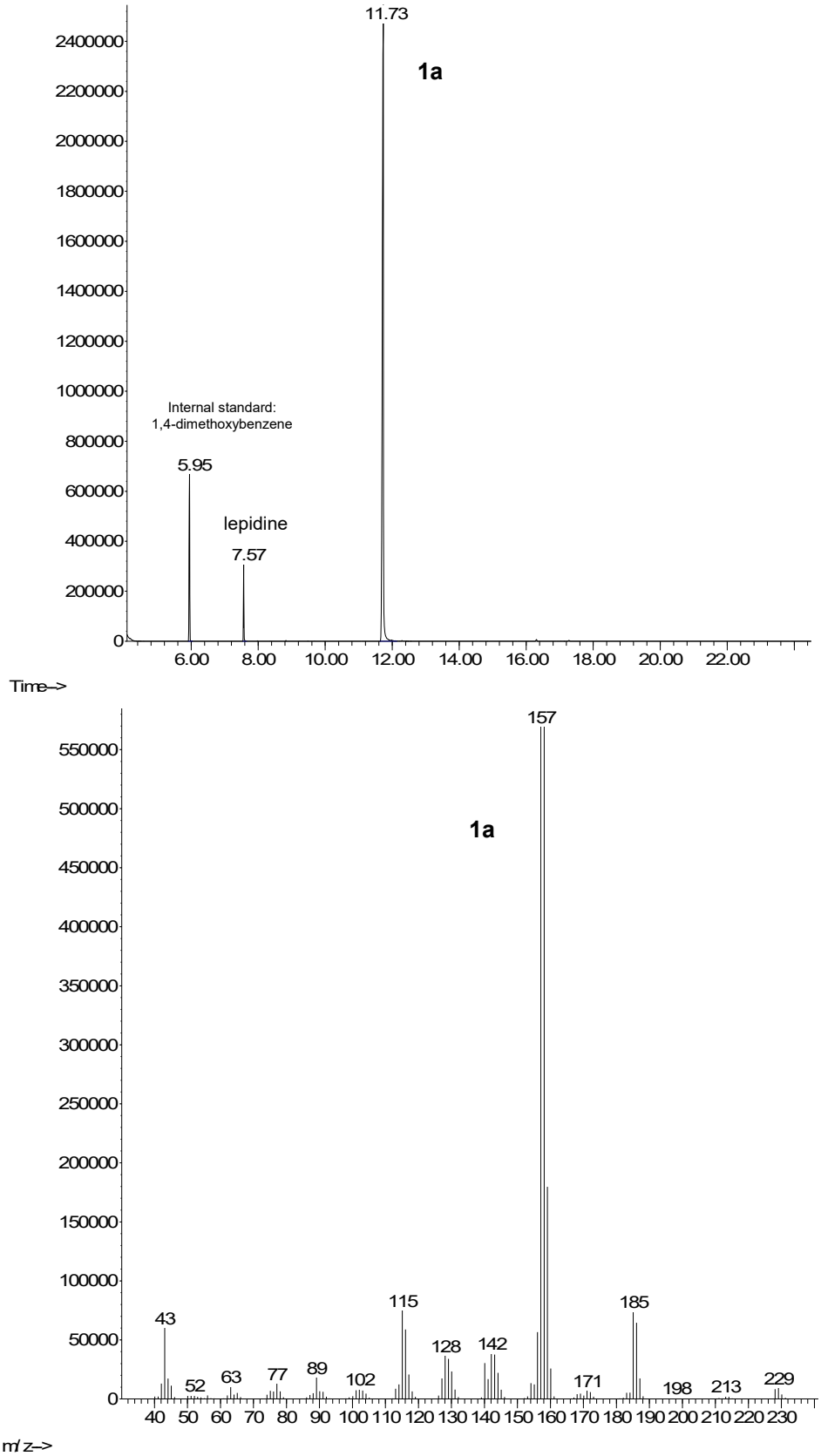
#1 ^{1}H NMR and GC-MS identification of product **1a**



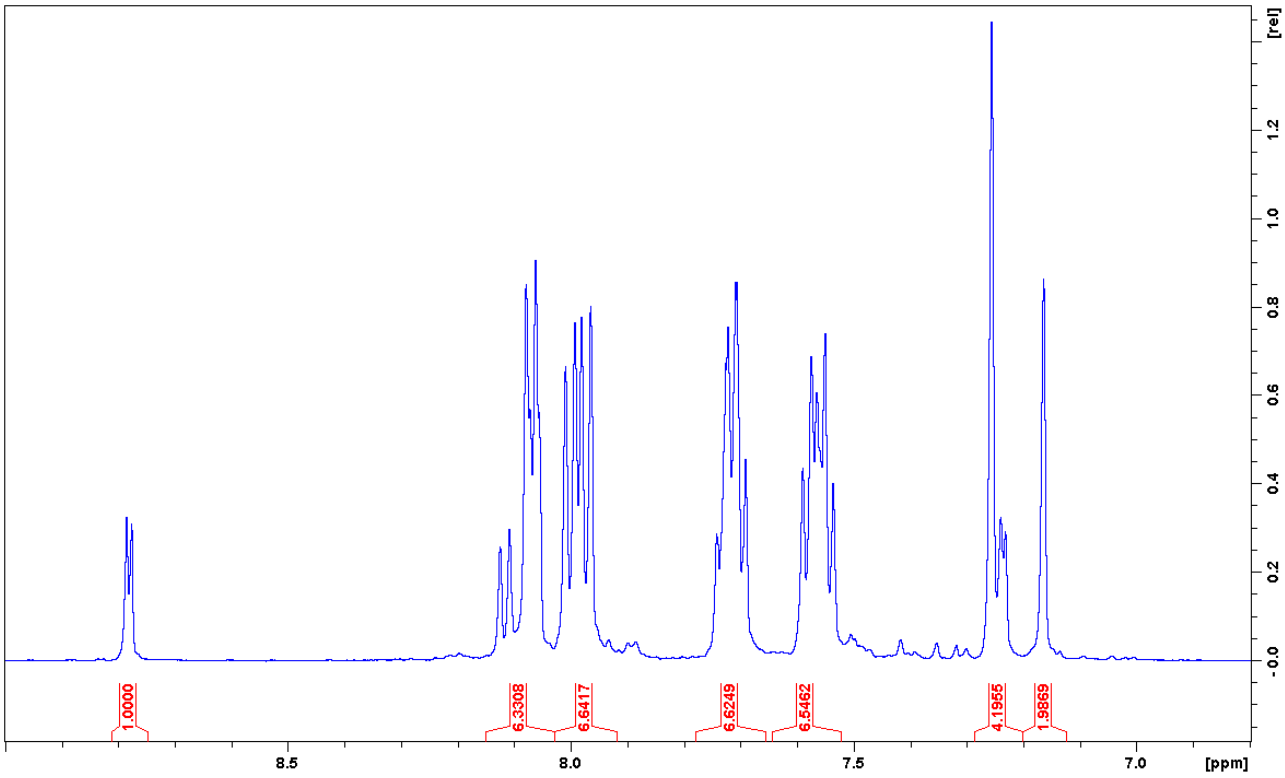
^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture
Reaction conditions: lepidine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'



^{1}H NMR (400 MHz) in $CDCl_3$ of the extracted reaction mixture.
Reaction conditions: lepidine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

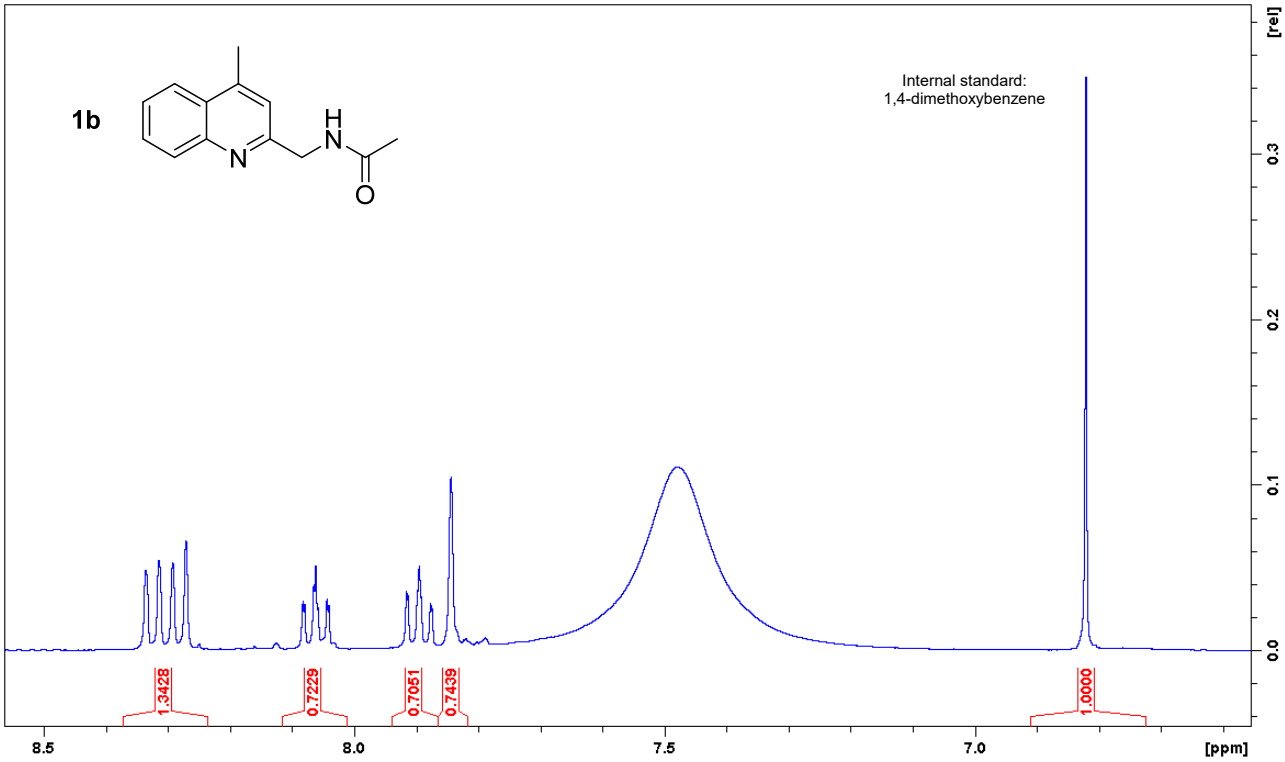


GC-MS of the extracted reaction mixture. Reaction conditions: lepidine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

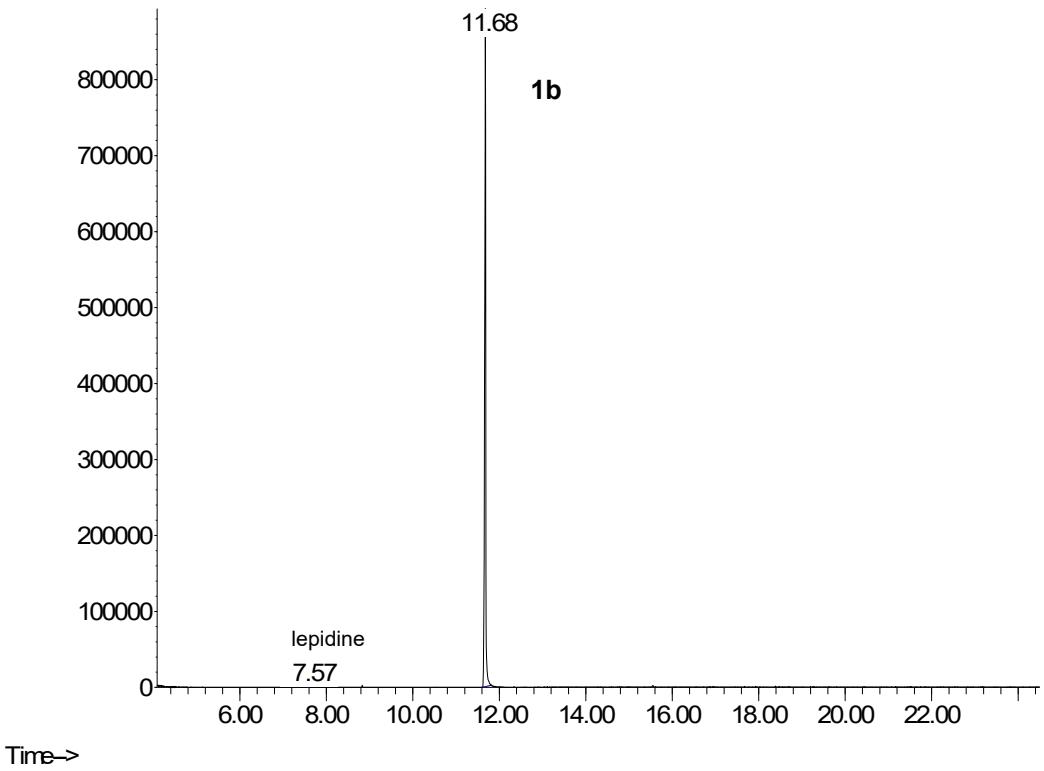


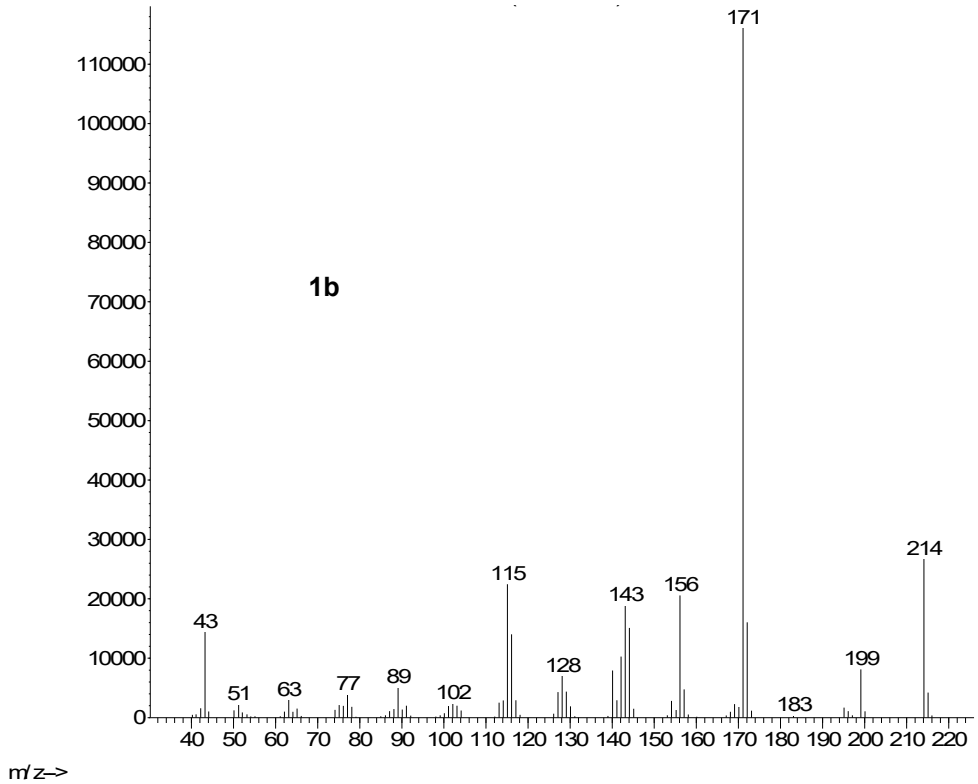
^{1}H NMR (400 MHz) in $CDCl_3$ of the deeply washed organic layer. The chemical shift are very similar to those reported in literature. Reaction conditions: lepidine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

#2 ^{1}H NMR and GC-MS identification of product **1b**



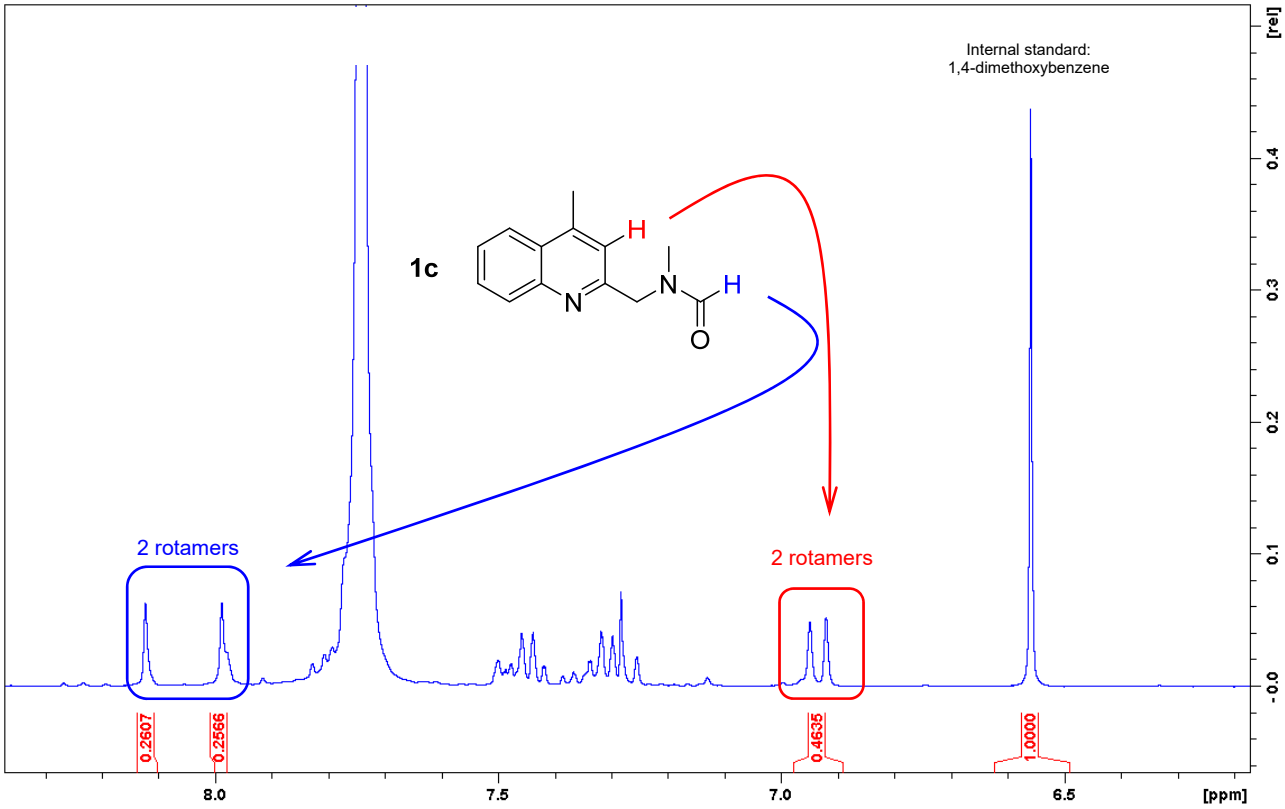
^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture.
Reaction conditions: lepidine + NMA 80 °C, 2:1 $Na_2S_2O_8$, 15'



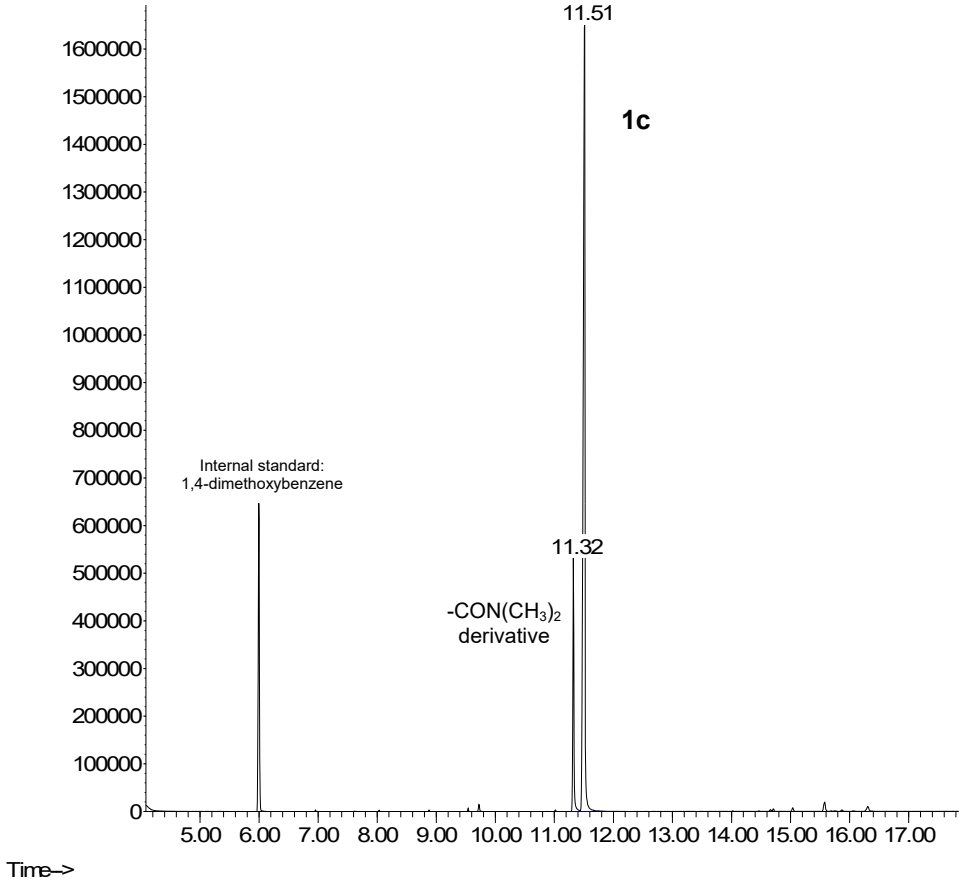


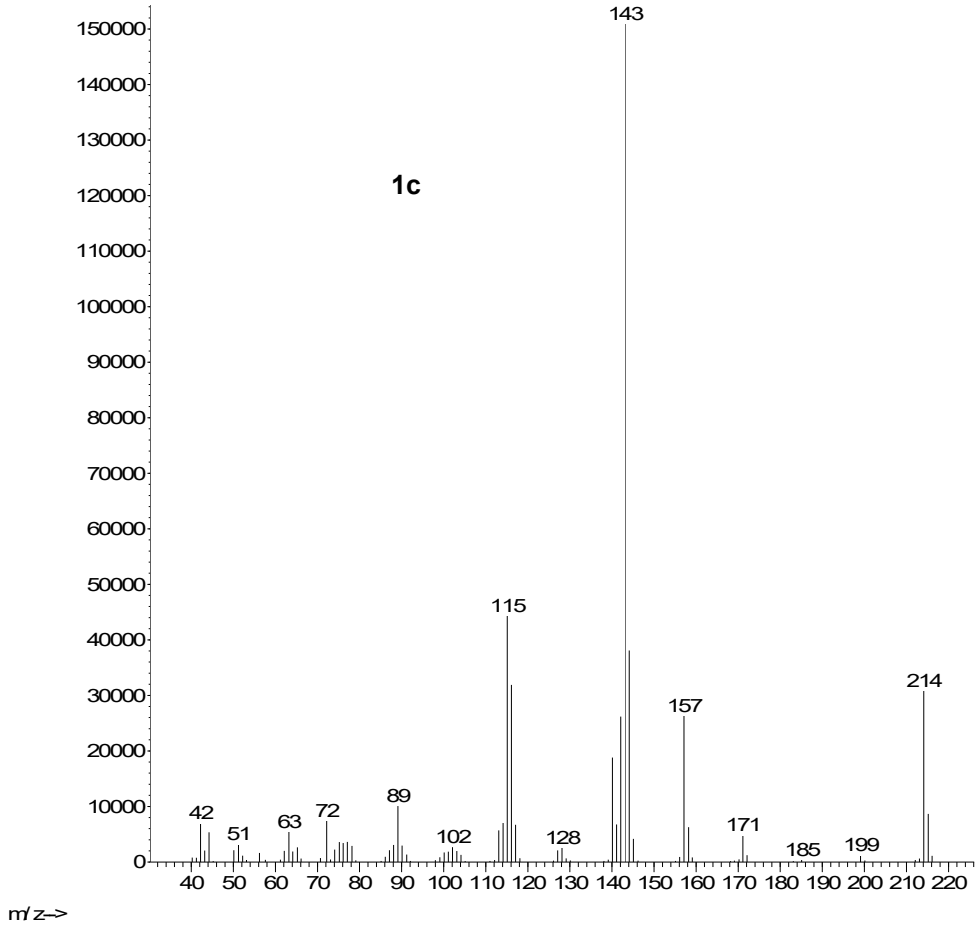
GC-MS of the extracted reaction mixture. Reaction conditions: lepidine + NMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

#3 ^{1}H NMR and GC-MS identification of product **1c**



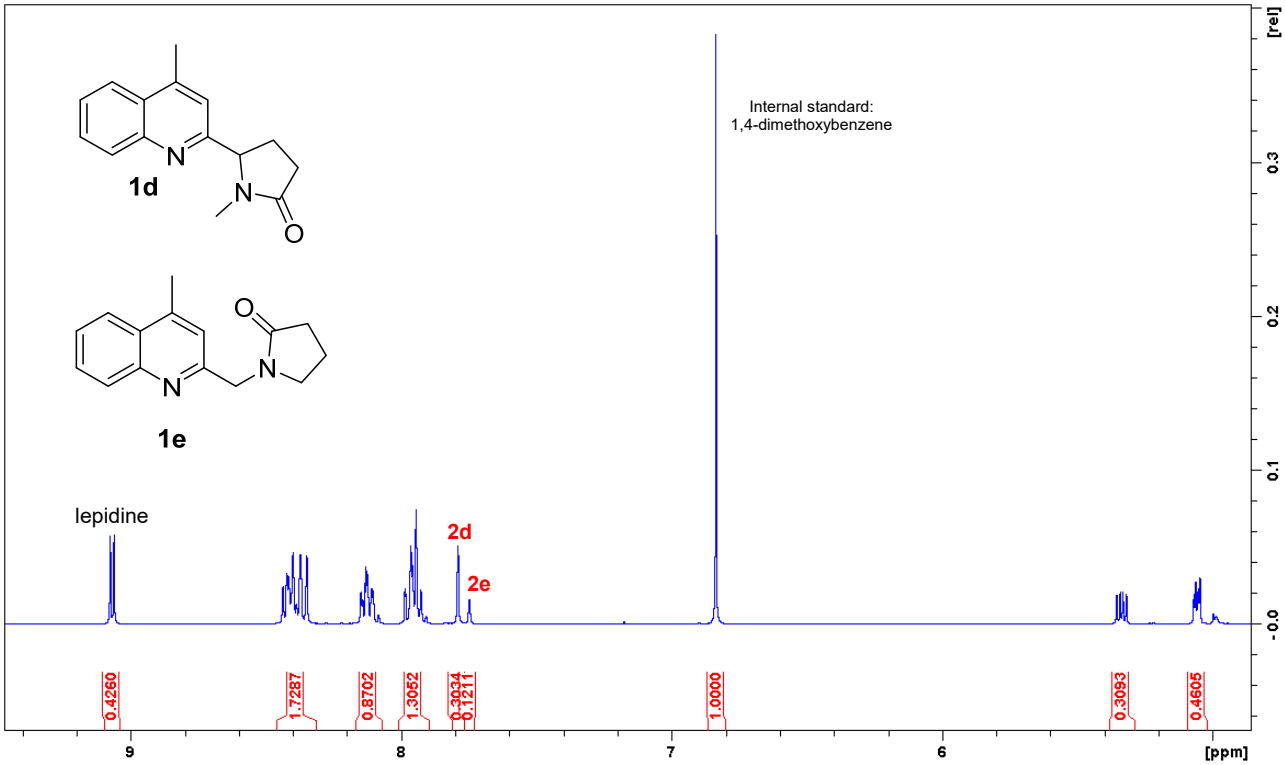
^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture.
Reaction conditions: lepidine + DMF 80 °C, 2:1 $Na_2S_2O_8$, 15'



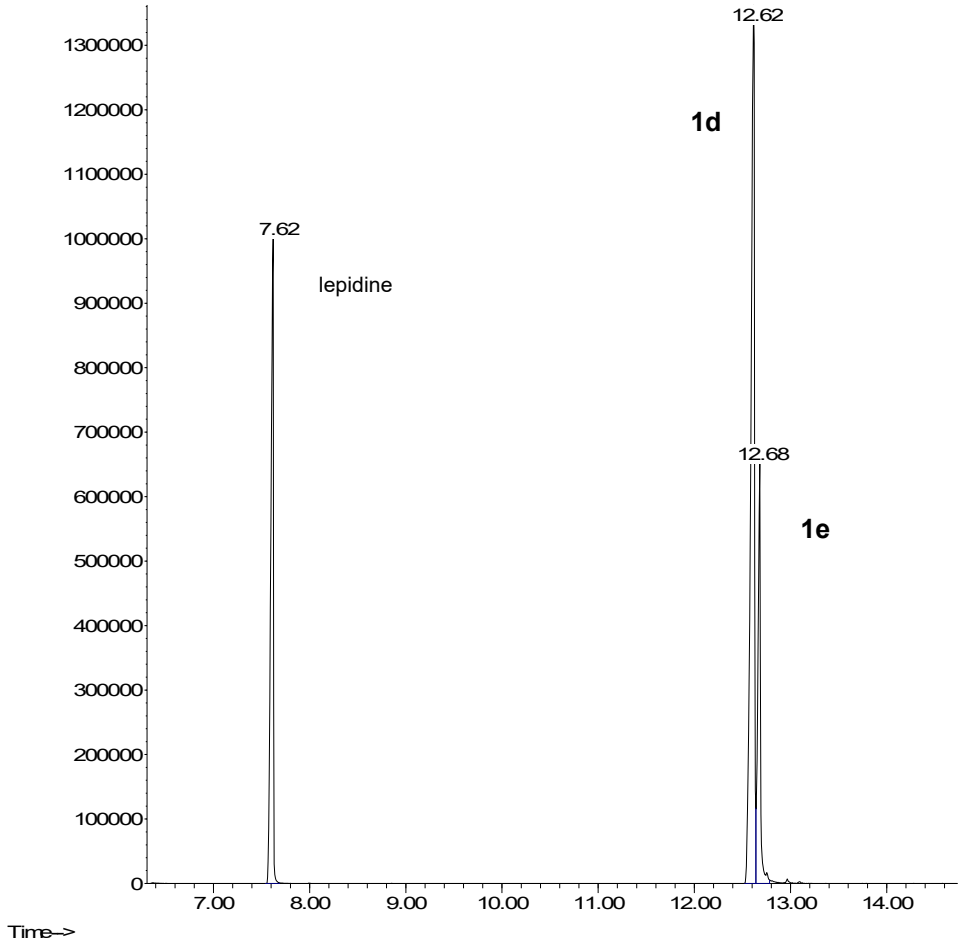


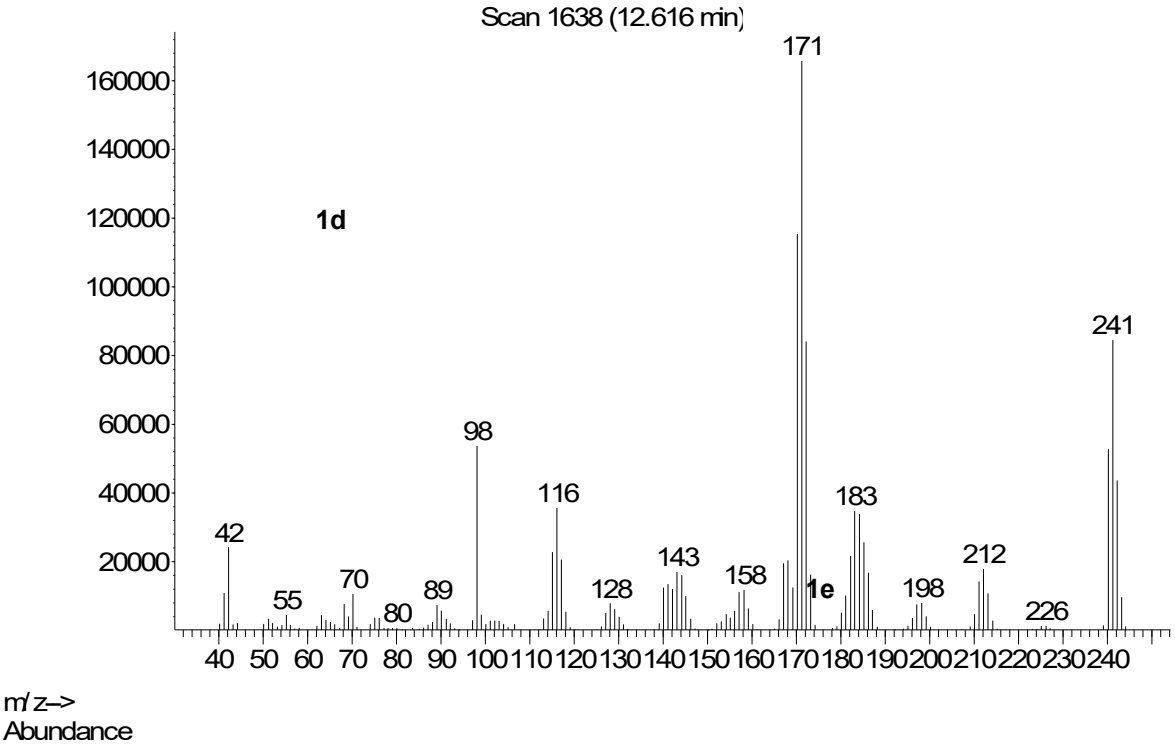
GC-MS of the extracted reaction mixture. Reaction conditions: lepidine + DMF 80 °C, 2:1 $Na_2S_2O_8$, 15'

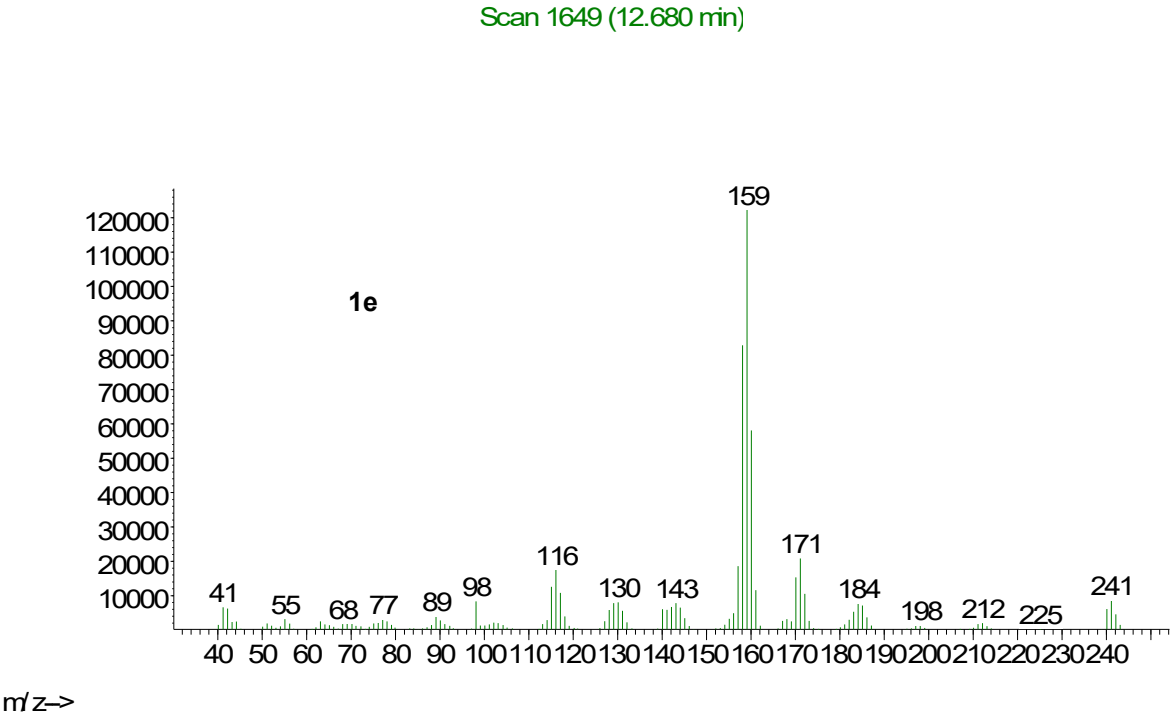
#4 ^{1}H NMR and GC-MS identification of products **1d** and **1e**



^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture.
Reaction conditions: lepidine + NMP 80 °C, 2:1 $Na_2S_2O_8$, 60'

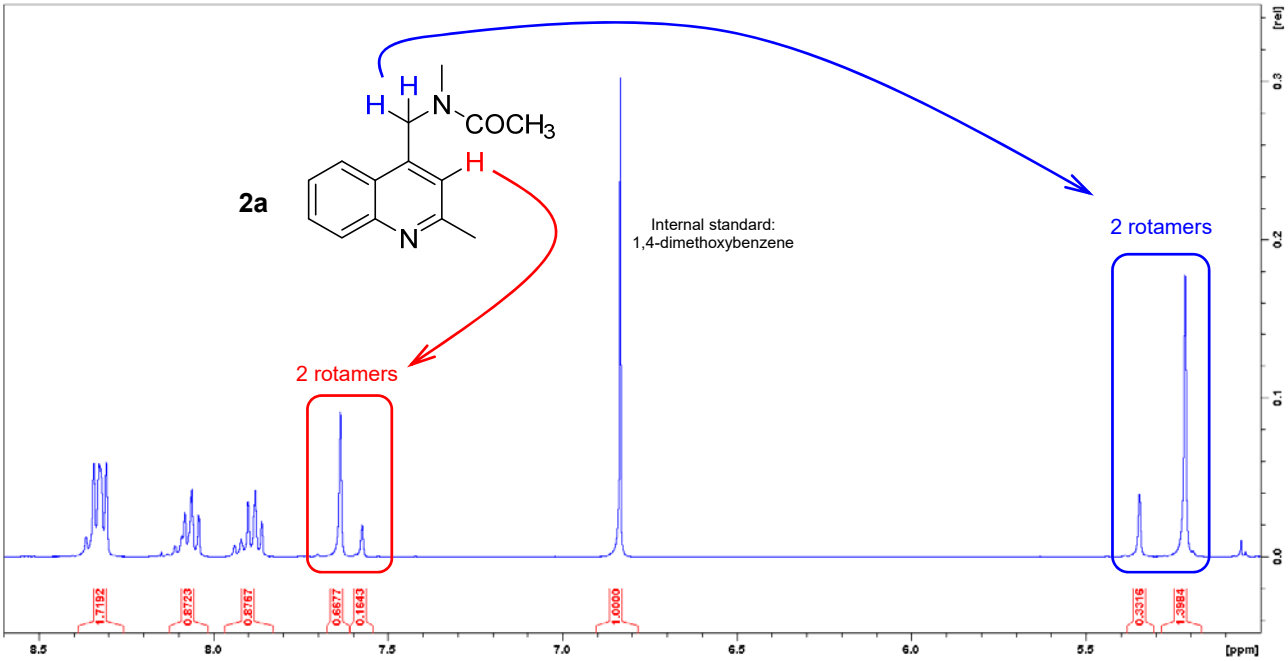




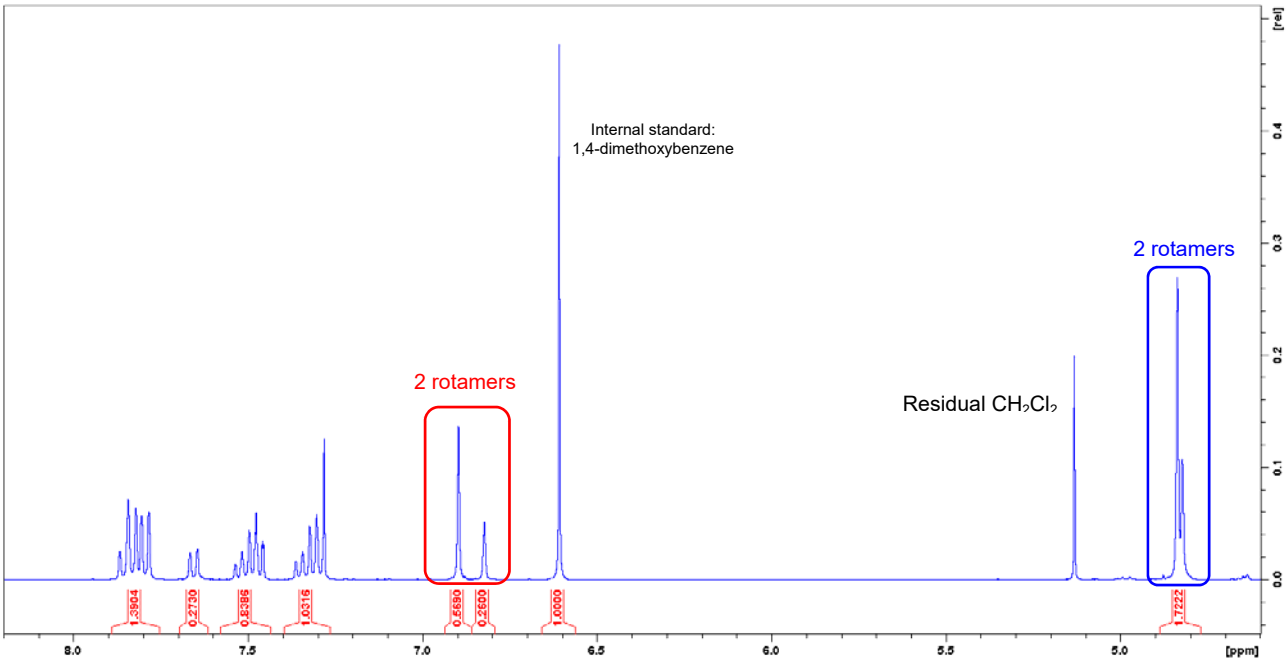


GC-MS of the extracted reaction mixture. Reaction conditions: lepidine + NMP 80 °C, 2:1 $Na_2S_2O_8$, 60'

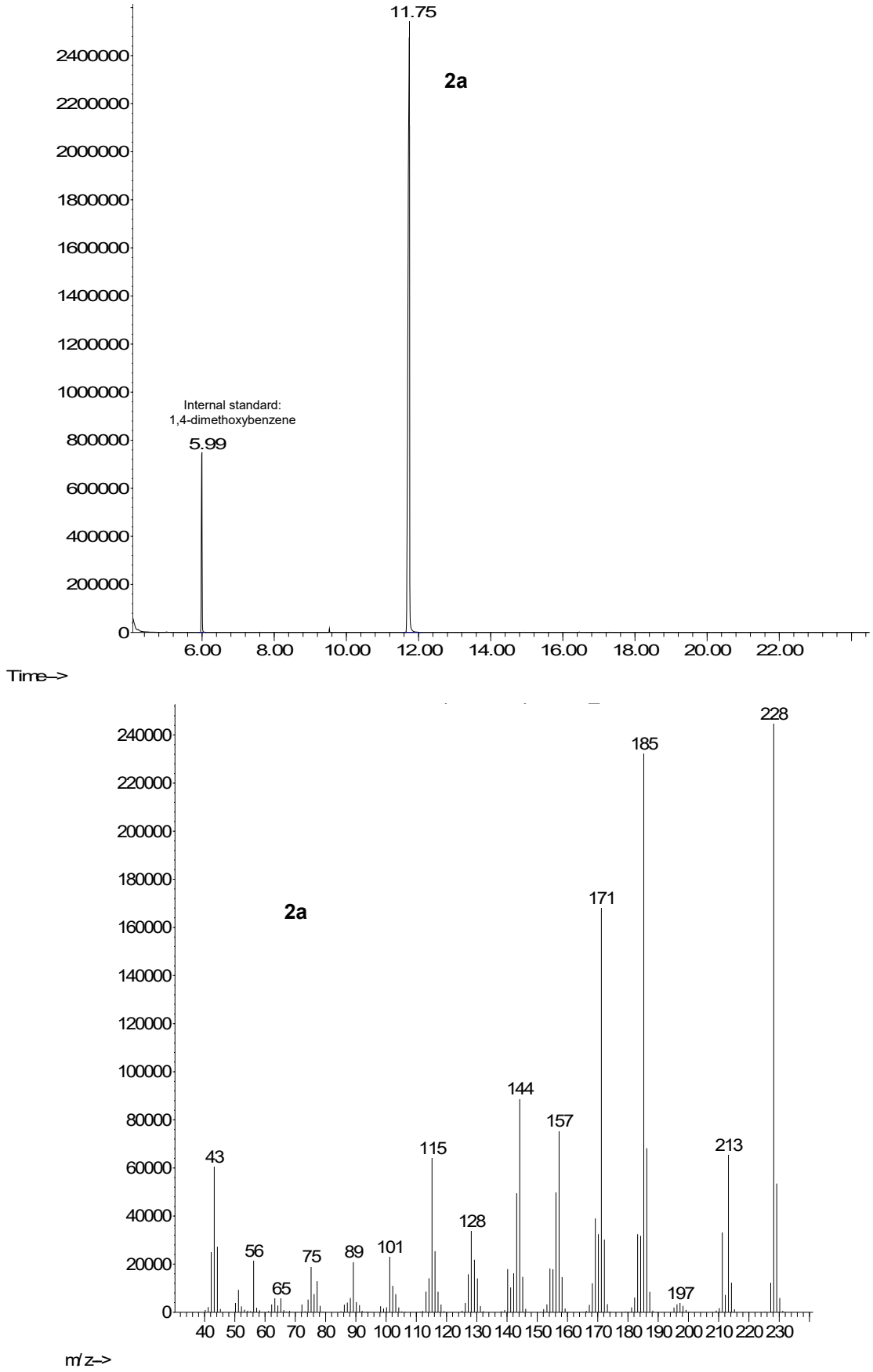
#5 ^{1}H NMR and GC-MS identification of product **2a**



^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture
Reaction conditions: quinaldine + DMA 50 °C, 2:1 $Na_2S_2O_8$, 15'

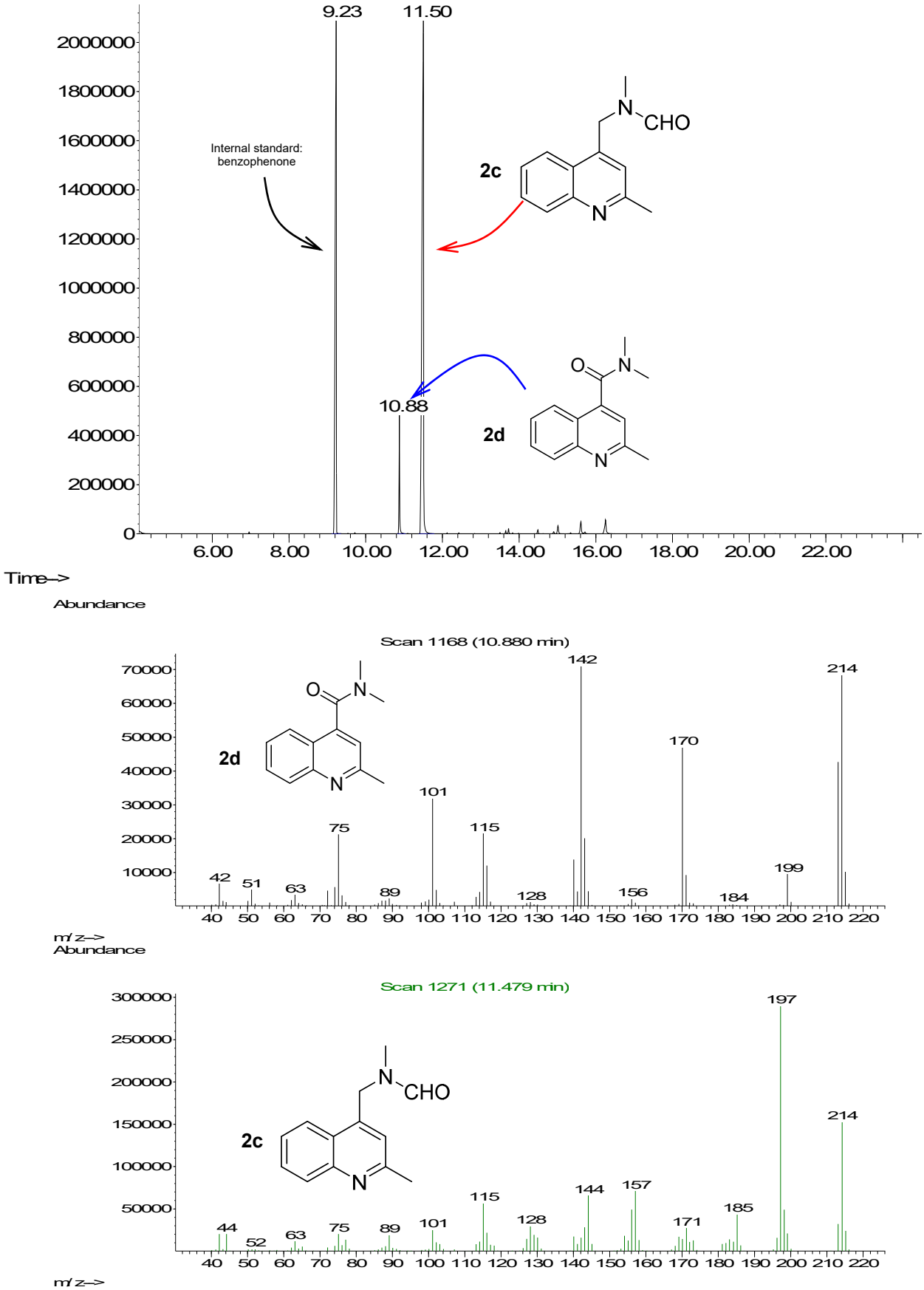


^{1}H NMR (400 MHz) in $CDCl_3$ of the extracted reaction mixture.
Reaction conditions: quinaldine + DMA 50 °C, 2:1 $Na_2S_2O_8$, 15'



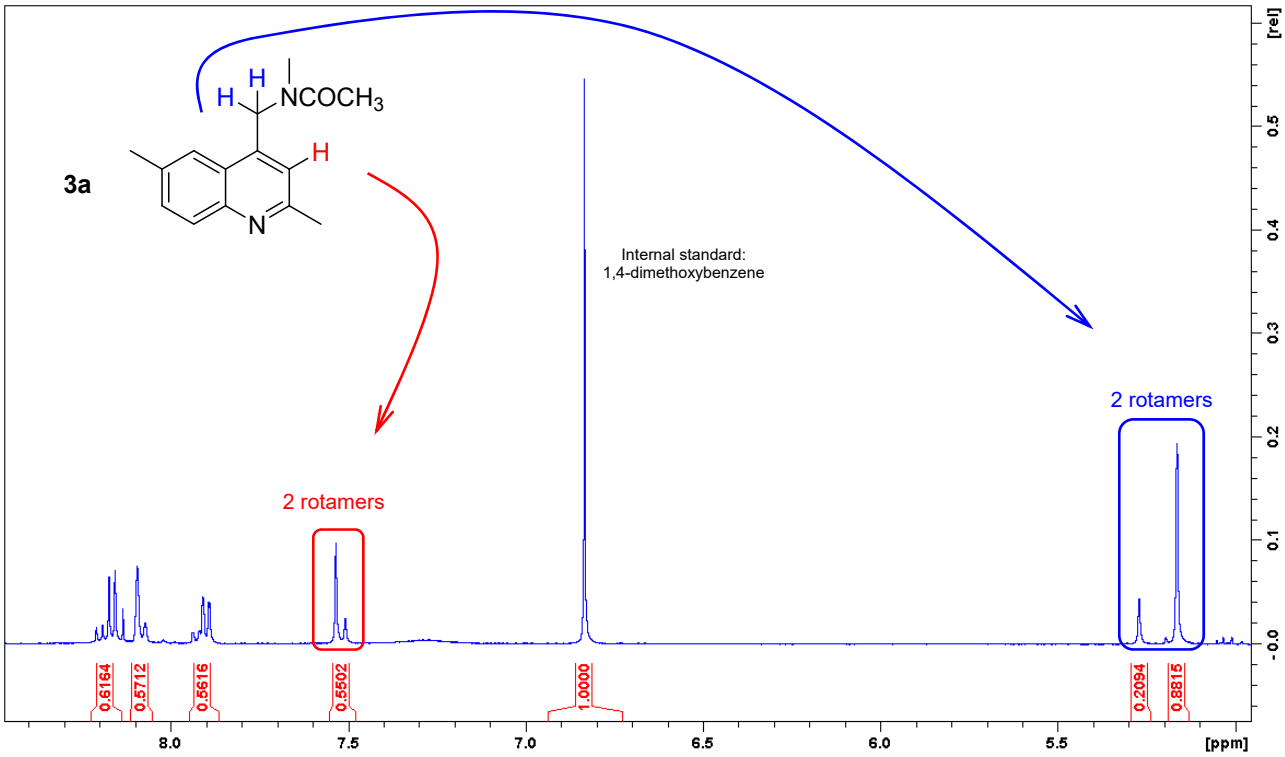
GC-MS of the extracted reaction mixture. Reaction conditions: quinaldine + DMA 50 °C, 2:1 $Na_2S_2O_8$, 15'

#6 GC-MS identification of product **2c**

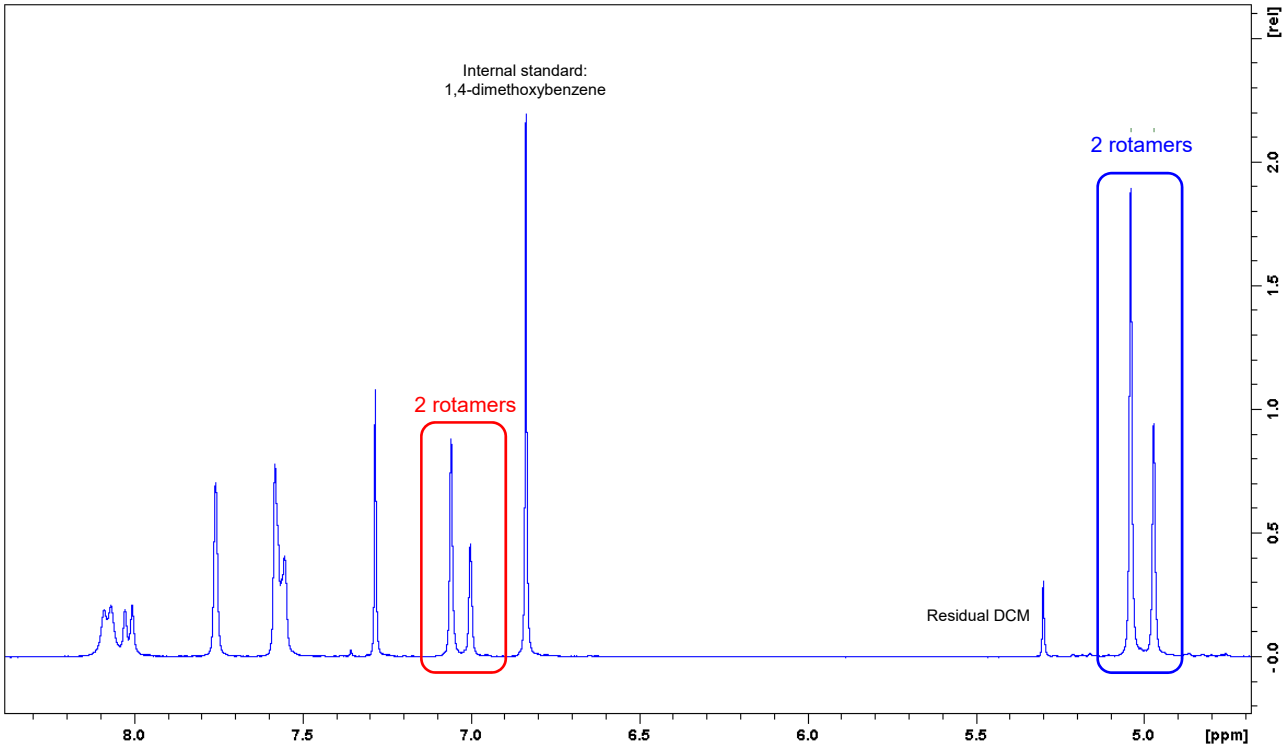


GC-MS of the extracted reaction mixture. Reaction conditions: quinaldine + DMF 80 °C, 2:1 $Na_2S_2O_8$, 15'

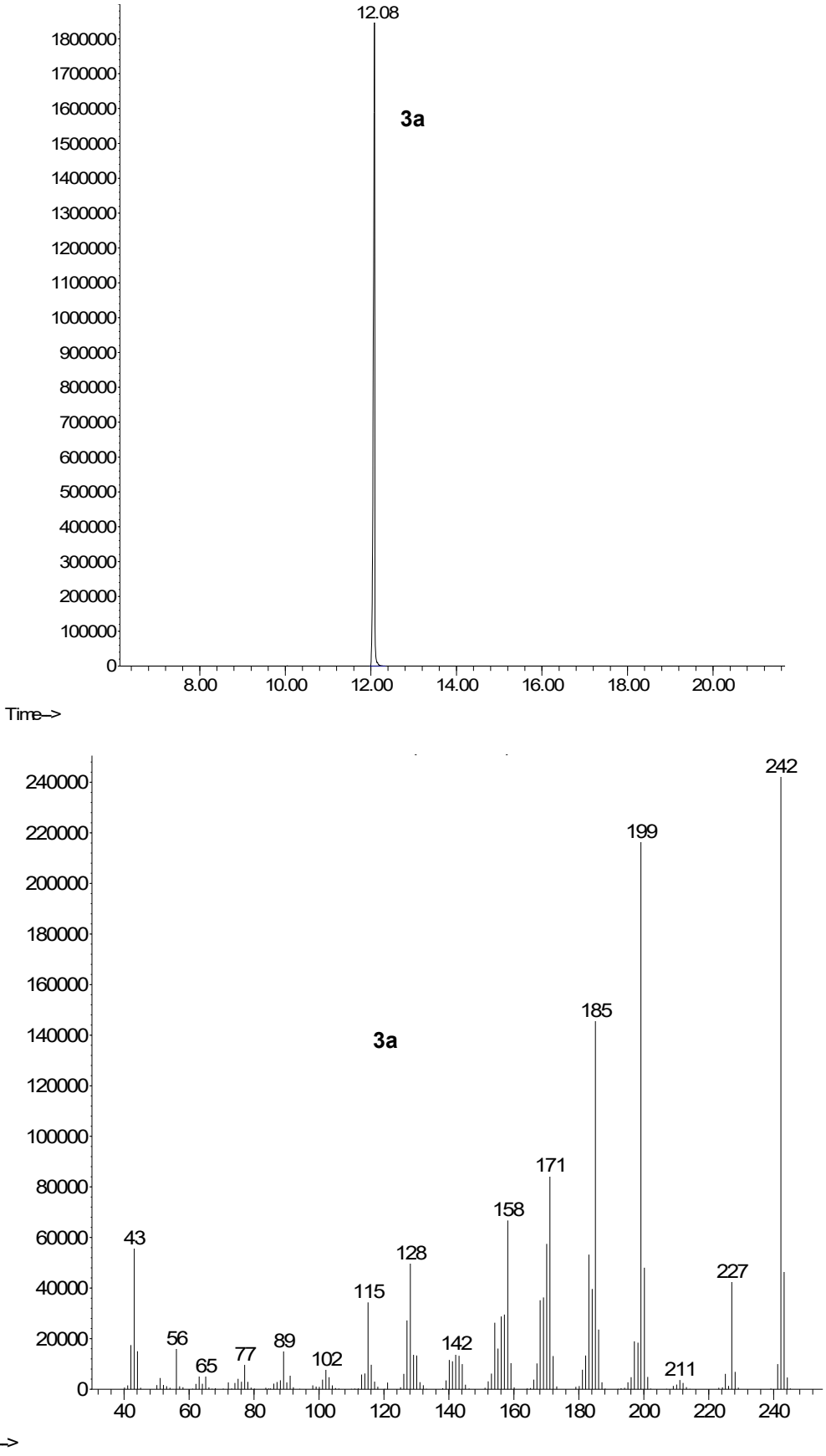
#7 ^{1}H NMR and GC-MS identification of product **3a**



^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture.
Reaction conditions: 2,6-dimethylquinoline + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

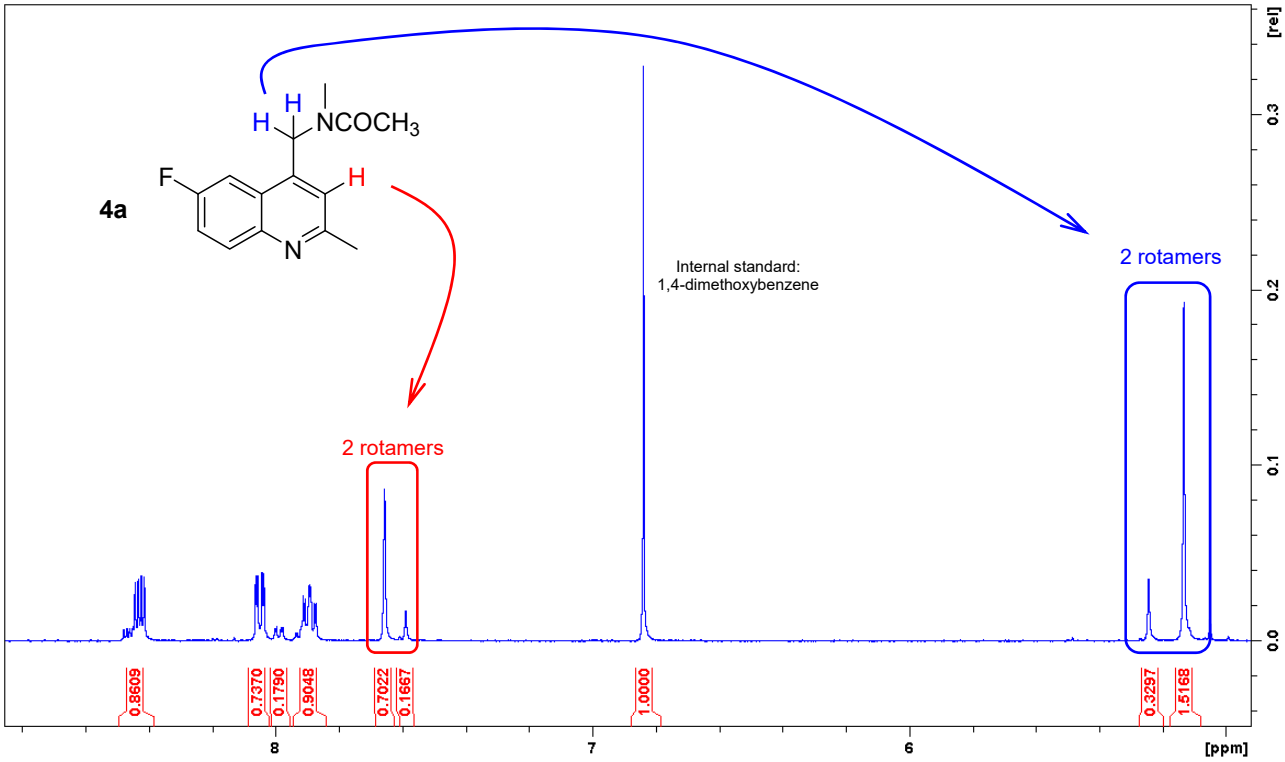


^{1}H NMR (400 MHz) in $CDCl_3$ of the extracted reaction mixture.
Reaction conditions: 2,6-dimethylquinoline + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

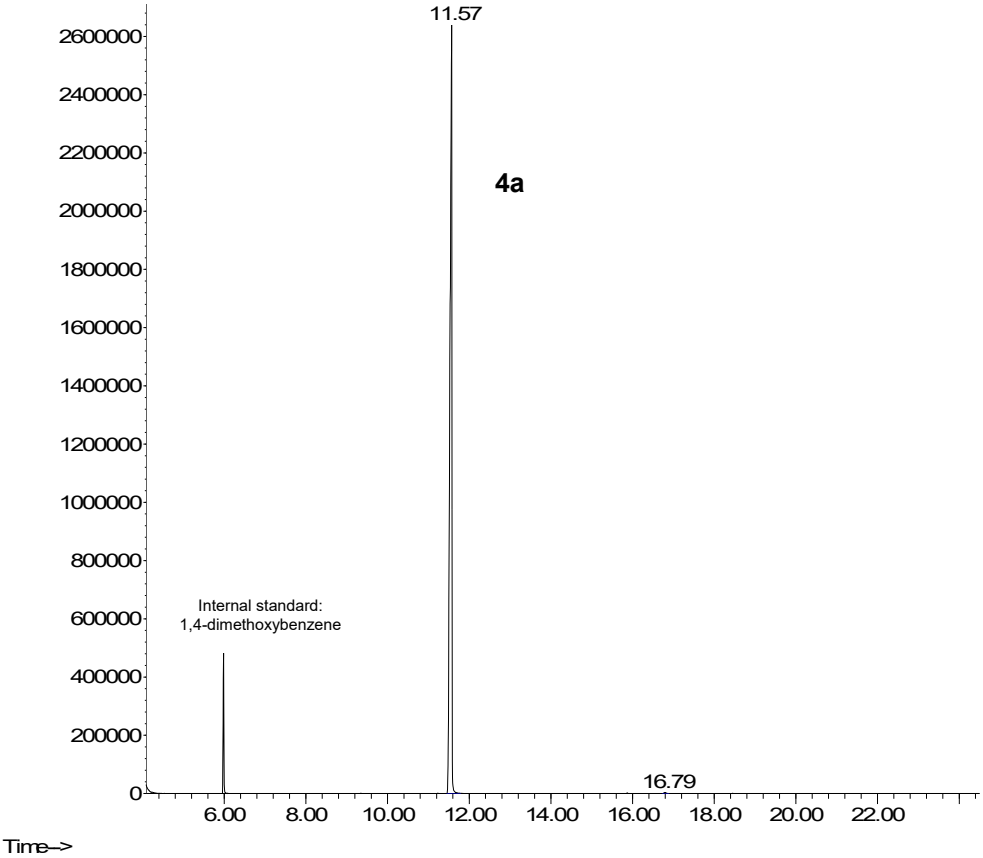


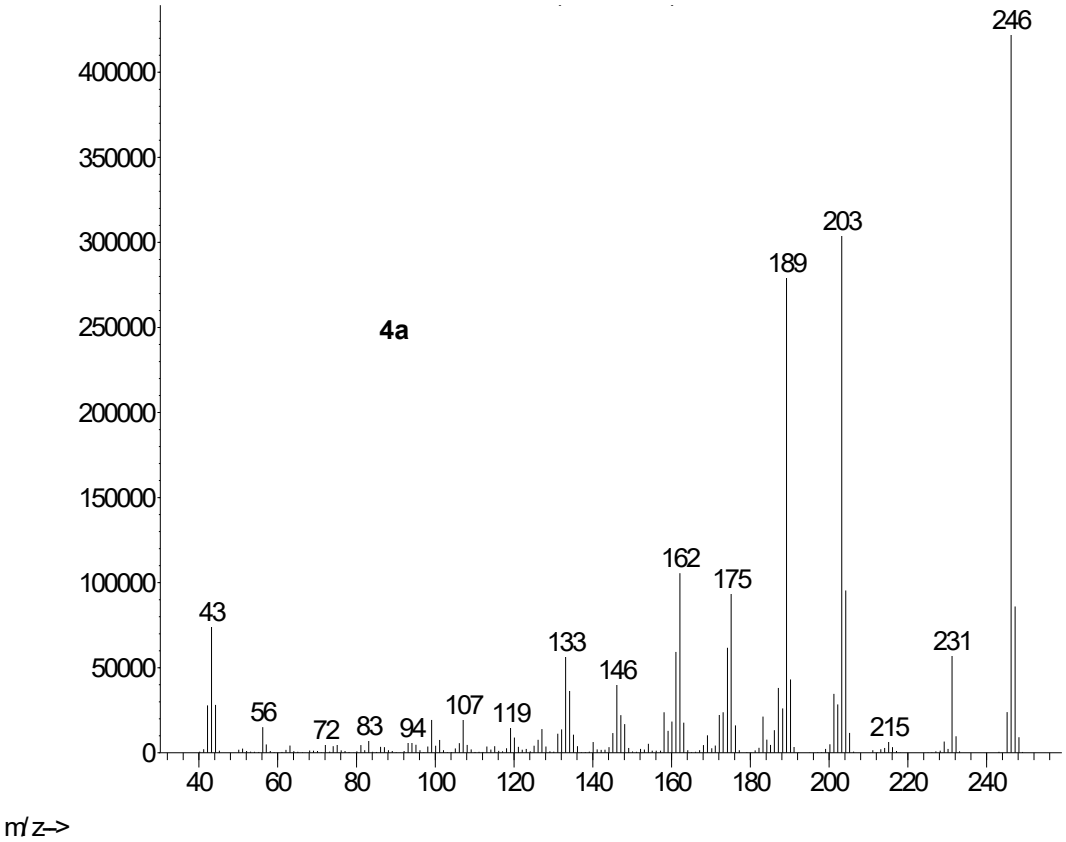
GC-MS of the extracted reaction mixture. Reaction conditions: 2,6-dimethylquinoline + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

#8 ^{1}H NMR and GC-MS identification of product **4a**



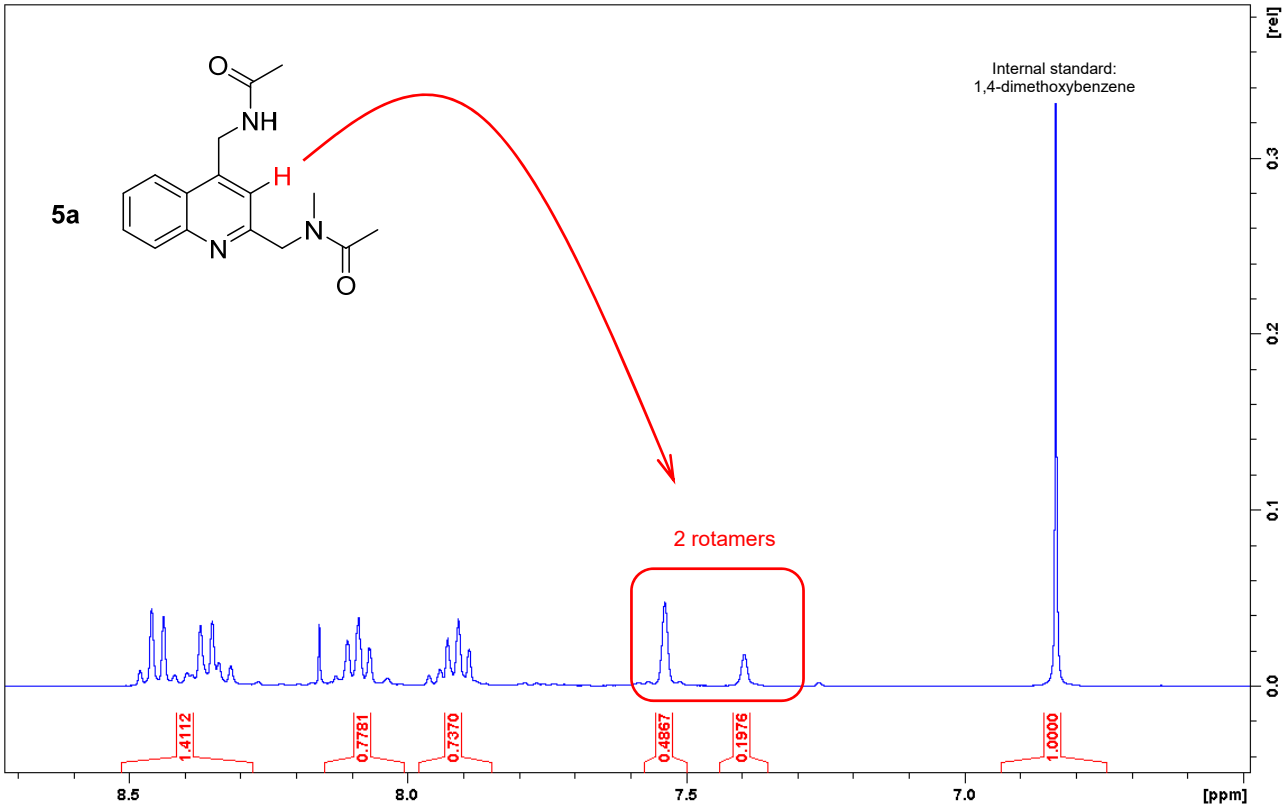
^{1}H NMR (500 MHz) in CD_3CN of the reaction mixture.
Reaction conditions: 6-fluoro-2-methyl-quinoline + DMA 50 °C, 2:1 $Na_2S_2O_8$, 15'



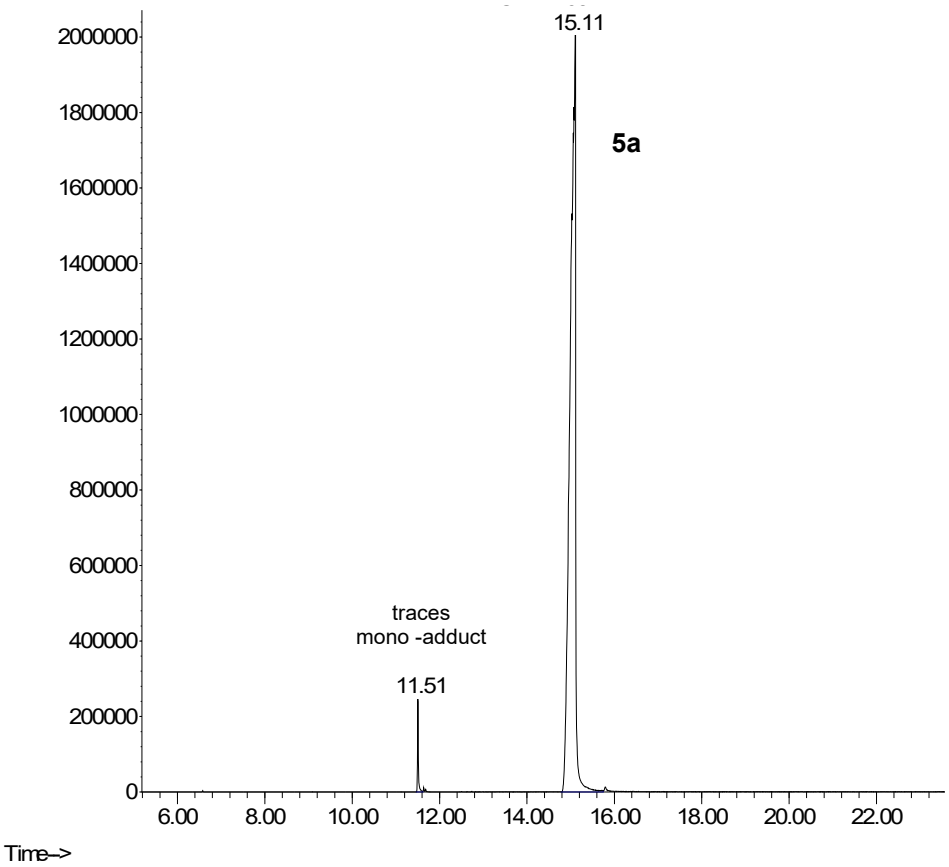


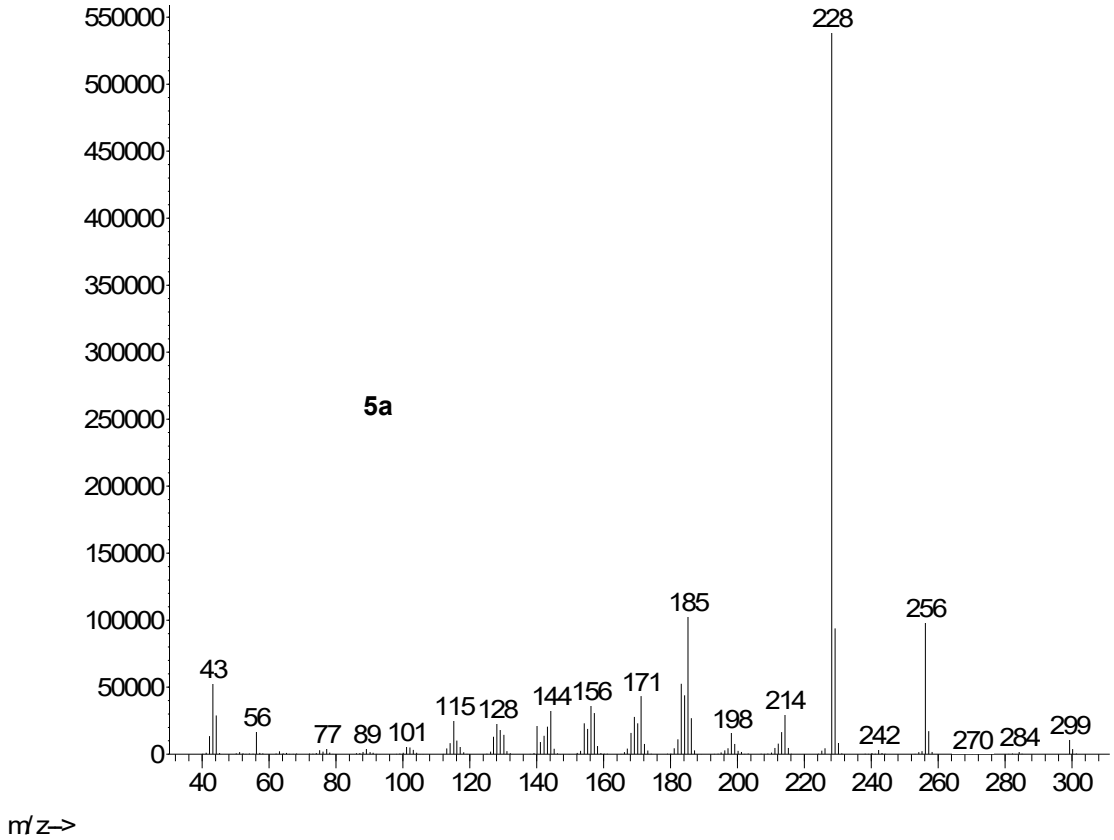
GC-MS of the extracted reaction mixture. Reaction conditions: 6-fluoro-2-methyl-quinoline + DMA 50 °C, 2:1 $Na_2S_2O_8$, 15'

#9 ^{1}H NMR and GC-MS identification of product **5a**



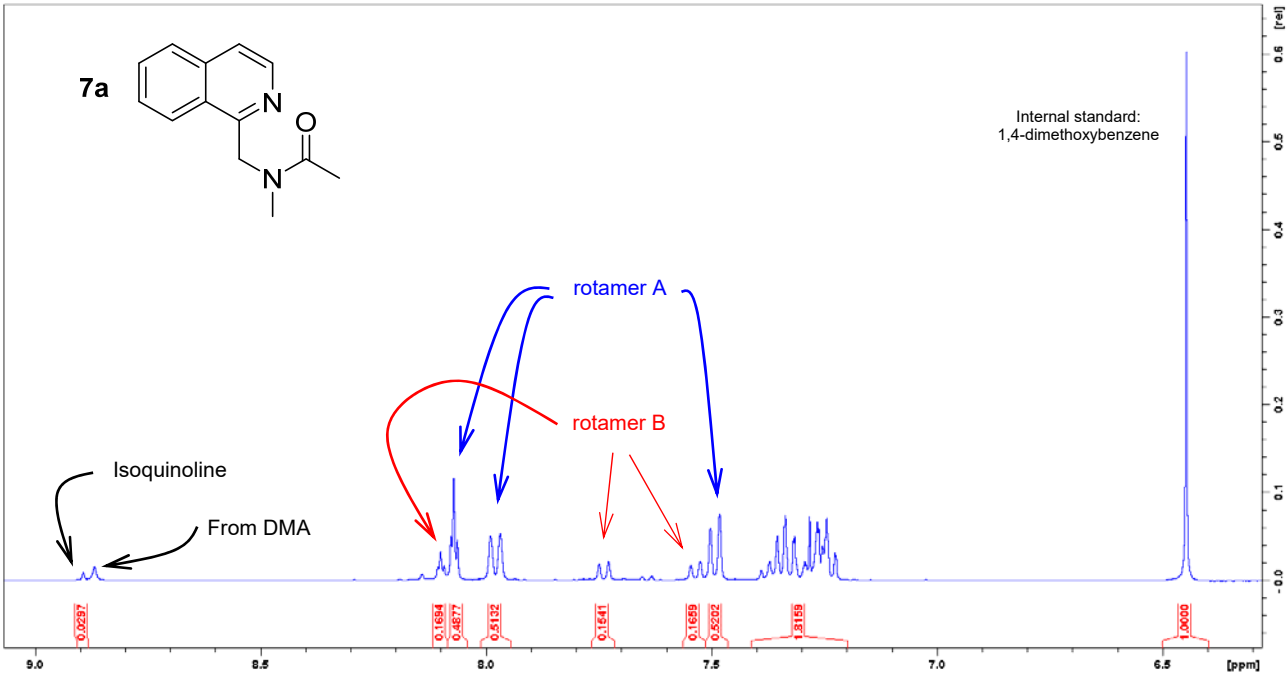
^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture.
Reaction conditions: quinoline + DMA 80 °C, 3:1 $Na_2S_2O_8$, 15'



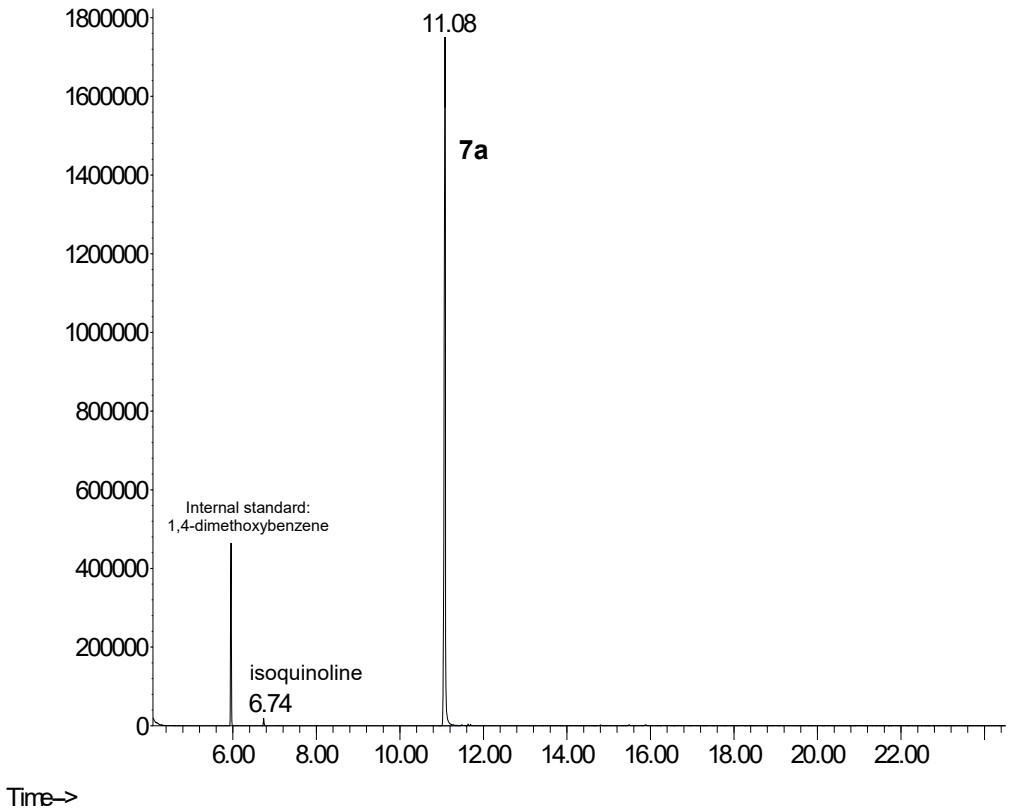


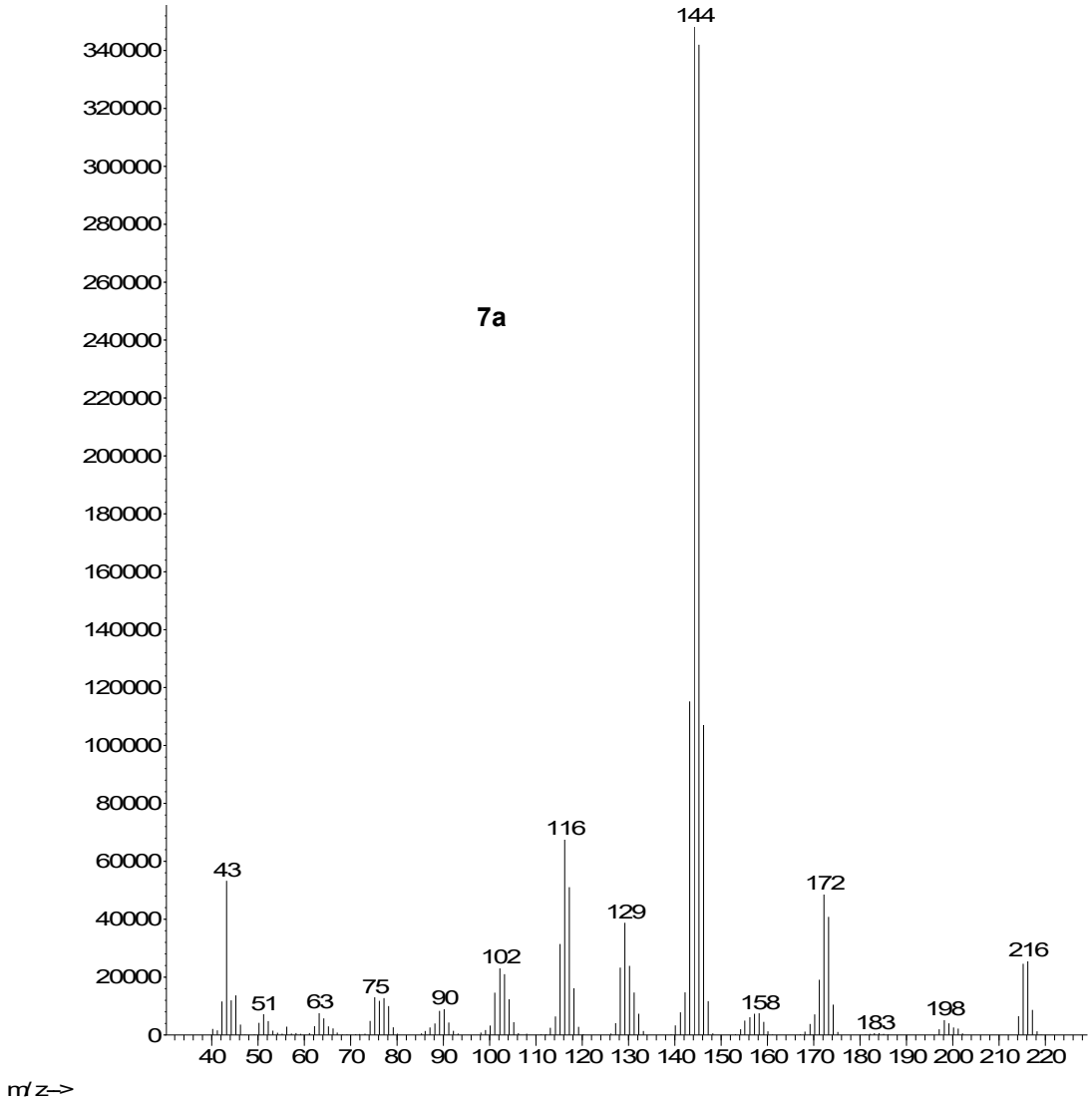
GC-MS of the extracted reaction mixture. Reaction conditions: quinoline + DMA 80 °C, 3:1 $Na_2S_2O_8$, 15'

#10 ^{1}H NMR and GC-MS identification of product **7a**



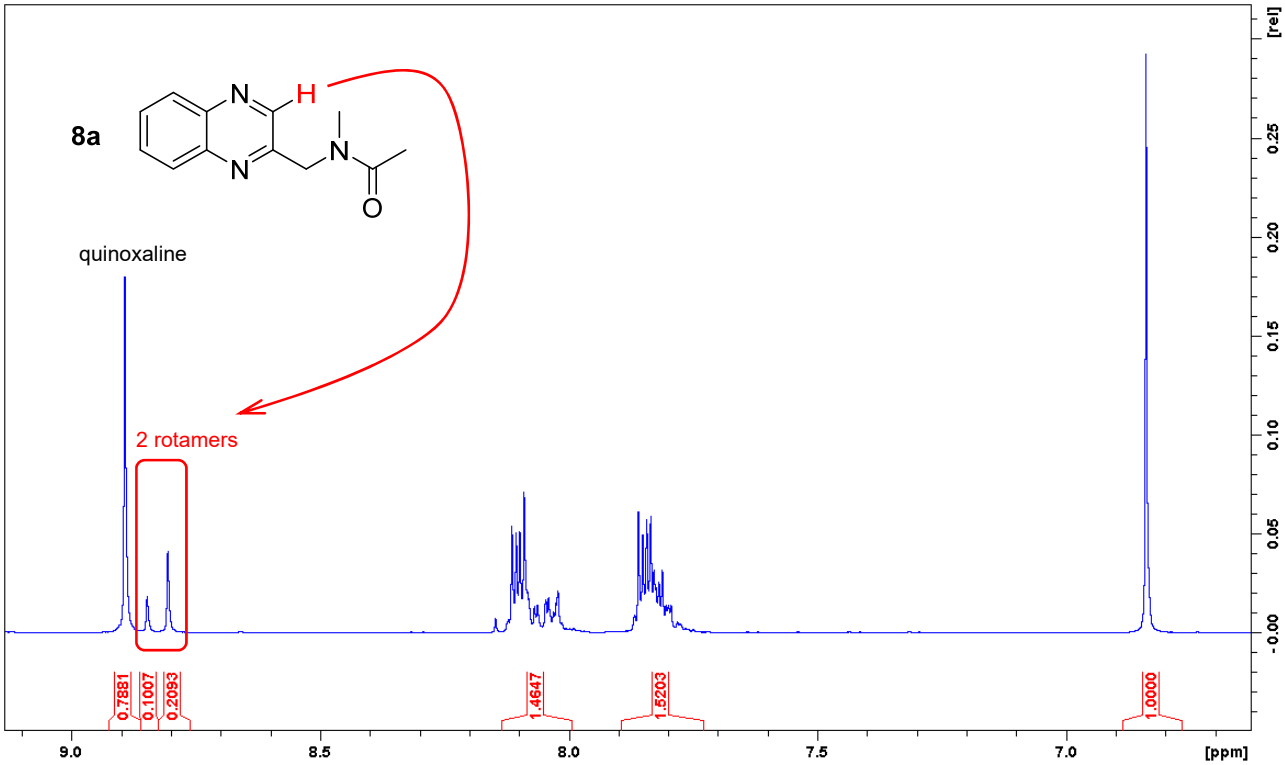
^{1}H NMR (400 MHz) in $CDCl_3$ of the extracted reaction mixture.
Reaction conditions: isoquinoline + DMA 80 °C, 1.2:1 $Na_2S_2O_8$, 15'



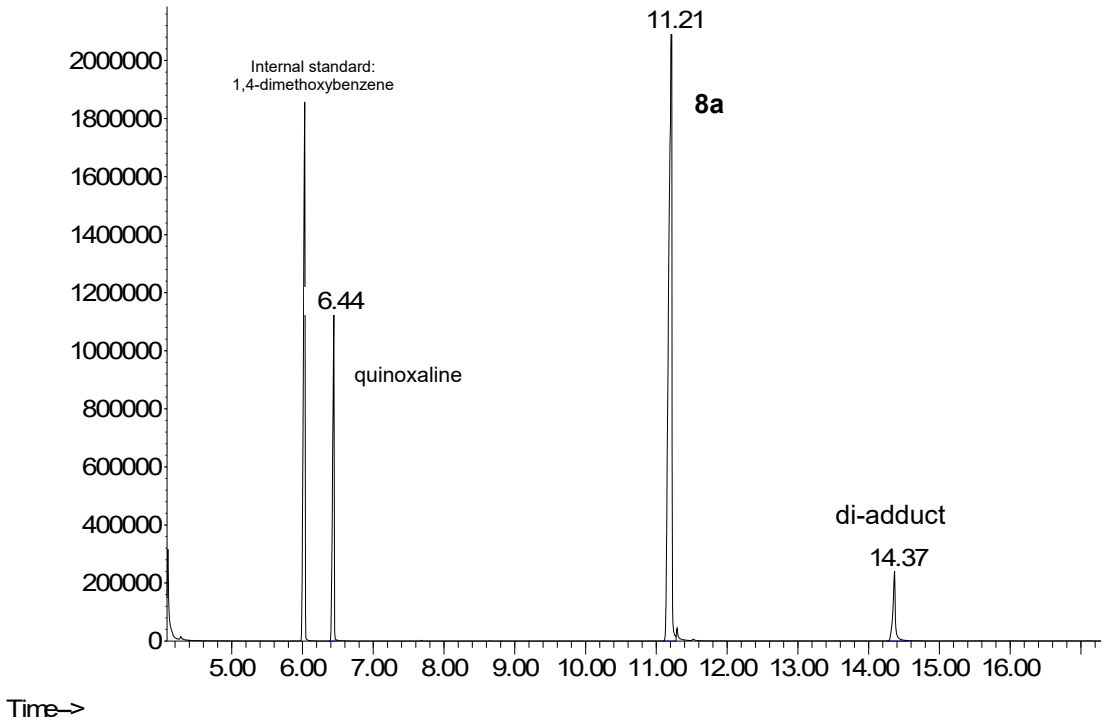


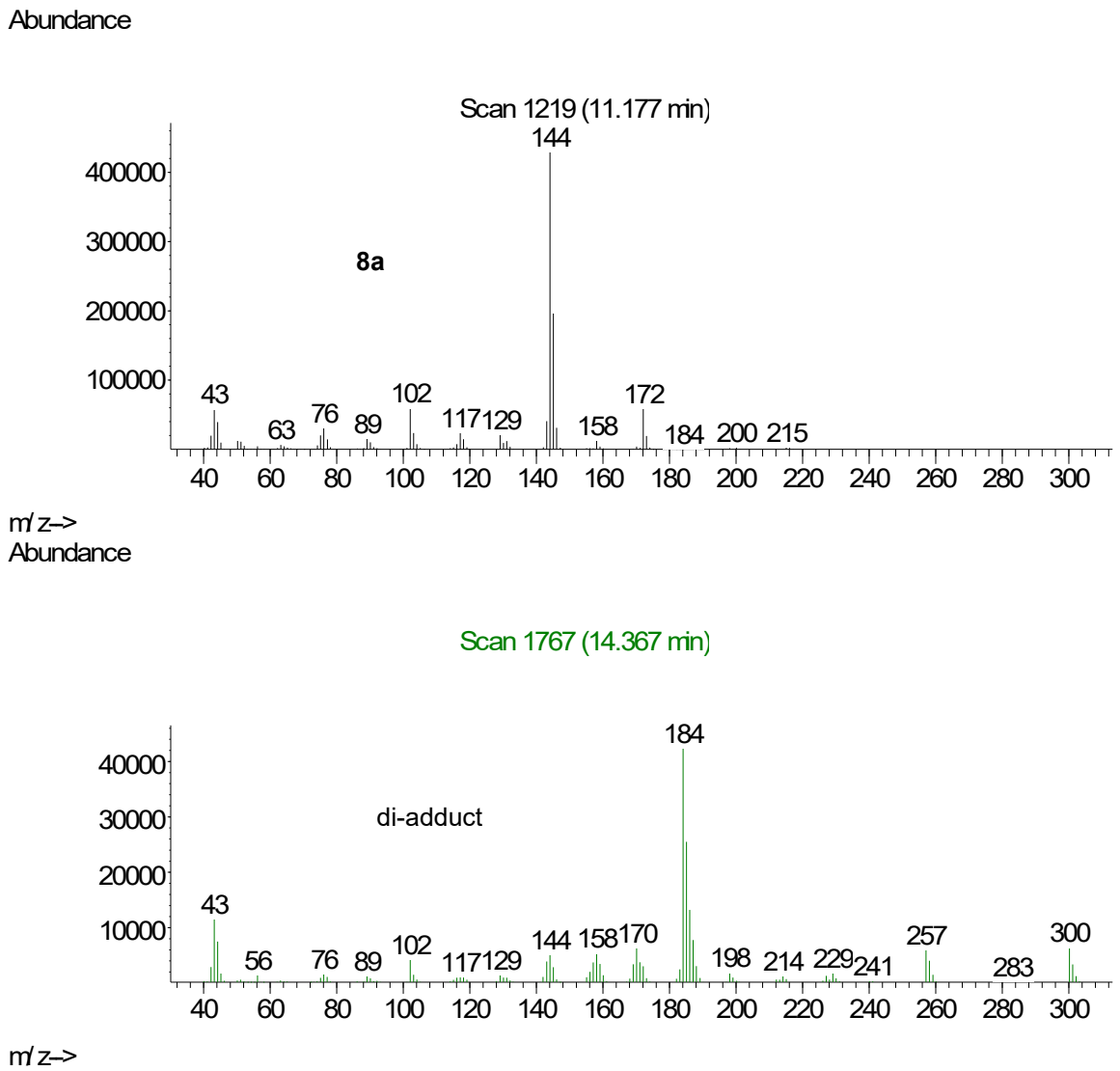
GC-MS of the extracted reaction mixture. Reaction conditions: isoquinoline + DMA 80 °C, 1.2:1 $Na_2S_2O_8$, 15'

#11 ^{1}H NMR and GC-MS identification of product **8a**



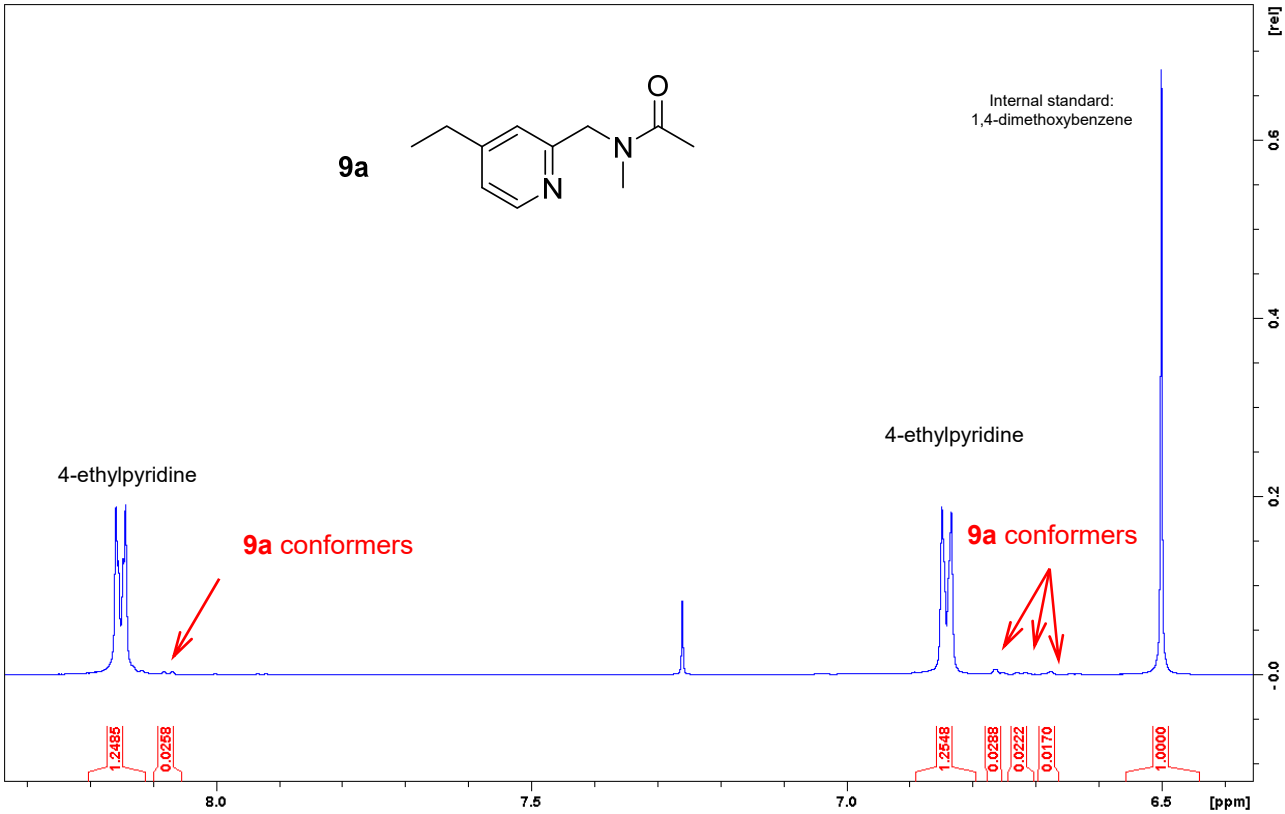
^{1}H NMR (400 MHz) in CD_3CN of the reaction mixture.
Reaction conditions: quinoxaline + DMA 80 °C, 1.2:1 $Na_2S_2O_8$, 15'



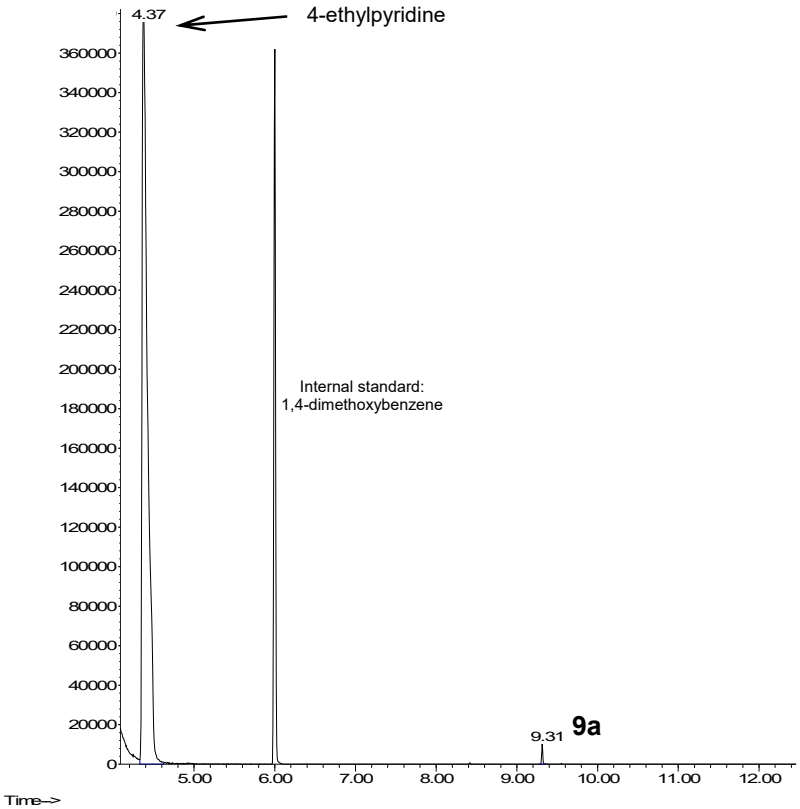


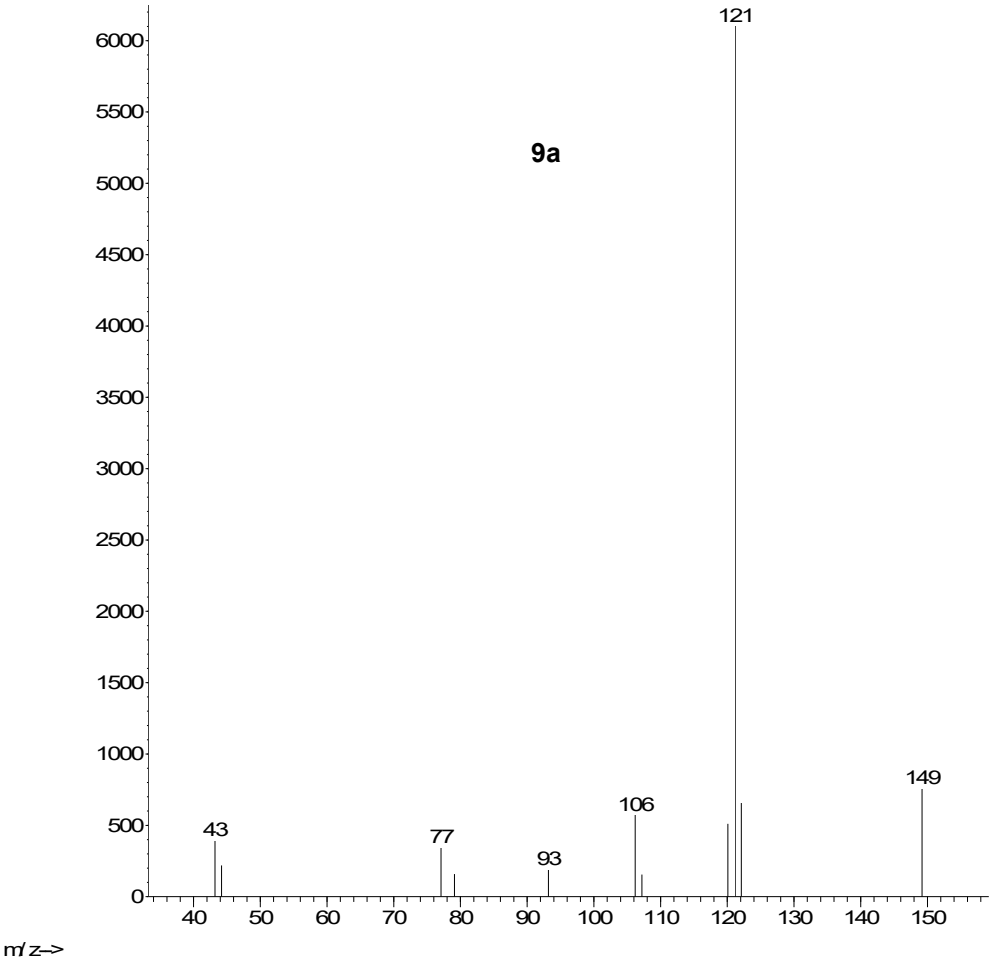
GC-MS of the extracted reaction mixture. Reaction conditions: quinoxaline + DMA 80 °C, 1.2:1 $Na_2S_2O_8$, 15'

#12 ^{1}H NMR and GC-MS identification of product **9a**



^{1}H NMR (400 MHz) in $CDCl_3$ of the extracted reaction mixture.
Reaction conditions: 4-ethylpyridine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 2 hours

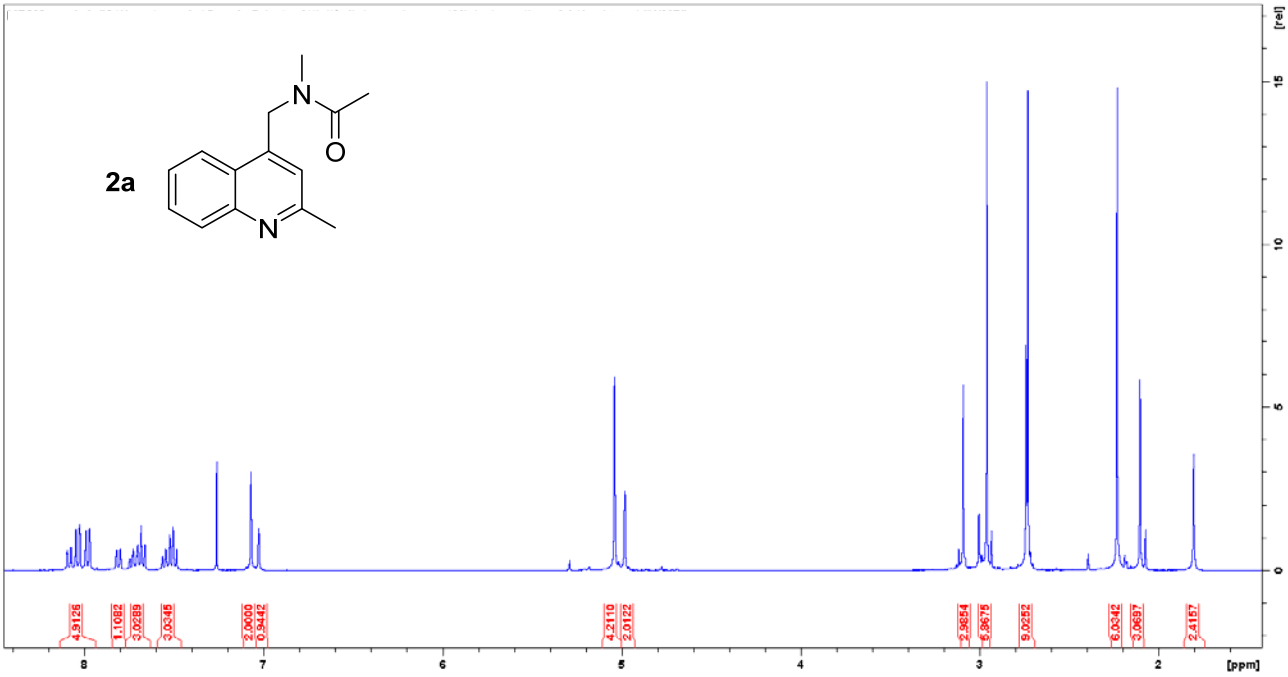




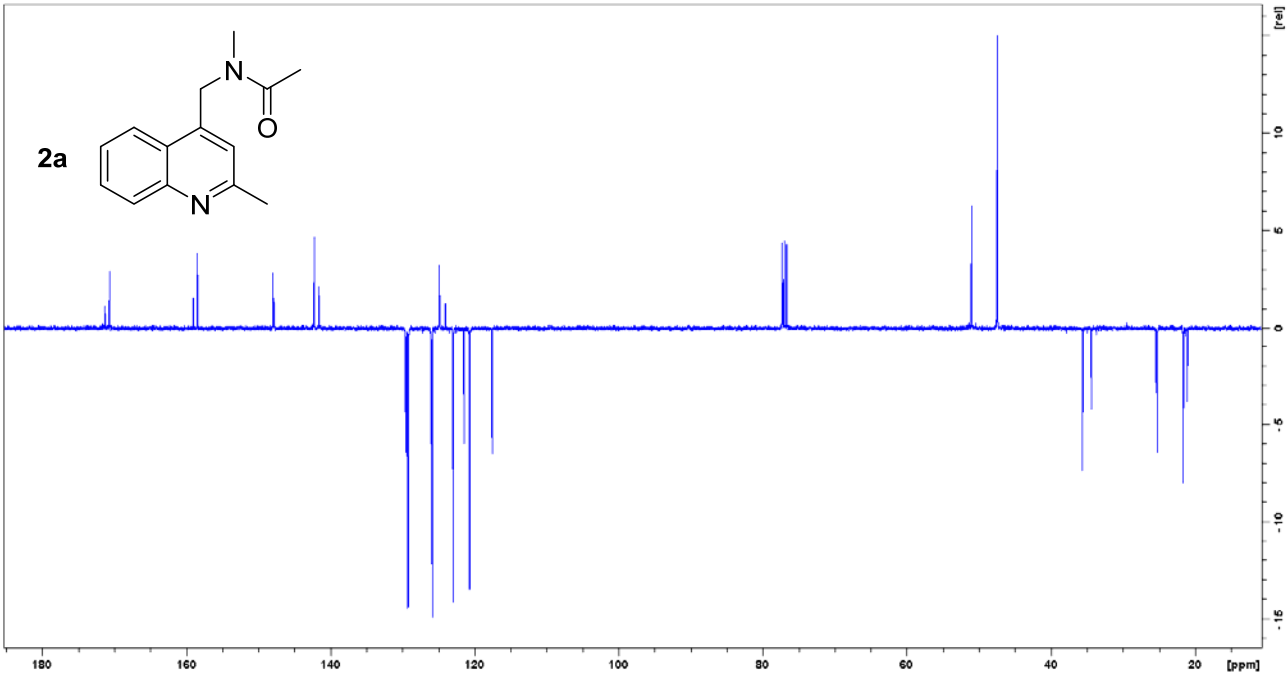
GC-MS of the extracted reaction mixture. Reaction conditions: 4-ethylpyridine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 2 hours

Part 3: Scale-up spectra

^{1}H NMR and ^{13}C of purified product **2a – Scale-up**

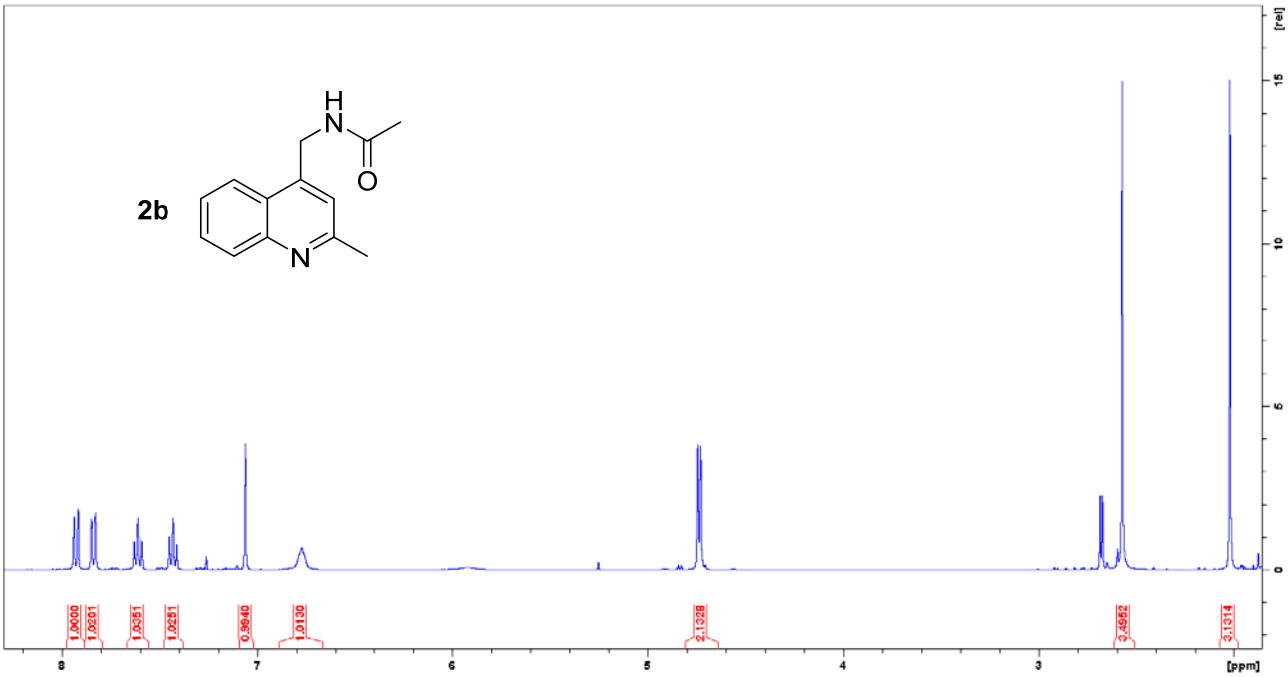


^{1}H NMR (400 MHz) in $CDCl_3$ of the purified reaction mixture.
Reaction conditions: quinaldine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

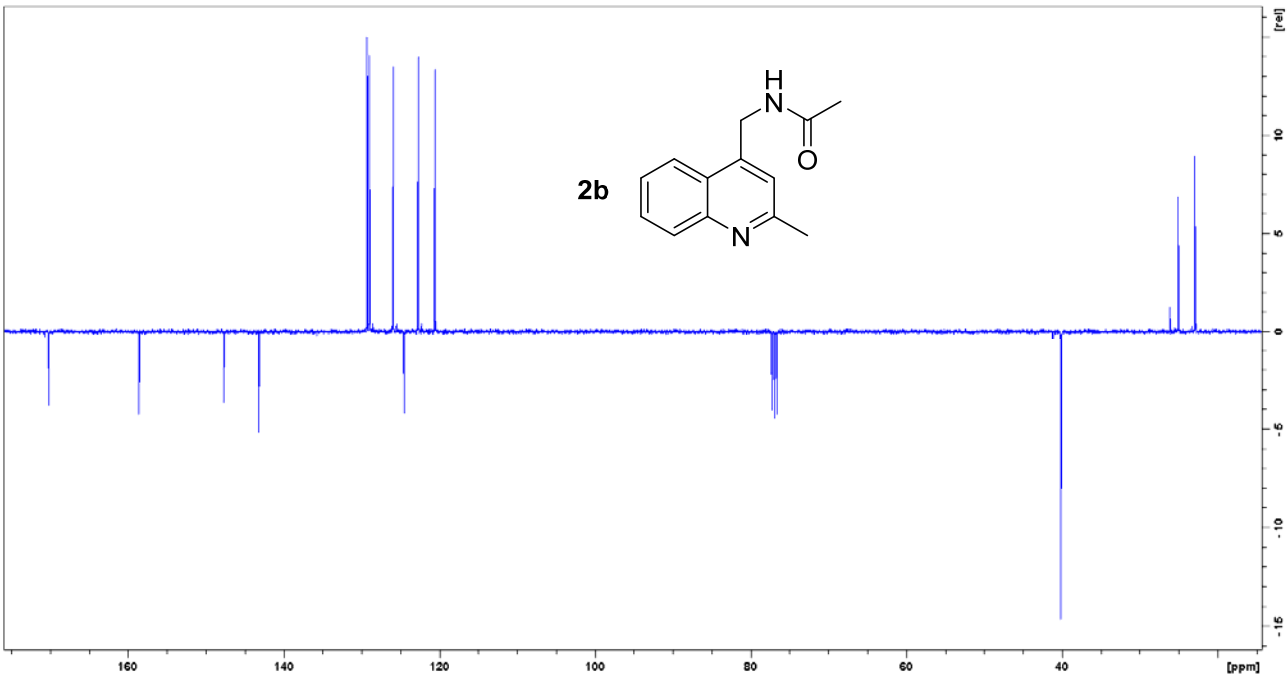


^{13}C APT NMR (100 MHz) in $CDCl_3$ of the purified reaction mixture.
Reaction conditions: quinaldine + DMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

^{1}H NMR and ^{13}C of purified product **2b – Scale-up**

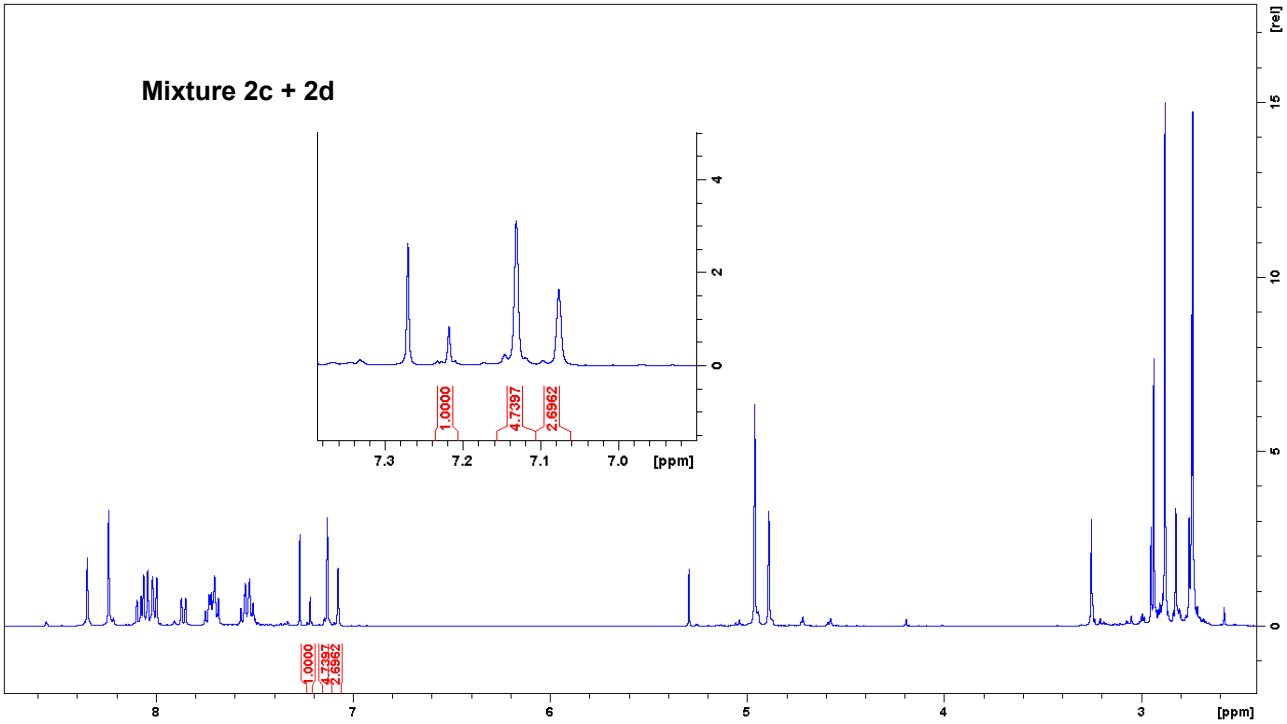


^{1}H NMR (400 MHz) in $CDCl_3$ of the purified reaction mixture.
Reaction conditions: quinaldine + NMA 80 °C, 2:1 $Na_2S_2O_8$, 15'



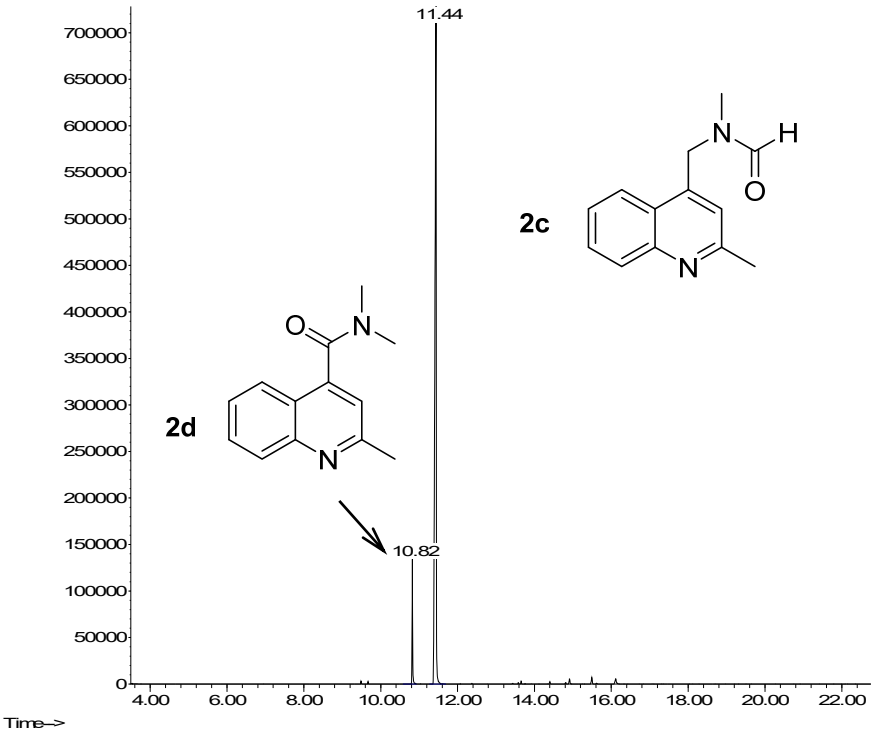
^{13}C APT NMR (100 MHz) in $CDCl_3$ of the purified reaction mixture.
Reaction conditions: quinaldine + NMA 80 °C, 2:1 $Na_2S_2O_8$, 15'

^{1}H NMR and ^{13}C of purified product **2c – Scale-up**

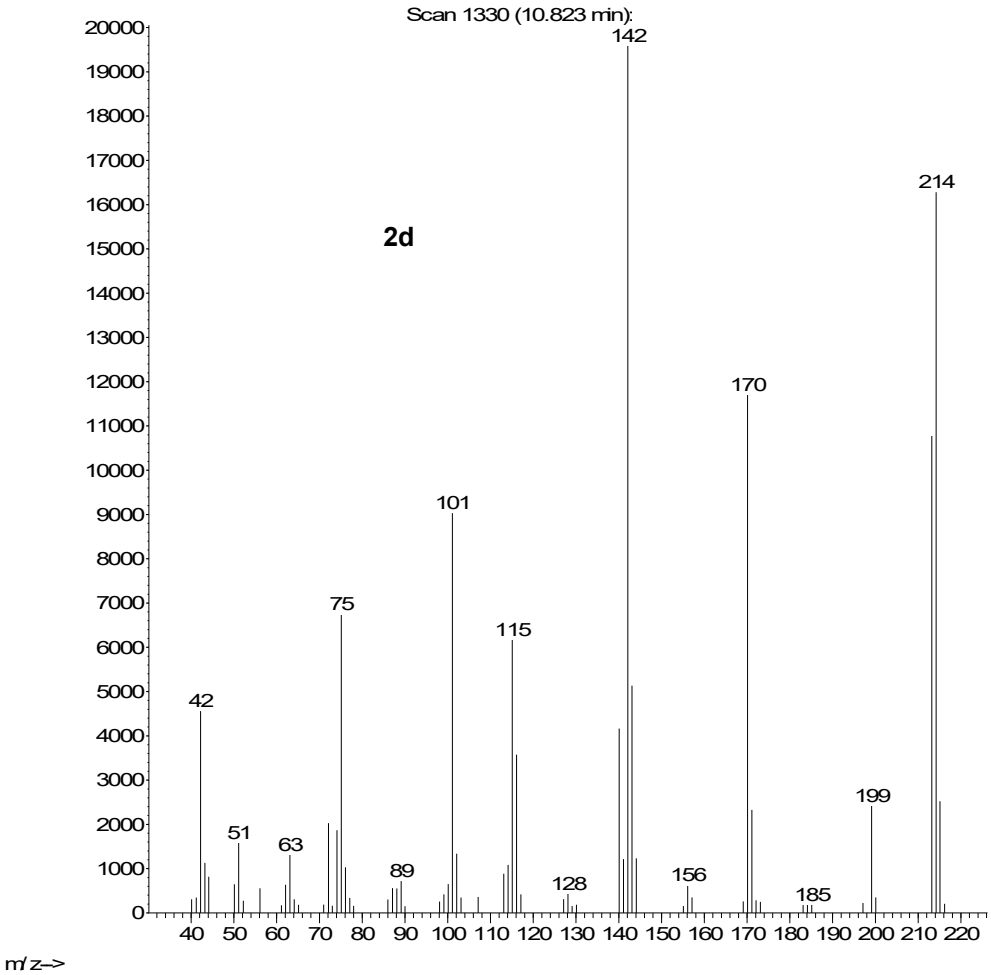


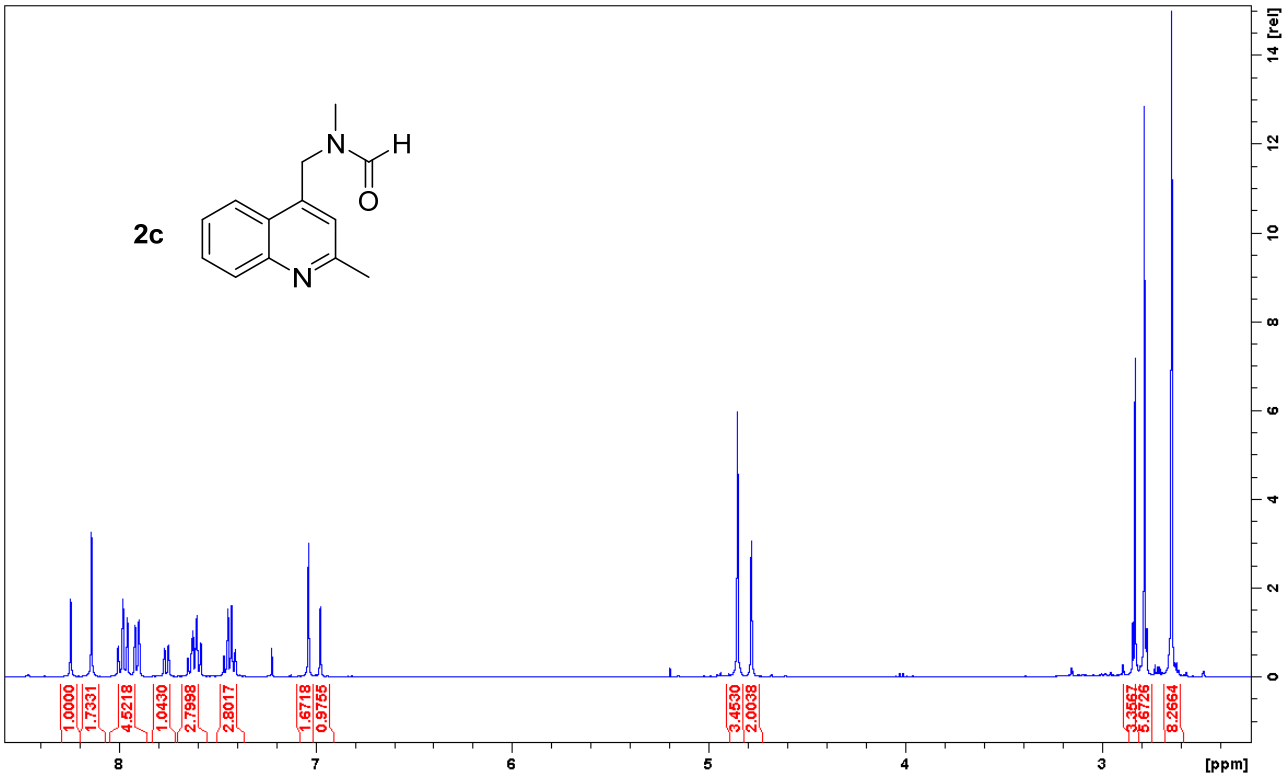
^{1}H NMR (400 MHz) in $CDCl_3$ of the purified reaction mixture.
Reaction conditions: quinaldine + DMF 80 °C, 2:1 $Na_2S_2O_8$, 15'

For the ^{1}H and 13C NMR of the pure **2c** and enriched fraction containing carboxamido derivative see part 2, #6

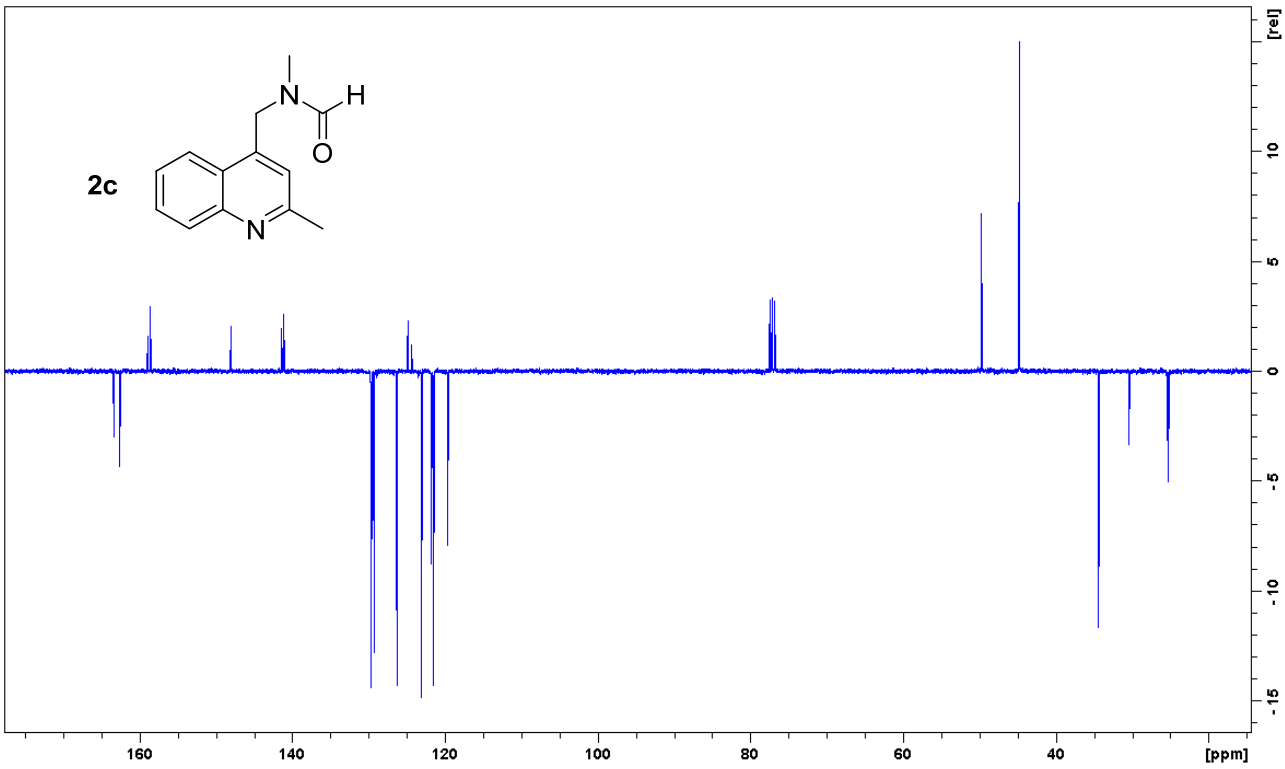


GC-MS of the purified reaction mixture.
Reaction conditions: quinaldine + DMF 80 °C, 2:1 $Na_2S_2O_8$, 15'


Scan 1330 (10.823 min):
2d
142
214
170
101
75
115
42
51
63
89
128
156
185
199
m/z-->
Scan 1436 (11.440 min)
2c
197
214
115
144
157
44
75
101
128
185
171
63
89
52
m/z-->



^{1}H NMR (400 MHz) in $CDCl_3$ of the purified **2c**.
Reaction conditions: quinaldine + DMF 80 °C, 2:1 $Na_2S_2O_8$, 15'



^{13}C APT NMR (100.6 MHz) in $CDCl_3$ of the purified **2c**.
Reaction conditions: quinaldine + DMF 80 °C, 2:1 $Na_2S_2O_8$, 15'