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Supporting Information

# Strong Antibiotic Activity of the Myxocoumarin Scaffold *in vitro* and *in vivo*

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## 1. General Information

Myxocoumarin B (**5**)[1] and derivatives **11g**[1], **17**[1], **24**[1], **29**[1] as well as β-ketoester ethyl 2-methyl-3-oxododecanoate (**6g**)[1] were synthesized as described in the literature. All solvents used in the reactions were p.A. grade. If necessary, reactions under argon atmosphere were carried out in dry solvents, which were purchased or prepared by distillation and dried over suitable molecular sieves (3 Å, 4 Å). Solvents for column chromatography were technical grade and distilled prior to use. Solvents for MPLC and HPLC were purchased from Fisher Scientific and VWR in a purity of over 99% (HPLC-grade). Commercial materials were purchased at the highest commercial quality from the providers Acros Organics, Alfa Aesar, Carbolution, Carl Roth, Sigma Aldrich, Thermo Fisher Scientific and Tokyo Chemical Industry. These chemicals were used without further purification. Silica sulfuric acid was prepared according to the literature[2] and the $H^+$ content determined prior to use according to the literature[3]. Pechmann condensations were carried out in 10 mL pressure vials equipped with a stirring bar using a Discover LabMate microwave from CEM, as well as a Monowave 50 from Anton-Paar. Reactions under high pressure were conducted in glass pressure tubes sealed with Teflon screw caps. Silica gel Geduran® Si 60 (particle size 0.40-0.60 mm), purchased from Merck was used for flash column chromatography. Solvent mixtures are understood as volume/volume. For TLC analysis, TLC-silica gel 60 $F_{254}$ plates were purchased from Merck. Applied substances were observed using a UV lamp at 254 nm and 365 nm. For UV-inactive substances, dyeing reagents, such as 2.4% anisaldehyde solution in ethanol were used. For product isolation the Reveleris® X2 medium pressure liquid chromatography (MPLC) system (Grace) was used. Reveleris® Reverse Phase (RP) C18 finished columns (Grace) in different sizes were used as required. The system was run with the Reveleris® Navigator®software (Grace) and UV detection was carried out at 220 nm, 250 nm and 254 nm. Applied column sizes and solvent gradients are noted in the respective experimental procedures. Semi-preparative HPLC separation was used for product isolation as well. Semi-preparative high performance liquid chromatography (HPLC) separation was carried out using a computer-controlled Jasco system (UV-1575 Intelligent UV/VIS Detector, two PU-1580 Intelligent HPLC Pumps, MIKA 1000 Dynamic Mixing Chamber, 1000 µL Portmann Instruments AG Biel-Benken, LC-NetII/ ADC, Rheodyne injection valve). Program control and interpretation of the recorded data was carried out using Galaxie software. Eurospher II 100-5 C18 A columns (Knauer) (250 mm x 8 mm) with integrated pre-columns were used. Applied solvent gradients are noted in the respective experimental procedures. After product-isolation with MPLC or semi-preparative HPLC the respective fractions were combined and acetonitrile removed under reduced pressure. The aqueous layer was then lyophilized. NMR spectra were recorded on Bruker AVHD300, Bruker AVHD400, Bruker AVHD500, or Bruker AV500-cryo spectrometers. The chemical shifts δ are listed as parts per million [ppm]. The spectra were calibrated

on the residual peak of the deuterated solvent ($\delta(CDCl_3)$ = 7.26 ppm, $\delta((CD_3)_2CO)$ = 2.05 ppm, $\delta((CD_3)_2SO)$ = 2.50 ppm, $\delta(CD_3OD)$ = 3.31 for $^1$H-NMR; $\delta(CDCl_3)$ = 77.2 ppm, $\delta((CD_3)_2CO)$ = 29.8 ppm, $\delta((CD_3)_2SO)$ = 39.5 ppm, $\delta(CD_3OD)$ = 49.0 for $^{13}$C-NMR). The following abbreviations (or combinations thereof) are used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad. Multiplicities resulting from coincidentally identical coupling constants of magnetically non-equivalent protons are indicated as virtual (*virt.*) multiplicities. The following abbreviations for chemicals are used: $Ac_2O$ = Acetic anhydride, ACN = acetonitrile, DCM = dichloromethane, DIPA = diisopropylamine, DMF = dimethylformamide, EtOAc = ethyl acetate, *n*-BuLi = *n*-butyl lithium, $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0), SSA = silica sulfuric acid, *t*-BuBrettPhos = 2-(di-*t*-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl, *t*-BuOH = *t*-butanol, TDA = tris-(3,5-dioxaheptyl)-amine, TFA = trifluoroacetic acid, $Tf_2O$ = triflic anhydride, THF = tetrahydrofuran, TLC = thin layer chromatography, rt = room temperature. For high resolution mass spectrometry (HRMS) a Thermo LTQ FT Ultra mass spectrometer with ESI and linear ion trap as well as an Agilent mass spectrometer 6538 with ESI, high resolution Q-TOF mass analyzer and microchannel plate detector were used.

## 2. Biological Activity Tests

Biological activity data were determined against *Candida albicans* ATCC 10231 and a panel of bacteria (all obtained from the National Collection of Type Cultures (NCTC) and the American Type Culture Collection (ATCC)).

Initially, the antimicrobial activity was determined against *C. albicans* ATCC 10231, *Enterococcus faecalis* ATCC 29212 and S*taphylococcus aureus* NCTC 6571 using standard diffusion assay with 250 µg of each compound added per disc or well in the agar plate inoculated with the test organism. Plates were incubated at 24 h of incubation at 37°C for 24 h and assessed for the zones of clearance, indicating antimicrobial potential.


**Figure S1.** Representative photograph of the agar diffusion assay using S*. aureus* NCTC 6571 where a selection of different myxocoumarin derivatives was dissolved in DMSO (50 mg/mL) and 5 µL (250 µg of compound) was added to each well. Asterix mark the zones of clearance, after 24-h incubation period.

### 2.1 Minimal inhibitory concentration (MIC) assay

MIC values (the lowest concentrations inhibiting visible growth) against *Bacillus subtilis* NCTC 5398, *Staphylococcus aureus* NCTC 6571, *Staphylococcus aureus* ATCC 43300 (*S. aureus* MRSA), *Staphylococcus aureus* ATCC 9144, *Staphylococcus* clinical isolates (*Staphylococcus* sp. 80103770, 80100861 and 80100865) and *Enterococcus faecium* ATCC 6057 were determined in accordance with the standard broth microdilution assay, recommended by CLSI (Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Tenth Edition M07-A10. CLSI). The highest tested concentration was 250 µg/mL, the inoculum was $5\times10^5$ cfu/mL and the MIC value was read after 24 h of incubation at 37°C.

### 2.2 MTT assay

Cytotoxicity in terms of antiproliferative effects was tested by the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay with normal human lung fibroblasts (MRC-5), as previously described.[4] Briefly, the assay was carried out after 48 h of cell monolayer incubation in the medium containing different concentrations of the compounds two times in four replicates. Cytotoxicity was expressed as the concentration of the compound inhibiting cell growth by 50% (IC50) in comparison to untreated control.

### 2.3 Multistep Resistance Selection of *S. aureus* to 5, 25 and 11e

To assess the ability of *S. aureus* to develop resistance to **5**, **25** and **11e** after repeated exposure, a multistep resistance selection experiment was performed as previously described.[5] The broth microdilution method for MIC determination against *S. aureus* was performed in accordance with the standard broth microdilution assay and repeated for 20 passages over a period of 2 months. In each succesive passage the inoculum was adjusted to a final density of approximately $5 \times 10^5$ cfu/mL using the contents of a well containing a subinhibitory concentration of the compound. Resistance was classified as a greater than 4-fold increase in the initial MIC as reported elsewhere.

### 2.4 Embryotoxicity using the zebrafish (*Danio rerio*) model

The evaluation of the toxicity of all compounds on zebrafish embryos was carried out according to the general rules of the OECD Guidelines for the Testing of Chemicals.[6] All experiments involving zebrafish were performed in compliance with the European directive 2010/63/EU and the ethical guidelines of the Guide for Care and Use of Laboratory Animals of the Institute of Molecular Genetics and Genetic Engineering, University of Belgrade. Adult zebrafish (*Danio rerio*, wild type) were obtained from a commercial supplier (Pet Center, Belgrade, Serbia), housed in a temperature- and light-controlled facility with 28 °C and standard 14:10-hour light-dark photoperiod, and regularly fed with commercially dry flake food (TetraMin™ flakes; Tetra Melle, Germany) twice a day and *Artemia nauplii* once daily. Zebrafish embryos were produced by pair-wise mating, collected and distributed into 24-well plates containing 10 embryos per well and 1 mL distilled water with 0.2 g/L of Instant Ocean® Salt, and raised at 28 °C. For assessing lethal and developmental toxicity, embryos at 6 hours post fertilization (hpf) stage were treated with six different concentrations of all compounds. DMSO (0.25%) was used as a negative control. Experiments were performed three times using 20 embryos per concentration. Apical endpoints for the toxicity evaluation were recorded at 24, 48, 72, 96 and 114 hpf using an inverted microscope (CKX41; Olympus, Tokyo, Japan). Dead embryos were counted and discarded every 24 h.

At 114 hpf, embryos were inspected for heartbeat rate, anesthetized by addition of 0.1% (w/v) tricaine solution (Sigma-Aldrich, St. Louis, MO), photographed and killed by freezing at -20 °C for ≥ 24 h.

### 2.5 Antimicrobial efficacy compounds *in vivo*

To examine anti-Staphylococcus efficacy of the selected myxocoumarins **5** and **25** *in vivo*, wild type zebrafish embryos were challenged to *S. aureus* ATCC43300 (MRSA) infections using the zebrafish - *S. aureus* model of systemic infection, according the protocol of Prajsnar.[7]

***S. aureus* culture and preparation of the cells for microinjection.** Briefly, the overnight bacterial culture grown in BHI broth were diluted at 1:100 ration and incubated at 37 °C with shaking (180 rpm) to reach a mid-exponential phase (OD600 0.6-0.7). Following centrifugation at 2000 × g for 5 min (Centrifuge 5415D, Eppendorf, Hamburg, Germany), bacterial cells in pellet were washed three times in sterile PBS and labelled with 2 µM CellTrackerTM RedCMTPX (Thermofisher Scientific) according to the manufacturer's instructions. In order to prepare bacterial inoculum for microinjection, the labelled cells were centrifuged 2000 × g for 5 min, washed in PBS to remove dye excess and resuspended in 2% polyvinylpyrrolidone (PVP) to achieve a final concentration of ~5×108 cells/mL.

**Infection of zebrafish embryos.** At 30-hpf, manually dechorionated embryos were anesthetized with 170 µg/mL of tricaine (MS-222) solution and microinjected with 4 nL containing 1200-1300 labelled-MRSA cells into the circulation valley by a pneumatic picopump (PV820, World Precision Instruments, USA). To confirm the number of injected MRSA cells (the viable counts – CFU), 4-5 infected embryos were crashed, plated on BHU agar and incubated at 37 °C for 2 days. Immediately after injection, embryos were allowed to recover for 1 h at 28 °C and then alive embryos were transferred into 24-well plates containing 1 mL of E3 medium and 10 embryos per well. In individual experiments, the infected embryos were treated with three doses (½ × MIC, 1 × MIC and 2× MIC) of each myxocoumarin analog and maintained at 31 °C by 120 hpf. Linezolid and vancomycin were used as positive controls. Embryos microinjected with 5% PVP were used as the control (mock) groups. Twenty embryos were used per concentration and each experiment was performed two times. The survival and development of MRSA-infected embryos was recorded every day until 120 hpf. Anti-staphylococcal efficacy of the selected compounds was assessed by the survival rate of treated embryos and the bacterial burden in relation to those in the untreated group. Also, the effect of applied myxocoumarins on infection eradication was followed in real time by fluorescence microscopy.

**Table S1.** Heat map of the antibacterial activity profile of myxocoumarin B (**5**) and its structural analogs **10-31** against *B. subtilis* NCTC5398, *S. aureus* NCTC6571, *S. aureus* MRSA compared to toxicity in zebrafish embryos. NCTC = National Collection of Type Cultures (NCTC, Culture Collection of Public Health, Salisbury, UK). Green color indicates antibiotic activity (darker green equals higher activity), orange color toxicity (darker orange equals higher toxicity). Activities are provided in µg/mL and µmol/mL.

| | ***B. subtilis*** **NCTC5398** | | ***S. aureus*** **NCTC6571** | | ***S. aureus*** **MRSA** | | ***Zebrafish*** $LC_{50}$ | |
|---|---|---|---|---|---|---|---|---|
| | [µg/mL] | [µmol/mL] | [µg/mL] | [µmol/mL] | [µg/mL] | [µmol/mL] | [µg/mL] | [µmol/mL] |
| **5** | 8 | 0.02 | 0.3 | 0.00086 | 0.6 | 0.0017 | 119.6 | 0.34 |
| **10a** | >250 | >1.31 | >250 | >1.31 | >250 | >1.31 | 8.9 | 0.05 |
| **10b** | 31.2 | 0.13 | 62.5 | 0.27 | 62.5 | 0.27 | 2.1 | 0.01 |
| **10c** | 200 | 0.81 | 200 | 0.81 | 200 | 0.81 | 2.5 | 0.01 |
| **10d** | 200 | 0.77 | 200 | 0.77 | 200 | 0.77 | 1.5 | 0.01 |
| **10e** | 2 | 0.01 | 2 | 0.01 | 2 | 0.01 | 2.7 | 0.01 |
| **10f** | 15.6 | 0.05 | 7.8 | 0.03 | 7.8 | 0.03 | 21.5 | 0.07 |
| **10g** | 2 | 0.01 | 3.9 | 0.01 | 7.8 | 0.03 | >151.2 | >0.50 |
| **10h** | 7.8 | 0.02 | >250 | >0.79 | 250 | 0.79 | 30.5 | 0.10 |
| **10i** | 62.5 | 0.19 | >250 | >0.76 | >250 | >0.76 | >82.6 | >0.25 |
| **10j** | >250 | >0.70 | >250 | >0.70 | >250 | >0.70 | >89.6 | >0.25 |
| **10k** | 15.6 | 0.06 | >250 | >0.96 | >250 | >0.96 | 5.2 | 0.02 |
| **11a** | 125 | 0.61 | 125 | 0.61 | 62.5 | 0.30 | 14.7 | 0.07 |
| **11b** | 15.6 | 0.06 | 15.6 | 0.06 | 15.6 | 0.06 | 9.0 | 0.04 |
| **11c** | 7.8 | 0.03 | 7.8 | 0.03 | 7.8 | 0.03 | 5.2 | 0.02 |
| **11d** | 7.8 | 0.03 | 4 | 0.01 | 2 | 0.01 | 4 | 0.01 |
| **11e** | 7.8 | 0.03 | 2.5 | 0.01 | 4 | 0.01 | 24.3 | 0.08 |
| **11f** | 4 | 0.01 | 15.6 | 0.05 | 7.8 | 0.03 | >152.2 | >0.50 |
| **11g** | 31.2 | 0.10 | 7.8 | 0.02 | 31.2 | 0.10 | >159.2 | >0.50 |
| **11h** | >250 | >0.75 | 250 | 0.75 | 250 | 0.75 | >158.2 | >0.48 |
| **11i** | >250 | >0.72 | >250 | >0.72 | >250 | >0.72 | >173.2 | >0.50 |
| **11j** | >250 | >0.67 | >250 | >0.67 | >250 | >0.67 | >187.3 | >0.50 |
| **11k** | 250 | 0.90 | 10 | 0.04 | 10 | 0.04 | 10.9 | 0.04 |
| **12** | 250 | 0.82 | 100 | 0.33 | 100 | 0.33 | >250 | >0.82 |
| **13** | 5 | 0.02 | 12.5 | 0.04 | 50 | 0.15 | >250 | >0.75 |
| **14** | >250 | >1.22 | >250 | >1.22 | >250 | >1.22 | 12.7 | 0.06 |
| **15** | >250 | >1.07 | >250 | >1.07 | >250 | >1.07 | 1.3 | 0.01 |
| **16** | 250 | 0.79 | >250 | >0.79 | >250 | >0.79 | >158.2 | >0.50 |
| **17** | 62.5 | 0.18 | >250 | >0.72 | >250 | >0.72 | >166.2 | >0.48 |
| **18** | 250 | 1.08 | >250 | >1.08 | >250 | >1.08 | 18.4 | 0.08 |
| **19** | 125 | 0.43 | >250 | >0.86 | >250 | >0.86 | 11.3 | 0.04 |
| **20** | 15.6 | 0.05 | 31.2 | 0.09 | 15.6 | 0.05 | 118.9 | 0.35 |
| **21** | 31.2 | 0.08 | 31.2 | 0.08 | 62.5 | 0.16 | 180.2 | 0.45 |
| **22** | >250 | >1.14 | >250 | >1.14 | >250 | >1.14 | 25.8 | 0.12 |
| **23** | >250 | >0.75 | >250 | >0.75 | >250 | >0.75 | >165.7 | >0.50 |
| **24** | >250 | >0.69 | >250 | >0.69 | >250 | >0.69 | >180.7 | >0.50 |
| **25** | 0.3 | 0.00077 | 0.15 | 0.00039 | 0.15 | 0.00039 | 27.8 | 0.07 |
| **26** | >250 | >0.72 | >250 | 0.72 | >250 | >0.72 | >172.7 | >0.50 |
| **27** | >250 | >0.83 | >250 | 0.83 | >250 | >0.83 | 21.5 | 0.07 |
| **28** | 125 | 0.37 | 250 | 0.74 | >250 | >0.74 | >168.4 | >0.50 |
| **29** | 62.5 | 0.15 | >250 | 0.58 | 250 | 0.58 | 67.6 | 0.16 |
| **30** | 2 | 0.0063 | 0.3 | 0.00094 | 0.3 | 0.00094 | 20.2 | 0.06 |
| **31** | 1 | 0.0028 | 0.15 | 0.00042 | 1.25 | 0.0035 | 18.6 | 0.05 |

**Table S2.** Selection of potent antimicrobial myxocoumarin derivatives. MICs against Gram(+) bacteria *Staphylococcus aureus*, *Staphylococcus aureus* MRSA, and *Bacillus subtilis* in comparison to $IC_{50}$ and $LC_{50}$ values

| **Compound** | ***S. aureus*** [µg/mL] | ***S. aureus* MRSA** [µg/mL] | ***B. subtilis*** [µg/mL] | ***MRC-5 IC50*** [µg/mL] | ***Zebrafish $LC_{50}$*** [µg/mL] | ***SI cytotox*** | ***SI embryotox*** |
|---|---|---|---|---|---|---|---|
| **5** | **0.3** | **0.6** | **8** | 35 | 119.60 | 87.5 | 299 |
| **10e** | **2** | **2** | **2** | 18 | 2.74 | 9 | 1.4 |
| **10f** | **7.8** | **7.8** | **15.6** | 28 | 21.53 | 3.6 | 2.7 |
| **10g** | **3.9** | **7.8** | **2** | 8 | >151.20 | 4 | 75 |
| **11b** | **15.6** | **15.6** | **15.6** | 20 | 9.03 | 1.3 | 0.6 |
| **11c** | **7.8** | **7.8** | **7.8** | 15 | 5.21 | 1.9 | 0.7 |
| **11d** | **4** | **2** | **7.8** | 15 | 4.00 | 7.5 | 2 |
| **11e** | **2.5** | **4** | **7.8** | 15 | 24.32 | 3.8 | 6 |
| **11f** | **15.6** | **7.8** | **4** | 12 | 152.20 | 3 | 19.51 |
| **11g** | **7.8** | **31.2** | **31.2** | 6 | >159.20 | 0.77 | 20 |
| **11k** | **10** | **10** | 250 | 14 | 10.92 | 1.4 | 1.1 |
| **13** | **12.5** | 50 | **5** | 27 | >250 | 5.4 | 50 |
| **20** | **31.2** | **15.6** | **15.6** | 7 | 118.90 | 0.45 | 7 |
| **25** | **0.2** | **0.15** | **0.3** | 5 | 27.80 | 25 | 139 |
| **30** | **0.3** | **0.3** | **2** | 3 | 20.19 | 10 | 67.30 |
| **31** | **0.15** | **1.25** | **1** | 3 | 18.61 | 20 | 124.1 |

## 3. Chemical Procedures

### 3.1 General Procedures

#### 3.1.1 Synthesis of β-keto esters

β-Keto esters **6b-k**, **S2** and **S4** were prepared as follows:

Lithium diisopropylamide was freshly prepared by the addition of *n*-BuLi (2.5 M in hexane, 2.5 eq.) to a solution of DIPA (2.5 eq.) in THF (0.8 mL/mmol) at −78 °C under argon atmosphere and stirred for 1 h. To this solution, the respective β-keto ester (1.0 eq.) was added at 0 °C. The resulting deep yellow clear solution was stirred for 1 h at 0 °C. After cooling the solution to −78 °C, the respective 1-iodoalkane (1.2 eq.) was added slowly. The reaction mixture was allowed to warm up to rt overnight. The reaction was quenched by adding 10% aqueous HCl and the mixture was then extracted with diethyl ether (3x). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography. Applied gradients are indicated in the respective section.

#### 3.1.2 Synthesis of coumarins by TFA-catalyzed Pechmann condensation

Coumarins **10b-k**, **11a-k**, **12**, **13**, **15**, **16**, **26** and **27** were prepared as follows:

Phenol (1.2 eq.) and β-keto ester (1.0 eq.) were dissolved in TFA (6.0 eq.) and heated either in the microwave or the synthesis reactor for 60 min at 110 °C. The dark red reaction mixture was poured into stirred ice-cold water. The formed precipitate was dissolved by adding EtOAc. The organic layer was separated, the aqueous phase extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography. Applied gradients are indicated in the respective section.

#### 3.1.3 Synthesis of *O*-acetylated coumarins

Coumarins **18**, **19**, **20** and **21** were prepared as follows:

The corresponding hydroxycoumarin (1.0 eq.) was dissolved in pyridine and acetic anhydride was added dropwise (volumes are indicated in the respective section). The solution was stirred for 24 h at rt. Subsequently, pyridine and acetic anhydride were removed under reduced pressure. The crude product was purified by semi-preparative HPLC or MPLC. Applied gradients are indicated in the respective section.

Coumarins **25** and **31** were prepared as follows:

The hydroxycoumarin (1.0 eq.) was dissolved under argon atmosphere in DCM (27 µL/µmol), pyridine (excess) and acetic anhydride (excess). The solution was stirred at rt for 15 min. The reaction mixture was diluted with EtOAc, washed with 10% aqueous HCl, water and brine (1-2x each). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography. Applied gradients are indicated in the respective section.

### 3.1.4 Synthesis of triflated coumarins

Coumarins **S7**, **S8** and **S12** were prepared as follows:

Into a suspension of hydroxycoumarin (1.0 eq.) in DCM and pyridine (2.0 eq.) was added triflic anhydride (1.2 eq.) in DCM (volumes are indicated in the respective section) under argon atmosphere dropwise using a syringe at 0 °C. The reaction mixture was warmed up to rt under continuous stirring over 30 min. Afterwards, the reaction mixture was diluted with DCM, washed with 10% aqueous HCl, water and brine (1-2x each). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography. Applied gradients are indicated in the respective section.

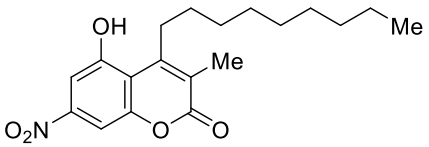
### 3.1.5 Synthesis of nitrocoumarins

Coumarins **22**, **23** and **30** were prepared as follows:

An oven dried glass pressure tube was flushed with argon and charged with the triflated coumarin (1.0 eq.), $Pd_2(dba)_3$ (0.5 mol%), *t*-BuBrettPhos (1.2 mol%), TDA (5.0 mol%) and sodium nitrite (2.0 eq.). After addition of *t*-BuOH (2.0 mL/mmol coumarin) the pressure tube was sealed with a Teflon screw cap and heated up to 130 °C for 24 h. The dark red reaction mixture was cooled to rt, diluted with EtOAc and washed with water (1-2x). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography. Applied gradients are indicated in the respective section.

3.2 Experimental Data

3.2.1 Myxocoumarin B (**5**)

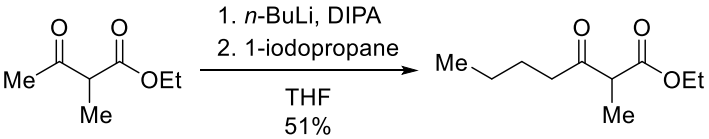



**5**

**Figure 1.** Structure of Myxocoumarin B (**5**).

**5** was synthesized as described in the literature.[1] $^{1}$H-NMR (500 MHz, $CD_3OD$) $\delta$ = 7.52 (d, $J$ = 2.4 Hz, 1H), 7.48 (d, $J$ = 2.4 Hz, 1H), 3.12 - 3.08 (m, 2H), 2.17 (s, 3H), 1.62 - 1.56 (m, 2H), 1.50 - 1.45 (m, 2H), 1.40 - 1.28 (m, 10H), 0.90 - 0.89 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $CD_3OD$) $\delta$ = 162.7, 157.9, 155.0, 153.1, 149.2, 124.3, 115.2, 106.5, 104.0, 33.1, 32.5, 31.1, 30.7, 30.4, 30.4, 30.1, 23.7, 14.4, 13.0 ppm. HRMS (+): m/z = 348.1806 $[M+H]^+$, calc.: 348.1805. The spectroscopic data were in agreement with those described in the literature.[1,8]

3.2.2 ethyl 2-methyl-3-oxoheptanoate (**6b**)

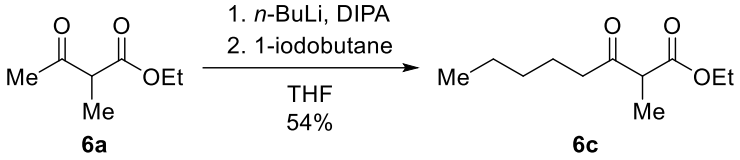



**6a** **6b**

**Scheme 1.** Synthesis of β-keto ester **6b**.

**6b** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/2, $R_f$ = 0.6) afforded an orange oil (286 mg, 1.54 mmol, 51%). $^{1}$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.17 (q, $J$ = 7.1 Hz, 2H), 3.50 (q, $J$ = 7.1 Hz, 1H), 2.63 - 2.41 (m, 2H), 1.64 - 1.49 (m, 2H), 1.32 (d, $J$ = 7.2 Hz, 3H), 1.29 - 1.21 (m, 5H), 0.89 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.1, 170.8, 61.4, 53.0, 41.2, 25.8, 22.3, 14.2, 13.9, 12.9 ppm. HRMS (+): m/z = 187.1328 $[M+H]^+$, calc.: 187.1328. The spectroscopic data were in agreement with those described in the literature.[9]

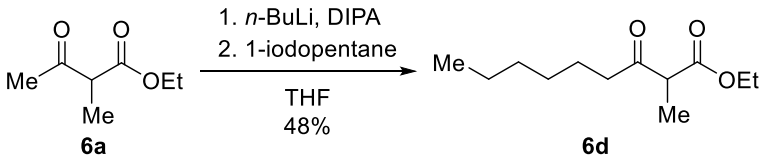
3.2.3 ethyl 2-methyl-3-oxooctanoate (**6c**)




**Scheme 2.** Synthesis of β-keto ester **6c**.

**6c** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/1, $R_f$ = 0.6) afforded a yellow oil (326 mg, 1.63 mmol, 54%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, $J$ = 7.1 Hz, 2H), 3.50 (q, $J$ = 7.2 Hz, 1H), 2.63 - 2.40 (m, 2H), 1.58 ($p_{virt}$, $J \approx$ 7.3 Hz, 2H), 1.32 (d, $J$ = 7.2 Hz, 3H), 1.30 - 1.20 (m, 7H), 0.88 (t, $J$ = 7.0 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.2, 170.8, 61.4, 53.0, 41.5, 31.4, 23.4, 22.6, 14.2, 14.0, 12.9 ppm. HRMS (+): m/z = 201.1485 $[M+H]^+$, calc.: 201.1485. The spectroscopic data were in agreement with those described in the literature.[10]

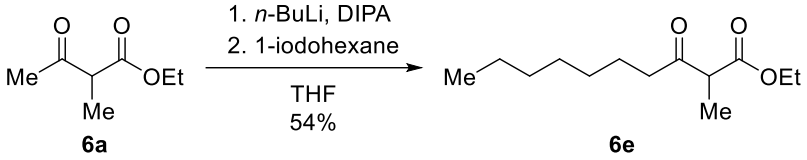
3.2.4 ethyl 2-methyl-3-oxononanoate (**6d**)




**Scheme 3.** Synthesis of β-keto ester **6d**.

**6d** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/2, $R_f$ = 0.7) afforded a yellow oil (311 mg, 1.45 mmol, 48%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, $J$ = 7.1 Hz, 2H), 3.50 (q, $J$ = 7.1 Hz, 1H), 2.63 - 2.41 (m, 2H), 1.63 - 1.52 (m, 2H), 1.32 (d, $J$ = 7.2 Hz, 3H), 1.30 - 1.22 (m, 9H), 0.91 - 0.83 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.2, 170.8, 61.4, 53.0, 41.5, 31.7, 28.9, 23.7, 22.6, 14.2, 14.1, 12.9 ppm. HRMS (+): m/z = 215.1642 $[M+H]^+$, calc.: 215.1641. The spectroscopic data were in agreement with those described in the literature.[11]

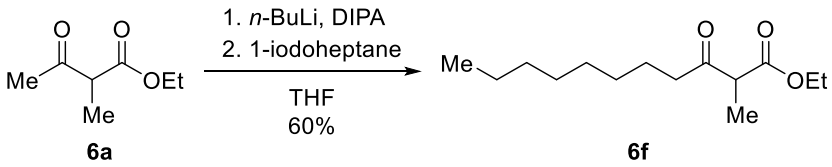
3.2.5 ethyl 2-methyl-3-oxodecanoate (**6e**)




**Scheme 4.** Synthesis of β-keto ester **6e**.

**6e** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/2, $R_f$ = 0.7) afforded a yellow oil (374 mg, 1.64 mmol, 54%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, *J* = 7.0 Hz, 2H), 3.50 (q, *J* = 7.1 Hz, 1H), 2.64 - 2.40 (m, 2H), 1.68 - 1.50 (m, 2H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.30 - 1.22 (m, 11H), 0.90 - 0.83 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.2, 170.8, 61.4, 53.0, 41.5, 31.8, 29.2, 29.2, 23.7, 22.7, 14.22, 14.18, 12.9 ppm. HRMS (+): m/z = 229.1798 $[M+H]^+$, calc.: 229.1798.

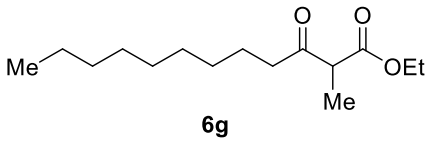
3.2.6 ethyl 2-methyl-3-oxoundecanoate (**6f**)




**Scheme 5.** Synthesis of β-keto ester **6f**.

**6f** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/3, $R_f$ = 0.9) afforded an orange oil (360 mg, 1.49 mmol, 60%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, *J* = 7.1 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 1H), 2.65 - 2.41 (m, 2H), 1.64 - 1.50 (m, 2H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.30 - 1.18 (m, 13H), 0.93 - 0.82 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.2, 170.8, 61.4, 53.0, 41.5, 31.9, 29.5, 29.3, 29.2, 23.7, 22.8, 14.2, 14.2, 12.9 ppm. HRMS (+): m/z = 243.1955 $[M+H]^+$, calc.: 243.1954.

3.2.7 ethyl 2-methyl-3-oxododecanoate (**6g**)

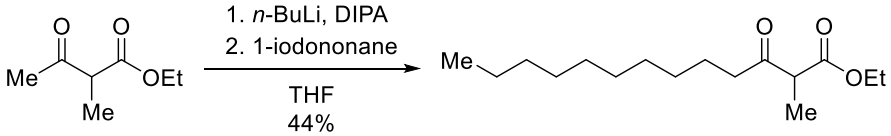



**6g**

**Figure 2.** Structure of β-keto ester **6g**.

**6g** was synthesized as described in the literature.[1] $^{1}$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.15 (q, $J$ = 7.1 Hz, 2H), 3.48 (q, $J$ = 7.1 Hz, 1H), 2.64 - 2.35 (m, 2H), 1.58 - 1.53 (m, 2H), 1.30 (d, $J$ = 7.1 Hz, 3H), 1.26 - 1.21 (m, 15H), 0.85 (t, $J$ = 6.3 Hz, 3H) ppm. $^{13}$C-NMR (101 MHz, $CDCl_3$) $\delta$ = 206.1, 170.7, 61.3, 53.0, 41.5, 32.0, 29.50, 29.48, 29.4, 29.2, 23.7, 22.7, 14.2 (2C), 12.9 ppm. HRMS (+): m/z = 257.2112 $[M+H]^+$, calc.: 257.2111. The spectroscopic data were in agreement with those described in the literature.[1]

3.2.8 ethyl 2-methyl-3-oxotridecanoate (**6h**)

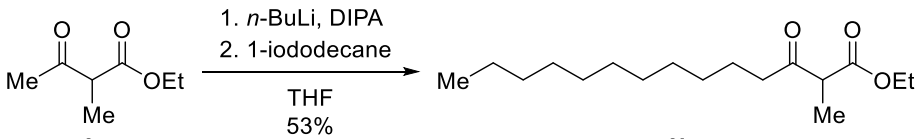



**6a** **6h**

**Scheme 6.** Synthesis of β-keto ester **6h**.

**6h** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/1, $R_f$ = 0.7) afforded a yellow oil (437 mg, 1.62 mmol, 44%). $^{1}$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, $J$ = 7.1 Hz, 2H), 3.50 (q, $J$ = 7.2 Hz, 1H), 2.64 - 2.39 (m, 2H), 1.58 ($p_{virt}$, $J \approx$ 7.6 Hz, 2H), 1.32 (d, $J$ = 7.2 Hz, 3H), 1.30 - 1.21 (m, 17H), 0.91 - 0.83 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.2, 170.8, 61.4, 53.0, 41.5, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 23.7, 22.8, 14.2 (2C), 12.9 ppm. HRMS (+): m/z = 271.2269 $[M+H]^+$, calc.: 271.2267.

3.2.9 ethyl 2-methyl-3-oxotetradecanoate (**6i**)



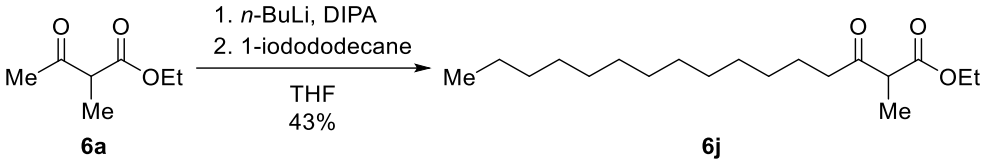

**6a** **6i**

**Scheme 7.** Synthesis of β-keto ester **6i**.

**6i** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/1, $R_f$ = 0.7) afforded a yellow oil (527 mg, 1.85 mmol, 53%). $^{1}$H-NMR

(300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, $J$ = 7.1 Hz, 2H), 3.50 (q, $J$ = 7.1 Hz, 1H), 2.64 - 2.40 (m, 2H), 1.58 ($p_{virt}$, $J \approx$ 7.3 Hz, 2H), 1.32 (d, $J$ = 7.1 Hz, 3H), 1.30 - 1.23 (m, 19H), 0.91 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.2, 170.8, 61.4, 53.0, 41.5, 32.1, 29.7, 29.7, 29.6, 29.53, 29.47, 29.2, 23.7, 22.8, 14.24, 14.23, 12.9 ppm. HRMS (+): m/z = 285.2424 $[M+H]^+$, calc.: 285.2424.

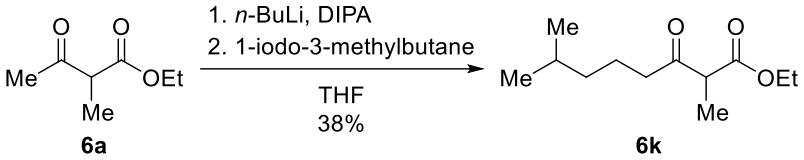
### 3.2.10 ethyl 2-methyl-3-oxohexadecanoate (**6j**)




**Scheme 8.** Synthesis of β-keto ester **6j**.

**6j** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/1, $R_f$ = 0.5) afforded a yellow oil (430 mg, 1.38 mmol, 43%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, $J$ = 7.1 Hz, 2H), 3.50 (q, $J$ = 7.1 Hz, 1H), 2.63 - 2.40 (m, 2H), 1.58 ($p_{virt}$, $J \approx$ 7.3 Hz, 2H), 1.32 (d, $J$ = 7.1 Hz, 3H), 1.30 - 1.22 (m, 23H), 0.91 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.2, 170.8, 61.4, 53.0, 41.5, 32.1, 29.81, 29.79 (2C), 29.75, 29.6, 29.53, 29.49, 29.2, 23.7, 22.8, 14.3, 14.2, 12.9 ppm. HRMS (+): m/z = 313.2737 $[M+H]^+$, calc.: 313.2737.

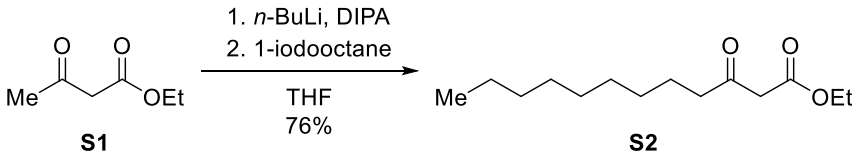
### 3.2.11 ethyl 2,7-dimethyl-3-oxooctanoate (**6k**)




**Scheme 9.** Synthesis of β-keto ester **6k**.

**6k** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/1, $R_f$ = 0.6) afforded a yellow oil (378 mg, 1.76 mmol, 38%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.18 (q, $J$ = 7.2 Hz, 2H), 3.50 (q, $J$ = 7.2 Hz, 1H), 2.63 - 2.39 (m, 2H), 1.67 - 1.45 (m, 3H), 1.33 (d, $J$ = 7.2 Hz, 3H), 1.26 (t, $J$ = 7.1 Hz, 3H), 1.20 - 1.10 (m, 2H), 0.87 (d, $J$ = 6.6 Hz, 6H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 206.1, 170.8, 61.4, 53.0, 41.7, 38.4, 28.0, 22.6 (2C), 21.6, 14.2, 12.9 ppm. HRMS (+): m/z = 215.1642 $[M+H]^+$, calc.: 215.1641.

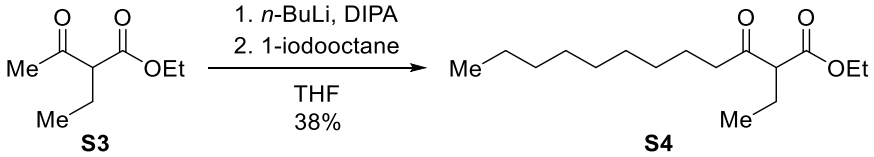
3.2.12 ethyl 3-oxododecanoate (**S2**)




**Scheme 10.** Synthesis of β-keto ester **S2**.

**S2** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 7/1, $R_f$ = 0.5) afforded a yellow oil (458 mg, 1.89 mmol, 76%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.19 (q, $J$ = 7.2 Hz, 2H), 3.42 (s, 2H), 2.52 (t, $J$ = 7.4 Hz, 2H), 1.58 ($p_{virt}$, $J \approx$ 6.9 Hz, 2H), 1.34 - 1.19 (m, 15H), 0.91 - 0.83 (m, 3H) ppm. $^{13}$C-NMR (151 MHz, $CDCl_3$) $\delta$ = 203.1, 167.4, 61.5, 49.5, 43.2, 32.0, 29.53, 29.49, 29.4, 29.2, 23.6, 22.8, 14.3, 14.2 ppm. HRMS (+): m/z = 265.1777 $[M+Na]^+$, calc.: 265.1774. The spectroscopic data were in agreement with those described in the literature.[12]

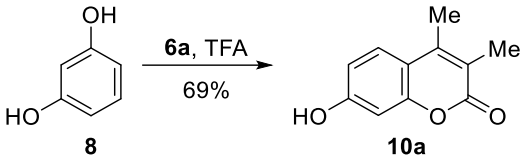
3.2.13 ethyl 2-ethyl-3-oxododecanoate (**S4**)




**Scheme 11.** Synthesis of β-keto ester **S4**.

**S4** was synthesized according to the general procedure 3.1.1. Purification by column chromatography (cyclohexane/EtOAc = 15/1, $R_f$ = 0.4) afforded a yellow oil (77.0 mg, 285 µmol, 38%). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ = 4.17 (q, $J$ = 7.1 Hz, 2H), 3.34 (t, $J$ = 7.4 Hz, 1H), 2.61 - 2.38 (m, 2H), 1.94 - 1.78 (m, 2H), 1.64 - 1.49 (m, 2H), 1.33 - 1.19 (m, 15H), 0.91 (t, $J$ = 7.4 Hz, 3H), 0.86 (t, $J$ = 6.4 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ = 205.7, 170.0, 61.3, 60.8, 42.0, 32.0, 29.52, 29.50, 29.4, 29.2, 23.6, 22.8, 21.7, 14.23, 14.20, 12.1 ppm. HRMS (+): m/z = 293.2087 $[M+Na]^+$, calc.: 293.2087.

3.2.14 7-hydroxy-3,4-dimethylcoumarin (**10a**)

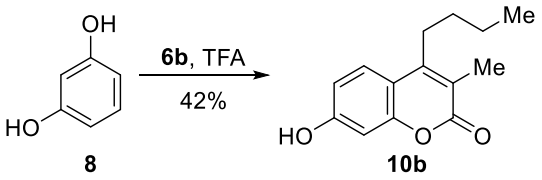



**8** **10a**

**Scheme 12.** Synthesis of coumarin **10a**.

**8** (430 mg, 3.91 mmol, 1.0 eq.) and **6a** (650 mg, 4.51 mmol, 1.2 eq.) were dissolved in TFA (1.8 mL, 23.5 mmol, 6.0 eq.) and microwave-irradiated for 35 min at 100 °C. The reaction mixture was poured into stirred ice-cold water (50 mL). The formed precipitate was filtered off, washed with water and dried for two days at 80°C. Purification by column chromatography (cyclohexane/acetone = 3/2, $R_f$ = 0.6) afforded a colourless solid (513 mg, 2.70 mmol, 69%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 10.33 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 2.33 (s, 3H), 2.05 (s, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 160.0, 153.1, 147.0, 126.2, 116.8, 112.7, 112.5, 101.9, 14.8, 12.8 ppm. HRMS (+): m/z = 191.0702 $[M+H]^+$, calc.: 191.0703. The spectroscopic data were in agreement with those described in the literature.[13]

3.2.15 4-butyl-7-hydroxy-3-methylcoumarin (**10b**)

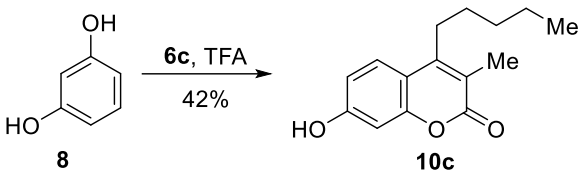



**8** **10b**

**Scheme 13.** Synthesis of coumarin **10b**.

**10b** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 4/3, $R_f$ = 0.6) afforded a yellow solid (71.0 mg, 306 µmol, 42%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.21 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.7 Hz, 2.5 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 2.86 - 2.78 (m, 2H), 2.11 (s, 3H), 1.64 - 1.45 (m, 4H), 1.01 - 0.94 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.4, 160.6, 155.1, 151.3, 126.9, 118.4, 113.5, 113.3, 103.3, 31.7, 29.0, 23.6, 14.2, 12.9 ppm. HRMS (+): m/z = 233.1171 $[M+H]^+$, calc.: 233.1172.

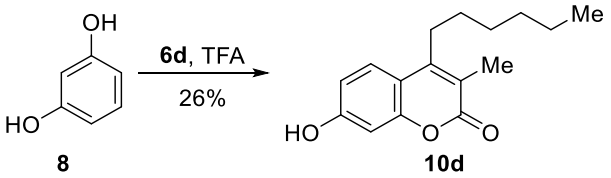
3.2.16 7-hydroxy-3-methyl-4-pentylcoumarin (**10c**)




**Scheme 14.** Synthesis of coumarin **10c**.

**10c** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ = 0.5) afforded a yellow solid (85.0 mg, 345 µmol, 42%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.22 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 2.88 - 2.79 (m, 2H), 2.11 (s, 3H), 1.66 - 1.54 (m, 2H), 1.54 - 1.32 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.5, 160.7, 155.1, 151.4, 126.8, 118.3, 113.5, 113.2, 103.3, 32.7, 29.23, 29.20, 23.1, 14.3, 12.9 ppm. HRMS (+): m/z = 247.1328 $[M+H]^+$, calc.: 247.1329.

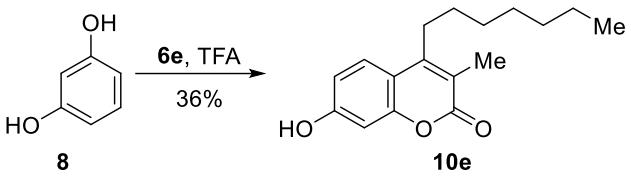
3.2.17 4-hexyl-7-hydroxy-3-methylcoumarin (**10d**)




**Scheme 15.** Synthesis of coumarin **10d**.

**10d** was synthesized according to the general procedure 3.1.2. Purification by MPLC (A = $H_2O$ + 0.05% TFA, B = ACN + 0.05% TFA, 0 - 1 min 5% B, 1 - 13 min 5 - 95% B, 13 - 16 min 95% B; column: Reveleris® C18, 12 g; flow rate: 30 mL/min) afforded a yellow solid (49.0 mg, 188 µmol, 26%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.23 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 2.87 - 2.79 (m, 2H), 2.11 (s, 3H), 1.67 - 1.43 (m, 4H), 1.42 - 1.26 (m, 4H), 0.94 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.5, 160.7, 155.1, 151.4, 126.8, 118.2, 113.5, 113.2, 103.2, 32.3, 30.2, 29.5, 29.3, 23.3, 14.3, 12.9 ppm. HRMS (+): m/z = 261.1485 $[M+H]^+$, calc.: 261.1485.

3.2.18 4-heptyl-7-hydroxy-3-methylcoumarin (**10e**)

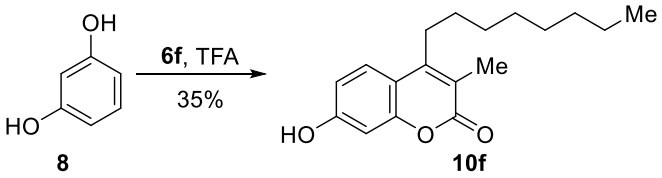



8 **10e**

**Scheme 16.** Synthesis of coumarin **10e**.

**10e** was synthesized according to the general procedure 3.1.2. Purification by MPLC (A = $H_2O$ + 0.05% TFA, B = ACN + 0.05% TFA, 0 - 1 min 5% B, 1 - 13 min 5 - 95% B, 13 - 16 min 95% B; column: Reveleris® C18, 12 g; flow rate: 30 mL/min) afforded a yellow solid (81.0 mg, 295 µmol, 36%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.18 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 2.88 - 2.78 (m, 2H), 2.11 (s, 3H), 1.67 - 1.44 (m, 4H), 1.44 - 1.19 (m, 6H), 0.94 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.5, 159.9, 153.5, 150.9, 126.1, 116.5, 112.9, 111.5, 102.1, 31.2, 29.1, 28.5, 28.4, 28.1, 22.0, 13.9, 12.5 ppm. HRMS (+): m/z = 275.1641 $[M+H]^+$, calc.: 275.1642.

3.2.19 7-hydroxy-3-methyl-4-octylcoumarin (**10f**)

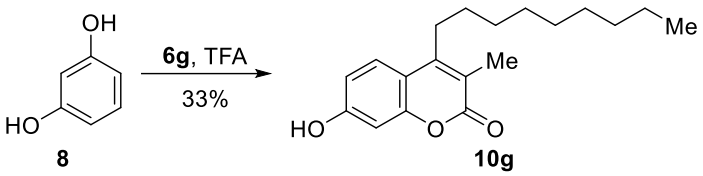



8 **10f**

**Scheme 17.** Synthesis of coumarin **10f**.

**10f** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/EtOAc = 2/1, $R_f$ = 0.5) afforded a yellow solid (34.0 mg, 118 µmol, 35%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.20 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 2.88 - 2.79 (m, 2H), 2.11 (s, 3H), 1.67 - 1.45 (m, 4H), 1.44 - 1.20 (m, 8H), 0.91 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (126 MHz, $(CD_3)_2SO$) $\delta$ = 161.6, 160.0, 153.5, 151.0, 126.2, 116.5, 113.0, 111.5, 102.1, 31.3, 29.2, 28.8, 28.7, 28.4, 28.1, 22.1, 14.0, 12.6 ppm. HRMS (+): m/z = 289.1797 $[M+H]^+$, calc.: 289.1798.

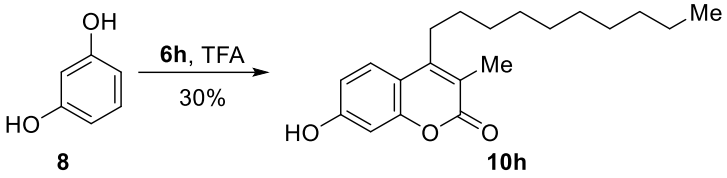
3.2.20 7-hydroxy-3-methyl-4-nonylcoumarin (**10g**)




**Scheme 18.** Synthesis of coumarin **10g**.

**10b** was synthesized according to the general procedure 3.1.2 with the following adjustments. The reaction mixture was microwave-irradiated for 75 min at 110 °C. Purification by column chromatography (cyclohexane/EtOAc = 3/1, $R_f$ = 0.4) afforded a light yellow solid (0.31 g, 1.03 mmol, 33%). $^1$H-NMR (400 MHz, $(CD_3)_2CO$) $\delta$ = 9.28 (br s, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 2.84 - 2.81 (m, 2H), 2.11 (s, 3H), 1.63 - 1.55 (m, 2H), 1.53 - 1.46 (m, 2H), 1.42 - 1.27 (m, 10H), 0.89 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.4, 160.7, 155.1, 151.4, 126.9, 118.3, 113.5, 113.2, 103.3, 32.6, 30.4, 30.24, 30.15, 30.0, 29.8, 29.5, 23.3, 14.3, 12.9 ppm. HRMS (+): m/z = 303.1954 $[M+H]^+$, calc.: 303.1960.

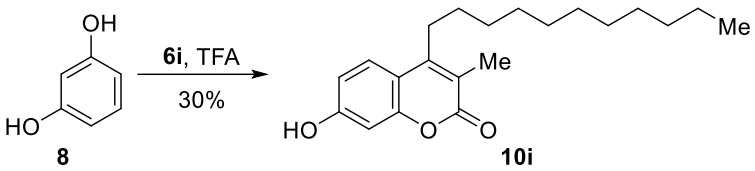
3.2.21 4-decyl-7-hydroxy-3-methylcoumarin (**10h**)




**Scheme 19.** Synthesis of coumarin **10h**.

**10h** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ = 0.4) afforded a yellow solid (74.0 mg, 234 µmol, 30%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.21 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 6.84 (dd, *J* = 8.7 Hz, 2.5 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 2.89 - 2.78 (m, 2H), 2.11 (s, 3H), 1.66 - 1.44 (m, 4H), 1.43 - 1.21 (m, 12H), 0.92 - 0.83 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.5, 159.9, 153.5, 150.9, 126.0, 116.5, 112.9, 111.5, 102.1, 31.3, 29.1, 28.9 (2C), 28.8, 28.7, 28.3, 28.1, 22.1, 13.9, 12.5 ppm. HRMS (+): m/z = 317.2110 $[M+H]^+$, calc.: 317.2111.

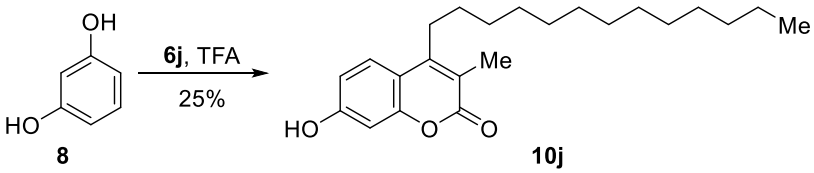
3.2.22 7-hydroxy-3-methyl-4-undecylcoumarin (**10i**)




**Scheme 20.** Synthesis of coumarin **10i**.

**10i** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ = 0.5) afforded a white solid (90.0 mg, 272 µmol, 30%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.20 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 6.84 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 2.89 - 2.79 (m, 2H), 2.11 (s, 3H), 1.68 - 1.44 (m, 4H), 1.44 - 1.19 (m, 14H), 0.94 - 0.81 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.5, 159.9, 153.5, 150.9, 126.1, 116.5, 112.9, 111.5, 102.1, 31.3, 29.1, 29.0 (2C), 28.9, 28.8, 28.7, 28.3, 28.1, 22.1, 13.9, 12.5 ppm. HRMS (+): m/z = 331.2267 $[M+H]^+$, calc.: 331.2268.

3.2.23 7-hydroxy-3-methyl-4-tridecylcoumarin (**10j**)

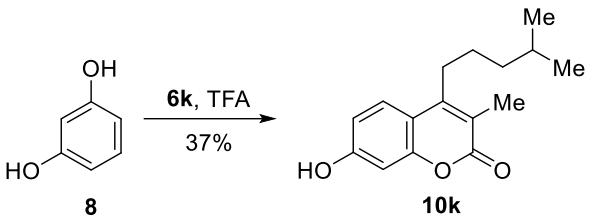



**Scheme 21.** Synthesis of coumarin **10j**.

**10j** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ = 0.5) afforded a yellow solid (60.0 mg, 167 µmol, 25%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.23 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 2.87 - 2.79 (m, 2H), 2.11 (s, 3H), 1.67 - 1.44 (m, 4H), 1.44 - 1.21 (m, 18H), 0.91 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.5, 159.9, 153.5, 150.8, 126.0, 116.4, 112.9, 111.5, 102.1, 31.3, 29.1, 29.0*, 28.9*, 28.8, 28.7, 28.3, 28.1, 22.1, 13.9, 12.5 ppm. HRMS (+): m/z = 359.2580 $[M+H]^+$, calc.: 359.2581.

* Total of 5 signals not fully resolved due to signal overlap.

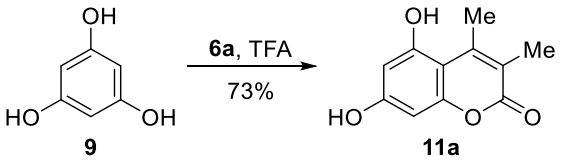
3.2.24 7-hydroxy-3-methyl-4-(4-methylpentyl)coumarin (**10k**)




**Scheme 22.** Synthesis of coumarin **10k**.

**10k** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ = 0.6) afforded a yellow solid (81.0 mg, 311 µmol, 37%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.22 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 2.87 - 2.78 (m, 2H), 2.11 (s, 3H), 1.69 - 1.54 (m, 3H), 1.45 - 1.32 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.5, 160.7, 155.1, 151.4, 126.8, 118.3, 113.5, 113.2, 103.3, 39.7, 29.5, 28.6, 27.4, 22.8 (2C), 13.0 ppm. HRMS (+): m/z = 261.1485 $[M+H]^+$, calc.: 261.1485.

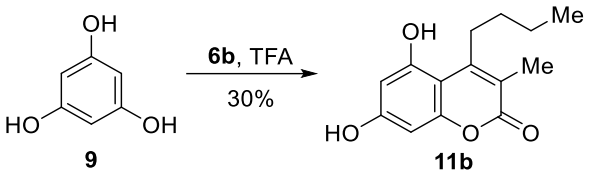
3.2.25 5,7-dihydroxy-3,4-dimethylcoumarin (**11a**)




**Scheme 23.** Synthesis of coumarin **11a**.

**11a** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 1/1, $R_f$ = 0.5) afforded a yellow solid (487 mg, 2.36 mmol, 73%). $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ = 6.22 (d, *J* = 2.4 Hz, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 2.62 (s, 3H), 2.08 (s, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.2, 159.7, 157.2, 154.5, 148.8, 114.8, 102.5, 99.3, 94.1, 19.0, 12.5 ppm. HRMS (+): m/z = 207.0651 $[M+H]^+$, calc.: 207.0657. The spectroscopic data were in agreement with those described in the literature.[14]

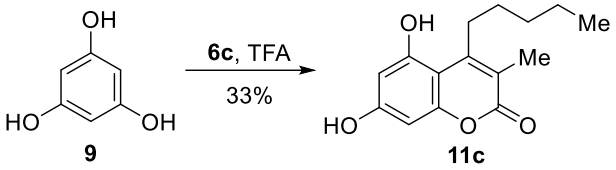
3.2.26 4-butyl-5,7-dihydroxy-3-methylcoumarin (**11b**)




**Scheme 24.** Synthesis of coumarin **11b**.

**11b** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 10/9, $R_f$ = 0.6) afforded a yellow solid (32.0 mg, 129 µmol, 30%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.43 (s, 1H), 9.07 (s, 1H), 6.37 (d, $J$ = 2.4 Hz, 1H), 6.26 (d, $J$ = 2.4 Hz, 1H), 3.12 - 3.03 (m, 2H), 2.08 (s, 3H), 1.66 - 1.52 (m, 2H), 1.51 - 1.39 (m, 2H), 0.95 (t, $J$ = 7.2 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.2, 160.5, 157.4, 156.7, 153.2, 116.7, 103.4, 100.5, 95.9, 32.0, 31.9, 23.8, 14.2, 12.5 ppm. HRMS (+): m/z = 249.1121 $[M+H]^+$, calc.: 249.1121.

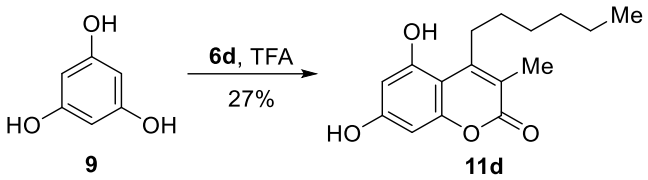
3.2.27 5,7-dihydroxy-3-methyl-4-pentylcoumarin (**11c**)




**Scheme 25.** Synthesis of coumarin **11c**.

**11c** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 10/9, $R_f$ = 0.6) afforded a yellow solid (48.0 mg, 183 µmol, 33%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 10.43 (s, 1H), 10.11 (s, 1H), 6.26 (d, $J$ = 2.4 Hz, 1H), 6.14 (d, $J$ = 2.4 Hz, 1H), 3.01 - 2.92 (m, 2H), 2.00 (s, 3H), 1.58 - 1.44 (m, 2H), 1.43 - 1.26 (m, 4H), 0.91 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 159.7, 156.7, 155.1, 152.8, 114.5, 101.7, 99.5, 94.4, 31.7, 30.9, 28.3, 21.9, 13.9, 12.0 ppm. HRMS (+): m/z = 263.1278 $[M+H]^+$, calc.: 263.1278.

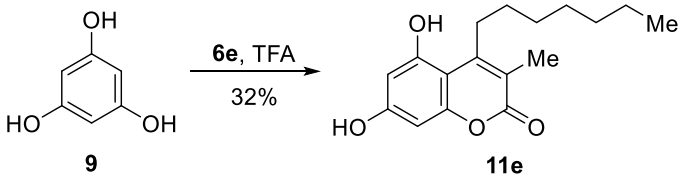
3.2.28 4-hexyl-5,7-dihydroxy-3-methylcoumarin (**11d**)




**Scheme 26.** Synthesis of coumarin **11d**.

**11d** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 10/9, $R_f$ = 0.7) afforded a yellow solid (41.0 mg, 148 µmol, 27%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.44 (s, 1H), 9.08 (s, 1H), 6.37 (d, $J$ = 2.5 Hz, 1H), 6.26 (d, $J$ = 2.4 Hz, 1H), 3.11 - 3.03 (m, 2H), 2.08 (s, 3H), 1.67 - 1.53 (m, 2H), 1.52 - 1.40 (m, 2H), 1.39 - 1.24 (m, 4H), 0.92 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 159.7, 156.7, 155.1, 152.8, 114.5, 101.7, 99.5, 94.4, 30.98, 30.95, 29.2, 28.6, 22.1, 13.9, 12.0 ppm. HRMS (+): m/z = 277.1434 $[M+H]^+$, calc.: 277.1434.

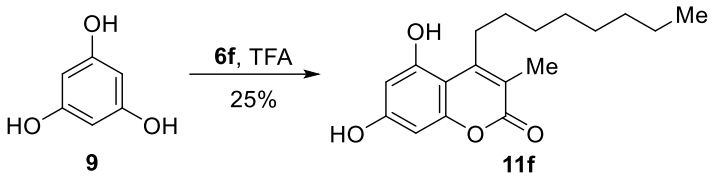
3.2.29 4-heptyl-5,7-dihydroxy-3-methylcoumarin (**11e**)




**Scheme 27.** Synthesis of coumarin **11e**.

**11e** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 4:3, $R_f$ = 0.5) afforded a yellow solid (67.0 mg, 231 µmol, 32%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 10.42 (s, 1H), 10.11 (s, 1H), 6.26 (d, $J$ = 2.5 Hz, 1H), 6.14 (d, $J$ = 2.4 Hz, 1H), 3.02 - 2.91 (m, 2H), 2.00 (s, 3H), 1.57 - 1.44 (m, 2H), 1.44 - 1.17 (m, 8H), 0.91 - 0.82 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 159.7, 156.7, 155.1, 152.8, 114.5, 101.7, 99.5, 94.4, 31.3, 31.0, 29.5, 28.6, 28.5, 22.1, 14.0, 12.0 ppm. HRMS (+): m/z = 291.1591 $[M+H]^+$, calc.: 291.1591.

3.2.30 5,7-dihydroxy-3-methyl-4-octylcoumarin (**11f**)




**Scheme 28.** Synthesis of coumarin **11f**.

**11f** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 4/3, $R_f$ = 0.6) afforded a yellow solid (47.0 mg, 154 µmol, 25%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 10.43 (s, 1H), 10.11 (s, 1H), 6.26 (d, $J$ = 2.4 Hz, 1H), 6.14 (d, $J$ = 2.4 Hz, 1H), 3.01 - 2.92 (m, 2H), 2.00 (s, 3H), 1.56 - 1.43 (m, 2H), 1.43 - 1.34 (m, 2H), 1.34 - 1.16 (m, 8H), 0.90 - 0.81 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 159.7, 156.7, 155.1, 152.8, 114.5, 101.7, 99.5, 94.4, 31.3, 31.0, 29.6, 28.8, 28.71, 28.65, 22.1, 14.0, 12.0 ppm. HRMS (+): m/z = 305.1747 $[M+H]^+$, calc.: 305.1747.

3.2.31 5,7-dihydroxy-3-methyl-4-nonylcoumarin (**11g**)

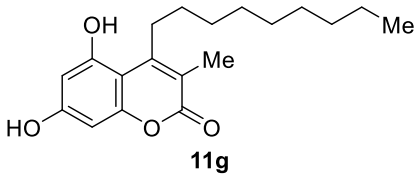
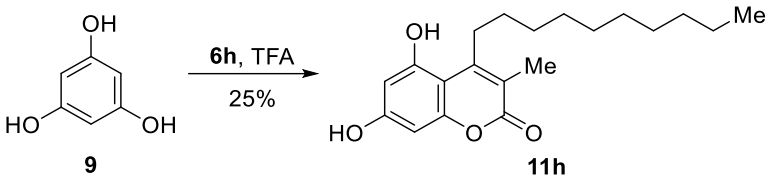



**Figure 3.** Structure of coumarin **11g**.

**11g** was synthesized as described in the literature.[1] $^1$H-NMR (400 MHz, $(CD_3)_2CO$) $\delta$ = 9.41 (s, 1H), 9.04 (s, 1H), 6.37 (d, $J$ = 2.4 Hz, 1H), 6.26 (d, $J$ = 2.4 Hz, 1H), 3.09 - 3.05 (m, 2H), 2.08 (s, 3H), 1.65 - 1.57 (m, 2H), 1.49 - 1.42 (m, 2H), 1.38 - 1.28 (m, 10H), 0.89 - 0.86 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.3, 160.5, 157.4, 156.6, 153.3, 116.6, 103.4, 100.5, 95.9, 32.6, 32.2, 30.9, 30.3, 30.2, 30.1, 29.9, 23.3, 14.4, 12.5 ppm. HRMS (+): m/z = 319.1902 $[M+H]^+$, calc.: 319.1909. The spectroscopic data were in agreement with those described in the literature.[1]

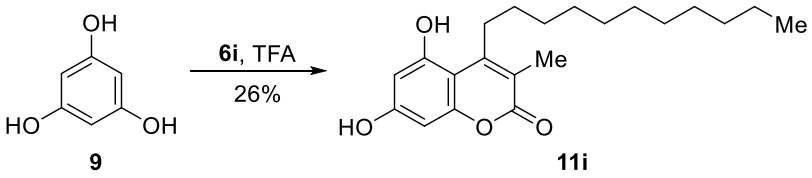
3.2.32 4-decyl-5,7-dihydroxy-3-methylcoumarin (**11h**)




**Scheme 29.** Synthesis of coumarin **11h**.

**11h** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 4/3, $R_f$ = 0.6) afforded a yellow solid (52.0 mg, 156 µmol, 25%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 10.42 (s, 1H), 10.11 (s, 1H), 6.26 (d, $J$ = 2.5 Hz, 1H), 6.14 (d, $J$ = 2.4 Hz, 1H), 3.02 - 2.91 (m, 2H), 2.00 (s, 3H), 1.56 - 1.43 (m, 2H), 1.43 - 1.34 (m, 2H), 1.34 - 1.14 (m, 12H), 0.90 - 0.80 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 159.7, 156.7, 155.1, 152.8, 114.5, 101.7, 99.5, 94.4, 31.3, 31.0, 29.5, 29.1, 29.0, 28.8, 28.7, 28.6, 22.1, 14.0, 12.0 ppm. HRMS (+): m/z = 333.2060 $[M+H]^+$, calc.: 333.2060.

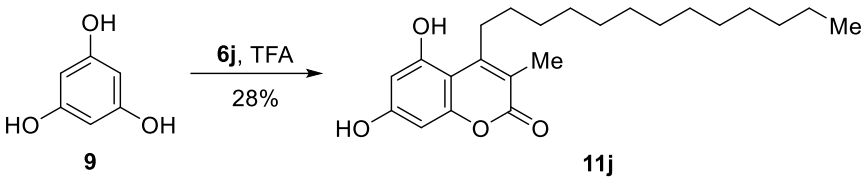
3.2.33 5,7-dihydroxy-3-methyl-4-undecylcoumarin (**11i**)




**Scheme 30.** Synthesis of coumarin **11i**.

**11i** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 4/3, $R_f$ = 0.6) afforded a yellow solid (50.0 mg, 144 µmol, 26%). $^1$H-NMR (500 MHz, $(CD_3)_2CO$) $\delta$ = 9.42 (s, 1H), 9.05 (s, 1H), 6.37 (d, $J$ = 2.2 Hz, 1H), 6.26 (d, $J$ = 2.4 Hz, 1H), 3.10 - 3.04 (m, 2H), 2.08 (s, 3H), 1.65 - 1.56 (m, 2H), 1.50 - 1.42 (m, 2H), 1.40 - 1.21 (m, 14H), 0.91 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 159.7, 156.8, 155.1, 152.8, 114.4, 101.7, 99.5, 94.3, 31.3, 31.0, 29.5, 29.1 (2C), 29.0, 28.8, 28.7, 28.6, 22.1, 13.9, 12.0 ppm. HRMS (+): m/z = 347.2217 $[M+H]^+$, calc.: 347.2217.

3.2.34 5,7-dihydroxy-3-methyl-4-tridecylcoumarin (**11j**)

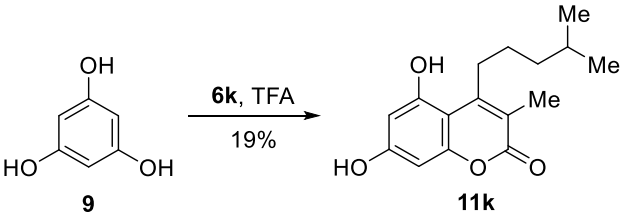



**Scheme 31.** Synthesis of coumarin **11j**.

**11j** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 4/3, $R_f$ = 0.6) afforded a white solid (40.0 mg, 107 µmol, 28%). $^1$H-NMR (500 MHz, $(CD_3)_2CO$) $\delta$ = 9.42 (s, 1H), 9.06 (s, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 3.11 - 3.04 (m, 2H), 2.08 (s, 3H), 1.65 - 1.56 (m, 2H), 1.50 - 1.42 (m, 2H), 1.40 - 1.23 (m, 18H), 0.91 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.3, 159.7, 156.7, 155.1, 152.8, 114.5, 101.7, 99.5, 94.4, 31.3, 31.0, 29.5, 29.04*, 29.01*, 28.8, 28.7, 28.6, 22.1, 13.9, 12.0 ppm. HRMS (+): m/z = 375.2529 $[M+H]^+$, calc.: 375.2530.

* Total of 5 signals not fully resolved due to signal overlap.

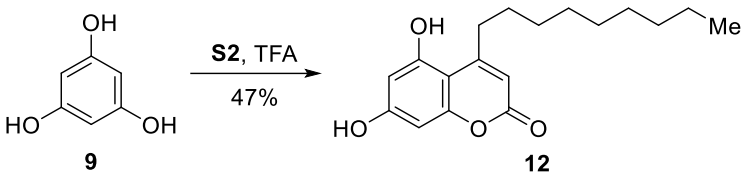
3.2.35 5,7-dihydroxy-3-methyl-4-(4-methylpentyl)coumarin (**11k**)




**Scheme 32.** Synthesis of coumarin **11k**.

**11k** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 4/3, $R_f$ = 0.2) afforded a yellow solid (50.0 mg, 181 µmol, 19%). $^1$H-NMR (500 MHz, $(CD_3)_2CO$) $\delta$ = 9.50 (s, 1H), 9.13 (s, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 3.08 - 3.02 (m, 2H), 2.08 (s, 3H), 1.65 - 1.55 (m, 3H), 1.38 - 1.31 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H) ppm. $^{13}$C-NMR (126 MHz, $(CD_3)_2CO$) $\delta$ = 162.2, 160.4, 157.3, 156.6, 153.2, 116.6, 103.3, 100.4, 95.9, 40.2, 32.4, 28.5, 27.7, 23.0 (2C), 12.5 ppm. HRMS (+): m/z = 299.1252 $[M+Na]^+$, calc.: 299.1254.

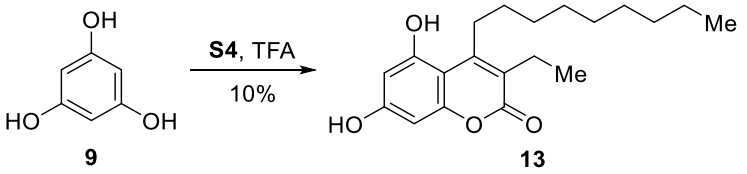
3.2.36 5,7-dihydroxy-4-nonylcoumarin (**12**)




**Scheme 33.** Synthesis of coumarin **12**.

**12** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ = 0.4) afforded a yellow solid (176 mg, 578 µmol, 47%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 10.58 (s, 1H), 10.29 (s, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 5.82 (s, 1H), 2.89 - 2.81 (m, 2H), 1.61 - 1.47 (m, 2H), 1.40 - 1.16 (m, 14H), 0.89 - 0.80 (m, 3H) ppm. $^{13}$C-NMR (151 MHz, $(CD_3)_2CO$) $\delta$ = 161.7, 161.1, 159.5, 158.4, 158.0, 110.0, 103.0, 100.2, 96.3, 36.7, 32.6, 30.8, 30.4, 30.3, 30.2, 30.0, 23.3, 14.4 ppm. HRMS (+): m/z = 327.1568 $[M+Na]^+$, calc.: 327.1567.

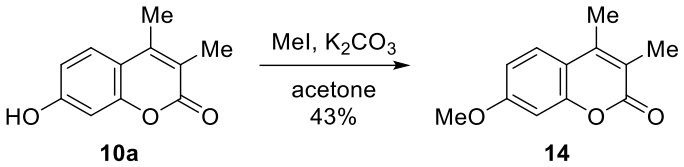
3.2.37 3-ethyl-5,7-dihydroxy-4-nonylcoumarin (**13**)




**Scheme 34.** Synthesis of coumarin **13**.

**13** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ =0.3) afforded a yellow solid (19.0 mg, 57.2 µmol, 10%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 9.44 (s, 1H), 9.06 (s, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 3.10 - 2.98 (m, 2H), 2.57 (q, *J* = 7.4 Hz, 2H), 1.70 - 1.54 (m, 2H), 1.54 - 1.19 (m, 15H), 1.10 (t, *J* = 7.4 Hz, 3H), 0.92 - 0.81 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 161.8, 160.5, 157.5, 156.8, 152.8, 122.7, 103.4, 100.5, 96.0, 32.6, 31.7, 31.1, 31.0, 30.3, 30.2, 30.1, 23.3, 20.7, 14.4, 14.1 ppm. HRMS (+): m/z = 355.1881 $[M+Na]^+$, calc.: 355.1880.

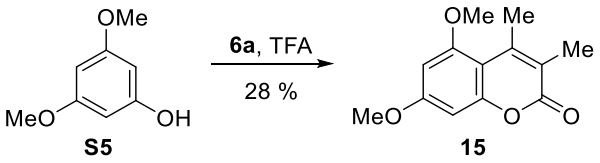
3.2.38 7-methoxy-3,4-dimethylcoumarin (**14**)




**Scheme 35.** Synthesis of coumarin **14**.

**10a** (0.12 g, 0.63 mmol, 1.0 eq.) was dissolved in acetone (6.6 mL) and methyl iodide (0.7 mL) as well as $K_2CO_3$ (0.25 g, 1.81 mmol, 3.0 eq.) were added to the solution. The mixture was heated under reflux for 5 h, filtrated and acetone removed under vacuum. Purification by MPLC (A = $H_2O$ + 0.05% TFA, B = ACN + 0.05% TFA, 0 - 3 min 100% A, 3 - 8 min 95% B, 8 - 9 min 95% B; column: Reveleris® C18, 12 g; flow rate: 30 mL/min) afforded a light yellow solid (0.06 g, 0.27 mmol, 43%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 7.64 (d, $J$ = 8.9 Hz, 1H), 6.89 (dd, $J$ = 8.9 Hz, 2.6 Hz, 1H), 6.81 (d, $J$ = 2.6 Hz, 1H), 3.89 (s, 3H), 2.38 (q, $J$ = 0.9 Hz, 3H), 2.11 (q, $J$ = 0.9 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 162.7, 162.1, 154.6, 147.0, 126.6, 119.5, 114.9, 112.6, 101.1, 56.2, 15.1, 13.2 ppm. HRMS (+): m/z = 205.0858 $[M+H]^+$, calc.: 205.0865. The spectroscopic data were in agreement with those described in the literature.[15]

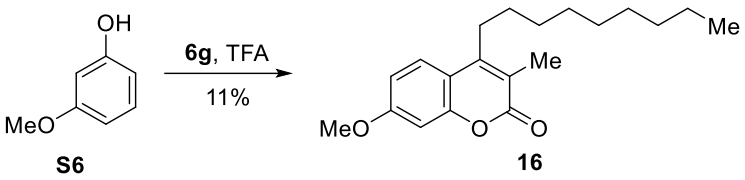
3.2.39 5,7-dimethoxy-3,4-dimethylcoumarin (**15**)




**Scheme 36.** Synthesis of coumarin **15**.

**15** was synthesized according to the general procedure 3.1.2 with the following adjustments. In the synthesis, 1.0 eq. of phenol were used. The reaction mixture was microwave-irradiated for 30 min at 100 °C. Purification by column chromatography (cyclohexane/acetone = 3/1, $R_f$ = 0.6) afforded a colorless solid (283 mg, 1.21 mmol, 28%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 6.53 (d, $J$ = 2.5 Hz, 1H), 6.47 (d, $J$ = 2.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.47 (q, $J$ = 0.8 Hz, 3H), 2.02 (q, $J$ = 0.8 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.5, 160.8, 158.42, 154.36, 147.9, 116.8, 104.4, 95.8, 93.2, 56.2, 55.7, 19.2, 12.7 ppm. HRMS (+): m/z = 235.0966 $[M+H]^+$, calc.: 235.0965. The spectroscopic data were in agreement with those described in the literature.[16]

3.2.40 7-methoxy-3-methyl-4-nonylcoumarin (**16**)




**Scheme 37.** Synthesis of coumarin **16**.

**16** was synthesized according to the general procedure 3.1.2. Purification by column chromatography (cyclohexane/acetone = 5/1, $R_f$ = 0.4) afforded a yellow solid (33.0 mg, 104 µmol, 11%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) δ = 7.67 (d, *J* = 8.9 Hz, 1H), 6.91 (dd, *J* = 8.9 Hz, 2.6 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 3.90 (s, 3H), 2.88 - 2.83 (m, 2H), 2.12 (s, 3H), 1.66 - 1.44 (m, 4H), 1.42 - 1.20 (m, 10H), 0.90 - 0.83 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) δ = 161.4, 161.3, 153.5, 150.7, 125.9, 117.5, 112.6, 112.1, 100.6, 55.8, 31.3, 29.1, 28.9, 28.8, 28.7, 28.3, 28.1, 22.1, 13.9, 12.6 ppm. HRMS (+): m/z = 339.1931 $[M+Na]^+$, calc.: 339.1931.

3.2.41 5,7-dimethoxy-3-methyl-4-nonylcoumarin (**17**)

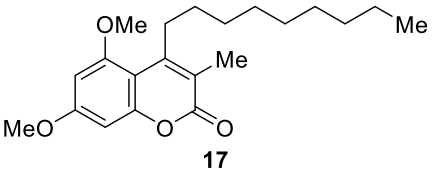
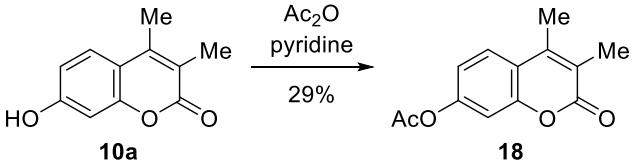



**Figure 4.** Structure of coumarin **17**.

**17** was synthesized as described in the literature.[1] $^1$H-NMR (300 MHz, $(CD_3)_2SO$) *δ* = 6.52 (d, *J* = 2.5 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.92 - 2.83 (m, 2H), 2.02 (s, 3H), 1.46 - 1.34 (m, 4H), 1.30 - 1.20 (m, 10H), 0.87 - 0.82 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) *δ* = 161.4, 160.9, 157.9, 154.8, 151.7, 116.5, 103.6, 95.8, 93.5, 56.2, 55.7, 31.4, 31.3, 29.5, 28.9, 28.8, 28.7, 28.4, 22.1, 13.9, 12.1 ppm. HRMS (+): m/z = 347.2218 $[M+H]^+$, calc.: 347.2217. The spectroscopic data were in agreement with those described in the literature.[1]

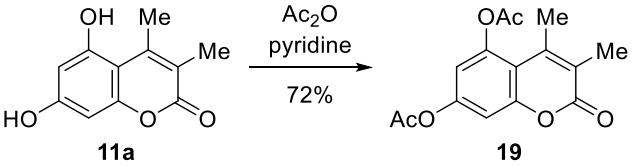
3.2.42 7-*O*-acyl-3,4-dimethylcoumarin (**18**)




**Scheme 38.** Synthesis of coumarin **18**.

**18** was synthesized according to the general procedure 3.1.3 with 16.7 mL pyridine/mmol coumarin and 9.8 mL $Ac_2O$/mmol coumarin. Purification by MPLC (A = $H_2O$ + 0.05% TFA, B = ACN + 0.05% TFA, 0 - 10 min 95 - 0% B, 10 - 11 min 100% A; column: Reveleris® C18, 4 g; flow rate: 18 mL/min) afforded a colourless solid (0.02 mg, 0.08 mmol, 29%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 7.79 (d, $J$ = 9.3 Hz, 1H), 7.14 - 7.10 (m, 2H), 2.45 (q, $J$ = 0.9 Hz, 3H), 2.30 (s, 3H), 2.16 (q, $J$ = 0.9 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 169.2, 161.5, 153.4, 153.2, 146.7, 126.5, 122.2, 118.9, 113.3, 110.6, 20.9, 15.3, 13.5 ppm. HRMS (+): m/z = 233.0808 $[M+H]^+$, calc.: 233.0814. The spectroscopic data were in agreement with those described in the literature.[16]

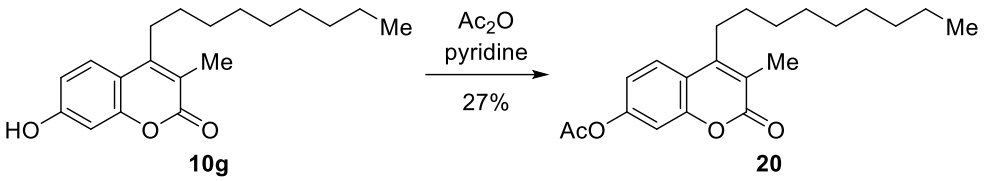
3.2.43 5,7-*O*-diacyl-3,4-dimethylcoumarin (**19**)




**Scheme 39.** Synthesis of coumarin **19**.

**19** was synthesized according to the general procedure 3.1.3 with 21.2 mL pyridine/mmol coumarin and 21.2 mL $Ac_2O$/mmol coumarin. Purification by semi-preparative HPLC (A = $H_2O$ + 0.05% TFA, B = ACN + 0.05% TFA, 0 - 2 min 95% A, 2 - 25 min 95% B, 25 - 27 min 95% B, 27 - 27.1 min 95% A, 27.1 - 35 min 95% A; flow rate: 5 mL/min) afforded a light yellow solid (0.05 g, 0.18 mmol, 72%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 7.06 (d, $J$ = 2.4 Hz, 1H), 6.92 (d, $J$ = 2.4 Hz, 1H), 2.50 (q, $J$ = 0.9 Hz, 3H), 2.39 (s, 3H), 2.30 (s, 3H), 2.15 (q, $J$ = 0.9 Hz, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 169.6, 169.0, 160.8, 154.2, 152.3, 148.9, 145.3, 123.6, 114.9, 113.1, 108.8, 21.3, 21.0, 18.4, 13.4 ppm. HRMS (+): m/z = 291.0863 $[M+H]^+$, calc.: 291.0869.

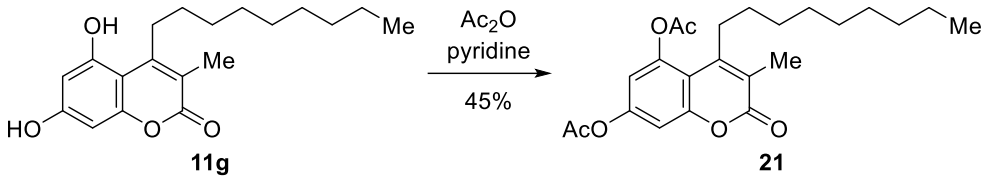
3.2.44 7-*O*-acyl-3-methyl-4-nonylcoumarin (**20**)




**Scheme 40.** Synthesis of coumarin **20**.

**20** was synthesized according to the general procedure 3.1.3 with 18.8 mL pyridine/mmol coumarin and 18.8 mL $Ac_2O$/mmol coumarin. Purification by semi-preparative HPLC (A = $H_2O$ + 0.05% TFA, B = ACN + 0.05% TFA, 0 - 2 min 95% A, 2 - 25 min 95% B, 25 - 27 min 95% B, 27 - 27.1 min 95% A, 27.1 - 35 min 95% A; flow rate: 5 mL/min) afforded a colourless solid (6.00 mg, 17.4 µmol, 27%). $^1$H-NMR (400 MHz, $(CD_3)_2SO$) $\delta$ = 7.82 (d, $J$ = 8.8 Hz, 1H), 7.23 (d, $J$ = 2.3 Hz, 1H), 7.15 (dd, $J$ = 8.8 Hz, 2.3 Hz, 1H), 2.84 - 2.80 (m, 2H), 2.30 (s, 3H), 2.10 (s, 3H), 1.54 - 1.39 (m, 4H), 1.33 - 1.22 (m, 10H), 0.86 - 0.83 (m, 3H) ppm. $^{13}$C-NMR (400 MHz, $(CD_3)_2SO$) $\delta$ = 168.9, 152.3, 151.8, 150.0, 129.6, 125.9, 120.5, 118.4, 117.0, 110.0, 31.3, 29.1, 28.9, 28.8, 28.6, 28.2, 28.1, 22.1, 20.9, 13.9, 12.8 ppm. HRMS (+): m/z = 345.2060 $[M+H]^+$, calc.: 345.2066.

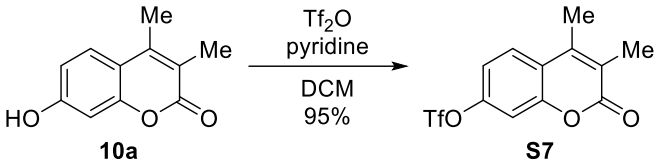
3.2.45 5,7-*O*-diacyl-3-methyl-4-nonylcoumarin (**21**)




**Scheme 41.** Synthesis of coumarin **21**.

**21** was synthesized according to the general procedure 3.1.3 with 32.8 mL pyridine/mmol coumarin and 32.8 mL $Ac_2O$/mmol coumarin. Purification by MPLC (A = $H_2O$ + 0.05% TFA, B = ACN + 0.05% TFA, 0 - 1 min 95% B, 1 - 6 min 80% B, 6 - 8.9 50% B; column: Reveleris® C18, 4 g; flow rate: 18 mL/min) afforded a colourless solid (23.2 mg, 57.6 µmol, 45%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 7.07 (d, $J$ = 2.5 Hz, 1H), 6.94 (d, $J$ = 2.5 Hz, 1H), 2.96 - 2.91 (m, 2H), 2.42 (s, 3H), 2.30 (s, 3H), 2.18 (s, 3H), 1.63 - 1.47 (m, 4H), 1.41 - 1.29 (m, 10H), 0.90 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (100 MHz, $(CD_3)_2SO$) $\delta$ = 169.2, 168.8, 160.3, 153.3, 151.0, 148.7, 147.3, 122.5, 114.9, 110.9, 108.5, 31.4, 30.9, 29.5, 29.1, 29.0, 28.8, 28.6, 22.2, 21.3, 21.0, 14.1, 13.0 ppm. HRMS (+): m/z = 403.2114 $[M+H]^+$, calc.: 403.2115.

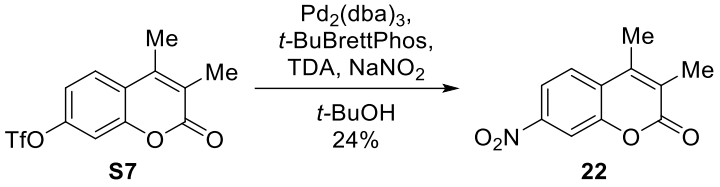
3.2.46 3,4-dimethyl-7-trifluoromethanesulfonylcoumarin (**S7**)




**Scheme 42.** Synthesis of compound **S7**.

**S7** was synthesized according to the general procedure 3.1.4 in DCM (2.5 mL/mmol) with $Tf_2O$ in DCM (0.23 mL/mmol). Purification by column chromatography (pentane/EtOAc = 3/1, $R_f$ = 0.7) afforded a slightly yellow solid (644 mg, 2.00 mmol, 95%). $^1$H-NMR (400 MHz, $(CD_3)_2SO$) $\delta$ = 7.94 (d, $J$ = 9.0 Hz, 1H), 7.66 (d, $J$ = 2.5 Hz, 1H), 7.46 (dd, $J$ = 9.0 Hz, 2.6 Hz, 1H), 2.39 (d, $J$ = 0.9 Hz, 3H), 2.11 (d, $J$ = 0.9 Hz, 3H) ppm. $^{13}$C-NMR (101 MHz, $(CD_3)_2SO$) $\delta$ = 160.2, 151.8, 149.3, 145.5, 127.3, 122.5, 120.6, 118.2 (q, $CF_3$), 117.2, 109.9, 15.0, 13.2 ppm. HRMS (+): m/z = 323.0196 $[M+H]^+$, calc.: 323.0196.

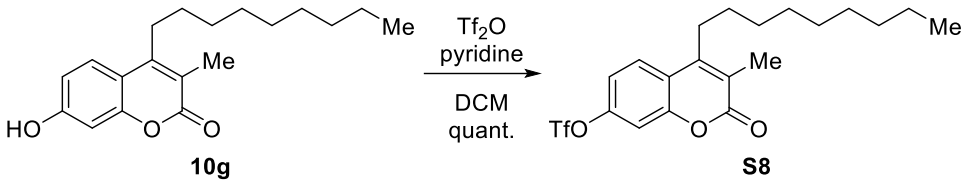
3.2.47 3,4-dimethyl-7-nitrocoumarin (**22**)




**Scheme 43.** Synthesis of coumarin **22**.

**22** was synthesized according to the general procedure 3.1.5. Purification by column chromatography (cyclohexane/EtOAc = 3/1, $R_f$ = 0.3) afforded a yellow solid (56.3 mg, 260 µmol, 24%). $^1$H-NMR (300 MHz, $(CD_3)_2CO$) $\delta$ = 8.16 (dd, $J$ = 8.8 Hz, 2.3 Hz, 1H), 8.10 (dd, $J$ = 2.3 Hz, 0.4 Hz, 1H), 8.06 (d, $J$ = 8.8 Hz, 1H), 2.54 (q, $J$ = 0.9 Hz, 3H), 2.23 (q, $J$ = 0.9 Hz, 3H) ppm. $^{13}$C-NMR (126 MHz, $(CD_3)_2CO$) $\delta$ = 160.9, 152.6, 149.1, 145.7, 127.2, 126.7, 126.5, 119.3, 112.4, 15.4, 13.9 ppm. HRMS (+): m/z = 220.0605 $[M+H]^+$, calc.: 220.0604.

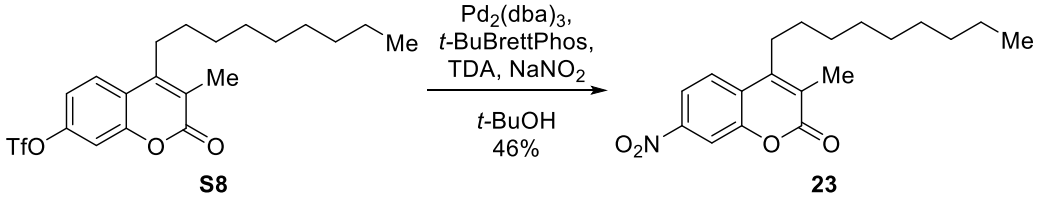
3.2.48 3-methyl-4-nonyl-7-trifluoromethanesulfonylcoumarin (**S8**)




**Scheme 44.** Synthesis of compound **S8**.

**S8** was synthesized according to the general procedure 3.1.4 in DCM (3.2 mL/mmol) with the following adjustments. In the synthesis, 1.3 eq. $Tf_2O$ in DCM (0.43 mL/mmol) were used. Purification by column chromatography (cyclohexane/EtOAc= 4/1, $R_f$ = 0.7) afforded a slightly yellow solid (135 mg, 310 µmol, quant.). $^1$H-NMR (500 MHz, $(CD_3)_2SO$) $\delta$ = 7.96 (d, $J$ = 9.0 Hz, 1H), 7.69 (d, $J$ = 2.6 Hz, 1H), 7.47 (dd, $J$ = 9.0 Hz, 2.6 Hz, 1H), 2.82 (t, $J$ = 7.2 Hz, 2H), 2.11 (s, 3H), 1.52 - 1.37 (m, 4H), 1.33 - 1.18 (m, 10H), 0.83 (t, $J$ = 6.8 Hz, 3H) ppm. $^{13}$C-NMR (101 MHz, $(CD_3)_2SO$) $\delta$ = 160.4, 152.2, 149.28, 149.26, 127.2, 122.4, 119.7, 118.2 (q, $CF_3$), 117.4, 110.2, 31.3, 29.1, 28.9, 28.8, 28.6, 28.1, 26.3, 22.0, 13.9, 13.0 ppm. HRMS (+): m/z = 435.1447 $[M+H]^+$, calc.: 435.1448.

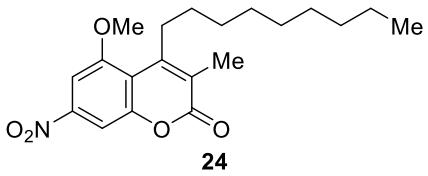
3.2.49 3-methyl-7-nitro-4-nonylcoumarin (**23**)




**Scheme 45.** Synthesis of coumarin **23**.

**23** was synthesized according to the general procedure 3.1.5. Purification by column chromatography (cyclohexane/EtOAc = 9/1, $R_f$ = 0.3) afforded a yellow solid (45.4 mg, 137 µmol, 46%). $^1$H-NMR (500 MHz, $(CD_3)_2SO$) $\delta$ = 8.19 (d, $J$ = 2.3 Hz, 1H), 8.14 (dd, $J$ = 8.9 Hz, 2.3 Hz, 1H), 8.05 (d, $J$ = 8.9 Hz, 1H), 2.87 (t, $J$ = 7.2 Hz, 2H), 2.16 (s, 3H), 1.53 - 1.39 (m, 4H), 1.33 - 1.20 (m, 10H), 0.85 (t, $J$ = 6.8 Hz, 3H) ppm. $^{13}$C-NMR (126 MHz, $(CD_3)_2SO$) $\delta$ = 160.3, 151.5, 148.9, 147.7, 126.5, 125.0, 124.6, 118.8, 111.9, 31.3, 29.1, 29.0, 28.9, 28.7, 28.2, 28.1, 22.1, 14.0, 13.4 ppm. HRMS (+): m/z = 332.1857 $[M+H]^+$, calc.: 332.1856.

3.2.50 5-methoxy-3-methyl-7-nitro-4-nonylcoumarin (**24**)

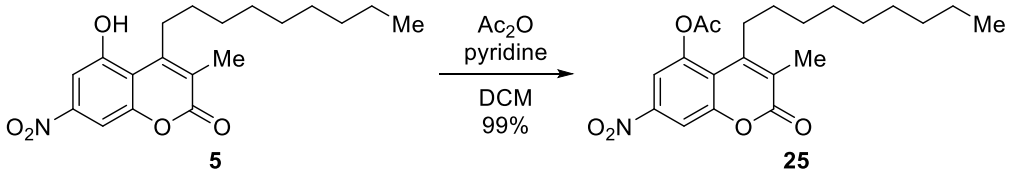



**24**

**Figure 5.** Structure of coumarin **24**.

**24** was synthesized as described in the literature.[1] $^{1}$H-NMR (500 MHz, $(CD_3)_2SO$) $\delta$ = 7.78 (d, $J$ = 2.3 Hz, 1H), 7.67 (d, $J$ = 2.3 Hz, 1H), 4.03 (s, 3H), 3.00 - 2.95 (m, 2H), 2.14 (s, 3H), 1.51 - 1.38 (m, 4H), 1.37 - 1.19 (m, 10H), 0.87 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (126 MHz, $(CD_3)_2SO$) $\delta$ = 159.9, 157.5, 152.9, 150.0, 147.7, 124.1, 114.8, 104.8, 101.8, 57.1, 31.5, 31.3, 29.5, 29.0, 29.8, 28.7, 28.3, 22.1, 14.0, 13.0 ppm. HRMS (+): m/z = 362.1963 $[M+H]^+$, calc.: 362.1962. The spectroscopic data were in agreement with those described in the literature.[1]

3.2.51 5-*O*-acyl-3-methyl-7-nitro-4-nonylcoumarin (**25**)

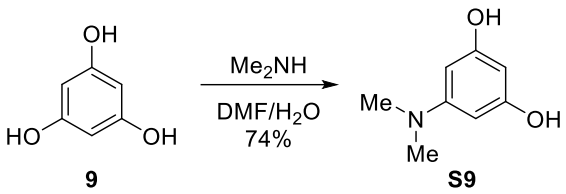



**5** **25**

**Scheme 46.** Synthesis of coumarin **25**.

**25** was synthesized according to the general procedure 3.1.3. Purification by column chromatography (cyclohexane/EtOAc = 6/1, $R_f$ = 0.4) afforded a yellow solid (22.3 mg, 57.2 µmol, 99%). $^{1}$H-NMR (500 MHz, $(CD_3)_2SO$) $\delta$ = 8.15 (d, $J$ = 2.5 Hz, 1H), 8.10 (d, $J$ = 2.5 Hz, 1H), 2.87 (t, $J$ = 6.9 Hz, 2H), 2.41 (s, 3H), 2.17 (s, 3H), 1.50 - 1.37 (m, 4H), 1.35 - 1.18 (m, 10H), 0.85 (t, $J$ = 6.9 Hz, 3H) ppm. $^{13}$C-NMR (126 MHz, $(CD_3)_2SO$) $\delta$ = 169.0, 159.5, 152.6, 147.4, 147.2, 146.6, 126.7, 118.3, 115.2, 109.6, 31.3, 30.7, 29.4, 29.0, 28.9, 28.7, 28.4, 22.1, 21.4, 14.0, 13.3 ppm. HRMS (+): m/z = 390.1912 $[M+H]^+$, calc.: 390.1911.

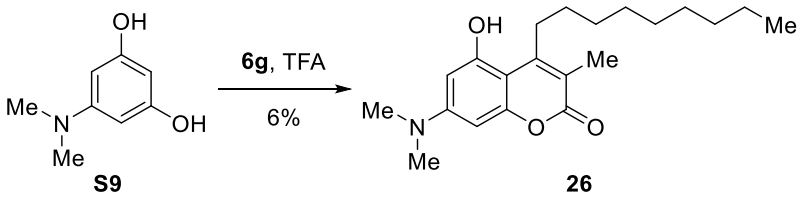
3.2.52 5-(dimethylamino)benzene-1,3-diol (**S9**)




**Scheme 47.** Synthesis of compound **S9**.

**9** (0.82 g, 6.53 mmol, 1.0 eq.) was dissolved in DMF (11.6 mL) and $H_2O$ (7.40 mL) and dimethylamine (0.96 mL, 40 wt. % in $H_2O$, 8.49 mmol, 1.3 eq.) was added. The solution was stirred under argon atmosphere at rt for 5 d. The reaction mixture was diluted with 150 mL EtOAc and 150 mL brine. The aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine (6x), dried over $MgSO_4$ and concentrated under reduced pressure. A pink solid was obtained (0.74 g, 4.84 mmol, 74%) and directly used in the next reaction step. $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 8.82 (s, 2H), 5.59 (s, 3H), 2.77 (s, 6H) ppm. $^{13}$C-NMR (101 MHz, $(CD_3)_2CO$) $\delta$ = 159.8 (2C), 153.8, 92.83, 92.80 (2C), 40.6 (2C) ppm. HRMS (+): m/z = 154.0864 $[M+H]^+$, calc.: 154.0863. The spectroscopic data were in agreement with those described in the literature.[17]

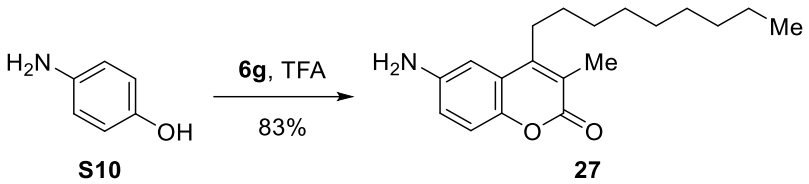
3.2.53 7-(dimethylamino)-5-hydroxy-3-methyl-4-nonylcoumarin (**26**)




**Scheme 48.** Synthesis of coumarin **26**.

**26** was synthesized according to the general procedure 3.1.2 with the following adjustments. The reaction mixture was microwave-irradiated for 160 min at 110 °C. Purification by column chromatography (cyclohexane/acetone = 2/1, $R_f$ = 0.4) afforded a yellow solid (4.00 mg, 11.6 µmol, 6%). $^1$H-NMR (500 MHz, $(CD_3)_2CO$) $\delta$ = 9.19 (s, 1H), 6.20 (d, $J$ = 2.6 Hz, 1H), 6.08 (d, $J$ = 2.6 Hz, 1H), 3.08 - 3.02 (m, 2H), 2.98 (s, 6H), 2.06 (s, 3H), 1.64 - 1.56 (m, 2H), 1.49 - 1.41 (m, 2H), 1.39 - 1.23 (m, 10H), 0.90 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (126 MHz, $CD_3OD$) $\delta$ = 165.5, 157.8, 157.0, 156.8, 153.5, 113.7, 101.2, 96.7, 92.0, 40.0 (2C), 33.1, 32.5, 31.3, 30.8, 30.52, 30.48, 30.3, 23.8, 14.5, 12.2 ppm. HRMS (+): m/z = 346.2376 $[M+H]^+$, calc.: 346.2377.

3.2.54 6-amino-3-methyl-4-nonylcoumarin (**27**)

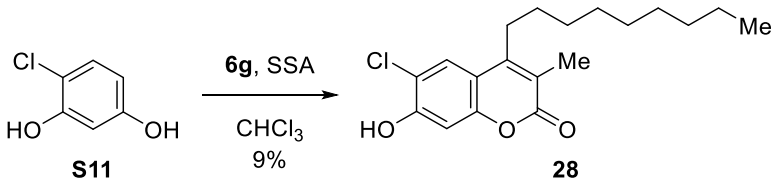



**S10** **27**

**Scheme 49.** Synthesis of coumarin **27**.

**27** was synthesized according to the general procedure 3.1.2 with the following adjustments. In the synthesis, 1.0 eq. of phenol were used. The reaction mixture was microwave-irradiated for 90 min at 110 °C. Purification by column chromatography (DCM/methanol = 20/1, $R_f$ = 0.8) afforded a light brown solid (0.47 g, 1.6 mmol, 83%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 7.65 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 2.6 Hz, 1H), 7.30 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 5.86 (br s, 2H), 2.85 - 2.79 (m, 2H), 2.15 (s, 3H), 1.67 - 1.57 (m, 2H), 1.35 - 1.23 (m, 12H), 0.86 - 0.81 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 154.8, 152.5, 132.6, 123.2, 122.6, 120.1, 112.9, 109.6, 105.7, 31.8, 31.2, 28.84, 28.79, 28.7, 28.6, 28.3, 22.1, 13.9, 10.6 ppm. HRMS (+): m/z = 302.2113 $[M+H]^+$, calc.: 302.2120.

3.2.55 6-chloro-7-hydroxy-3-methyl-4-nonylcoumarin (**28**)

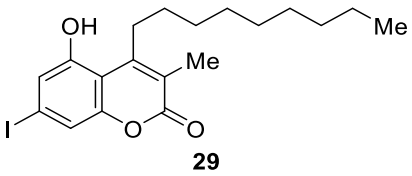



**S11** **28**

**Scheme 50.** Synthesis of coumarin **28**.

**S11** (0.29 g, 2.01 mmol, 1.0 eq.) and **6g** (0.52 g, 2.03 mmol, 1.0 eq.) were dissolved in chloroform (6.50 mL) and SSA (4.0 g, 19.3 mmol $H^+$, 9.6 eq.) was then added to the clear red solution. The reaction mixture was heated under reflux for 19 h. After completion, hot ethanol was added and SSA filtered off. The filtrate was concentrated under vacuum and purified by column chromatography (cyclohexane/EtOAc = 3/1, $R_f$ = 0.4) to give a light brown solid (62.0 mg, 1.85 mmol, 9%). $^1$H-NMR (400 MHz, $(CD_3)_2SO$) $\delta$ = 7.69 (s, 1H), 6.87 (s, 1H), 2.75 - 2.71 (m, 2H), 2.03 (s, 3H), 1.46 - 1.37 (m, 4H), 1.31 - 1.22 (m, 10H), 0.84 - 0.81 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 161.1, 155.1, 151.7, 150.1, 125.5, 117.9, 116.9, 112.4, 103.4, 31.3, 29.0, 28.9, 28.8, 28.7, 28.2, 27.9, 22.1, 13.9, 12.7 ppm. HRMS (+): m/z = 337.1564 $[M+H]^+$, calc.: 337.1571.

3.2.56 5-hydroxy-7-iodo-3-methyl-4-nonylcoumarin (**29**)

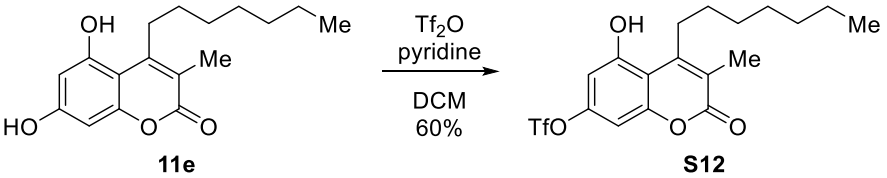



**29**

**Figure 6.** Structure of coumarin **29**.

**29** was synthesized as described in the literature.[1] $^1$H-NMR (400 MHz, $(CD_3)_2SO$) $\delta$ = 7.16 (d, *J* = 1.7 Hz, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 3.01 - 2.98 (m, 2H), 2.04 (s, 3H), 1.52 - 1.46 (m, 2H), 1.42 - 1.36 (m, 2H), 1.31 - 1.23 (m, 10H), 0.87 - 0.84 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$) $\delta$ = 161.0, 156.5, 155.1, 152.2, 121.4, 121.2, 118.1, 109.7, 95.0, 32.6, 32.2, 30.8, 30.3, 30.14, 30.05, 29.8, 23.3, 14.4, 12.9 ppm. HRMS (+): m/z = 429.0920 $[M+H]^+$, calc.: 429.0927. The spectroscopic data were in agreement with those described in the literature.[1]

3.2.57 4-heptyl-5-hydroxy-3-methyl-7-trifluoromethanesulfonylcoumarin (**S12**)

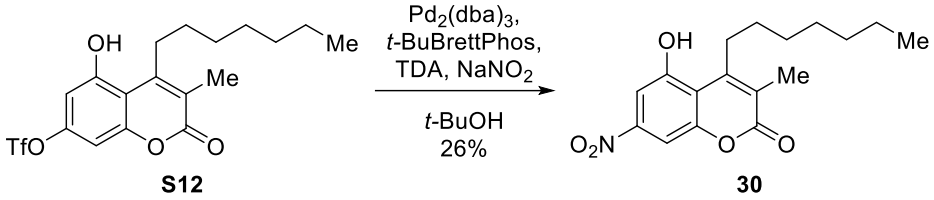



**11e** **S12**

**Scheme 51.** Synthesis of compound **S12**.

**S12** was synthesized according to the general procedure 3.1.4 in DCM (5.0 mL/mmol) with the following adjustments. $Tf_2O$ in DCM (0.35 mL/mmol) was added portion-wise using a syringe over 45 min at 0 °C. The reaction mixture was stirred at 0 °C for 90 min and worked up afterwards. Purification by column chromatography (cyclohexane/acetone = 5/1, $R_f$ = 0.3) afforded a slightly yellow solid (613 mg, 1.45 mmol, 60%). $^1$H-NMR (300 MHz, $(CD_3)_2SO$) $\delta$ = 11.50 (s, 1H), 7.04 (d, *J* = 2.6 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 3.06 - 2.96 (m, 2H), 2.08 (s, 3H), 1.57 - 1.45 (m, 2H), 1.45 - 1.35 (m, 2H), 1.35 - 1.19 (m, 6H), 0.90 - 0.82 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 160.2, 157.0, 154.0, 151.1, 149.0, 120.3, 118.2 (q, *C*$F_3$), 108.9, 104.1, 100.9, 31.3, 30.9, 29.4, 28.44, 28.39, 22.1, 13.9, 12.4 ppm. HRMS (+): m/z = 423.1079 $[M+H]^+$, calc.: 423.1084.

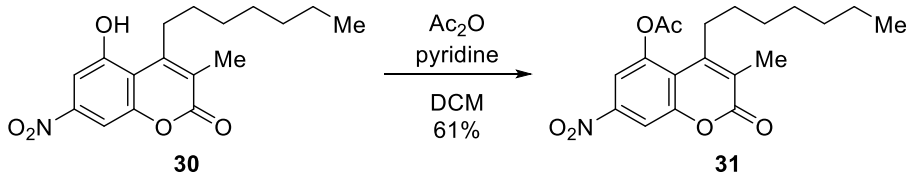
3.2.58 4-heptyl-5-hydroxy-3-methyl-7-nitrocoumarin (**30**)




**Scheme 52.** Structure of coumarin **30**.

**30** was synthesized according to the general procedure 3.1.5 with the following adjustments. In the synthesis, 2.5 mol% $Pd_2(dba)_3$ and 6.0 mol% *t*-BuBrettPhos were used. Purification by column chromatography (cyclohexane/acetone = 10/1, $R_f$ = 0.2) afforded a yellow solid (98.0 mg, 307 µmol, 26%). $^1$H-NMR (500 MHz, $CD_3OD$) $\delta$ = 7.49 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H) ,3.10 - 3.05 (m, 2H), 2.16 (s, 3H), 1.61 - 1.54 (m, 2H), 1.50 - 1.43 (m, 2H), 1.42 - 1.27 (m, 6H), 0.93 - 0.89 (m, 3H) ppm. $^{13}$C-NMR (151 MHz, $CD_3OD$) $\delta$ = 162.6, 157.9, 155.0, 153.1, 149.2, 124.2, 115.1, 106.5, 104.0, 33.0, 32.5, 31.1, 30.07, 30.05, 23.7, 14.4, 13.0 ppm. HRMS (+): m/z = 342.1312 $[M+Na]^+$, calc.: 342.1312.

3.2.59 5-*O*-acyl-4-heptyl-3-methyl-7-nitrocoumarin (**31**)

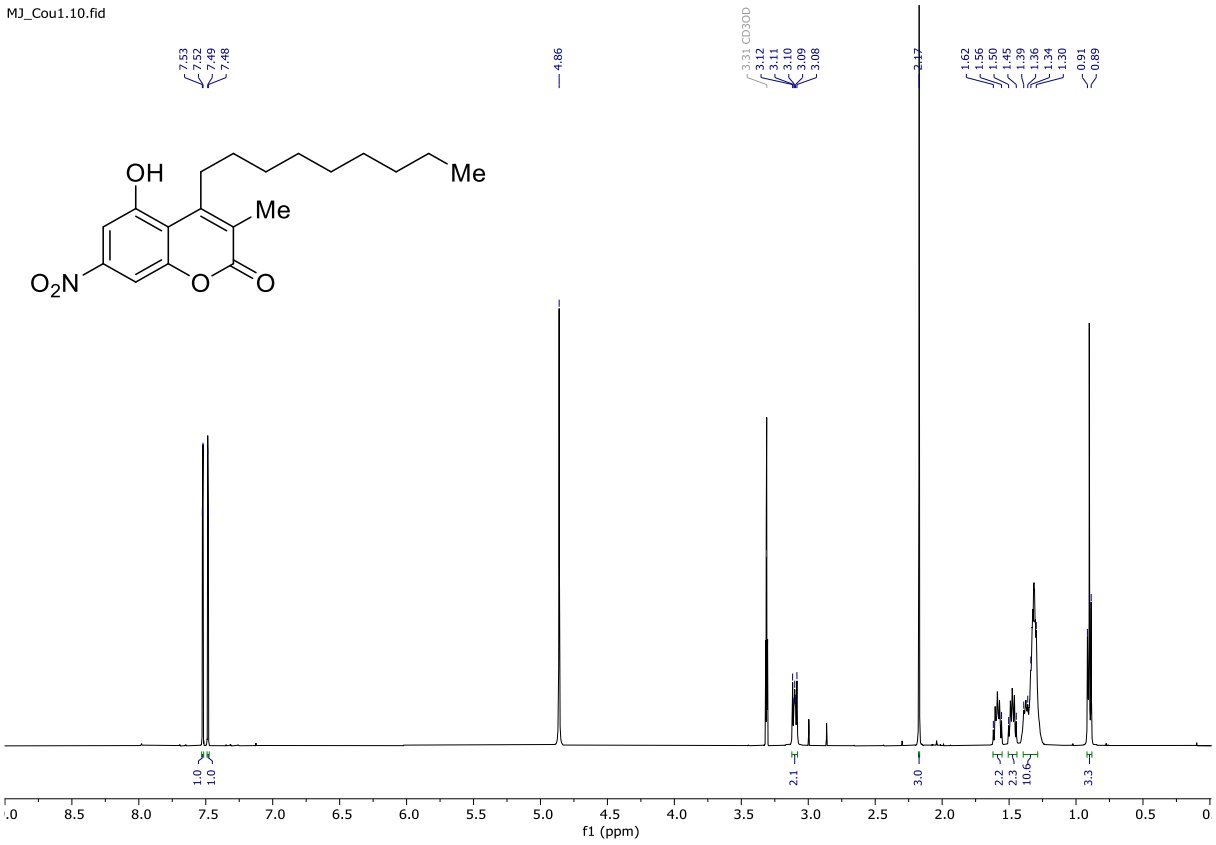


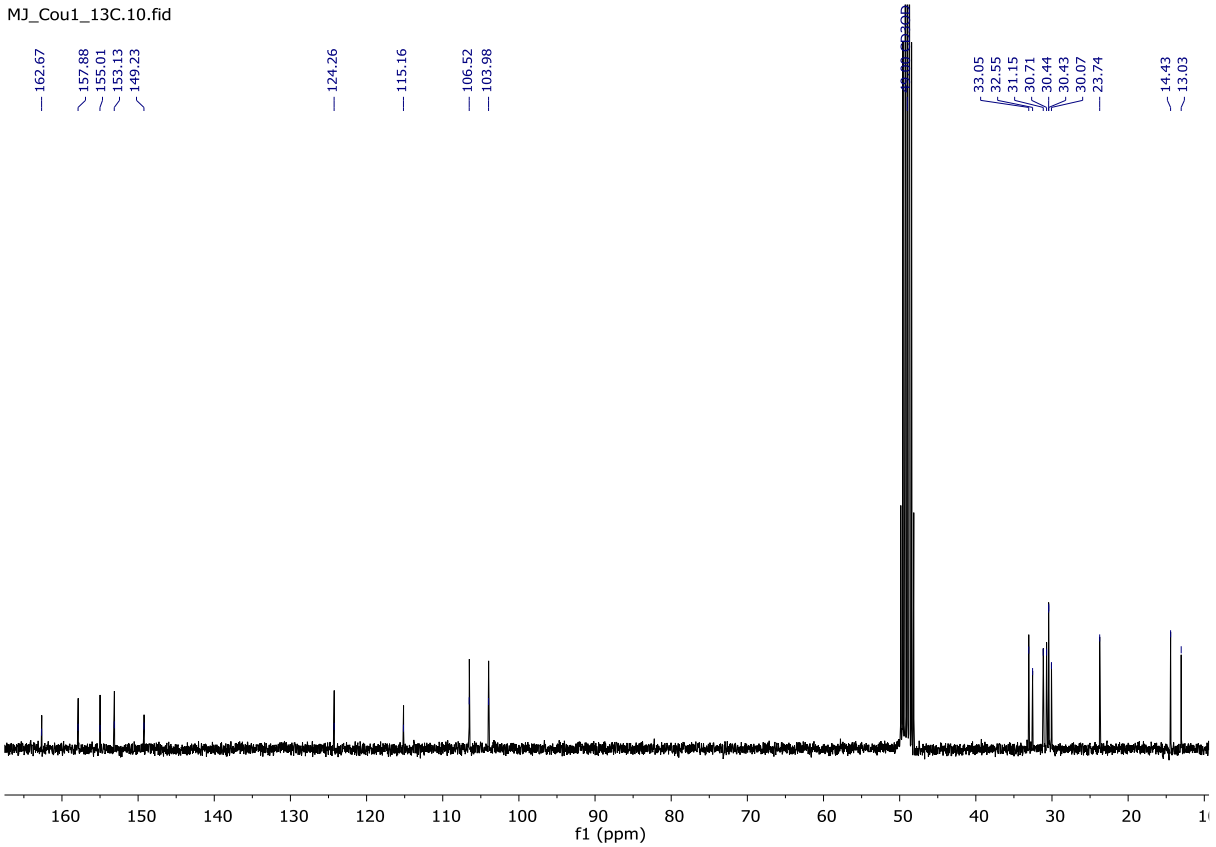

**Scheme 53.** Synthesis of coumarin **31**.

**31** was synthesized according to the general procedure 3.1.3. Purification by column chromatography (cyclohexane/EtOAc = 6/1, $R_f$ = 0.4) afforded a yellow solid (24.0 mg, 66.4 µmol, 61%). $^1$H-NMR (500 MHz, $(CD_3)_2CO$) $\delta$ = 8.01 (s, 2H), 3.03 - 2.98 (m, 2H), 2.49 (s, 3H), 2.25 (s, 3H), 1.64 - 1.56 (m, 2H), 1.56 - 1.49 (m, 2H), 1.43 - 1.26 (m, 6H), 0.91 - 0.85 (m, 3H) ppm. $^{13}$C-NMR (75 MHz, $(CD_3)_2SO$) $\delta$ = 169.0, 159.5, 152.6, 147.4, 147.2, 146.6, 126.6, 118.2, 115.2, 109.6, 31.2, 30.7, 29.4, 28.7, 28.4, 22.1, 21.3, 14.0, 13.3 ppm. HRMS (+): m/z = 362.1590 $[M+H]^+$, calc.: 362.1598.

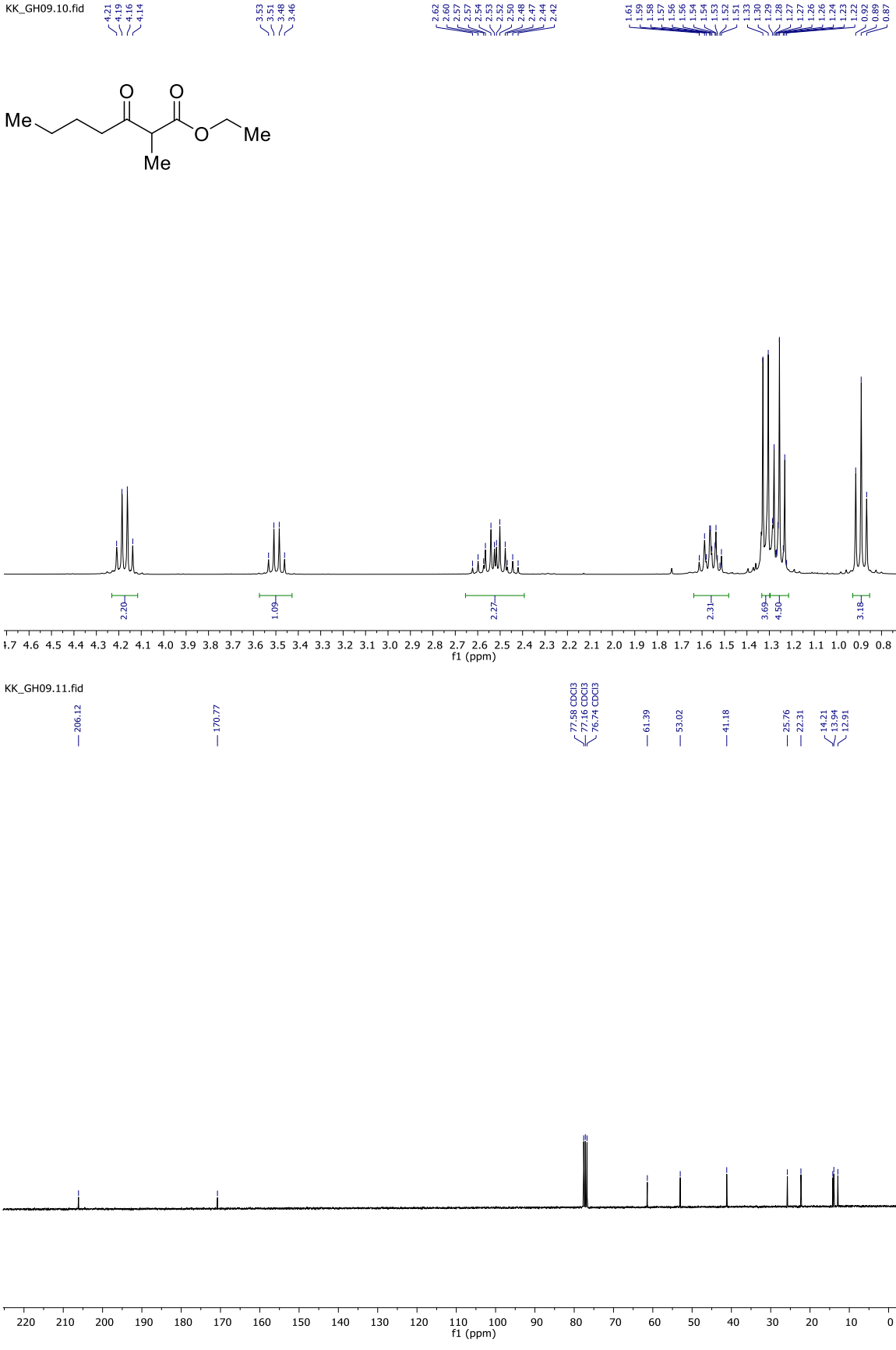
## 4. NMR-Spectra

### 4.1 Myxocoumarin B (**5**)

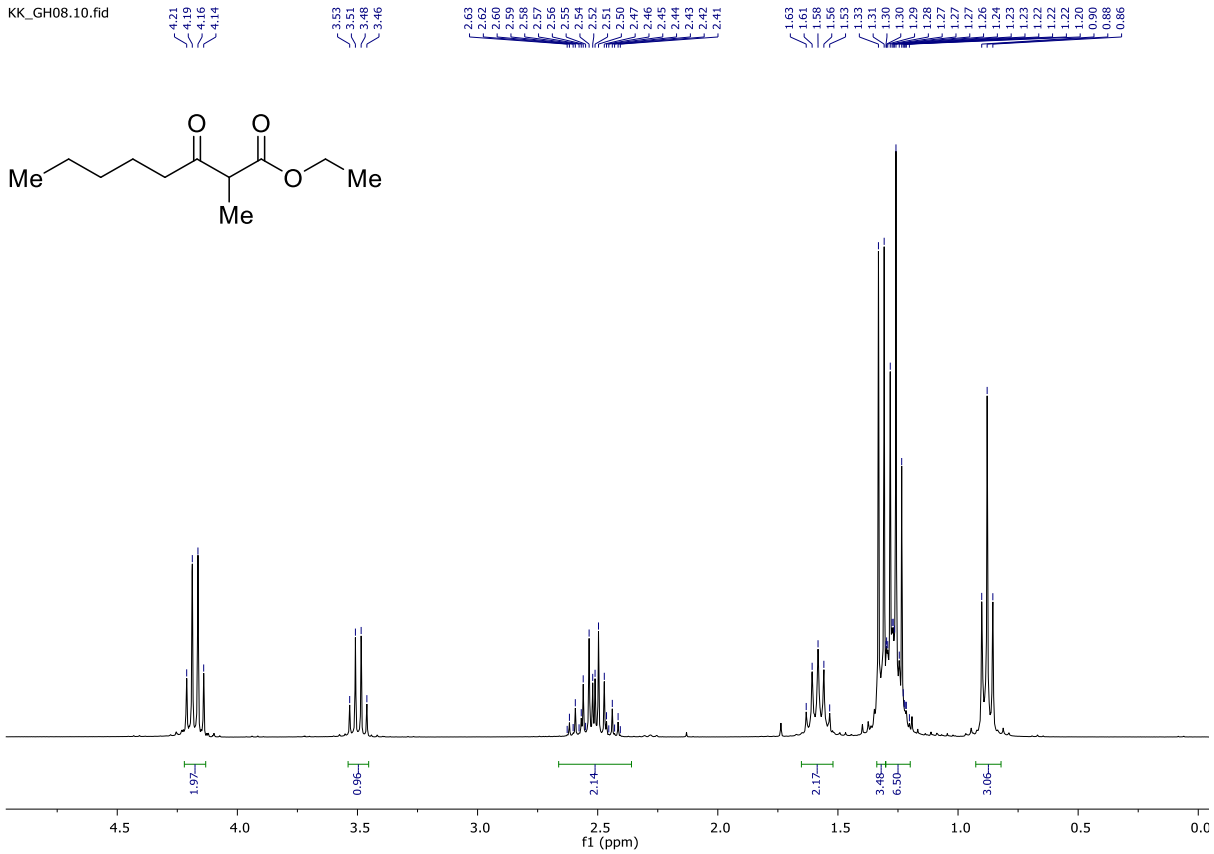


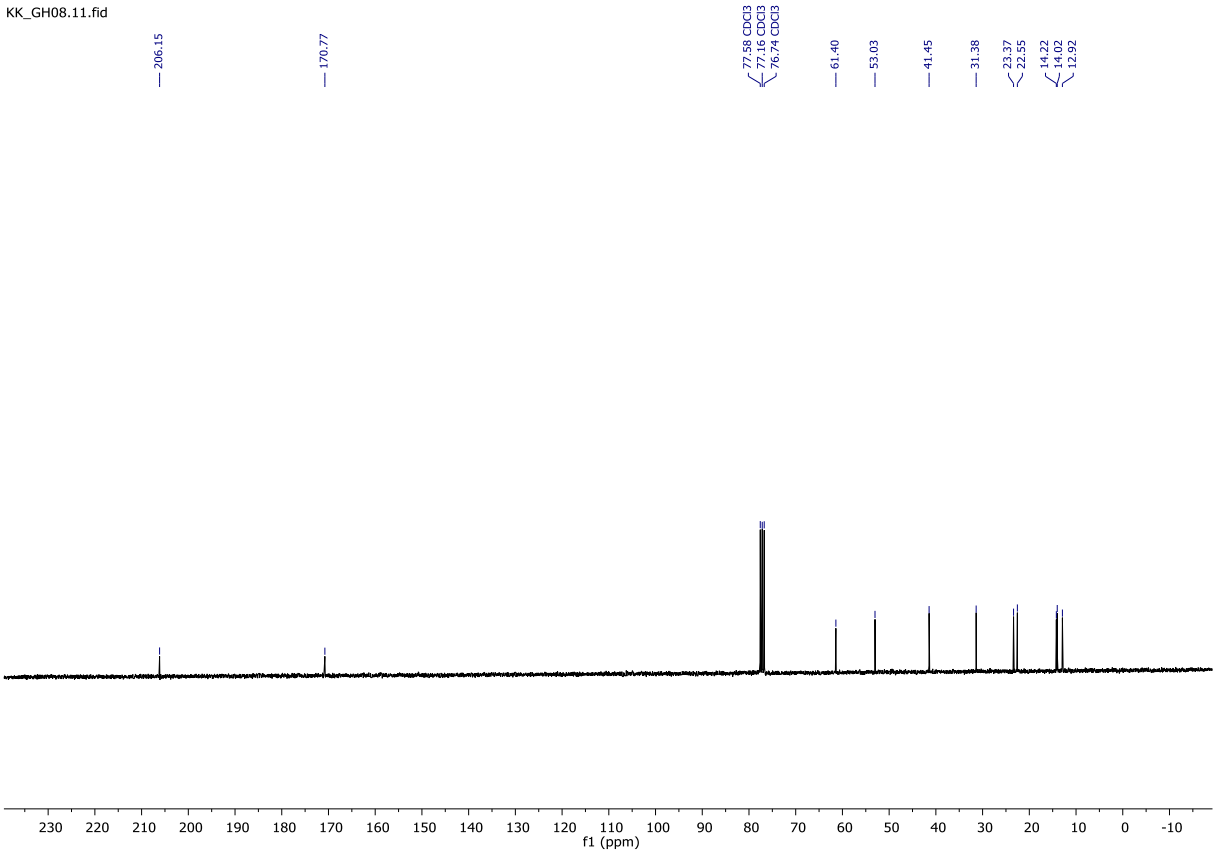



## 4.2 ethyl 2-methyl-3-oxoheptanoate (**6b**)

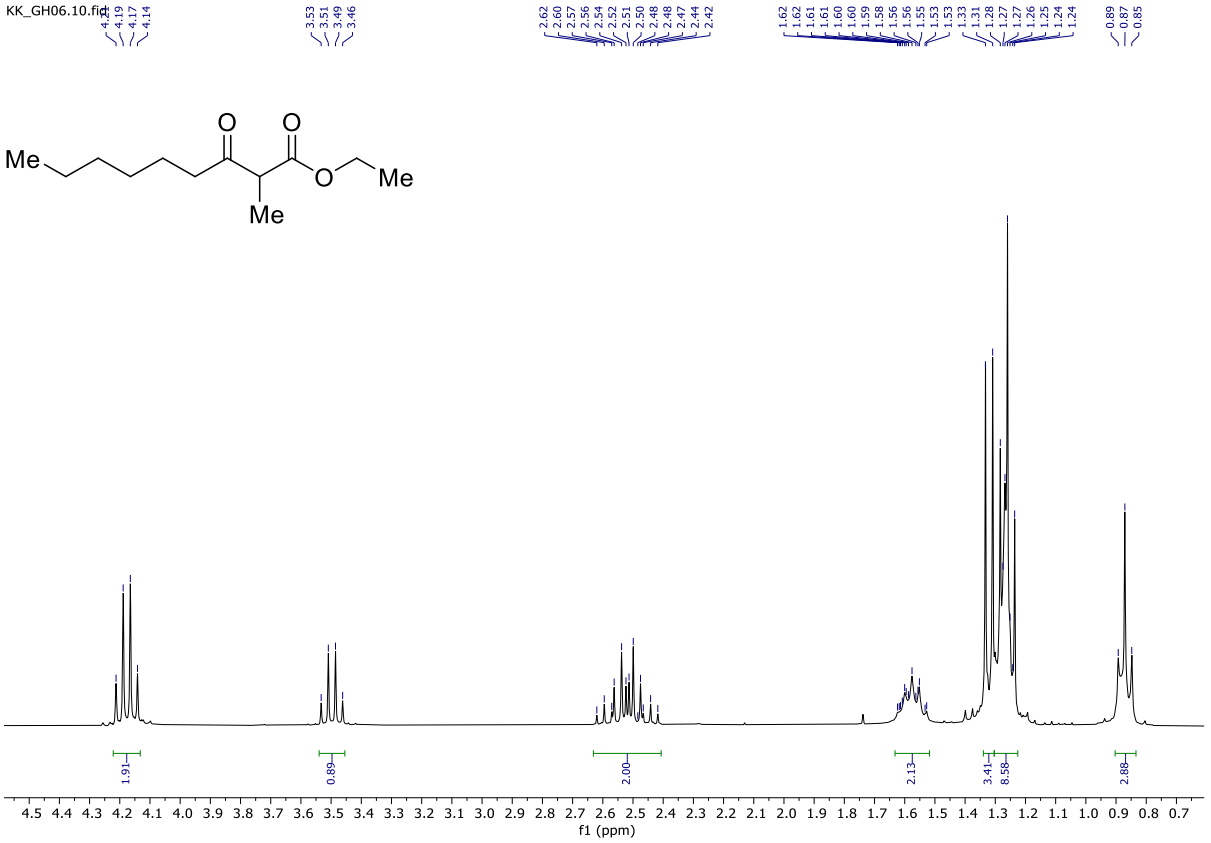


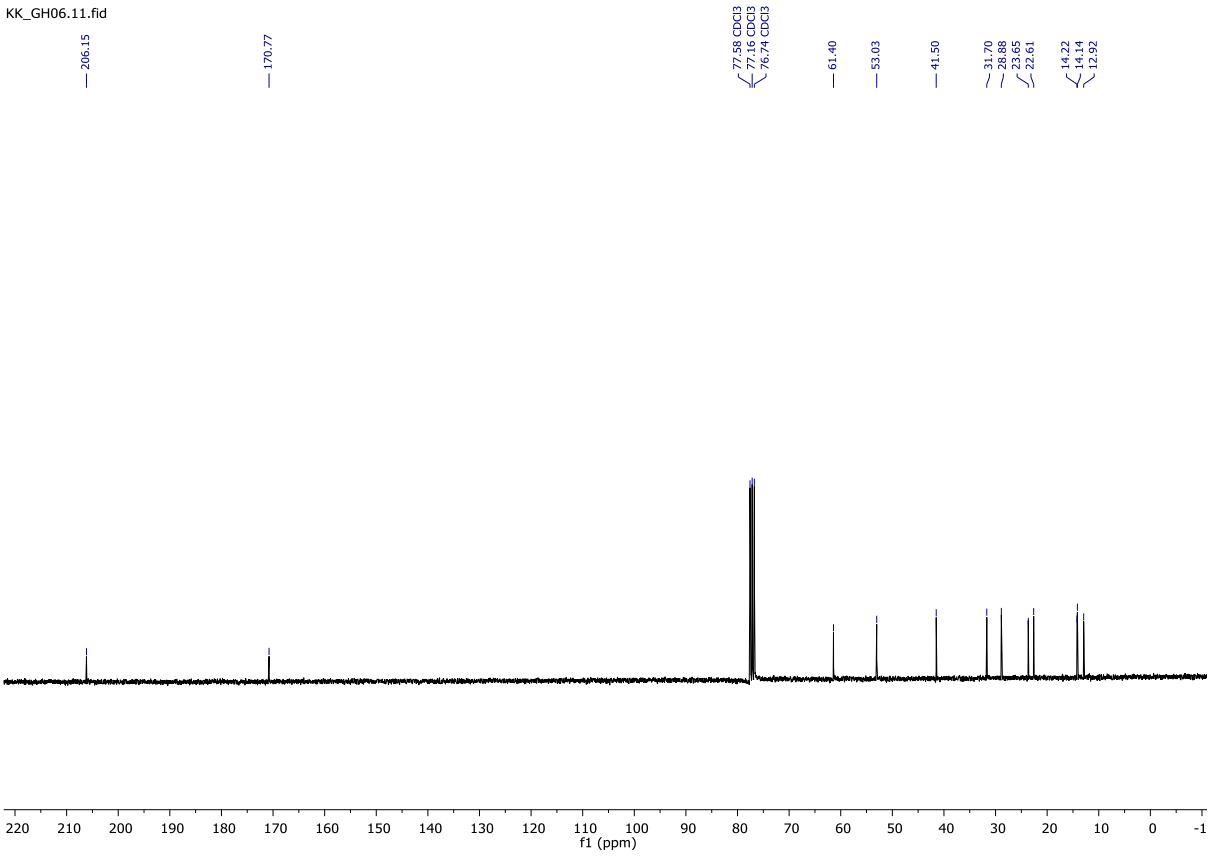
## 4.3 ethyl 2-methyl-3-oxooctanoate (**6c**)



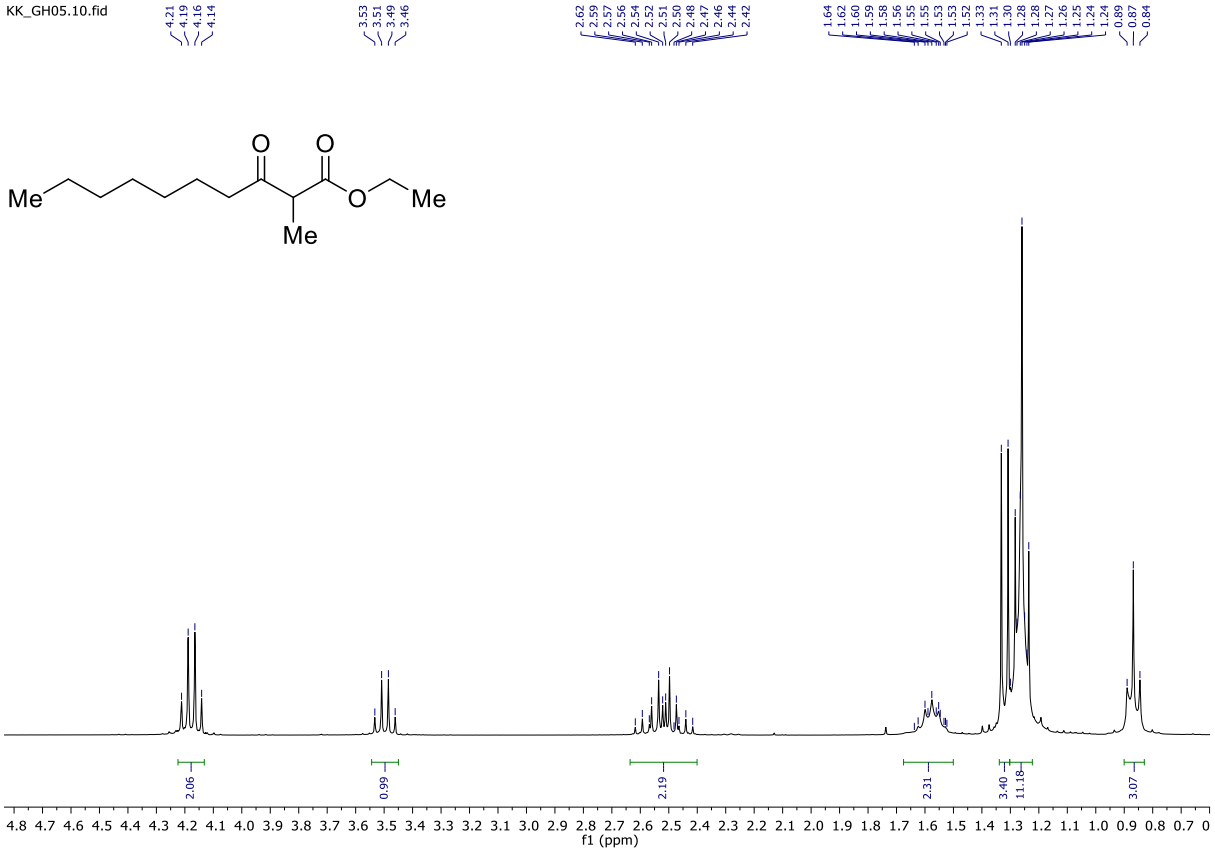



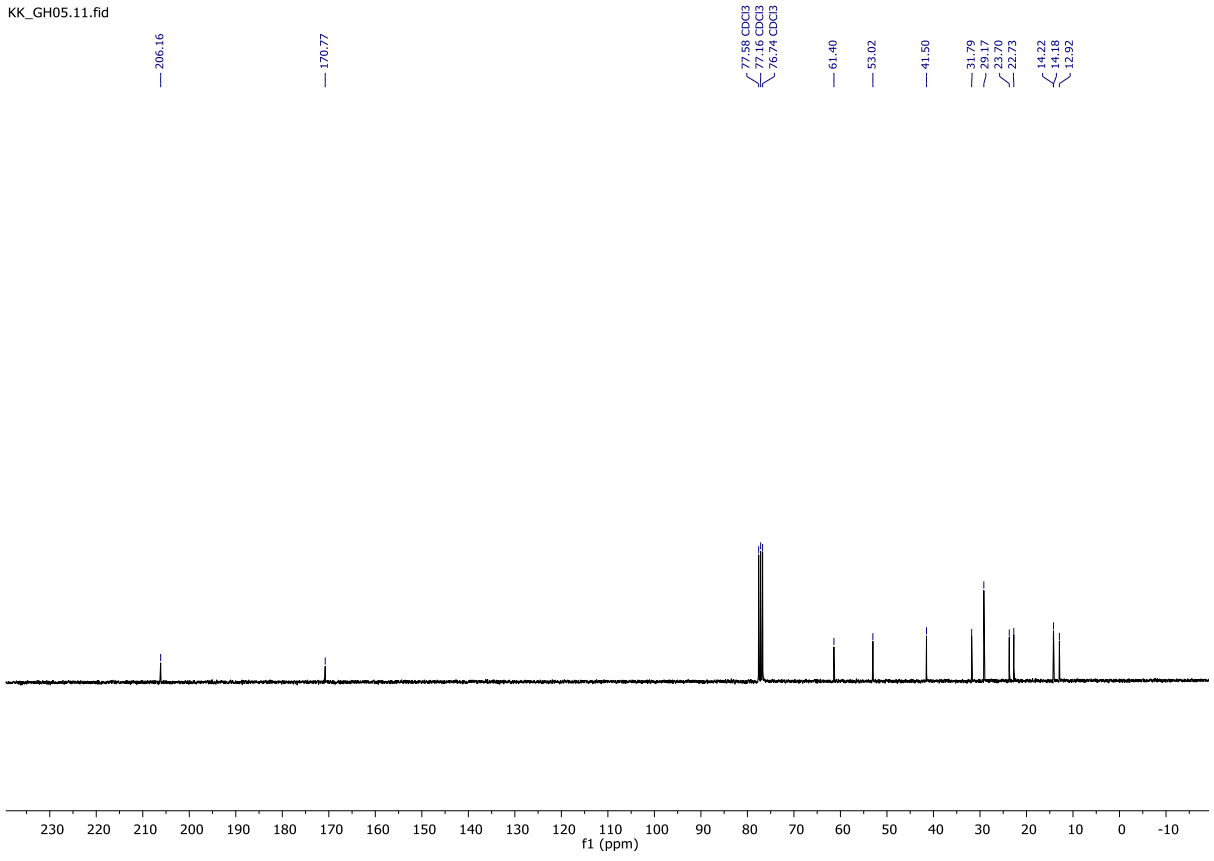
## 4.4 ethyl 2-methyl-3-oxononanoate (**6d**)



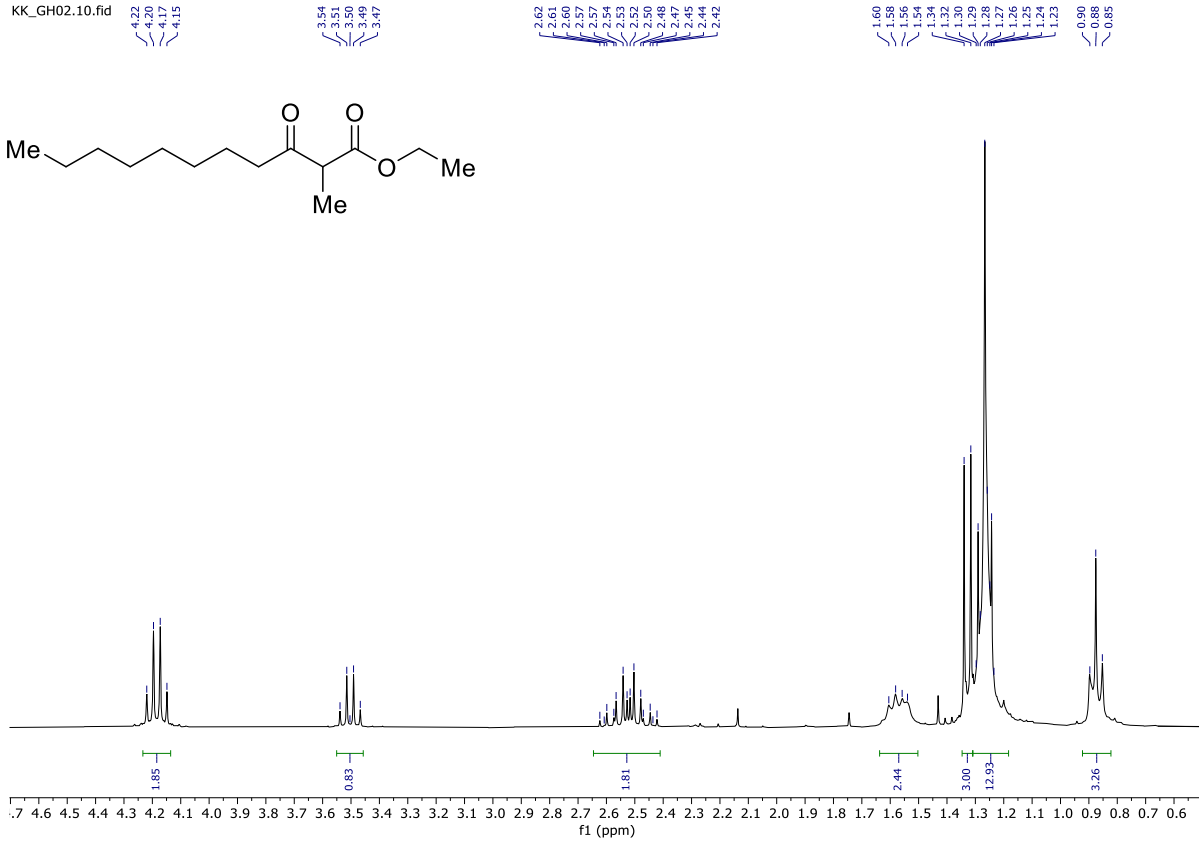



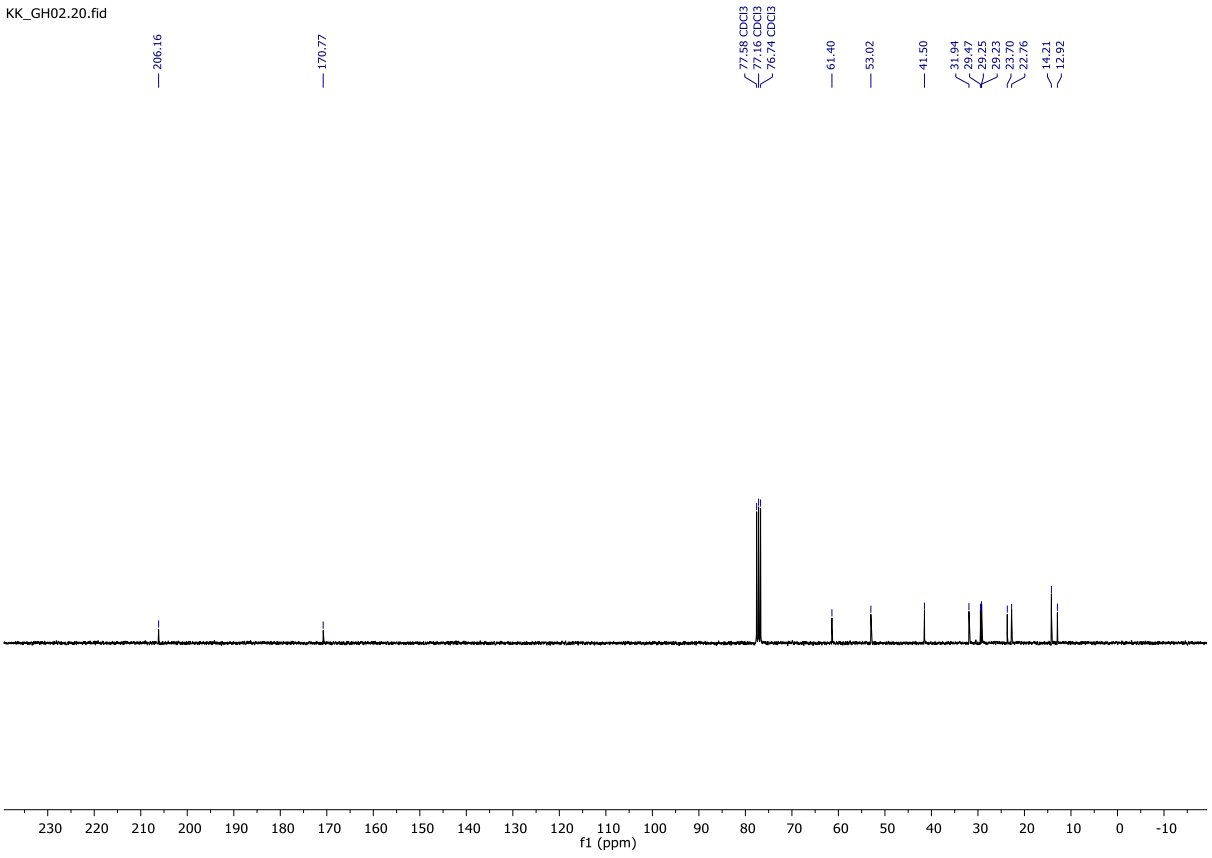
## 4.5 ethyl 2-methyl-3-oxodecanoate (**6e**)



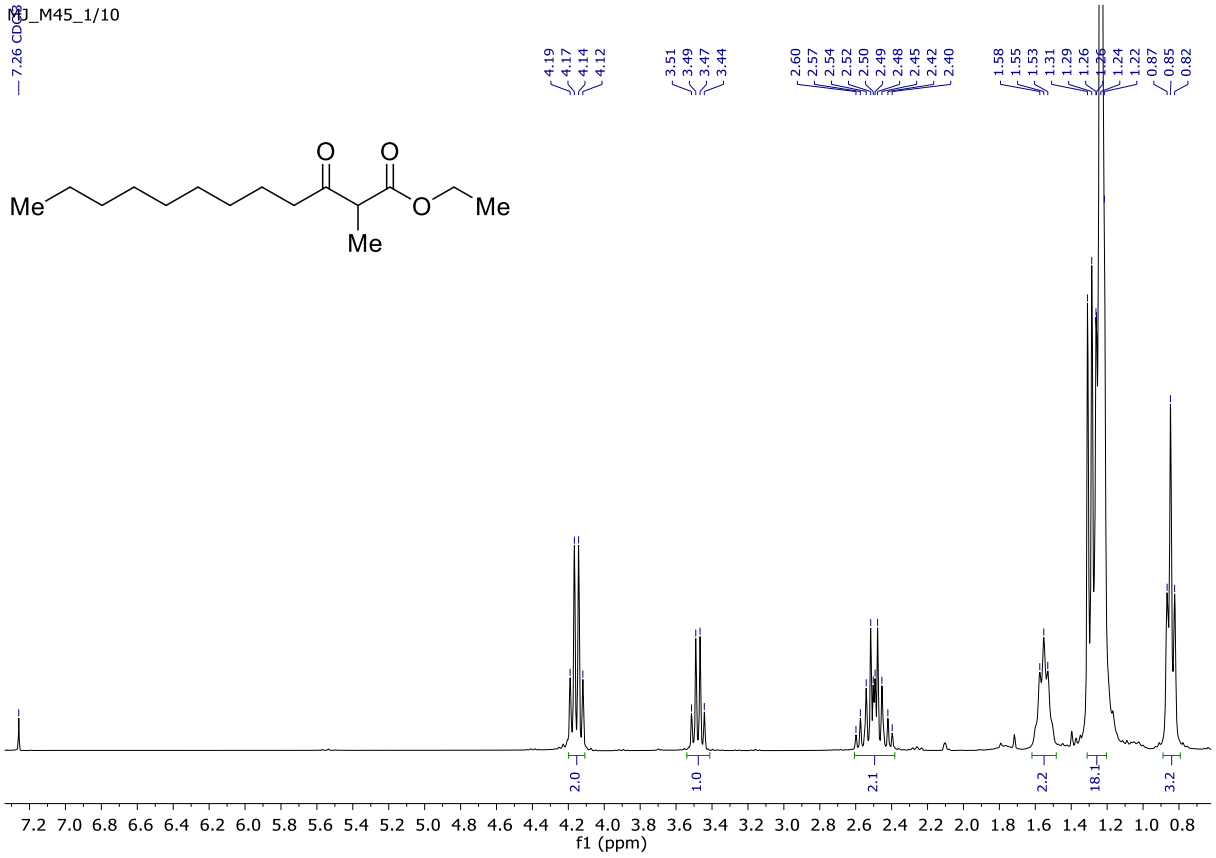



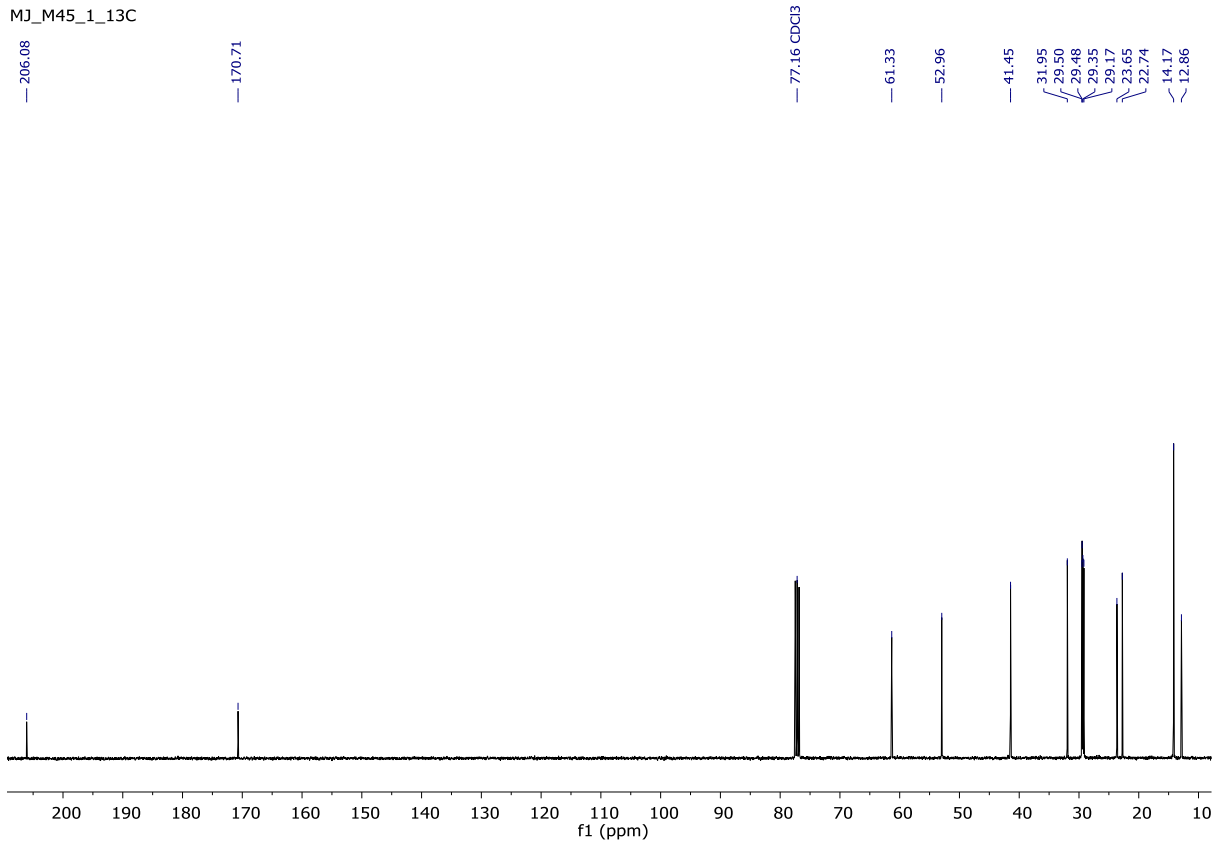
## 4.6 ethyl 2-methyl-3-oxoundecanoate (**6f**)



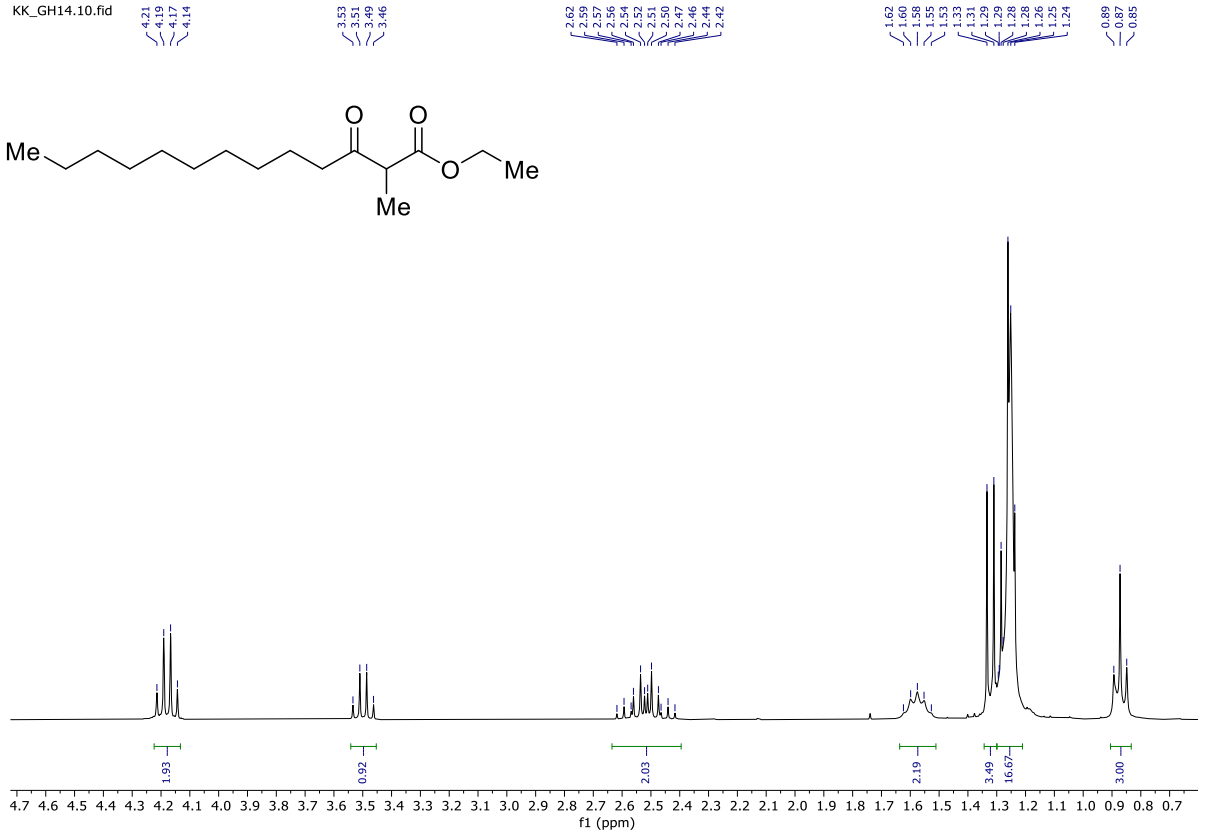



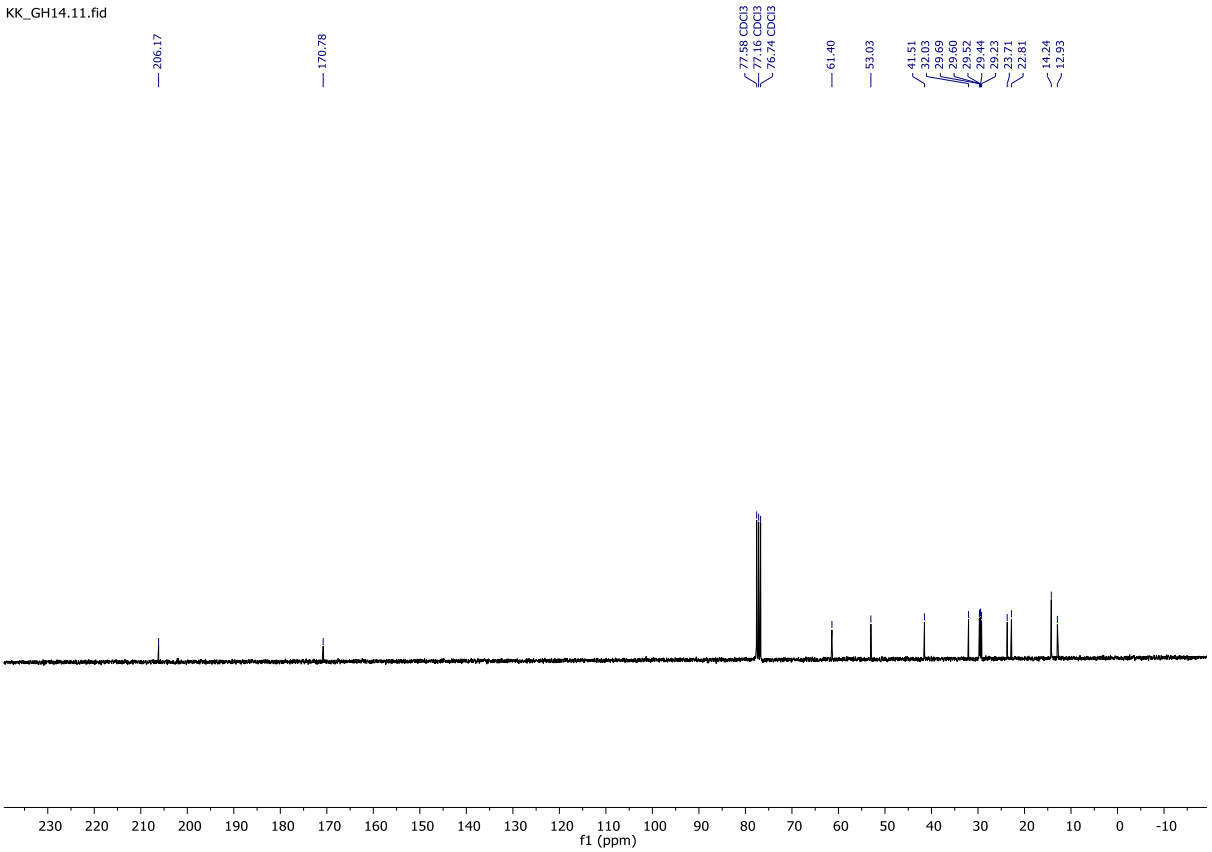
## 4.7 ethyl 2-methyl-3-oxododecanoate (**6g**)



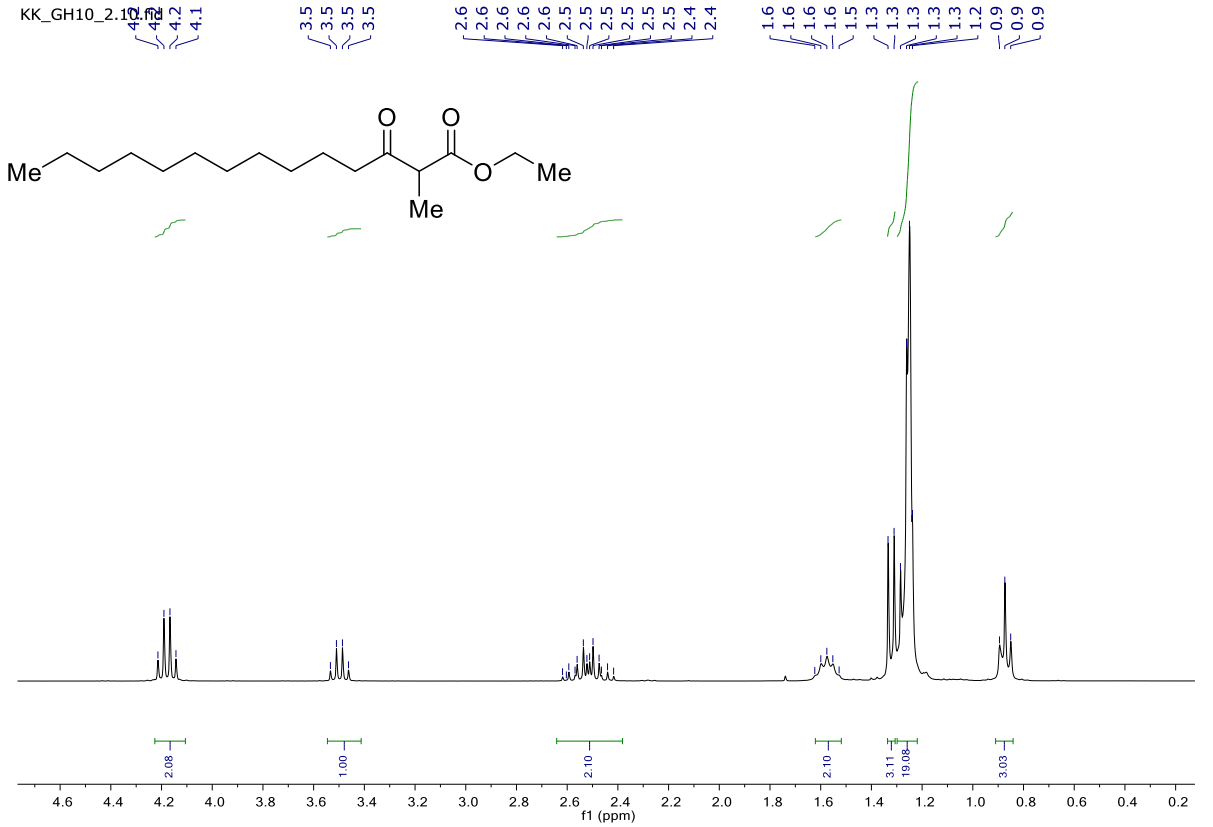



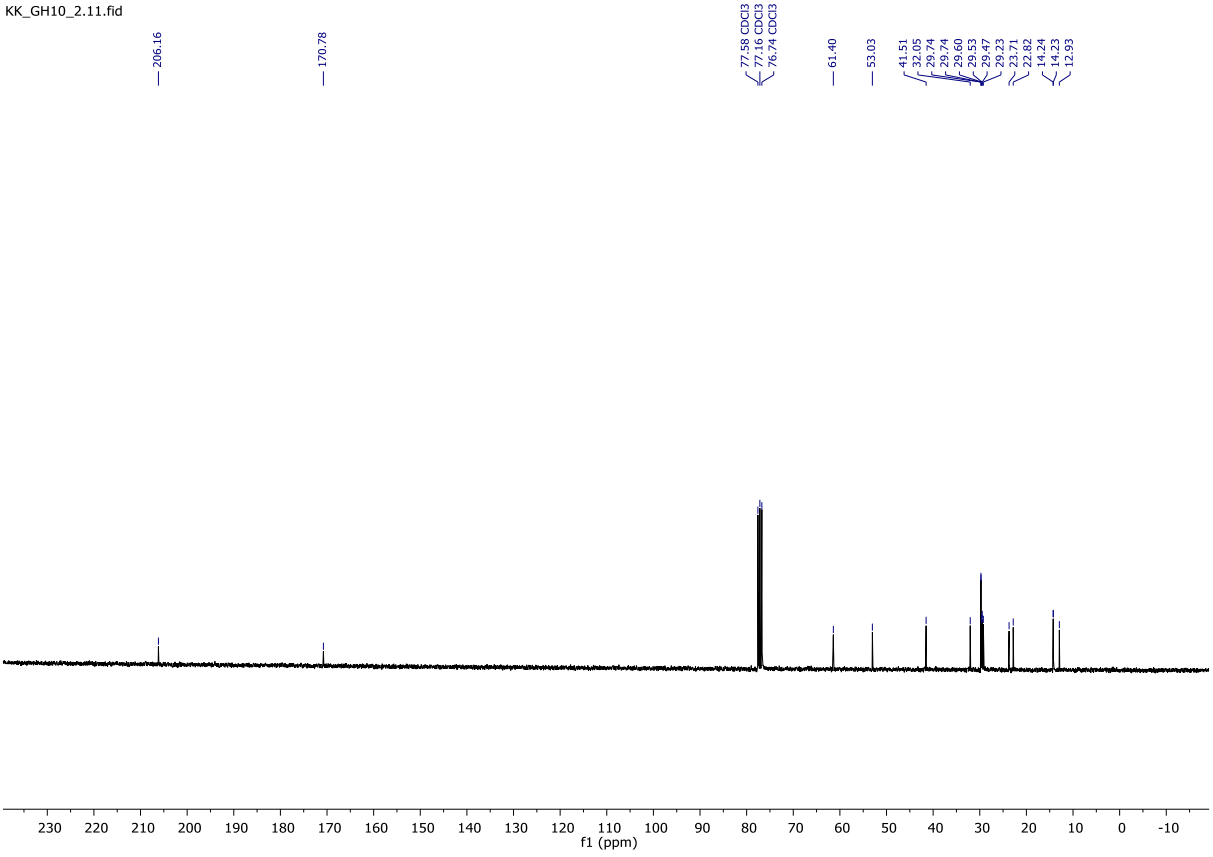
## 4.8 ethyl 2-methyl-3-oxotridecanoate (**6h**)



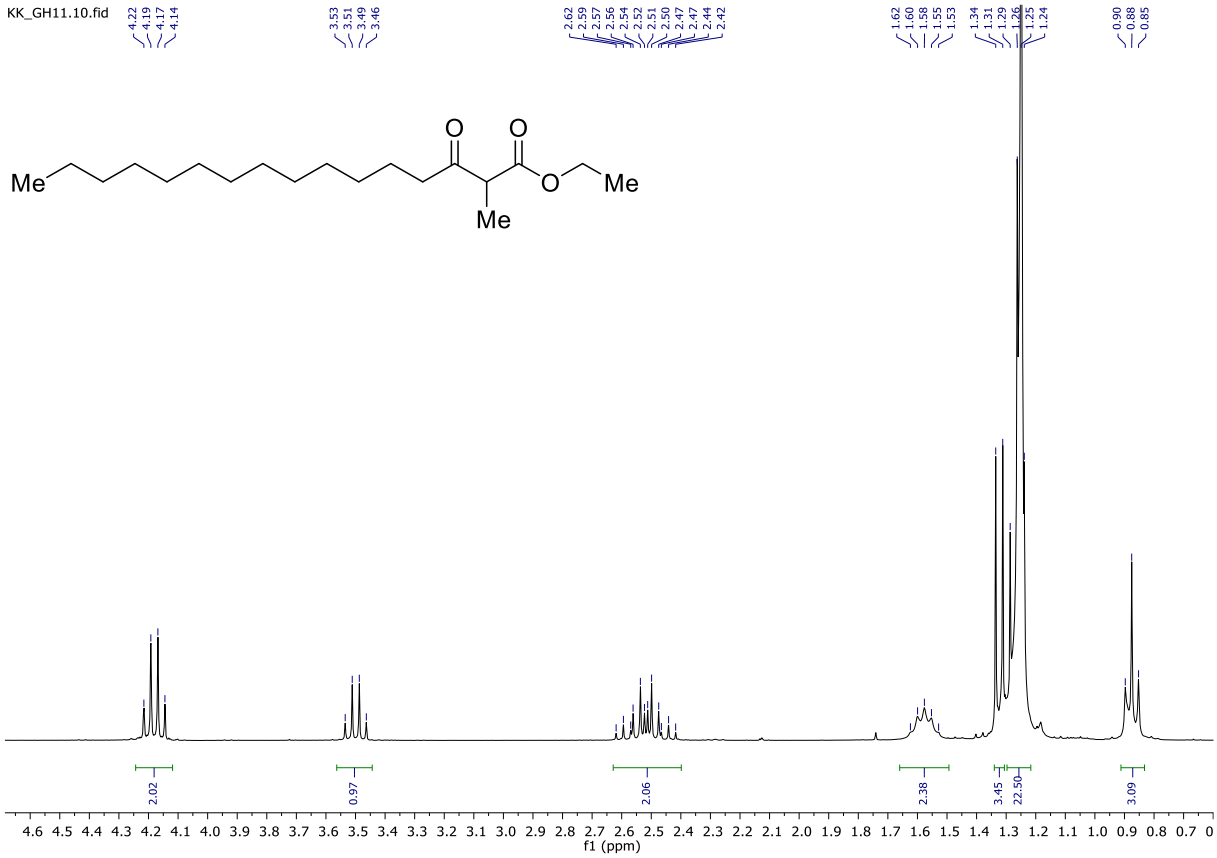



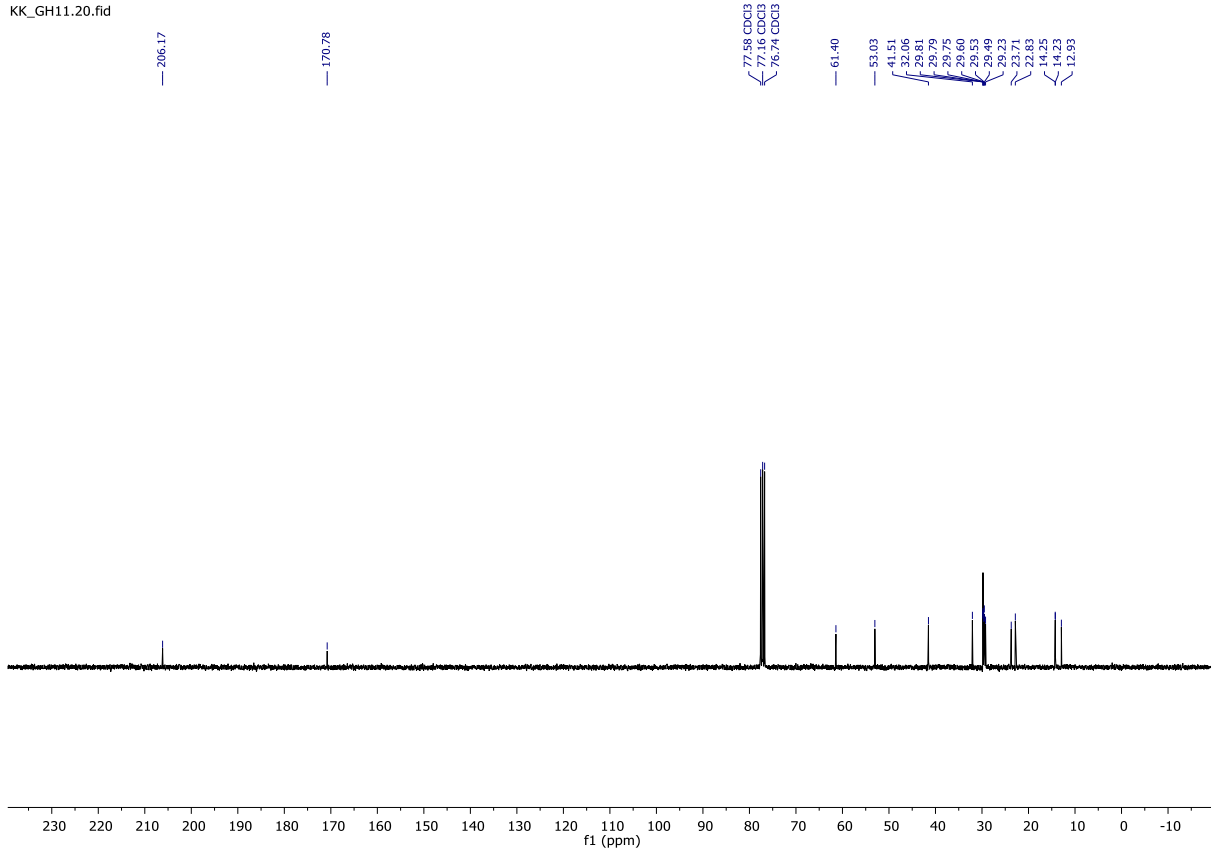
## 4.9 ethyl 2-methyl-3-oxotetradecanoate (**6i**)



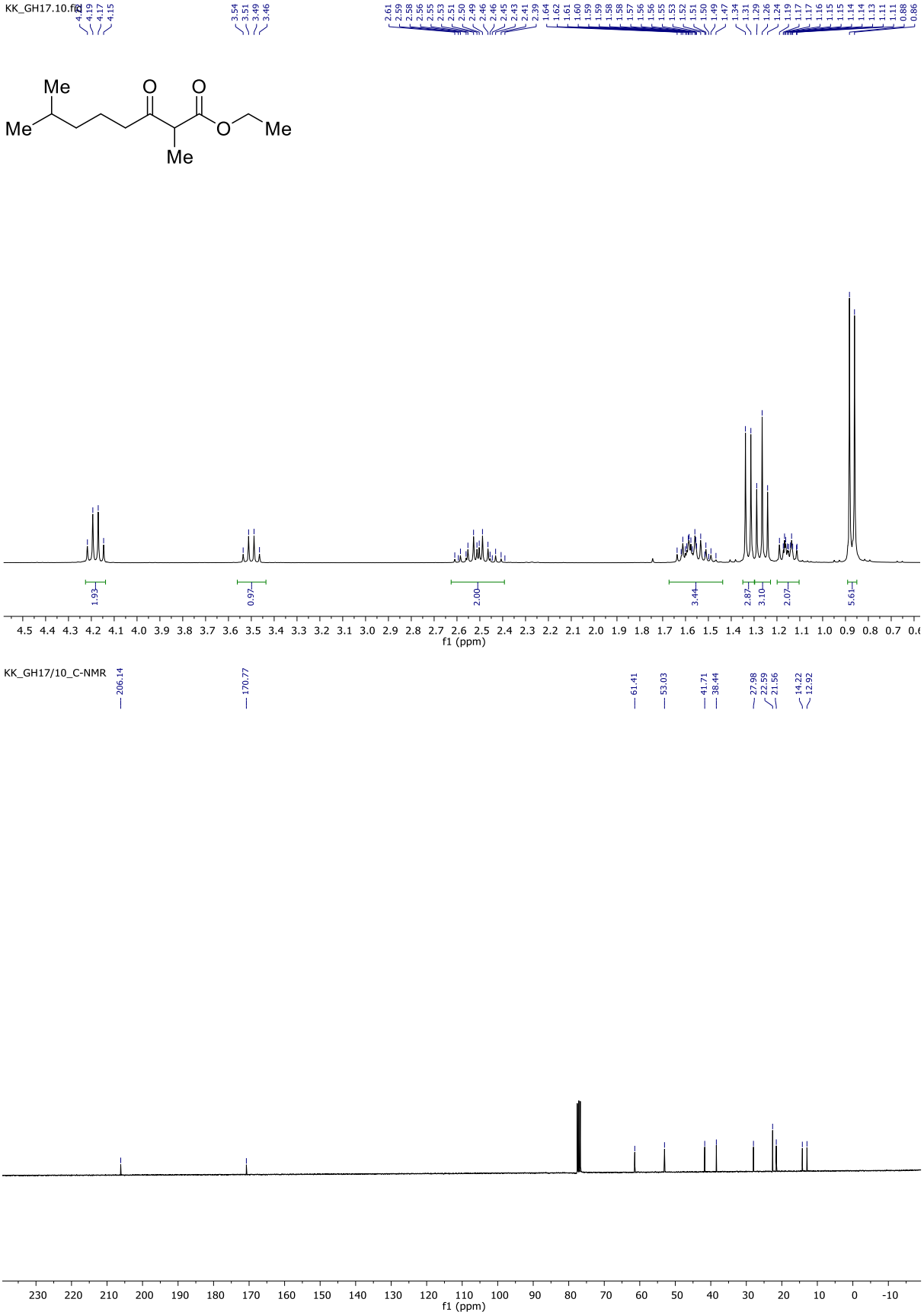



## 4.10 ethyl 2-methyl-3-oxohexadecanoate (**6j**)

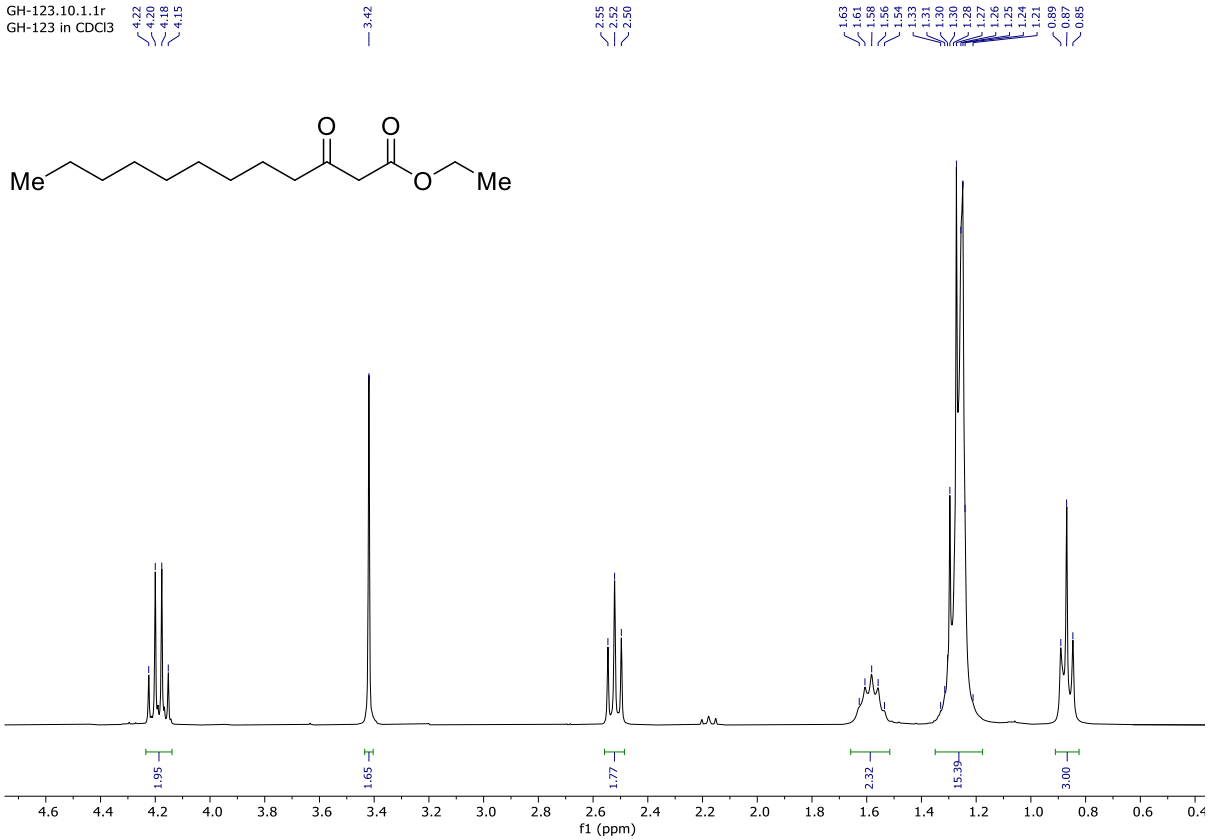


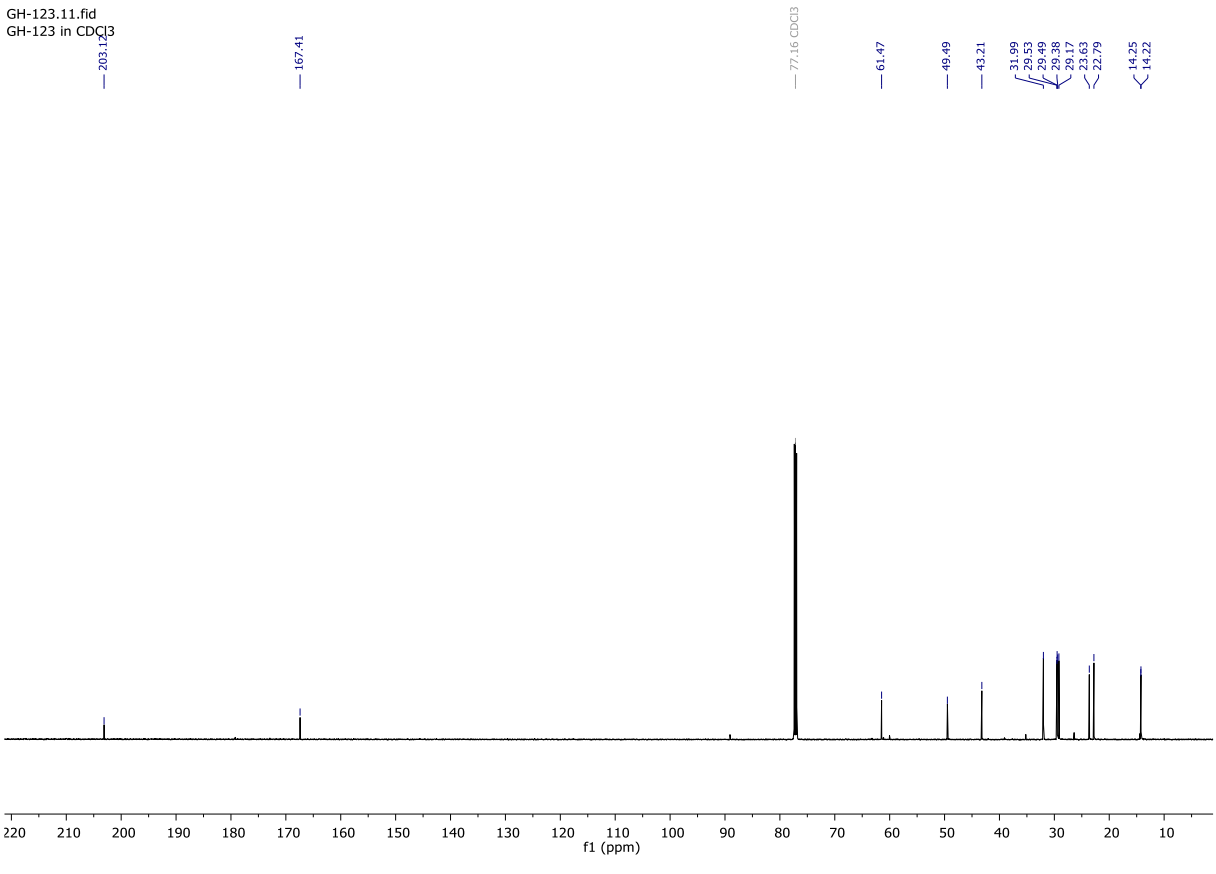



## 4.11 ethyl 2,7-dimethyl-3-oxooctanoate (**6k**)

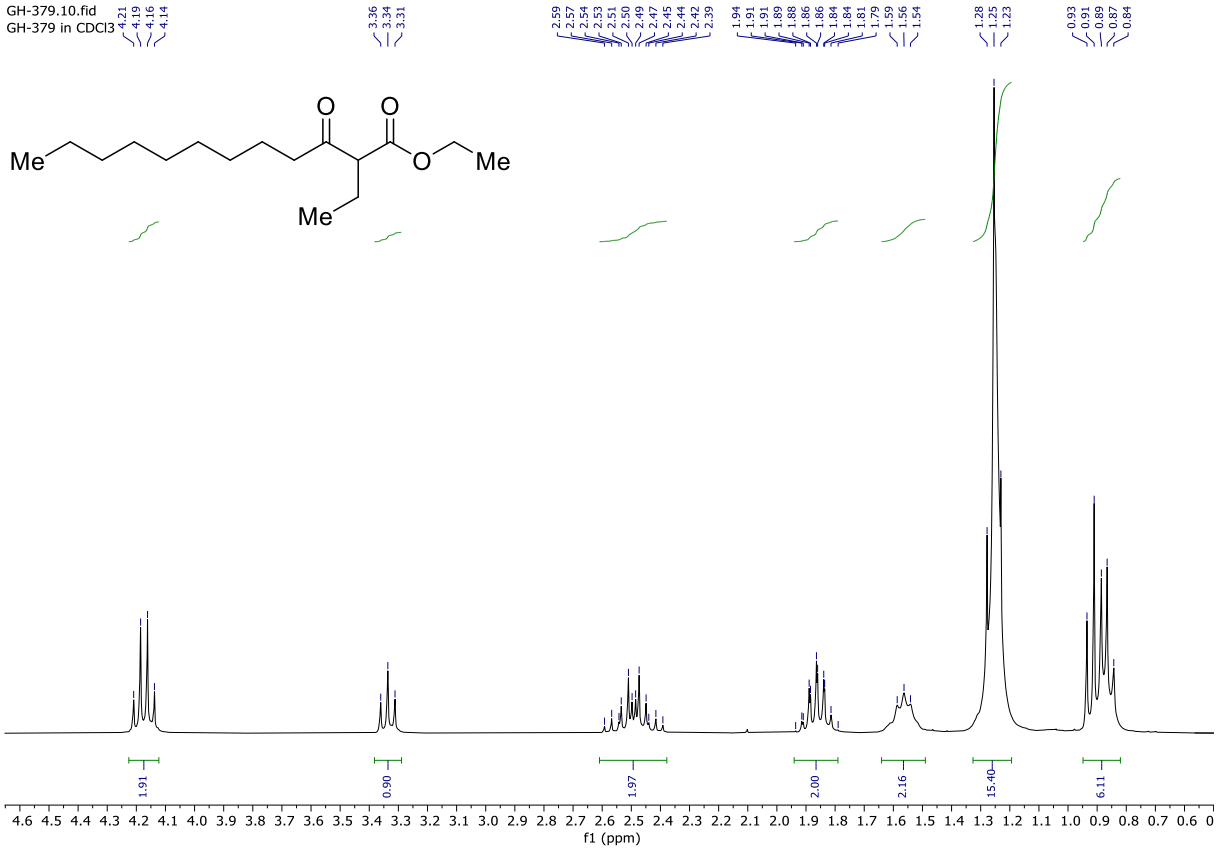


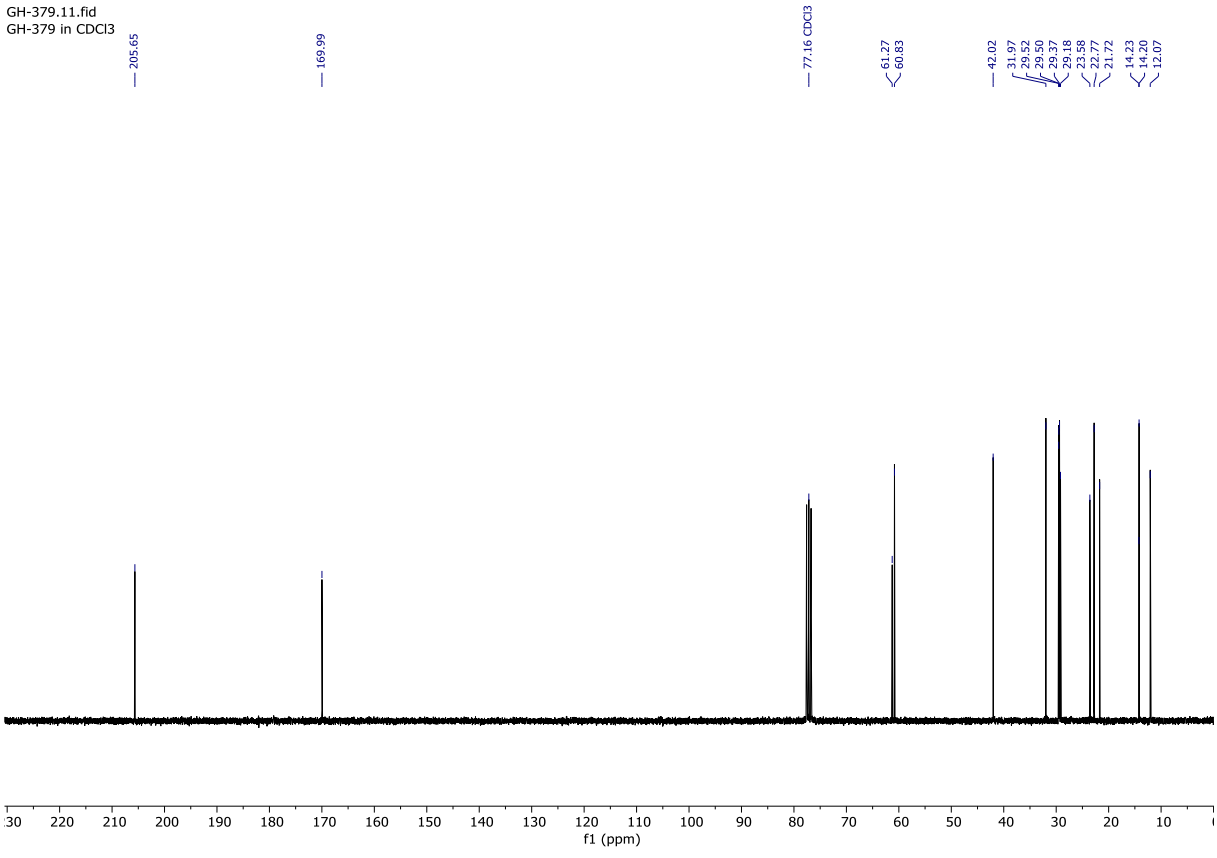
## 4.12 ethyl 3-oxododecanoate (**S2**)



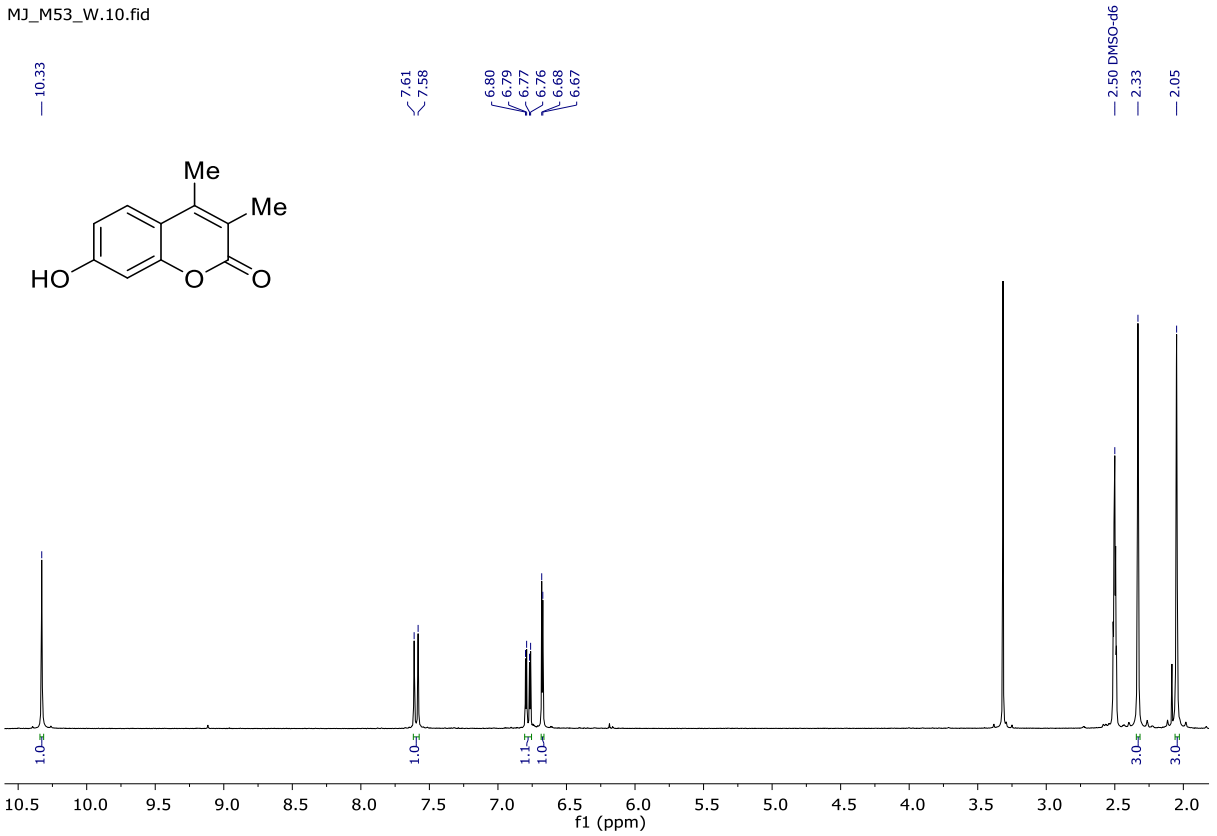



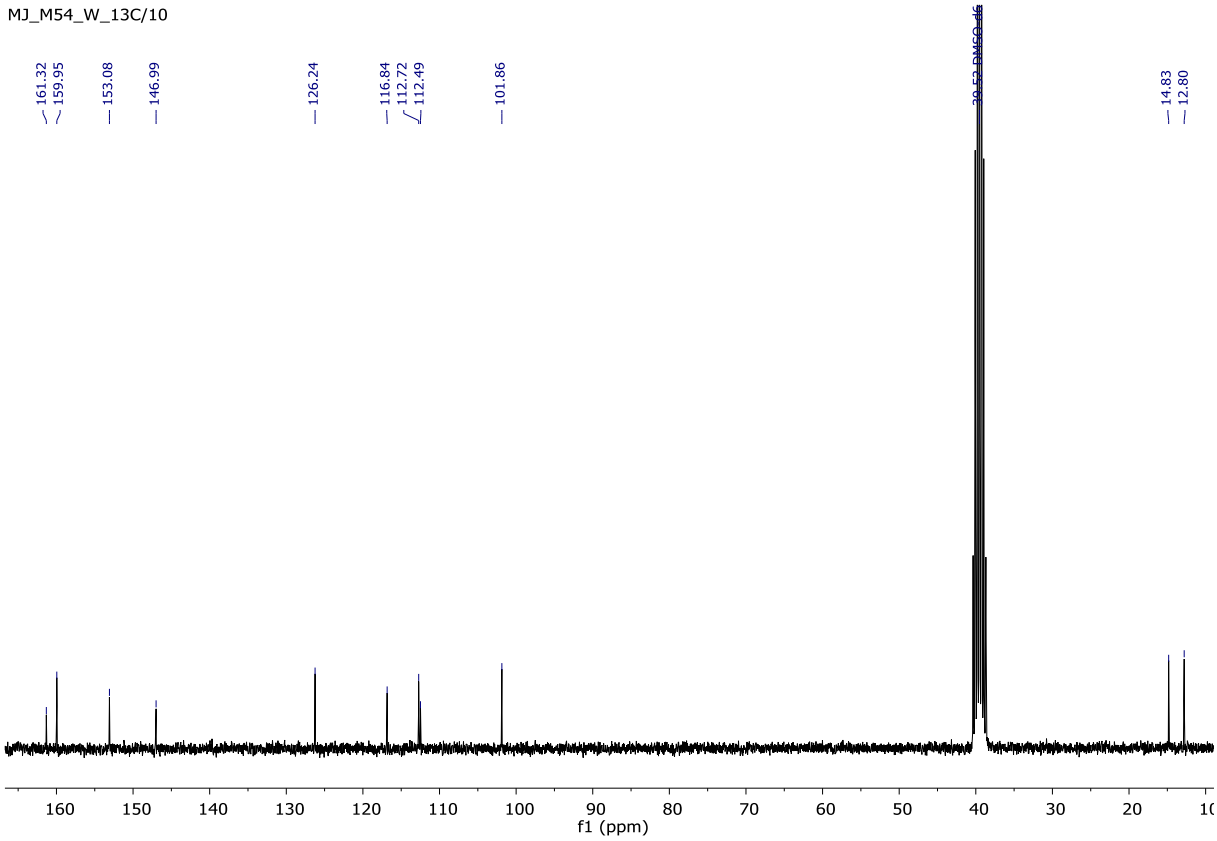
## 4.13 ethyl 2-ethyl-3-oxododecanoate (**S4**)



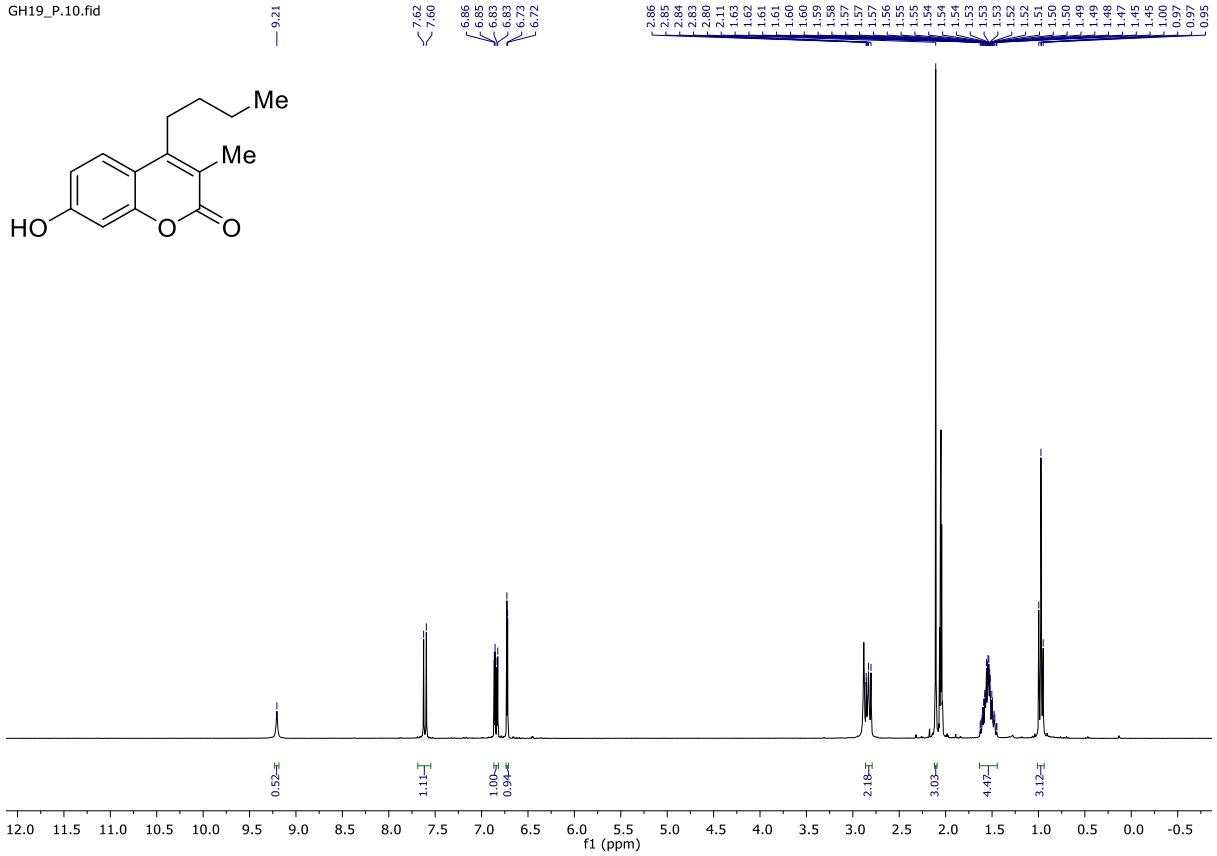



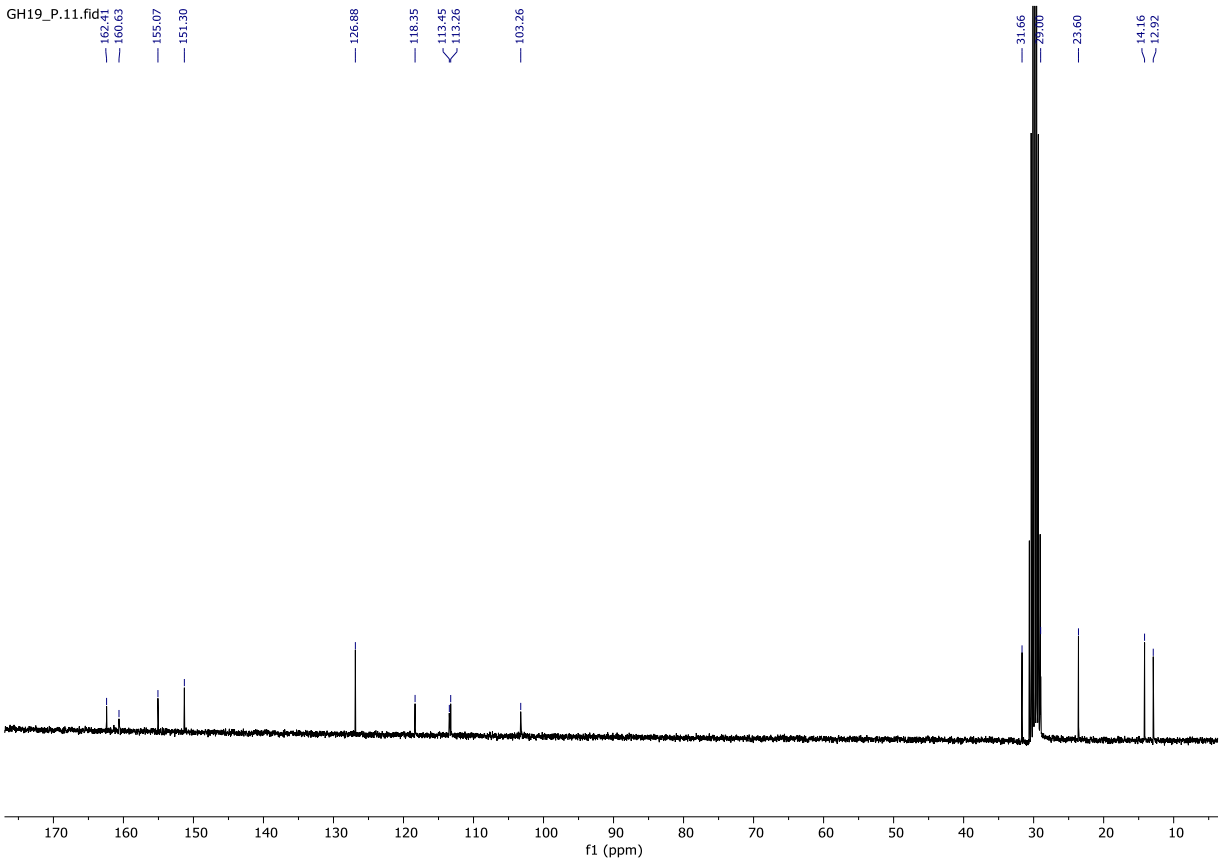
## 4.14 7-hydroxy-3,4-dimethylcoumarin (**10a**)



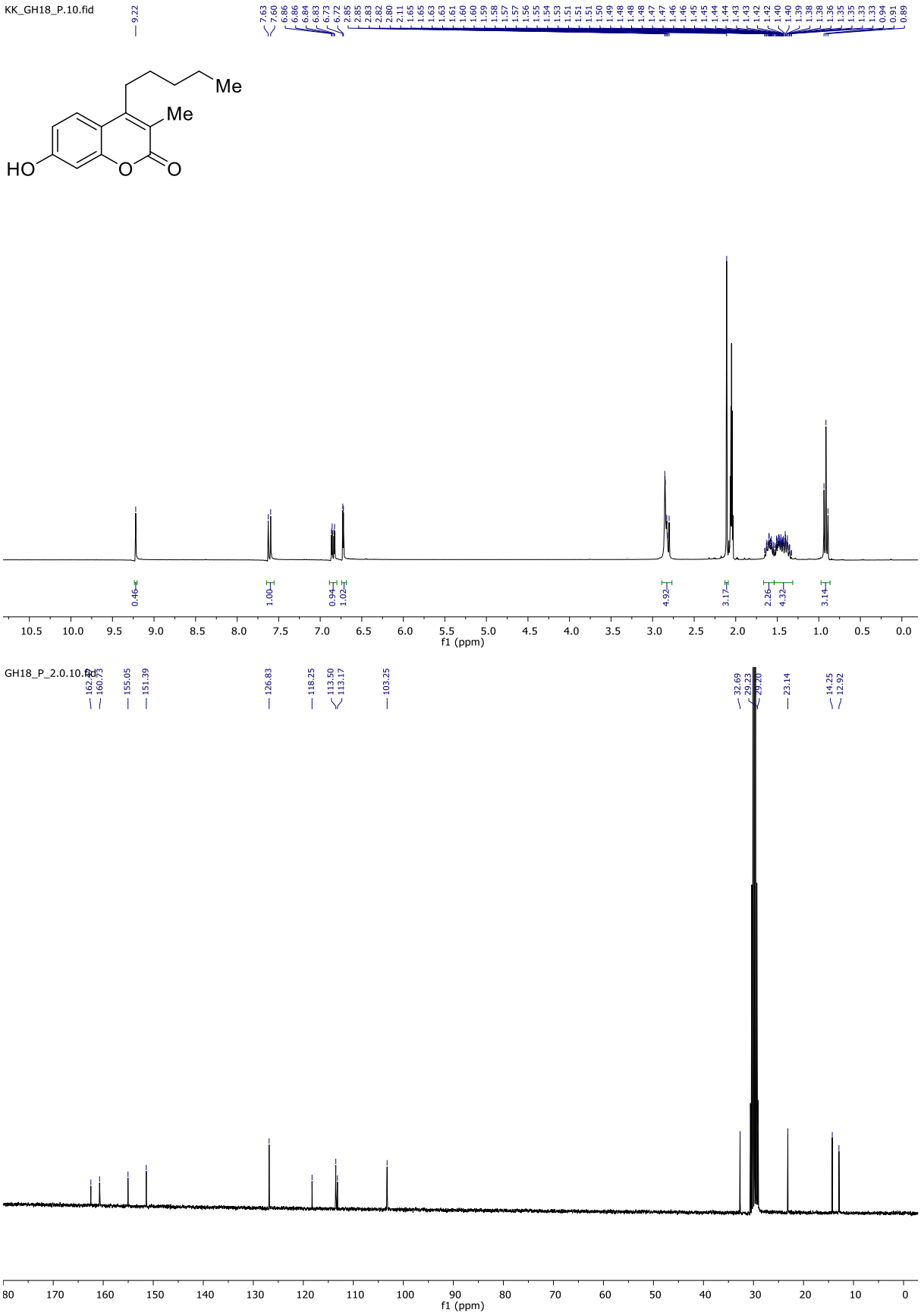



## 4.15 4-butyl-7-hydroxy-3-methylcoumarin (**10b**)

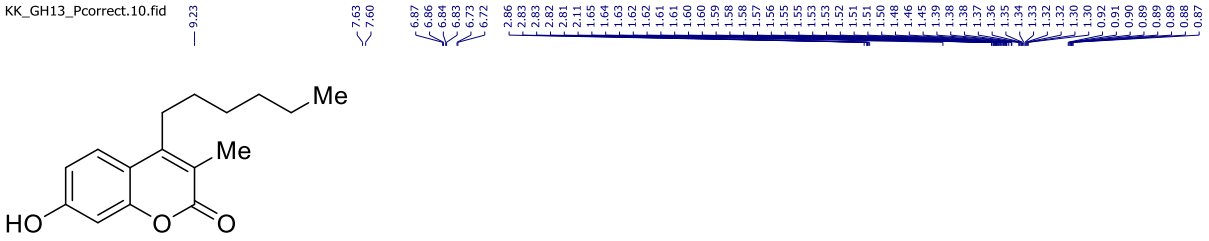


## 4.16 7-hydroxy-3-methyl-4-pentylcoumarin (**10c**)

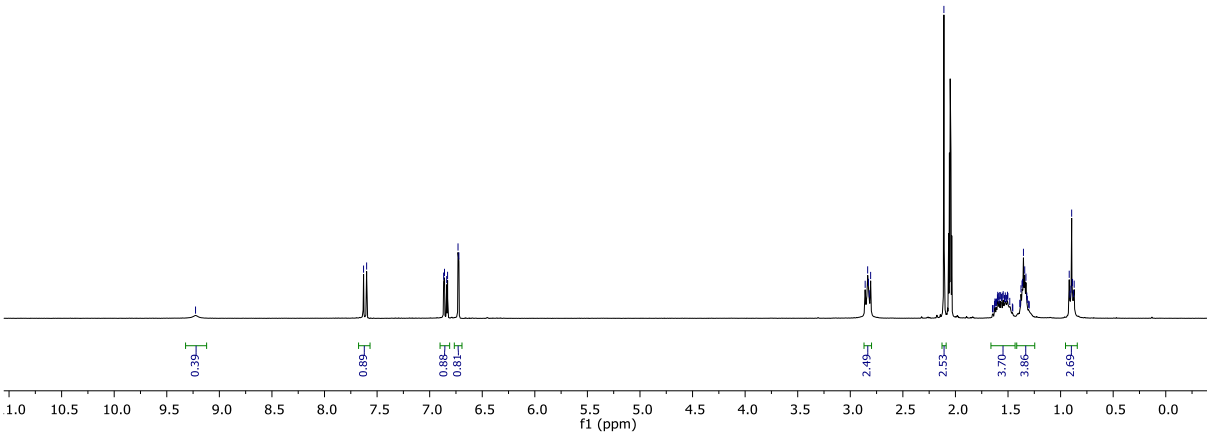


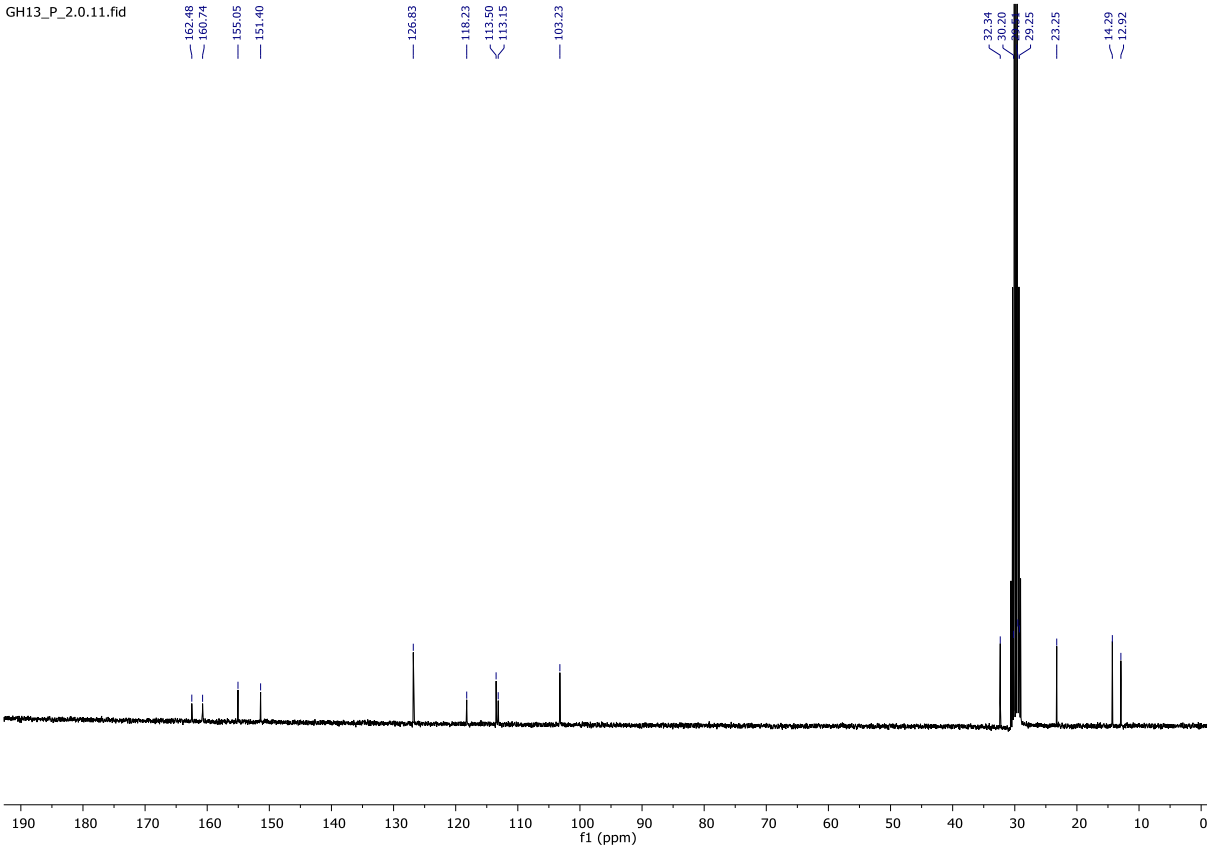
## 4.17 4-hexyl-7-hydroxy-3-methylcoumarin (**10d**)



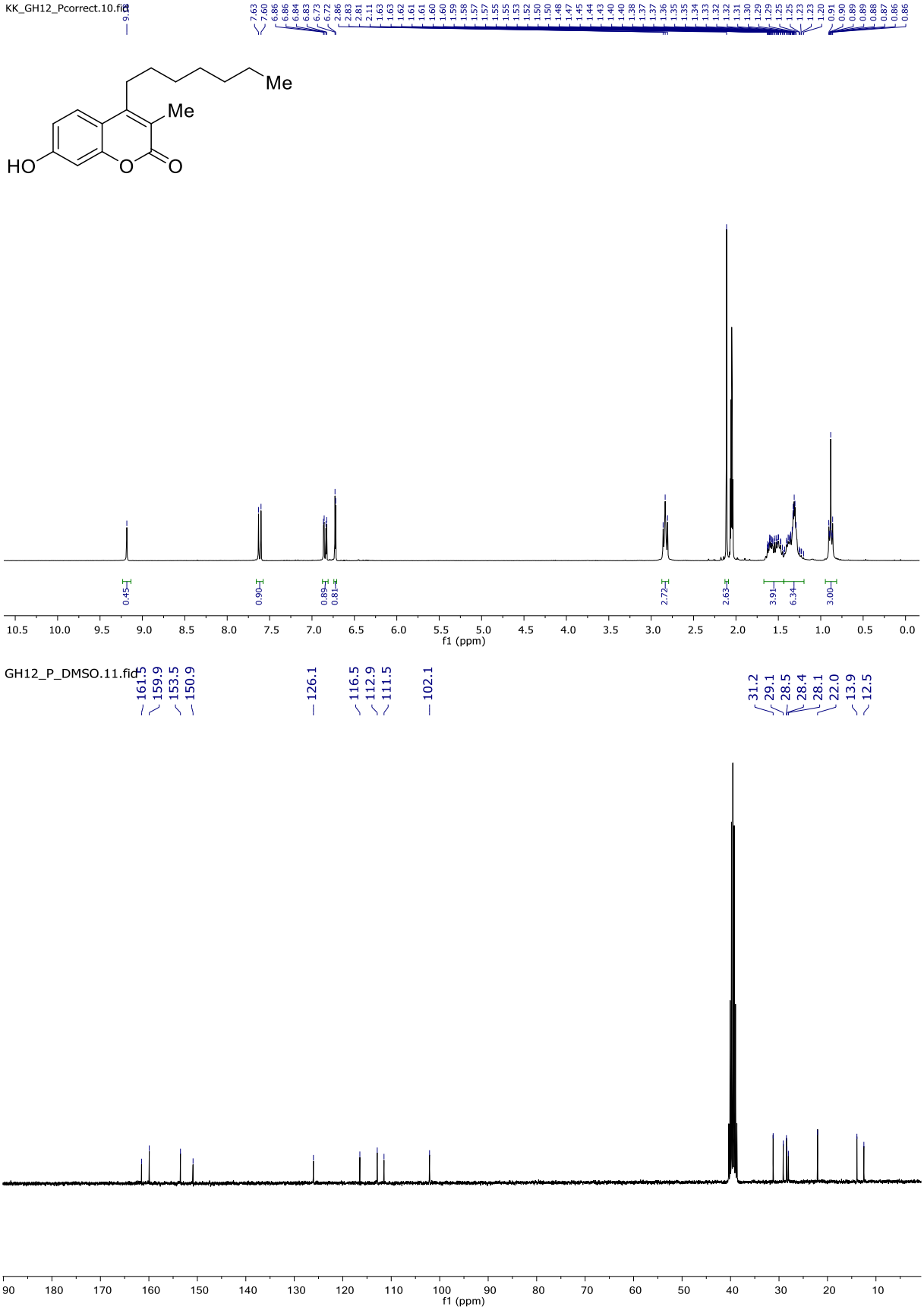




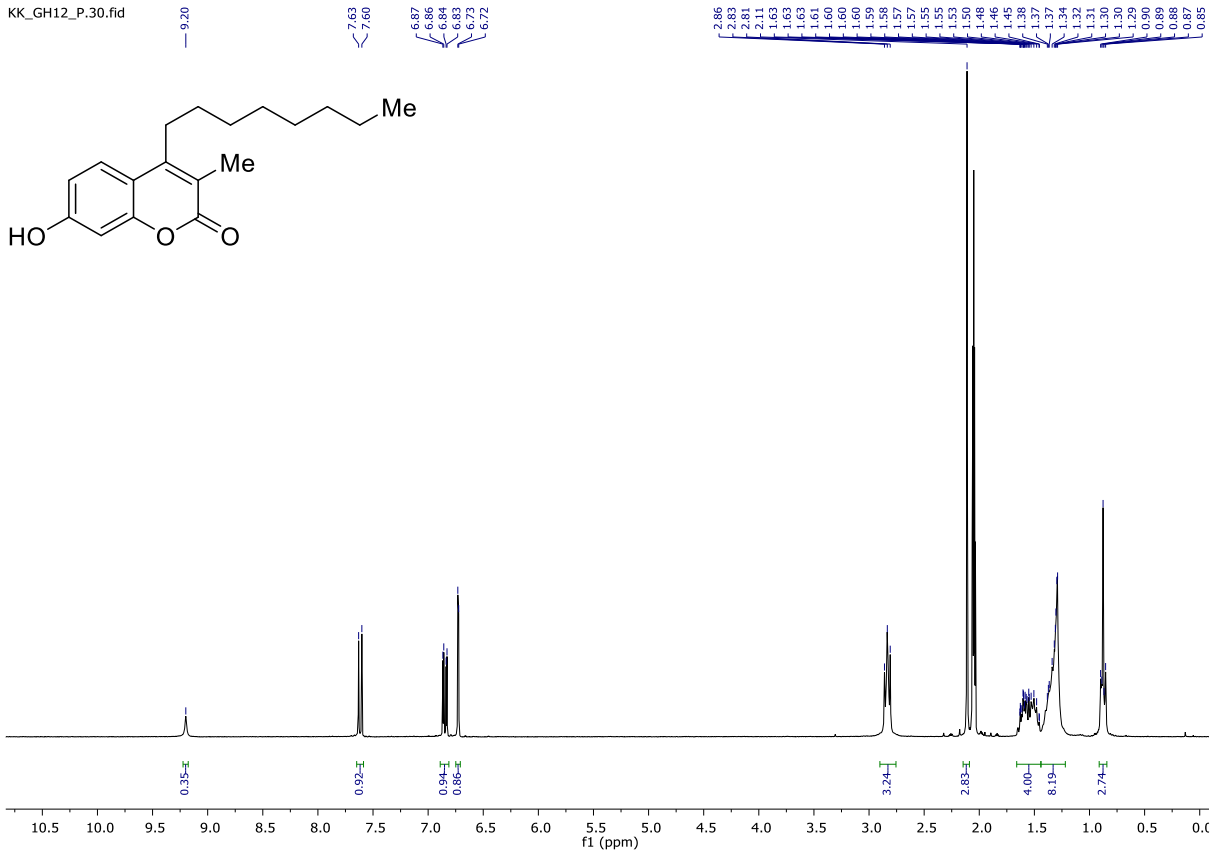


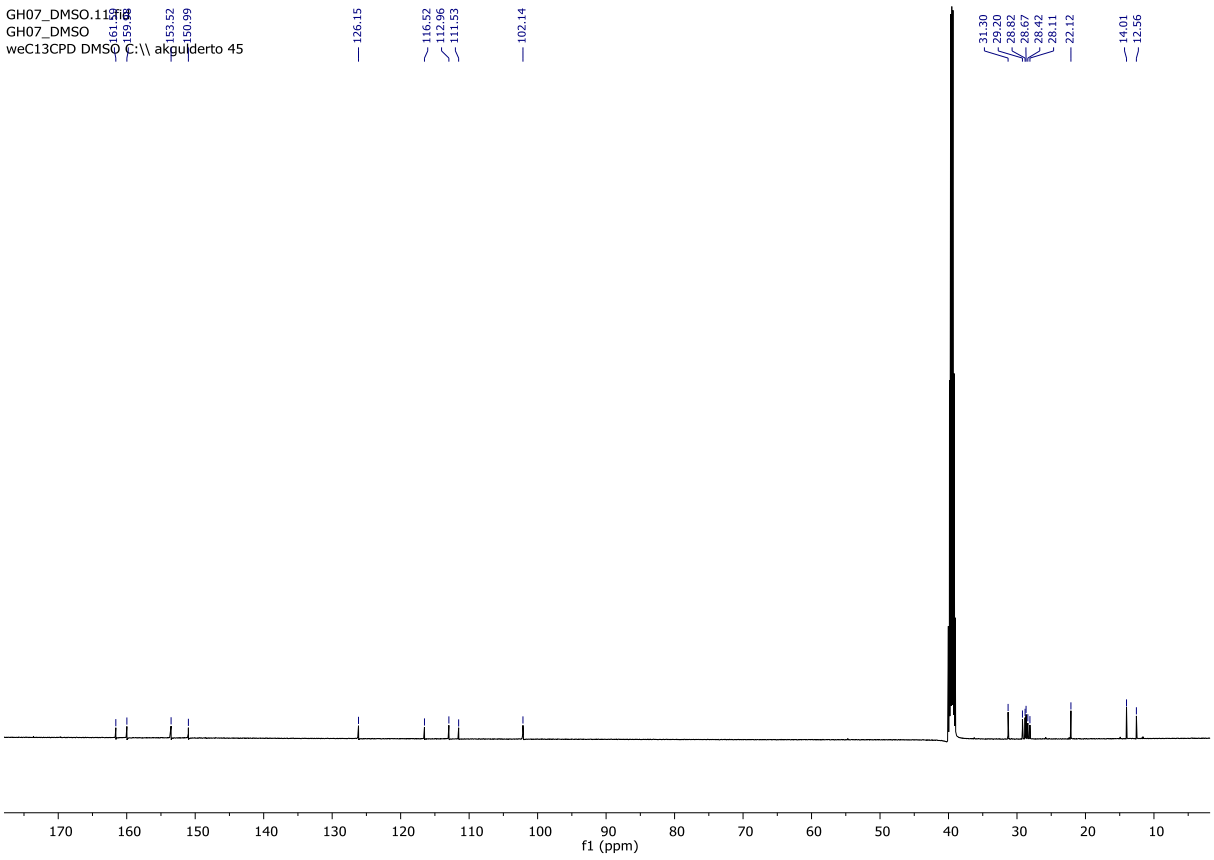



## 4.18 4-heptyl-7-hydroxy-3-methylcoumarin (**10e**)

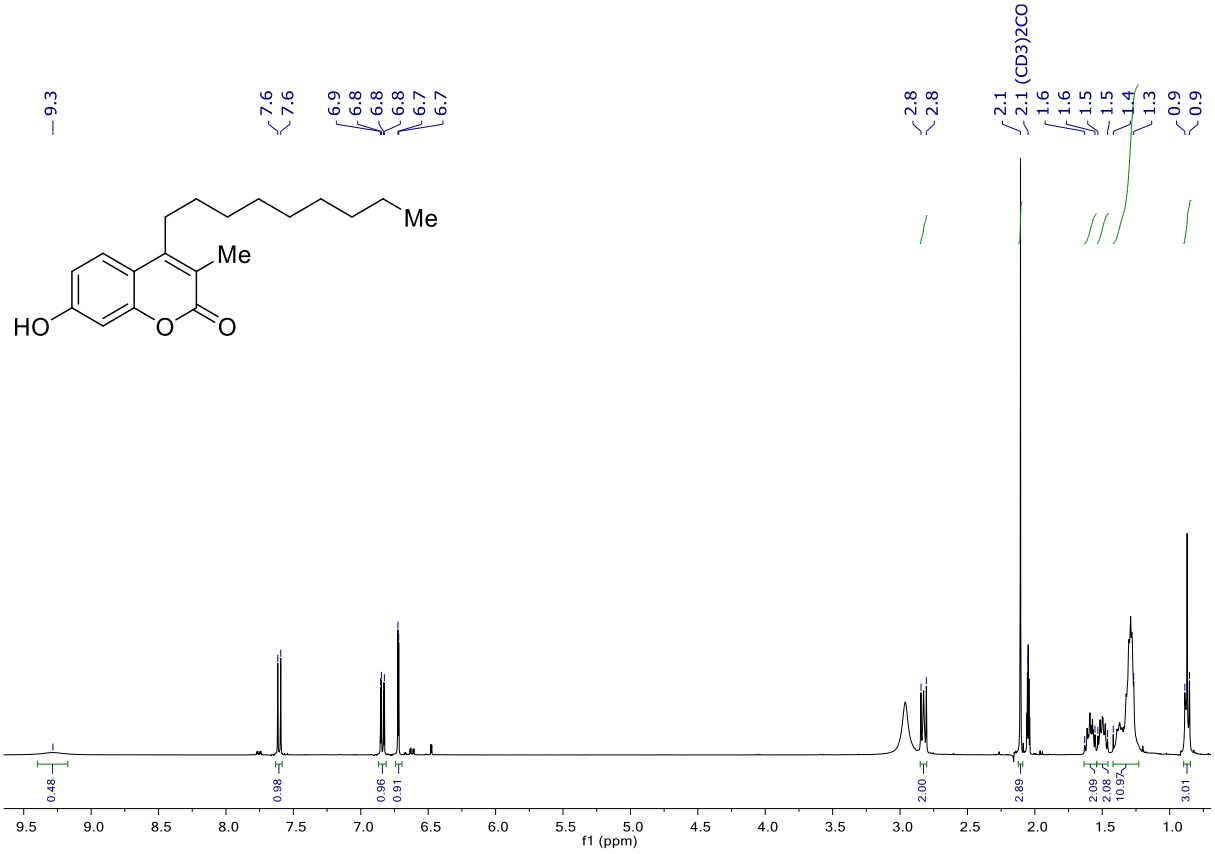


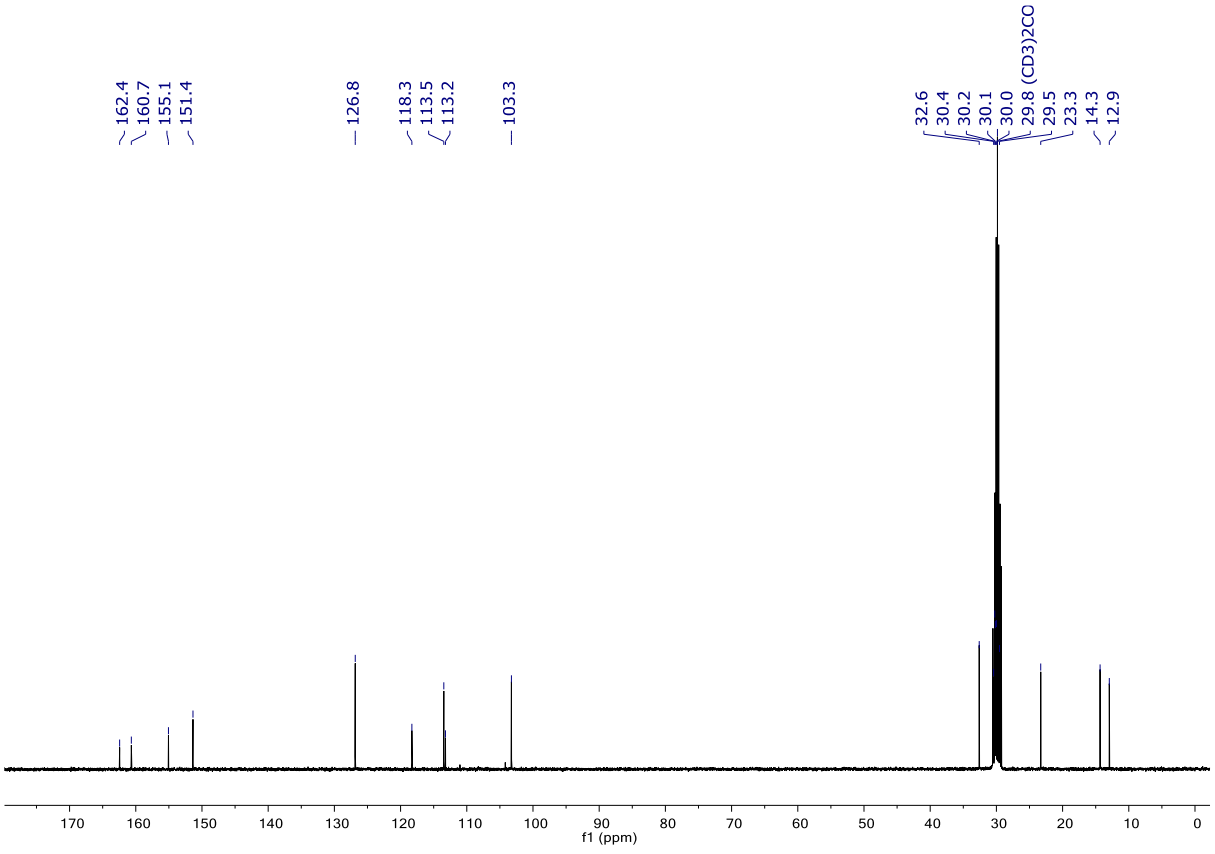
## 4.19 7-hydroxy-3-methyl-4-octylcoumarin (**10f**)



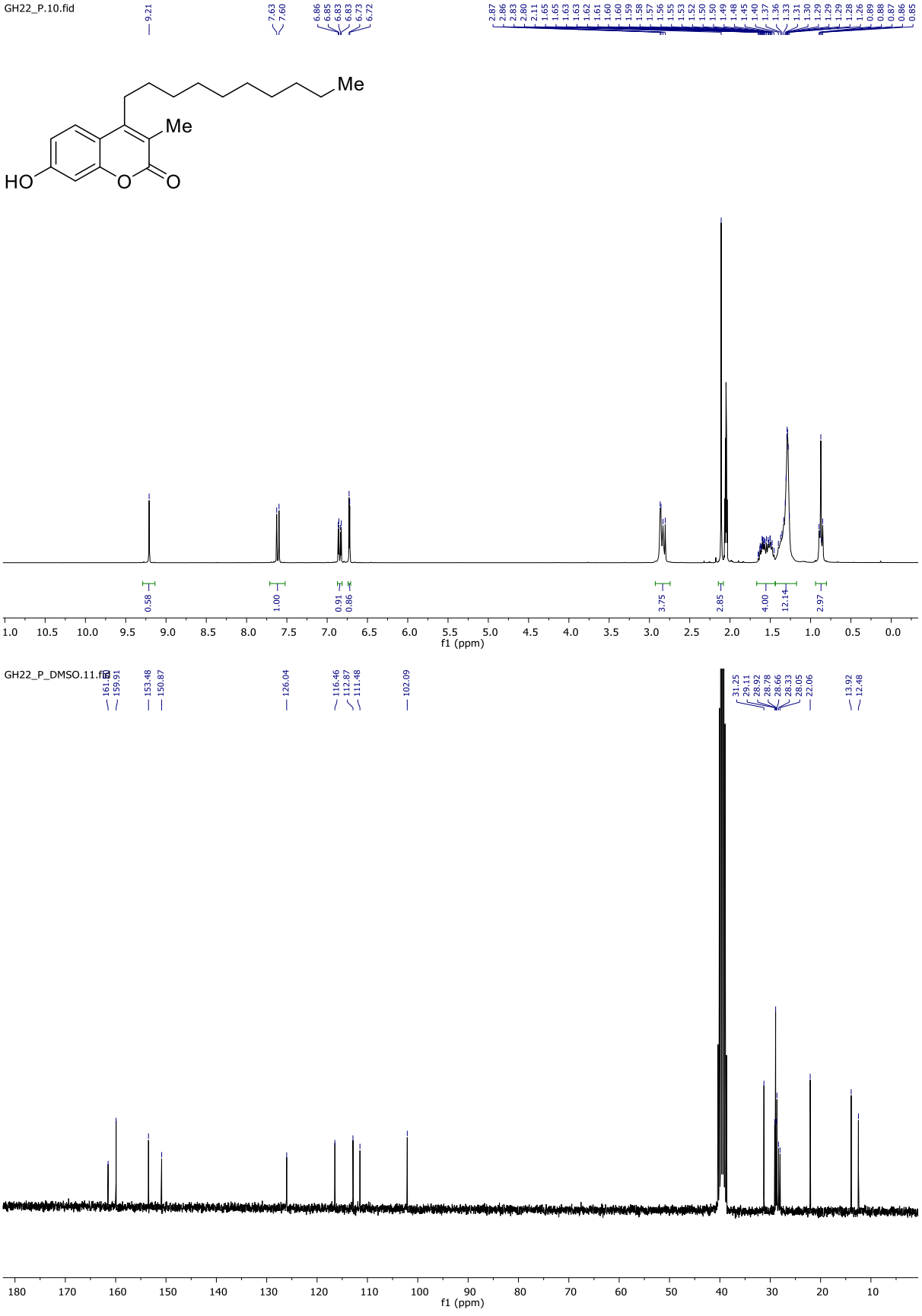



4.20 7-hydroxy-3-methyl-4-nonylcoumarin (**10g**)

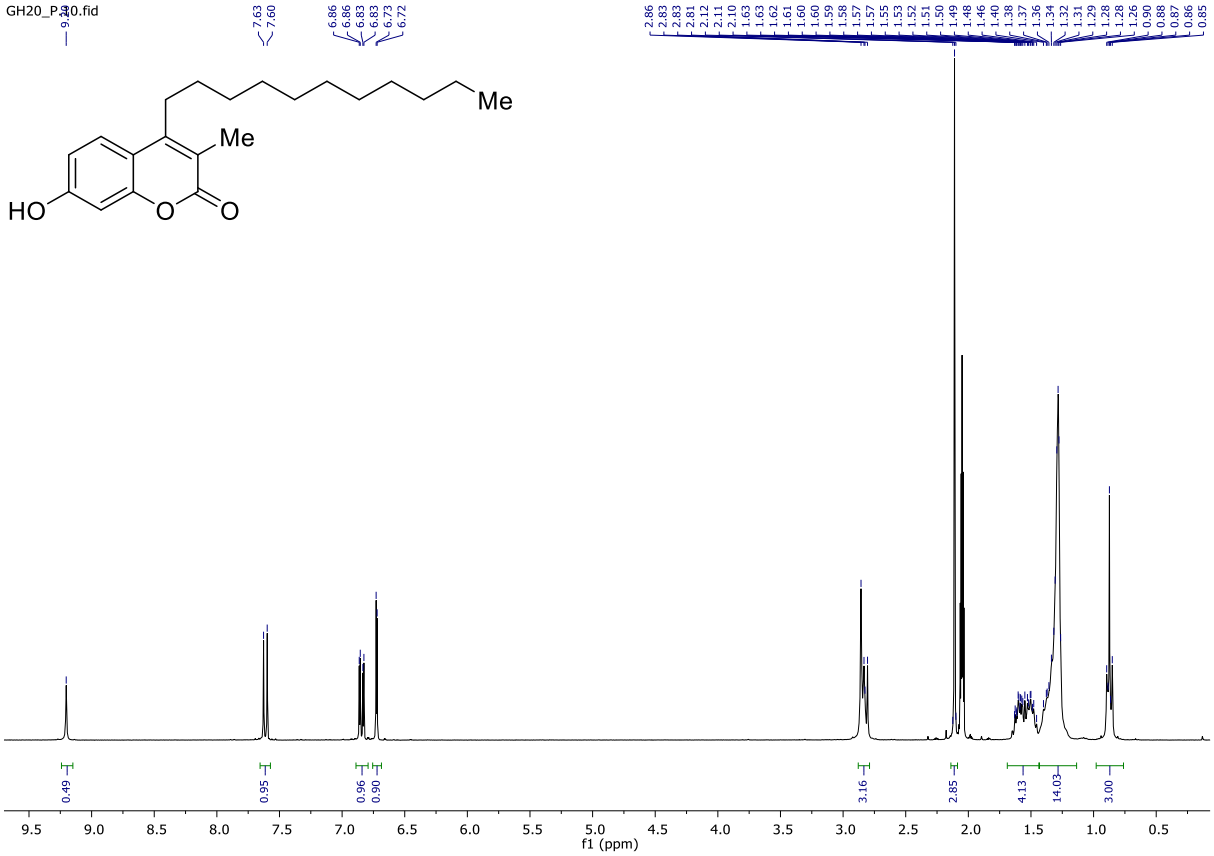


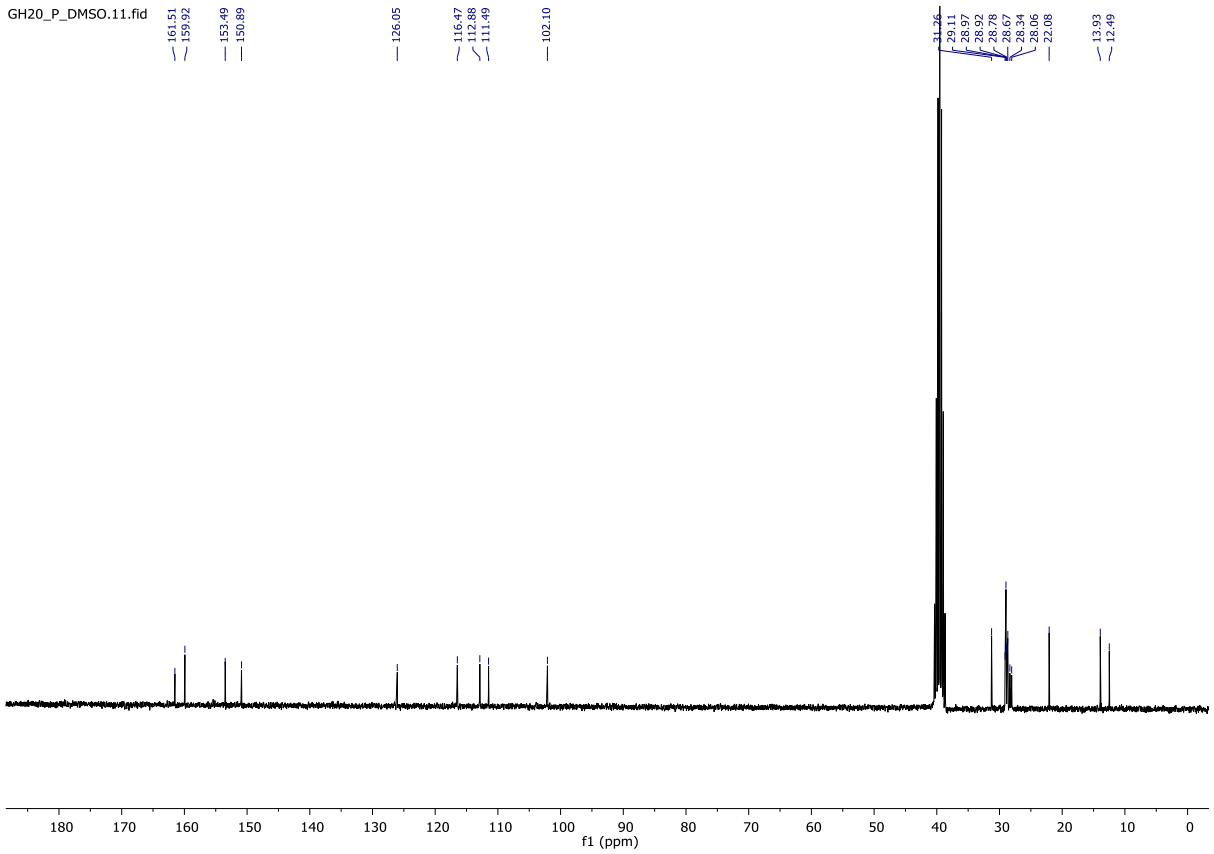



## 4.21 4-decyl-7-hydroxy-3-methylcoumarin (**10h**)

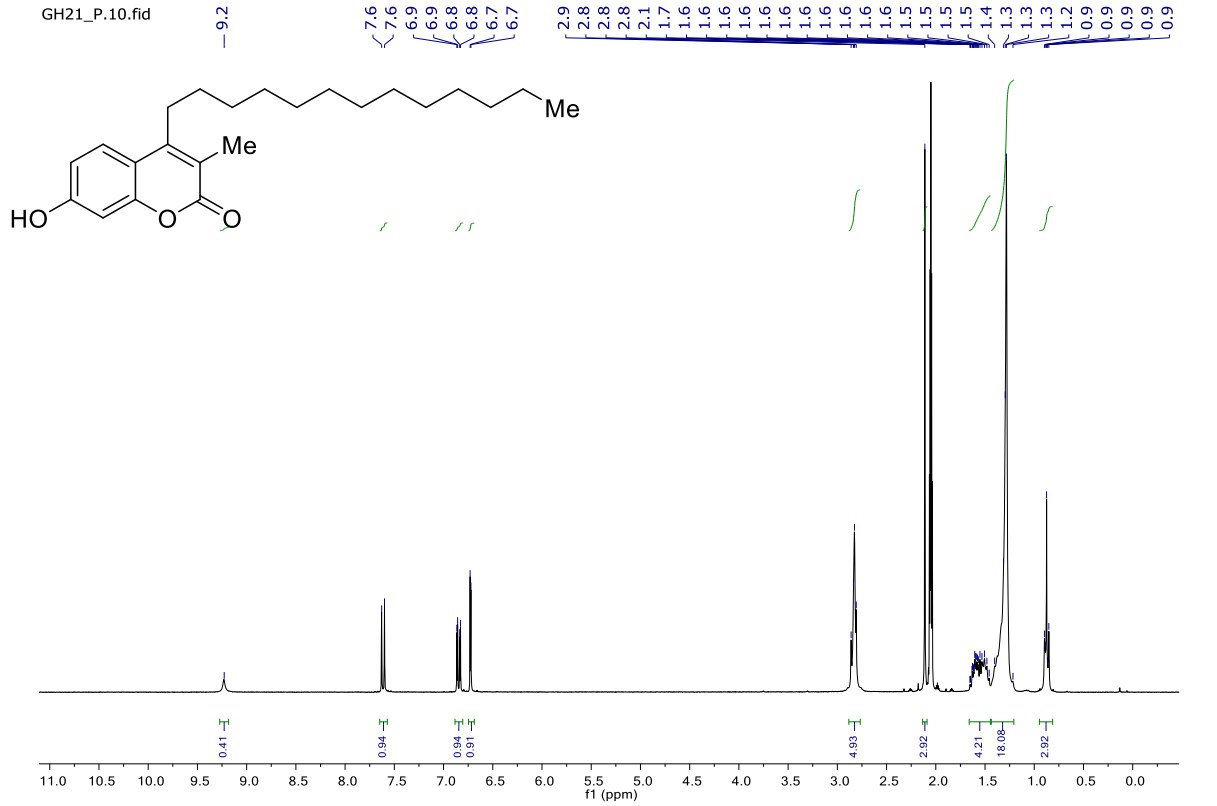


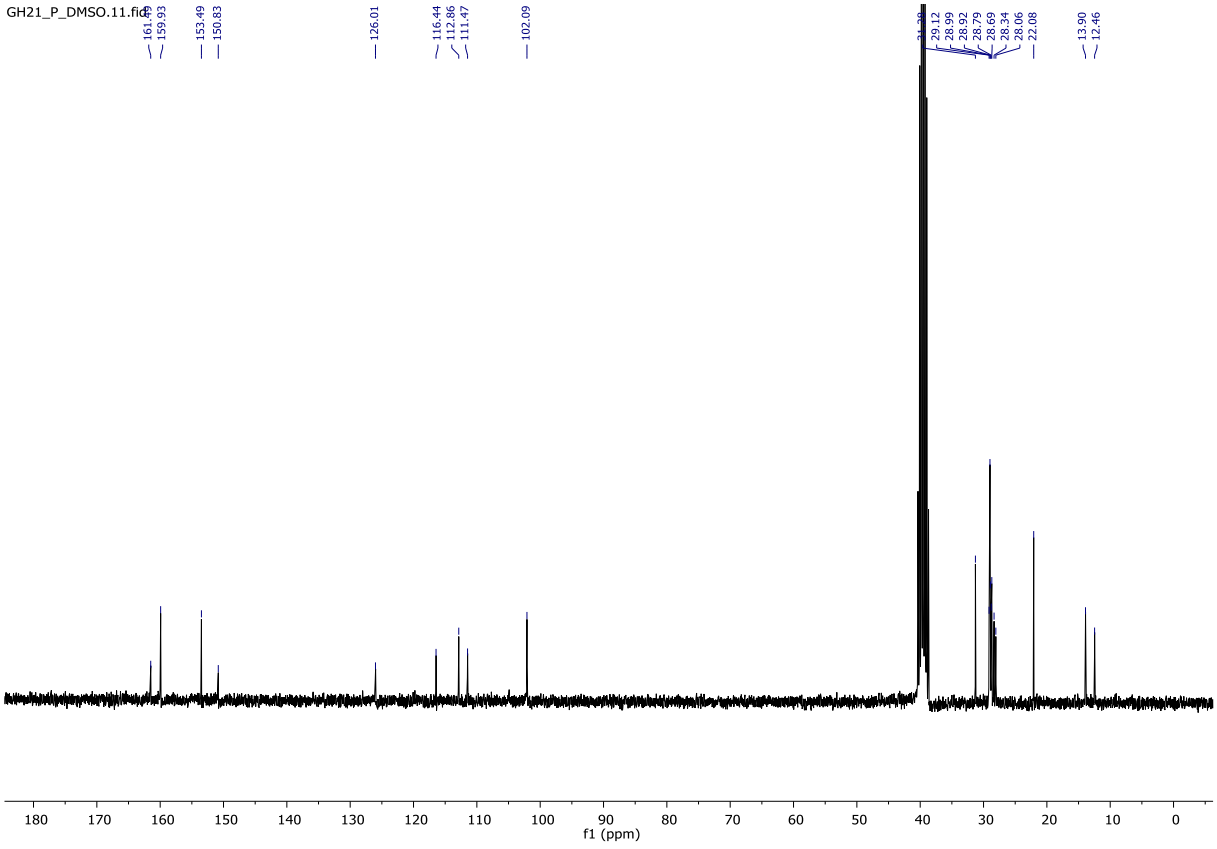
## 4.22 7-hydroxy-3-methyl-4-undecylcoumarin (**10i**)



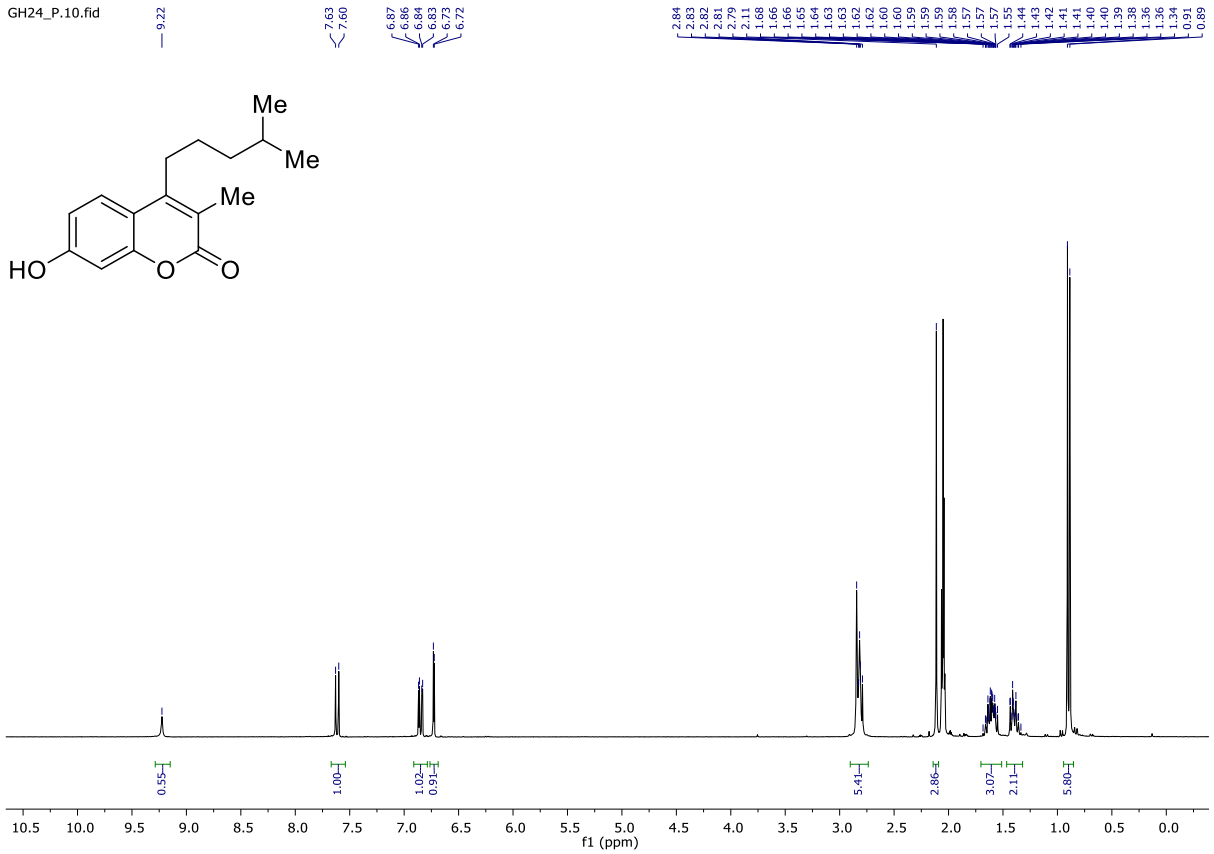



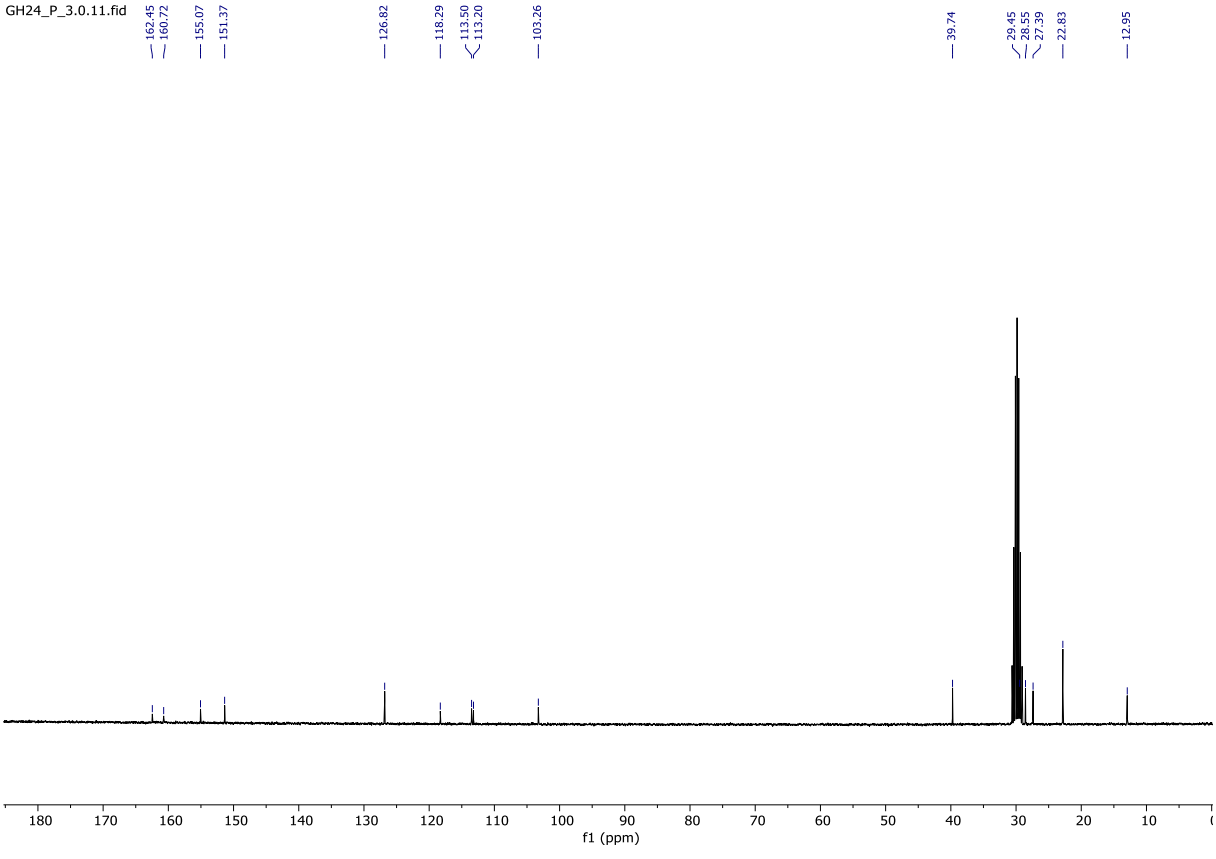
4.23 7-hydroxy-3-methyl-4-tridecylcoumarin (**10j**)



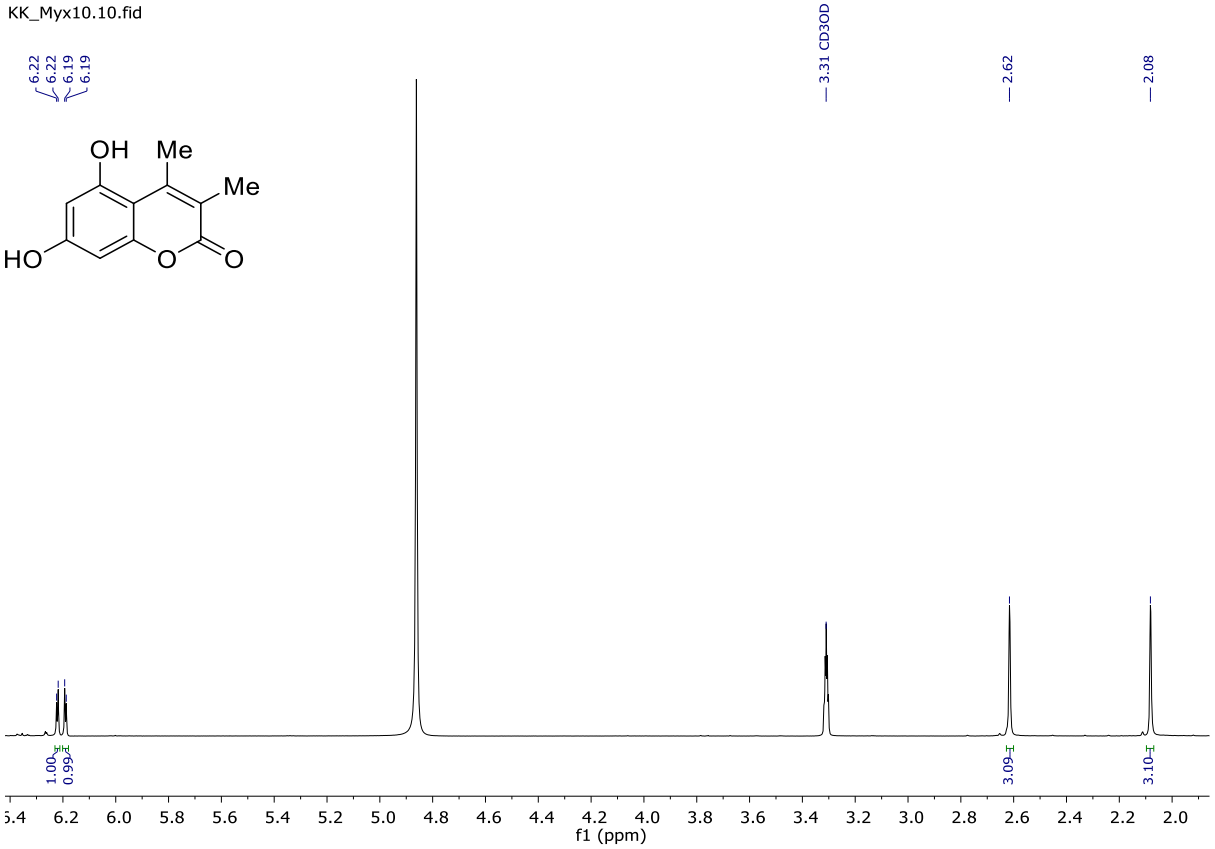



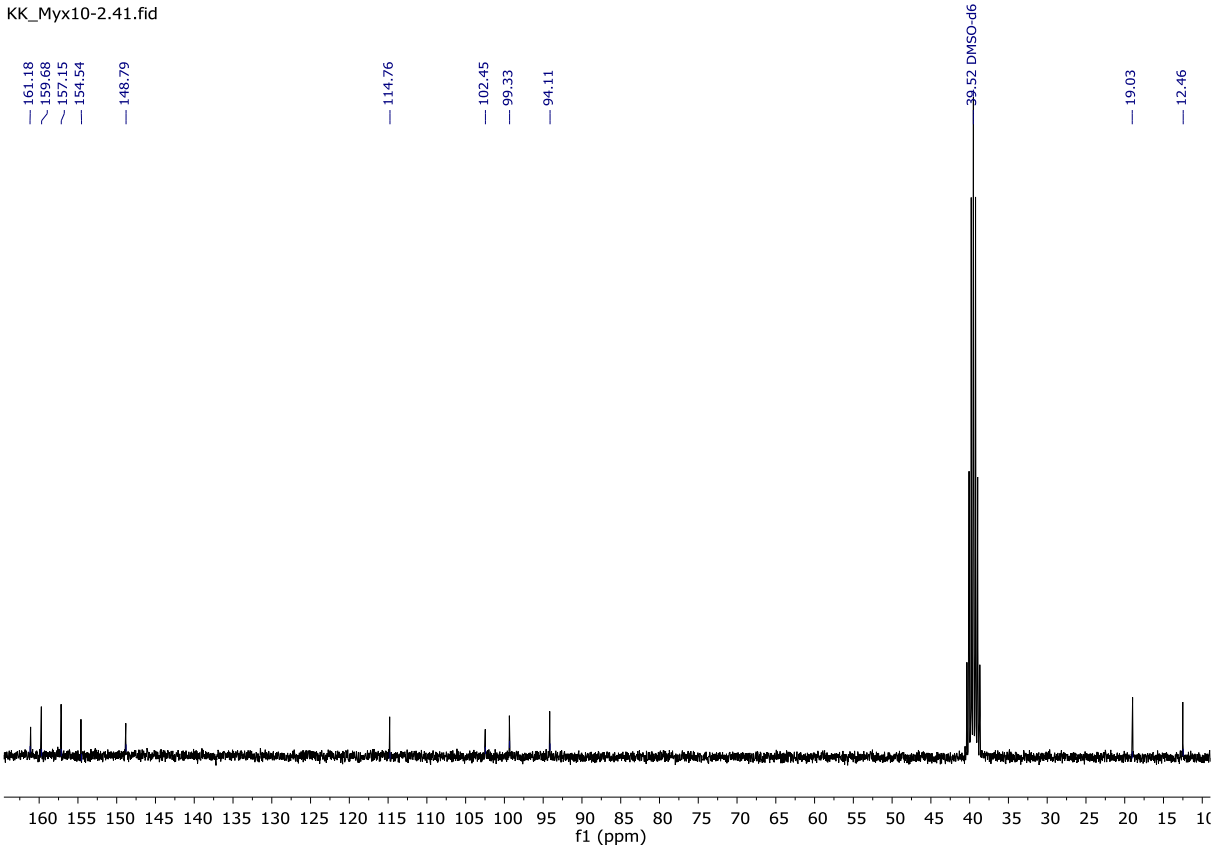
## 4.24 7-hydroxy-3-methyl-4-(4-methylpentyl)coumarin (**10k**)



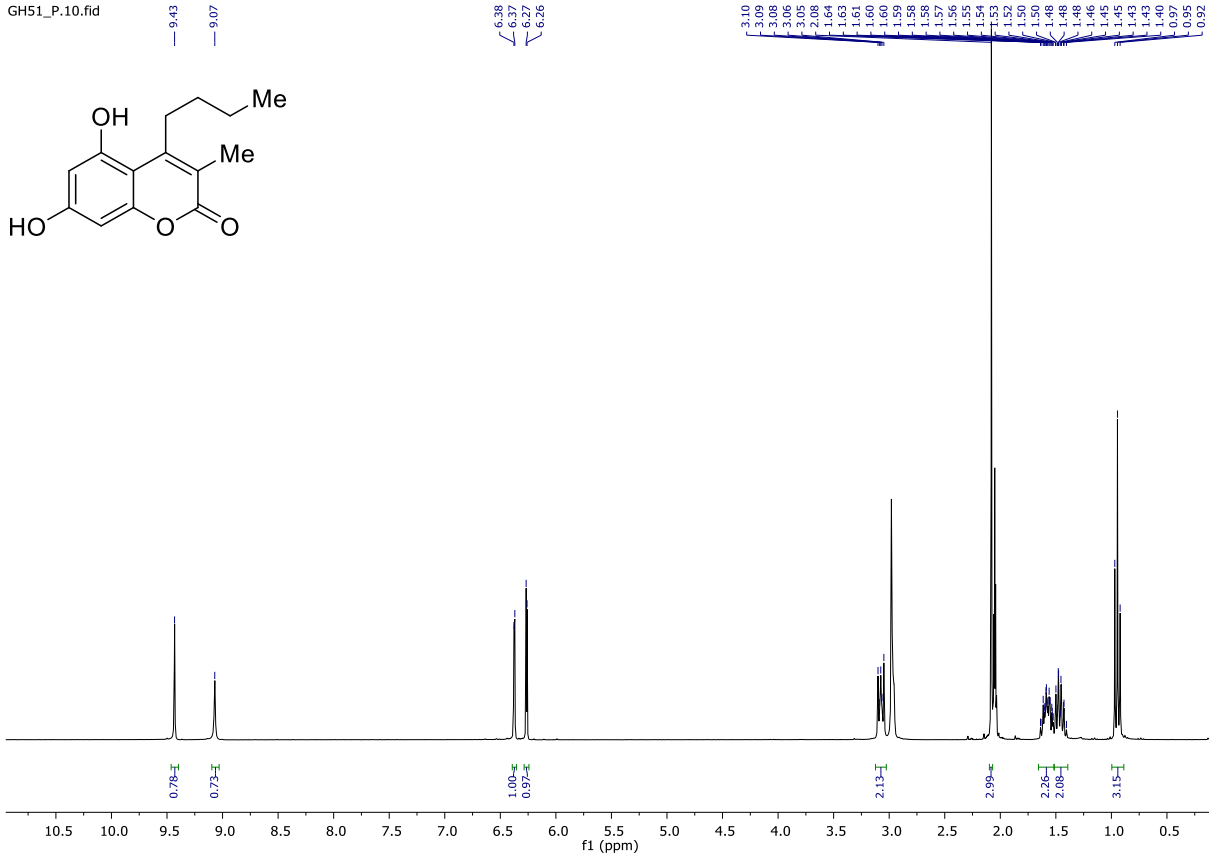



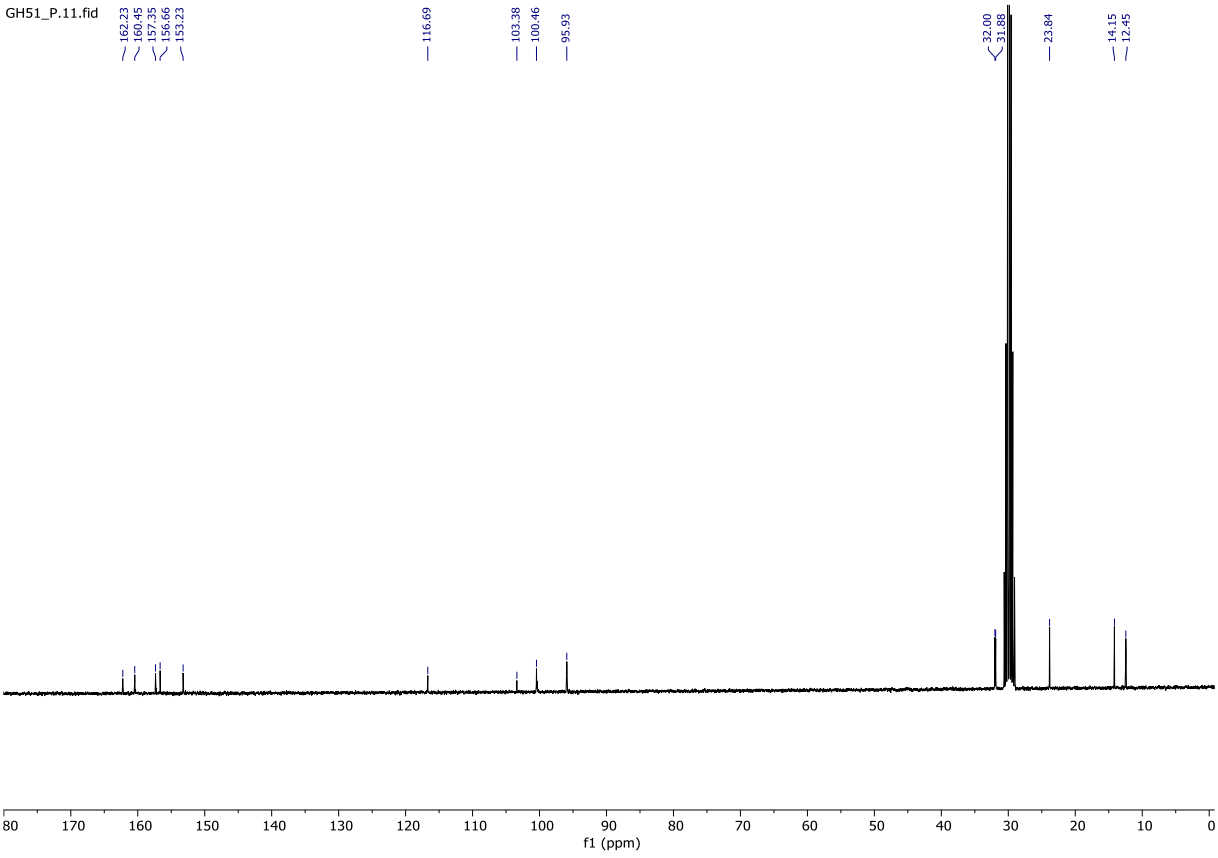
4.25 5,7-dihydroxy-3,4-dimethylcoumarin (**11a**)



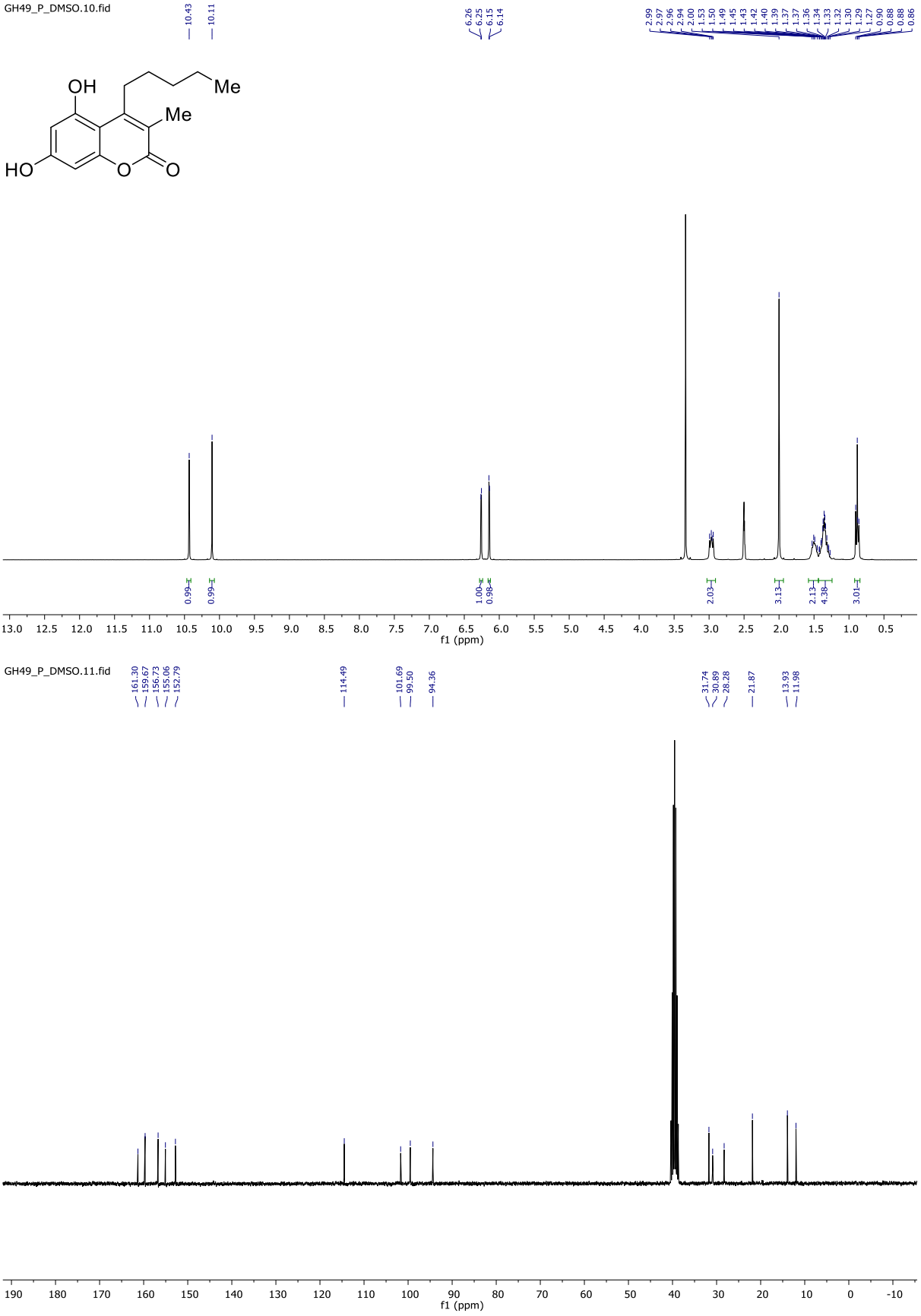



## 4.26 4-butyl-5,7-dihydroxy-3-methylcoumarin (**11b**)

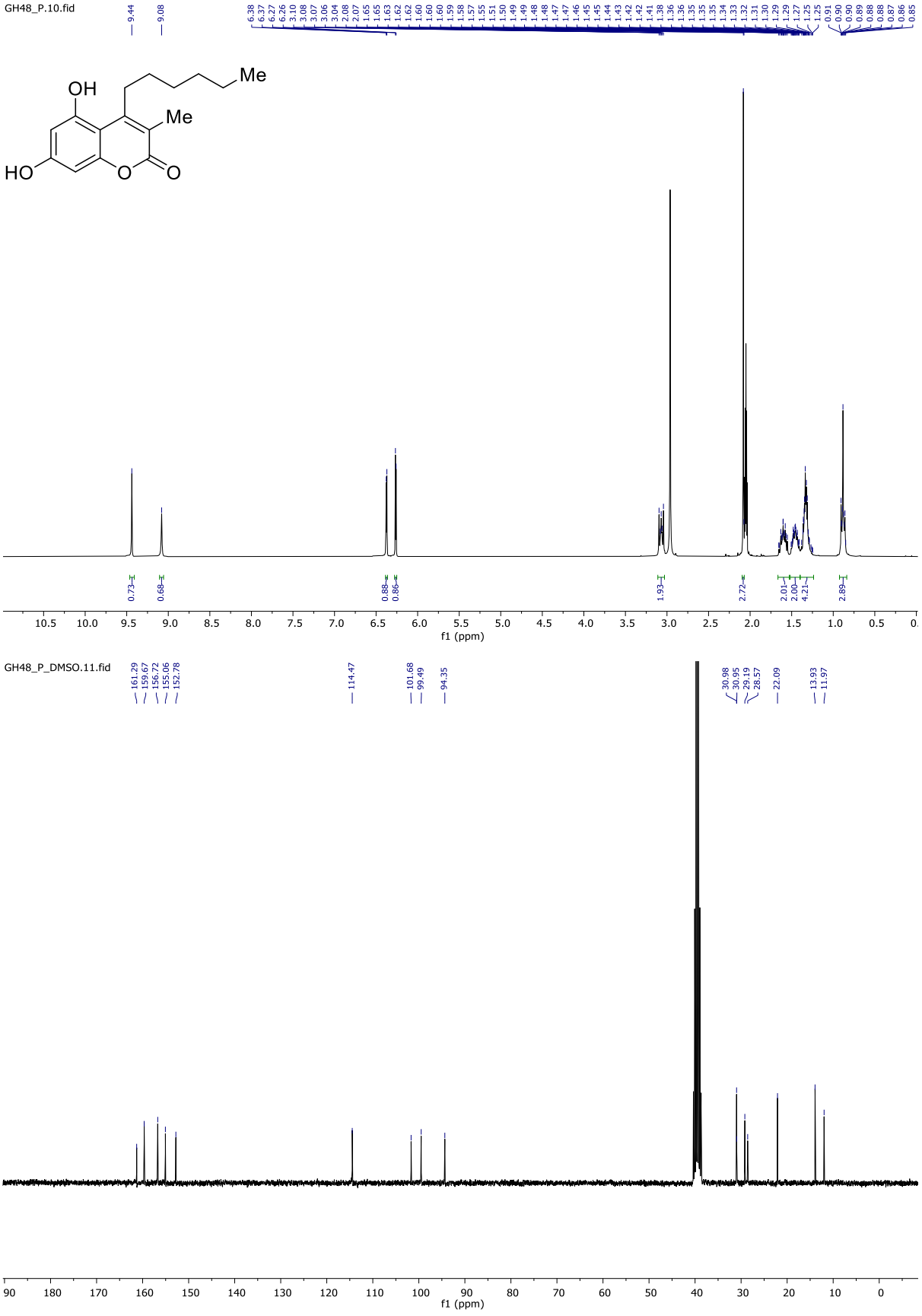


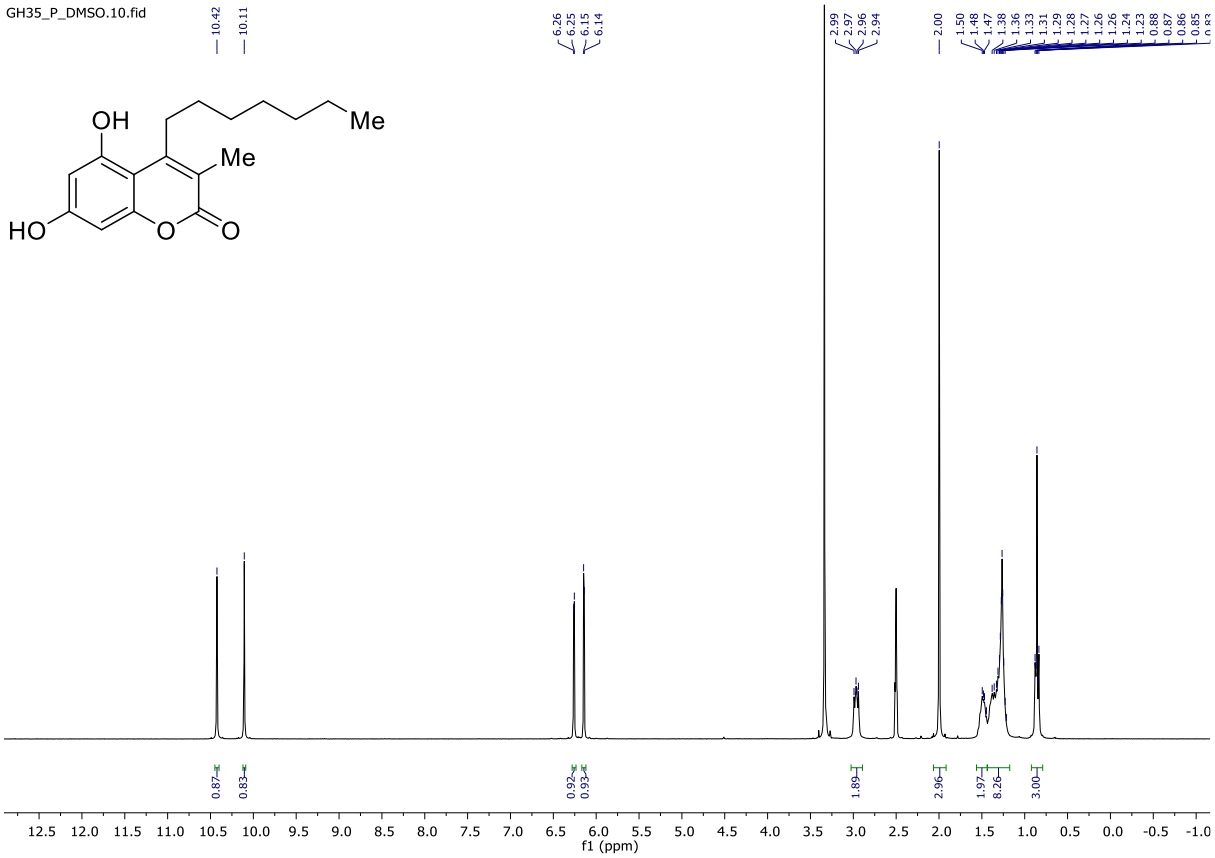
## 4.27 5,7-dihydroxy-3-methyl-4-pentylcoumarin (**11c**)

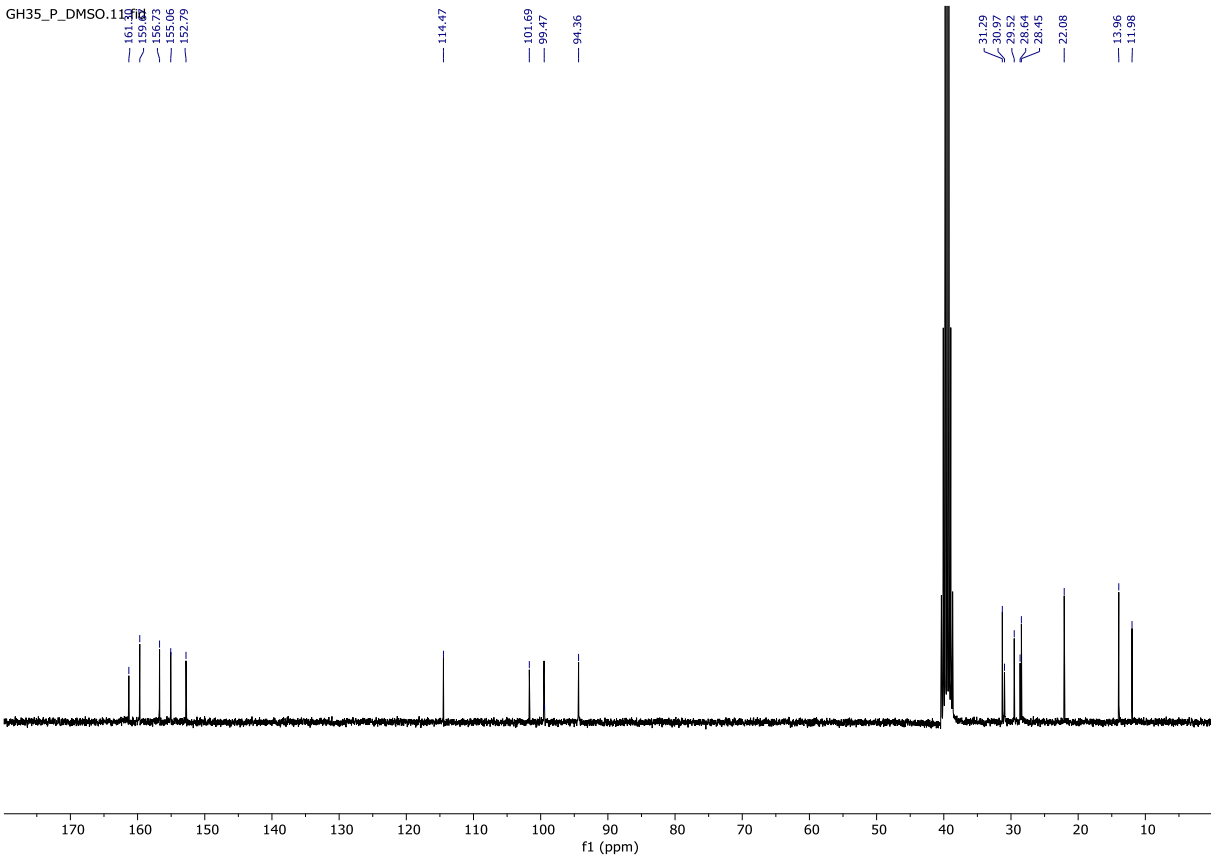


## 4.28 4-hexyl-5,7-dihydroxy-3-methylcoumarin (**11d**)

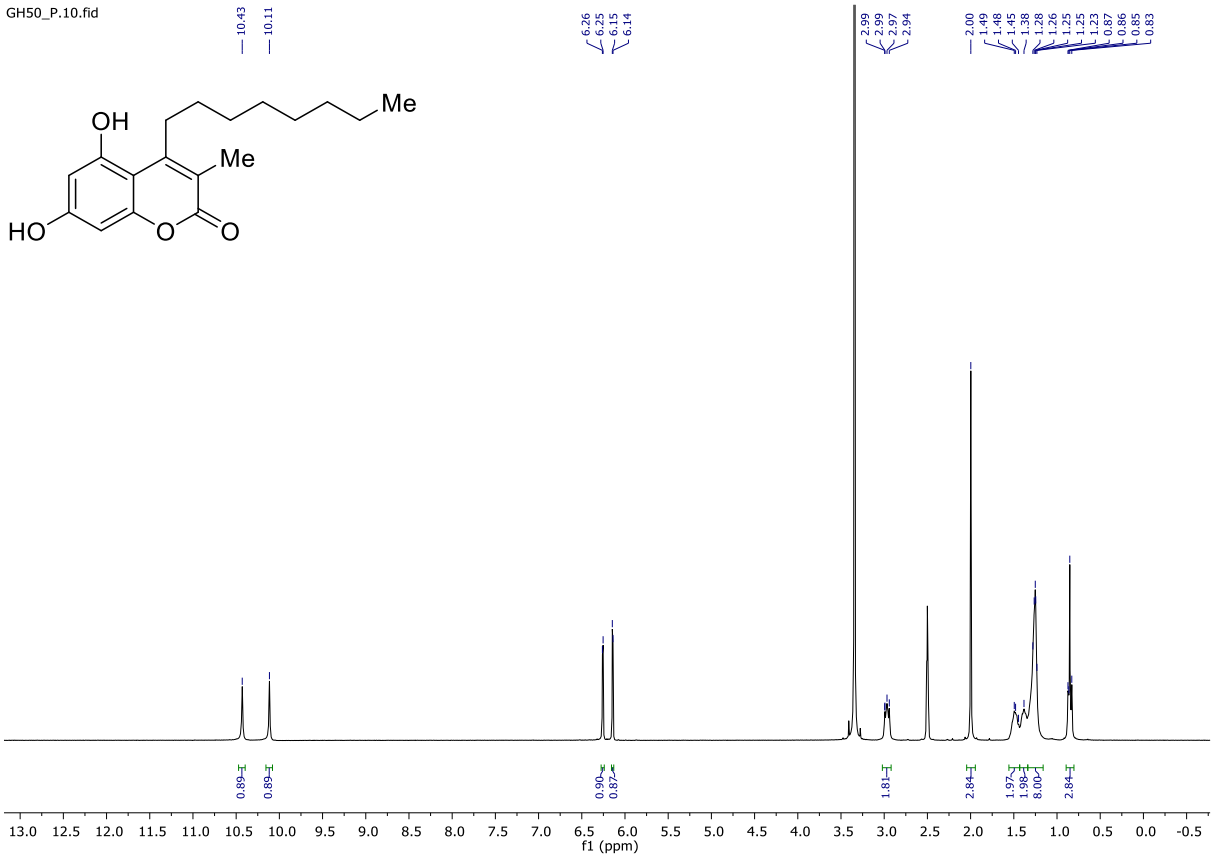


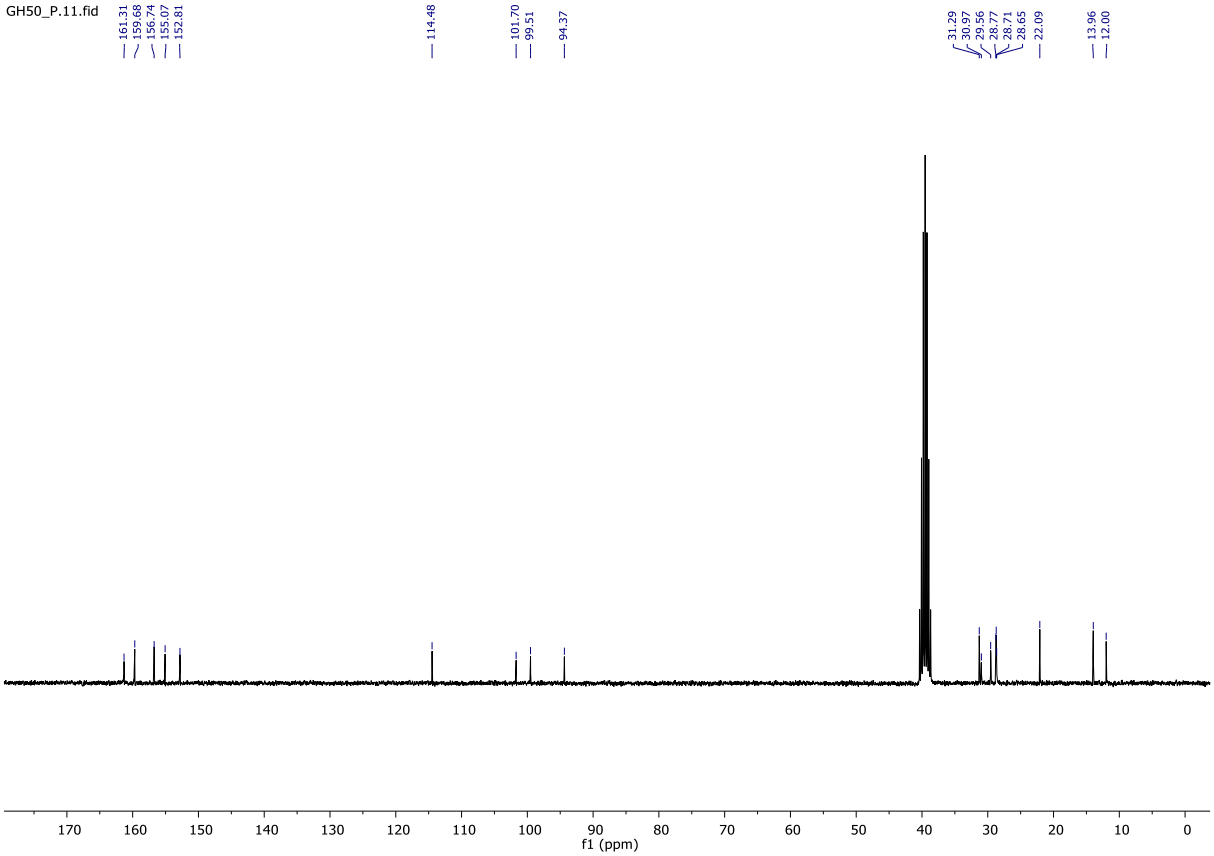
## 4.29 4-heptyl-5,7-dihydroxy-3-methylcoumarin (**11e**)



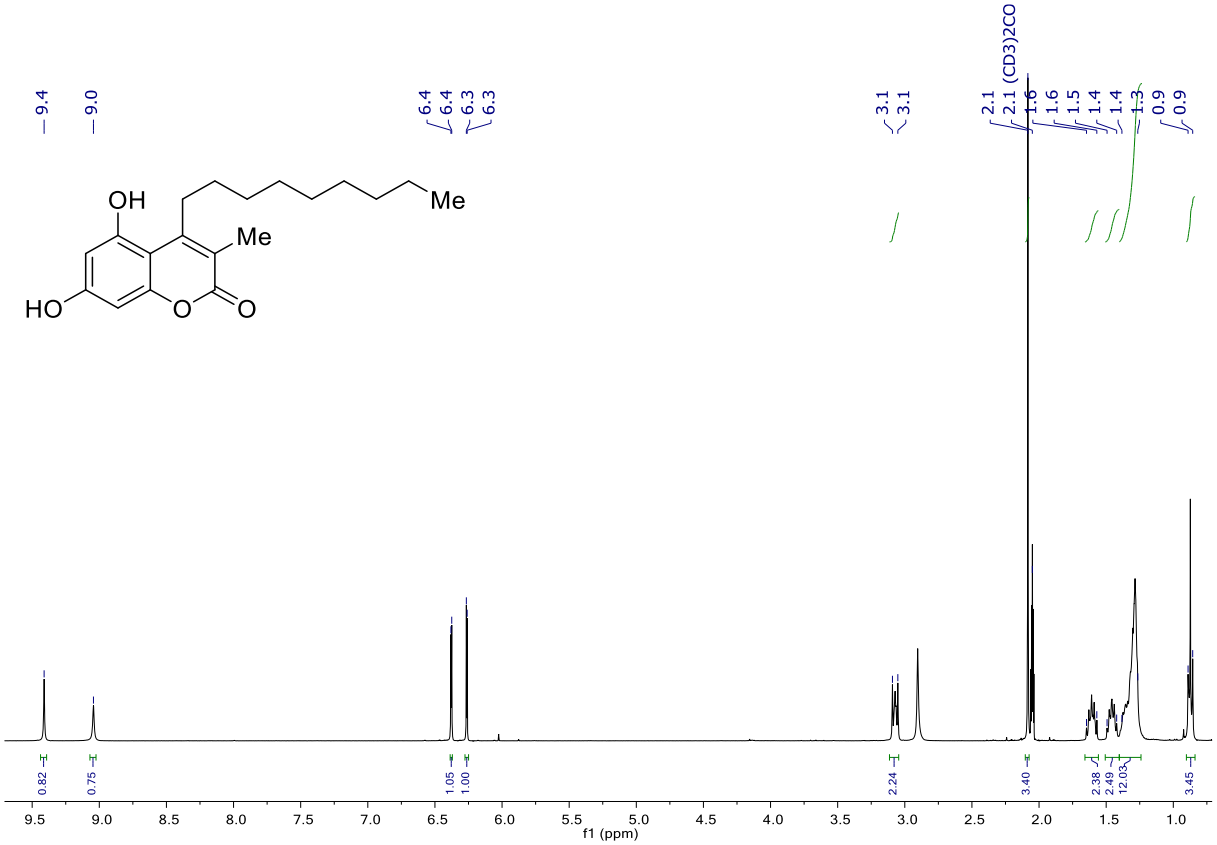



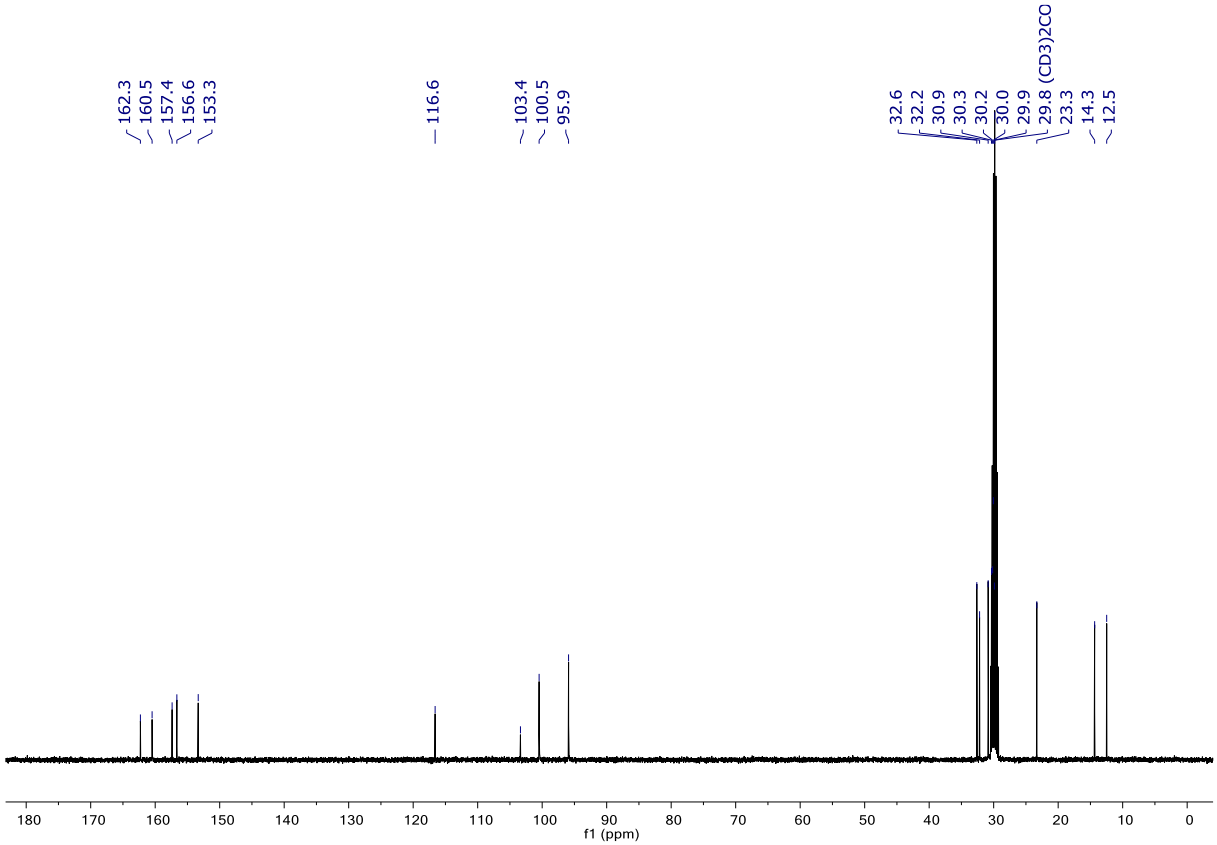
4.30 5,7-dihydroxy-3-methyl-4-octylcoumarin (**11f**)



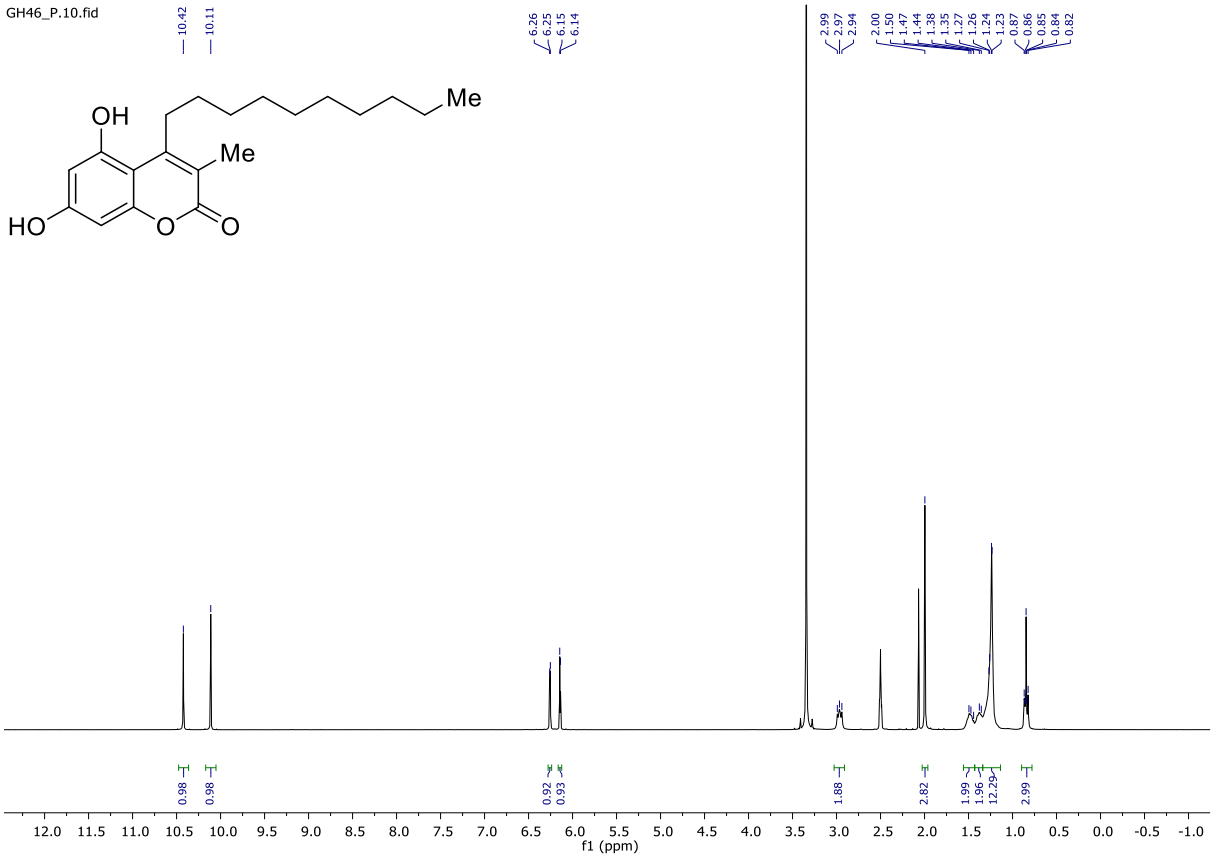



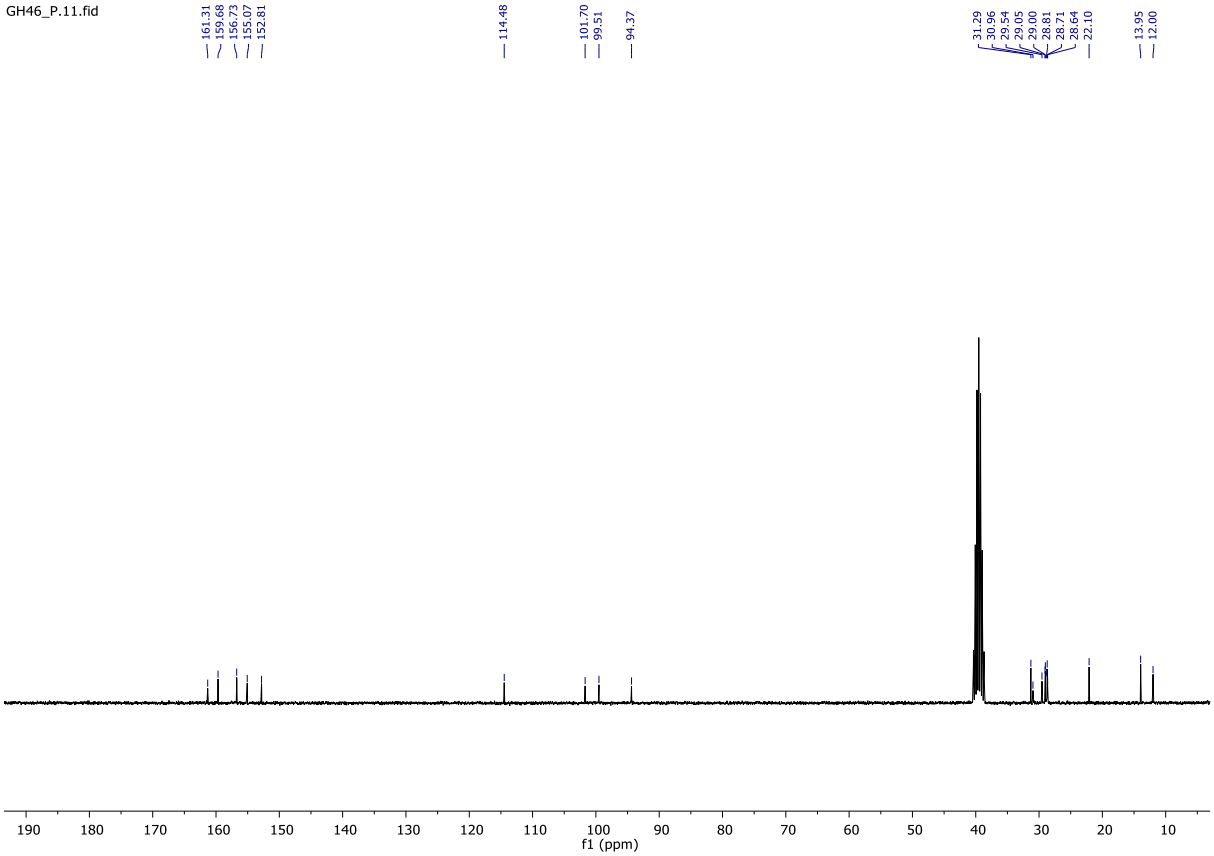
4.31 5,7-dihydroxy-3-methyl-4-nonylcoumarin (**11g**)



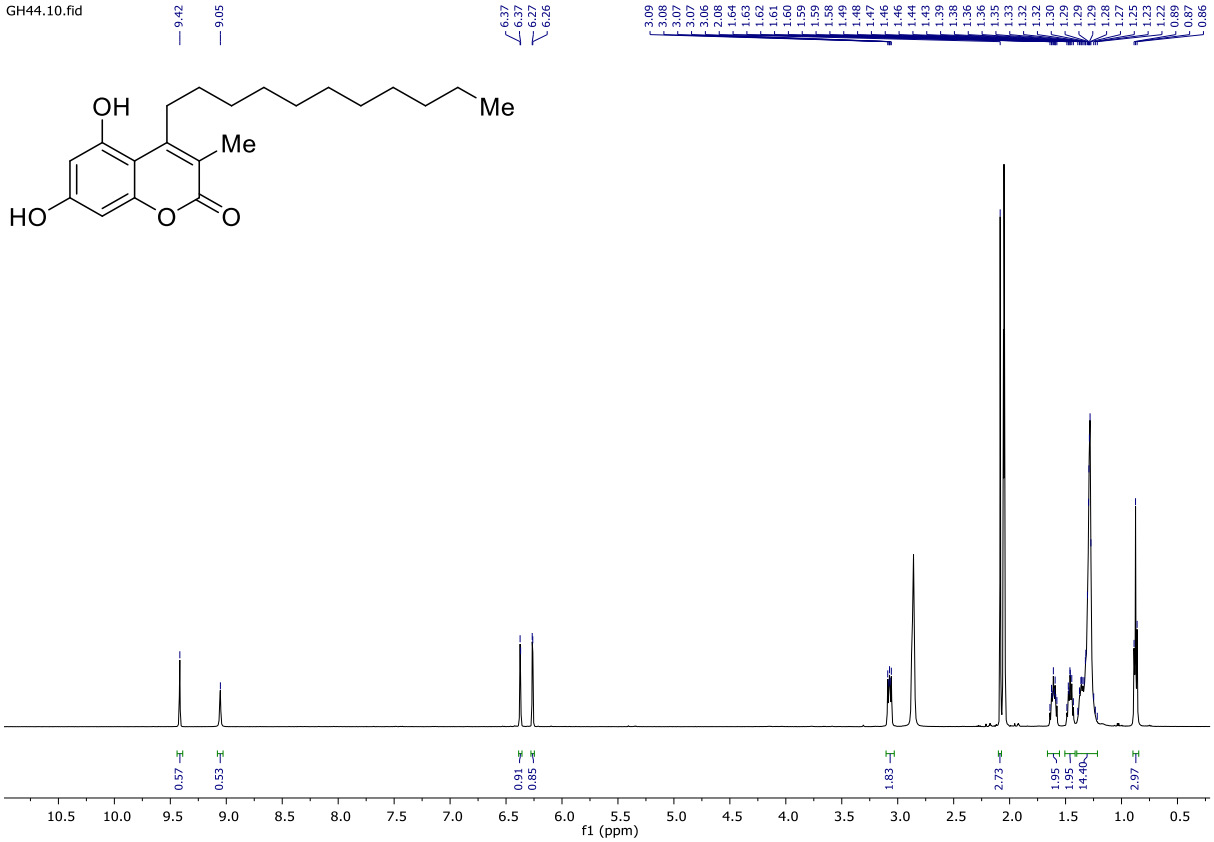



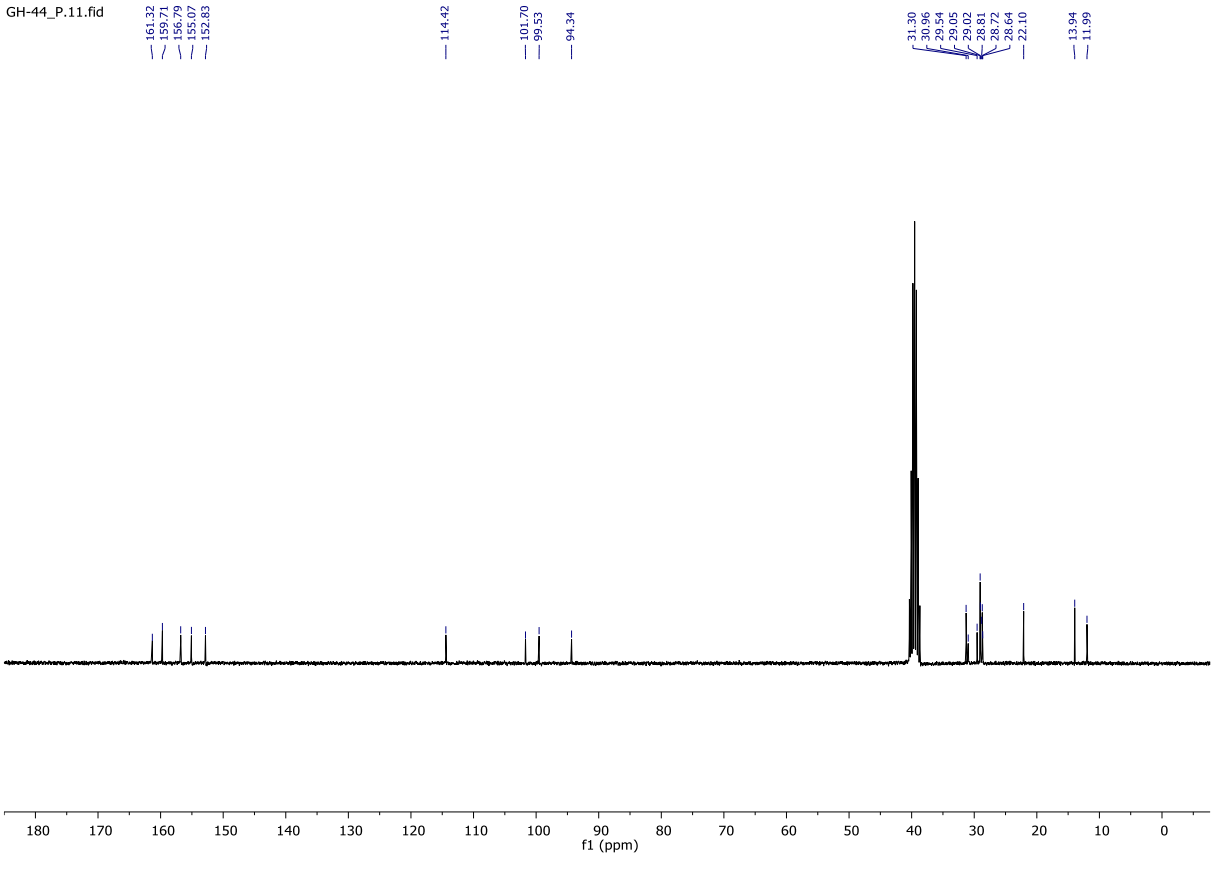
4.32 4-decyl-5,7-dihydroxy-3-methylcoumarin (**11h**)



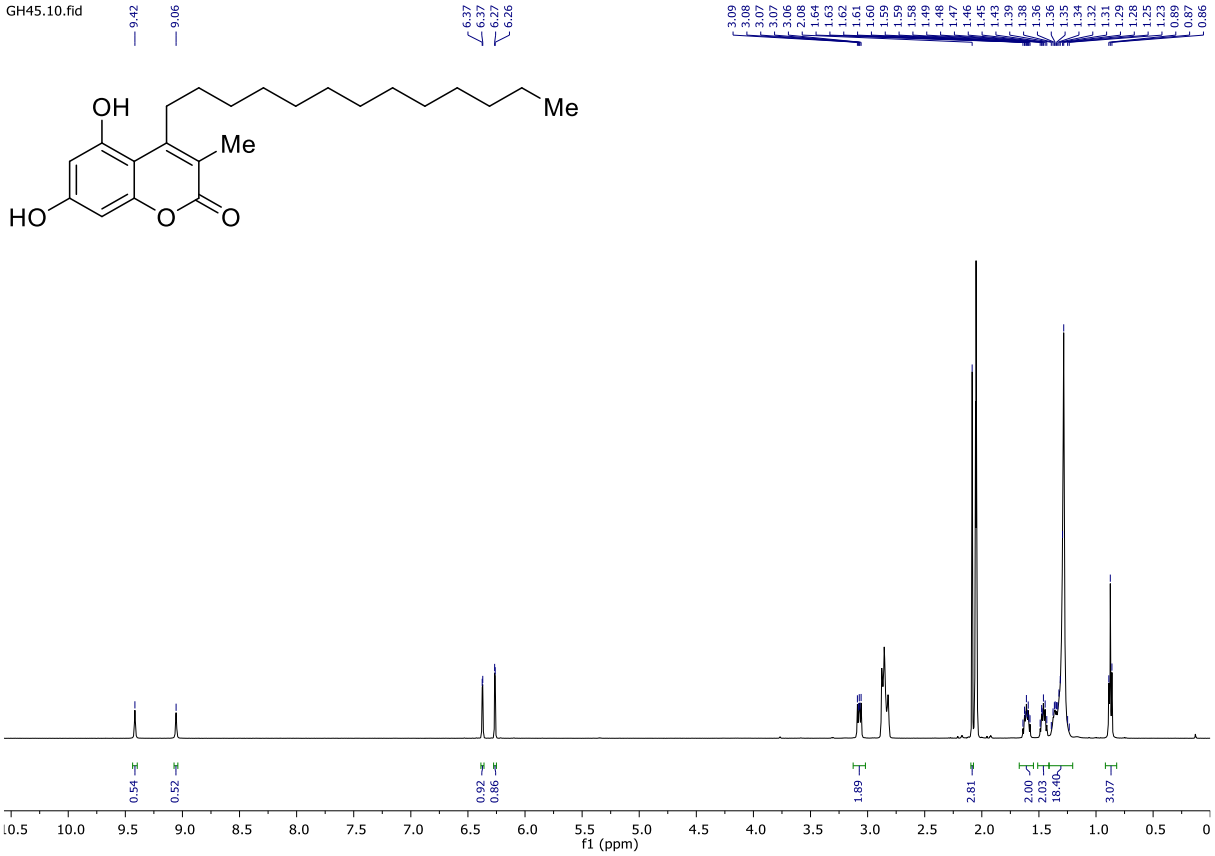



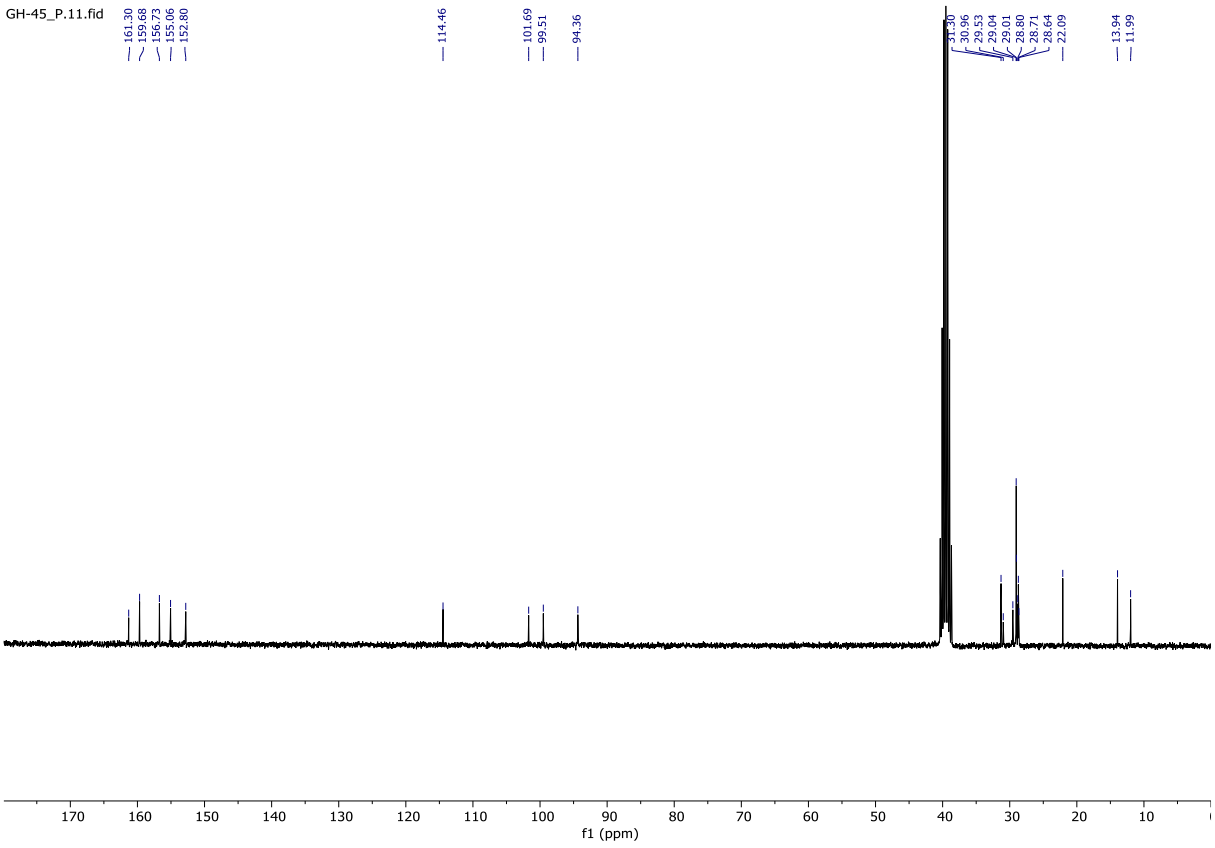
## 4.33 5,7-dihydroxy-3-methyl-4-undecylcoumarin (**11i**)



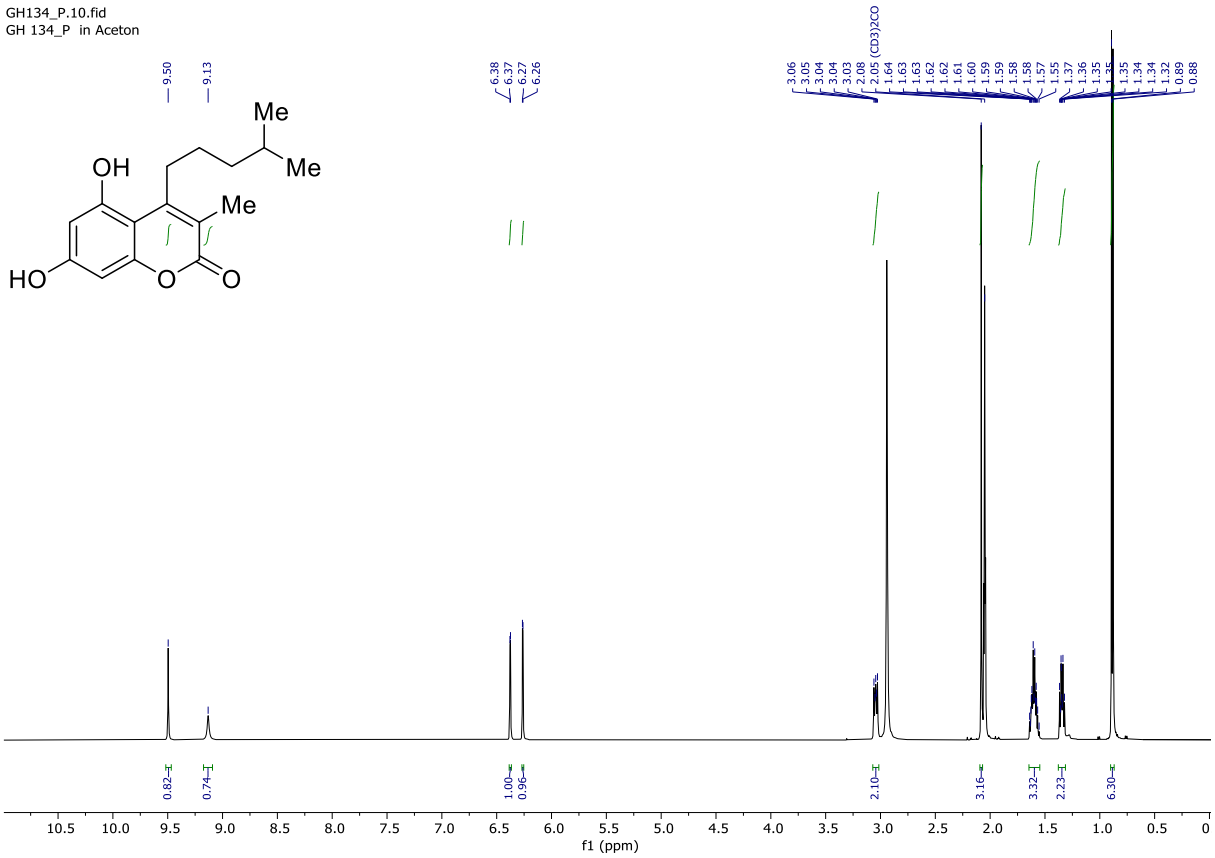



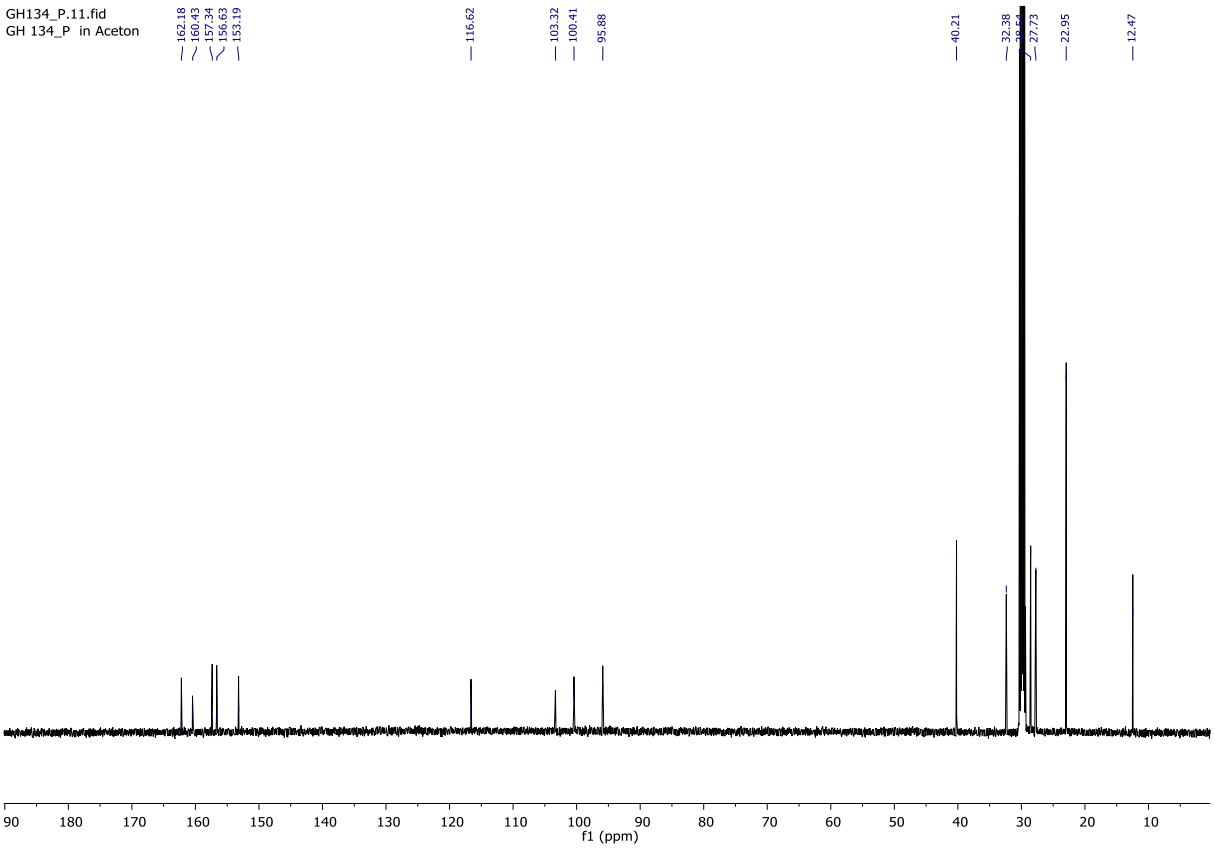
4.34 5,7-dihydroxy-3-methyl-4-tridecylcoumarin (**11j**)



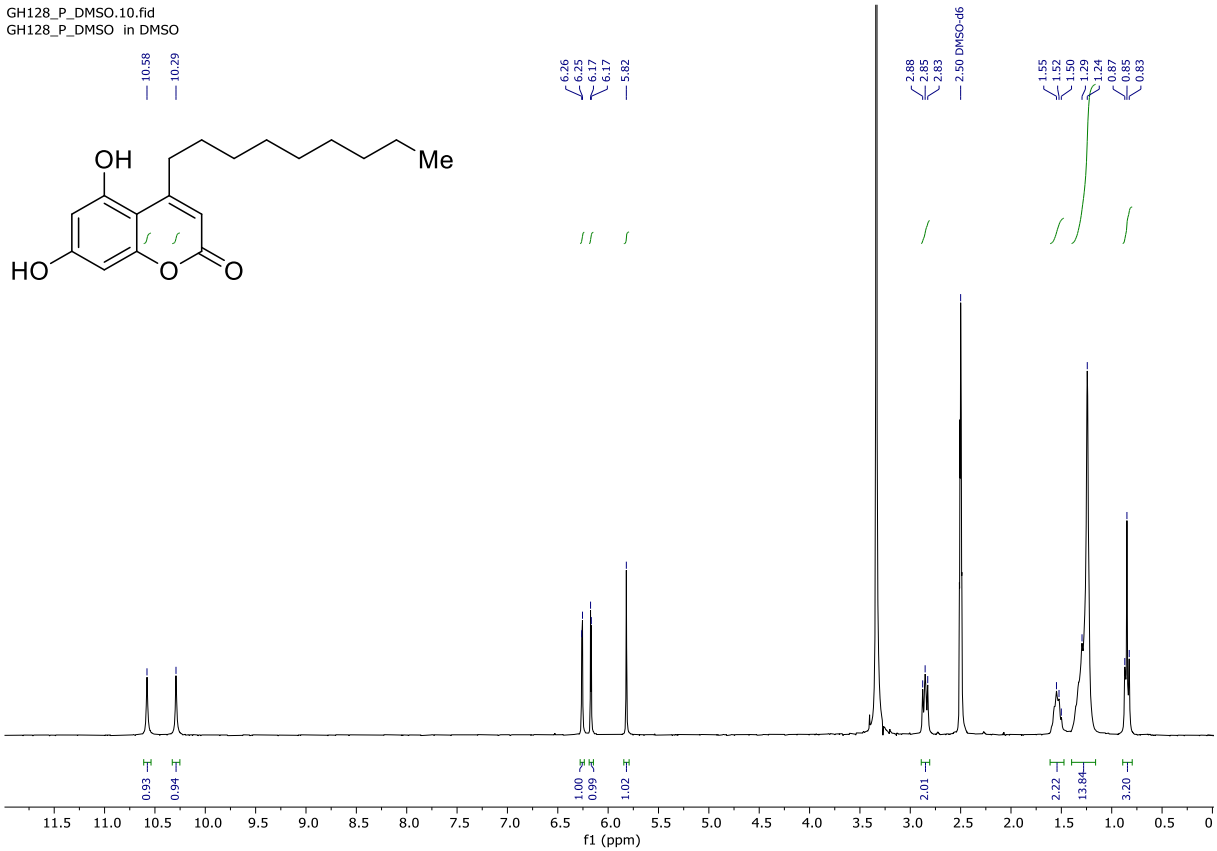



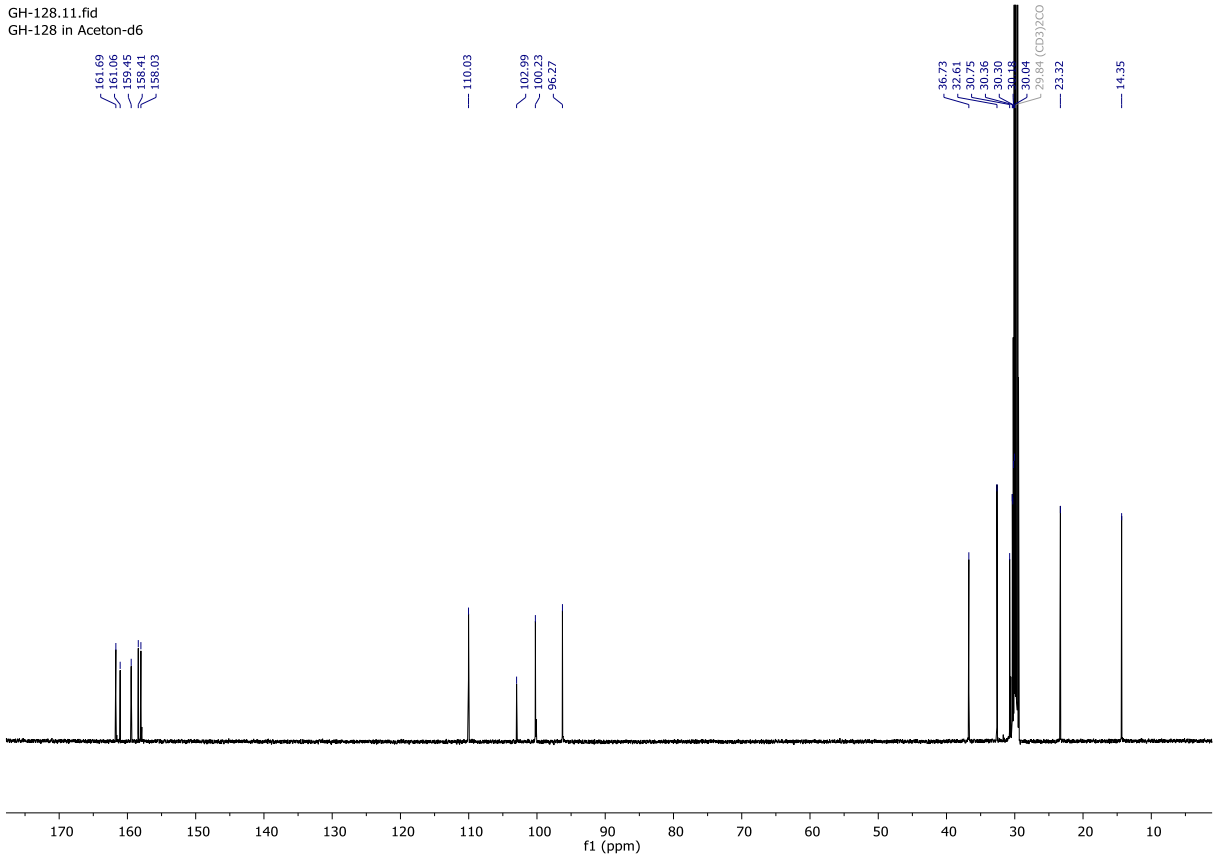
## 4.35 5,7-dihydroxy-3-methyl-4-(4-methylpentyl)coumarin (**11k**)



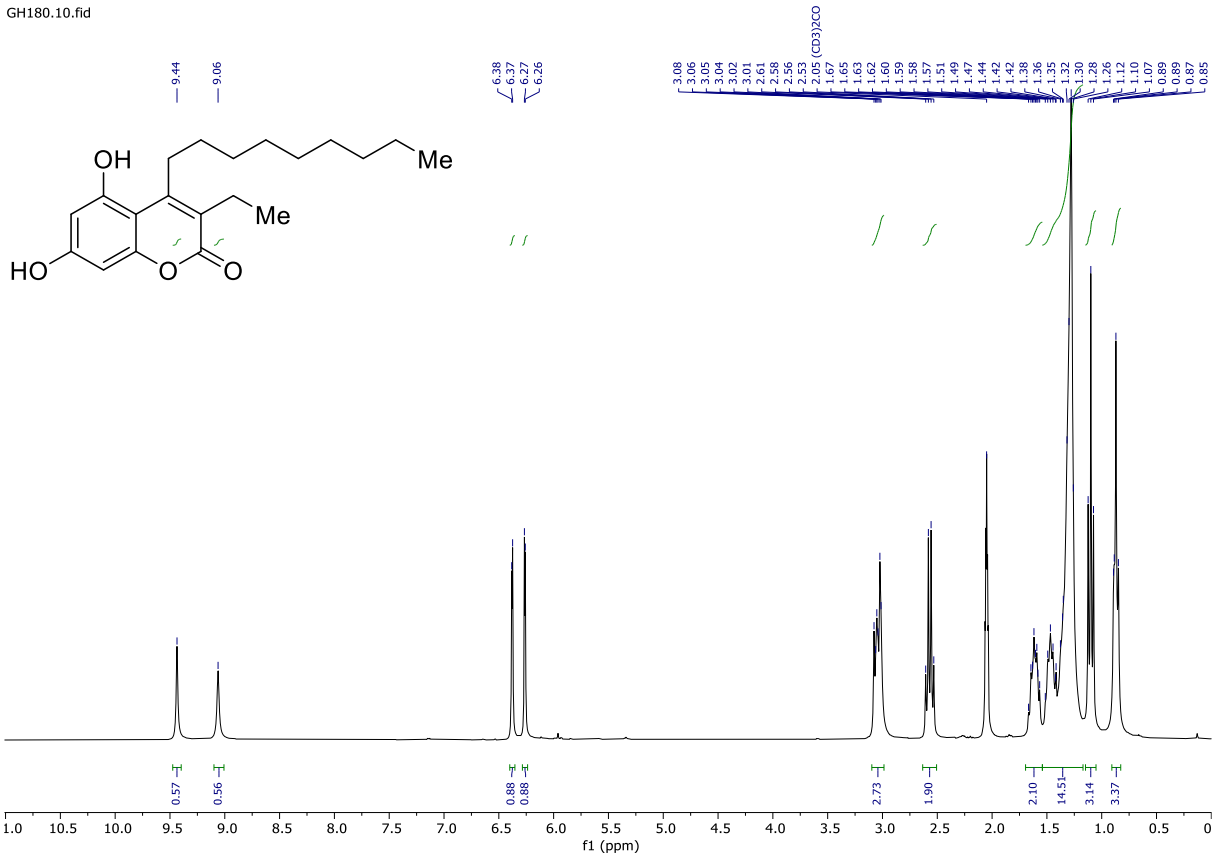



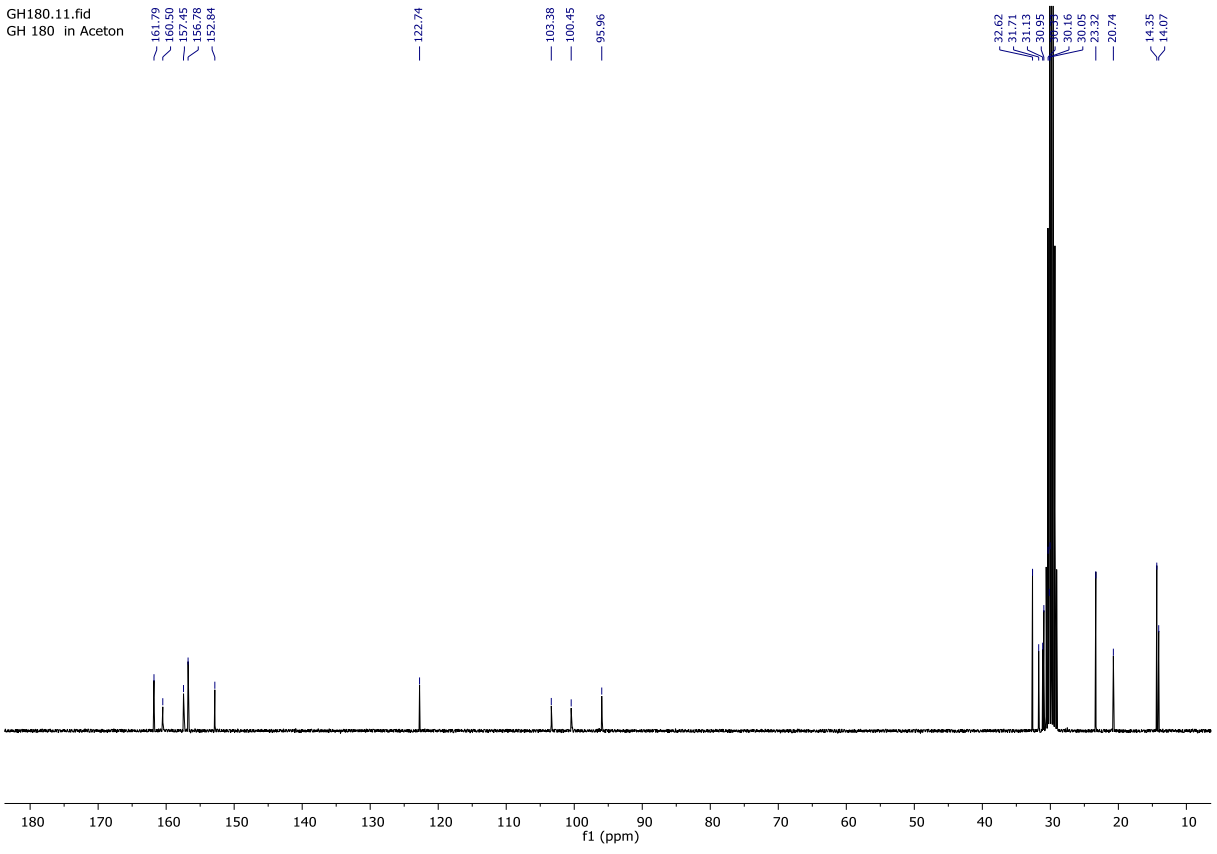
## 4.36 5,7-dihydroxy-4-nonylcoumarin (**12**)



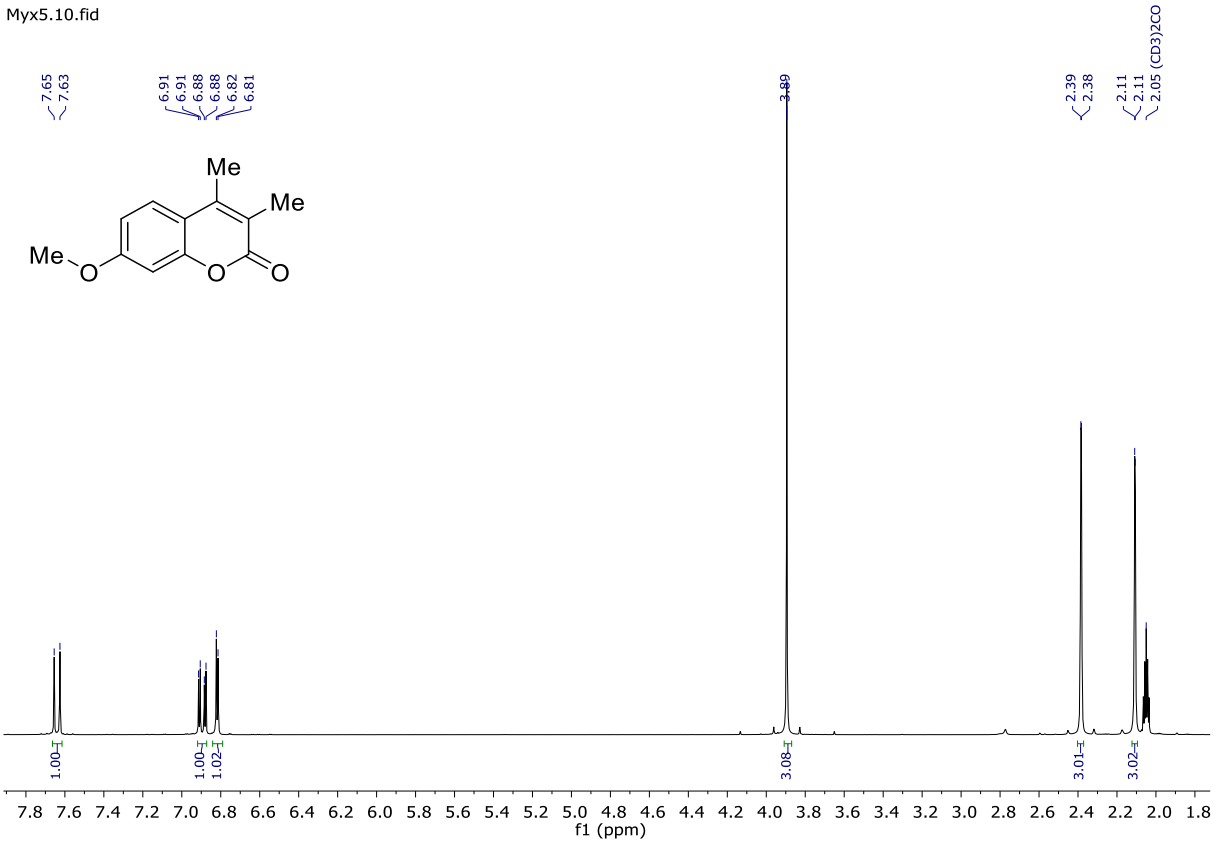
## 4.37 3-ethyl-5,7-dihydroxy-4-nonylcoumarin (**13**)



## 4.38 7-methoxy-3,4-dimethylcoumarin (**14**)

Myx5.10.fid

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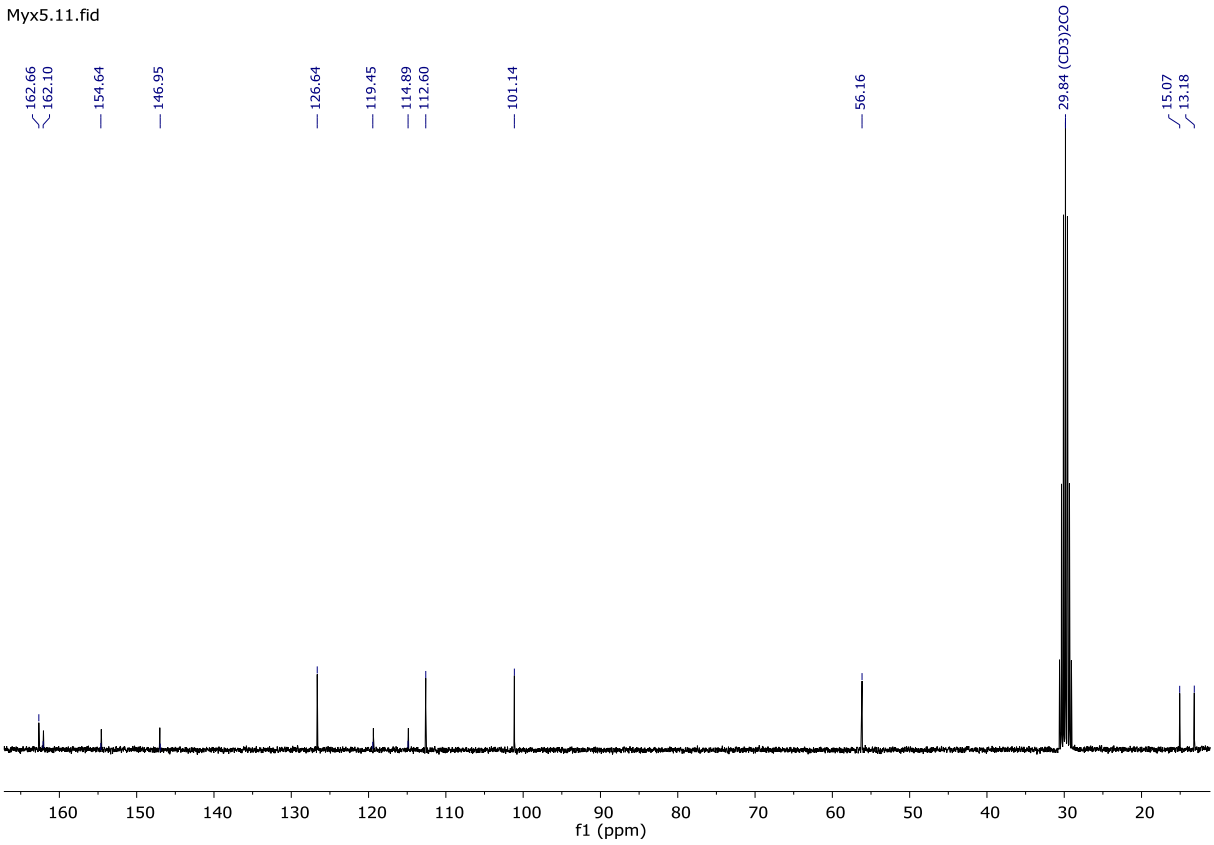
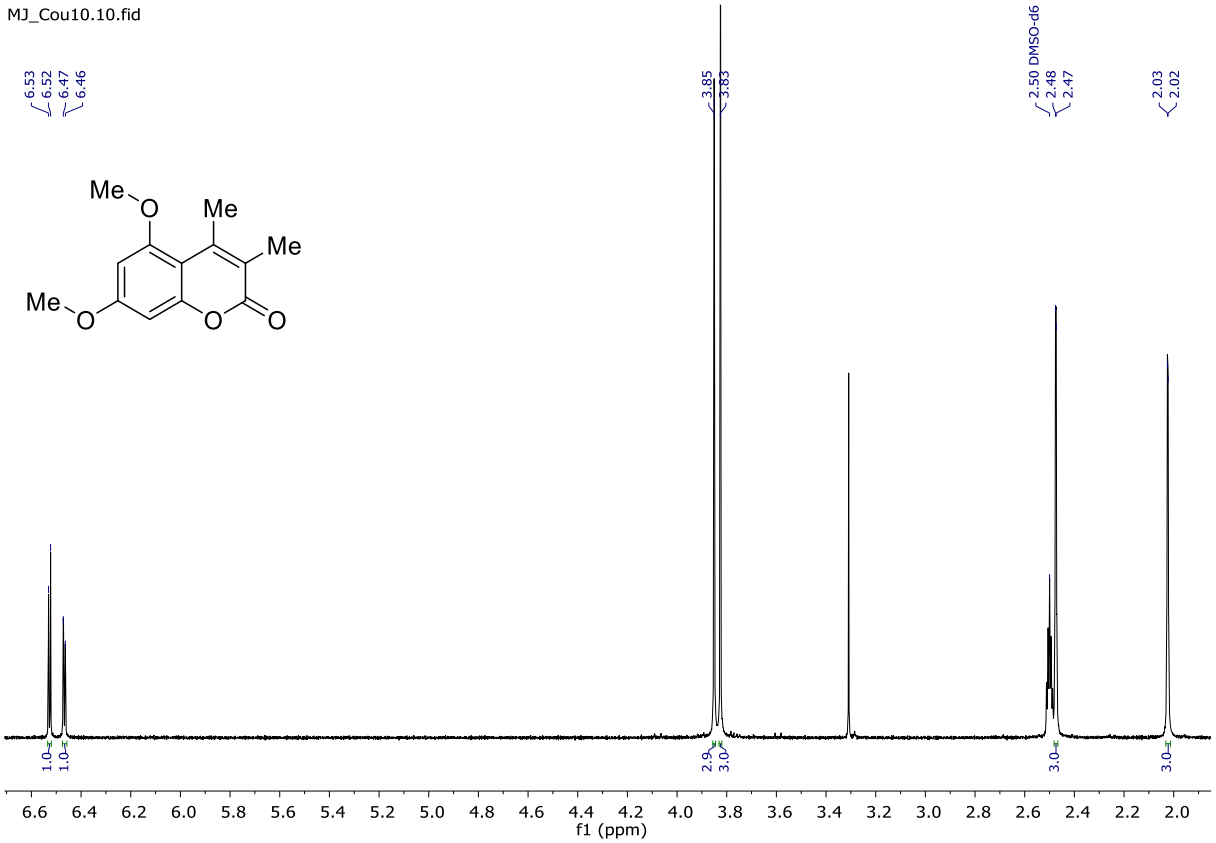
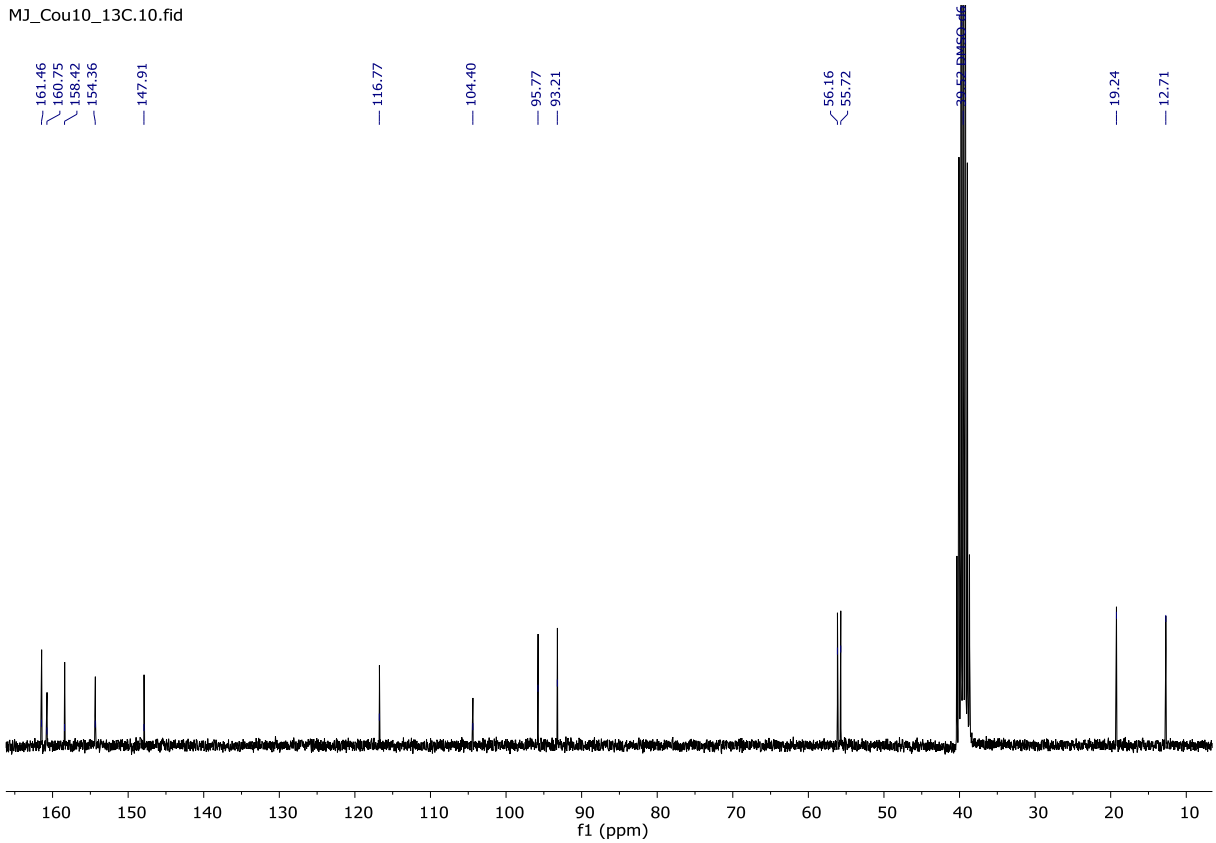
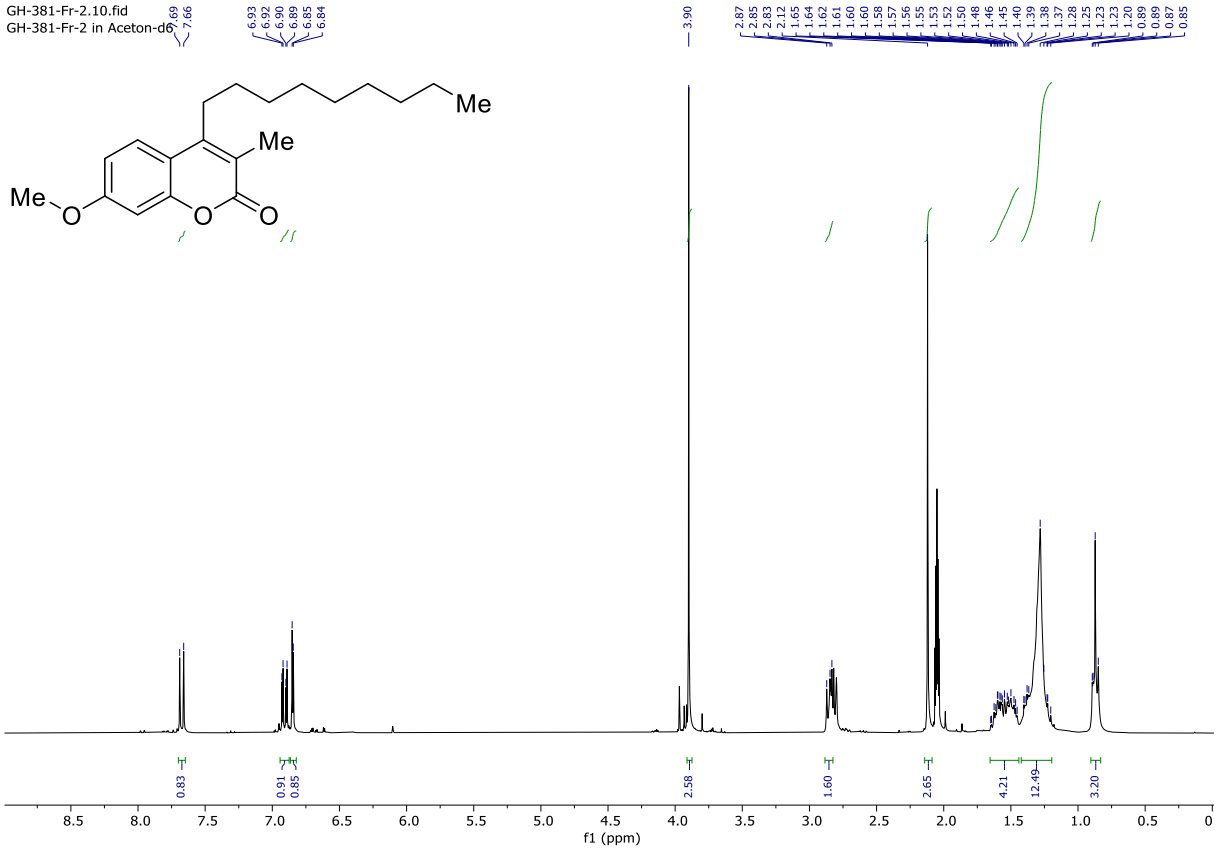


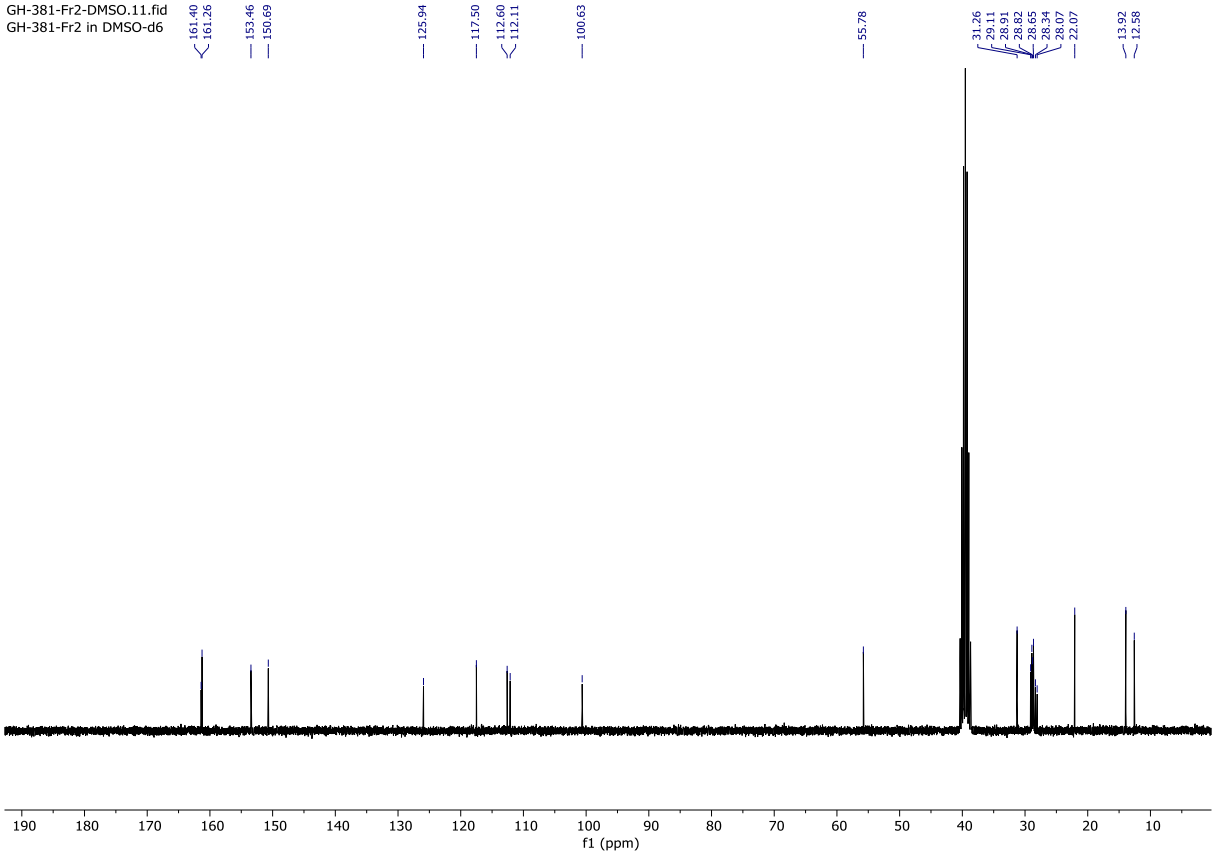
4.39 5,7-dimethoxy-3,4-dimethylcoumarin (**15**)



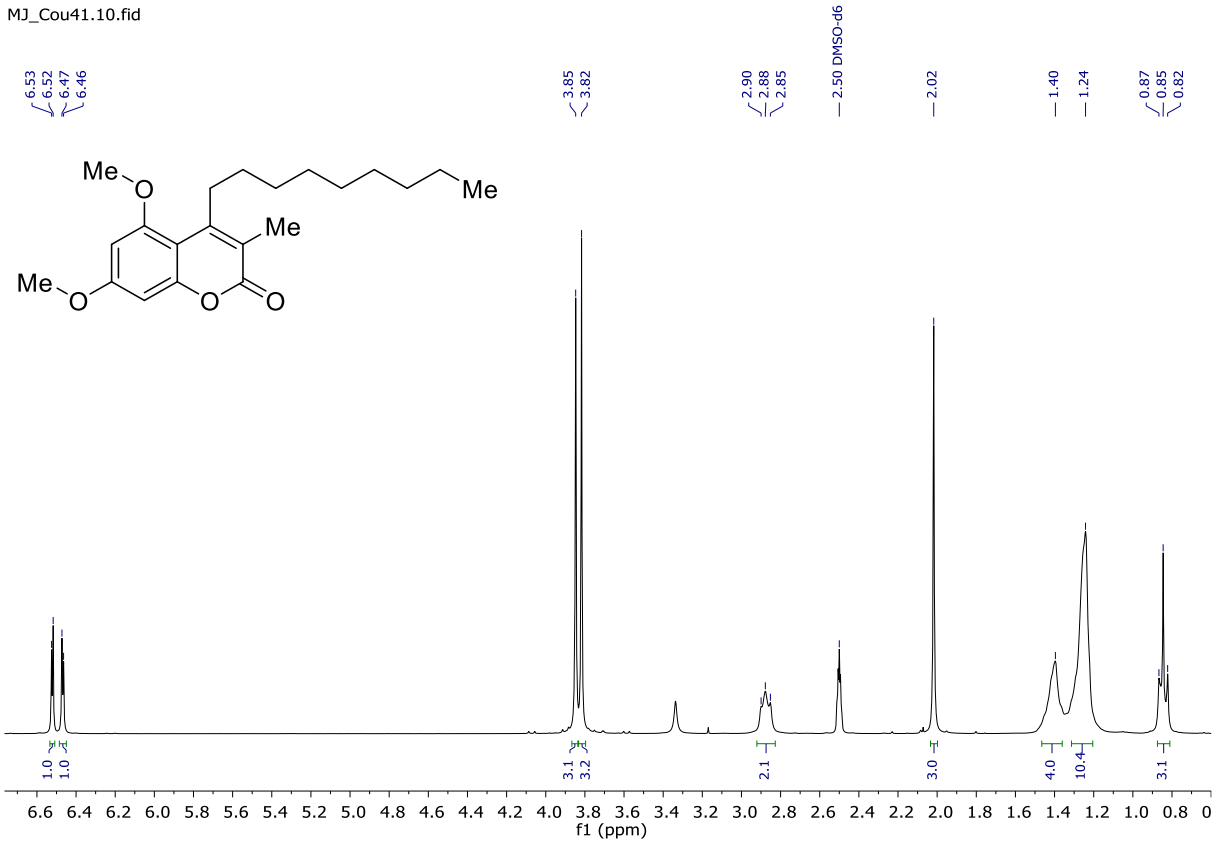
## 4.40 7-methoxy-3-methyl-4-nonylcoumarin (**16**)



## 4.41 5,7-dimethoxy-3-methyl-4-nonylcoumarin (**17**)

MJ_Cou41.10.fid

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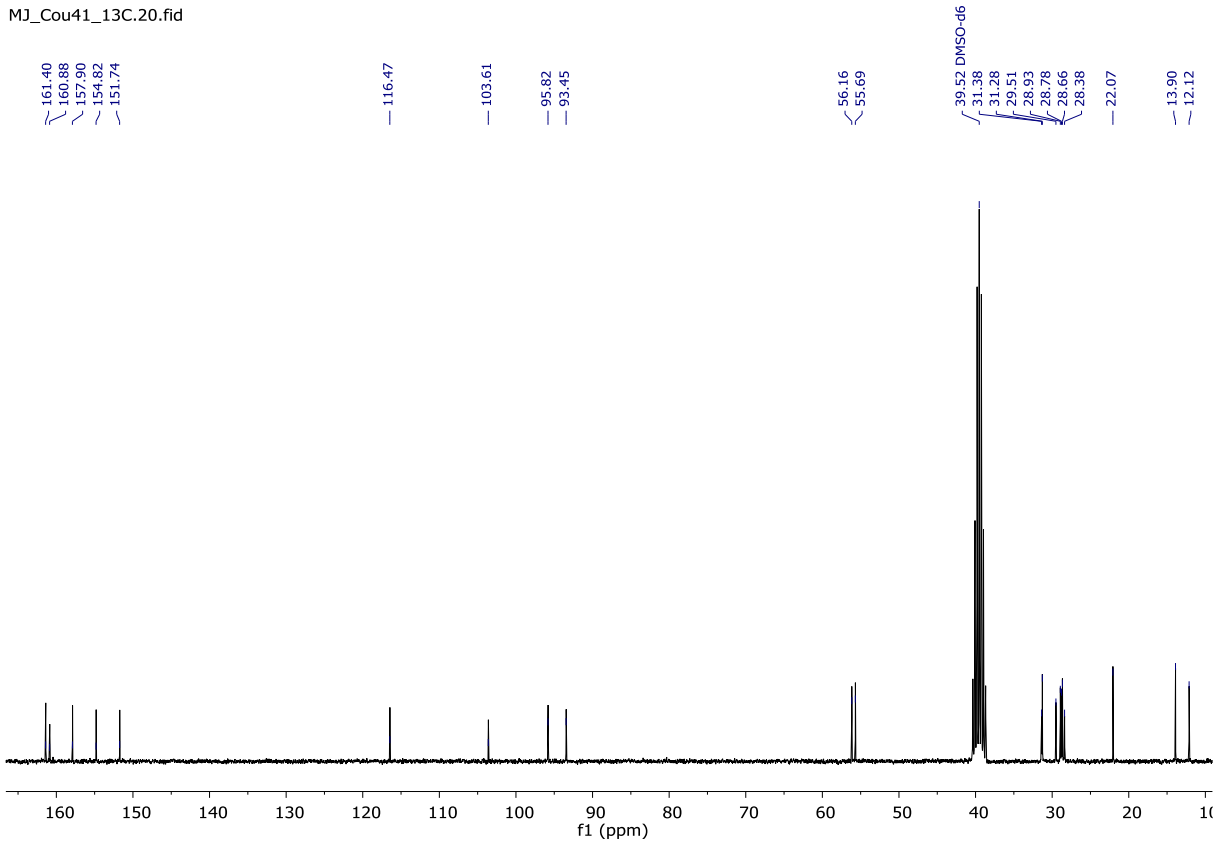
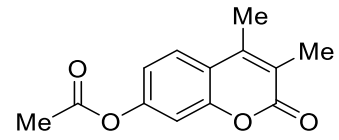


## 4.42 7-*O*-acyl-3,4-dimethylcoumarin (**18**)

KK_Myx6.20.fid







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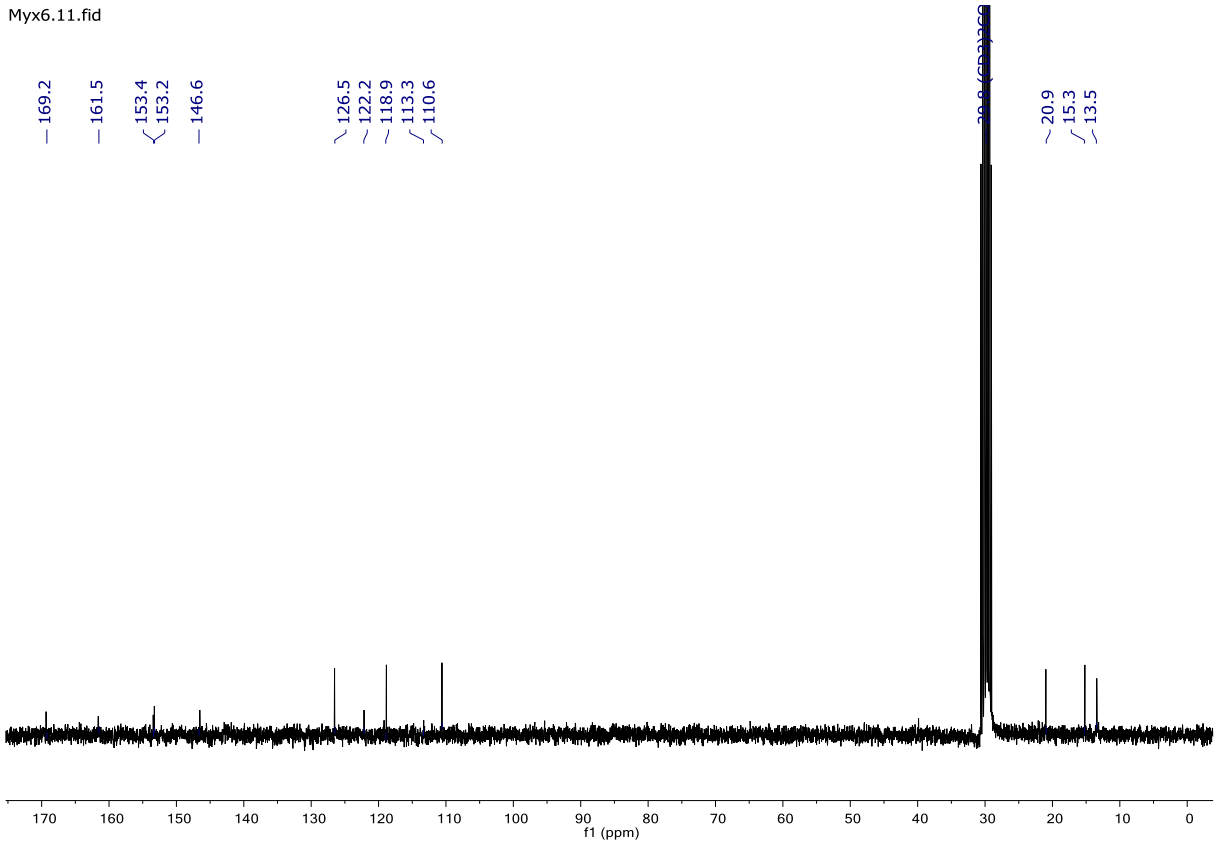
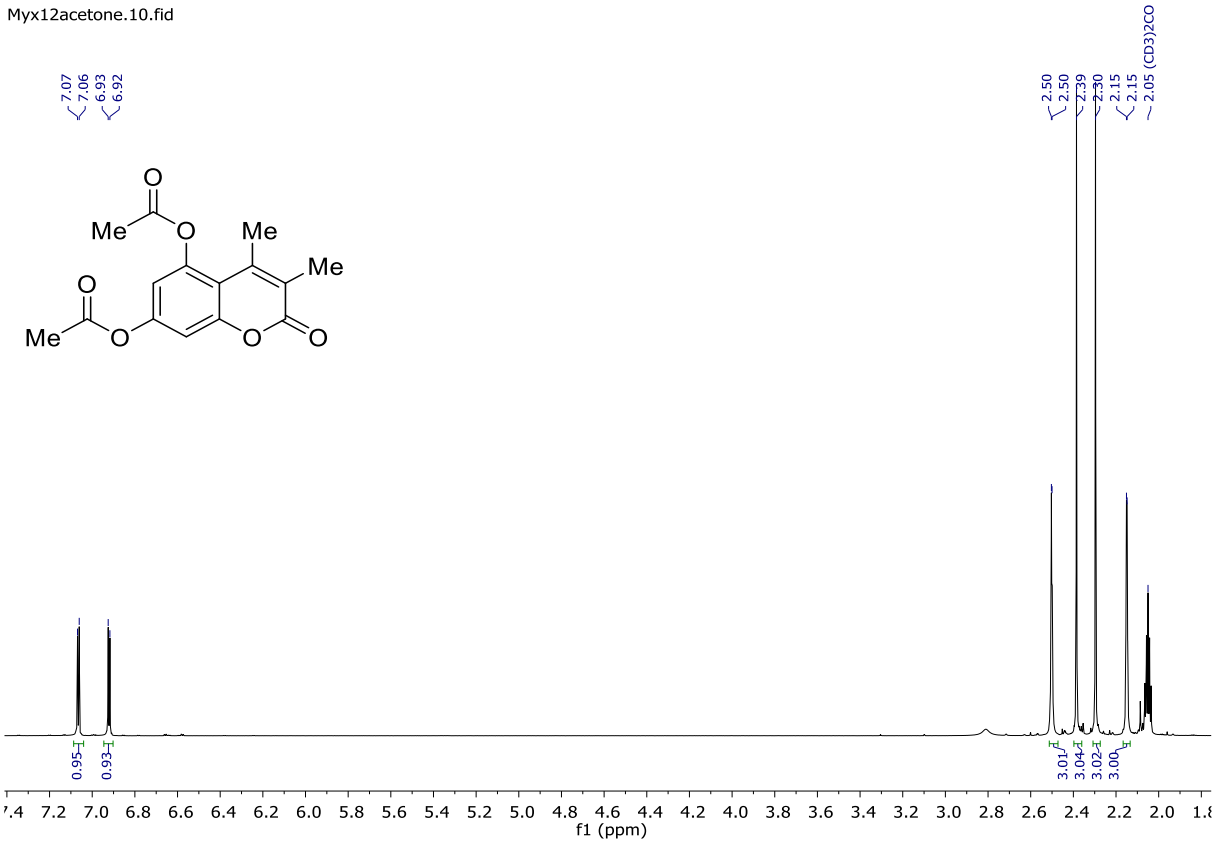
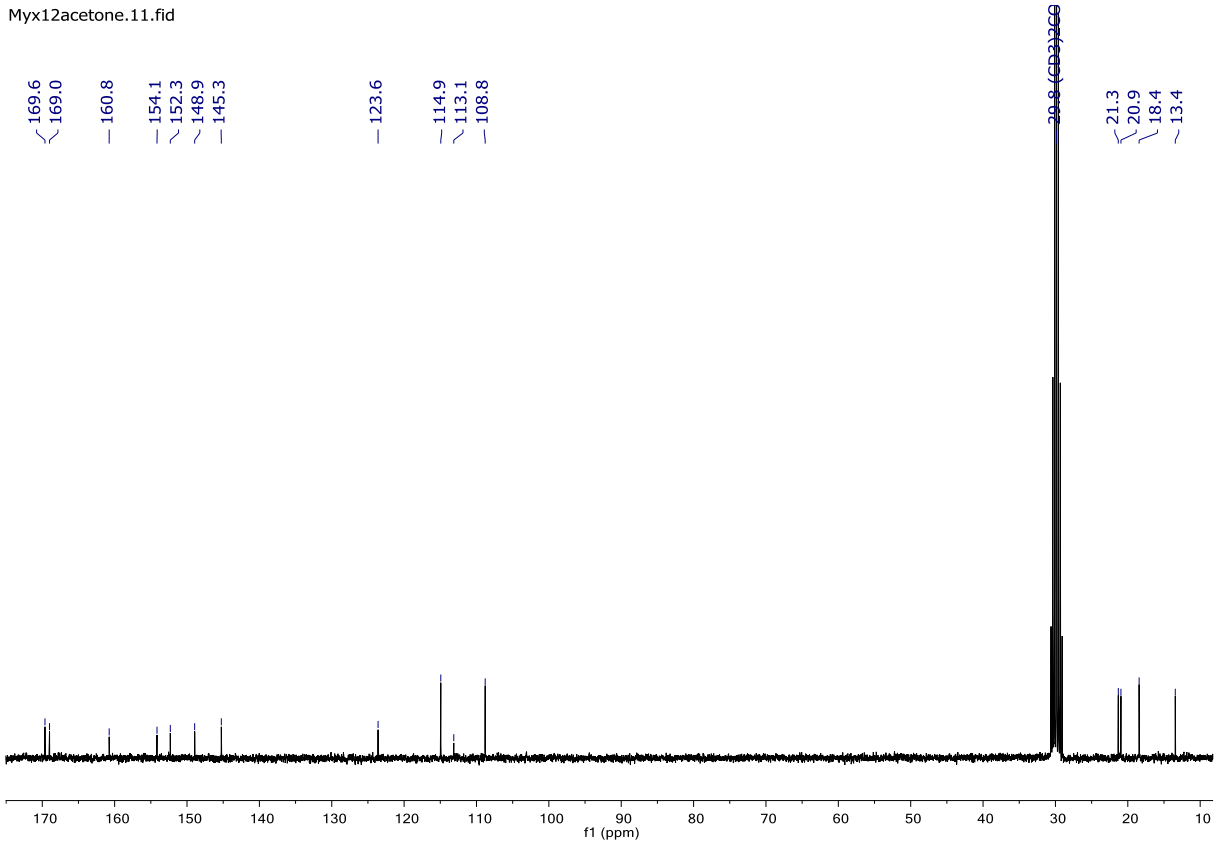
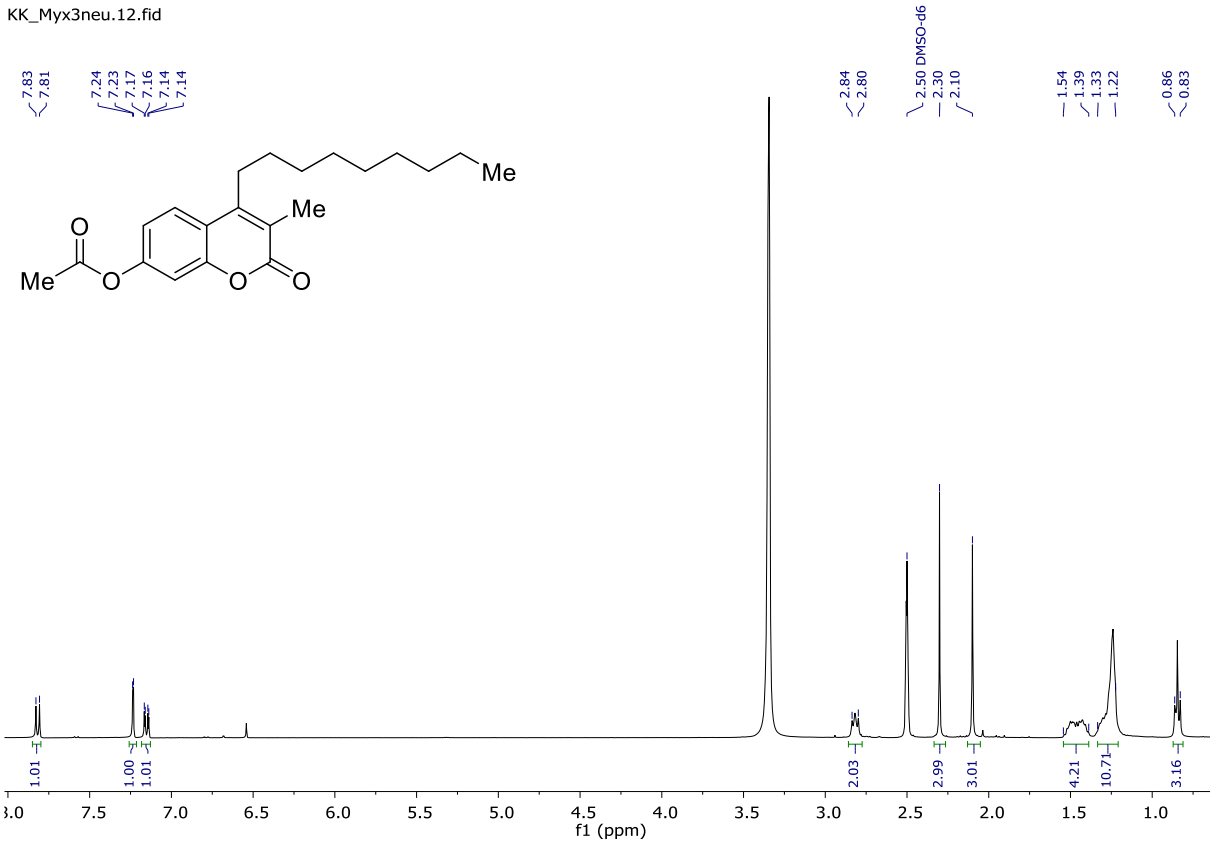


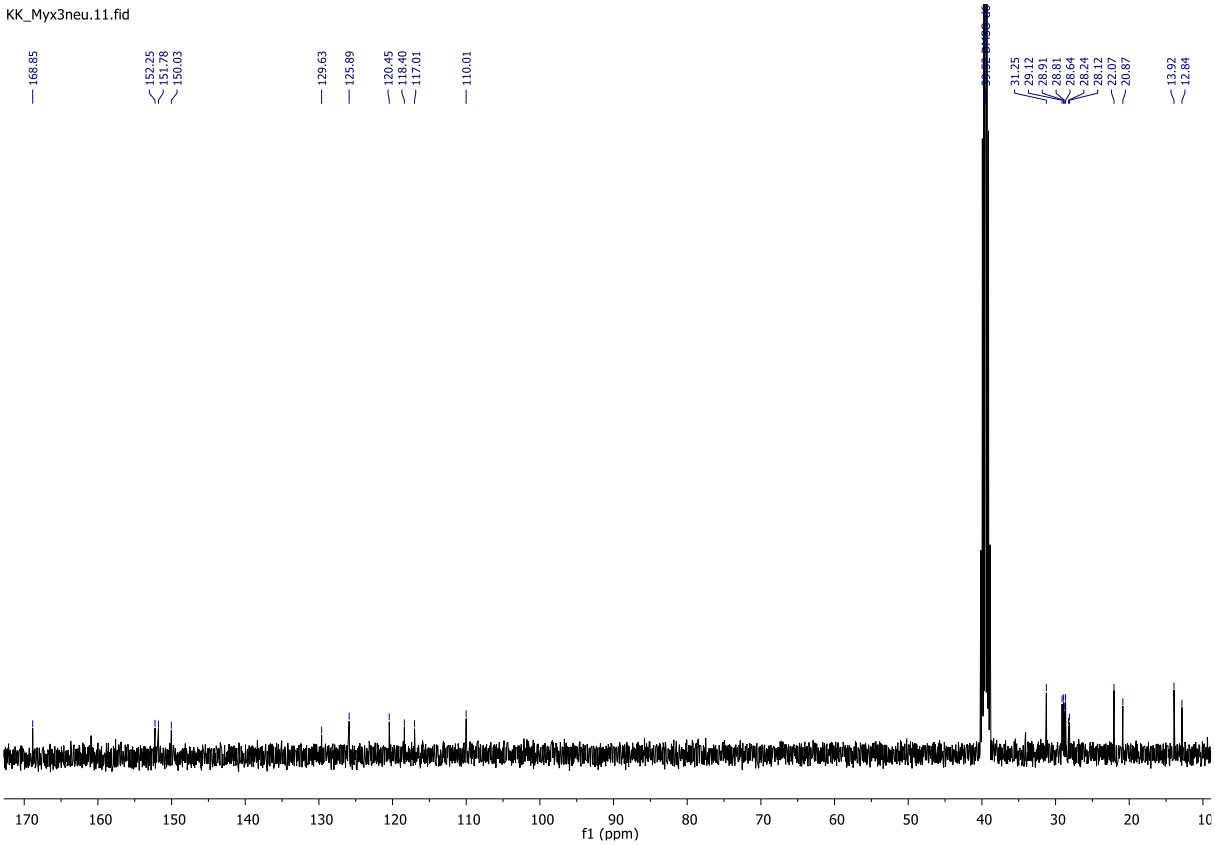
4.43 5,7-*O*-diacyl-3,4-dimethylcoumarin (**19**)



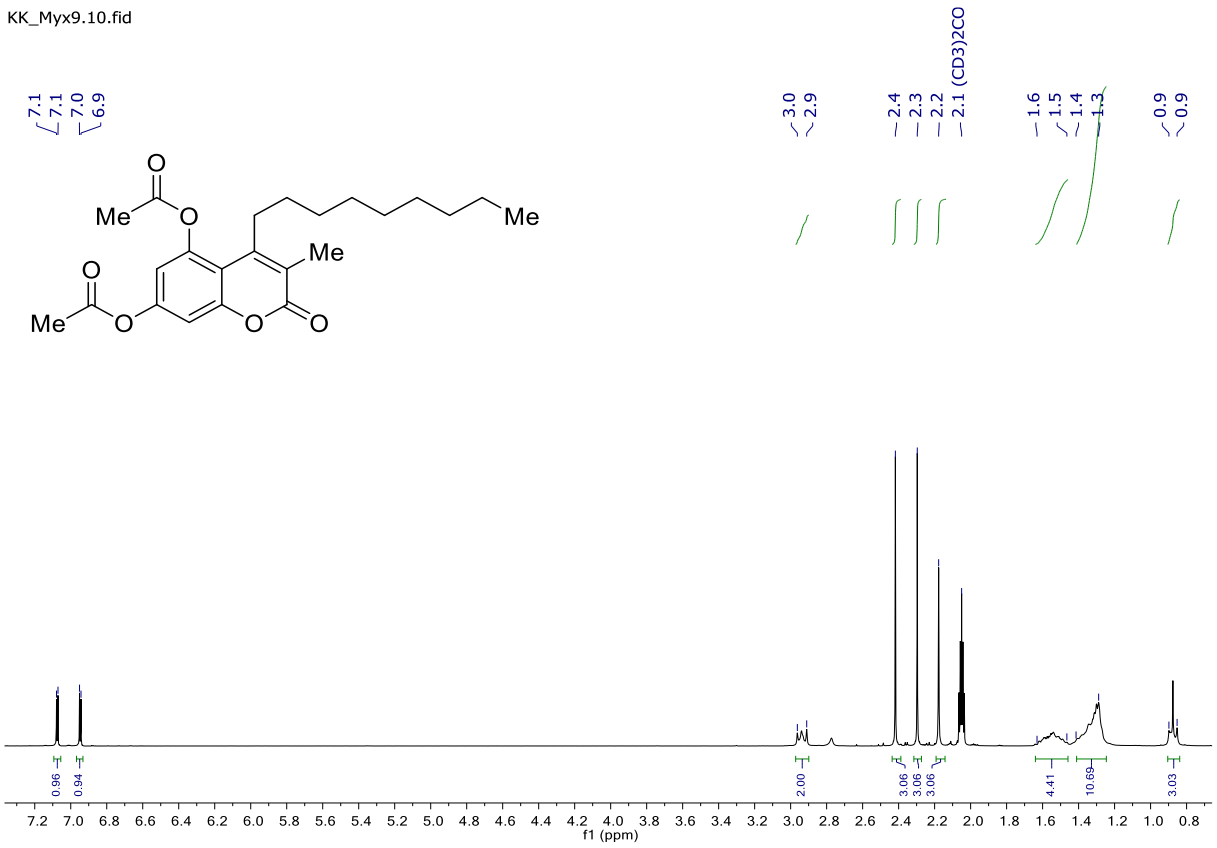



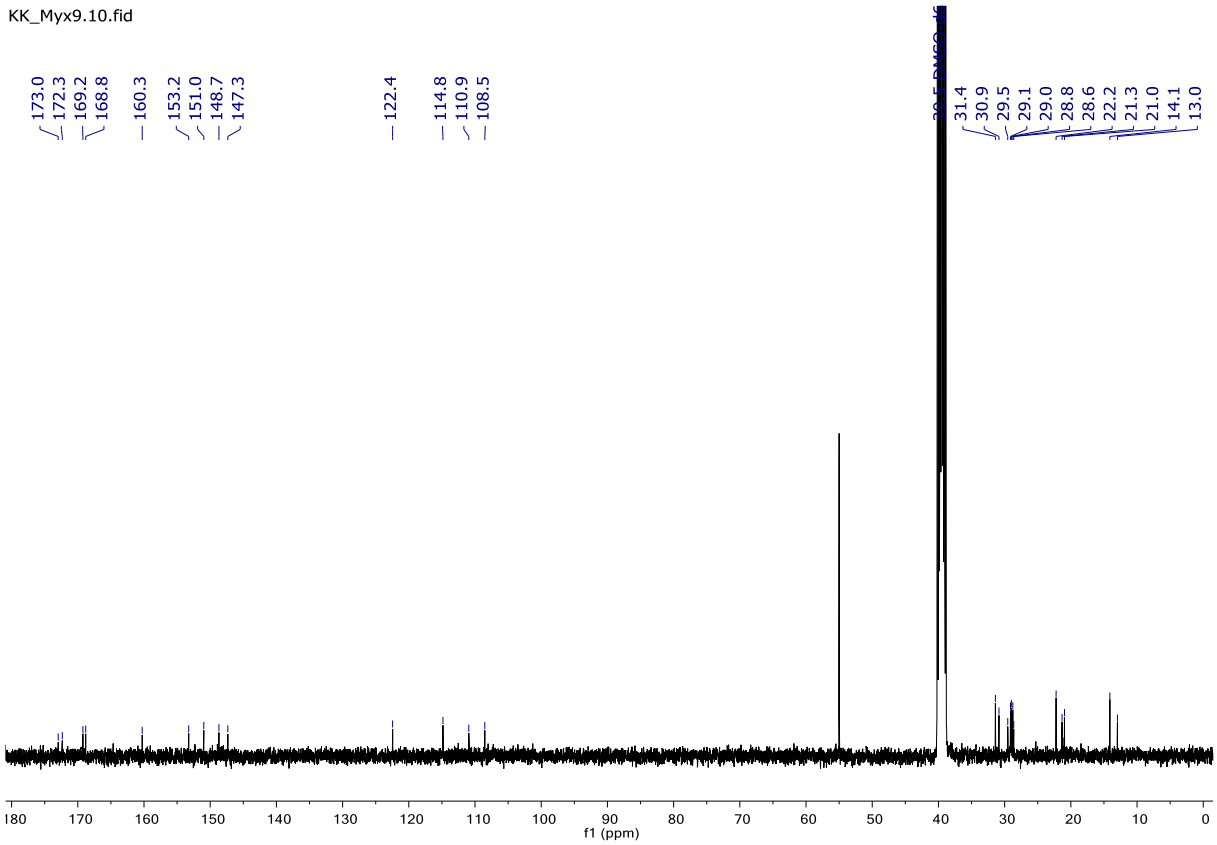
## 4.44 7-*O*-acyl-3-methyl-4-nonylcoumarin (**20**)



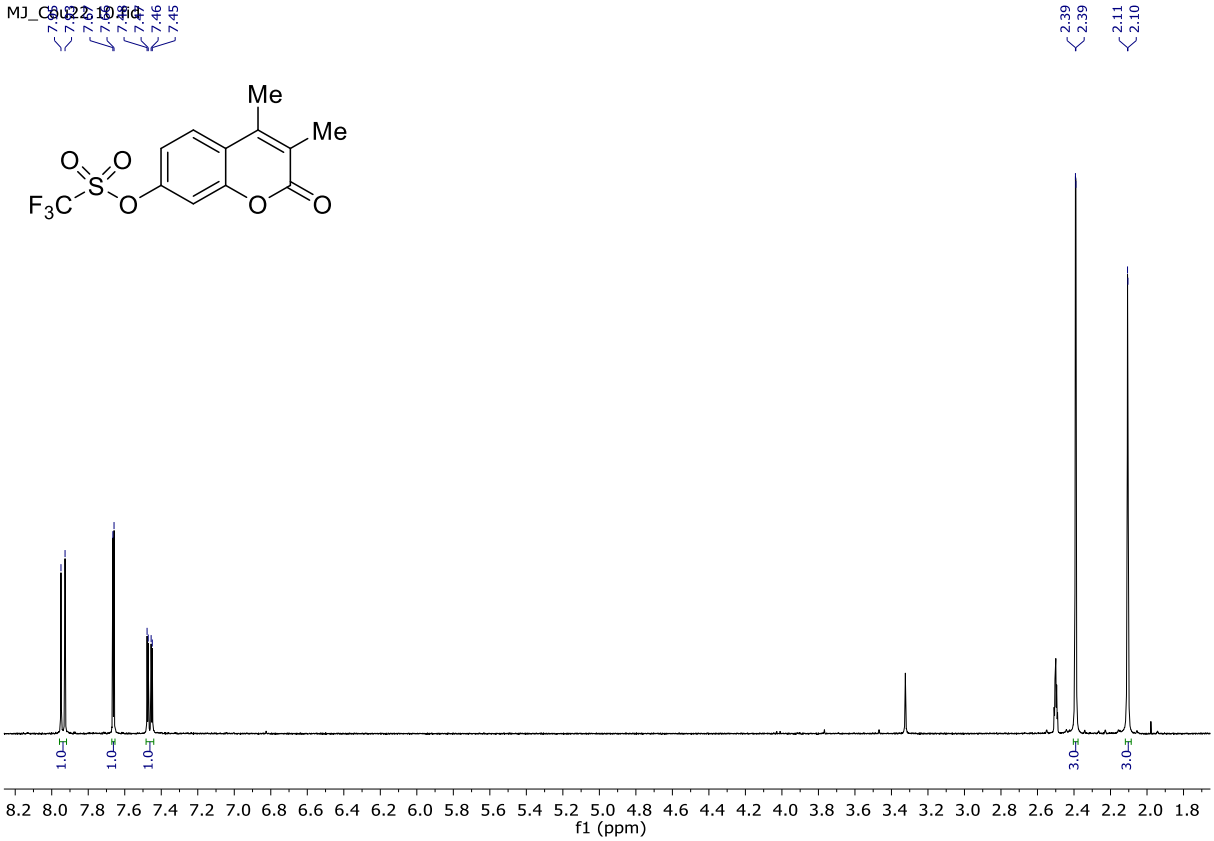



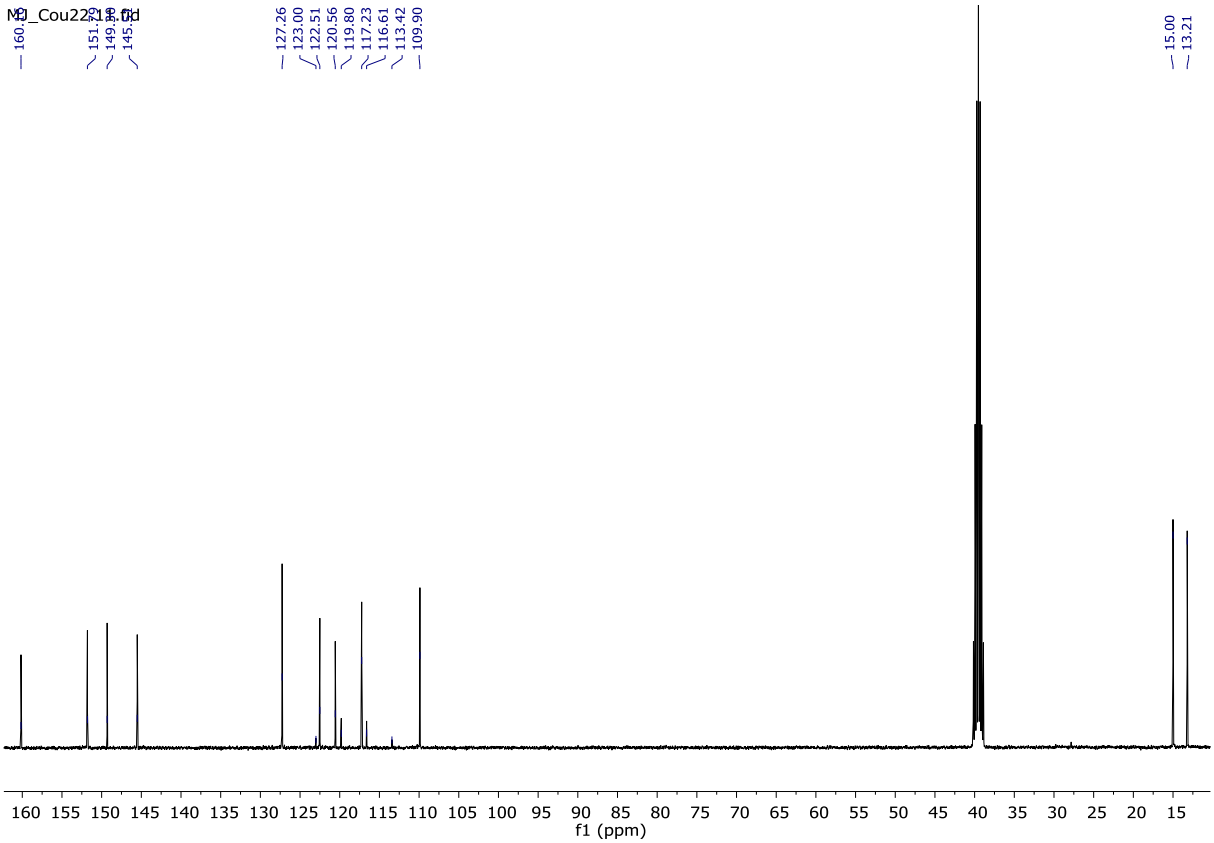
4.45 5,7-*O*-diacyl-3-methyl-4-nonylcoumarin (**21**)



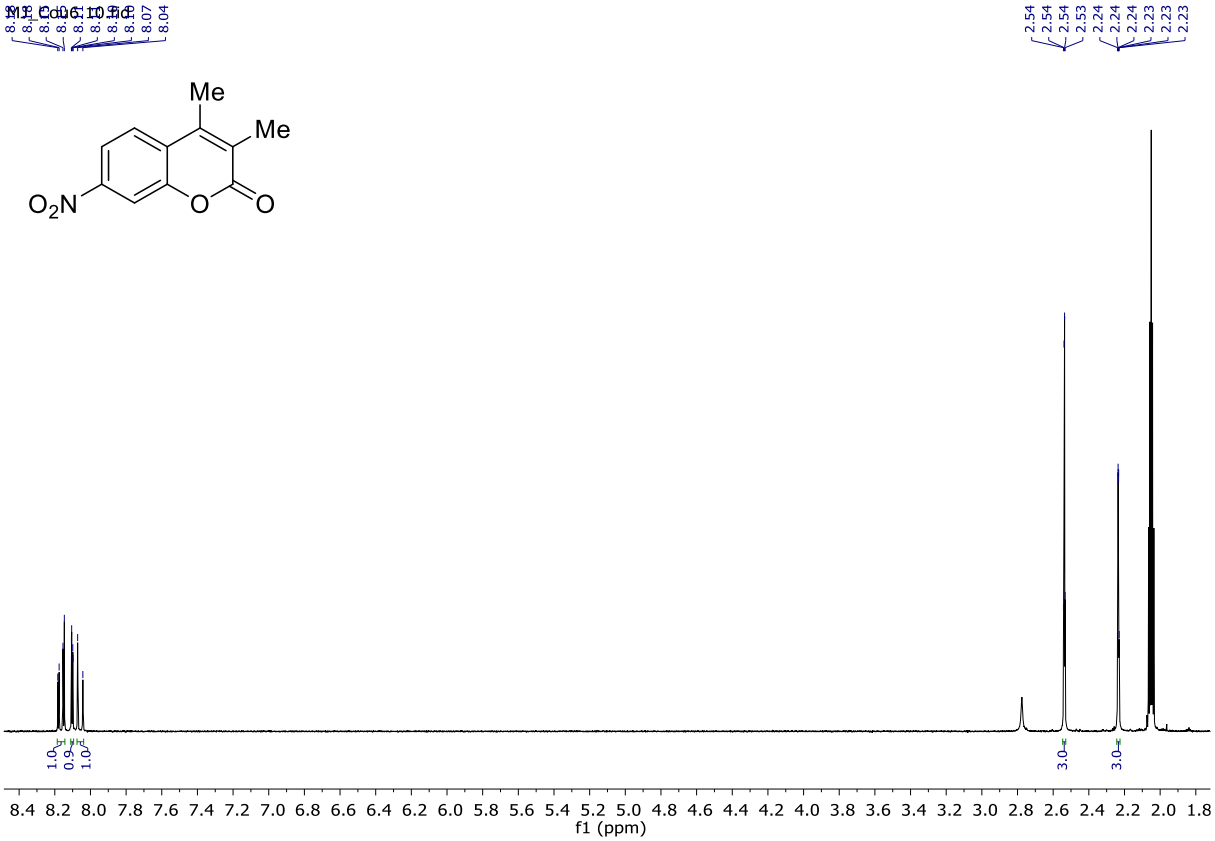



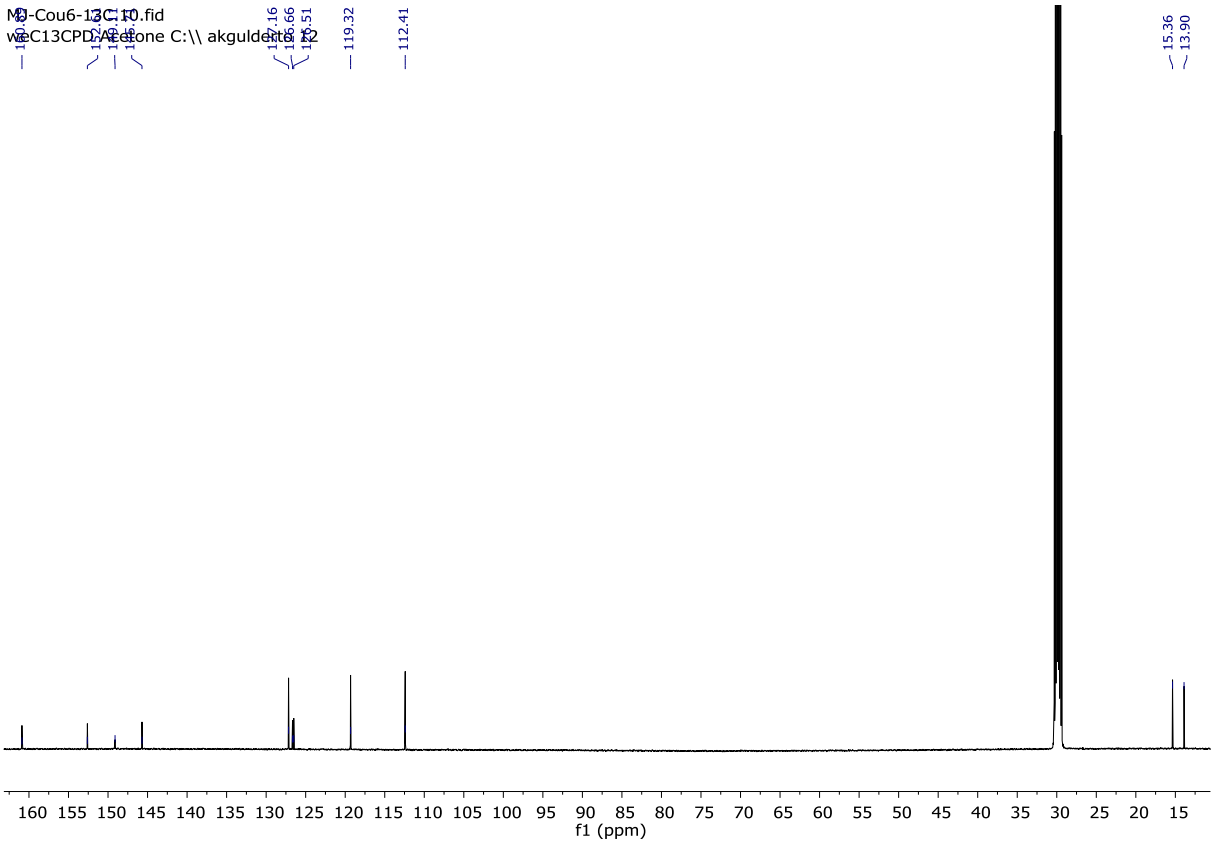
4.46 3,4-dimethyl-7-trifluoromethanesulfonylcoumarin (**S7**)



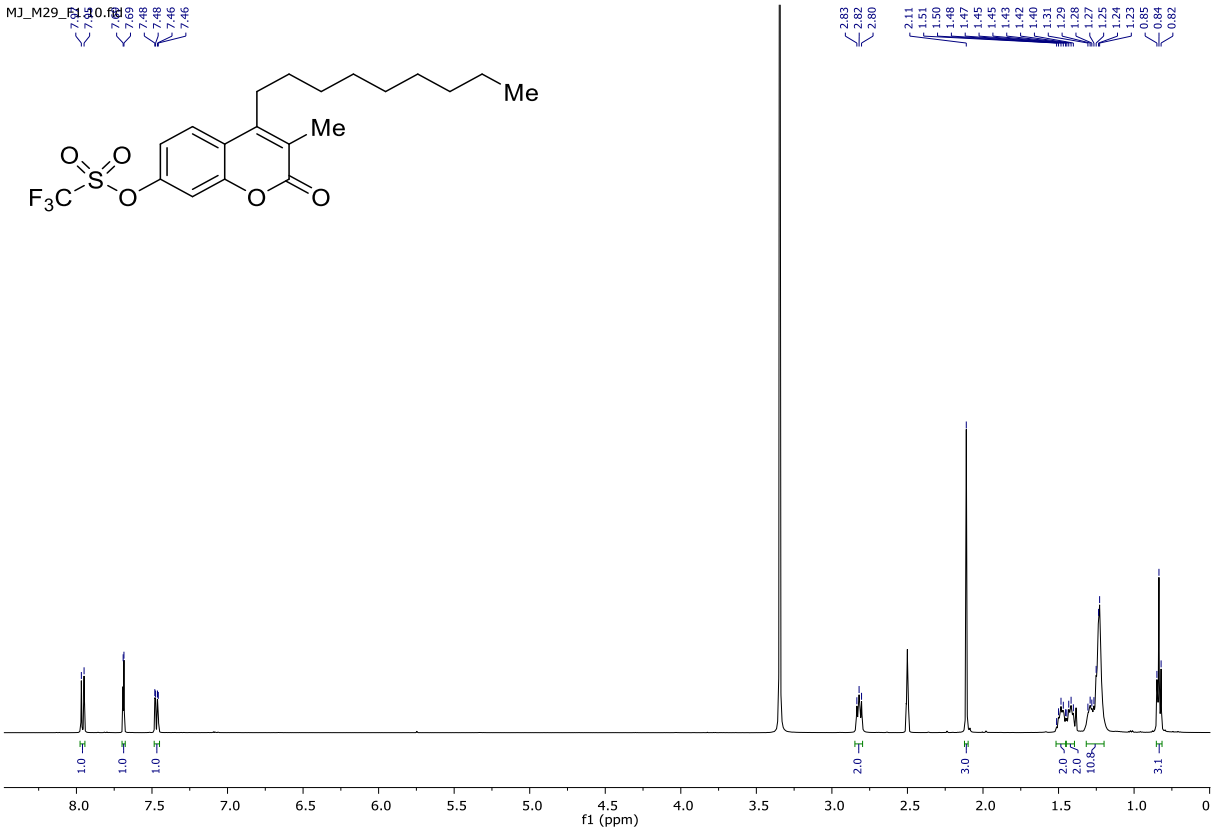



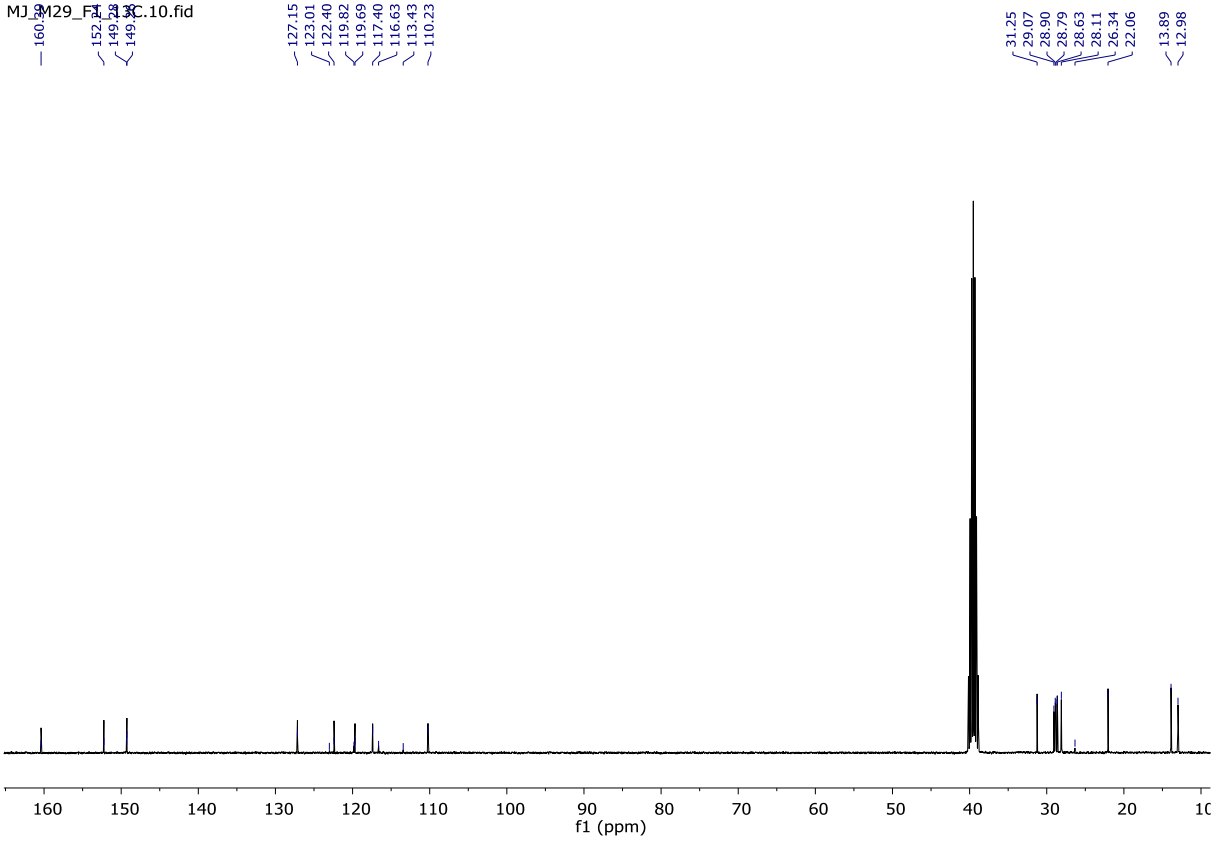
4.47 3,4-dimethyl-7-nitrocoumarin (**22**)



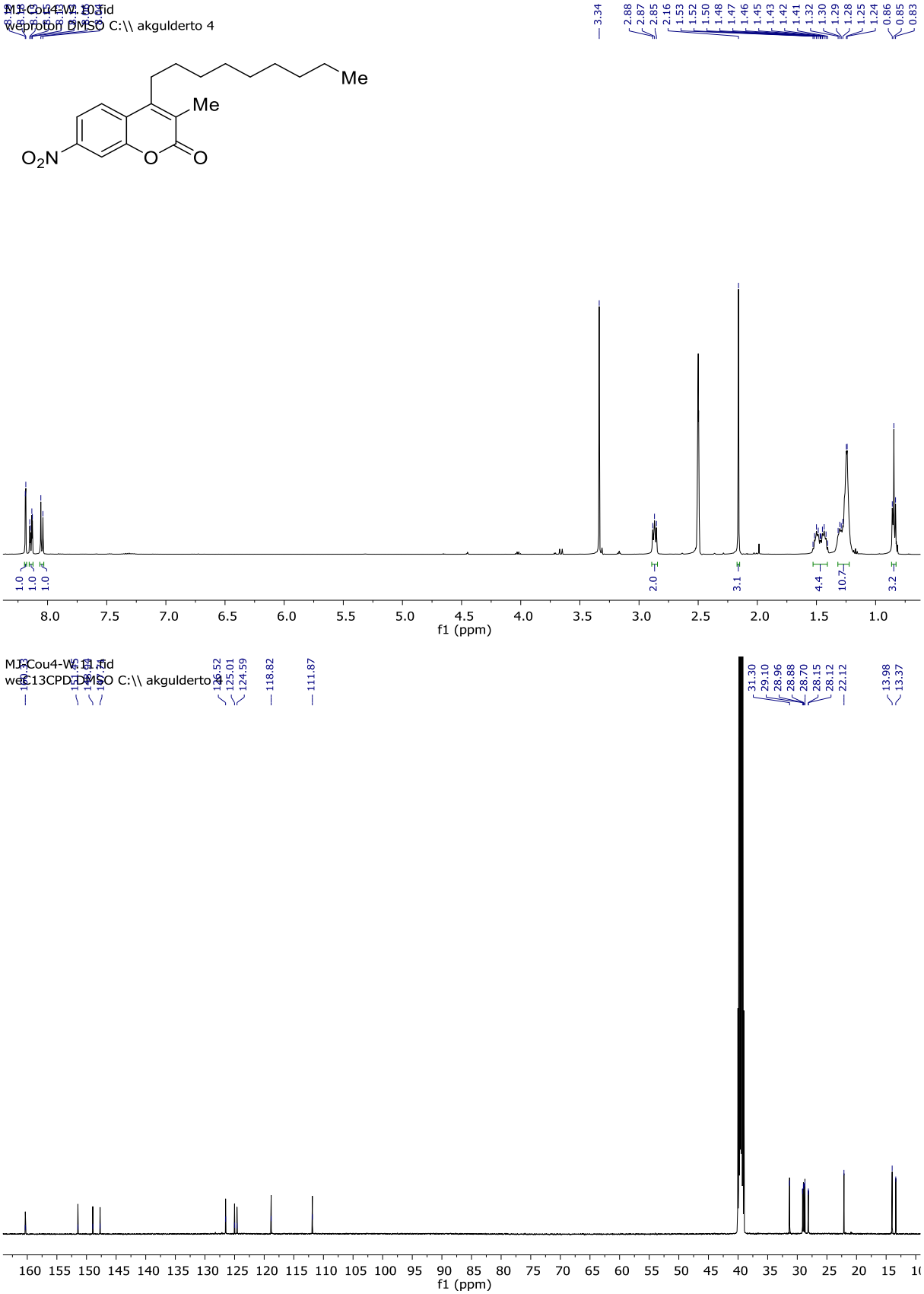



4.48 3-methyl-4-nonyl-7-trifluoromethanesulfonylcoumarin (**S8**)

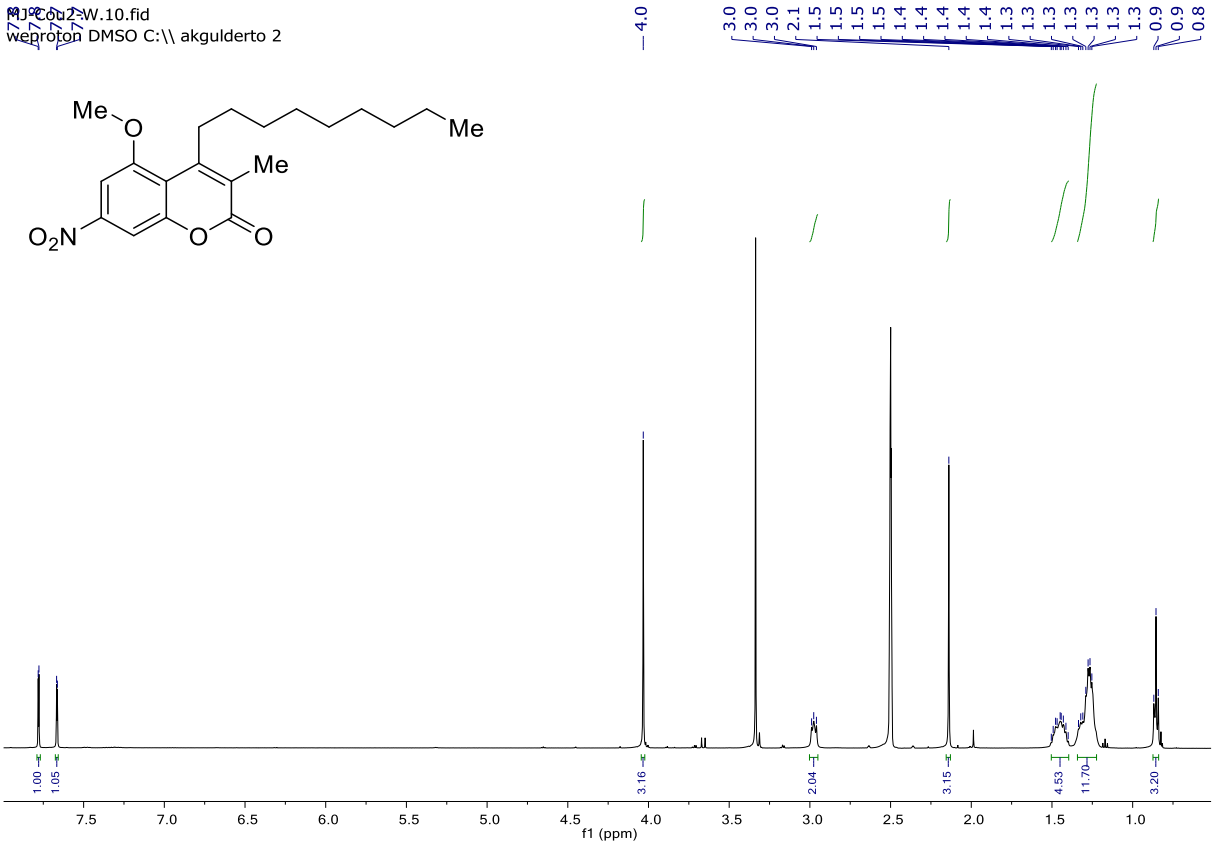


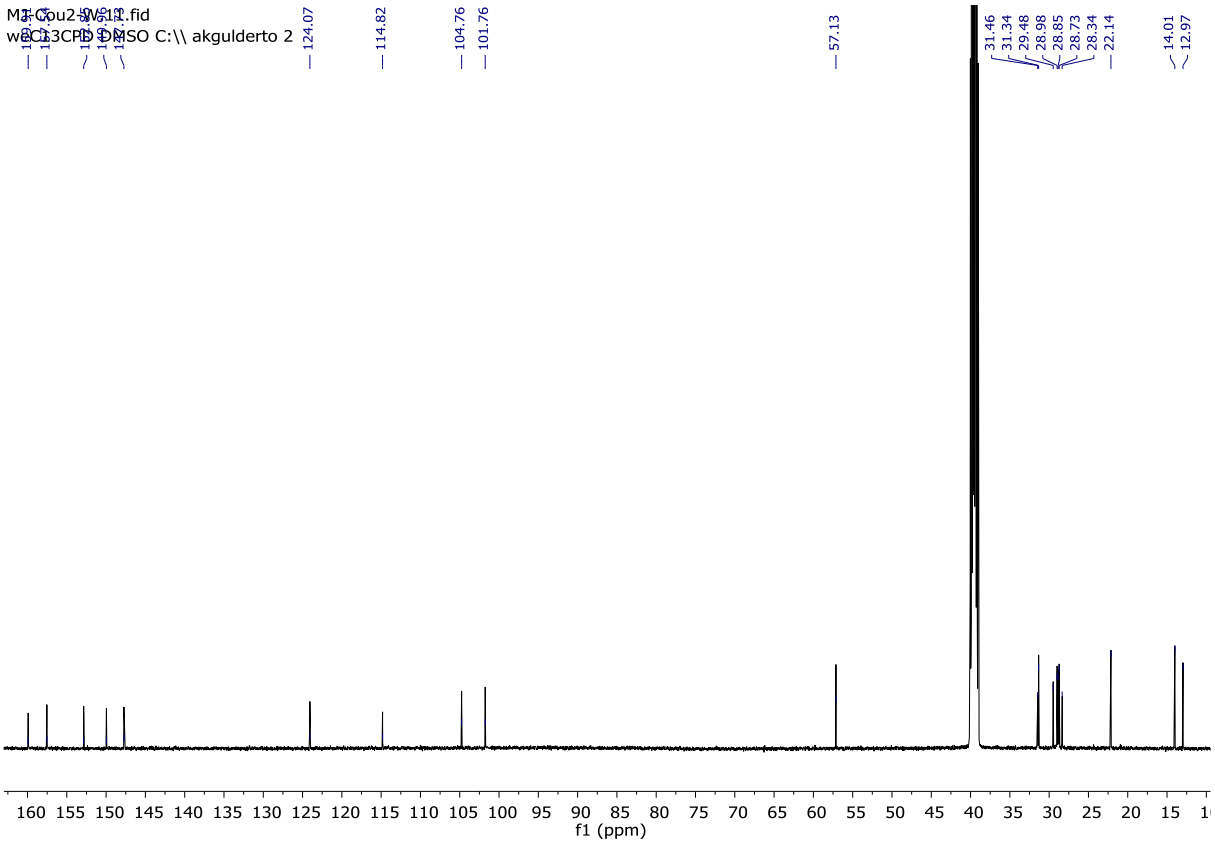



## 4.49 3-methyl-7-nitro-4-nonylcoumarin (**23**)

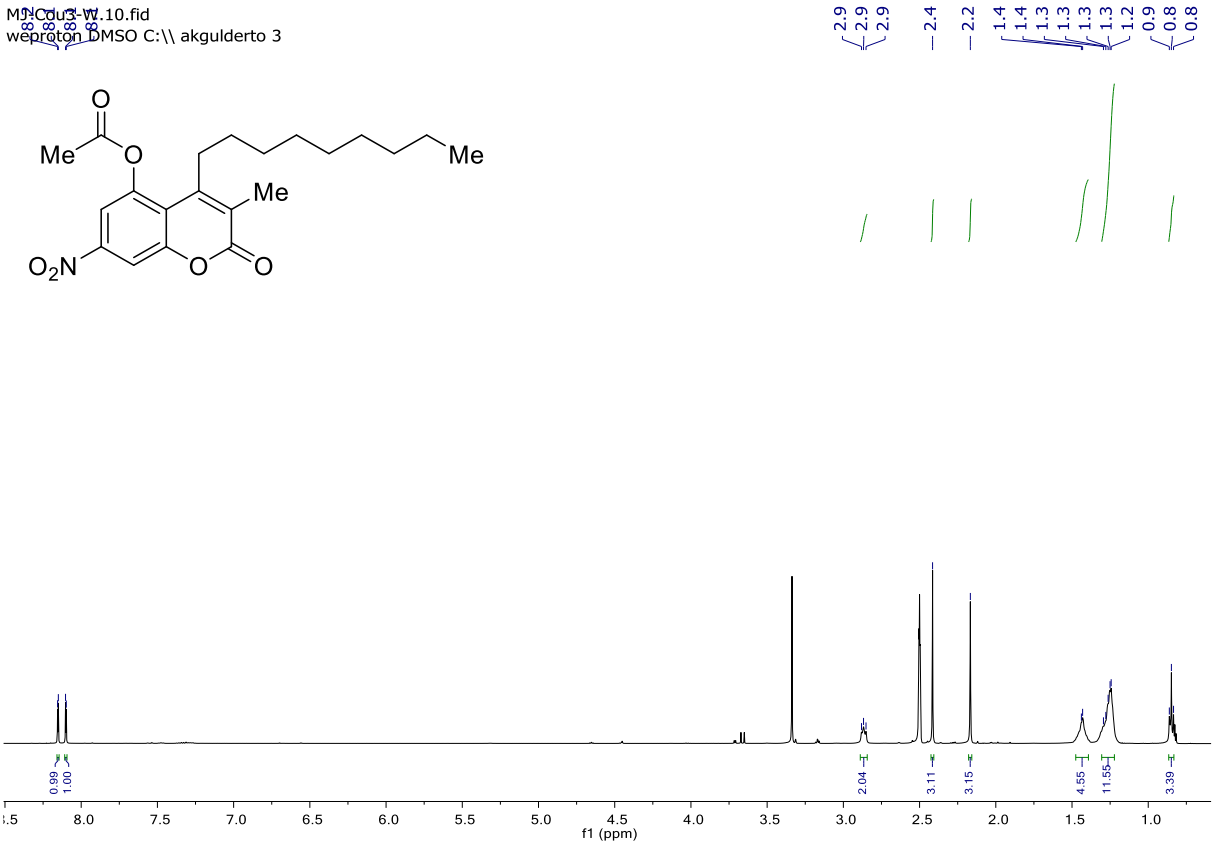


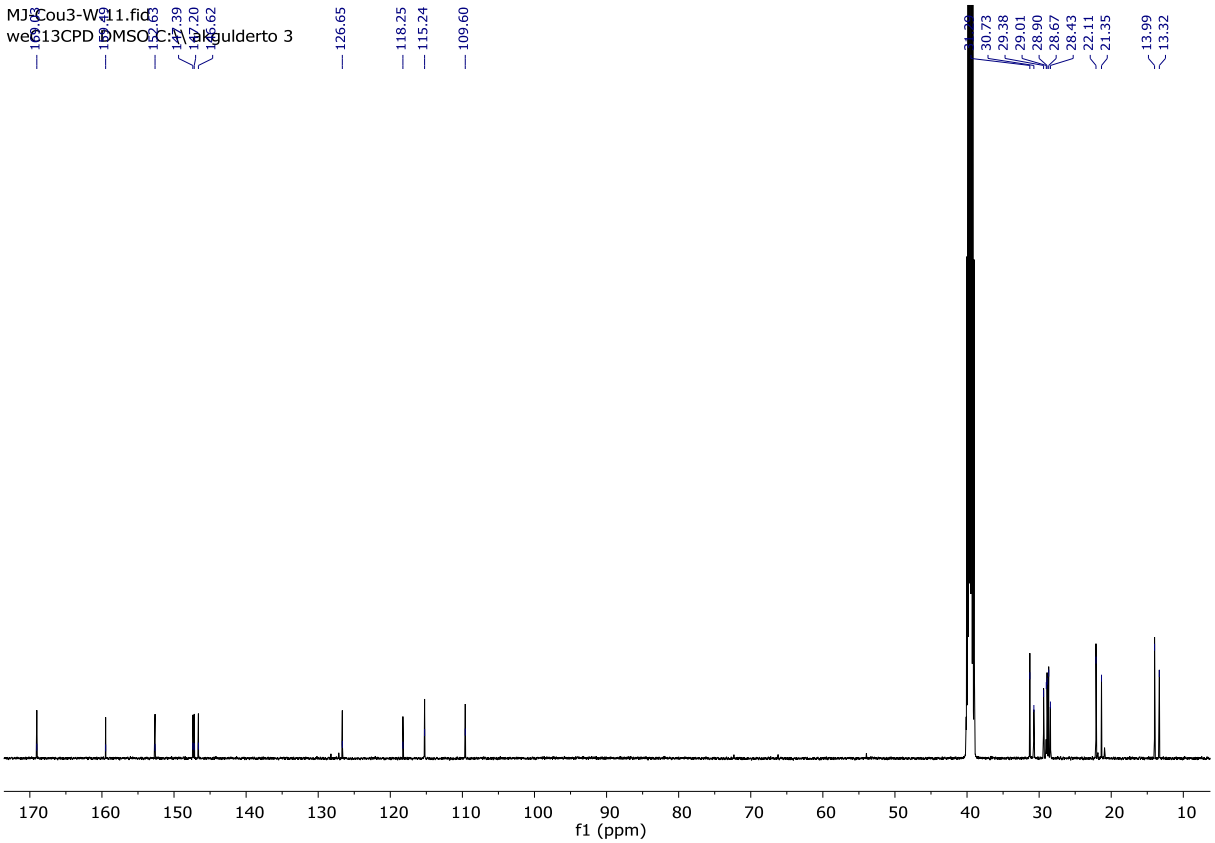
## 4.50 5-methoxy-3-methyl-7-nitro-4-nonylcoumarin (**24**)



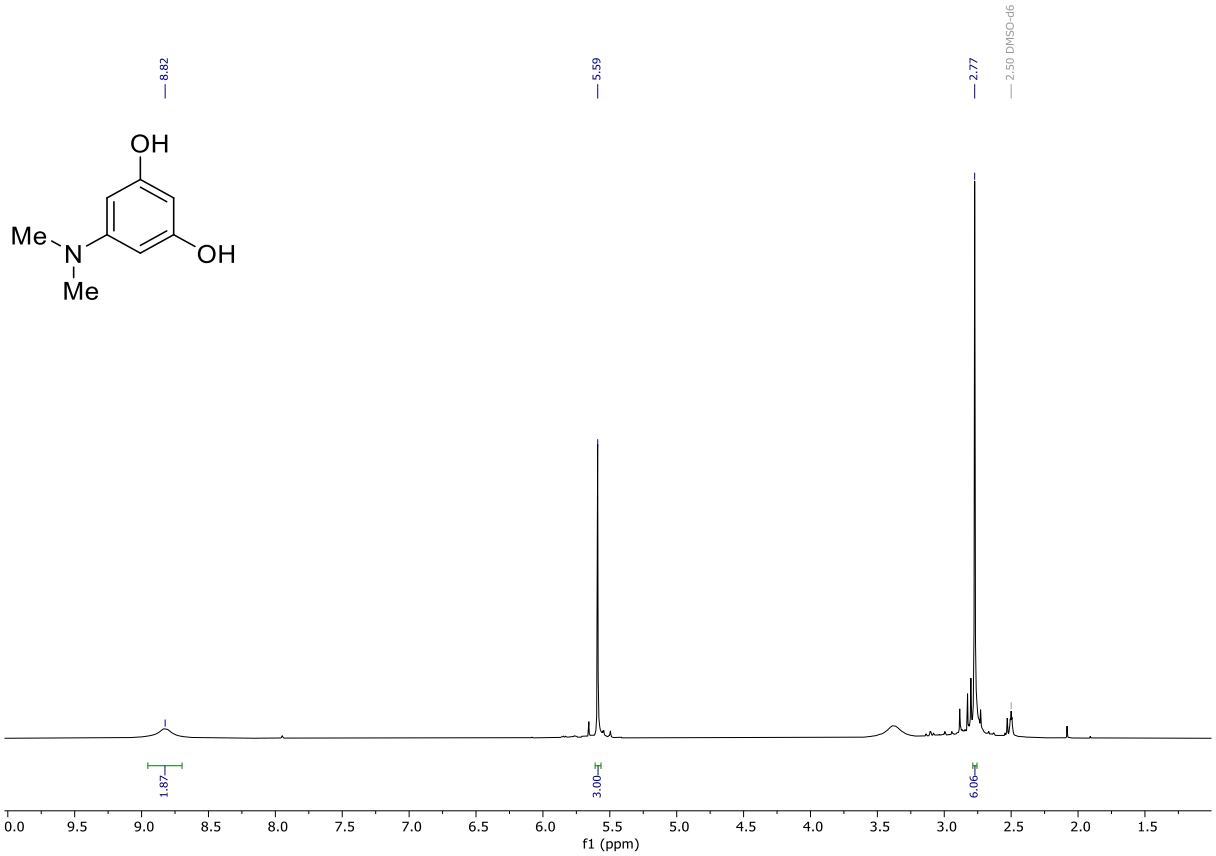



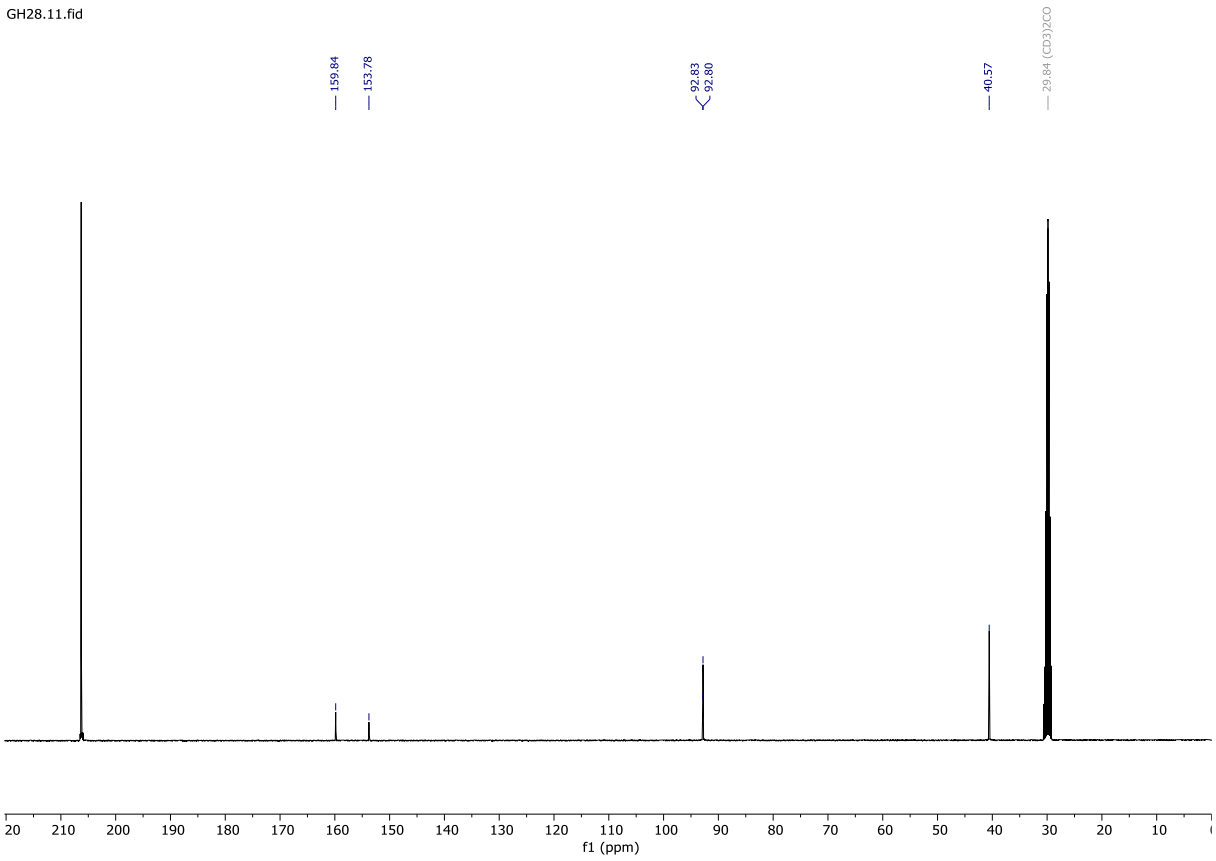
4.51 5-*O*-acyl-3-methyl-7-nitro-4-nonylcoumarin (**25**)



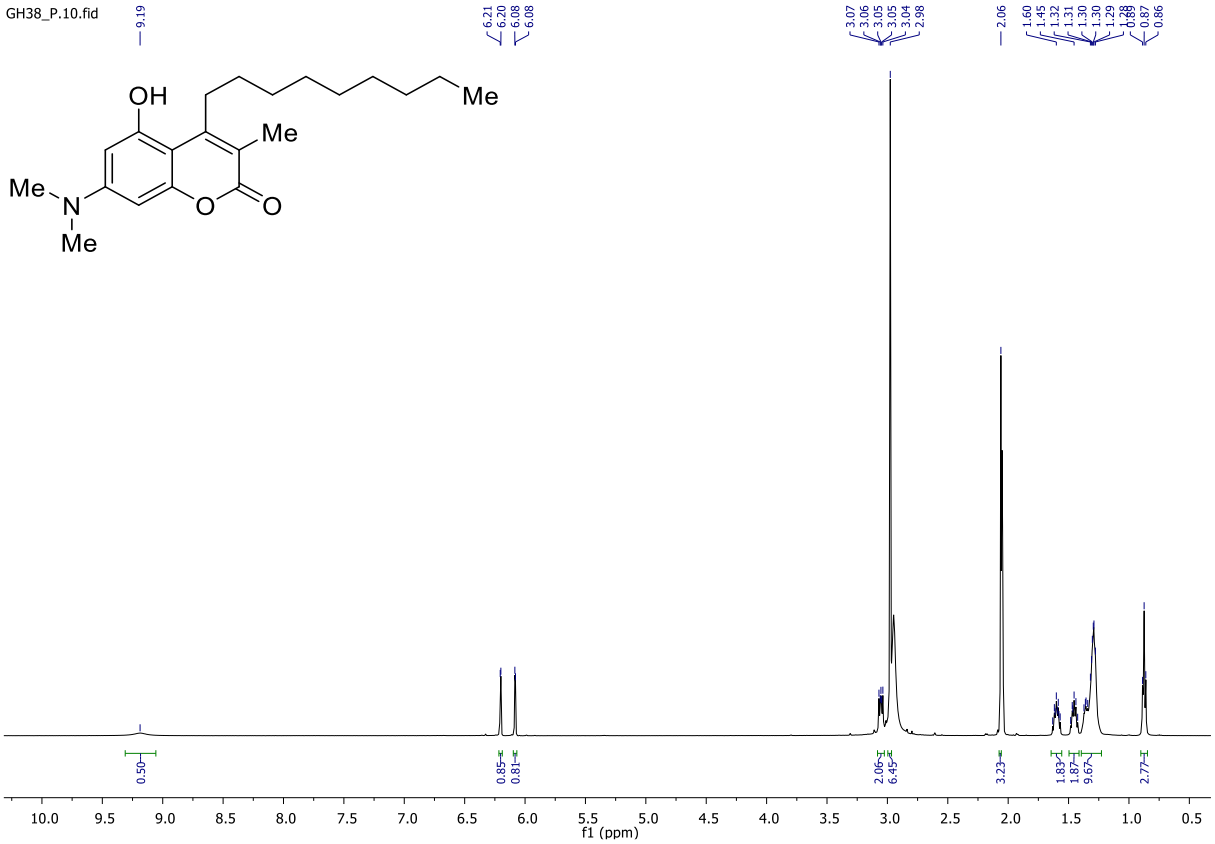



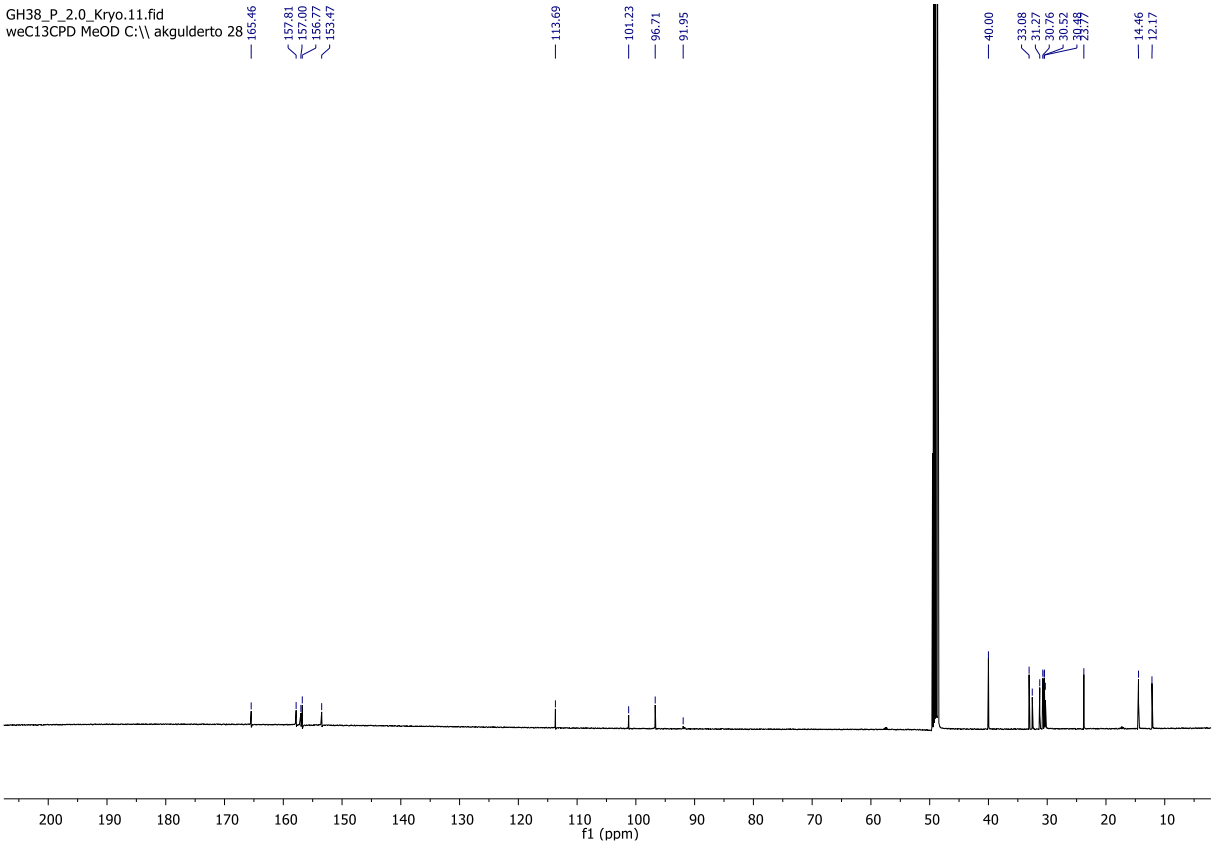
4.52 5-(dimethylamino)benzene-1,3-diol (**S9**)



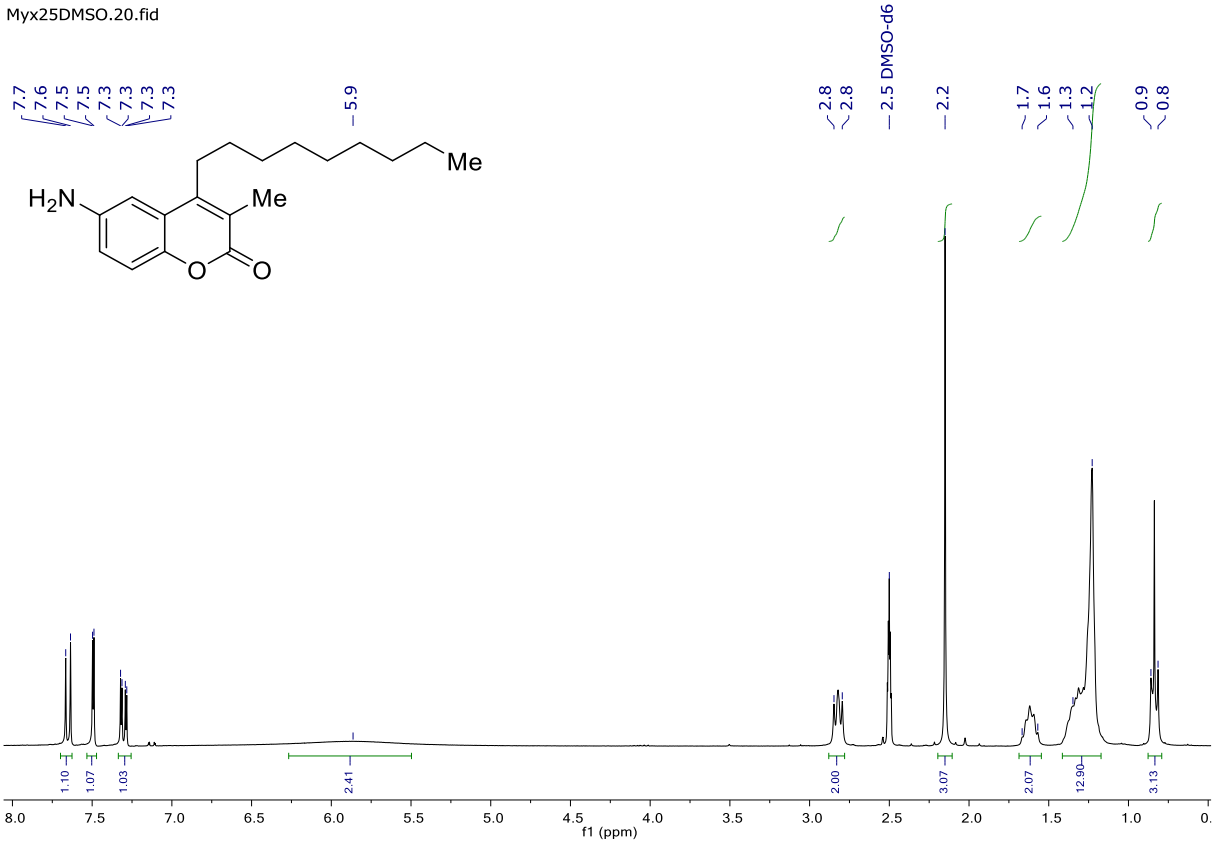
4.53 7-(dimethylamino)-5-hydroxy-3-methyl-4-nonylcoumarin (**26**)



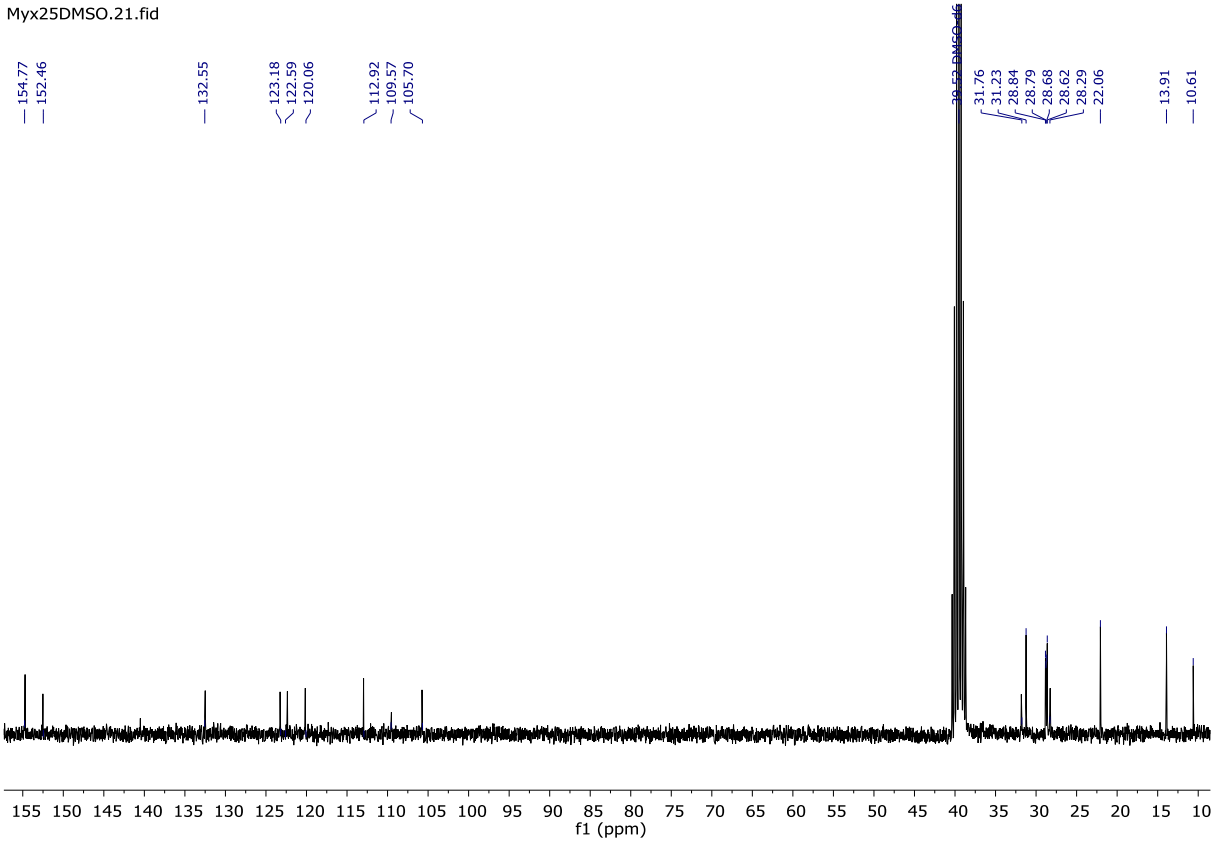



## 4.54 6-amino-3-methyl-4-nonylcoumarin (**27**)

Myx25DMSO.20.fid




Myx25DMSO.21.fid



## 4.55 6-chloro-7-hydroxy-3-methyl-4-nonylcoumarin (**28**)

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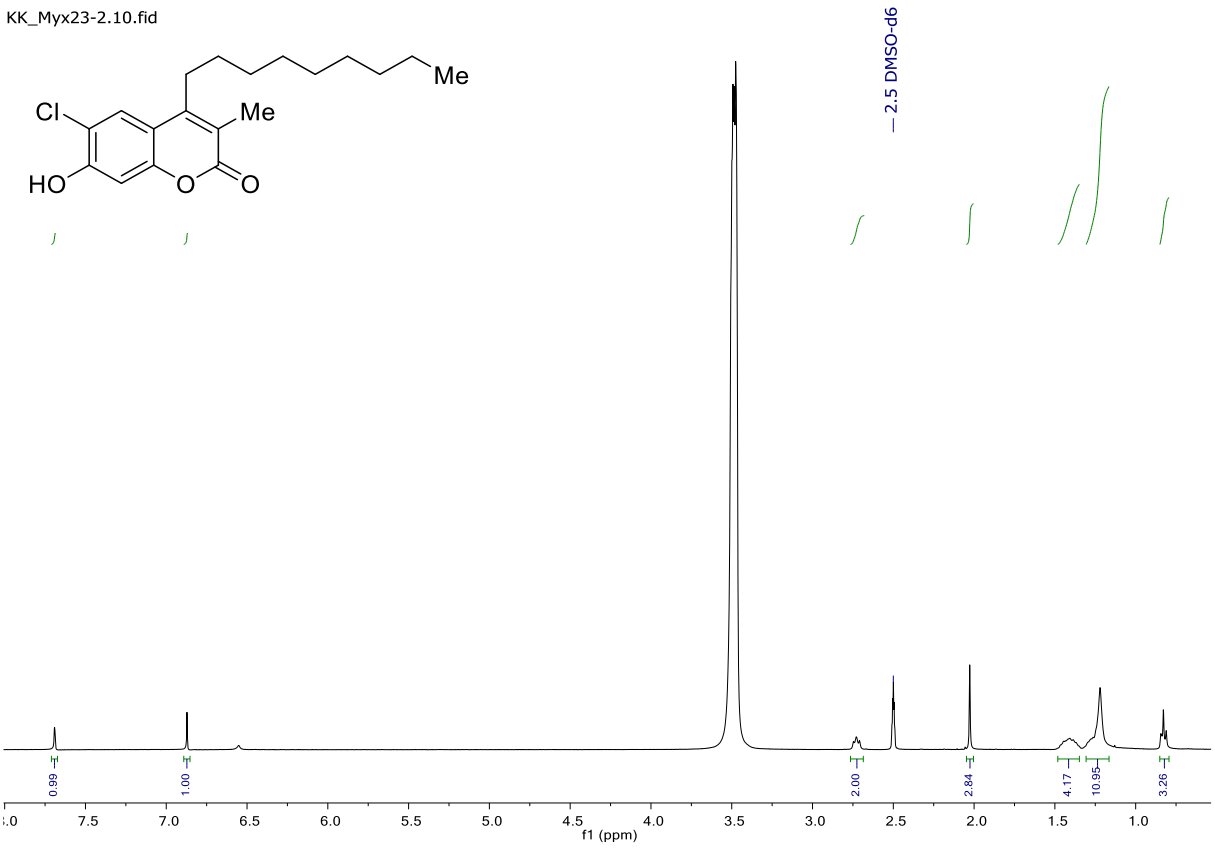


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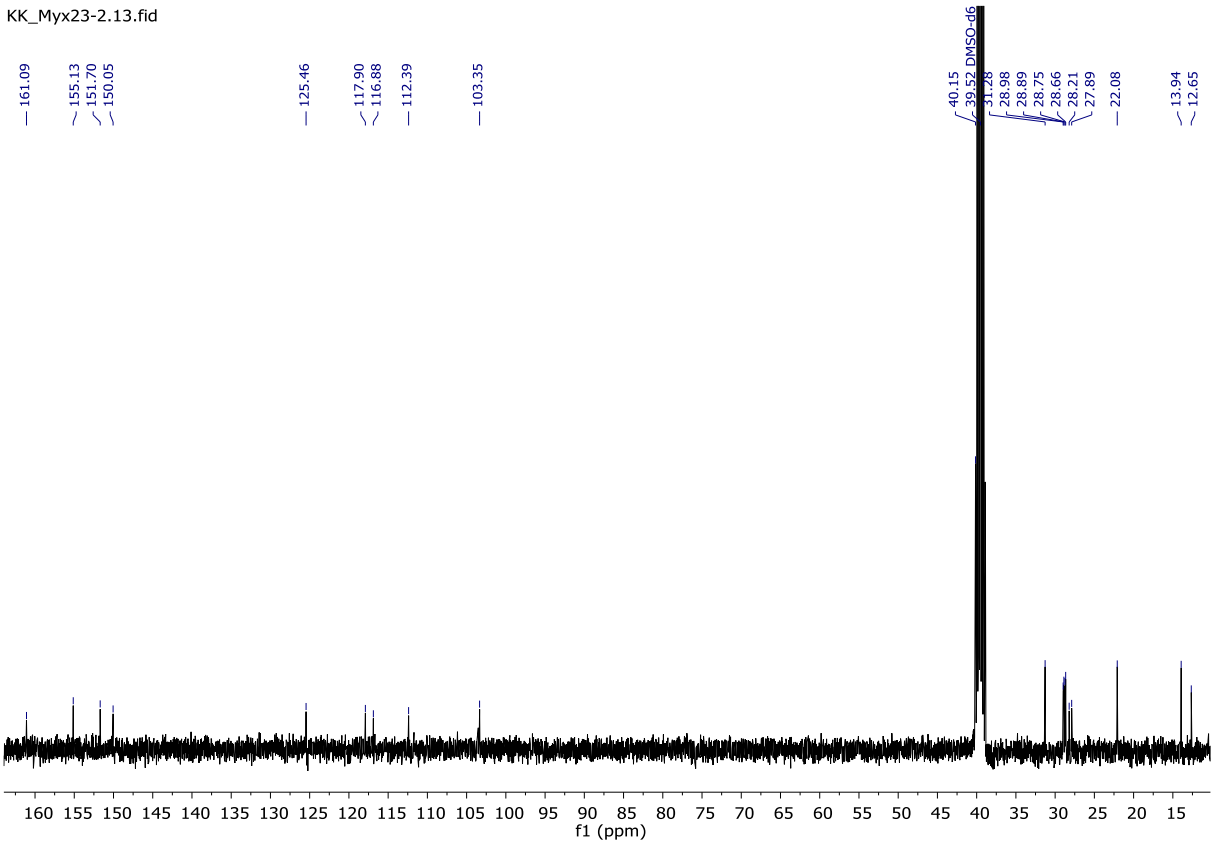
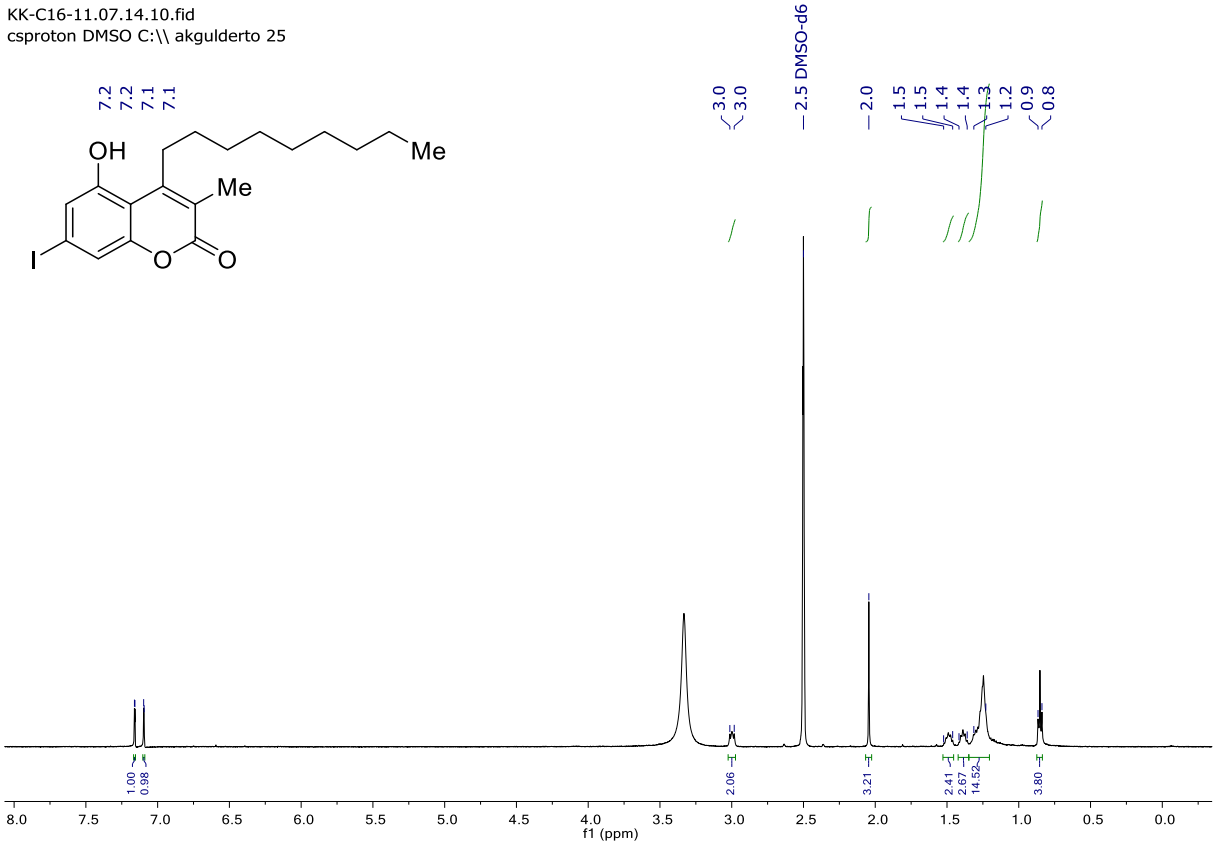
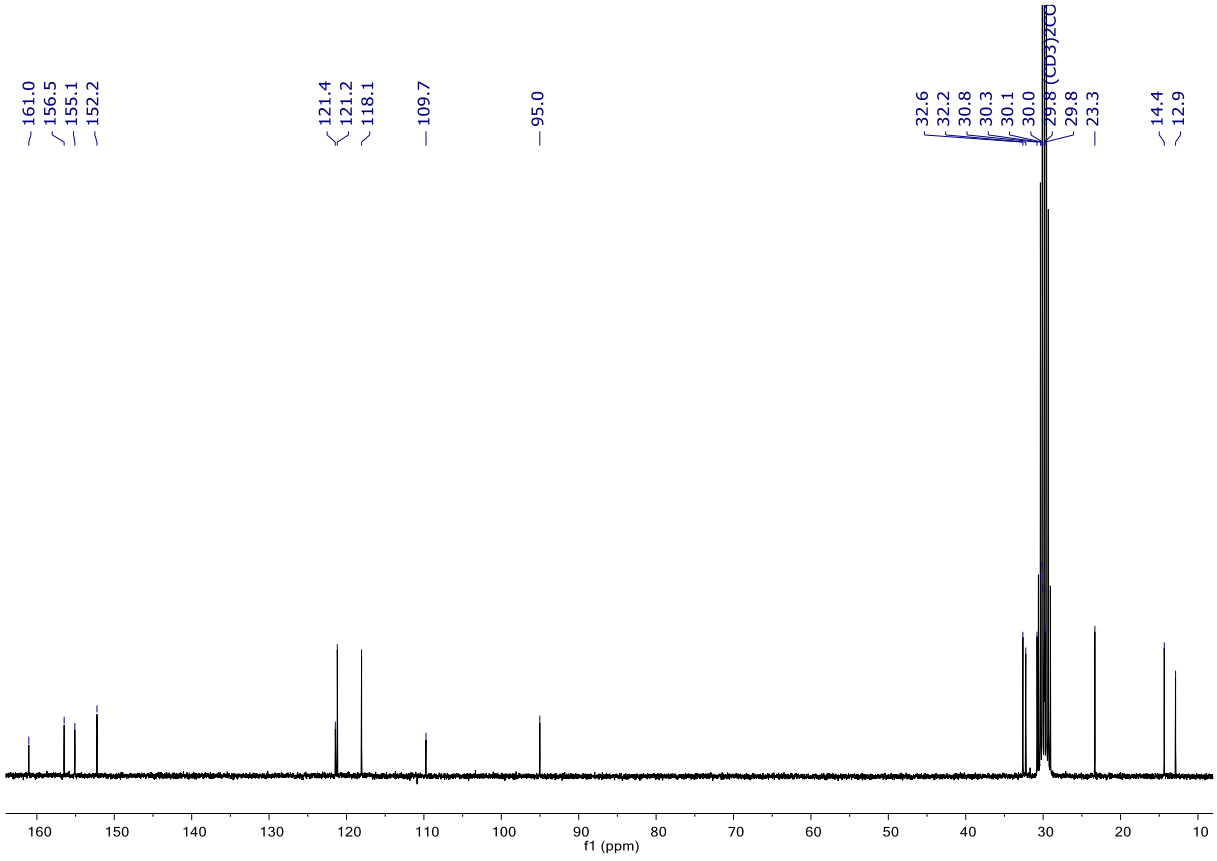


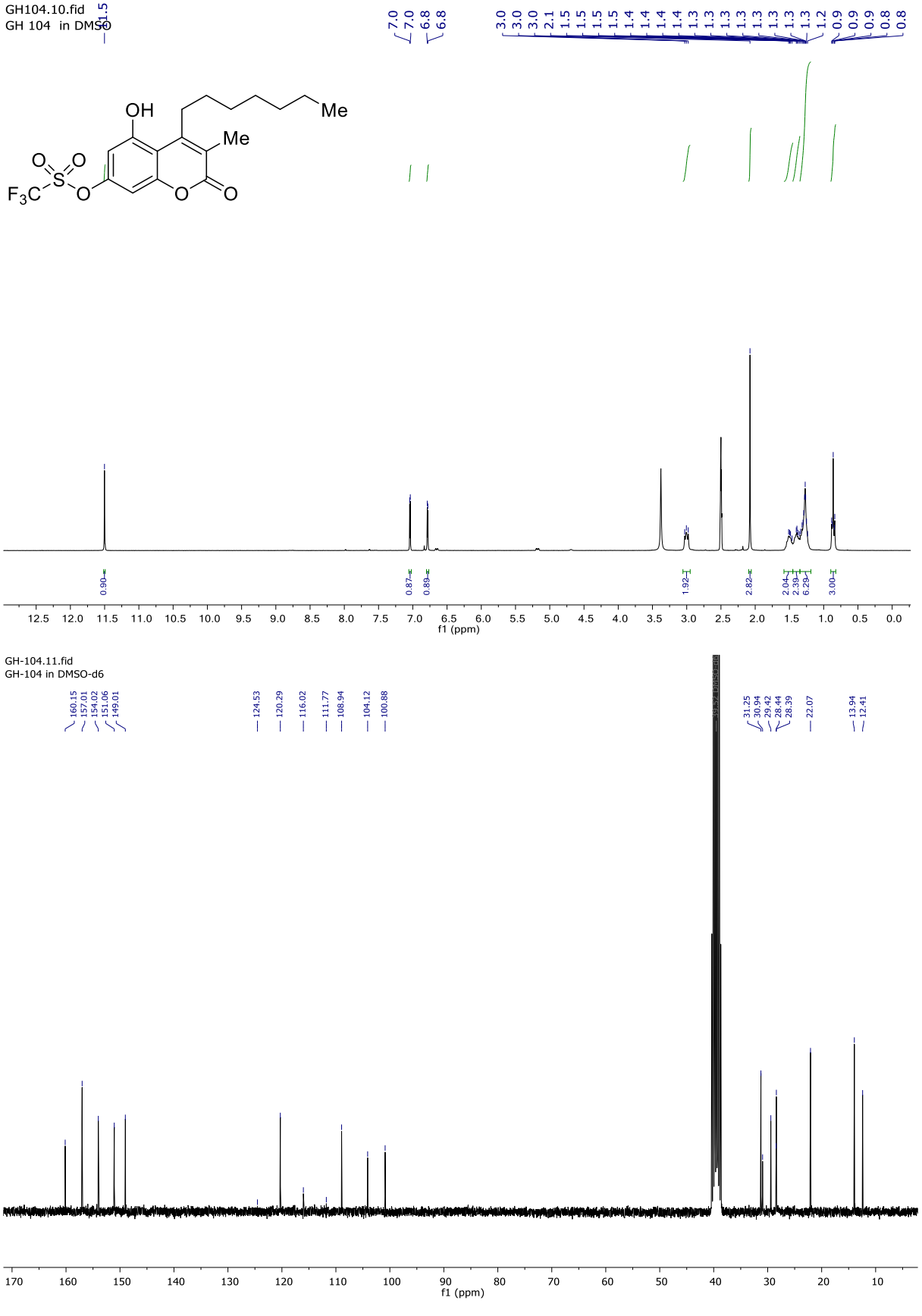
## 4.56 5-hydroxy-7-iodo-3-methyl-4-nonylcoumarin (**29**)

KK-C16-11.07.14.10.fid
csproton DMSO C:\\ akgulderto 25

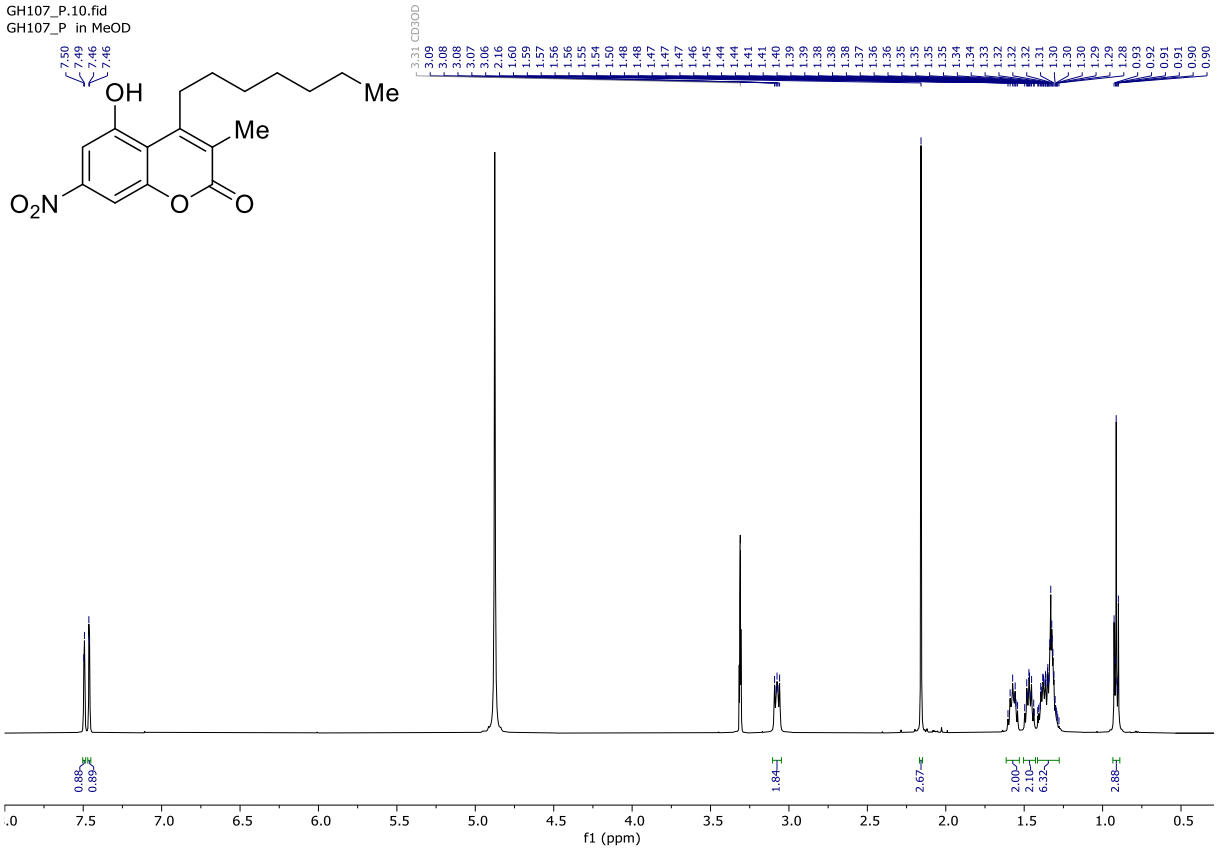


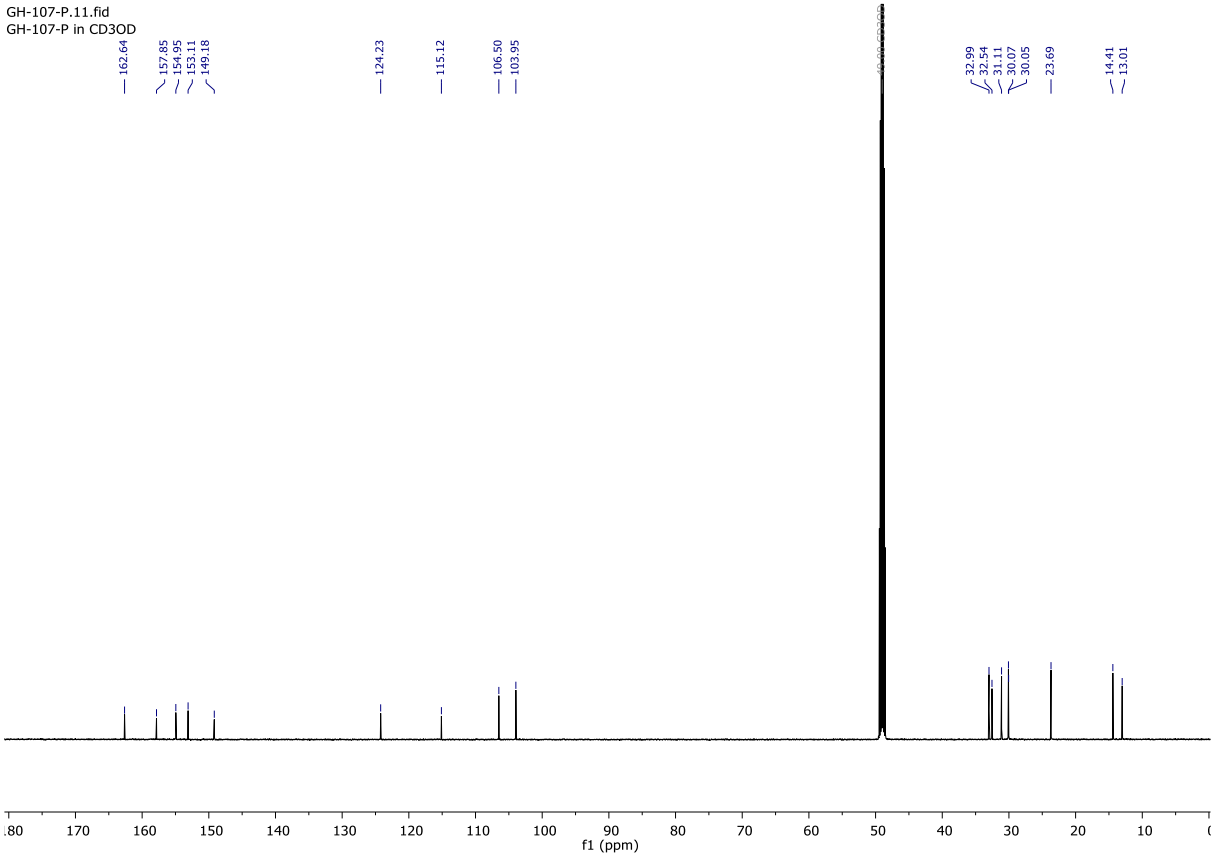



4.57 4-heptyl-5-hydroxy-3-methyl-7-trifluoromethanesulfonylcoumarin (**S12**)

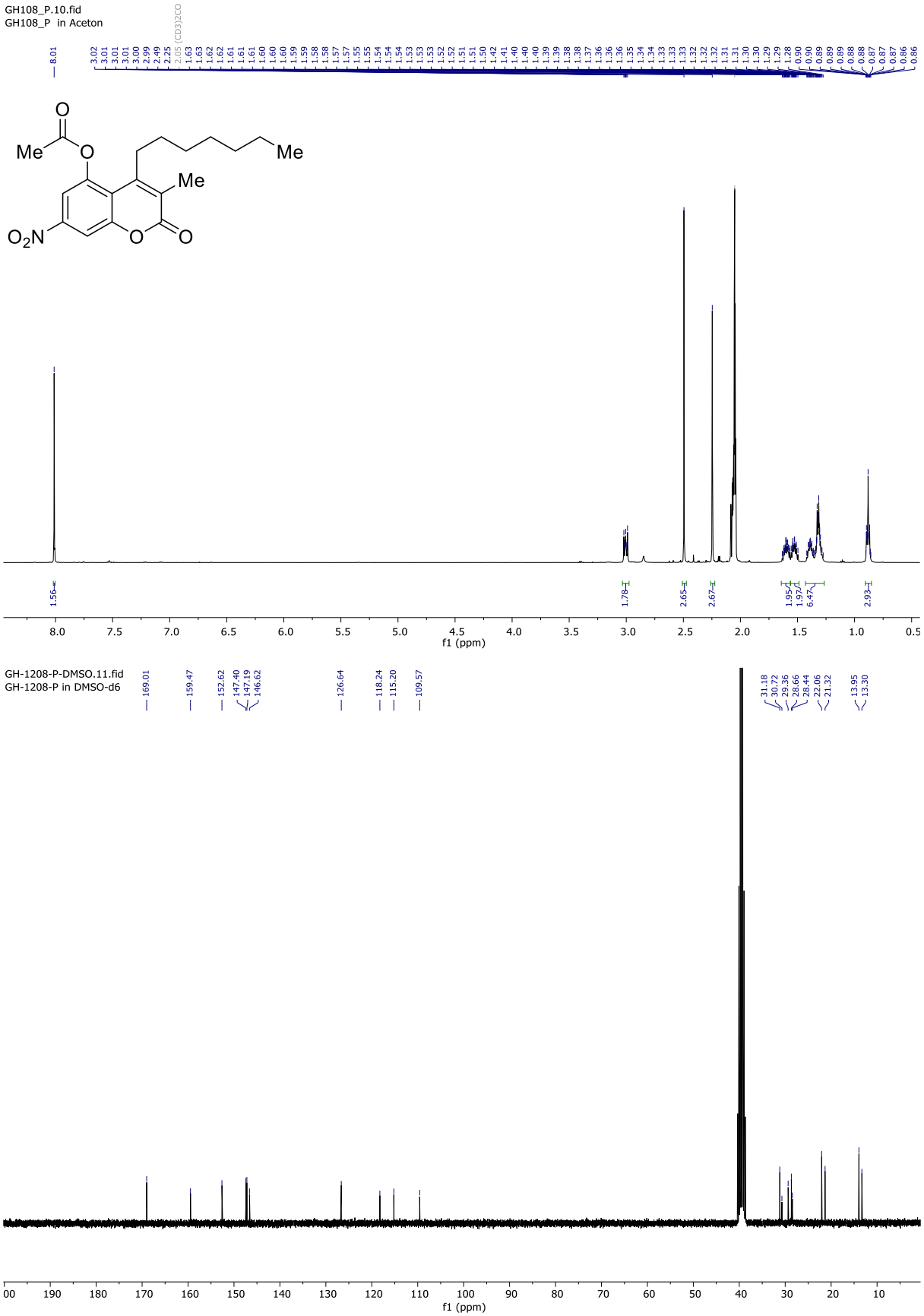


## 4.58 4-heptyl-5-hydroxy-3-methyl-7-nitrocoumarin (**30**)



## 4.59 5-*O*-acyl-4-heptyl-3-methyl-7-nitrocoumarin (**31**)



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