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# Supplementary Materials: Enzymatic Synthesis of Thioesters from Thiols and Vinyl Esters in a Continuous-Flow Microreactor

**Nani Zhou [1], Le Shen [1], Zhen Dong [1], Jiahong Shen [1], Lihua Du [1,*] and Xiping Luo [2,*]**

## 3. Materials and Methods

### *3.2. Thioester Synthesis Operating Conditions*

#### 3.2.1. General Procedure for Thioesters Synthesis under Shaker Conditions

**Method A:** Benzyl mercaptan (1 mmol) and vinyl laurate (3 mmol) were added to 5 mL DMSO. The biocatalyst lipozyme TL IM (0.22 g, 44 mg $mL^{-1}$) was then added and the suspension maintained at 50 °C for 24 h under Shaker Conditions. The mixture was cooled and filtered. Then evaporated under reduced pressure and the residue was submitted to column chromatography on silica gel (200-300 mesh). The products were eluted with a gradient of normal petroleum ether: ethyl acetate (20: 1, by vol). The purification was monitored by TLC. The fractions containing the main products were pooled, the solvent evaporated, and the residue analyzed by $^{1}H$ NMR, $^{13}C$ NMR and ESI-MS.

#### 3.2.2. General Procedure for Thioester Synthesis in Continuous Flow Microreactors

**Method B:** 4 mmol of the benzyl mercaptan was dissolved in 10 mL DMSO (feed **1**) and 8 mmol vinyl laurate were dissolved in 10 mL DMSO (feed **2**). Lipozyme TL IM (0.87 g, 44 mg $mL^{-1}$) was weighed, then filled the MVQ reactor coil (inner diameter ID: 2.0 mm, length: 1 m). Feeds **1** and **2** were mixed together at a flow rate of 10.4 μL $min^{-1}$ in a Y-mixer at 50 °C and the resulting stream (20.8 μL $min^{-1}$) was connected to a sample vial which was used to collect the final mixture. The final mixture was then evaporated, and the residue was submitted to column chromatography on silica gel (200-300 mesh). The products were eluted with a gradient of normal petroleum ether: ethyl acetate (20: 1, by vol). The purification was monitored by TLC. The fractions containing the main products were pooled, the solvent evaporated, and the residue analyzed by $^{1}H$ NMR, $^{13}C$ NMR and ESI-MS.

In order to examine the reproducibility of the method, we repeated the reaction five times, the result are illustrate in Figure S1.

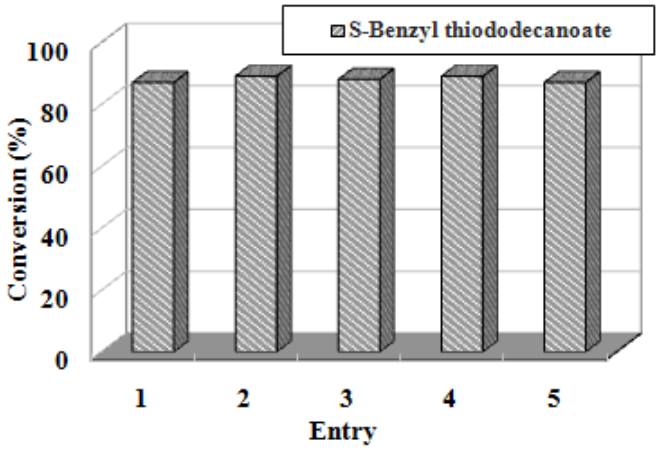
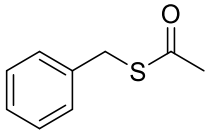
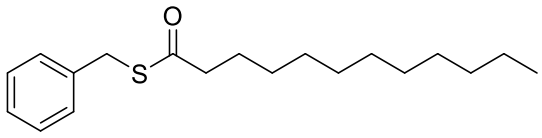



**Figure S1.** The reproducibility of the reaction on the conversion of S-Benzyl thiododecanoate catalysed by Lipozyme TL IM in a continuous flow microreactor.

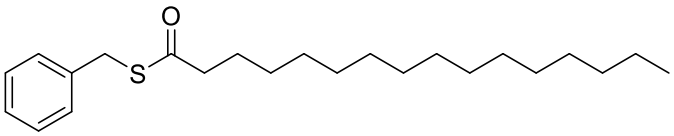
**Nuclear magnetic resonance (NMR) analysis**



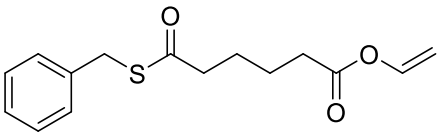
***S-benzyl thioacetate (3a):*** Light yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.32 - 7.26 (m, 5H), 4.15 (s, 2H), 2.37 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 195.0, 137.6, 128.8, 128.6, 127.2, 33.4, 30.2. ESI-MS: *m*/*z* = 189.1 $[M+Na]^+$.



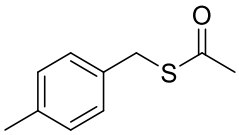
***S-benzyl thiododecanoate (3b):*** White crystals; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.36 - 7.27 (m, 5H), 4.17 (s, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.73 (m, 2H), 1.35 (m, 16H), 0.98 (t, *J* = 6.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.2, 137.7, 128.6, 128.4, 127.0, 43.6, 32.9, 31.8, 29.5, 29.4 - 29.1, 28.8, 25.5, 22.6, 14.0. ESI-MS: *m*/*z* = 329.2 $[M+Na]^+$.



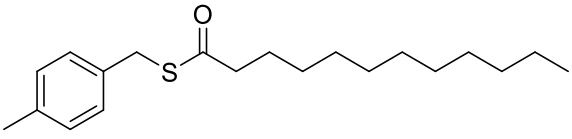
***S-benzyl thiohexadecanoate (3c):*** White solid; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.34 - 7.25 (m, 5H), 4.14 (s, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.66 (m, 2H), 1.47 - 1.23 (m, 24H), 0.91 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.9, 137.8, 129.3, 129.0, 128.8, 128.6, 127.2, 43.9, 33.1, 31.9, 29.7, 29.6 – 29.1, 29.0, 25.6, 22.7, 14.1. ESI-MS: *m*/*z* = 385.2 $[M+Na]^+$.



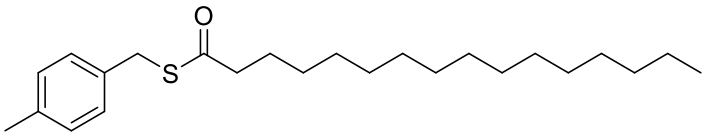
***6-oxo.-6-((benzyl)thio)-hexanoate vinyl ester (3d):*** Yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.35 - 7.24 (m, 6H), 4.89 (ddd, *J* = 14.0, 3.4, 1.6 Hz, 1H), 4.59 (ddd, *J* = 6.3, 2.4, 1.7 Hz, 1H), 4.14 (s, 2H), 2.59 (m, 2H), 2.43 (m, 2H), 1.72 (m, 4H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.1, 170.1, 141.1, 137.5, 128.7, 128.6, 127.2, 97.6, 43.2, 33.4, 33.1, 24.7, 23.8. ESI-MS: *m*/*z* = 301.1 $[M+Na]^+$.



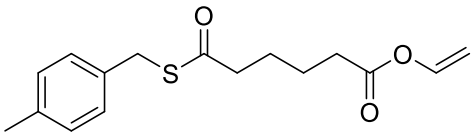
***S-(4-methylbenzyl) ethanethioate (3e):*** Light yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 4.10 (s, 2H), 2.35 (s, 3H), 2.33 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 195.0, 137.9, 134.2, 129.8, 129.7, 33.4, 30.2, 21.1. ESI-MS: *m*/*z* = 203.1 $[M+Na]^+$.



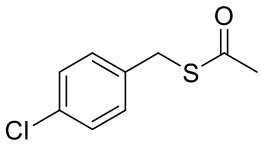
***S-(4-methylbenzyl) thiododecanoate (3f):*** Yellow liquid oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 4.10 (s, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.33 (s, 3H), 1.64 (m, 2H), 1.31 (m, 16H), 0.89 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.1, 137.0, 134.7, 129.4, 128.8, 43.9, 32.9, 32.0, 29.7, 29.6 - 29.3, 29.0, 25.7, 22.8, 21.1, 14.2. ESI-MS: *m*/*z* = 343.2 $[M+Na]^+$.



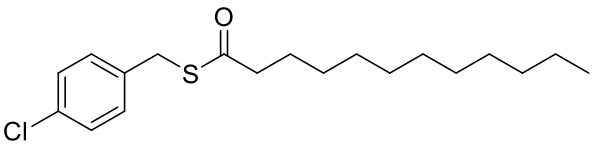

***S-(4-methylbenzyl) thiohexadecanoate (3g):*** Light yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 4.10 (s, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 1.68 (m, 2H), 1.32 - 1.27 (m, 24H), 0.90 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.0, 136.9, 134.7, 129.3, 128.7, 43.9, 32.9, 32.0, 29.7, 29.6 - 29.3, 29.0, 25.6, 22.7, 21.1, 14.1. ESI-MS: *m*/*z* = 399.3 $[M+Na]^+$.



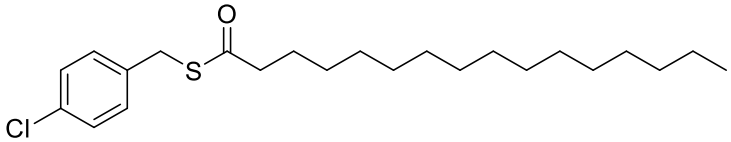

***6-oxo.-6-((4-methylbenzyl)thio)-hexanoate vinyl ester (3h):*** Light yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.31 - 7.20 (m, 5H), 4.87 (ddd, *J* = 14.0, 3.3, 1.7 Hz, 1H), 4.56 (ddd, *J* = 6.2, 2.0, 1.7 Hz, 1H), 4.11 (s, 2H), 2.59 (m, 2H), 2.41 (m, 2H), 2.39 (s, 3H), 1.71 (m, 4H).$^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.0, 170.1, 141.0, 137.5, 128.7, 128.5, 127.2, 97.6, 43.1, 33.4, 33.1, 24.7, 23.8, 23.7. ESI-MS: *m*/*z* = 315.1 $[M+Na]^+$.




***S-(4-chlorobenzyl) ethanethioate (3i):*** Light yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 8.6, 6.6 Hz, 2H), 7.23 (dd, *J* = 8.5, 6.1 Hz, 2H), 4.08 (s, 2H), 2.36 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 195.0, 135.7, 132.7, 130.8, 128.8, 33.1, 30.5. ESI-MS: *m*/*z* = 223.0 $[M+Na]^+$.

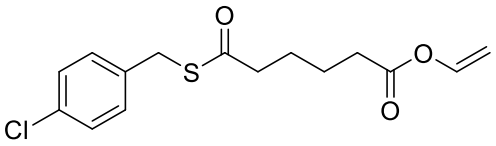



***S-(4-chlorobenzyl) thiododecanoate (3j):*** Yellow liquid oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 8.5, 6.5 Hz, 2H), 7.23 (dd, *J* = 8.5, 6.0 Hz, 2H), 4.08 (s, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.66 (m, 2H), 1.29 (m, 16H), 0.90 (t, *J* = 6.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.7, 141.2, 136.5, 133.0, 130.2, 128.7, 43.8, 34.0, 32.4, 31.9, 29.6 - 29.0, 28.9, 25.6, 24.6, 22.7, 14.1. ESI-MS: *m*/*z* = 363.2 $[M+Na]^+$.




***S-(4-chlorobenzyl) thiohexadecanoate (3k):*** Yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 8.4, 6.3 Hz, 2H), 7.23 (dd, *J* = 8.3, 6.0 Hz, 2H), 4.23 (s, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.78 (d, *J* = 7.1 Hz, 2H), 1.58 - 1.32 (m, 24H), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.0, 135.9, 132.8,

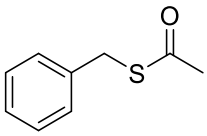
131.9, 131.7, 129.2, 128.8, 44.2, 33.6, 32.9, 30.1, 29.8 - 29.2, 28.0, 26.5, 23.4, 14.9. ESI-MS: *m*/*z* = 419.2 $[M+Na]^+$.

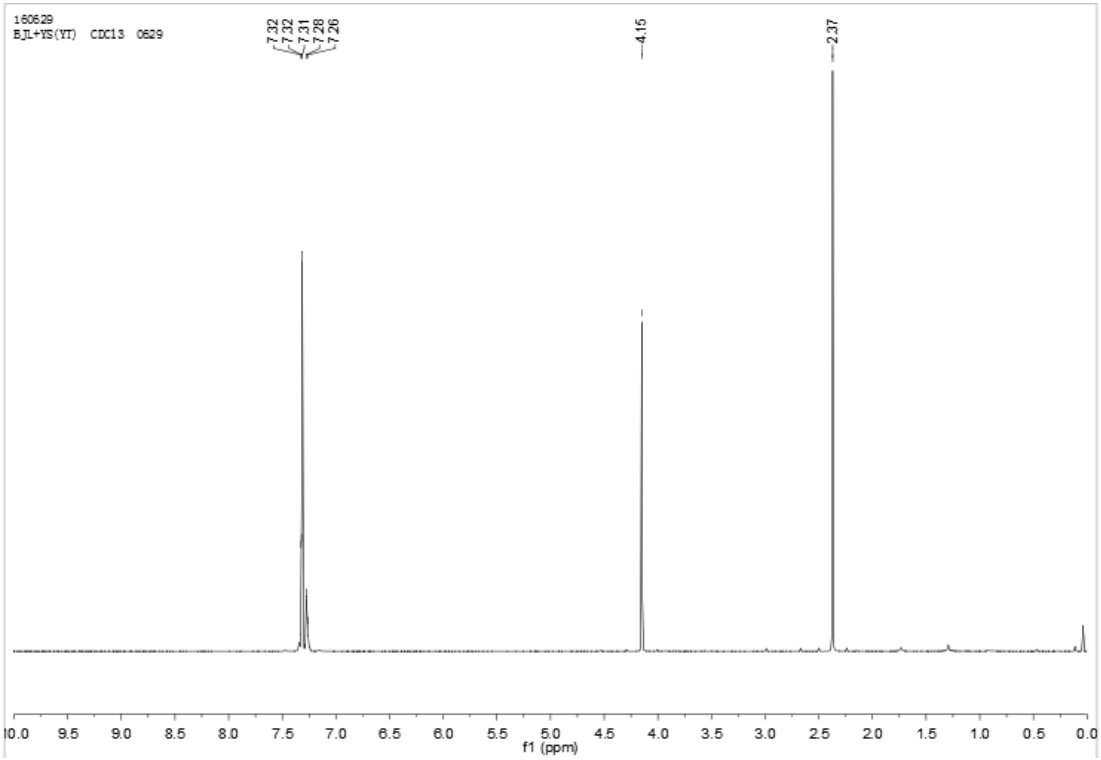



***6-oxo.-6-((4-chlorobenzyl)thio)-hexanoate vinyl ester(3l):*** Yellow oil; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.32 - 7.20 (m, 5H), 4.89 (ddd, *J* = 14.0, 3.4, 1.6 Hz, 1H), 4.59 (ddd, *J* = 6.3, 2.4, 1.6 Hz, 1H), 4.08 (s, 2H), 2.61 (m, 2H), 2.41 (m, 2H), 1.72 (m, 4H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.0, 170.2, 141.1, 136.3, 133.1, 130.2, 128.8, 97.7, 43.2, 33.4, 32.5, 24.8, 23.8. ESI-MS: *m*/*z* = 335.1 $[M+Na]^+$.

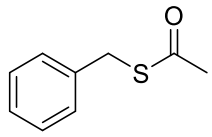
**Copy of $^1$H NMR and $^{13}$C Spectra of Products**

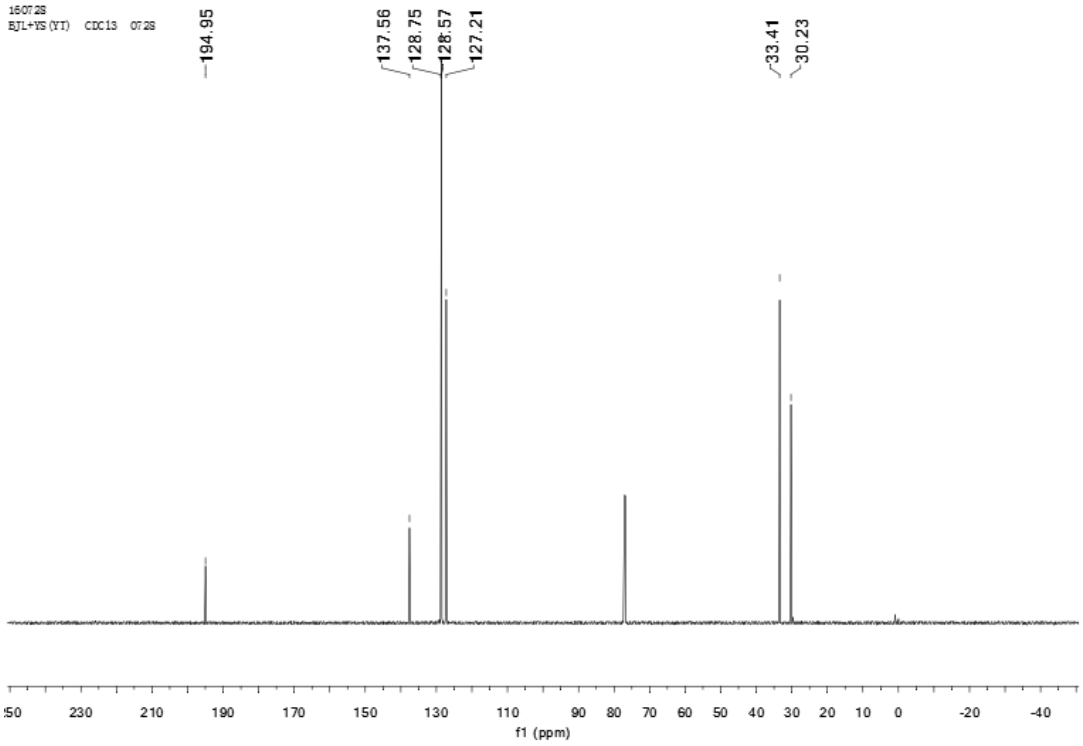
$^1$H-NMR of compound **3a**



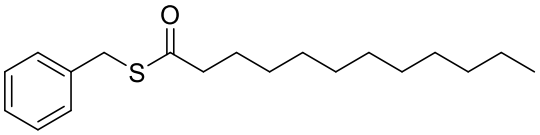



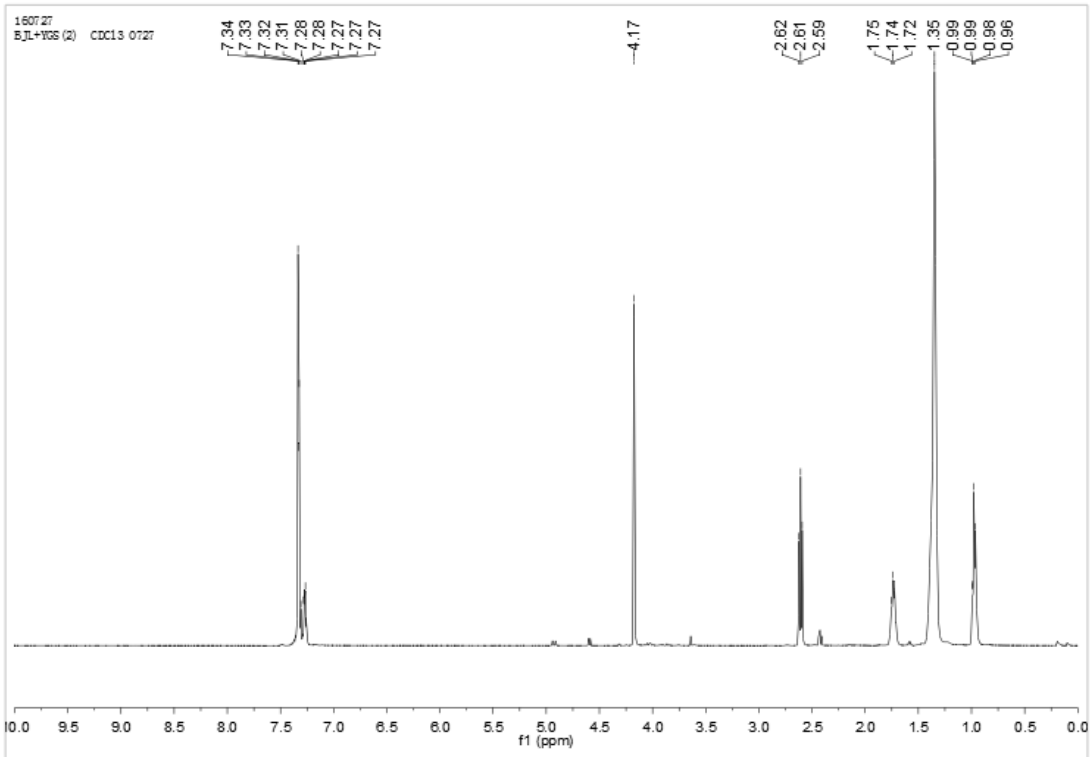
$^{13}$C-NMR of compound **3a**



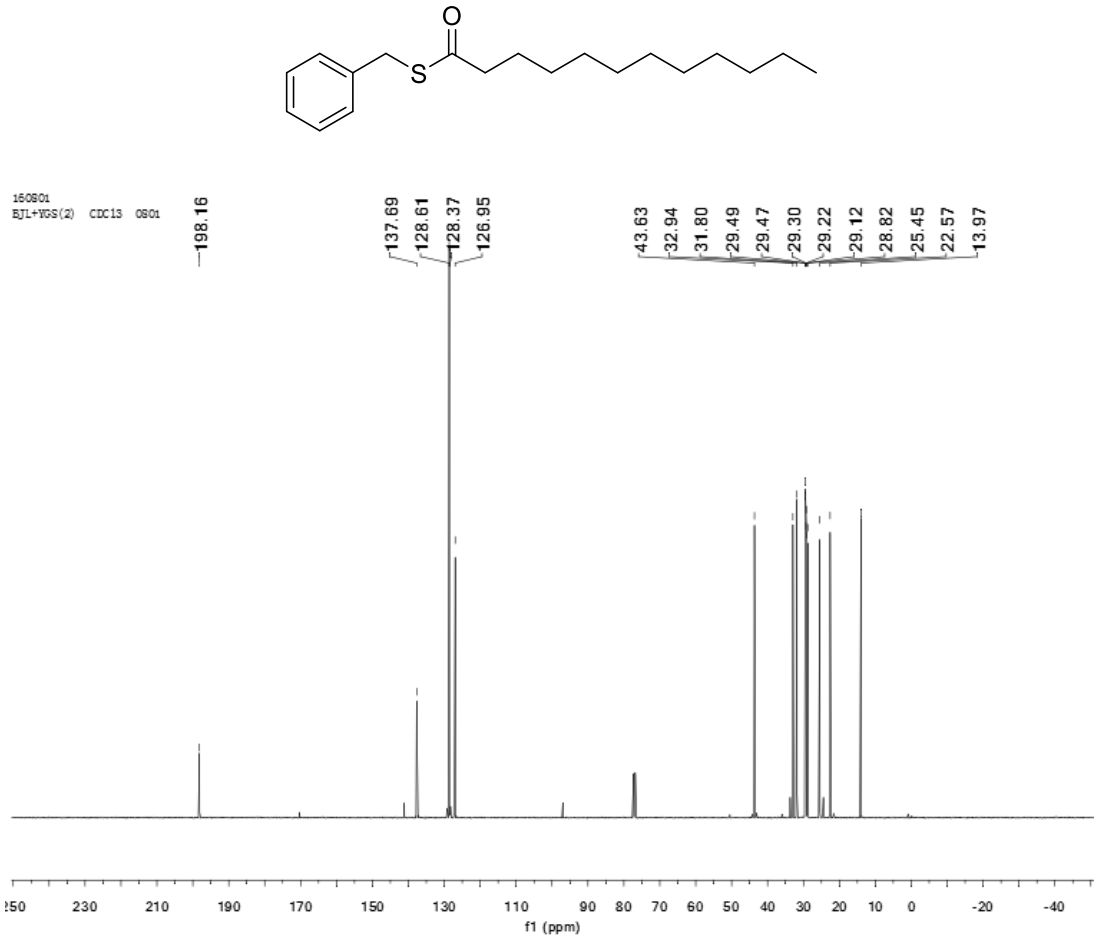



$^{1}$H-NMR of compound **3b**

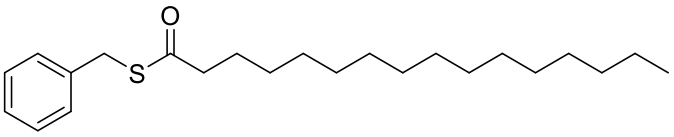


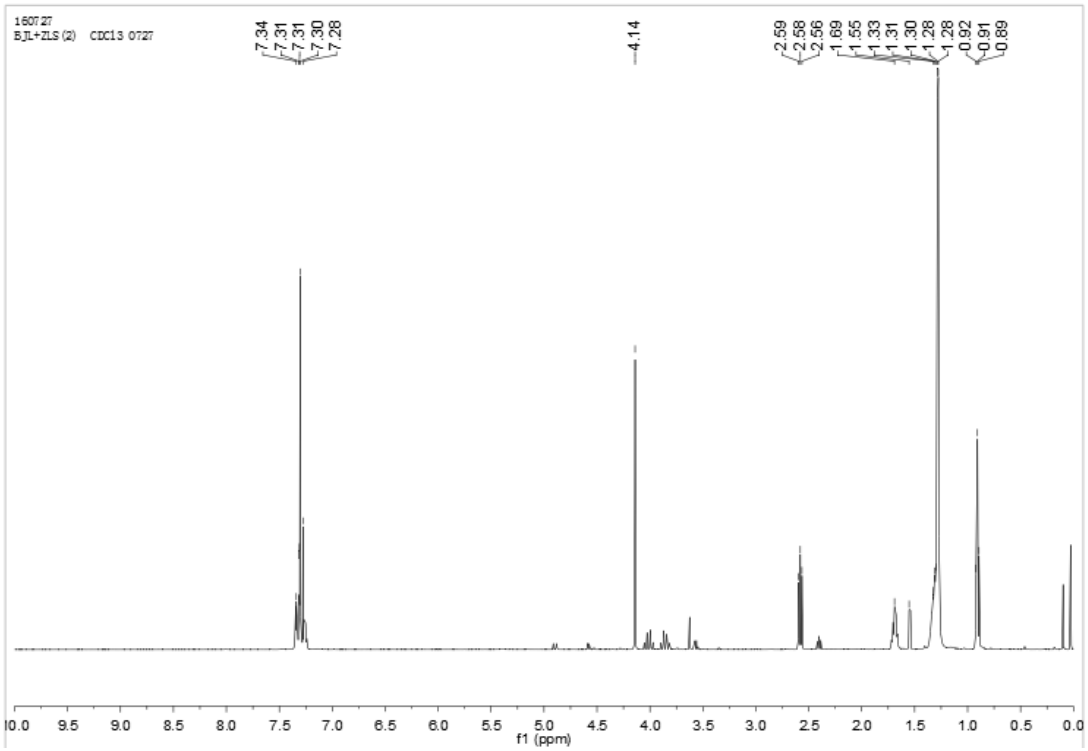



$^{13}$C-NMR of compound **3b**

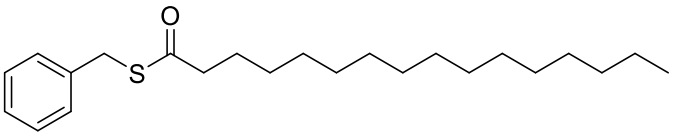


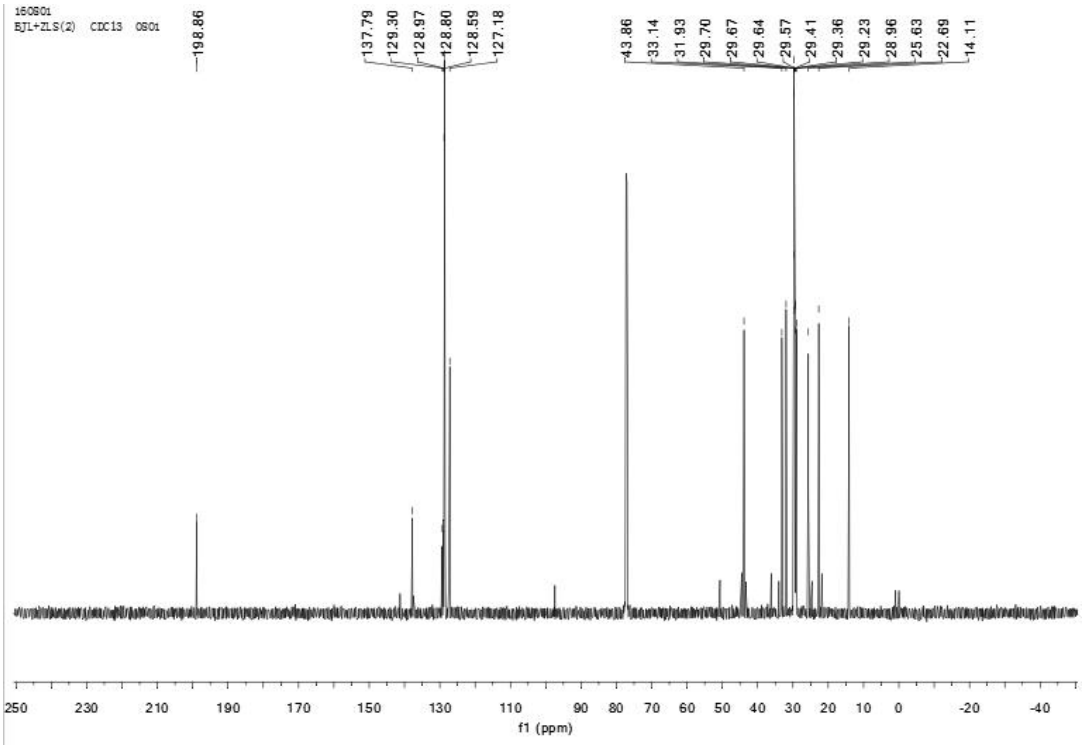
$^{1}$H-NMR of compound **3c**



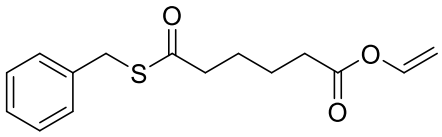



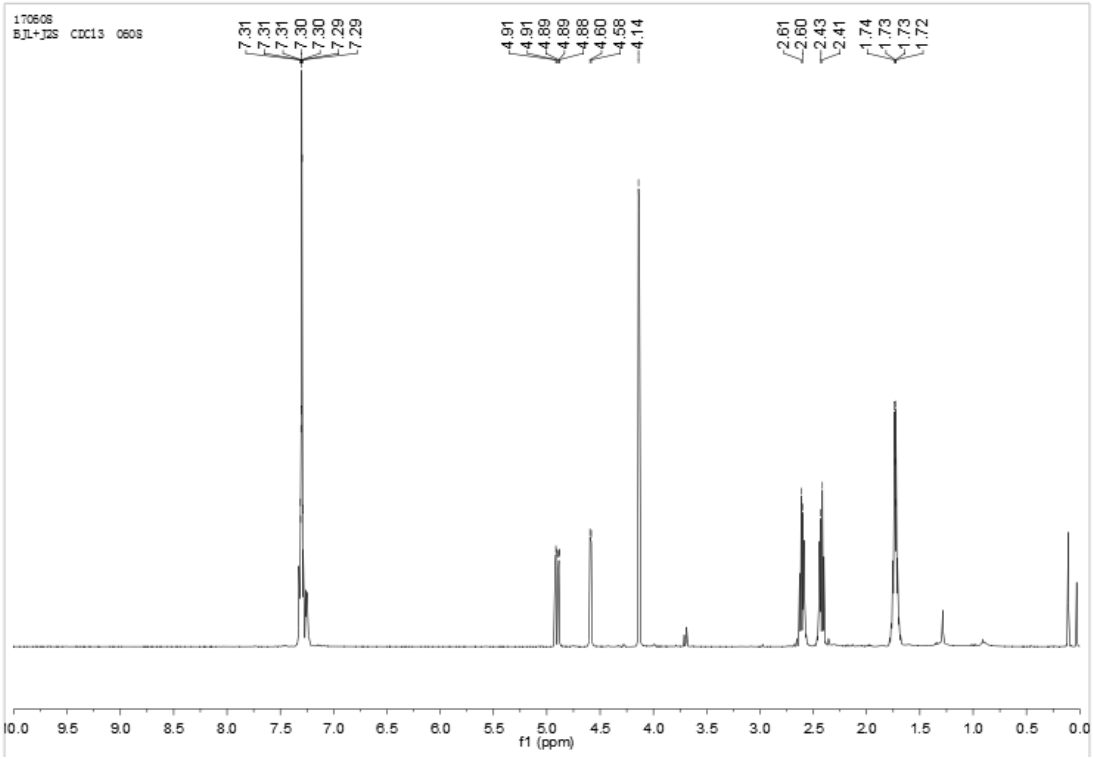
$^{13}$C-NMR of compound **3c**



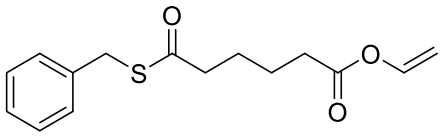



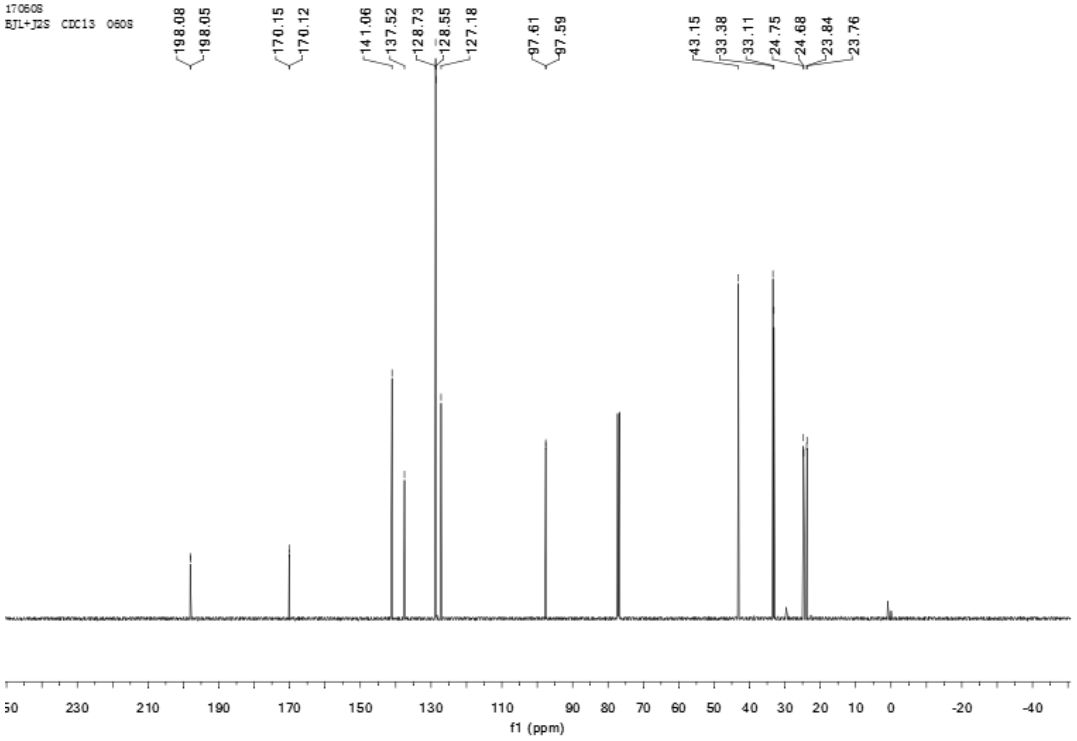
$^{1}$H-NMR of compound **3d**



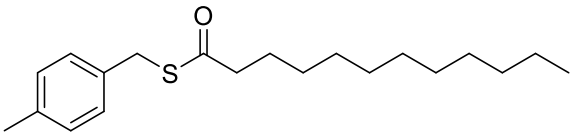



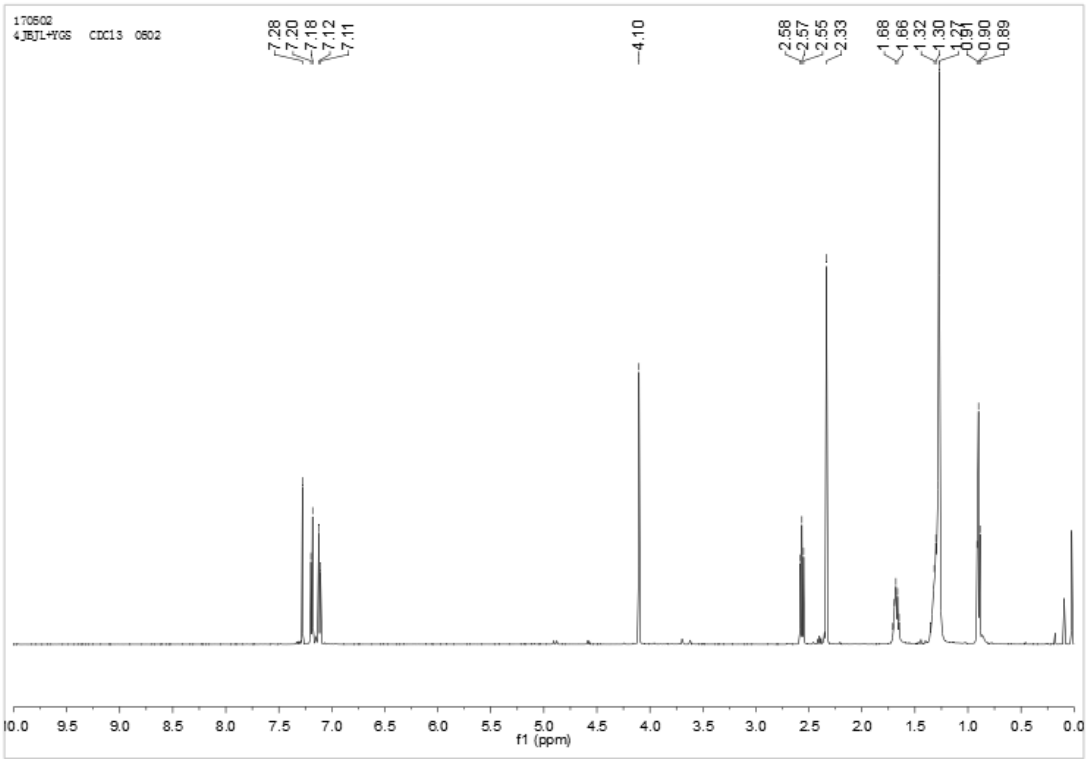
$^{13}$C-NMR of compound **3d**



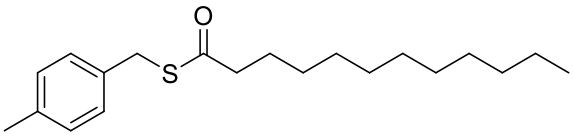



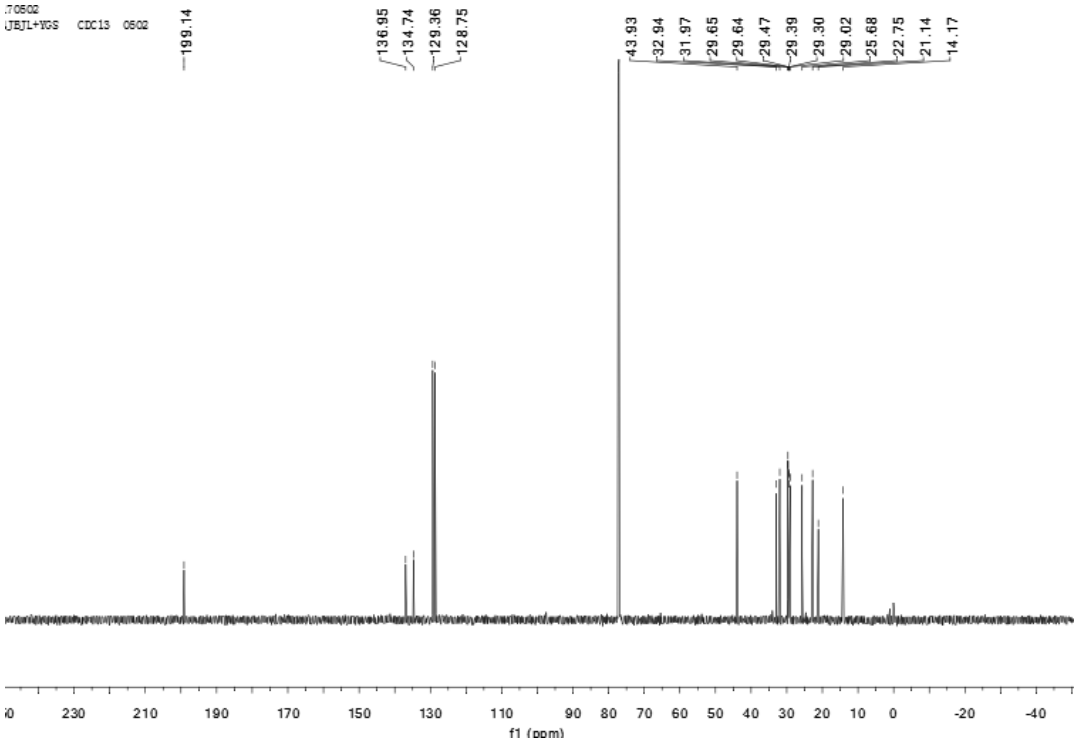
$^{1}$H-NMR of compound **3f**



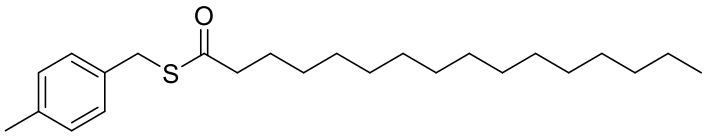



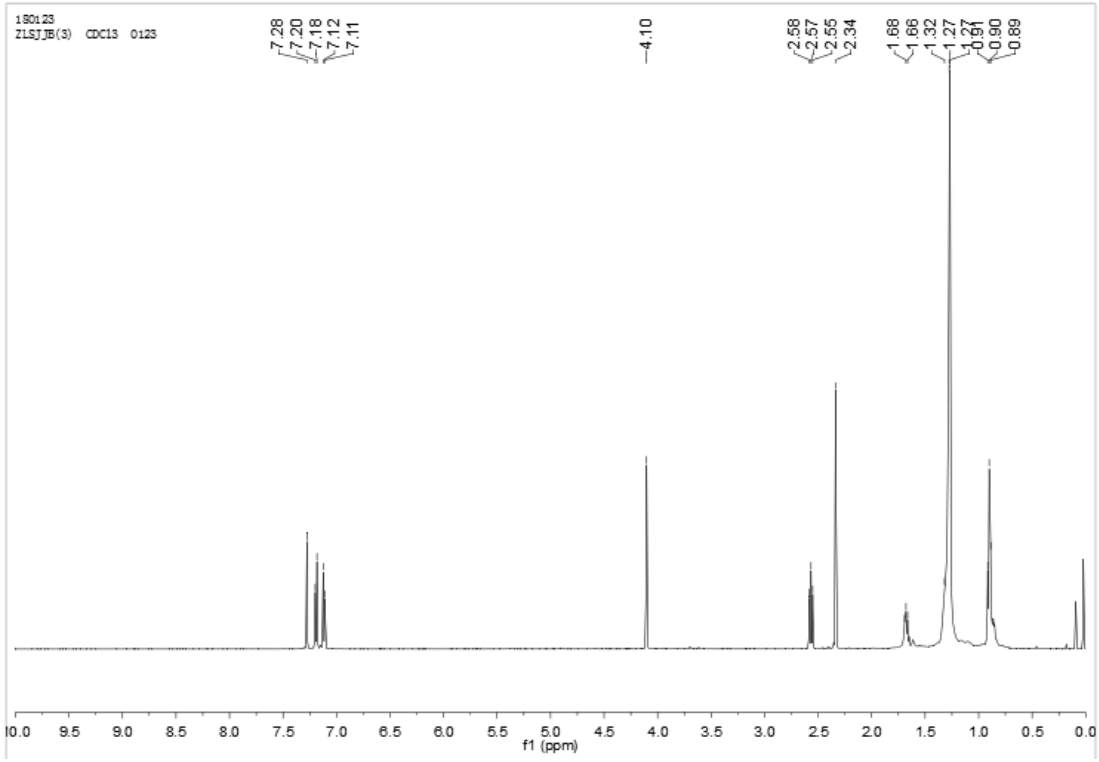
$^{13}$C-NMR of compound **3f**



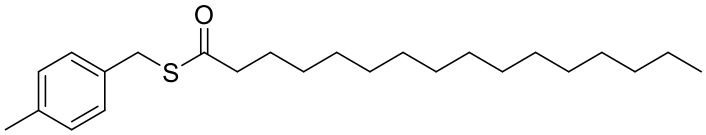



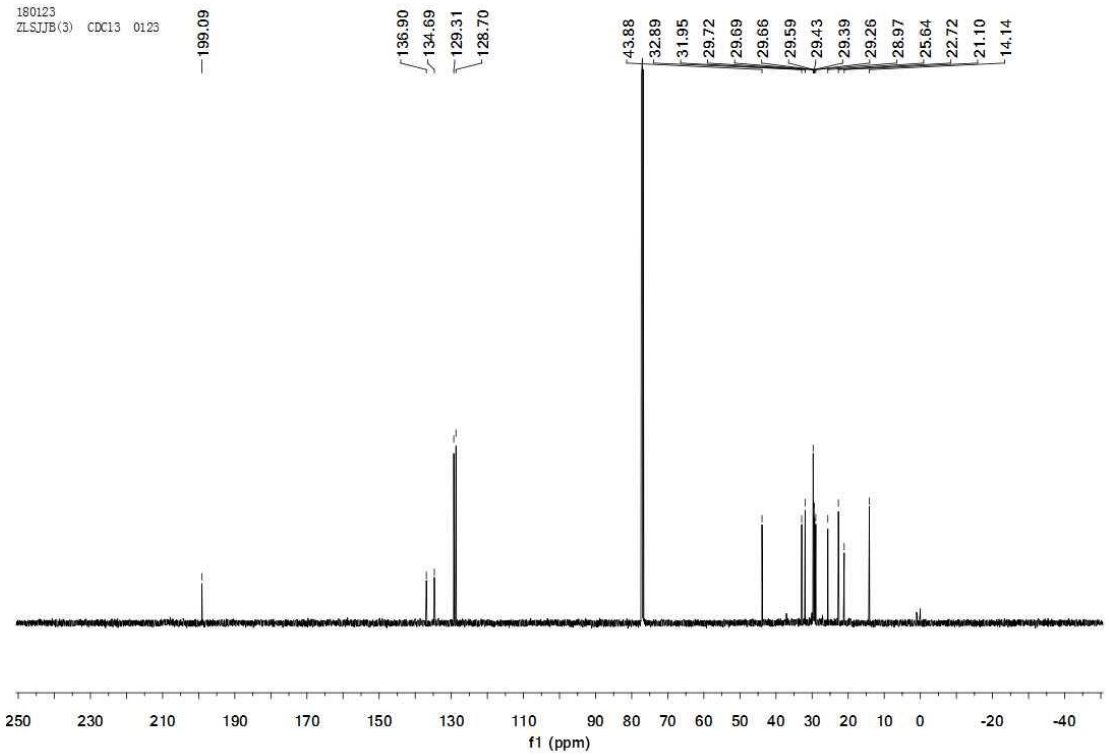
$^{1}$H-NMR of compound **3g**



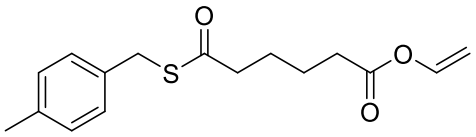



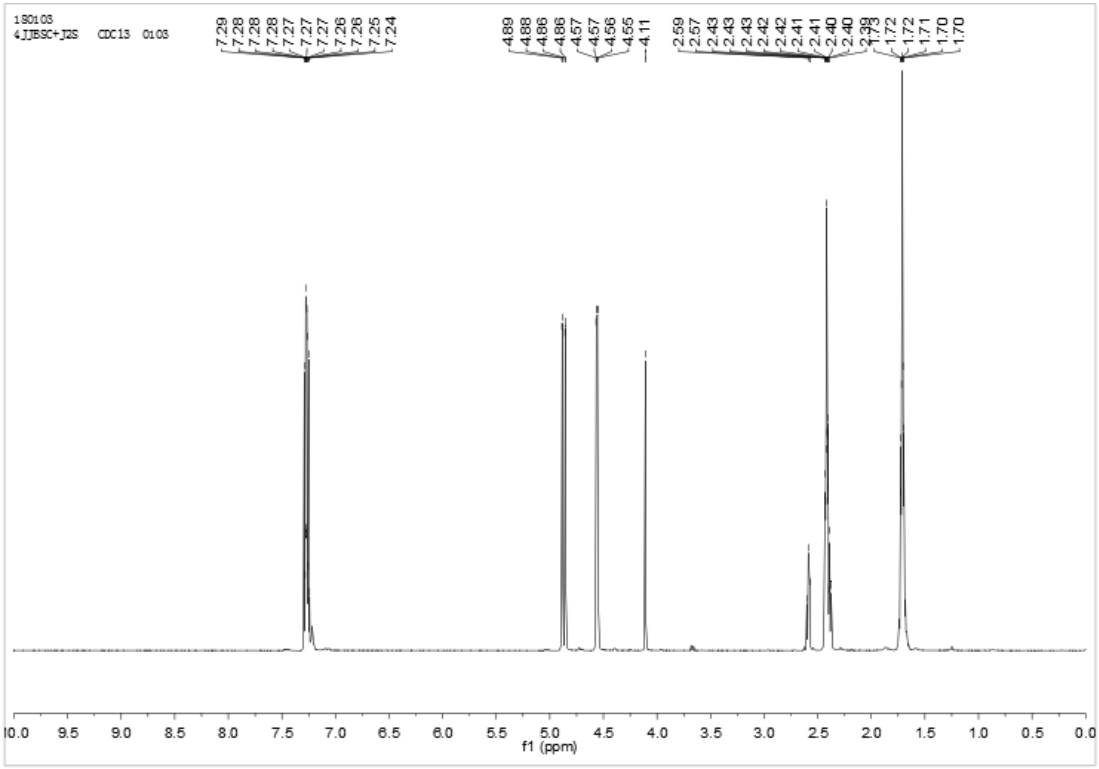
$^{13}$C-NMR of compound **3g**



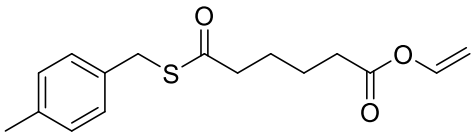



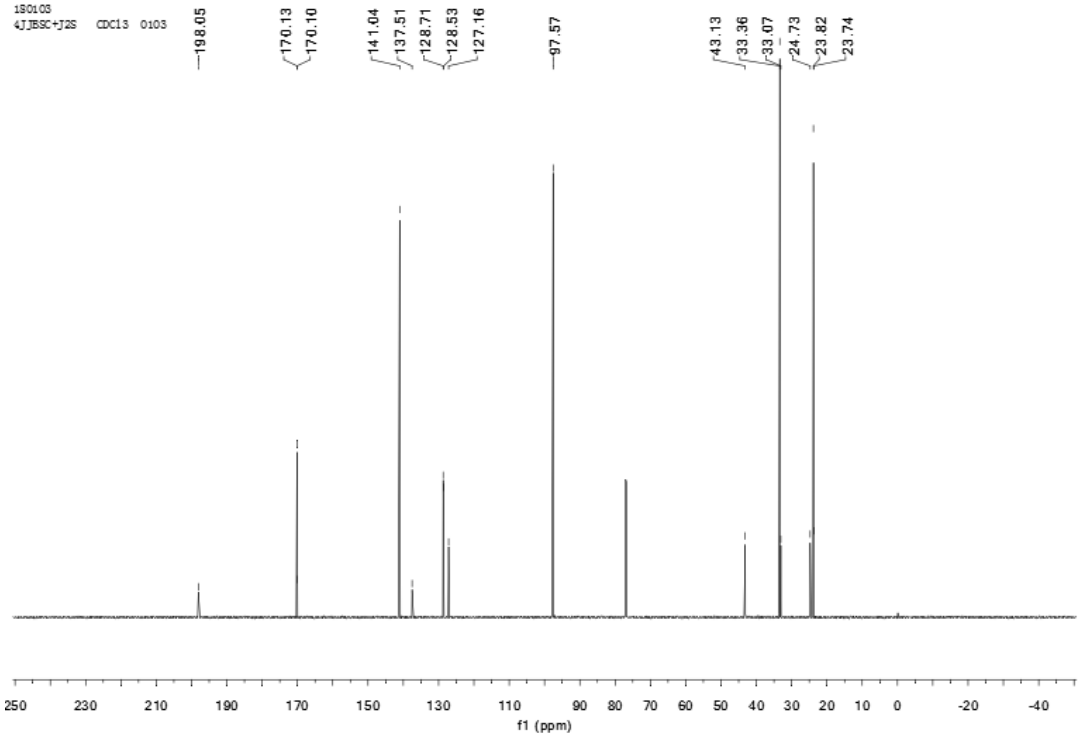
$^{1}$H-NMR of compound **3h**



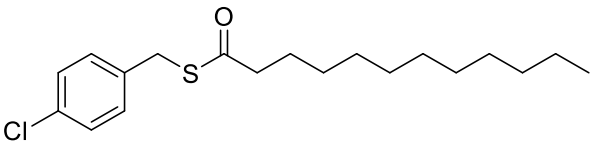



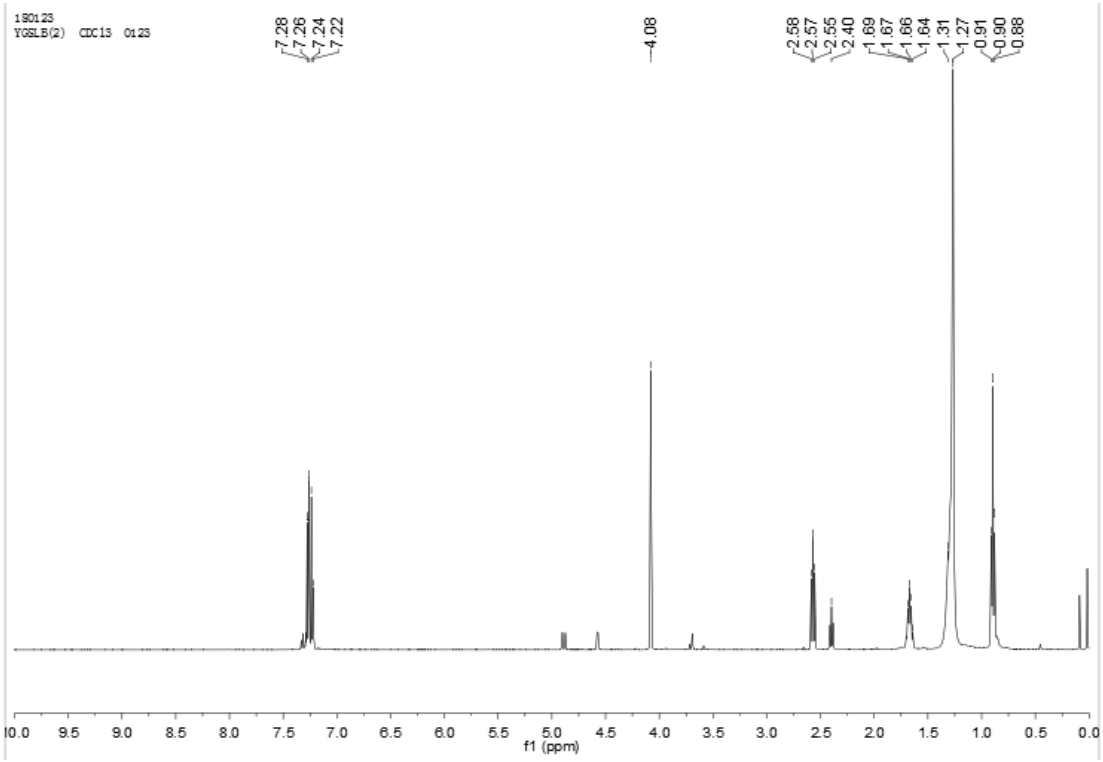
$^{13}$C-NMR of compound **3h**



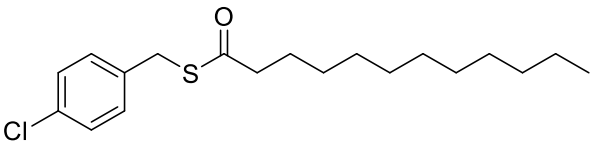



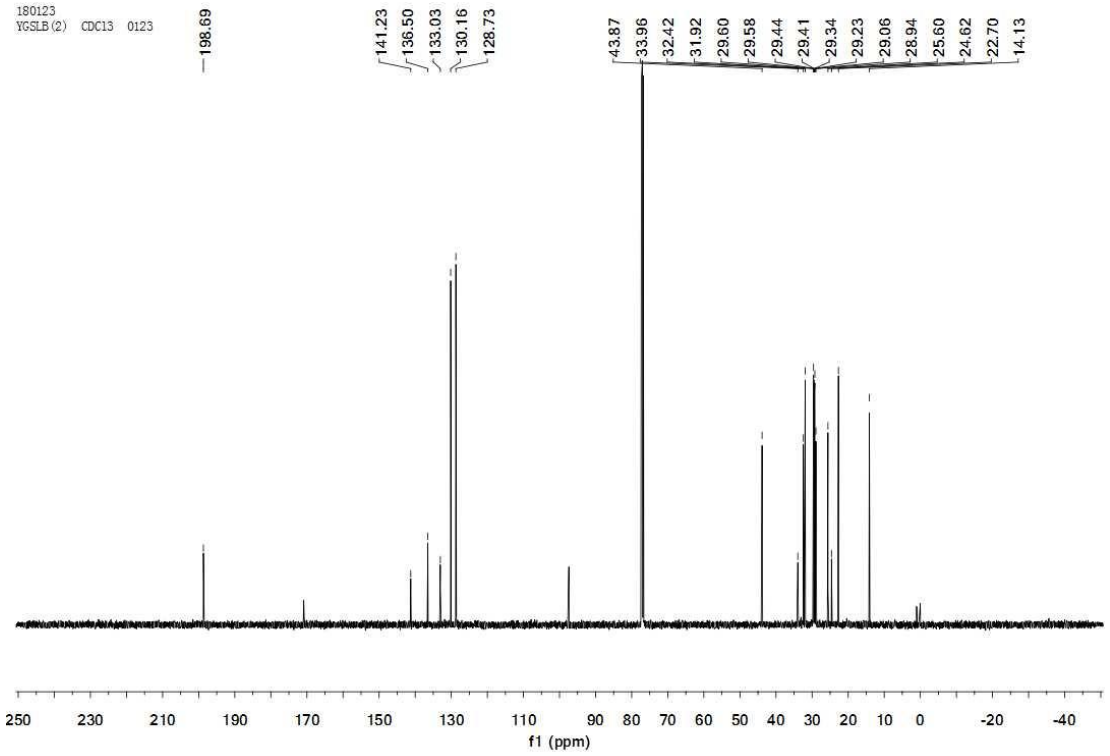
$^{1}$H-NMR of compound **3j**



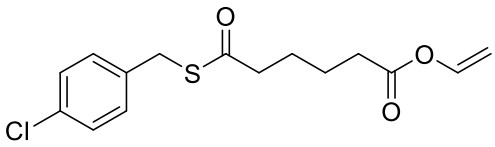



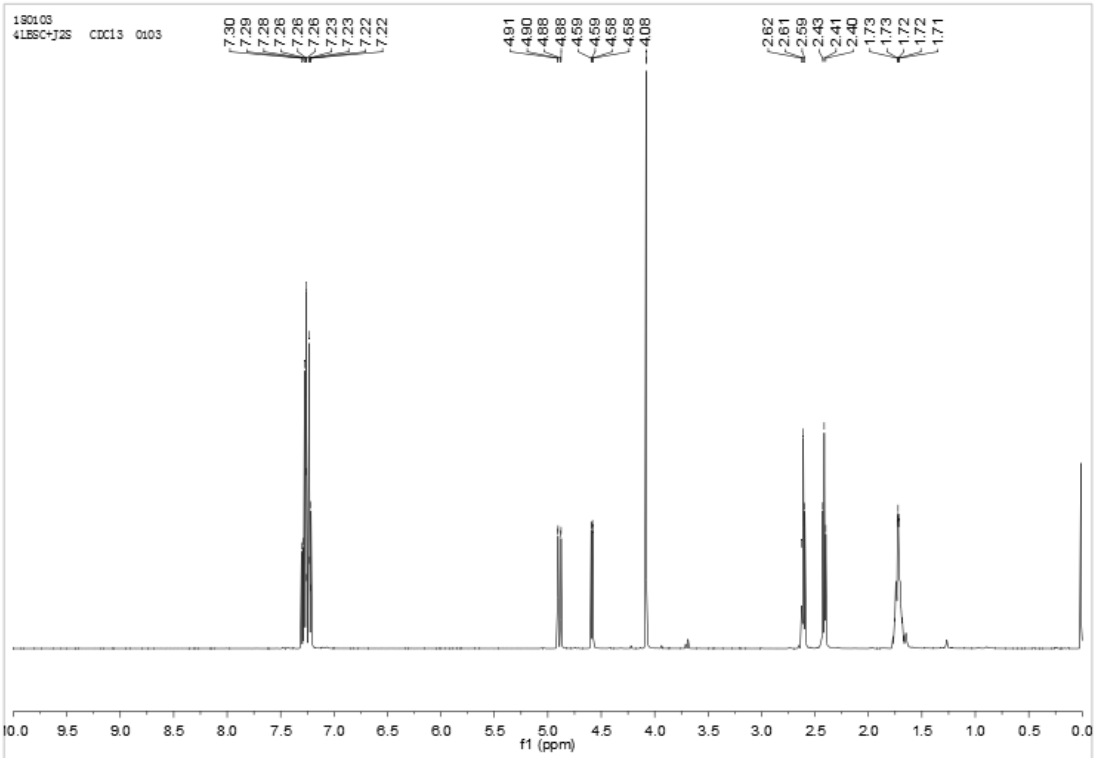
$^{13}$C-NMR of compound **3j**



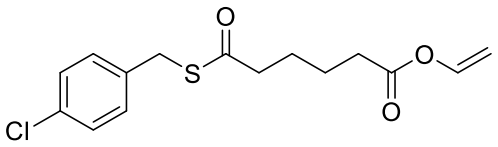



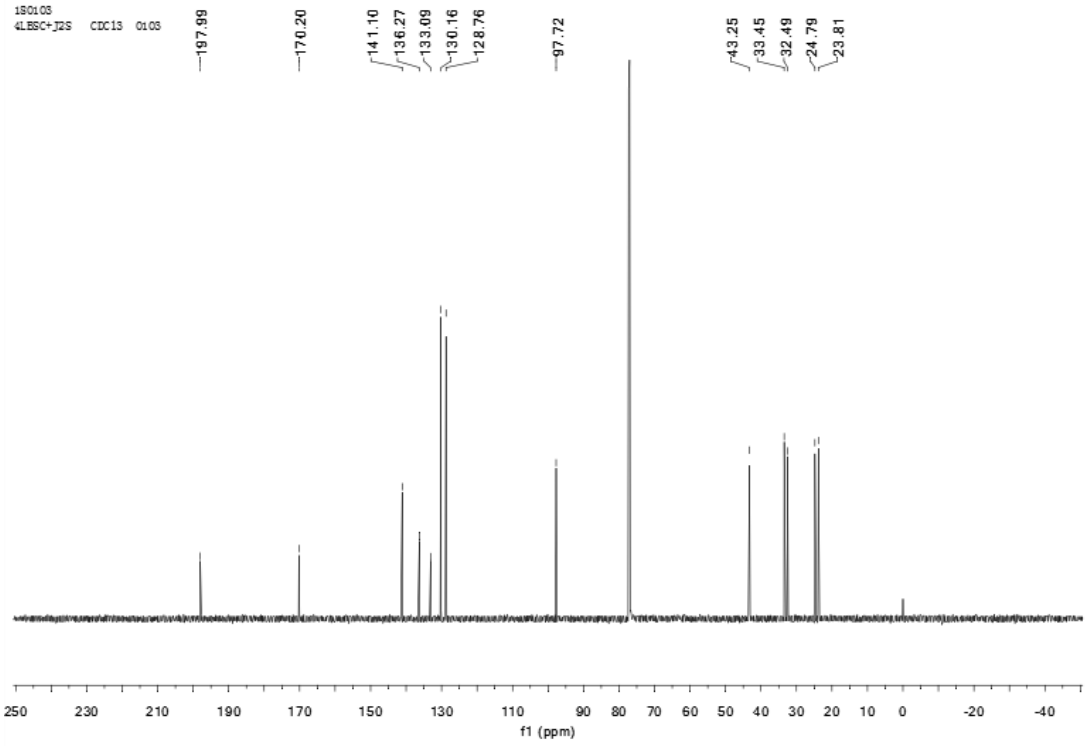
$^{1}$H-NMR of compound **3l**



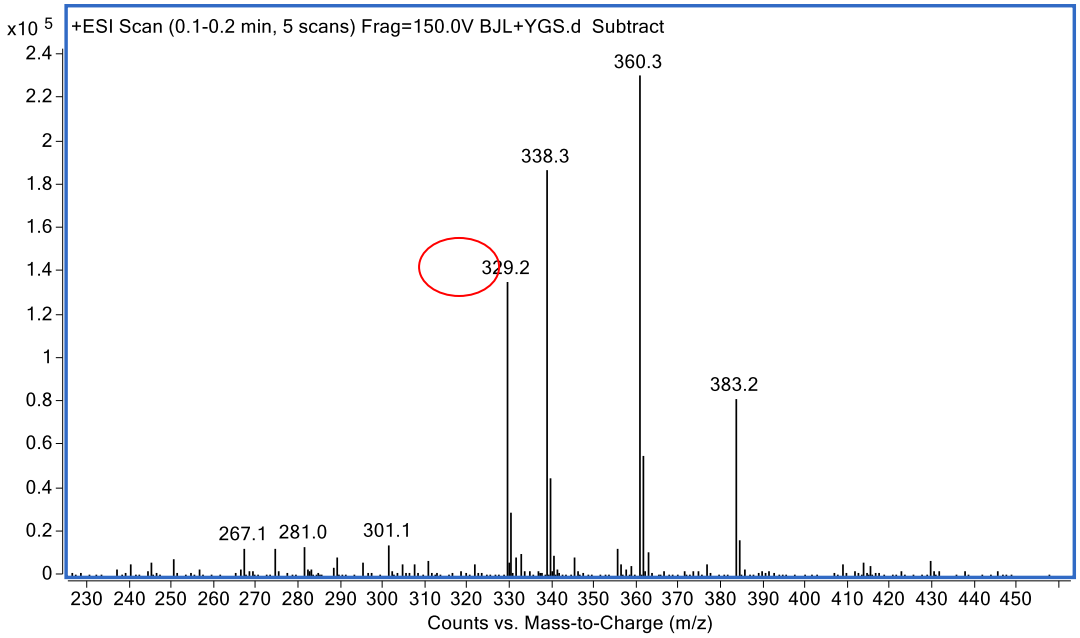
$^{13}$C-NMR of compound **3l**



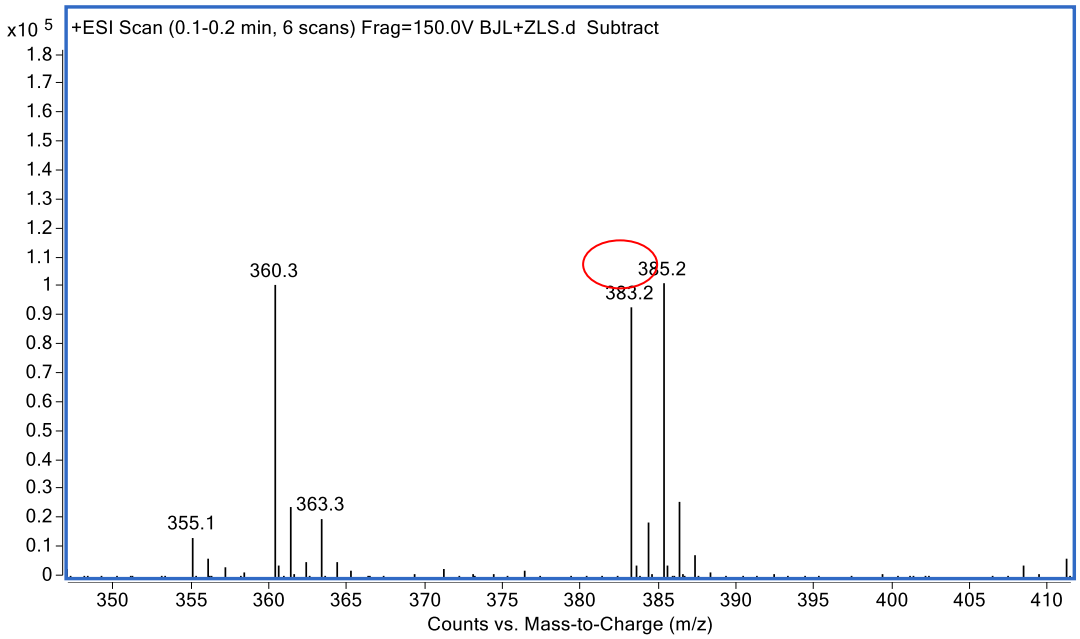



## The Mass spectrum of compound

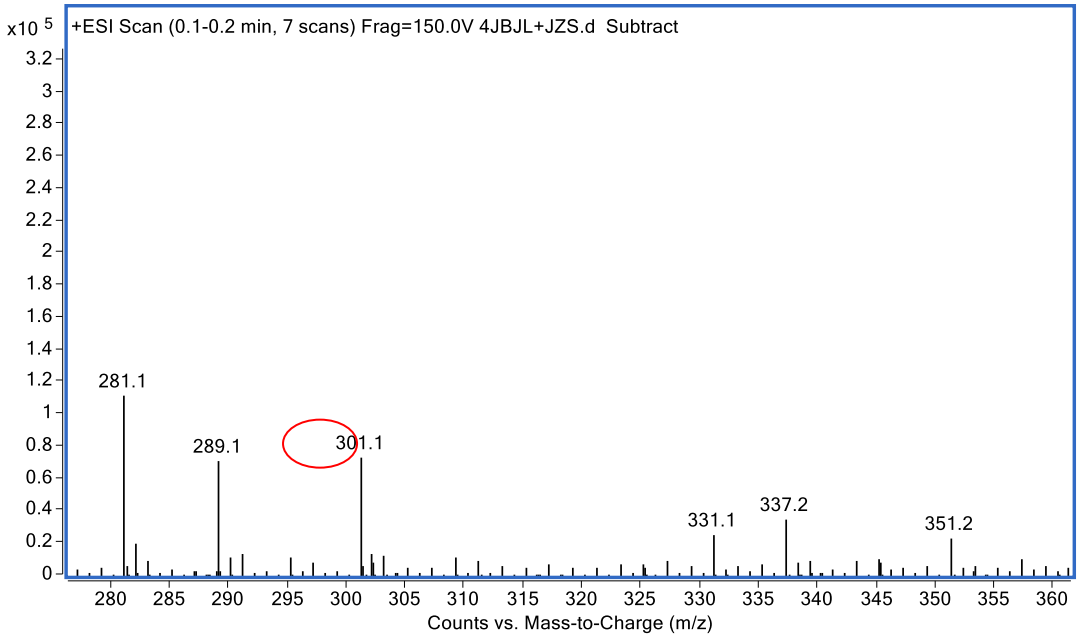
compound **3b**




compound **3c**



compound **3d**


x10 5
+ESI Scan (0.1-0.2 min, 7 scans) Frag=150.0V 4JBJL+JZS.d Subtract
3.2
3
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
281.1
289.1
301.1
331.1
337.2
351.2
280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360
Counts vs. Mass-to-Charge (m/z)