



## Supporting Information

for

### **Derivatives of benzo-1,4-thiazine-3-carboxylic acid and the corresponding amino acid conjugates**

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**Experimental procedures and characterization data, additional experimental results, pictures of NMR and HRMS spectra**

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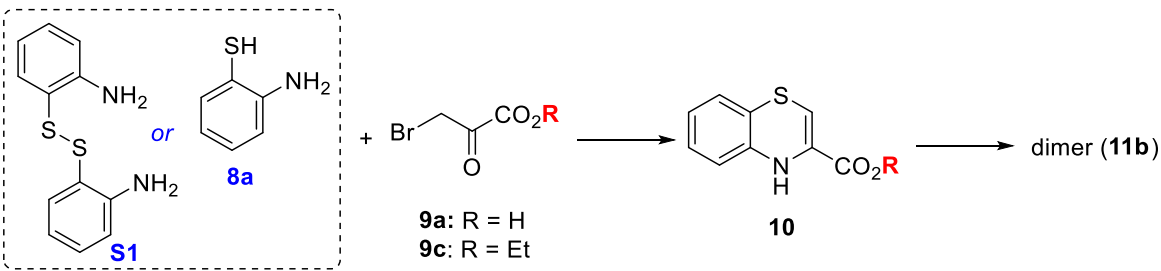
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## 1. General information

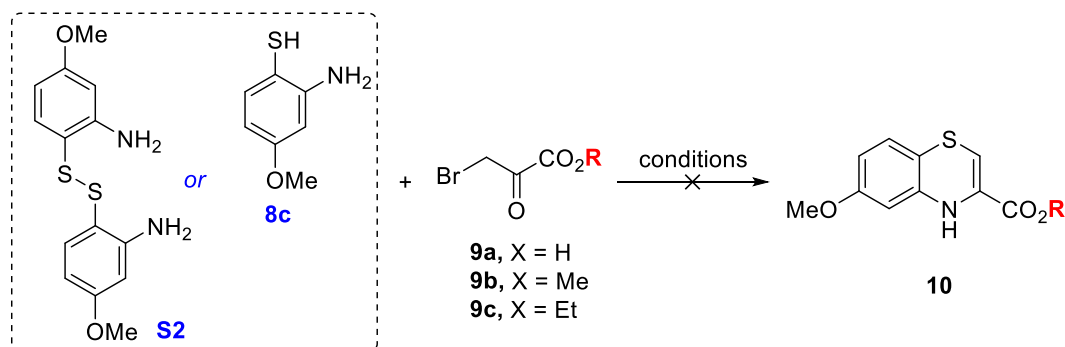
Chemicals were purchased from Merck (previously Sigma Aldrich), Alfa Aesar, Acros Organics and TCI, and if not otherwise noted, they were used as provided. Reactions were monitored by thin-layer chromatography (TLC) analysis using Merck silica gel 60 F<sub>254</sub> plates. Following the general workup, products were purified by flash chromatography using Isolera Biotage FSKO-1107-0010 or Büchi Pure C-810 Flash system and Std, HC or HP Puriflash columns by Interchim. NMR spectra were measured on a Varian VNMRs 600 spectrometer (600 MHz for <sup>1</sup>H NMR experiments, 150 MHz for <sup>13</sup>C NMR spectra) and Bruker Avance NEO 400 MHz (400 MHz for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR). Chemical shifts ( $\delta$ ) were referenced to TMS as an internal standard and are given in ppm. Interaction constants (*J*) are in Hz. The following abbreviations are used to describe the multiplicity of observed signals: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectroscopy was measured by using Orbitrap Thermo Scientific Velos pro with HESI/heated electrospray ionization. Low-resolution mass spectroscopy was measured on an Advion Expression CMS Compact Mass Spectrometer using Atmospheric Solids Analysis Probe (ASAP<sup>®</sup>) or a TLC plate reader. Enantiomeric purities were determined by Chiralcel and Chiralpak (Daicel Chemical Industries Ltd.) columns on HPLC Agilent Technologies 1200 Infinity series using Chemstation software for LC systems. IR spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were measured on an M-565 Büchi device.

## 2. Additional experimental results

**Table S1.** Reactions of **9** with 2-aminobenzenethiol (**8a**) and 2-aminophenyl disulfide (**S1**).

|  <p> <math>\text{Br}-\text{CH}_2-\text{C}(=\text{O})-\text{CO}_2\text{R}</math><br/> <b>9a:</b> R = H<br/> <b>9c:</b> R = Et         </p> <p> <b>10</b><br/> <b>11b</b> </p> |              |          |                                                    |              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|----------|----------------------------------------------------|--------------|
| entry                                                                                                                                                                                                                                                          | <b>8a/S1</b> | <b>R</b> | conditions                                         | yield        |
| 1                                                                                                                                                                                                                                                              | <b>S1</b>    | Et       | EtOH, rt, 24 h                                     | —            |
| 2                                                                                                                                                                                                                                                              | <b>S1</b>    | Et       | EtOH, rt, 168 h                                    | —            |
| 3                                                                                                                                                                                                                                                              | <b>S1</b>    | Et       | EtOH, reflux, 30 min                               | —            |
| 4                                                                                                                                                                                                                                                              | <b>8a</b>    | Et       | EtOH, MWI, 100 °C, 5 min                           | —            |
| 5                                                                                                                                                                                                                                                              | <b>8a</b>    | Et       | EtOH, rt, 24 h                                     | —            |
| 6                                                                                                                                                                                                                                                              | <b>8a</b>    | Et       | EtOH, MWI, 100 °C, 20 min                          | (dimer, 28%) |
| 7                                                                                                                                                                                                                                                              | <b>8a</b>    | Et       | EtOH, MWI, 100 °C, 1 h                             | (dimer, 11%) |
| 8                                                                                                                                                                                                                                                              | <b>8a</b>    | Et       | EtOH, MWI, 60 °C, 1 h                              | (dimer, 20%) |
| 9                                                                                                                                                                                                                                                              | <b>S1</b>    | Et       | EtOH, MWI, 100 °C, 20 min                          | —            |
| 10                                                                                                                                                                                                                                                             | <b>8a</b>    | Et       | EtOH, MWI, 100 °C, 20 min                          | —            |
| 11                                                                                                                                                                                                                                                             | <b>S1</b>    | Et       | EtOH, reflux, 10 min, NaBH <sub>4</sub>            | —            |
| 12                                                                                                                                                                                                                                                             | <b>8a</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h          | (dimer, 15%) |
| 13                                                                                                                                                                                                                                                             | <b>S1</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt→reflux, 2 h   | —            |
| 14                                                                                                                                                                                                                                                             | <b>8a</b>    | Et       | EtOH, rt, 40 min                                   | 51%          |
| 15                                                                                                                                                                                                                                                             | <b>8a</b>    | Et       | EtOAc, rt, 1 h                                     | —            |
| 16                                                                                                                                                                                                                                                             | <b>S1</b>    | Et       | EtOAc, rt, 1 h                                     | —            |
| 17                                                                                                                                                                                                                                                             | <b>8a</b>    | Et       | EtOH, 0 °C→rt, 2h                                  | 29%          |
| 18                                                                                                                                                                                                                                                             | <b>S1</b>    | H        | EtOH, reflux, 30 min                               | —            |
| 19                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | EtOH, reflux, 30 min                               | —            |
| 20                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | EtOH, MWI, 60 °C, 1 h                              | —            |
| 21                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | CH <sub>2</sub> Cl <sub>2</sub> , MWI, 100 °C, 1 h | —            |
| 22                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | Et <sub>2</sub> O, reflux, 10 min                  | —            |
| 23                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | Et <sub>2</sub> O, rt, 10 min                      | —            |
| 24                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | Et <sub>2</sub> O, 0 °C→rt, 10 min                 | —            |
| 25                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | Et <sub>2</sub> O, 0 °C, 15 min                    | traces       |
| 26                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | Et <sub>2</sub> O, 0 °C, 1 h                       | traces       |
| 27                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | EtOH, 0 °C, 30 min                                 | —            |
| 28                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | THF, 0 °C, 30 min                                  | —            |
| 29                                                                                                                                                                                                                                                             | <b>S1</b>    | H        | DMF, rt, 24h                                       | —            |
| 30                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | DMF, rt, 24h                                       | —            |
| 31                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | EtOAc, 0 °C, 1 h                                   | —            |
| 32                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | Et <sub>2</sub> O, rt, 1 h                         | —            |
| 33                                                                                                                                                                                                                                                             | <b>8a</b>    | H        | Et <sub>2</sub> O, 0 °C, 1 h                       | 75%          |

**Table S2.** Reactions of **9** with 2-amino-4-methoxybenzenethiol (**8c**) and 2-amino-4-methoxyphenyl disulfide (**S2**).



| entry | <b>8c/S2</b> | <b>R</b> | conditions                                                       | yield |
|-------|--------------|----------|------------------------------------------------------------------|-------|
| 1     | <b>S2</b>    | Et       | EtOH, MWI, 100 °C, 20 min                                        | —     |
| 2     | <b>S2</b>    | Et       | EtOH, reflux, 10 min                                             | —     |
| 3     | <b>S2</b>    | Et       | EtOH, rt, 10 min→24 h                                            | —     |
| 4     | <b>S2</b>    | Et       | EtOH, rt, 10 min, TsOH                                           | —     |
| 5     | <b>S2</b>    | Et       | EtOH, reflux, 10 min, NaBH <sub>4</sub>                          | —     |
| 6     | <b>S2</b>    | Et       | EtOH, MWI, 100 °C, 20 min (2 equiv of ester)                     | —     |
| 7     | <b>S2</b>    | Et       | EtOH, rt, 24 h                                                   | —     |
| 8     | <b>S2</b>    | Et       | Et <sub>2</sub> O, rt, 24 h                                      | —     |
| 9     | <b>S2</b>    | Et       | MeOH, rt, 24 h                                                   | —     |
| 10    | <b>S2</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 24 h                       | —     |
| 11    | <b>S2</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 1 h                        | —     |
| 12    | <b>S2</b>    | Et       | EtOH, MWI, 100 °C, 5 min                                         | —     |
| 13    | <b>S2</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h (2 equiv of disulfide) | —     |
| 14    | <b>S2</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h                        | —     |
| 15    | <b>S2</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h (2 equiv of ester)     | —     |
| 16    | <b>S2</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h (3 equiv of ester)     | —     |
| 17    | <b>S2</b>    | Et       | EtOH, rt, 1 h (2.5 equiv of ester)                               | —     |
| 18    | <b>S2</b>    | Et       | CH <sub>2</sub> Cl <sub>2</sub> , rt, 1 h (2.5 equiv of ester)   | —     |
| 19    | <b>S2</b>    | Et       | Et <sub>2</sub> O, rt, 1 h (2.5 equiv of ester)                  | —     |
| 20    | <b>8c</b>    | Et       | EtOH, rt, 40 min                                                 | —     |
| 21    | <b>8c</b>    | Et       | EtOH, 0 °C – rt, 1 h                                             | —     |
| 22    | <b>S2</b>    | H        | Et <sub>2</sub> O, rt, 20 min                                    | —     |
| 23    | <b>S2</b>    | H        | Et <sub>2</sub> O, rt, 24 h                                      | —     |
| 24    | <b>S2</b>    | H        | Et <sub>2</sub> O, rt, 20 h (acid–base extraction)               | —     |
| 25    | <b>S2</b>    | H        | Et <sub>2</sub> O, rt, 1 h                                       | —     |
| 26    | <b>S2</b>    | H        | Et <sub>2</sub> O, rt, 1 h (acid–base extraction)                | —     |
| 27    | <b>8c</b>    | H        | Et <sub>2</sub> O, 0 °C, 1 h                                     | —     |
| 28    | <b>S2</b>    | H        | EtOH, rt, 2 h                                                    | —     |
| 29    | <b>S2</b>    | H        | EtOH, reflux, 10 min                                             | —     |
| 30    | <b>8c</b>    | H        | Et <sub>2</sub> O, 0 °C, 1 h                                     | —     |
| 31    | <b>8c</b>    | H        | Et <sub>2</sub> O, rt, 24 h                                      | —     |
| 32    | <b>8c</b>    | H        | EtOH, rt, 24 h                                                   | —     |
| 33    | <b>8c</b>    | H        | EtOH, reflux, 1 h                                                | —     |
| 34    | <b>8c</b>    | Me       | EtOH, rt, 3 h                                                    | —     |
| 35    | <b>S2</b>    | Me       | EtOH, rt, 3 h                                                    | —     |

**Table S3.** Reactions of **9** with 2-amino-4-chlorobenzenethiol (**8b**).

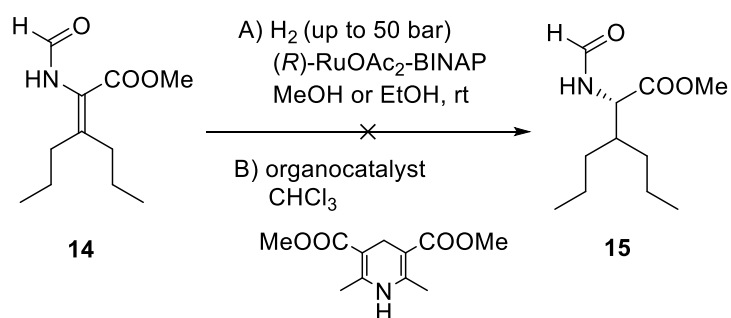
$\text{SH}$   
 $\text{NH}_2$   
 $\text{Cl}$   
**8b**

$\text{Br}-\text{CH}_2-\text{C}(=\text{O})-\text{CO}_2\text{R}$   
**9a**, X = H  
**9b**, X = Me

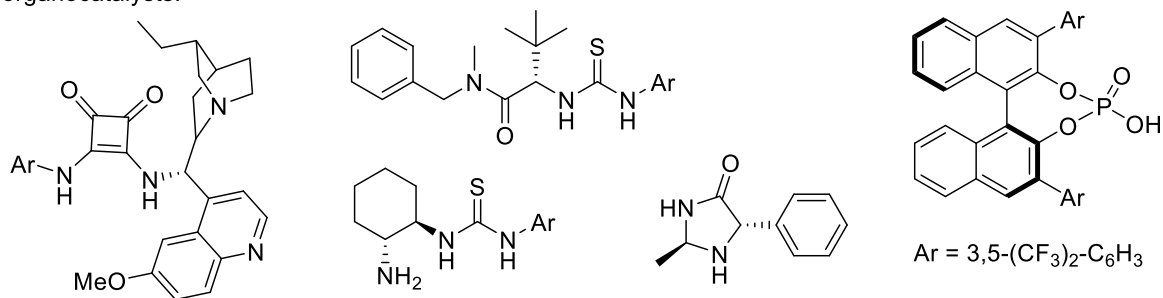
conditions  $\longrightarrow$

$\text{Cl}$   
 $\text{S}$   
 $\text{NH}$   
 $\text{CO}_2\text{R}$   
**10**

| entry | R  | conditions                 | yield (%) |
|-------|----|----------------------------|-----------|
| 1     | Me | EtOH, rt, 30 min           | 50        |
| 2     | Me | Et <sub>2</sub> O, rt, 1 h | 30        |
| 3     | Me | EtOH, rt, 1 h              | 44        |
| 4     | H  | EtOH, rt, 30 min           | 43        |
| 5     | H  | EtOH, rt, 60 min           | 66        |



organocatalysts:



**Scheme S1.** Unsuccessful stereoselective syntheses of formyl-protected amino acid methyl ester **15**.

**Table S4.** Reaction of benzothiazine acid **10aa** with L-valine (**S3**).

**10aa** + **S3**  $\xrightarrow[\text{rt, 24 h}]{\text{conditions}}$  Product

| entry | <b>10aa</b> (equiv) | <b>S3</b> (equiv) | reagents (equiv)                                             | solvent                         | yield (%) |
|-------|---------------------|-------------------|--------------------------------------------------------------|---------------------------------|-----------|
| 1     | 1.0                 | 1.0               | EDC (1.0), DIPEA (1.0)                                       | CH <sub>2</sub> Cl <sub>2</sub> | —         |
| 2     | 1.0                 | 1.0               | EDC (1.0), DIPEA (1.0)                                       | CH <sub>3</sub> CN              | —         |
| 3     | 1.0                 | 1.0               | EDC (1.0), DIPEA (1.5)                                       | CH <sub>2</sub> Cl <sub>2</sub> | —         |
| 4     | 1.5                 | 1.0               | T <sub>3</sub> P <sup>®</sup> (1.2), DMAP (0.1), DIPEA (2.0) | CH <sub>2</sub> Cl <sub>2</sub> | —         |
| 5     | 1.7                 | 1.1               | HOBt (2.0), DIPEA (1,1)                                      | CH <sub>2</sub> Cl <sub>2</sub> | —         |
| 6     | 1.0                 | 1.1               | HOBt (2.0), DIPEA (1,1)                                      | CH <sub>2</sub> Cl <sub>2</sub> | —         |
| 7     | 1.0                 | 1.1               | HOBt (2.0), EDC (1.0), DIPEA (1.1)                           | CH <sub>2</sub> Cl <sub>2</sub> | —         |

**Table S5.** Reaction of benzothiazine acid **10aa** with methyl L-valinate **S3·HCl**.

**10aa** + **S3·HCl**  $\xrightarrow[\text{conditions}]{\text{X}}$  Product

| entry | <b>10aa</b> (equiv) | <b>S3·HCl</b> (equiv) | reagents (equiv)                               | solvent                         | T (°C) | t (h)  | yield (%) |
|-------|---------------------|-----------------------|------------------------------------------------|---------------------------------|--------|--------|-----------|
| 1     | 1.0                 | 1.1                   | HOBt (1.0), DIPEA (1.1)                        | CH <sub>2</sub> Cl <sub>2</sub> | rt     | 24     | —         |
| 2     | 1.2                 | 1.0                   | EDC (1.0), HOBt (0.1), DMAP (1.0), DIPEA (1.0) | CH <sub>3</sub> CN              | rt     | 24     | —         |
| 3     | 1.0                 | 1.0                   | EDC (1.4), DCC (1.2), DIPEA (1.0)              | BM (25 Hz), EtOAc (LAG)         |        | 10 min | —         |
| 4     | 1.0                 | 1.0                   | EDC (1.4), DCC (1.2), DIPEA (1.0)              | BM (25 Hz), EtOAc (LAG)         |        | 1      | —         |
| 5     | 1.0                 | 1.0                   | EDC (1.4), DCC (1.2), DIPEA (1.0)              | EtOAc                           | 0      | 24     | —         |

**Table S6.** Unsuccessful connection of the amino acid methyl ester **16a**·HCl with the benzothiazine **10**.

**16a**·HCl + **10** (R = H or Et)  $\xrightarrow{\text{conditions}}$  Product

| entry | <b>16a</b> ·HCl (equiv) | R  | <b>10</b> (equiv) | reagents (equiv)                                  | solvent                               | T (°C)    | t (h) | yield (%) |
|-------|-------------------------|----|-------------------|---------------------------------------------------|---------------------------------------|-----------|-------|-----------|
| 1     | 1.2                     | Et | 1.0               | KOt-Bu (1.85)                                     | BM (30 Hz), no solvent                | —         | 2.5   | —         |
| 2     | 1.0                     | H  | 1.0               | EDC (1.0), DIPEA (1.0)                            | CH <sub>2</sub> Cl <sub>2</sub>       | rt        | o/n   | —         |
| 3     | 1.0                     | H  | 1.0               | EDC (1.2), HOBT (1.2), DIPEA (3.5)                | DMF                                   | 0 °C → rt | o/n   | —         |
| 4     | 1.0                     | H  | 1.0               | SOCl <sub>2</sub> (1.0), TEA (4.0)                | CH <sub>2</sub> Cl <sub>2</sub>       | rt        | o/n   | —         |
| 5     | 1.2                     | H  | 1.0               | SOCl <sub>2</sub> (138.0), DMF (cat), DIPEA (3.0) | THF                                   | rt        | o/n   | —         |
| 6     | 1.0                     | H  | 1.5               | (COCl) <sub>2</sub> , DMF (cat), TEA              | CH <sub>2</sub> Cl <sub>2</sub> , DMF | rt        | o/n   | —         |
| 7     | 1.0                     | H  | 1.0               | COMU (1.0), TEA (3.0)                             | DMF                                   | rt        | o/n   | traces    |

**Table S7.** Reaction of benzothiazine ester **10bb** with racemic amino acid methyl ester **16a**.

**10bb** + **16a**  $\xrightarrow{\text{conditions}}$  Product

| entry | <b>10bb</b> (equiv) | <b>16a</b> (equiv) | reagents (equiv)                   | solvent                               | T (°C)    | t (h) | yield (%) |
|-------|---------------------|--------------------|------------------------------------|---------------------------------------|-----------|-------|-----------|
| 1     | 1.2                 | 1.0                | <i>t</i> -BuOK (0.85)              | BM (30 Hz), no solvent                | —         | 10    | —         |
| 2     | 1.2                 | 1.0                | <i>t</i> -BuOK (0.85)              | BM (30 Hz), EtOAc (LAG)               | —         | 60    | —         |
| 3     | 1.0                 | 1.0                | EDC (1.0), DIPEA (1.0)             | CH <sub>2</sub> Cl <sub>2</sub>       | rt        | 24    | —         |
| 4     | 1.0                 | 1.0                | EDC (1.0), DIPEA (2.0)             | CH <sub>2</sub> Cl <sub>2</sub> , DMF | rt        | 48    | —         |
| 5     | 1.0                 | 1.0                | EDC (1.2), HOBT (1.2), DIPEA (1.0) | DMF                                   | 0 °C → rt | 24    | —         |
| 6     | 1.0                 | 1.0                | EDC (1.0), HOBT (1.0), DIPEA (1.0) | CH <sub>3</sub> CN, DMF               | 0 °C → rt | 24    | —         |

|   |     |     |                                    |     |      |    |   |
|---|-----|-----|------------------------------------|-----|------|----|---|
| 7 | 1.0 | 1.0 | EDC (1.0), HOBT (1.0), DIPEA (1.0) | DMF | 0 °C | 15 | — |
| 8 | 1.0 | 1.0 | TBTU (1.0), DIPEA (1.0)            | DMF | 0 °C | 15 | — |

**Table S8.** Reaction of benzothiazine acid **10ba** with methyl L-valinate **S3**·HCl.

**10ba** + **S3**·HCl  $\xrightarrow{\text{conditions}}$  Product

| entry | <b>10ba</b> (equiv) | <b>S3</b> ·HCl (equiv) | reagents (equiv)                   | solvent | <i>T</i> (°C) | <i>t</i> (h) | yield (%) |
|-------|---------------------|------------------------|------------------------------------|---------|---------------|--------------|-----------|
| 1     | 1.0                 | 1.0                    | EDC (2.0), HOBT (2.0), DIPEA (2.0) | DMF     | 0 °C → rt     | 24           | —         |

**Table S9.** Unsuccessful reaction of bromopyruvic acid (**9a**) and **16a**·HCl.

**16a**·HCl + **9a**  $\xrightarrow{\text{conditions}}$  Product

| entry | <b>16a</b> ·HCl (equiv) | <b>9a</b> (equiv) | reagents (equiv)                   | solvent                         | <i>T</i> (°C) | <i>t</i> (h) | yield (%) |
|-------|-------------------------|-------------------|------------------------------------|---------------------------------|---------------|--------------|-----------|
| 1     | 1.0                     | 1.0               | EDC (1.2), HOBT (1.2), DIPEA (3.5) | CH <sub>2</sub> Cl <sub>2</sub> | 0 °C → rt     | o/n          | —         |
| 2     | 1.0                     | 1.1               | EDC (1.2), TEA (1.0)               | CH <sub>3</sub> CN              | 0 °C → rt     | o/n          | —         |

**Table S10.** Reaction of amine **16a** with pyruvic acid.

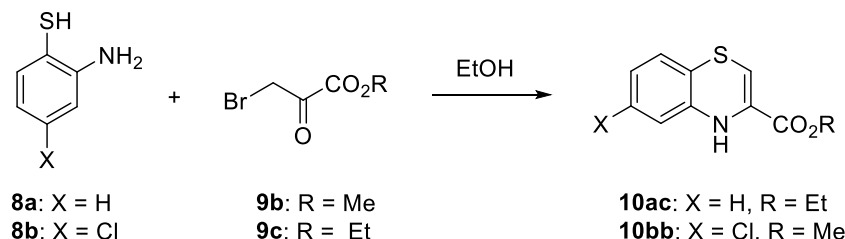
**16a** + Pyruvic acid  $\xrightarrow{\text{conditions}}$  **17a**

| entry | <b>16a</b> (equiv) | acid (equiv) | reagents (equiv)                                                   | solvent                         | <i>T</i> (°C) | <i>t</i> (h) | yield (%) |
|-------|--------------------|--------------|--------------------------------------------------------------------|---------------------------------|---------------|--------------|-----------|
| 1     | 1.1                | 1.0          | T <sub>3</sub> P <sup>®</sup> (2.0), <i>N</i> -Me-morpholine (3.0) | CH <sub>3</sub> CN              | rt            | o/n          | 34        |
| 2     | 1.0                | 1.2          | DCC (2.2), DMAP (1.0)                                              | CH <sub>2</sub> Cl <sub>2</sub> | 0 °C → rt     | 24           | 18        |

|   |     |     |                                                    |                                 |                    |     |    |
|---|-----|-----|----------------------------------------------------|---------------------------------|--------------------|-----|----|
| 3 | 1.0 | 1.0 | SOCl <sub>2</sub> (1.1), TEA (3.0)                 | THF                             | reflux,<br>then rt | o/n | 19 |
| 4 | 1.1 | 1.0 | (COCl) <sub>2</sub> (1.2), DMF<br>(cat), TEA (3.0) | CH <sub>2</sub> Cl <sub>2</sub> | rt                 | o/n | 10 |

### 3. Experimental procedures

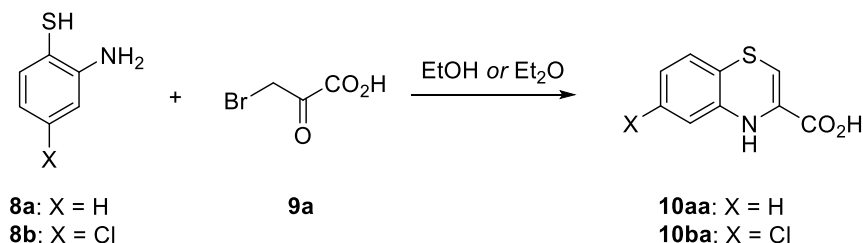
#### General procedure for the synthesis of benzothiazine esters



Aminothiols **8a** or **8b** (16.0 mmol) was dissolved in absolute EtOH (25 mL, 99.8% grade) at room temperature under nitrogen atmosphere and was cooled down with an ice bath. Next, ester **9b** or **9c** (19.0 mmol) was added dropwise, and the reaction mixture was stirred at the same temperature for 0.5–2 h. The conversion of the starting material was monitored by TLC analysis (hexane/EtOAc 5:1 or 7:1, anisaldehyde visualization). The reaction was quenched by the addition of cold distilled water (25 mL). Then, CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added. The separated organic phase was washed with 1 M NaOH aqueous solution (1 × 25 mL), saturated NaCl solution (1 × 25 mL), and dried over MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography (SiO<sub>2</sub>, hexane/EtOAc 7:1 to 5:1). If necessary, the product was crystallized from MeOH in the freezer overnight. The products were obtained as orange or red solids.

Notes: The unsubstituted ethyl ester **10ac** is unstable, and the purification is problematic. Products decompose also when the reaction mixture is stirred for a longer time (e.g., overnight) or if a solution stands in an NMR tube for a few hours. Unexpected side products **11a** and **11b** were obtained when the reaction was proceeded under microwave irradiation or reflux.

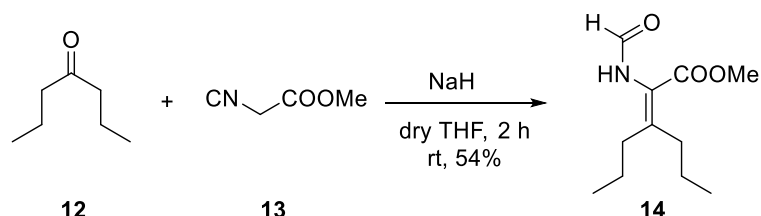
#### General procedure for the synthesis of benzothiazine carboxylic acids



Aminothiols **8a** or **8b** (4.0 mmol) was dissolved in absolute EtOH or dry Et<sub>2</sub>O (15 mL) at room temperature under nitrogen atmosphere and was cooled down with an ice bath. Then, a solution of carboxylic acid **9a** (4.2 mmol) in EtOH or Et<sub>2</sub>O (5 mL) was added dropwise, and the reaction was stirred vigorously at the same temperature for 0.5–1 h. The mixture was warmed to room temperature and the conversion of the starting material was monitored by TLC (hexane/EtOAc 5:1, anisaldehyde visualization). The reaction was quenched with saturated

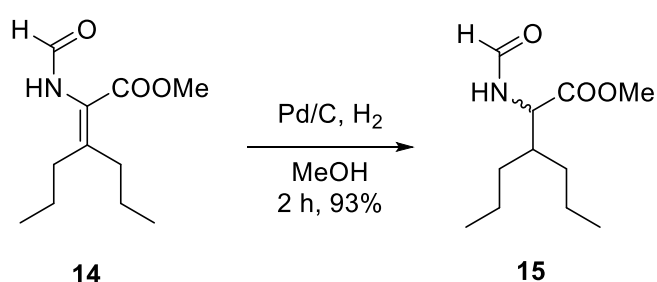
NaHCO<sub>3</sub> solution (25 mL) and was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The aqueous phase was transferred to a beaker and was stirred vigorously. Then, it was acidified dropwise (Pasteur pipette) with conc HCl to roughly pH 1 (as controlled with litmus paper). The resulting solid was filtered off, washed with distilled water and hexane and then dried under high vacuum. Products were obtained as red or orange solids.

### Methyl 2-formamido-3-propylhex-2-enoate (**14**)

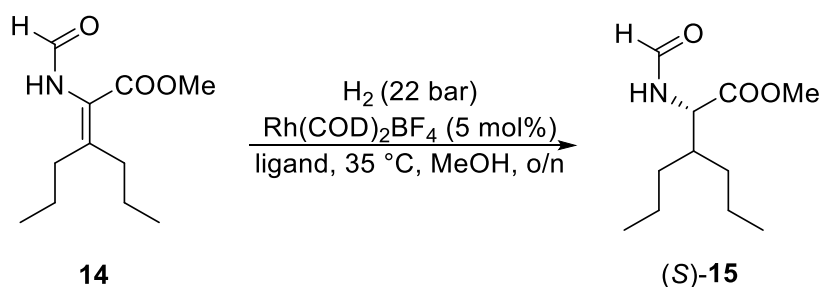


A solution of methyl cyanoacetate (**13**, 910  $\mu$ L, 10.0 mmol) and heptan-4-one (**12**, 1.4 mL, 10.0 mmol) in dry THF (10 mL) was added dropwise to a mixture of NaH (60% dispersion in mineral oil, 0.48 g, 12.0 mmol) in dry THF (10 mL). The reaction mixture was stirred at ambient temperature for 2 h. The progress of the reaction was monitored by TLC analysis (hexane/EtOAc 2:1, KMnO<sub>4</sub> visualization). Next, the mixture was cooled down with an ice bath, and water was added slowly dropwise until the remaining NaH was consumed. Then, the volatile components were removed by evaporation under vacuum. The remaining aqueous aliquot was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>, hexane/EtOAc 1.5:1) to yield the product **14** as a colorless liquid (1.15 g, 54%). While standing in the fridge, the product slowly solidified.

### Methyl 2-formamido-3-propylhexanoate (**15**)

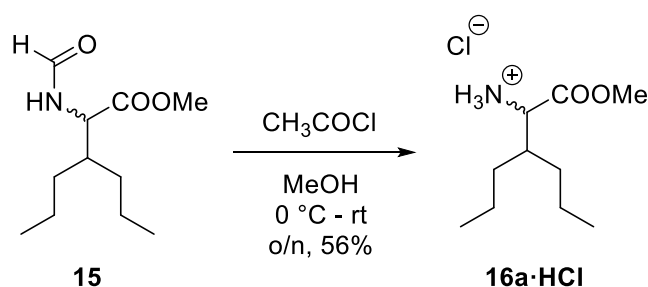


**Method A:** The starting material methyl 2-formamido-3-propylhex-2-enoate (**14**, 1.15 g, 5.4 mmol) was dissolved in MeOH (50 mL). Next, 10% Pd/C (280 mg, 25 wt %) was added, and the mixture was hydrogenated (using a balloon) for 2 h at room temperature. The reaction mixture was filtered through celite, and the solvent was evaporated under reduced pressure to gain the title compound **15** as a colorless oil (1.07 g, 93%). The product was used without further purification. While standing in the fridge, the product slowly solidified. The rotation of the amide bond was partially restricted. Based on the <sup>1</sup>H NMR, the isomeric ratio was 9:1.

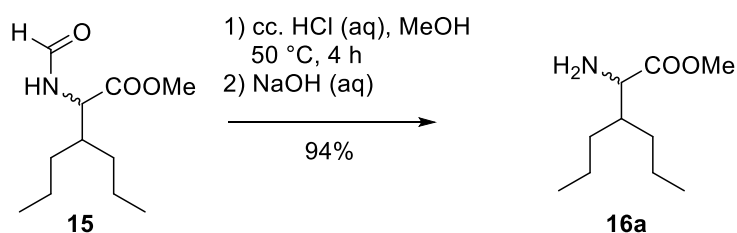


**Method B (general procedure for stereoselective hydrogenation):** The starting material methyl 2-formamido-3-propylhex-2-enoate (**14**, 50 mg, 0.23 mmol), ligand (0.06 equiv), and Rh(COD)<sub>2</sub>BF<sub>4</sub> (5 or 6 mol %) were dissolved in degassed MeOH (2 mL, Ar). The mixture was hydrogenated (22 bar) for 24 h at 35 °C. The reaction mixture was filtered through celite, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>, hexane/EtOAc 2:1) to yield the product **15** as a colorless oil.

### Methyl 2-amino-3-propylhexanoate (**16a**)



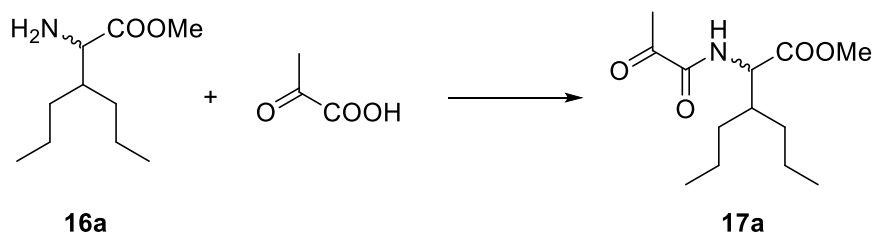
**Method A:** First, the starting material methyl 2-formamido-3-propylhexanoate (**15**, 1.068 g, 4.9 mmol) was dissolved in MeOH (20 mL), and the solution was cooled with an ice bath. Next, acetyl chloride (1.3 mL, 18.3 mmol) was added dropwise to the reaction mixture. After the addition, the ice bath was removed, and the reaction mixture was stirred at ambient temperature overnight. Next, a few drops of water were added to discharge the remaining acetyl chloride, and the volatile components were removed under reduced pressure. The remaining material was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with water (3 × 50 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> with up to 5% MeOH) to yield **16a·HCl** as an off-white solid (620 mg, 56%).



**Method B:** First, the starting material methyl 2-formamido-3-propylhexanoate (**15**, 3 g, 13.9 mmol) was dissolved in MeOH (70 mL). Next, conc HCl (7 mL) was added dropwise. The reaction mixture was stirred at 50 °C for 4 h. After the reaction, 10% NaOH (aq) was added

(roughly pH 12), and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure to gain the title compound **16a** as a colorless oil (2.466 g, 94%). The product was used without further purification.

### Methyl 2-(2-oxopropanamido)-3-propylhexanoate (**17a**)



**Method A:** First, methyl 2-amino-3-propylhexanoate (**16a**, 100 mg, 0.5 mmol) and *N*-methylmorpholine (160  $\mu$ L, 1.0 mmol) were dissolved in dry MeCN (2 mL). Pyruvic acid (34  $\mu$ L, 0.5 mmol) and T<sub>3</sub>P<sup>®</sup> (50 wt % in EtOAc, 577  $\mu$ L, 1.0 mmol) were then added to this mixture, and the reaction mixture was stirred at room temperature for 24 h. Next, the mixture was diluted with EtOAc (50 mL) and washed first with saturated NaHCO<sub>3</sub> (aq, 20 mL) and then with water (2 × 50 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>, hexane with EtOAc up to 10%) to yield the title compound (**17a**) as a colorless oil (42.4 mg, 34%).

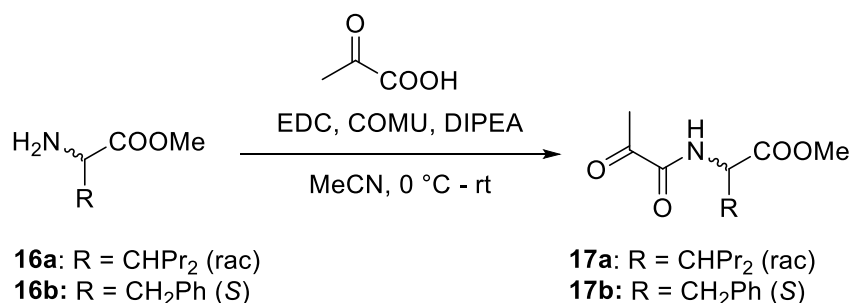
**Method B:** Pyruvic acid (705  $\mu$ L, 10.0 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Then, SOCl<sub>2</sub> (798  $\mu$ L, 11.0 mmol) was added, and the mixture was refluxed for 2 h. Then, the volatile components were removed under reduced pressure to gain pyruvoyl chloride, which was used without further purification in the next step. Next, methyl 2-amino-3-propylhexanoate (**16a**, 100 mg, 0.5 mmol) and triethyl amine (223  $\mu$ L, 1.6 mmol) were dissolved in dry THF (1 mL). A solution of the previously prepared pyruvoyl chloride (110 mg, 1.1 mmol) in dry THF (1 mL) was added, and the mixture was stirred at room temperature for 24 h. Next, the volatile components were evaporated under reduced pressure, and the remaining mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>, hexane with up to 10% EtOAc) to yield the title compound **17a** as a colorless oil (24.3 mg, 19%).

**Method C:** Pyruvic acid (270  $\mu$ L, 3.8 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and the mixture was cooled down with an ice bath. Next, DCC (792 mg, 3.8 mmol), DMAP (78 mg, 0.6 mmol), and a solution of methyl 2-amino-3-propylhexanoate (**16a**, 600 mg, 3.2 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were added, and the reaction mixture was stirred at ambient temperature. The next day, an additional amount of DCC (660 mg, 3.2 mmol) and DMAP (312 mg, 2.6 mmol) were added, and the stirring was continued for 2 days. The mixture was diluted with water (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic phase was washed with saturated NaHCO<sub>3</sub> (aq, 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>,

hexane with EtOAc up to 10%) to yield the title compound **17a** as a colorless oil (146 mg, 18%).

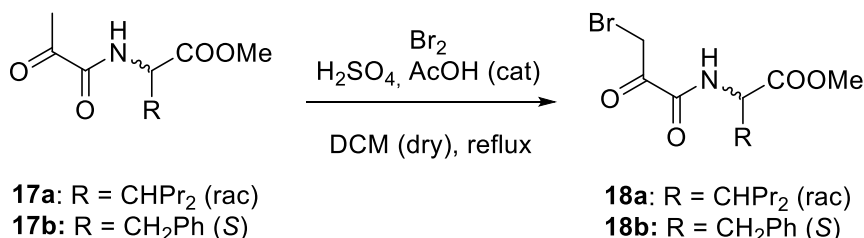
**Method D:** Pyruvic acid (342  $\mu$ L, 4.9 mmol) and a few drops of DMF were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (20 mL). Next, oxalyl chloride (505  $\mu$ L, 5.9 mmol) was added, and the mixture was stirred for 2 h. The volatile components were removed under reduced pressure. The remaining oil was taken up in dry  $\text{CH}_2\text{Cl}_2$  (20 mL) and was dropwise added to a solution of methyl 2-amino-3-propylhexanoate (**16a**, 1 g, 5.3 mmol) and triethyl amine (2 mL, 14.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with water (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 50$  mL). The combined organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography ( $\text{SiO}_2$ , hexane with up to 10% EtOAc) to yield the title compound **17a** as a colorless oil (120 mg, 10%).

### General procedure for the peptide couplings (**17a** and **17b**):



The amino acid methyl ester **16a** or **16b** (2.0 mmol), pyruvic acid (138  $\mu$ L, 2.0 mmol), and COMU (1.3 g, 2.4 mmol) were dissolved in dry  $\text{CH}_3\text{CN}$  (20 mL), and the mixture was cooled with an ice bath to 0  $^\circ\text{C}$ . Next, a mixture of EDC $\cdot$ HCl (460 mg, 2.4 mmol) and DIPEA (1.22 mL, 7.0 mmol) in  $\text{CH}_3\text{CN}$  (20 mL) was slowly added to the reaction mixture. After 1 h, the ice bath was removed, and the mixture was stirred at ambient temperature for 2 days. After that, water (50 mL) and EtOAc (50 mL) were added, and the phases were separated. The organic phase was washed with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude product was purified by flash chromatography ( $\text{SiO}_2$ , hexane/EtOAc 6:1 to 3:1) to yield the product as a colorless oil.

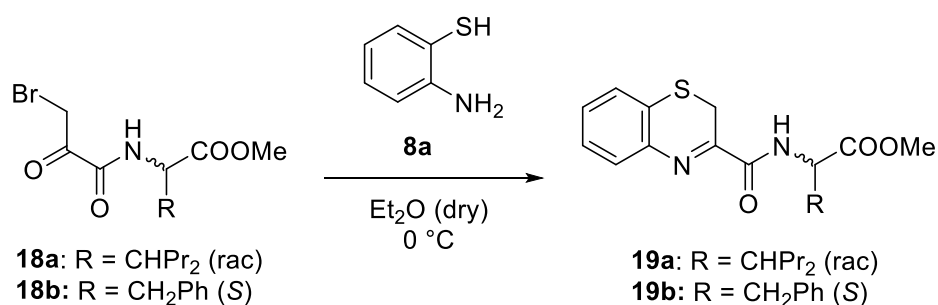
### General procedure for the $\alpha$ -bromination reactions



Starting material **17a** or **17b** (0.6 mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (20 mL). Then, bromine (60  $\mu$ L, 1.1 mmol), three drops of conc  $\text{H}_2\text{SO}_4$ , and three drops of acetic acid were added. The reaction mixture was refluxed for 8 h. Then, 5 wt %  $\text{Na}_2\text{S}_2\text{O}_3$  (aq, 10 mL) was added, and this

was stirred for 10 min, followed by extraction with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 50$  mL). The combined organic phase was washed with saturated  $\text{NaHCO}_3$  (50 mL), water (50 mL), and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography ( $\text{SiO}_2$ , hexane:EtOAc 10:1) to yield the title compound **18a** or **18b** as a yellow oil.

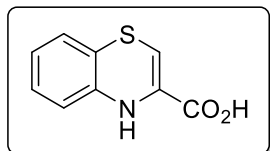
### General procedure for the cyclization reactions



Bromine derivative **18a** or **18b** (0.4 mmol) was dissolved in freshly distilled dry  $\text{Et}_2\text{O}$  (20 mL) in an Ar atmosphere and cooled down with an ice bath. Then, 2-aminothiophenol (**8a**, 48  $\mu\text{L}$ , 0.4 mmol) was added, and this was stirred at the same temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash chromatography ( $\text{SiO}_2$ , hexane/EtOAc 10:1) to yield the title compound **19a** or **19b** as a yellow oil.

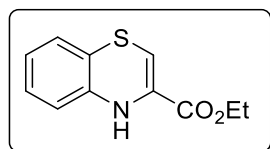
## 4. Characterization data

### 4*H*-Benzo[*b*][1,4]thiazine-3-carboxylic acid (10aa)



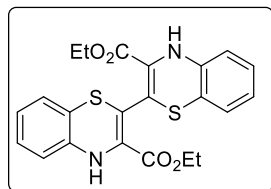
Orange solid, **Mp** 140 – 143 °C. **<sup>1</sup>H NMR** (600 MHz, DMSO):  $\delta$  13.08 (br s, 1H), 7.27 (d,  $J$  = 1.9 Hz, 1H), 6.84 (m, 1H), 6.73 (d,  $J$  = 7.5 Hz, 1H), 6.65 (m, 2H), 5.72 (d,  $J$  = 1.8 Hz, 1H) ppm. **<sup>13</sup>C NMR** (150 MHz, DMSO)  $\delta$  162.0, 142.5, 132.0, 128.5, 126.5, 123.4, 115.7, 114.7, 102.9 ppm. **2D NMR**: HSQC, COSY, HMBC. **IR** (ATR): 3340, 2816, 2718, 2626, 2528, 2475, 1654, 1617, 1576, 1437, 734 cm<sup>-1</sup>. **MS** (APCI):  $m/z$  [M+H]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>8</sub>NO<sub>2</sub>S: 194.0, found: 194.0; [M-CO<sub>2</sub>H]<sup>+</sup> calcd. for C<sub>8</sub>H<sub>6</sub>NS: 148.0, found: 148.0. **HRMS** (HESI):  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>8</sub>NO<sub>2</sub>S: 194.0270; found: 194.0271; [M]<sup>+</sup> calcd for C<sub>9</sub>H<sub>7</sub>NO<sub>2</sub>S: 193.0192, found: 193.0193.

### Ethyl 4*H*-benzo[*b*][1,4]thiazine-3-carboxylate (10ac)



Orange solid, **Mp** 77 – 78 °C. **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta$  6.91 (m, 1H), 6.80 – 6.66 (m, 2H), 6.37 (d,  $J$  = 7.9 Hz, 1H), 5.86 (s, 2H), 4.24 (q,  $J$  = 7.1 Hz, 2H), 1.30 (t,  $J$  = 7.1 Hz, 3H) ppm. **<sup>13</sup>C NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  160.7, 141.5, 130.7, 128.2, 126.6, 123.6, 115.2, 114.8, 105.2, 61.8, 14.2 ppm. **IR** (ATR): 3366, 2974, 1692, 1578, 1462, 1440, 1370, 1321, 1286, 1226, 1090, 761, 721 cm<sup>-1</sup>. **MS** (APCI):  $m/z$  [M+H]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>12</sub>NO<sub>2</sub>S: 222.1, found: 222.0; [M-CO<sub>2</sub>Et]<sup>+</sup> calcd. for C<sub>8</sub>H<sub>6</sub>NS: 148.0, found: 148.0. **HRMS** (HESI):  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>12</sub>NO<sub>2</sub>S: 222.0583; found: 222.0539; [M]<sup>+</sup> calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>S: 221.0505, found: 221.0505.

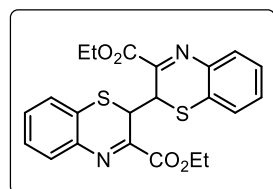
### Diethyl 4*H*,4'*H*-[2,2'-bibenzo[*b*][1,4]thiazine]-3,3'-dicarboxylate (11a)



Pale red solid, **Mp** 188 – 192 °C. **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta$  6.98 (td,  $J$  = 7.6, 1.5 Hz, 1H), 6.91 (dd,  $J$  = 7.7, 1.5 Hz, 1H), 6.84 (td,  $J$  = 7.5, 1.2 Hz, 1H), 6.55 (dd,  $J$  = 7.8, 1.3 Hz, 1H), 6.44 (br s, 1H), 4.23 – 4.10 (m, 2H), 1.15 (t,  $J$  = 7.2 Hz, 3H) ppm. **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>):  $\delta$  161.3, 141.8, 129.6, 127.8, 126.5, 123.7, 118.1, 115.1, 114.6, 62.3, 13.8 ppm. **2D NMR**: HSQC, COSY, HMBC. **IR** (ATR): 3359, 1669, 1576, 1466, 1427, 1369, 1293, 1176, 1007, 746 cm<sup>-1</sup>. **MS** (APCI):  $m/z$  [M+H]<sup>+</sup> calcd. for C<sub>22</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: 441.1, found: 440.8; [M-OEt]<sup>+</sup> calcd. for

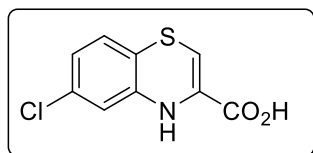
$C_{20}H_{15}N_2O_3S_2$ : 395.1, found: 394.7. **HRMS** (HESI):  $m/z$   $[M+H]^+$  calcd. for  $C_{22}H_{21}N_2O_4S_2$ : 441.0937, found: 441.0942;  $[M+Na]^+$  calcd. for  $C_{22}H_{20}N_2O_4S_2Na$ : 463.0757, found: 463.0756;  $[M+K]^+$  calcd. for  $C_{22}H_{20}N_2O_4S_2K$ : 479.0496, found: 479.0498.

### Diethyl 2*H*,2'*H*-[2,2'-bibenzo[*b*][1,4]thiazine]-3,3'-dicarboxylate (11b)



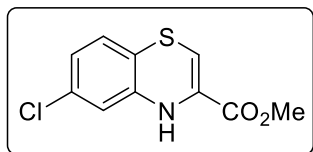
Yellow solid, **Mp** 205 – 209 °C.  **$^1H$  NMR** (600 MHz,  $CDCl_3$ ):  $\delta$  7.75 (dd,  $J$  = 7.4, 1.8 Hz, 2H), 7.43 – 7.26 (m, 6H), 4.44 (dq,  $J$  = 10.8, 7.1 Hz, 2H), 4.32 – 4.19 (m, 4H), 1.33 (t,  $J$  = 7.1 Hz, 6H) ppm.  **$^{13}C$  NMR** (150 MHz,  $CDCl_3$ ):  $\delta$  162.4, 146.5, 139.9, 129.0, 128.7, 127.0, 126.2, 120.4, 61.8, 29.1, 13.1 ppm. **IR** (ATR): 2979, 1709, 1441, 1330, 1286, 1224, 1084, 1063, 862, 762  $cm^{-1}$ . **MS** (APCI):  $m/z$   $[M+H]^+$  calcd. for  $C_{22}H_{21}N_2O_4S_2$ : 441.1, found: 440.7;  $[M-OEt]^+$  calcd. for  $C_{20}H_{15}N_2O_3S_2$ : 395.1, found: 394.6. **HRMS** (HESI):  $m/z$   $[M+H]^+$  calcd. for  $C_{22}H_{21}N_2O_4S_2$ : 441.0937, found: 441.0937;  $[M+Na]^+$  calcd. for  $C_{22}H_{20}N_2O_4S_2Na$ : 463.0757, found: 463.0757;  $[M+K]^+$  calcd. for  $C_{22}H_{20}N_2O_4S_2K$ : 479.0496, found: 479.0495.

### 6-chloro-4*H*-benzo[*b*][1,4]thiazine-3-carboxylic acid (10ba)



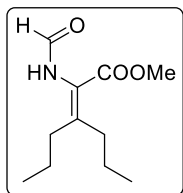
Red solid, **Mp** 192 – 195 °C.  **$^1H$  NMR** (600 MHz, DMSO):  $\delta$  7.51 (s, 1H), 6.81 (d,  $J$  = 2.1 Hz, 1H), 6.69 – 6.62 (m, 2H), 5.74 (d,  $J$  = 1.8 Hz, 1H) ppm.  **$^{13}C$  NMR** (150 MHz, DMSO):  $\delta$  161.7, 144.2, 132.9, 131.4, 127.6, 122.7, 115.0, 113.9, 103.5 ppm. **IR** (ATR): 3354, 1653, 1623, 1573, 1437, 1235, 1090, 880, 843, 796, 729  $cm^{-1}$ . **MS** (APCI):  $m/z$   $[M+H]^+$  calcd. for  $C_9H_7ClNO_2S$ : 228.0, found: 227.8;  $[M-CO_2H]^+$  calcd. for  $C_8H_5ClNS$ : 182.0, found: 181.8. **HRMS** (HESI):  $m/z$   $[M]^+$  calcd for  $C_9H_6ClNO_2S$ : 226.9802, found: 226.9803; (APPI):  $[M+H]^+$  calcd for  $C_9H_7ClNO_2S$ : 227.9881; found: 227.9882.

### Methyl 6-chloro-4*H*-benzo[*b*][1,4]thiazine-3-carboxylate (10bb)



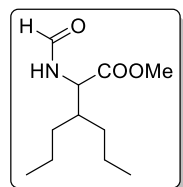
Red solid, **Mp** 144 – 146 °C.  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.70 (dd,  $J = 8.0, 2.0$  Hz 1H), 6.61 (d,  $J = 8.0$  Hz, 1H), 6.37 (d,  $J = 2.0$  Hz, 1H), 5.86 (br s, 2H), 3.79 (s, 3H) ppm.  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  160.9, 142.7, 133.9, 129.8, 127.2, 123.3, 114.2, 113.8, 105.9, 52.7 ppm. **IR** (ATR): 3373, 1696, 1628, 1472, 1432, 1384, 1253, 1094, 860, 802, 771, 727  $\text{cm}^{-1}$ . **MS** (APCI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_9\text{ClNO}_2\text{S}$ : 242.0, found: 241.9. **HRMS** (HESI):  $m/z$   $[\text{M}]^+$  calcd for  $\text{C}_{10}\text{H}_8\text{ClNO}_2\text{S}$ : 240.9959; found: 240.9961;  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{10}\text{H}_8\text{ClNO}_2\text{SNa}$ : 263.9857, found: 263.9814.

### Methyl 2-formamido-3-propylhex-2-enoate (14)



White solid, **Mp** 56 – 58 °C.  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.20 (d,  $J = 1.4$  Hz, 0.6H), 7.95 (d,  $J = 11.6$  Hz, 0.4H), 6.67 (br s, 0.6H), 6.55 (d,  $J = 11.6$  Hz, 0.4H), 3.76 (s, 1.2H), 3.75 (s, 1.8H), 2.54 (m, 0.8H), 2.47 (m, 1.2H), 2.25 (m, 0.8H), 2.15 (m, 1.2H), 1.56 – 1.43 (m, 4H), 1.00 – 0.92 (m, 6H) ppm.  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.96, 164.94, 164.82, 159.81, 157.26, 153.30, 120.61, 120.04, 52.07, 51.91, 35.62, 35.41, 34.33, 34.12, 22.24, 22.15, 21.17, 20.74, 14.37, 14.35, 14.29 ppm. **IR** (ATR): 3266, 2957, 2932, 2870, 1723, 1685, 1657, 1506, 1463, 1435, 1385, 1316, 1274, 1251, 1203, 1134, 1095, 1034, 1000, 939, 873, 789, 746, 722, 677, 633, 548, 479  $\text{cm}^{-1}$ . **MS** (MM-ES+APCI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{11}\text{H}_{20}\text{NO}_3$ : 214.1, found: 214.1;  $[\text{M}-\text{H}]^+$  calcd. for  $\text{C}_{11}\text{H}_{18}\text{NO}_3$ : 212.1, found: 212.1. **HRMS** (HESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{11}\text{H}_{20}\text{NO}_3$ : 214.14377, found: 214.14382;  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{11}\text{H}_{19}\text{NO}_3\text{Na}$ : 236.1257, found: 236.1255;  $[\text{M}+\text{K}]^+$  calcd. for  $\text{C}_{11}\text{H}_{19}\text{NO}_3\text{K}$ : 252.0997, found: 252.0995.

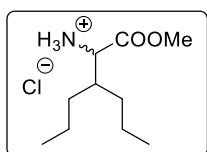
### Methyl 2-formamido-3-propylhexanoate (15)



White solid, **Mp** 53 – 56 °C. The rotation of the amide bond is restricted. Based on the  $^1\text{H NMR}$ , the isomeric ratio is 9:1.  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.25 (d,  $J = 1.6$  Hz, 0.9H), 7.99 (d,  $J = 11.8$  Hz, 0.1H), 6.02 (d,  $J = 8.5$  Hz, 0.9H), 5.92 (m, 0.1H), 4.85 (dd,  $J = 9.2, 3.7$  Hz, 0.9H), 4.14 (dd,  $J = 10.2, 4.1$  Hz, 0.1H), 3.77 (s, 0.35H), 3.75 (s, 2.65H), 1.91 (m, 1H), 1.50 – 1.14 (m, 8H), 0.96 – 0.85 (m, 6H) ppm.  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.57, 171.92, 163.62, 160.78, 56.90,

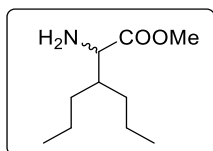
52.57, 52.52, 52.33, 40.71, 40.42, 32.85, 32.41, 32.31, 31.67, 20.27, 20.25, 20.10, 20.03, 14.18, 14.15, 14.07 ppm. **IR** (ATR): 3234, 3047, 2958, 2931, 2872, 1743, 1644, 1544, 1458, 1439, 1377, 1345, 1322, 1284, 1242, 1204, 1130, 1116, 1049, 1003, 932, 787, 736, 669, 597, 454, 430  $\text{cm}^{-1}$ . **MS** (APCI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{11}\text{H}_{22}\text{NO}_3$ : 216.2, found: 216.0;  $[\text{M}-\text{CO}_2\text{CH}_3]^+$  calcd. for  $\text{C}_9\text{H}_{18}\text{NO}$ : 156.1, found: 155.9;  $[\text{M}-\text{H}]^+$  calcd. for  $\text{C}_{11}\text{H}_{20}\text{NO}_3$ : 214.2, found: 213.8. **HRMS** (HESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{11}\text{H}_{22}\text{NO}_3$ : 216.1594, found: 216.1595;  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{11}\text{H}_{21}\text{NO}_3\text{Na}$ : 238.1414, found: 238.1412;  $[\text{M}+\text{K}]^+$  calcd. for  $\text{C}_{11}\text{H}_{21}\text{NO}_3\text{K}$ : 254.1153, found: 254.1152. **HPLC**: Chiralpak IA, hexane/*i*-PrOH 90:10, 1.0  $\text{mL min}^{-1}$ , 215 nm,  $t_{\text{R}}(\text{minor})$  = 5.536 min,  $t_{\text{R}}(\text{major})$  = 7.360 min.

### Methyl 2-amino-3-propylhexanoate·HCl (16a·HCl)



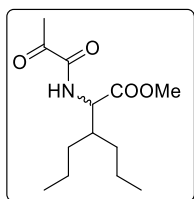
Off-white solid. **M.p.** 114.0 – 117.4  $^{\circ}\text{C}$ .  **$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.91 (s, 3H), 4.05 (s, 1H), 3.82 (s, 3H), 2.14 (m, 1H), 1.67 (m, 1H), 1.52 – 1.29 (m, 7H), 0.99 – 0.86 (m, 6H) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.03, 55.40, 53.03, 39.09, 32.00, 31.95, 20.28, 20.22, 13.97, 13.92 ppm. **IR** (ATR): 2953, 2929, 2867, 2611, 1738, 1579, 1507, 1465, 1449, 1436, 1375, 1305, 1229, 1170, 1128, 1068, 1045, 1003, 967, 933, 901, 880, 814, 785, 740, 643, 544, 503, 438  $\text{cm}^{-1}$ . **MS** (APCI):  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{10}\text{H}_{22}\text{NO}_2$ : 188.2, found: 188.0. **HRMS** (HESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_{22}\text{NO}_2$ : 188.1645, found: 188.1643.

### Methyl 2-amino-3-propylhexanoate (16a)



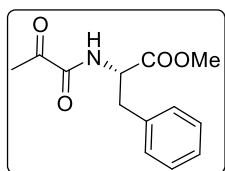
Transparent oil.  **$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.72 (s, 3H), 3.52 (d,  $J$  = 3.8 Hz, 1H), 1.78 (m, 1H), 1.48 – 1.16 (m, 8H), 0.92 (t,  $J$  = 6.8 Hz, 3H), 0.87 (t,  $J$  = 7.0 Hz, 3H) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  176.81, 56.32, 51.79, 41.23, 33.11, 31.72, 20.45, 20.41, 14.32, 14.26 ppm. **IR** (ATR): 3387, 2956, 2929, 2871, 1732, 1601, 1458, 1436, 1378, 1206, 1167, 1095, 1004, 922, 840, 743  $\text{cm}^{-1}$ . **MS** (APCI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_{22}\text{NO}_2$ : 187.2, found: 188.0;  $[\text{M}-\text{CO}_2\text{CH}_3]^+$  calcd. for  $\text{C}_8\text{H}_{18}\text{N}$ : 128.1, found: 128.0. **HRMS** (HESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_{22}\text{NO}_2$ : 188.1645, found: 188.1644.

### Methyl 2-(2-oxopropanamido)-3-propylhexanoate (17a)



Colorless oil. **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>): δ 7.31 (d, *J* = 9.3 Hz, 1H), 4.66 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.75 (s, 3H), 2.49 (s, 3H), 1.96 (m, 1H), 1.45 – 1.17 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 6H) ppm. **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 196.39, 171.82, 159.92, 54.26, 52.37, 40.40, 32.85, 32.26, 24.44, 20.27, 20.24, 14.15, 14.12 ppm. **IR** (ATR): 3402, 2957, 2931, 2872, 1741, 1686, 1514, 1458, 1436, 1353, 1251, 1208, 1168, 1015, 917, 822, 734, 592 cm<sup>-1</sup>. **MS** (APCI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>13</sub>H<sub>24</sub>NO<sub>4</sub>: 258.2, found: 258.2; [M-CO<sub>2</sub>CH<sub>3</sub>]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>20</sub>NO<sub>2</sub>: 198.2, found: 198.2; [M-H]<sup>-</sup> calcd. for C<sub>13</sub>H<sub>22</sub>NO<sub>4</sub>: 256.2, found: 256.1. **HRMS** (HESI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>13</sub>H<sub>24</sub>NO<sub>4</sub>: 258.1700, found: 258.1699; [M+Na]<sup>+</sup> calcd. for C<sub>13</sub>H<sub>23</sub>NO<sub>4</sub>Na: 280.1519, found: 280.1518.

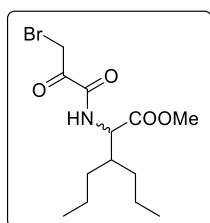
### Methyl (2-oxopropanoyl)-L-phenylalaninate (17b)



Colorless oil. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.36 – 7.22 (m, 4H), 7.14 – 7.07 (m, 2H), 4.81 (dt, *J* = 8.5, 6.2 Hz, 1H), 3.72 (s, 3H), 3.14 (qd, *J* = 13.9, 6.1 Hz, 2H), 2.44 (s, 3H) ppm. **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>): δ 196.01, 170.91, 159.53, 135.29, 129.11 (2 × C<sub>Ar</sub>), 128.73 (2 × C<sub>Ar</sub>), 127.34, 53.22, 52.50, 37.89, 24.33 ppm. **IR** (ATR): 3339, 3028, 2953, 1741, 1680, 1517, 1498, 1437, 1355, 1248, 1219, 1197, 1165, 1105, 1079, 1030, 1016, 989, 746, 701, 609, 589 cm<sup>-1</sup>. **MS** (APCI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>13</sub>H<sub>16</sub>NO<sub>4</sub>: 250.1, found: 249.9; [M-CO<sub>2</sub>CH<sub>3</sub>]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>12</sub>NO<sub>2</sub>: 190.1, found: 189.8; [M-H]<sup>-</sup> calcd. for C<sub>13</sub>H<sub>14</sub>NO<sub>4</sub>: 248.1, found: 247.6. **HRMS** (HESI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>13</sub>H<sub>16</sub>NO<sub>4</sub>: 250.1074, found: 250.1073; [M+Na]<sup>+</sup> calcd. for C<sub>13</sub>H<sub>15</sub>NO<sub>4</sub>Na: 272.0893, found: 272.0894.

Spectral data are fully consistent with those reported in the literature [1].

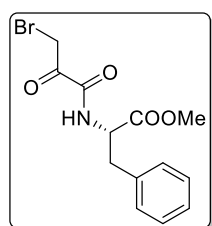
### Methyl 2-(3-bromo-2-oxopropanamido)-3-propylhexanoate (18a)



Colorless oil. The rotation of the amide bond is partially restricted which leads to the duplication of some signals. Based on the <sup>1</sup>H NMR, the isomeric ratio is 7:3. **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>): δ 7.36 (d, *J* = 9.2 Hz, 0.3H), 7.31 (d, *J* = 9.3 Hz, 0.7H), 4.72 (dd, *J* = 9.2, 3.7 Hz, 0.3H), 4.69

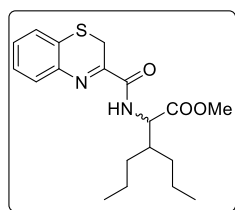
(dd,  $J = 9.3, 3.7$  Hz, 0.7H), 4.49 (dd,  $J = 58.4, 30.9$  Hz, 2H), 3.78 (s, 0.9H), 3.76 (s, 2.1H), 1.98 (m, 1H), 1.45 – 1.15 (m, 8H), 0.90 (t,  $J = 7.2$  Hz, 6H) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  188.98, 182.44, 171.50, 171.31, 158.19, 156.40, 54.77, 54.46, 52.58, 52.51, 40.58, 40.47, 36.99, 32.84, 32.82, 32.24, 30.10, 20.25, 20.23, 14.14, 14.11 ppm. **IR** (ATR): 3396, 2956, 2930, 2871, 1740, 1682, 1519, 1458, 1436, 1380, 1355, 1264, 1207, 1176, 1143, 1093, 1008, 938, 910, 734, 645  $\text{cm}^{-1}$ . **MS** (APCI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{17}\text{H}_{23}\text{BrNO}_4$ : 336.1 and 338.1 (97.3%), found: 336.0 and 338.0;  $[\text{M}-\text{CO}_2\text{CH}_3]^+$  calcd. for  $\text{C}_{11}\text{H}_{19}\text{BrNO}_2$ : 276.1 and 278.1, found: 275.9 and 277.9;  $[\text{M}-\text{H}]^-$  calcd. for  $\text{C}_{13}\text{H}_{21}\text{BrNO}_4$ : 334.1 (100%) and 336.1, found: 333.8 and 335.7. **HRMS** (HESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{13}\text{H}_{23}\text{BrNO}_4$ : 336.0805 and 338.0785, found: 336.0805 and 338.0784;  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{13}\text{H}_{22}\text{BrNO}_4\text{Na}$ : 358.0624 and 360.0604, found: 358.0624 and 360.0603.

### Methyl (3-bromo-2-oxopropanoyl)-L-phenylalaninate (18b)



Yellow oil.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37 – 7.25 (m, 4H), 7.14 – 7.08 (m, 2H), 4.84 (ddd,  $J = 8.4, 6.5, 5.7$  Hz, 1H), 4.44 (dd,  $J = 38.7, 11.4$  Hz, 2H), 3.74 (s, 3H), 3.24 – 3.09 (m, 2H) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  188.68, 170.64, 157.86, 135.08, 129.15, 128.82, 127.47, 53.41, 52.67, 37.77, 29.97 ppm. **IR** (ATR): 3346, 3060, 3028, 2951, 1812, 1738, 1676, 1520, 1497, 1437, 1363, 1271, 1205, 1176, 1120, 1081, 1047, 1030, 911, 882, 732, 700, 648, 594, 487  $\text{cm}^{-1}$ . **MS** (APCI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{13}\text{H}_{15}\text{BrNO}_4$ : 328.0 (100%) and 329.0 (97.3%), found: 327.7 and 329.6;  $[\text{M}-\text{COOCH}_3]^+$  calcd. for  $\text{C}_{11}\text{H}_{11}\text{BrNO}_2$ : 268.0 and 270.0, found: 267.7 and 269.7. **HRMS** (HESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{13}\text{H}_{15}\text{BrNO}_4$ : 328.0179 and 330.0159, found: 328.0178 and 330.0158;  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{13}\text{H}_{14}\text{BrNO}_4\text{Na}$ : 349.9998 and 351.9978, found: 349.9997 and 351.9976.

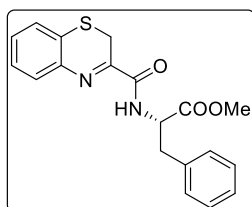
### Methyl 2-(2*H*-benzo[*b*][1,4]thiazine-3-carboxamido)-3-propylhexanoate (19a)



Yellow oil.  **$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02 (d,  $J = 9.3$  Hz, 1H), 7.47 (dd,  $J = 7.8, 1.5$  Hz, 1H), 7.31 (dd,  $J = 7.7, 1.5$  Hz, 1H), 7.23 (td,  $J = 7.6, 1.6$  Hz, 1H), 7.19 (td,  $J = 7.5, 1.5$  Hz, 1H), 4.81 (dd,  $J = 9.3, 3.9$  Hz, 1H), 3.76 (s, 3H), 3.64 (dd,  $J = 90.1, 15.2$  Hz, 2H), 2.01 (m, 1H), 1.48 – 1.25 (m, 9H), 0.91 (m, 6H) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.49, 162.64, 150.41, 141.83, 129.12, 128.80, 127.32, 126.53, 125.20, 54.60, 52.28, 40.52, 32.91, 32.36, 20.30 ( $2 \times \text{C}$ ), 19.97, 14.22, 14.18 ppm. **IR** (ATR): 3360, 2956, 2928, 2871, 1738, 1670, 1618, 1592, 1512, 1477, 1465, 1437, 1376, 1351, 1314, 1261, 1203, 1154, 1028, 908, 731, 647  $\text{cm}^{-1}$ . **MS** (APCI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_3\text{S}$ : 363.2, found: 363.1;  $[\text{M}-\text{CO}_2\text{CH}_3]^+$  calcd. for

$C_{17}H_{23}N_2O_3S$ : 303.2, found: 303.1;  $[M-H]^-$  calcd. for  $C_{19}H_{25}N_2O_3S$ : 361.2, found: 361.0. **HRMS** (HESI):  $m/z$   $[M+H]^+$  calcd. for  $C_{19}H_{27}N_2O_3S$ : 363.1737, found: 363.1737;  $[M+Na]^+$  calcd. for  $C_{19}H_{26}N_2O_3SNa$ : 385.1556, found: 385.1556.

### Methyl (2*H*-benzo[*b*][1,4]thiazine-3-carbonyl)-L-phenylalaninate (19b)



Yellow oil.  **$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  8.02 (d,  $J = 8.4$  Hz, 1H), 7.41 (m, 1H), 7.34 – 7.26 (m, 4H), 7.25 – 7.16 (m, 4H), 4.96 (dt,  $J = 8.4, 6.2$  Hz, 1H), 3.74 (s, 3H), 3.62 (q,  $J = 15.2$  Hz, 2H), 3.21 (dd,  $J = 6.2, 1.7$  Hz, 2H) ppm.  **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ ):  $\delta$  171.56, 162.33, 150.20, 141.76, 135.74, 129.28, 129.07, 128.85, 128.67, 127.33, 127.25, 126.55, 125.15, 53.59, 52.41, 38.25, 19.88 ppm. **IR** (ATR): 3378, 3058, 3027, 3001, 2950, 2928, 2850, 1740, 1670, 1616, 1508, 1442, 1410, 1364, 1304, 1262, 1211, 1174, 1127, 1077, 1057, 1030, 909, 843, 763, 730, 701, 650, 598, 541, 494, 466, 437  $cm^{-1}$ . **MS** (APCI):  $m/z$   $[M+H]^+$  calcd. for  $C_{19}H_{19}N_2O_3S$ : 355.1, found: 354.8;  $[M-CO_2CH_3]^+$  calcd. for  $C_{17}H_{15}N_2O_3S$ : 295.1, found: 294.8;  $[M-H]^-$  calcd. for  $C_{19}H_{17}N_2O_3S$ : 353.1, found: 352.5. **HRMS** (HESI):  $m/z$   $[M+H]^+$  calcd. for  $C_{19}H_{19}N_2O_3S$ : 355.1111, found: 355.1110;  $[M+Na]^+$  calcd. for  $C_{19}H_{18}N_2O_3SNa$ : 377.0930, found: 377.0930;  $[M+K]^+$  calcd. for  $C_{19}H_{18}N_2O_3SK$ : 393.0670, found: 393.0668.

## 5. Pictures of NMR, MS, HRMS, and HPLC spectra

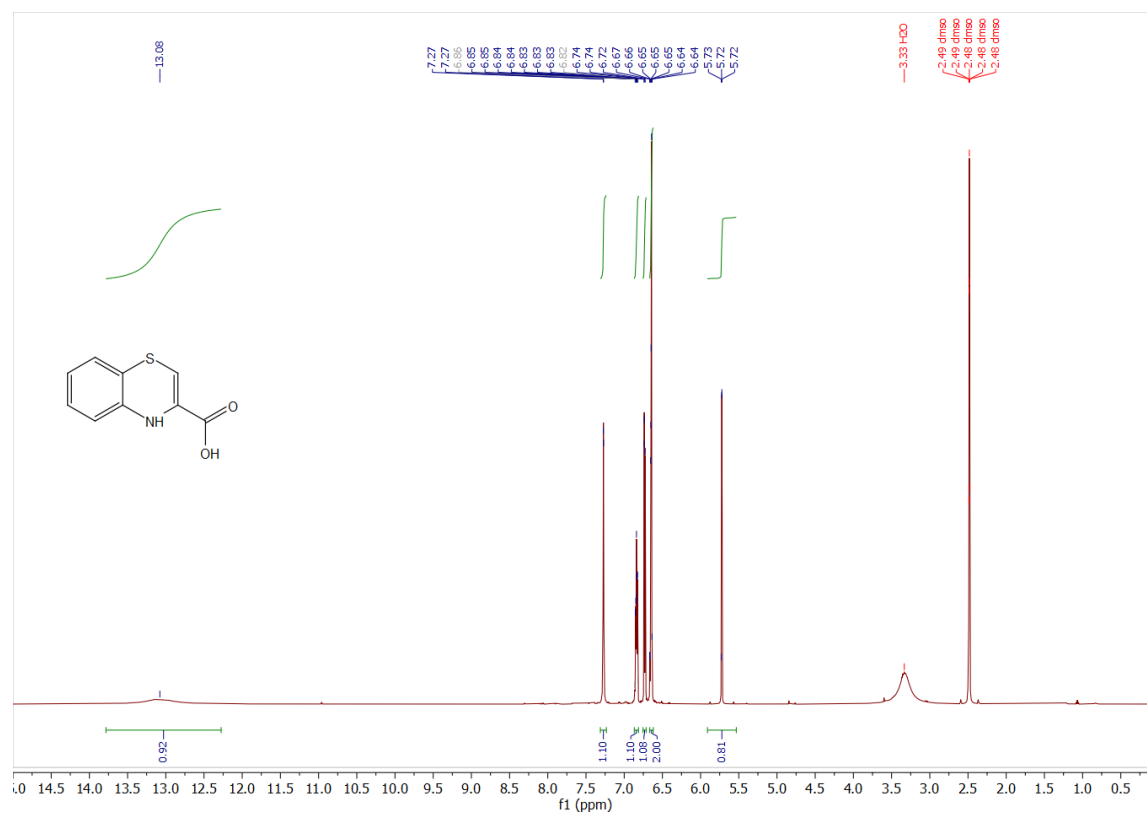


Figure S1. <sup>1</sup>H NMR spectrum of compound 10aa.

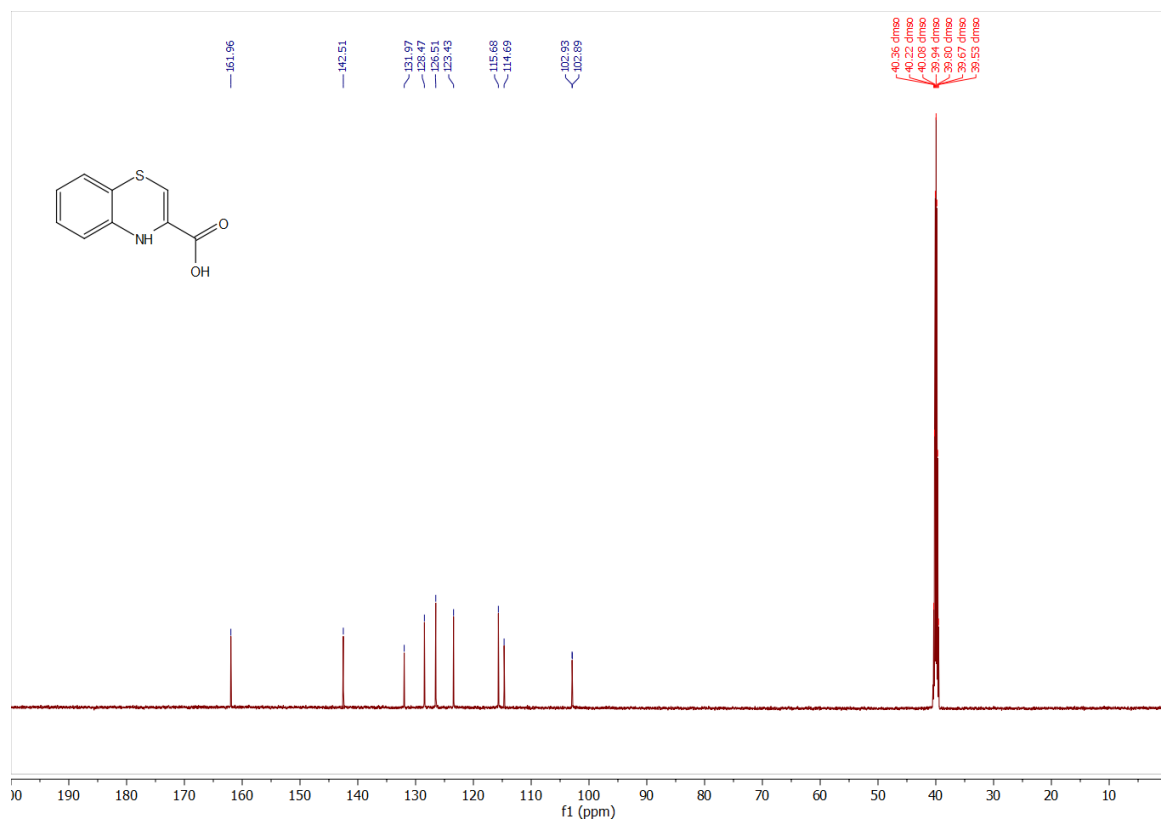
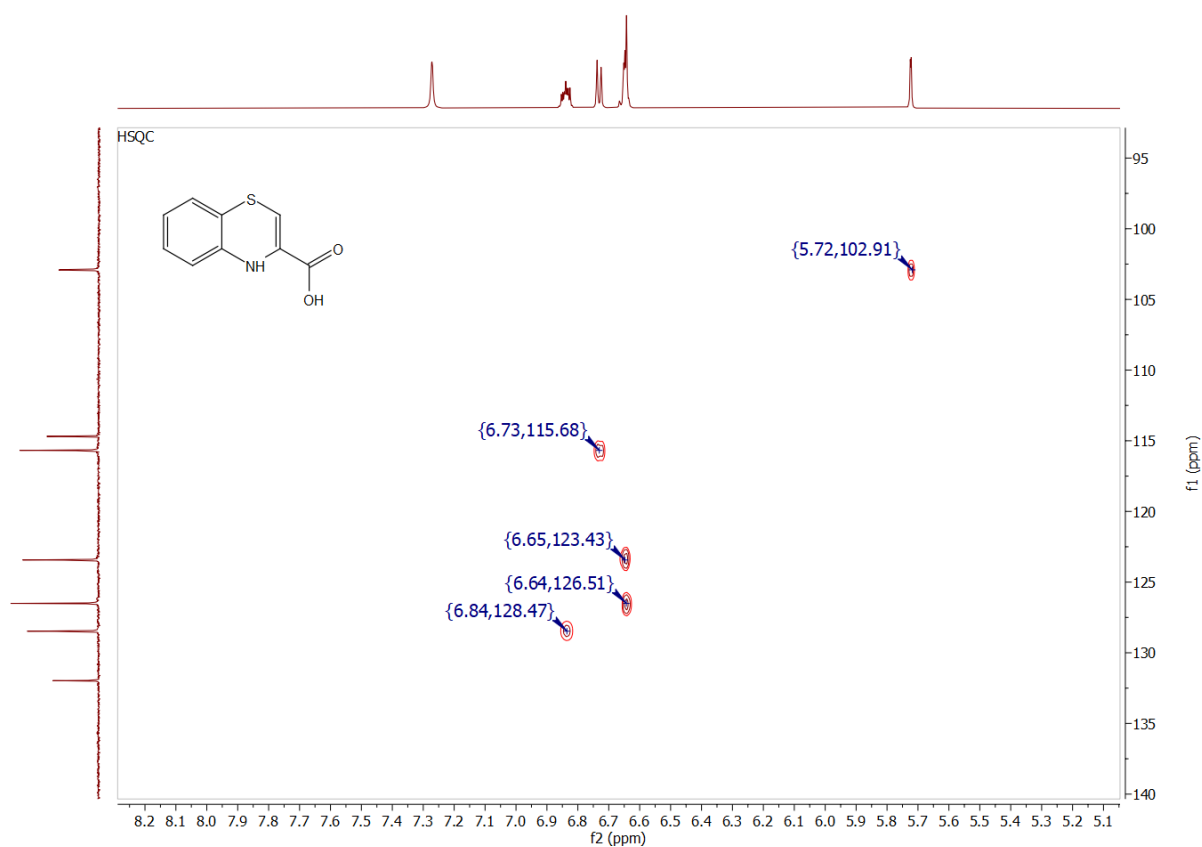
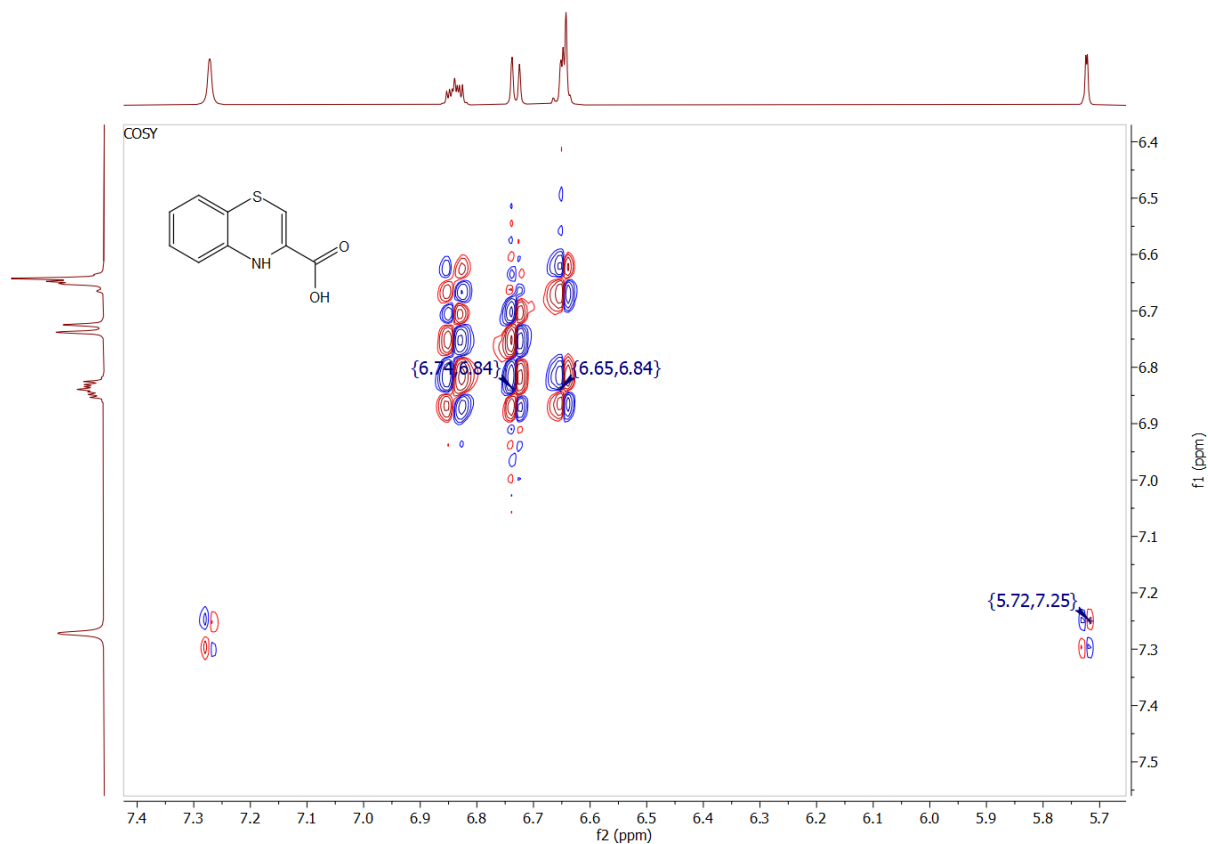


Figure S2. <sup>13</sup>C NMR spectrum of compound 10aa.



**Figure S3.** HSQC spectrum of compound **10aa**.



**Figure S4.** COSY spectrum of compound **10aa**.

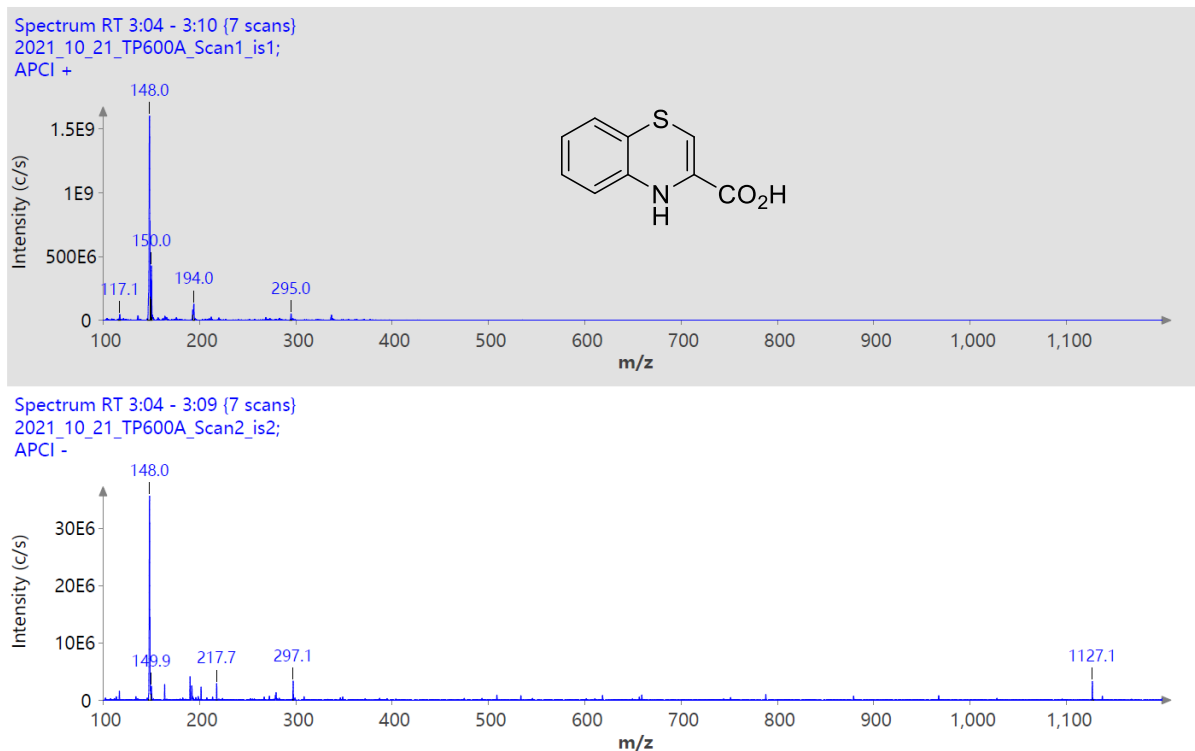


Figure S5. MS spectrum of compound 10aa.

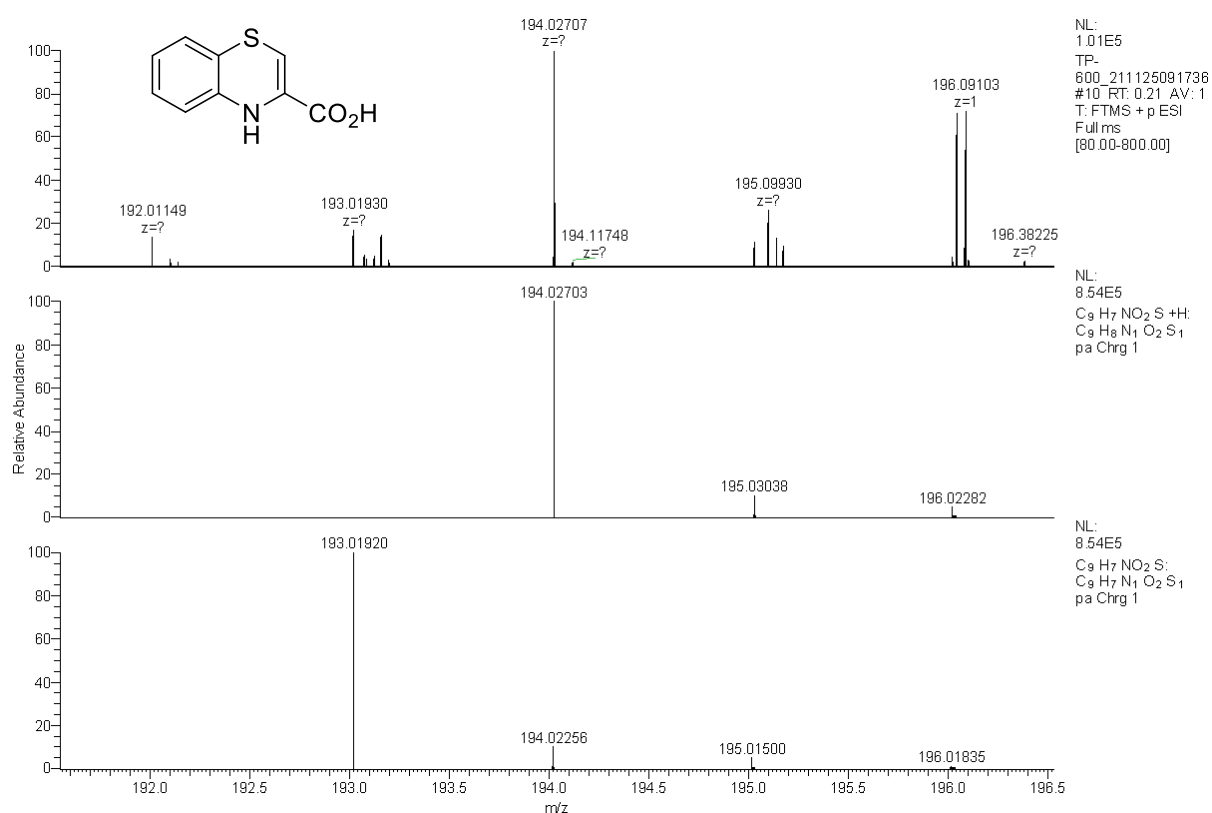


Figure S6. HRMS spectrum of compound 10aa.

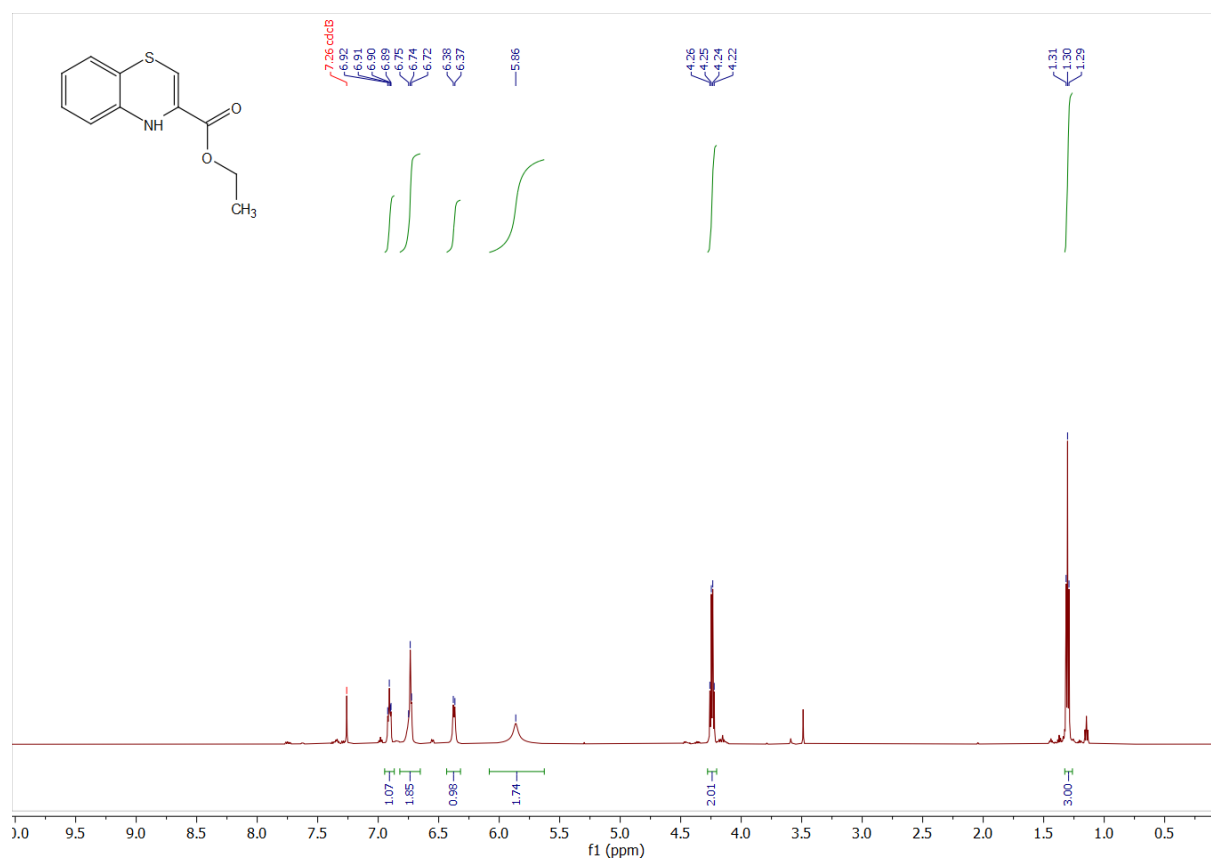


Figure S7. <sup>1</sup>H NMR spectrum of compound 10ac.

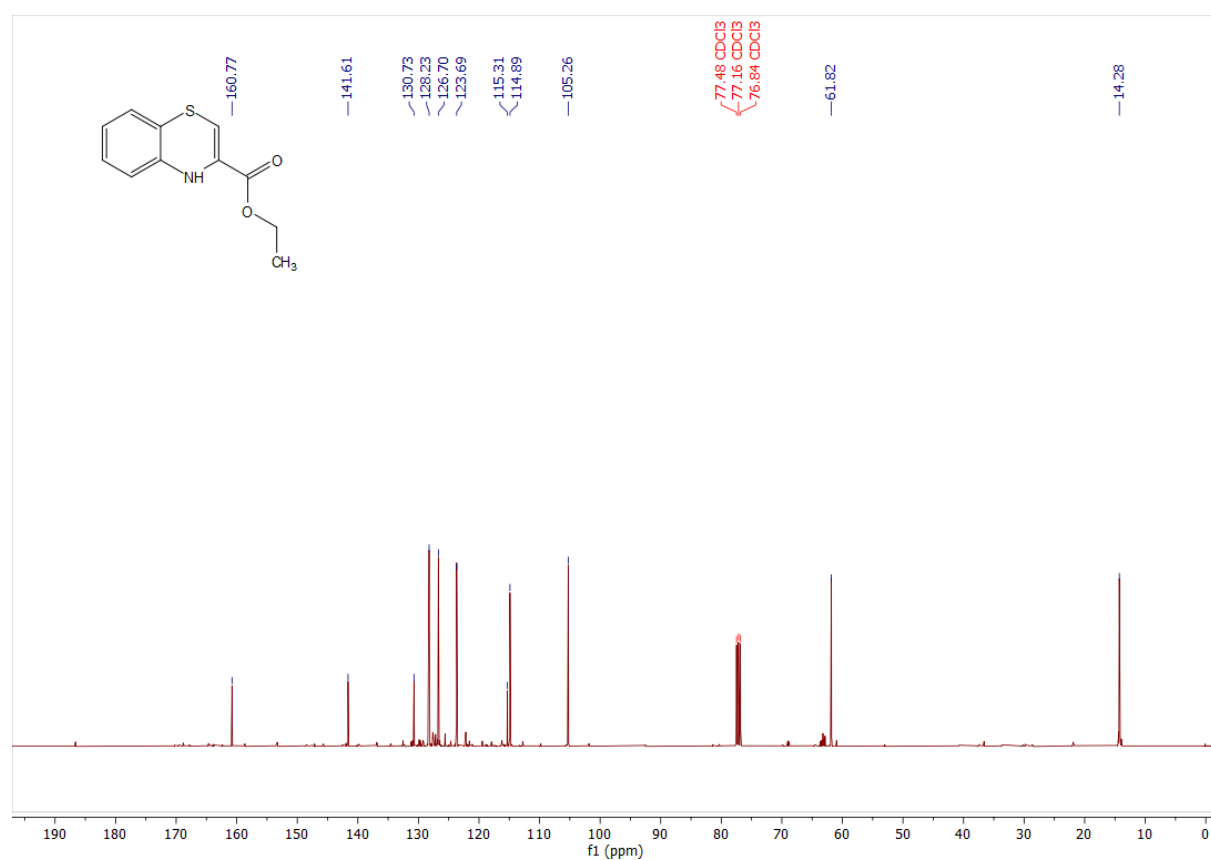
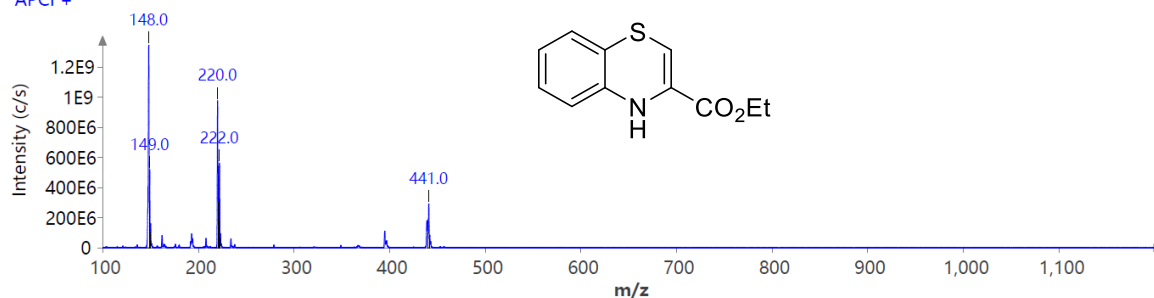
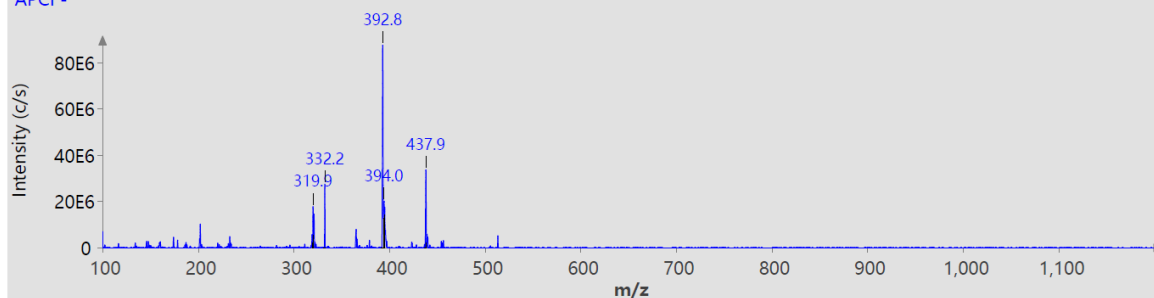


Figure S8. <sup>13</sup>C NMR spectrum of compound 10ac.

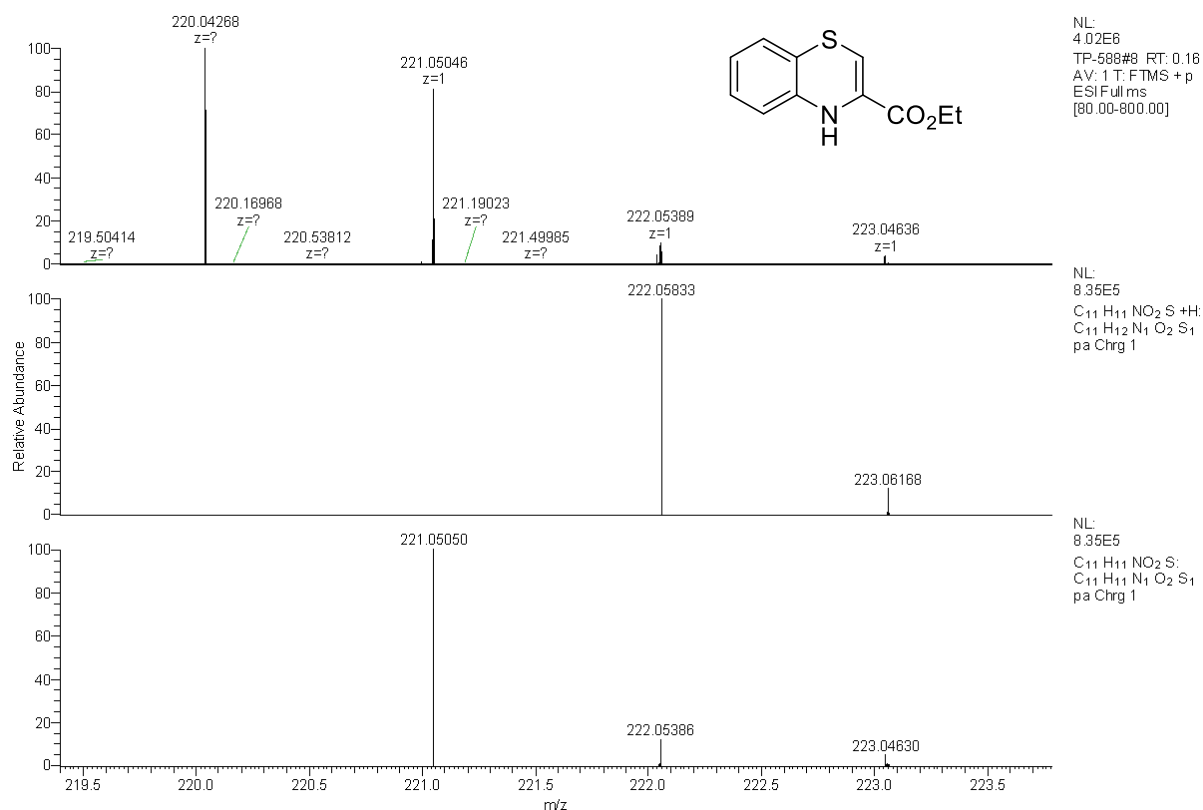
Spectrum RT 1:24 - 1:32 (10 scans)  
2021\_10\_21\_TP588A\_Scan1\_is1;  
APCI +



Spectrum RT 1:30 (1 scans)  
2021\_10\_21\_TP588A\_Scan2\_is2;  
APCI -



**Figure S9.** MS spectrum of compound **10ac**.



**Figure S10.** HRMS spectrum of compound **10ac**.

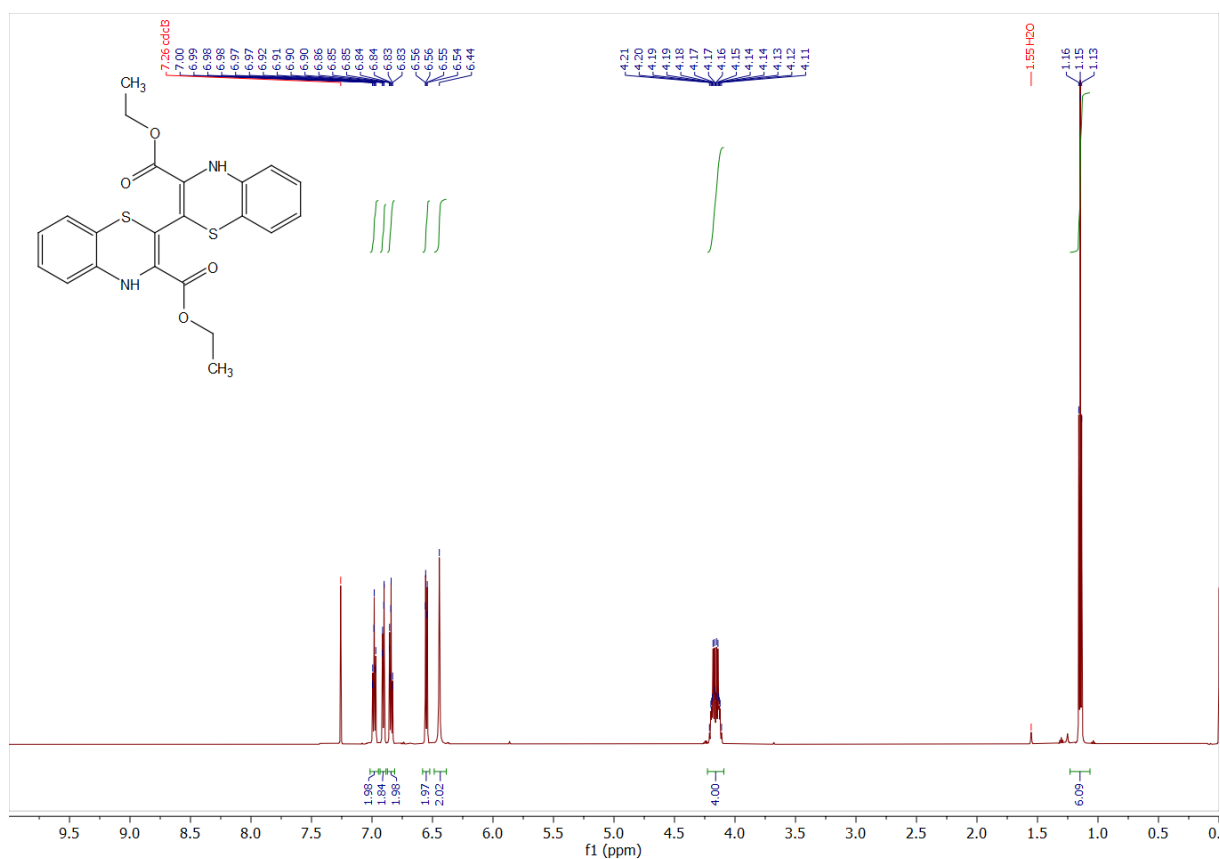


Figure S11. <sup>1</sup>H NMR spectrum of compound 11a.

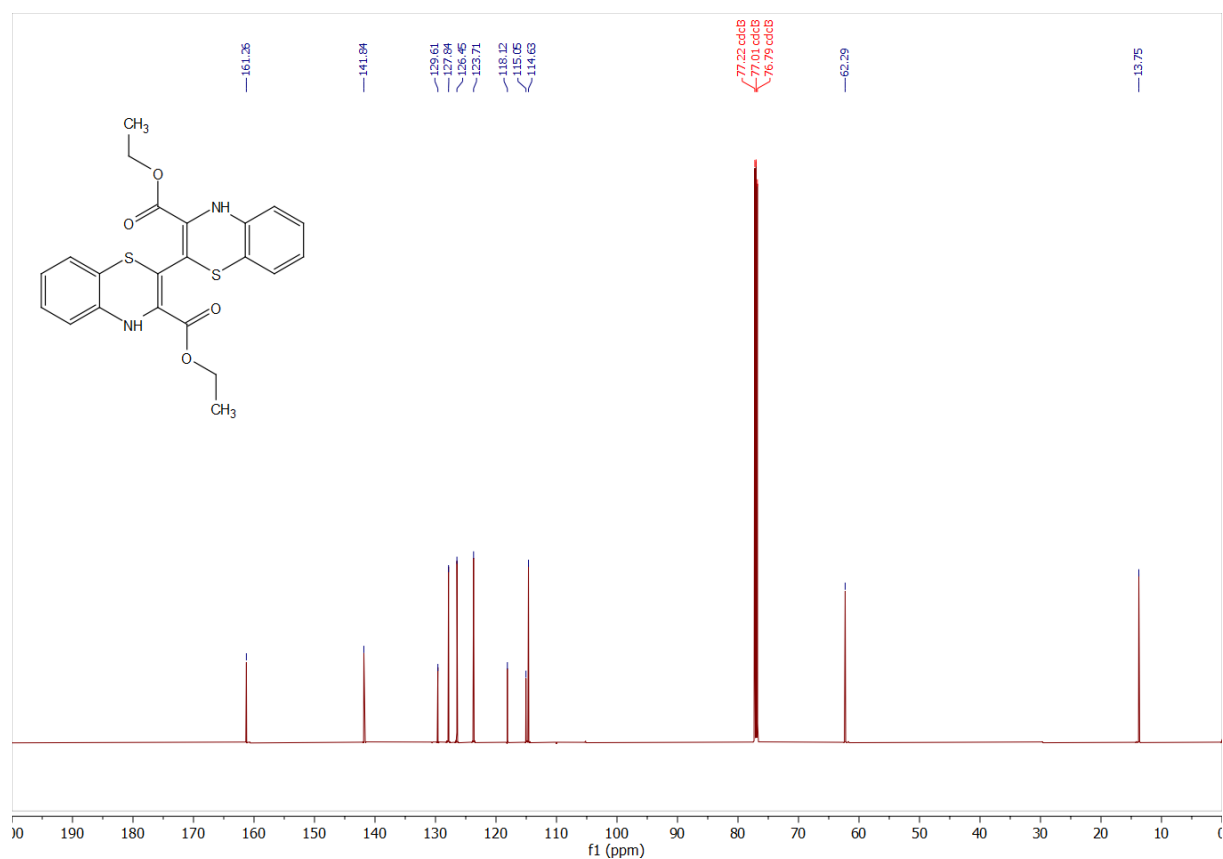
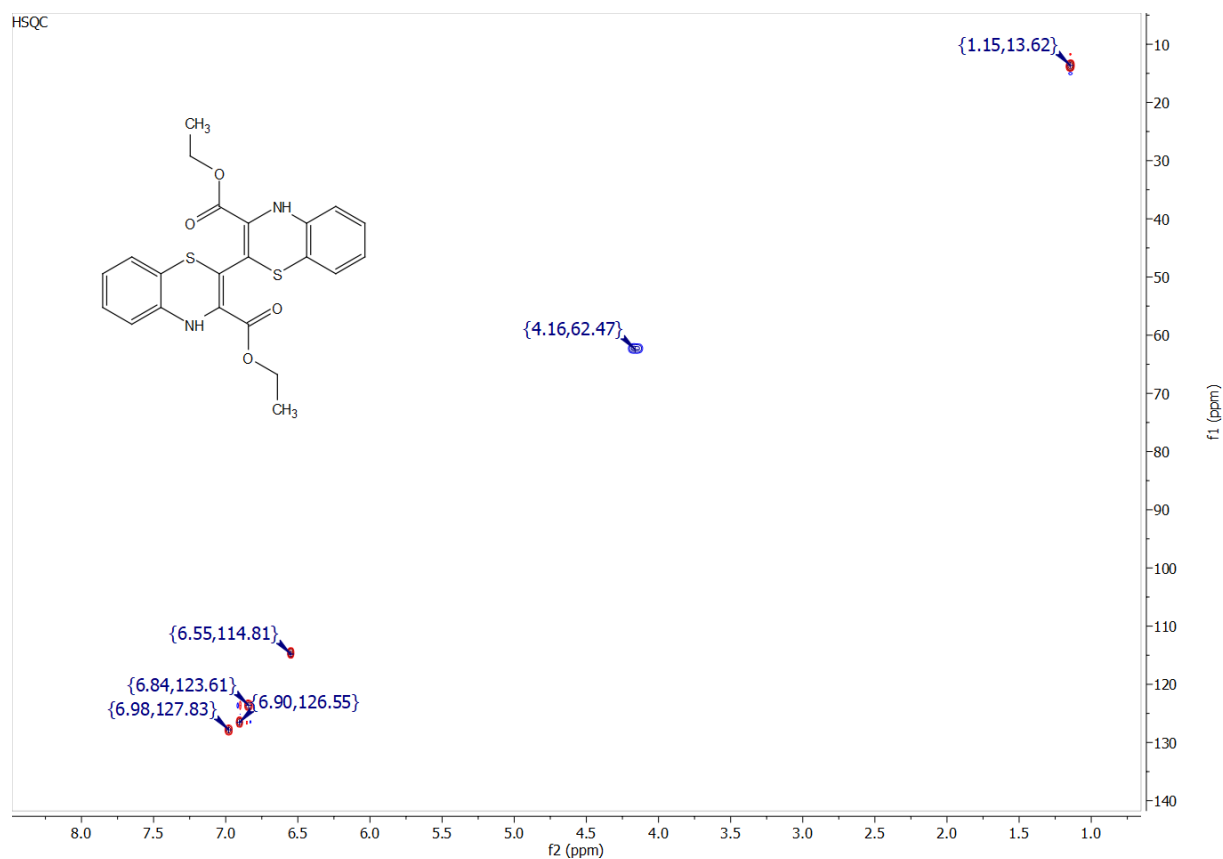
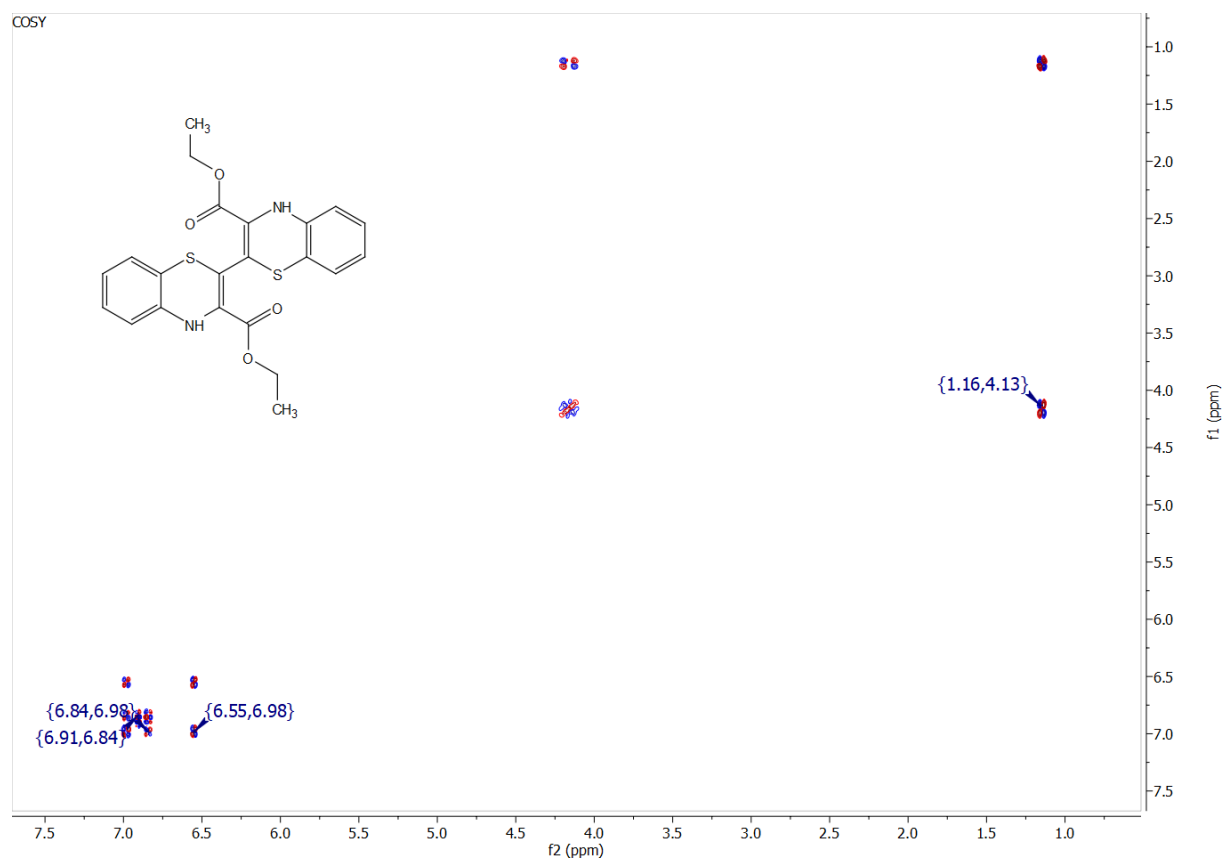


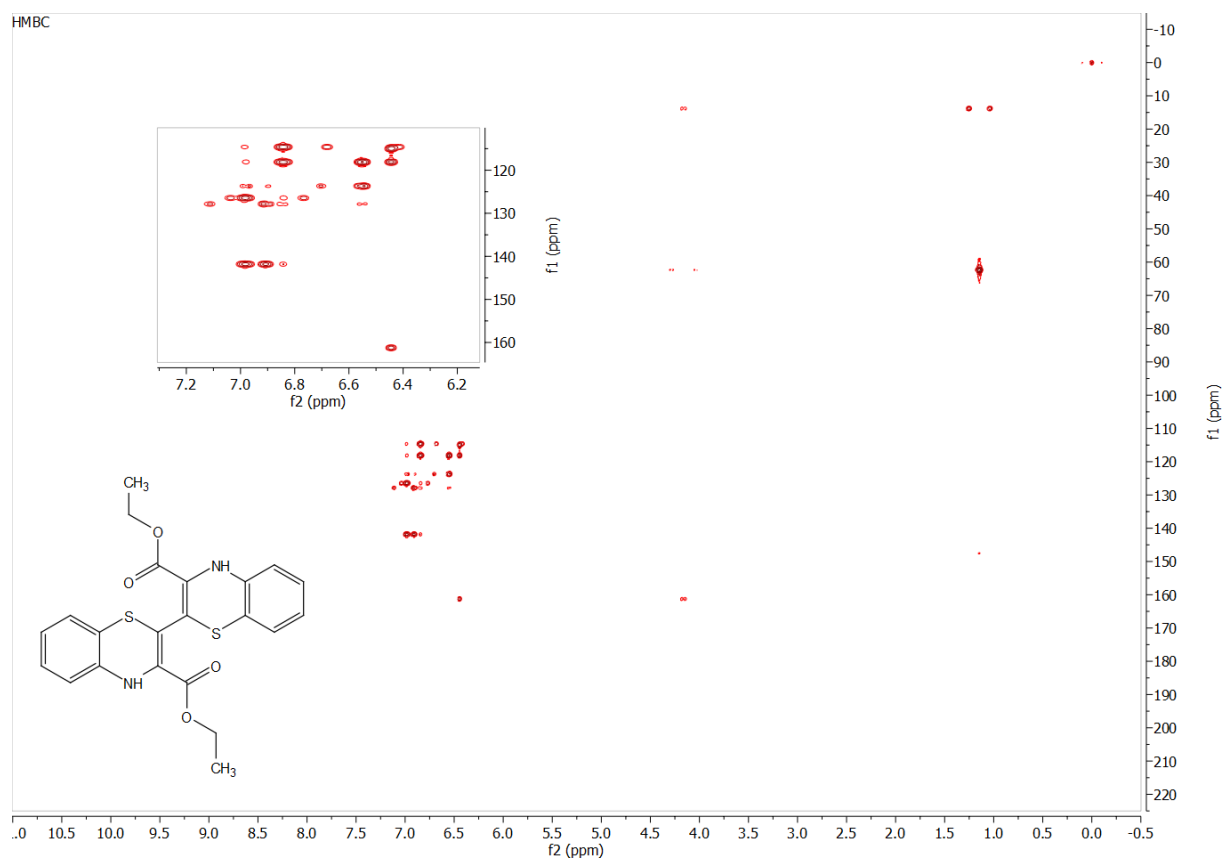
Figure S12. <sup>13</sup>C NMR spectrum of compound 11a.



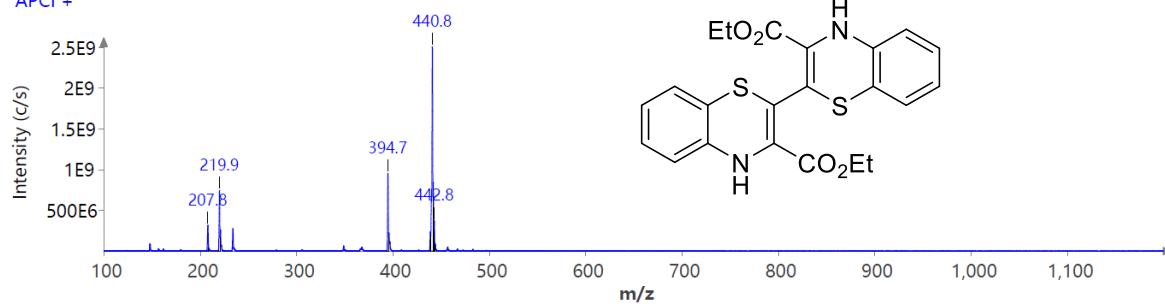
**Figure S13.** HSQC spectrum of compound **11a**.



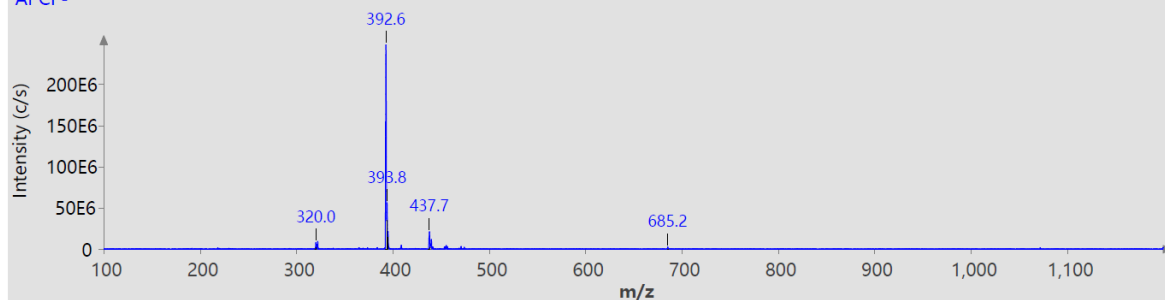
**Figure S14.** COSY spectrum of compound **11a**.

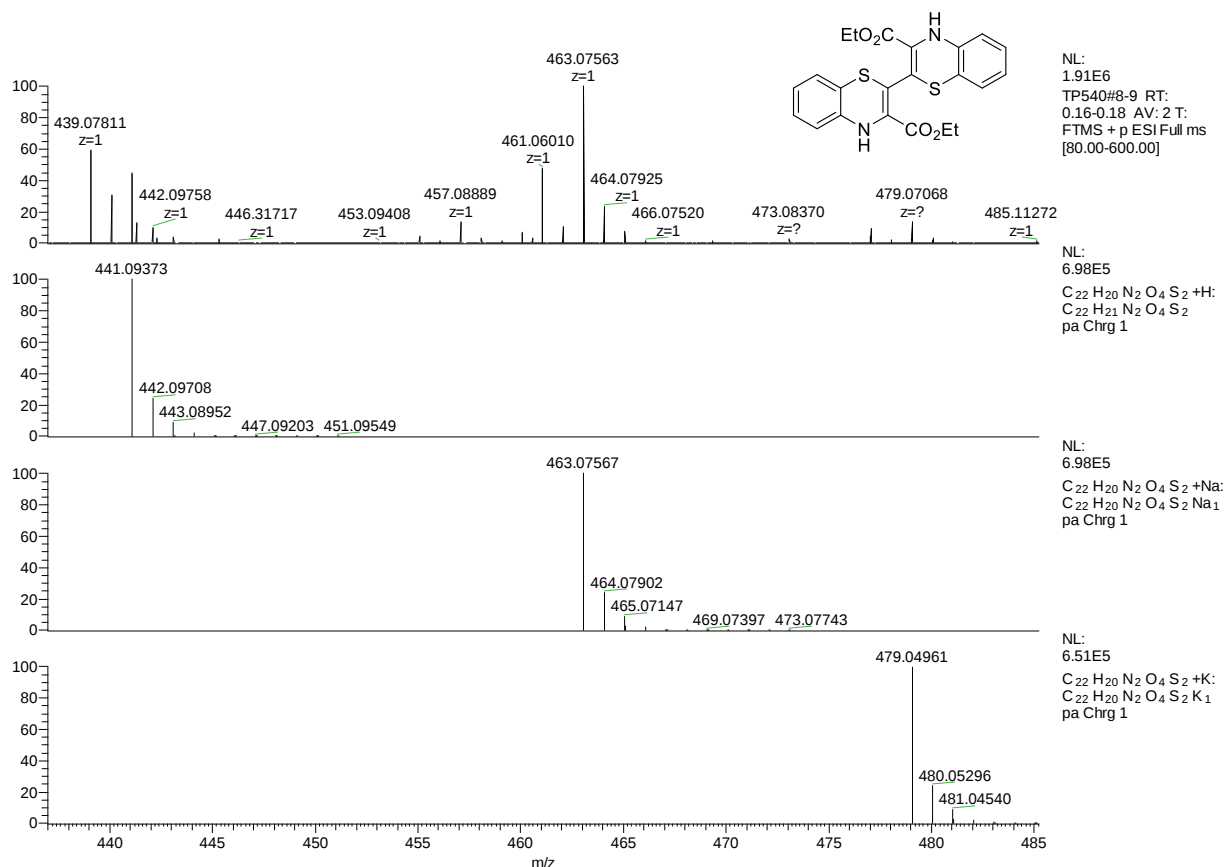


Spectrum RT 0:45 - 0:59 (17 scans)  
2021\_12\_13\_tp540\_Scan1\_is1;  
APCI +

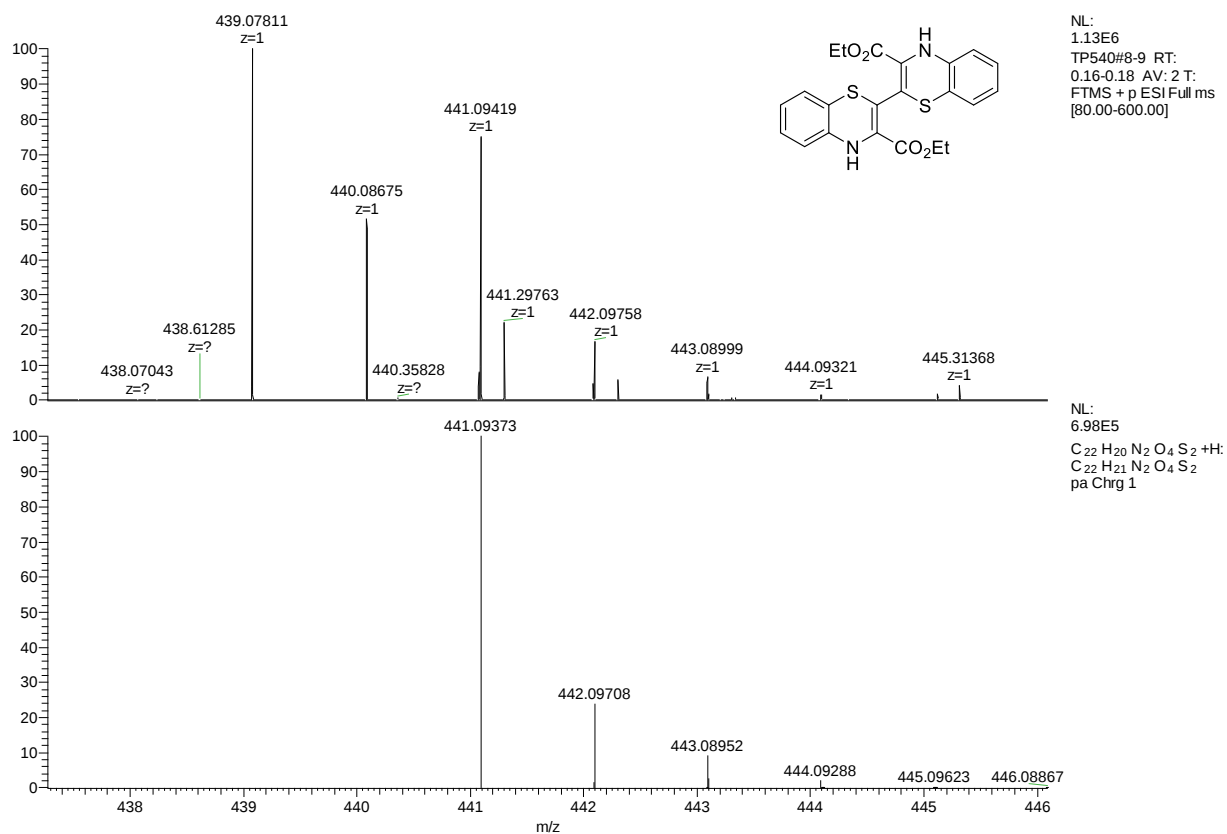


Spectrum RT 0:54 (1 scans)  
2021\_12\_13\_tp540\_Scan2\_is2;  
APCI -

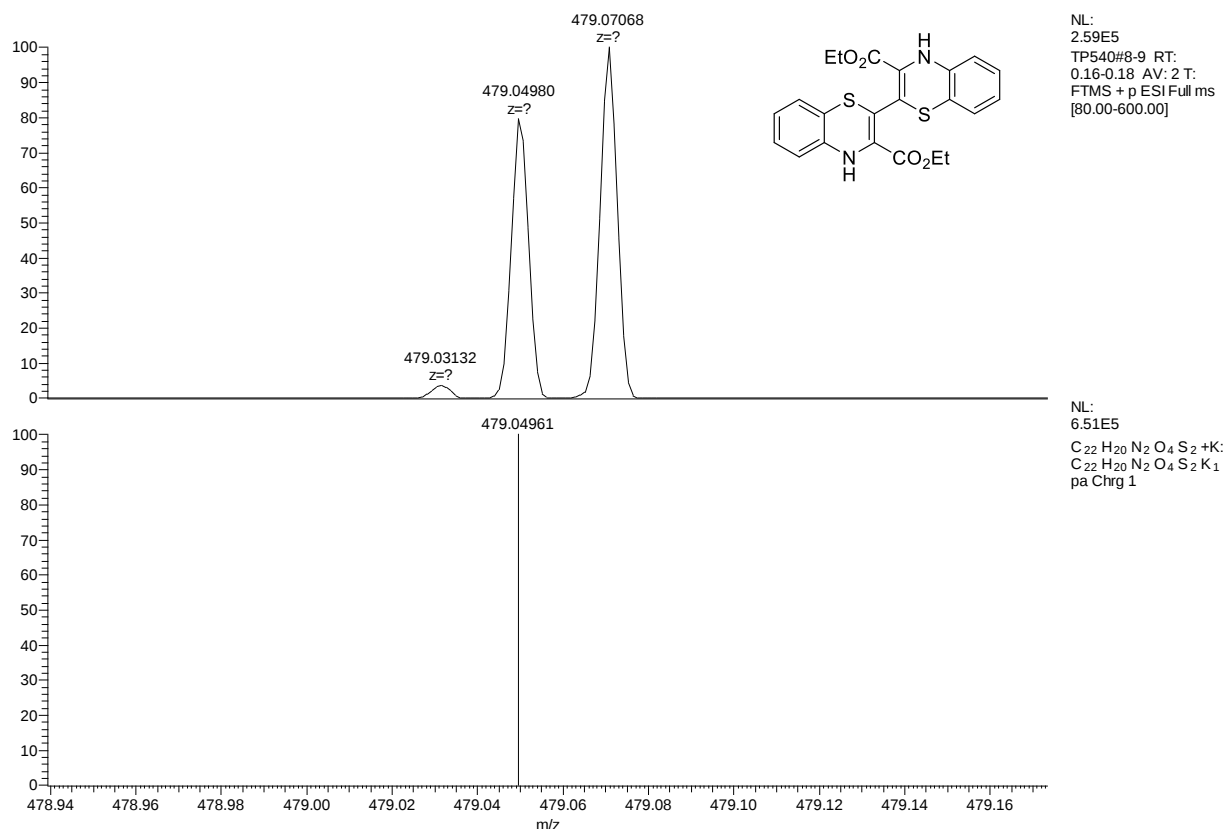




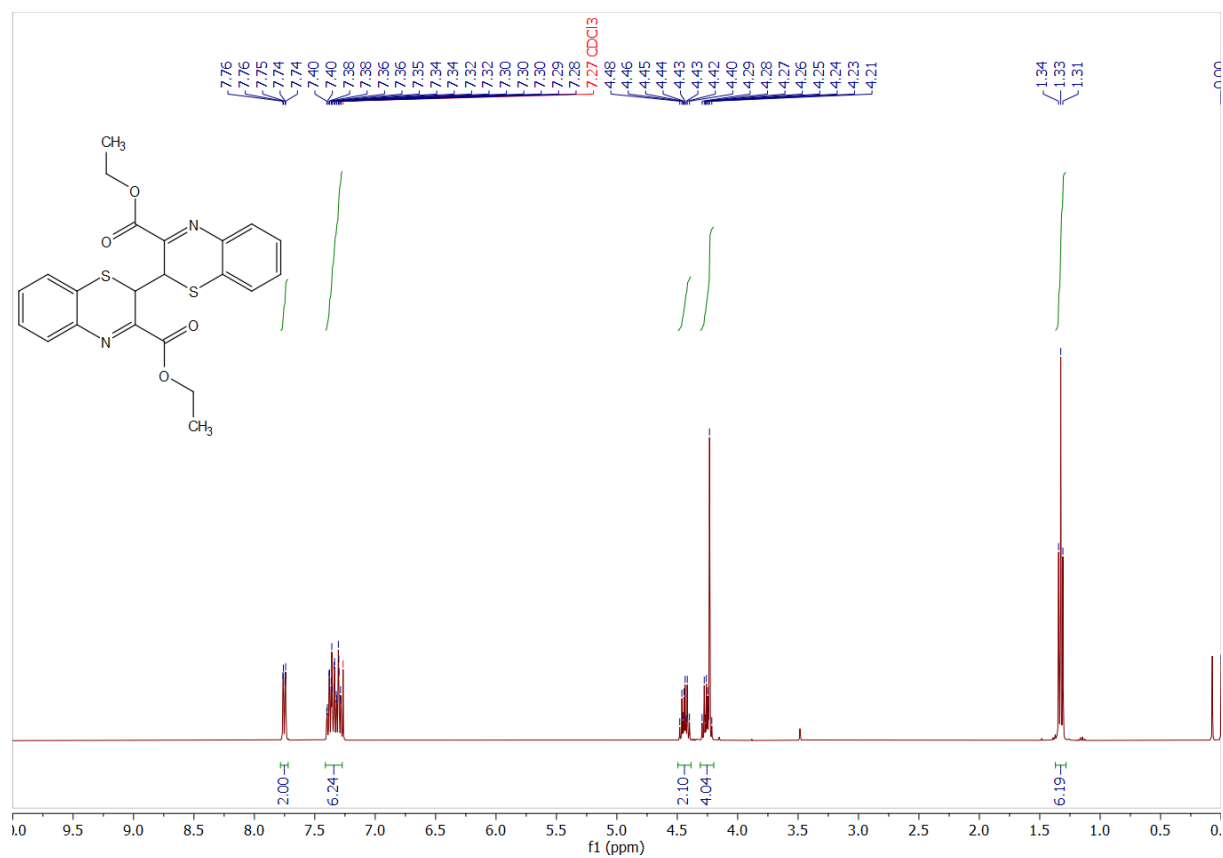
**Figure S17.** HRMS spectrum of compound **11a**.



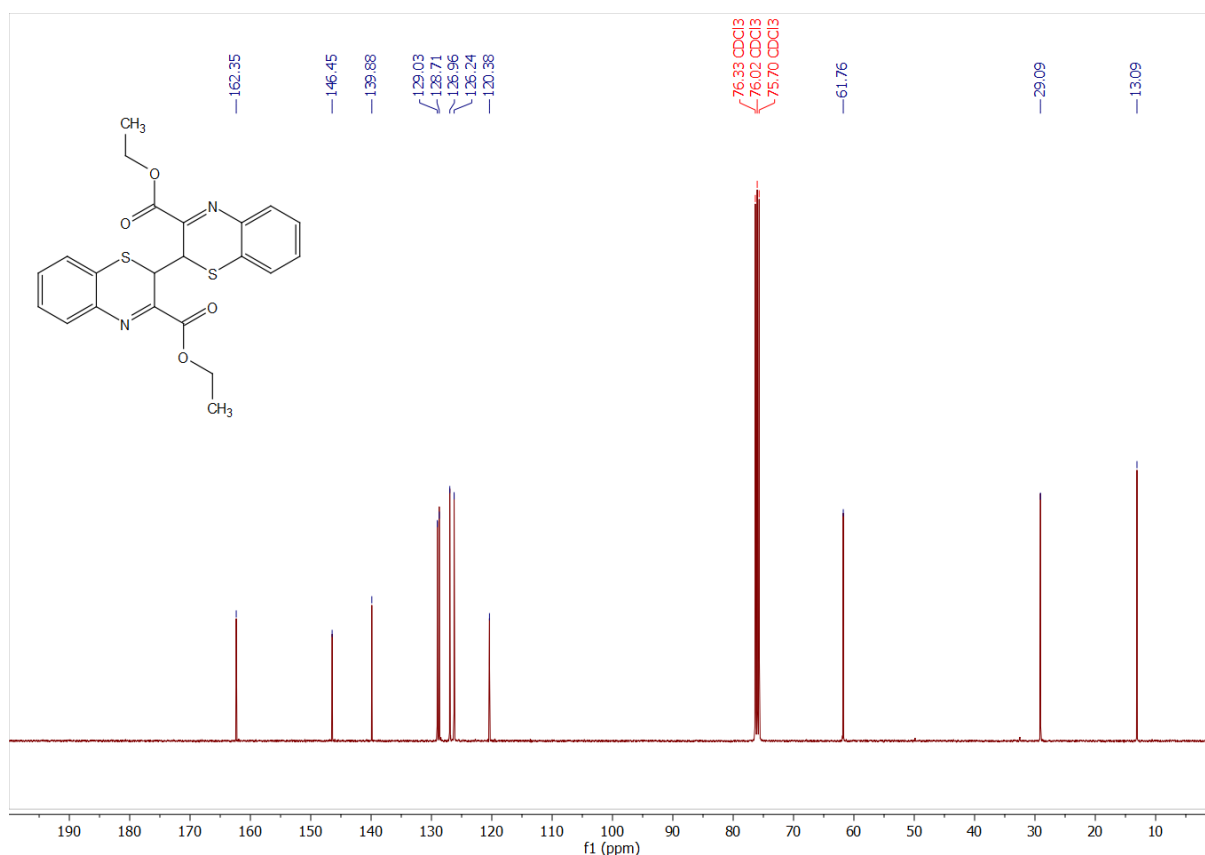
**Figure S18.** HRMS spectrum of compound **11a** (enlarged for [M+H]<sup>+</sup>).



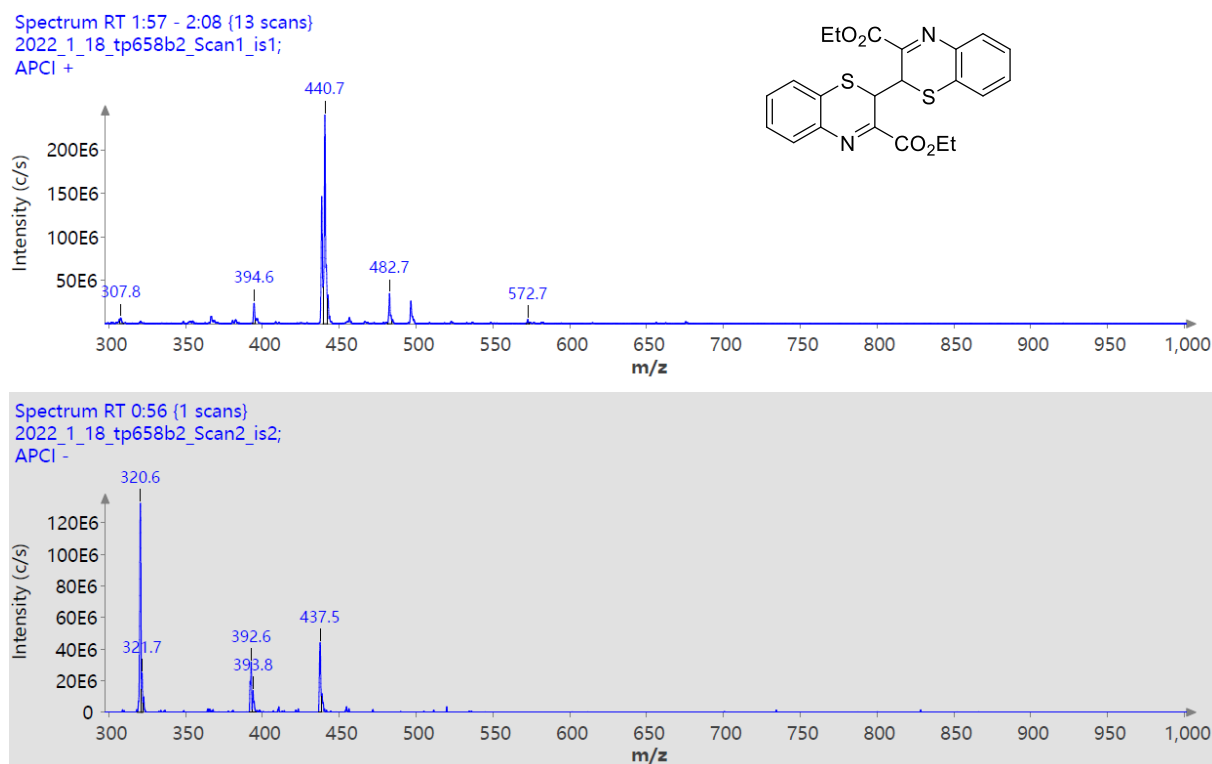
**Figure S19.** HRMS spectrum of compound **11a** (enlarged for  $[M+K]^+$ ).



**Figure S20.**  $^1H$  NMR spectrum of compound **11b**.



**Figure S21.** <sup>13</sup>C NMR spectrum of compound **11b**.



**Figure S22.** MS spectrum of compound **11b**.

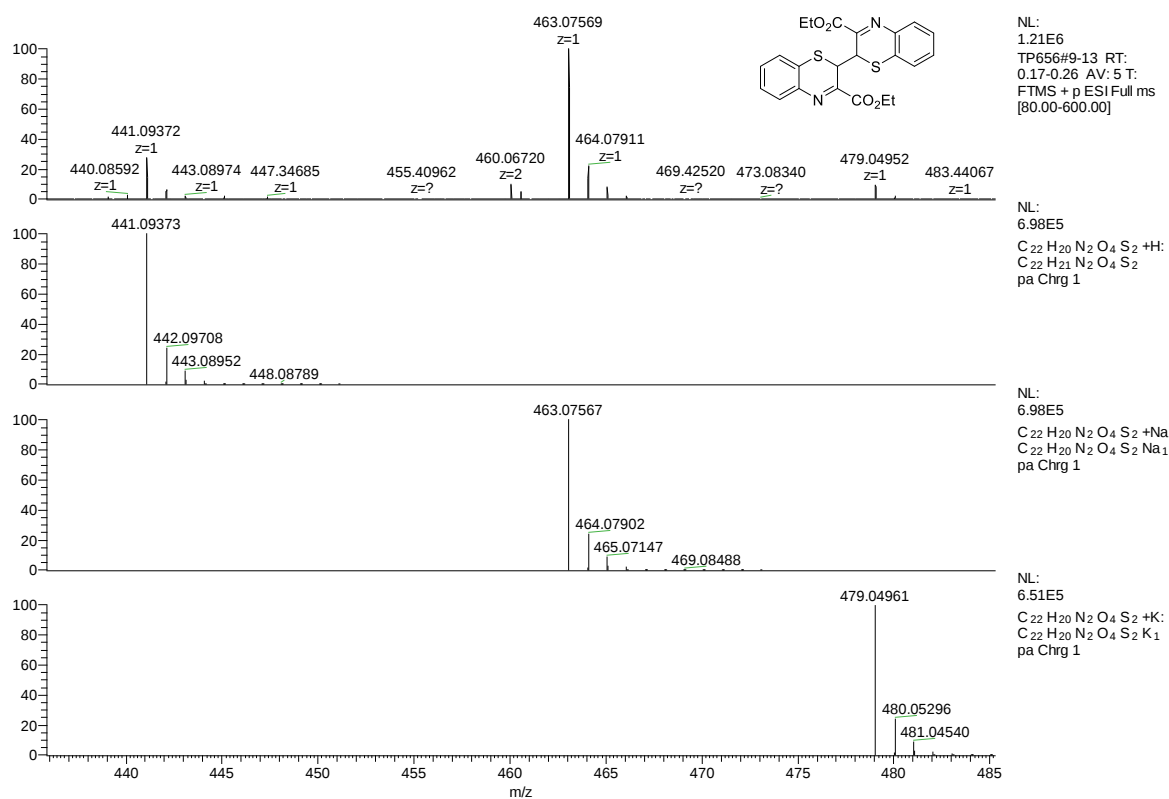


Figure S23. HRMS spectrum of compound 11b.

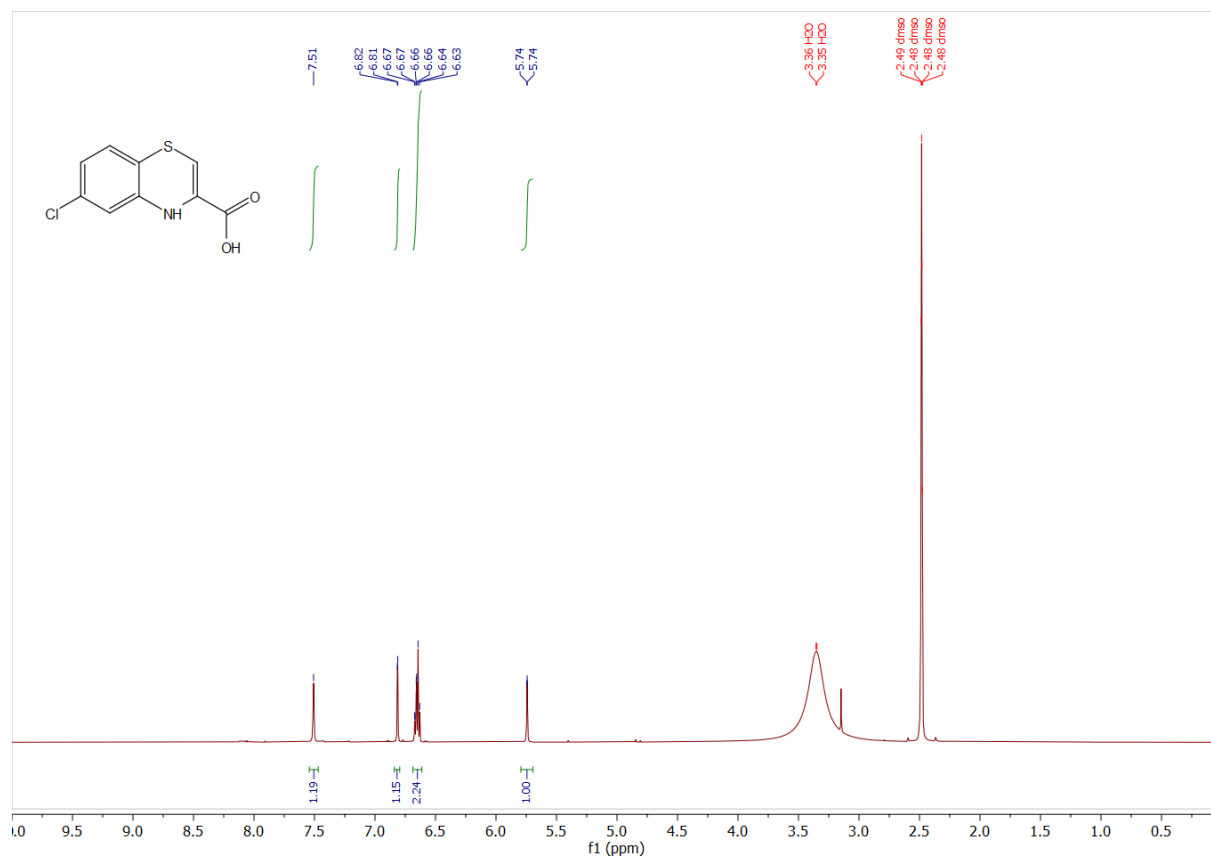
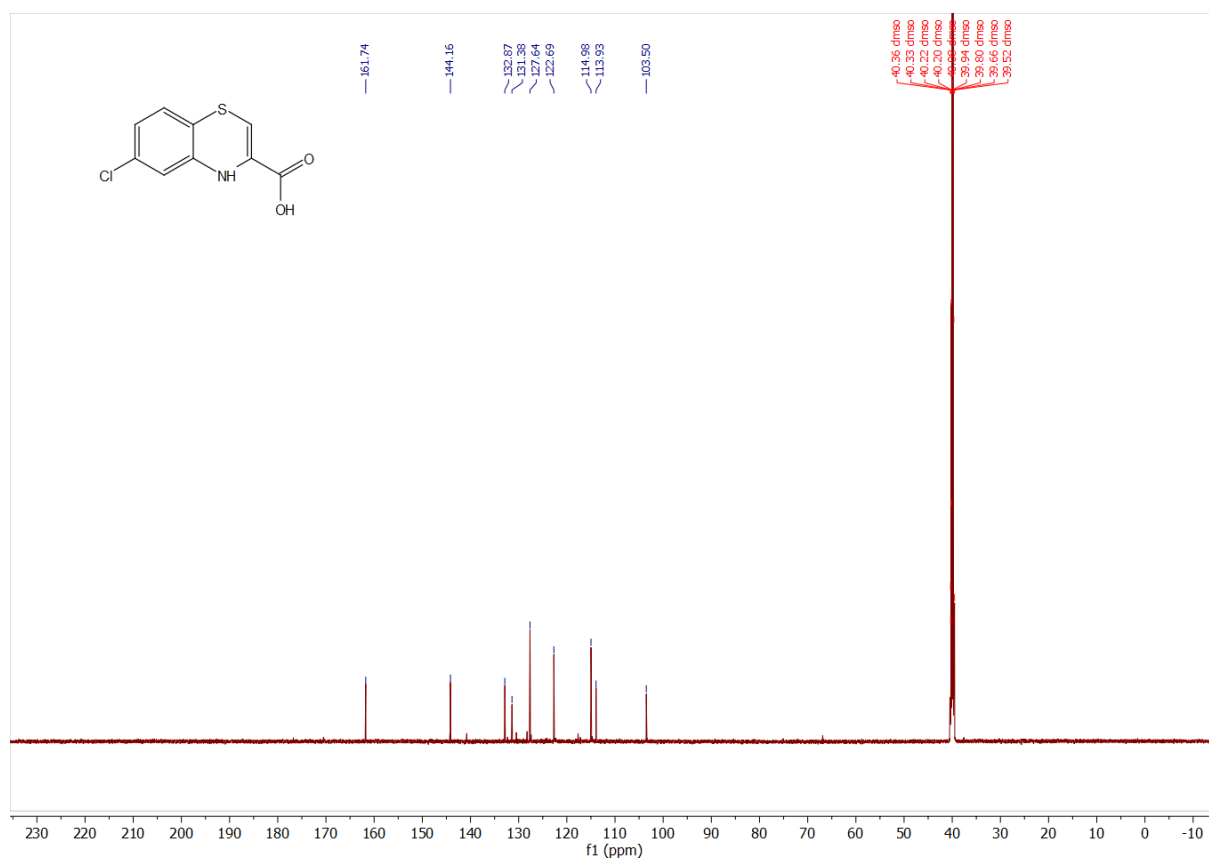
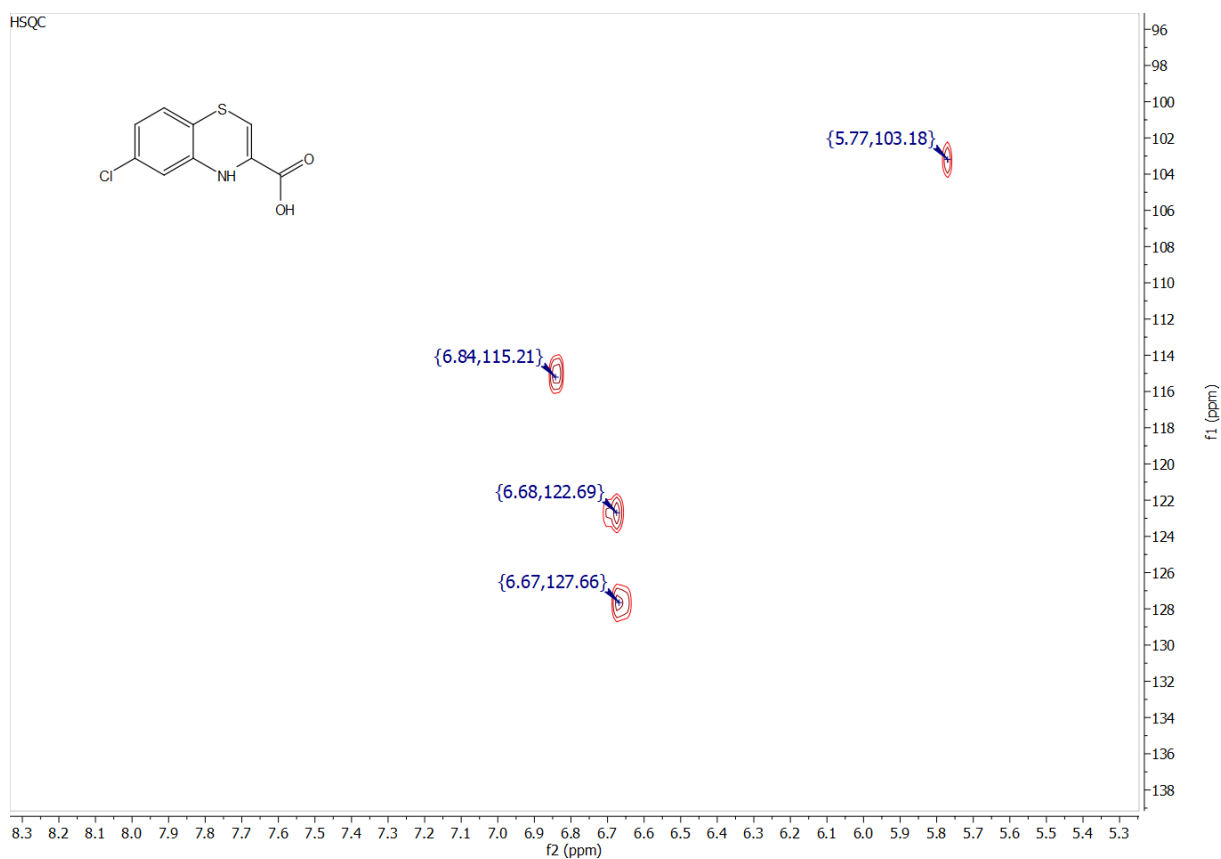


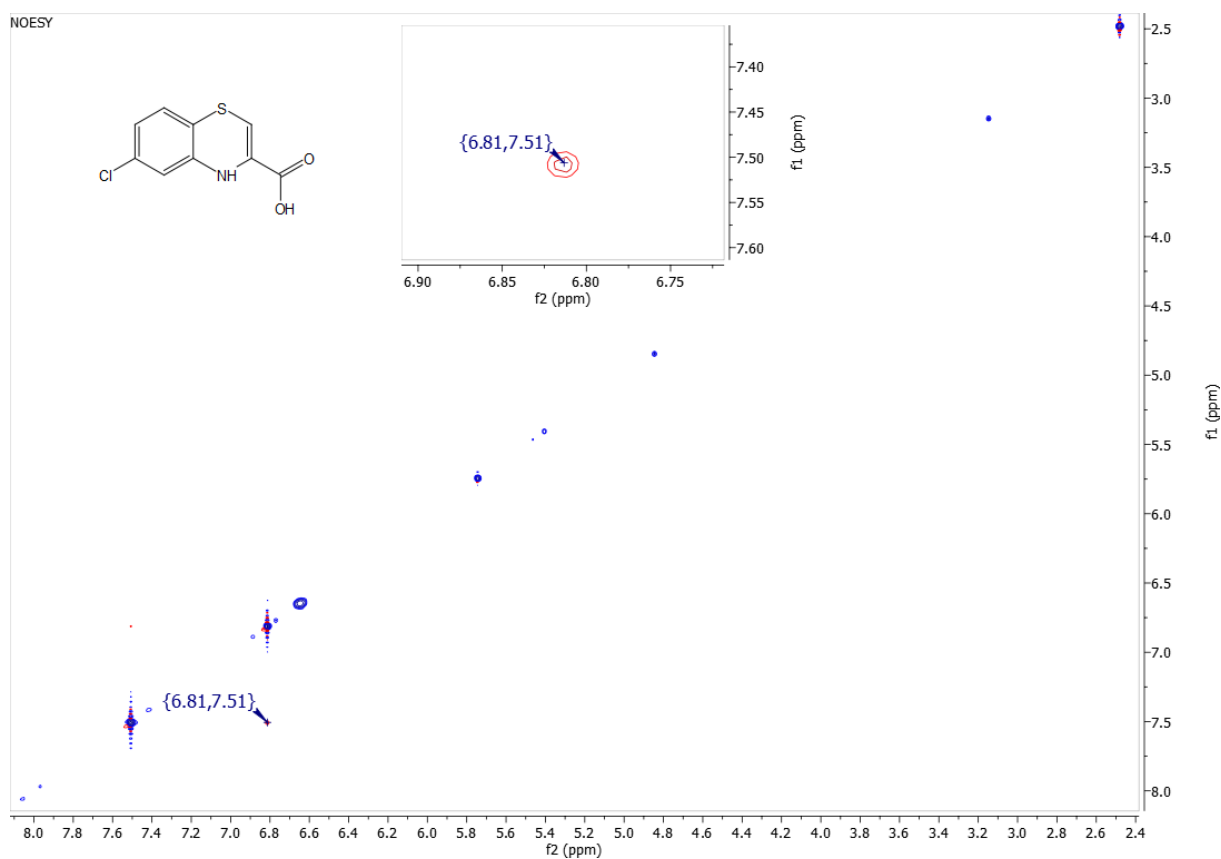
Figure S24. <sup>1</sup>H NMR spectrum of compound 10ba.



**Figure S8.** <sup>13</sup>C NMR spectrum of compound **10ba**.

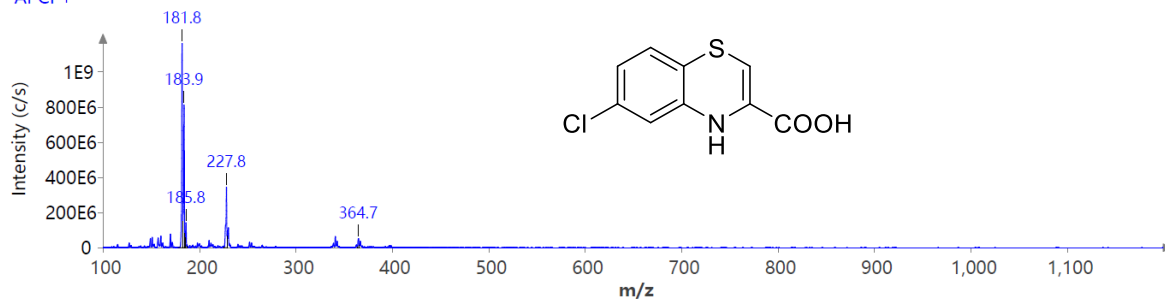


**Figure S9.** HSQC spectrum of compound **10ba**.

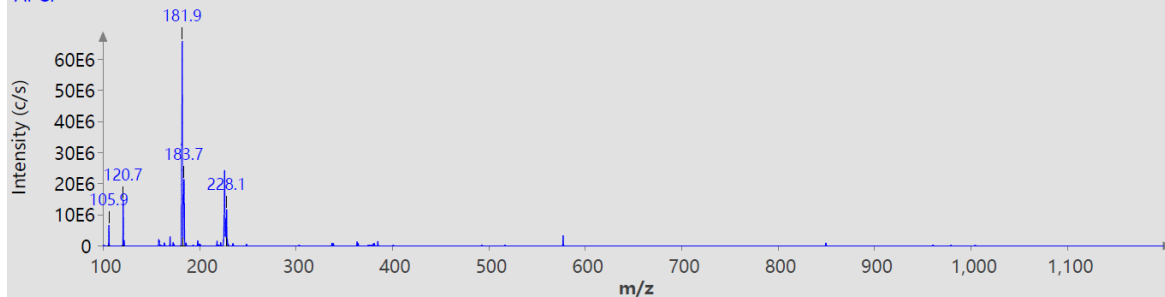


**Figure S10.** NOESY spectrum of compound **10ba**.

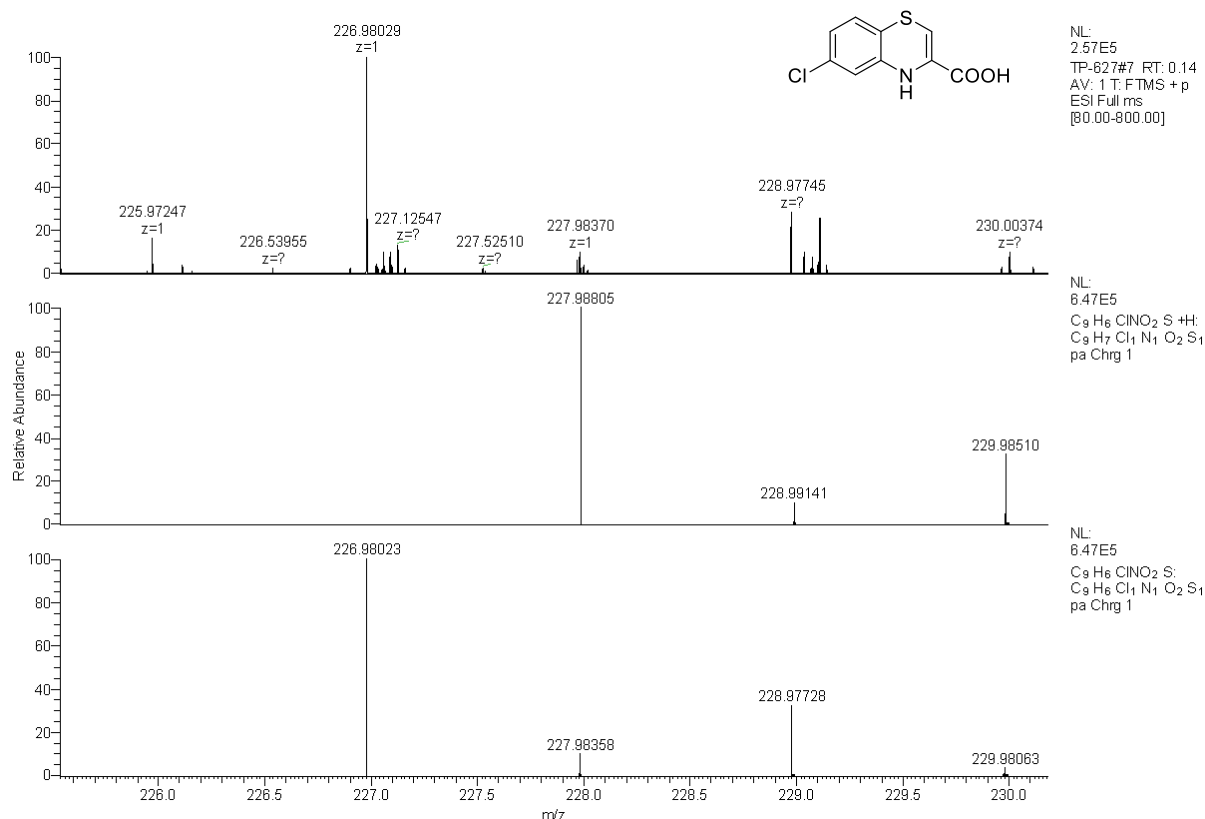
Spectrum RT 1:15 - 1:21 {8 scans}  
2021\_10\_27\_tp626\_Scan1\_is1;  
APCI +



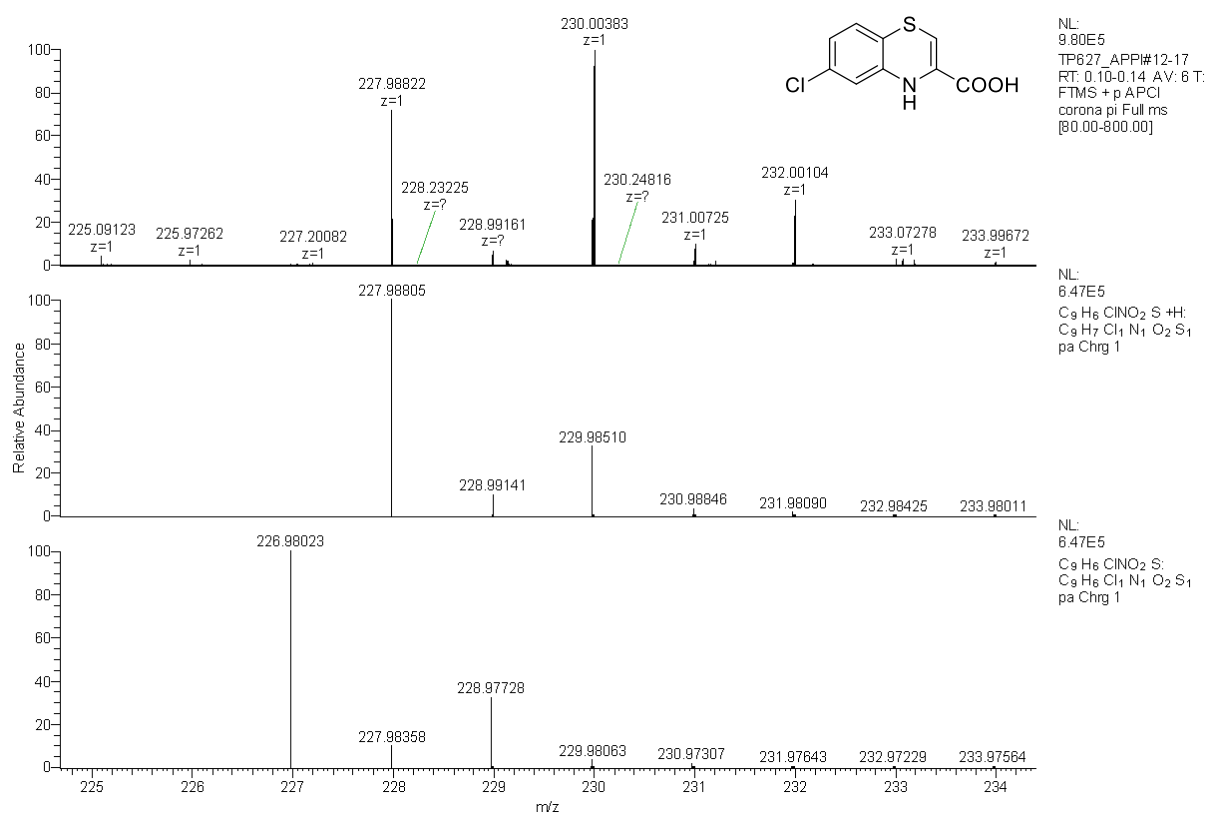
Spectrum RT 1:19 {1 scans}  
2021\_10\_27\_tp626\_Scan2\_is2;  
APCI -



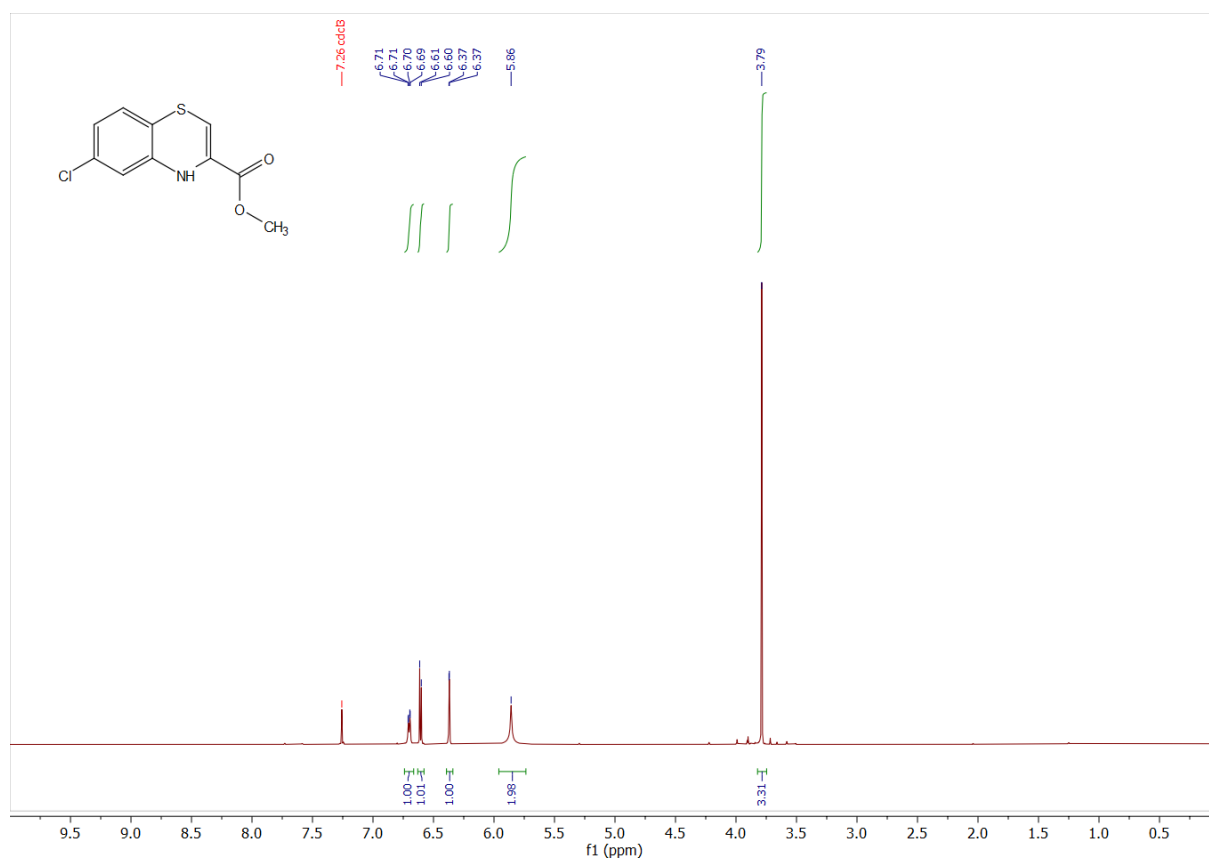
**Figure S11.** MS spectrum of compound **10ba**.



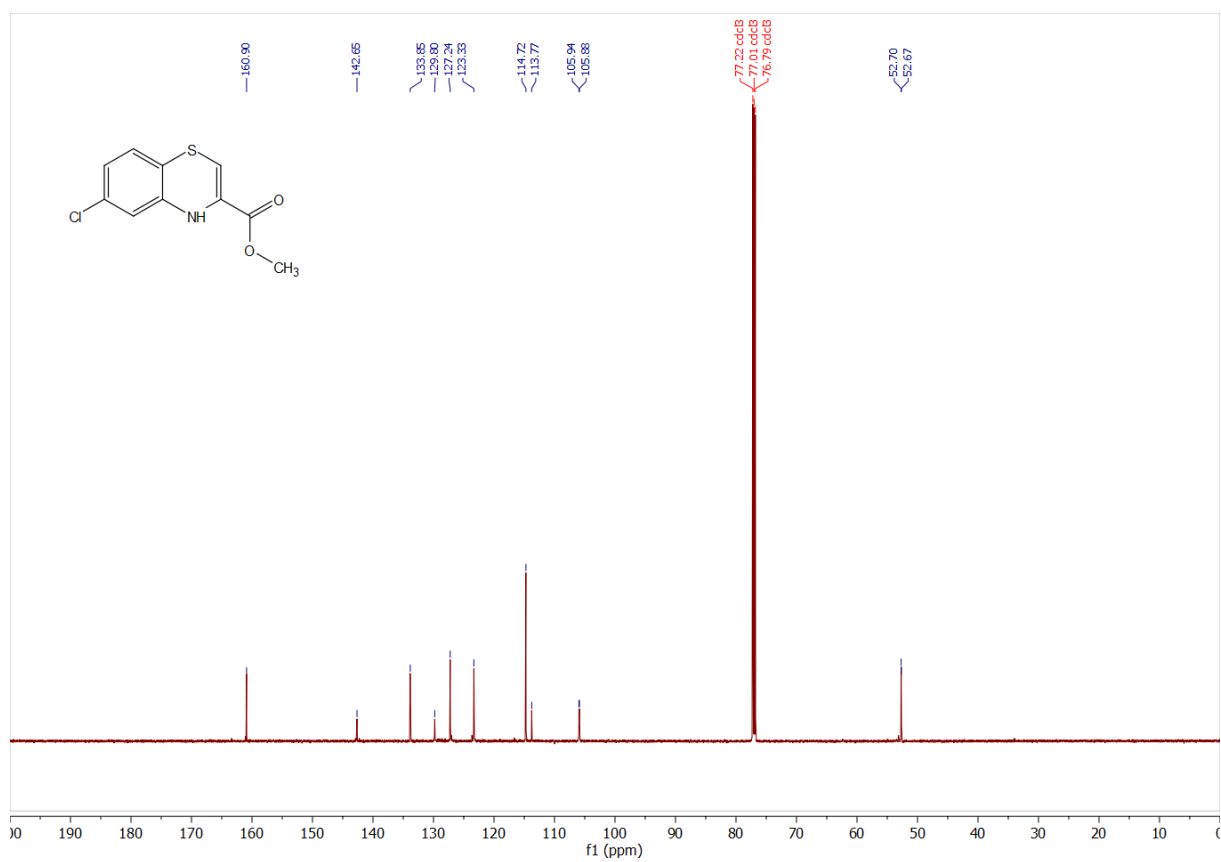
**Figure S29.** HRMS spectrum of compound **10ba** (HESI).



**Figure S30.** HRMS spectrum of compound **10ba** (APPI).

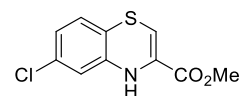
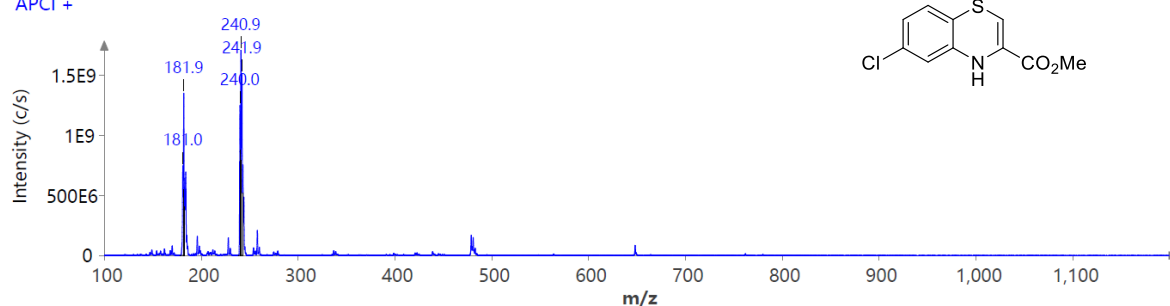


**Figure S31.** <sup>1</sup>H NMR spectrum of compound **10bb**.

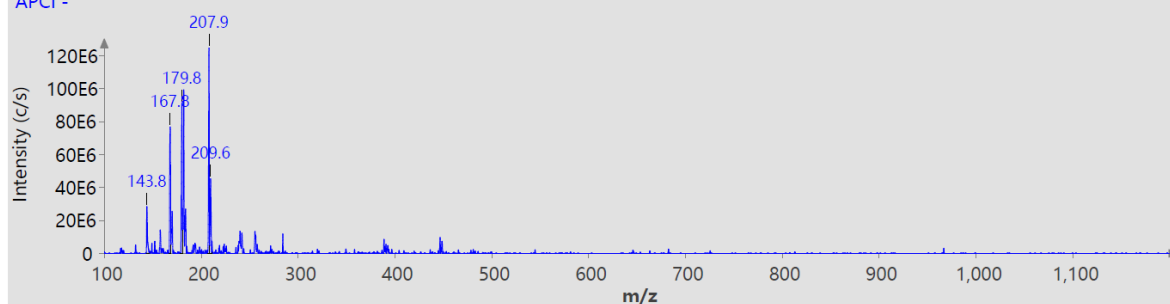


**Figure S32.** <sup>13</sup>C NMR spectrum of compound **10bb**.

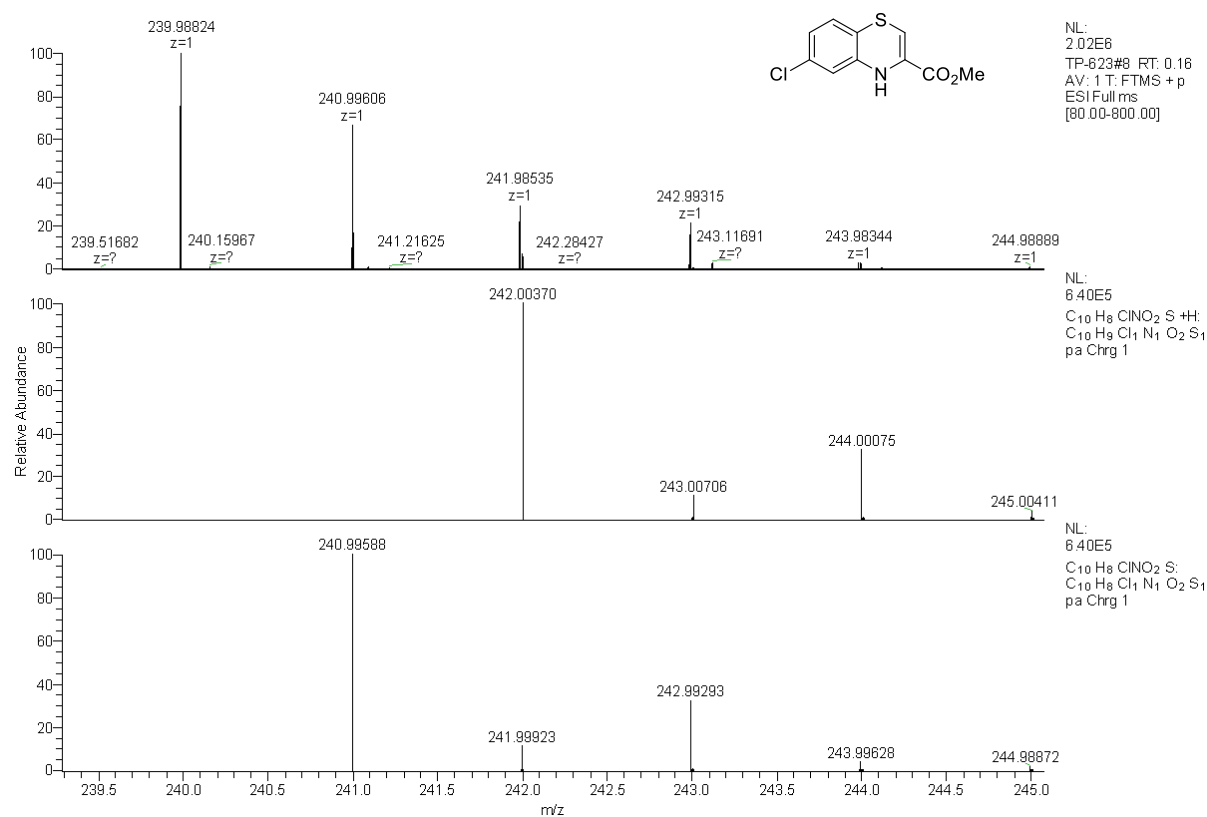
Spectrum RT 2:29 - 2:41 (15 scans)  
2021\_10\_21\_TP623a\_Scan1\_is1;  
APCI +



Spectrum RT 2:35 (1 scans)  
2021\_10\_21\_TP623a\_Scan2\_is2;  
APCI -



**Figure S33.** MS spectrum of compound **10bb**.



**Figure S34.** HRMS spectrum of compound **10bb**.

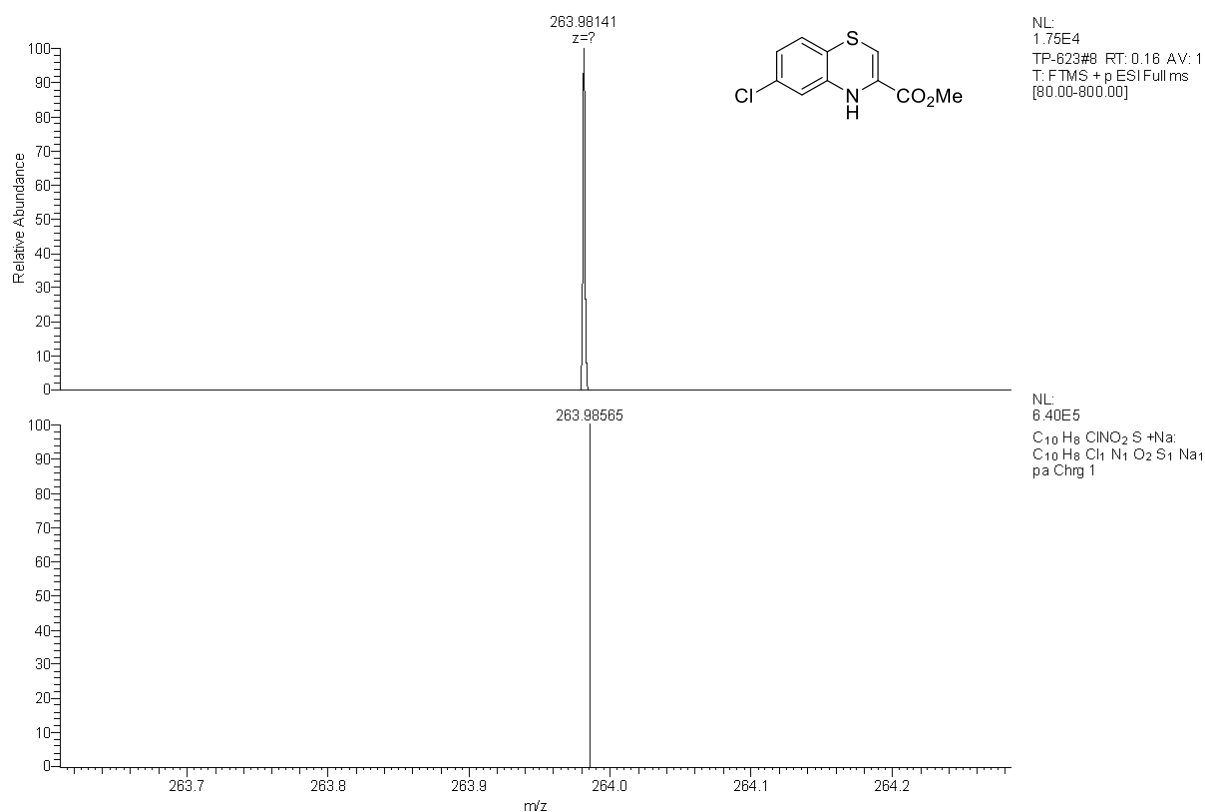


Figure S35. HRMS spectrum of compound 10bb.

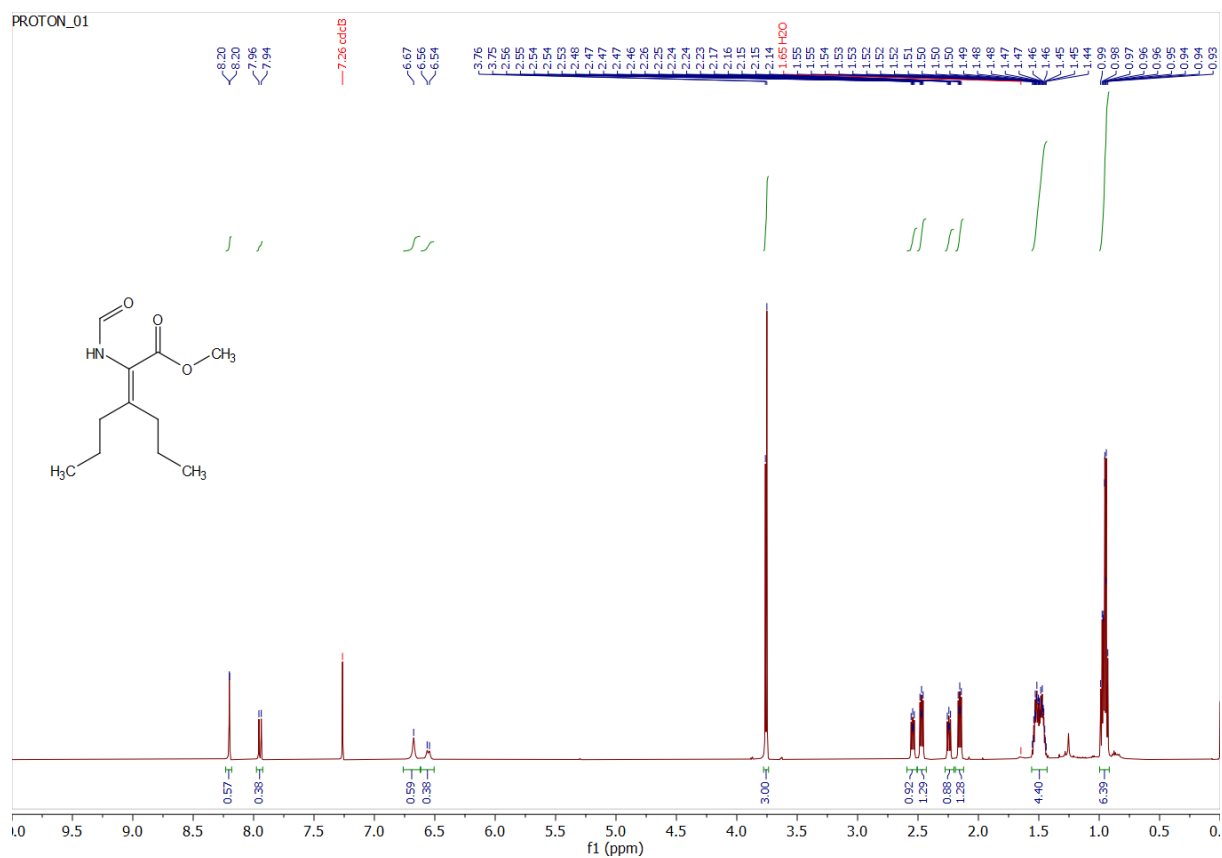
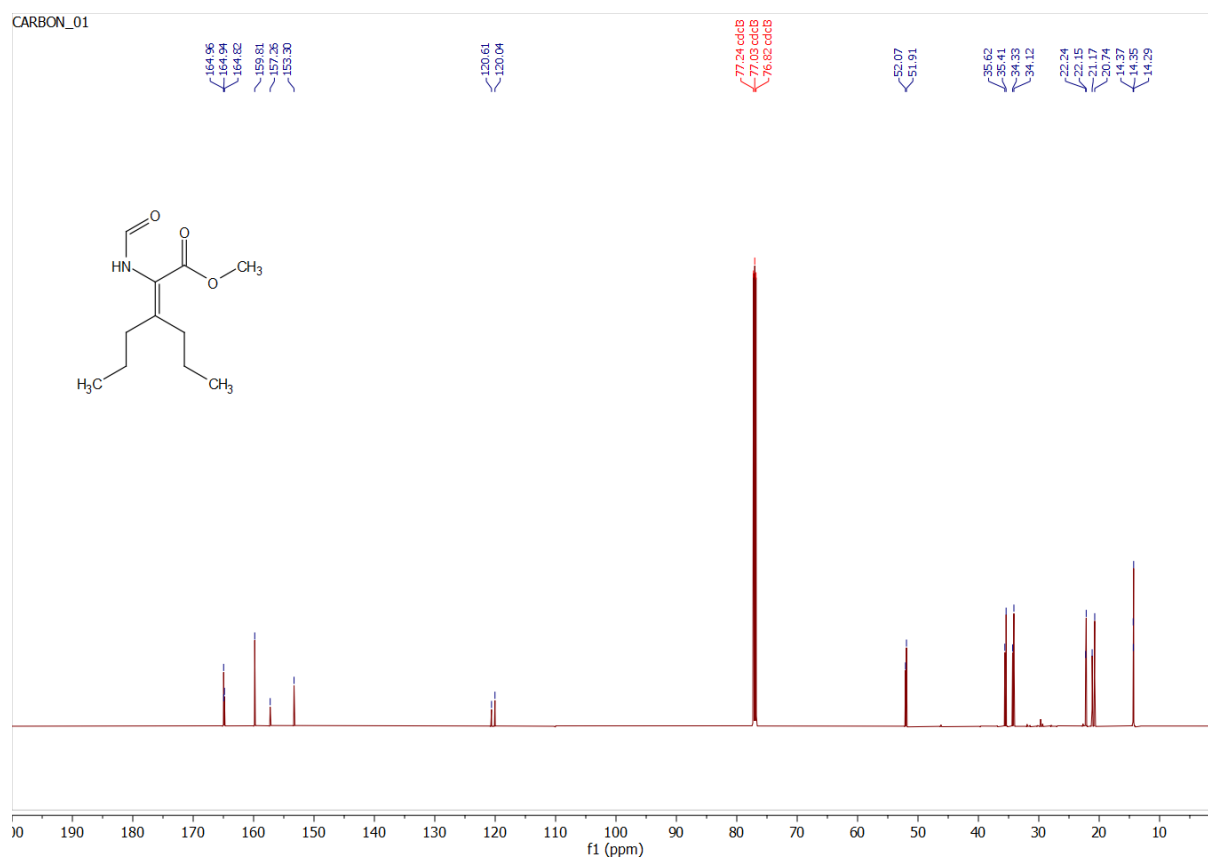
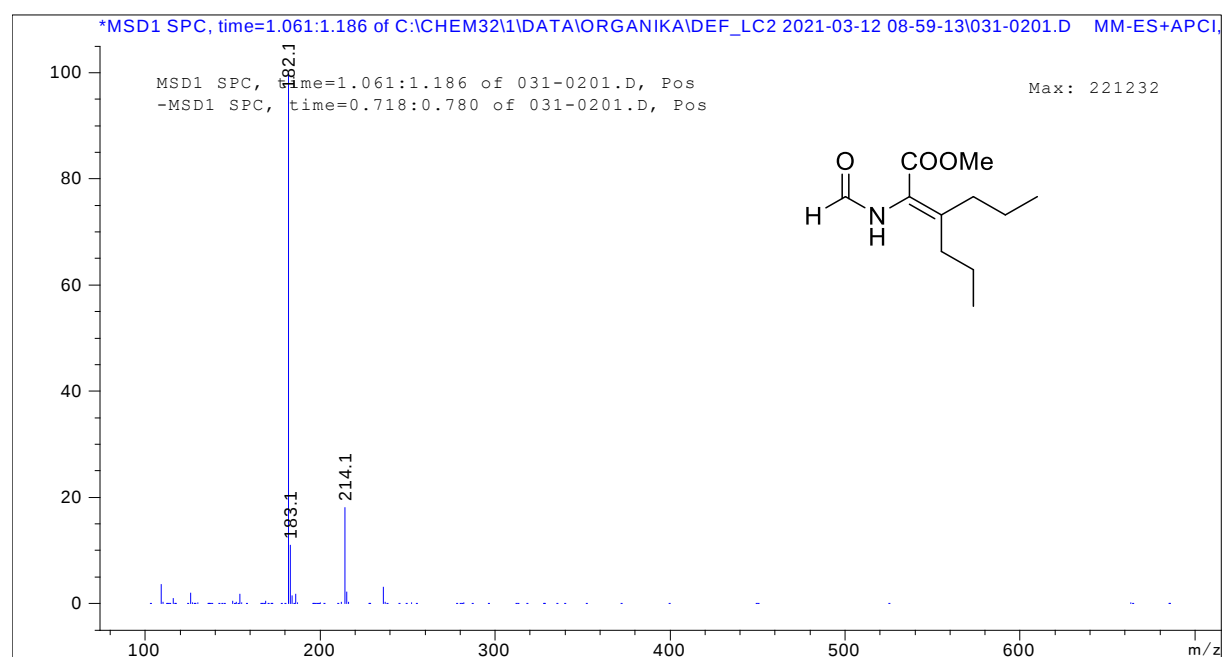


Figure S36. <sup>1</sup>H NMR spectrum of compound 14.



**Figure S37.**  $^{13}\text{C}$  NMR spectrum of compound **14**.



**Figure S38.** MS spectrum of compound **14** (MM-ES+APCI positive mode).

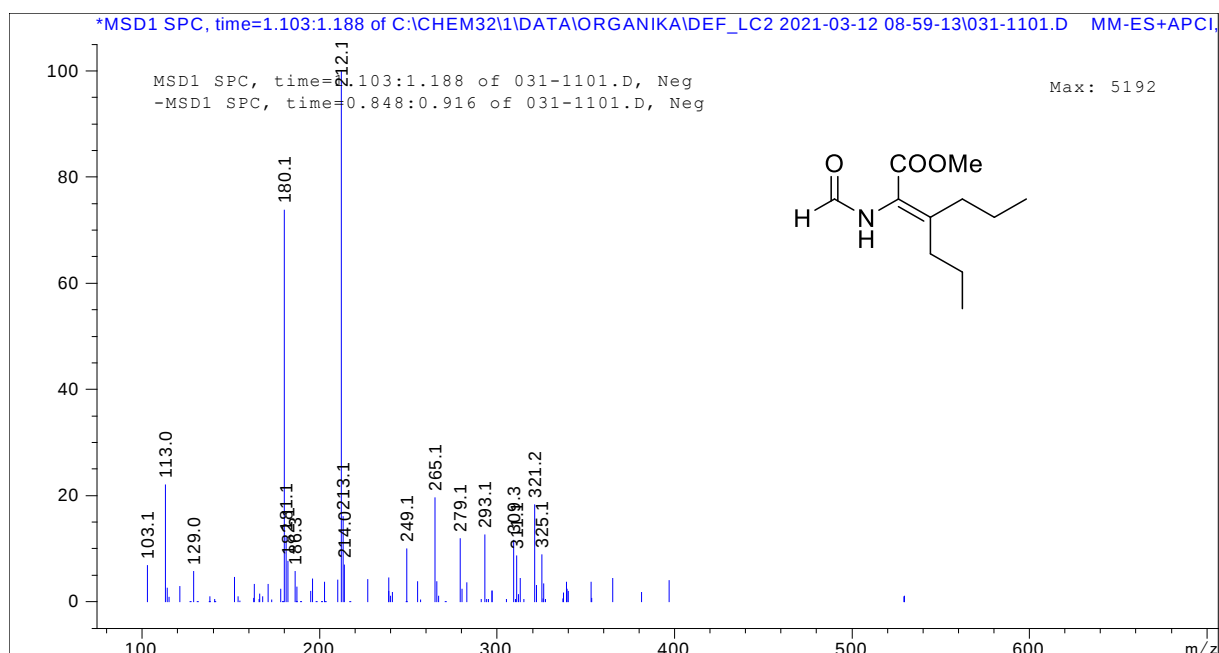


Figure S39. MS spectrum of compound 14 (MM-ES+APCI negative mode).

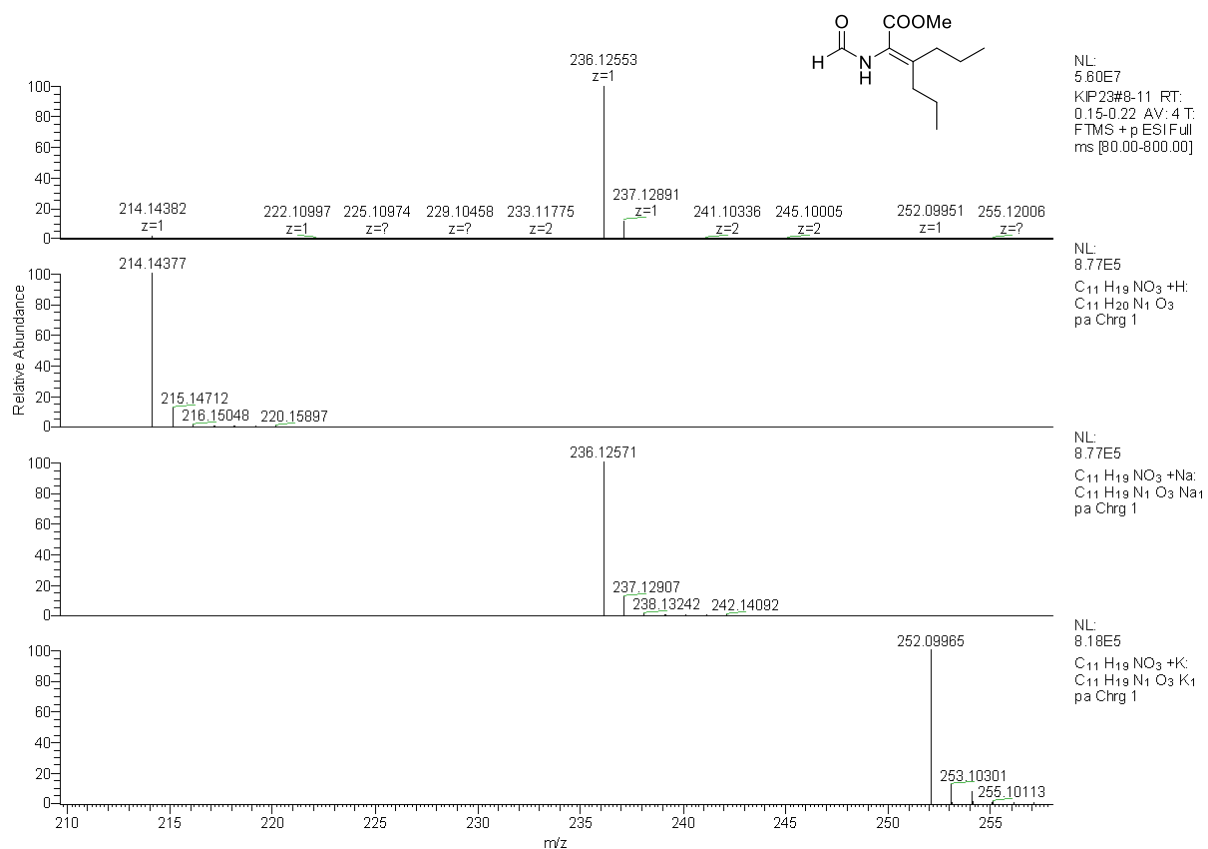


Figure S40. HRMS spectrum of compound 14.

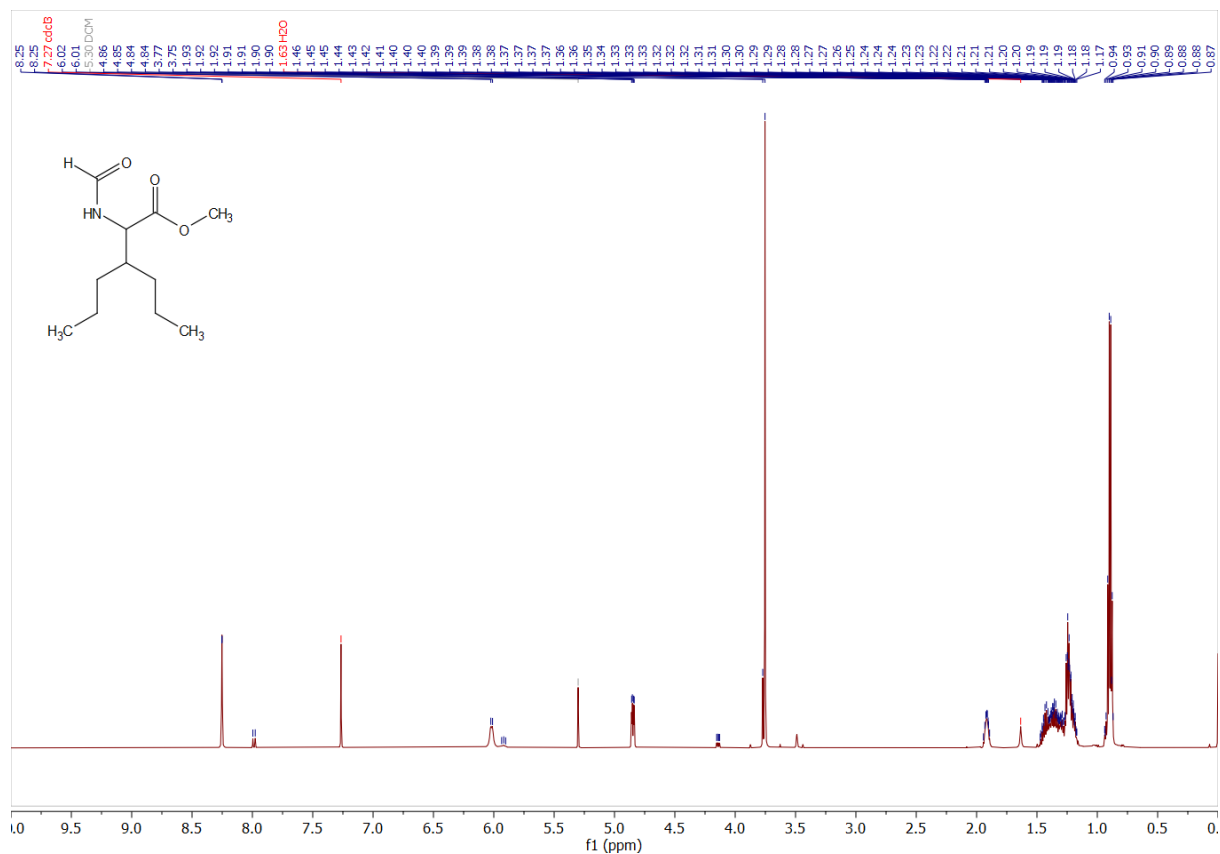


Figure S41. <sup>1</sup>H NMR spectrum of compound 15.

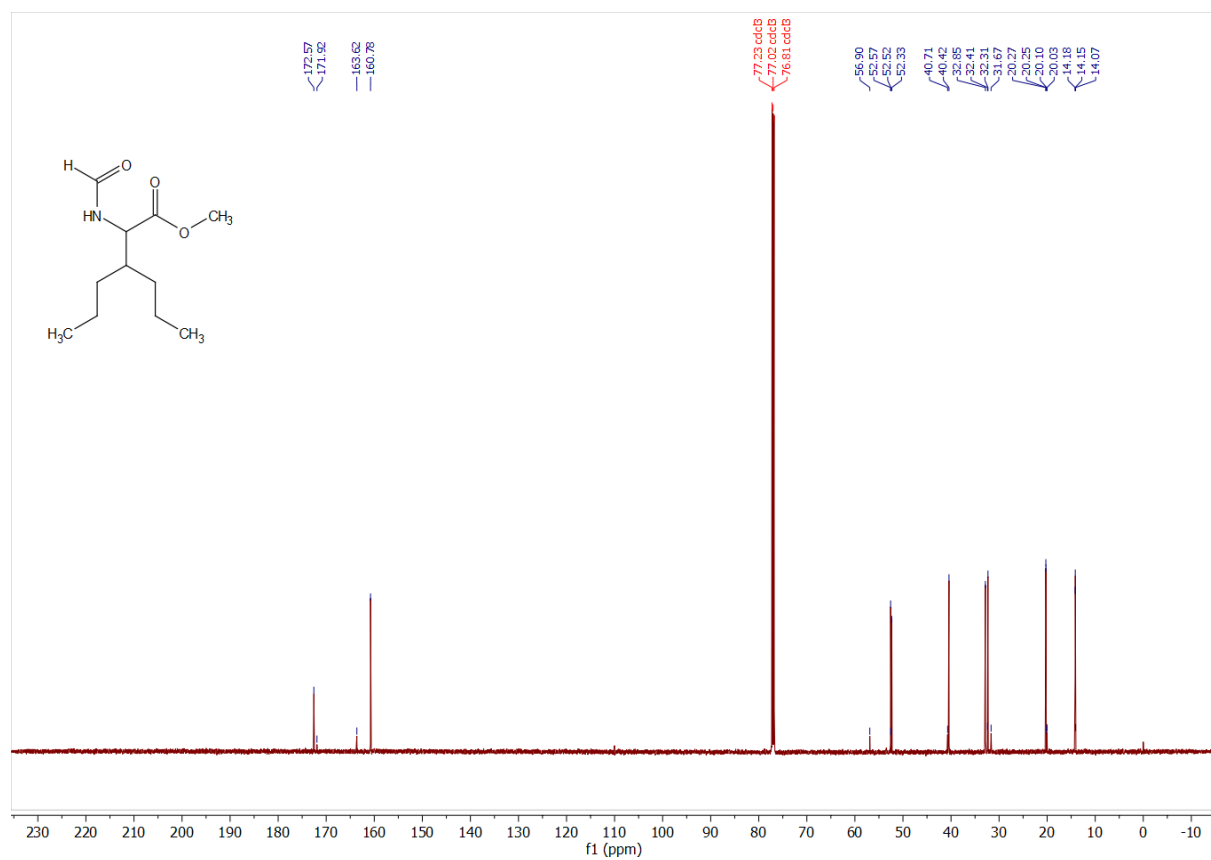
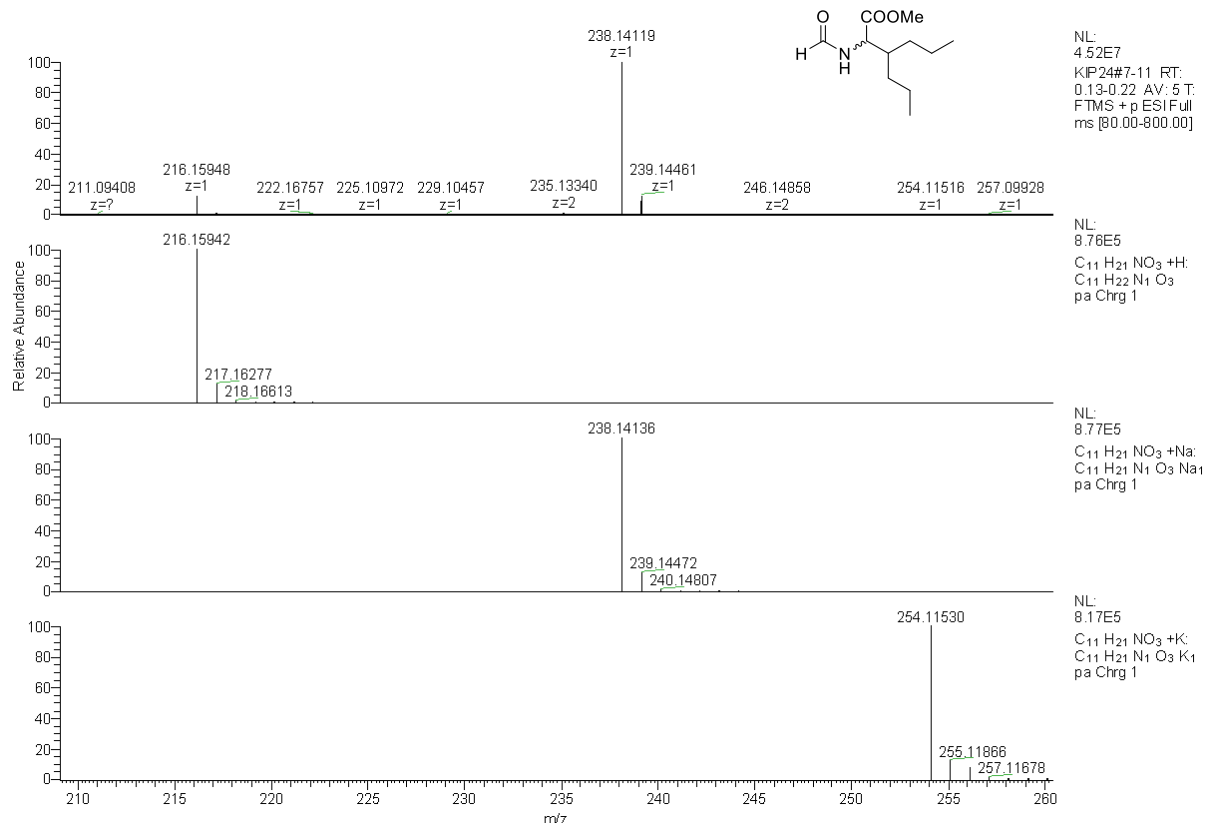
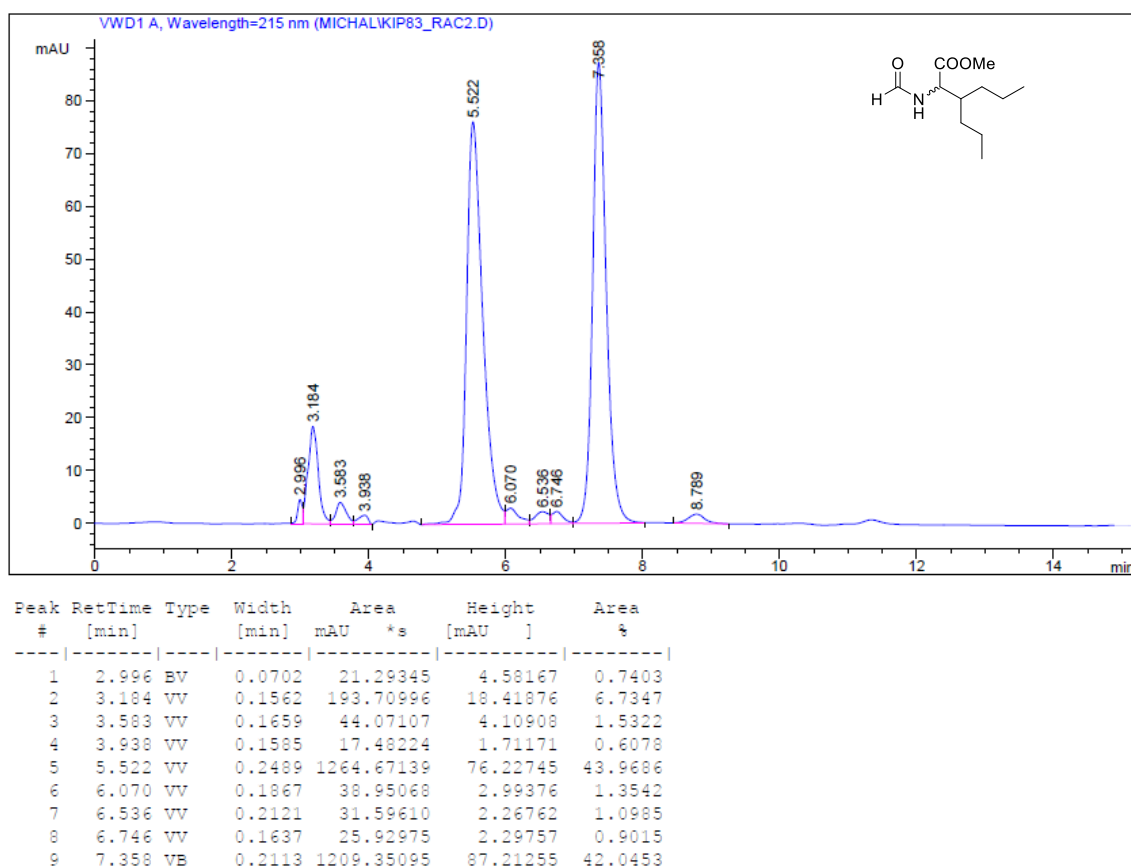


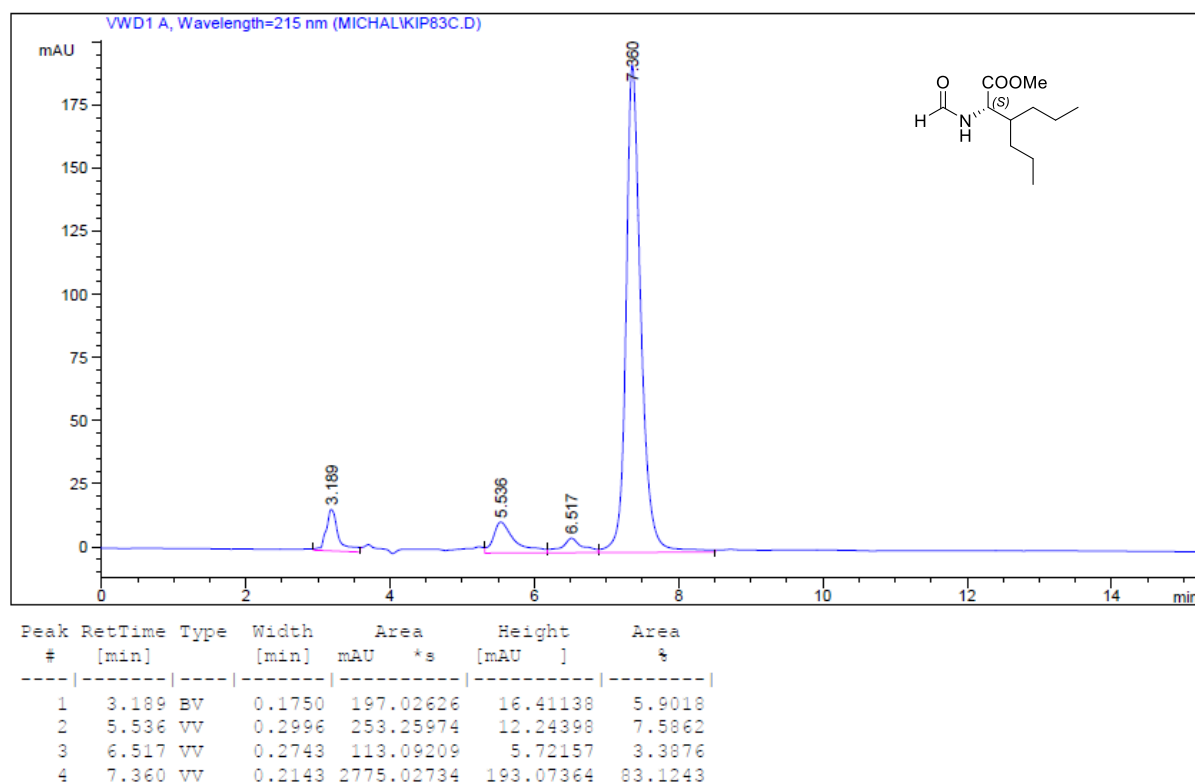
Figure S42. <sup>13</sup>C NMR spectrum of compound 15.



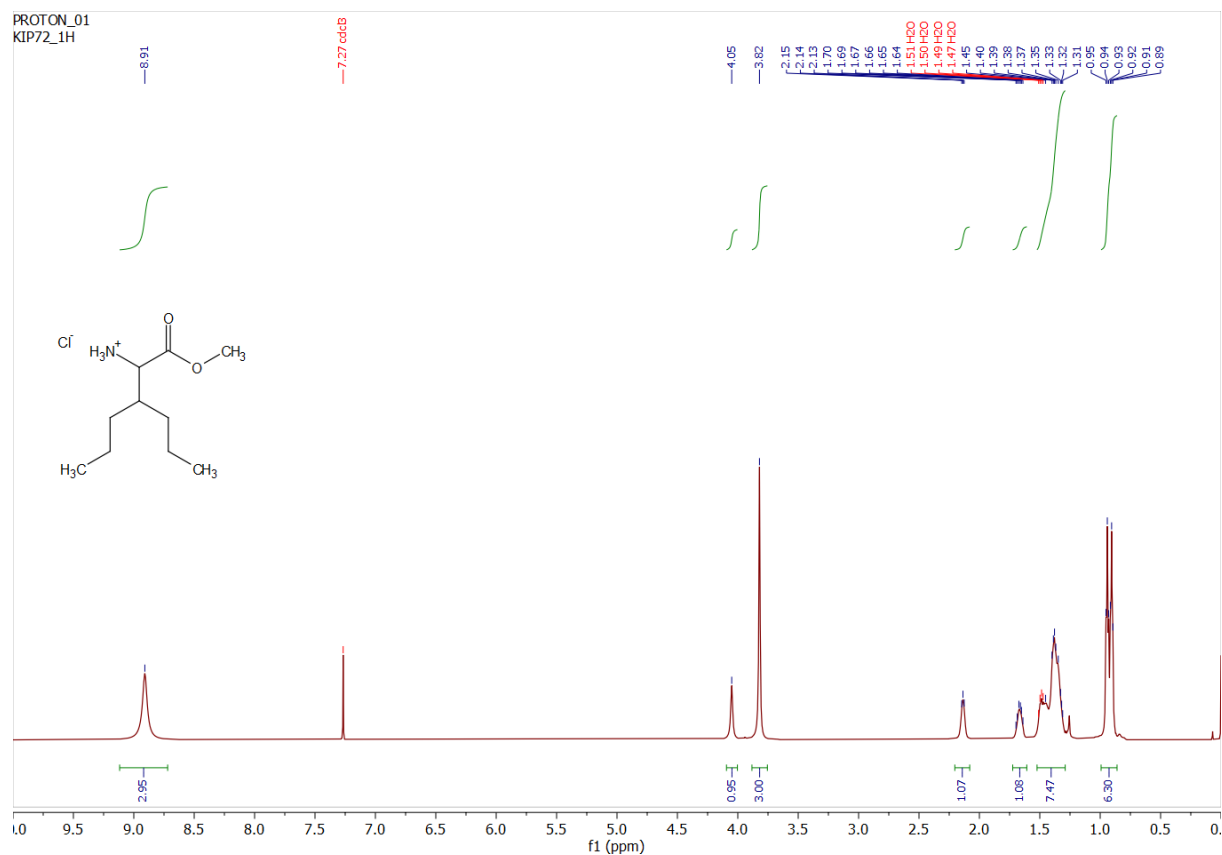
**Figure S43.** HRMS spectrum of compound **15**.



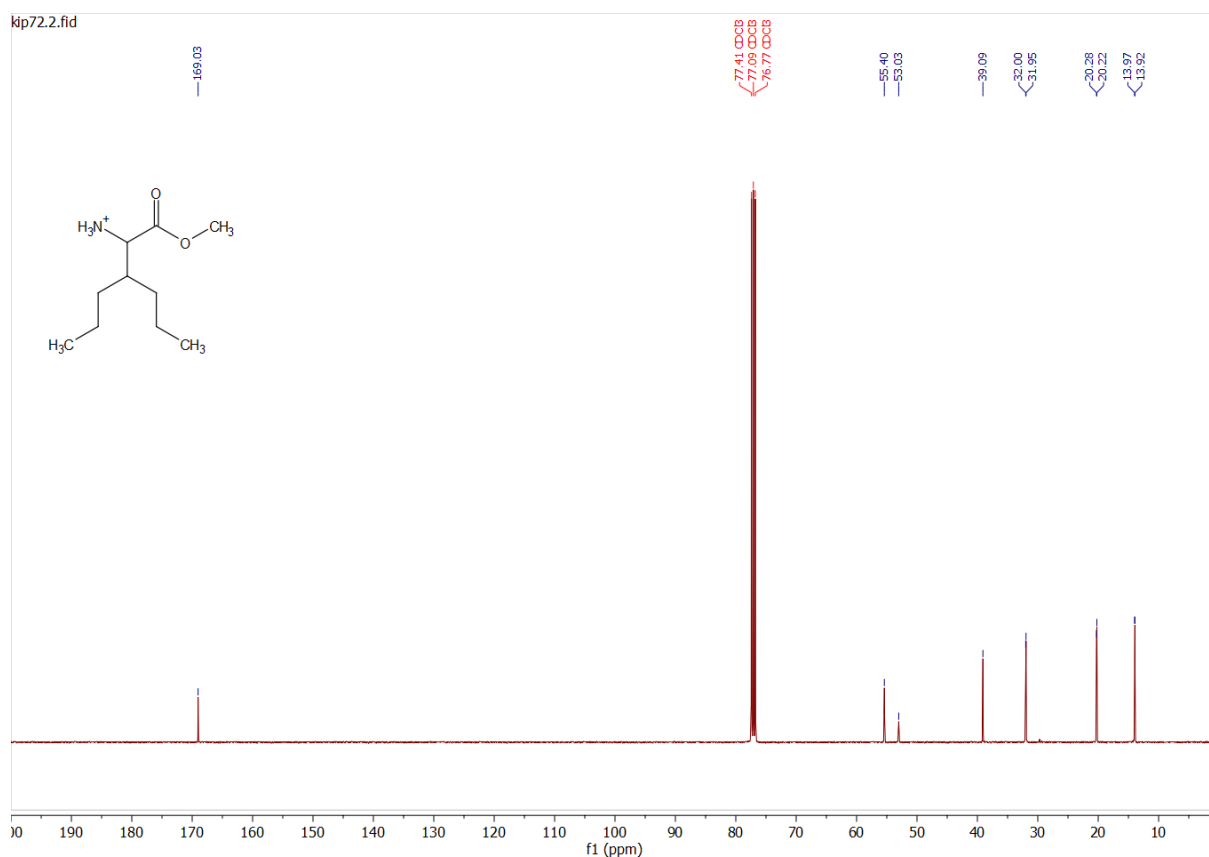
**Figure S44.** HPLC chromatogram of compound **15** (racemic).



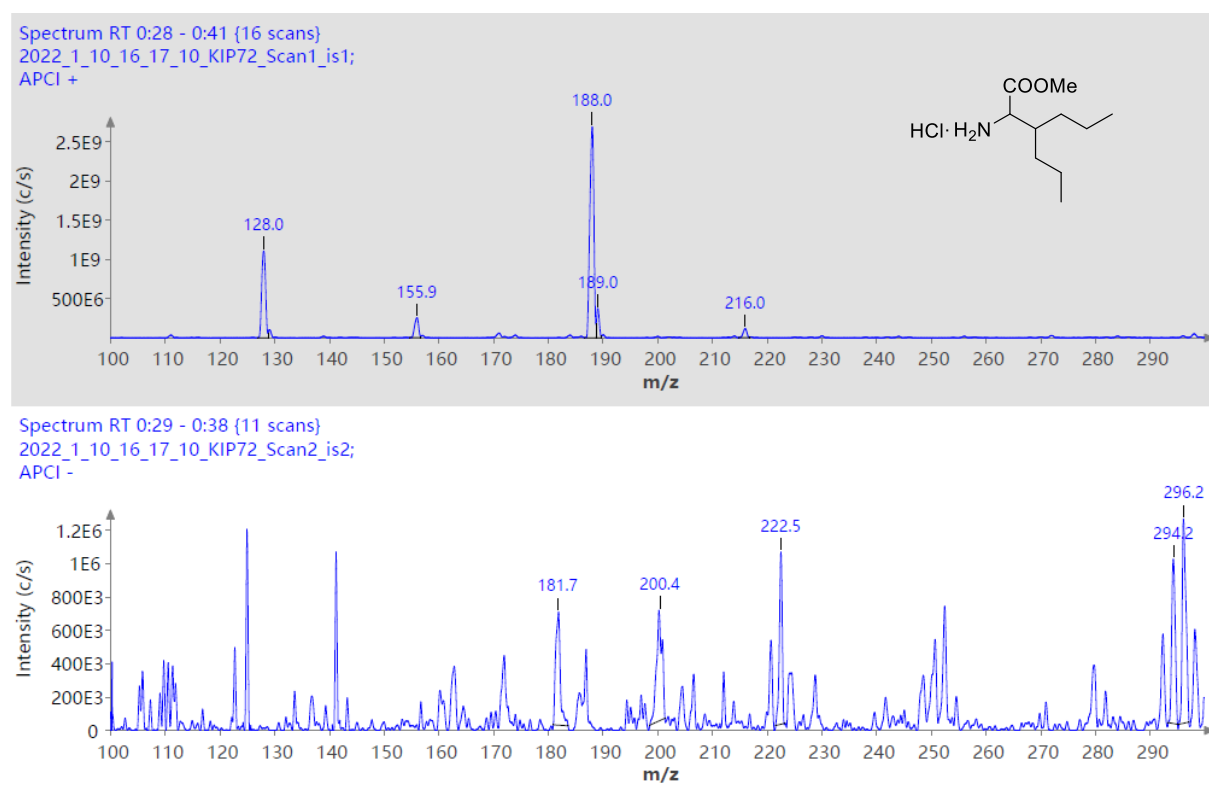
**Figure S45.** HPLC chromatogram of compound (S)-15 (83% ee).



**Figure S46.**  $^1\text{H}$  NMR spectrum of compound 16·HCl.



**Figure S47.**  $^{13}\text{C}$  NMR spectrum of compound **16**·HCl.



**Figure S48.** MS spectrum of compound **16**·HCl.

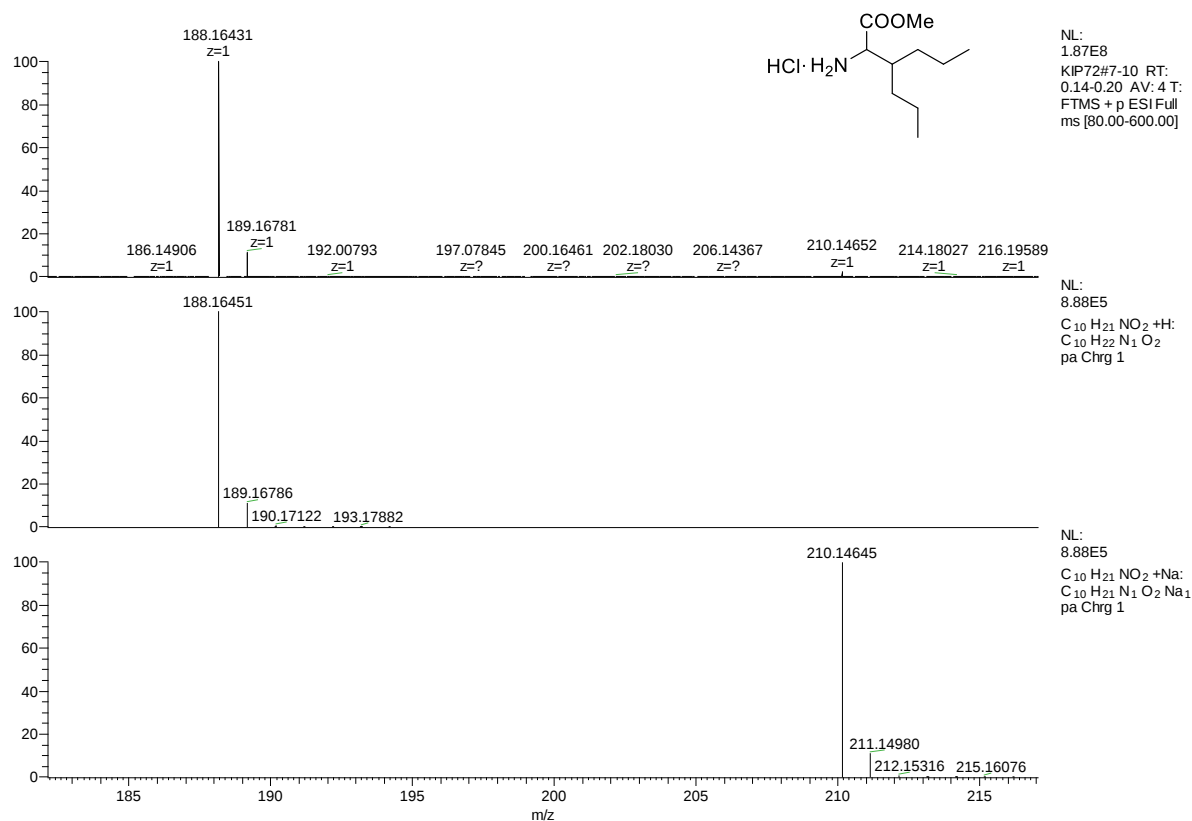


Figure S49. HRMS spectrum of compound 16·HCl.

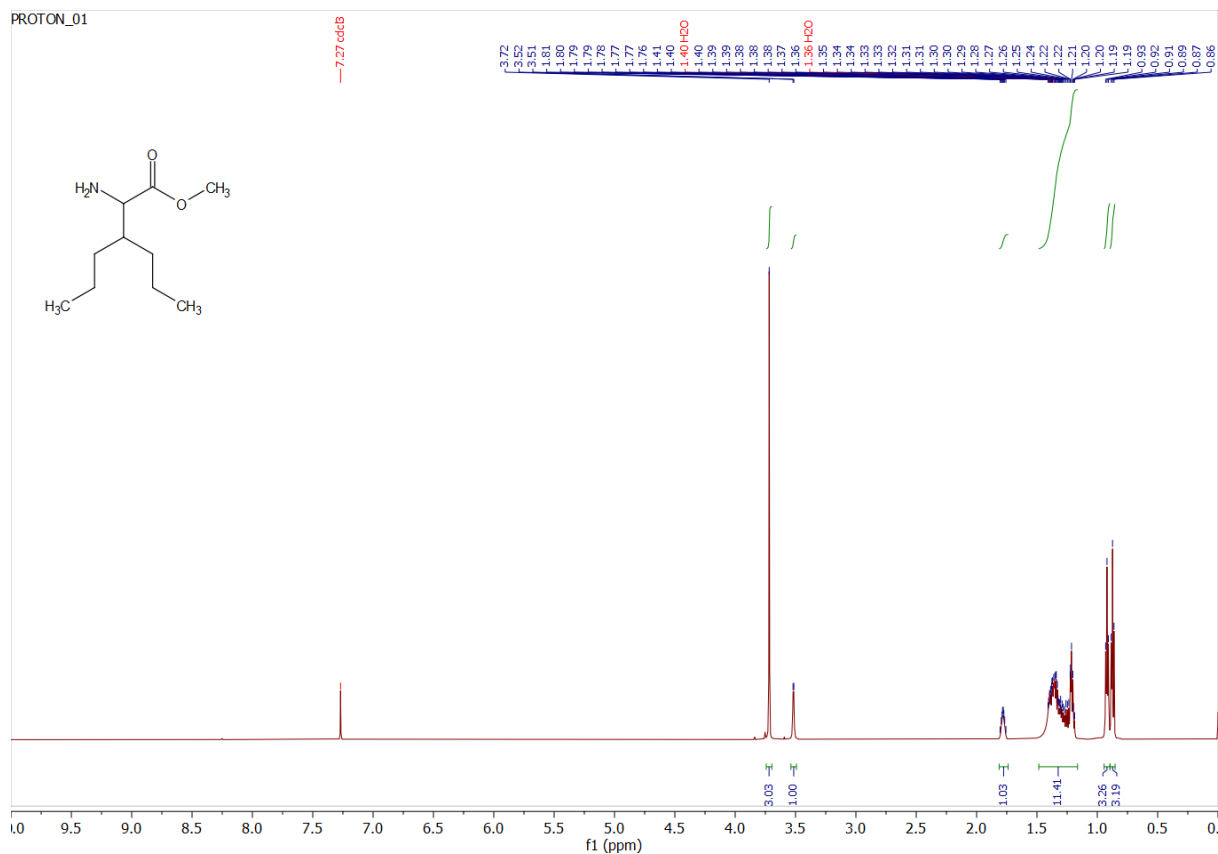
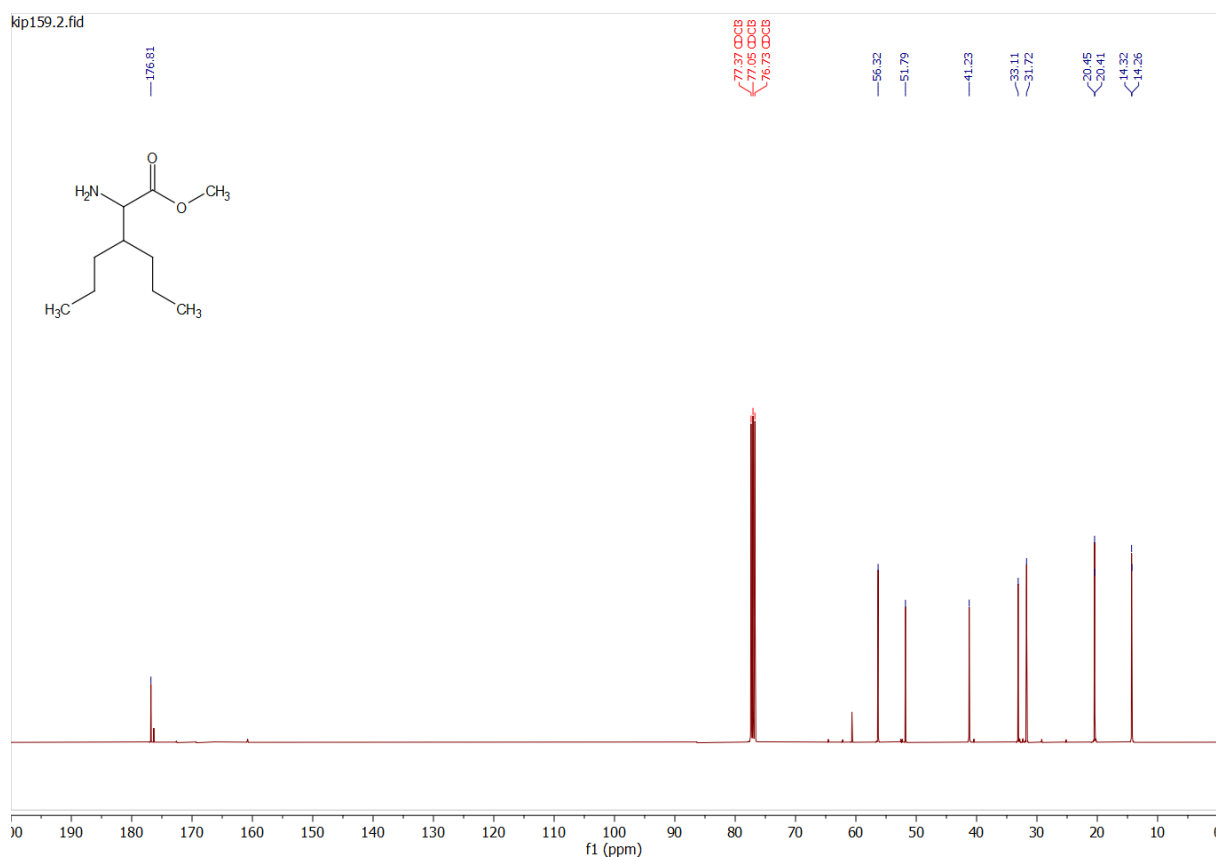
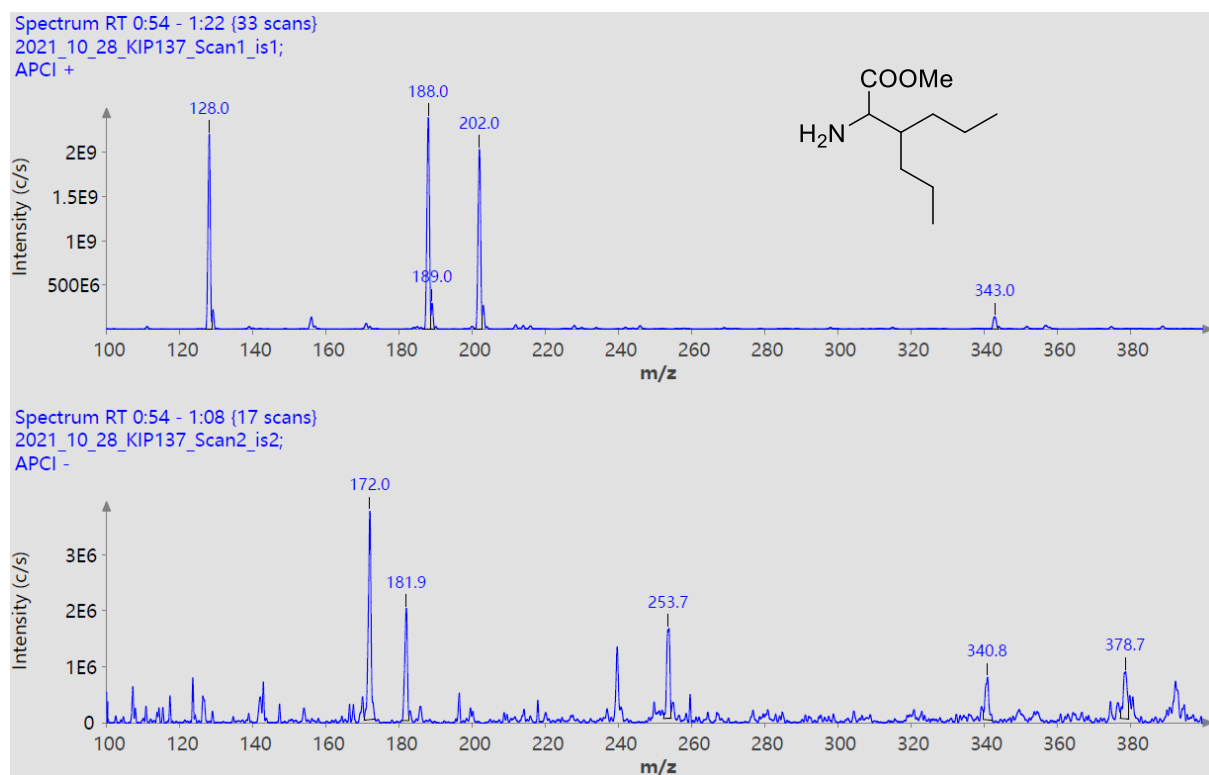


Figure S50. <sup>1</sup>H NMR spectrum of compound 16.



**Figure S51.**  $^{13}\text{C}$  NMR spectrum of compound **16**.



**Figure S52.** MS spectrum of compound **16**.

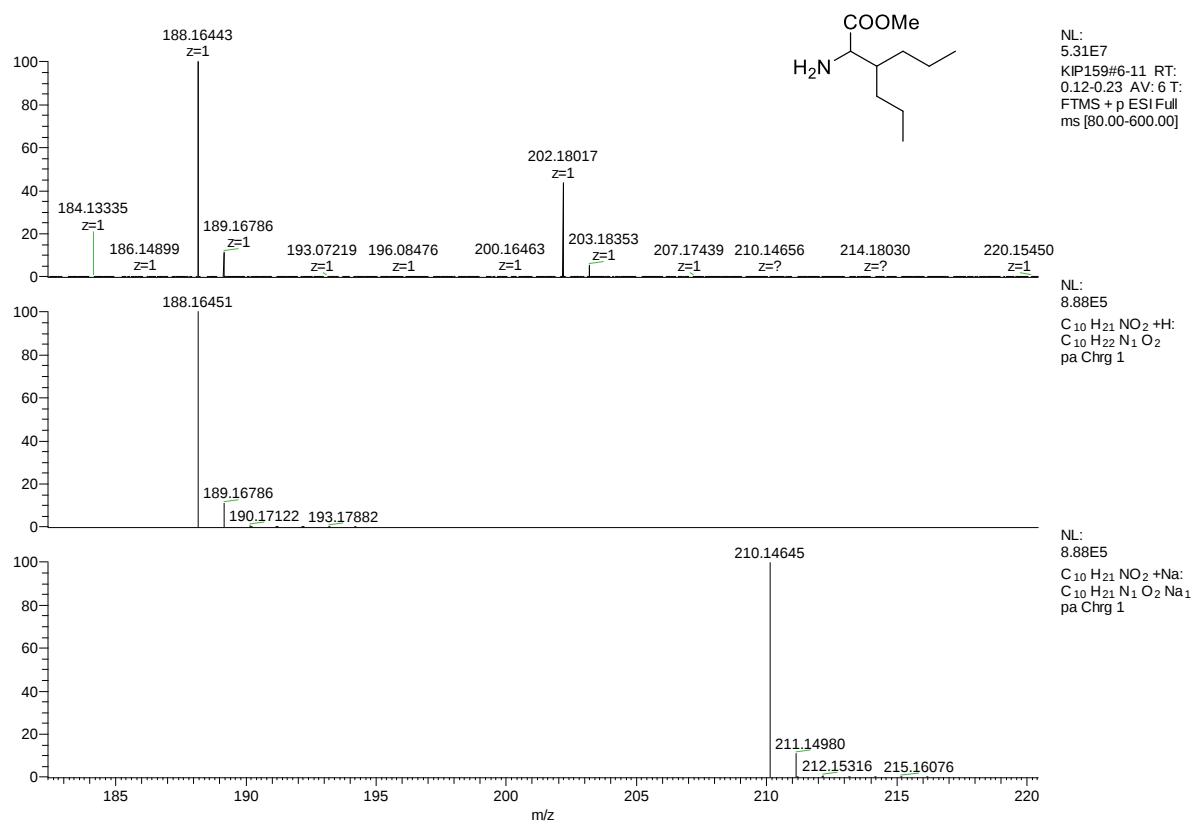


Figure S53. HRMS spectrum of compound 16.

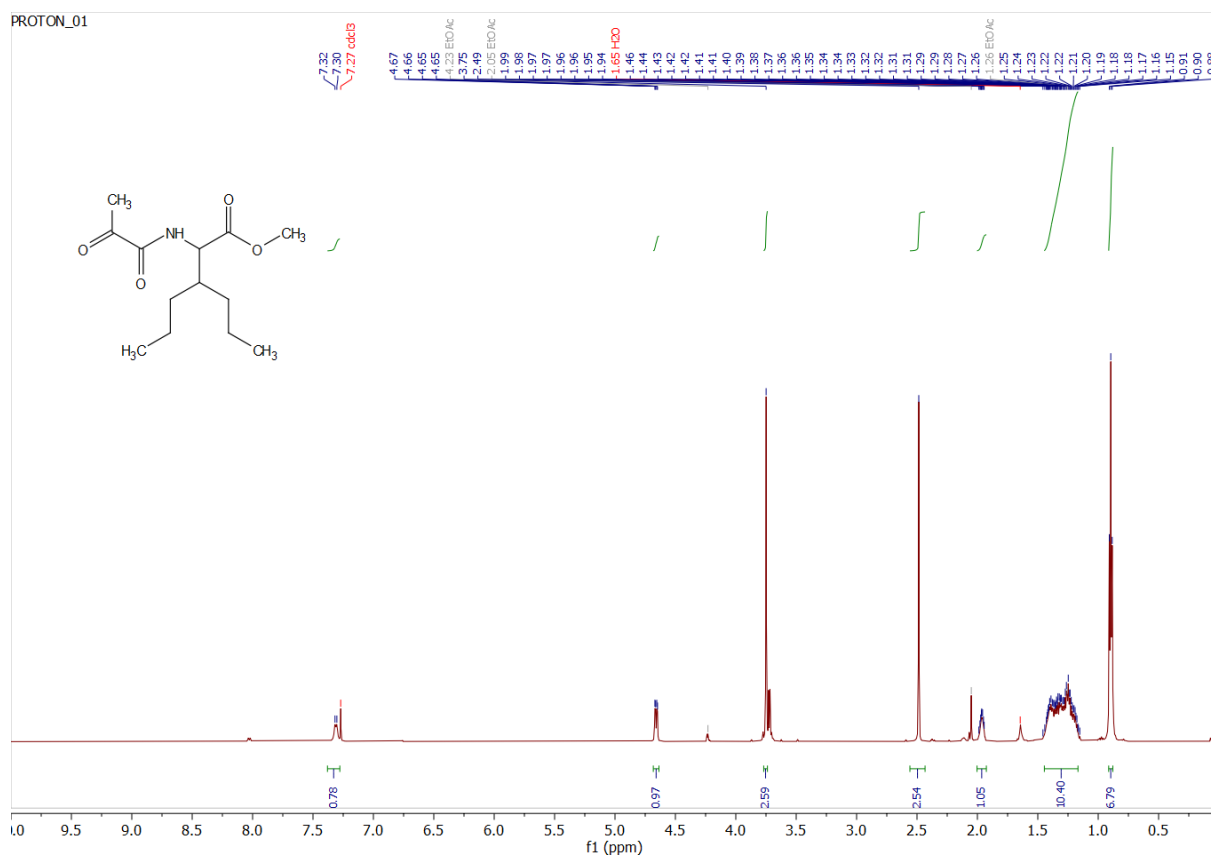


Figure S54. <sup>1</sup>H NMR spectrum of compound 17a.

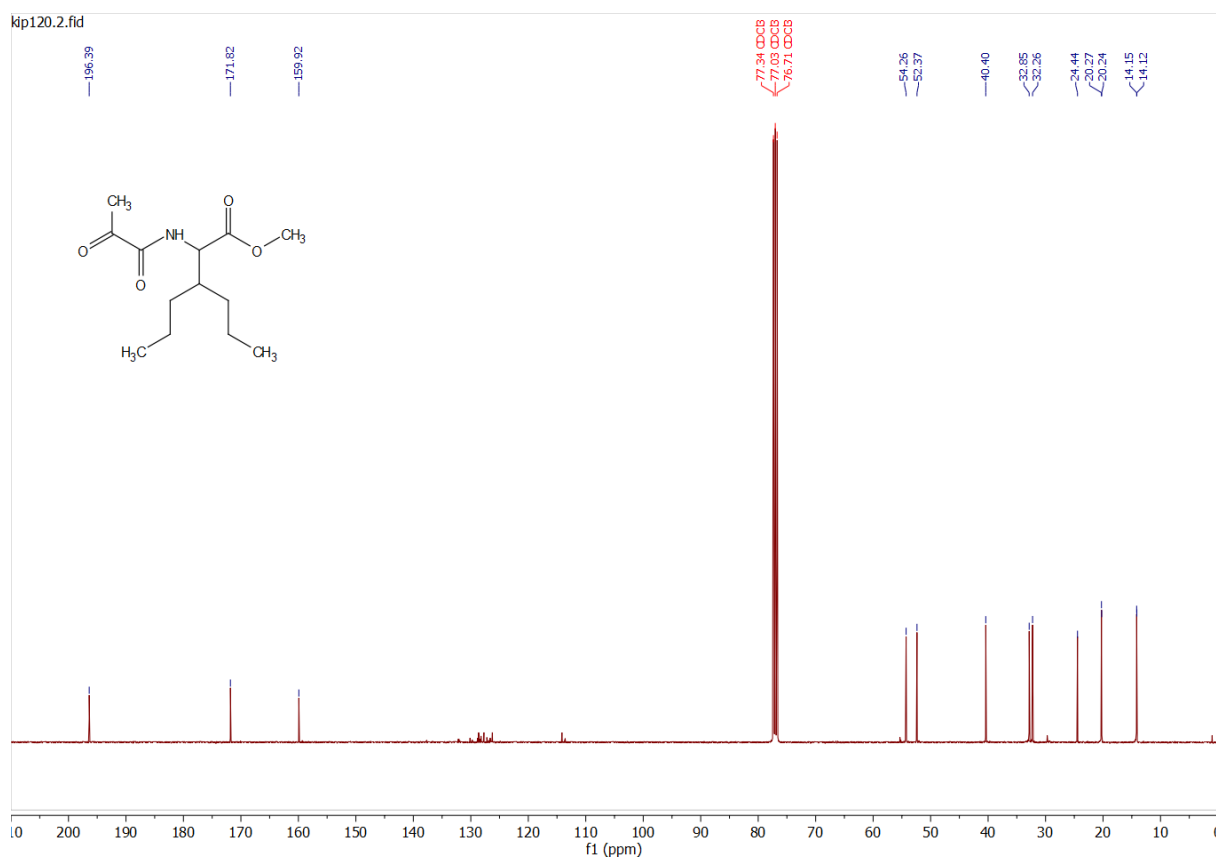


Figure S55.  $^{13}\text{C}$  NMR spectrum of compound 17a.

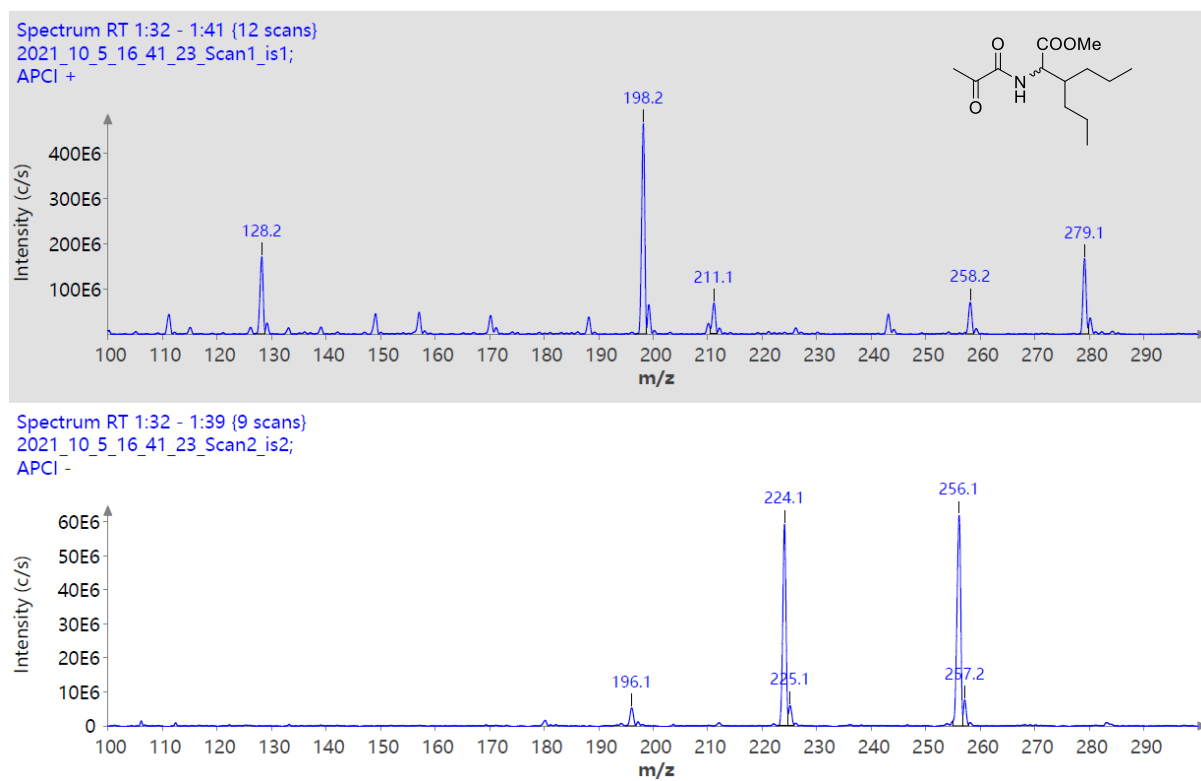
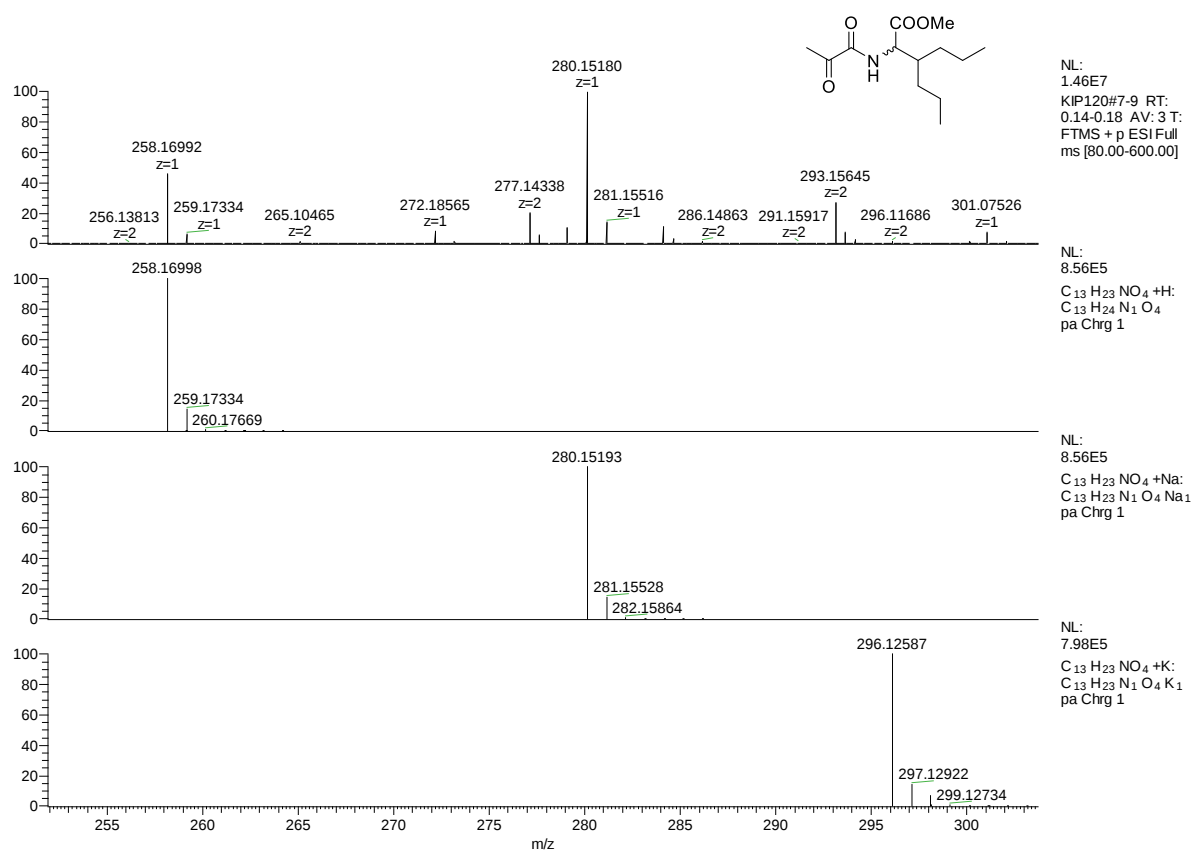
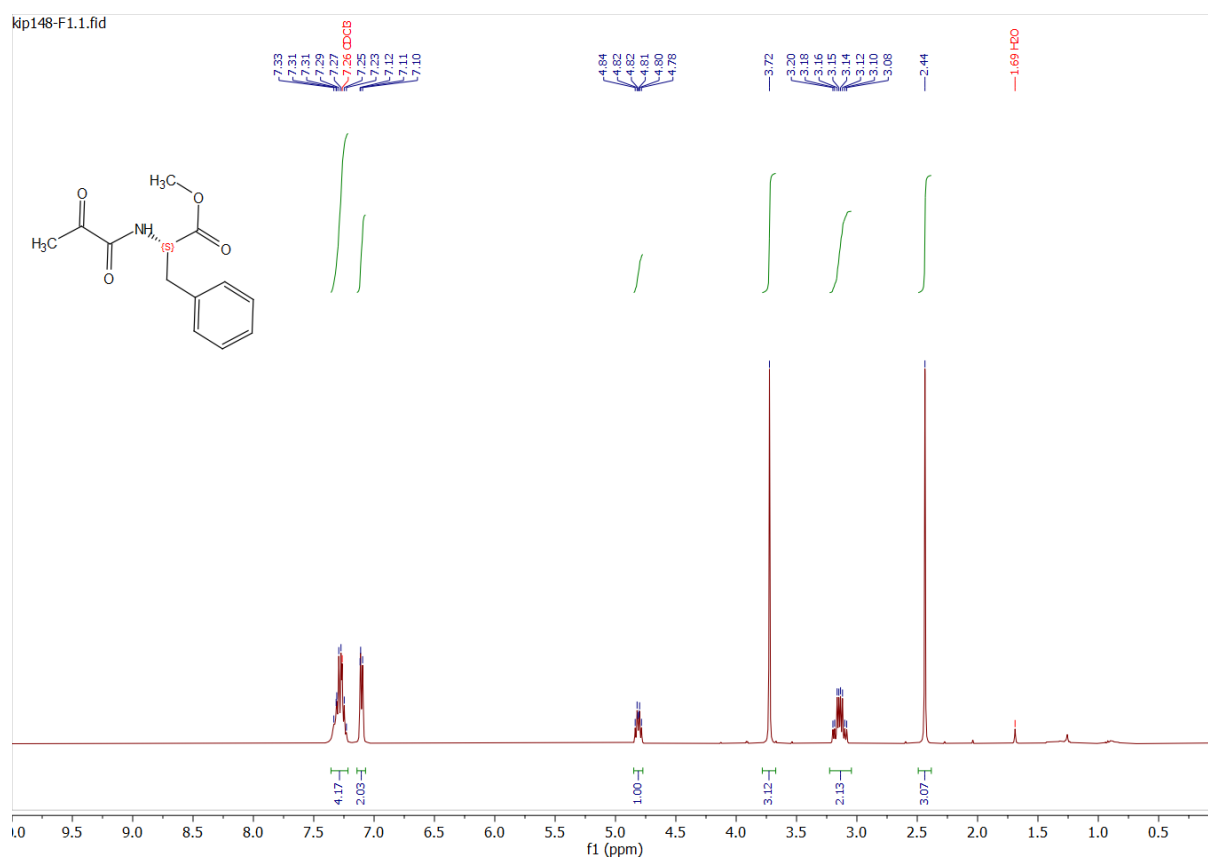


Figure S56. MS spectrum of compound 17a.



**Figure S57.** HRMS spectrum of compound **17a**.



**Figure S58.** <sup>1</sup>H NMR spectrum of compound **17b**.

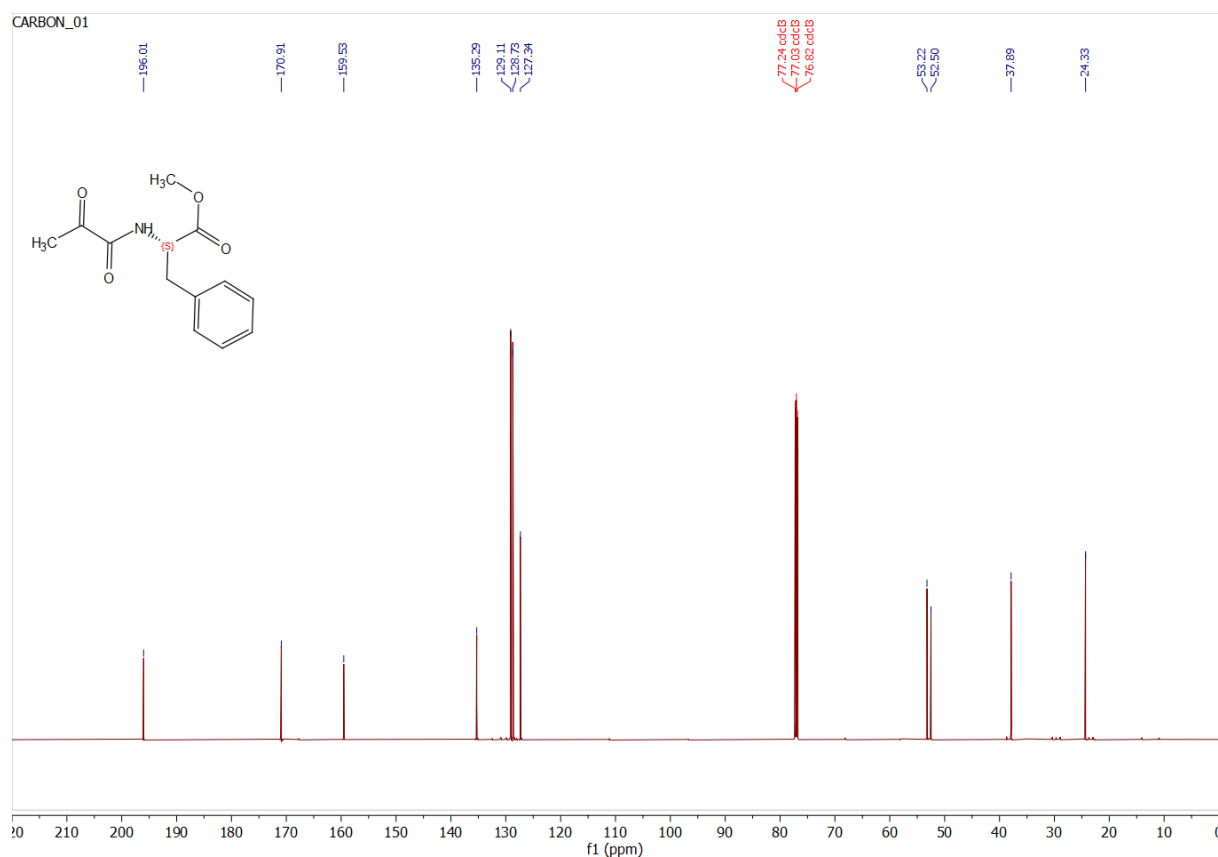


Figure S59. <sup>13</sup>C NMR spectrum of compound 17b.

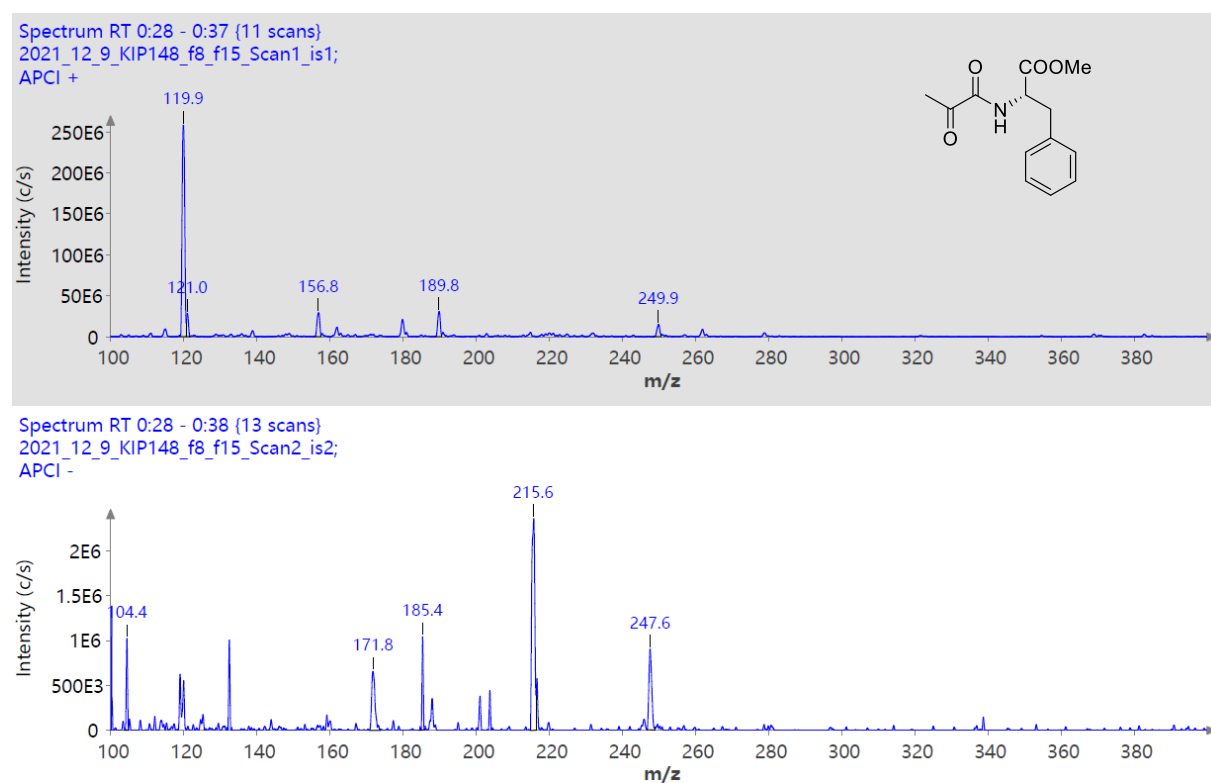


Figure S60. MS spectrum of compound 17b.

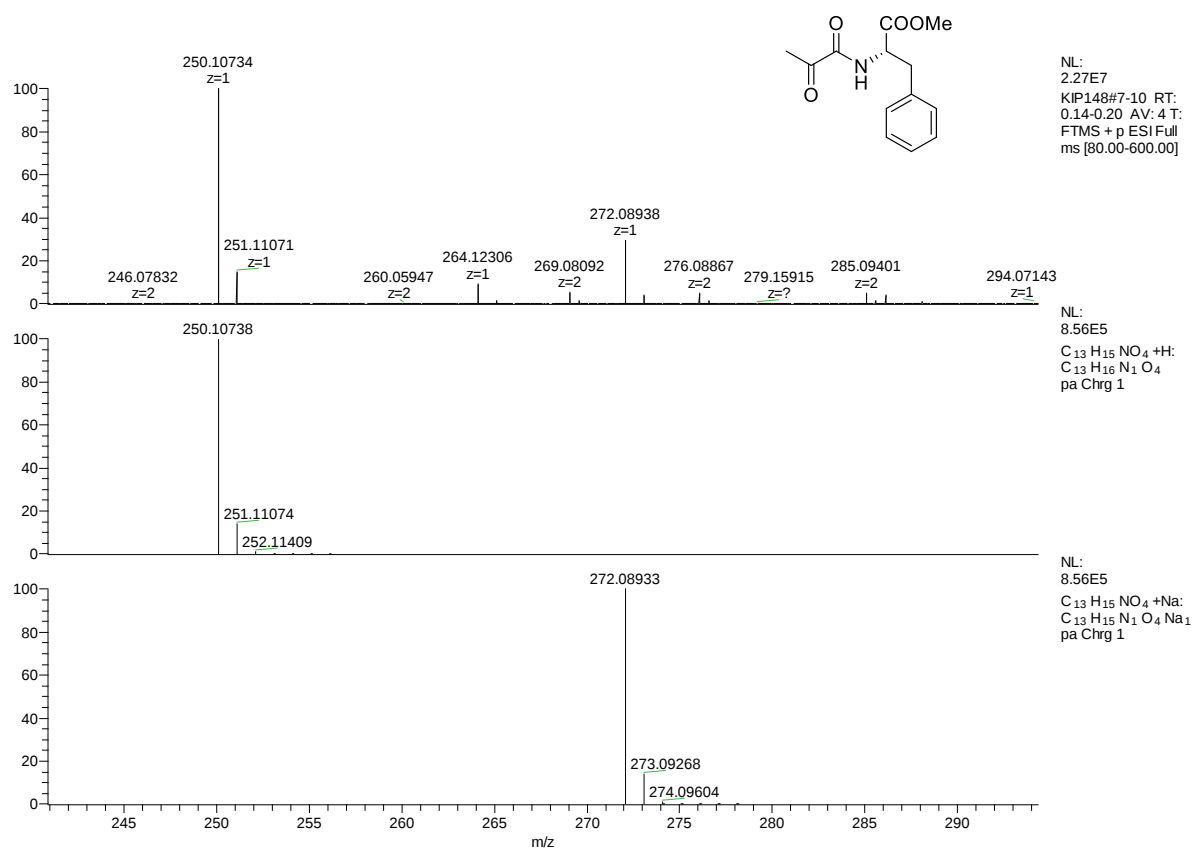


Figure S61. HRMS spectrum of compound 17b.

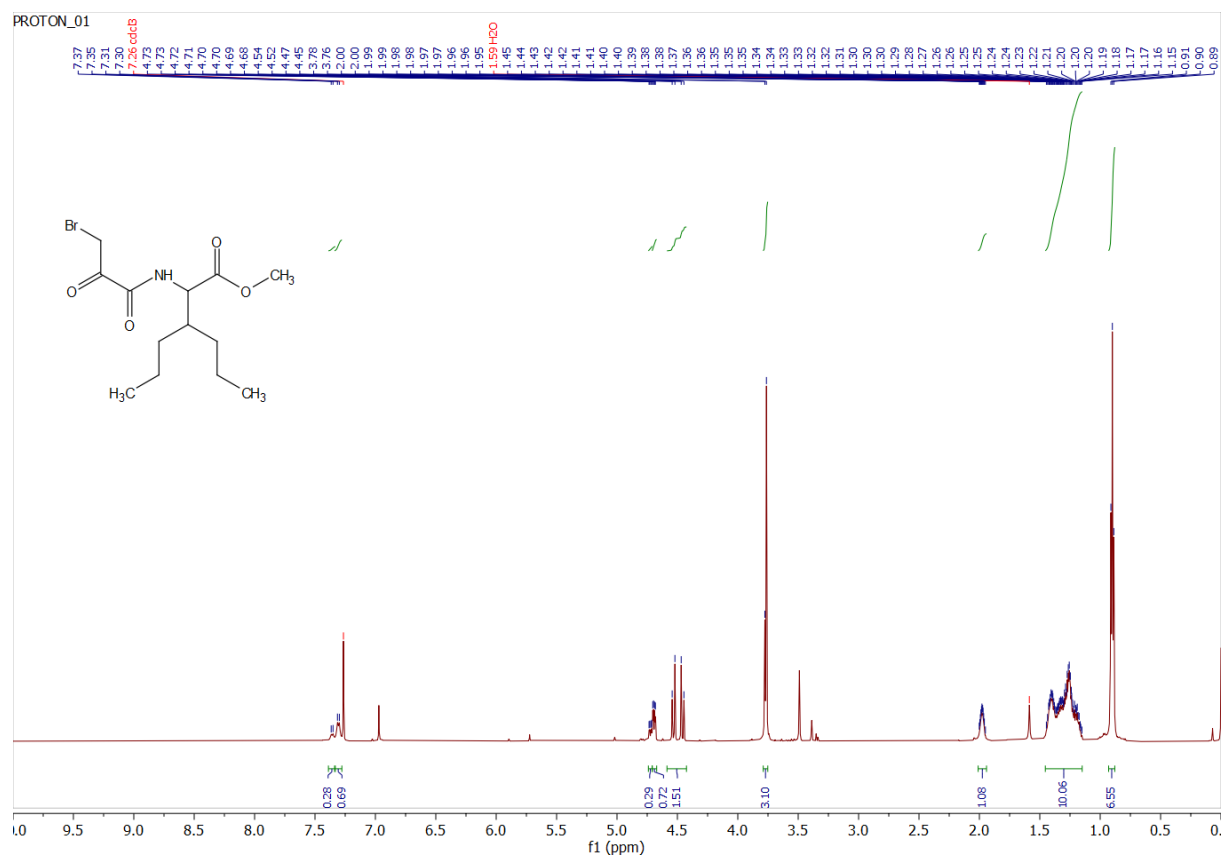
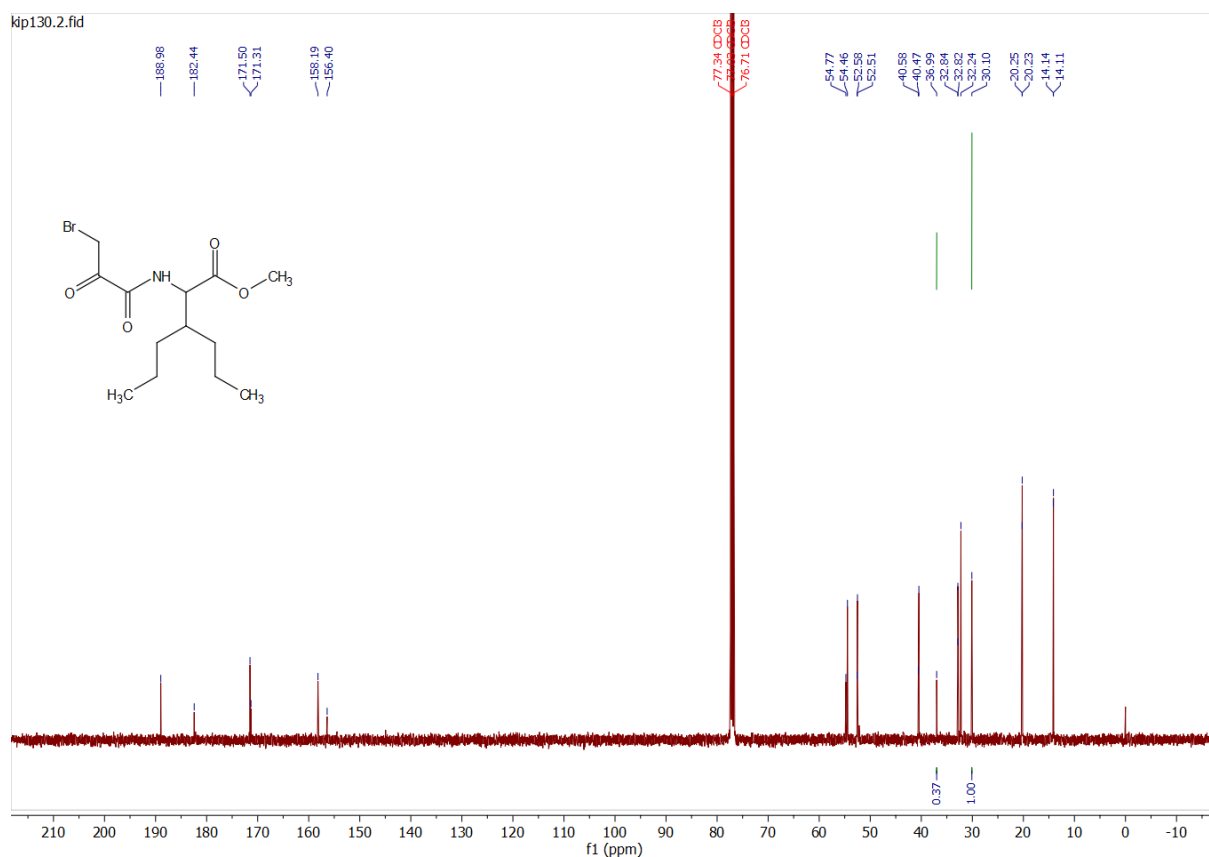
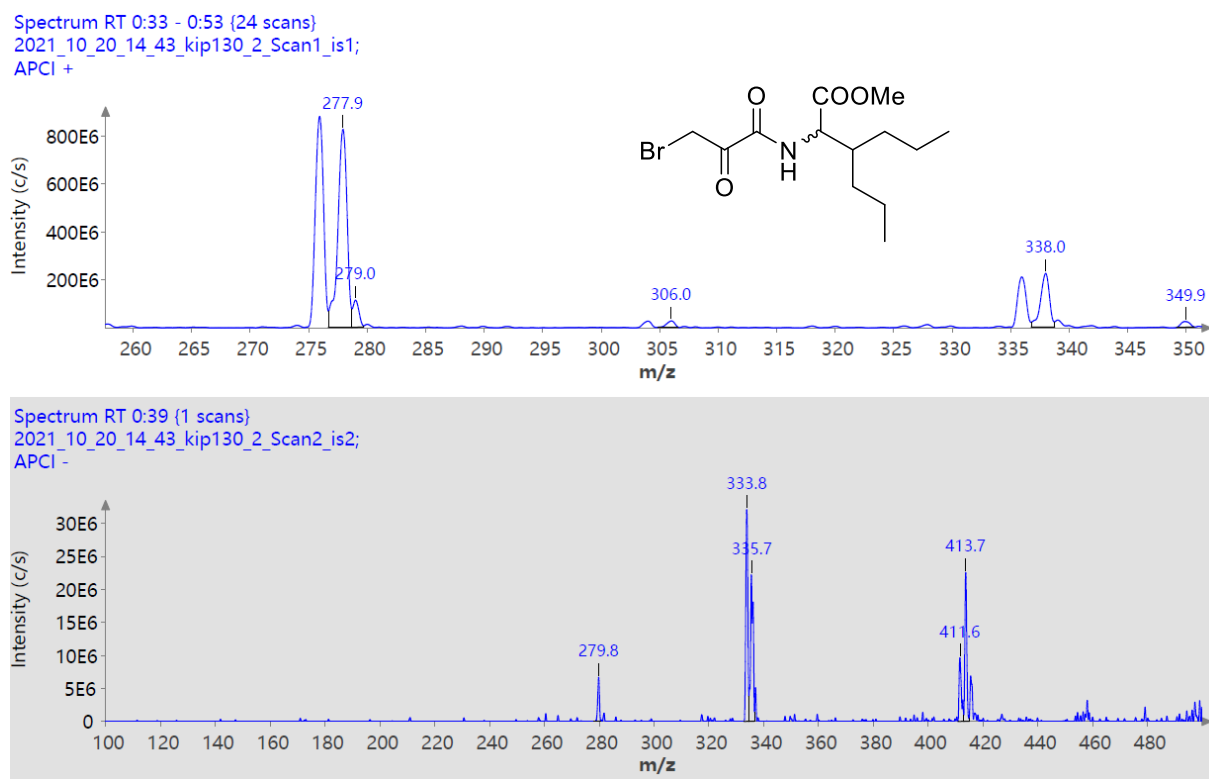


Figure S62. <sup>1</sup>H NMR spectrum of compound 18a.



**Figure S63.**  $^{13}\text{C}$  NMR spectrum of compound **18a**.



**Figure S63.** MS spectrum of compound **18a**.

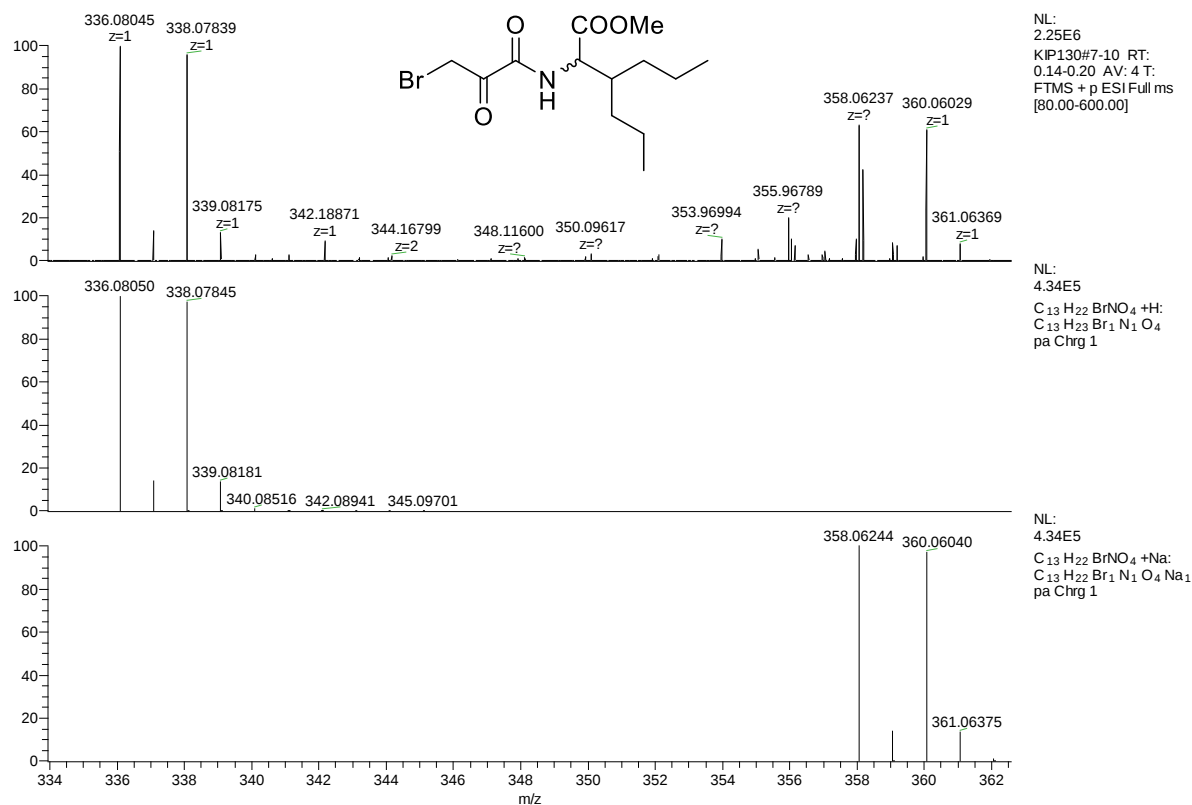


Figure S65. HRMS spectrum of compound 18a.

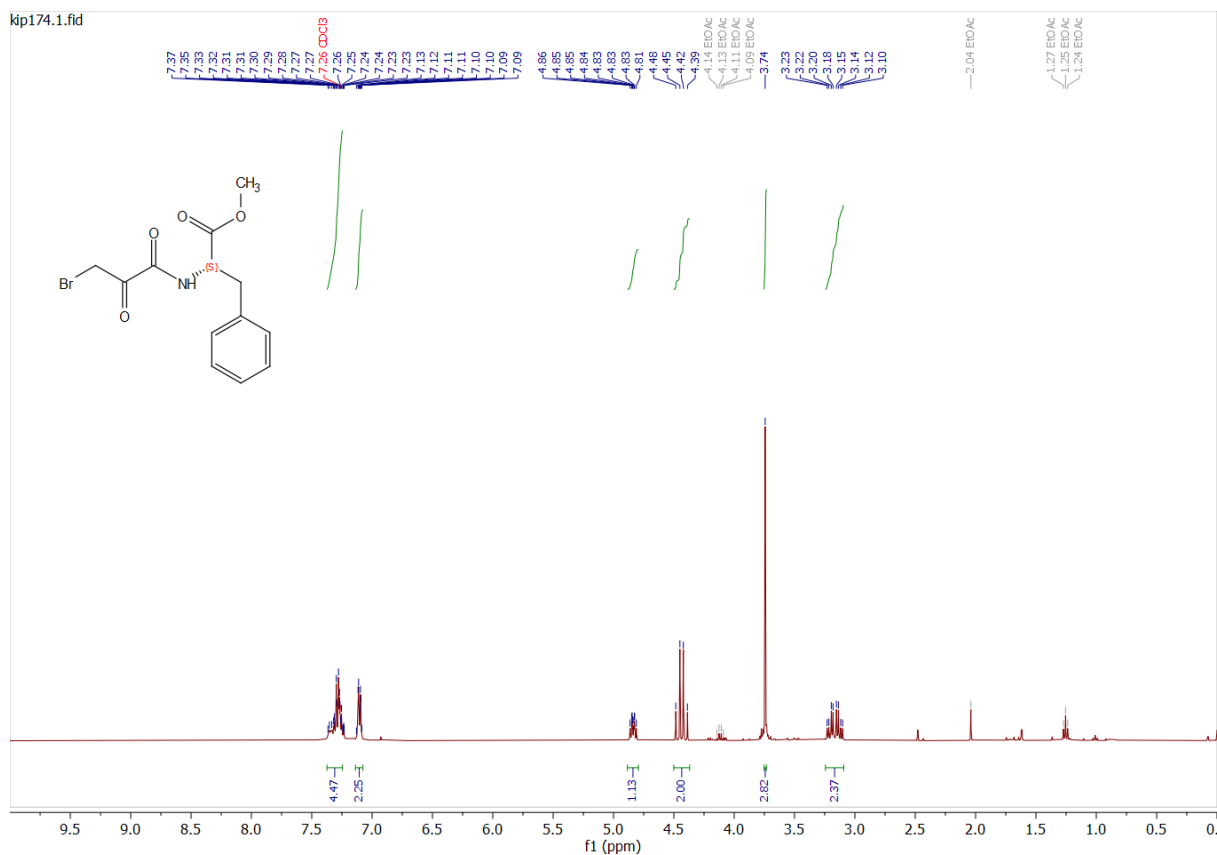
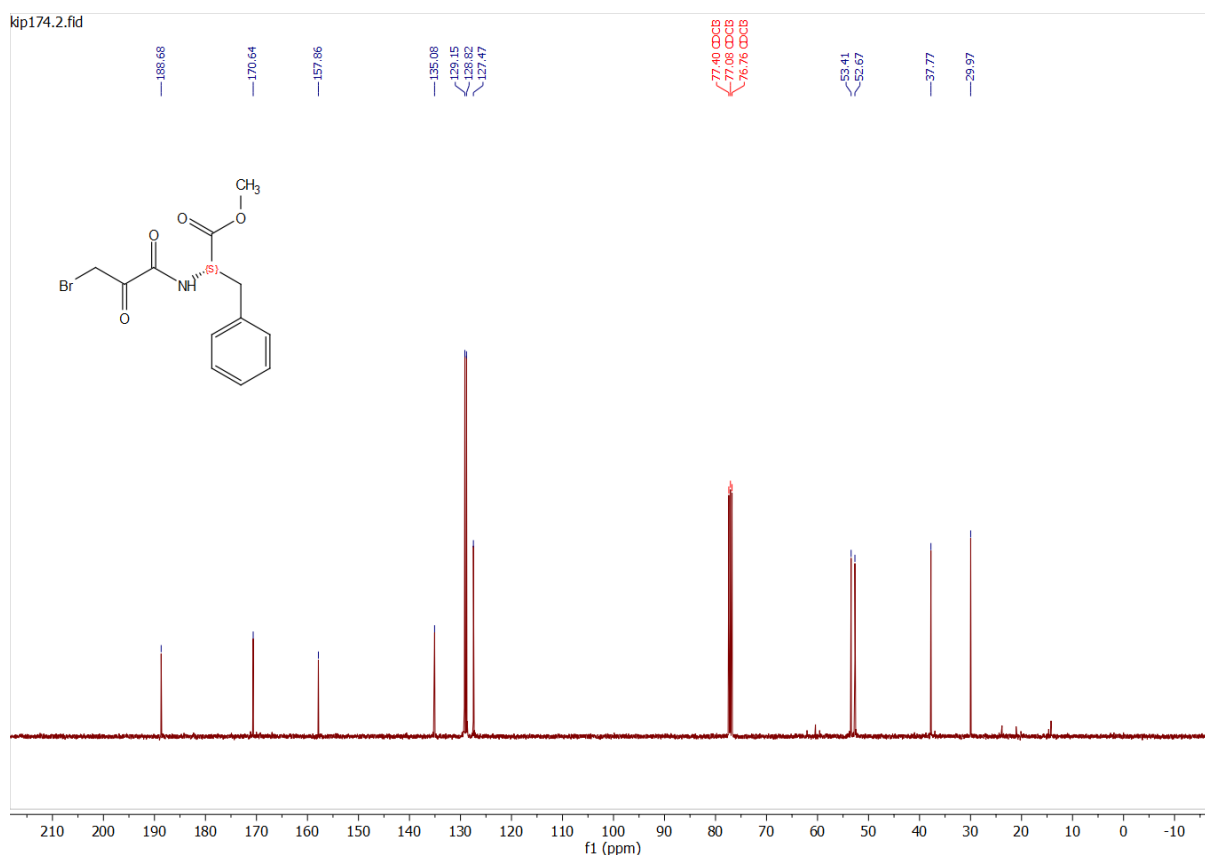
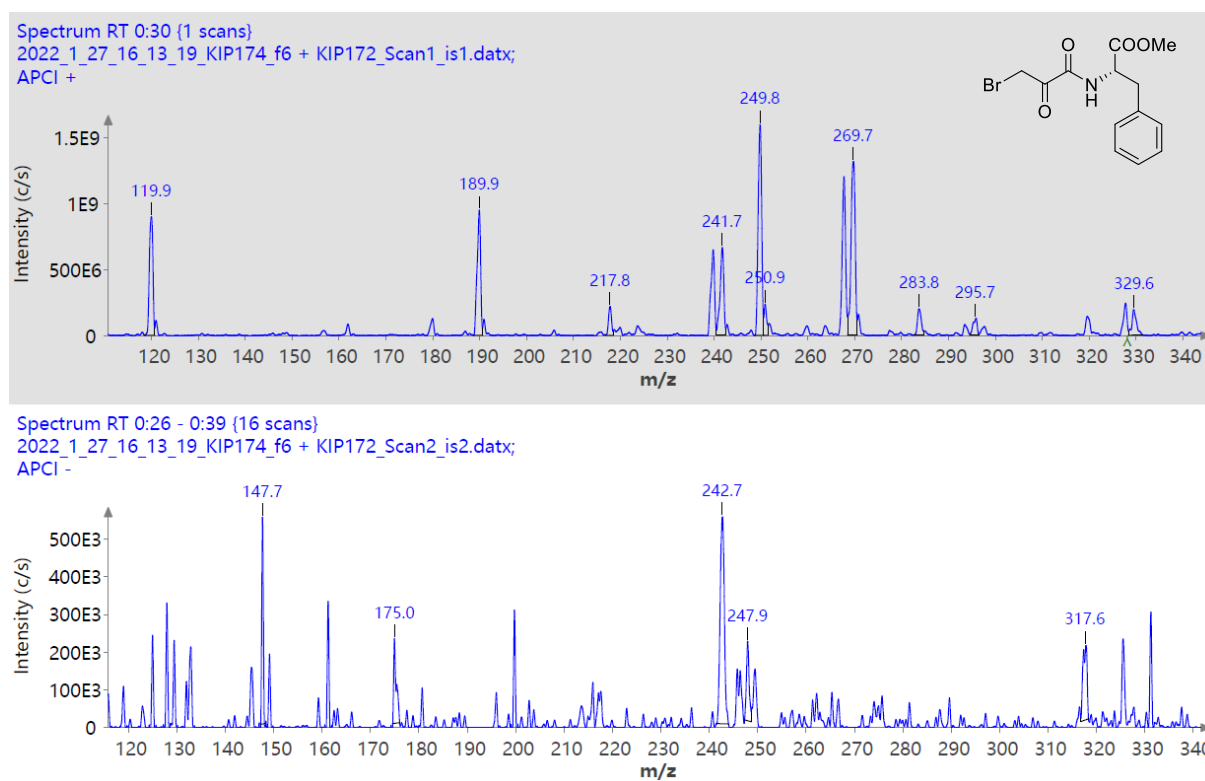


Figure S66. <sup>1</sup>H NMR spectrum of compound 18b.



**Figure S67.**  $^{13}\text{C}$  NMR spectrum of compound **18b**.



**Figure S68.** MS spectrum of compound **18b**.

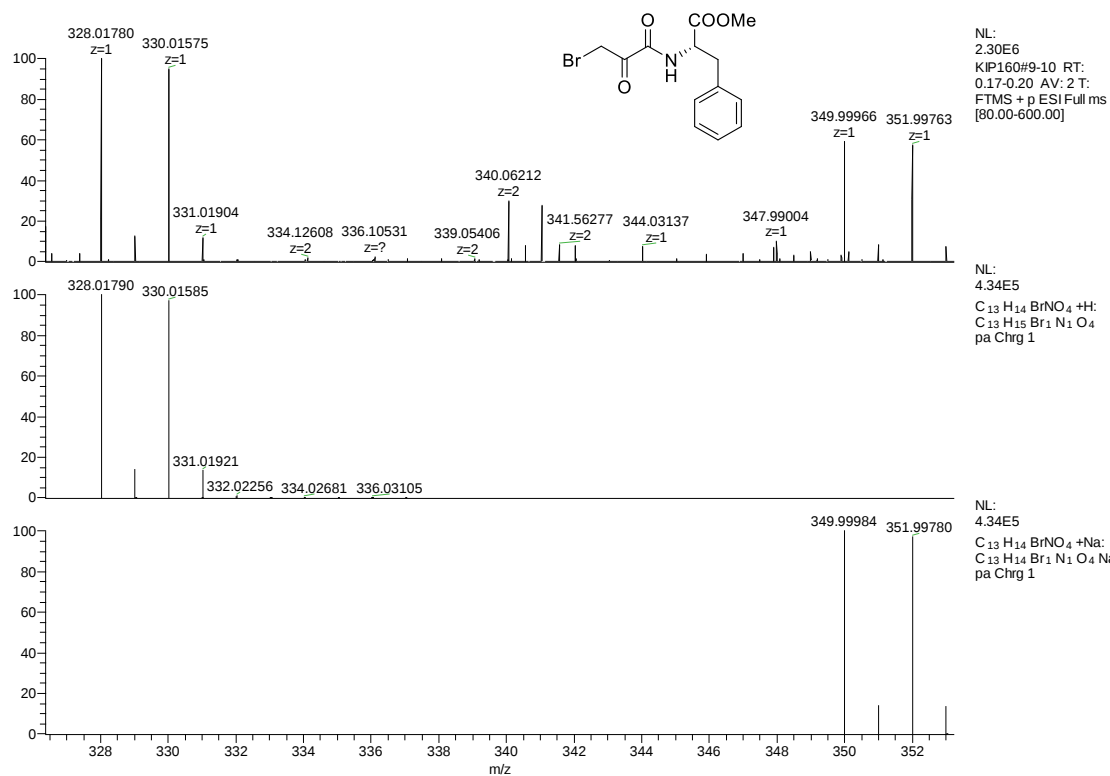


Figure S69. HRMS spectrum of compound 18b.

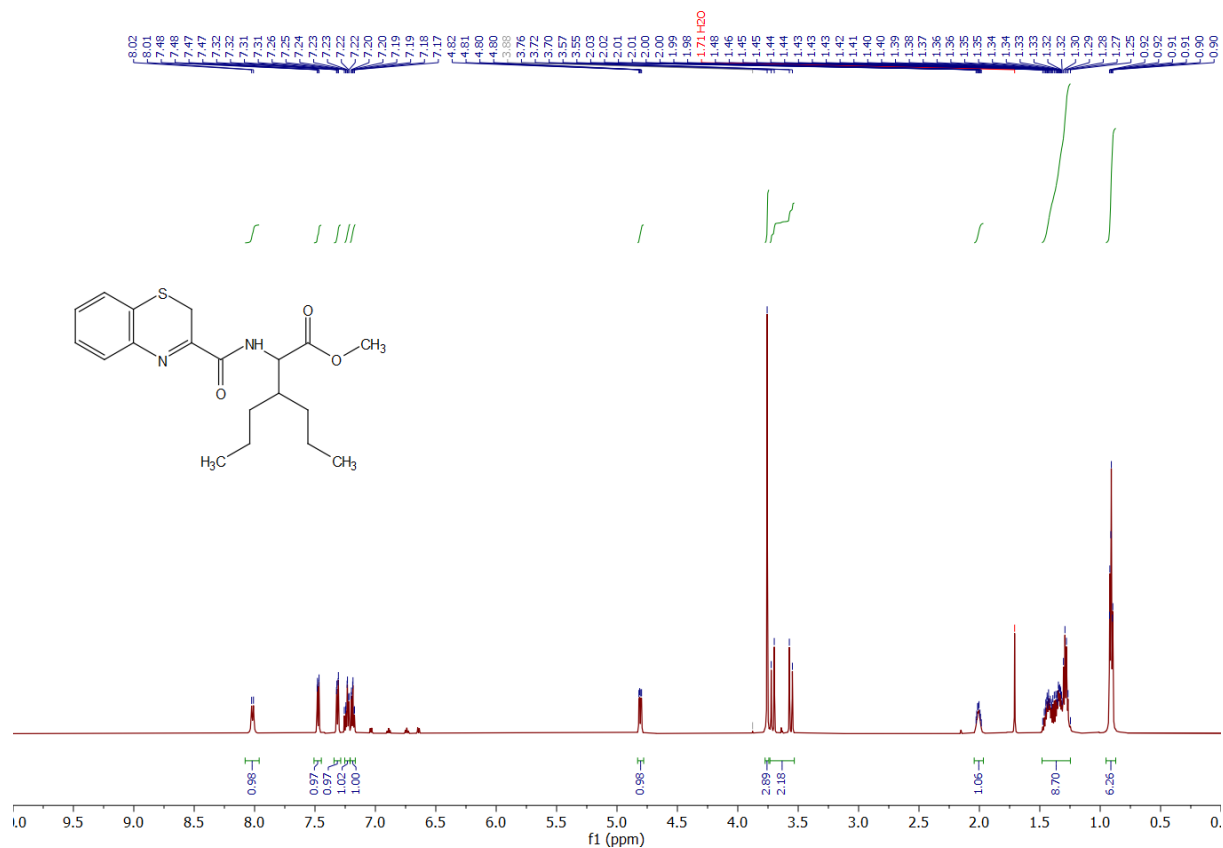
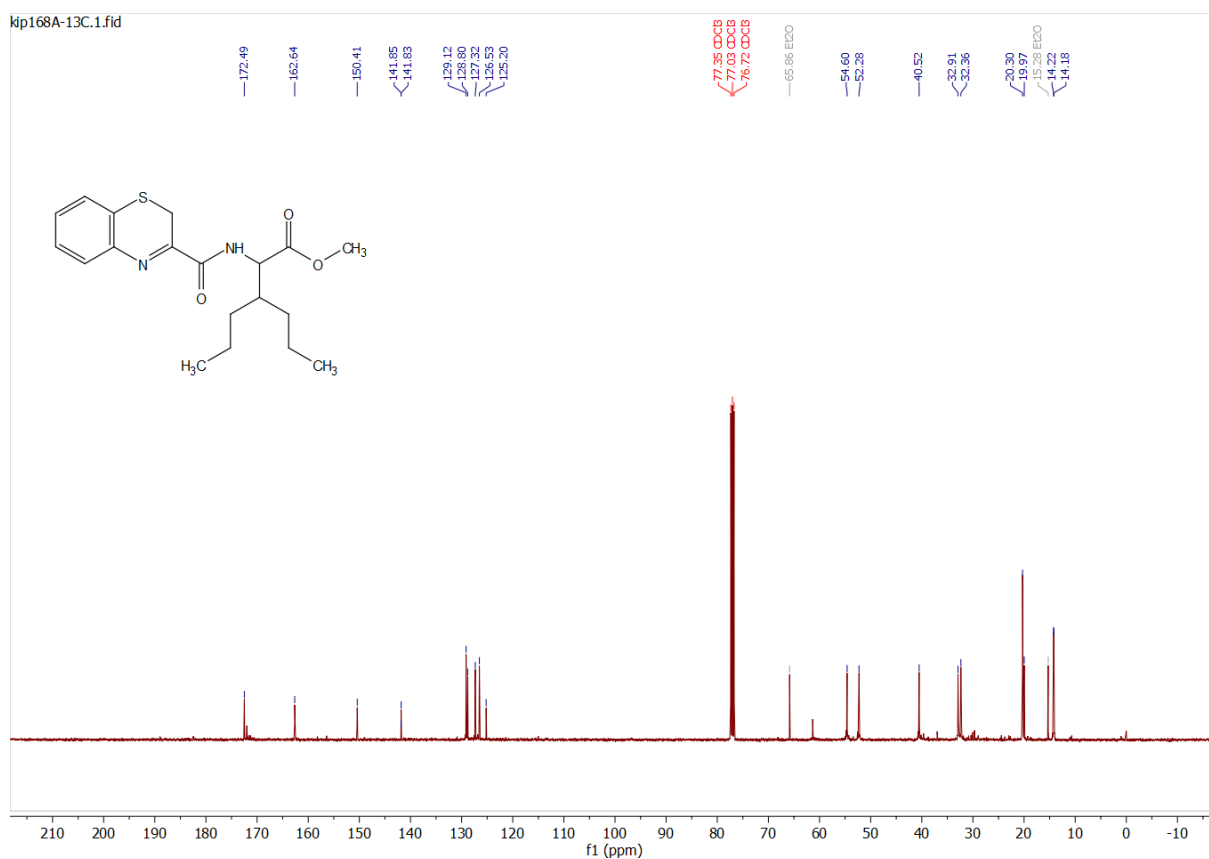
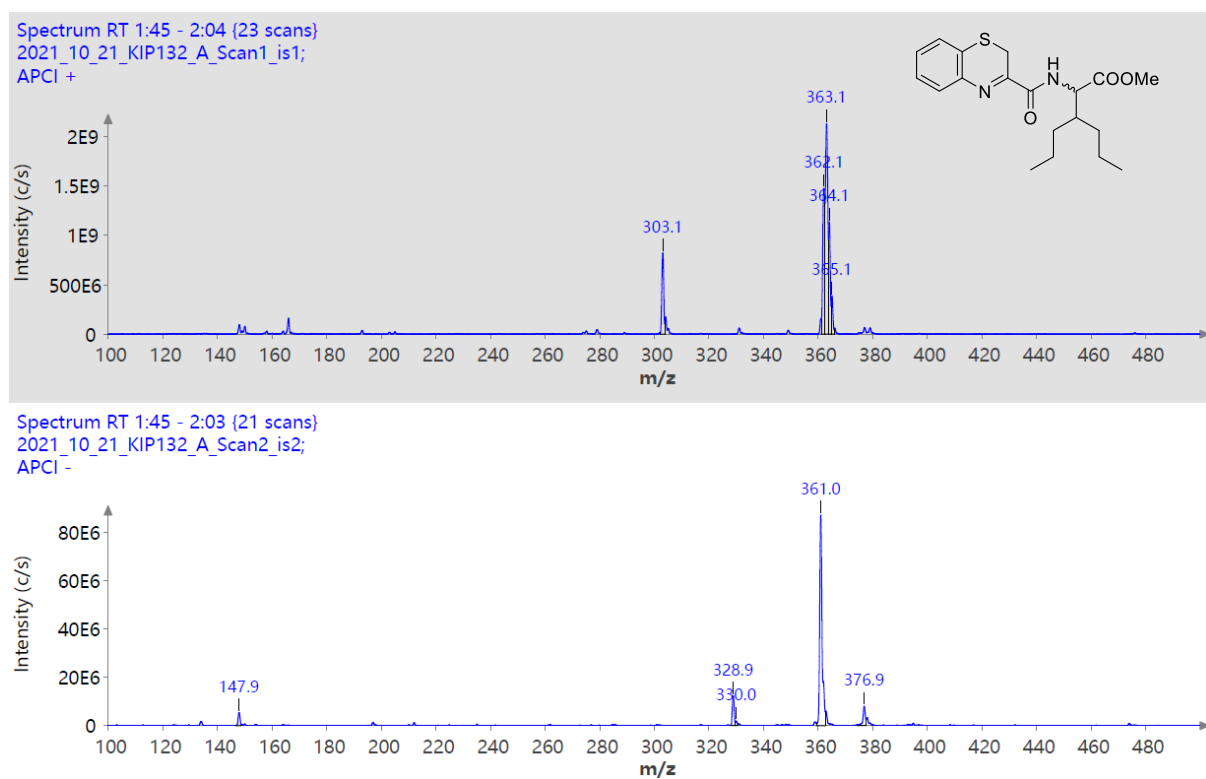


Figure S70. <sup>1</sup>H NMR spectrum of compound 19a.



**Figure S71.**  $^{13}\text{C}$  NMR spectrum of compound **19a**.



**Figure S72.** MS spectrum of compound **19a**.

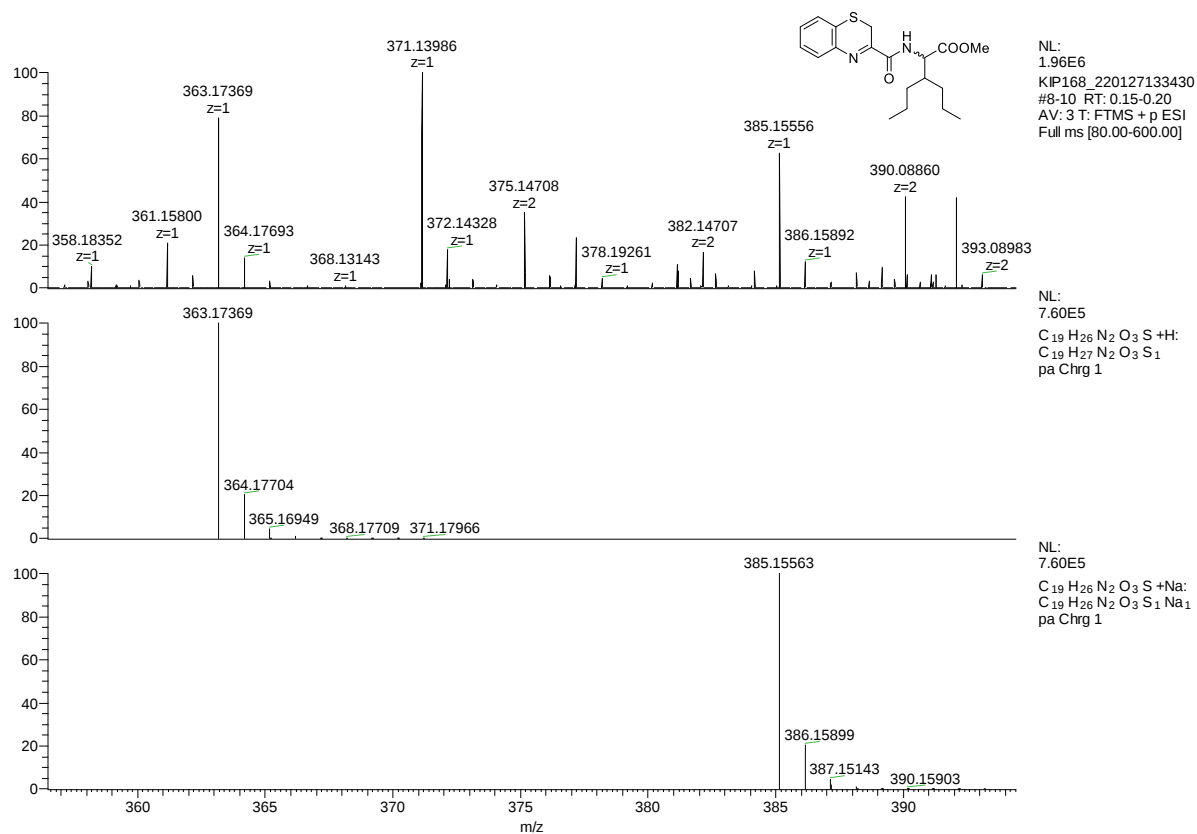


Figure S73. HRMS spectrum of compound 19a.

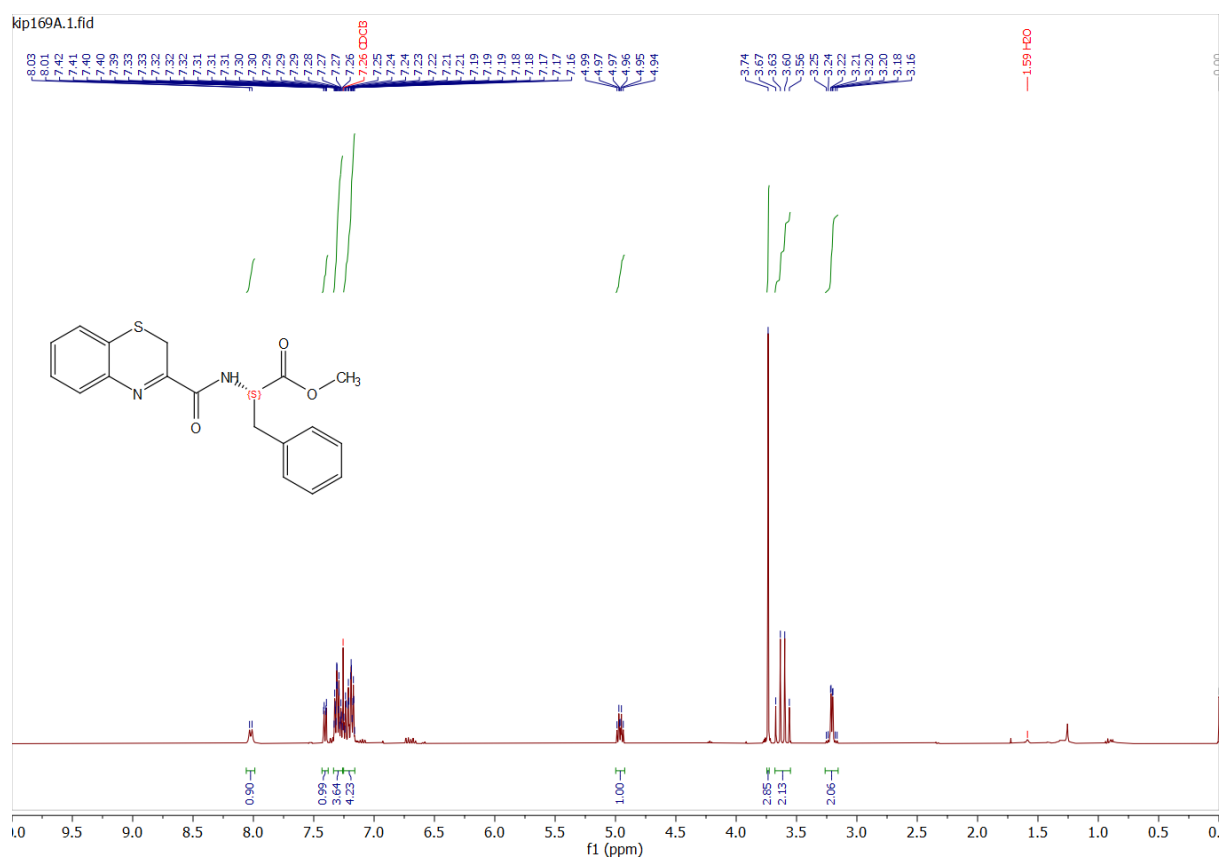
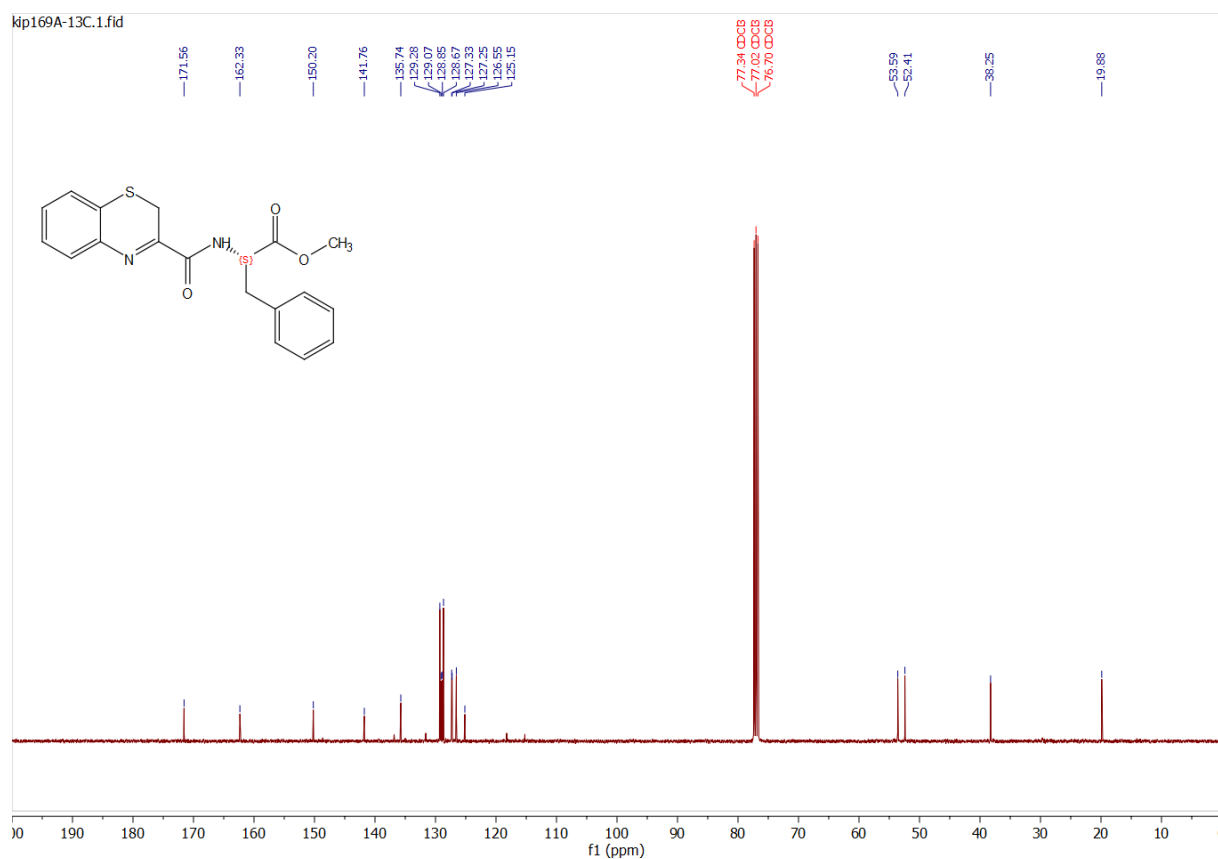
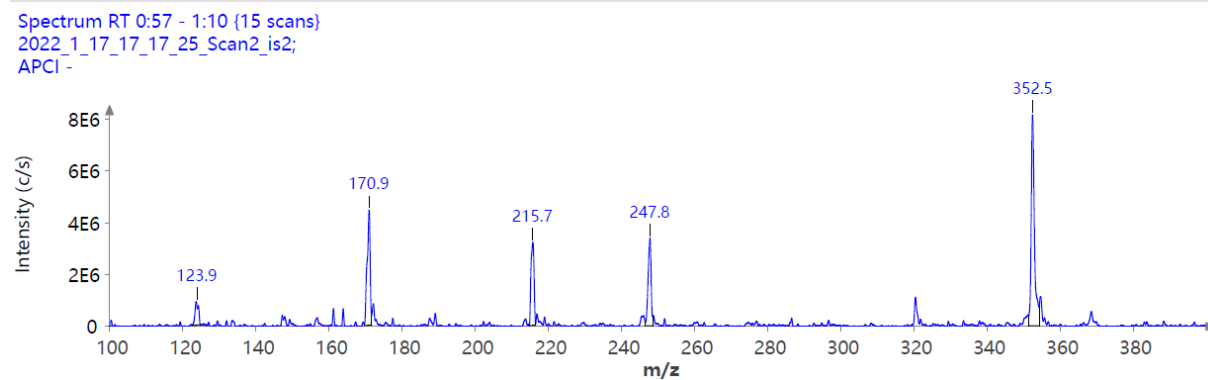
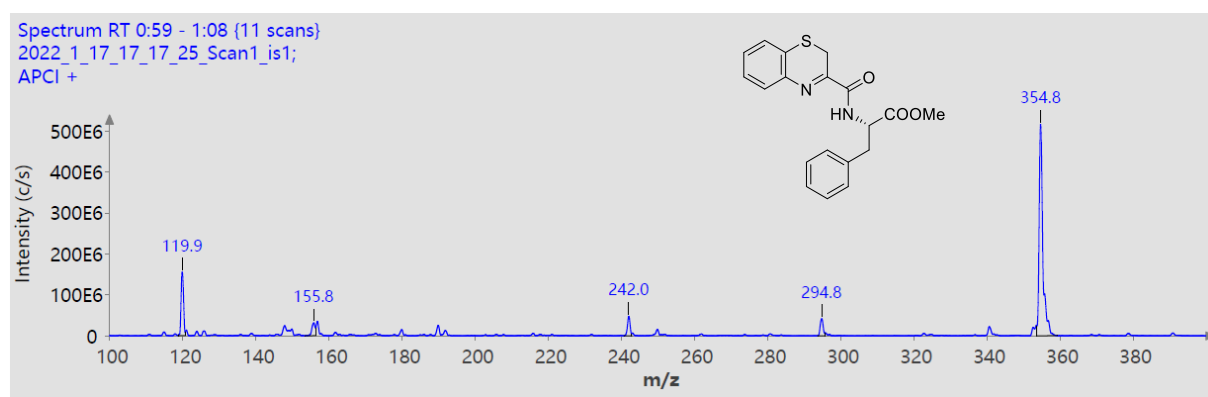


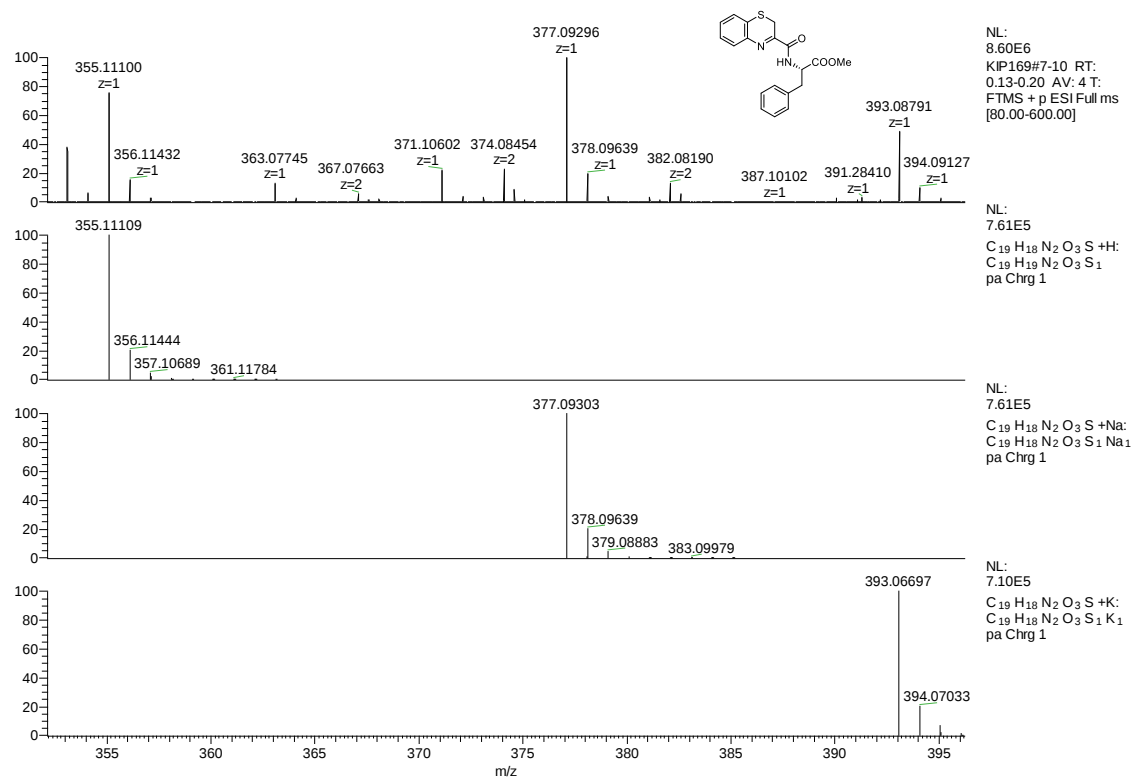
Figure S74. <sup>1</sup>H NMR spectrum of compound 19b.



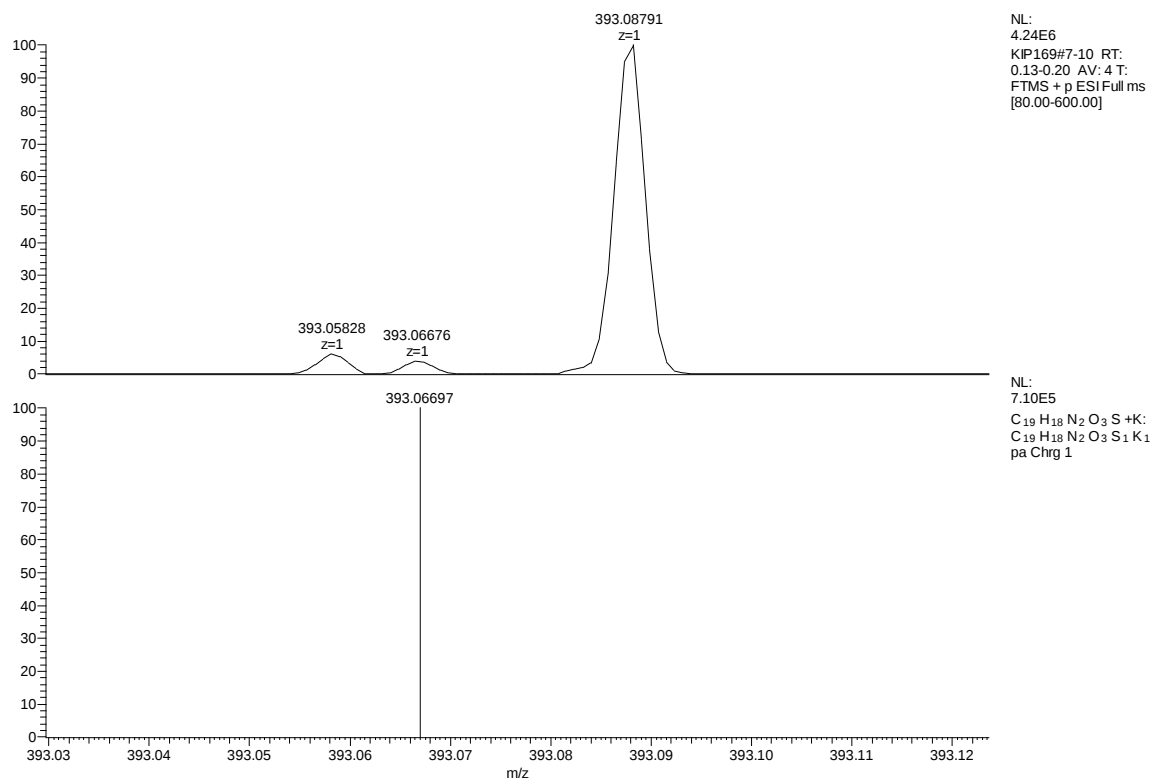
**Figure S75.**  $^{13}\text{C}$  NMR spectrum of compound **19b**.



**Figure S76.** MS spectrum of compound **19b**.



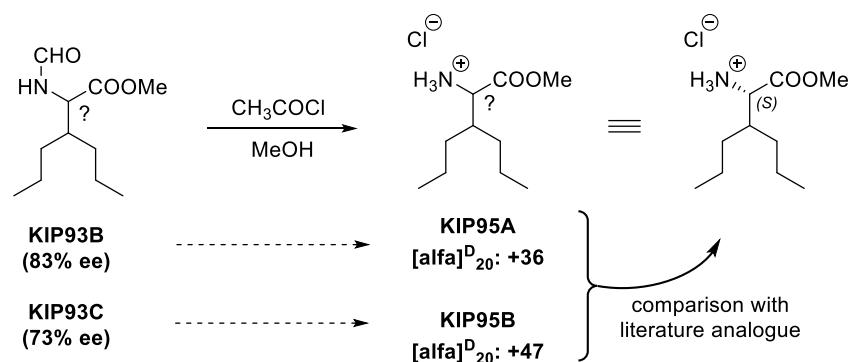
**Figure S77.** HRMS spectrum of compound **19b**.



**Figure S78.** HRMS spectrum of compound **19b** (enlarged for [M+K]<sup>+</sup>).

## 6. Stereochemical description of 16·HCl

In the literature [2], the optical rotation of a highly similar deprotected ester is given. Thus, the product of the stereoselective reduction was deprotected using AcCl, and then the optical rotation was measured and compared with the literature analogue.

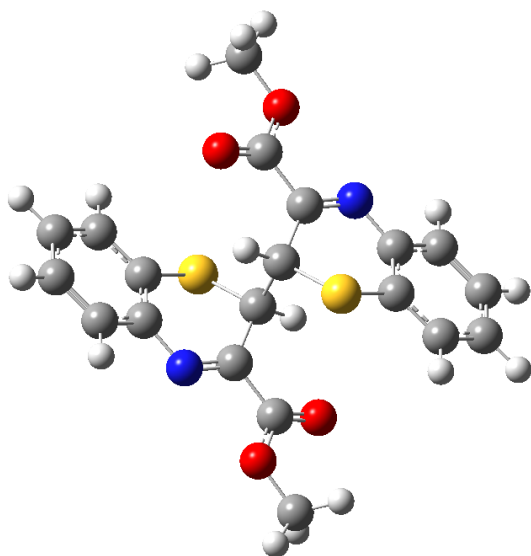


Purified by flash chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$  with up to 5%  $\text{MeOH}$ ). Optical rotation measured in  $\text{MeOH}$  ( $c = 0.35$  and  $0.31$ , respectively)

## 7. Details of DFT calculations

Structures were built and preoptimized using a semiempirical RM1 method and by HF/3-21G using Spartan program package [3]. Then, the structures were fully geometrically optimized at the wB97xD/6-31G(d) level [4]. Single-point energies were calculated at the MN15/6-311+G(2d,p) level [5]. DFT calculations were performed using the Gaussian program package [6].

### Benzothiazine-imine-dimer



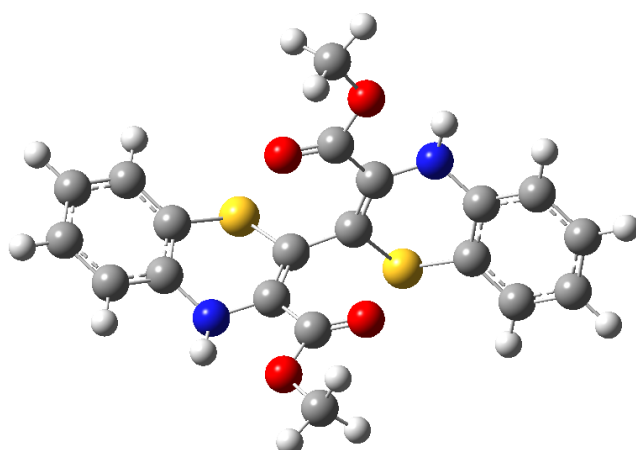
```
Imaginary Freq 0
Temperature      298.15      Kelvin
Pressure 1      atm
Frequencies scaled by 1
Electronic Energy (EE)  -1978.1239      Hartree
Zero-point Energy Correction  0.333555      Hartree
Thermal Correction to Energy  0.357944      Hartree
Thermal Correction to Enthalpy      0.358888      Hartree
Thermal Correction to Free Energy  0.277595      Hartree
EE + Zero-point Energy  -1977.7904      Hartree
EE + Thermal Energy Correction      -1977.766      Hartree
EE + Thermal Enthalpy Correction  -1977.7651      Hartree
EE + Thermal Free Energy Correction      -1977.8463
Hartree
E (Thermal)      224.613      kcal/mol
Heat Capacity (Cv)  91.871      cal/mol-kelvin
Entropy (S)      171.096      cal/mol-kelvin
Energy (FREE) = -5.192835576172E6 kJ.mol-1

Single point energy MN15/6-311+G(2d,p)
E(RMN15)  -1977.3584      Hartree
```

Cartesian coordinates

|    | Atom | X       | Y       | Z       |
|----|------|---------|---------|---------|
| 1  | C    | -0.0654 | 0.7068  | -3.9573 |
| 2  | C    | 2.1731  | -0.8965 | -3.5436 |
| 3  | C    | 0.5587  | 0.7039  | -2.7105 |
| 4  | C    | 0.4210  | -0.0929 | -4.9827 |
| 5  | C    | 1.5355  | -0.9059 | -4.7738 |
| 6  | C    | 1.6955  | -0.0985 | -2.4978 |
| 7  | N    | 2.4394  | -0.0881 | -1.3103 |
| 8  | C    | 1.9017  | 0.2841  | -0.2158 |
| 9  | C    | 0.4389  | 0.6352  | -0.0378 |
| 10 | S    | -0.0502 | 1.7272  | -1.4062 |
| 11 | C    | 2.7551  | 0.3923  | 1.0215  |
| 12 | O    | 2.3672  | 0.9379  | 2.0317  |
| 13 | O    | 3.9538  | -0.1624 | 0.8789  |
| 14 | C    | 4.7960  | -0.0801 | 2.0277  |
| 15 | H    | -0.9498 | 1.3171  | -4.1106 |
| 16 | H    | -0.0793 | -0.0909 | -5.9460 |
| 17 | H    | 1.9094  | -1.5363 | -5.5740 |
| 18 | H    | 3.0560  | -1.4992 | -3.3571 |
| 19 | H    | 4.3309  | -0.5835 | 2.8791  |
| 20 | H    | 4.9856  | 0.9634  | 2.2908  |
| 21 | H    | 5.7221  | -0.5794 | 1.7459  |
| 22 | H    | 0.3259  | 1.2216  | 0.8769  |
| 23 | C    | 0.0654  | -0.7068 | 3.9573  |
| 24 | C    | -2.1731 | 0.8965  | 3.5436  |
| 25 | C    | -0.5587 | -0.7039 | 2.7105  |
| 26 | C    | -0.4210 | 0.0929  | 4.9827  |
| 27 | C    | -1.5355 | 0.9059  | 4.7738  |
| 28 | C    | -1.6955 | 0.0985  | 2.4978  |
| 29 | N    | -2.4394 | 0.0881  | 1.3103  |
| 30 | C    | -1.9017 | -0.2841 | 0.2158  |
| 31 | C    | -0.4389 | -0.6352 | 0.0378  |
| 32 | S    | 0.0502  | -1.7272 | 1.4062  |
| 33 | C    | -2.7551 | -0.3923 | -1.0215 |
| 34 | O    | -2.3672 | -0.9379 | -2.0317 |
| 35 | O    | -3.9538 | 0.1624  | -0.8789 |
| 36 | C    | -4.7960 | 0.0801  | -2.0277 |
| 37 | H    | 0.9498  | -1.3171 | 4.1106  |
| 38 | H    | 0.0793  | 0.0909  | 5.9460  |
| 39 | H    | -1.9094 | 1.5363  | 5.5740  |
| 40 | H    | -3.0560 | 1.4992  | 3.3571  |
| 41 | H    | -0.3259 | -1.2216 | -0.8769 |
| 42 | H    | -4.9856 | -0.9634 | -2.2908 |
| 43 | H    | -4.3309 | 0.5835  | -2.8791 |
| 44 | H    | -5.7221 | 0.5794  | -1.7459 |

# Benzothiazine-enamine-dimer



```

Imaginary Freq 0
Temperature      298.15      Kelvin
Pressure        1          atm
Frequencies scaled by 1
Electronic Energy (EE)      -1978.1133      Hartree
Zero-point Energy Correction  0.333367      Hartree
Thermal Correction to Energy  0.358322      Hartree
Thermal Correction to Enthalpy      0.359266      Hartree
Thermal Correction to Free Energy  0.276511      Hartree
EE + Zero-point Energy      -1977.7799      Hartree
EE + Thermal Energy Correction      -1977.755      Hartree
EE + Thermal Enthalpy Correction  -1977.754      Hartree
EE + Thermal Free Energy Correction      -1977.8368
Hartree
E (Thermal)      224.85      kcal/mol
Heat Capacity (Cv)  93.939      cal/mol-kelvin
Entropy (S)      174.171      cal/mol-kelvin
Energy (FREE) = -5.1928104422605E6 kJ.mol-1
  
```

```

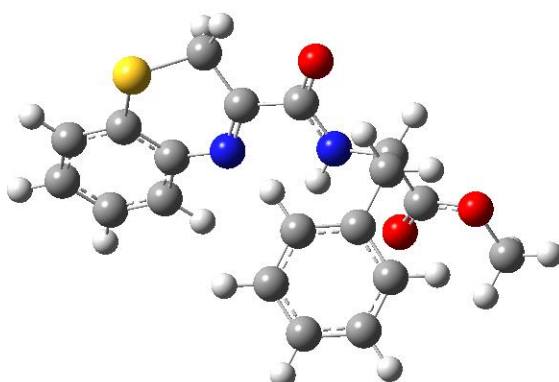
Single point energy MN15/6-311+G(2d,p)
E(RMN15)  -1977.3563      Hartree
  
```

## Cartesian coordinates

|    | Atom | X       | Y       | Z       |
|----|------|---------|---------|---------|
| 1  | C    | -4.5475 | 0.5321  | -1.2239 |
| 2  | C    | -4.5355 | 0.4879  | 1.5573  |
| 3  | C    | -3.5670 | -0.1802 | -0.5450 |
| 4  | C    | -5.5520 | 1.1890  | -0.5163 |
| 5  | C    | -5.5456 | 1.1577  | 0.8736  |
| 6  | C    | -3.5435 | -0.1918 | 0.8522  |
| 7  | N    | -2.5211 | -0.8849 | 1.5189  |
| 8  | C    | -1.2182 | -0.8756 | 0.9993  |
| 9  | C    | -0.9838 | -0.9518 | -0.3246 |
| 10 | S    | -2.3599 | -1.1357 | -1.4350 |
| 11 | C    | -0.1064 | -0.7244 | 1.9757  |
| 12 | O    | 1.0721  | -0.6817 | 1.7144  |

|    |   |         |         |         |
|----|---|---------|---------|---------|
| 13 | O | -0.5800 | -0.6530 | 3.2380  |
| 14 | C | 0.4155  | -0.5329 | 4.2530  |
| 15 | H | -4.5335 | 0.5561  | -2.3093 |
| 16 | H | -6.3313 | 1.7216  | -1.0515 |
| 17 | H | -6.3216 | 1.6684  | 1.4354  |
| 18 | H | -4.5168 | 0.4861  | 2.6443  |
| 19 | H | -2.5415 | -0.7946 | 2.5246  |
| 20 | H | 0.9949  | 0.3823  | 4.1116  |
| 21 | H | 1.0914  | -1.3906 | 4.2270  |
| 22 | H | -0.1290 | -0.5008 | 5.1962  |
| 23 | C | 3.7807  | -2.8398 | -0.3197 |
| 24 | C | 4.5451  | -0.4588 | -1.5379 |
| 25 | C | 2.8291  | -2.0407 | -0.9406 |
| 26 | C | 5.1249  | -2.4742 | -0.3434 |
| 27 | C | 5.5027  | -1.2868 | -0.9599 |
| 28 | C | 3.2026  | -0.8341 | -1.5384 |
| 29 | N | 2.2197  | -0.0221 | -2.1256 |
| 30 | C | 0.9572  | 0.0900  | -1.5248 |
| 31 | C | 0.3457  | -0.9686 | -0.9600 |
| 32 | S | 1.1315  | -2.5613 | -1.0380 |
| 33 | C | 0.3460  | 1.4457  | -1.4932 |
| 34 | O | -0.7218 | 1.7362  | -1.0091 |
| 35 | O | 1.1432  | 2.3479  | -2.1042 |
| 36 | C | 0.6297  | 3.6784  | -2.1491 |
| 37 | H | 3.4691  | -3.7592 | 0.1667  |
| 38 | H | 6.5469  | -0.9904 | -0.9818 |
| 39 | H | 4.8385  | 0.4821  | -1.9967 |
| 40 | H | 2.5627  | 0.8584  | -2.4818 |
| 41 | H | 0.4824  | 4.0638  | -1.1376 |
| 42 | H | -0.3237 | 3.7009  | -2.6817 |
| 43 | H | 1.3798  | 4.2651  | -2.6782 |
| 44 | H | 5.8682  | -3.1151 | 0.1194  |

# **Benzothiazine-imine-Phe**



Imaginary Freq 0  
Temperature 298.15 Kelvin  
Pressure 1 atm  
Frequencies scaled by 1

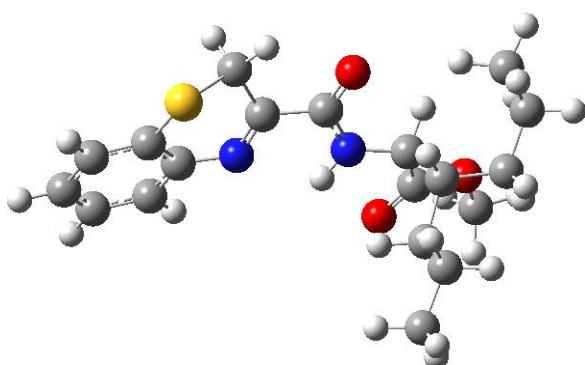
Electronic Energy (EE) -1467.899 Hartree  
 Zero-point Energy Correction 0.344768 Hartree  
 Thermal Correction to Energy 0.366783 Hartree  
 Thermal Correction to Enthalpy 0.367727 Hartree  
 Thermal Correction to Free Energy 0.289259 Hartree  
 EE + Zero-point Energy -1467.5542 Hartree  
 EE + Thermal Energy Correction -1467.5322 Hartree  
 EE + Thermal Enthalpy Correction -1467.5313 Hartree  
 EE + Thermal Free Energy Correction -1467.6097 Hartree  
 E (Thermal) 230.16 kcal/mol  
 Heat Capacity (Cv) 83.421 cal/mol-kelvin  
 Entropy (S) 165.15 cal/mol-kelvin  
 Energy (FREE) = -3.8532093224855E6 kJ.mol-1

# Cartesian coordinates

|    | Atom | X       | Y       | Z       |
|----|------|---------|---------|---------|
| 1  | H    | 1.0479  | 4.4209  | -4.5328 |
| 2  | C    | 0.2794  | 3.9707  | -3.9114 |
| 3  | C    | -1.6956 | 2.8089  | -2.3333 |
| 4  | C    | 0.4748  | 2.6869  | -3.4013 |
| 5  | C    | -0.8987 | 4.6585  | -3.6474 |
| 6  | C    | -1.8955 | 4.0725  | -2.8678 |
| 7  | C    | -0.5161 | 2.1030  | -2.5895 |
| 8  | H    | -1.0411 | 5.6534  | -4.0579 |
| 9  | H    | -2.8183 | 4.6071  | -2.6667 |
| 10 | H    | -2.4394 | 2.3395  | -1.6974 |
| 11 | N    | -0.3500 | 0.8712  | -1.9377 |
| 12 | C    | 0.4822  | 0.0104  | -2.3783 |
| 13 | C    | 1.2904  | 0.1511  | -3.6395 |
| 14 | S    | 1.9853  | 1.8232  | -3.7199 |
| 15 | H    | 2.1087  | -0.5697 | -3.6346 |
| 16 | C    | 0.6809  | -1.2629 | -1.5811 |
| 17 | O    | 1.5256  | -2.0891 | -1.9085 |
| 18 | N    | -0.1285 | -1.3801 | -0.5130 |
| 19 | H    | -0.7808 | -0.6309 | -0.3115 |
| 20 | C    | -0.0171 | -2.4773 | 0.4127  |
| 21 | H    | 0.0451  | -3.4156 | -0.1501 |
| 22 | C    | -1.2809 | -2.4927 | 1.2557  |
| 23 | O    | -2.1479 | -1.6534 | 1.2106  |
| 24 | O    | -1.2977 | -3.5451 | 2.0800  |
| 25 | C    | -2.4077 | -3.5950 | 2.9789  |
| 26 | H    | -2.2630 | -4.4967 | 3.5728  |
| 27 | H    | -2.4149 | -2.7083 | 3.6175  |
| 28 | H    | -3.3475 | -3.6458 | 2.4246  |
| 29 | C    | 1.2454  | -2.3762 | 1.3077  |
| 30 | H    | 2.1049  | -2.3554 | 0.6316  |
| 31 | H    | 0.6592  | -0.0369 | -4.5159 |
| 32 | H    | 1.3136  | -3.2916 | 1.9028  |
| 33 | C    | 1.2240  | -1.1604 | 2.1999  |
| 34 | C    | 1.0664  | 1.1219  | 3.8220  |

|    |   |        |         |        |
|----|---|--------|---------|--------|
| 35 | C | 1.6436 | 0.0839  | 1.7224 |
| 36 | C | 0.7308 | -1.2444 | 3.5046 |
| 37 | C | 0.6524 | -0.1134 | 4.3116 |
| 38 | C | 1.5639 | 1.2172  | 2.5252 |
| 39 | H | 2.0381 | 0.1653  | 0.7131 |
| 40 | H | 0.4088 | -2.2090 | 3.8903 |
| 41 | H | 0.2703 | -0.1979 | 5.3248 |
| 42 | H | 1.8931 | 2.1763  | 2.1365 |
| 43 | H | 1.0058 | 2.0060  | 4.4497 |

### Benzothiazine-imine-norleucine



Imaginary Freq 0  
 Temperature 298.15 Kelvin  
 Pressure 1 atm  
 Frequencies scaled by 1  
 Electronic Energy (EE) -1472.744 Hartree  
 Zero-point Energy Correction 0.435646 Hartree  
 Thermal Correction to Energy 0.461386 Hartree  
 Thermal Correction to Enthalpy 0.46233 Hartree  
 Thermal Correction to Free Energy 0.376848 Hartree  
 EE + Zero-point Energy -1472.3083 Hartree  
 EE + Thermal Energy Correction -1472.2826 Hartree  
 EE + Thermal Enthalpy Correction -1472.2817 Hartree  
 EE + Thermal Free Energy Correction -1472.3671 Hartree  
 E (Thermal) 289.524 kcal/mol  
 Heat Capacity (Cv) 94.884 cal/mol-kelvin  
 Entropy (S) 179.913 cal/mol-kelvin  
 Energy (FREE) = -3.865699941823E6 kJ.mol<sup>-1</sup>

### Cartesian coordinates

|   | Atom | X       | Y      | Z       |
|---|------|---------|--------|---------|
| 1 | H    | 1.8542  | 4.7238 | -5.0486 |
| 2 | C    | 0.9641  | 4.1959 | -4.7193 |
| 3 | C    | -1.3133 | 2.8319 | -3.8881 |
| 4 | C    | 1.0949  | 3.0863 | -3.8836 |
| 5 | C    | -0.2921 | 4.6085 | -5.1462 |
| 6 | C    | -1.4341 | 3.9181 | -4.7415 |
| 7 | C    | -0.0569 | 2.4038 | -3.4487 |

|    |   |         |         |         |
|----|---|---------|---------|---------|
| 8  | H | -0.3785 | 5.4687  | -5.8029 |
| 9  | H | -2.4149 | 4.2362  | -5.0799 |
| 10 | H | -2.1857 | 2.2932  | -3.5319 |
| 11 | N | -0.0260 | 1.3545  | -2.5167 |
| 12 | C | 1.0355  | 0.6678  | -2.3457 |
| 13 | C | 2.3044  | 0.8187  | -3.1403 |
| 14 | S | 2.6939  | 2.5793  | -3.3226 |
| 15 | H | 3.1270  | 0.3292  | -2.6181 |
| 16 | C | 1.0266  | -0.4093 | -1.2794 |
| 17 | O | 2.0309  | -1.0767 | -1.0526 |
| 18 | N | -0.1492 | -0.5498 | -0.6434 |
| 19 | H | -0.9240 | 0.0420  | -0.9207 |
| 20 | C | -0.3477 | -1.5252 | 0.4032  |
| 21 | H | 0.1417  | -2.4559 | 0.1022  |
| 22 | C | -1.8423 | -1.7652 | 0.5069  |
| 23 | O | -2.6857 | -1.0073 | 0.0850  |
| 24 | O | -2.1185 | -2.9040 | 1.1477  |
| 25 | C | -3.5071 | -3.1725 | 1.3544  |
| 26 | H | -3.5440 | -4.1180 | 1.8936  |
| 27 | H | -3.9659 | -2.3748 | 1.9432  |
| 28 | H | -4.0260 | -3.2544 | 0.3967  |
| 29 | C | 0.2679  | -1.0519 | 1.7530  |
| 30 | H | 1.2929  | -0.7657 | 1.4857  |
| 31 | C | 0.3481  | -2.1596 | 2.8151  |
| 32 | H | 0.9165  | -1.7579 | 3.6633  |
| 33 | H | -0.6588 | -2.3767 | 3.1928  |
| 34 | C | -0.4528 | 0.2003  | 2.2725  |
| 35 | H | -1.4592 | -0.0699 | 2.6258  |
| 36 | H | -0.5984 | 0.8978  | 1.4376  |
| 37 | C | 1.0140  | -3.4688 | 2.3745  |
| 38 | H | 0.3793  | -3.9825 | 1.6421  |
| 39 | H | 1.0555  | -4.1332 | 3.2466  |
| 40 | C | 0.2890  | 0.9366  | 3.3897  |
| 41 | H | 0.3643  | 0.2990  | 4.2786  |
| 42 | H | 1.3183  | 1.1390  | 3.0648  |
| 43 | C | -0.3956 | 2.2482  | 3.7707  |
| 44 | H | 0.1428  | 2.7601  | 4.5750  |
| 45 | H | -1.4214 | 2.0703  | 4.1136  |
| 46 | H | -0.4459 | 2.9286  | 2.9131  |
| 47 | C | 2.4231  | -3.2871 | 1.8081  |
| 48 | H | 2.4203  | -2.7149 | 0.8741  |
| 49 | H | 2.8883  | -4.2571 | 1.6036  |
| 50 | H | 3.0629  | -2.7547 | 2.5226  |
| 51 | H | 2.1888  | 0.3540  | -4.1265 |

## 8. References

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- 4 J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, 10, 6615-6620.
- 5 H. S. Yu, X. He, S. L. Li, D. G. Truhlar, *Chem. Sci.* **2016**, 7, 5032-5051.
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