

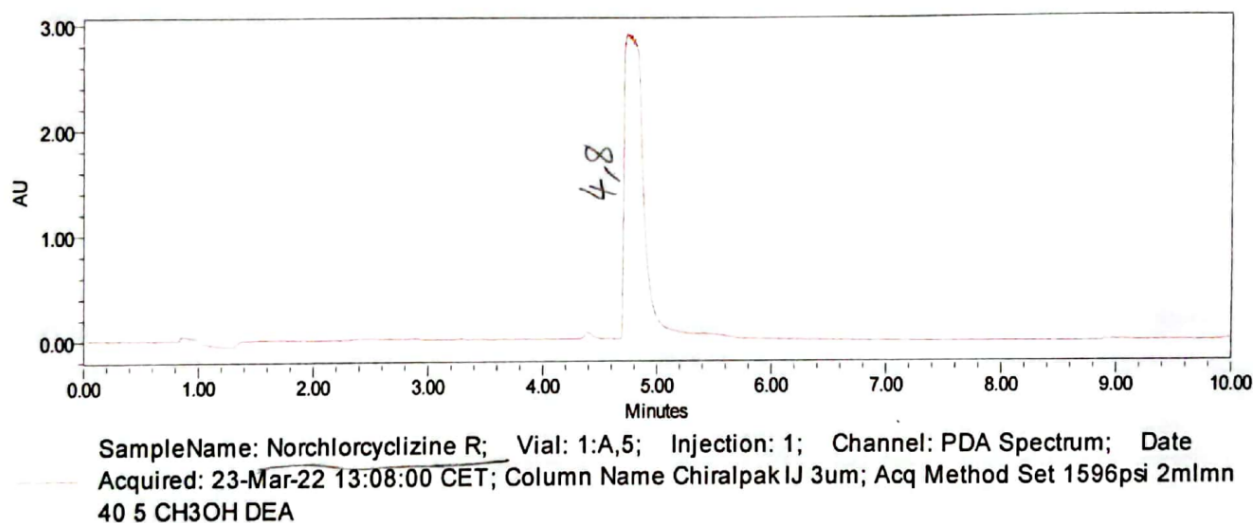
## Supporting Information

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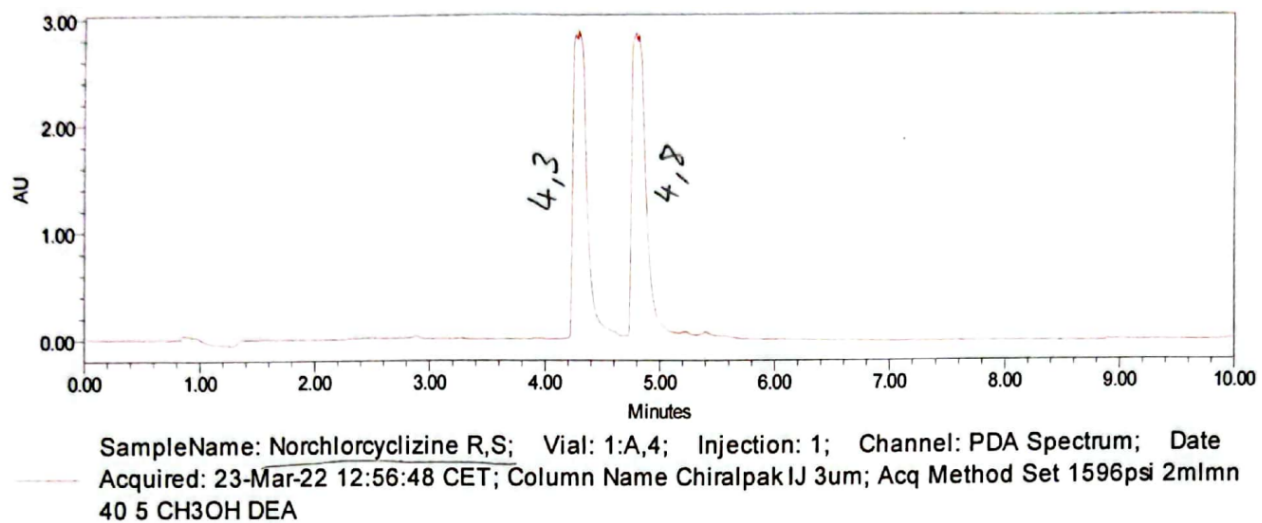
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# 1. Chiral HPLC of (R)-norchlorcyclizine and (R,S)-norchlorcyclizine

1.1. HPLC of (R)-norchlorcyclizine,  $R_t = 4.8$  min.

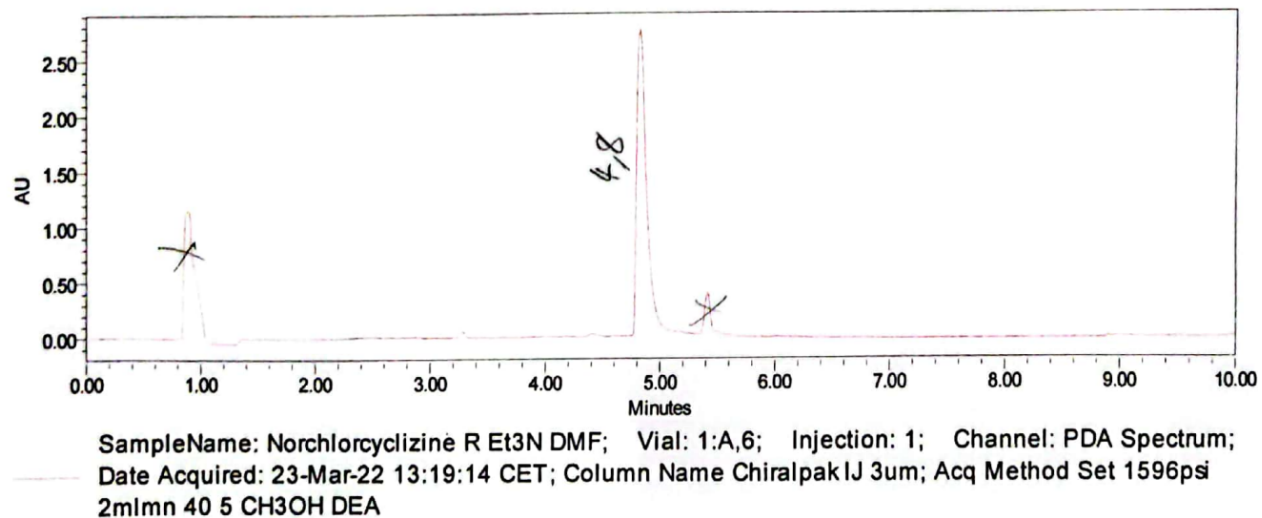


1.2. HPLC of (R,S)-norchlorcyclizine,  $R_t = 4.8$  min (R) and 4.3 (S).

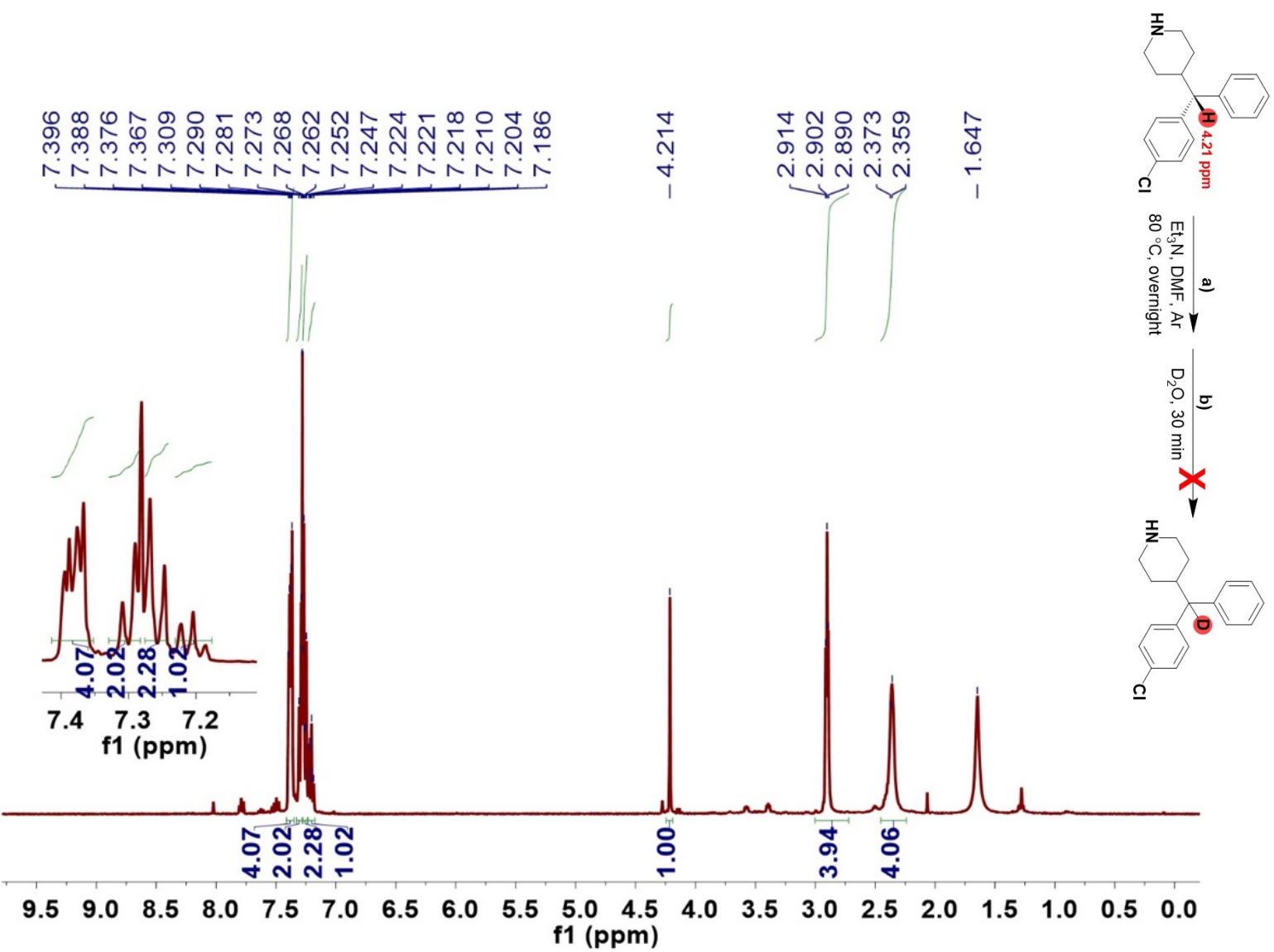


## 2. Retention of configuration of (*R*)-norchlorcyclizine after reaction in DMF/Et<sub>3</sub>N, 80 °C

### 2.1. Chiral HPLC

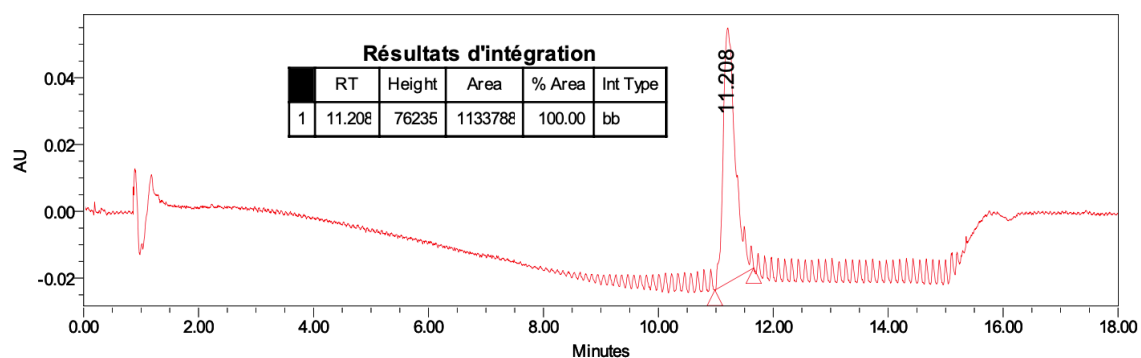


2.2.  $^1\text{H}$  NMR in  $\text{CDCl}_3$  (*R*)-norchlorcyclizine after heating overnight at  $80^\circ\text{C}$  in DMF/TEA, and quenching by  $\text{D}_2\text{O}$ .

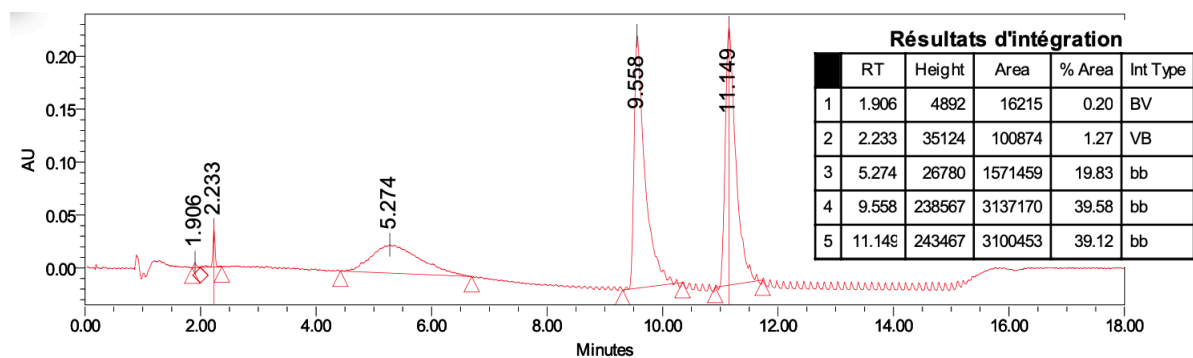


### 3. Chiral HPLC of (*R*)-emoxyzine-2 and (*R,S*)-emoxyzine-2

#### 3.1. Chiral HPLC of (*R*)-emoxyzine-2 ( $R_t = 11.2$ min)

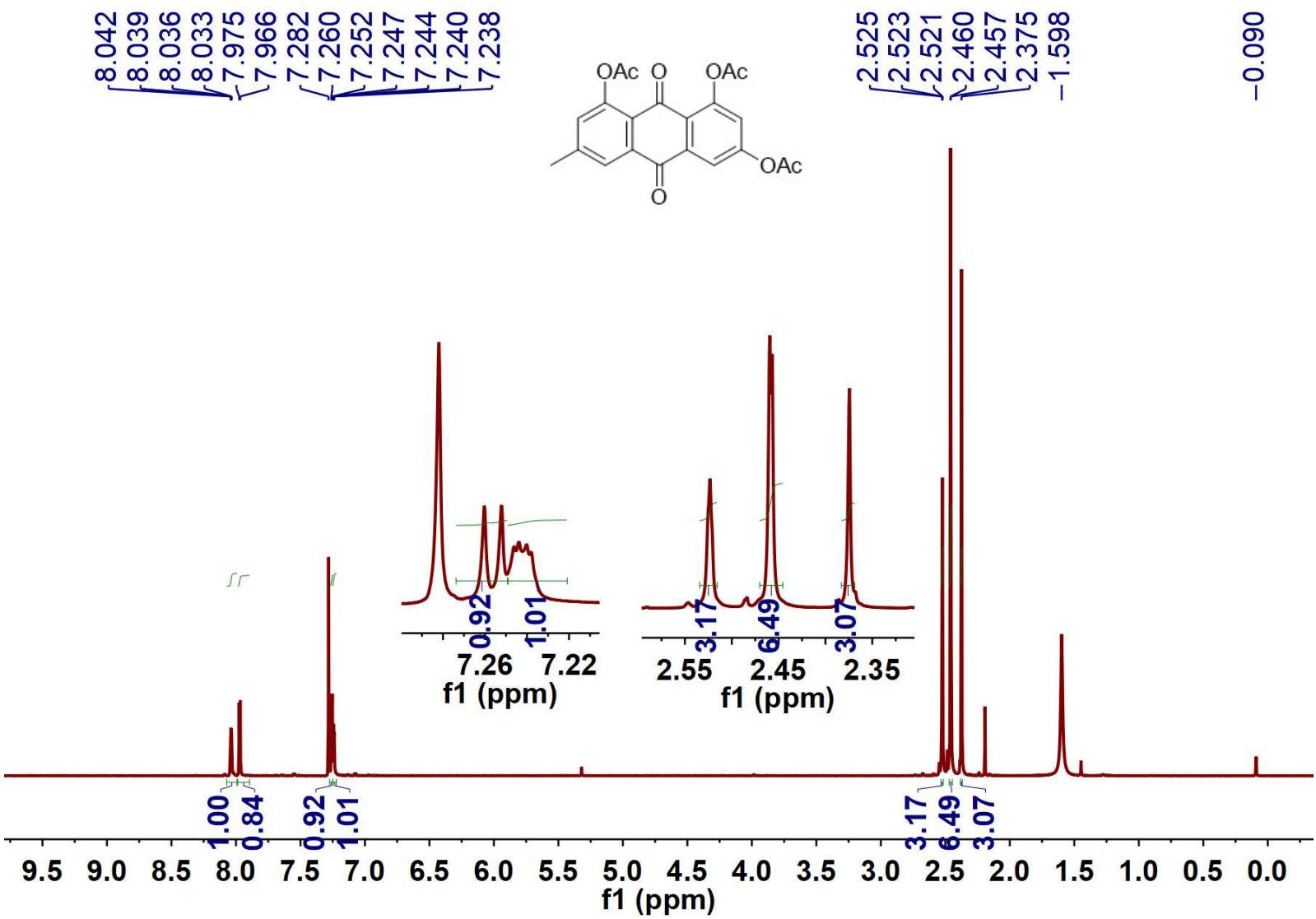


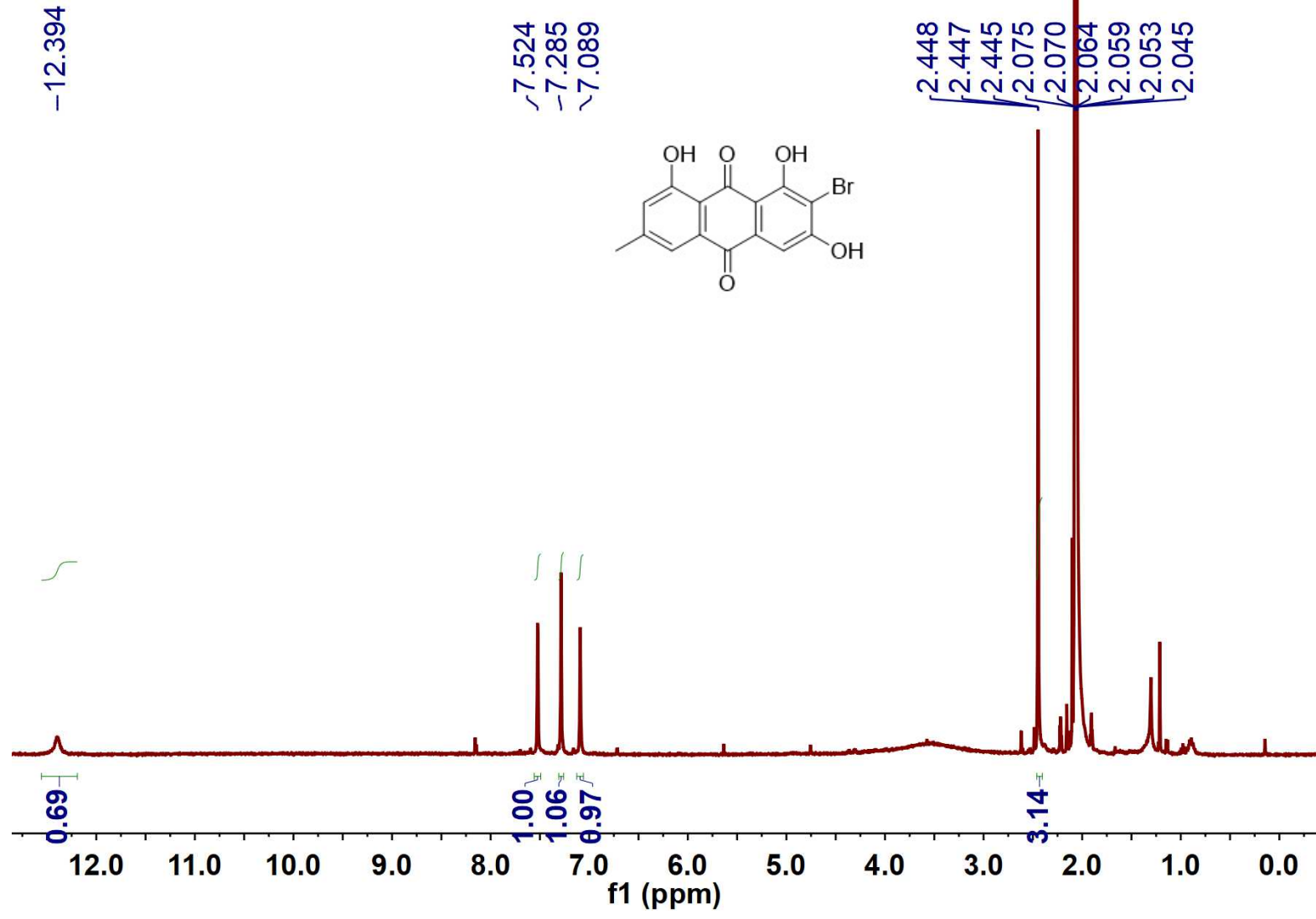
#### 3.2. Chiral HPLC of (*R,S*)-emoxyzine-2. $R_t = 9.6$ min (*S*, 50%), $R_t = 11.1$ min (*R*, 50%)

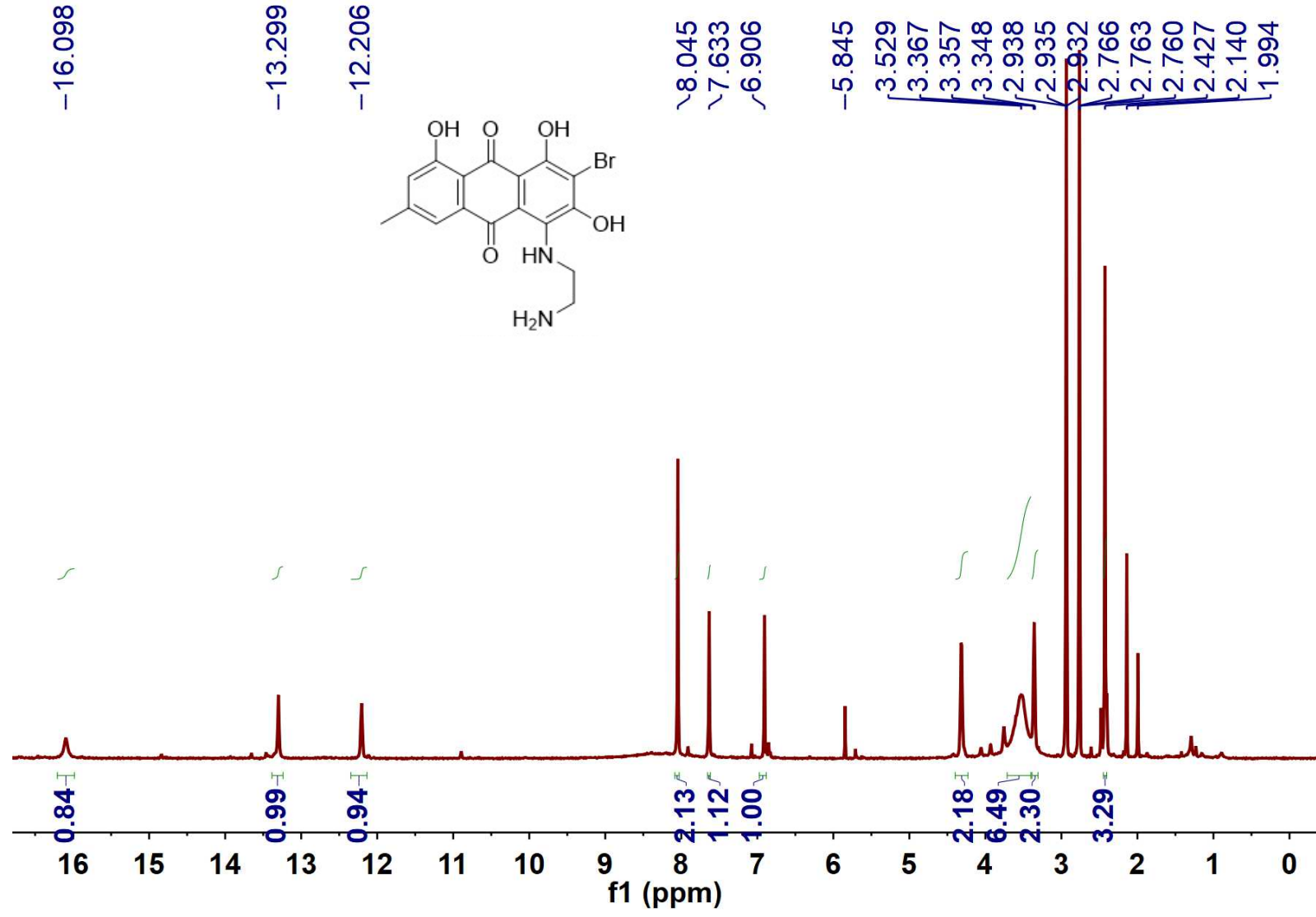


#### 4. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR of emodin-PA and emoxyzine derivatives, and synthesis intermediates

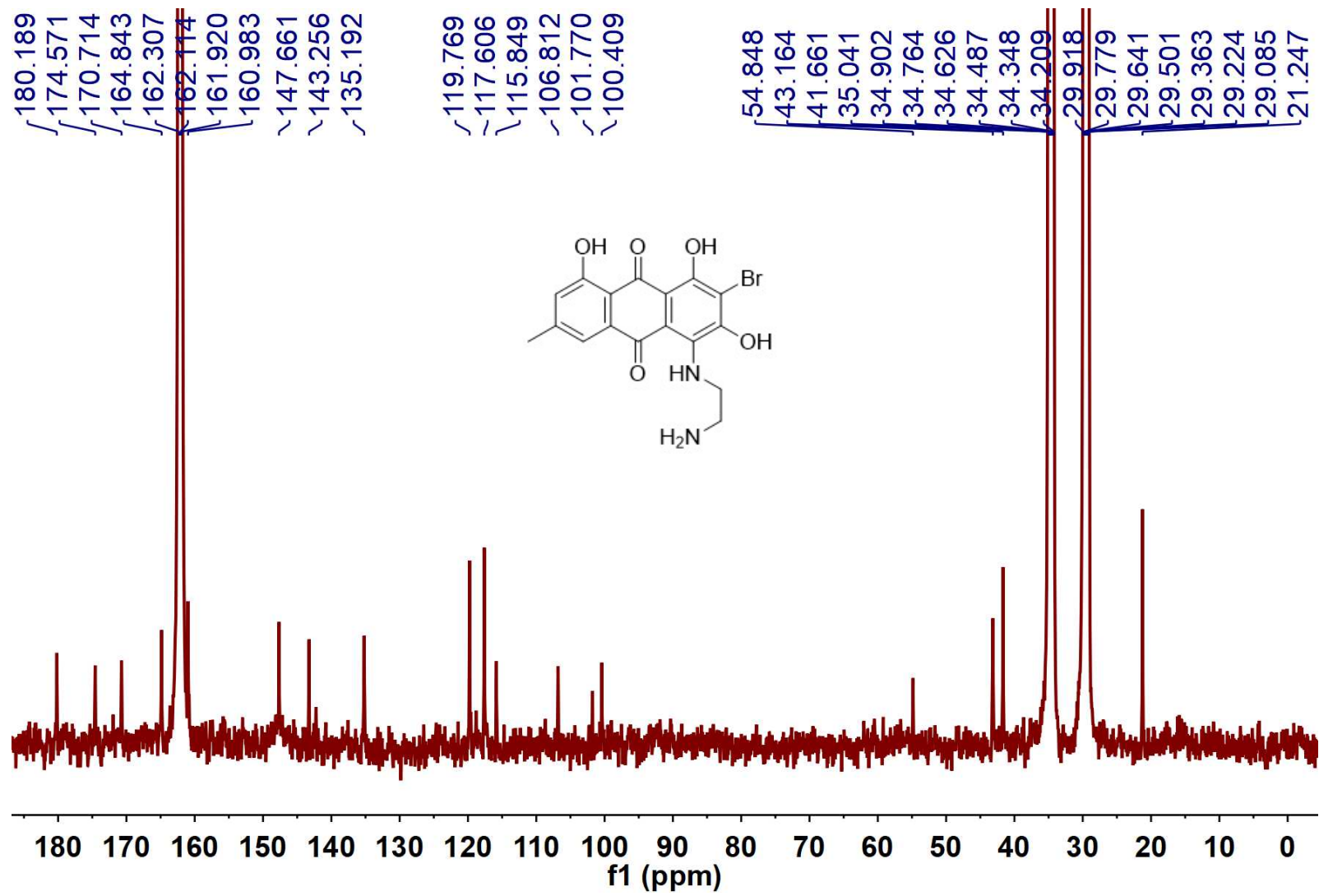
##### 4.1. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) spectrum of 1,3,8-triacety/emodin

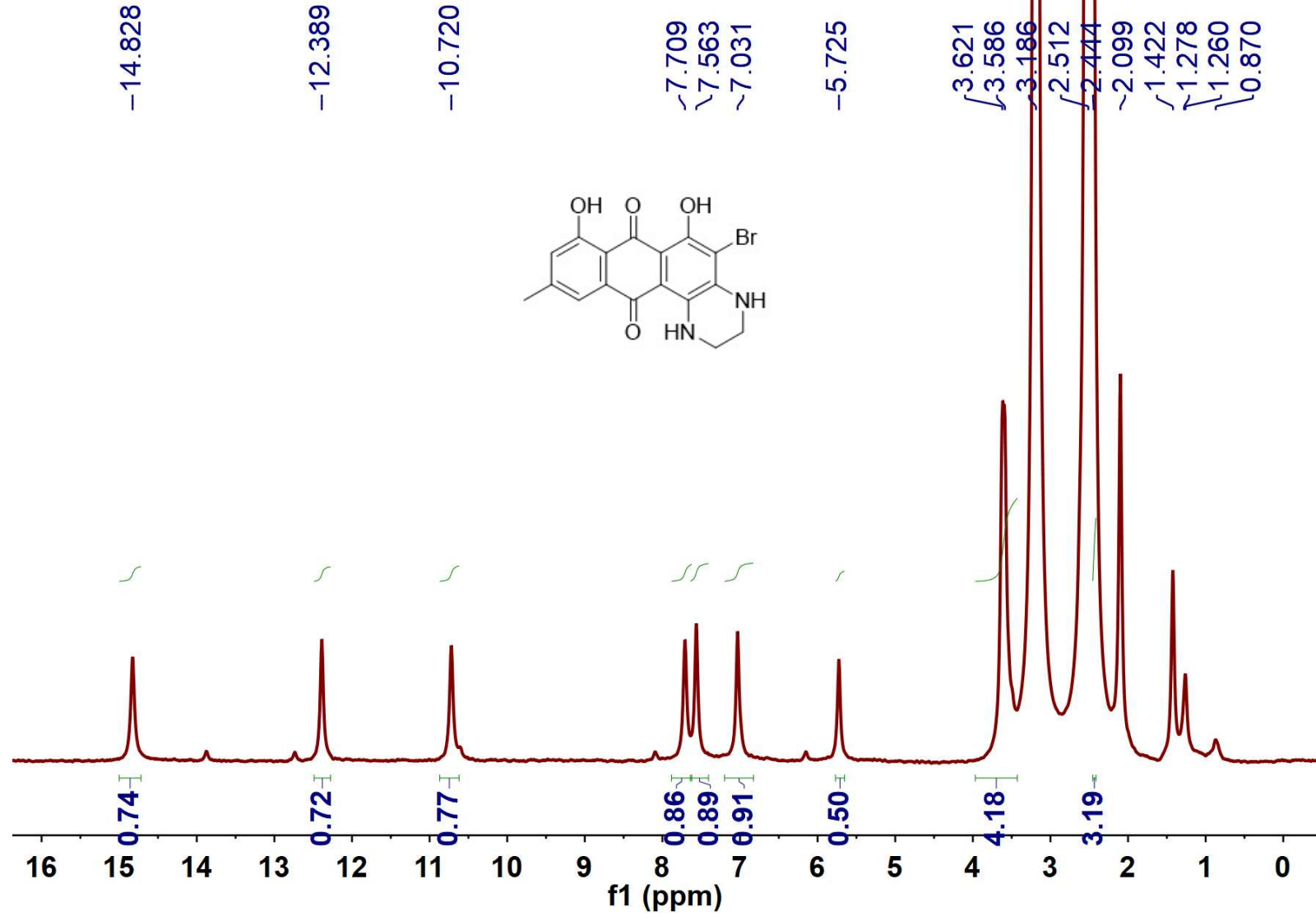


4.2.  $^1\text{H NMR}$  (400 MHz, acetone- $d_6$ ) spectrum of 2-bromoemodin

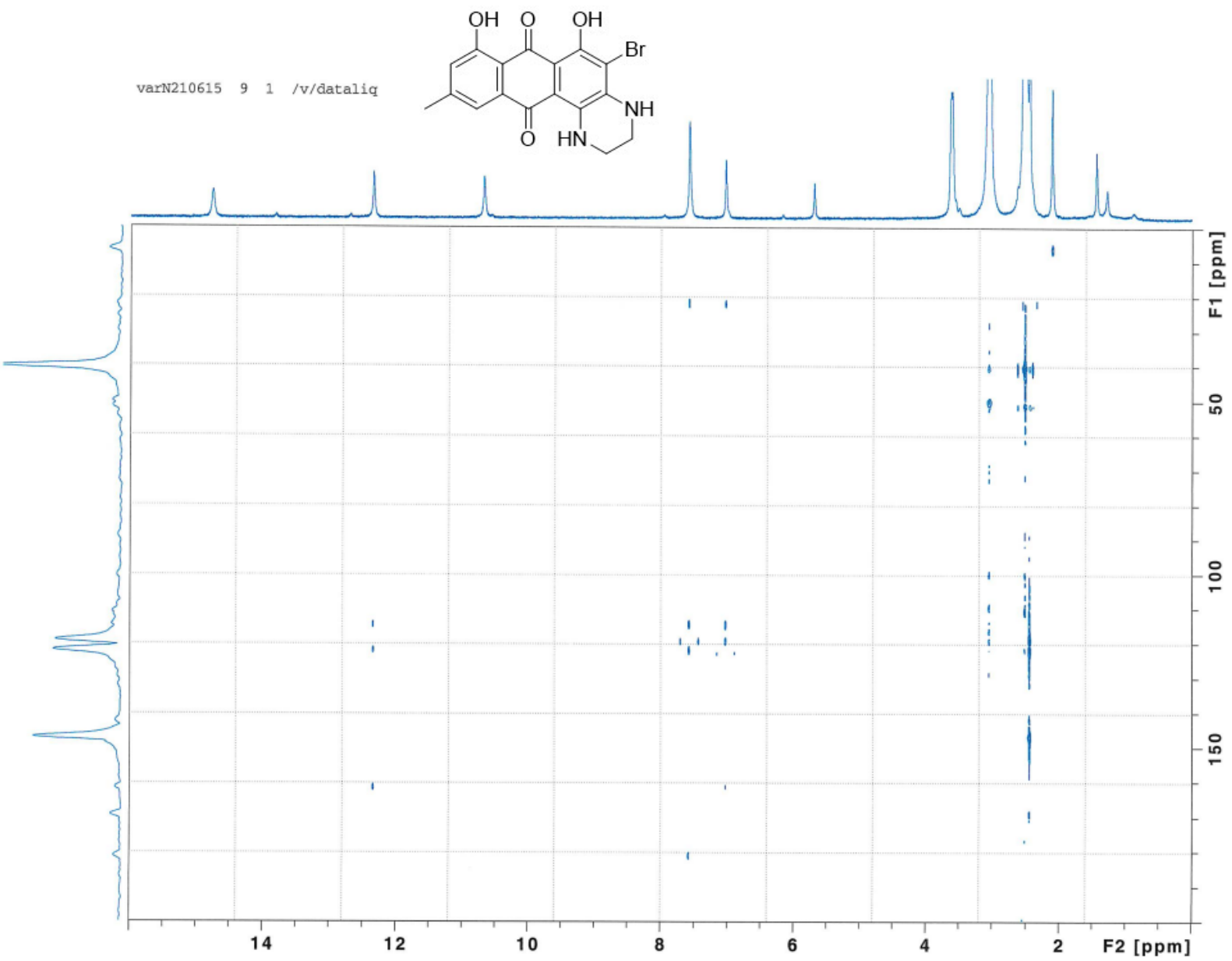
4.3.a. <sup>1</sup>H NMR (600 MHz, DMF-*d*<sub>7</sub>) spectrum of emodin-PA-1

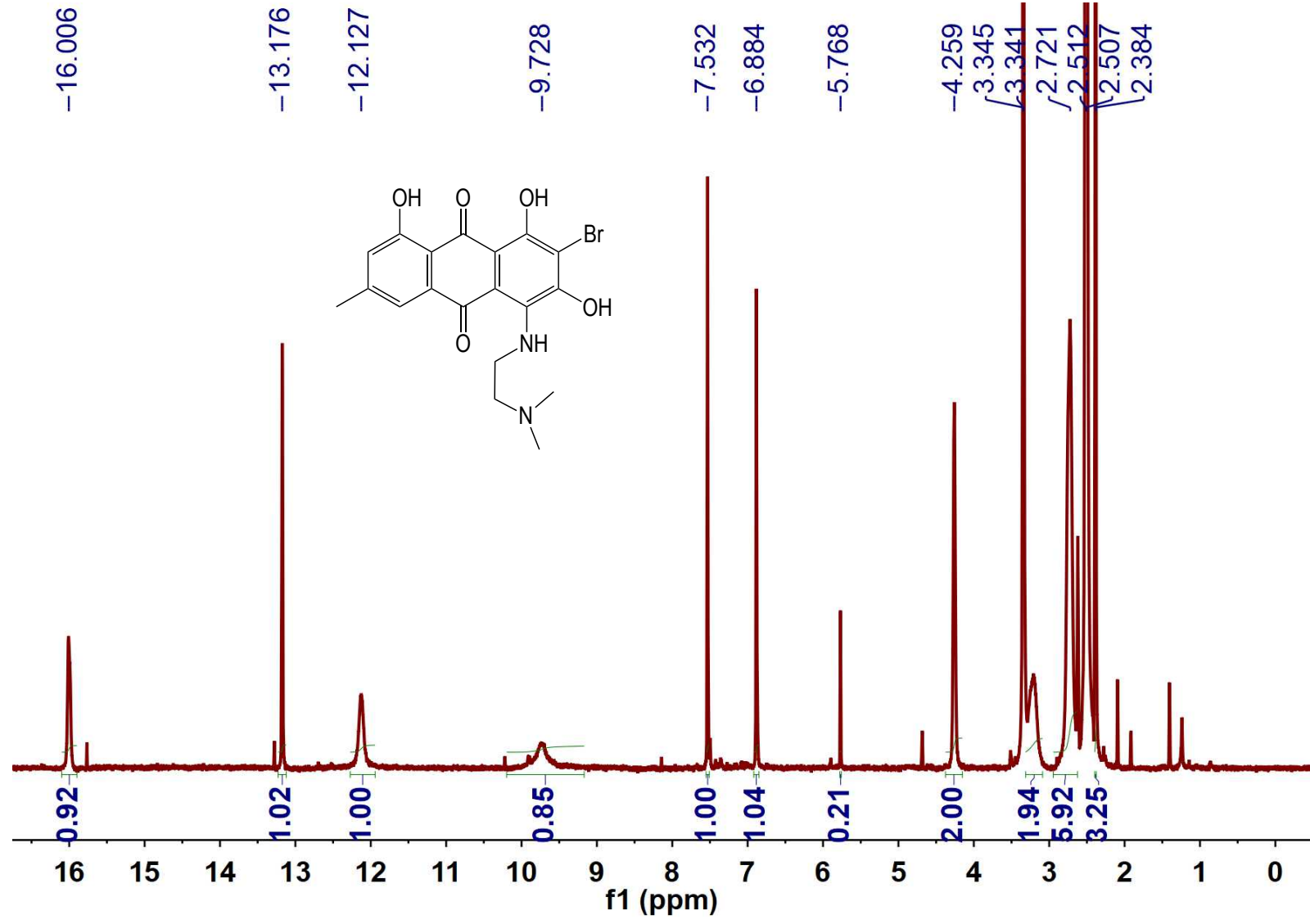


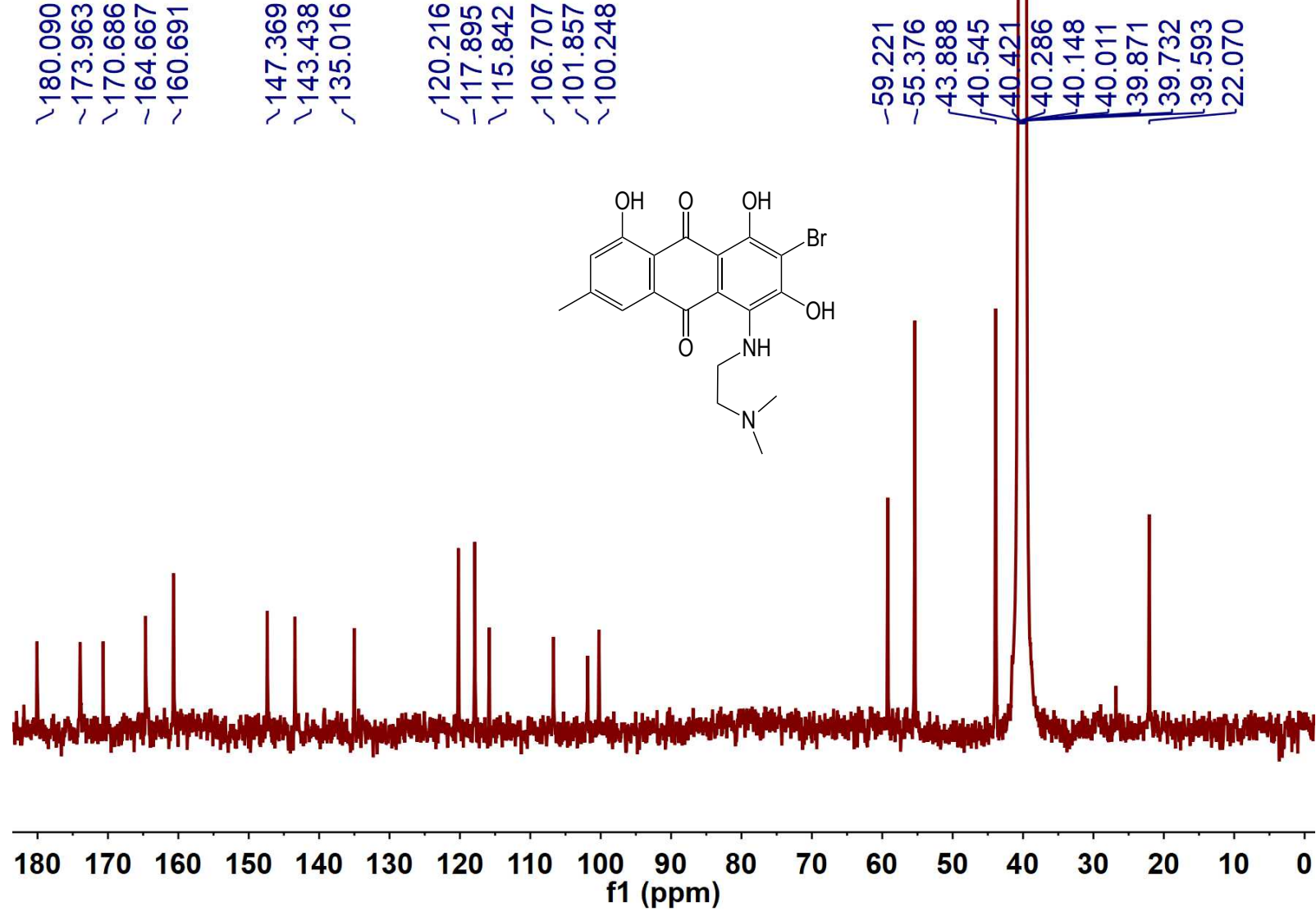
4.3.b.  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMF-}d_7$ ) spectrum of emodin-PA-1

4.4.a.  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ , 373 K) spectrum of emodin-PA-2

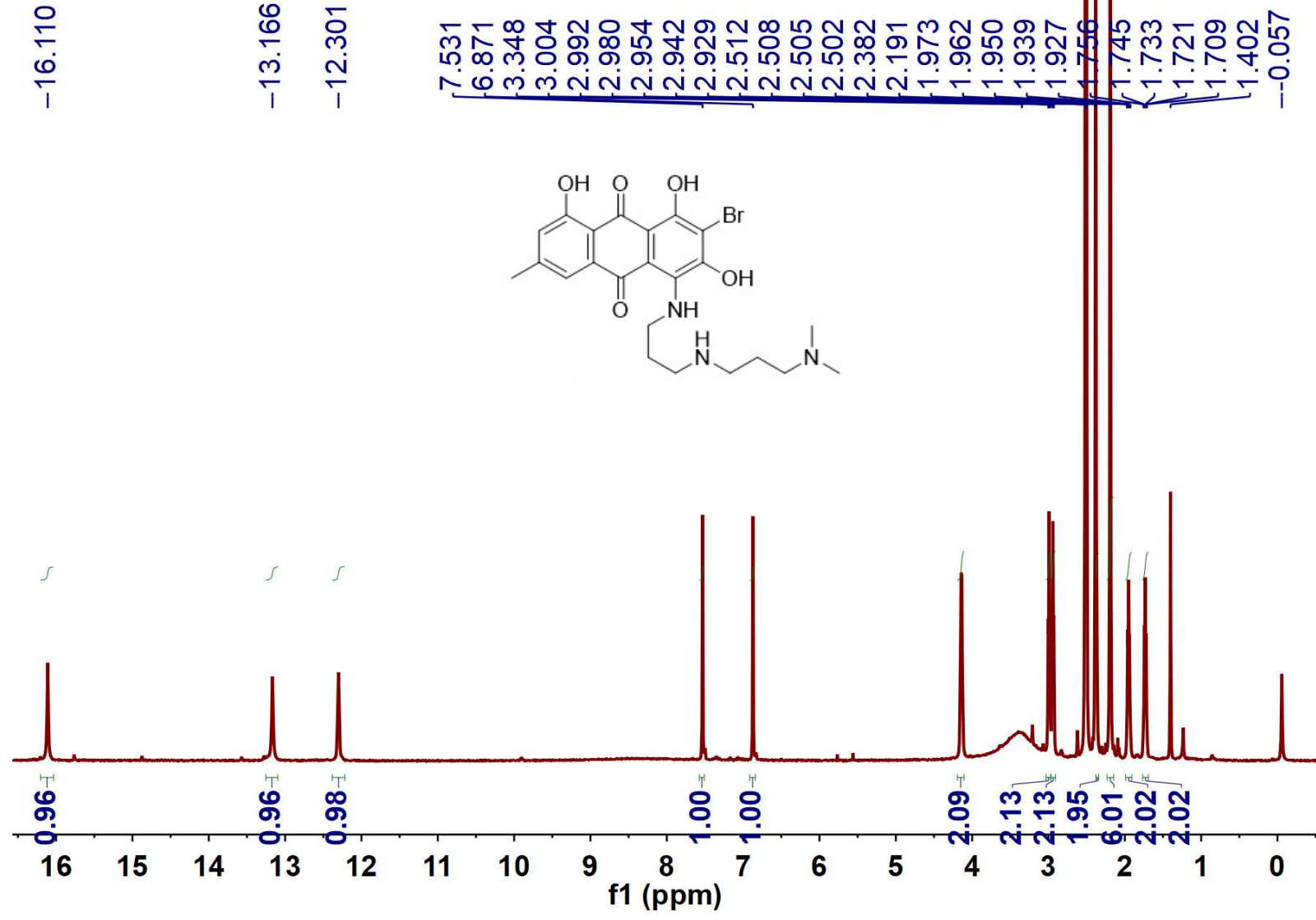
4.4.b. HMBC (600 MHz, DMSO-*d*<sub>6</sub>, 373 K) spectrum of emodin-P-A-2

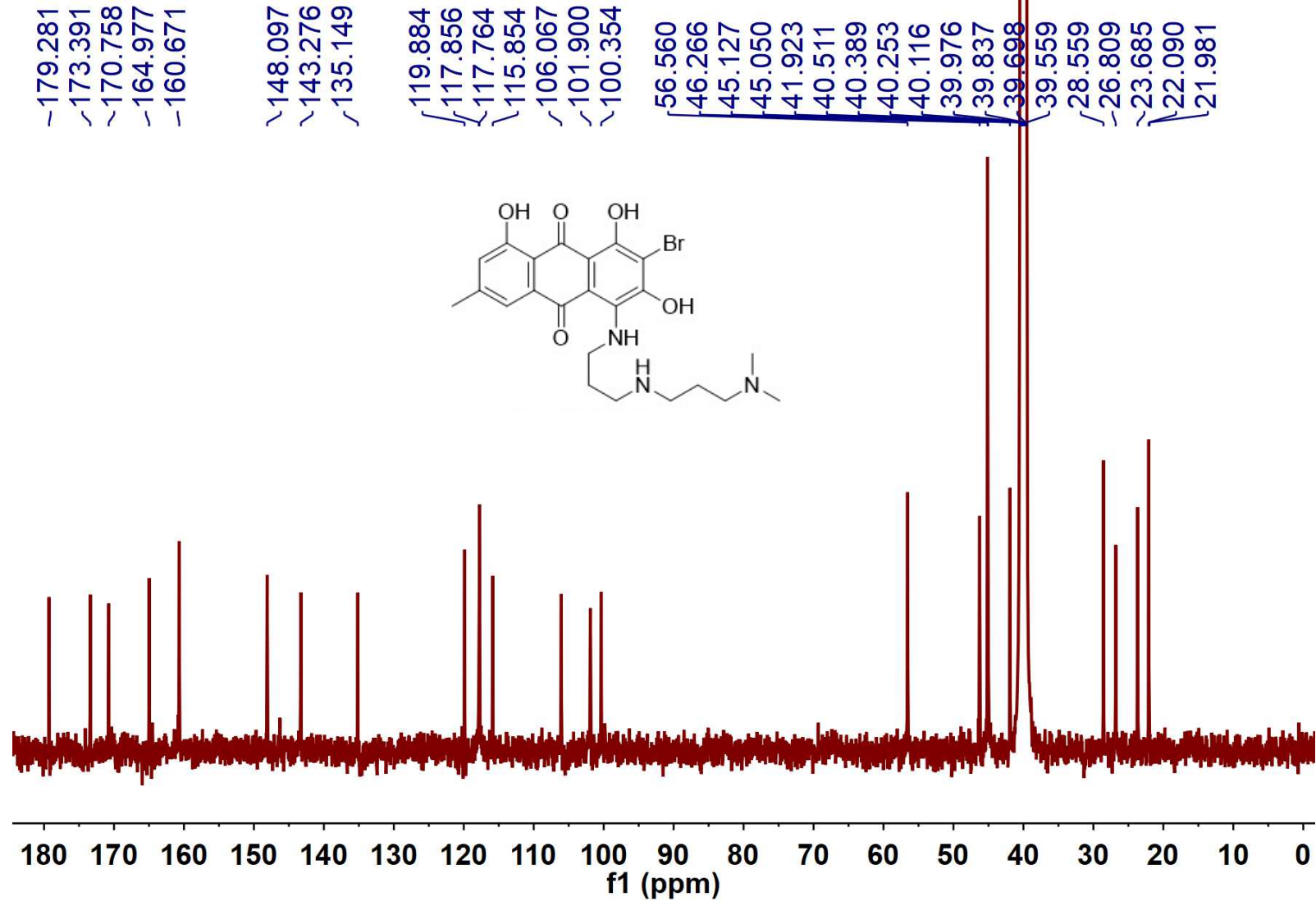


4.5.a. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) spectrum of emodin-PA-3



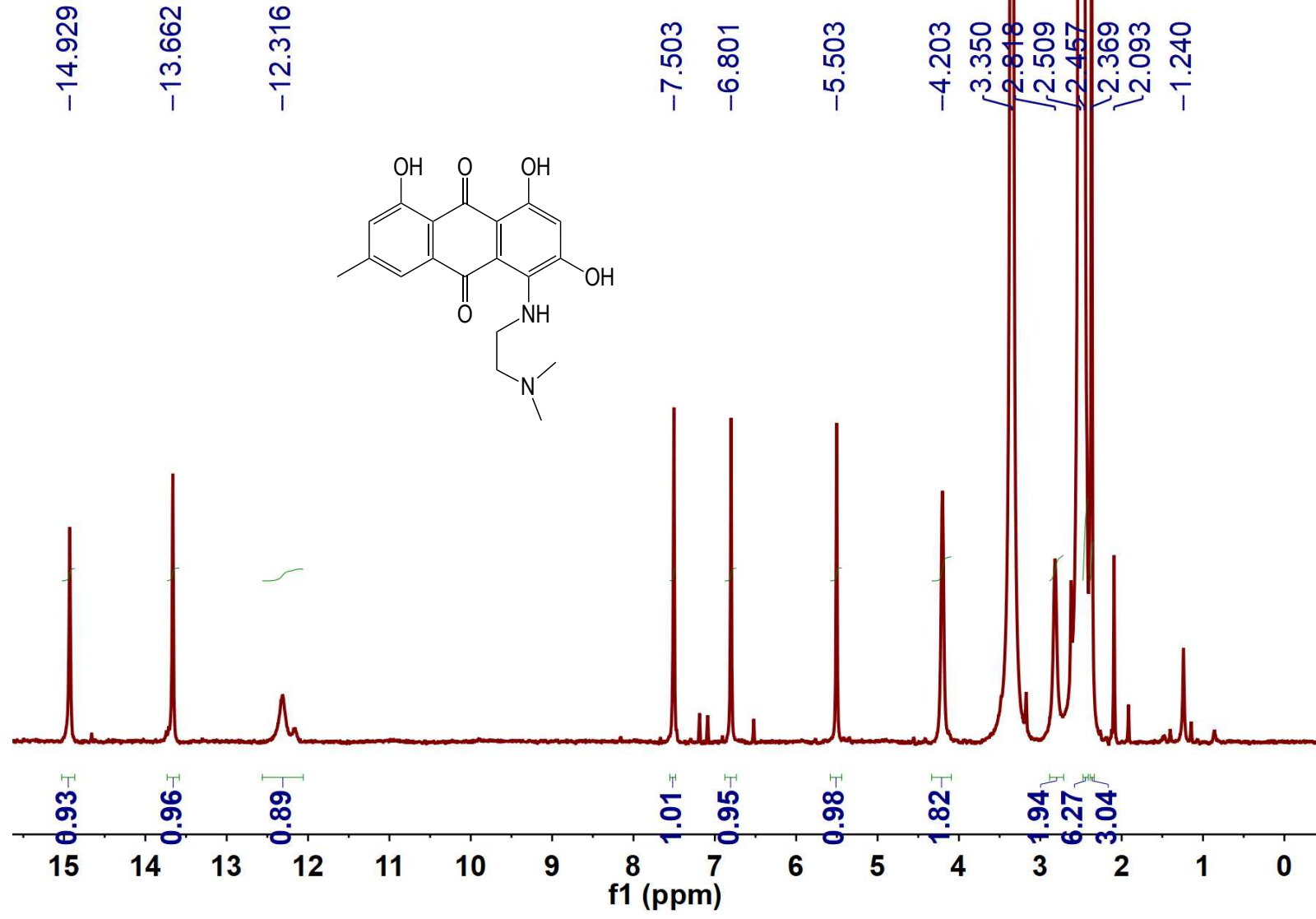
4.5.b. <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) spectrum of emodin-PA-3

4.6.a. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) spectrum of emodin-PA-4

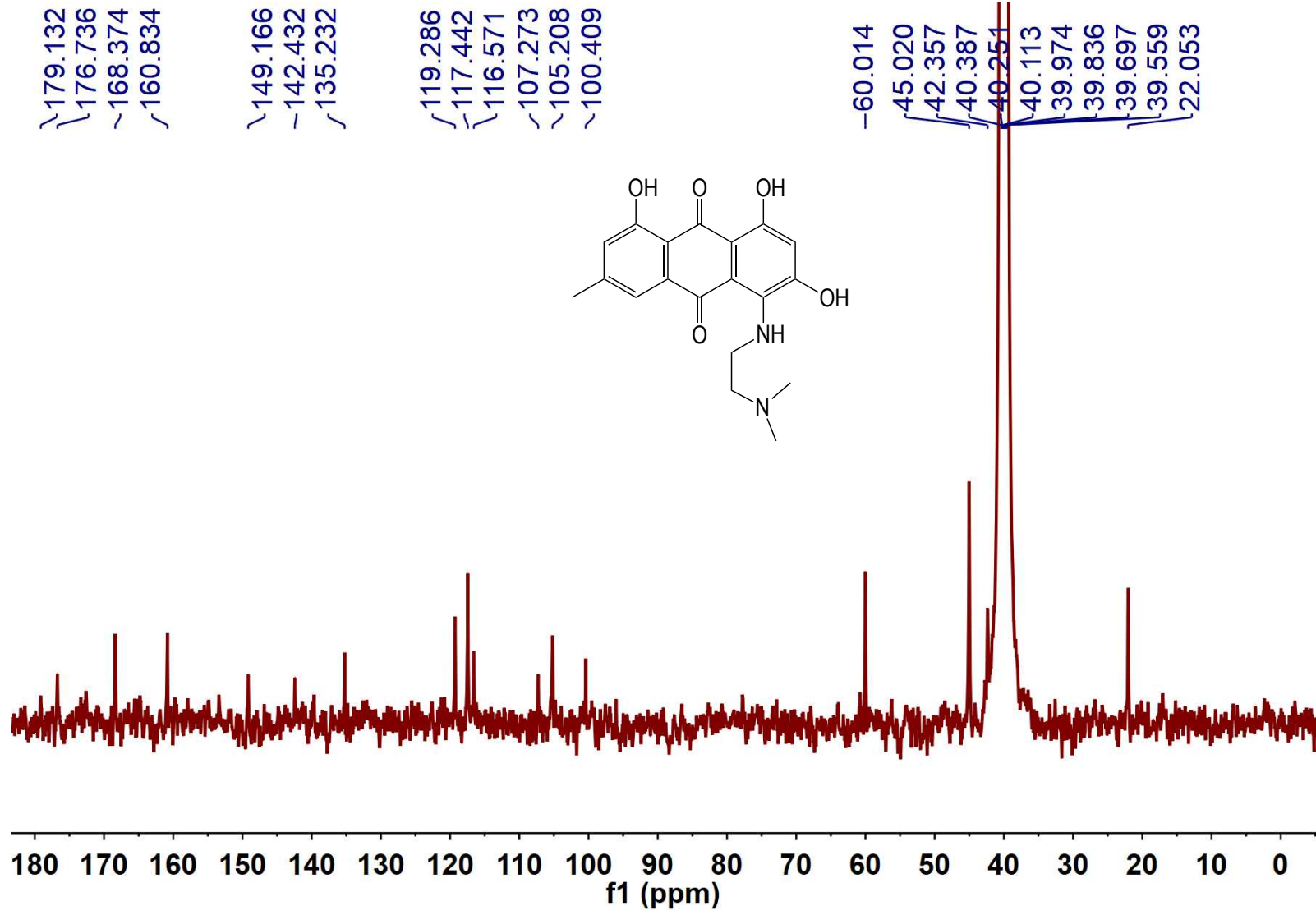


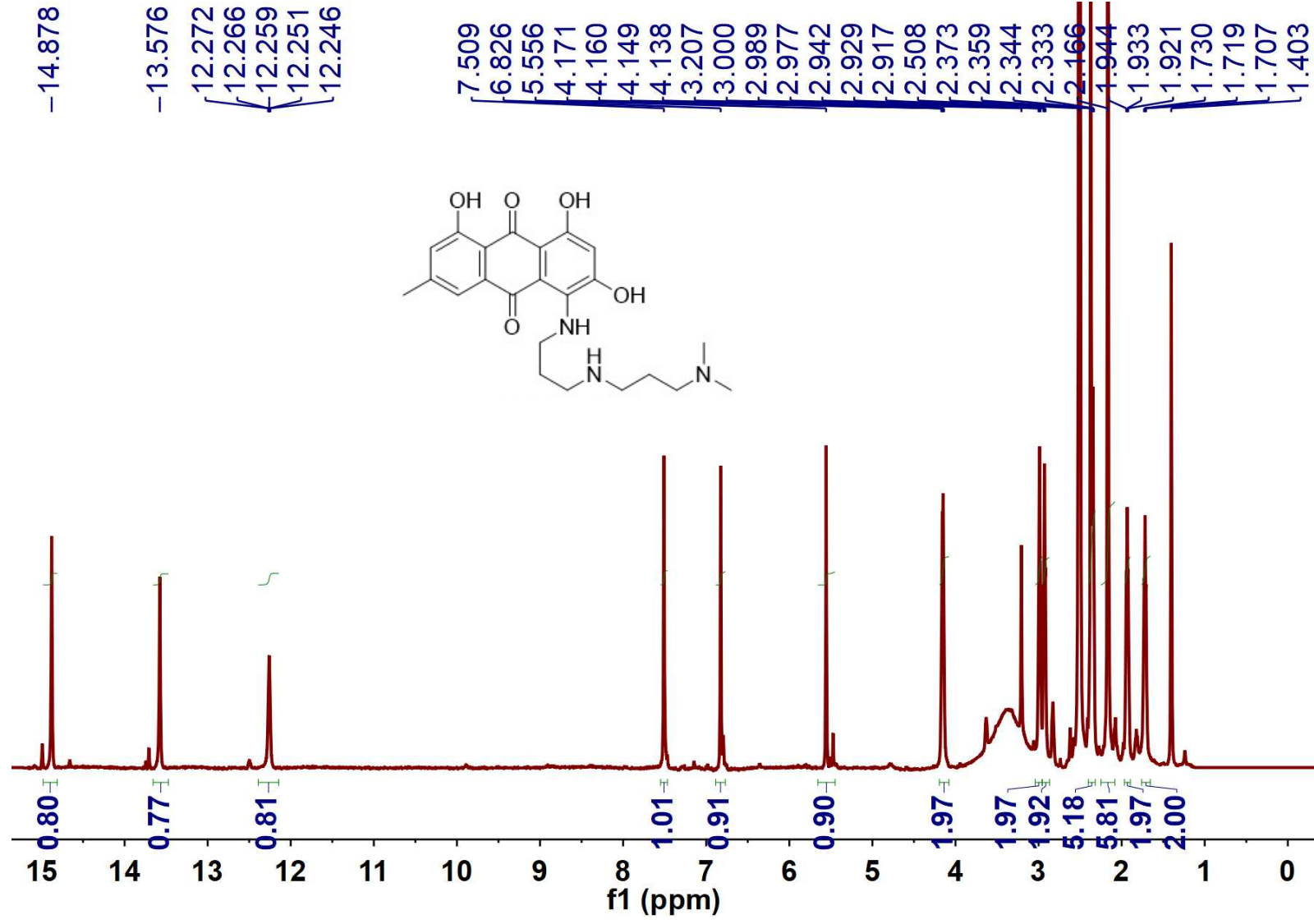
4.6.b.  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ) spectrum of emodin-PA4

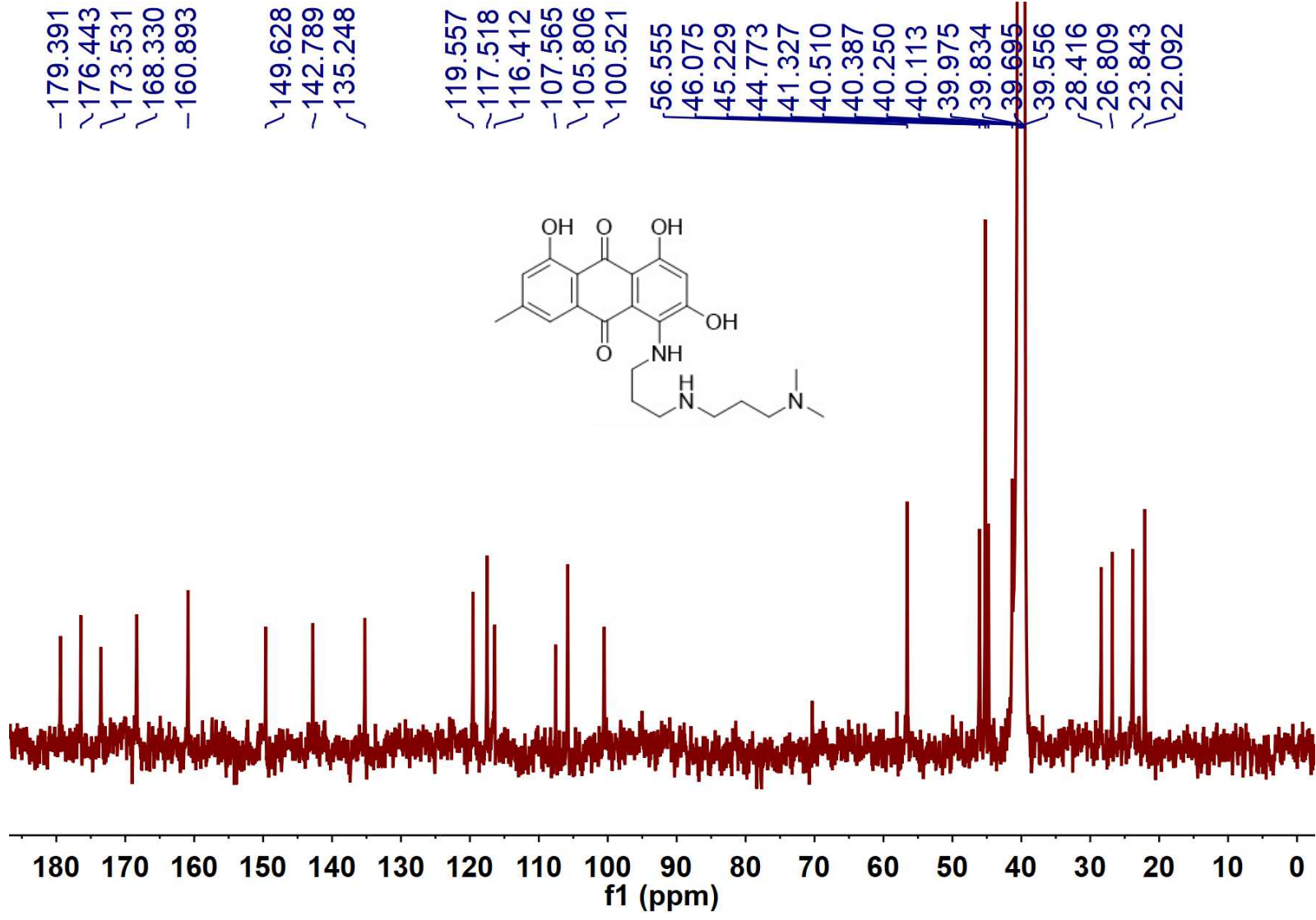


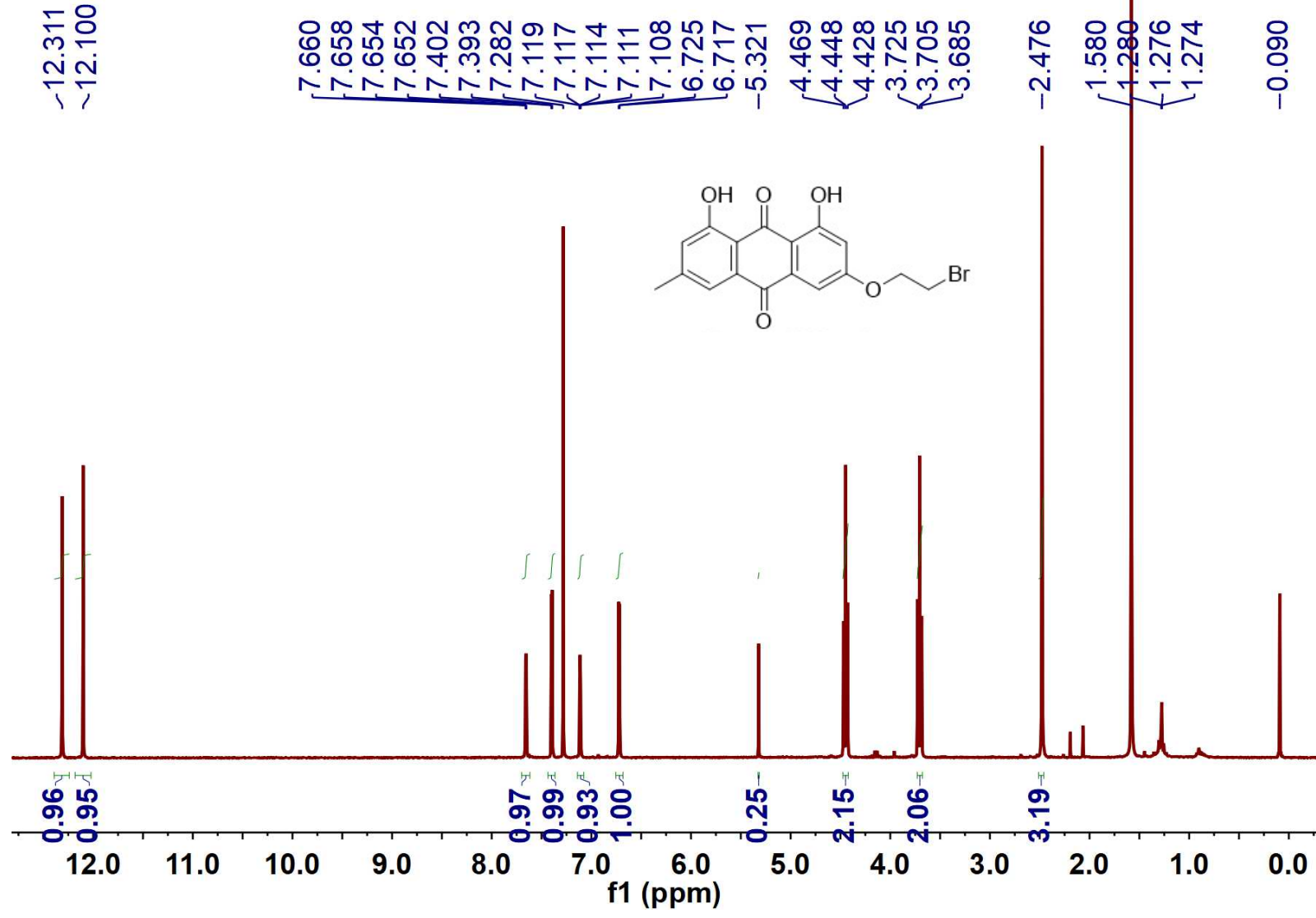
4.7.a. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) spectrum of emodin-PA-5

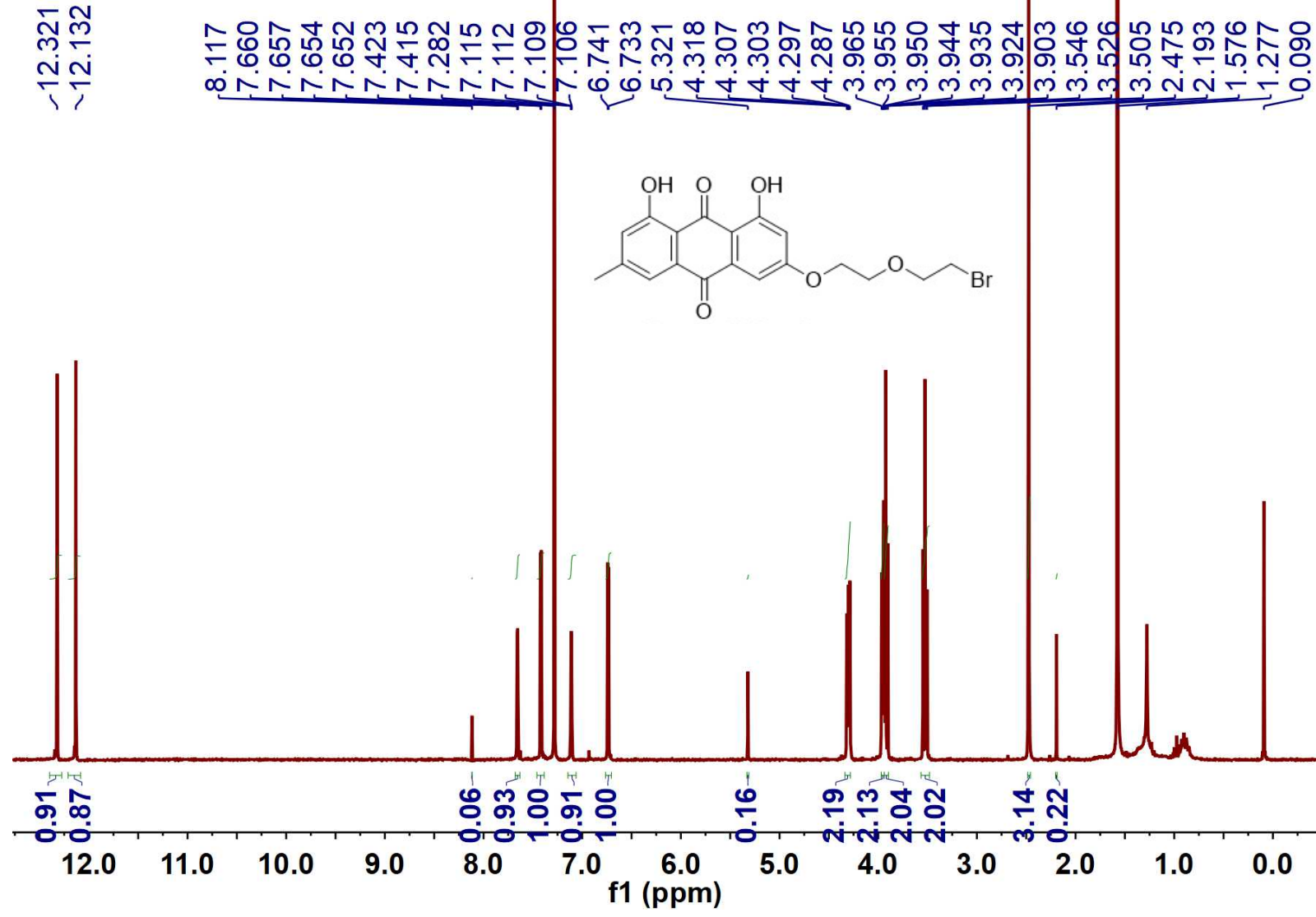


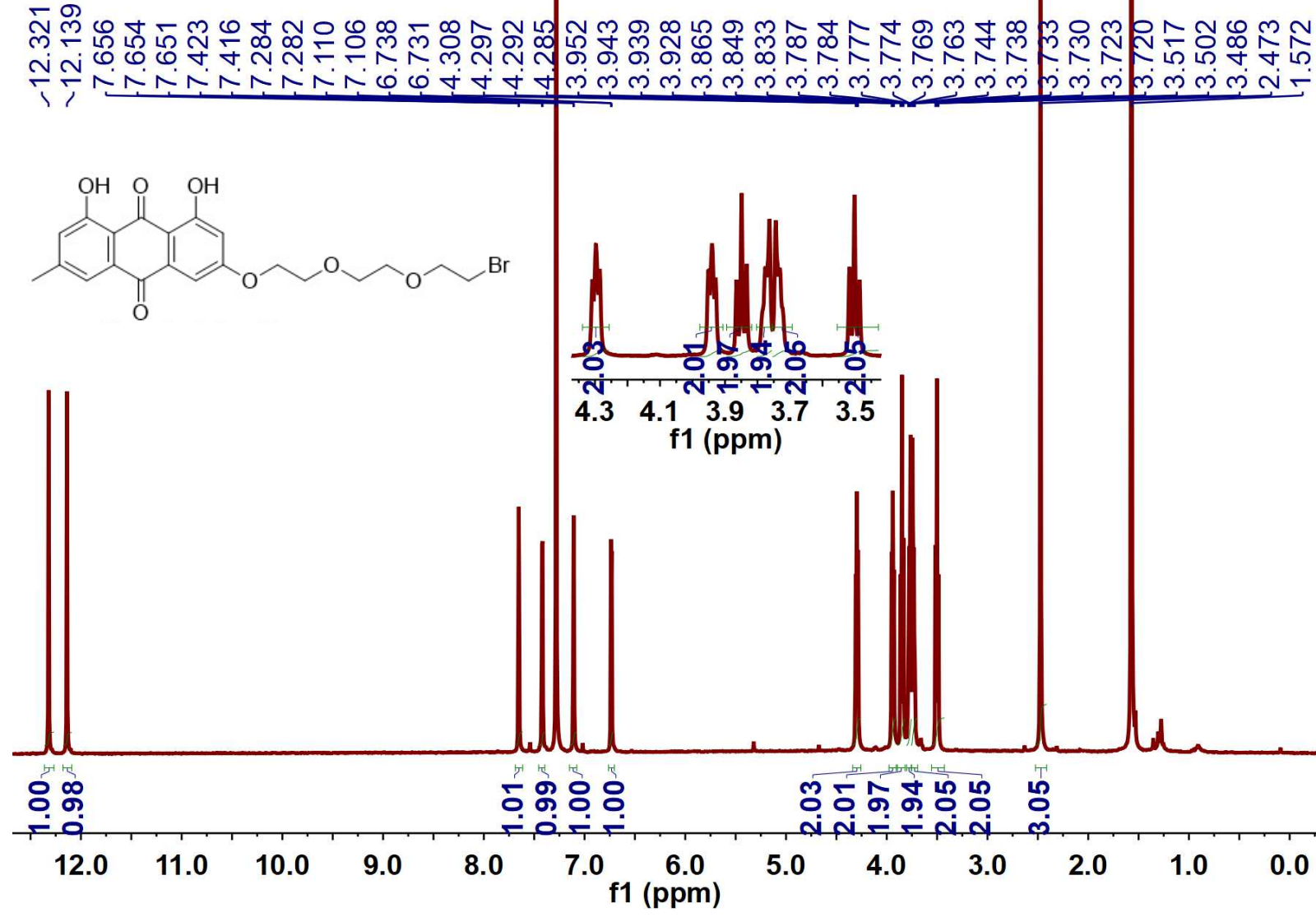
4.7.b.  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ) spectrum of emodin-PA-5

4.8.a. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) spectrum of emodin-PA-6

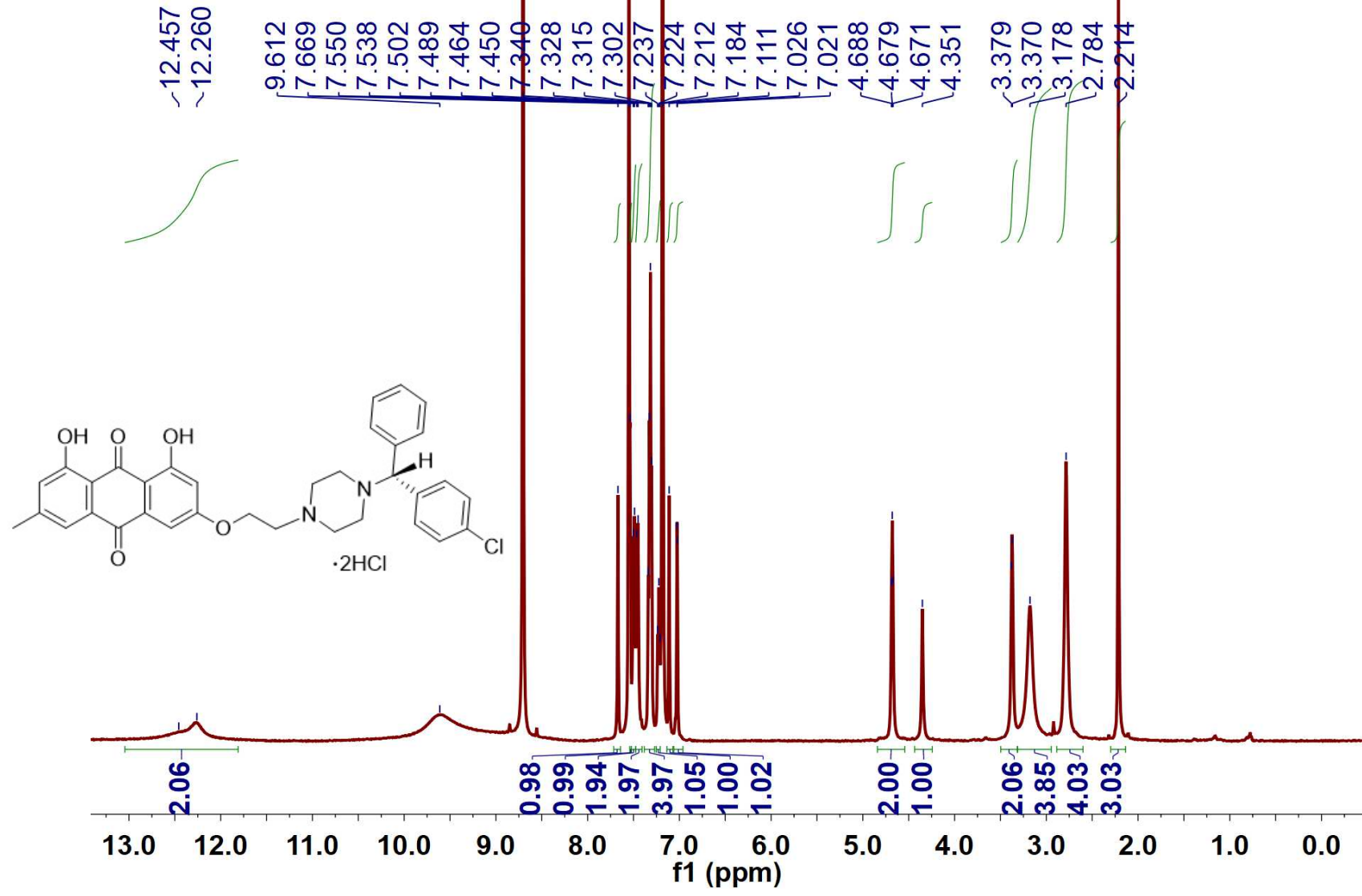


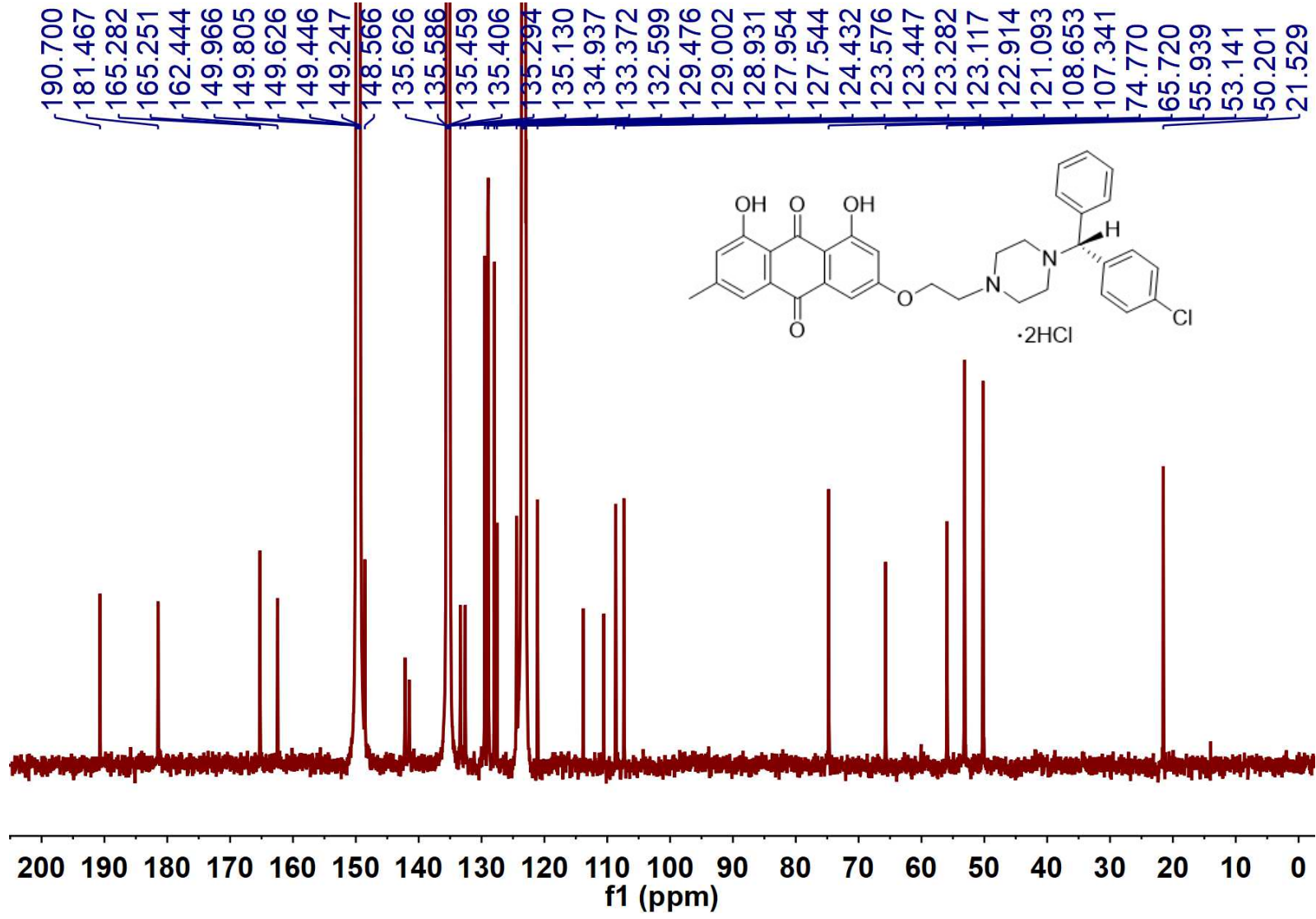
4.9.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) spectrum of emodin-link-1

4.10.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) spectrum of emodin-link-2

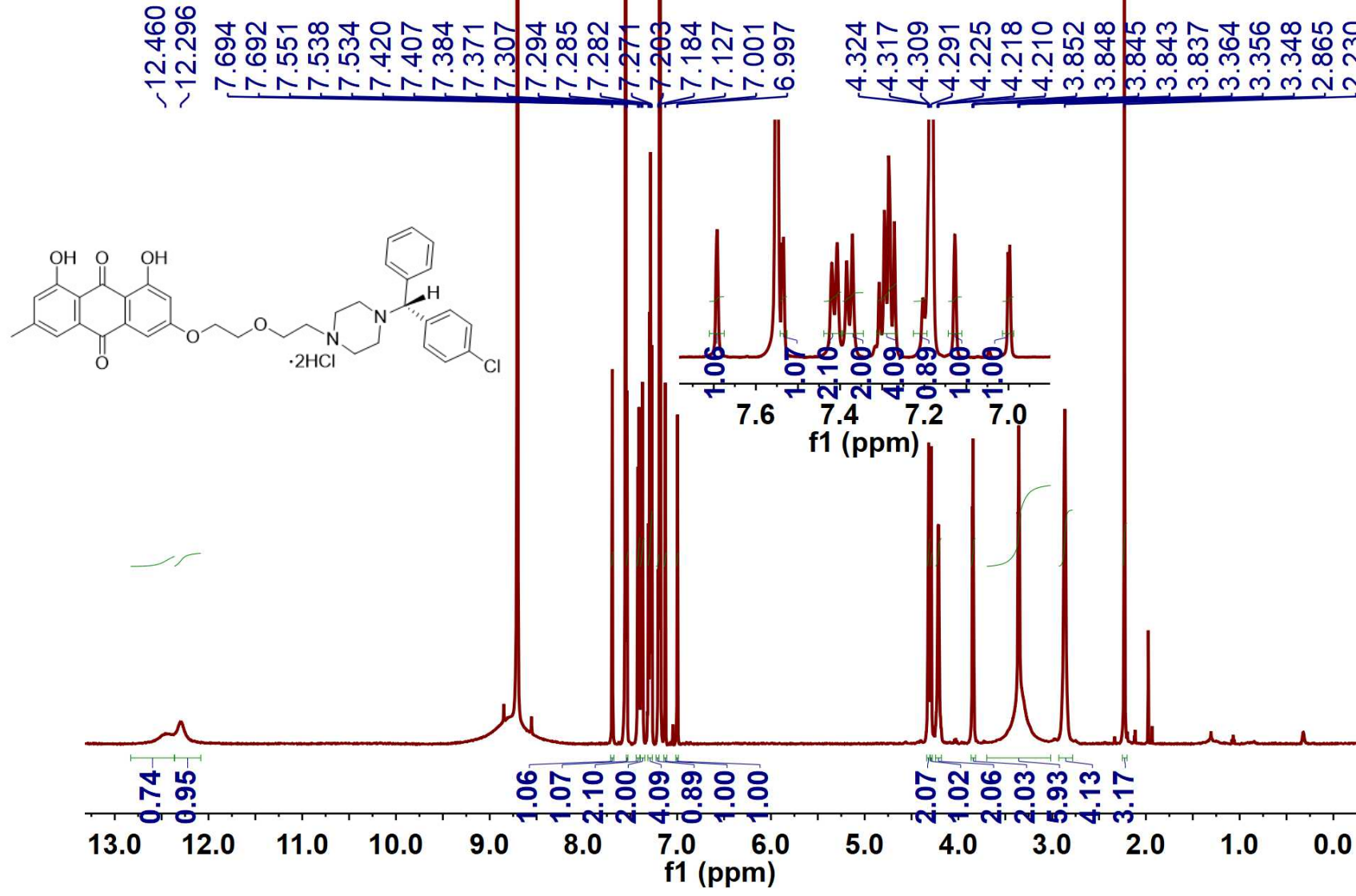
4.11. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of emodin-link-3

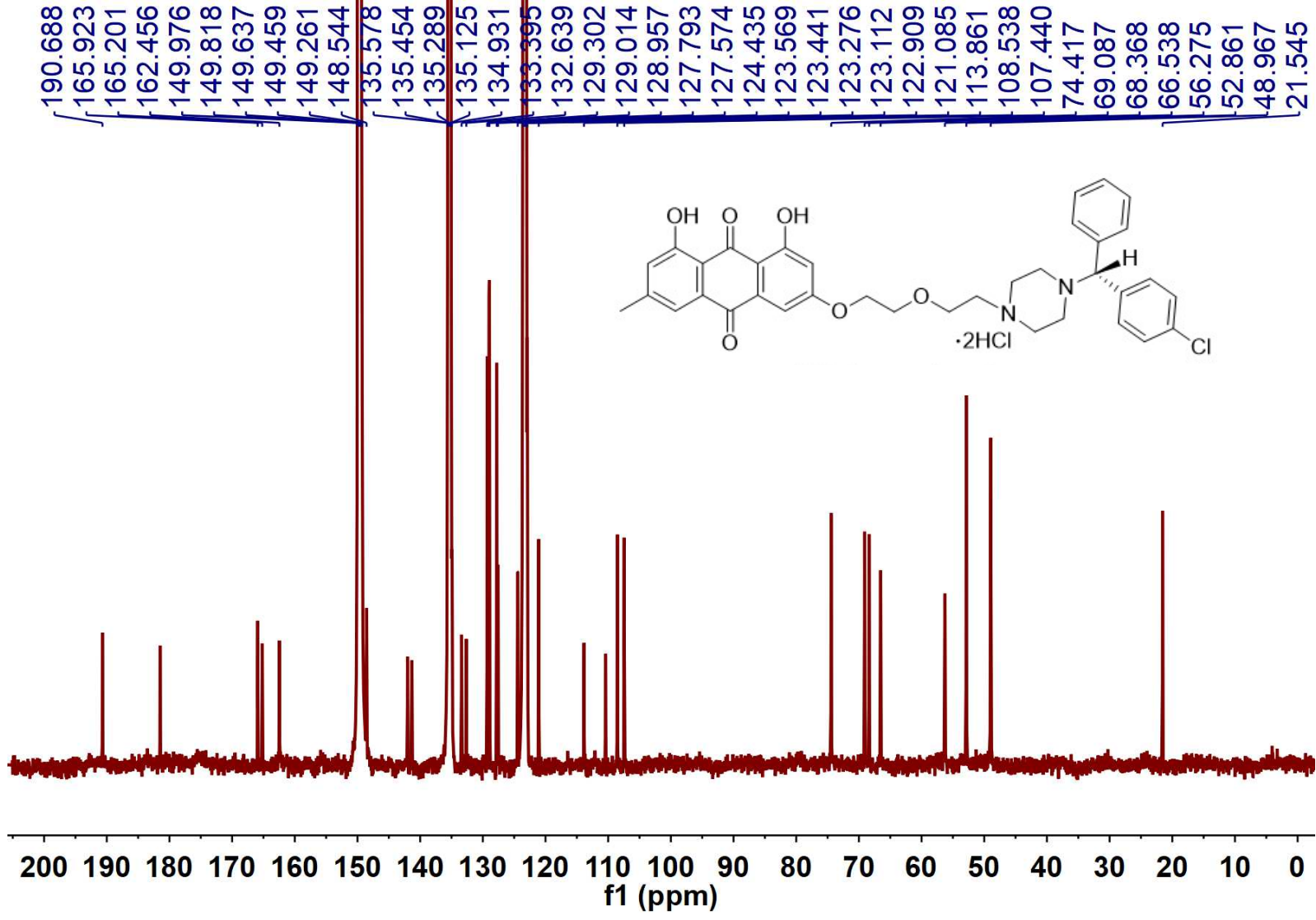


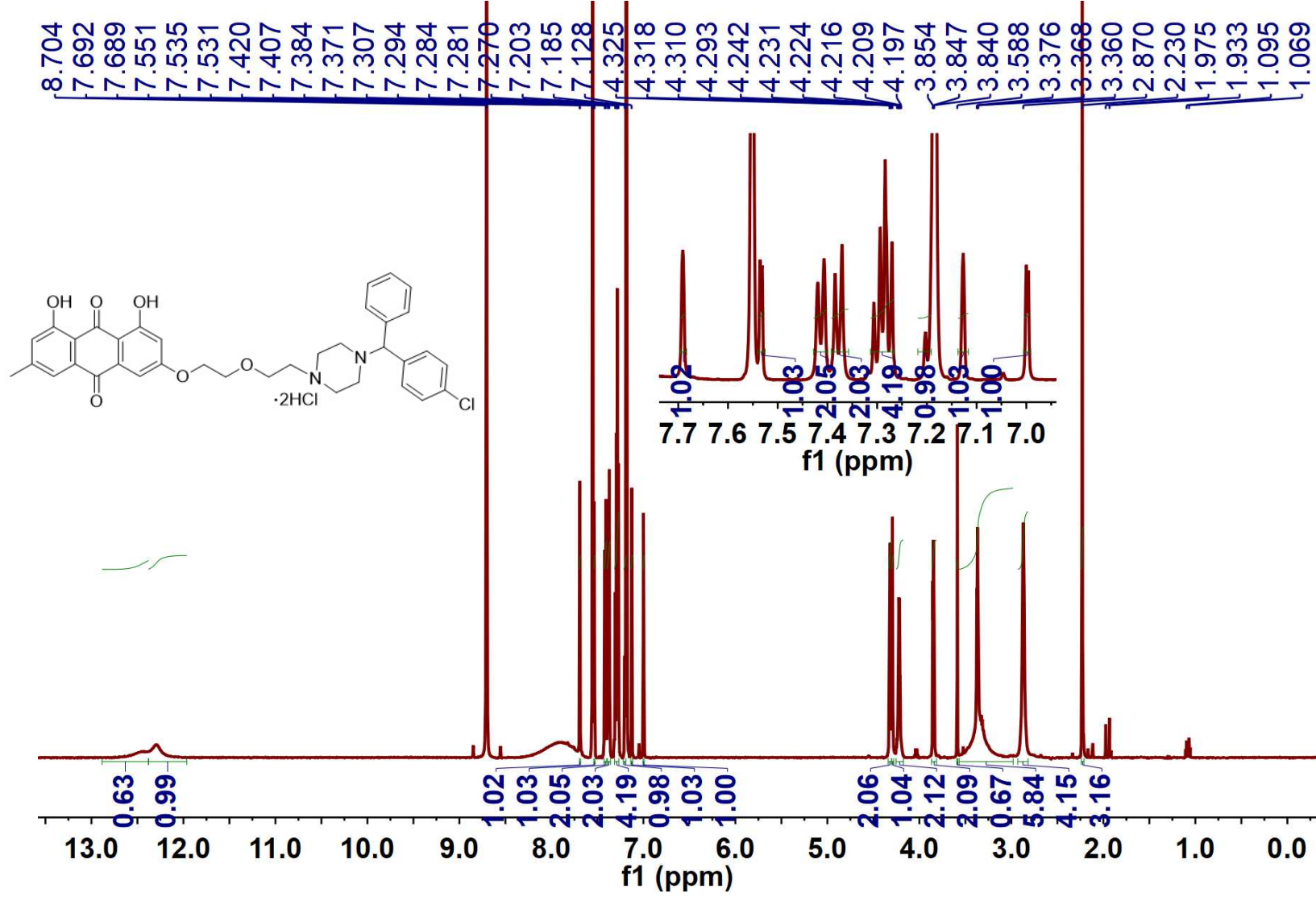
4.12.a. <sup>1</sup>H NMR (600 MHz, pyridine-*d*<sub>5</sub>) spectrum of (R)-emoxyzine-1

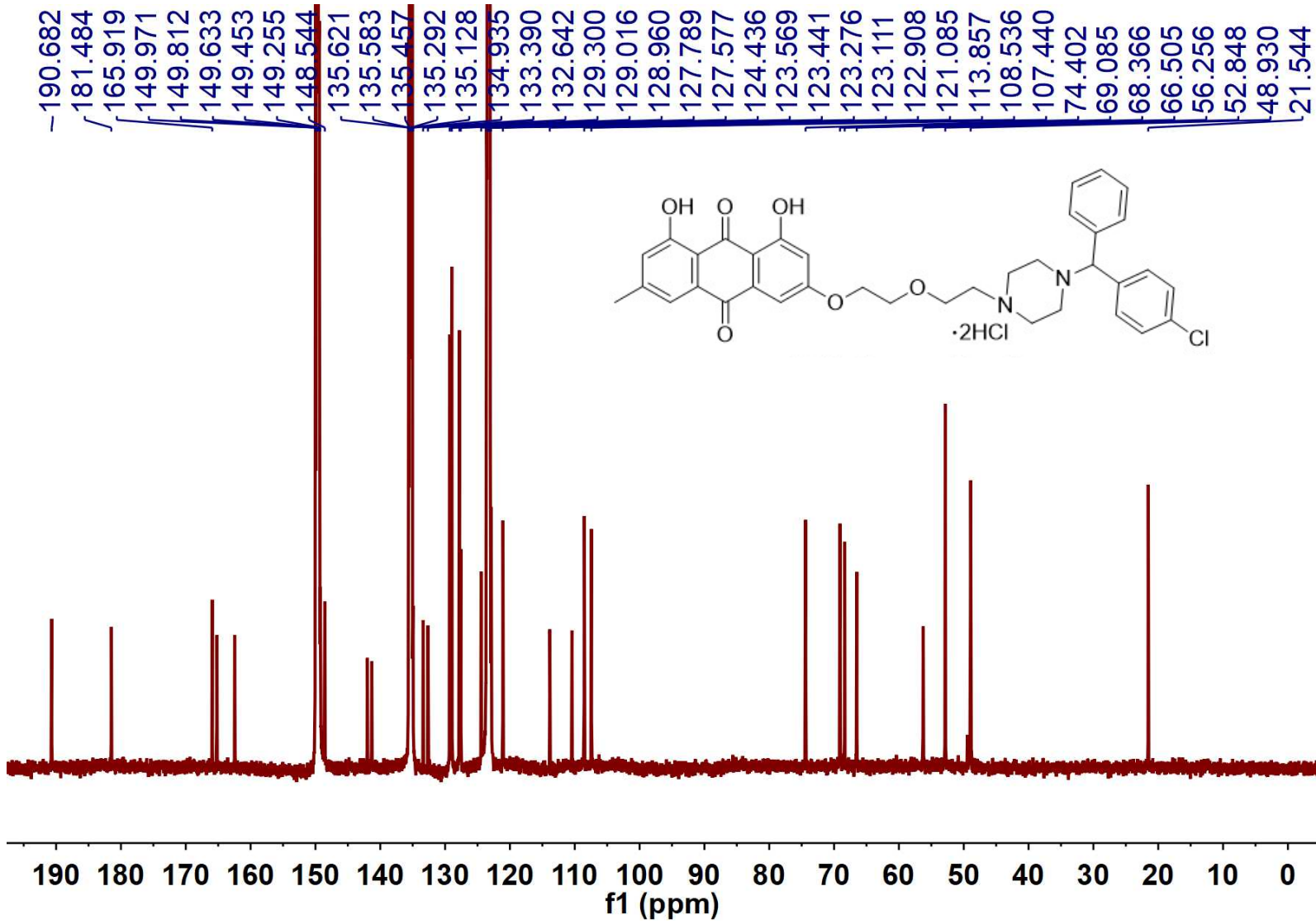
4.12.b.  $^{13}\text{C}$  NMR (150 MHz, pyridine- $d_5$ ) spectrum of (R)-emoxyzine-1

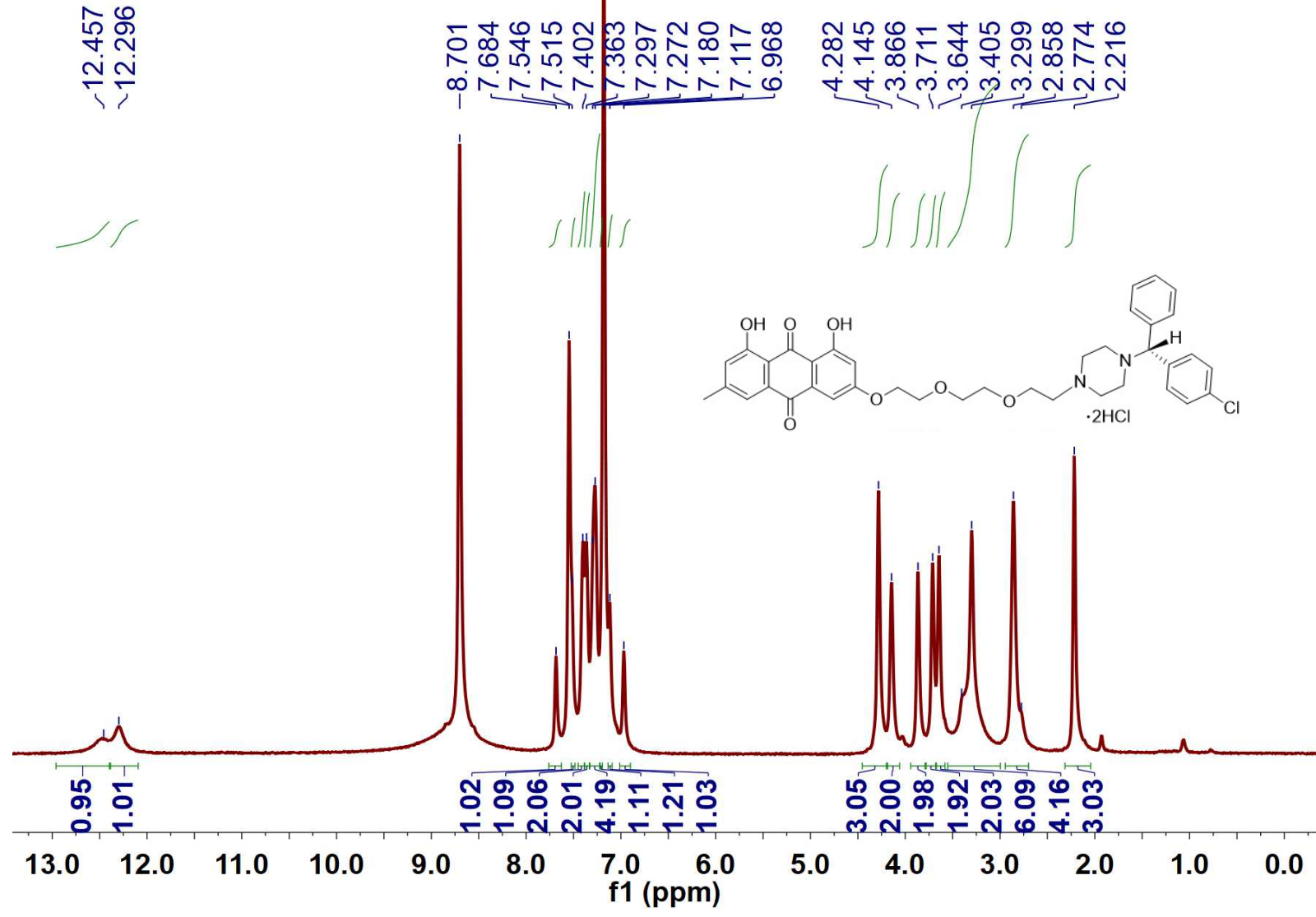


4.13.a. <sup>1</sup>H NMR (600 MHz, pyridine-*d*<sub>5</sub>) spectrum of (*R*)-emoxyzine-2

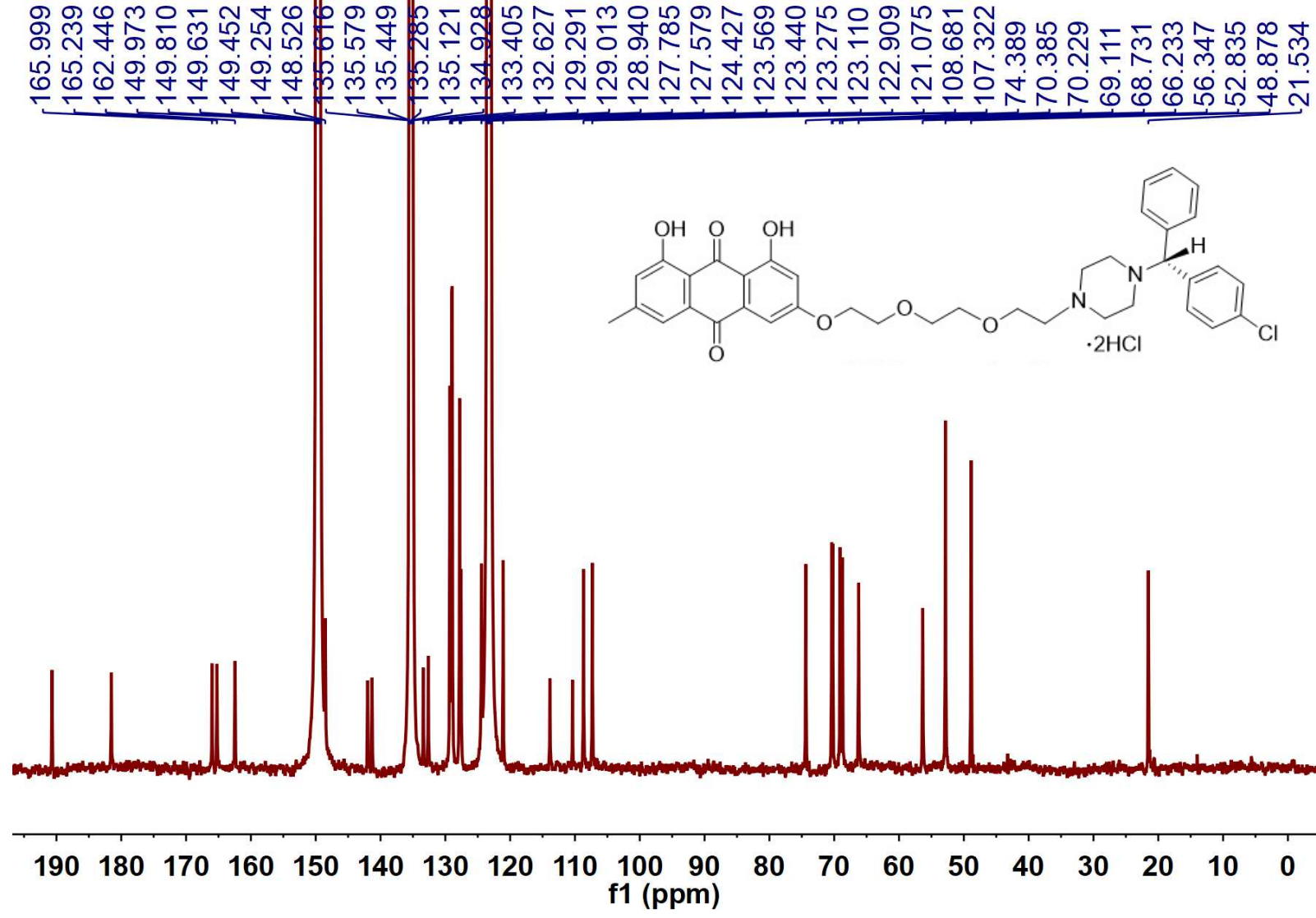
4.13.b.  $^{13}\text{C}$  NMR (150 MHz, pyridine- $d_5$ ) spectrum of (R)-emoxyzine-2

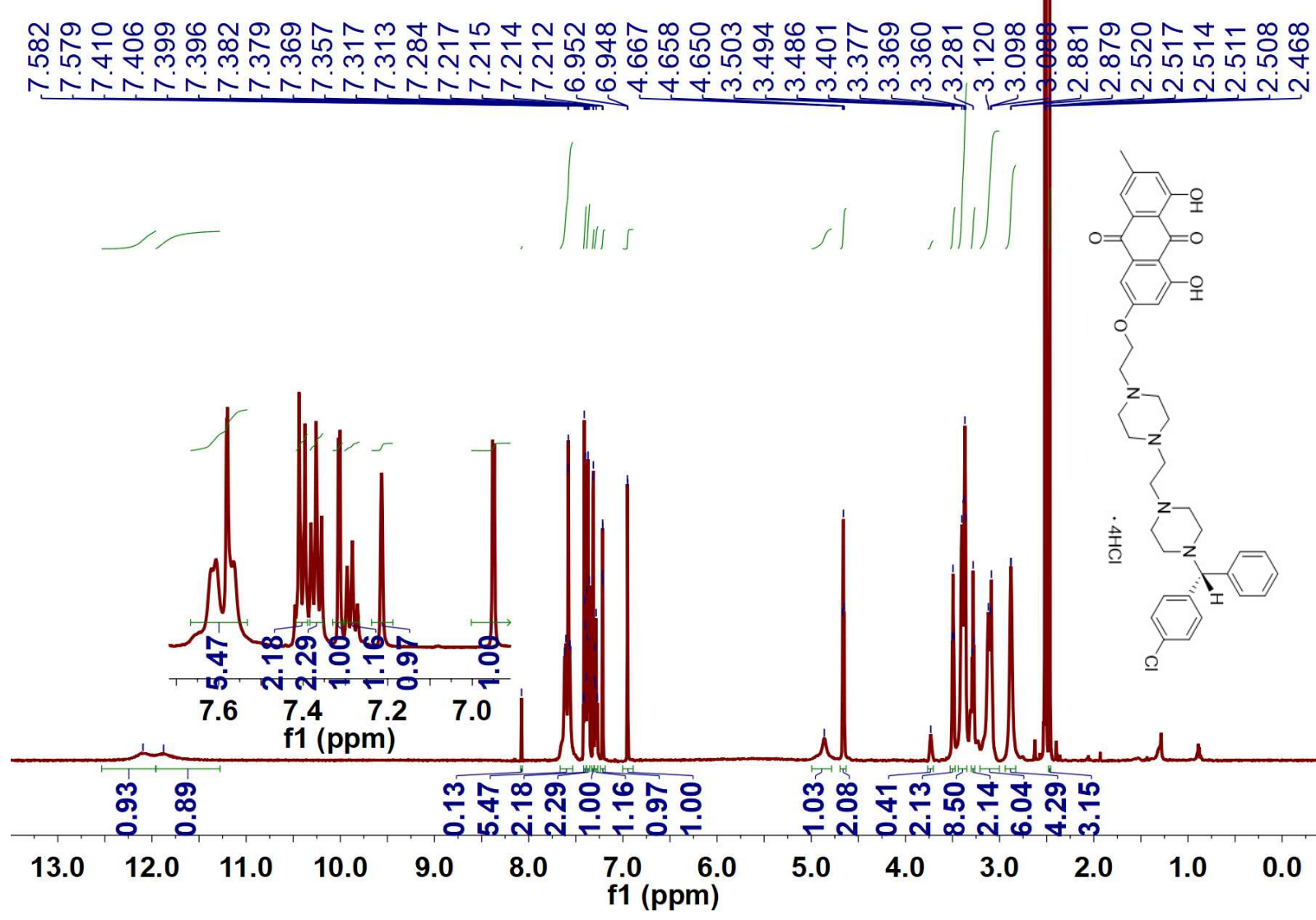


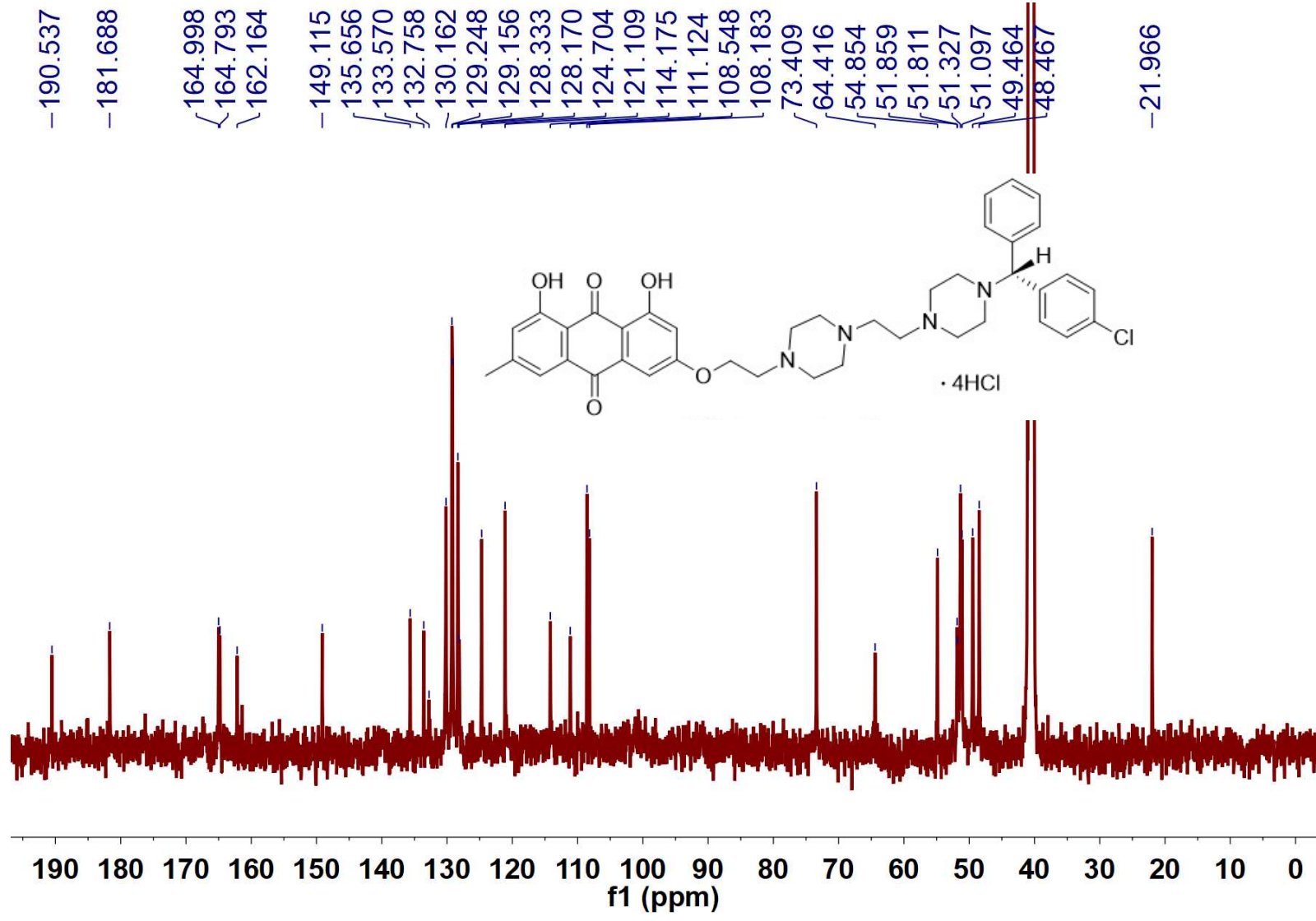
4.14.b.  $^{13}\text{C}$  NMR (150 MHz, pyridine- $d_5$ ) spectrum of (R,S)-emoxazine-2

4.15.a. <sup>1</sup>H NMR (600 MHz, pyridine-*d*<sub>5</sub>) spectrum of (*R*)-emoxazine-3



4.15.b.  $^{13}\text{C}$  NMR (150 MHz, pyridine- $d_5$ ) spectrum of (*R*)-emoxyzine-3

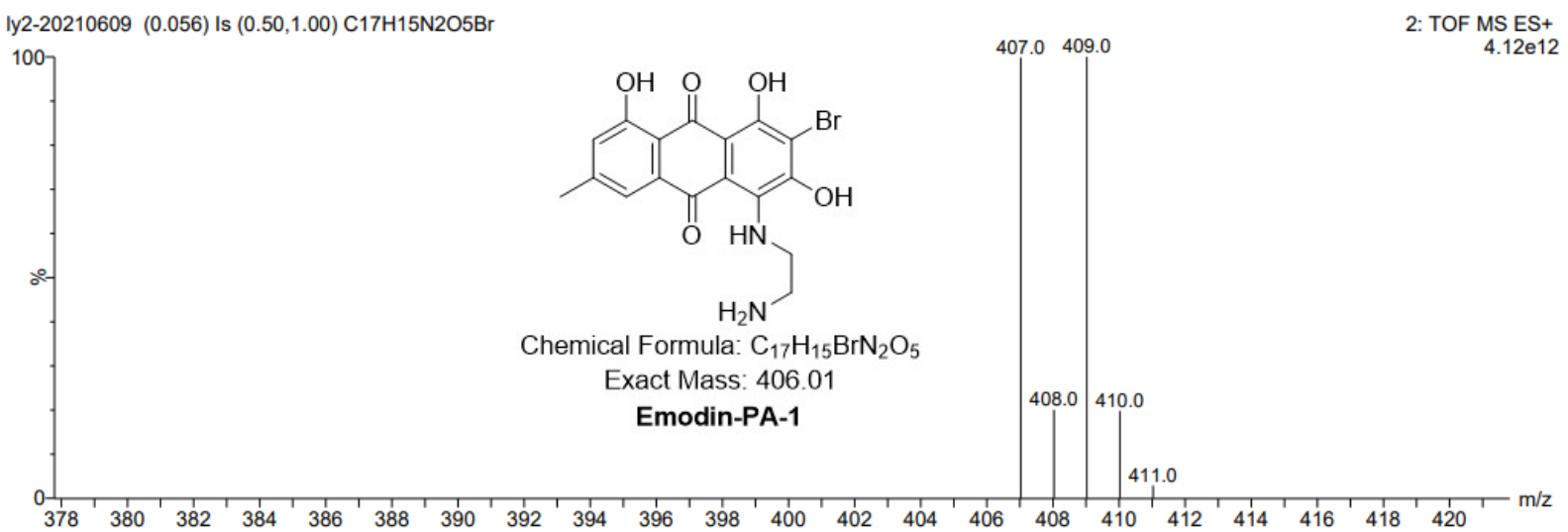
4.16.a.  $^1\text{H}$  NMR (600 MHz, pyridine- $d_5$ ) spectrum of (R)-emoxyzine-7

4.16.b.  $^{13}\text{C}$  NMR (150 MHz, pyridine- $d_3$ ) spectrum of (R)-emoxyzine-7

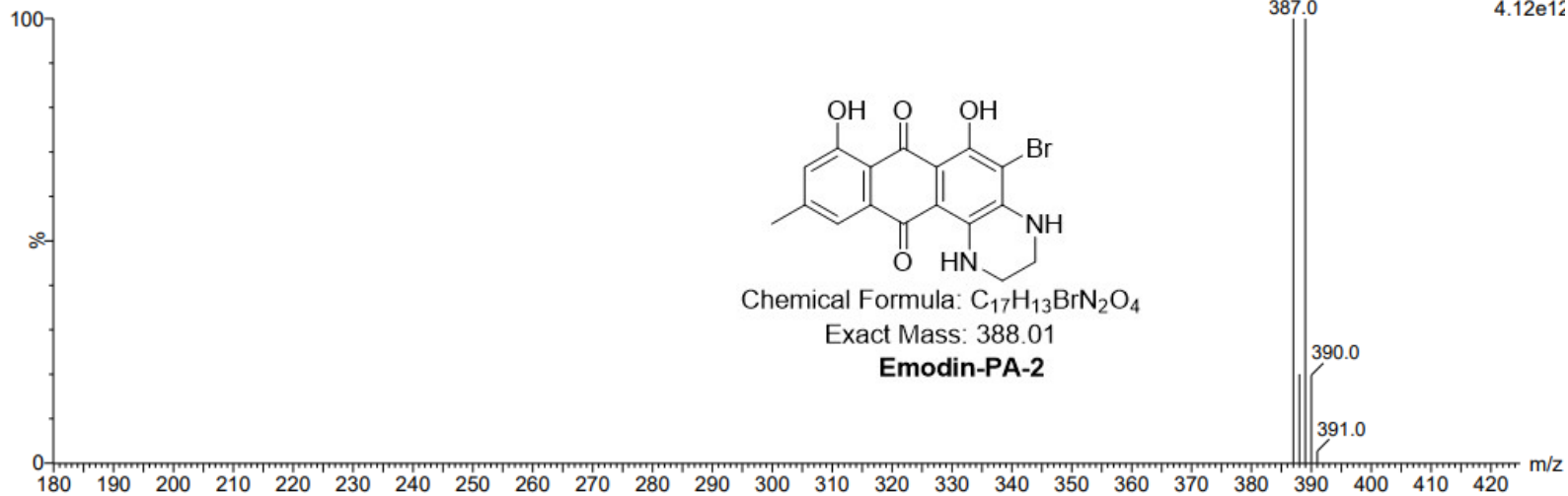


## 5. Mass spectra of emodin-PA and emoxyzine derivatives

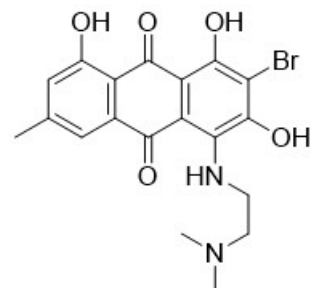
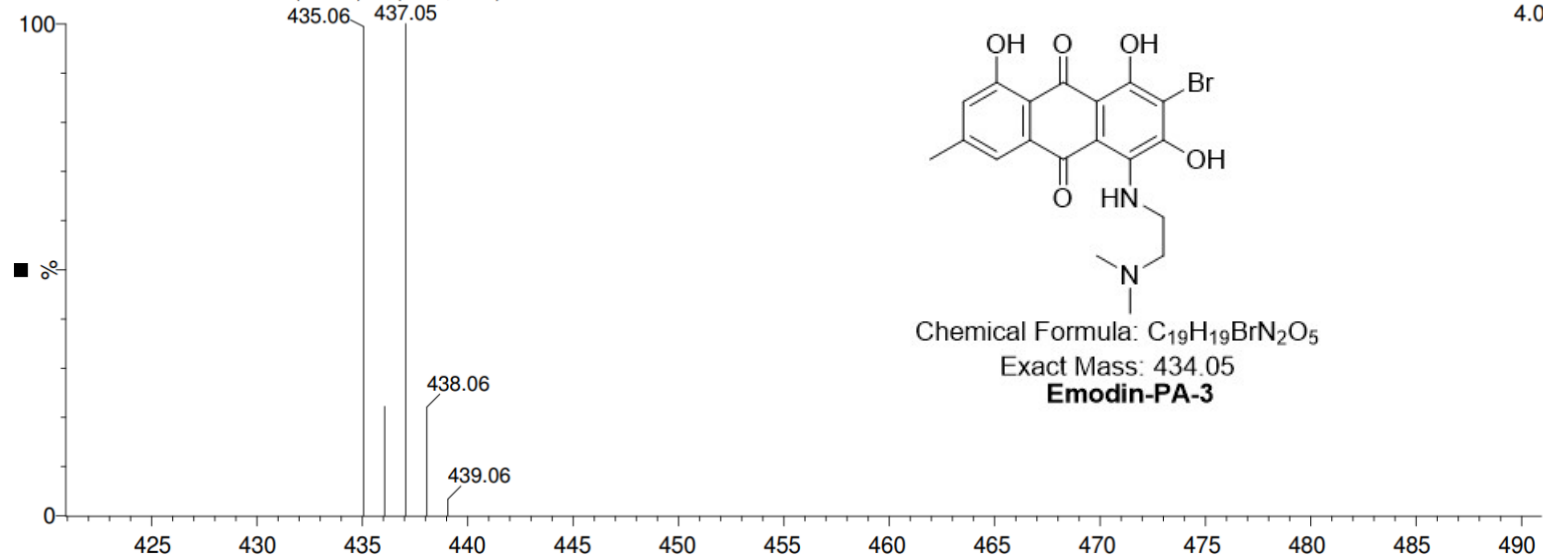
### 5.1. MS (ESI<sup>+</sup>) of emodin-PA-1



ly2-20210603a-A-neg (0.031) Is (0.50,1.00) C<sub>17</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>Br



20210517-LY2-20210427b (0.017) Is (1.00,1.00) C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>Br



Chemical Formula: C<sub>19</sub>H<sub>19</sub>BrN<sub>2</sub>O<sub>5</sub>

Exact Mass: 434.05

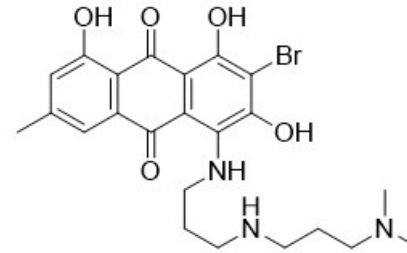
**Emodin-PA-3**

TOF MS Cl<sup>+</sup>  
4.04e12

5.3. MS (DCI<sup>+</sup>-CH<sub>4</sub>) of emodin-PA-3

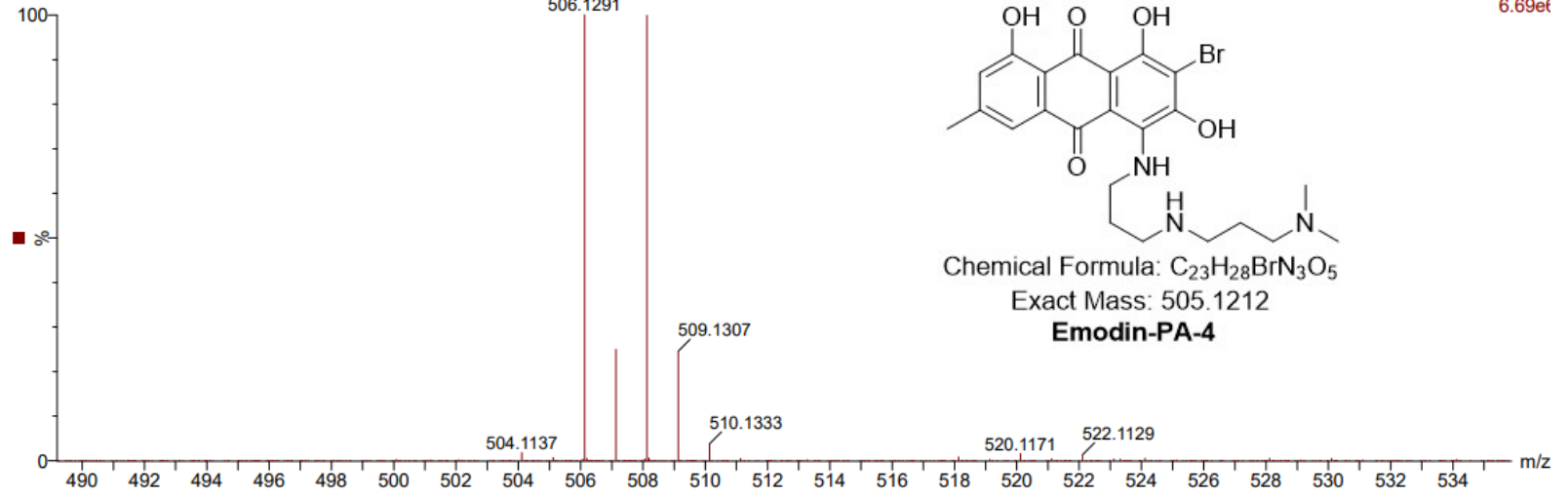
5.4. HRMS (ESI<sup>+</sup>) of emodin-PA-4

1: TOF MS ES+  
6.69e6



Chemical Formula: C<sub>23</sub>H<sub>28</sub>BrN<sub>3</sub>O<sub>5</sub>  
Exact Mass: 505.1212  
**Emodin-PA-4**

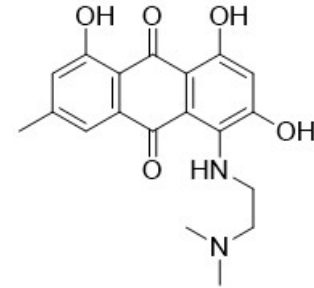
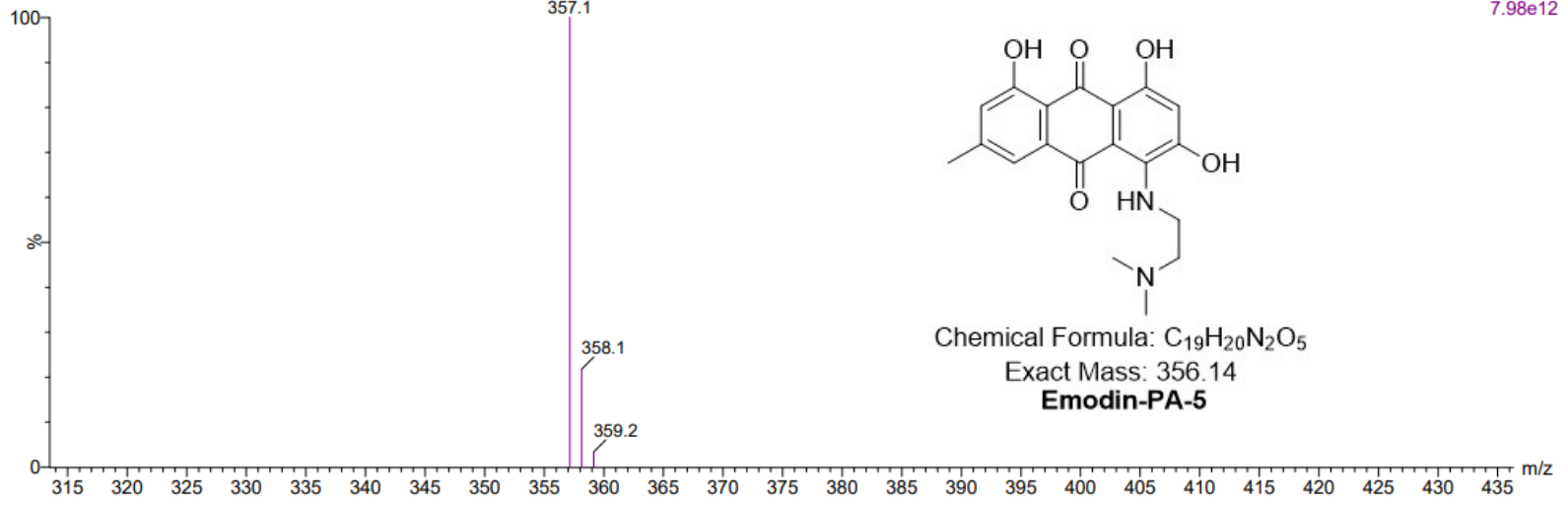
ly2-20210510 83 (0.526) AM2 (Ar,20000.0,0.00,0.00); Cm (77:91-34:61x2.000)



5.5. MS (ESI<sup>+</sup>) of emodin-PA-5

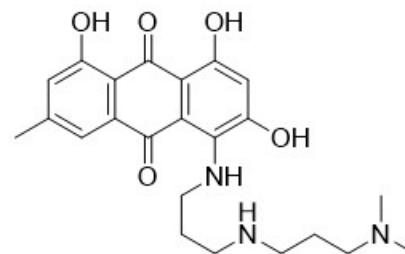
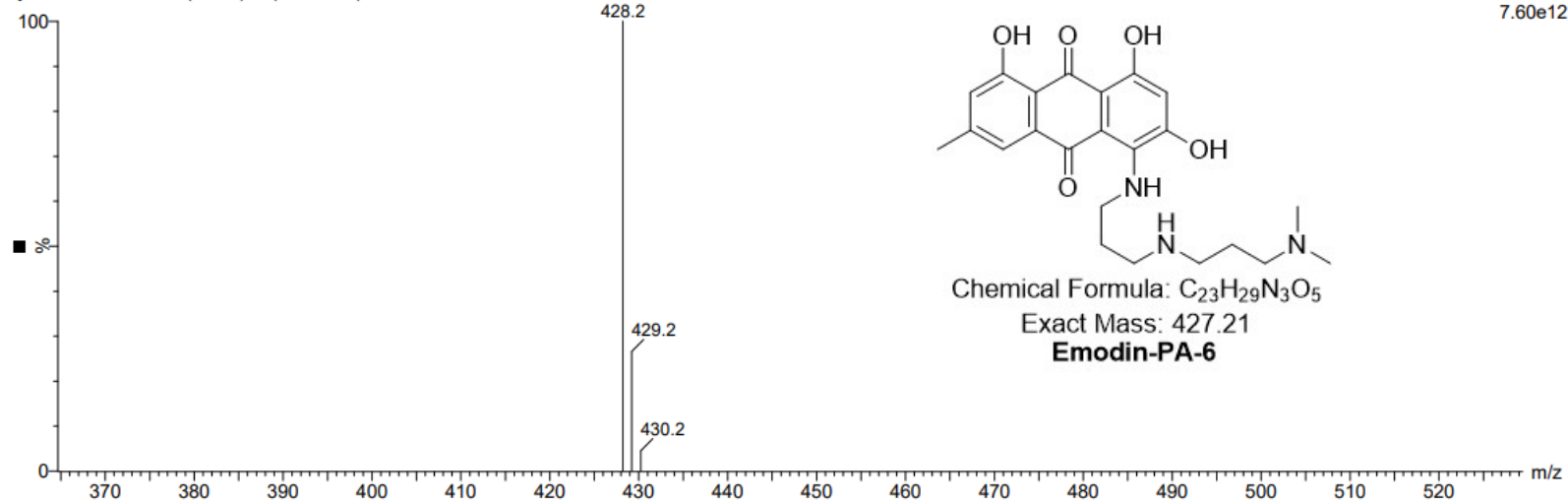
1: TOF MS ES+  
7.98e12

ly2-20210506-purple (0.031) Is (1.00,1.00) C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>



Chemical Formula: C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>  
Exact Mass: 356.14  
**Emodin-PA-5**

ly2-20210607a-ESI (0.031) Is (1.00,1.00) C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>



Chemical Formula: C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>

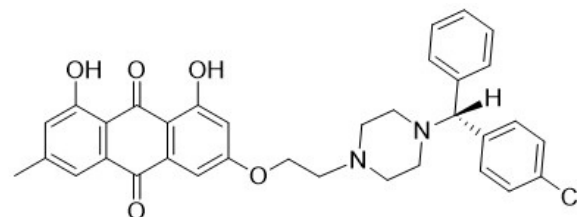
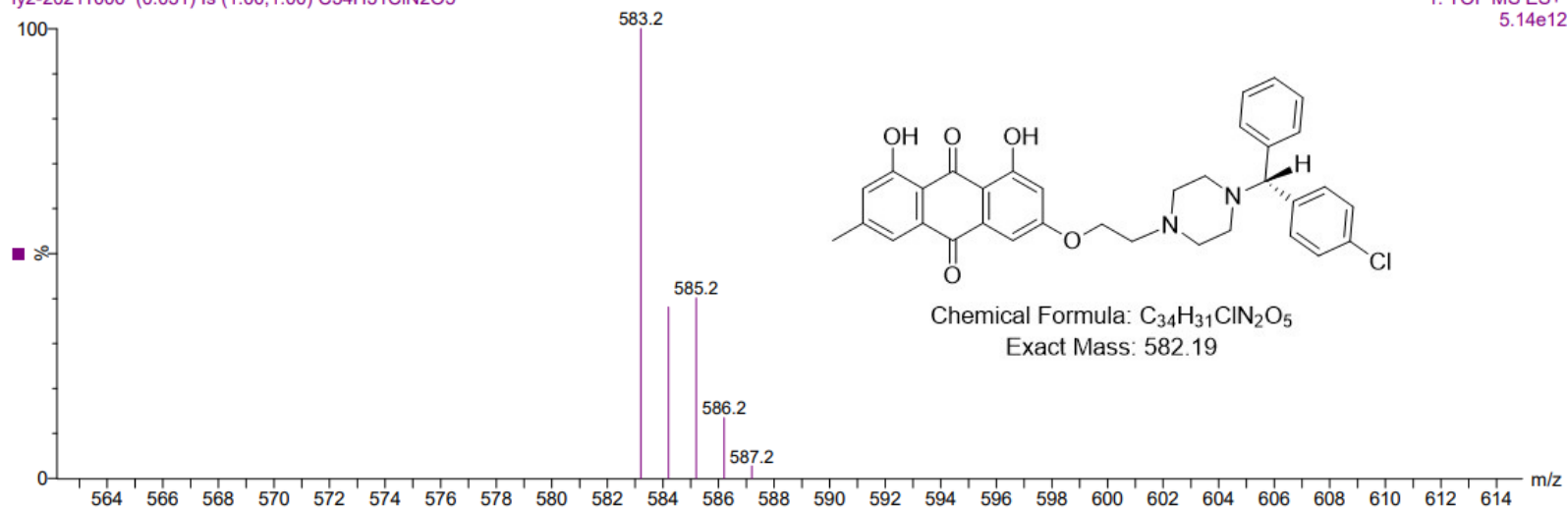
Exact Mass: 427.21

**Emodin-PA-6**

1: TOF MS ES+  
7.60e12

5.6. MS (ESI<sup>+</sup>) of emodin-PA-6

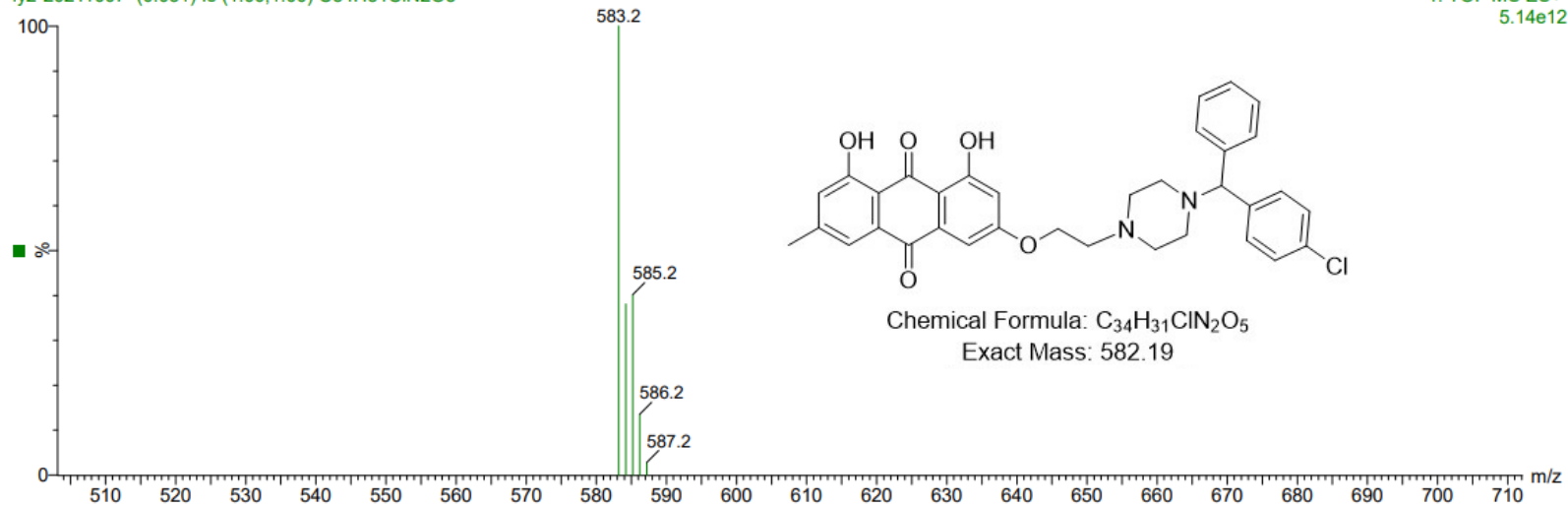
ly2-20211006 (0.031) Is (1.00,1.00) C<sub>34</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>5</sub>



Chemical Formula: C<sub>34</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>5</sub>  
Exact Mass: 582.19

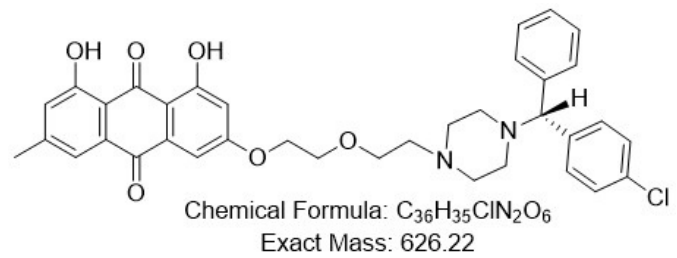
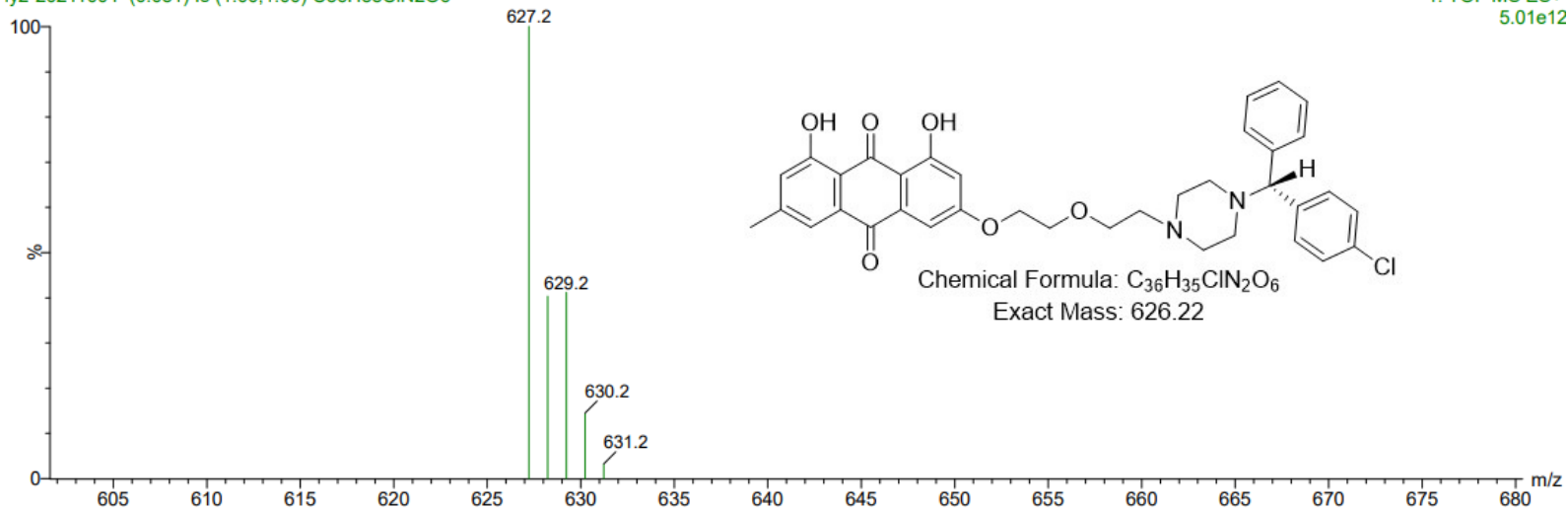
1: TOF MS ES+  
5.14e12

5.7. MS (ESI<sup>+</sup>) of (R)-emoxazine-1

ly2-20211007 (0.031) Is (1.00,1.00) C<sub>34</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>5</sub>1: TOF MS ES+  
5.14e125.8. MS (ESI<sup>+</sup>) of (R,S)-emoxazine-1



ly2-20211004 (0.031) Is (1.00,1.00) C<sub>36</sub>H<sub>35</sub>ClN<sub>2</sub>O<sub>6</sub>



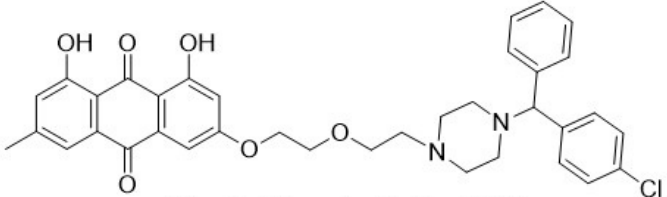
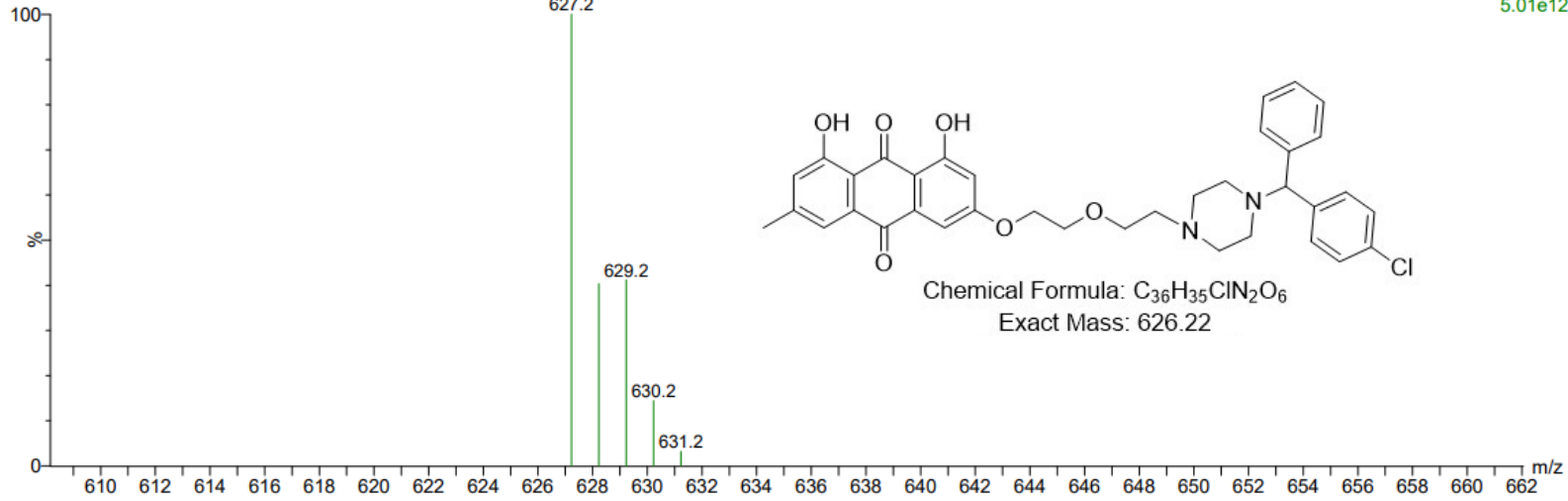
1: TOF MS ES+  
5.01e12

5.9. MS (ESI<sup>+</sup>) of (R)-emoxazine-2

5.10. MS (ESI<sup>+</sup>) of (R,S)-emoxazine-2

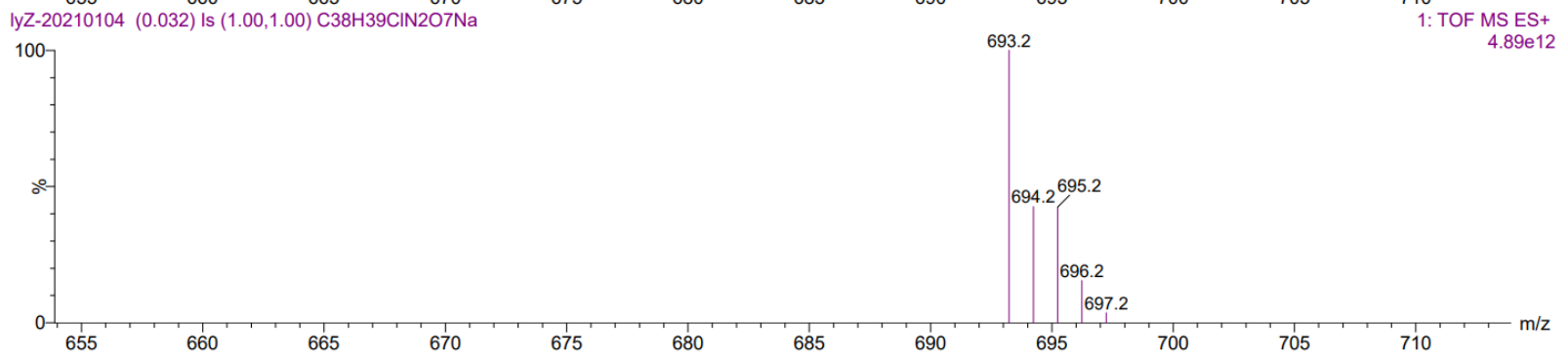
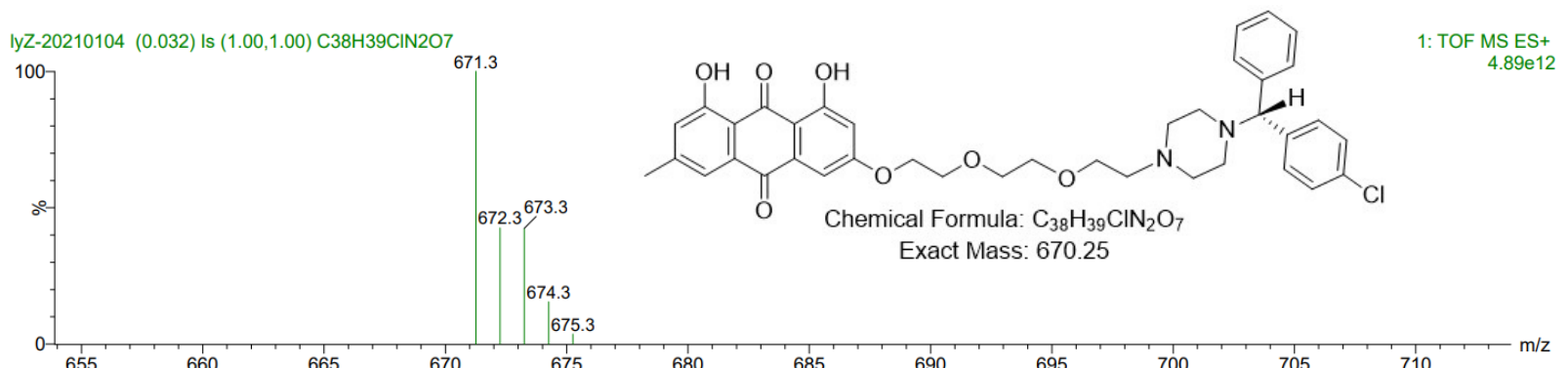
1: TOF MS ES+  
5.01e12

ly2-20210929 (0.031) Is (1.00,1.00) C<sub>36</sub>H<sub>35</sub>ClN<sub>2</sub>O<sub>6</sub>



Chemical Formula: C<sub>36</sub>H<sub>35</sub>ClN<sub>2</sub>O<sub>6</sub>  
Exact Mass: 626.22

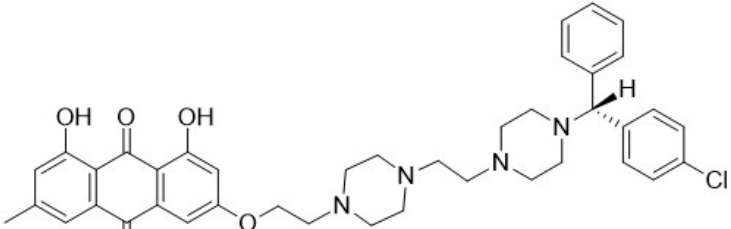
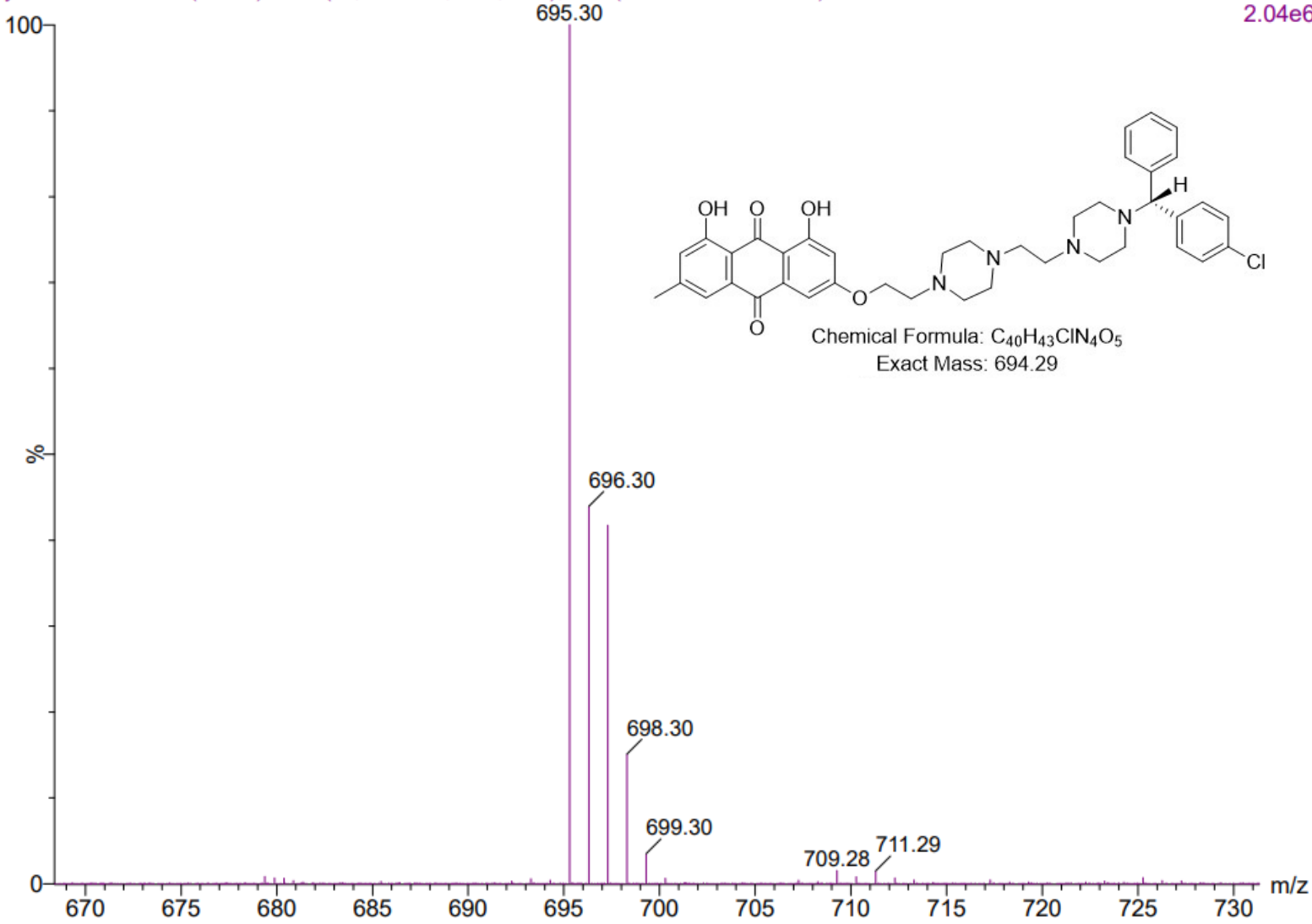
5.11. MS (ESI<sup>+</sup>) of (R)-emoxazine-3



5.12. MS (ESI<sup>+</sup>) of (R)-emoxyzine-7

lyz-20220117b 79 (0.492) AM2 (Ar,20000.0,0.00,0.00); Cm (76:86-57:62x2.000)

1: TOF MS ES+  
2.04e6



Chemical Formula: C<sub>40</sub>H<sub>43</sub>ClN<sub>4</sub>O<sub>5</sub>  
Exact Mass: 694.29