

**Design, Synthesis, In Vitro and In Vivo Evaluation of Tacrine-Cinnamic Acid Hybrids as Multi-Target Acetyl- and Butyrylcholinesterase Inhibitors against Alzheimer's Disease**

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*<sup>b</sup>State Key Laboratory Cultivation Base for TCM Quality and Efficacy, Nanjing University of Chinese Medicine, Nanjing, 210023, China;*

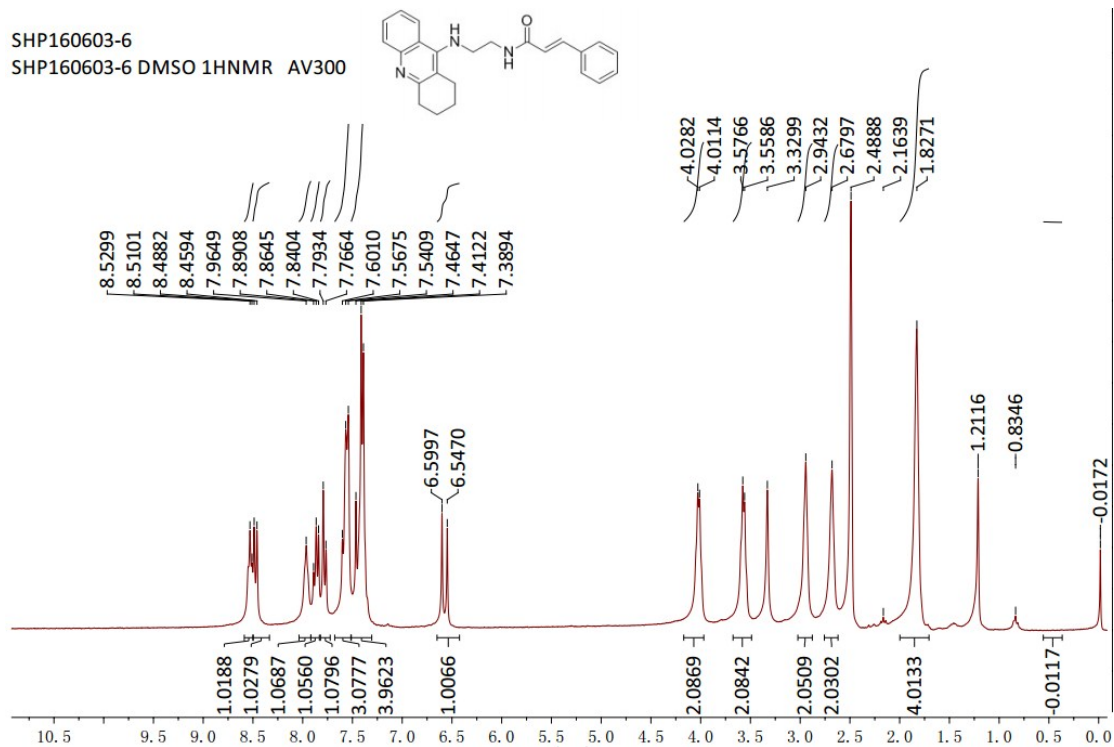
*<sup>c</sup>Jiangsu Key Laboratory for Functional Substance of Chinese Medicine, Nanjing University of Chinese Medicine, Nanjing, 210023, China;*

*<sup>d</sup>School of Nursing, Nanjing University of Chinese Medicine, Nanjing, 210023, China;*

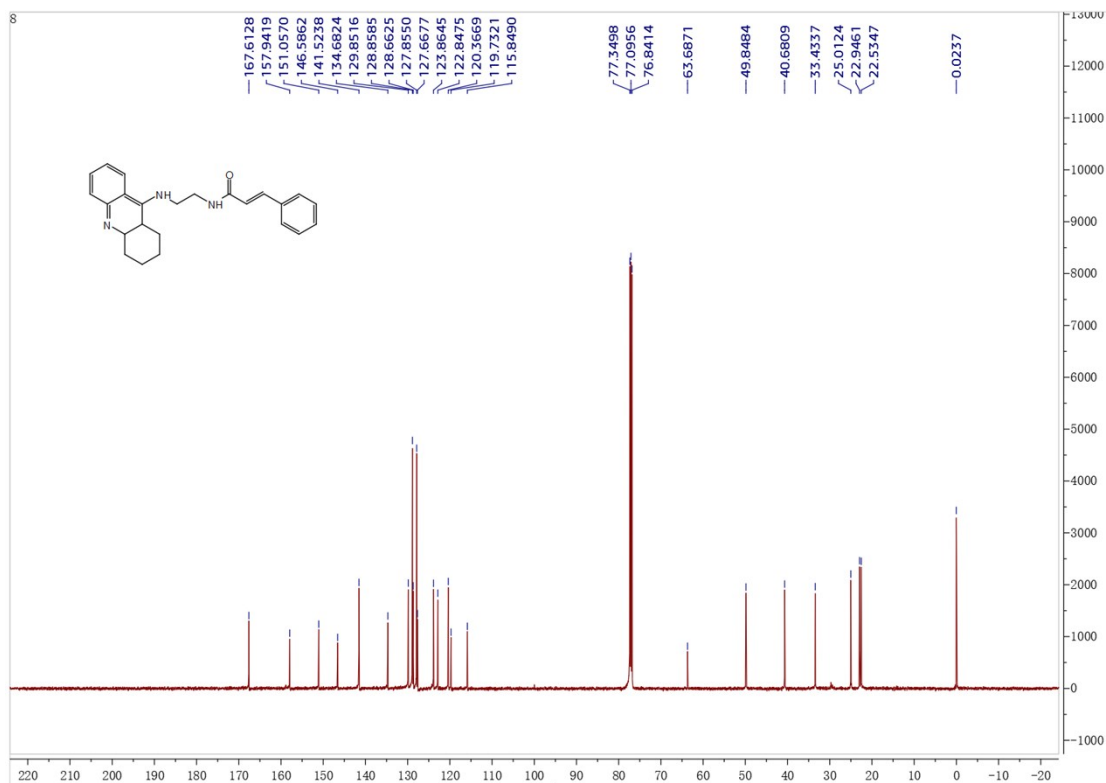
*<sup>e</sup>Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, 210009, China;*

### 8 <sup>1</sup>H NMR spectrum

SHP160603-6  
SHP160603-6 DMSO 1HNMR AV300

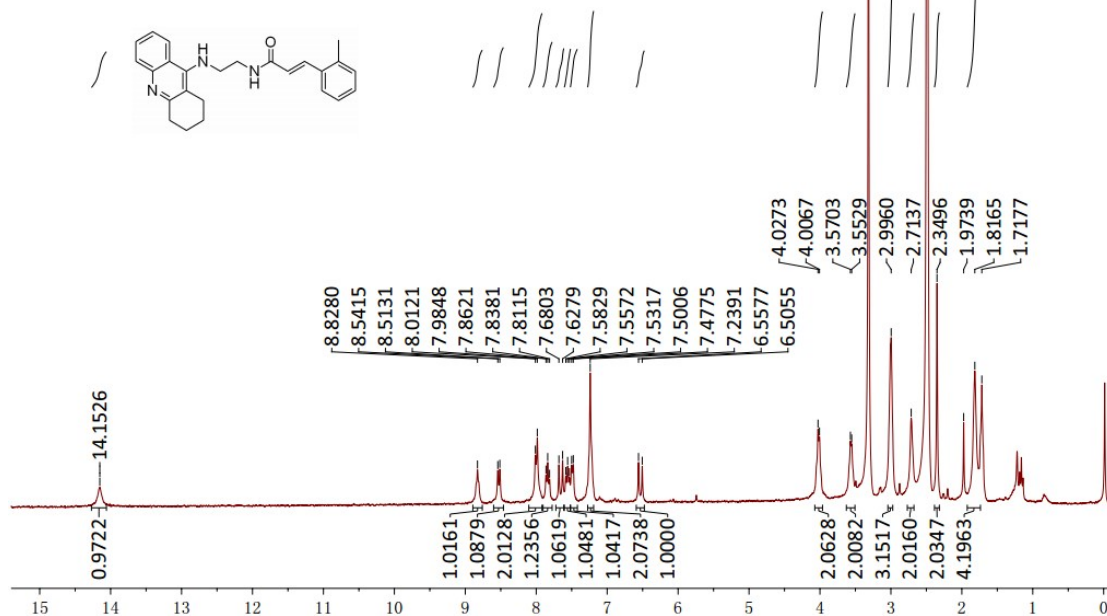


### 8 <sup>13</sup>C NMR spectrum

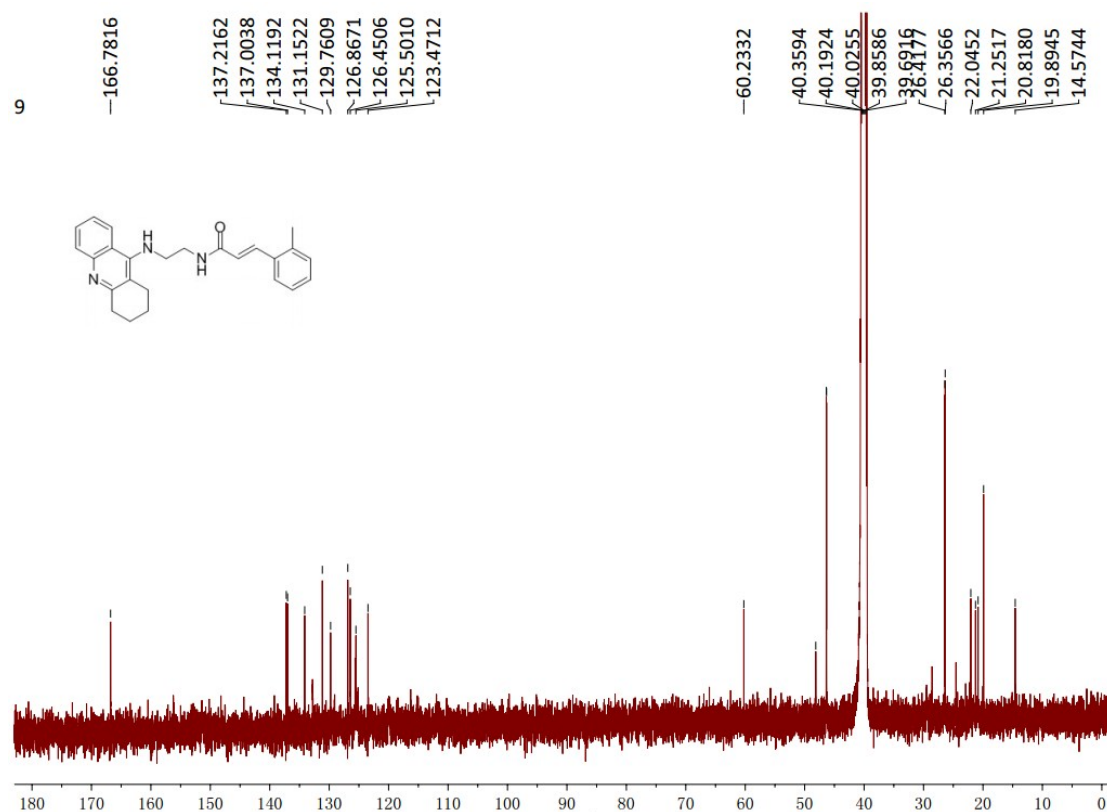


# 9 <sup>1</sup>H NMR spectrum

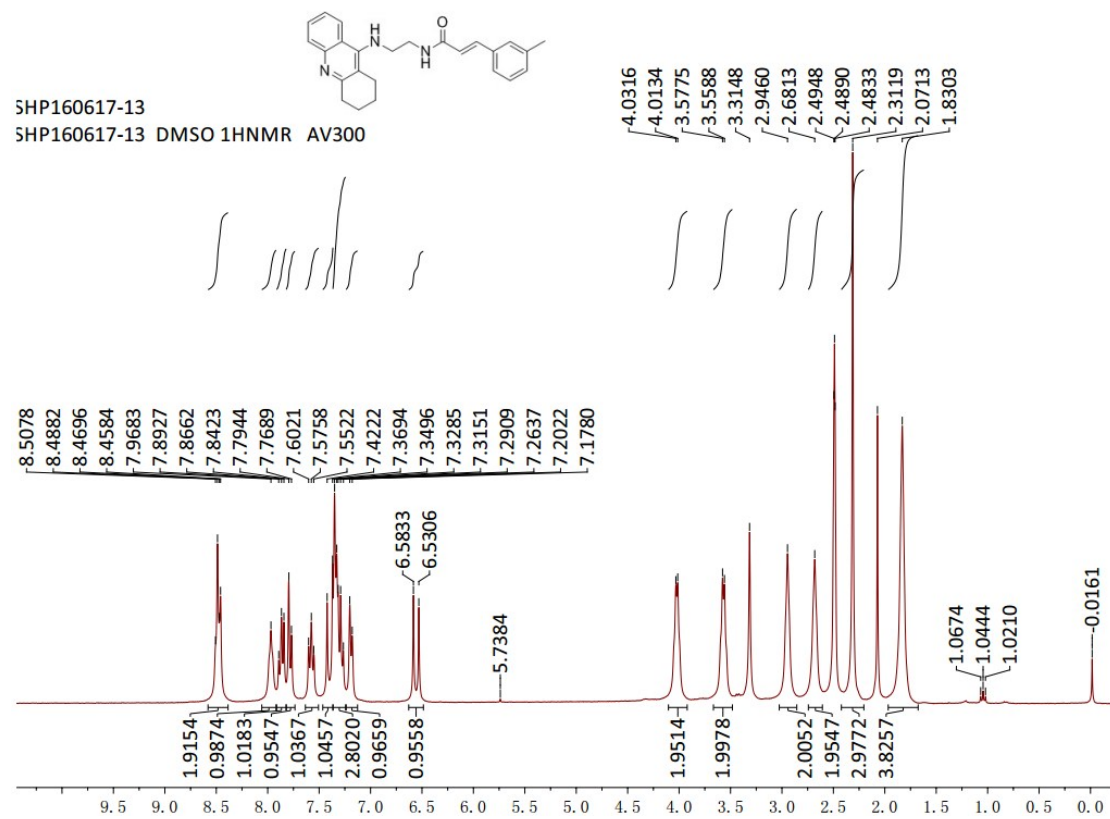
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SHP160617-15 DMSO 1HNMR AV300



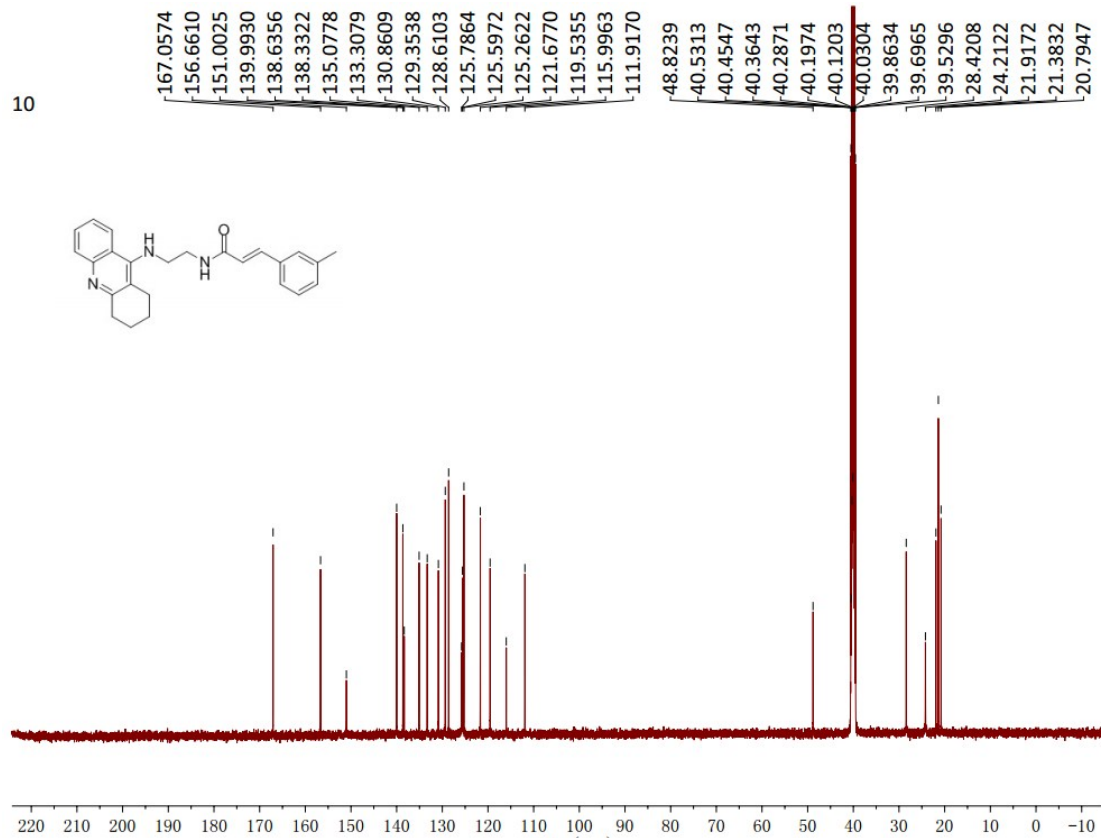
# 9 <sup>13</sup>C NMR spectrum



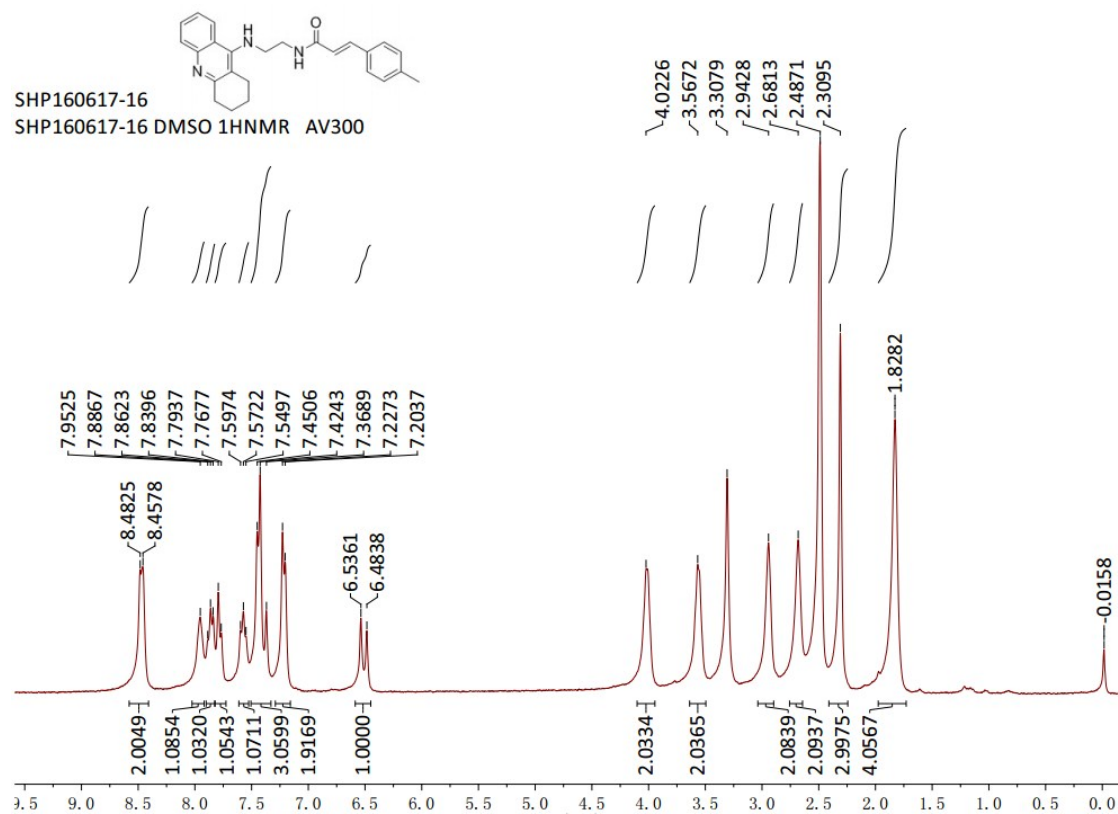
# 10 <sup>1</sup>H NMR spectrum



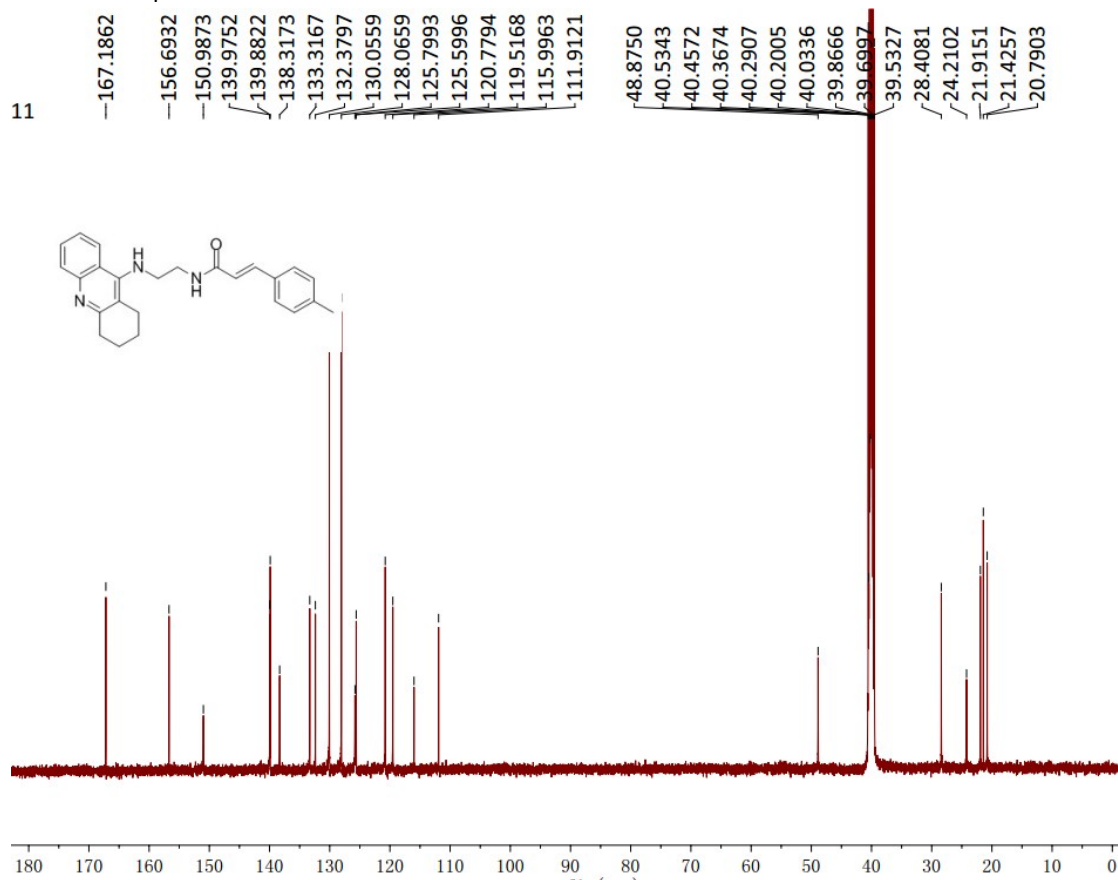
# 10 <sup>13</sup>C NMR spectrum



**11** <sup>1</sup>H NMR spectrum



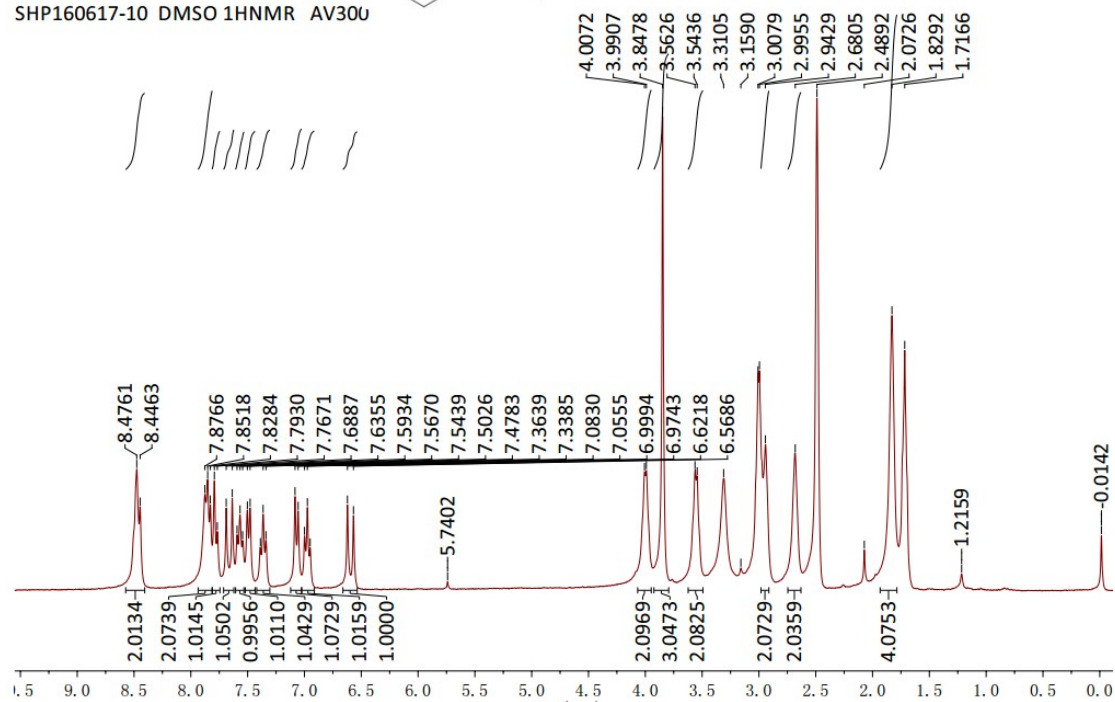
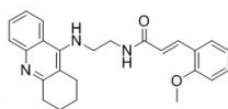
**11** <sup>13</sup>C NMR spectrum



**12** <sup>1</sup>H NMR spectrum

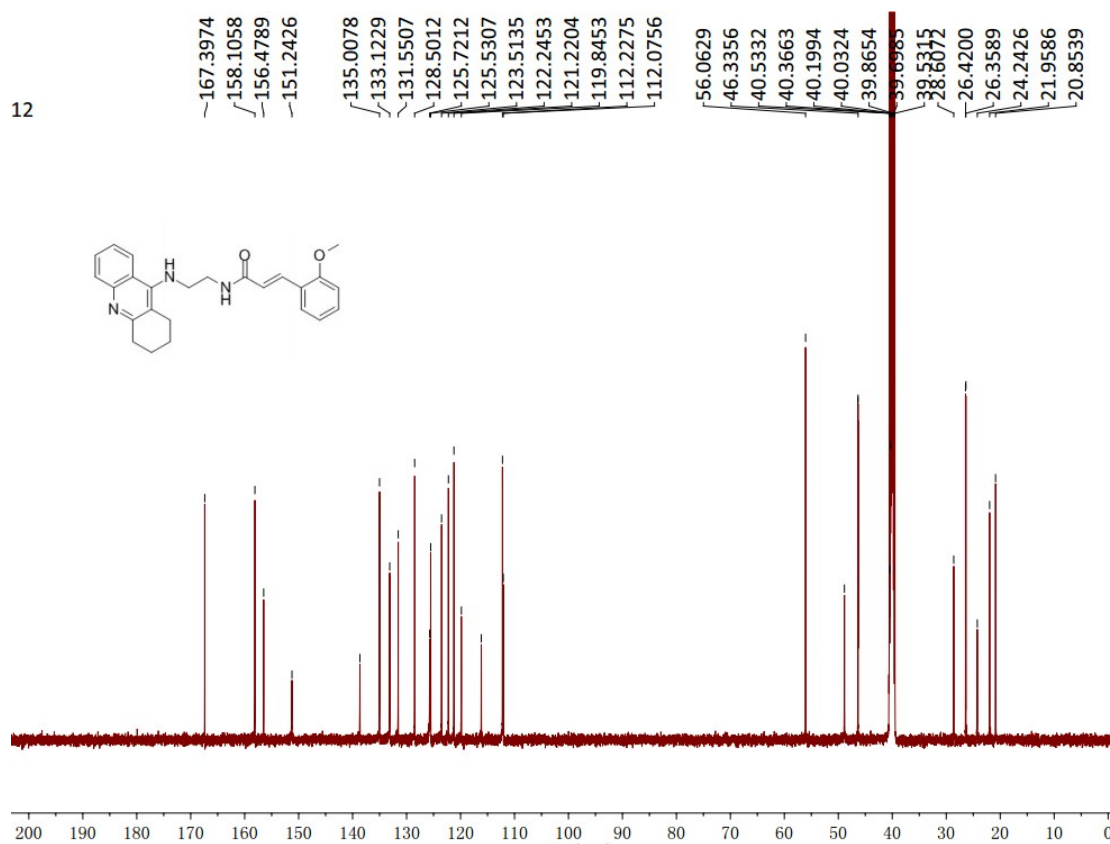
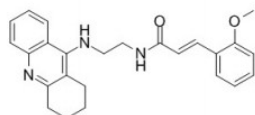
SHP160617-10

SHP160617-10 DMSO 1HNMR AV300



**12** <sup>13</sup>C NMR spectrum

12

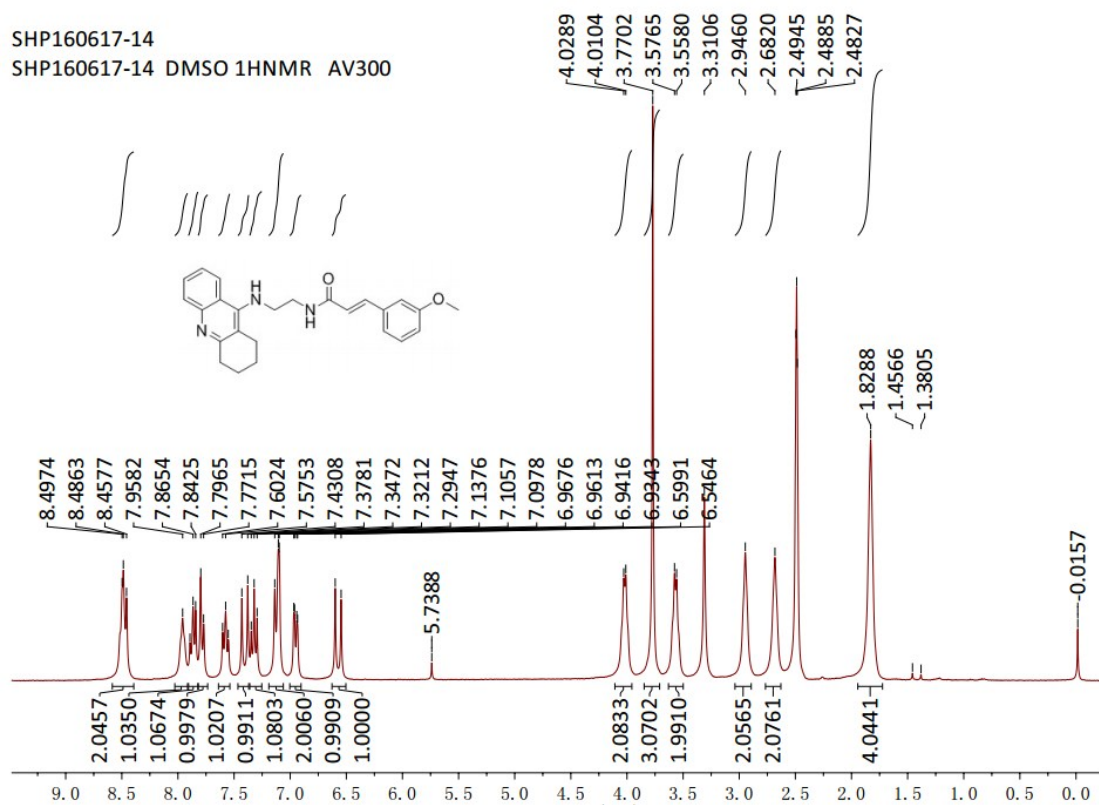




**13** <sup>1</sup>H NMR spectrum

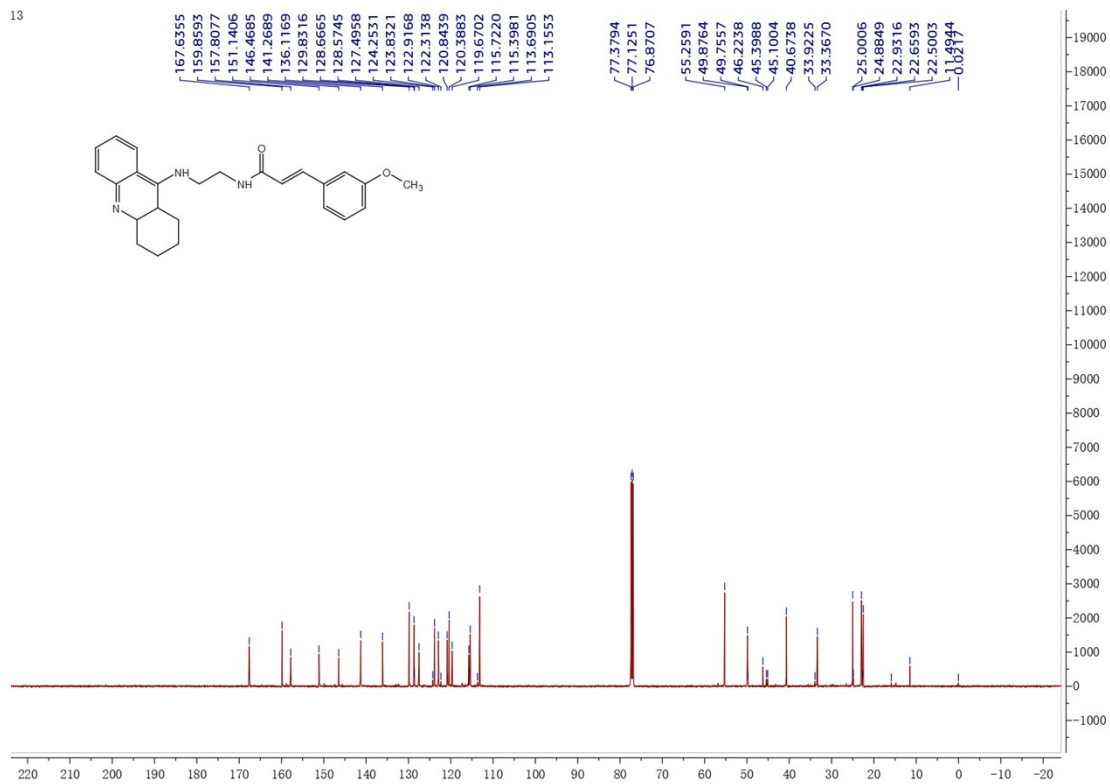
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SHP160617-14 DMSO 1HNMR AV300



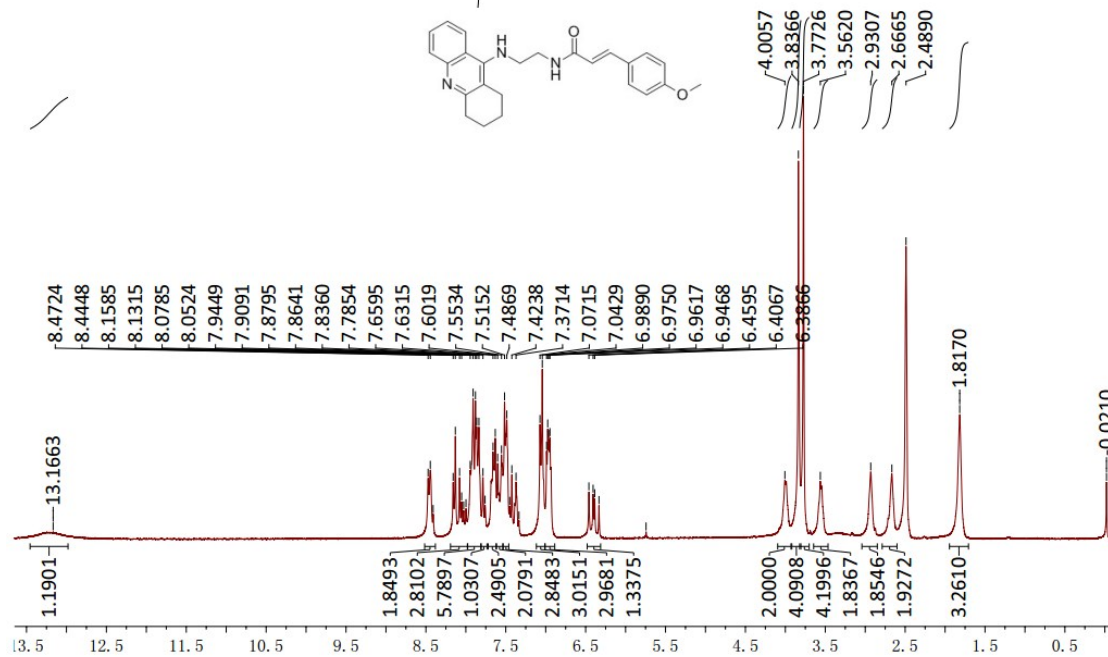
**13** <sup>13</sup>C NMR spectrum

13

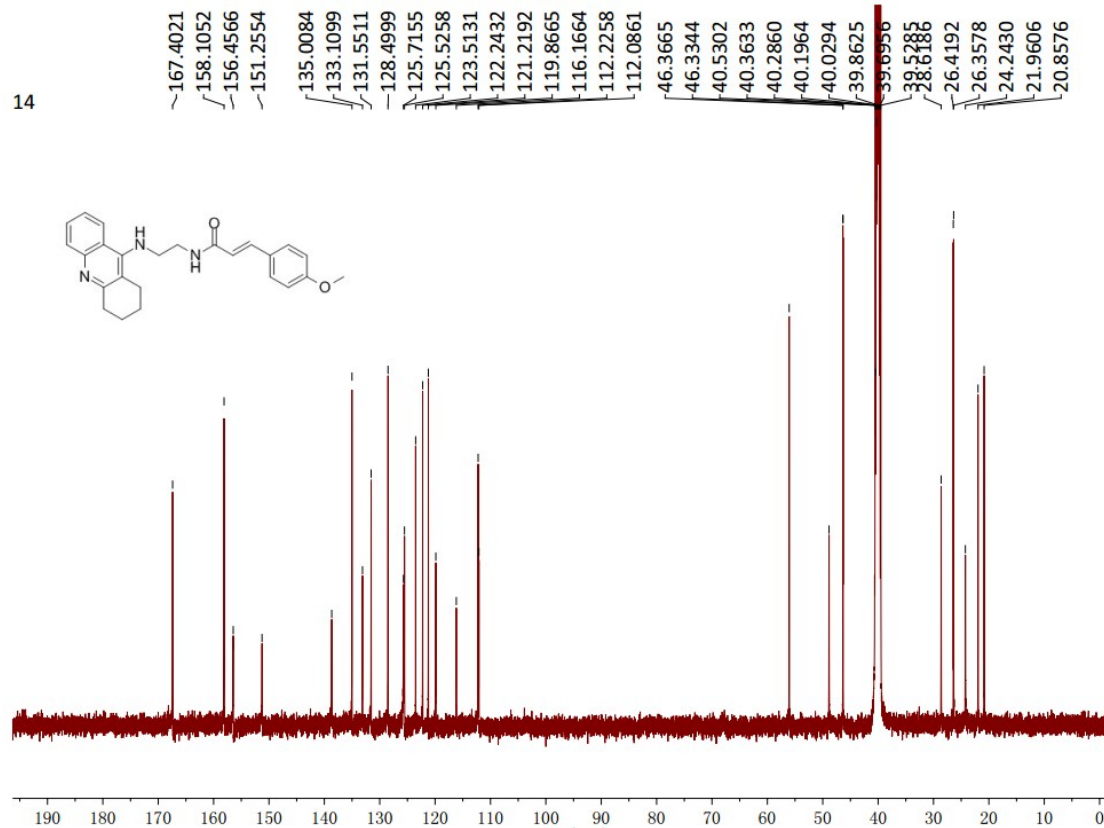


# 14 <sup>1</sup>H NMR spectrum

SHP160603-4  
SHP160603-4 DMSO 1HNMR AV300



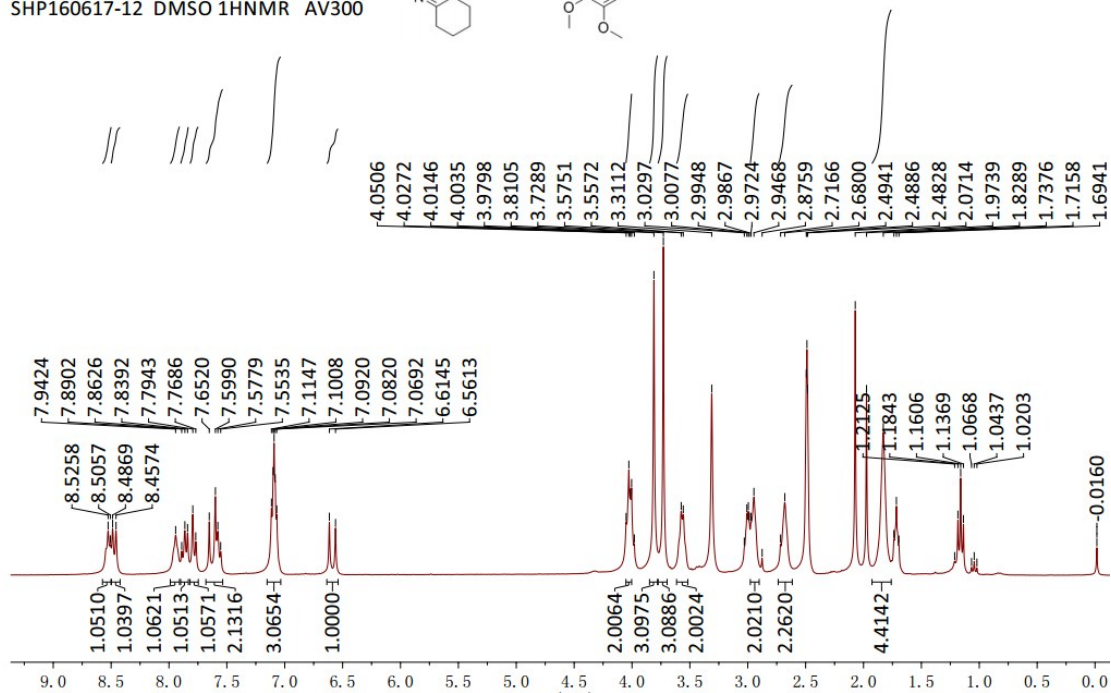
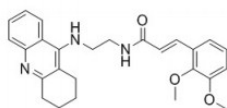
# 14 <sup>13</sup>C NMR spectrum



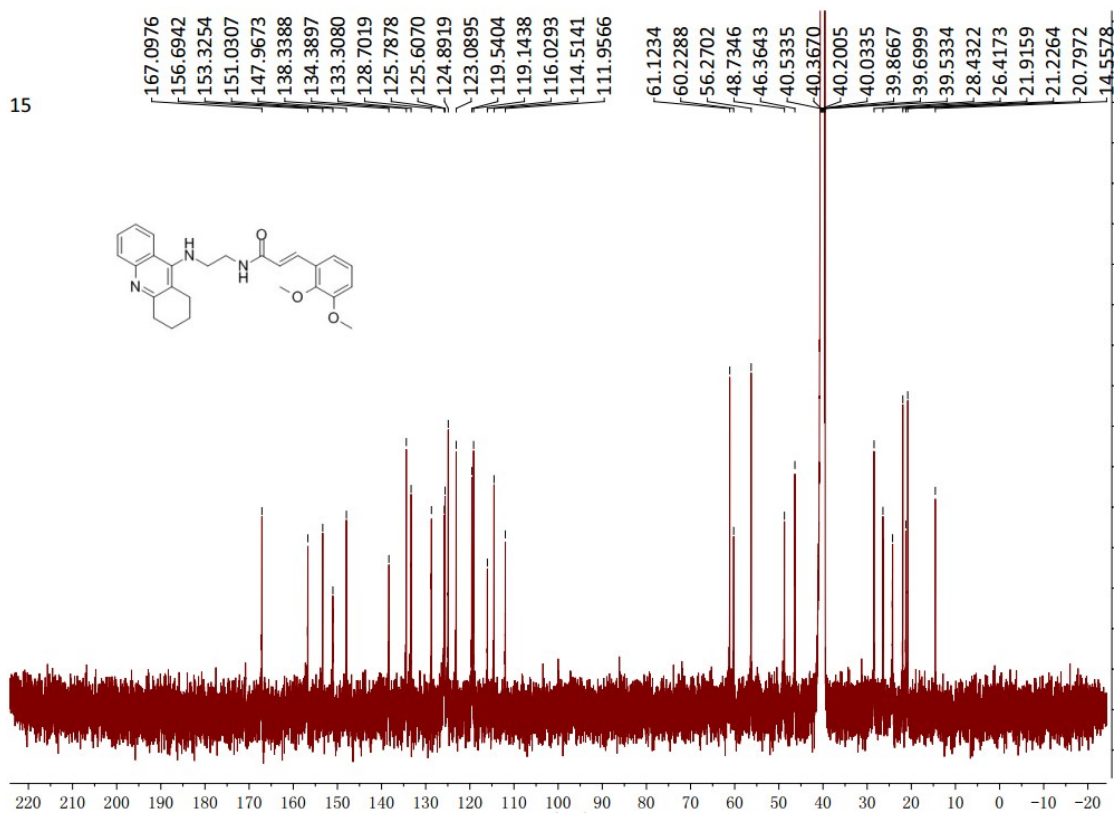


15 <sup>1</sup>H NMR spectrum

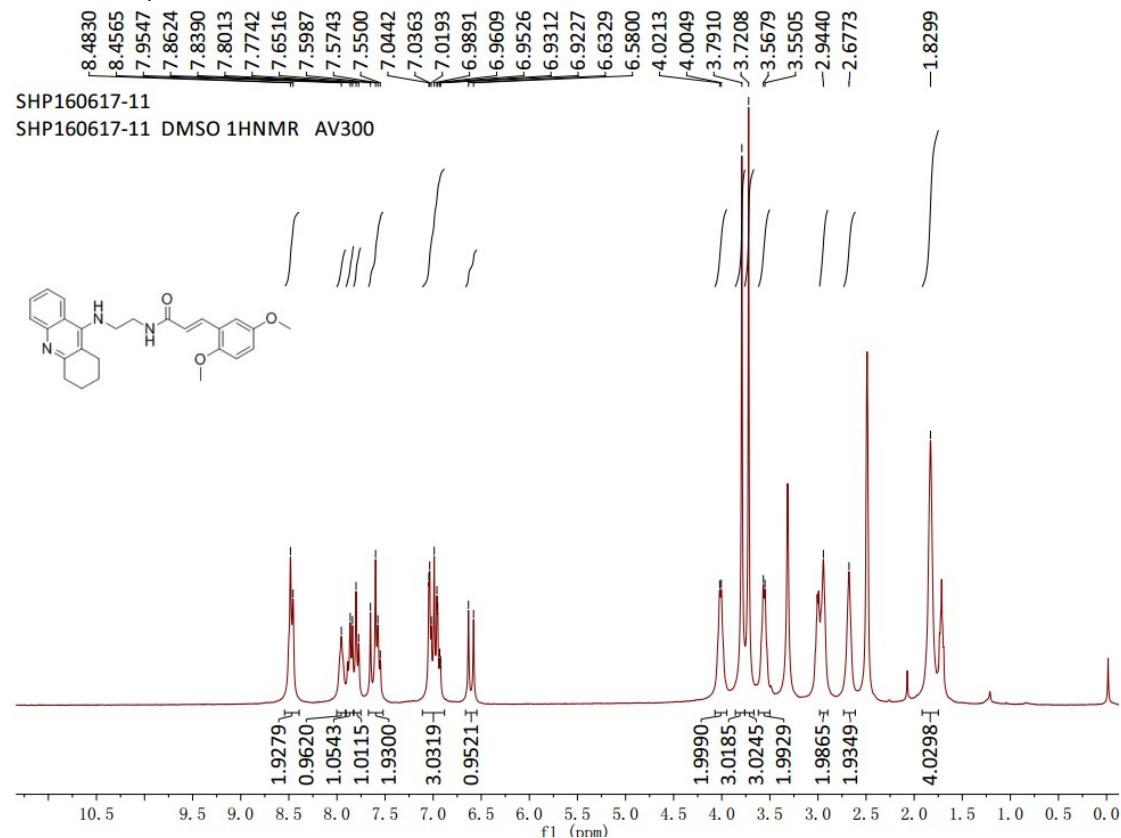
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 SHP160617-12 DMSO 1HNMR AV300



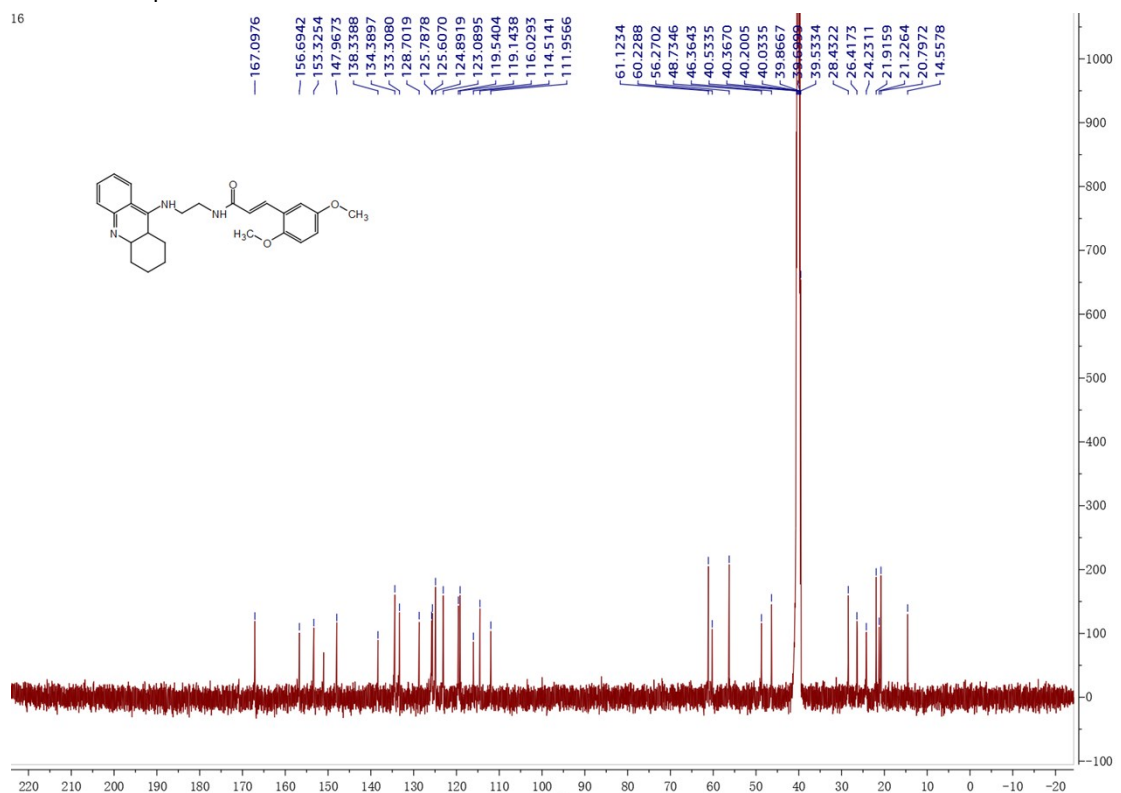
15 <sup>13</sup>C NMR spectrum



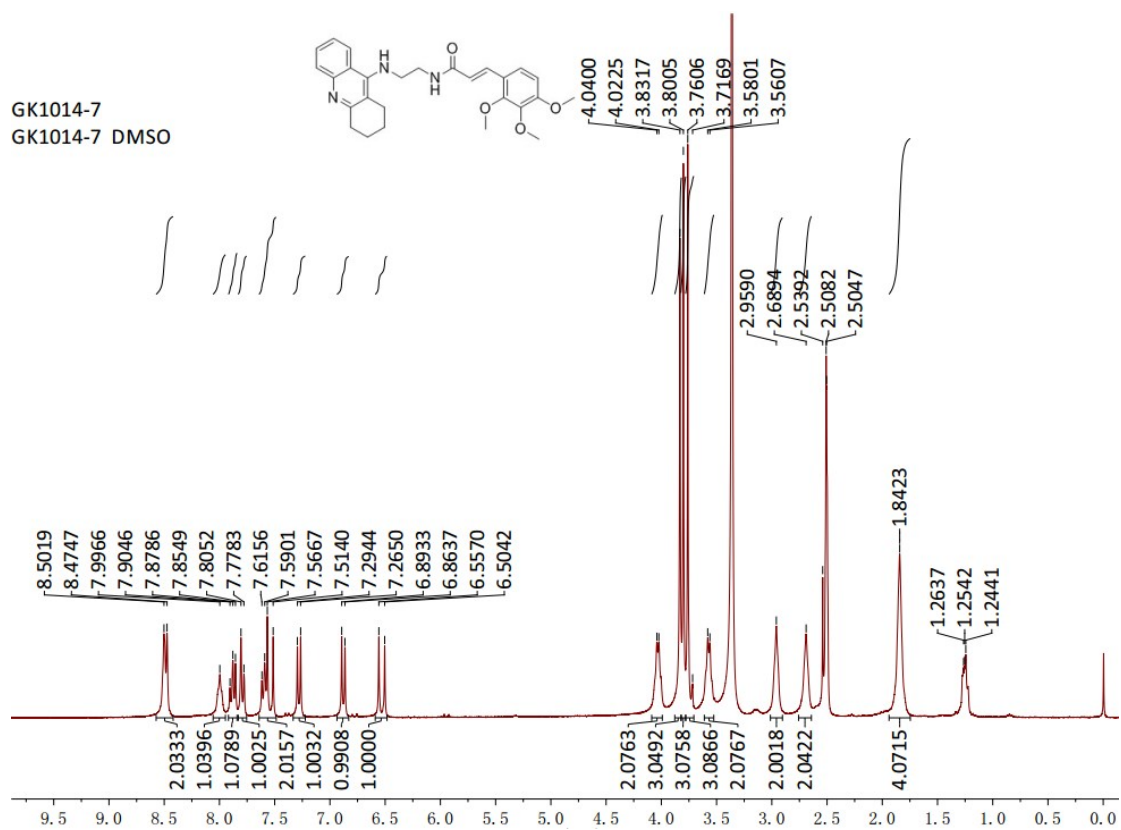
**16** <sup>1</sup>H NMR spectrum



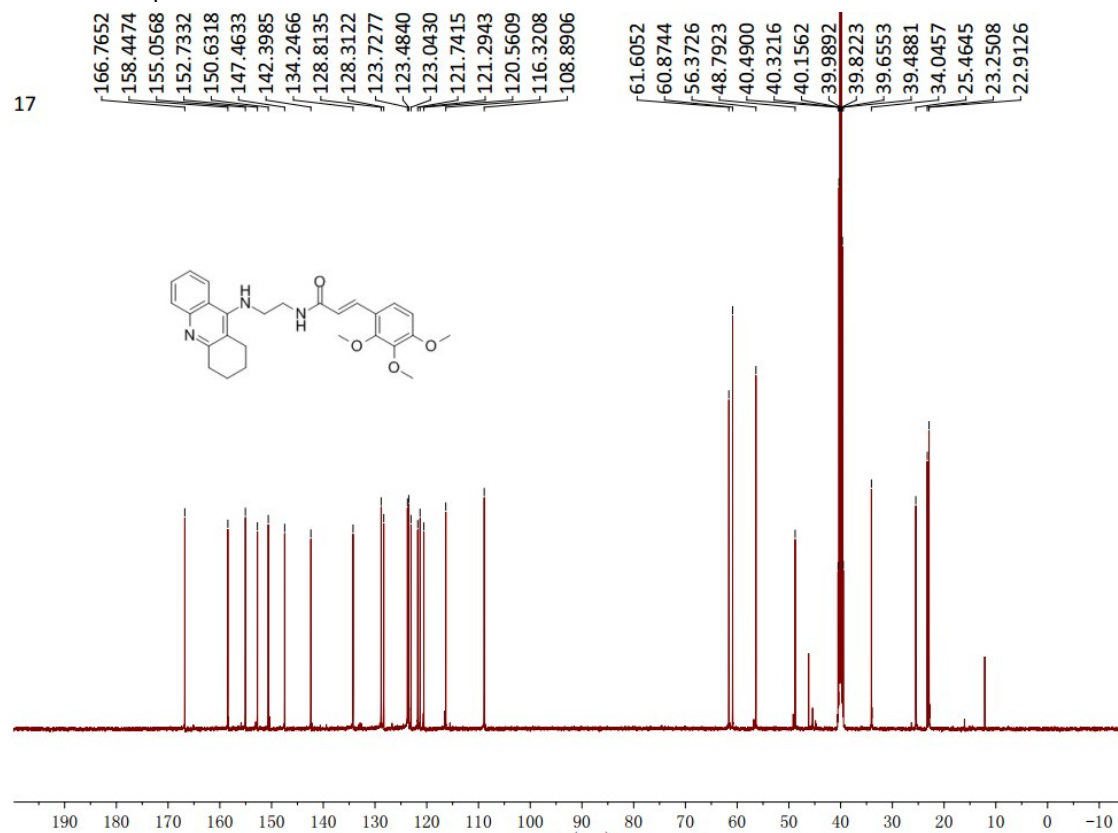
**16** <sup>13</sup>C NMR spectrum



17 <sup>1</sup>H NMR spectrum

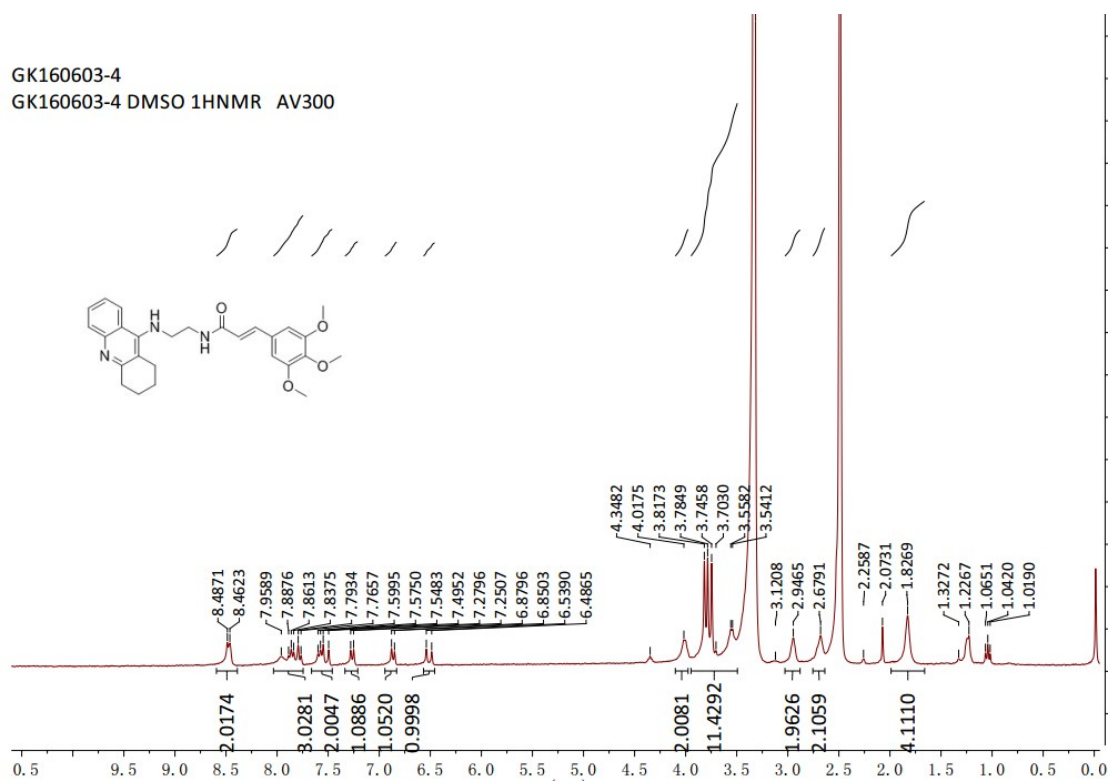


17 <sup>13</sup>C NMR spectrum

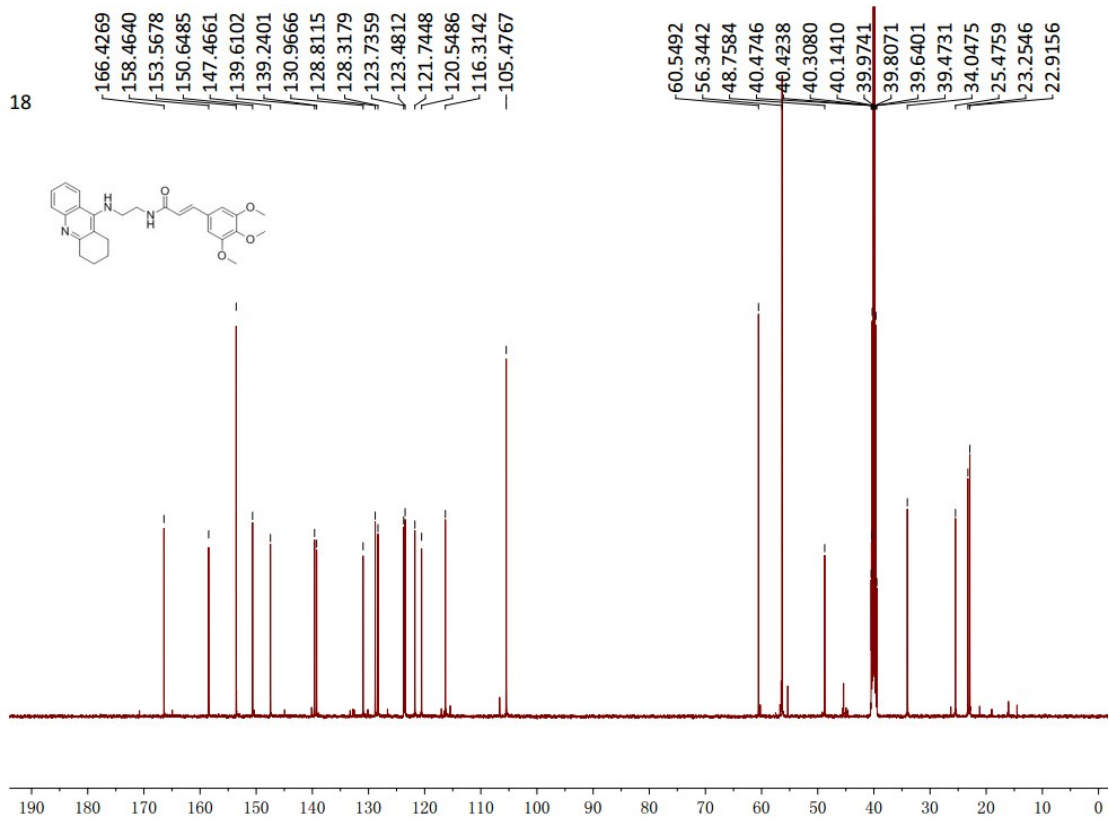


# 18 <sup>1</sup>H NMR spectrum

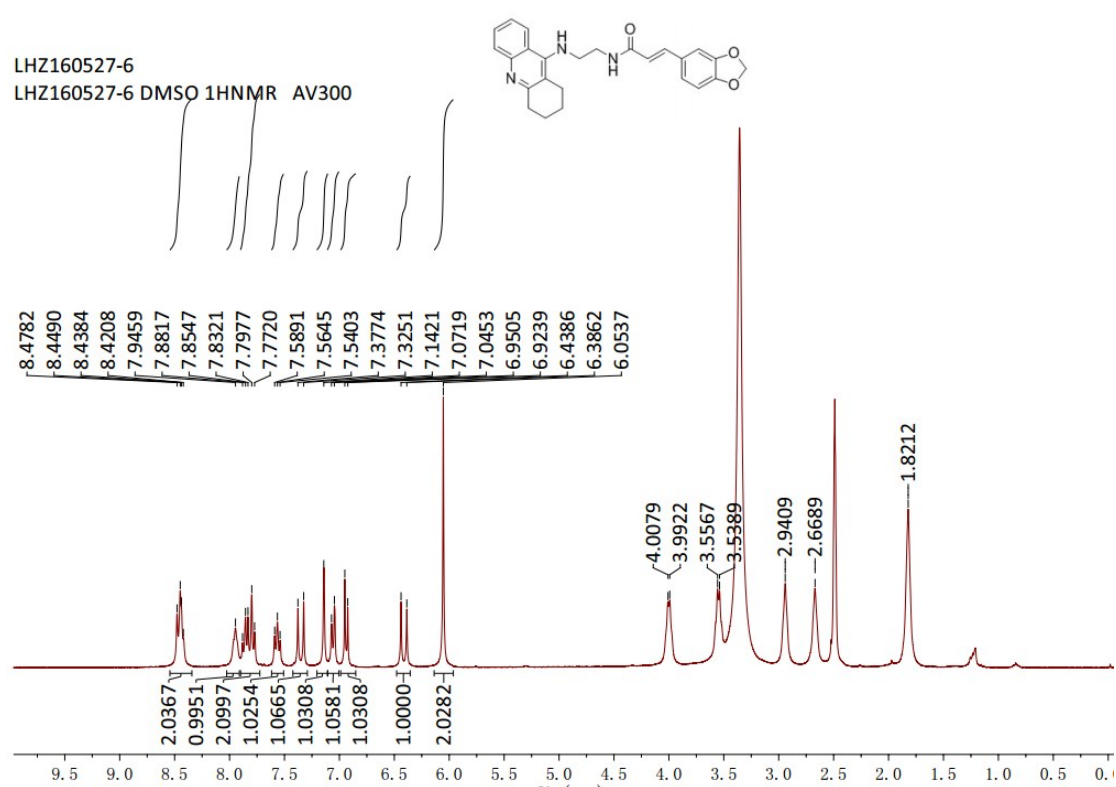
GK160603-4  
GK160603-4 DMSO 1HNMR AV300



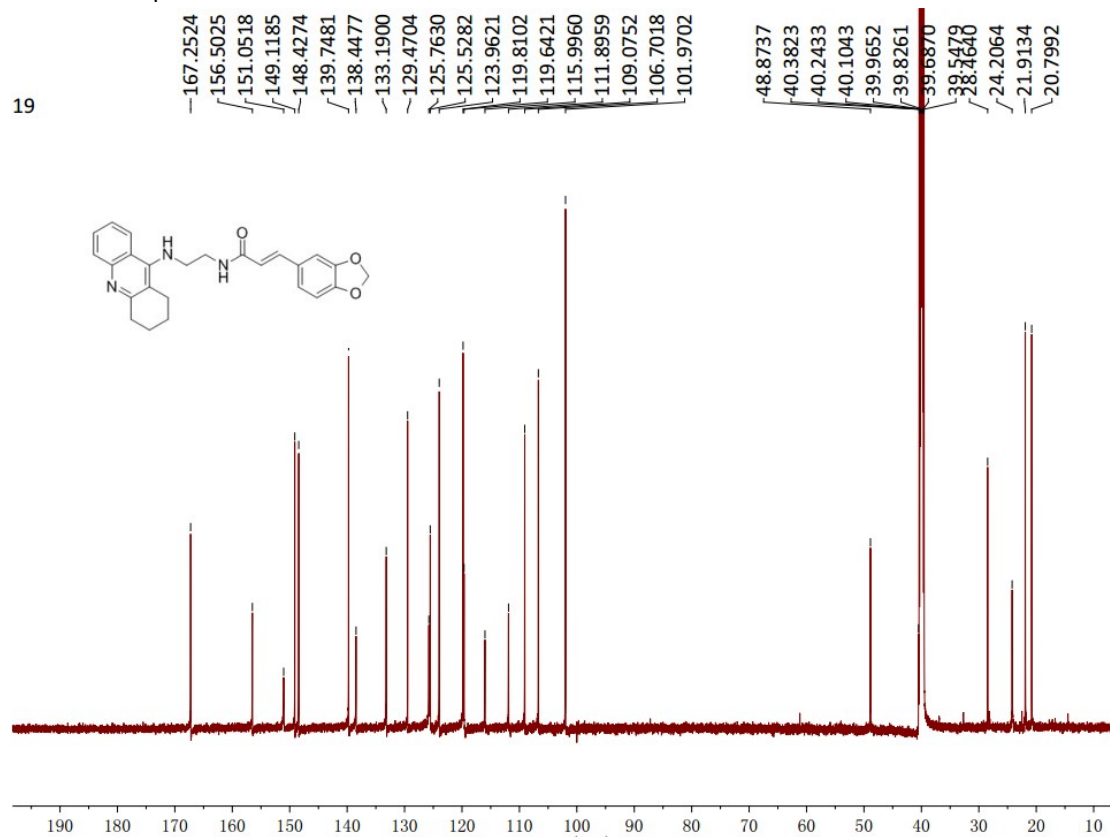
# 18 <sup>13</sup>C NMR spectrum



### 19 <sup>1</sup>H NMR spectrum



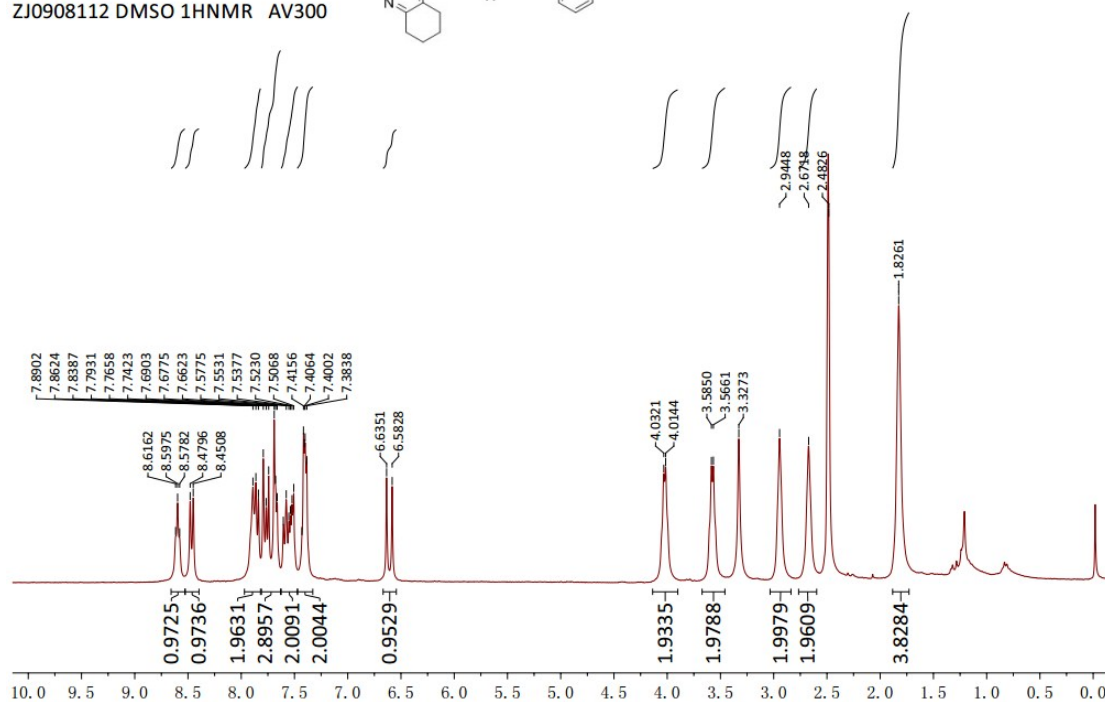
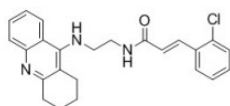
### 19 <sup>13</sup>C NMR spectrum



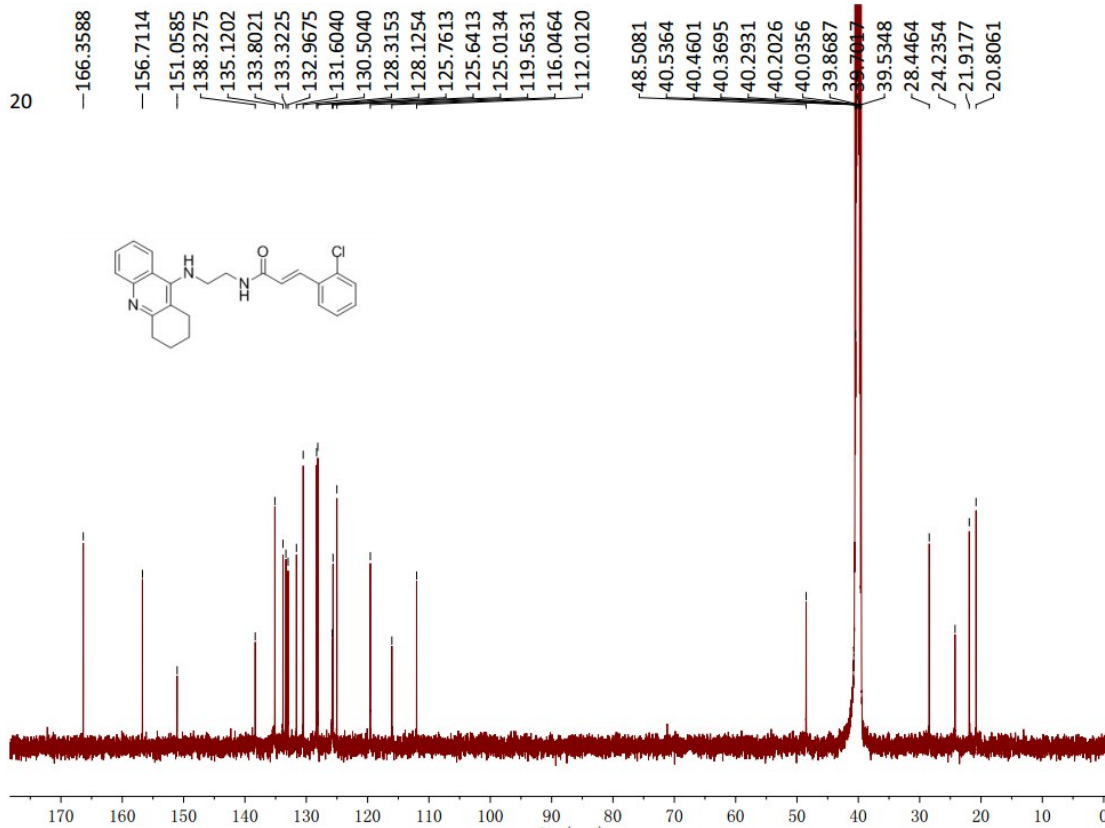


## 20 <sup>1</sup>H NMR spectrum

ZJ0908112  
ZJ0908112 DMSO 1HNMR AV300



## 20 <sup>13</sup>C NMR spectrum

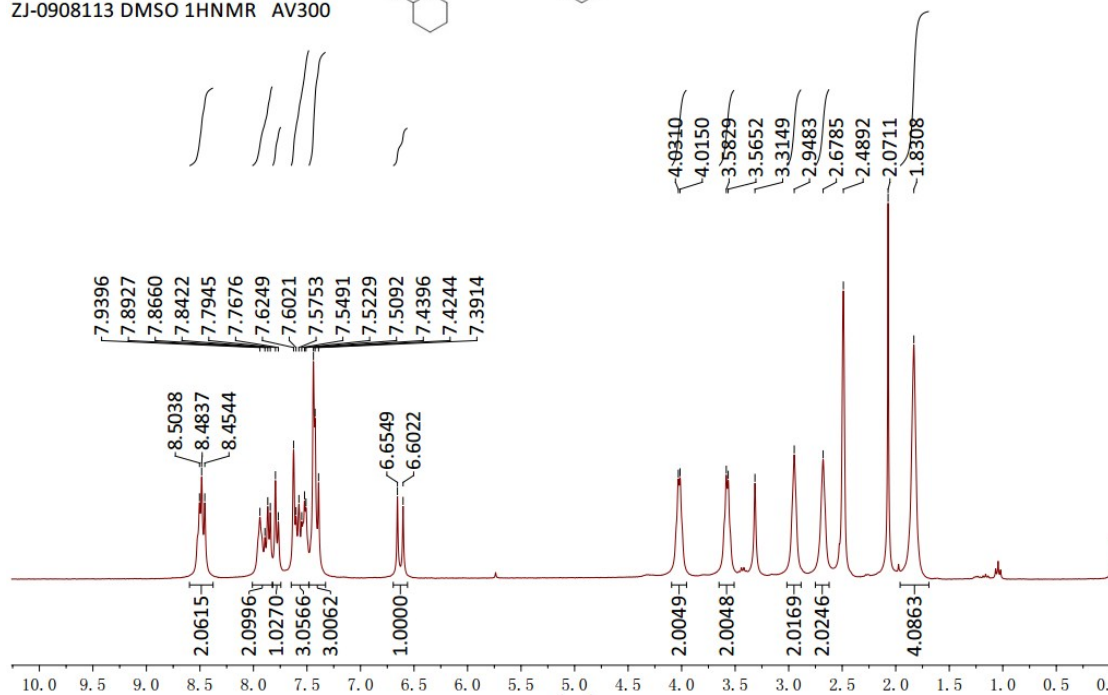
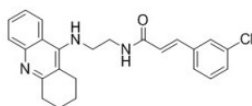




# 21 <sup>1</sup>H NMR spectrum

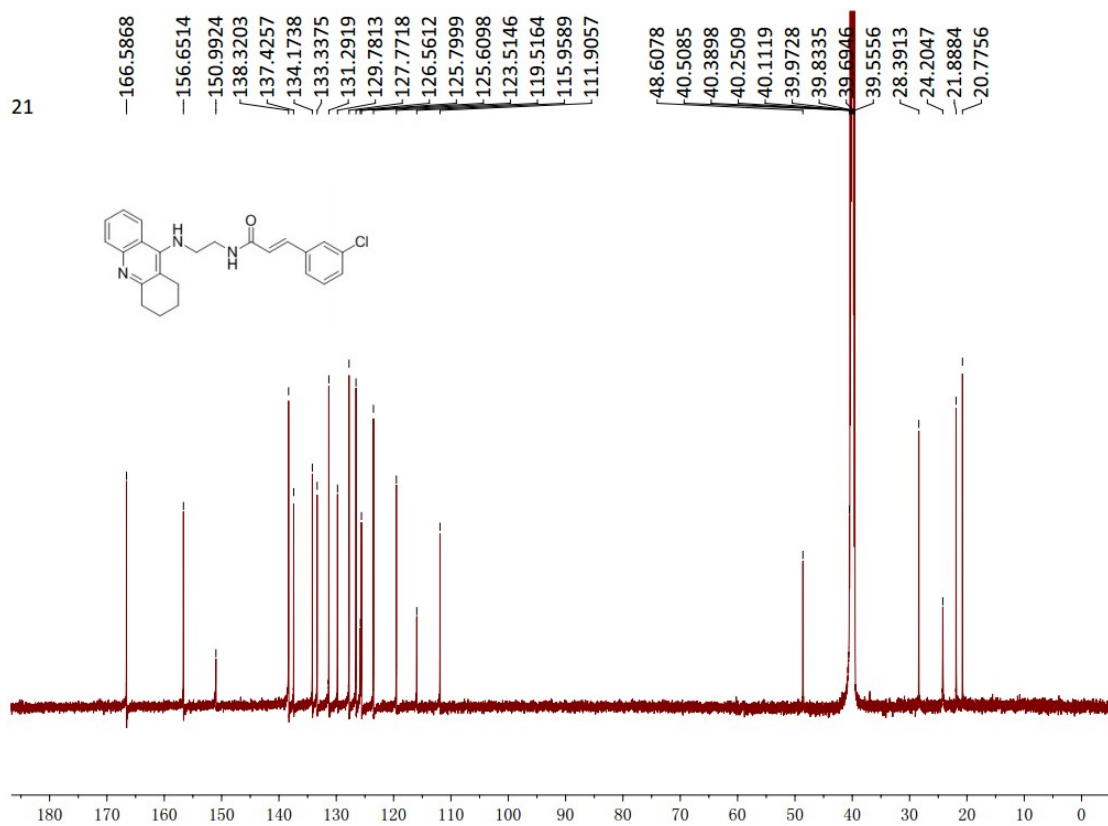
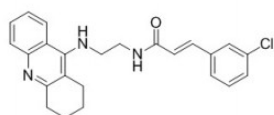
ZJ-0908113

ZJ-0908113 DMSO 1HNMR AV300



# 21 <sup>13</sup>C NMR spectrum

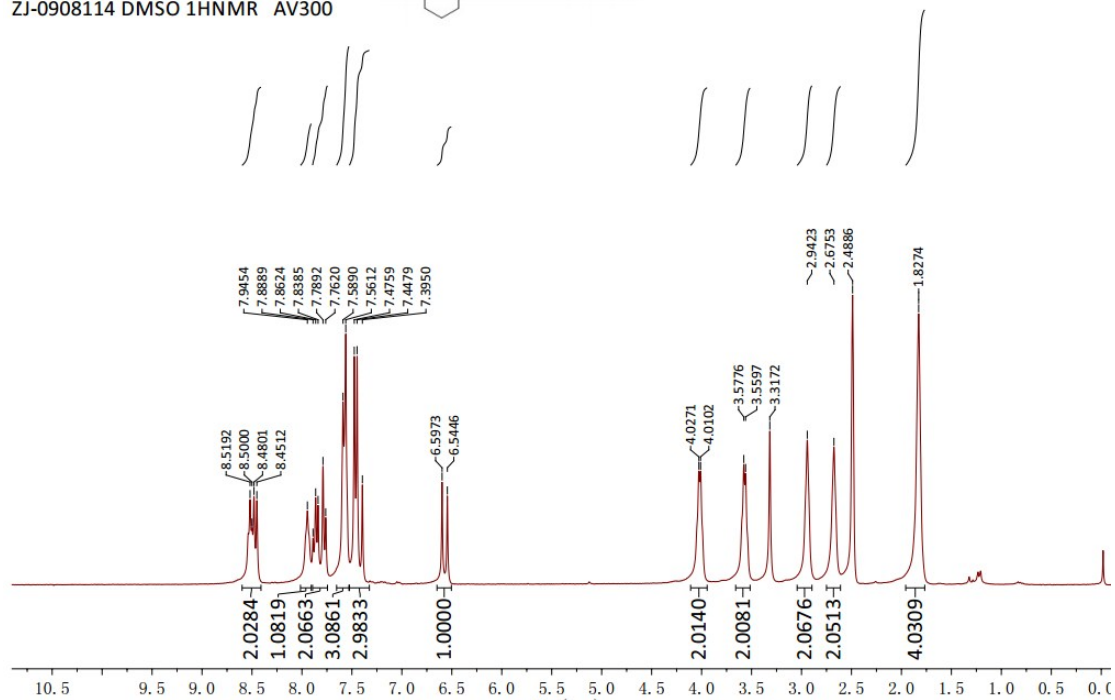
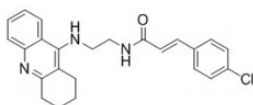
21



## 22 <sup>1</sup>H NMR spectrum

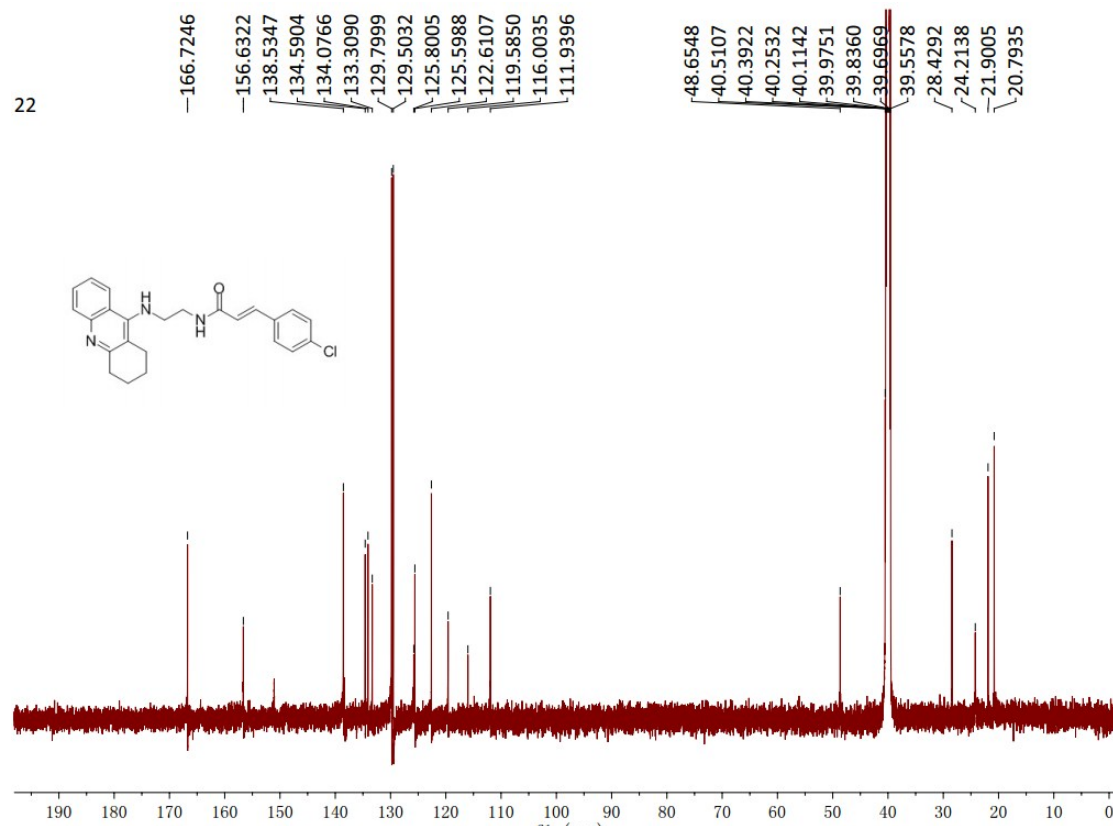
ZJ-0908114

ZJ-0908114 DMSO 1HNMR AV300



## 22 <sup>13</sup>C NMR spectrum

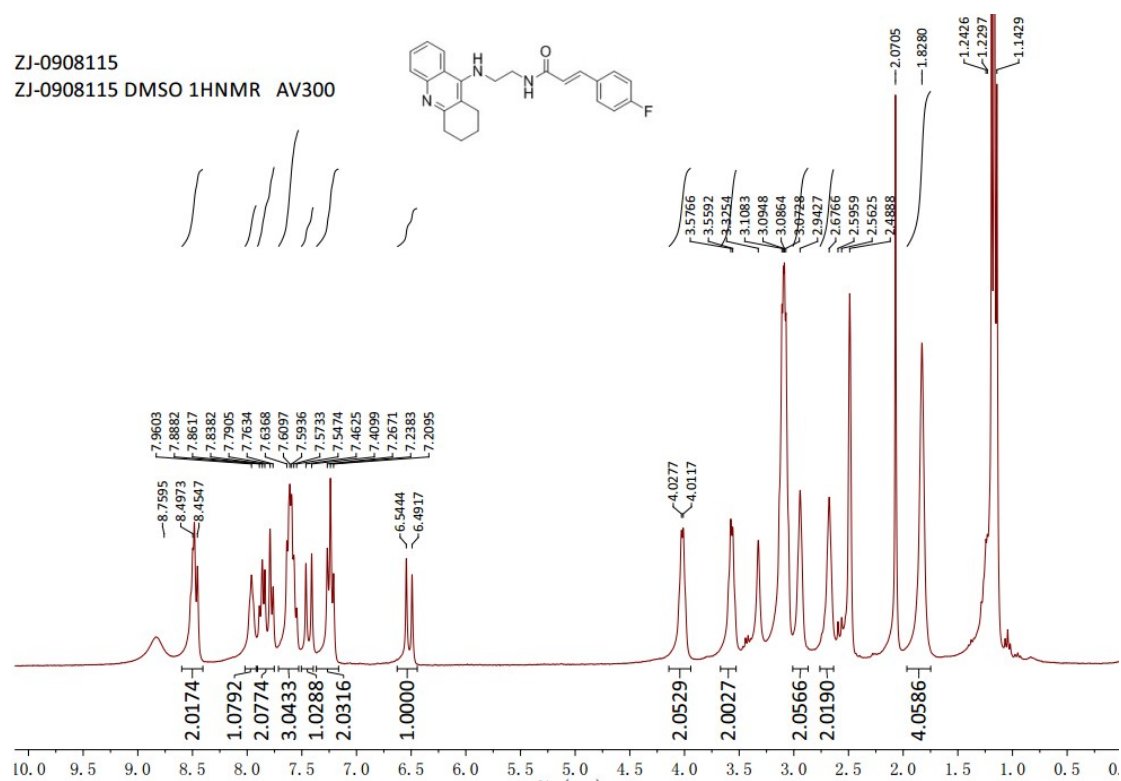
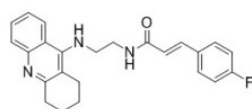
22



### 23 <sup>1</sup>H NMR spectrum

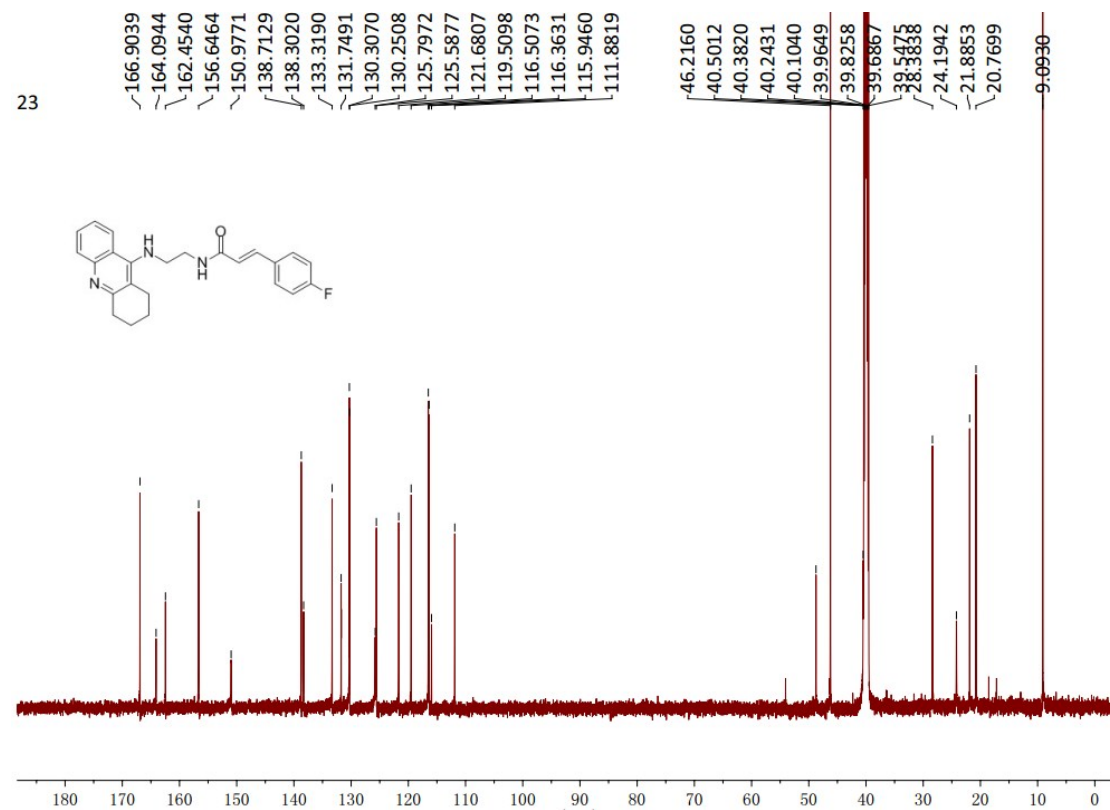
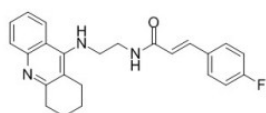
ZJ-0908115

ZJ-0908115 DMSO 1HNMR AV300



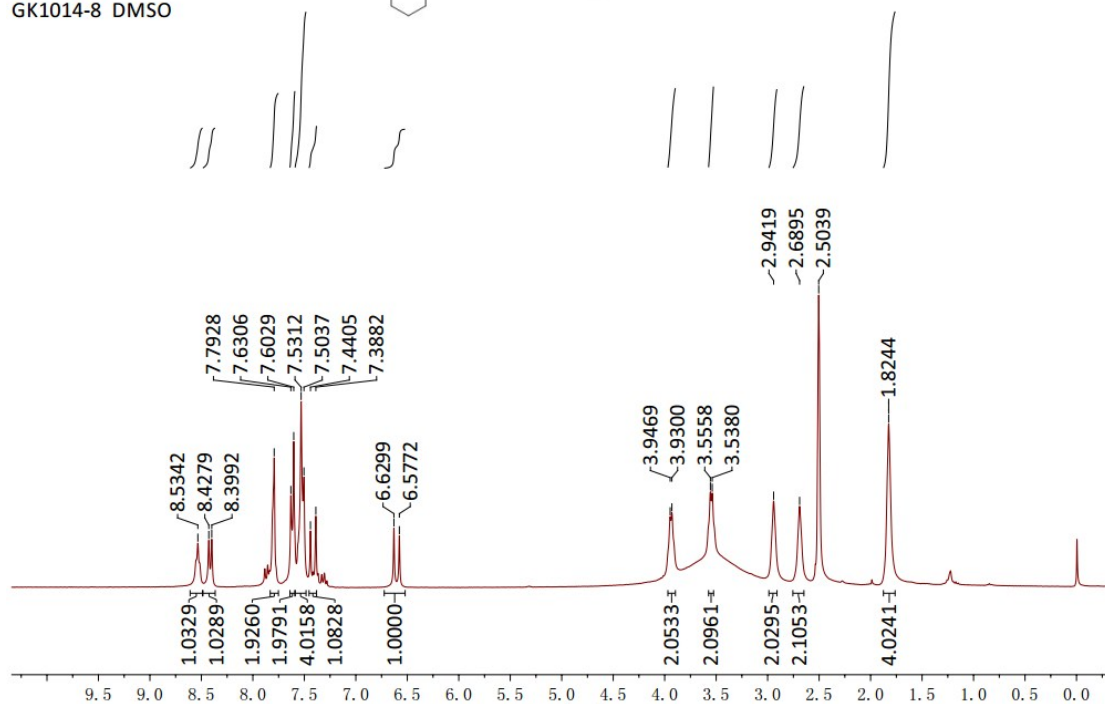
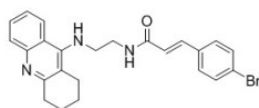
### 23 <sup>13</sup>C NMR spectrum

23



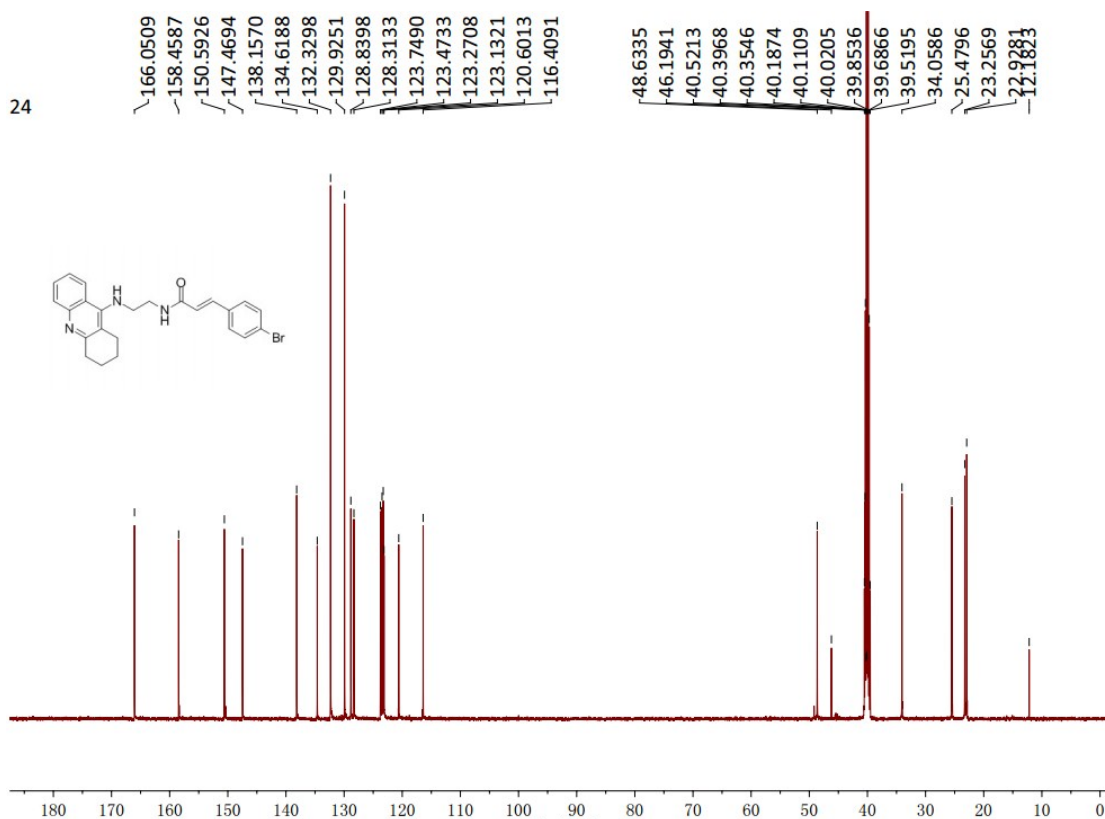
### 24 <sup>1</sup>H NMR spectrum

GK1014-8  
GK1014-8 DMSO

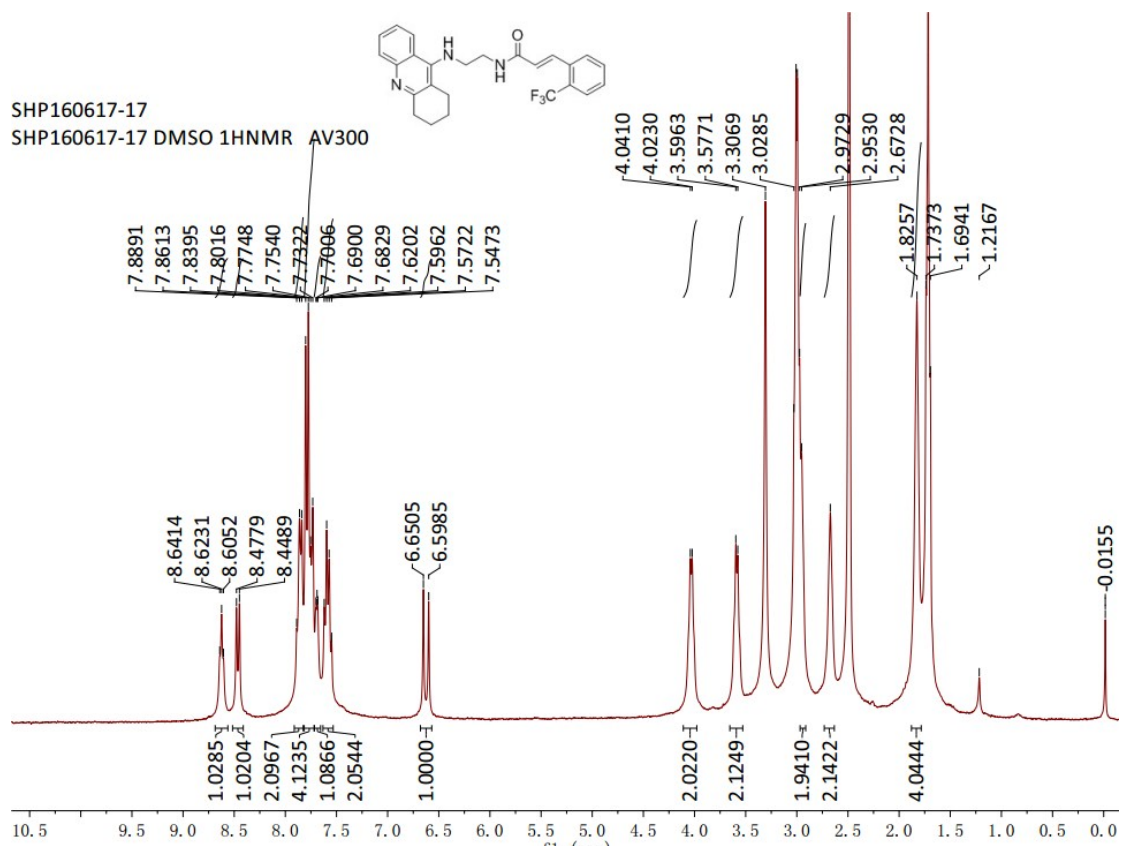


### 24 <sup>13</sup>C NMR spectrum

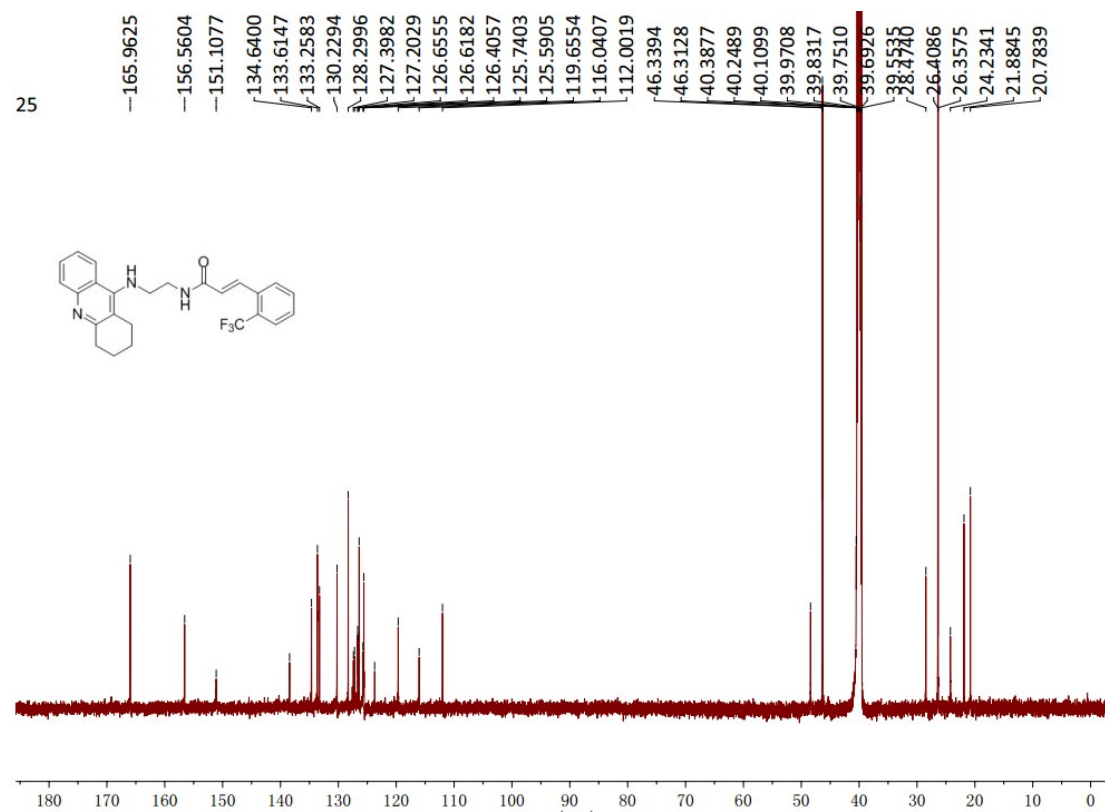
24



### 25 <sup>1</sup>H NMR spectrum



### 25 <sup>13</sup>C NMR spectrum

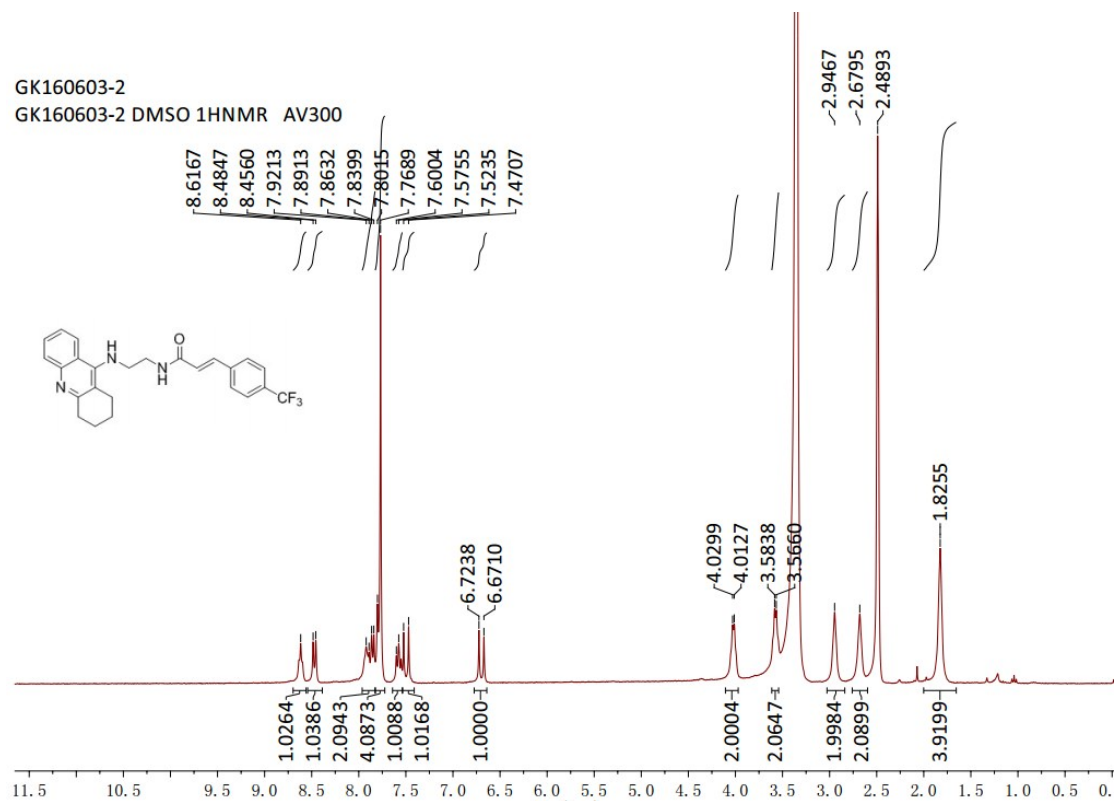




## 26 <sup>1</sup>H NMR spectrum

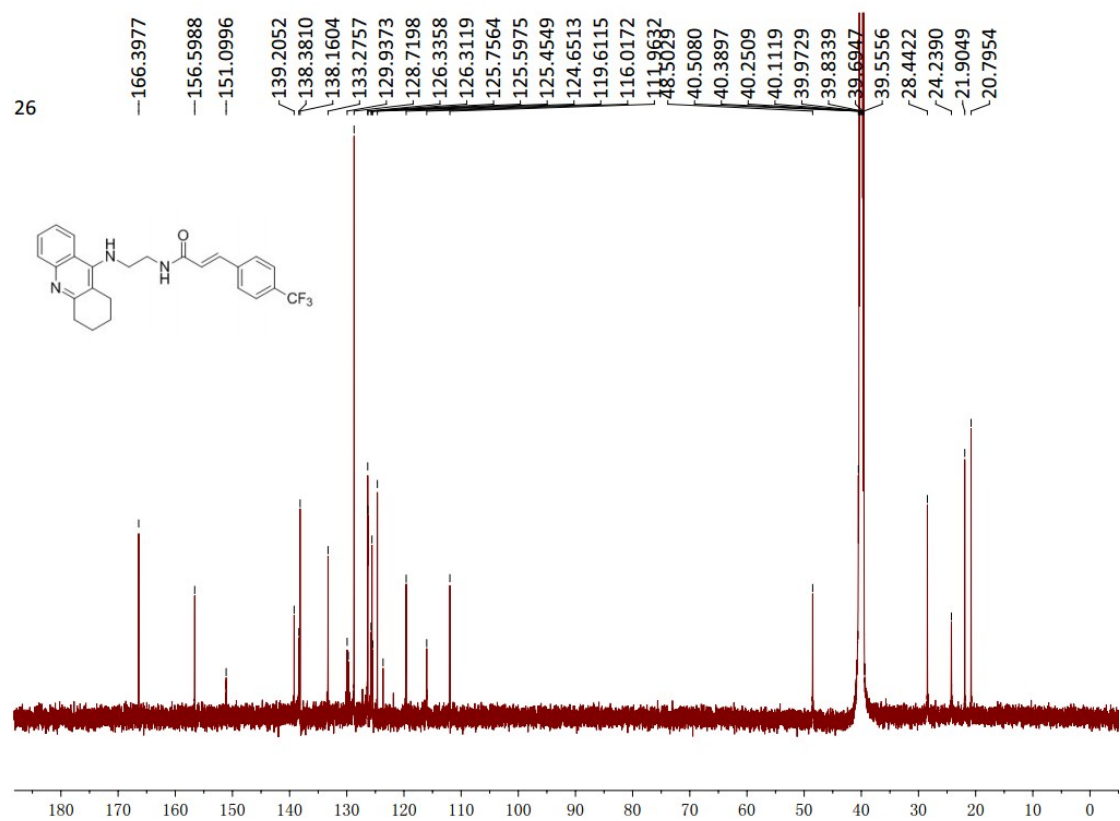
GK160603-2

GK160603-2 DMSO 1HNMR AV300



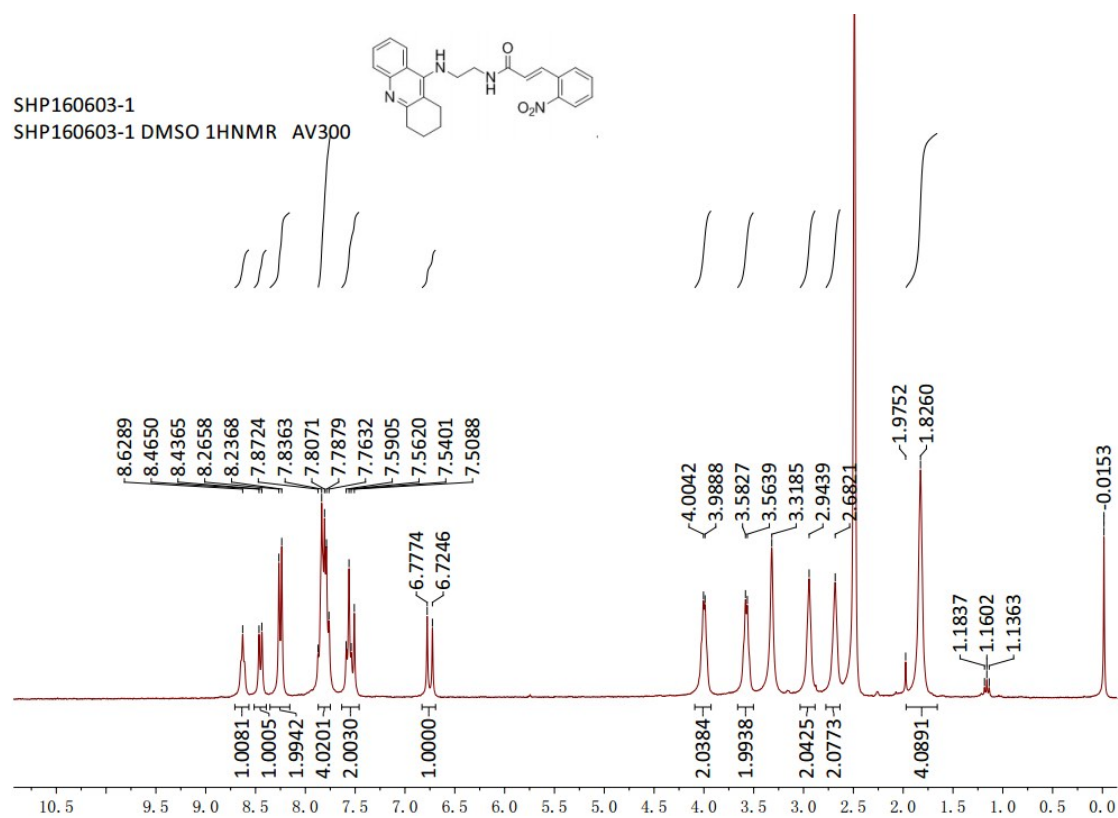
## 26 <sup>13</sup>C NMR spectrum

26

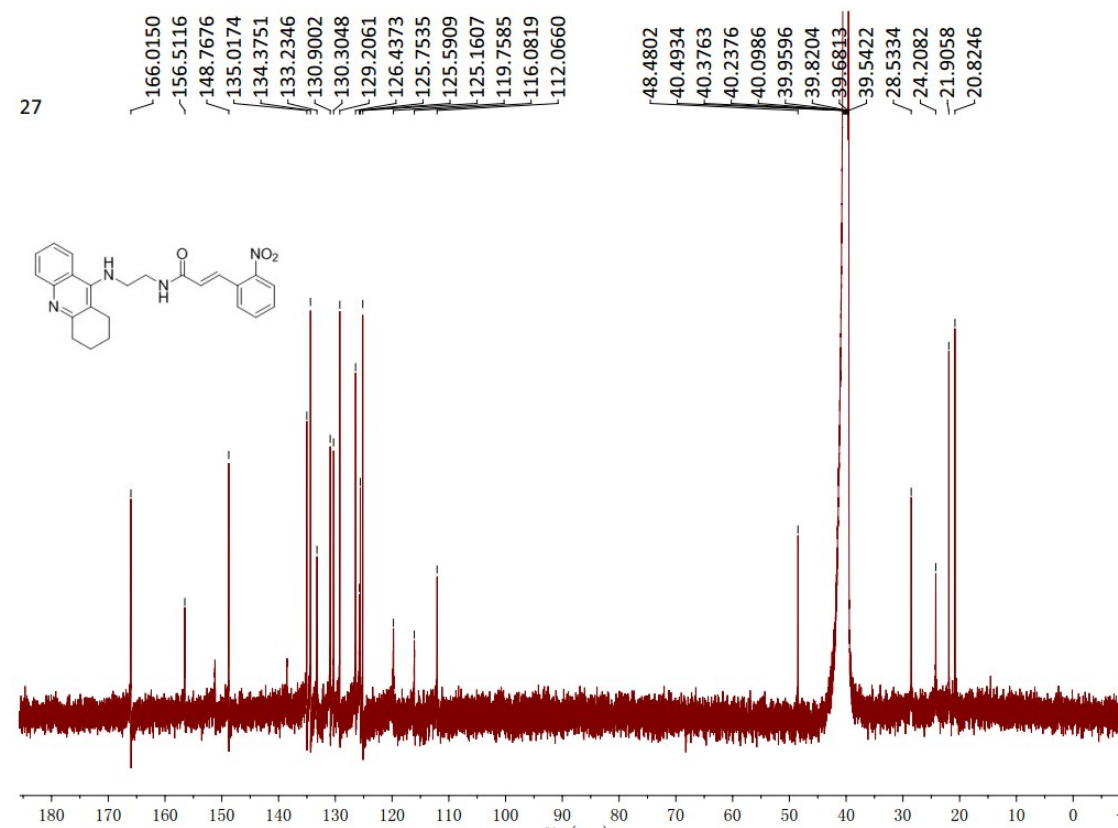




27 <sup>1</sup>H NMR spectrum

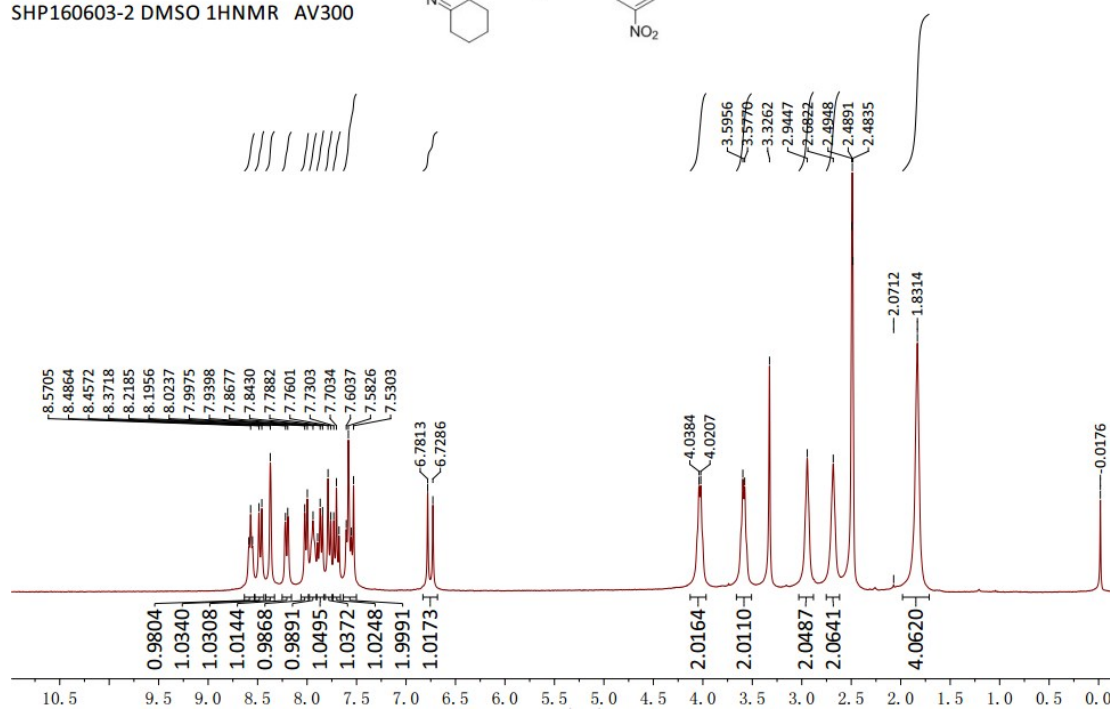
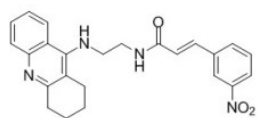


27 <sup>13</sup>C NMR spectrum



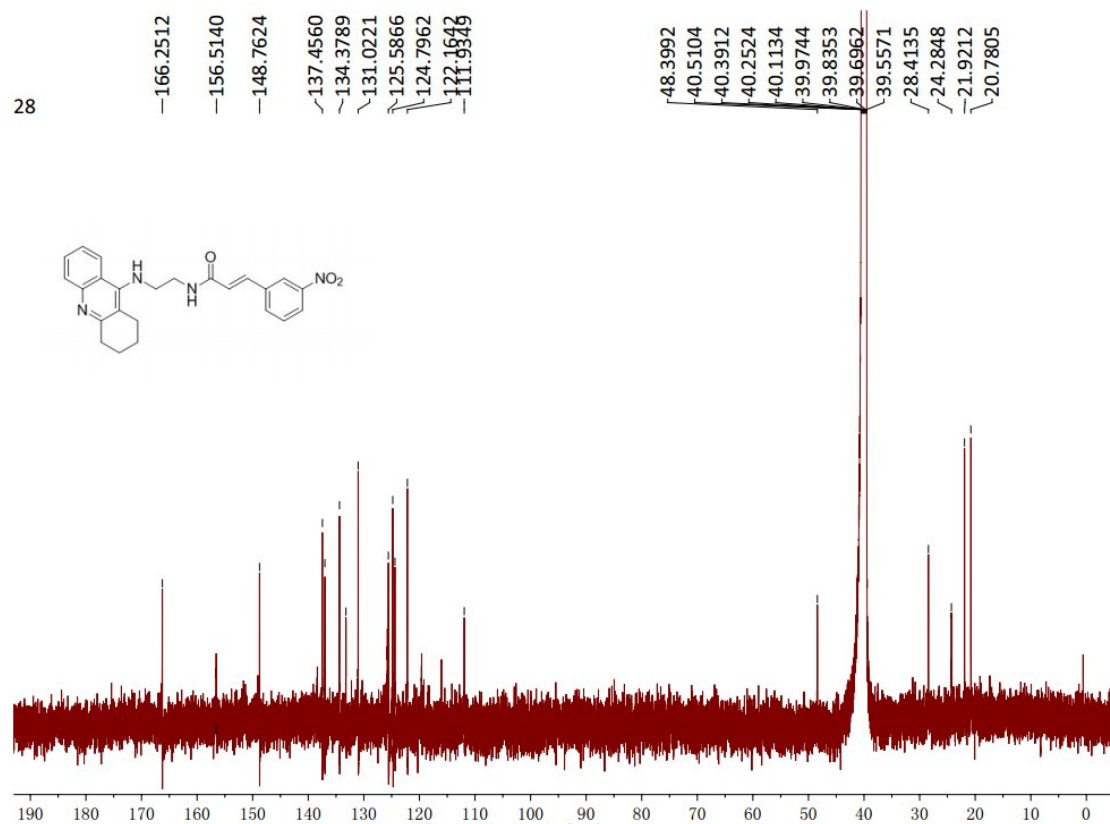
**28**  $^1\text{H}$  NMR spectrum

SHP160603-2  
SHP160603-2 DMSO  $1\text{H}$ NMR AV300



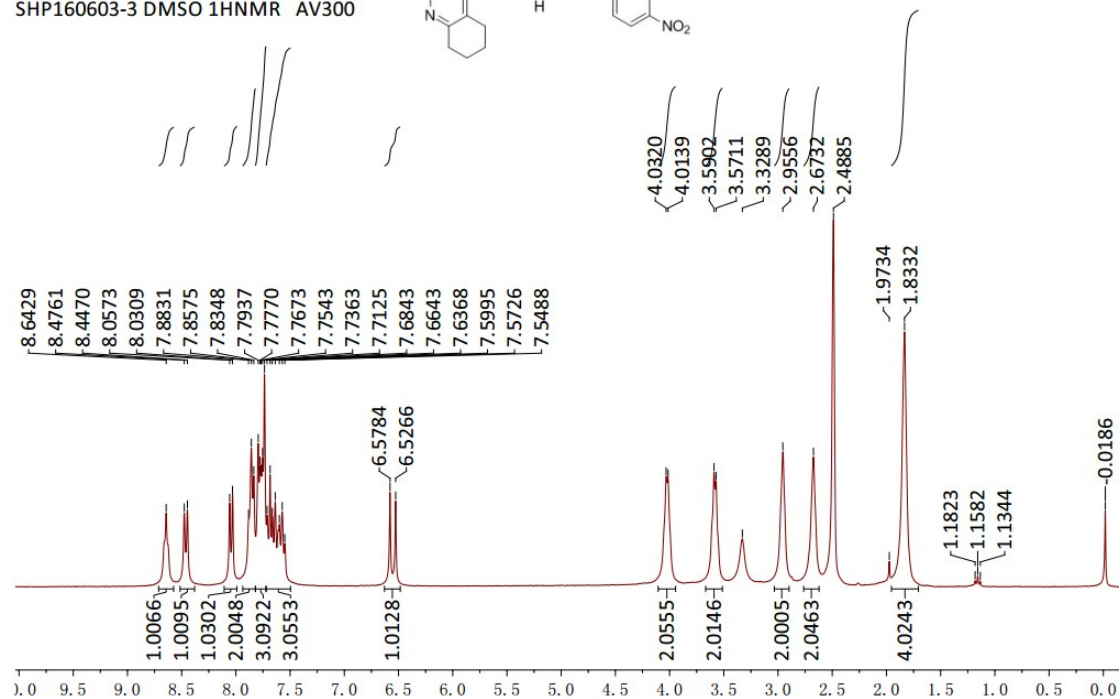
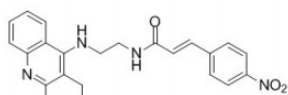
**28**  $^{13}\text{C}$  NMR spectrum

28



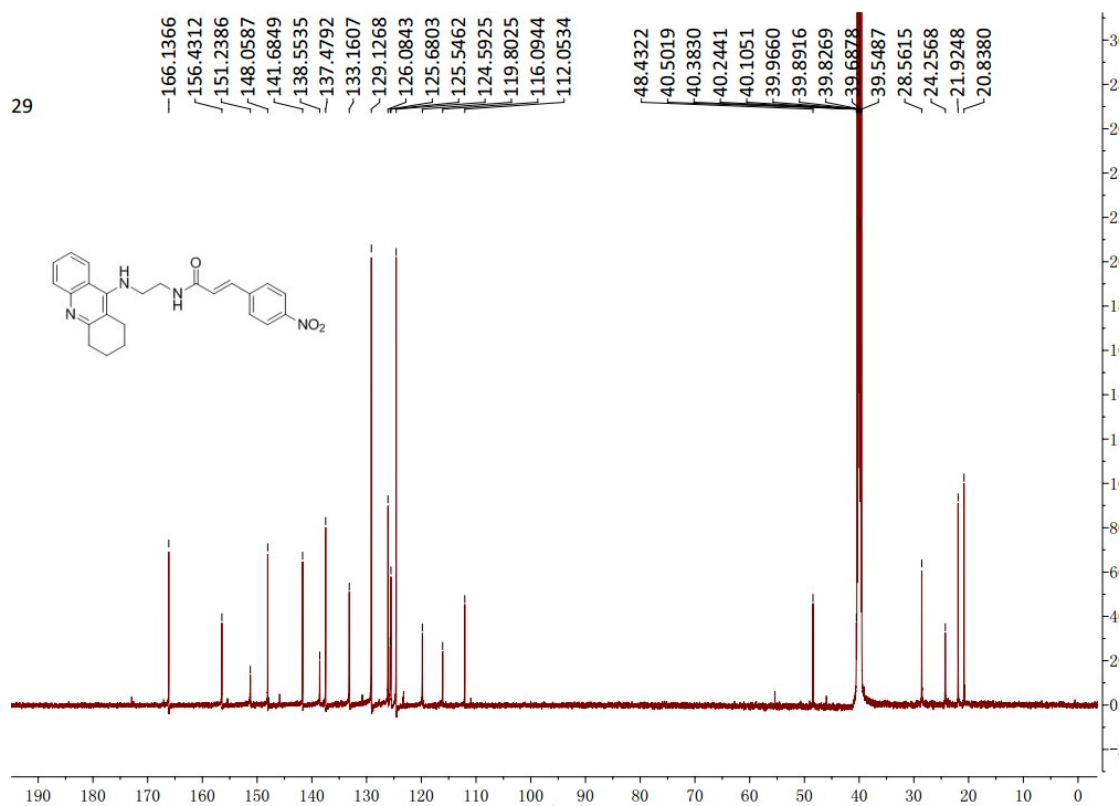
# 29 <sup>1</sup>H NMR spectrum

SHP160603-3  
SHP160603-3 DMSO 1HNMR AV300

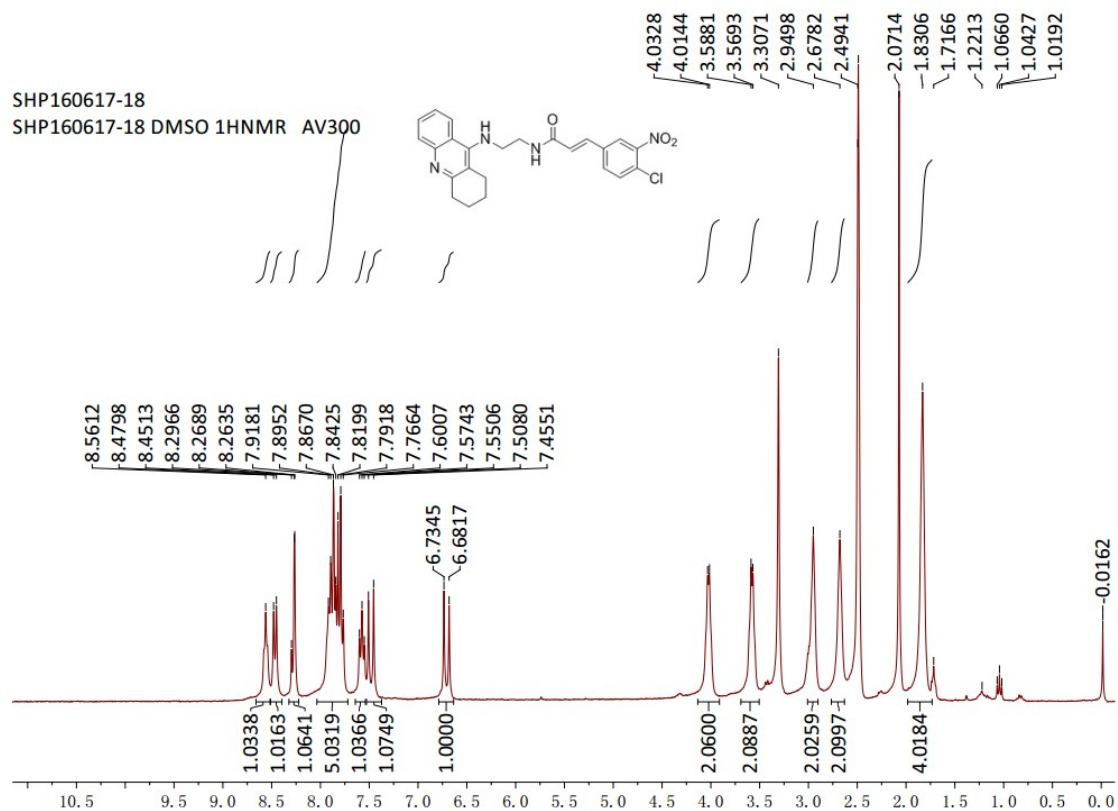


# 29 <sup>13</sup>C NMR spectrum

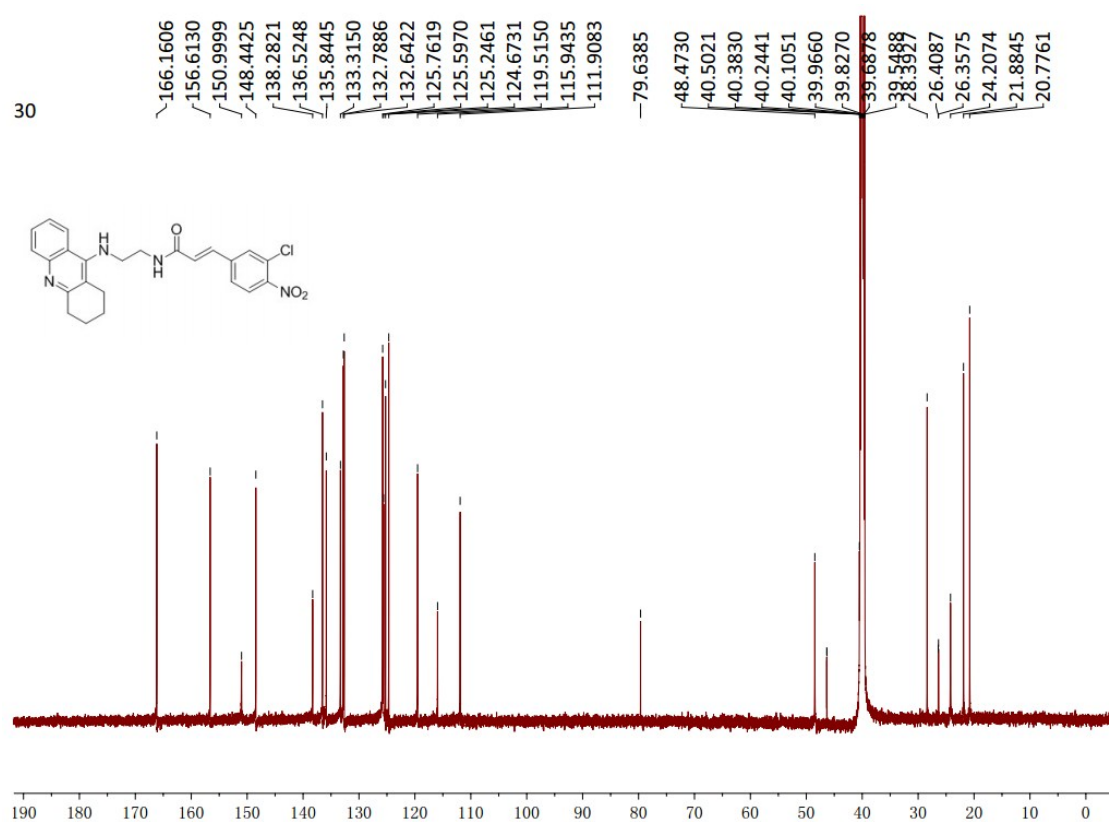
29



### 30 <sup>1</sup>H NMR spectrum



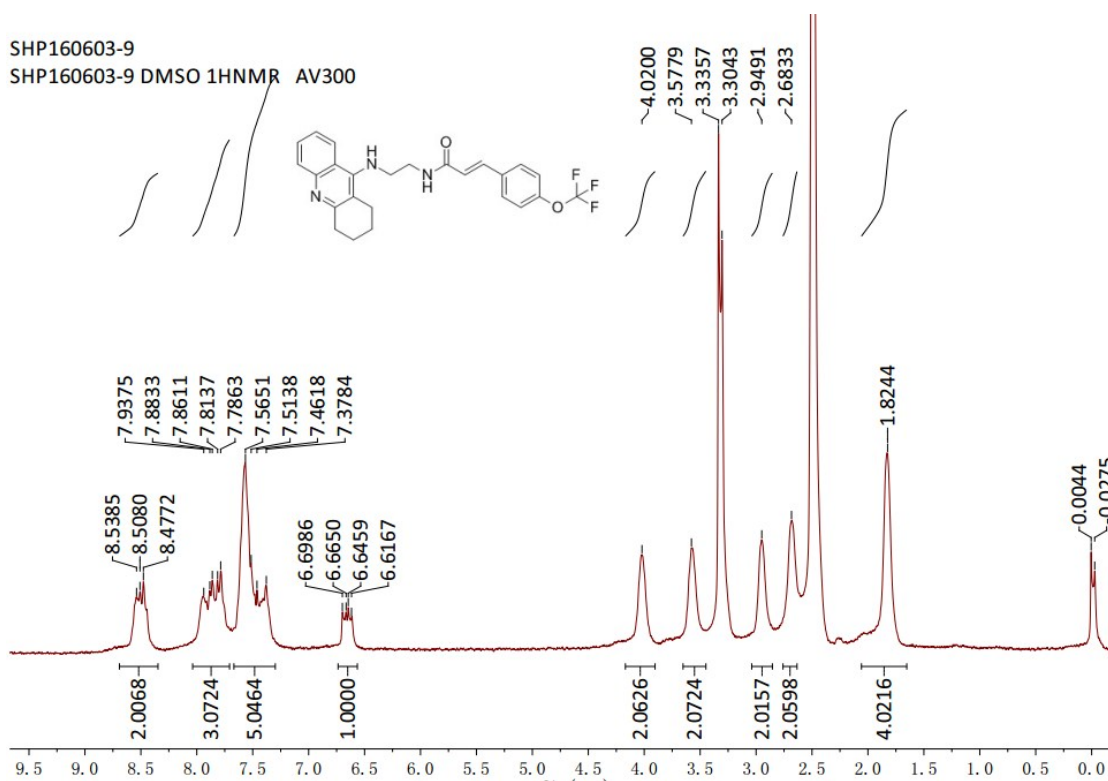
### 30 <sup>13</sup>C NMR spectrum



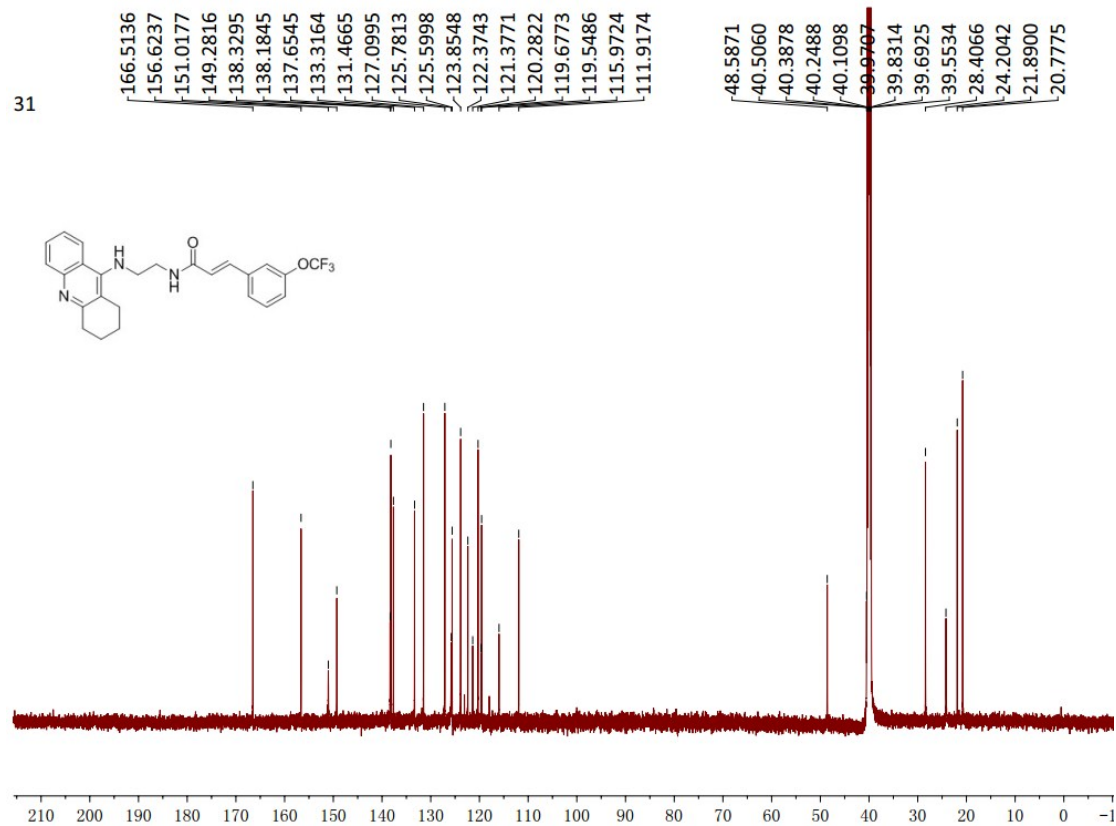
### 31 <sup>1</sup>H NMR spectrum

SHP160603-9

SHP160603-9 DMSO 1HNMR AV300



### 31 <sup>13</sup>C NMR spectrum

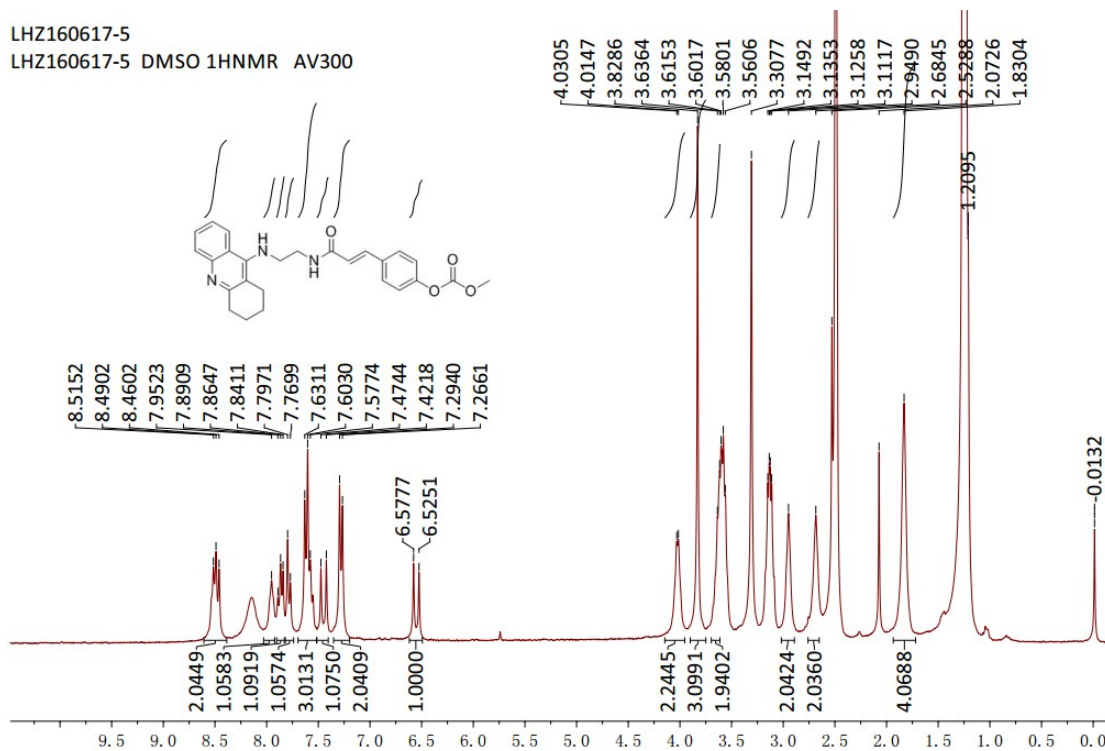




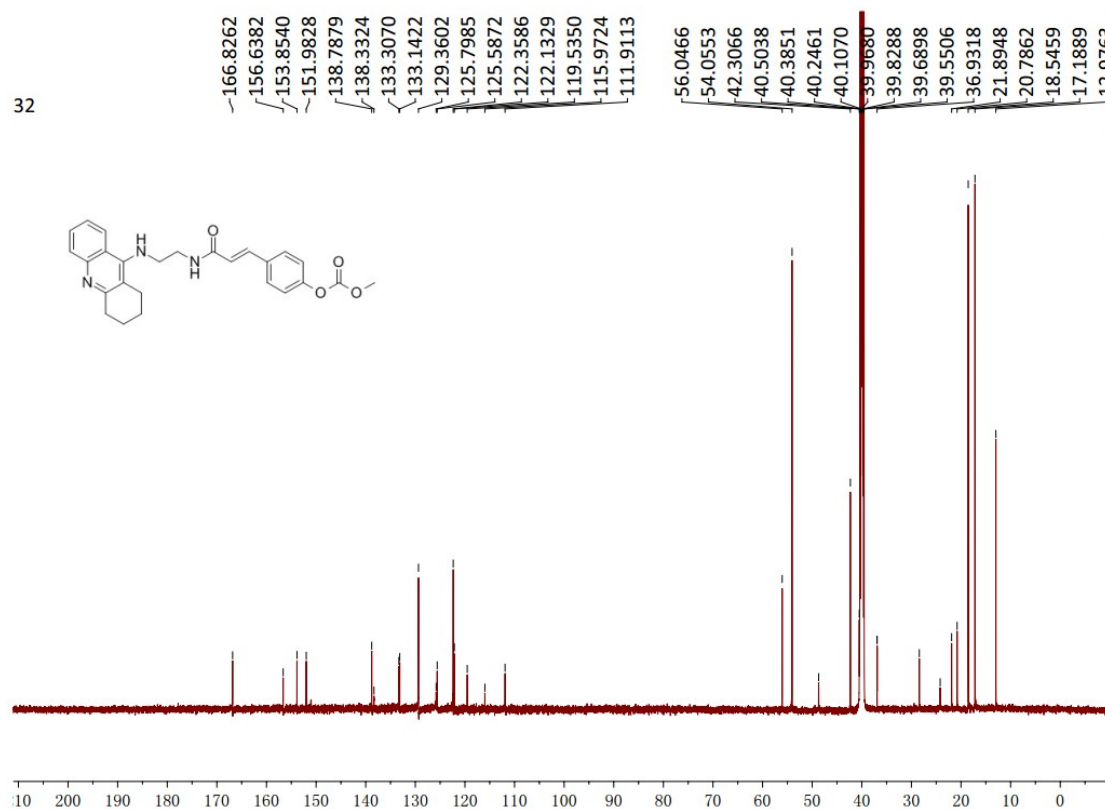
### 32 <sup>1</sup>H NMR spectrum

LHZ160617-5

LHZ160617-5 DMSO 1HNMR AV300

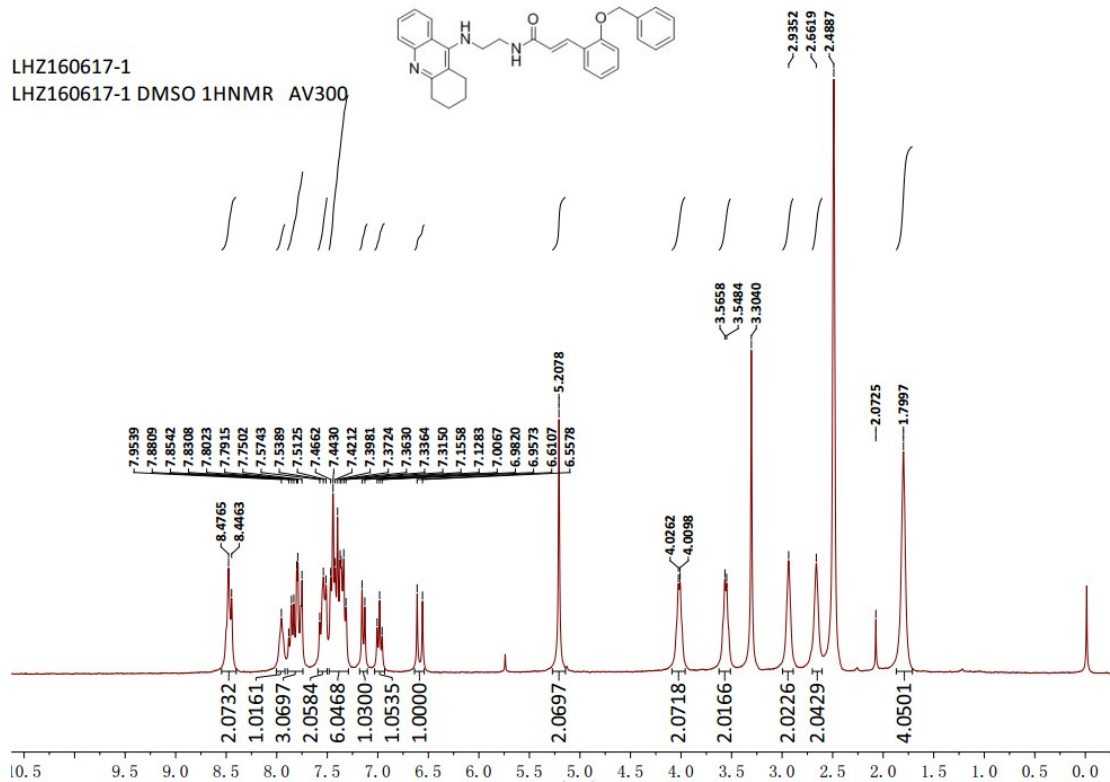


### 32 <sup>13</sup>C NMR spectrum

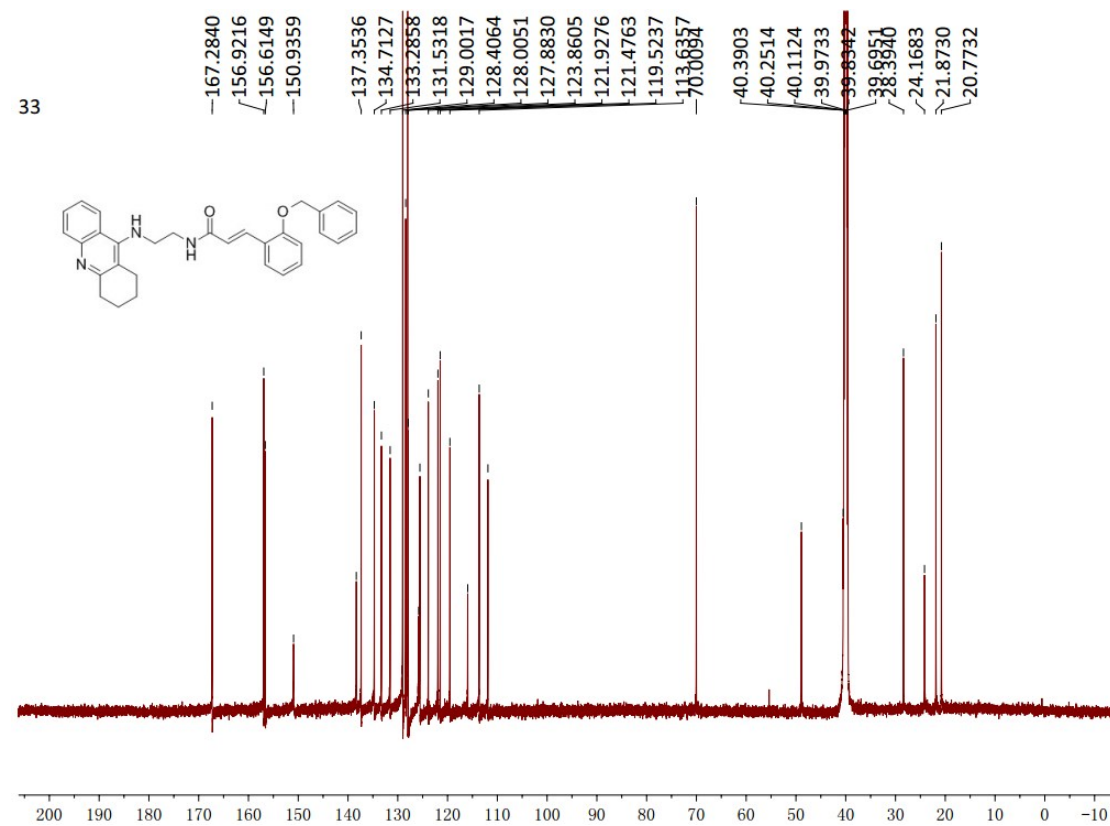




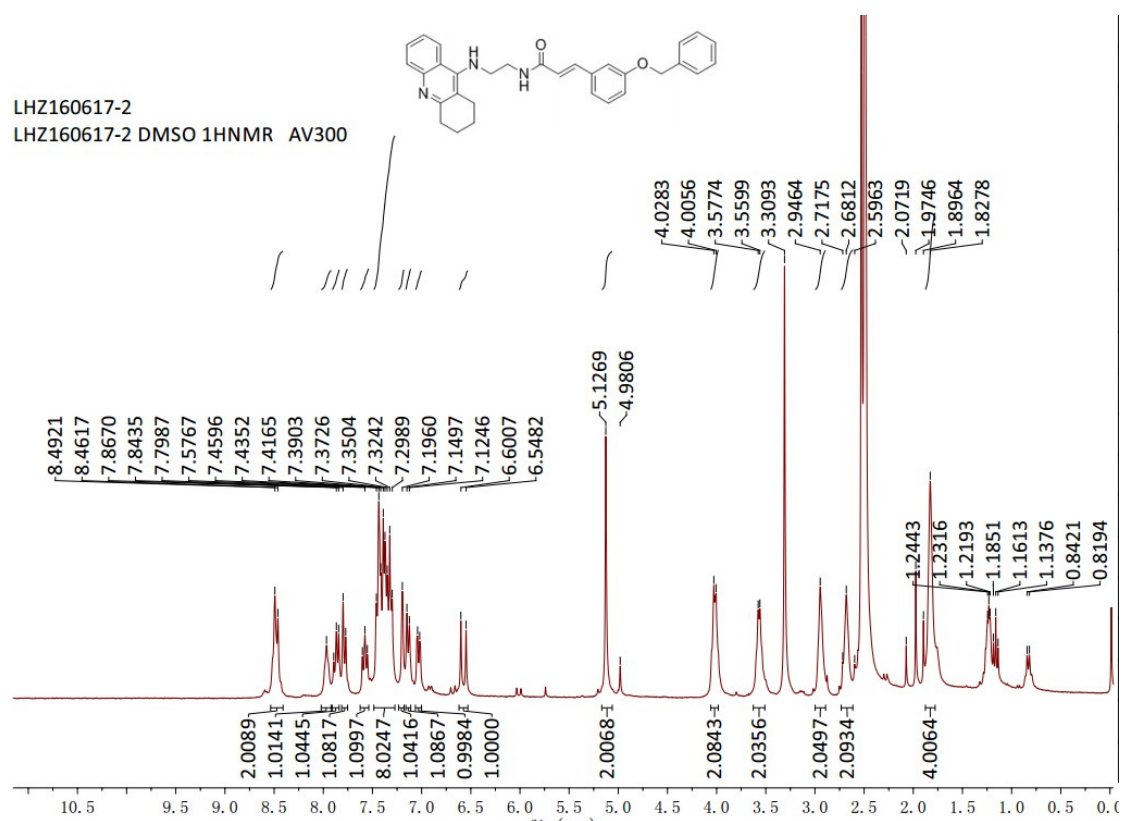
### 33 <sup>1</sup>H NMR spectrum



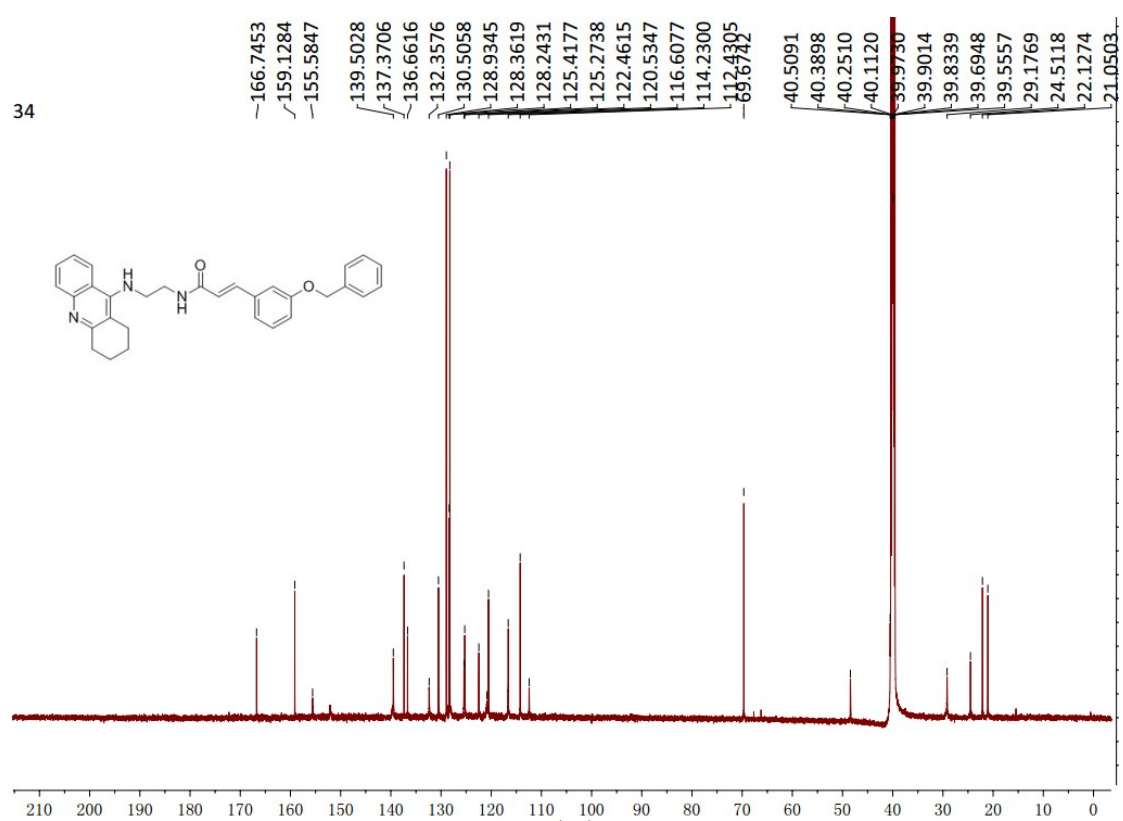
### 33 <sup>13</sup>C NMR spectrum



### 34 <sup>1</sup>H NMR spectrum

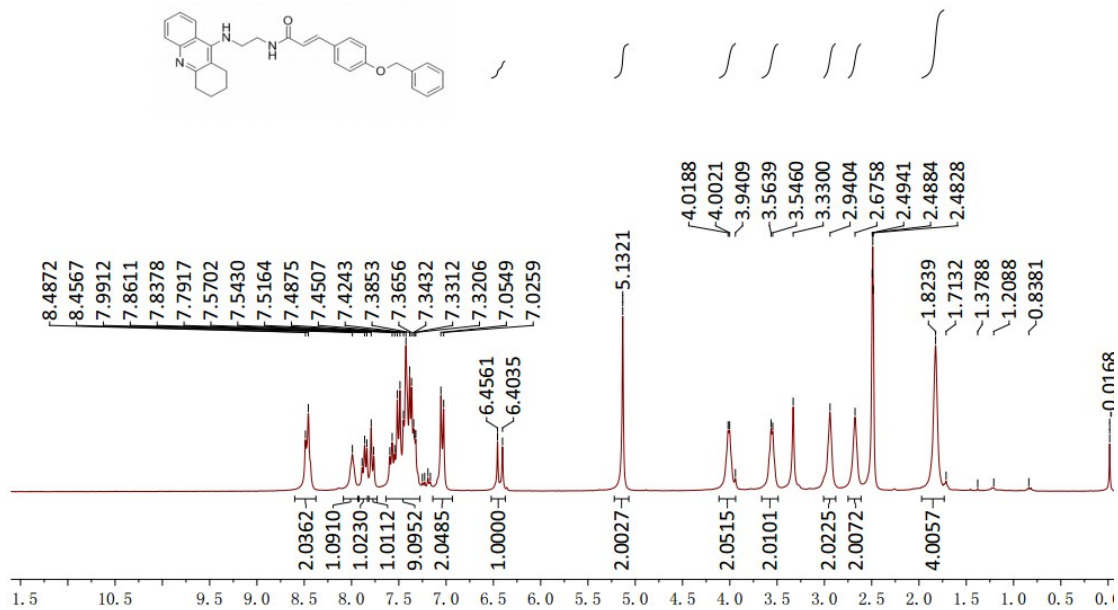


### 34 <sup>13</sup>C NMR spectrum

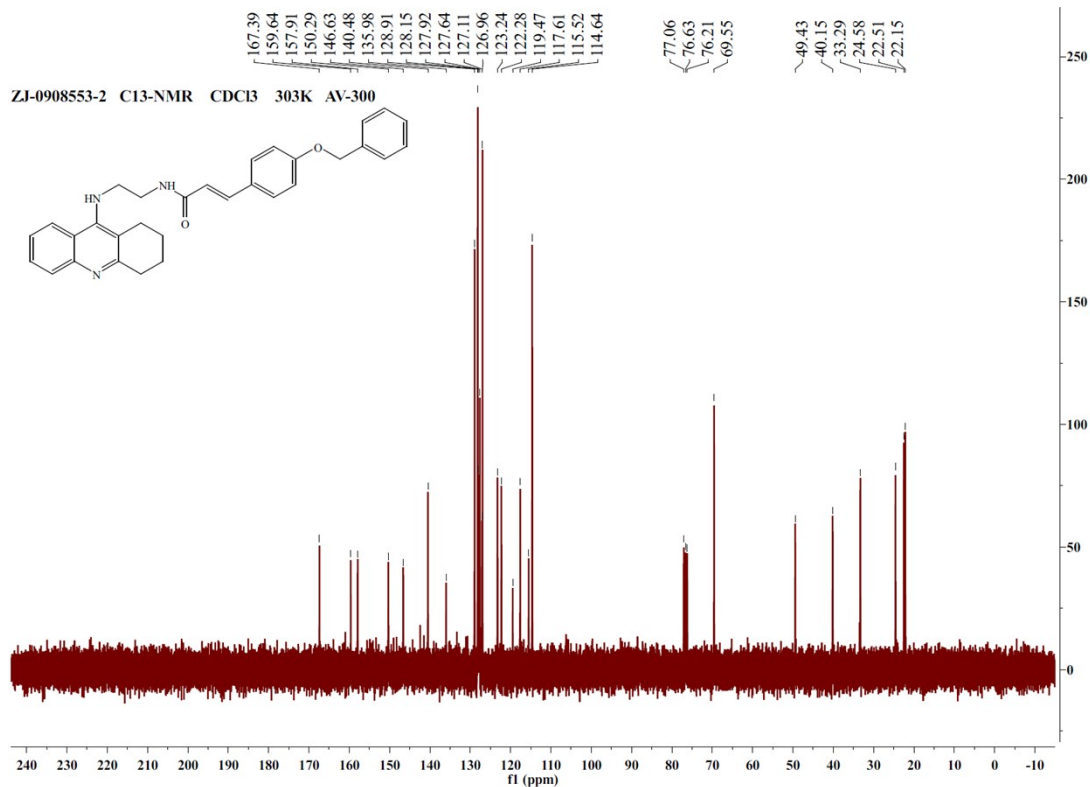


### 35 <sup>1</sup>H NMR spectrum

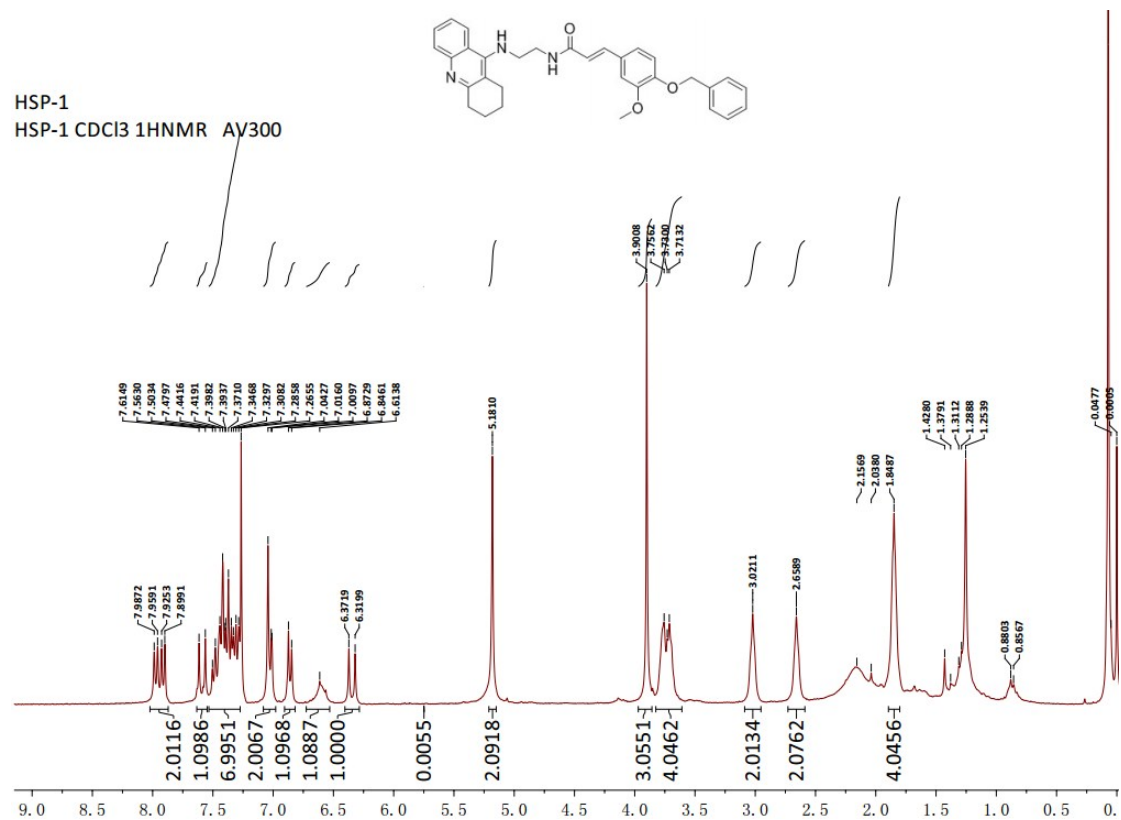
SHP160603-5  
SHP160603-5 DMSO 1HNMR AV300



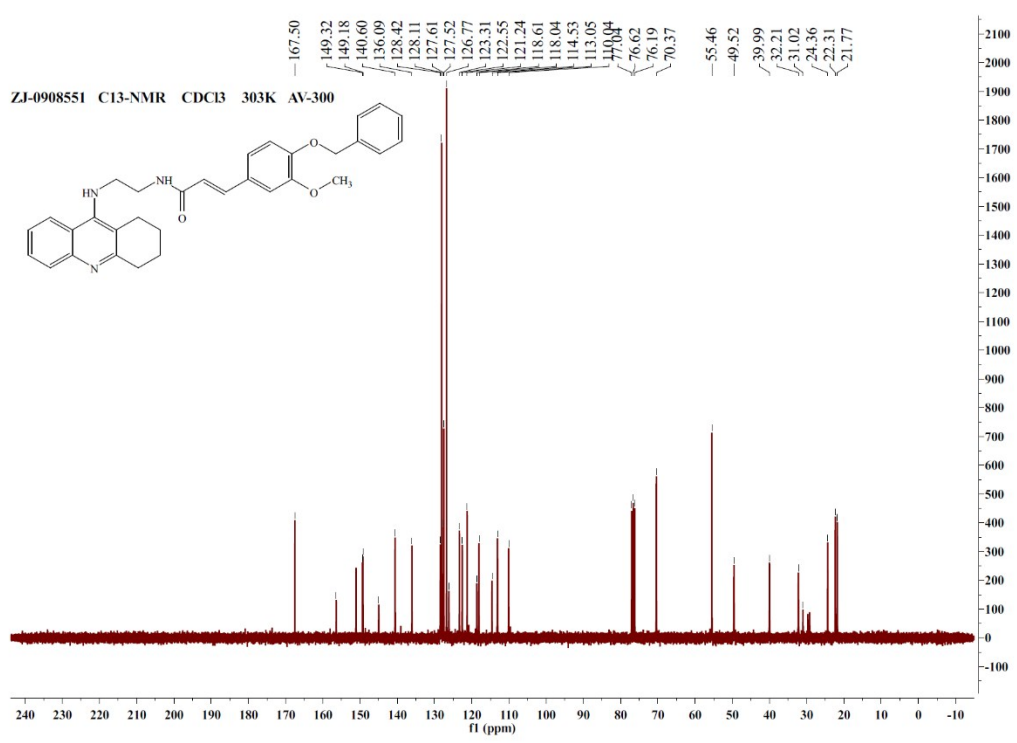
### 35 <sup>13</sup>C NMR spectrum



**36**  $^1\text{H}$  NMR spectrum



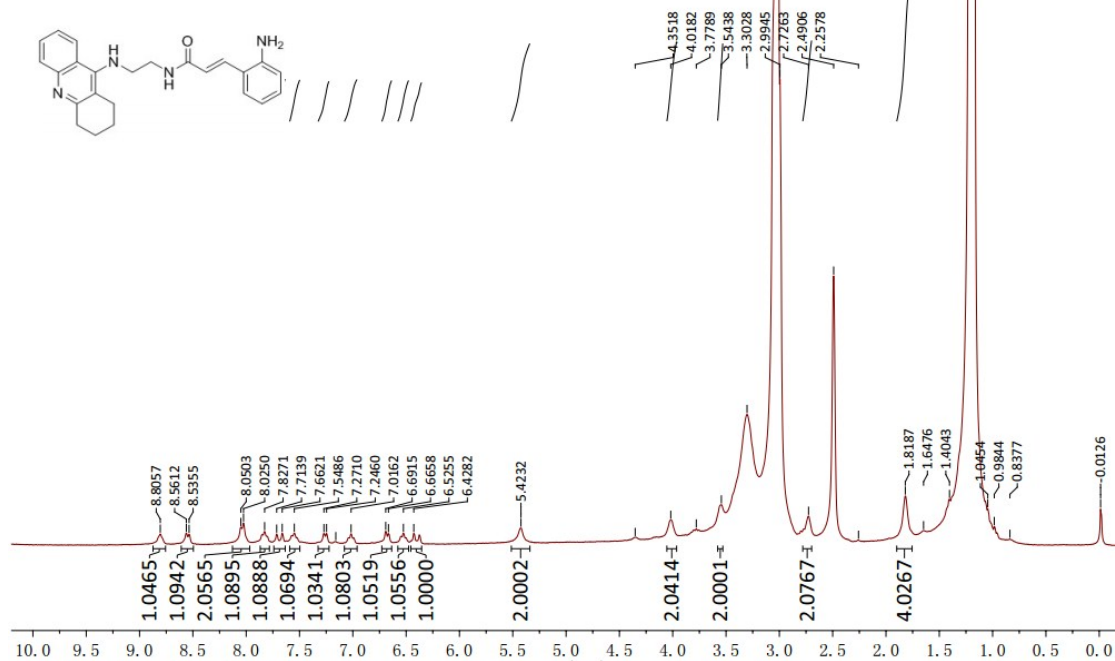
**36**  $^{13}\text{C}$  NMR spectrum



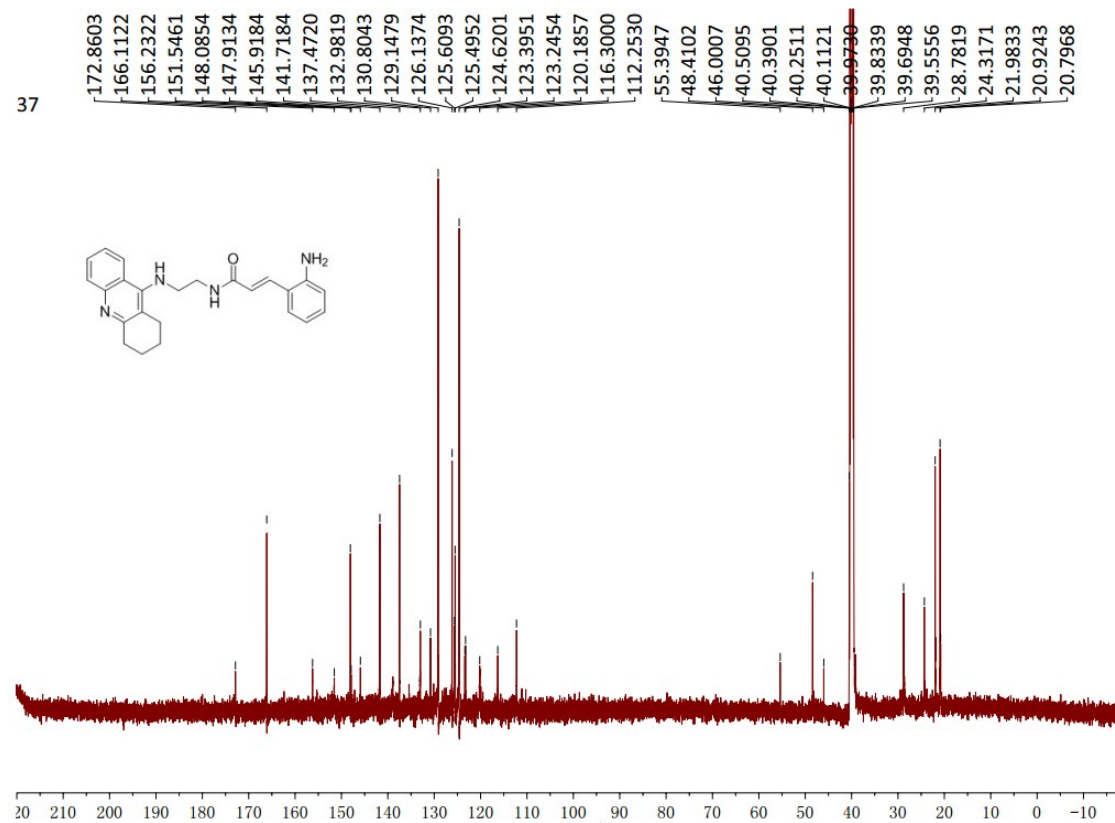
### 37 <sup>1</sup>H NMR spectrum

LHZ20160822-1

LHZ20160822-1 DMSO 1HNMR AV300



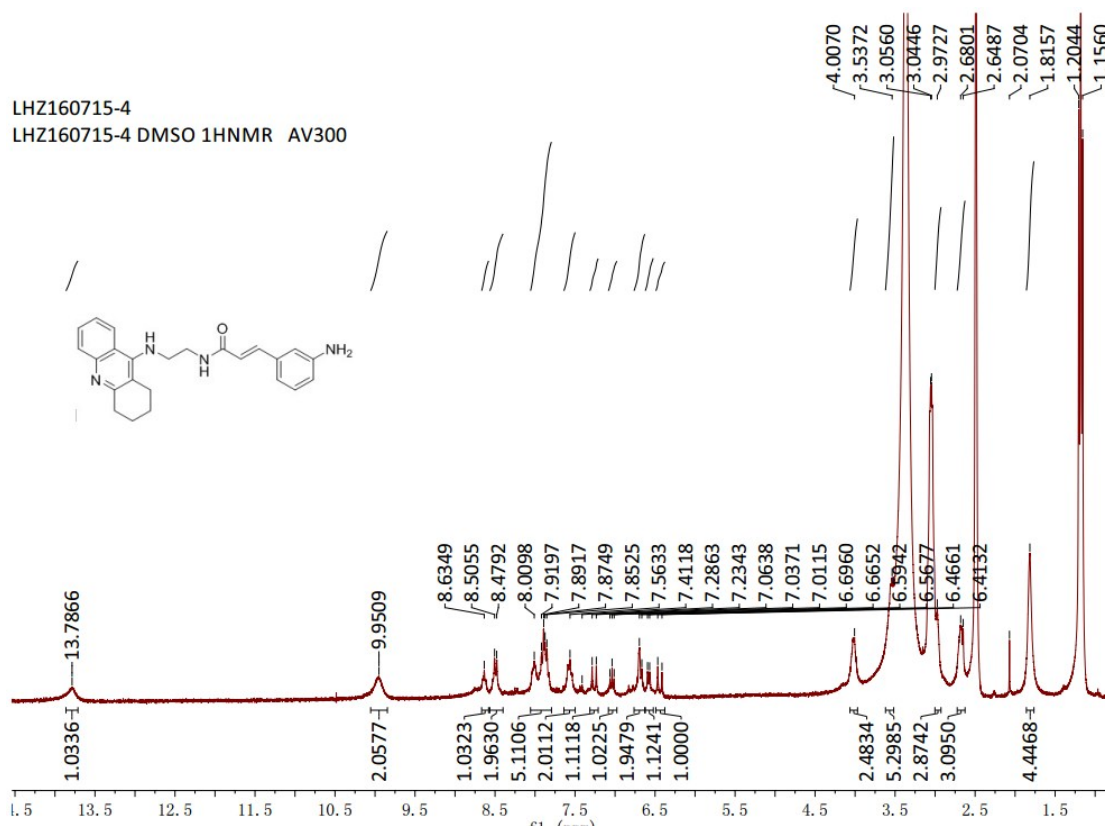
### 37 <sup>13</sup>C NMR spectrum



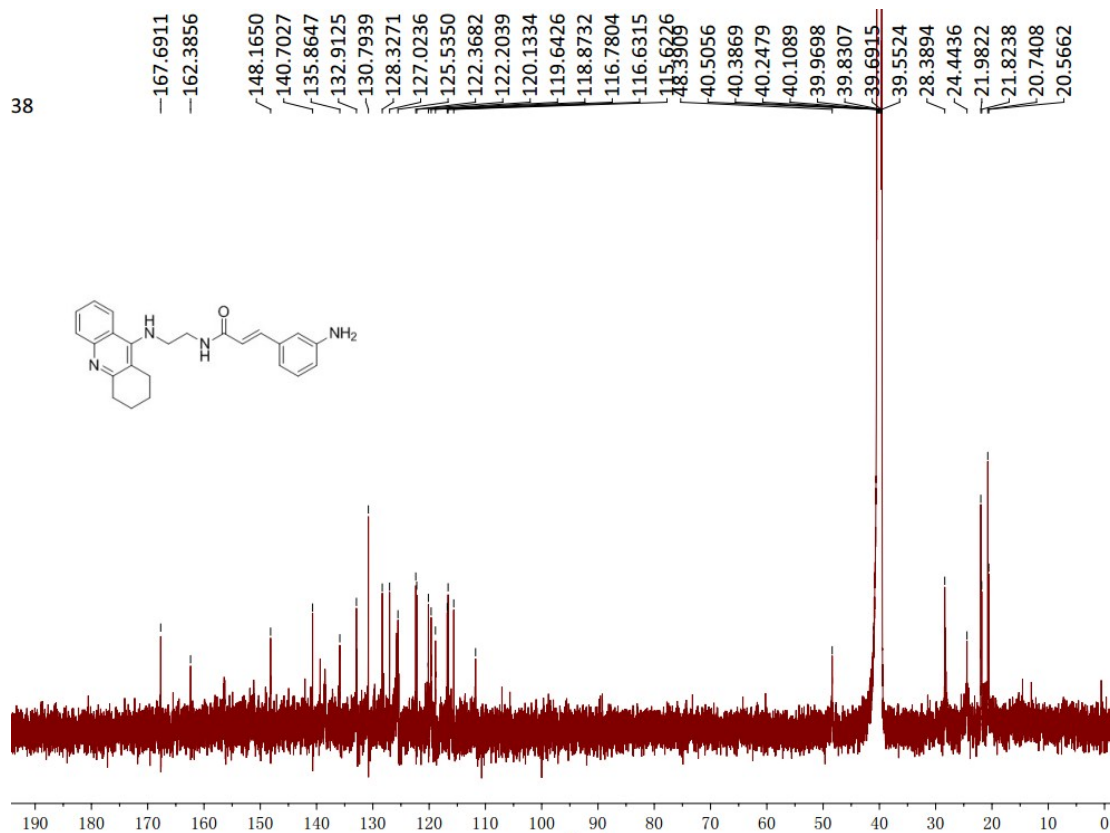


### 38 <sup>1</sup>H NMR spectrum

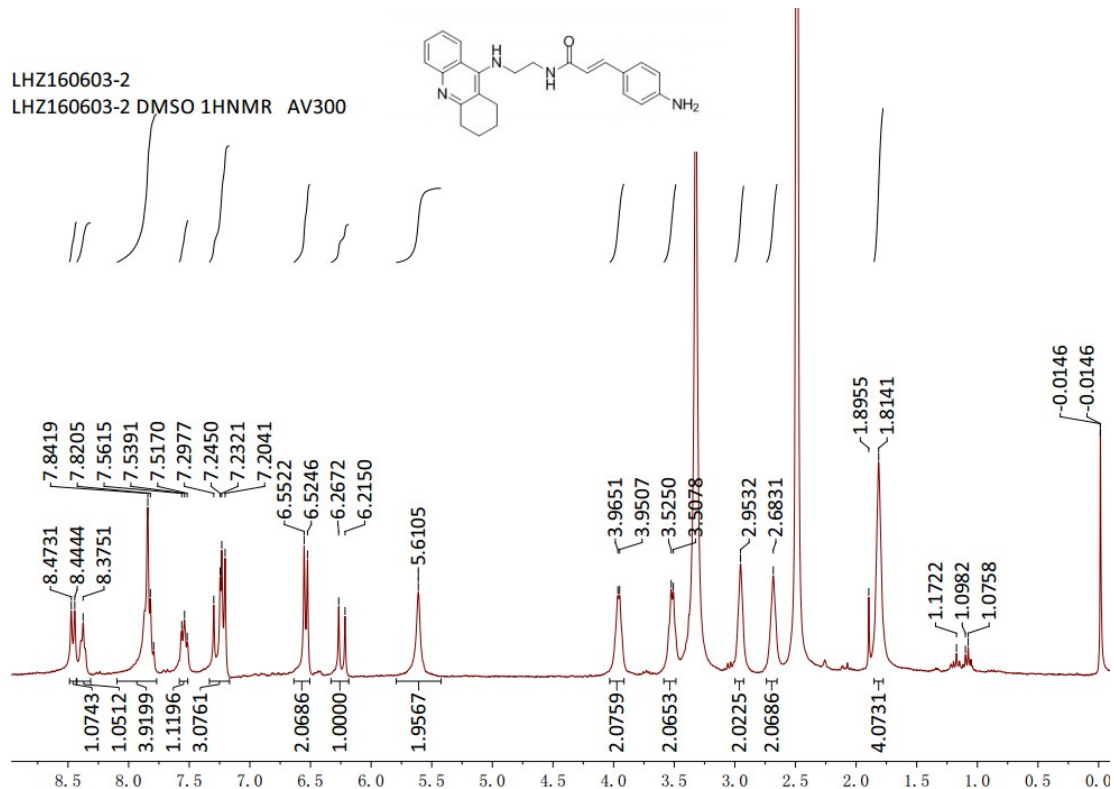
LHZ160715-4  
LHZ160715-4 DMSO 1HNMR AV300



### 38 <sup>13</sup>C NMR spectrum



**39** <sup>1</sup>H NMR spectrum



**39** <sup>13</sup>C NMR spectrum,

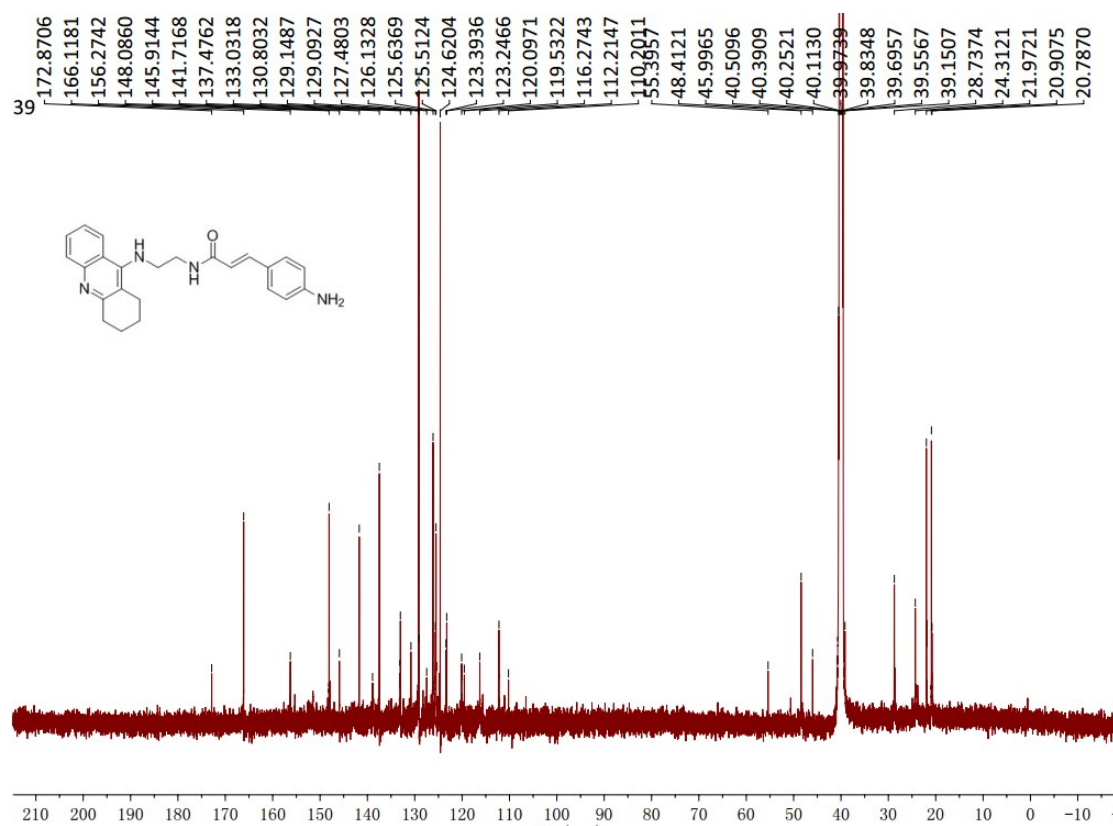


Table S1. The fluorescence intensity data of thioflavin T-based fluorometric assay.

<b>Cpd.</b>	<b>Intensity (OD value)</b>	<b>Cpd.</b>	<b>Intensity (OD value)</b>
<b>8</b>	1.269	<b>26</b>	1.079
<b>9</b>	0.946	<b>27</b>	1.282
<b>10</b>	0.949	<b>28</b>	1.287
<b>11</b>	0.850	<b>29</b>	1.188
<b>12</b>	1.304	<b>30</b>	1.116
<b>13</b>	1.252	<b>31</b>	0.985
<b>14</b>	1.258	<b>32</b>	1.138
<b>15</b>	1.293	<b>33</b>	0.853
<b>16</b>	0.942	<b>34</b>	0.912
<b>17</b>	1.091	<b>35</b>	0.889
<b>18</b>	1.000	<b>36</b>	0.834
<b>19</b>	0.969	<b>37</b>	1.110
<b>20</b>	0.984	<b>38</b>	1.178
<b>21</b>	0.999	<b>39</b>	1.046
<b>22</b>	0.920	<b>Curcumin</b>	0.785
<b>23</b>	1.075	<b>A<math>\beta</math><sub>1-42</sub></b>	1.356
<b>24</b>	1.089	<b>ThT</b>	0.120
<b>25</b>	1.269		