# Supporting Information

**Synthesis and anti-influenza virus effects of novel substituted polycyclic pyridone derivatives modified from Baloxavir**

Lin Tang[a†], Haiyan Yan[b†], Weibin Wu[a,c], Dawei Chen[a], Zhenxiong Gao[d], Jinqiang Hou[e], Cunlong Zhang[a,c,*], Yuyang Jiang[f,g,*]

a Shenzhen Kivita Innovative Drug Discovery Institute, Shenzhen 518057, PR China.

*b* Beijing Key Laboratory of Antimicrobial Agents, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, PR China.

*c* National & Local United Engineering Lab for Personalized Anti-tumor Drugs, The Graduate School at Shenzhen, Tsinghua University, Shenzhen 518055, PR China.

*d* Department of Chemistry, Tsinghua University, Beijing 100084, PR China.

*e* Department of Chemistry, Lakehead University and Thunder Bay Regional Health Research Institute, 980 Oliver Road, Thunder Bay, On, P7B 6V4, Canada.

*f* Joint Key State Laboratory of Tumor Chemogenomics, Tsinghua Shenzhen International Graduate School, Tsinghua University, Shenzhen 518055, PR China.

*g* School of pharmaceutical sciences, Tsinghua University, Beijing 100084, PR China.

[†]These authors contributed equally to this work.

*Corresponding authors.

E-mail: zhcunl@126.com (Cunlong Zhang); jiangyy@sz.tsinghua.edu.cn (Yuyang Jiang).

## Table of Contents:

## 1. Compound purity information

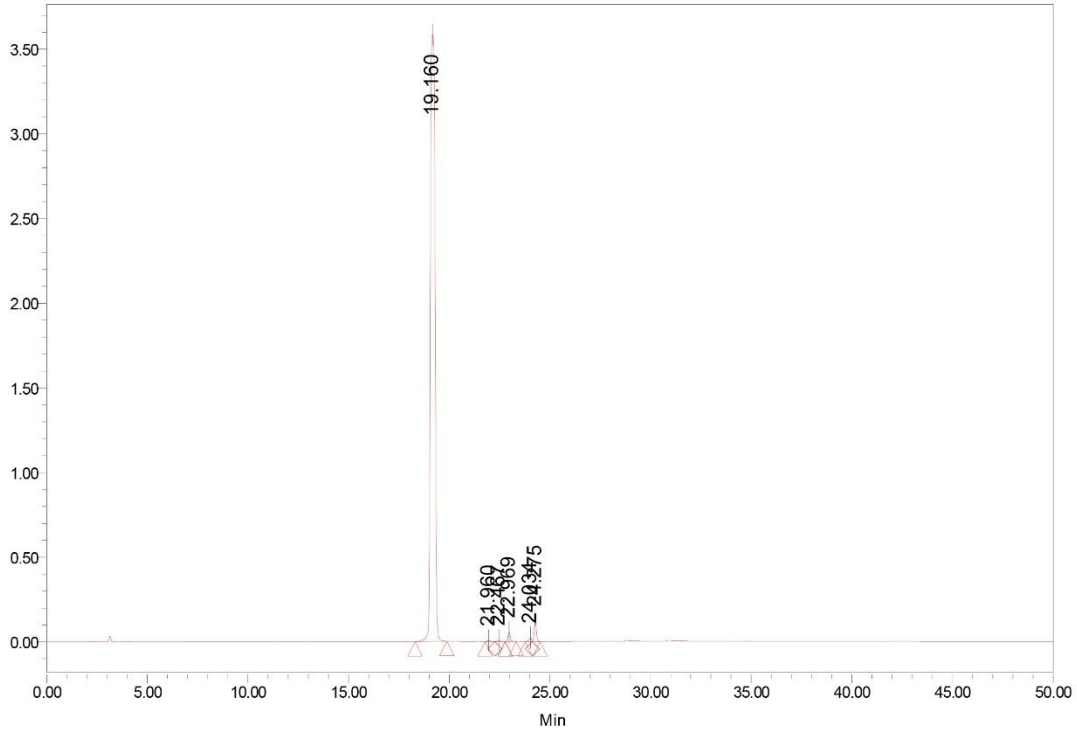
The purity of all tested compounds was determined by HPLC (**Table S1**). In **Figure S1** and **Figure S2**, HPLC traces of the key compound (**10a**) and the lead compound (**Baloxavir**) were shown.

**Table S1.** Compound purity information.

| Compound | Purity (HPLC) |
|---|---|
| **10a** | 96.99 % |
| **10b** | 95.66 % |
| **10c** | 97.56 % |
| **10d** | 99.83 % |
| **10e** | 96.41 % |
| **10f** | 98.95 % |
| **10g** | 99.15 % |
| **10h** | 96.18 % |
| **10i** | 98.75 % |
| **10j** | 95.31 % |
| **10k** | 96.01 % |
| **Baloxavir** | 99.51 % |

Sample information

| | | | |
|---|---|---|---|
| Sample name | 10a | | |
| | | Sample group name | 20210719_1 |
| Sample bottle | 97 | Collection method group | 20210617 50min |
| Number of injections | 1 | Approach | 10a_2 |
| Injection volume | 20.00 ul | Channel name | W2489 ChA |
| Run time | 50.0 Minutes | Processing channel description | W2489 ChA 220nm |
| Acquisition time | 2021/7/19 16:42:27 CST | | |
| Processing time | 2021/7/20 11:25:51 CST | | |




| Name | Retention time (min) | Area (μV*S) | % Area | Height (μV) | % Height | Symmetry factor | Resolution | Theoretical plate number | s/n |
|---|---|---|---|---|---|---|---|---|---|
| | 19.160 | 57370058 | 96.99 | 3587480 | 94.22 | 1.17 | | 45753 | 21446 |
| | 21.960 | 71920 | 0.12 | 6795 | 0.18 | 1.49 | 8.30 | 126818 | 41 |
| | 22.467 | 87101 | 0.15 | 9443 | 0.25 | 1.27 | 2.16 | 147535 | 56 |



2021/7/20
11:51:11 PRC

**Figure S1.** The HPLC trace of compound 10a.

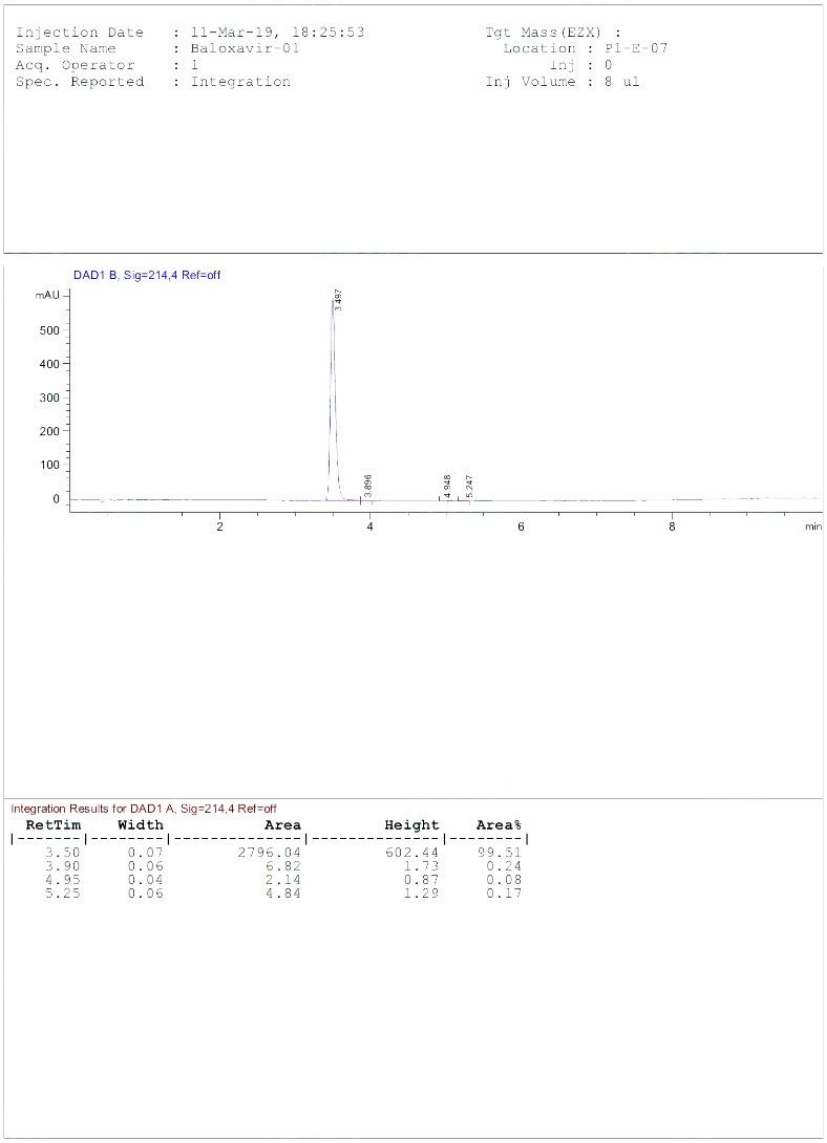



**Figure S2.** The HPLC trace of Baloxavir.

## 2. Animal care and use

The pharmacokinetic study of **10a** in male SD rats was outsourced to Sundia Pharmaceutical Technology (Shanghai) Co., LTD. The animal study was performed with the approval of the Sundia Animal Care and Use Committee.

## 3. Synthetic procedures of intermediates

***3.1.*** *Synthetic procedure for methyl 2-(bromomethyl)benzoate* (**3**)

To a solution of chlorobenzene (30mL) were added **2** (3.15g, 21.0mmol), N-Bromosuccinimide (4.09g, 23.0mmol), the NBS was used without freshly crystallized before. Then a solution of azodiisobutyronitrile (0.13g, 0.80mmol) in chlorobenzene (10mL) was added, and the mixture was heated to 70°C. This mixture was stirred for 1h at 70°C, then cooled to room temperature, and the solvent was evaporated in vacuo. The residue containing compound **3** was used for the next step without purification.

***3.2.*** *General synthetic procedures for the synthesis of compounds* (**5b-5k**)

The unpurified **3** was added to a solution of triphenylphosphine (5.51g, 21.0mmol) in acetone (25mL), and the mixture was refluxed for 1h. The precipitate was collected and dried after the mixture was cooled to room temperature. The precipitate and sodium methoxide (1.35g, 25.0mmol) were dissolved in methanol (30mL), and the solution was firstly stirred for 30min at room temperature, and then heated to reflux. The corresponding substituted benzaldehyde **4** (**4b**-**4k** , 11mmol) was added, and stirring was continued for 6h under reflux. After cooling to room temperature, the mixture was poured into ice water, and the suspension was extracted with dichloromethane, the organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was added to 50mL petroleum ether, most of the impurities were precipitated and then filtered out. The filtrate was concentrated in vacuo to give the preliminary purified **5** (**5b-5k**) , which was used for the next step without further purification.

*methyl (Z)-2-(3-bromostyryl)benzoate* (**5b**)

Obtained as a Z-isomer. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.01 (m, 1H), 7.34 – 7.32 (m, 2H), 7.25 – 7.13 (m, 3H), 7.11 (d, *J* = 12.0 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.57 (d, *J* =12.0 Hz, 1H), 3.90 (s, 3H).

The other compounds (**5c-5k**) were used for the next step without purification.

***3.3.*** *General synthetic procedures for the synthesis of compounds* (**6b-6k**)

A mixture of **5** (**5b-5k**, 5.0mmol) and potassium hydroxide (0.56g, 10.0mmol) in methanol (20mL) and water (1.0mL) was heated under reflux for 4h, and then cooled to room temperature. The mixture was poured into ice water, acidified with aqueous hydrochloric acid, and the

product was precipitated as light yellow solid. The precipitate was filtered and dried, then washed with petroleum ether to afford the preliminary purified **6** (**6b-6k**) , which was also used for the next step without further purification.

*(Z)-2-(3-bromostyryl)benzoic acid* (**6b**)

Obtained as a Z-isomer. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.13-8.11 (m, 1H), 7.38 – 7.34 (m, 2H), 7.24 – 7.18 (m, 3H), 7.14 (d, *J* = 12.0 Hz, 1H).7.01 – 6.94 (m, 2H), 6.59 (d, *J* = 12.0 Hz, 1H).

*(Z)-2-(4-bromostyryl)benzoic acid* (**6c**)

Obtained as a Z-isomer. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.14 (m, 1H), 7.42 – 7.36 (m, 2H), 7.29 (d, *J* = 1.9 Hz, 1H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.16 (d, *J* = 12.1 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.61 (d, *J* = 12.2 Hz, 1H).

The other compounds (**6d-6k**) were used for the next step without purification.

***3.4.*** *General synthetic procedures for the synthesis of compounds* (**7b-7k**)

The unpurified **6** (**6b-6k**, 1.0 mmol) was dissolved in dichloromethane (20mL), and thionyl chloride (0.13g, 1.1mmol) was slowly added to the solution. The mixture was heated under reflux for 1.5h, then aluminium chloride (0.17 g) was added to it, and stirring was continued for 3h at room temperature. The mixture was poured into ice water, and the aqueous phase was extracted with dichloromethane. The organic phase was dried over sodium sulfate, and the solvent was evaporated in vacuo. The residues containing compounds **7b-7k** were used for the next step without purification.

*2-bromo-5H-dibenzo[a,d][7]annulen-5-one* (**7b**)

$^1$H NMR (400 MHz, Chloroform-*d*) δ 8.26 – 8.22 (m, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.62 – 7.55 (m, 2H), 7.12 (d, *J* = 12.1 Hz, 1H), 6.97 (d, *J* = 12.1 Hz, 1H).

*3-bromo-5H-dibenzo[a,d][7]annulen-5-one* (**7c**)

δ 8.37 (d, *J* = 2.4 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.72 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.59 – 7.54 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 12.0 Hz, 1H), 7.00 (d, *J* = 12.0 Hz, 1H).

The other compounds (**7d-5k**) were used for the next step without purification.

***3.5**. General synthetic procedures for the synthesis of compounds* (**8a-8k**)

To a solution of tetrahydrofuran (10mL) and ethanol (2mL) was added 20mmol **7a** or unpurified **7b-7k**. Sodium borohydride (10mmol) was slowly added to the solution at 0℃. The mixture was then stirred for 1.5h at room temperature. The mixture was poured into ice water and most of the organic solvent in the mixture was then evaporated in vacuo. The aqueous phase was extracted with dichloromethane. The organic phase was dried over sodium sulfate, and the solvent was evaporated in vacuo. The residues containing compounds **8a-8k** were used for the next step without purification.

*5H-dibenzo[a,d][7]annulen-5-ol* (**8a**)

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.68 (dt, $J$ = 7.8, 1.1 Hz, 2H), 7.39 (td, $J$ = 7.5, 1.4 Hz, 2H), 7.34 (dd, $J$ = 7.6, 1.4 Hz, 2H), 7.22 (td, $J$ = 7.4, 1.4 Hz, 2H), 7.13 (s, 2H), 6.08 (s, 1H), 4.99 (d, $J$ = 4.1 Hz, 1H).

*2-bromo-5H-dibenzo[a,d][7]annulen-5-ol* (**8b**)

$^1$H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, $J$ = 7.8 Hz, 1H), 7.58 (d, $J$ = 8.3 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.46 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.38 (dd, $J$ = 7.7, 1.4 Hz, 1H), 7.32 (dd, $J$ = 7.4, 1.3 Hz, 1H), 7.17 (d, $J$ = 11.7 Hz, 1H), 7.03 (d, $J$ = 11.7 Hz, 1H), 5.37 (s, 1H).

The other compounds (**8c-8k**) were used for the next step without purification.

***3.6.** General synthetic procedures for the synthesis of compounds* (**9a-9k**)

To a solution of ethyl acetate (20mL) were added **1** (1mmol), **8** (**8a-8k**, 1.2mmol) and 50wt.% T3P in ethyl acetate (2.5 mmol). The mixture was stirred overnight at 50℃. The mixture was poured into ice water and extracted with ethyl acetate. The obtained organic layer was washed with saturated brine and dried over sodium sulfate, then the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (methanol : dichloromethane = 1 : 20), affording a mixture of diastereoisomers (**9b-9k**) , expect **9a**, as colorless solids.

*(R)-7-(benzyloxy)-12-(5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9a**)

Obtained in 46.0% yield, m.p. 151.2℃. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.57 (m, 2H), 7.48 (dt, $J$ = 4.9, 2.9 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.40 – 7.33 (m, 4H), 7.31 – 7.25

(m, 2H), 7.04 (d, *J* = 6.3 Hz, 3H), 6.56 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.25 (d, *J* = 7.7 Hz, 1H), 5.68 – 5.53 (m, 2H), 5.41 (d, *J* = 10.8 Hz, 1H), 5.33 (s, 1H), 4.58 (dd, *J* = 13.6, 2.5 Hz, 1H), 3.90 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.61 (dd, *J* = 11.8, 3.3 Hz, 1H), 3.51 (dd, *J* = 10.8, 3.1 Hz, 1H), 3.18 (td, *J* = 11.8, 2.7 Hz, 1H), 3.12 – 3.01 (m, 1H), 2.76 (ddd, *J* = 13.5, 11.8, 3.5 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.47, 155.54, 151.58, 139.25, 136.79, 134.53, 134.31, 133.11, 133.09, 130.79, 130.68, 130.47, 130.23, 130.10, 129.63, 129.35, 129.23, 129.11, 128.24, 128.23, 127.90, 113.56, 75.61, 73.65, 68.89, 68.83, 66.47, 45.74.

*(R)-7-(benzyloxy)-12-((R/S)-2-bromo-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9b**)

Obtained in 47.1% yield, m.p. 70.2℃. A mixture (3:4) of diastereoisomers. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.63 (m, 4H), 7.62 – 7.59 (m, 3H), 7.55 – 7.52 (m, 3H), 7.48 – 7.45 (m, 4H), 7.38 – 7.35 (m, 4H), 7.34 – 7.31 (m, 2H), 7.16 – 7.02 (m, 4H), 6.93 (dd, *J* = 11.8, 1.5 Hz, 2H), 6.59 – 6.18 (m, 4H), 5.77 – 5.55 (m, 4H), 5.43 (t, *J* = 11.4 Hz, 2H), 5.29 (d, *J* = 13.2 Hz, 2H), 4.59 (ddd, *J* = 13.5, 7.1, 2.5 Hz, 2H), 3.87 (ddd, *J* = 25.7, 9.9, 3.0 Hz, 2H), 3.63 (td, *J* = 11.5, 3.3 Hz, 2H), 3.53 (ddd, *J* = 10.0, 6.5, 3.0 Hz, 2H), 3.26 – 3.13 (m, 2H), 3.07 (t, *J* = 10.4 Hz, 2H), 2.76 (dddd, *J* = 25.1, 13.5, 11.7, 3.5 Hz, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.50, 175.43, 155.57, 155.50, 151.71, 151.68, 139.12, 139.09, 136.75, 136.24, 136.09, 134.20, 133.95, 133.33, 132.95, 132.91, 132.78, 132.63, 132.13, 132.09, 132.06, 132.04, 132.00, 131.97, 131.95, 131.67, 130.98, 130.69, 130.42, 130.32, 129.80, 129.71, 129.63, 129.47, 129.35, 129.14, 128.74, 128.57, 128.49, 128.31, 128.26, 128.25, 128.23, 127.74, 127.71, 123.20, 123.01, 113.74, 113.60, 75.00, 74.79, 73.63, 73.61, 69.00, 68.88, 68.82, 68.79, 66.48, 66.47, 45.81, 45.74.

*(R)-7-(benzyloxy)-12-((R/S)-3-bromo-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9c**)

Obtained in 49.1% yield, m.p. 75.7℃. A mixture (1:1) of diastereoisomers. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.59 (m, 5H), 7.57 – 7.53 (m, 2H), 7.50 – 7.42 (m, 5H), 7.39 – 7.29 (m, 9H), 7.09 – 7.02 (m, 4H), 6.97 (dd, *J* = 14.3, 11.8 Hz, 2H), 6.53 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.34 (d, *J* = 7.7 Hz, 1H), 6.23 (d, *J* = 7.7 Hz, 1H), 5.74 (d, *J* = 7.7 Hz, 1H), 5.66 – 5.57 (m, 2H), 5.50 – 5.37 (m, 3H), 5.34 – 5.24 (m, 2H), 4.59 (ddd, *J* = 23.4, 13.5, 2.5 Hz, 2H), 3.90

(ddd, *J* = 10.9, 9.9, 3.0 Hz, 2H), 3.63 (ddd, *J* = 18.5, 11.8, 3.3 Hz, 2H), 3.52 (ddd, *J* = 10.7, 6.3, 3.0 Hz, 2H), 3.18 (dtd, *J* = 16.3, 11.9, 2.7 Hz, 2H), 3.11 – 2.98 (m, 2H), 2.79 (dddd, *J* = 38.5, 13.5, 11.8, 3.5 Hz, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.43, 175.24, 155.54, 155.37, 151.92, 151.64, 139.26, 139.12, 136.75, 136.73, 134.72, 134.68, 134.42, 134.21, 133.55, 133.29, 133.22, 132.97, 132.75, 132.70, 132.55, 132.26, 132.23, 132.15, 132.10, 132.04, 132.01, 131.99, 131.47, 131.35, 130.89, 130.84, 130.76, 130.51, 130.22, 129.63, 129.61, 129.58, 129.55, 129.52, 129.49, 129.40, 129.18, 128.58, 128.50, 128.27, 128.24, 128.17, 127.89, 127.70, 123.21, 123.10, 113.79, 113.58, 74.87, 74.66, 74.23, 73.68, 69.06, 68.92, 68.80, 68.74, 66.47, 66.46, 45.84, 45.77.

*(R)-7-(benzyloxy)-12-((R/S)-1-fluoro-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9d**)

Obtained in 58.3% yield, m.p. 107.4℃. A mixture (1:1) of diastereoisomers. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.70 – 7.59 (m, 5H), 7.56 – 7.44 (m, 5H), 7.42 – 7.29 (m, 9H), 7.23 – 7.11 (m, 4H), 7.11 – 6.97 (m, 3H), 6.56 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.35 (t, *J* = 8.3 Hz, 2H), 6.26 (d, *J* = 7.7 Hz, 1H), 5.70 (d, *J* = 7.7 Hz, 1H), 5.65 – 5.56 (m, 3H), 5.46 – 5.34 (m, 4H), 4.60 (ddd, *J* = 13.5, 5.2, 2.5 Hz, 2H), 3.92 (ddd, *J* = 21.7, 9.9, 3.0 Hz, 2H), 3.64 (ddd, *J* = 10.9, 6.9, 3.3 Hz, 2H), 3.60 – 3.49 (m, 2H), 3.20 (tt, *J* = 11.9, 3.1 Hz, 2H), 3.09 (td, *J* = 10.4, 2.7 Hz, 2H), 2.77 (dtd, *J* = 13.4, 11.8, 3.5 Hz, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.45, 175.41, 161.62, 161.17, 159.94, 159.50, 155.46, 155.44, 151.66, 151.63, 139.16, 139.10, 136.75, 135.78, 135.71, 134.31, 134.09, 133.02, 132.96, 132.75, 132.09, 132.06, 132.02, 131.99, 131.98, 131.90, 131.54, 130.93, 130.64, 130.42, 130.36, 130.34, 130.26, 129.68, 129.62, 129.61, 129.58, 129.45, 129.31, 128.56, 128.48, 128.25, 128.24, 128.21, 127.81, 127.75, 126.10, 126.08, 125.90, 125.88, 122.73, 122.70, 122.65, 122.62, 121.80, 121.75, 121.28, 121.22, 116.15, 116.00, 115.89, 115.74, 113.66, 113.57, 74.99, 74.98, 74.92, 73.60, 73.58, 69.08, 68.92, 68.79, 68.75, 66.45, 66.44, 45.76, 45.73.

*(R)-7-(benzyloxy)-12-((R/S)-2-fluoro-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9e**)

Obtained in 52.1% yield, m.p. 118.4℃. A mixture (1:1) of diastereoisomers. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.65 (m, 2H), 7.62 (ddd, *J* = 11.1, 5.5, 3.0 Hz, 4H), 7.54 – 7.52

(m, 1H), 7.46 (ddt, *J* = 8.1, 2.9, 1.7 Hz, 5H), 7.38 (ddt, *J* = 7.4, 3.6, 1.7 Hz, 5H), 7.32 (dt, *J* = 7.1, 1.3 Hz, 2H), 7.10 – 7.03 (m, 4H), 6.95 (d, *J* = 11.9 Hz, 2H), 6.72 (td, *J* = 8.2, 2.7 Hz, 1H), 6.55 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.45 (dd, *J* = 8.5, 5.5 Hz, 1H), 6.25 (dd, *J* = 21.3, 7.7 Hz, 2H), 5.73 – 5.56 (m, 4H), 5.42 (dd, *J* = 10.9, 6.5 Hz, 2H), 5.32 (d, *J* = 7.9 Hz, 2H), 4.59 (dt, *J* = 13.5, 2.9 Hz, 2H), 3.89 (ddd, *J* = 11.7, 9.9, 3.0 Hz, 2H), 3.63 (ddd, *J* = 11.9, 6.5, 3.3 Hz, 2H), 3.53 (ddd, *J* = 10.7, 7.7, 3.0 Hz, 2H), 3.19 (td, *J* = 11.8, 2.7 Hz, 2H), 3.13 – 3.02 (m, 2H), 2.77 (dtd, *J* = 14.3, 11.5, 3.5 Hz, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.47, 175.43, 163.47, 163.41, 161.82, 161.75, 155.56, 155.49, 151.65, 151.63, 139.17, 139.15, 136.78, 136.75, 136.57, 136.51, 136.43, 136.37, 134.17, 133.93, 133.13, 133.13, 132.75, 132.52, 132.46, 132.41, 132.35, 132.10, 132.04, 132.01, 131.99, 131.92, 131.49, 130.98, 130.61, 130.40, 130.31, 129.73, 129.67, 129.63, 129.61, 129.45, 129.44, 129.39, 129.32, 129.31, 129.29, 129.25, 129.00, 128.99, 128.57, 128.49, 128.28, 128.25, 128.23, 128.22, 127.80, 127.78, 116.98, 116.83, 116.32, 116.28, 116.22, 116.17, 116.14, 116.07, 113.59, 113.58, 74.78, 74.68, 73.62, 73.58, 68.90, 68.81, 66.46, 45.81, 45.74.

*(R)-7-(benzyloxy)-12-((R/S)-3-fluoro-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9f**)

Obtained in 53.4% yield, m.p. 80.3℃. A mixture (1:1) of diastereoisomers. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.63 (m, 3H), 7.61 – 7.58 (m, 3H), 7.54 – 7.51 (m, 1H), 7.48 – 7.44 (m, 5H), 7.39 – 7.34 (m, 6H), 7.30 (tdd, *J* = 7.8, 2.9, 1.4 Hz, 3H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.01 (q, *J* = 2.6 Hz, 4H), 6.54 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.41 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.32 (d, *J* = 7.7 Hz, 1H), 6.25 (d, *J* = 7.7 Hz, 1H), 5.72 (d, *J* = 7.8 Hz, 1H), 5.65 – 5.51 (m, 3H), 5.43 (t, *J* = 10.6 Hz, 2H), 5.27 (d, *J* = 1.9 Hz, 2H), 4.59 (ddd, *J* = 21.5, 13.5, 2.5 Hz, 2H), 3.89 (ddd, *J* = 28.1, 9.9, 3.0 Hz, 2H), 3.63 (ddd, *J* = 15.7, 11.8, 3.3 Hz, 2H), 3.52 (ddd, *J* = 11.0, 8.2, 3.0 Hz, 2H), 3.18 (qd, *J* = 11.7, 2.7 Hz, 2H), 3.11 – 3.00 (m, 2H), 2.78 (dddd, *J* = 42.6, 13.4, 11.8, 3.5 Hz, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.45, 175.40, 163.99, 162.32, 155.54, 155.44, 151.70, 151.66, 139.23, 139.16, 136.75, 136.60, 135.07, 135.03, 134.89, 134.84, 134.45, 134.17, 132.75, 132.70, 132.43, 132.33, 132.11, 132.05, 132.01, 131.99, 131.95, 131.89, 131.00, 130.97, 130.79, 130.75, 130.71, 130.39, 130.18, 130.11, 129.78, 129.63, 129.56, 129.49, 129.47, 129.40, 129.36, 129.15, 128.58, 128.50, 128.30, 128.27, 128.23,

127.85, 127.73, 117.33, 117.19, 116.97, 116.82, 116.54, 116.40, 116.36, 116.21, 113.75, 113.57, 74.98, 74.90, 73.84, 73.66, 69.10, 68.87, 68.81, 68.72, 66.48, 66.44, 45.84, 45.79.

*(R)-7-(benzyloxy)-12-((R/S)-1-chloro-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9g**)

Obtained in 57.8% yield, m.p. 112.7℃. A mixture (1:1) of diastereoisomers. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.58 (m, 5H), 7.51 (dt, *J* = 7.6, 1.2 Hz, 2H), 7.48 – 7.42 (m, 4H), 7.41 – 7.34 (m, 8H), 7.33 – 7.30 (m, 3H), 7.18 (dd, *J* = 12.2, 5.6 Hz, 2H), 7.07 (td, *J* = 7.5, 1.4 Hz, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 6.51 (ddd, *J* = 31.7, 7.8, 1.2 Hz, 2H), 6.30 (dd, *J* = 25.6, 7.7 Hz, 2H), 5.76 – 5.54 (m, 4H), 5.41 (d, *J* = 10.9 Hz, 2H), 5.32 (d, *J* = 1.3 Hz, 2H), 4.59 (ddd, *J* = 13.5, 5.6, 2.5 Hz, 2H), 3.92 (ddd, *J* = 26.3, 9.9, 3.0 Hz, 2H), 3.63 (ddd, *J* = 11.3, 7.6, 3.3 Hz, 2H), 3.55 (ddd, *J* = 15.4, 10.8, 3.1 Hz, 2H), 3.26 – 3.14 (m, 2H), 3.08 (ddd, *J* = 11.4, 10.0, 1.6 Hz, 2H), 2.85 – 2.69 (m, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.45, 175.43, 155.50, 155.44, 151.73, 151.68, 139.11, 136.75, 136.74, 135.81, 135.45, 134.67, 133.91, 133.72, 133.38, 133.36, 132.11, 132.05, 132.00, 131.98, 131.87, 131.66, 131.60, 131.54, 130.77, 130.72, 130.54, 130.41, 130.20, 130.06, 129.80, 129.74, 129.63, 129.52, 129.40, 129.18, 128.99, 128.57, 128.49, 128.26, 128.23, 127.81, 127.74, 126.35, 125.90, 113.72, 113.63, 75.28, 75.15, 73.61, 73.59, 69.19, 68.99, 68.80, 68.78, 66.48, 45.76, 45.72.

*(R)-7-(benzyloxy)-12-((R/S)-2-chloro-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9h**)

Obtained in 47.6% yield, m.p. 116.4℃. A mixture (1:1) of diastereoisomers. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.64 (m, 5H), 7.52 – 7.50 (m, 5H), 7.44 (d, *J* = 1.5 Hz, 6H), 7.35 (dd, *J* = 6.6, 2.0 Hz, 5H), 7.09 – 7.02 (m, 3H), 6.92 (dd, *J* = 11.8, 1.4 Hz, 2H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 8.2 Hz, 1H), 6.24 (dd, *J* = 19.4, 7.7 Hz, 2H), 5.75 – 5.54 (m, 4H), 5.42 (t, *J* = 10.7 Hz, 2H), 5.29 (d, *J* = 11.1 Hz, 2H), 4.58 (ddd, *J* = 13.5, 6.1, 2.5 Hz, 2H), 3.86 (ddd, *J* = 21.3, 9.9, 3.0 Hz, 2H), 3.62 (ddd, *J* = 12.5, 9.7, 3.3 Hz, 2H), 3.51 (ddd, *J* = 10.0, 6.6, 3.1 Hz, 2H), 3.17 (td, *J* = 11.8, 11.4, 2.6 Hz, 2H), 3.05 (t, *J* = 10.4 Hz, 2H), 2.75 (dddd, *J* = 20.8, 13.4, 11.8, 3.5 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 175.43, 175.38, 155.52, 155.45, 151.68, 151.66, 139.11, 139.08, 136.78, 136.00, 135.82, 135.07, 134.91, 134.22, 133.96, 132.98, 132.09, 132.00, 131.95, 131.92, 131.83, 131.76, 131.63, 131.54, 130.95, 130.65, 130.38,

130.32, 130.29, 129.71, 129.63, 129.57, 129.42, 129.28, 129.20, 129.02, 128.97, 128.79, 128.55, 128.43, 128.23, 128.19, 128.17, 127.75, 127.72, 113.66, 113.54, 74.90, 74.72, 73.62, 73.59, 69.00, 68.90, 68.77, 66.41, 45.80, 45.73.

*(R)-7-(benzyloxy)-12-((R/S)-3-chloro-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9i**)

Obtained in 47.0% yield, m.p. 76.7℃. A mixture (1:1) of diastereoisomers. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.60 (m, 5H), 7.58 – 7.52 (m, 2H), 7.48 – 7.43 (m, 5H), 7.40 – 7.30 (m, 10H), 7.07 – 6.99 (m, 4H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 7.7 Hz, 1H), 6.24 (d, *J* = 7.7 Hz, 1H), 5.74 (d, *J* = 7.7 Hz, 1H), 5.67 – 5.56 (m, 2H), 5.49 – 5.39 (m, 3H), 5.30 (d, *J* = 17.6 Hz, 2H), 4.60 (ddd, *J* = 23.5, 13.6, 2.6 Hz, 2H), 3.90 (ddd, *J* = 15.8, 9.9, 3.0 Hz, 2H), 3.64 (ddd, *J* = 18.2, 11.8, 3.3 Hz, 2H), 3.53 (ddd, *J* = 10.1, 6.7, 3.1 Hz, 2H), 3.19 (dtd, *J* = 14.8, 11.8, 2.7 Hz, 2H), 3.07 (q, *J* = 10.1 Hz, 2H), 2.84 (ddd, *J* = 13.4, 11.7, 3.5 Hz, 1H), 2.74 (ddd, *J* = 13.5, 11.8, 3.5 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 175.42, 175.26, 155.54, 155.41, 151.92, 151.70, 139.17, 139.04, 136.78, 136.73, 135.31, 135.14, 134.56, 134.48, 134.41, 134.21, 133.10, 132.98, 132.83, 132.72, 132.57, 132.12, 132.03, 131.99, 131.95, 131.93, 131.22, 131.11, 130.84, 130.77, 130.70, 130.46, 130.39, 130.17, 130.07, 129.63, 129.59, 129.49, 129.37, 129.31, 129.21, 129.13, 128.55, 128.43, 128.24, 128.20, 128.15, 127.82, 127.67, 113.75, 113.55, 74.99, 74.82, 74.13, 73.70, 69.10, 68.95, 68.81, 68.74, 66.47, 66.44, 45.84, 45.77.

*(R)-7-(benzyloxy)-12-((R/S)-3-methyl-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9j**)

Obtained in 59.5% yield, m.p. 88.3℃. A mixture (1:1) of diastereoisomers. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.60 (m, 5H), 7.52 (dq, *J* = 6.6, 1.9, 1.5 Hz, 1H), 7.44 (ddt, *J* = 14.5, 7.2, 2.0 Hz, 4H), 7.39 – 7.28 (m, 9H), 7.19 (d, *J* = 1.7 Hz, 1H), 7.12 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.05 – 6.95 (m, 5H), 6.64 (d, *J* = 1.8 Hz, 1H), 6.55 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.30 (d, *J* = 7.7 Hz, 1H), 6.26 (d, *J* = 7.7 Hz, 1H), 5.66 (d, *J* = 7.7 Hz, 1H), 5.63 – 5.56 (m, 2H), 5.49 – 5.37 (m, 3H), 5.35 (s, 1H), 5.28 (s, 1H), 4.59 (ddd, *J* = 13.2, 10.3, 2.5 Hz, 2H), 3.99 – 3.87 (m, 2H), 3.62 (ddd, *J* = 11.1, 7.2, 3.3 Hz, 2H), 3.51 (dd, *J* = 10.8, 3.1 Hz, 2H), 3.18 (dtd, *J* = 14.5, 11.8, 2.7 Hz, 2H), 3.05 (q, *J* = 10.1 Hz, 2H), 2.83 – 2.69 (m, 2H), 2.40 (s, 3H), 2.16 (s, 3H); $^{13}$C NMR

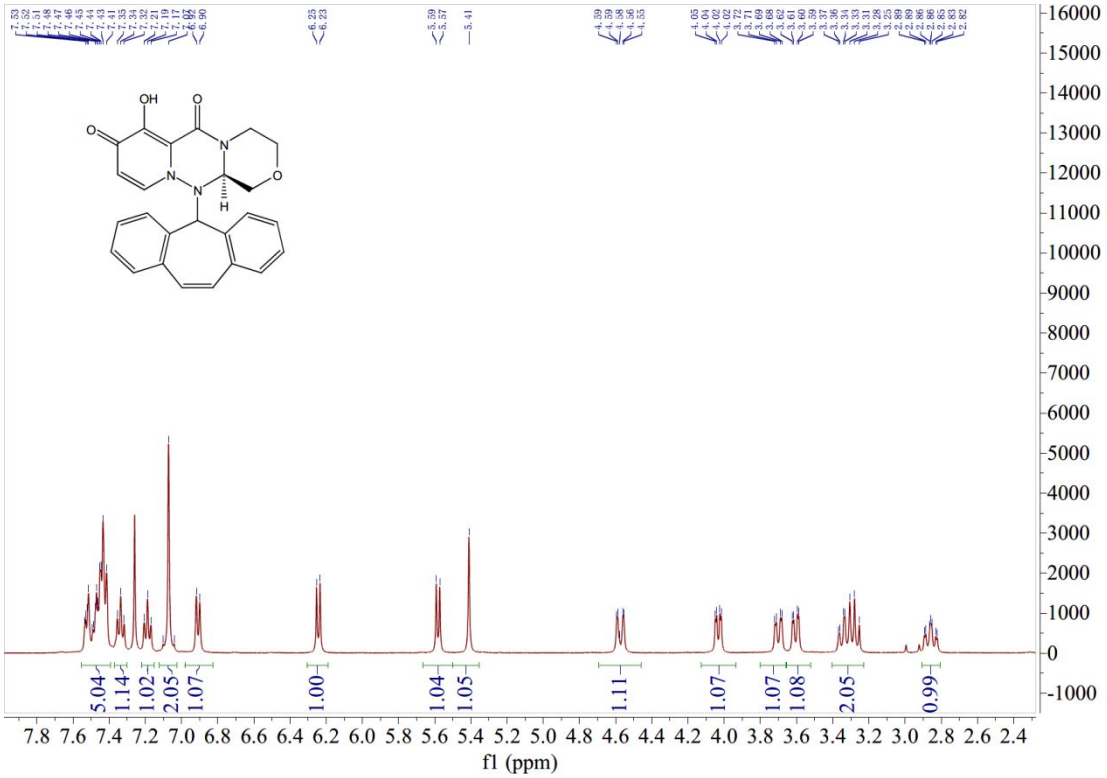
(101 MHz, $CDCl_3$) δ 175.44, 175.29, 155.58, 155.55, 151.70, 151.61, 139.82, 139.57, 139.40, 139.23, 136.88, 136.85, 134.72, 134.55, 133.13, 133.12, 133.05, 132.96, 132.13, 132.03, 132.01, 131.96, 131.94, 131.74, 131.36, 130.89, 130.78, 130.71, 130.66, 130.59, 130.46, 130.18, 130.17, 130.03, 129.99, 129.91, 129.79, 129.58, 129.39, 129.36, 129.15, 129.12, 129.02, 129.00, 128.57, 128.45, 128.19, 128.09, 127.99, 127.87, 113.57, 113.54, 75.69, 73.81, 73.68, 68.93, 68.88, 68.85, 66.47, 45.72, 21.07, 20.88.

*(R)-7-(benzyloxy)-12-((R/S)-3-methoxy-5H-dibenzo[a,d][7]annulen-5-yl)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione* (**9k**)

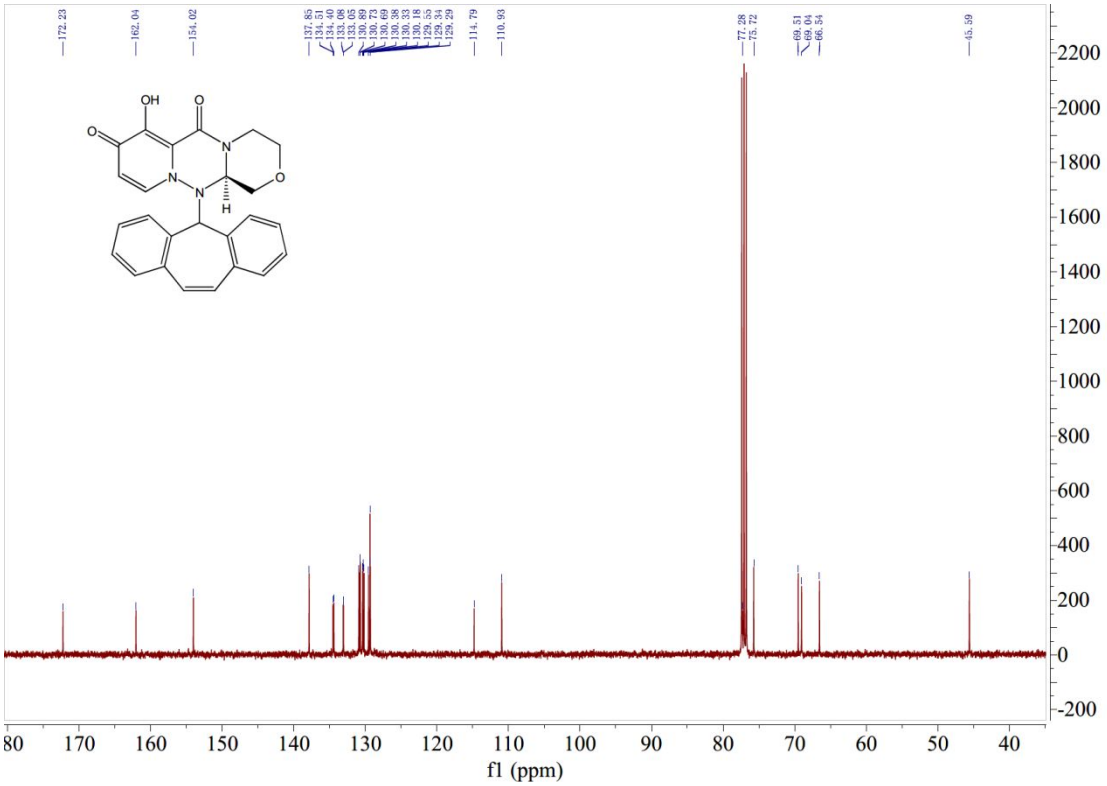
Obtained in 46.4% yield, m.p. 72.9℃. A mixture (1:1) of diastereoisomers. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.58 (m, 5H), 7.55 – 7.51 (m, 1H), 7.45 (ddd, *J* = 13.9, 6.0, 2.8 Hz, 4H), 7.39 – 7.28 (m, 9H), 7.06 – 6.92 (m, 5H), 6.91 – 6.86 (m, 2H), 6.61 – 6.54 (m, 1H), 6.42 – 6.33 (m, 2H), 6.28 (d, *J* = 7.7 Hz, 1H), 5.72 (d, *J* = 7.7 Hz, 1H), 5.65 – 5.53 (m, 2H), 5.46 – 5.32 (m, 4H), 5.27 (s, 1H), 4.60 (ddd, *J* = 16.9, 13.5, 2.5 Hz, 2H), 3.99 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.90 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.85 (s, 3H), 3.69 – 3.59 (m, 5H), 3.53 (dt, *J* = 10.9, 3.6 Hz, 2H), 3.19 (dtd, *J* = 19.0, 11.8, 2.7 Hz, 2H), 3.07 (dt, *J* = 14.0, 10.3 Hz, 2H), 2.79 (dddd, *J* = 29.4, 13.4, 11.8, 3.5 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 175.44, 175.29, 160.86, 160.73, 155.59, 155.54, 151.73, 151.67, 139.46, 139.25, 136.87, 136.79, 134.87, 134.68, 134.55, 134.50, 132.46, 132.36, 132.13, 132.03, 131.97, 131.94, 131.69, 130.72, 130.61, 130.47, 130.27, 129.89, 129.83, 129.55, 129.44, 129.18, 129.10, 129.00, 128.85, 128.57, 128.48, 128.45, 128.19, 128.10, 127.97, 127.82, 127.69, 127.47, 115.53, 115.36, 115.31, 115.03, 113.76, 113.54, 75.75, 73.77, 73.68, 68.99, 68.90, 68.87, 68.81, 66.47, 66.45, 55.66, 55.56, 45.73.

## 4. Copies of $^{1}$H-NMR and $^{13}$C-NMR for target compounds（10a~10k）

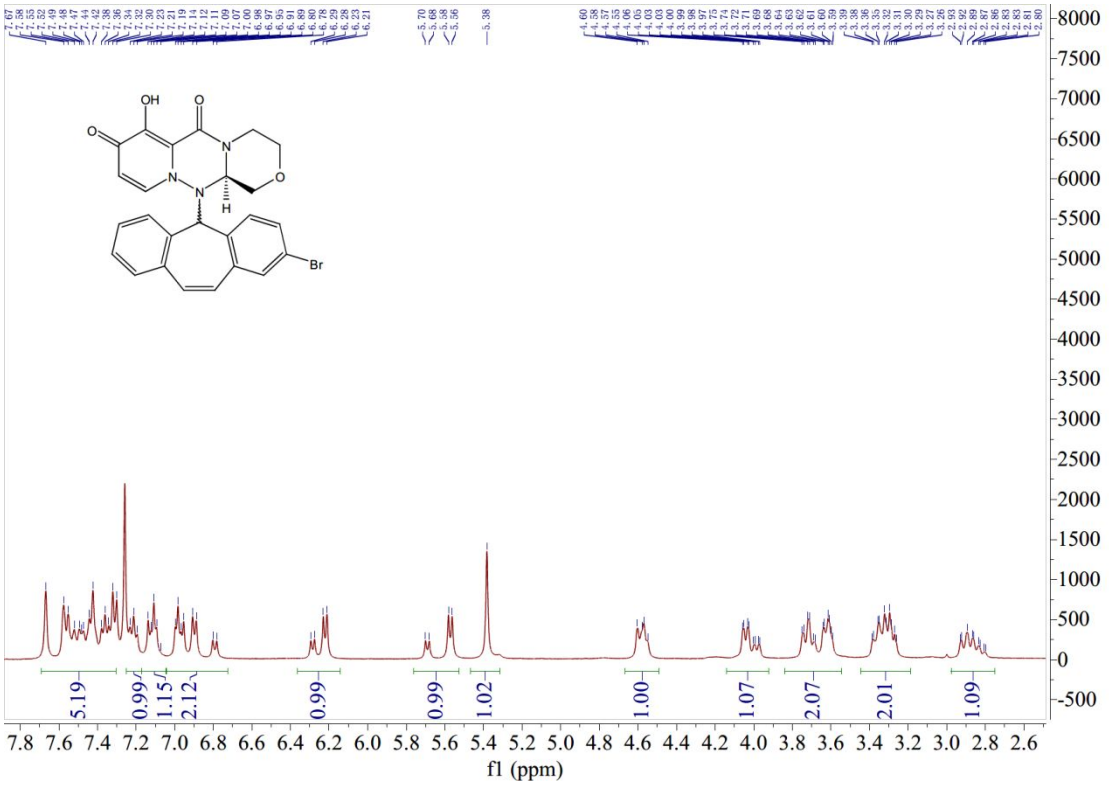
### $^{1}$H-NMR of Compound 10a:



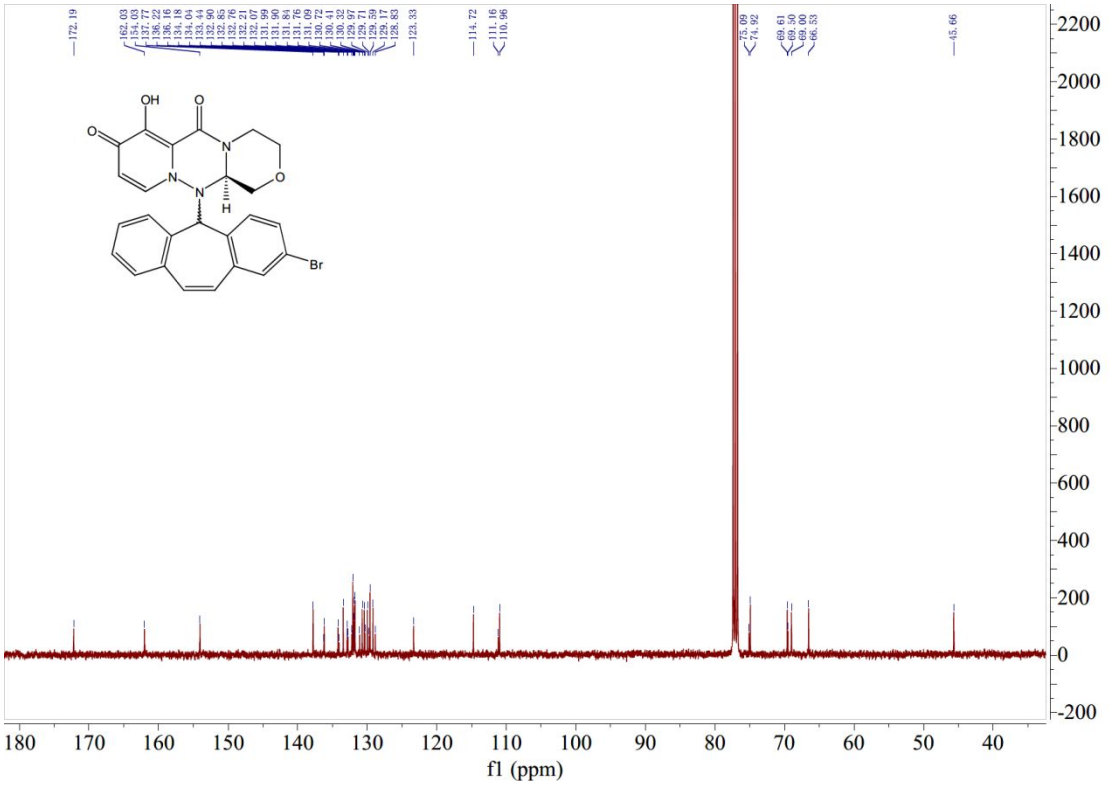

### $^{1}$C-NMR of Compound 10a:



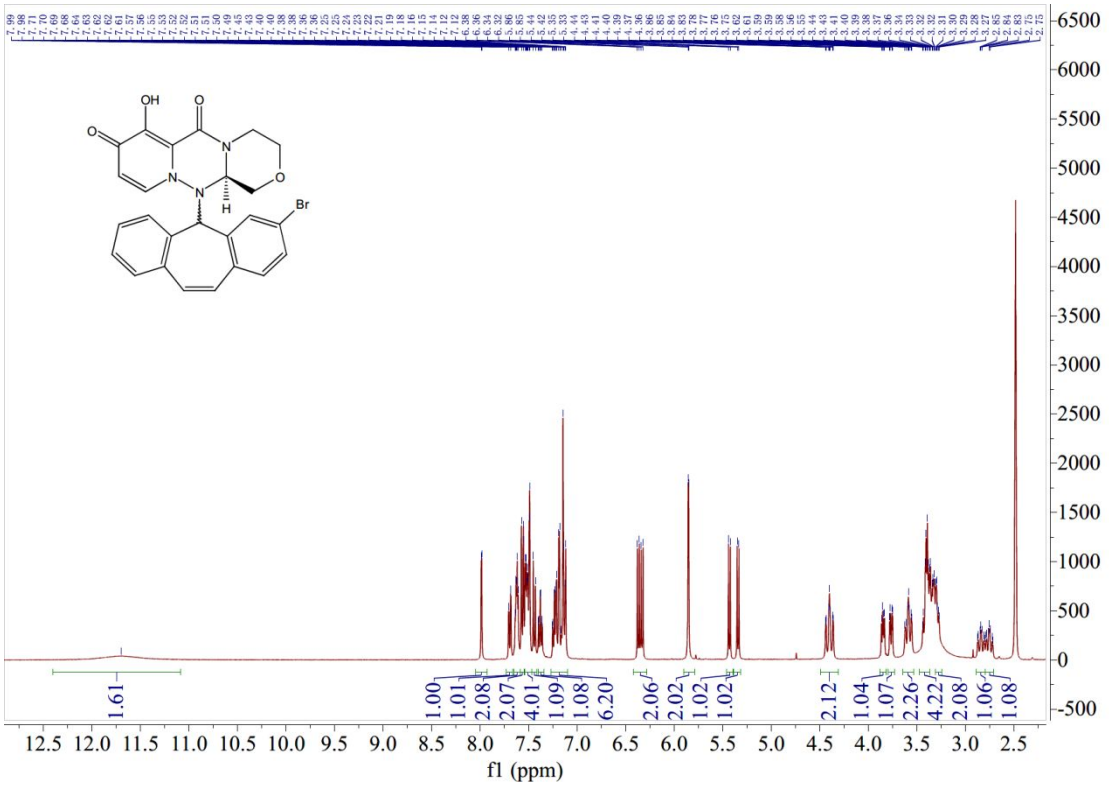
**[1]H-NMR of Compound 10b:**



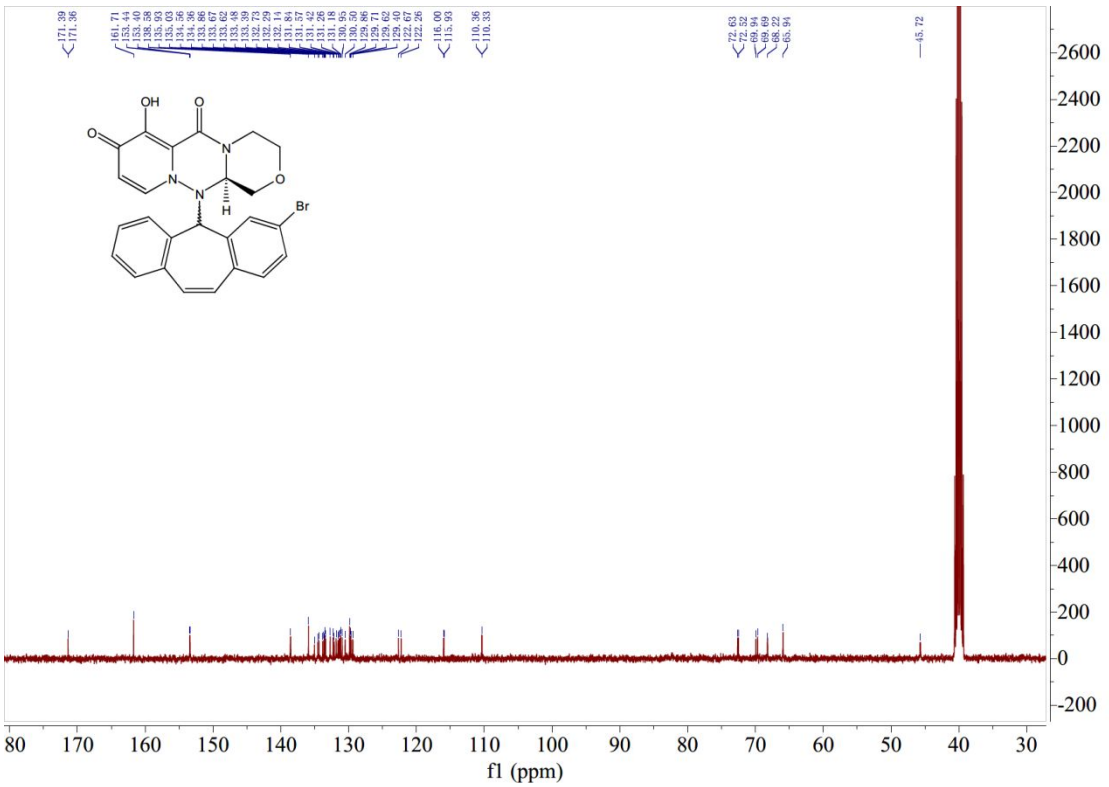

**[1]C-NMR of Compound 10b:**



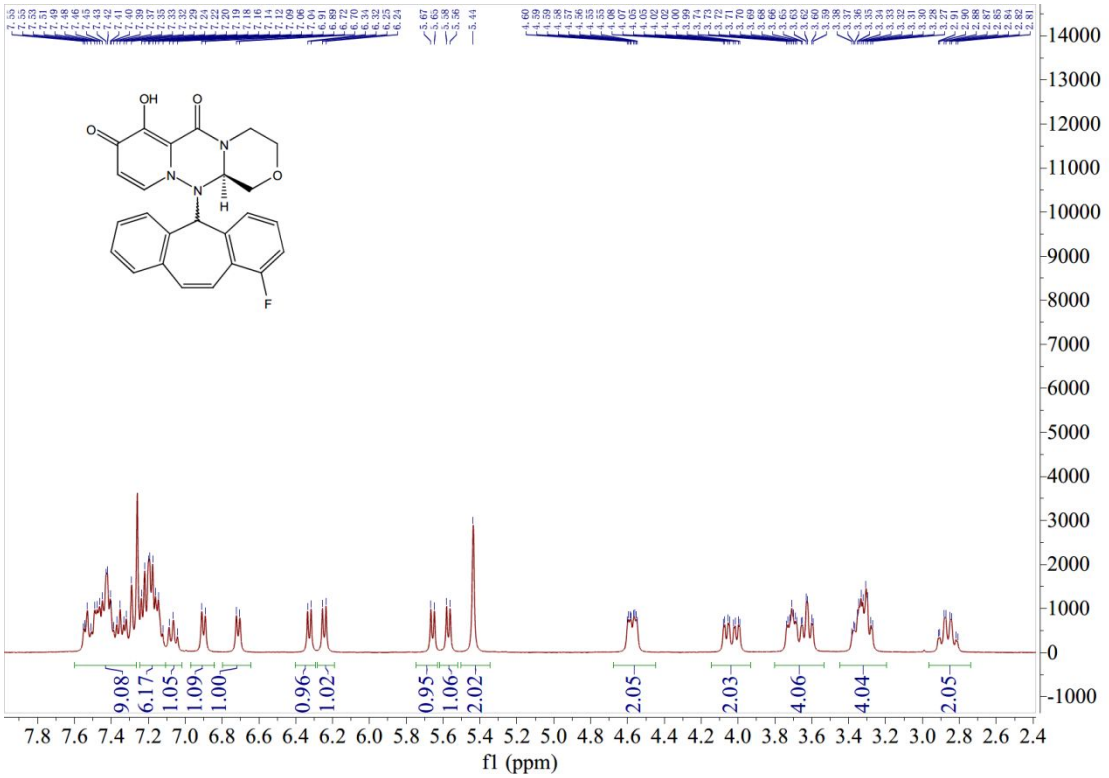

**[1]H-NMR of Compound 10c:**



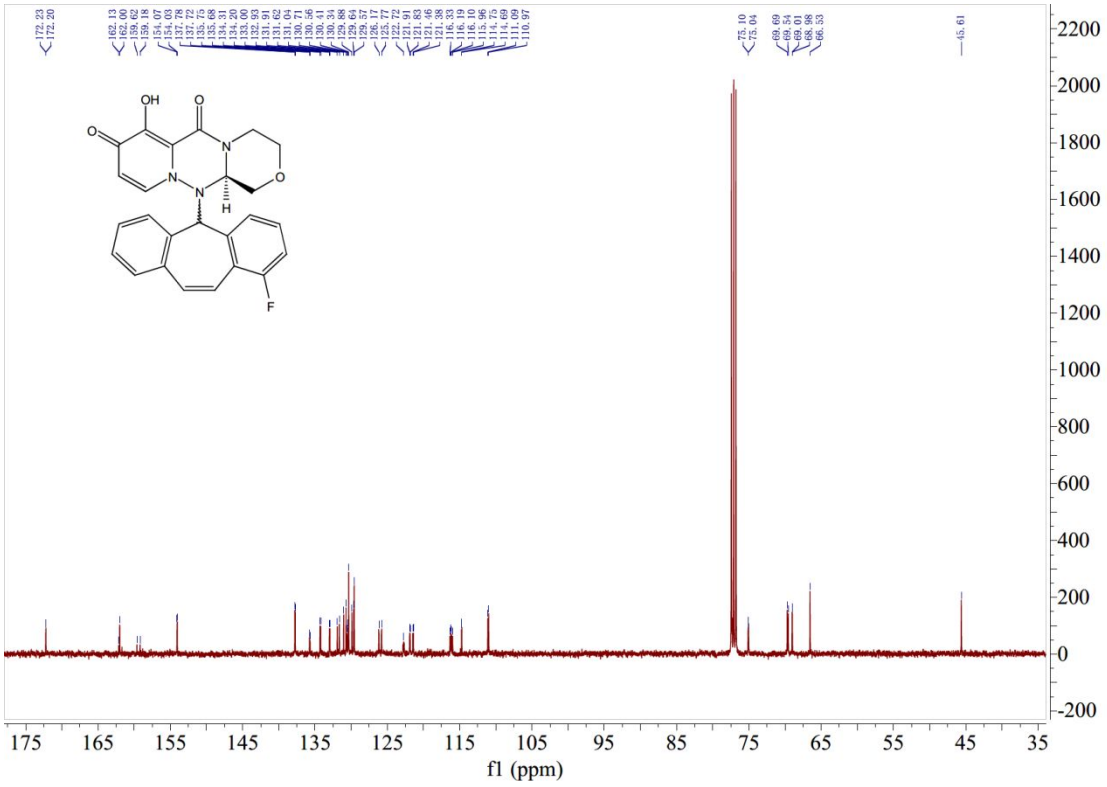
**[1]C-NMR of Compound 10c:**



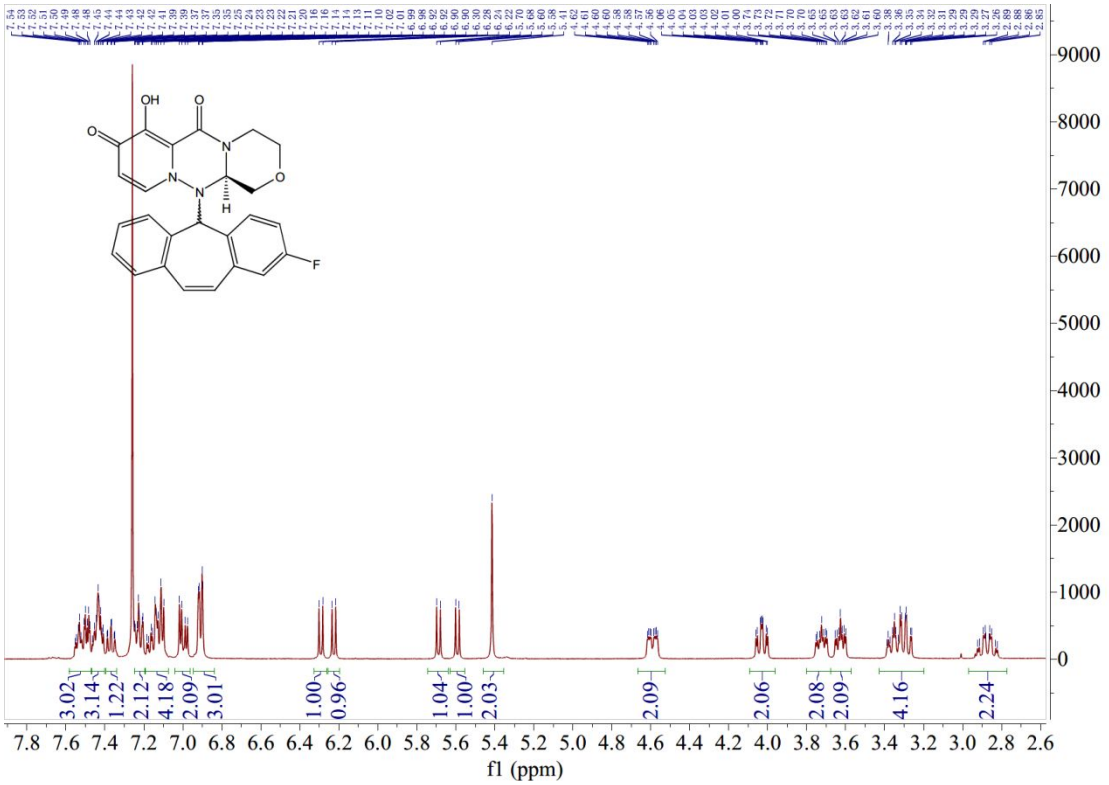

**[1]H-NMR of Compound 10d:**



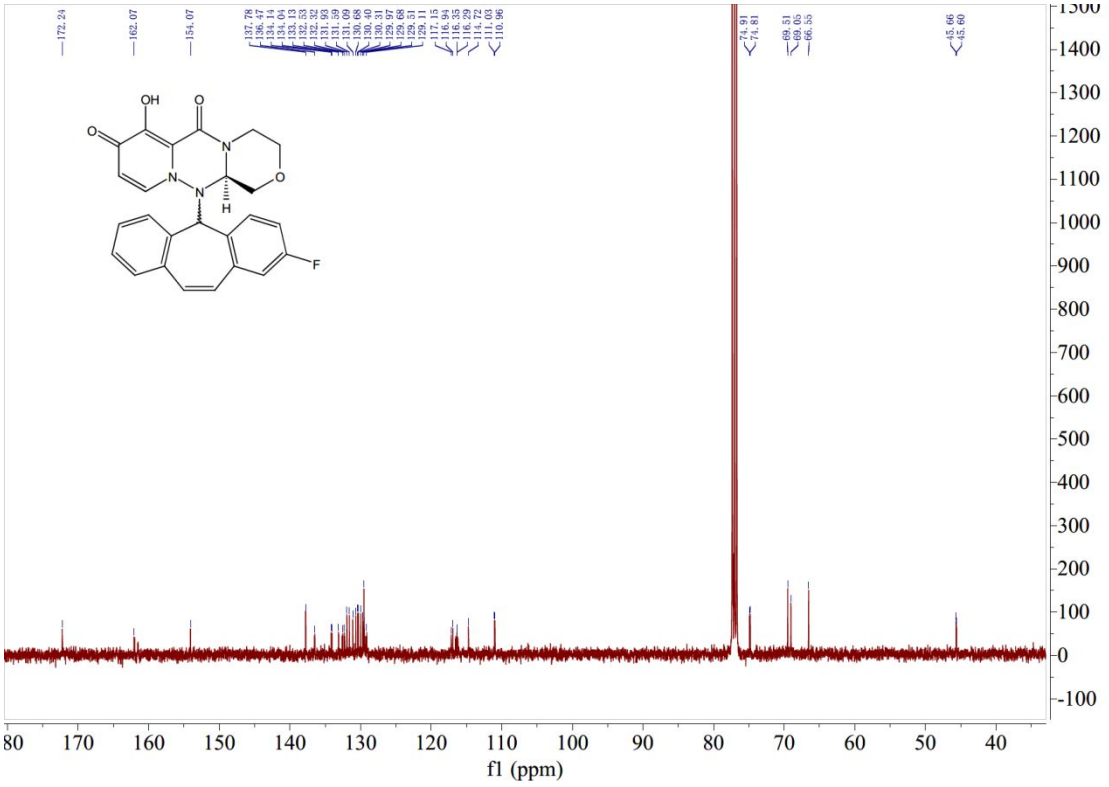
**[1]C-NMR of Compound 10d:**



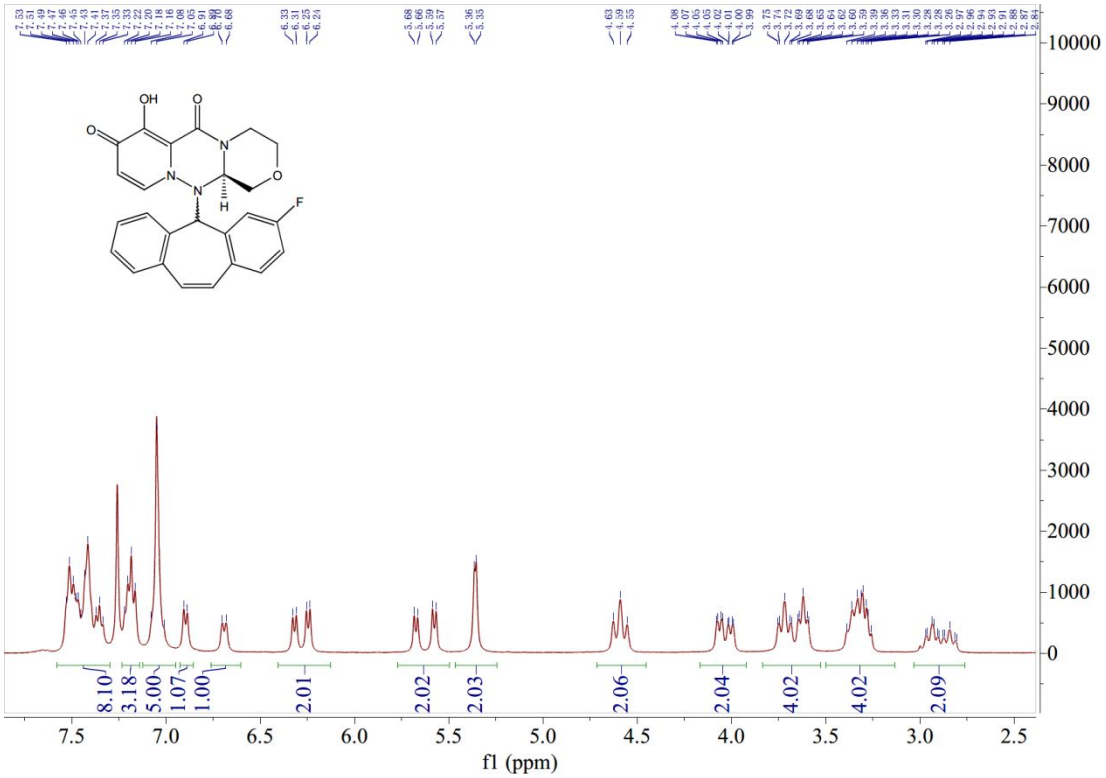

**[1]H-NMR of Compound 10e:**



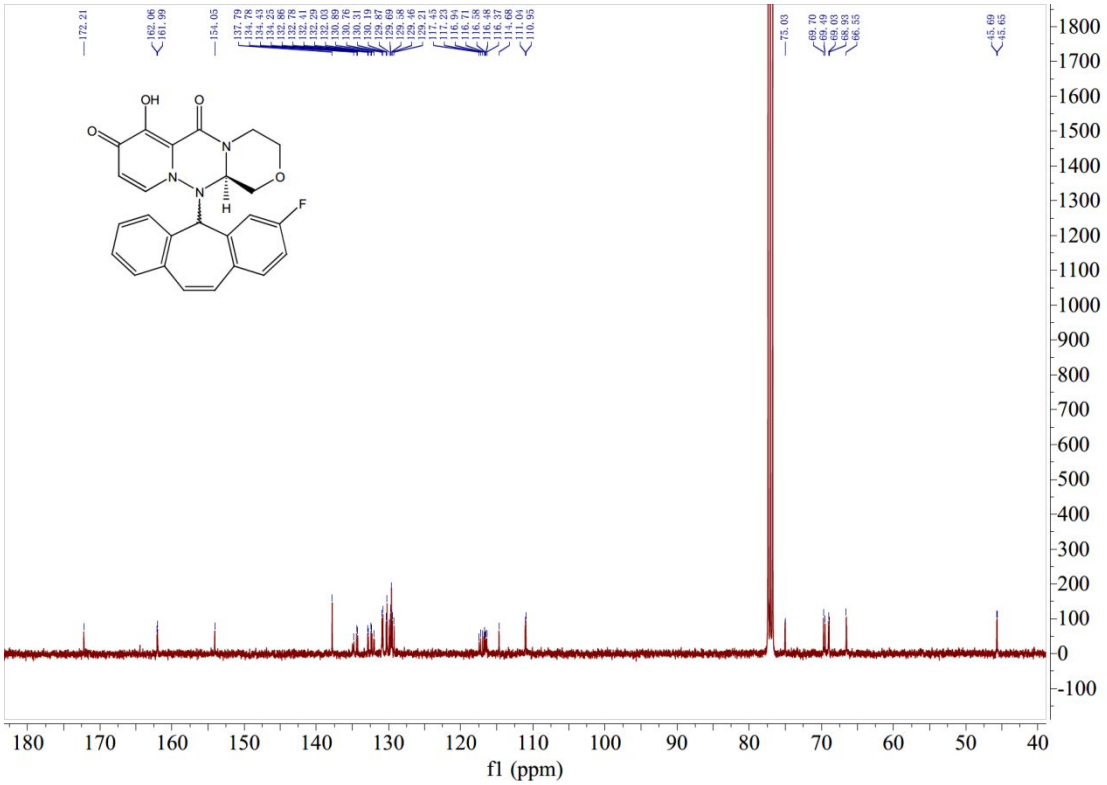

**[1]C-NMR of Compound 10e:**



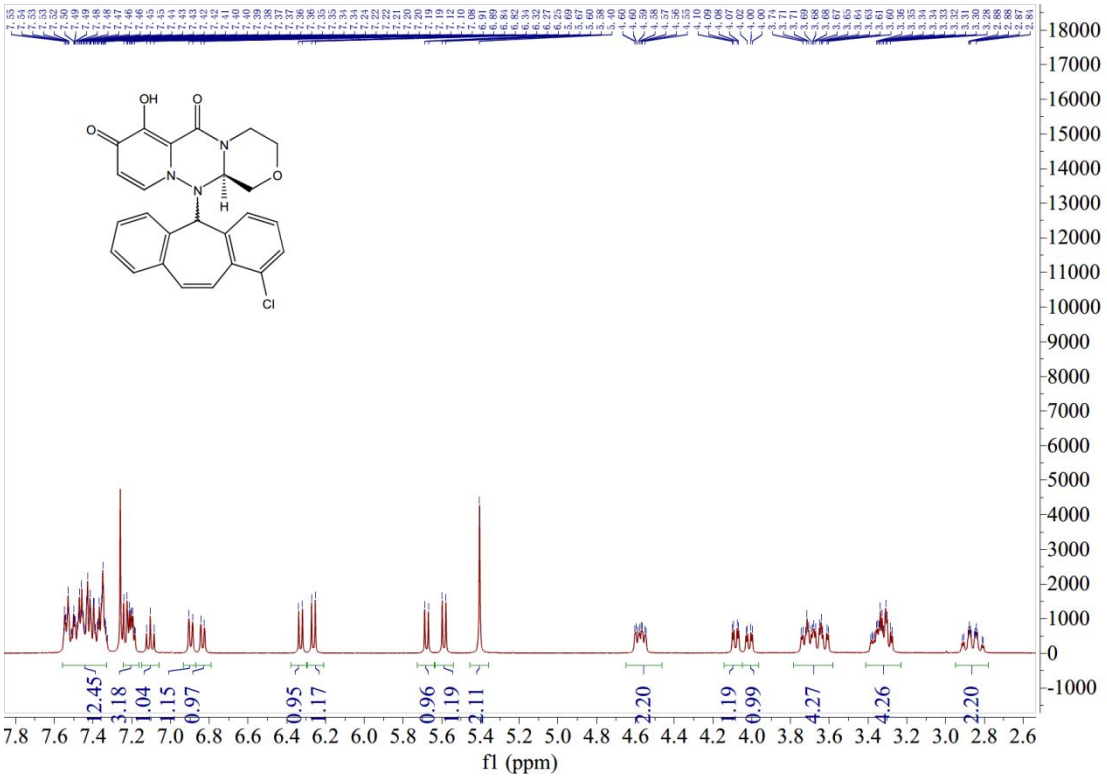
**[1]H-NMR of Compound 10f:**



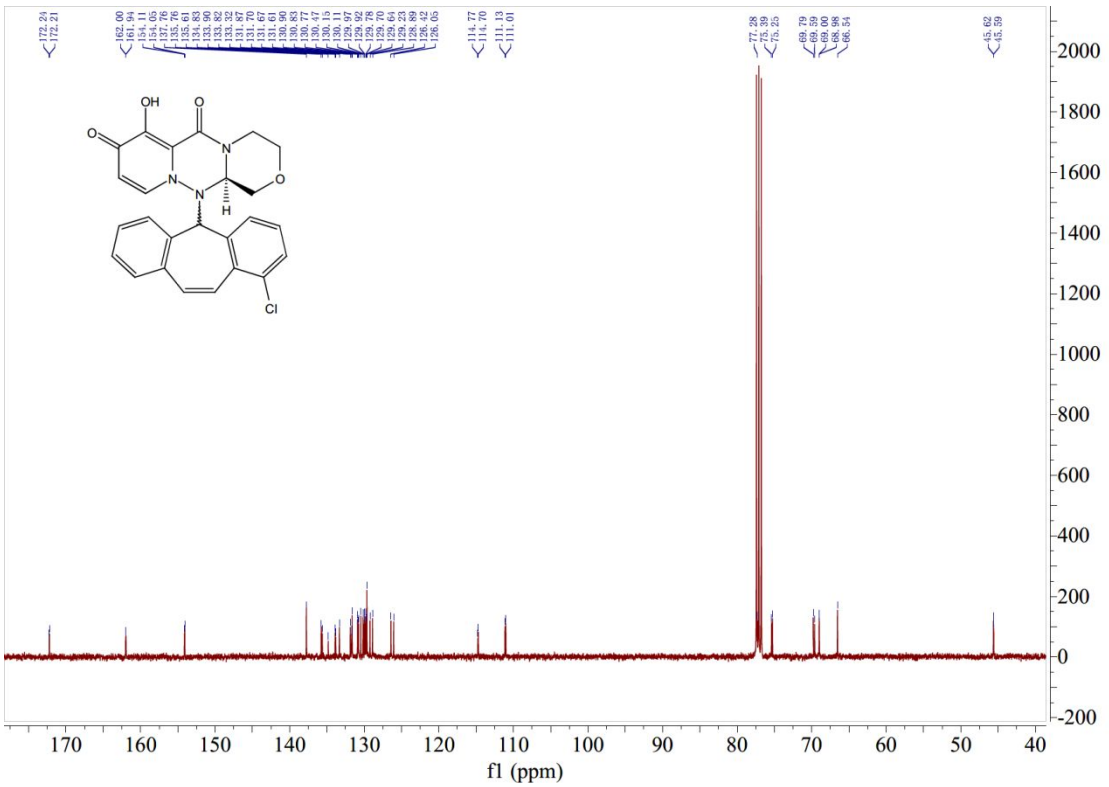

**[1]C-NMR of Compound 10f:**



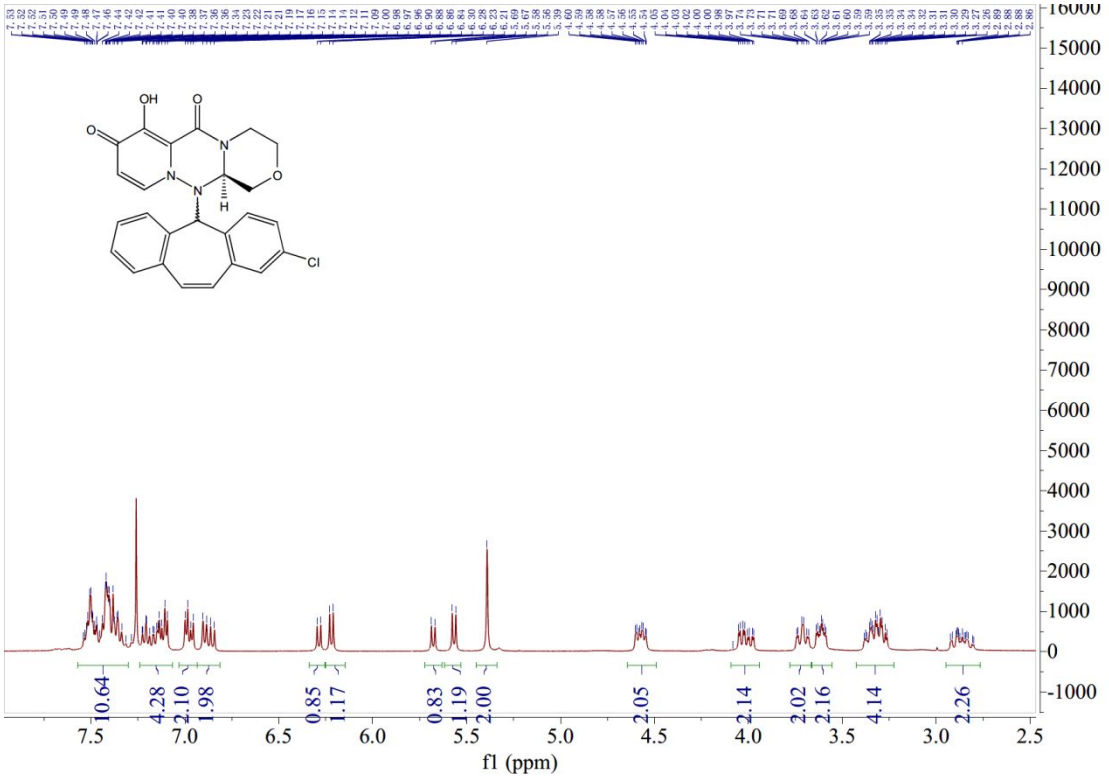

**[1]H-NMR of Compound 10g:**



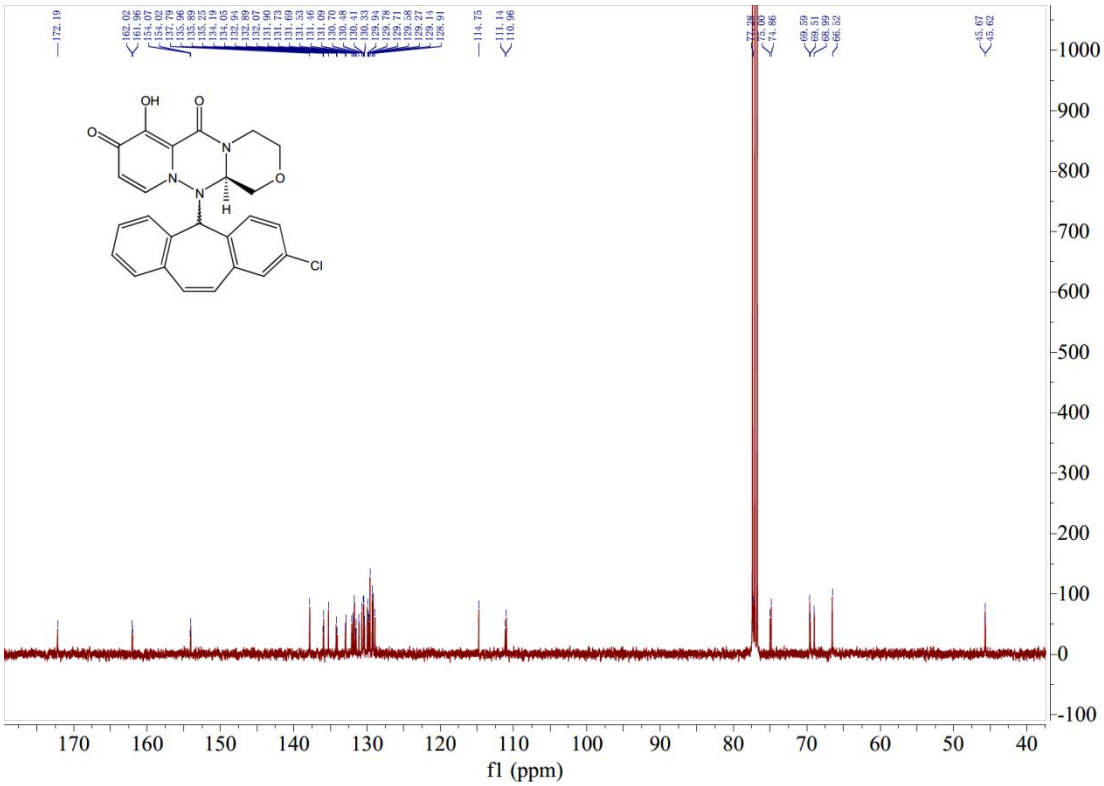
**[1]C-NMR of Compound 10g:**



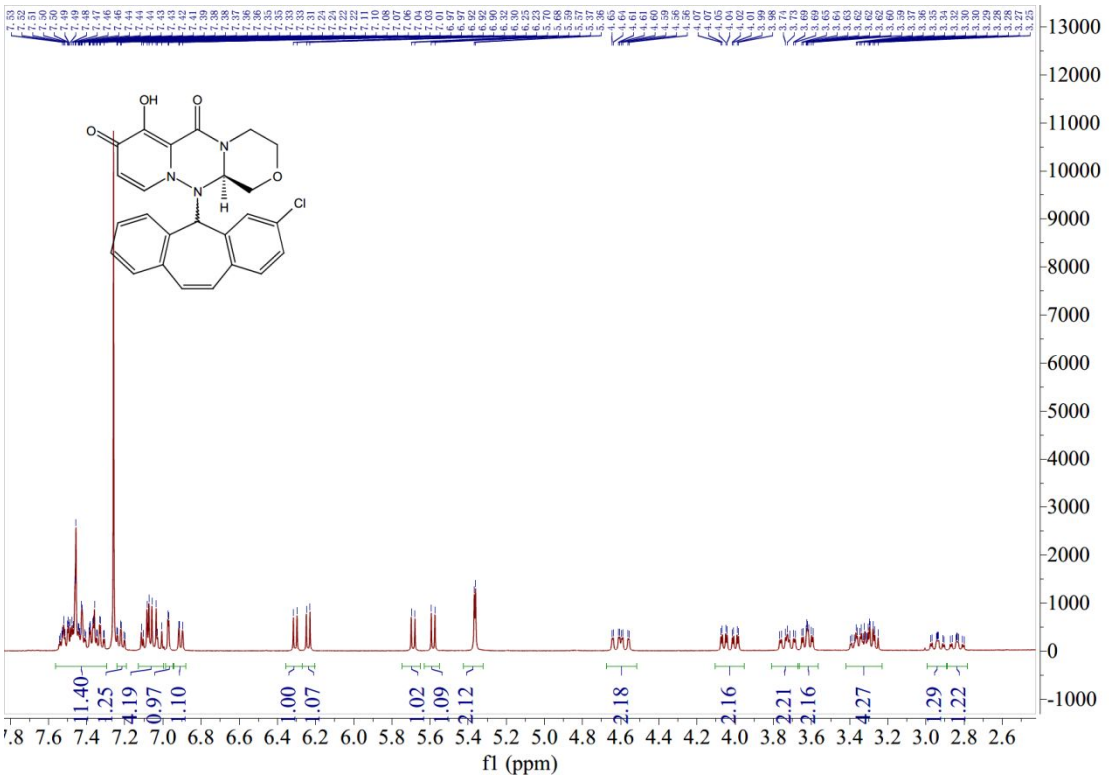

**[1]H-NMR of Compound 10h:**



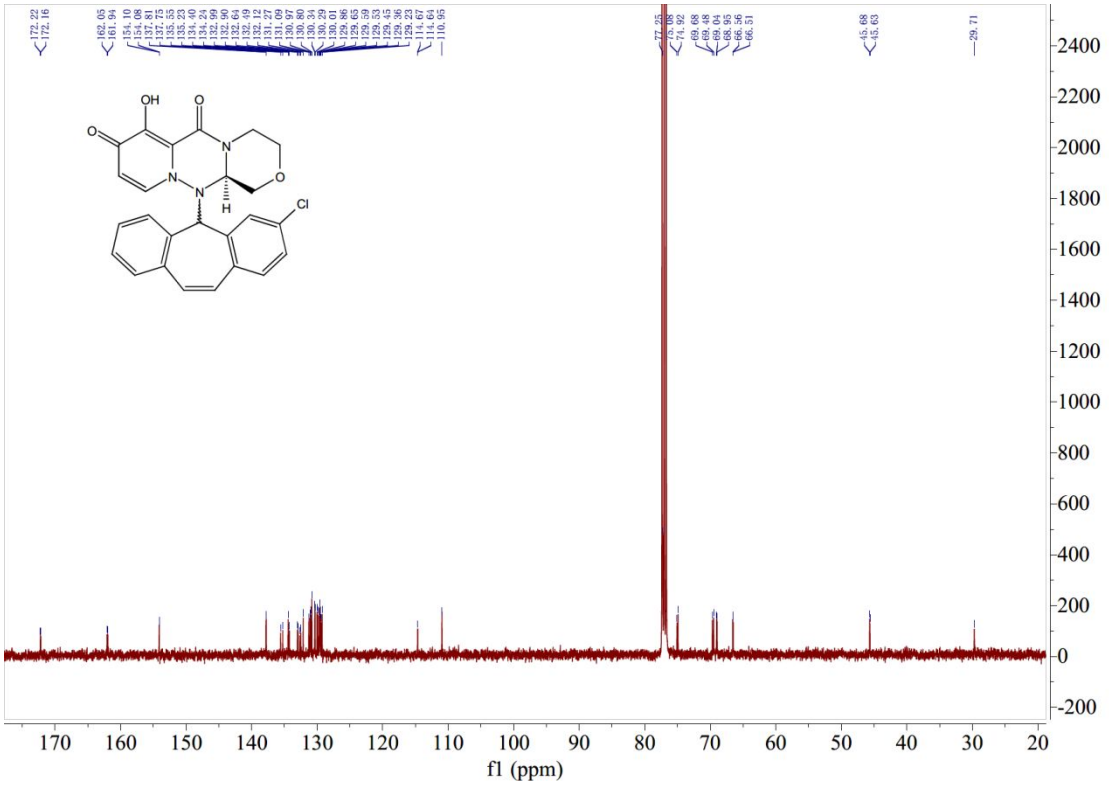
**[1]C-NMR of Compound 10h:**



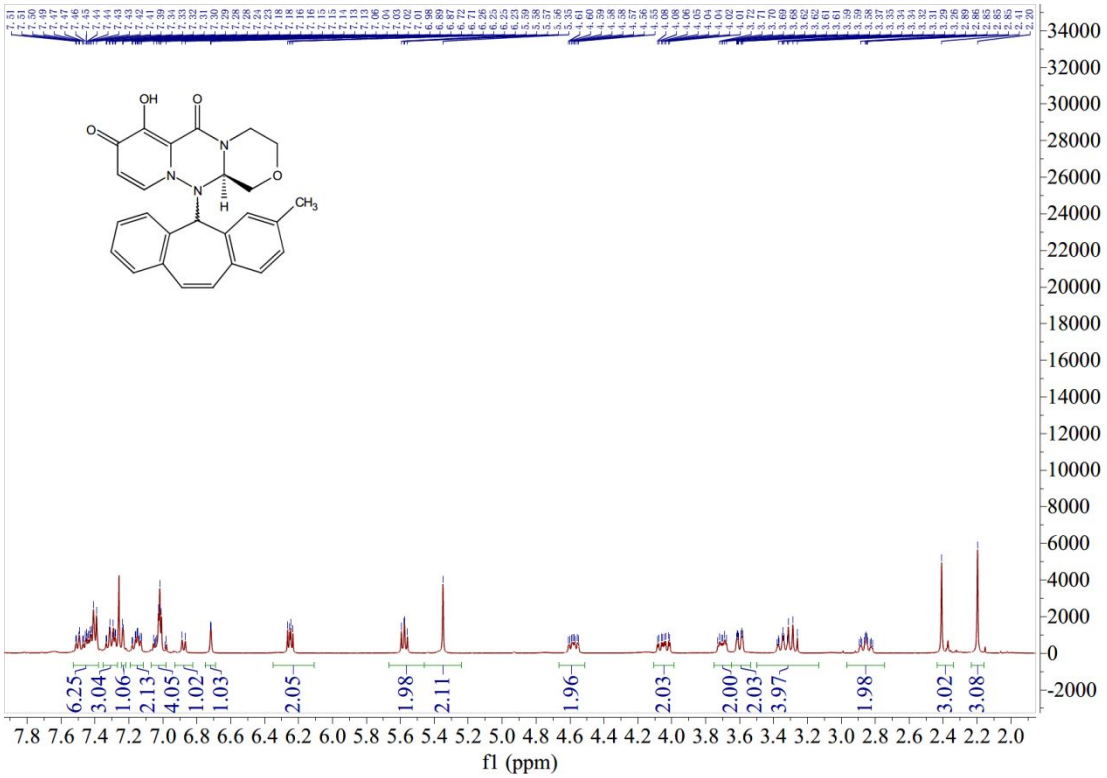

**[1]H-NMR of Compound 10i:**



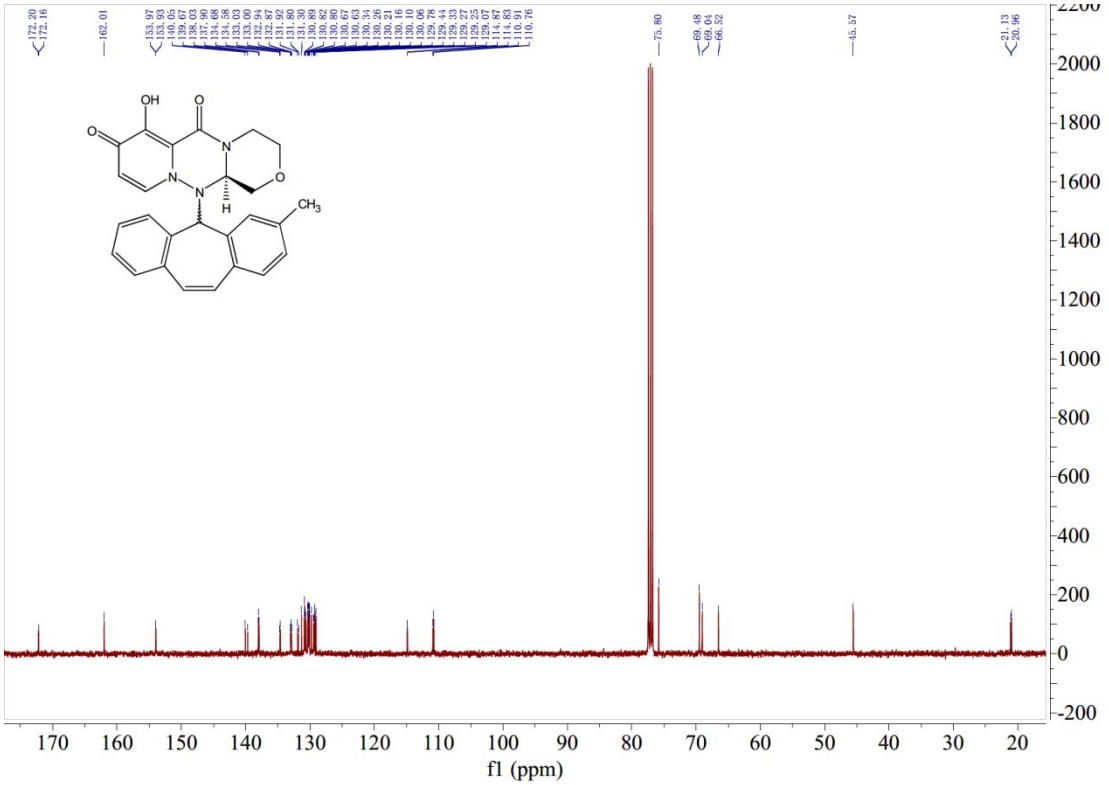

**[1]C-NMR of Compound 10i:**



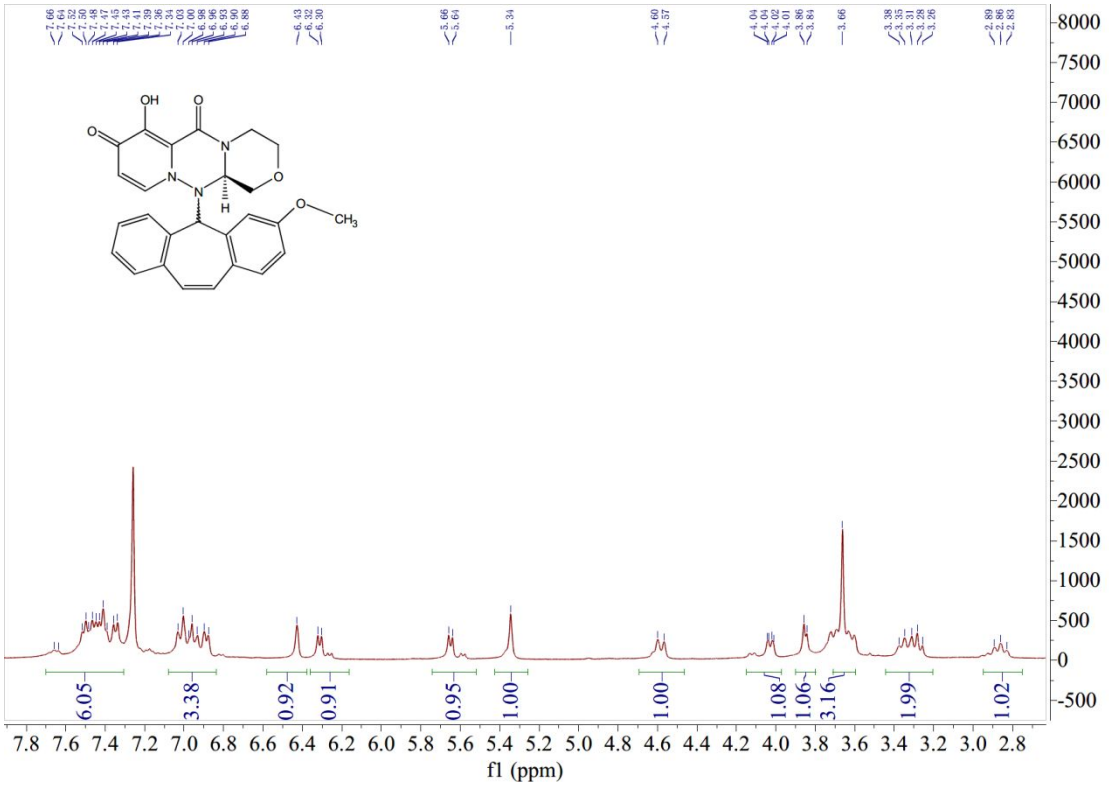
**[1]H-NMR of Compound 10j:**




**[1]C-NMR of Compound 10j:**




**[1]H-NMR of Compound 10k:**



**[1]C-NMR of Compound 10k:**