# Supporting Information

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## General Information

All commercially available reagents were directly used as received from vendors, unless otherwise stated. Anhydrous THF (tetrahydrofuran) and DMF (*N*, *N*-dimethylformamide) freshly distilled over metal sodium, prior to use. NMR spectra were recorded on either Brucker 400 MHz or 500 MHz spectrometer. All NMR spectra were measured in $CDCl_3$, MeOD or DMSO-$d_6$ solutions and referenced to the residual $CHCl_3$ signal ($^1$H, d= 7.26 ppm; $^{13}$C, d=77.16 ppm), MeOH signal ($^1$H, d=3.31 ppm; $^{13}$C, d=49.00 ppm) or DMSO-$d_6$ signal ($^1$H, d= 2.50 ppm; $^{13}$C, d= 39.52 ppm). All $^1$H and $^{13}$C shifts are given in ppm (s=singlet; d=doublet; t=triplet; q=quadruplet; m=multiplet; b=broad signal). High resolution mass spectra (HRMS) were performed with a Bruker ULTRAFLEX Ⅲ TOF/TOF 200 instrument.

## Antibacterial activity assay[1]

The antibacterial activities of the five compounds were tested against *S. aureus* strains. MIC values of tested compounds were determined using agar dilution assay. In brief, the *S. aureus* strains were cultivated on LB broth overnight and diluted. Approximate $10^4$ colony forming units (CFU) of each strain was spotted (2 μL) onto LB agar plates containing different concentration of the tested compounds, ranging from 0.5 - 64 μg/mL LB agar. Then the plates were incubated in 37 ℃ for 16 hours and monitored. The *S. aureus* strains were cultivated on LB broth overnight and diluted to an $OD_{600}$ = 0.25 ± 0.05, then diluted $10^4$ with LB broth, and approximate $10^4$ CFU of each strain was spotted (2 μL) onto LB agar plates.

**Table S1.** MIC values (μg/ml) of PTM (**1**) and selected variants against selected Gram-positive pathogens. (i) black: isolated from wild-type; (ii) purple: isolated from engineered strains; (iii) blue: from semisynthesis; (iv) red: from total synthesis; (v) green: from mutasynthesis.

| Compound | MSSA[a] | MRSA[b] | VRE[c] | Reference |
|---|---|---|---|---|
| **1** | 0.5 | 0.5-1 | 0.1 | [2] |
| **s-2a** | >64 | 37-58 | >58-64 | [3] |
| **s-2b** | >64 | -[d] | - | [3] |
| **s-2c** | >64 | - | >64 | [3] |
| **s-2d** | >64 | - | >64 | [3] |
| **s-2e** | 100 | - | - | [4] |
| **s-2f** | >64 | - | - | [4] |
| **s-2g** | >64 | - | - | [5] |
| **s-2h** | >64 | - | - | [5] |
| **s-2i** | >64 | - | >64 | [6] |
| **s-2j** | >64 | - | - | [4] |
| **s-2k** | >250 | - | - | [7] |
| **s-2l** | >250 | - | - | [7] |
| **s-2m** | >64 | - | - | [3] |
| **s-3a** | - | >85 | >85 | [8] |
| **s-3b** | - | >85 | >85 | [8] |
| **s-3c** | - | >82 | >82 | [8-9] |
| **s-3d** | - | >85 | >85 | [8] |
| **s-4a** | ND[e] | - | - | [10] |
| **s-4b** | ND | - | - | [10] |
| **s-4c** | >64 | >64 | - | [10] |
| **s-4d** | >64 | >64 | - | [10] |
| **s-4e** | >64 | >64 | - | [10] |
| **s-4f** | ND | - | - | [10] |
| **s-4g** | ND | - | - | [10] |
| **s-4h** | ND | - | - | [10] |
| **s-4i** | ND | - | - | [10] |
| **s-4j** | >64 | >64 | - | [9, 11] |
| **s-4k** | >64 | >64 | - | [9] |
| **s-4l** | >64 | >64 | - | [9] |
| **s-4m** | >64 | >64 | - | [9] |
| **s-4n** | >64 | >64 | - | [9] |
| **s-4o** | >64 | >64 | - | [9] |
| **s-4p** | >64 | >64 | - | [9] |
| **s-4q** | >64 | >64 | - | [9] |
| **s-4r** | >64 | >64 | - | [9] |
| **s-4s** | >64 | >64 | - | [9] |
| **s-4t** | >64 | >64 | - | [9] |

| | | | | |
|---|---|---|---|---|
| **s-4u** | >64 | >64 | - | [9] |
| **s-4v** | >64 | >64 | - | [9] |
| **s-4w** | >64 | >64 | - | [9] |
| **s-4x** | >64 | >64 | - | [9] |
| **s-4y** | >64 | >64 | - | [9] |
| **s-4z** | >64 | >64 | - | [9] |
| **s-4a’** | >64 | >64 | - | [9] |
| **s-4b’** | >64 | >64 | - | [9] |
| **s-4c’** | >64 | >64 | - | [9] |
| **s-4d’** | >64 | >64 | - | [9] |
| **s-4e’** | >64 | >64 | - | [9] |
| **s-4f’** | >64 | >64 | - | [9] |
| **s-4g’** | >64 | >64 | - | [9] |
| **s-4h’** | >64 | >64 | - | [9] |
| **s-4i’** | >64 | >64 | - | [9] |
| **s-4j’** | >64 | >64 | - | [9] |
| **s-4k’** | >64 | >64 | - | [9] |
| **s-4l’** | >64 | >64 | - | [9] |
| **s-4m’** | >64 | >64 | - | [9] |
| **s-4n’** | >64 | >64 | - | [9] |
| **s-4o’** | >64 | >64 | - | [9] |
| **s-4p’** | >64 | >64 | - | [9] |
| **s-4q’** | >64 | >64 | - | [3] |
| **s-4r’** | >64 | >64 | - | [7] |
| **s-4s’** | >64 | >64 | - | [7] |
| **s-4t’** | >64 | >64 | - | [3] |
| **s-4u’** | >64 | >64 | - | [3] |
| **s-5a** | NA[f] | - | - | [11] |
| **s-5b** | NA | - | - | [11] |
| **s-5c** | NA | - | - | [11] |
| **s-5d** | NA | - | - | [11] |
| **s-5e** | NA | - | - | [11] |
| **s-5f** | NA | - | - | [11] |
| **s-5g** | NA | - | - | [11] |
| **s-5h** | NA | - | - | [11] |
| **s-5i** | NA | - | - | [11] |
| **s-5j** | NA | - | - | [11] |
| **s-6a** | ND | ND | ND | [12] |
| **s-6b** | ND | ND | ND | [12] |

[a] methicillin-sensitive *S.aureus*. [b] methicillin-resistant *S. aureus*. [c] vancomycin-resistant *Entercocci*. [d] –, not tested against this pathogen. [e] ND, not determined (in some cases, compounds were reported as “less than that of PTM” without an MIC value). [f] NA, no activity without specifying the upper limit concentrations tested.

**Figure S1.** Summarize of platensimycin ADHBA variants. (i) black: isolated from wild-type; (ii) purple: isolated from engineered strains; (iii) blue: from semisynthesis; (iv) red: from total synthesis; (v) green: from mutasynthesis.

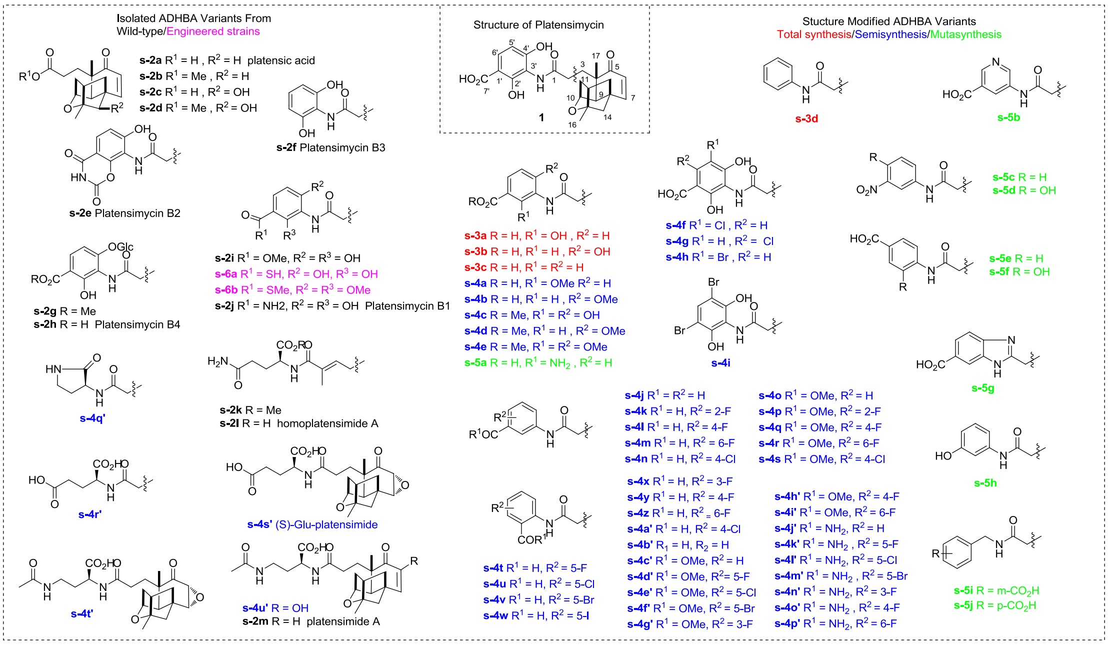
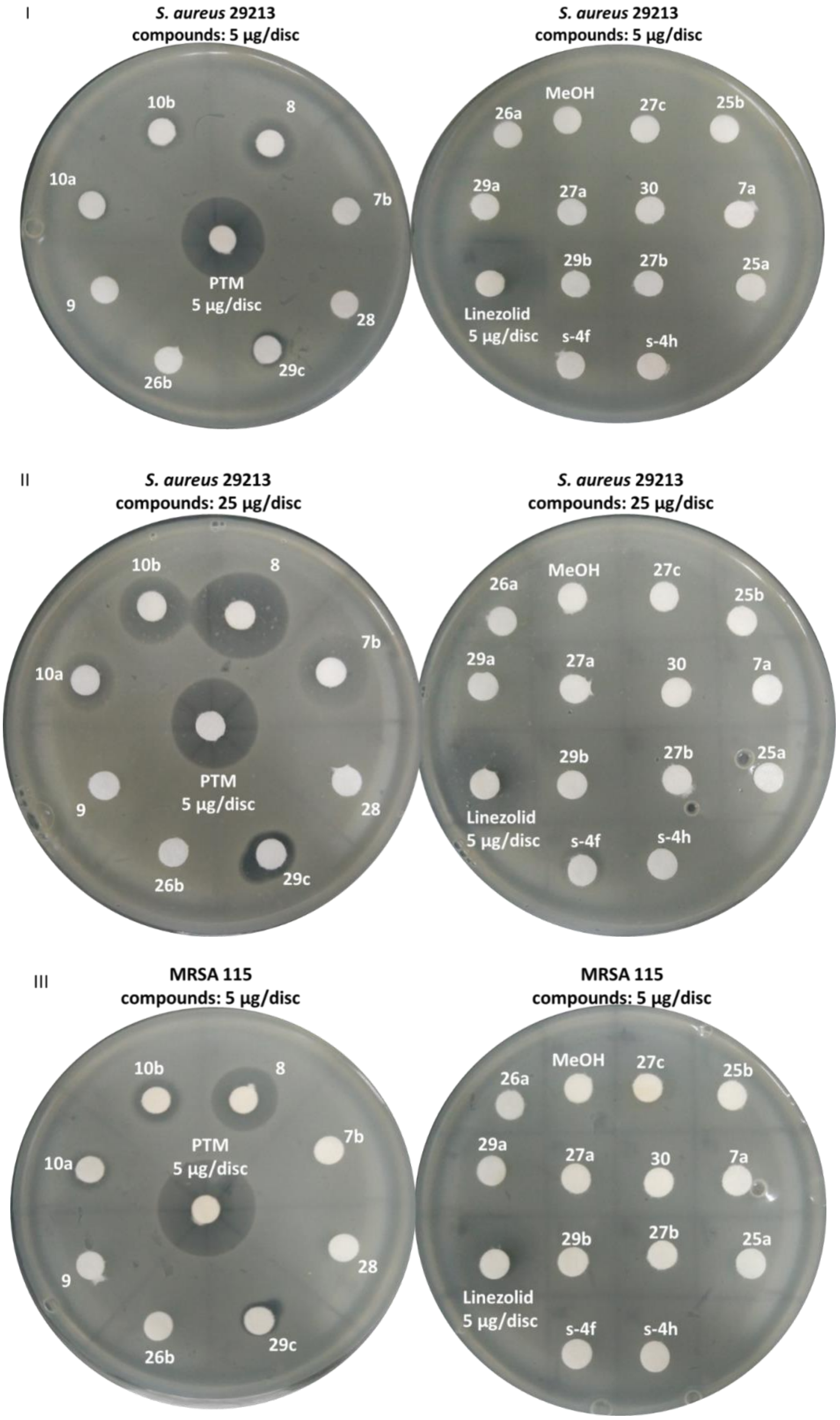
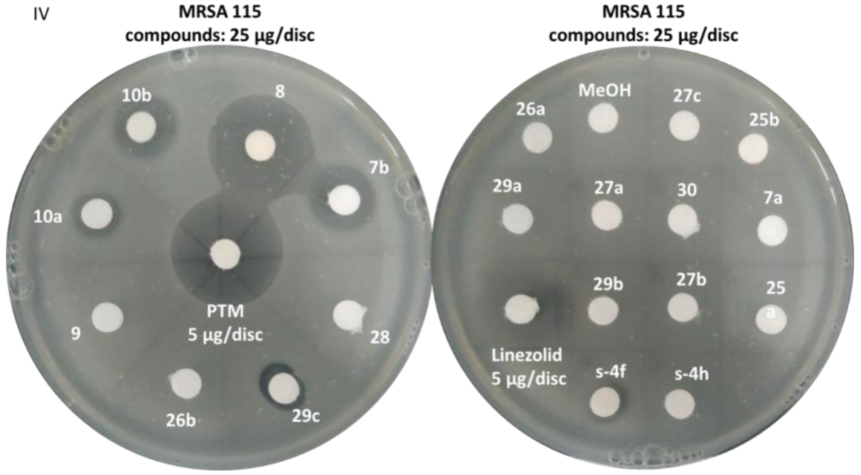


**Figure S2.** Paper Disc Method. Five PTM analogues **7b**, **8**, **10a**, **10b**, **29c** showed clear zone of inhibition against *S. aureus* 29213 and one MRSA strain, when tested in 25 µg/disk, using PTM and Linezolid (5 µg/disk) as a positive control and MeOH as a negative control. The 5'-Cl-platensimycin **s-4f** and 5'-Br-platensimycin **s-4h** were prepared based on a previous work.[10] The experiments were repeated at least for three times and only the results from one experiment were presented.

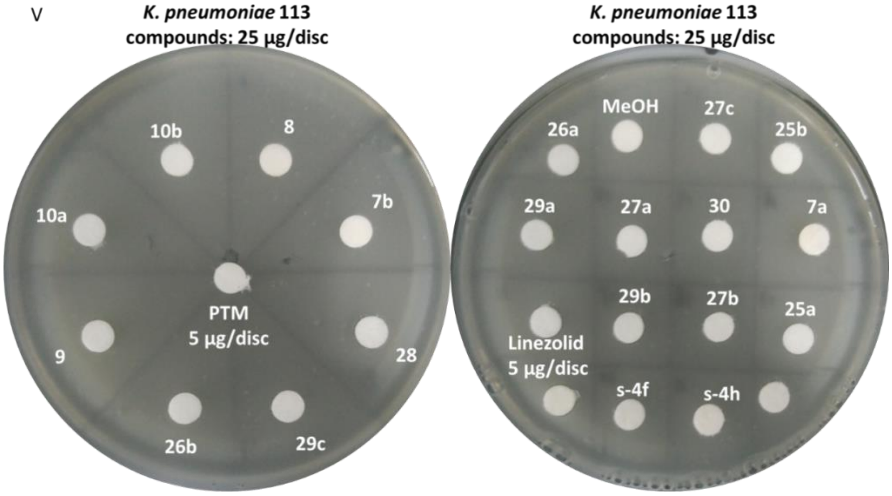


IV


**MRSA 115**
**compounds: 25 µg/disc**

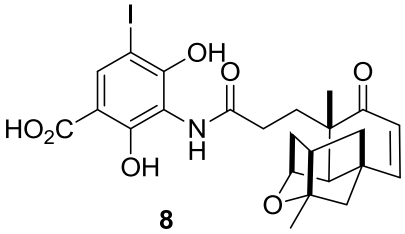
**MRSA 115**
**compounds: 25 µg/disc**

V

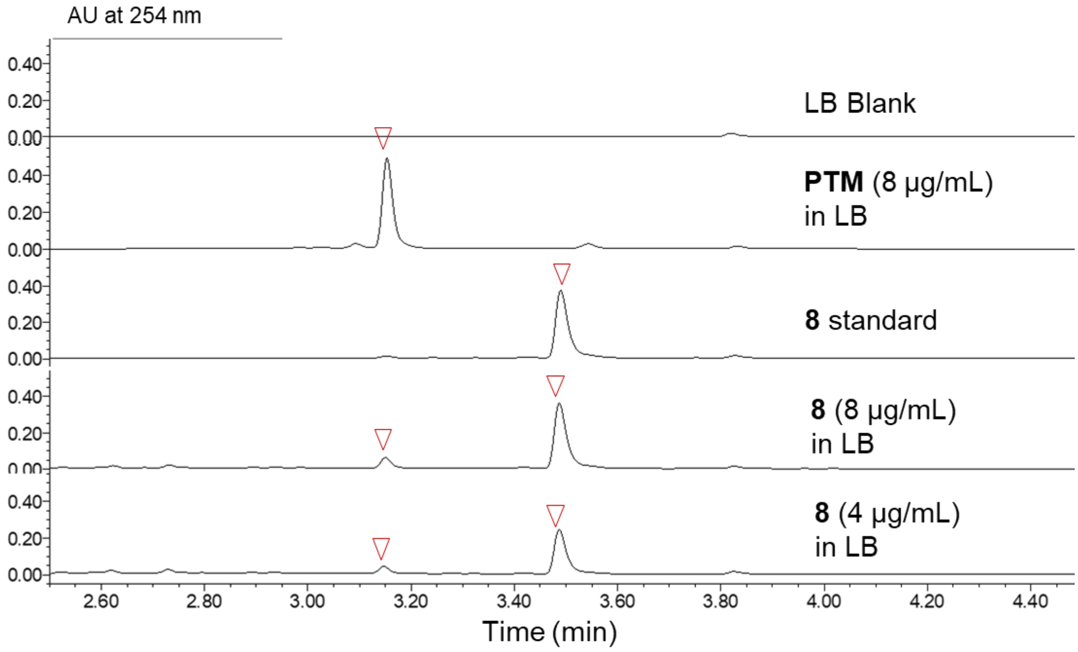

***K. pneumoniae* 113**
**compounds: 25 µg/disc**

***K. pneumoniae* 113**
**compounds: 25 µg/disc**

**Figure S3.** The stability analysis of **8** in LB agar. The compounds **8** (0.1 mg mL$^{-1}$) were diluted in 5 mL LB agar to 0.004 or 0.008 mg mL$^{-1}$, and the resulting LB agar plates were incubated at 37℃ for 16 h. PTM was used as control. The LB agar with the tested compounds were then extracted by $CH_2Cl_2$ (3 × 10 mL), dried by anhydrous $Na_2SO_4$, concentrated *in vacuum* and analyzed by HPLC.



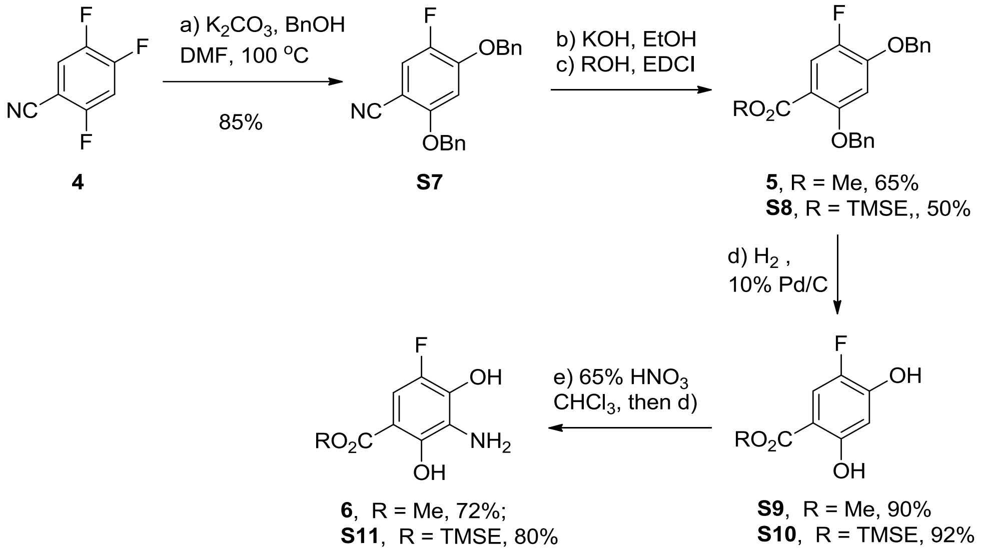
**8**



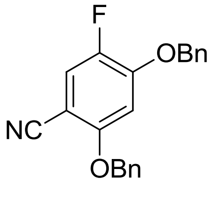
# Experimental procedure and physical data

Arylamines **6**,[13] **13**,[14] **15a**,[15] **15b**,[15] **17a**,[16] **17b**,[16] **19**,[16b] **21a**,[17] **21b**,[17] **24**,[14a] **S11**[13] were prepared by following the procedures based on the methods in the references. Others were purchased from commercial suppliers and used without further purification.

**Supporting Scheme S1.** Synthesis of anilines **6** and **S11**.



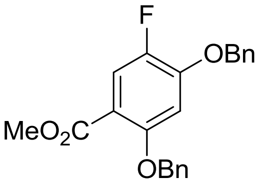
[a] Reagents and conditions: (a) $K_2CO_3$ (5 equiv.), BnOH (2.5 equiv.), DMF, 105 ℃ , 16 h, 85%; (b) 6 N KOH, EtOH, 140 ℃, 1.5 h, 95%; (c) MeOH, DMAP (0.1 equiv.), EDCI (1.2 equiv.), $Et_3N$ (2.5 equiv.) 10 h, 65% (for **5**), 50% (for **S8**); (d) $H_2$ (1.1 atm.),10% Pd/C (0.2 equiv.), MeOH, 25 ℃, 3 h, 90% (for **S9**), 92% (for **S10**); (e) 65%$HNO_3$, $CHCl_3$, 15 min, 72% (for **6**), 80% (for **S11**).



**S7**

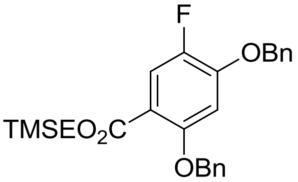
**2,4-bis(benzyloxy)-5-fluorobenzonitrile** (**S7**). To a solution of **4** (1.57 g, 10 mmol) in DMF (5 mL) was added benzyl alcohol (5 mL, 50 mmol) and potassium carbonate (6.9 g, 50 mmol). The vessel was heated to 105 ℃ for 16 h, subsequently placed under high vacuum for 2 h to remove DMF, followed by purification using column chromatography on silica gel (eluent: petroleum ether/ethyl acetate (10:1)) to afford **S7** (2.83 g, 85%) as a yellow solid. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 (dd, $J$ = 4.2, 2.2 Hz, 10H), 7.25 (d, $J$ = 4.9 Hz, 1H), 6.57 (d, $J$ = 6.8 Hz, 1H), 5.11 (d, $J$ = 2.7 Hz, 4H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 157.95 (s), 151.40 (d, J = 11.6 Hz), 147.62 (s), 145.21 (s), 135.28 (s), 135.03 (s), 128.93 – 128.51 (m), 128.37 (s), 127.31 (s), 126.98 (s), 119.92 (s), 119.70 (s), 115.70 (s), 101.18 (s), 93.30 (d, J = 4.9 Hz), 77.31 (s), 76.99 (s), 76.68 (s), 71.42 (d, J = 3.9 Hz). MS (ESI): m/z calcd for $C_{21}H_{17}FNO_2$ $[M+H]^+$: 334.1243; found: 334.0918.

**Methyl 2,4-bis(benzyloxy)-5-fluorobenzoate-2-(trimethylsilyl)ethyl** (**5**). To a suspension of benzonitrile **S7** (1.17 g, 3.5 mmol) in EtOH (6 mL) was added KOH (1.22 g, 21.8 mmol) in $H_2O$ (6 mL). The mixture was heated in a sealed tube at 140 ℃ in an oil bath for 1.5 hours and then concentrated under reduced pressure at 45 ℃. The resulting slurry was acidified with 2 N HCl (12 mL) and filtered. The filter cake was washed with $H_2O$ (3×10 mL) and dried *in vacuo* at ambient temperature to give 2,4-bis(benzyloxy)-5-fluorobenzoic acid as an off-white solid (1.07 g, 87%). A mixture of 2,4-bis(benzyloxy)-5-fluorobenzoic acid (704 mg, 2.0 mmol), alcohol methanol (160 µL, 4.0 mmol), DMAP (24.4 mg, 0.2 mmol), and EDCI (1.15 g, 6.0 mmol) in $CH_2Cl_2$ (25 mL) was stirred at room temperature overnight. The reaction mixture was washed with saturated NaCl. The $CH_2Cl_2$ solution was separated, dried over $Na_2SO_4$, and removed by rotary evaporation. The residue was purified by chromatography using 10 : 1 petroleum ether/ethyl acetate to obtain **5** (0.83 g ,65%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 11.8 Hz, 1H), 7.45 (d, $J$ = 7.3 Hz, 2H), 7.42 – 7.29 (m, 8H), 6.60 (d, $J$ = 6.9 Hz, 1H), 5.10 (d, $J$ = 15.6 Hz, 4H), 3.87 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 164.11 (s), 154.87 (s), 149.56 (d, $J$ = 11.9 Hz), 146.67 (s), 144.28 (s), 135.40 (s), 134.57 (s), 127.73 (s), 127.58 (s), 127.40 (s), 126.93 (s), 126.38 (s), 125.93 (s), 118.15 (s), 117.94 (s), 111.39 (s), 111.33 (s), 101.71 (s), 70.84 (s), 70.28 (s), 50.93 (s); HRMS (ESI): m/z calcd for $C_{22}H_{20}FO_4$ $[M+H]^+$: 367.1346; found:367.1339.



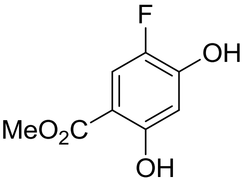
**5**

**2,4-bis(benzyloxy)-5-fluorobenzoate** (**S8**). To a suspension of benzonitrile **S7** (1.17 g, 3.5 mmol) in EtOH (6 mL) was added KOH (1.22 g, 21.8 mmol) in $H_2O$ (6 mL). The mixture was heated in a sealed tube at 140 ℃ in an oil bath for 1.5 hours and then concentrated under reduced pressure at 45 ℃. The resulting slurry was acidified with 2 N HCl (12 mL) and filtered. The filter cake was washed with $H_2O$ (3×10 mL) and dried *in vacuo* at ambient temperature to give 2,4-bis(benzyloxy)-5-fluorobenzoic acid as an off-white solid (1.07 g, 87%). A mixture of 2,4-bis(benzyloxy)-5-fluorobenzoic acid (704 mg, 2.0 mmol), 2-(trimethylsilyl) ethanol (236 mg, 2.0 mmol), DMAP (30 mg, 0.2 mmol), and EDCI (1.16 g, 6.0 mmol) in $CH_2Cl_2$ (25 mL) was stirred at room temperature overnight. The reaction mixture was washed with saturated NaCl. The $CH_2Cl_2$ solution was separated, dried over $Na_2SO_4$, and removed by rotary evaporation. The residue was purified by chromatography using 10 : 1 petroleum ether/ethyl acetate to obtain **S8** (0.79 g, 50%); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$ = 11.8 Hz, 1H), 7.48 (d, $J$ = 7.2 Hz, 2H), 7.45 – 7.30 (m, 8H), 6.62 (d, $J$ = 6.9 Hz, 1H), 5.11 (d, $J$ = 18.4 Hz, 4H), 4.48 – 4.27 (m, 3H), 1.15 – 1.06 (m, 2H), 0.09 (s, 9H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 164.95 (s), 155.78 (d, $J$ = 1.9 Hz), 150.38 (d, $J$ = 12.0 Hz), 147.74 (s), 145.35 (s), 136.51 (s), 135.71 (s), 128.76 (s), 128.56 (s), 128.42 (s), 127.97 (s), 127.43 (s), 127.13 (s), 119.12 (s), 118.91 (s), 113.09 (d, $J$ = 5.5 Hz), 102.78 (s), 77.34 (d, $J$ = 11.6 Hz), 77.08 (s), 76.76 (s), 71.88



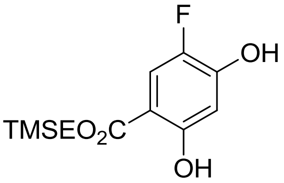
**S8**

(s), 71.35 (s), 66.09 (s), 65.81 (s), 63.12 (s), 44.25 (s), 28.87 (s), 25.75 (s), 17.46 (s), 17.23 (s), -1.51 (d, *J* = 7.1 Hz). MS (ESI): m/z calcd for $C_{26}H_{28}FO_4Si$ $[M+H]^-$: 451.1741; found: 451.4084.



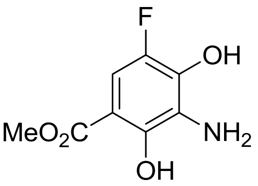
**S9**

**Methyl 5-fluoro-2,4-dihydroxybenzoate (S9)**. To a solution of **5** (431 mg, 1.18 mmol) in MeOH (12 mL) was added 10% Pd/C (43 mg) and the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give crude product. Purification by column chromatography on silica gel (ethyl acetate/petroleum ether = 1:10) to afford pure product **S9** (197 mg, 90%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.74 (s, 1H), 7.52 (d, *J* = 10.8 Hz, 1H), 6.57 (d, *J* = 7.4 Hz, 1H), 5.89 (s, 1H), 3.92 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 169.75 (s), 159.63 (s), 150.38 (d, *J* = 16.2 Hz), 145.53 (s), 143.23 (s), 115.47 (s), 115.26 (s), 104.98 (s), 104.25 (d, *J* = 6.3 Hz), 77.35 (s), 77.03 (s), 76.71 (s), 52.32 (s). MS (ESI): m/z calcd for $C_8H_6FO_4$ $[M+H]^-$: 185.0250; found: 185.1074.



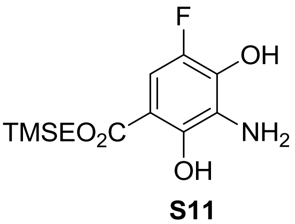
**S10**

**2-(trimethylsilyl)ethyl 5-fluoro-2,4-dihydroxybenzoate (S10)**. To a solution of **S8** (533mg, 1.18 mmol) in MeOH (12 mL) was added 10% Pd/C (53 mg) and the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give crude product. Purification by column chromatography on silica gel (ethyl acetate/petroleum ether = 1:10) to afford pure product **S10** (296 g, 92%).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.89 (s, 1H), 7.51 (d, *J* = 10.8 Hz, 1H), 6.56 (d, *J* = 7.4 Hz, 1H), 5.95 (s, 1H), 4.52 – 4.29 (m, 2H), 1.20 – 1.05 (m, 2H), 0.08 (s, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 169.55 (s), 159.66 (s), 150.21 (d, *J* = 16.0 Hz), 145.50 (s), 143.20 (s), 115.42 (s), 115.22 (s), 104.95 (s), 104.65 (d, *J* = 6.0 Hz), 77.29 (d, *J* = 11.6 Hz), 77.03 (s), 76.71 (s), 63.92 (s), 29.71 (s), 17.40 (s), -1.48 (s). MS (ESI): m/z calcd for $C_{12}H_{16}FO_4Si$ $[M+H]^-$: 271.0802; found: 271.1101.



**6**

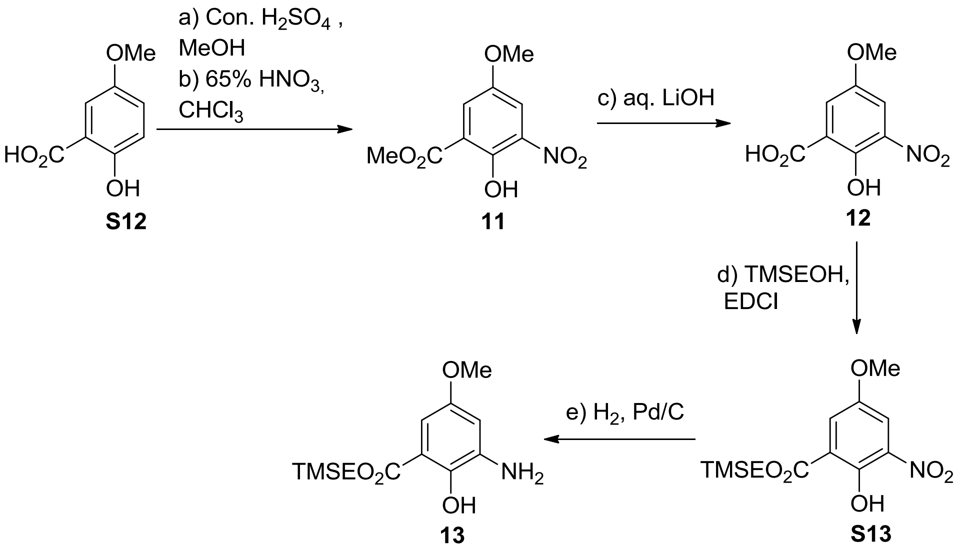
**Methyl 3-amino-5-fluoro-2,4-dihydroxybenzoate (6).** To a solution of Methyl 5-fluoro-2,4-dihydroxybenzoate **S9** (100 mg, 0.5 mmol) in $CHCl_3$ (25 mL) was slowly added 65% $HNO_3$ (40 μL) at 0 ℃, and the mixture was warmed to room temperature. After stirring at 25 ℃ for another 15 minutes, a yellowish precipitate was formed, and the solid was filtered off. Then the filtered cake was dried and dissolved in MeOH (12 mL), after that 10% Pd/C (12 mg) was added and the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give product **6** (72 mg, 72%) without further purification. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.52 (s, 1H), 6.84 (d, *J* = 11.2 Hz, 1H), 3.86 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 170.27 (d, *J* = 3.1 Hz), 146.98 (s), 146.03 (s), 144.69 (s), 137.43 (d, *J* = 17.9 Hz), 102.42 (d, *J* = 8.6 Hz), 102.00 (s), 101.79 (s), 52.76 (s); HRMS (ESI): m/z calcd for $C_8H_9FNO_4$ [M+H]$^+$: 202.0516; found: 202.0508.



**S11**

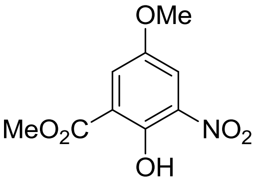
**2-(trimethylsilyl)ethyl 3-amino-5-fluoro-2,4-dihydroxybenzoate (S11).** To a solution of 2-(trimethylsilyl)ethyl-5-fluoro-2,4-dihydroxybenzoate **S10** (136 mg, 0.5 mmol) in $CHCl_3$ (25 mL) was slowly added 65% $HNO_3$ (40 µL) at 0 °C, and the mixture was warmed to room temperature. After stirring at 25 °C for another 15 minutes, a yellowish precipitate was formed, and the solid was filtered off. Then the filtered cake was dried and dissolved in MeOH (12 mL), after that 10% Pd/C (16 mg) was added the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give product **S11** (114 mg, 80%) without further purification. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.91 (s, 1H), 7.29 (s, 1H), 4.52 – 4.27 (m, 2H), 1.19 – 1.01 (m, 2H), 0.15 – 0.02 (m, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 158.25 – 157.75 (m), 125.52 (s), 77.37 (s), 77.05 (s), 76.73 (s), 66.10 (s), 65.73 (d, *J* = 17.3 Hz), 44.22 (s), 31.93 (s), 30.32 (s), 29.54 (d, *J* = 33.7 Hz), 28.86 (s), 28.86 – 28.71 (m), 25.74 (s), 22.70 (s), 17.84 – 17.02 (m), 14.13 (s), 1.02 (s), -1.53 (d, *J* = 9.9 Hz). MS (ESI): m/z calcd for $C_{12}H_{19}FO_4Si$ [M+H]$^+$: 288.1067; found: 288.0727.

**Supporting Scheme S2.** Synthesis of anilines **13.**



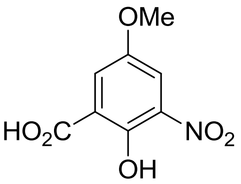
[a] Reagents and conditions: (a) Con. $H_2SO_4$, MeOH, 80 ℃, 24 h, 85%; (b) 65% $HNO_3$, $CHCl_3$, r.t, 2 h, 90%; (c) THF, aq. LiOH, 45 ℃, 4 h, 95%; (d) TMSEOH (1.2 equiv.), EDCI (1.0 equiv.), $NEt_3$ (2.0 equiv.), $CH_2Cl_2$, 25 ℃, 12 h, 89%; (e) $H_2$ (1.1 atm.), 10% Pd/C (0.2 equiv.), MeOH, 25 ℃, 3 h, 95%.

**Methyl 2-hydroxy-5-methoxy-3-nitrobenzoate（11）.** 2-hydroxy-5-methoxybenzoic acid (5.04 g, 30.0 mmol) was dissolved in MeOH (50 mL), to which con. $H_2SO_4$ (3 mL) was added. The mixture was heated under reflux for 24 h. The solvent was then removed in vacuo and the residue was dissolved in $CH_2Cl_2$ (100 mL), washed with water (3 × 50 mL) and dried over anhydrous $Na_2SO_4$. Removal of $CH_2Cl_2$ gave the pure product methyl 2-hydroxy-5-methoxybenzoate (4.64 g, 85%) as a light brown solid. To a solution of methyl 2-hydroxy-5-methoxybenzoate (1.82 g, 10 mmol) in $CHCl_3$ (25 mL) was slowly added 65% $HNO_3$ (400 μL) at 0 ℃, and the mixture was warmed to room temperature. After stirring at 25 ℃ for 2h, a yellowish precipitate was formed, and the solid was filtered off to give the title product **11** (2.04 g, 90%). MS (ESI): m/z calcd for $C_9H_8NO_6$ $[M+H]^-$: 226.0352; found: 226.1539.



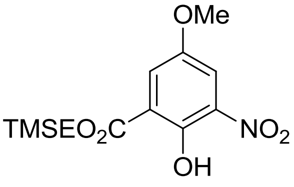
**11**

**2-hydroxy-5-methoxy-3-nitrobenzoic acid (12).** To a stirred solution of **11** (1.14 g, 5 mmol) in THF (5 mL) was added an aqueous solution of LiOH (2 M, 5 mL). The resulting mixture was stirred at 45 ℃ for 4 h. The resulting mixture was then cooled to room temperature, acidified with an aqueous solution of HCl (2 M, 10 mL) and extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (silica



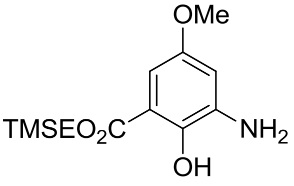
**12**

gel, ethyl acetate/methanol = 6:1) to give title compound **12** (1.01 g, 95%) as a yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.76 (s, 1H), 7.74 – 7.64 (m, 1H), 7.60 – 7.49 (m, 1H), 3.77 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 171.11 (s), 150.32 (s), 149.28 (s), 138.25 (s), 121.00 (s), 116.98 (s), 116.22 (s), 56.48 (s), 40.22 (s), 40.01 (s), 39.95 – 39.92 (m), 39.69 (d, $J$ = 21.0 Hz), 39.38 (s). MS (ESI): m/z calcd for $C_8H_6NO_6$ $[M+H]^-$: 212.0195; found: 212.1040.



**S13**

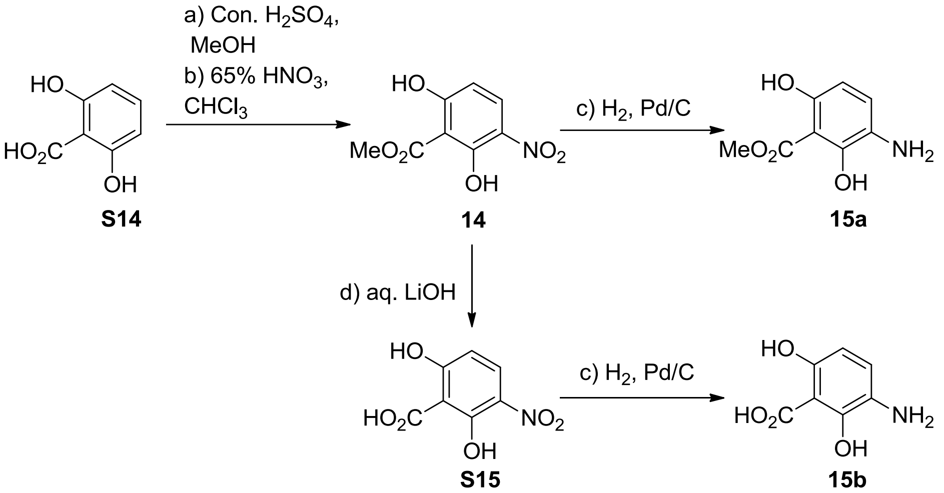
**2-(trimethylsilyl)ethyl 2-hydroxy-5-methoxy-3-nitrobenzoate (S13).** A mixture of **9**(567 mg, 2.5 mmol), 2-(trimethylsilyl)ethanol (307 mg, 2.6 mmol), DMAP (12.2 mg, 0. 1 mmol), and EDCI (443 mg, 3.75 mmol) in $CH_2Cl_2$ (15 mL) was stirred at 25 ℃ overnight. The reaction mixture was washed with water and then with saturated $NaHCO_3$. The ethyl acetate solution was separated, dried over $Na_2SO_4$, and ethyl acetate removed by rotary evaporation. The residue was purified by chromatography using ethyl acetate/petroleum ether = 1:10 to obtain **S13** (698 mg, 89%); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 11.68 (s, 1H), 7.71 (d, $J$ = 3.2 Hz, 1H), 7.68 (d, $J$ = 3.3 Hz, 1H), 4.55 – 4.46 (m, 2H), 3.85 (s, 3H), 1.21 – 1.16 (m, 2H), 0.11 (s, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.64 (s), 150.56 (s), 150.00 (s), 137.67 (s), 121.45 (s), 116.41 (d, $J$ = 4.8 Hz), 77.40 (s), 77.09 (s), 76.77 (s), 65.26 (s), 56.24 (s), 29.71 (s), 17.34 (s), -1.48 (s). MS (ESI): m/z calcd for $C_{13}H_{18}NO_6Si$ $[M+H]^-$: 312.0903; found: 312.1224.



**13**

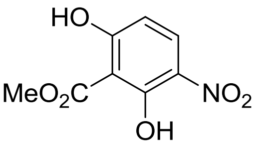
**2-(trimethylsilyl)ethyl 3-amino-2-hydroxy-5-methoxybenzoate (13).** To a solution of **65** (100 mg, 0.32 mmol) in MeOH (12 mL) was added 10% Pd/C (10 mg) and the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give product **13** (70 mg, 95%) without further purification. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.72 (s, 1H), 6.71 (d, $J$ = 2.9 Hz, 1H), 6.52 (d, $J$ = 2.8 Hz, 1H), 4.49 – 4.43 (m, 2H), 3.76 (s, 3H), 1.17 (s, 2H), 0.12 (s, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.71 (s), 152.03 (s), 144.99 (s), 136.84 (s), 111.33 (s), 108.07 (s), 99.91 (s), 77.38 (s), 77.06 (s), 76.74 (s), 63.78 (s), 55.59 (s), 29.73 (s), -1.40 (s); HRMS (ESI): m/z calcd for $C_{13}H_{22}NO_4Si$ $[M+H]^+$: 284.1318; found: 284.1312.

**Supporting Scheme S3.** Synthesis of anilines **15a** and **15b**.



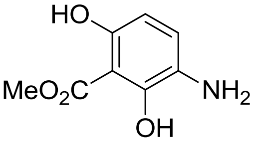
[a] Reagents and conditions: (a) Con. $H_2SO_4$, MeOH, 80 °C, 24 h, 72%; (b) 65% $HNO_3$, $CHCl_3$, r.t, 10 min, 95%; (d) THF, aq. LiOH, 45 °C, 91%; (c) $H_2$ (1.1 atm.), 10% Pd/C (0.2 equiv.), MeOH, 25 °C, 3 h, , 91% (for **15a**), 89% (for **15b**).

**Methyl 2,6-dihydroxy-3-nitrobenzoate (14).** 2,6-dihydroxybenzoic acid **S14** (4.62 g, 30.0 mmol) was dissolved in MeOH (50 mL), to which con. $H_2SO_4$ (3 mL) was added. The mixture was heated under reflux for 24 h. The solvent was then removed in vacuo and the residue was dissolved in $CH_2Cl_2$ (100 mL), washed with water (3 × 50 mL) and dried over anhydrous $Na_2SO_4$. Removal of $CH_2Cl_2$ gave the pure product methyl 2,6-dihydroxy benzoate (3.63 g, 21.6 mmol) as a light brown solid. To a solution of methyl 2,6-dihydroxy benzoate (1.68 g,10 mmol) in $CHCl_3$ (25 mL) was slowly added 65% $HNO_3$ (400 μL) at 0 °C, and the mixture was warmed to room temperature. After stirring at 25 °C for 2h, a yellowish precipitate was formed, and the solid was filtered off to give the title product **14** (2.02 g, 95%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 12.70 (s, 1H), 12.63 (s, 1H), 8.26 (d, $J$ = 9.6 Hz, 1H), 6.63 (d, $J$ = 9.6 Hz, 1H), 4.08 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 170.80 (s), 170.57 (s), 159.46 (s), 133.23 (s), 131.63 (s), 110.80 (s), 102.12 (s), 77.37 (s), 77.05 (s), 76.74 (s), 53.32 (s). MS (ESI): m/z calcd for $C_8H_6NO_6$ $[M+H]^-$: 212.0195; found: 212.0540.



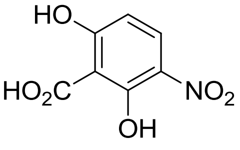
14

**Methyl 3-amino-2,6-dihydroxybenzoate (15a).** To a solution of **14** (106 mg, 0.5 mmol) in MeOH (12 mL) was added 10% Pd/C (10 mg) and the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give product **15a** (83 mg, 91%) without further purification. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 10.00 (s, 1H), 8.82 (s, 1H), 6.90 (d, $J$ = 8.6 Hz, 1H), 6.40 (d, $J$ = 8.6 Hz, 1H), 4.10 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$

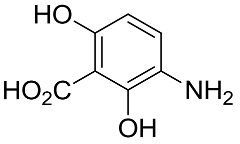


15a

170.17 (s), 152.44 (s), 147.96 (s), 144.51 (s), 127.52 (s), 123.18 (s), 107.13 (s), 99.89 (s), 77.35 (s), 77.03 (s), 76.72 (s), 52.84 (s), 29.71 (s); HRMS (ESI): m/z calcd for $C_8H_{10}NO_4$ $[M+H]^+$: 184.0610; found:184.0600.

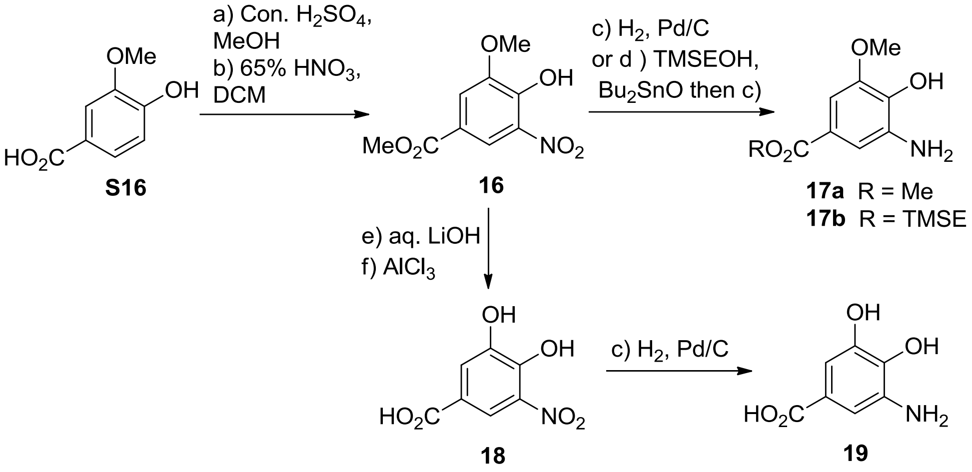

**S15**

**2,6-dihydroxy-3-nitrobenzoic acid (S15).** To a stirred solution of **14** (1.06 g, 5 mmol) in THF (5 mL) was added an aqueous solution of LiOH (2 M, 5 mL). The resulting mixture was stirred at 45 ℃ for 4 h. The resulting mixture was then cooled to room temperature, acidified with an aqueous solution of HCl (2 M, 10 mL) and extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue so obtained was purified by flash column chromatography (silica gel, ethyl acetate/methanol = 6:1) to give title compound **S15** (905 mg, 91%) as a yellow solid. $^1$H NMR (400 MHz, DMSO-*d*6) $\delta$ 9.90 (s, 3H), 7.95 (d, *J* = 9.4 Hz, 1H), 6.26 (d, *J* = 9.4 Hz, 1H). $^{13}$C NMR (101 MHz, DMSO-*d*6) $\delta$ 174.59 (s), 168.43 (s), 161.00 (s), 130.41 (s), 128.16 (s), 106.71 (s), 104.55 (s), 40.37 (d, *J* = 20.9 Hz), 40.08 (s), 40.11 – 39.62 (m), 39.43 (s), 39.43 (s), 39.33 (d, *J* = 20.8 Hz). MS (ESI): m/z calcd for $C_7H_4NO_6$ $[M+H]^-$: 198.0039; found: 198.1052.


**15b**

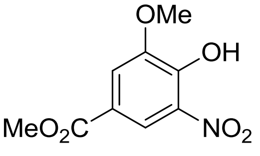
**3-amino-2,6-dihydroxybenzoic acid (15b).** To a solution of **S15** (100 mg, 0.5mmol) in MeOH (12 mL) was added 10% Pd/C (10 mg) and the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give product **15b** (75 mg, 89%) without further purification. $^1$H NMR (500 MHz, DMSO-*d*6) $\delta$ 7.90 (d, *J* = 9.1 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.04 (d, *J* = 8.3 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-*d*6) $\delta$ 175.39 (s), 168.00 (s), 165.61 (s), 128.28 (s), 124.22 (s), 106.21 (s), 103.60 (s), 41.80 – 39.91 (m), 39.80 (s), 39.67 (d, *J* = 21.0 Hz), 39.42 (s); HRMS (ESI): m/z calcd for $C_7H_8NO_4$ $[M+H]^+$: 170.0453; found:170.0445.

**Supporting Scheme S4.** Synthesis of anilines **17a**, **17b** and **19**.



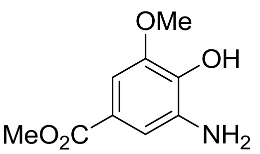
[a] Reagents and conditions: (a) Con. $H_2SO_4$, MeOH, 80 °C, 24 h, 95%; (b) 65% $HNO_3$, $CHCl_3$, r.t, 2 h, 91%; (c) $H_2$ (1.1 atm.), 10% Pd/C (0.2 equiv.), MeOH, 25 °C, 3 h, 93% (for **17a**), 82% (for **17b**), 89% (for **19**); (d) TMSEOH (1.5 equiv.), toluene, $Bu_2SnO$ (1.0 equiv.), 150 °C, 8 h, 85%; (e) THF, aq. LiOH, 45 °C, 4 h, 95%; (f) $AlCl_3$ (3.0 equiv.), 1,2-DCE, 90 °C, 2 h, 85%;

**Methyl 4-hydroxy-3-methoxy-5-nitrobenzoate (16).** To a solution of 4-hydroxy-3-methoxybenzoic acid **S16** (5.04 g, 30.0 mmol) in MeOH (50 mL), to which con. $H_2SO_4$ (3 mL) was added. The mixture was heated under reflux for 24 hrs. The solvent was then removed in vacuo and the residue was dissolved in $CH_2Cl_2$ (100 mL), washed with water (3 × 50 mL) and dried over anhydrous $Na_2SO_4$. Removal of $CH_2Cl_2$ gave the pure product methyl 4-hydroxy-5-methoxybenzoate (5.19 g, 95%) as a light brown solid. To a solution of methyl 4-hydroxy-5-methoxybenzoate (1.82 g, 10 mmol) in $CHCl_3$ (25 mL) was slowly added 65% $HNO_3$ (400 μL) at 0 °C, and the mixture was warmed to room temperature. After stirring at 25 °C for 2 h, a yellowish precipitate was formed, and the solid was filtered off to give title compound **16** (2.06 g, 91%) as a yellow solid. MS (ESI): m/z calcd for $C_9H_8NO_6$ $[M+H]^-$: 226.0352; found: 226.1539.



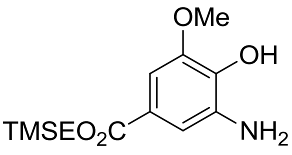
**16**

**Methyl 3-amino-4-hydroxy-5-methoxybenzoate (17a).** To a solution of **16** (113 mg, 0.5 mmol) in MeOH (12 mL) was added 10% Pd/C (11 mg) and the suspension was stirred for 3 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give product **17a** (91.6 mg, 93%) without further purification; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.17 (d, $J$ = 1.8 Hz, 1H), 7.10 (d, $J$ = 1.8 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H); $^{13}C$



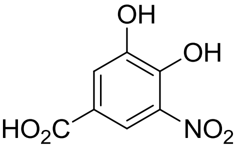
**17a**

NMR (101 MHz, $CDCl_3$) $\delta$ 167.21 (s), 146.13 (s), 137.03 (s), 133.84 (s), 121.65 (s), 111.23 (s), 103.09 (s), 77.35 (s), 77.03 (s), 76.72 (s), 56.23 (s), 51.93 (s); HRMS (ESI): m/z calcd for $C_9H_{12}NO_4$ $[M+H]^+$: 198.0766; found: 198.0759.



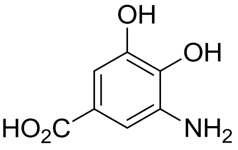
17b

**2-(trimethylsilyl)ethyl 3-amino-4-hydroxy-5-methoxybenzoate (17b).** To a stirred solution of methyl 4-hydroxy-3-methoxy-5-nitrobenzoate **16** (340 mg, 1.5 mmol) in toluene (10 mL) was added 2-(trimethylsilyl)ethanol (236 mg, 2.0 mmol) and $Bu_2SnO$ (375 mg, 1.5 mmol) respectively. The reaction mixture was heated in a sealed tube at 150 ℃ for 8 h before the solvent was removed using vacuum distillation. The residue was dissolved in $CH_2Cl_2$ the solid was filtered. The filtrate was concentrated in vacuo. Then dissolved in MeOH (12 mL) and added Pd/C (10 mg) and the reaction mixture was stirred under $H_2$ for 3h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to afford aniline **17b** (349 mg, 82%), which was used for next step without further purification. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.17 (s, 1H), 7.07 (s, 1H), 4.73 (s, 2H), 4.44 – 4.28 (m, 2H), 3.80 (s, 3H), 1.07 (s, 2H), 0.06 (s, 9H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 166.99 (s), 146.28 (s), 137.30 (s), 133.94 (s), 121.90 (s), 111.34 (s), 103.27 (s), 77.52 (s), 77.20 (s), 76.88 (s), 62.94 (s), 56.06 (s), 29.70 (s), 17.38 (s), -1.43 (s); HRMS (ESI): m/z calcd for $C_{13}H_{22}NO_4Si$ $[M+H]^+$: 284.1318; found: 284.1314.



18

**3,4-dihydroxy-5-nitrobenzoic acid (18).** To a stirred solution of **16** (1.13 g, 5 mmol) in THF (5 mL) was added an aqueous solution of LiOH (2 M, 5 mL). The resulting mixture was stirred at 45 ℃ for 4 h. The resulting mixture was then cooled to room temperature, acidified with an aqueous solution of HCl (2 M, 10 mL) and extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue was suspended in 1,2-dichloroethane (50 mL) at 0 ℃ and treated with $AlCl_3$ (2.01 g, 15 mmol) followed by addition of pyridine (2.37 g, 30 mmol) dropwise under argon. The red reaction mixture was heated at reflux for 2 h, then was cooled to room temperature, and poured onto a mixture of ice and 2 N HCl. The resulting yellow precipitate was filtered off, washed with water, and dried under vacuum to give **18** as a yellow solid (847 mg, 85%).$^1H$ NMR (400 MHz, MeOD) $\delta$ 8.19 (d, $J$ = 2.0 Hz, 1H), 7.68 (d, $J$ = 2.0 Hz, 1H). $^{13}C$ NMR (126 MHz, MeOD) $\delta$ 166.47 (s), 147.65 (s), 146.75 (s), 134.52 (s), 121.42 (s), 120.41 (s), 117.04 (s), 48.23 – 47.21 (m), 47.12 (s); MS (ESI): m/z calcd for $C_7H_4NO_6$ $[M+H]^-$: 198.0039; found: 198.1052.

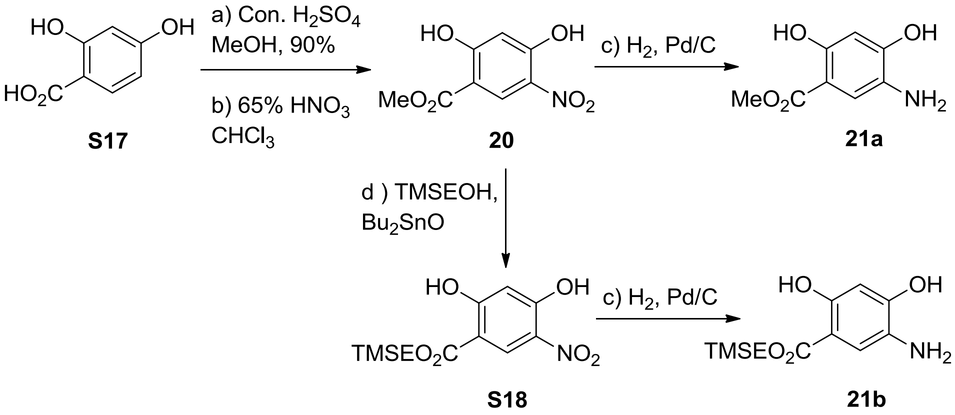


19

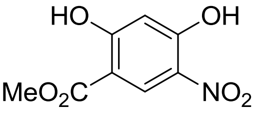
**3-amino-4,5-dihydroxybenzoic acid (19).** To a stirred solution of **18** (100 mg, 0.5 mmol) in MeOH (12 mL) was added Pd/C (10 mg) and the reaction mixture was stirred under $H_2$ for 3 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to afford **19** (75 mg, 89%), which was used for next step without further purification. $^1H$ NMR (400

MHz, DMSO-$d_6$) $\delta$ 8.52 (d, $J$ = 219.0 Hz, 2H), 6.83 (d, $J$ = 2.0 Hz, 1H), 6.77 (d, $J$ = 2.0 Hz, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 168.34 (s), 144.76 (s), 137.28 (s), 136.57 (s), 121.44 (s), 108.60 (s), 106.58 (s); HRMS (ESI): m/z calcd for $C_7H_8NO_4$ $[M+H]^+$: 170.0453; found: 170.0448.

**Supporting Scheme S5.** Synthesis of anilines **21a** and **21b**.

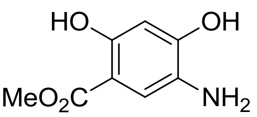


[a] Reagents and conditions: (a) Con. $H_2SO_4$, MeOH, 80 °C, 24 h, 90%; (b) 65% $HNO_3$, $CHCl_3$, r.t, 15 min, 42%; (c) $H_2$ (1.1 atm.), 10% Pd/C (0.2 equiv.), MeOH, 25 °C, 3 h, 84% (for **21a**) ; 92% (for **21b**); (d) TMSEOH (1.5 equiv.), toluene, $Bu_2SnO$ (1.0 equiv.) ,150 °C, 8 h, 95%;



**20**

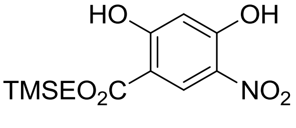
**Methyl 2,4-dihydroxy-5-nitrobenzoate (20).** To a stirred solution of 2,4-dihydroxybenzoic acid **S17** (4.62 g, 30.0 mmol) in MeOH (60 mL) was added con. $H_2SO_4$ (3 mL). The mixture was heated under reflux for 24 h. The solvent was then removed in vacuo and the residue was dissolved in $CH_2Cl_2$ (100 mL), washed with water (3 × 50 mL) and dried over anhydrous $Na_2SO_4$. Removal of $CH_2Cl_2$ gave the pure product methyl 2,4-dihydroxybenzoate as a light brown solid; To a solution of methyl 2,4-dihydroxybenzoate (1.68 g, 10 mmol) in $CHCl_3$ (25 mL) was slowly added 65% $HNO_3$ (400 µL) at 0 °C, and the mixture was warmed to room temperature. After stirring at 25 °C for a further 15 min after which an ochre-colored suspension had formed. $H_2O$ (130 mL) was added, where upon the mixture was aged for another 30 min without stirring. The precipitate was filtered, rinsed with small amounts of $H_2O$, and dried under vacuum to give crudeproduct, which was recrystallized (MTBE, 250 mL) to give pure **20** (2.68 g, 42%) as pale yellow cubes.



**21a**

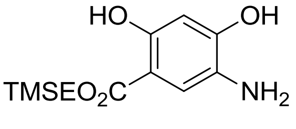
**Methyl 5-amino-2,4-dihydroxybenzoate (21a).** To a stirred solution of **20** (106 mg, 0.5 mmol) in MeOH (12 mL) was added Pd/C (10 mg) and the reaction mixture was stirred under $H_2$ for 3 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to afford **21a** (77 mg, 84%), which was used for next step without further purification. HRMS (ESI): m/z calcd for $C_8H_{10}NO_4$ $[M+H]^+$: 184.0610; found: 184.0602.

**2-(trimethylsilyl)ethyl 2,4-dihydroxy-5-nitrobenzoate (S18).** To a stirred solution of methyl 4-hydroxy-3-methoxy-5-nitrobenzoate **20** (320 mg, 1.5 mmol) in toluene (10 mL) was added 2-(trimethylsilyl) ethanol (236 mg, 2.0 mmol) and $Bu_2SnO$ (375 mg, 1.5 mmol) respectively. The reaction mixture was heated in a sealed tube at 150 ℃ for 8 h before the solvent was removed using vacuum distillation. The residue was dissolved in $CH_2Cl_2$ the solid was filtered. The filtrate was concentrated in vacuo. Flash chromatography on silica gel (ethyl acetate/ petroleum ether = 1:10) afforded **S18** (426 mg, 95%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 11.65 (s, 1H), 11.02 (s, 1H), 8.74 (s, 1H), 6.62 (s, 1H), 4.53 – 4.47 (m, 2H), 1.23 – 1.17 (m, 2H), 0.13 (s, 9H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 168.78 (s), 168.02 (s), 160.23 (s), 129.56 (s), 127.29 (s), 107.16 (s), 105.62 (s), 77.36 (s), 77.04 (s), 76.73 (s), 64.99 (s), 29.71 (s), 17.46 (s), -1.50 (s). MS (ESI): m/z calcd for $C_{12}H_{16}NO_6Si$ $[M+H]^-$: 298.0747; found: 298.0676.



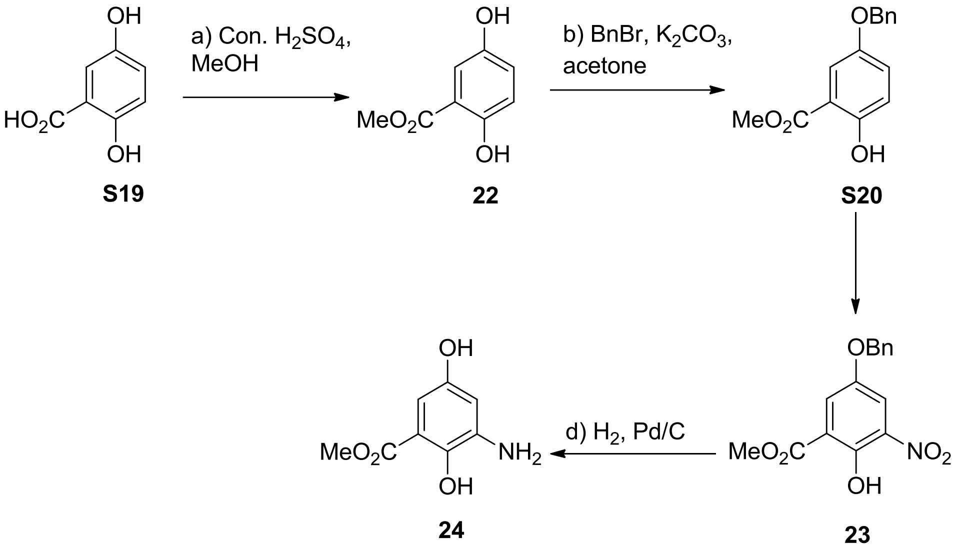
**S18**

**2-(trimethylsilyl)ethyl 5-amino-2,4-dihydroxybenzoate (21b).** To a stirred solution of **S18** (100 mg, 0.33 mmol) in MeOH (12 mL) was added Pd/C (10 mg) and the reaction mixture was stirred under $H_2$ for 3 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to afford **21b** (82 mg, 92%), which was used for next step without further purification. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 11.15 (s, 1H), 7.78 (s, 1H), 6.88 (s, 1H), 4.50 – 4.42 (m, 2H), 1.18 – 1.13 (m, 2H), 0.11 (s, 9H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 170.92 (s), 158.10 (s), 154.09 (s), 136.31 (s), 115.51 (s), 108.48 (s), 97.90 (s), 77.37 (s), 77.05 (s), 76.73 (s), 63.73 (s), 37.76 (s), -1.40 (s); HRMS (ESI): m/z calcd for $C_{12}H_{20}NO_4Si$ $[M+H]^+$: 270.1162; found: 270.1147.

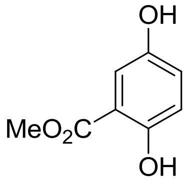


**21b**

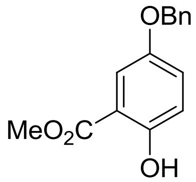
**Supporting Scheme S6.** Synthesis of aniline **24**.



[a] Reagents and conditions: (a) Con. $H_2SO_4$, MeOH, 80 °C, 10 h, 80%; (b) BnBr, $K_2CO_3$, acetone, 3 h, 87%; (c) $Bi(NO_3)_3.5\,H_2O$ (1.0 equiv.), MMT K10 (1.0 equiv.), THF, 25 °C, 2 h, 81%; (d) $H_2$ (1.1 atm.), 10% Pd/C (0.2 equiv.), MeOH, 25 °C, 3 h, 87%;

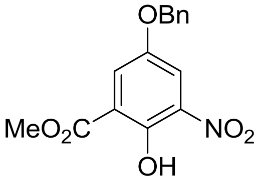

**22**

**Methyl 2,5-dihydroxybenzoate (22).** 2,5-dihydroxybenzoic acid **S19** (4.62 g, 30.0 mmol) was dissolved in MeOH (60 mL), to which concentrated $H_2SO_4$ (5 mL) was added. The mixture was heated under reflux for 24 h. The solvent was then removed in vacuo and the residue was dissolved in $CH_2Cl_2$ (100 mL), washed with water (3 × 50 mL) and dried over anhydrous $Na_2SO_4$. Removal of $CH_2Cl_2$ and flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:10) afforded the pure product **22** as a light brown solid. Yield: 4.0 g, 80%. MS (ESI): m/z calcd for $C_8H_7O_4$ $[M+H]^-$: 167.0344; found: 167.1126.


**S20**

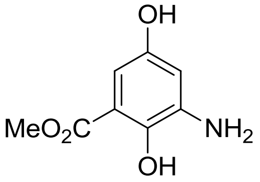
**Methyl 5-(benzyloxy)-2-hydroxybenzoate (S20).** A suspension of methyl 2,5-dihydroxybenzoate **22** (1.68 g, 10 mmol) and $K_2CO_3$ (2.06 g, 14.7 mmol) in acetone (50 mL) was stirred at rt for 5 min, then BnBr (2 mL, 2.55 g, 14.7 mmol) was added and the reaction mixture stirred at 60 °C for 3 h. After cooling to rt the suspension was diluted with EtOAc (250 mL), washed with 2 M $K_2CO_3$ (3 × 50 mL) and brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification via silica gel chromatography (ethyl acetate/petroleum ether = 1:10) yielded **S20** (2.24 g, 87%) as a pale yellow oil. MS (ESI): m/z calcd for $C_{15}H_{15}O_4$ $[M+H]^+$: 259.0970; found: 259.0640.

**Methyl 5-(benzyloxy)-2-hydroxy-3-nitrobenzoate (23).** To a suspension of **S20** (258 mg, 1.00 mmol) and Montmorillonite K10 (0.50 g) in THF (10 mL) was added bismuth nitrate (0.39 g, 1.00 mmol). The mixture was stirred at room temperature for 2 h and solid was filtered. Solvent was then removed *in vacuo* and the residue was dissolved in $CH_2Cl_2$. The filtrate was washed with 2 M HCl (2 ×10 mL), water (2 ×50 mL) and dried over anhydrous $Na_2SO_4$. Removal of $CH_2Cl_2$ gave the pure product **23** as a yellow solid. Yield: 245 mg, 81%. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.52 (s, 1H), 7.82 (d, $J$ = 13.4 Hz, 2H), 7.44 (s, 4H), 7.39 (s, 1H), 5.10 (s, 2H), 4.02 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 168.57 (s), 150.13 (s), 149.72 (s), 137.57 (s), 135.55 (s), 128.80 (s), 128.53 (s), 127.63 (s), 127.03 (s), 123.00 (s), 117.56 (s), 116.43 (s), 99.99 (s), 77.29 (s), 77.03 (s), 76.78 (s), 71.27 (s), 53.19 (s). MS (ESI): m/z calcd for $C_{15}H_{12}NO_6 [M+H]^-$: 302.0665; found: 302.1690.



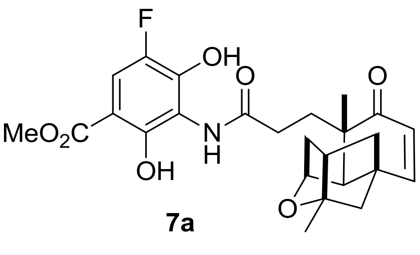
**23**

**Methyl 3-amino-2,5-dihydroxybenzoate (24).** To a stirred solution of **23** (100 mg, 0.33 mmol) in MeOH (12 mL) was added Pd/C (10 mg) and the reaction mixture was stirred under $H_2$ for 3 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to afford **24** (52.5 mg, 87%), which was used for next step without further purification; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.5 Hz, 2H), 3.87 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.42 (s), 149.46 (s), 136.02 (s), 135.39 (s), 122.17 (s), 112.81 (s), 107.07 (s), 77.32 (s), 77.01 (s), 76.69 (s), 52.15 (s); HRMS (ESI): m/z calcd for $C_8H_{10}NO_4 [M+H]^+$: 184.0610; found: 184.0605.



**24**

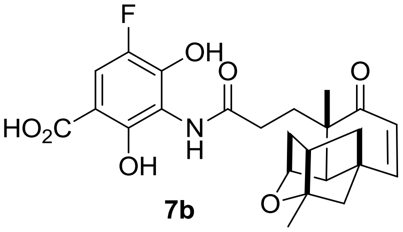
**Methyl 3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-5-fluoro-2,4-dihydroxybenzoate (7a).** To a solution of carboxylic acid PTMA (58.0 mg, 0.20 mmol) and aniline **6** (80.4 mg, 0.40 mmol) in DMF (2.0 mL) at room temperature were added $Et_3N$ (84.0 μL, 0.6 mmol) and HATU (152.2 mg, 0.40 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with $CH_2Cl_2$ (3×5.0 mL), and the combined organic portions dried over anhydrous $Na_2SO_4$. Concentration followed by flash column chromatography (eluent: EtOAc/light petroleum ether = 1:10~ 1:3) afforded the title compound **7a** (78.5 mg, 83%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 11.45 (s, 1H), 8.25 (s, 1H), 7.37 (d, $J$ = 10.8 Hz, 1H), 6.53 (d, $J$ = 10.1 Hz, 1H), 5.95 (d, $J$ = 10.1 Hz, 1H), 4.46 (s, 1H), 3.94 (s, 3H), 2.59 – 2.50 (m, 1H), 2.44 (d, $J$ = 5.0 Hz, 1H), 2.43 – 2.39 (m, 1H), 2.37 (dd, $J$ = 6.5, 4.0 Hz, 2H), 2.13 (d, $J$ = 5.3 Hz, 1H), 2.09 (d, $J$ = 3.6 Hz, 1H), 2.05 (dd, $J$ = 13.3, 7.4 Hz, 2H),



**7a**

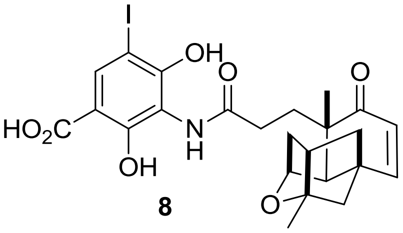
1.94 (d, $J$ = 6.0 Hz, 1H), 1.93 – 1.89 (m, 1H), 1.88 (d, $J$ = 3.4 Hz, 1H), 1.82 (d, $J$ = 6.8 Hz, 1H), 1.65 (d, $J$ = 11.2 Hz, 1H), 1.47 (s, 3H), 1.29 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 203.77 (s), 174.09 (s), 170.11 (s), 154.03 (s), 149.76 (s), 147.85 (s), 145.49 (s), 144.59 (d, $J$ = 16.4 Hz), 127.10 (s), 115.87 (s), 111.75 (s), 111.54 (s), 102.00 (d, $J$ = 7.7 Hz), 87.14 (s), 77.30 (d, $J$ = 11.6 Hz), 77.04 (s), 76.73 (s), 76.42 (s), 54.86 (s), 52.48 (s), 46.73 (s), 46.14 (d, $J$ = 5.9 Hz), 44.64 (s), 43.11 (s), 40.58 (s), 32.06 (s), 31.56 (s), 24.20 (s), 22.98 (s); HRMS (ESI): m/z calcd for $C_{25}H_{29}FNO_7$ $[M+H]^+$: 474.1928; found: 474.1916.

**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-5-fluoro-2,4-dihydroxybenzoic acid (7b).** To a stirred solution of **7a** (47.4 mg, 0.1 mmol) in MeOH (2 mL) was added aqueous solution of KOH (2 mL). The resulting mixture was stirred at 45 ℃ for 4 h. The resulting mixture was then cooled to room temperature, acidified with an aqueous solution of HCl (2 M, 5 mL) and extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, filtered. Concentration followed by flash column chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) afforded the title compound **7b** (40.9 mg, 89%); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.45 (s, 1H), 9.25 (d, $J$ = 5.3 Hz, 1H), 7.41 (d, $J$ = 9.9 Hz, 1H), 6.67 (d, $J$ = 7.7 Hz, 1H), 5.84 (d, $J$ = 8.8 Hz, 1H), 4.39 (s, 1H), 3.16 (d, $J$ = 8.3 Hz, 1H), 2.43 – 2.31 (m, 3H), 2.27 (s, 2H), 2.09 (s, 3H), 2.01 – 1.86 (m, 5H), 1.80 (s, 2H), 1.69 (s, 4H), 1.36 (d, $J$ = 6.7 Hz, 3H), 1.14 (s, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 203.37 (s), 172.69 (s), 171.97 (s), 155.57 (s), 155.26 (d, $J$ = 78.6 Hz), 147.78 (s), 145.80 (s), 143.96 (s), 126.94 (s), 115.38 (s), 113.43 (s), 103.40 (s), 86.82 (s), 75.96 (s), 54.70 (s), 49.05 (s), 46.28 (s), 46.62 – 45.46 (m), 46.06 (s), 44.71 (s), 42.81 (s), 31.48 (s), 30.76 (s), 24.67 (s), 23.40 (s); HRMS (ESI): m/z calcd for $C_{24}H_{27}FNO_7$ $[M+H]^+$: 460.1772; found: 460.1759.



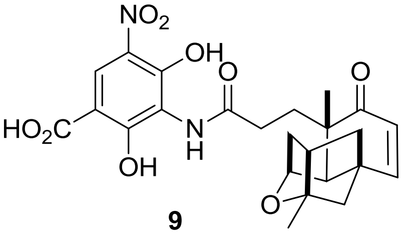
**7b**

**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxy-5-iodobenzoic acid (8).** To a mixture of iodine (38.1 mg, 0.30 mmol), DMAP (24.4 mg, 0.20 mmol), in 25 mL (pyridine/$CCl_4$ = 4:1) was added PTM (44.1 mg, 0.10 mmol) at room temperature under nitrogen. The resultant mixture was stirred at 110 ℃ for 4 h under nitrogen. TLC showed the starting material disappeared. The mixture was poured into 50 mL saturated $Na_2S_2O_3$ at 0 ℃ and the solid was removed by filtration, the filtrate was extracted with EtOAc (4 × 20 mL), then concentrated in vacuo and purified by flash chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) providing the title compound **8** (50 mg, 88%). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.54 (s, 1H), 9.24 (s, 1H), 8.00 (s, 1H), 6.68 (d, $J$ = 10.0 Hz, 1H), 5.84 (d, $J$ = 10.0 Hz, 1H), 4.39 (s,

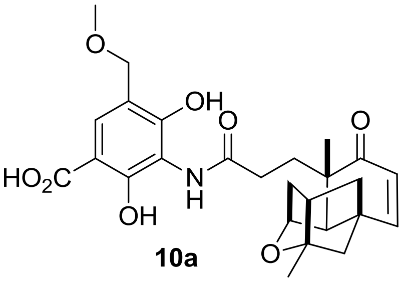


**8**

1H), 2.43 (t, *J* = 12.3 Hz, 1H), 2.35 (d, *J* = 5.8 Hz, 1H), 2.28 (s, 1H), 2.13 (d, *J* = 5.2 Hz, 1H), 2.12 (d, *J* = 8.3 Hz, 1H), 2.08 (s, 1H), 2.01 (s, 1H), 1.99 (s, 2H), 1.96 (s, 1H), 1.94 (s, 2H), 1.82 – 1.77 (m, 1H), 1.70 (s, 3H), 1.36 (s, 3H), 1.15 (s, 3H); $^{13}$C NMR (126 MHz, DMSO-*d*$_6$) $\delta$ 203.42 (s), 173.29 (s), 171.42 (s), 159.04 (s), 158.30 (s), 154.94 (s), 137.69 (s), 126.96 (s), 113.45 (s), 107.45 (s), 86.83 (s), 75.96 (s), 74.21 (s), 54.74 (s), 46.37 – 45.93 (m), 44.73 (s), 42.81 (s), 40.86 – 40.12 (m), 39.98 (s), 39.81 (s), 39.65 (s), 39.48 (s), 31.28 (s), 30.74 (s), 24.70 (s), 23.39 (s); HRMS (ESI): m/z calcd for $C_{24}H_{27}INO_7$ $[M+H]^+$: 568.0832; found: 568.0829.


**9**

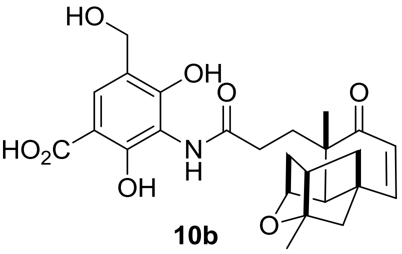
**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxy-5-nitrobenzoic acid (9) .** To a solution of PTM (44.1 mg, 0.10 mmol) in $CHCl_3$ (25 mL) was slowly added 65% $HNO_3$ (20 μL) at 0 ℃, and the mixture was warmed to room temperature. After stirring at 25 ℃ for 5 minutes, a yellowish precipitate was formed, and the solid was filtered off , the residue so obtained was purified by flash column chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) to give the title compound **9** (40.9 mg, 84%) as a yellow solid. $^1$H NMR (500 MHz, MeOD) $\delta$ 8.72 (s, 1H), 6.68 (d, *J* = 9.6 Hz, 1H), 5.92 (d, *J* = 9.4 Hz, 1H), 4.55 (s, 1H), 2.46 (s, 1H), 2.44 (s, 1H), 2.33 (s, 1H), 2.31 (s, 1H), 2.13 (d, *J* = 11.5 Hz, 1H), 2.11 (s, 1H), 2.09 (s, 1H), 1.87 (d, *J* = 13.5 Hz, 2H), 1.83 (s, 1H), 1.76 (d, *J* = 10.9 Hz, 1H), 1.46 (s, 3H), 1.28 (s, 3H); $^{13}$C NMR (126 MHz, MeOD) $\delta$ 204.31 (s), 173.85 (s), 166.04 – 165.48 (m), 154.98 – 154.78 (m), 154.67 (s), 130.99 – 130.96 (m), 129.46 – 129.42 (m), 128.48 (s), 127.16 (s), 112.90 – 112.37 (m), 87.34 (s), 76.61 (s), 54.42 (s), 48.14 (s), 47.97 (s), 47.80 (s), 47.62 (s), 47.45 (s), 47.28 (s), 47.11 (s), 46.38 (s), 45.94 (d, *J* = 6.7 Hz), 44.72 (s), 42.51 (s), 40.09 (s), 31.47 (s), 30.63 (s), 23.76 (s), 21.83 (s); HRMS (ESI): m/z calcd for $C_{24}H_{27}N2O_9$ $[M+H]^+$: 487.1717; found: 487.1710.


**10a**

**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxy-5-(methoxymethyl)benzoic acid (10a).** To a mixture of formaldehyde (50 μL, 0.50 mmol), KOH (16.8 mg, 0.30 mmol) and $CaCl_2$ (34 mg, 0.30 mmol) in 2 mL MeOH was added PTM (44.1 mg, 0.10 mmol). The resultant mixture was stirred at room temperature for 4 h. TLC showed the starting material disappeared. The mixture was added 2 mL $NH_3.H_2O$ then acidified with an aqueous solution of HCl (2 M, 5 mL) and extracted with EtOAc (4 × 20 mL), then concentrated in vacuo and purified by flash chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) providing the title compound **10a** (43.7 mg, 90%); $^1$H NMR (400 MHz, DMSO-*d*$_6$) $\delta$ 9.42 (s, 1H), 7.48 (s, 1H), 6.69 (d, *J* = 10.0 Hz, 1H), 5.85 (d, *J* = 10.0 Hz, 1H), 4.43 (s, 1H), 4.28 (s, 2H), 3.23 (s, 3H), 2.36 (t, *J* =

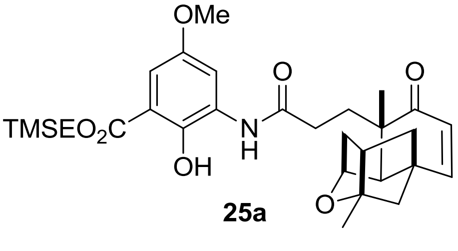
6.4 Hz, 1H), 2.29 (s, 1H), 2.19 – 2.09 (m, 2H), 1.98 (dd, $J$ = 15.8, 11.7 Hz, 3H), 1.81 (d, $J$ = 8.6 Hz, 1H), 1.72 (d, $J$ = 9.9 Hz, 3H), 1.68 – 1.60 (m, 1H), 1.37 (s, 3H), 1.15 (s, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 203.31 (s), 173.48 (s), 172.36 (s), 159.74 (s), 154.98 (s), 152.08 – 151.92 (m), 132.01 (s), 132.01 (s), 129.13 (s), 128.82 – 128.66 (m), 126.93 (s), 114.01 (s), 110.43 (s), 100.07 – 99.90 (m), 86.80 (s), 75.97 (s), 69.67 (s), 65.50 (s), 57.43 (s), 54.65 (s), 46.41 (s), 46.06 (s), 44.71 (s), 42.81 (s), 40.64 (s), 40.54 (s), 40.37 (s), 40.21 (s), 40.04 (s), 31.85 (s), 31.07 (s), 30.46 (s), 24.63 (s), 23.42 (s), 19.12 (s); HRMS (ESI): m/z calcd for $C_{26}H_{32}NO_8$ $[M+H]^+$: 486.2128; found: 486.2118.

**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxy-5-(hydroxymethyl)benzoic acid (10b).** To a mixture of formaldehyde (50 μL, 0.50 mmol), KOH (16.8 mg, 0.30 mmol) and $CaCl_2$ (34 mg, 0.30 mmol) in 2 mL MeOH was added PTM (44.1 mg, 0.10 mmol). The resultant mixture was stirred at room temperature for 4 h. TLC showed the starting material disappeared. Without any post-processing, the mixture was immediately purified by flash chromatography (eluent: EtOAc/MeOH = 6: 1) and providing the title compound **10b** (43.3 mg, 92%); $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.77 (d, $J$ = 12.2 Hz, 1H), 9.30 (s, 1H), 7.66 (s, 1H), 6.68 (d, $J$ = 10.0 Hz, 1H), 5.84 (d, $J$ = 10.0 Hz, 1H), 4.43 (d, $J$ = 12.1 Hz, 3H), 2.35 (t, $J$ = 6.0 Hz, 1H), 2.28 (s, 1H), 2.13 (t, $J$ = 11.6 Hz, 2H), 1.99 (d, $J$ = 11.9 Hz, 1H), 1.95 (d, $J$ = 11.6 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.70 (s, 2H), 1.36 (s, 3H), 1.23 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 203.37 (s), 173.35 (s), 173.01 (s), 172.50 (s), 154.97 (s), 126.94 (s), 120.88 (s), 113.39 (s), 113.23 (s), 106.16 (s), 86.80 (s), 79.70 (s), 75.94 (s), 58.52 (s), 54.68 (s), 46.36 – 45.91 (m), 44.71 (s), 42.79 (s), 41.05 – 40.19 (m), 40.34 (s), 40.24 (d, $J$ = 21.0 Hz), 39.95 (s), 39.82 (d, $J$ = 21.0 Hz), 39.53 (s), 39.40 (d, $J$ = 21.0 Hz), 31.56 (s), 30.86 (s), 29.46 (d, $J$ = 13.0 Hz), 24.70 (s), 23.41 (s), 22.58 (s), 21.58 (s); HRMS (ESI): m/z calcd for $C_{25}H_{30}NO_8$ $[M+H]^+$: 472.1971; found: 472.1969.



**10b**

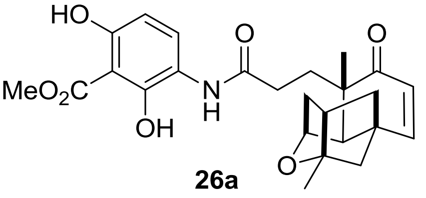
**2-(trimethylsilyl)ethyl 3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2-hydroxy-5-methoxybenzoate (25a).** To a solution of carboxylic acid PTMA (58.0 mg, 0.20 mmol) and aniline **13** (113.2 mg, 0.40 mmol) in $CH_2Cl_2$ (2.0 mL) at room temperature were added $Et_3N$ (84.0 μL, 0.60 mmol) and HATU (152.2 mg, 0.40 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with $CH_2Cl_2$ (3 × 5.0 mL), and the combined organic portions dried over anhydrous $Na_2SO_4$. Concentration followed by flash column chromatography (eluent: EtOAc/light petroleum ether =



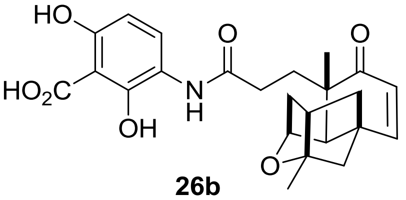
**25a**

1:10~ 1:3) afforded the title compound **25a** (95.5 mg, 86%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.97 (s, 1H), 8.32 (d, $J$ = 2.8 Hz, 1H), 7.99 (s, 1H), 7.01 (d, $J$ = 2.9 Hz, 1H), 6.50 (d, $J$ = 10.1 Hz, 1H), 5.92 (d, $J$ = 10.1 Hz, 1H), 4.46 (t, $J$ = 8.3 Hz, 3H), 3.78 (s, 3H), 2.43 (d, $J$ = 6.5 Hz, 1H), 2.40 (d, $J$ = 9.4 Hz, 2H), 2.33 (dd, $J$ = 12.4, 2.4 Hz, 1H), 2.27 (dd, $J$ = 13.4, 2.0 Hz, 1H), 2.09 (dd, $J$ = 8.6, 4.3 Hz, 1H), 2.03 (dd, $J$ = 11.8, 7.6 Hz, 2H), 1.87 (dd, $J$ = 11.2, 3.1 Hz, 2H), 1.82 – 1.75 (m, 1H), 1.63 (d, $J$ = 11.1 Hz, 1H), 1.45 (s, 3H), 1.27 (s, 3H), 1.18 – 1.14 (m, 2H), 0.10 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 203.81 (s), 171.07 (s), 170.32 (s), 153.76 (s), 151.74 (s), 144.95 (s), 128.14 (s), 127.20 (s), 112.77 (s), 111.45 (s), 106.49 (s), 86.98 (s), 77.38 (s), 77.06 (s), 76.75 (s), 76.48 (s), 64.12 (s), 55.87 (s), 54.88 (s), 46.65 (s), 46.11 (d, $J$ = 8.4 Hz), 44.67 (s), 43.12 (s), 40.56 (s), 32.94 (s), 31.30 (s), 29.70 (s), 24.33 (s), 23.02 (s), 17.31 (s), -1.43 (s); HRMS (ESI): m/z calcd for $C_{30}H_{42}NO_7Si$ $[M+H]^+$: 556.2731; found: 556.2726.

**Methyl 3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,6-dihydroxybenzoate (26a).** To a solution of carboxylic acid PTMA (29.0 mg, 0.10 mmol) and aniline **15a** (36.6 mg, 0.20 mmol) in DMF (1.0 mL) at room temperature were added $Et_3N$ (42.1 µL, 0.30 mmol) and HATU (76.1 mg, 0.20 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3 × 5.0 mL), and the combined organic portions dried over anhydrous $Na_2SO_4$. Concentration followed by flash column chromatography (eluent: EtOAc/light petroleum ether = 1:10~ 1:3) afforded the title compound **26a** (33.7 mg, 74%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.32 (s, 1H), 9.06 (s, 1H), 8.38 (d, $J$ = 9.1 Hz, 1H), 6.51 (d, $J$ = 9.2 Hz, 2H), 5.93 (d, $J$ = 10.1 Hz, 1H), 4.47 (s, 1H), 4.11 (s, 3H), 2.48 – 2.40 (m, 2H), 2.38 (d, $J$ = 7.8 Hz, 2H), 2.34 (s, 1H), 2.23 (d, $J$ = 13.2 Hz, 1H), 2.09 (d, $J$ = 2.9 Hz, 1H), 2.04 (dd, $J$ = 13.6, 7.5 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.83 – 1.73 (m, 2H), 1.64 (d, $J$ = 11.1 Hz, 1H), 1.46 (s, 3H), 1.27 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 204.07 (s), 170.88 (s), 169.94 (s), 155.68 (s), 153.89 (s), 149.60 (s), 128.46 (s), 127.20 (s), 119.54 (s), 107.51 (s), 99.43 (s), 86.98 (s), 77.30 (d, $J$ = 11.6 Hz), 77.04 (s), 76.73 (s), 76.50 (s), 54.90 (s), 53.10 (s), 46.80 (s), 46.10 (d, $J$ = 3.2 Hz), 44.67 (s), 43.12 (s), 40.57 (s), 32.89 (s), 31.56 (s), 29.71 (s), 24.33 (s), 23.03 (s); HRMS (ESI): m/z calcd for $C_{25}H_{30}NO_7$ $[M+H]^+$: 456.2022; found: 456.2015.

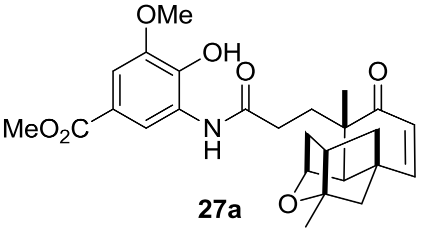


**26a**



**26b**

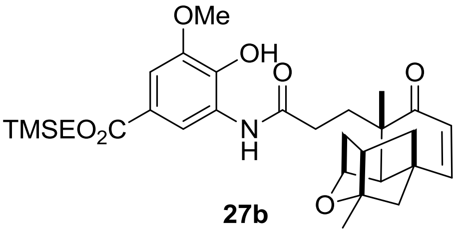
**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,6-dihydroxybenzoic acid (26b).** To a solution of carboxylic acid PTMA (29.0 mg, 0.10 mmol) and PyBOP (52.0 mg, 0.10 mmol) in $CH_2Cl_2$(2.0 mL) at room temperature were added $Et_3N$ (42.1 μL, 0.30 mmol). The mixture was stirred for 5 minutes, after which aniline **15b** (33.8 mg, 0.20 mmol) in 0.5 mL DMF was added. The mixture was stirred for extra 20 minutes, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3 × 5.0 mL), and the combined organic portions dried over anhydrous $Na_2SO_4$. Concentration followed by flash column chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) afforded the title compound **26b** (35.3 mg, 80%);$^1$H NMR (400 MHz, MeOD) $\delta$ 7.59 (d, $J$ = 8.8 Hz, 1H), 6.67 (d, $J$ = 10.1 Hz, 1H), 6.25 (d, $J$ = 8.8 Hz, 1H), 5.91 (d, $J$ = 10.1 Hz, 1H), 4.54 (s, 1H), 2.46 (s, 2H), 2.43 – 2.36 (m, 1H), 2.34 – 2.28 (m, 1H), 2.27 (d, $J$ = 2.2 Hz, 2H), 2.10 (dd, $J$ = 13.1, 4.9 Hz, 3H), 1.92 – 1.84 (m, 3H), 1.82 (d, $J$ = 3.4 Hz, 1H), 1.77 (d, $J$ = 2.1 Hz, 1H), 1.73 (d, $J$ = 6.4 Hz, 1H), 1.46 (d, $J$ = 4.8 Hz, 3H), 1.28 (s, 3H); $^{13}$C NMR (101 MHz, MeOD) $\delta$ 204.35 (s), 172.84 (s), 164.31 – 163.11 (m), 163.74 – 162.48 (m), 159.11 – 157.84 (m), 154.63 (s), 130.96 (s), 128.47 (s), 126.49 (s), 116.96 – 115.41 (m), 104.29 (s), 87.33 (s), 76.63 (s), 65.26 (s), 54.42 (s), 46.47 (s), 45.88 (s), 45.83 (s), 44.70 (s), 42.50 (s), 40.09 (s), 31.47 (s), 31.32 (s), 30.31 (s), 23.78 (s), 21.80 (s), 18.87 (s); HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_7$ $[M+H]^+$: 442.1866; found: 442.1856.



**27a**

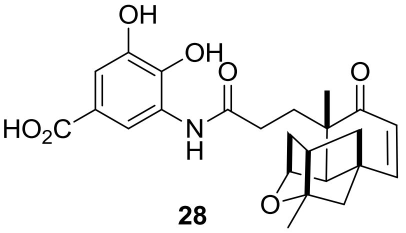
**Methyl 3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-4-hydroxy-5-methoxybenzoate (27a).** To a solution of carboxylic acid PTMA (29.0 mg, 0.10 mmol) and aniline **17a** (36.6 mg, 0.20 mmol) in DMF (1.0 mL) at room temperature were added $Et_3N$ (42.1 μL, 0.30 mmol) and HATU (76.1 mg, 0.20 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3 × 5.0 mL), and the combined organic portions dried over anhydrous $Na_2SO_4$. Concentration followed by flash column chromatography (eluent: EtOAc/light petroleum ether = 1:10~ 1:3) afforded the title compound **27a** (32.9 mg, 70%);$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 1.6 Hz, 1H), 8.12 (s, 1H), 7.73 (s, 1H), 7.39 (d, $J$ = 1.7 Hz, 1H), 6.53 (d, $J$ = 10.1 Hz, 1H), 5.94 (d, $J$ = 10.1 Hz, 1H), 4.47 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.44 (d, $J$ = 6.3 Hz, 2H), 2.39 (s, 1H), 2.36 – 2.32 (m, 1H), 2.09 (d, $J$ = 3.5 Hz, 1H), 2.07 – 2.02 (m, 2H), 1.90 (s, 1H), 1.87 (d, $J$ = 3.4 Hz, 1H), 1.82 (s, 2H), 1.64 (d, $J$ = 11.2 Hz, 1H), 1.46 (s, 2H), 1.43 (d, $J$ = 7.3 Hz, 1H), 1.28 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 204.28 (s), 172.21 (s), 166.85 (s), 154.16 (s), 147.46 (s), 140.32 – 140.28 (m), 127.12 (s), 125.67 (s), 121.62 (s), 116.00

(s), 108.27 (s), 87.07 (s), 56.35 (s), 54.86 (s), 52.08 (s), 46.86 (s), 46.11 (s), 44.66 (s), 44.42 (s), 43.09 (s), 40.56 (s), 32.58 (s), 31.53 (s), 29.70 (s), 24.28 (s), 23.00 (s); HRMS (ESI): m/z calcd for $C_{26}H_{32}NO_7$ $[M+H]^+$: 470.2179; found: 470.2173.



**27b**

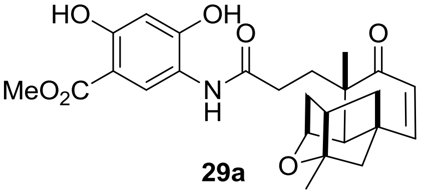
**2-(trimethylsilyl)ethyl 3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-4-hydroxy-5-methoxybenzoate (27b).** To a solution of carboxylic acid PTMA (58.0 mg, 0.20 mmol) and aniline **17b** (113.2 mg, 0.40 mmol) in DMF (2.0 mL) at room temperature were added Et$_3$N (84.0 µL, 0.60 mmol) and HATU (152.2 mg, 0.40 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3 × 5.0 mL), and the combined organic portions dried over anhydrous Na$_2$SO$_4$. Concentration followed by flash column chromatography (eluent: EtOAc/light petroleum ether = 1:10~ 1:3) afforded the title compound **27b** (88.8 mg, 80%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.43 (s, 1H), 8.07 (s, 1H), 7.34 (s, 1H), 6.47 (d, *J* = 3.8 Hz, 1H), 5.87 (d, *J* = 5.2 Hz, 1H), 4.45 (s, 1H), 4.40 – 4.31 (m, 2H), 3.88 (s, 3H), 2.43 – 2.37 (m, 2H), 2.35 (s, 1H), 2.31 (s, 1H), 2.24 (d, *J* = 12.4 Hz, 1H), 2.07 (d, *J* = 5.0 Hz, 1H), 2.04 – 1.99 (m, 2H), 1.96 (d, *J* = 4.9 Hz, 1H), 1.85 (dd, *J* = 16.7, 8.8 Hz, 2H), 1.75 (d, *J* = 5.3 Hz, 1H), 1.60 (d, *J* = 10.4 Hz, 1H), 1.42 (s, 3H), 1.24 (s, 3H), 1.13 – 1.07 (m, 2H), 0.06 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 204.17 (s), 172.46 (s), 170.70 (s), 166.53 (s), 154.14 (s), 147.77 (s), 140.76 (s), 127.07 (s), 121.91 (s), 116.19 (s), 108.44 (s), 87.14 (s), 77.36 (s), 77.10 (s), 76.85 (s), 76.41 (s), 63.15 (s), 56.28 (s), 54.81 (s), 46.71 (s), 46.05 (s), 44.66 (s), 43.04 (s), 40.50 (s), 31.55 (s), 29.66 (s), 24.29 (s), 22.96 (d, *J* = 5.7 Hz), 17.45 (s), 14.10 (s), -1.44 (s); HRMS (ESI): m/z calcd for $C_{30}H_{42}NO_7Si$ $[M+H]^+$: 556.2731; found: 556.2733.



**28**

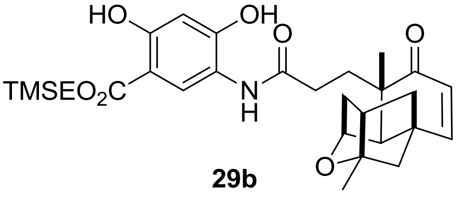
**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-4,5-dihydroxybenzoic acid (28).** To a solution of carboxylic acid PTMA (29.0 mg, 0.10 mmol) and PyBOP (52.0 mg, 0.10 mmol) in CH$_2$Cl$_2$ (2.0 mL) at room temperature was added Et$_3$N (42.1 µL, 0.30 mmol). The mixture was stirred for 5 minutes, after which aniline **19** (33.8 mg, 0.20 mmol) in 0.5 mL DMF was added. The mixture was stirred for extra 20 min, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3 × 5.0 mL), and the combined organic portions dried over anhydrous Na$_2$SO$_4$. Concentration followed by flash column chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) afforded the title compound **28** (33.5 mg, 75%); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.43 (s, 1H), 7.80 (s, 1H), 7.18 (s, 1H), 6.67 (d, *J* = 9.9 Hz, 1H), 5.83 (d, *J* = 10.0 Hz, 1H), 4.39 (s, 1H), 2.89 (s, 1H), 2.73 (s, 1H), 2.41 (d, *J* = 12.5 Hz, 1H), 2.34 (t, *J* = 5.8 Hz, 1H), 2.28 (s, 1H), 2.11 (t, *J* = 11.0 Hz, 2H), 1.98 (d, *J* = 11.3 Hz, 1H), 1.94 (d, *J* = 11.4 Hz, 2H), 1.82 – 1.75 (m, 1H), 1.69 (s, 2H), 1.35 (s, 3H), 1.14 (s, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 203.33 (s), 172.29 (s), 167.69 (s), 162.79 (s), 154.93 (s), 145.89 (s), 141.47 (s), 126.94 (s), 121.21 (s), 116.13 (s), 112.73 (s), 86.79 (s), 79.63 (s), 76.00 (s), 54.66 (s), 46.45 (s), 46.04 (s), 44.70 (s), 42.80 (s), 40.64 (s), 40.54 (s), 40.37 (s), 36.25 (s), 31.69 (s), 31.60 (s), 31.23 (s), 24.63 (s), 23.39 (s); HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_7$ [M+H]$^+$: 442.1866; found: 442.1848.

**Methyl 5-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxybenzoate (29a).** To a solution of carboxylic acid PTMA (29.0 mg, 0.10 mmol) and aniline **21a** (36.6 mg, 0.20 mmol) in DMF (1.0 mL) at room temperature were added $Et_3N$ (42.1 µL, 0.30 mmol) and HATU (76.1 mg, 0.20 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3×5.0 mL), and the combined organic portions dried over anhydrous $Na_2SO_4$. Concentration followed by flash column chromatography (eluent: EtOAc/light petroleum ether = 1:10~ 1:3) afforded the title compound **29a** (28.7 mg, 63%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.67 (s, 1H), 8.25 (s, 1H), 7.67 (s, 1H), 6.55 (d, *J* = 10.4 Hz, 1H), 6.53 (s, 1H), 5.94 (d, *J* = 10.1 Hz, 1H), 4.48 (s, 1H), 3.90 (s, 3H), 3.22 (s, 1H), 2.47 (t, *J* = 6.4 Hz, 2H), 2.41 – 2.36 (m, 2H), 2.31 (d, *J* = 3.0 Hz, 1H), 2.28 (d, *J* = 2.4 Hz, 1H), 2.12 (dd, *J* = 14.5, 3.5 Hz, 2H), 2.07 (s, 1H), 2.04 (s, 1H), 1.95 (d, *J* = 4.3 Hz, 1H), 1.90 (d, *J* = 3.9 Hz, 1H), 1.87 (d, *J* = 3.4 Hz, 1H), 1.82 (d, *J* = 4.8 Hz, 1H), 1.68 (s, 1H), 1.65 (s, 1H), 1.48 (s, 3H), 1.44 (d, *J* = 2.0 Hz, 1H), 1.28 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 204.65 (s), 173.32 (s), 169.89 (s), 161.02 (s), 155.96 (s), 154.55 (s), 127.06 (s), 123.49 (s), 119.18 (s), 106.04 (s), 104.55 (s), 87.36 (s), 77.30 (d, *J* = 11.5 Hz), 77.04 (s), 76.72 (s), 76.48 (s), 54.84 (s), 52.07 (s), 47.04 (s), 46.09 (d, *J* = 9.9 Hz), 44.66 (s), 43.06 (s), 40.54 (s), 31.97 (d, *J* = 7.4 Hz), 31.62 (s), 29.71 (s), 24.25 (s), 22.96 (s), 22.70 (s); HRMS (ESI): m/z calcd for $C_{25}H_{30}NO_7$ [M+H]$^+$: 456.2022; found: 456.2016.



**29a**

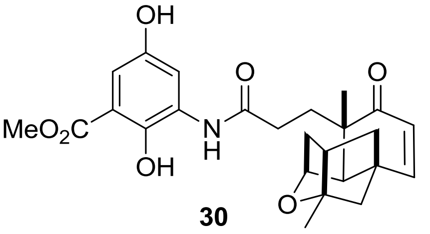
**2-(trimethylsilyl)ethyl 5-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxybenzoate (29b).** To a solution of carboxylic acid PTMA (58.0 mg, 0.20 mmol) and aniline **21b** (107.6 mg, 0.40 mmol) in DMF (2.0 mL) at room temperature were added $Et_3N$ (84.0 µL, 0.60 mmol) and HATU (152.2 mg, 0.40 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3 × 5.0 mL), and the combined organic portions dried over anhydrous $Na_2SO_4$. Concentration



**29b**

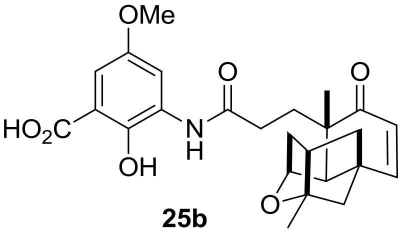
followed by flash column chromatography (eluent: EtOAc/light petroleum ether = 1:10~ 1:3) afforded the title compound **29b** (88.7 mg, 82%);$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.80 (s, 1H), 10.06 (s, 1H), 8.19 (s, 1H), 7.63 (s, 1H), 6.55 (d, *J* = 9.6 Hz, 2H), 5.94 (d, *J* = 10.0 Hz, 1H), 4.47 (s, 1H), 4.44 – 4.37 (m, 2H), 2.47 (d, *J* = 6.4 Hz, 1H), 2.44 (d, *J* = 6.6 Hz, 1H), 2.38 (s, 1H), 2.36 – 2.30 (m, 1H), 2.30 – 2.23 (m, 1H), 1.92 (s, 1H), 1.89 (d, *J* = 10.5 Hz, 1H), 1.82 (dd, *J* = 11.1, 6.7 Hz, 2H), 1.66 (d, *J* = 11.2 Hz, 1H), 1.48 (s, 3H), 1.28 (s, 3H), 1.17 – 1.13 (m, 2H), 0.10 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 204.56 (s), 173.44 (s), 169.65 (s), 161.20 (s), 155.96 (s), 154.50 (s), 127.07 (s), 123.51 (s), 119.08 (s), 106.35 (s), 105.07 (s), 87.24 (s), 77.28 (s), 77.03 (s), 76.77 (s), 76.44 (s), 63.58 (s), 54.87 (s), 47.03 (s), 46.12 (d, *J* = 6.5 Hz), 44.67 (s), 43.08 (s), 40.56 (s), 32.11 (s), 31.81 (s), 31.44 (s), 30.20 (s), 29.70 (s), 24.23 (s), 22.97 (s), 17.52 (s), -1.47 (s); HRMS (ESI): m/z calcd for C$_{29}$H$_{40}$NO$_7$Si [M+H]$^+$: 542.2574; found: 542.2570.

**Methyl 3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,5-dihydroxybenzoate (30).** To a solution of carboxylic acid PTMA (29.0 mg, 0.10 mmol) and aniline **24** (36.6 mg, 0.20 mmol) in DMF (1.0 mL) at room temperature were added Et$_3$N (42.1 μL, 0.30 mmol) and HATU (76.1 mg, 0.20 mmol). The mixture was stirred for 12 h, after which brine (5.0 mL) was added. The resulting mixture was extracted with EtOAc (3 × 5.0 mL), and the combined organic portions dried over anhydrous Na$_2$SO$_4$. Concentration followed by flash column chromatography (eluent: EtOAc/light petroleum ether = 1:10~ 1:3) afforded the title compound **30** (26.8 mg, 59%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.69 (s, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.09 (s, 1H), 7.04 (d, *J* = 2.9 Hz, 1H), 6.51 (d, *J* = 10.1 Hz, 1H), 5.94 (d, *J* = 10.1 Hz, 1H), 4.62 (s, 1H), 3.95 (s, 3H), 2.45 (t, *J* = 6.6 Hz, 2H), 2.41 – 2.35 (m, 2H), 2.32 (dd, *J* = 12.4, 2.2 Hz, 1H), 2.25 (dd, *J* = 13.8, 2.8 Hz, 1H), 2.16 (d, *J* = 5.0 Hz, 1H), 2.10 (d, *J* = 3.4 Hz, 1H), 2.07 (d, *J* = 1.6 Hz, 2H), 1.93 (d, *J* = 3.5 Hz, 1H), 1.90 (d, *J* = 3.4 Hz, 1H), 1.83 – 1.79 (m, 1H), 1.64 (d, *J* = 11.2 Hz, 1H), 1.48 (s, 3H), 1.44 (d, *J* = 1.7 Hz, 1H), 1.29 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 204.03 (s), 172.26 (s), 170.63 (s), 153.93 (s), 148.91 (s), 143.90 (s), 127.26 (d, *J* = 12.1 Hz), 113.71 (s), 111.62 (s), 108.95 (s), 87.25 (s), 77.29 (d, *J* = 11.5 Hz), 77.03 (s), 76.63 (d, *J* = 17.3 Hz), 54.85 (s), 52.43 (s), 46.80 (s), 46.08 (s), 44.72 (s), 44.46 (s), 43.15 (s), 40.61 (s), 33.18 (s), 31.93 (s), 31.37 (d, *J* = 14.3 Hz), 30.25 (d, *J* = 11.9 Hz), 29.37 (s), 24.27 (s), 22.98 (s), 22.70 (s); HRMS (ESI): m/z calcd for C$_{25}$H$_{30}$NO$_7$ [M+H]$^+$: 456.2022; found: 456.2008.



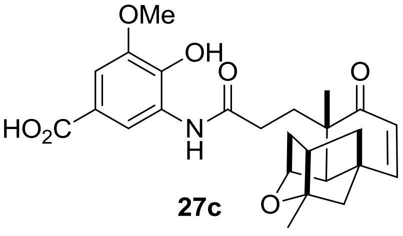
**30**

**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2-hydroxy-5-methoxybenzoic acid (25b).** To a stirred solution of TMSE-ester **25a** (55.5 mg, 0.1 mmol) in $CH_2Cl_2$ (2 mL) was added TBAF (52.2 mg, 0.2 mmol) at room temperature. The resulting reaction mixture was stirred at 40 ℃ for 12 h. Brine (5 mL) followed by water (5 mL) were added and the biphasic mixture was extracted first with $CHCl_3$ (3 × 5 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) to give title compound **25b** (34.6 mg, 76%);$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.28 (s, 1H), 7.88 (s, 1H), 6.98 (s, 1H), 6.66 (d, $J$ = 10.0 Hz, 1H), 5.83 (d, $J$ = 10.0 Hz, 1H), 4.39 (s, 1H), 3.70 (s, 3H), 2.34 (t, $J$ = 6.2 Hz, 1H), 2.28 (s, 1H), 2.11 (dd, $J$ = 16.7, 8.0 Hz, 2H), 1.98 (d, $J$ = 11.4 Hz, 1H), 1.92 (d, $J$ = 7.9 Hz, 2H), 1.79 (d, $J$ = 6.8 Hz, 1H), 1.69 (s, 2H), 1.35 (s, 3H), 1.31 – 1.20 (m, 2H), 1.13 (s, 3H);$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 203.38 (s), 172.48 (s), 171.87 (s), 154.92 (s), 150.82 (s), 147.40 (s), 128.35 (s), 126.97 (s), 115.12 (s), 113.33 – 112.95 (m), 106.80 (s), 86.77 (s), 76.02 (s), 55.87 (s), 54.66 (s), 46.50 (s), 46.00 – 45.72 (m), 44.69 (s), 42.81 (s), 40.64 (s), 40.53 (s), 40.36 (s), 31.92 (s), 31.44 (s), 24.67 (s), 23.41 (s), 21.53 (s);HRMS (ESI): m/z calcd for $C_{25}H_{30}NO_7$ $[M+H]^+$: 456.2022; found: 456.2013.

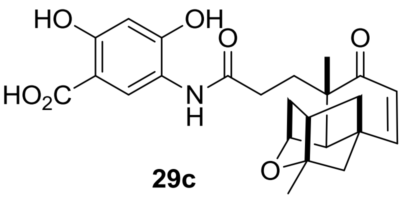


**25b**

**3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-4-hydroxy-5-methoxybenzoic acid (27c).** To a stirred solution of TMSE-ester **27b** (54.1 mg, 0.1 mmol) in $CH_2Cl_2$ (2 mL) was added TBAF (52.2 mg, 0.2 mmol) at room temperature. The resulting reaction mixture was stirred at 40 ℃ for 12 h. Brine (5 mL) followed by water (5 mL) were added and the biphasic mixture was extracted first with $CHCl_3$ (3 × 5 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) to give title compound **27c** (34.6 mg, 76%); $^1$H NMR (500 MHz, MeOD) $\delta$ 8.19 (d, $J$ = 1.8 Hz, 1H), 7.43 (d, $J$ = 1.7 Hz, 1H), 6.66 (d, $J$ = 10.1 Hz, 1H), 5.91 (d, $J$ = 10.1 Hz, 1H), 4.52 (s, 1H), 3.92 (s, 3H), 2.46 (s, 1H), 2.45 (s, 2H), 2.30 (td, $J$ = 14.1, 4.5 Hz, 2H), 2.12 – 2.06 (m, 3H), 1.91 – 1.84 (m, 2H), 1.84 – 1.79 (m, 1H), 1.75 (d, $J$ = 11.1 Hz, 1H), 1.45 (s, 3H), 1.27 (s, 3H); $^{13}$C NMR (126 MHz, MeOD) $\delta$ 204.31 (s), 172.99 (s), 168.41 (s), 154.62 (s), 147.45 (s), 142.22 (s), 126.47 (s), 125.37 (s), 120.69 (s), 117.77 (s), 108.59 (s), 87.36 (s), 76.63 (s), 55.25 (s), 54.41 (s), 46.42 (s), 45.89 (s), 45.86 (s), 44.69 (s), 42.49 (s), 40.09 (s), 31.43 (s), 31.22 (s), 23.73 (s), 21.80 (s); HRMS (ESI): m/z calcd for $C_{25}H_{30}NO_7$ $[M+H]^+$: 456.2022; found: 456.2015.

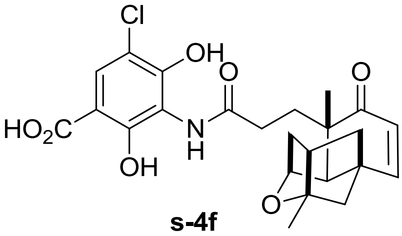


**27c**



29c

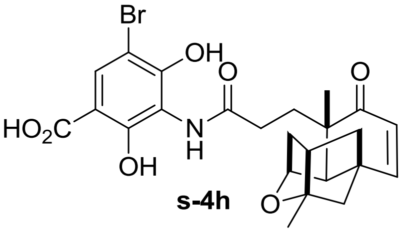
**5-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxybenzoic acid (29c).** To a stirred solution of TMSE-ester **29b** (54.1 mg, 0.1 mmol) in $CH_2Cl_2$ (2 mL) was added TBAF (52.2 mg, 0.2 mmol) at room temperature. The resulting reaction mixture was stirred at 40 °C for 12 h. Brine (5 mL) followed by water (5 mL) were added and the biphasic mixture was extracted first with $CHCl_3$ (3 × 5 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (eluent: light petroleum ether/EtOAc/AcOH = 2: 3: 0.5) to give title compound **29c** (37.5 mg, 85%); $^1$H NMR (400 MHz, MeOD) $\delta$ 7.98 (s, 1H), 6.66 (d, $J$ = 10.1 Hz, 1H), 6.31 (s, 1H), 5.91 (d, $J$ = 10.1 Hz, 1H), 4.51 (s, 1H), 2.46 (d, $J$ = 5.8 Hz, 1H), 2.43 (s, 1H), 2.30 (dd, $J$ = 14.6, 3.2 Hz, 1H), 2.27 – 2.19 (m, 1H), 2.12 (d, $J$ = 11.3 Hz, 2H), 2.07 (d, $J$ = 3.4 Hz, 1H), 1.96 (s, 1H), 1.88 (d, $J$ = 5.3 Hz, 1H), 1.85 (d, $J$ = 5.7 Hz, 1H), 1.81 (d, $J$ = 3.2 Hz, 1H), 1.75 (d, $J$ = 10.9 Hz, 1H), 1.45 (s, 3H), 1.27 (d, $J$ = 9.6 Hz, 3H); $^{13}$C NMR (101 MHz, MeOD) $\delta$ 204.38 (s), 173.18 (s), 160.40 (s), 154.59 (d, $J$ = 21.2 Hz), 154.48 (s), 130.97 (s), 128.47 (s), 126.47 (s), 126.37 (s), 116.89 (s), 109.55 (s), 102.36 (s), 87.37 (s), 76.61 (s), 54.40 (s), 48.24 (s), 48.03 (s), 47.82 (s), 47.61 (s), 47.39 (s), 47.18 (s), 46.97 (s), 46.42 (s), 45.87 (d, $J$ = 3.5 Hz), 44.69 (s), 42.49 (s), 40.09 (s), 31.41 (s), 31.14 (s), 23.74 (s), 21.81 (s); HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_7$ $[M+H]^+$: 442.1866; found: 442.1856.



s-4f

**5-chloro-3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxybenzoic acid (s-4f).** $^1$H NMR (400 MHz, MeOD) $\delta$ 7.77 (s, 1H), 6.67 (d, $J$ = 10.1 Hz, 1H), 5.92 (d, $J$ = 10.1 Hz, 1H), 4.53 (s, 1H), 2.56 – 2.49 (m, 1H), 2.46 (t, $J$ = 5.8 Hz, 2H), 2.41 – 2.36 (m, 1H), 2.34 (d, $J$ = 3.1 Hz, 1H), 2.11 (d, $J$ = 4.6 Hz, 2H), 2.08 (d, $J$ = 3.5 Hz, 1H), 2.02 (d, $J$ = 8.7 Hz, 1H), 1.90 (d, $J$ = 5.9 Hz, 1H), 1.88 – 1.84 (m, 1H), 1.83 (d, $J$ = 3.2 Hz, 1H), 1.76 (d, $J$ = 11.2 Hz, 1H), 1.45 (d, $J$ = 3.6 Hz, 3H), 1.28 (d, $J$ = 3.2 Hz, 3H); $^{13}$C NMR (126 MHz, MeOD) $\delta$ 204.39 (s), 175.32 – 174.41 (m), 168.50 – 166.97 (m), 154.70 (s), 132.87 – 131.62 (m), 130.95 (s), 128.47 (s), 126.47 (s), 87.38 (s), 76.61 (s), 65.25 (s), 54.41 (s), 47.89 – 47.88 (m), 46.43 (s), 45.91 (s), 44.70 (s), 42.50 (s), 40.09 (s), 31.24 (s), 30.70 (s), 30.32 (s), 29.39 (s), 23.72 (s), 21.81 (s); HRMS (ESI): m/z calcd for $C_{24}H_{27}ClNO_7$ $[M+H]^+$: 476.1476; found: 476.1471.

**5-bromo-3-(3-((4S,4aR,5S,7R,8S,9aS)-4,8-dimethyl-3-oxo-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-4-yl)propanamido)-2,4-dihydroxybenzoic acid (s-4h).** $^1$H NMR (400 MHz, MeOD) $\delta$ 7.94 (s, 1H), 6.67 (d, $J$ = 10.1 Hz, 1H), 5.92 (d, $J$ = 10.1 Hz, 1H), 4.53 (s, 1H), 2.53 (dd, $J$ = 11.6, 5.5 Hz, 1H), 2.45 (d, $J$ = 6.5 Hz, 2H), 2.42 – 2.35 (m, 1H), 2.33 (dd, $J$ = 9.2, 4.5 Hz, 1H), 2.09 (dd, $J$ = 12.6, 4.2 Hz, 3H), 2.03 (t, $J$ = 5.9 Hz, 1H), 1.88 (dd, $J$ = 12.6, 5.8 Hz, 2H), 1.83 (d, $J$ = 3.0 Hz, 1H), 1.76 (d, $J$ = 11.2 Hz, 1H), 1.45 (s, 3H), 1.28 (s, 3H). $^{13}$C NMR (101 MHz, MeOD) $\delta$ 204.41 (s), 174.86 (s), 156.29 (s), 154.72 (s), 131.55 (s), 126.47 (s), 113.84 (s), 100.48 (s), 87.39 (s), 76.62 (s), 62.86 (s), 54.43 (s), 48.47 (s), 46.43 (s), 45.93 (d, $J$ = 3.2 Hz), 44.71 (s), 42.52 (s), 40.09 (s), 31.16 (s), 30.66 (s), 29.34 (s), 23.71 (s), 21.79 (s), 13.07 (s); HRMS (ESI): m/z calcd for $C_{24}H_{27}BrNO_7$ [M+H]$^+$: 520.0971; found: 520.0966.



s-4h

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## NMR spectra Data of Products.

**Figure S4.** $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **7a** in CDCl$_3$

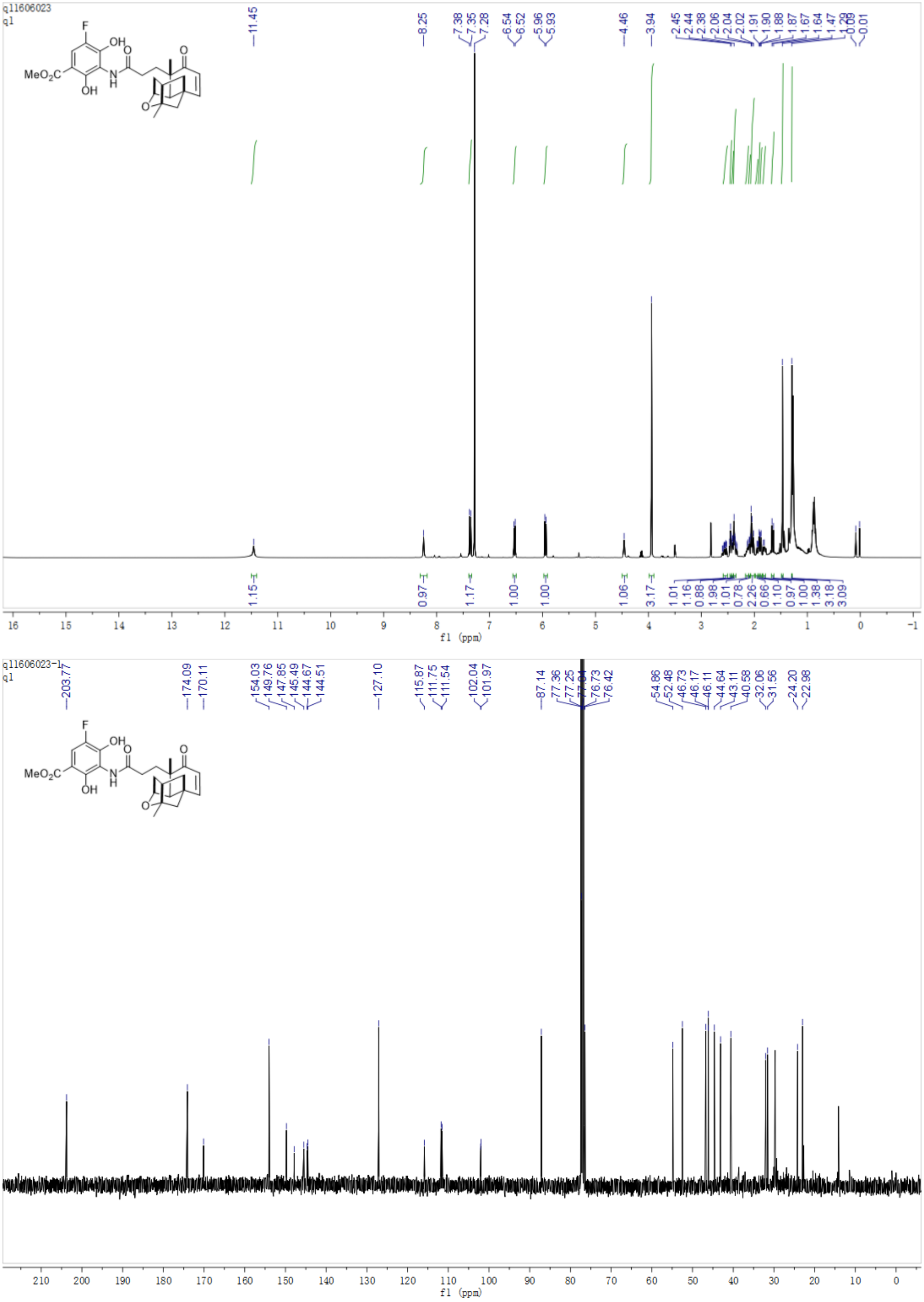


**Figure S5.** $^{1}$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **7b** in DMSO-$d_6$

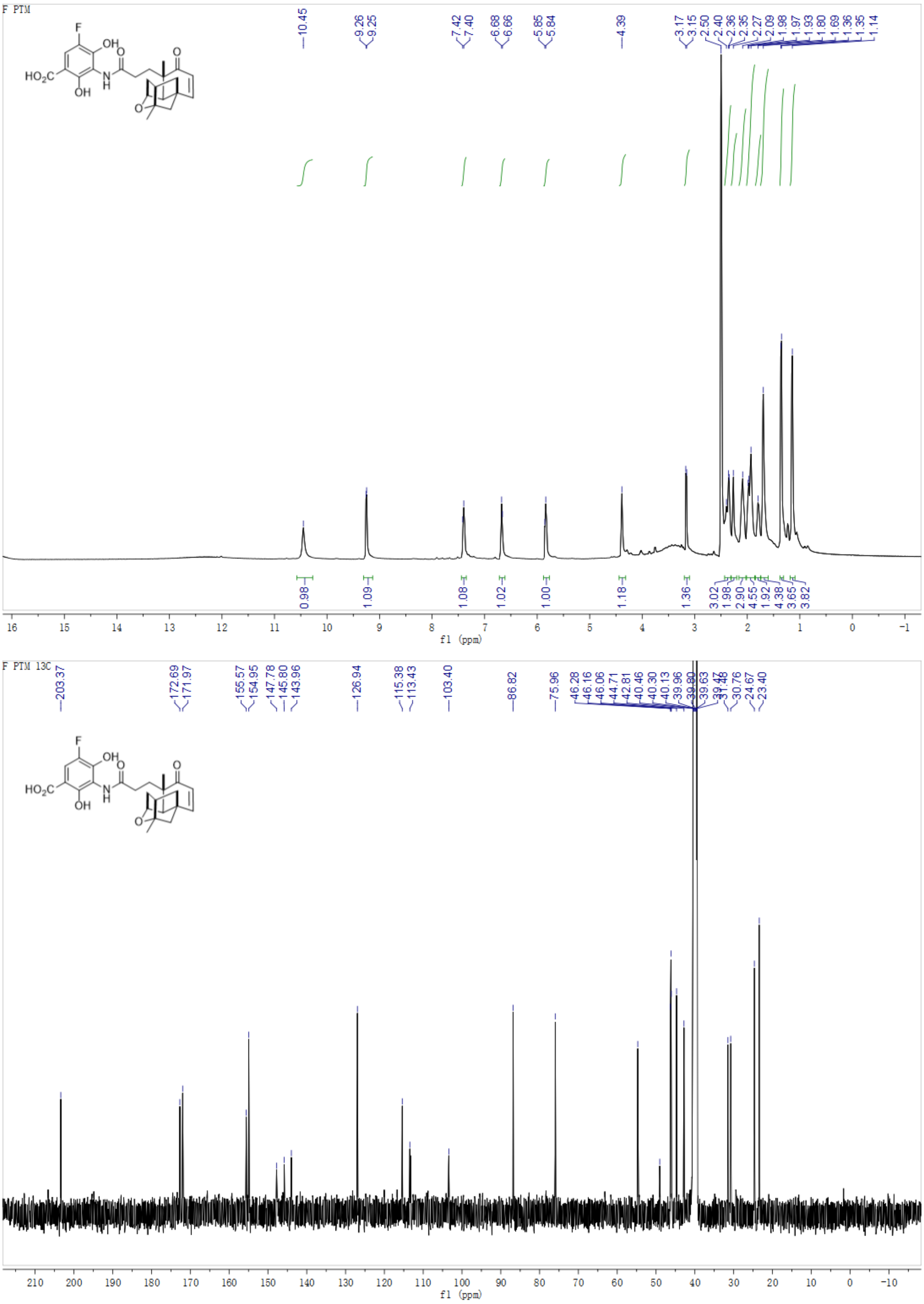


**Figure S6**. $^1H$–$^{13}C$ HSQCspectrum of **7b** in DMSO-*d*$_6$

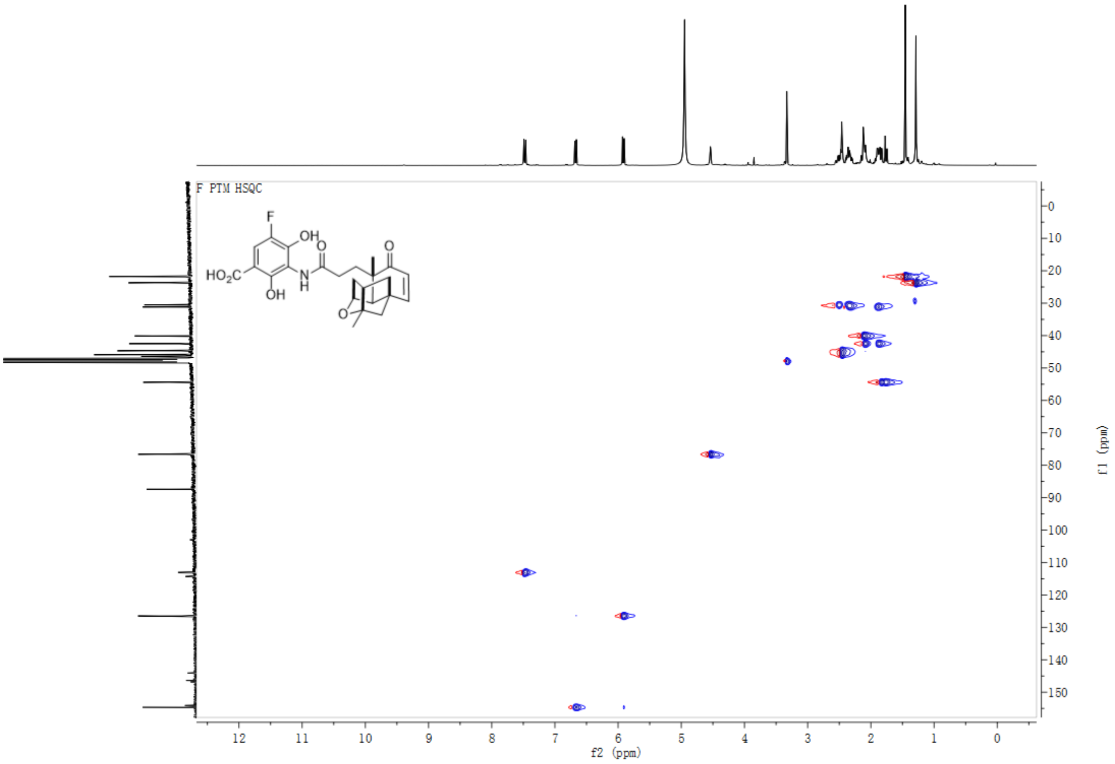
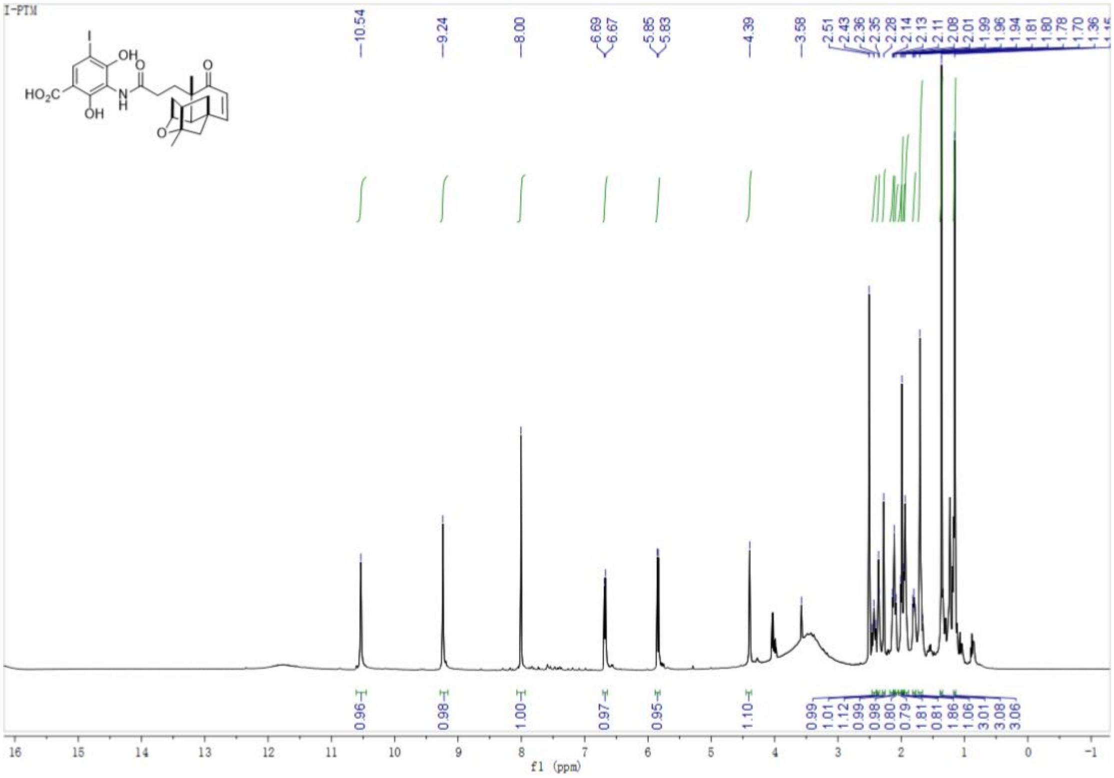


**Figure S7.** $^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **8** in DMSO-$d_6$



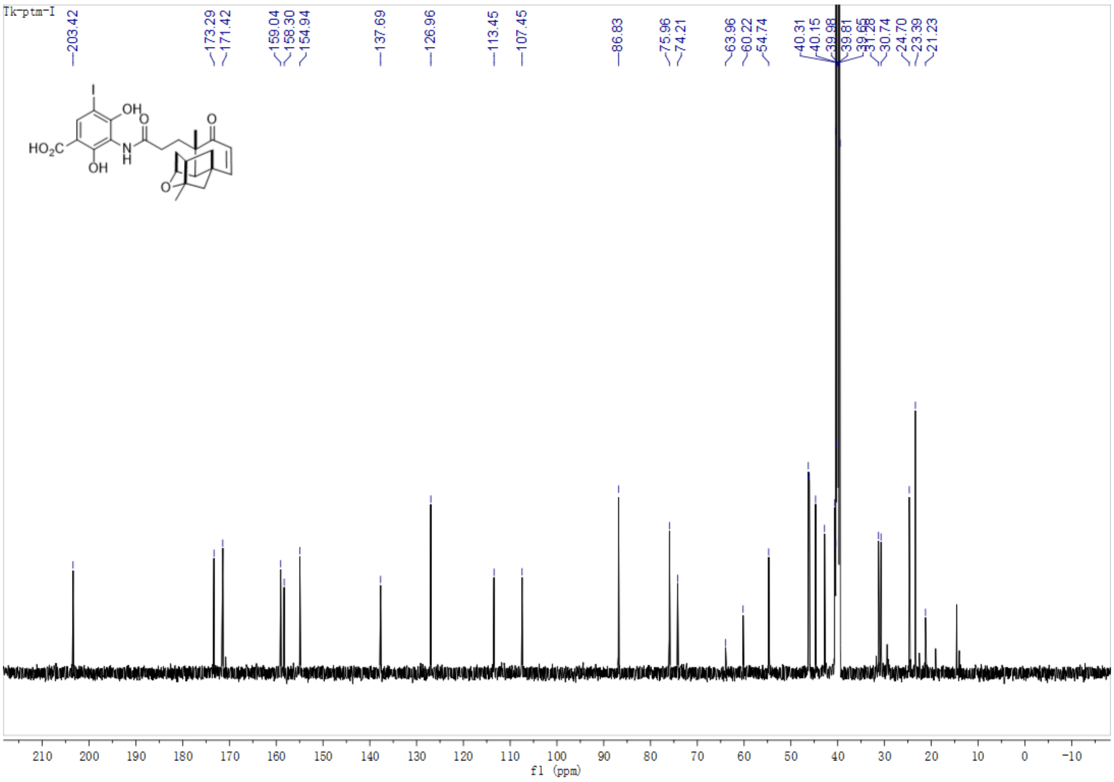


**Figure S8**. $^1H$–$^{13}C$ HSQC spectrum of **8** in DMSO-$d_6$

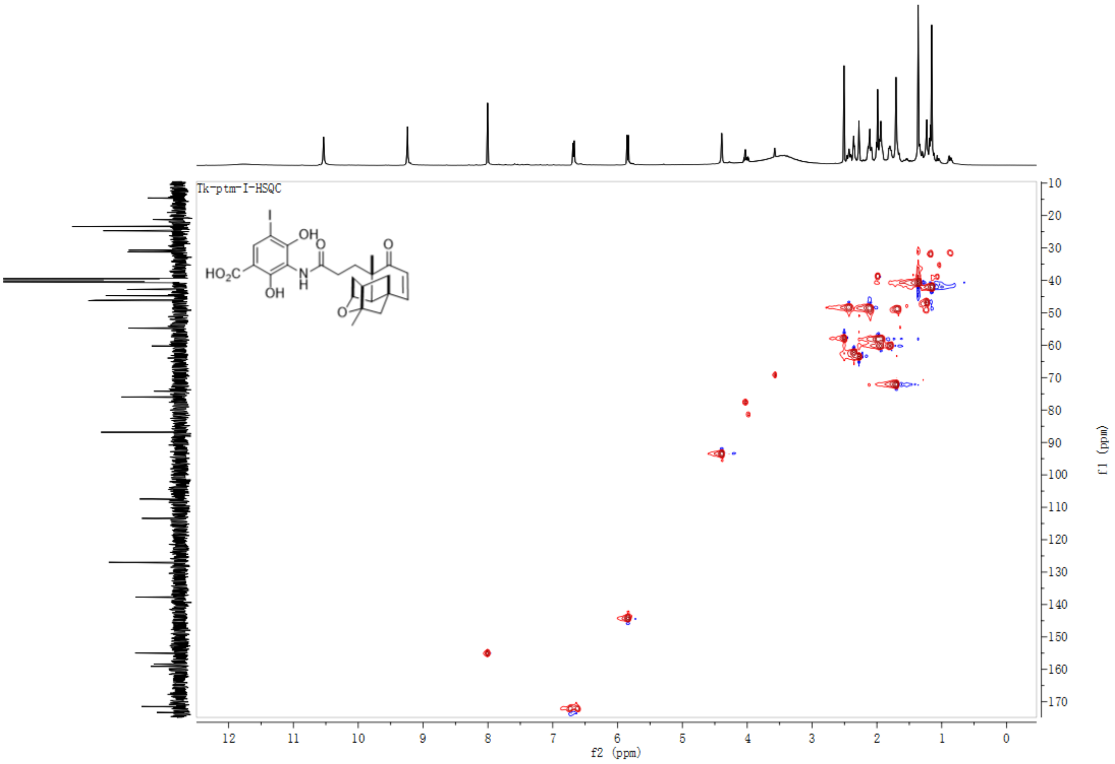


**Figure S9**. $^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **9** in MeOD

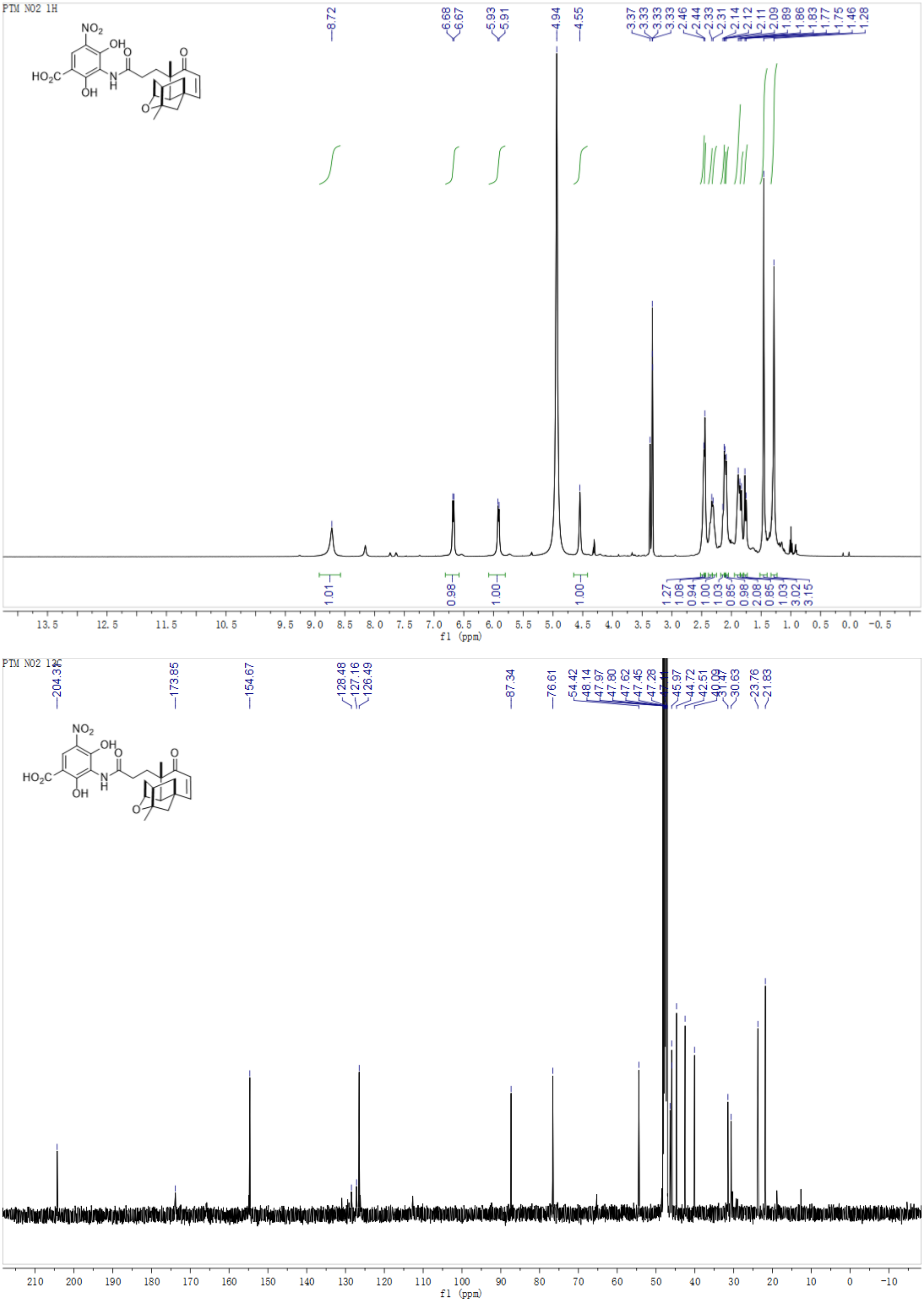


**Figure S10**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (126 MHz) spectrum of **10a** in DMSO-$d_6$

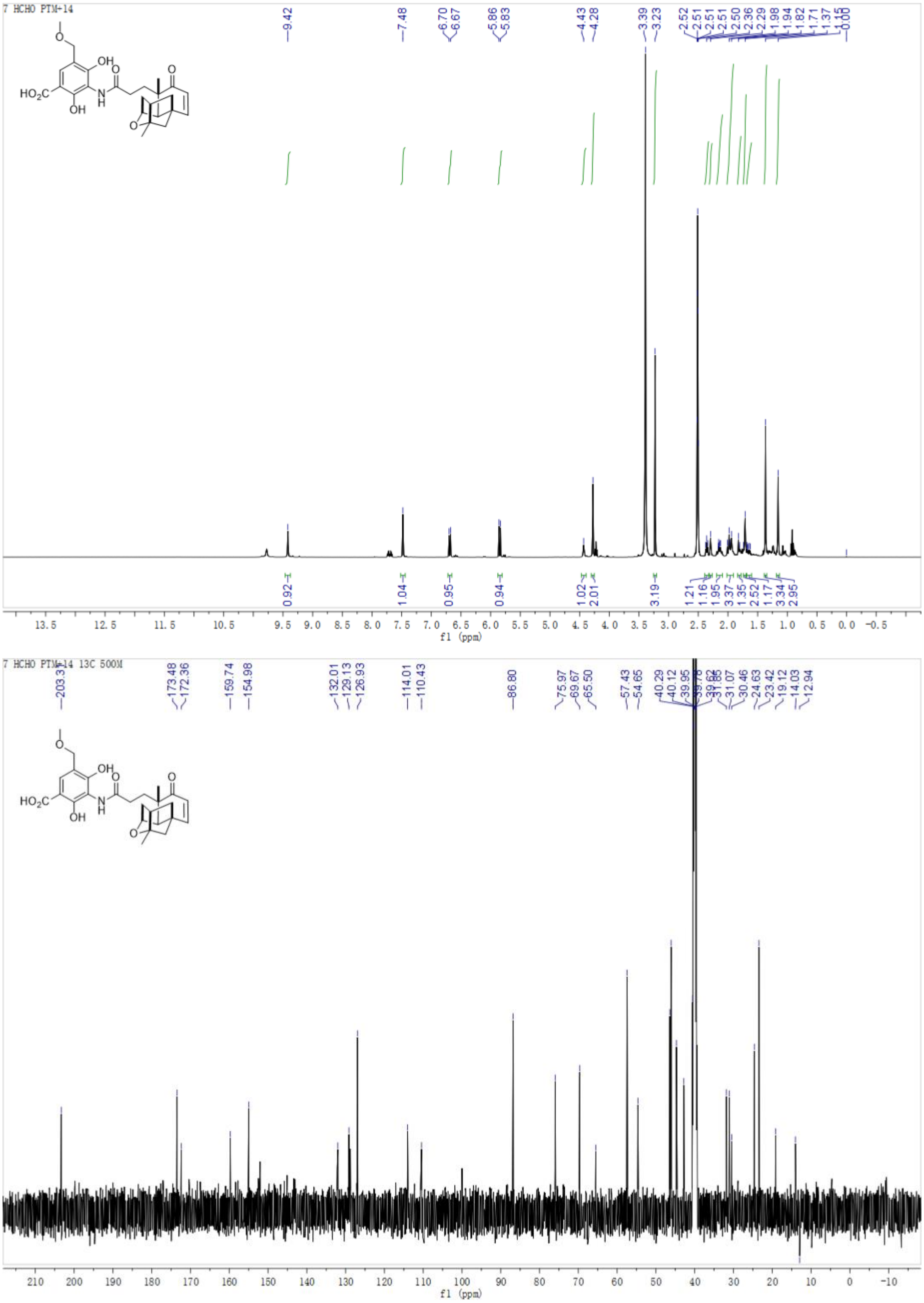


**Figure S11**. $^{1}$H–$^{13}$C HSQC spectrum of **10a** in DMSO-*d*$_6$

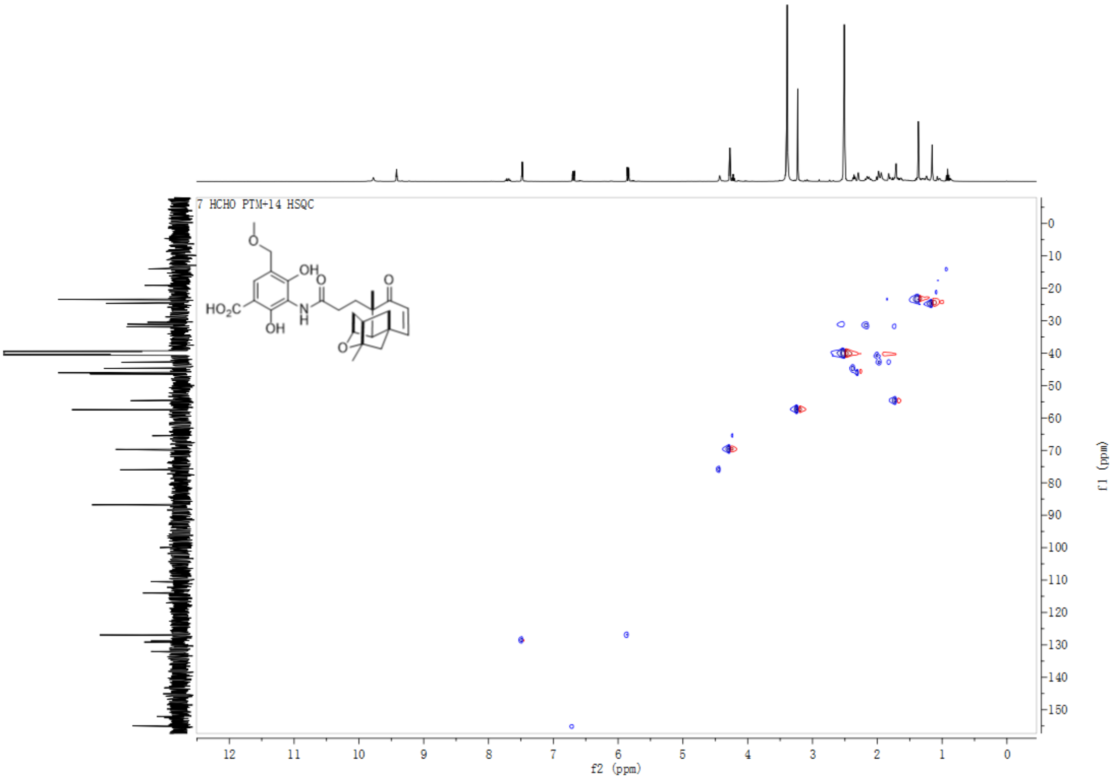


**Figure S12**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **10b** in DMSO-$d_6$

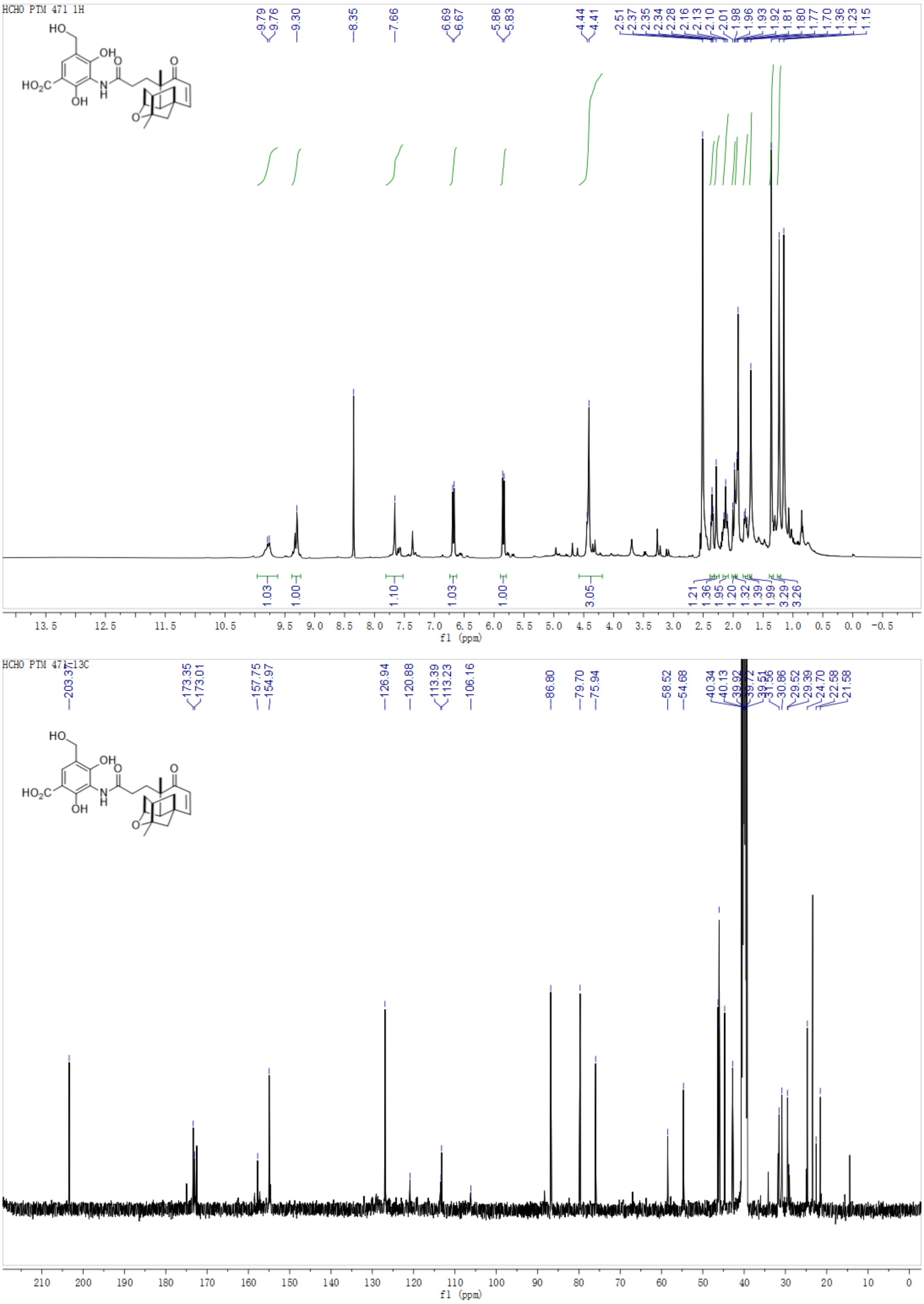


**Figure S13**. $^{1}H$–$^{13}C$ HSQC spectrum of **10b** in DMSO-$d_6$

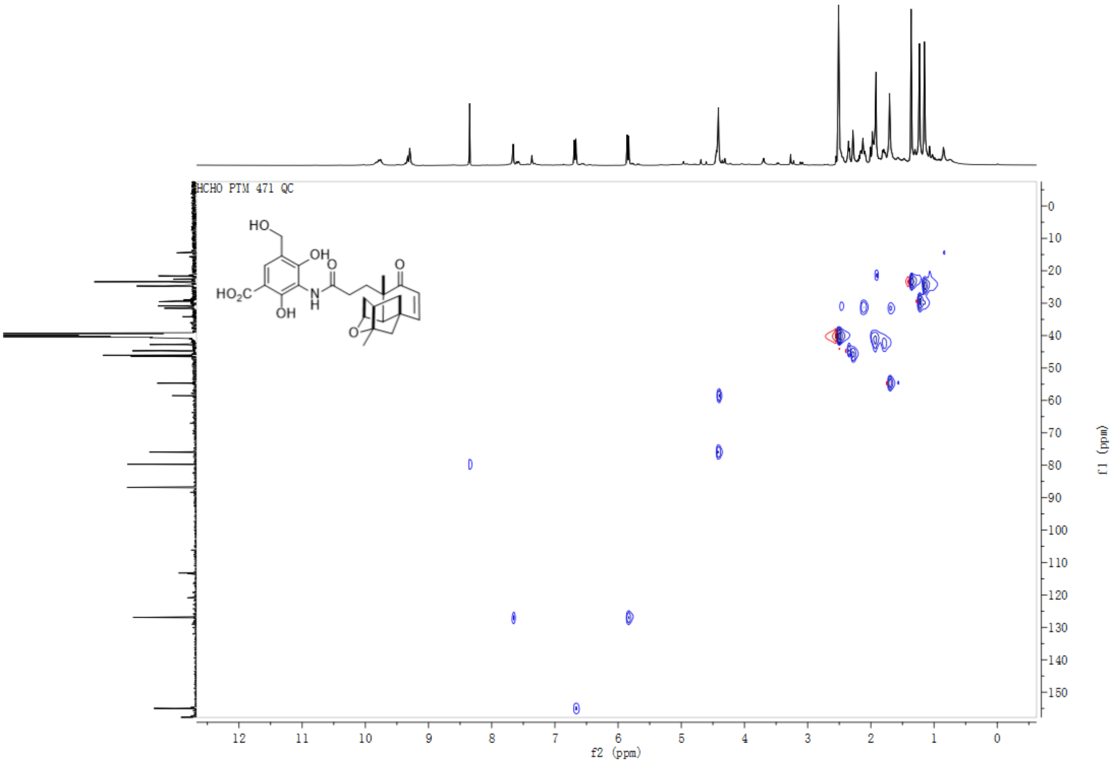


**Figure S14**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **25a** in CDCl$_3$

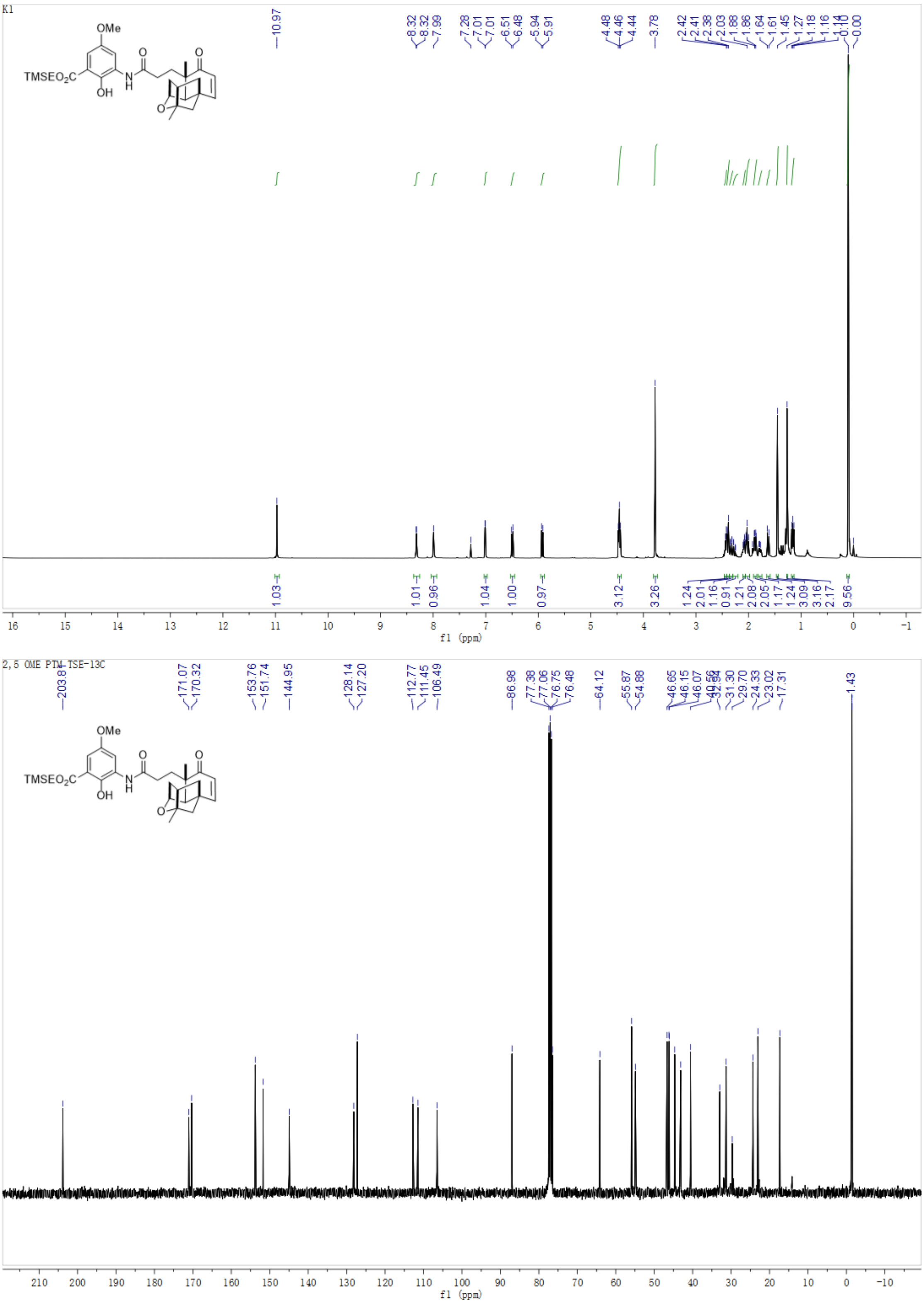


**Figure S15**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **26a** in $CDCl_3$

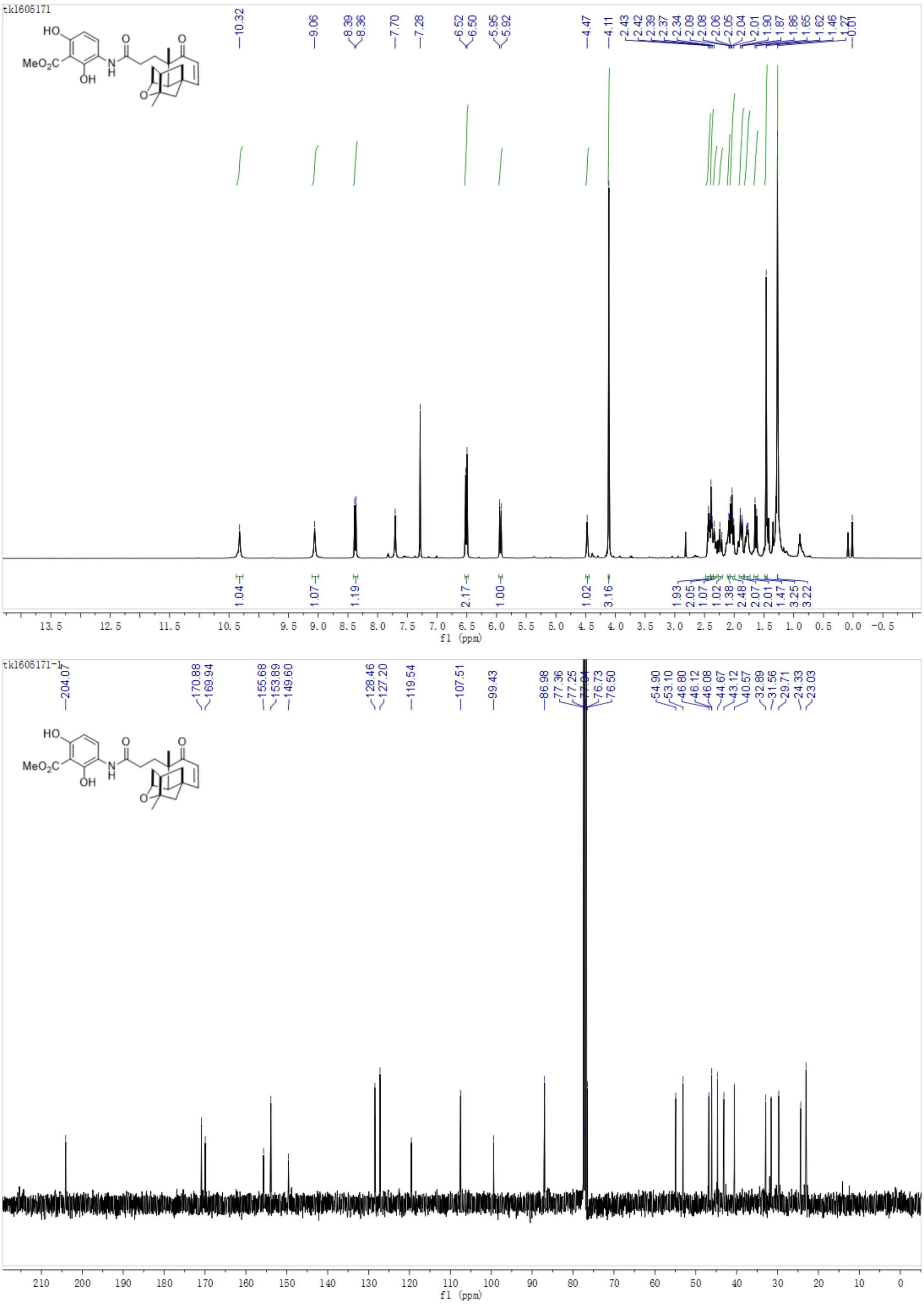


**Figure S16.** $^1H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) spectrum of **26b** in MeOD

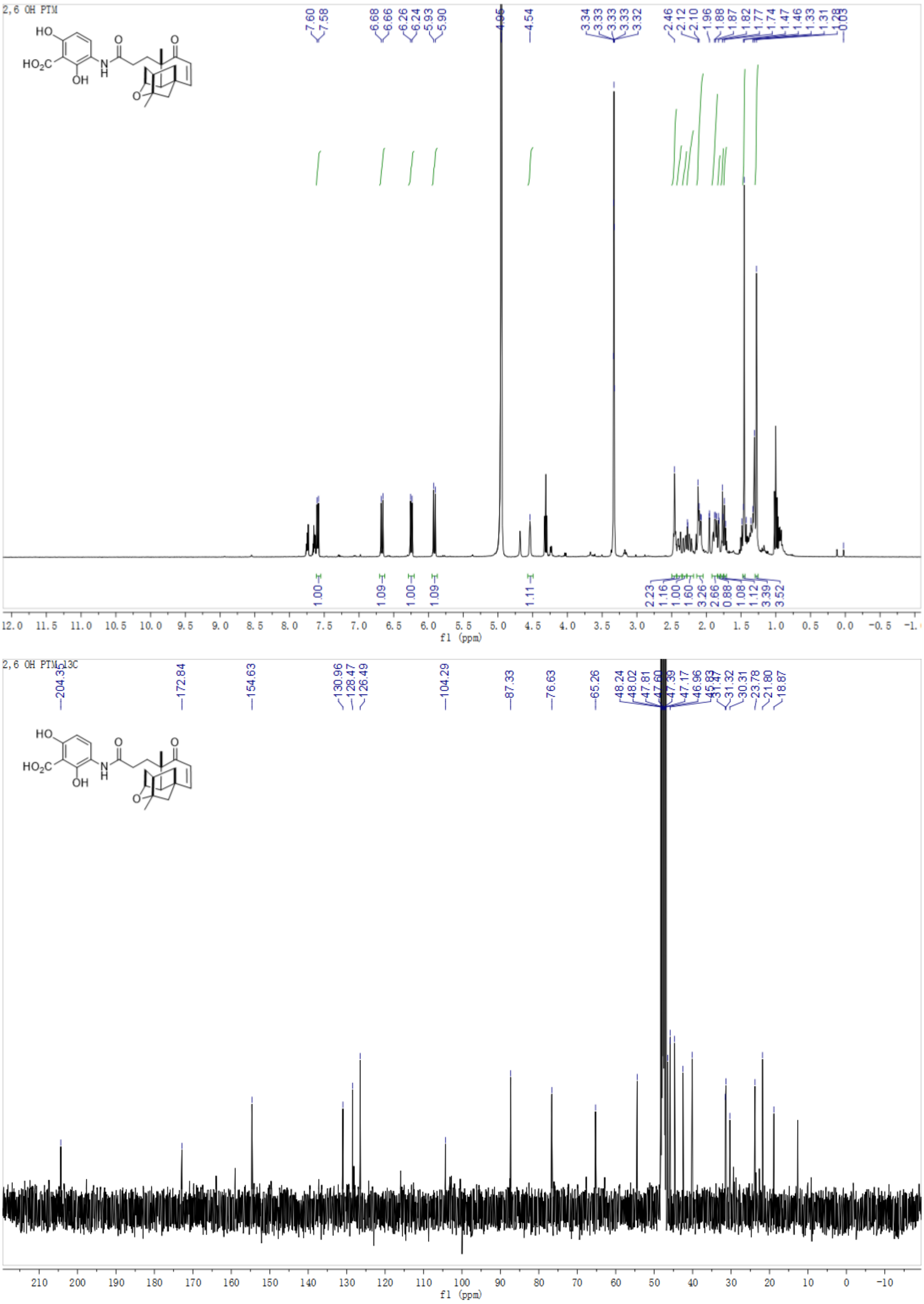


**Figure S17**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **27a** in $CDCl_3$

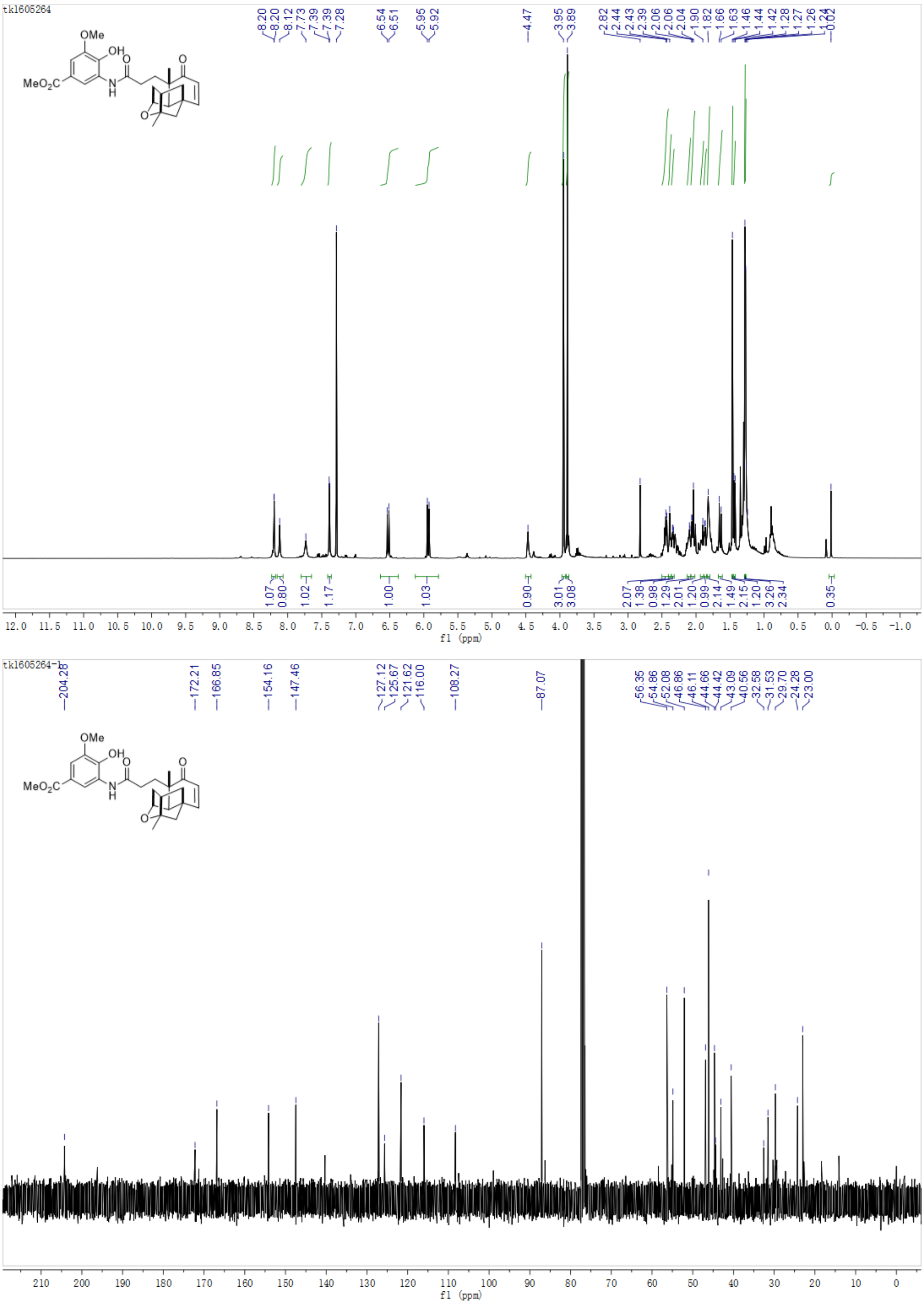
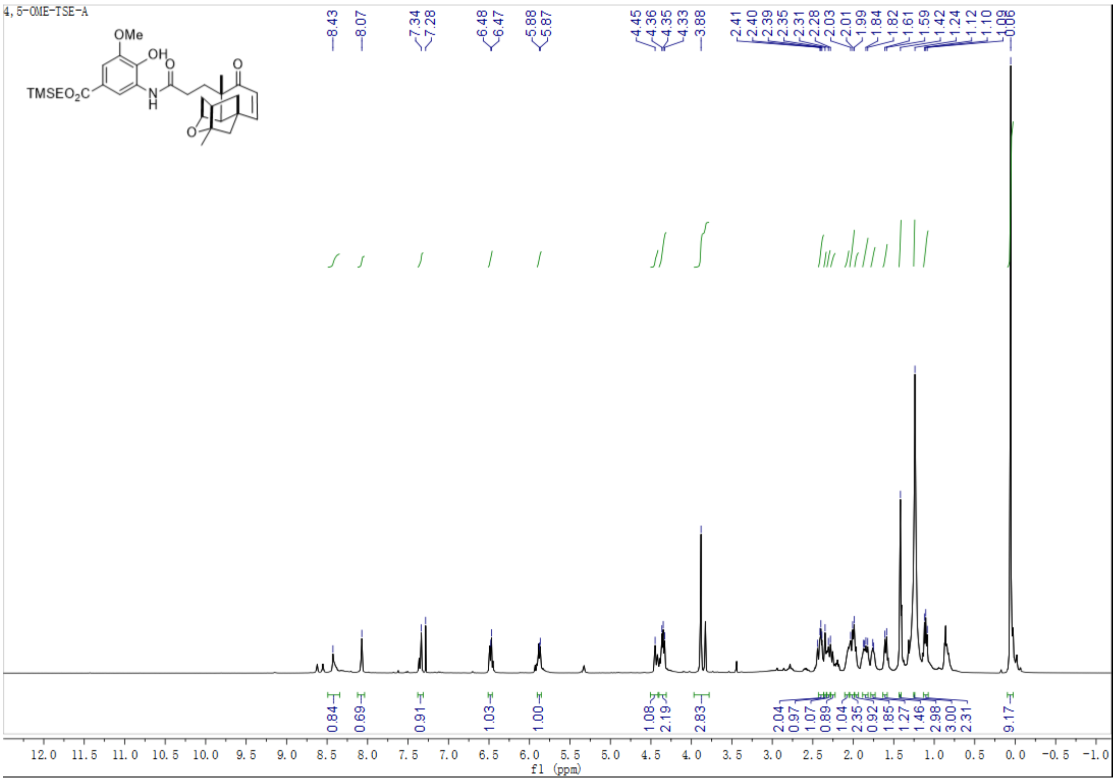


**Figure S18**. $^1H$ NMR (500 MHz) and $^{13}C$ NMR (126 MHz) spectrum of **27b** in $CDCl_3$



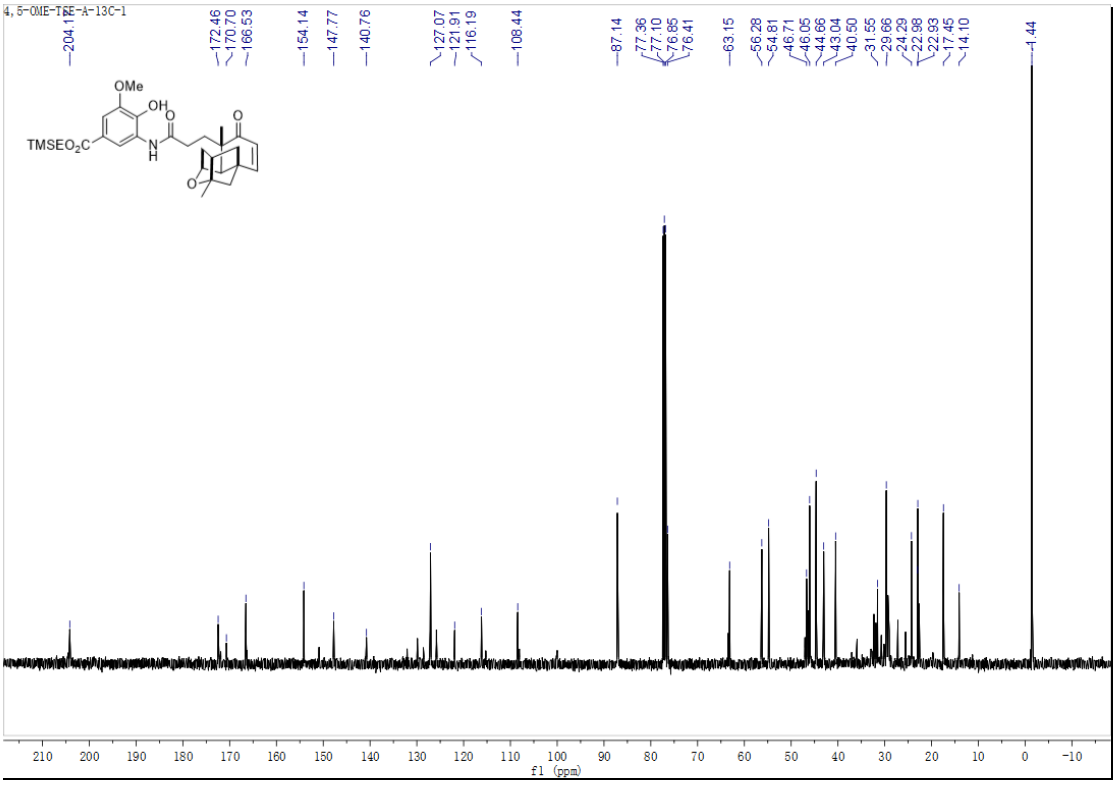


**Figure S19**. $^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **28** in DMSO-$d_6$

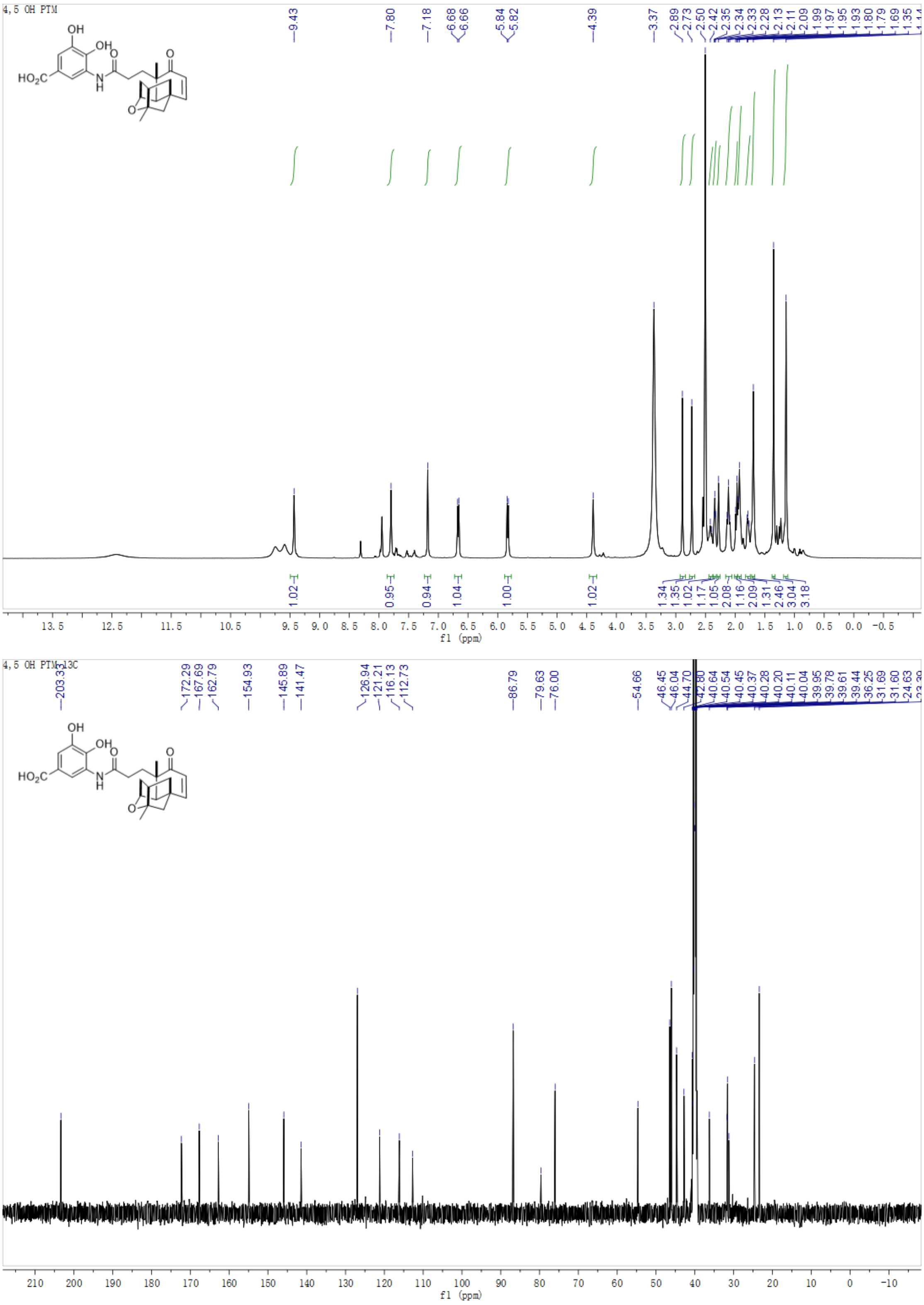
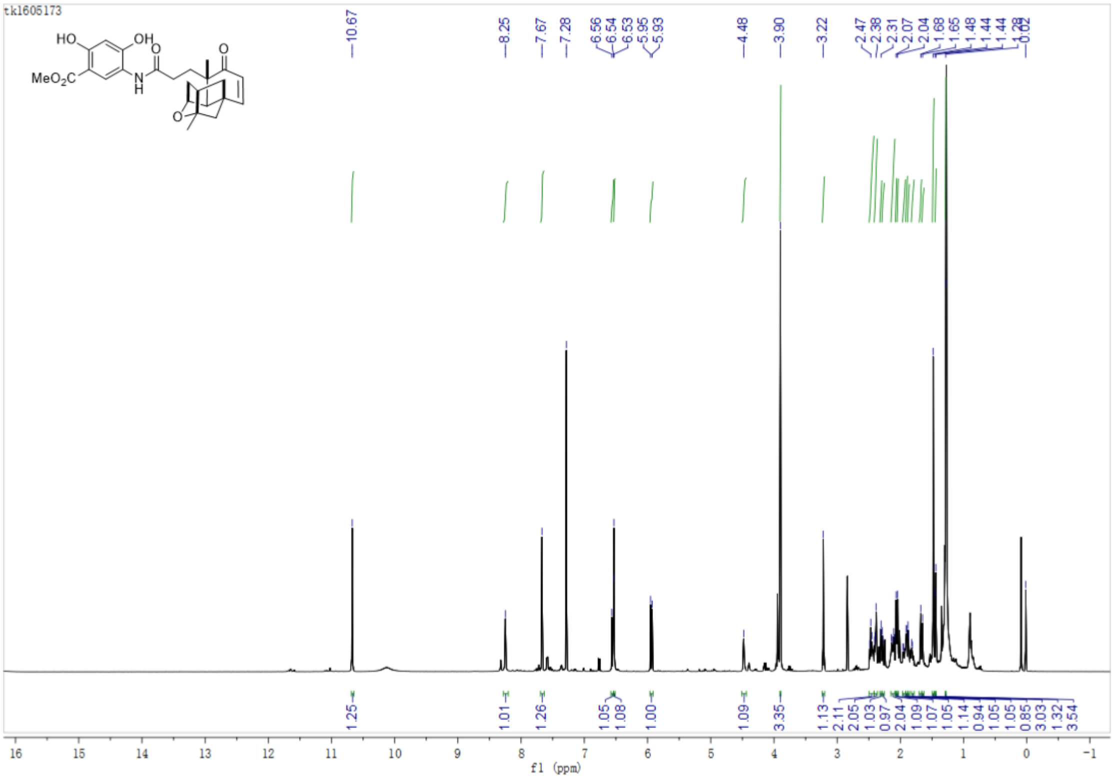


**Figure S20**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **29a** in $CDCl_3$



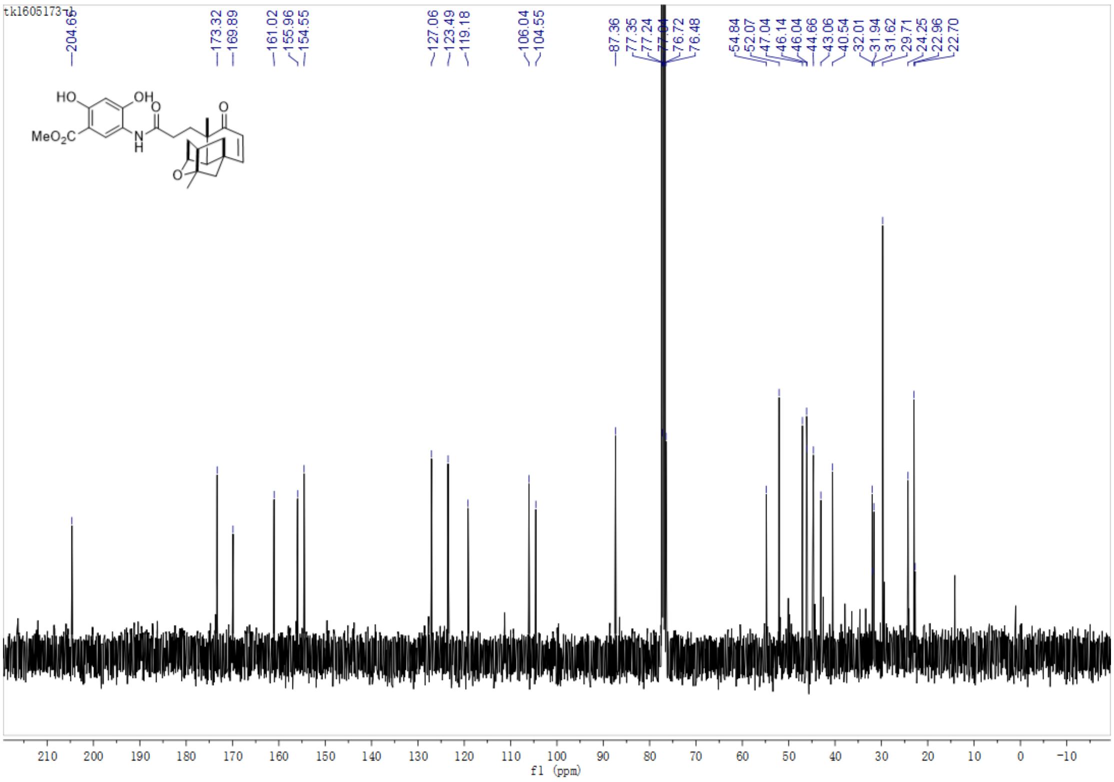


**Figure S21**. ${}^{1}$H NMR (500 MHz) and ${}^{13}$C NMR (126 MHz) spectrum of **29b** in $CDCl_3$

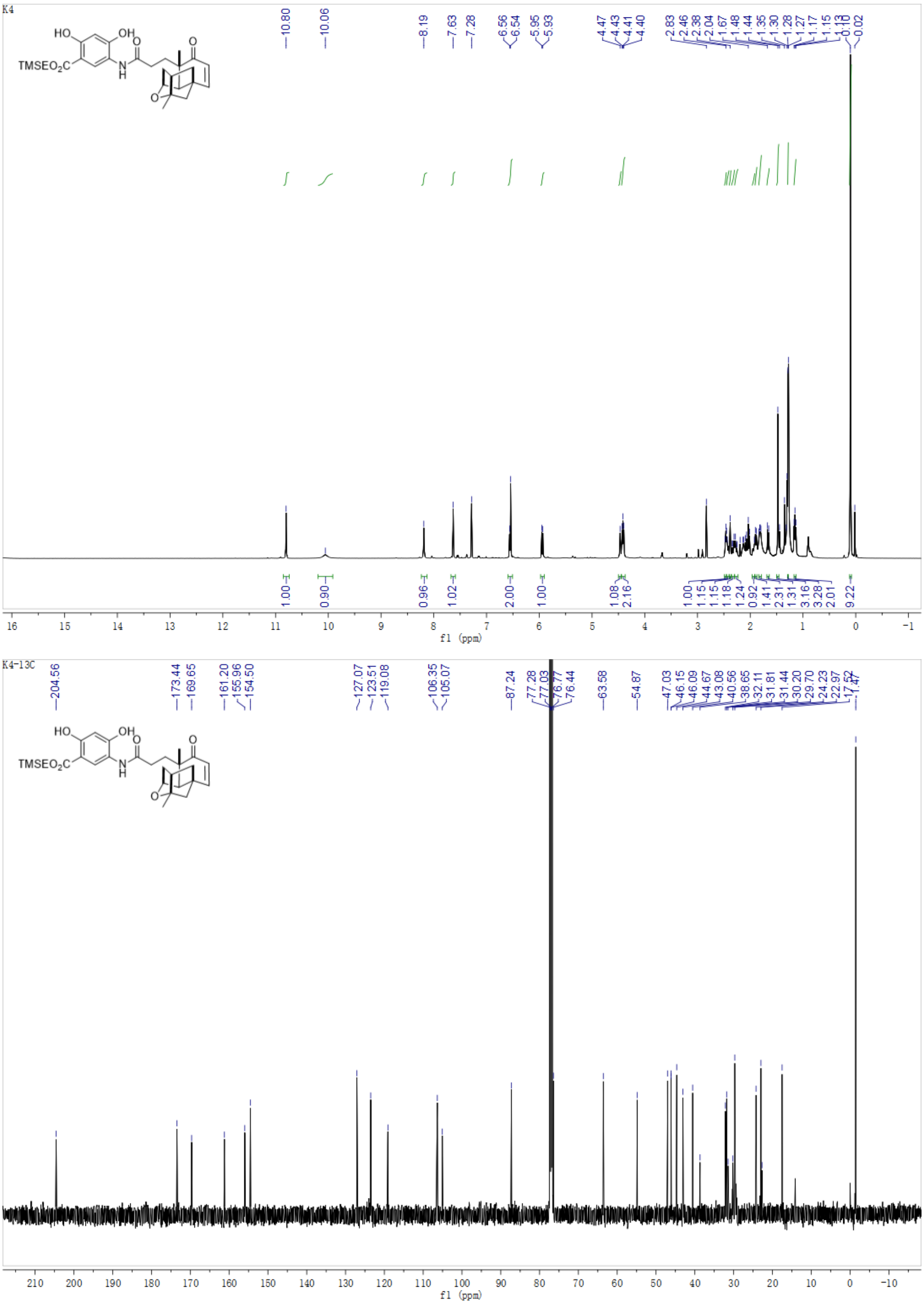


**Figure S22**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **30** in $CDCl_3$

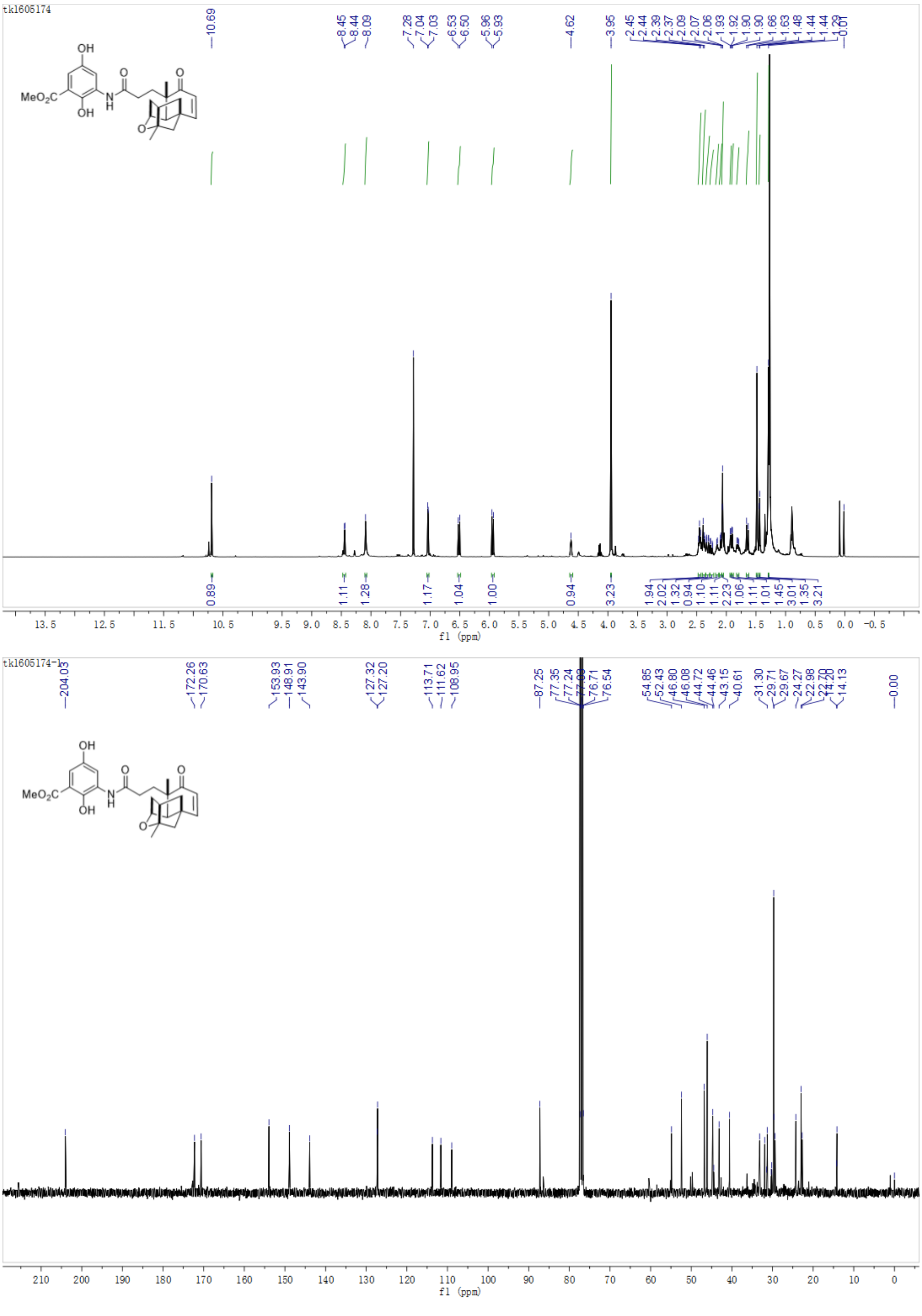


**Figure S23.** $^{1}$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **25b** in DMSO-$d_6$

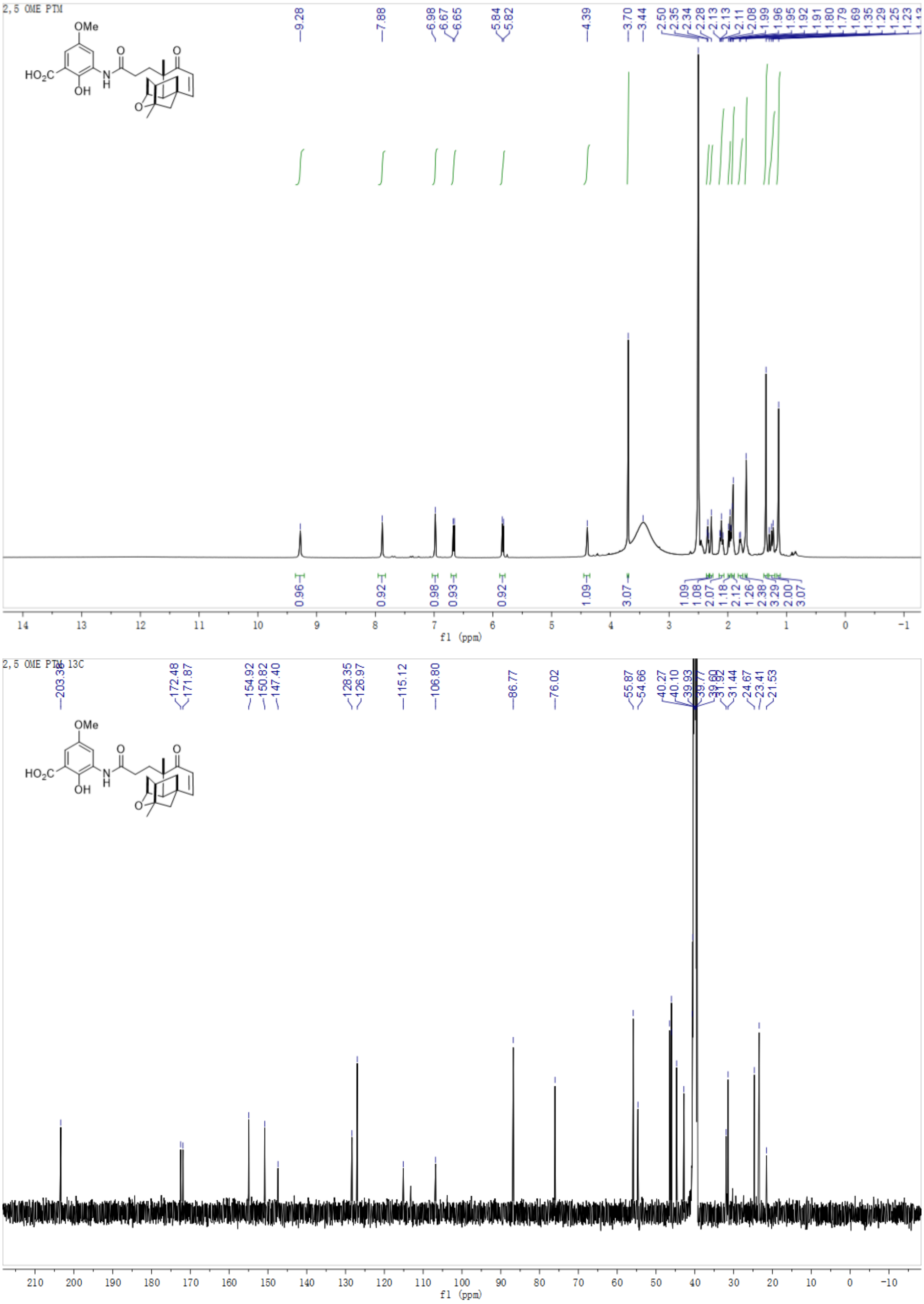


**Figure S24**. $^{1}$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **27c** in MeOD

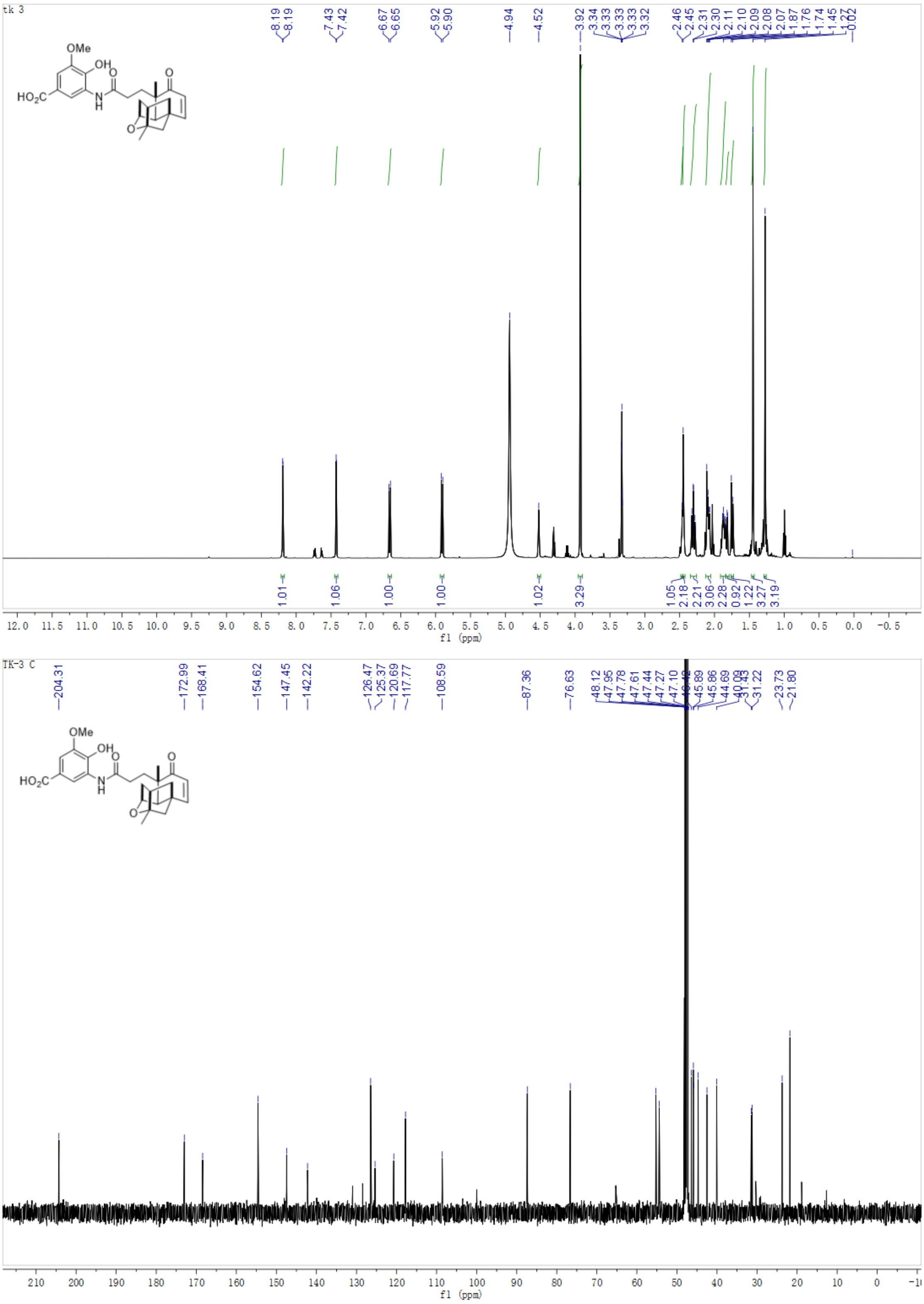


**Figure S25**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **29c** in MeOD

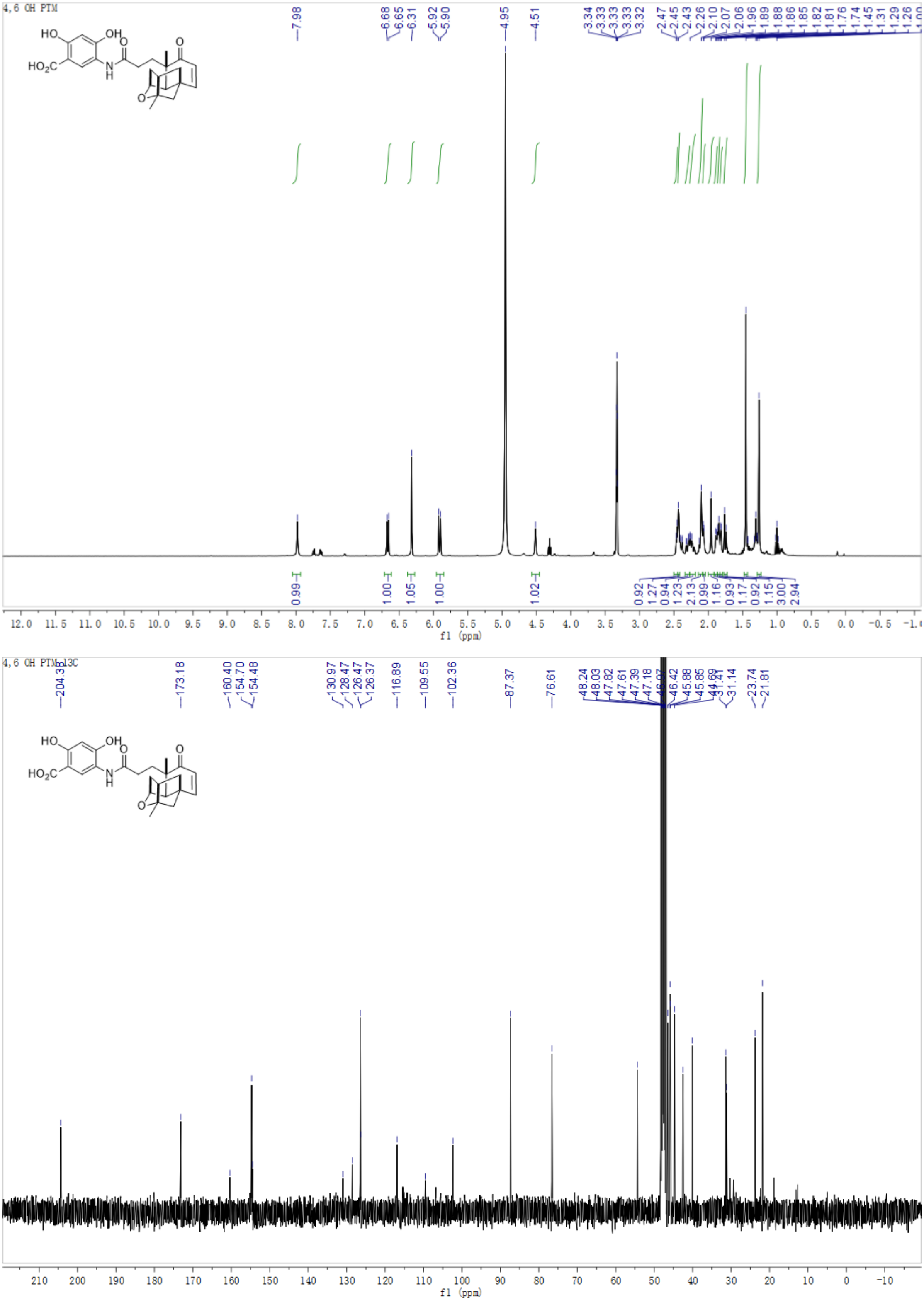


**Figure S26**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **4** in $CDCl_3$

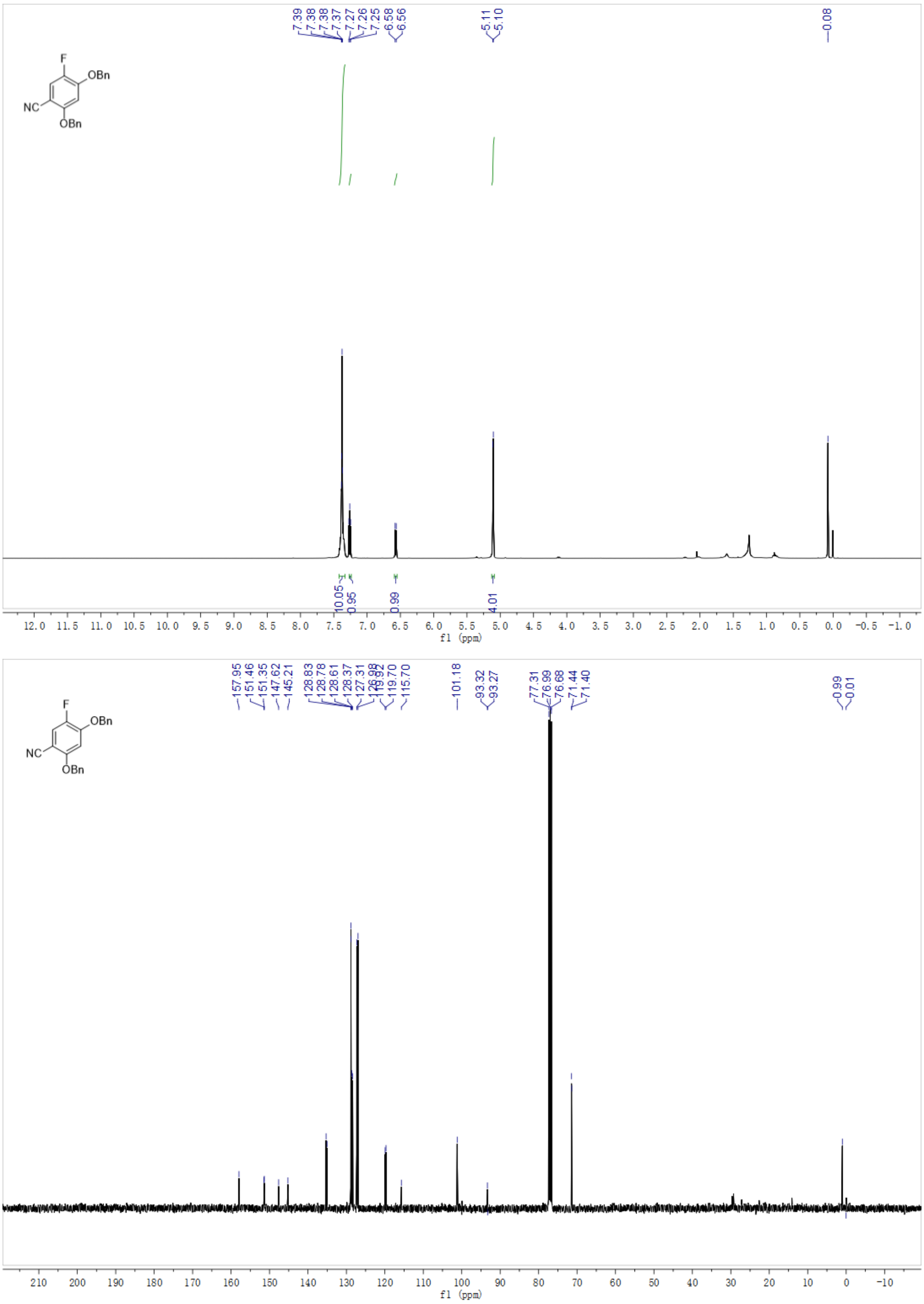


**Figure S27**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **5** in $CDCl_3$

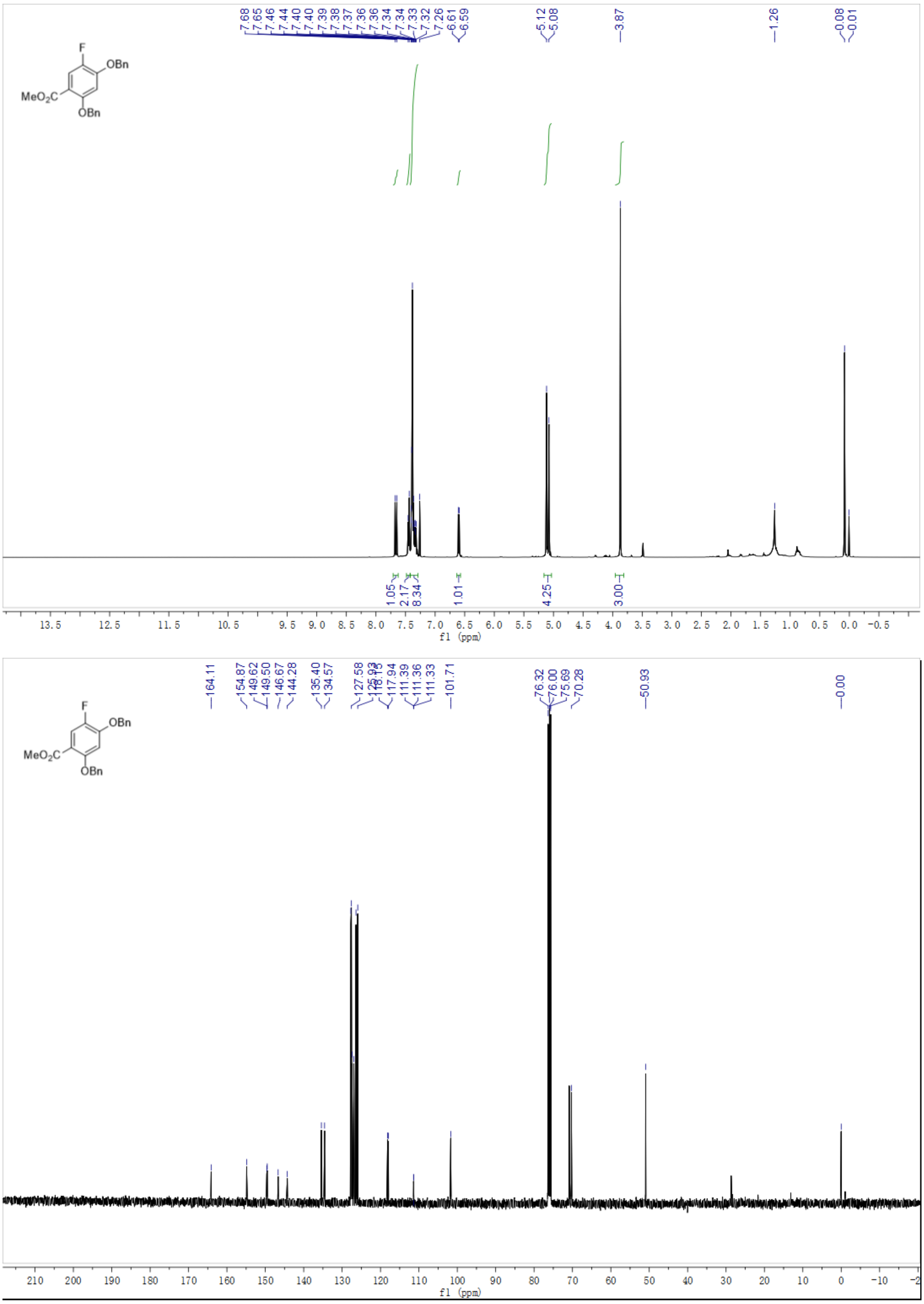


**Figure S28**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **S9** in $CDCl_3$

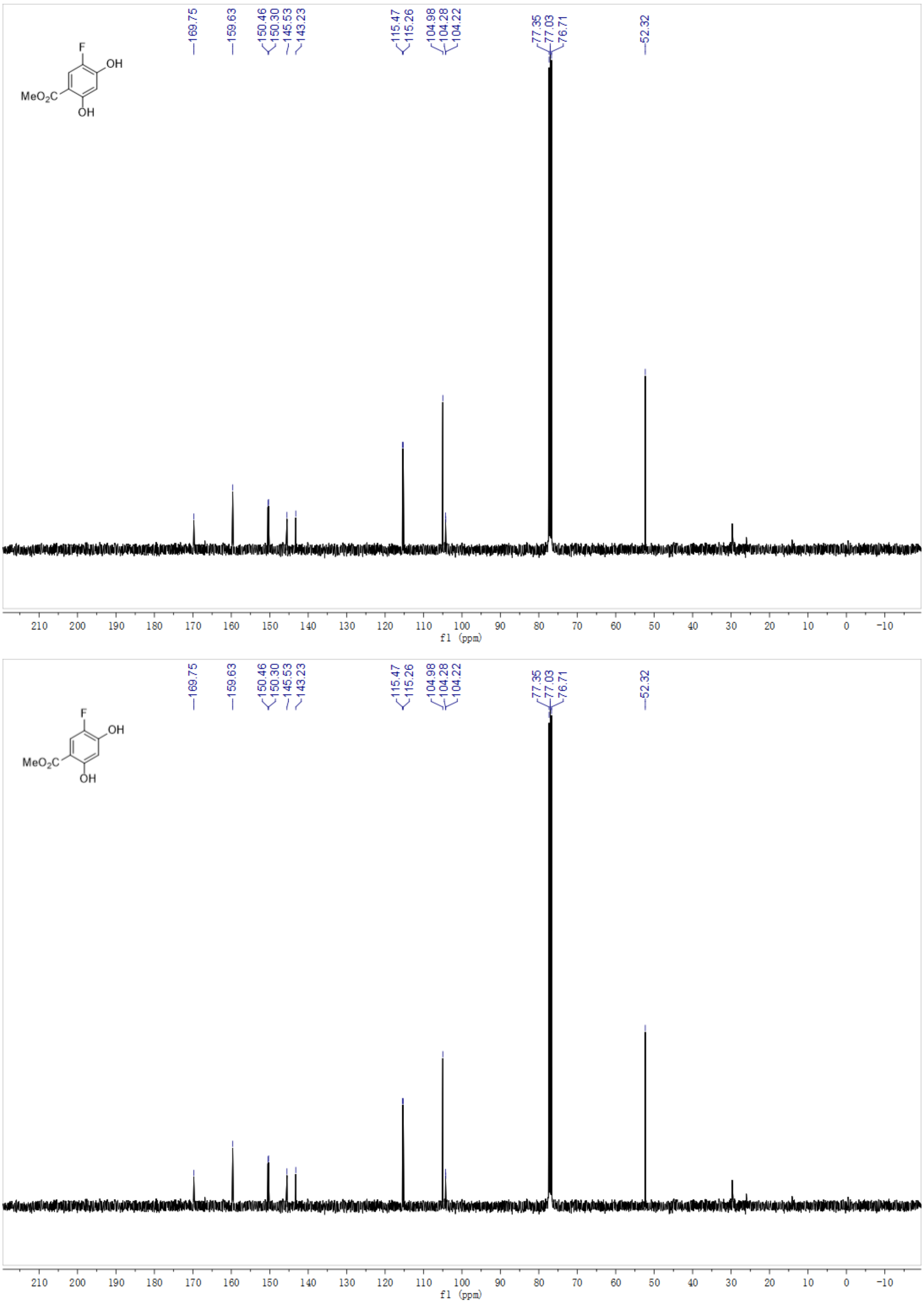


**Figure S29**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **6** in DMSO-$d_6$

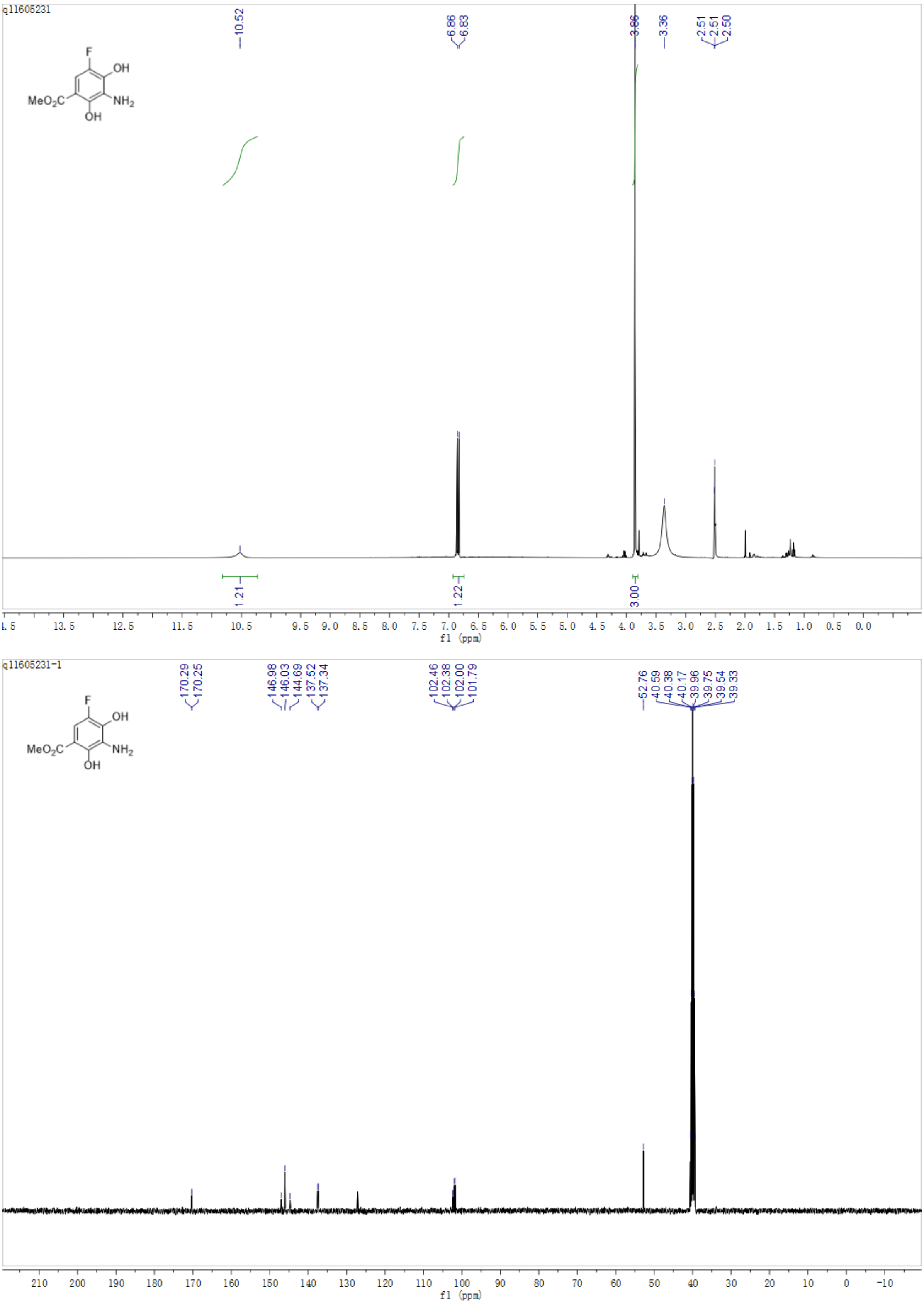


**Figure S30**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **13** in CDCl$_3$.

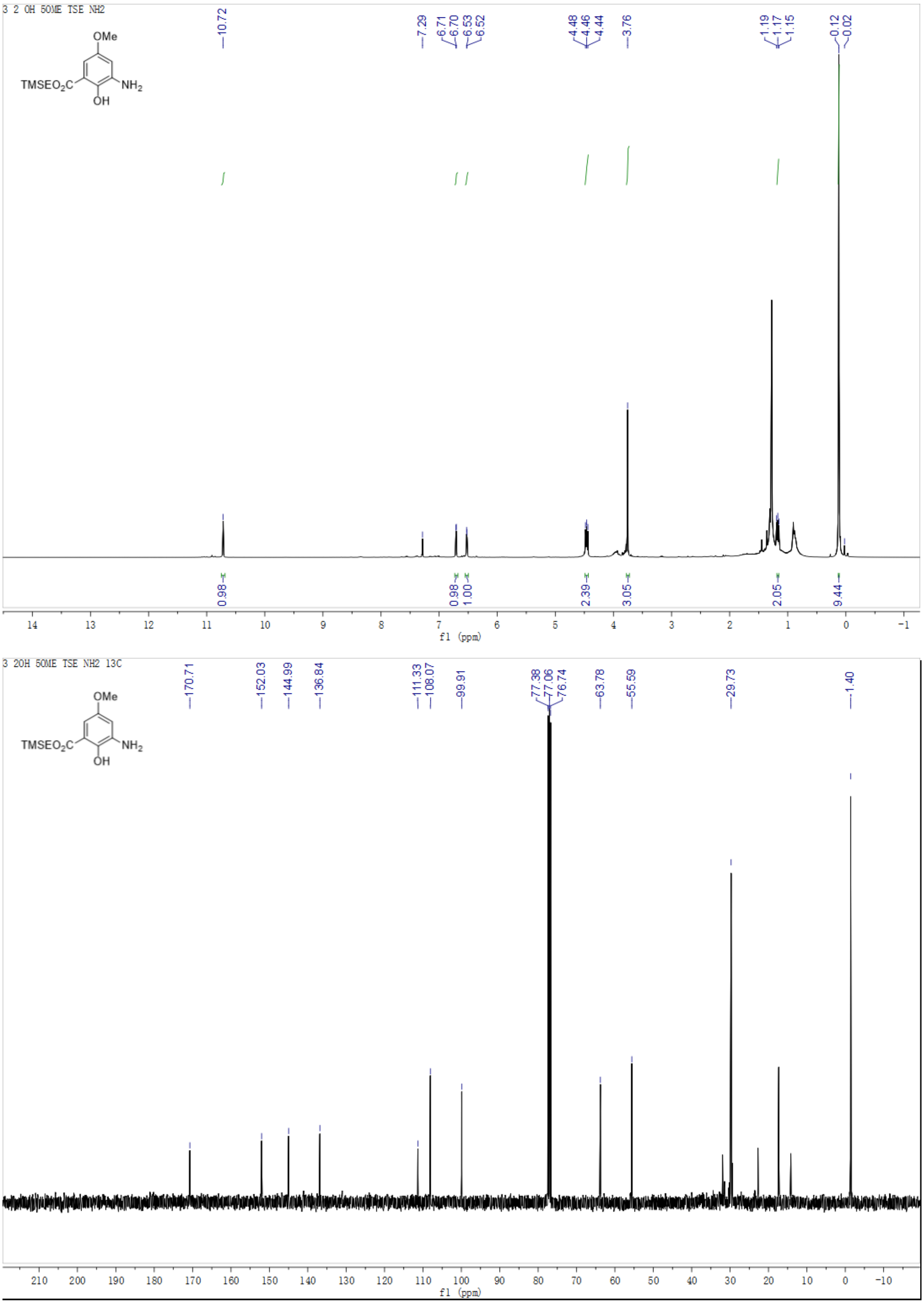


**Figure S31**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **15a** in $CDCl_3$.

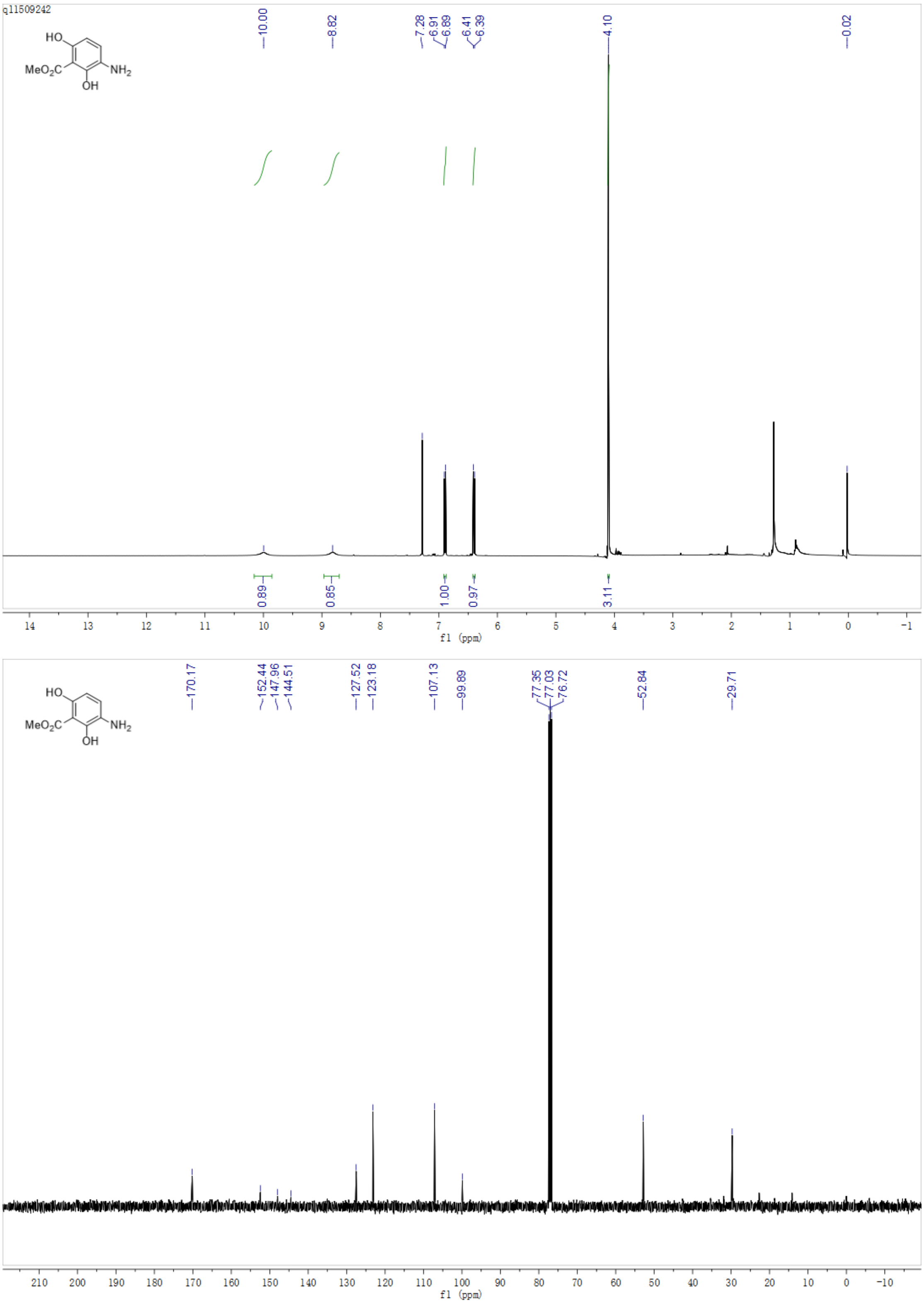


**Figure S32**. $^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **15b** in DMSO-$d_6$

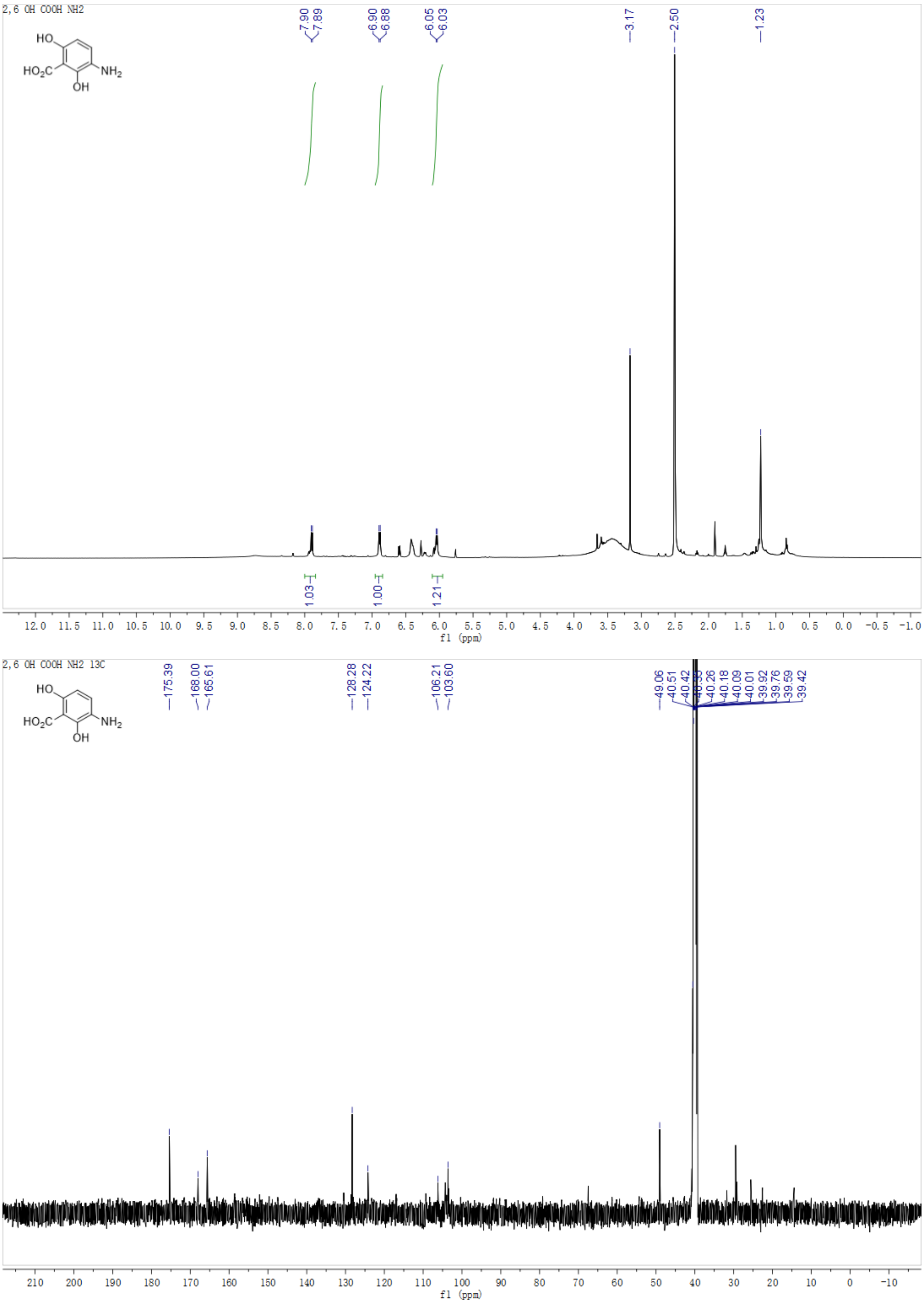


**Figure S33**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) spectrum of **17a** in $CDCl_3$.

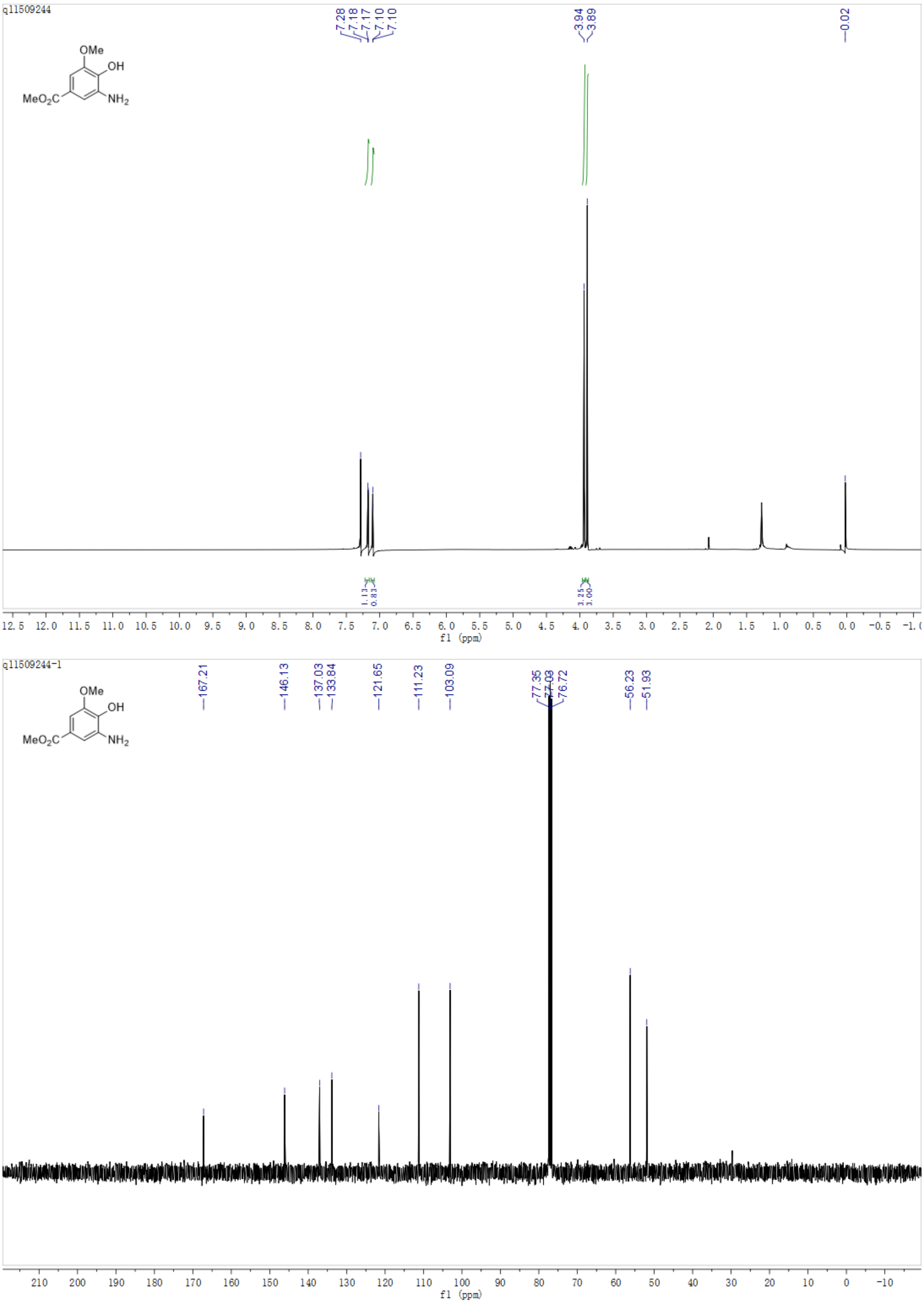


**Figure S34**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) spectrum of **17b** in $CDCl_3$.

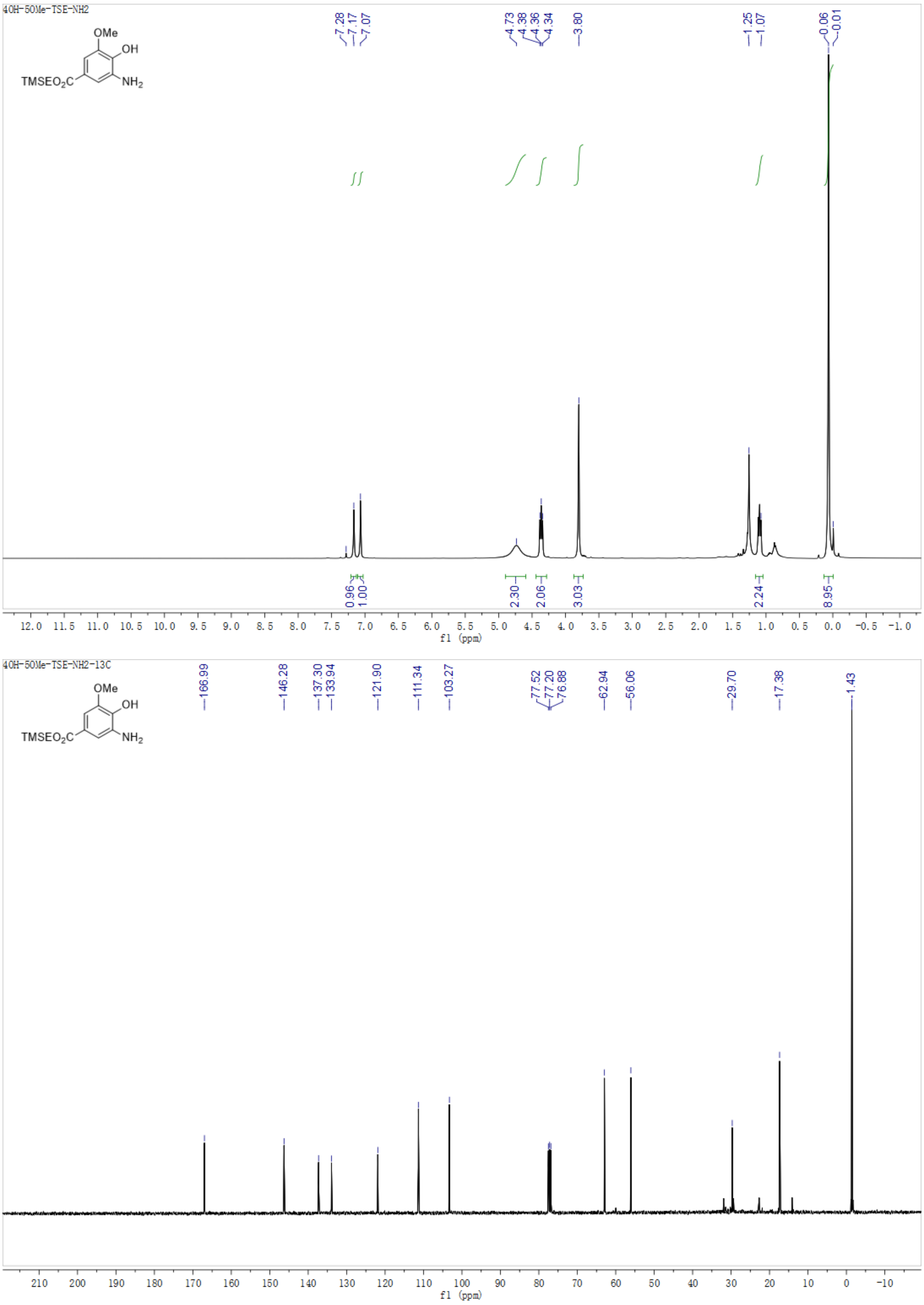


**Figure S35**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **19** in DMSO-$d_6$

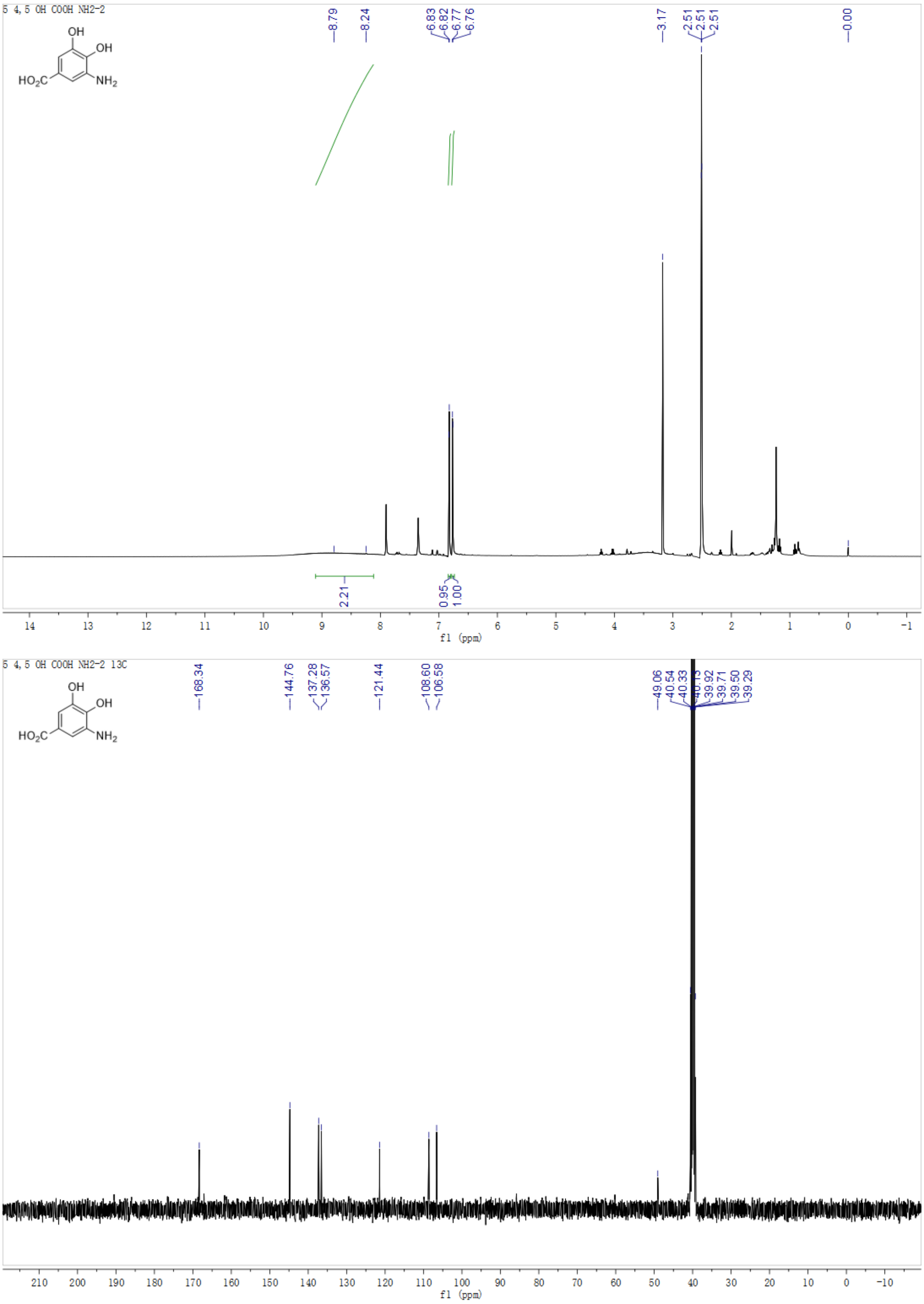


**Figure S36**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **21b** in $CDCl_3$

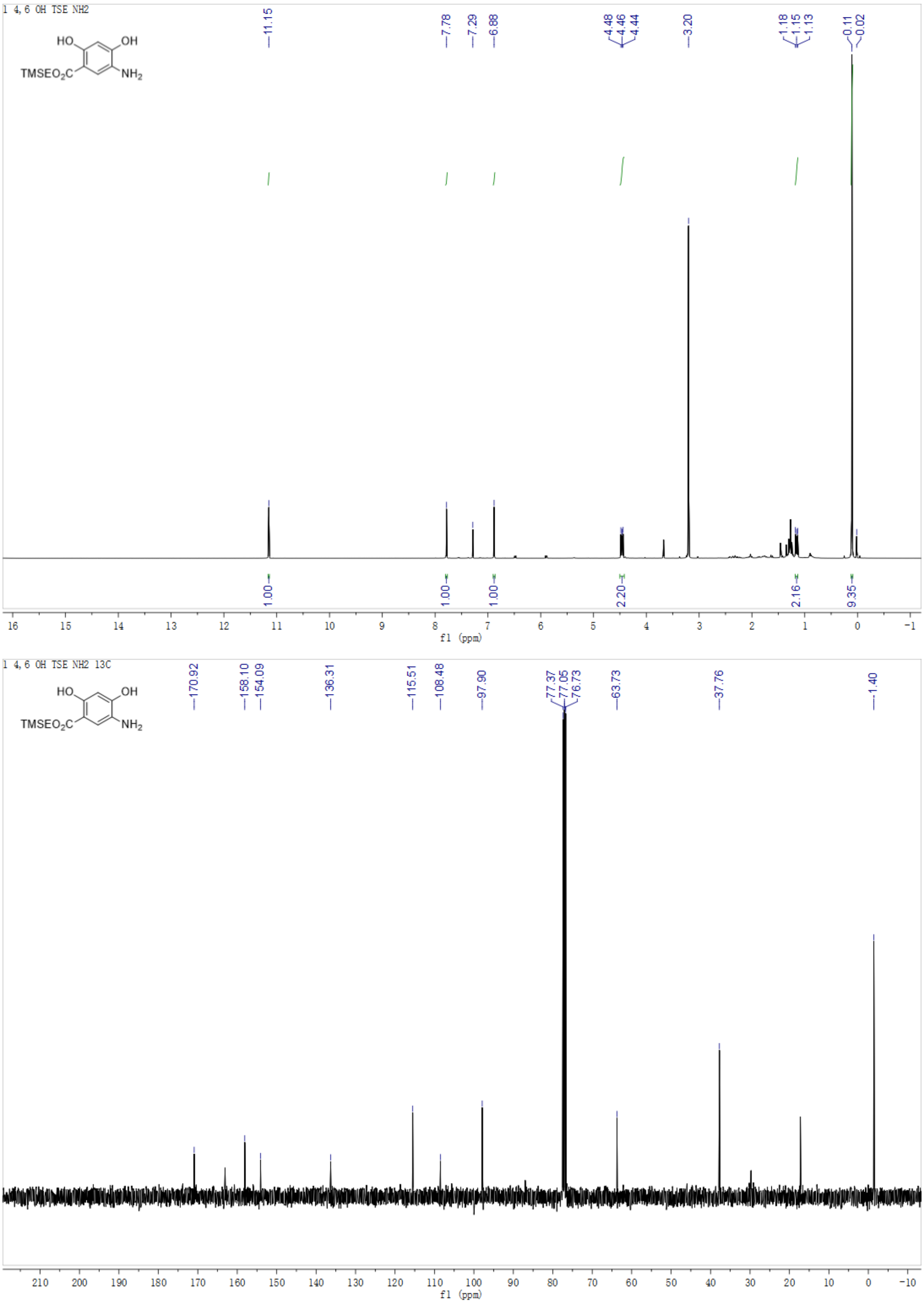


**Figure S37**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **24** in $CDCl_3$

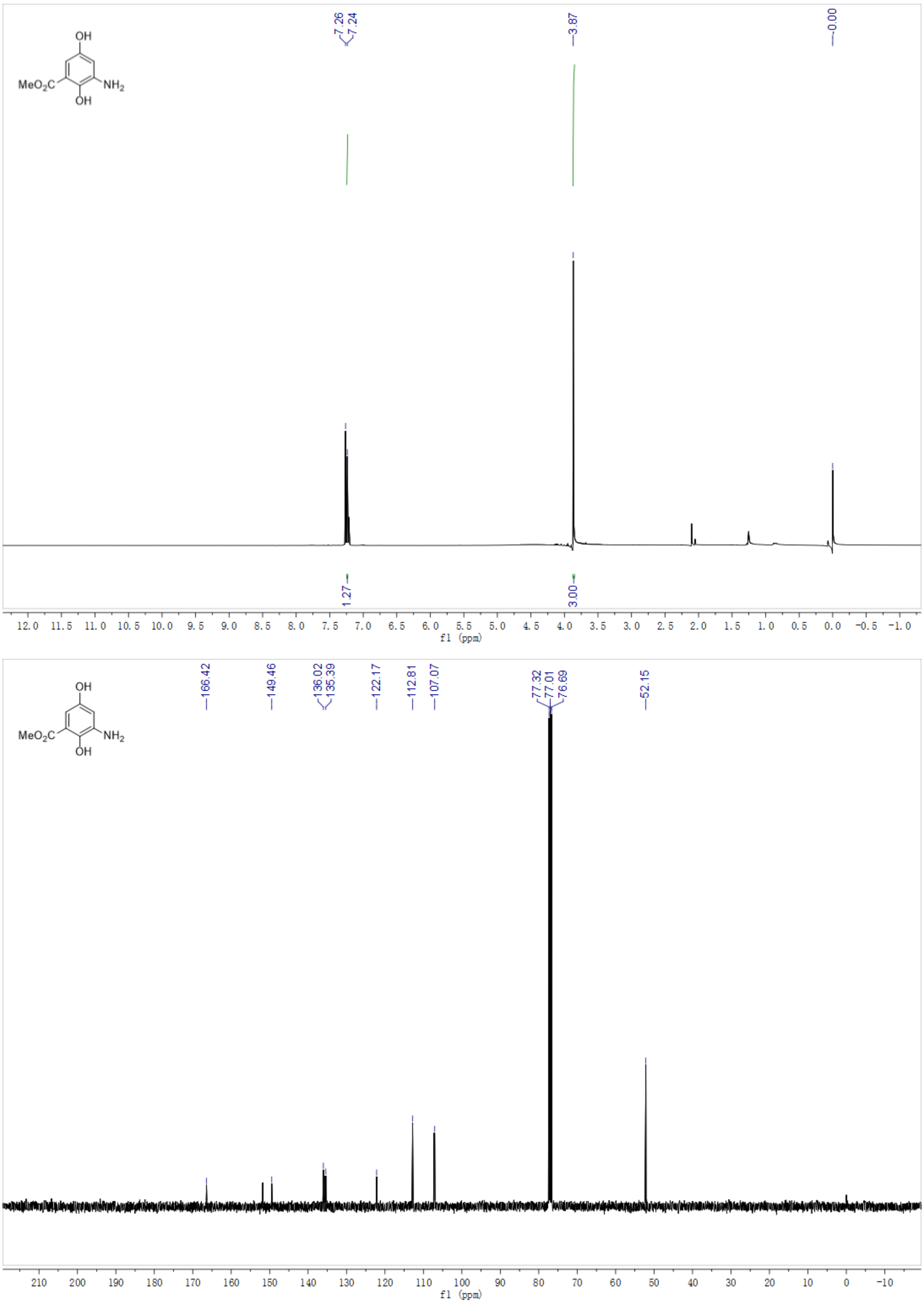


**Figure S38**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **12** in CDCl$_3$.

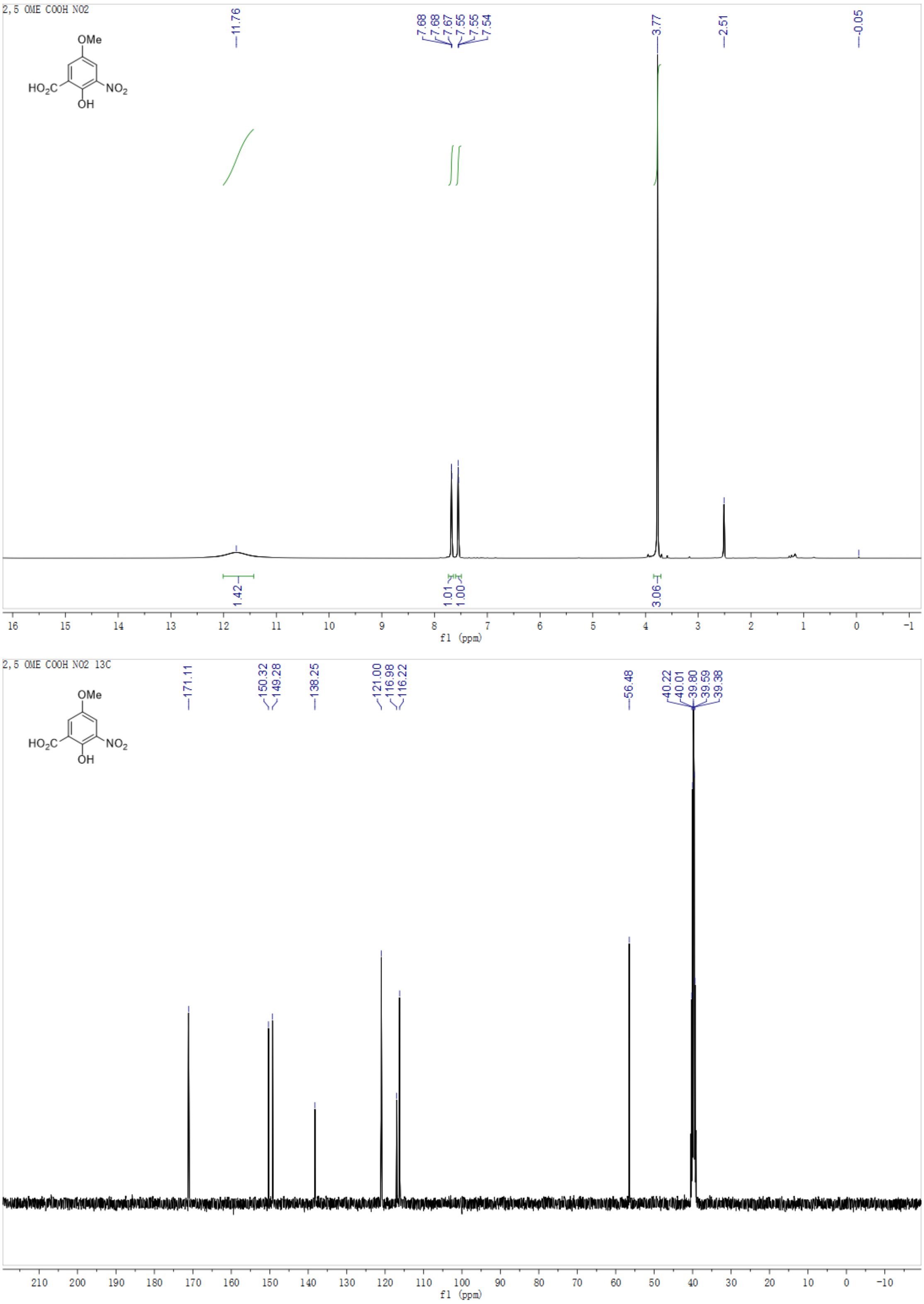
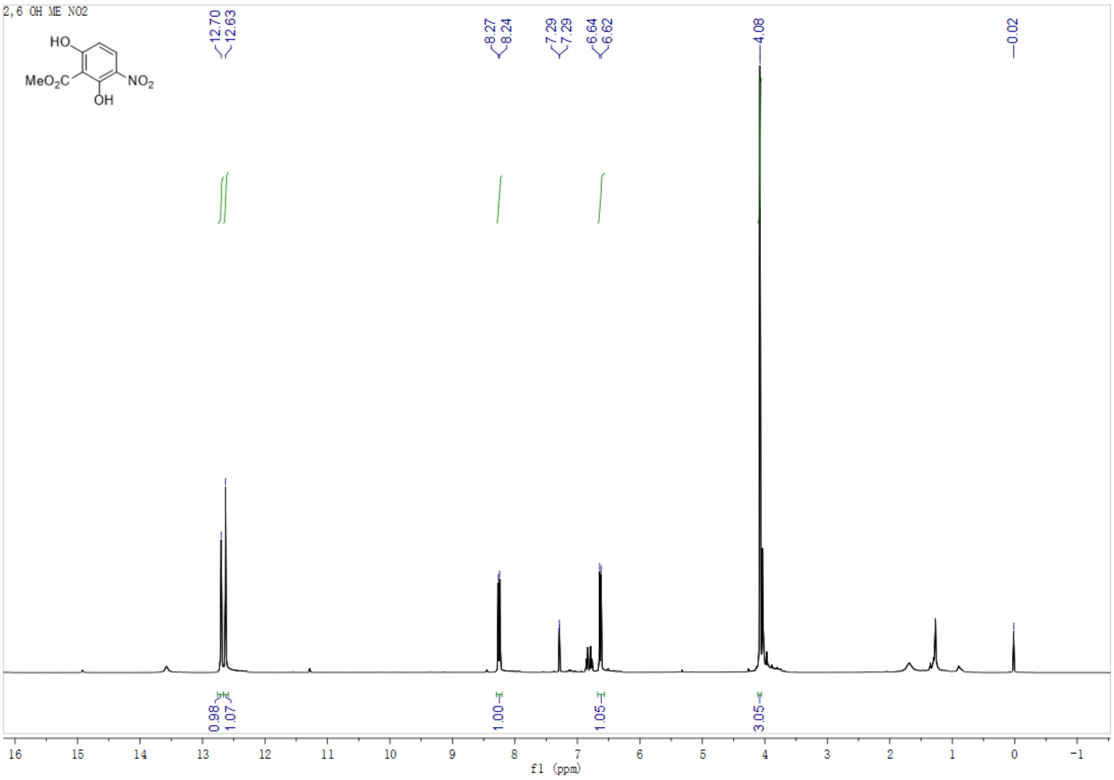


**Figure S39**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **14** in $CDCl_3$.



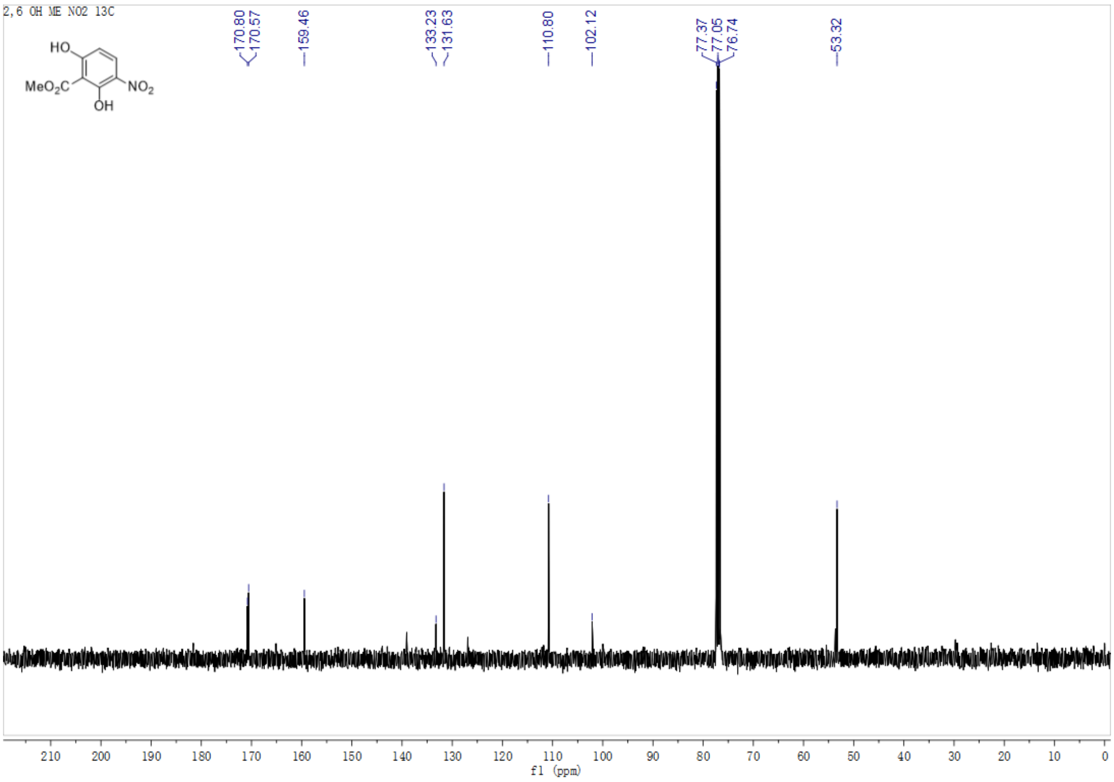


**Figure S40**. $^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectrum of **23** in CDCl$_3$.

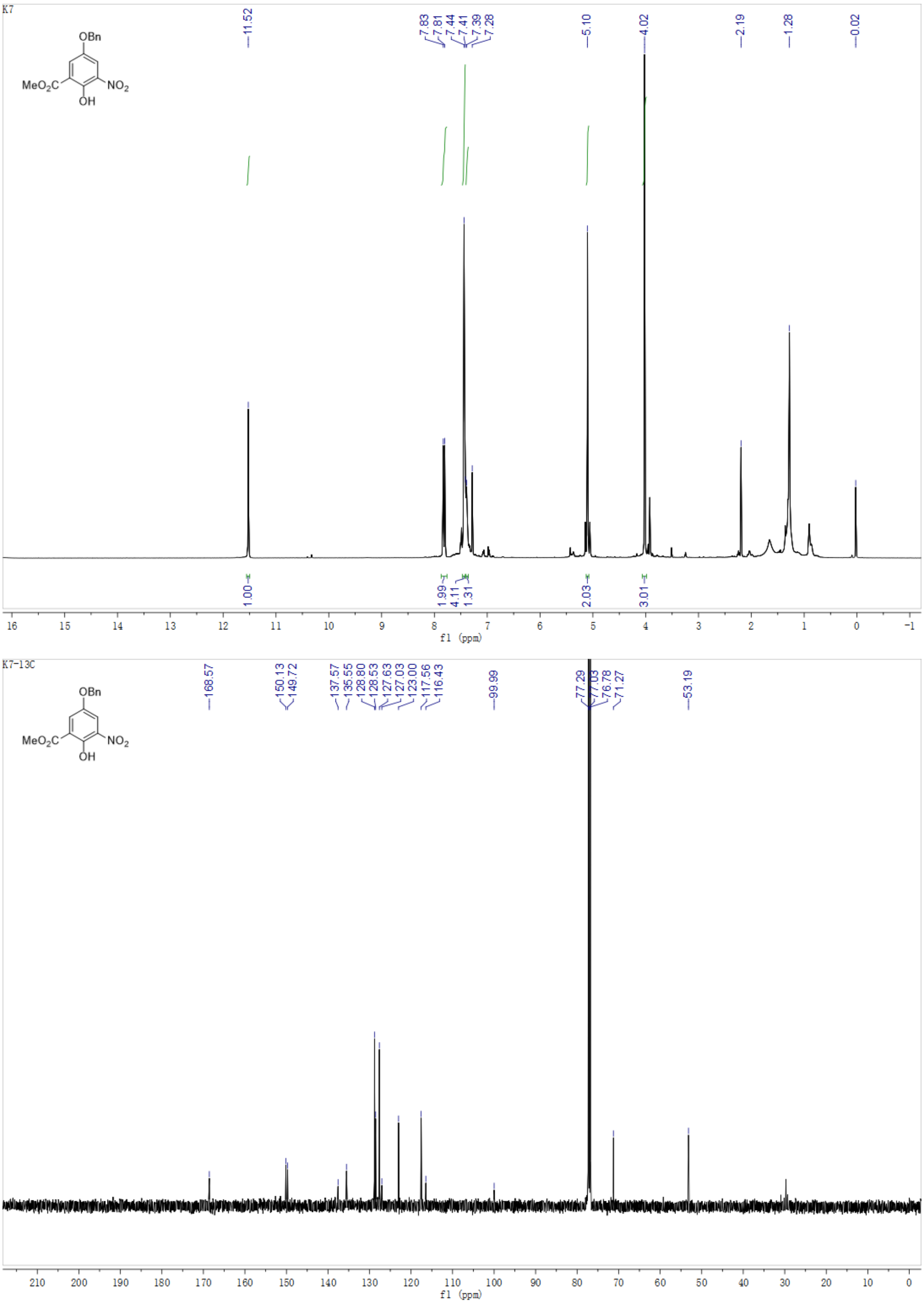


**Figure S41**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **S8** in $CDCl_3$.

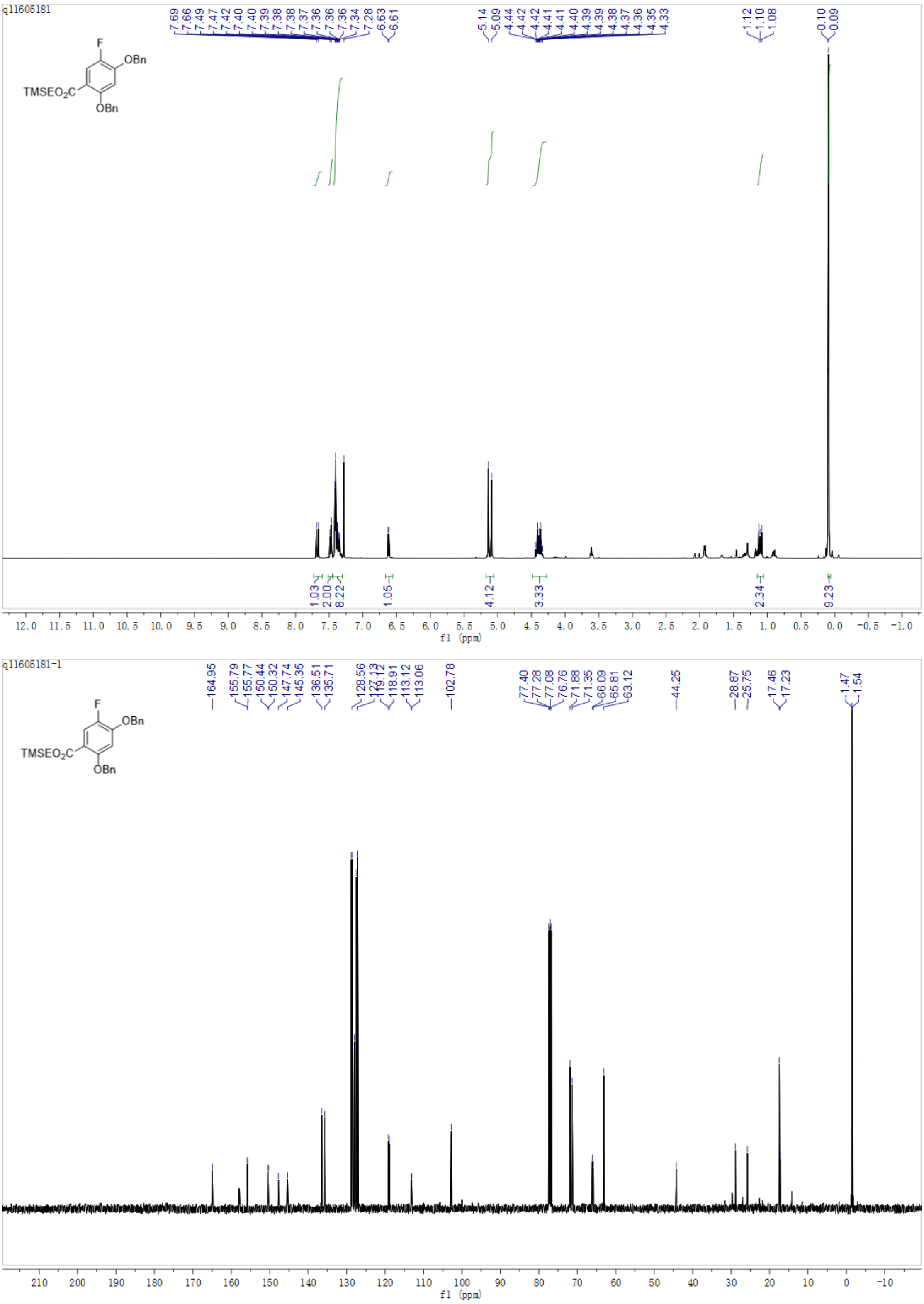
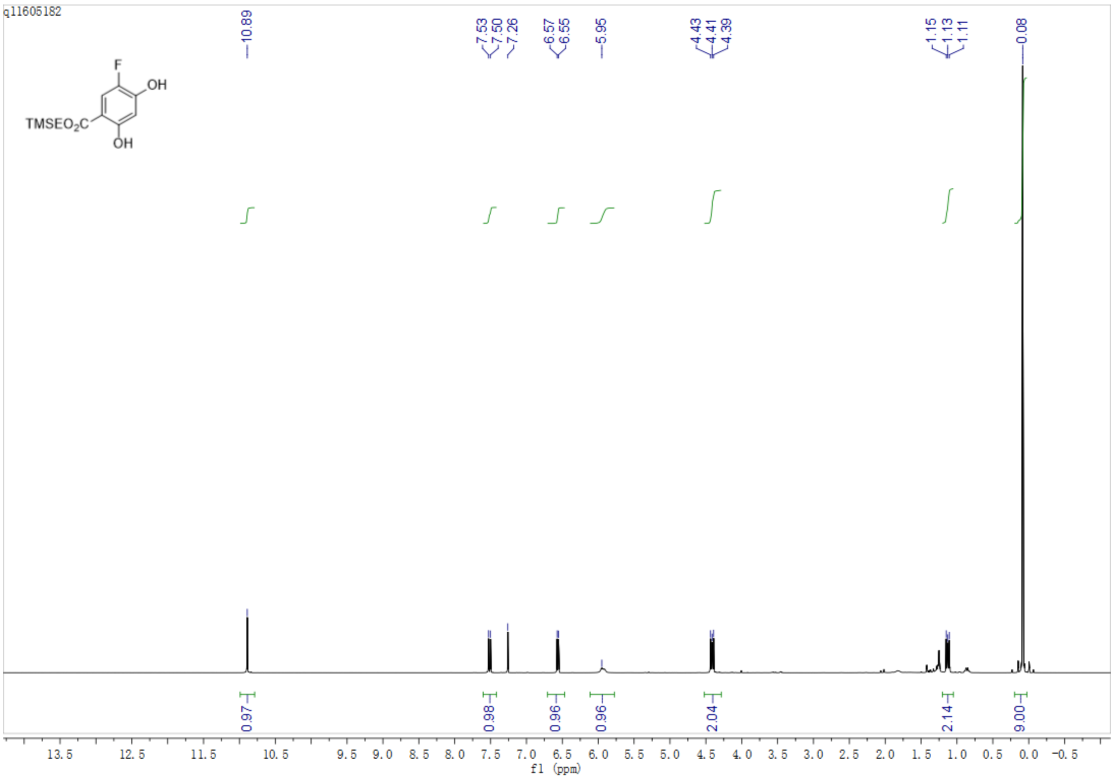


**Figure S42**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **S10** in CDCl$_3$.



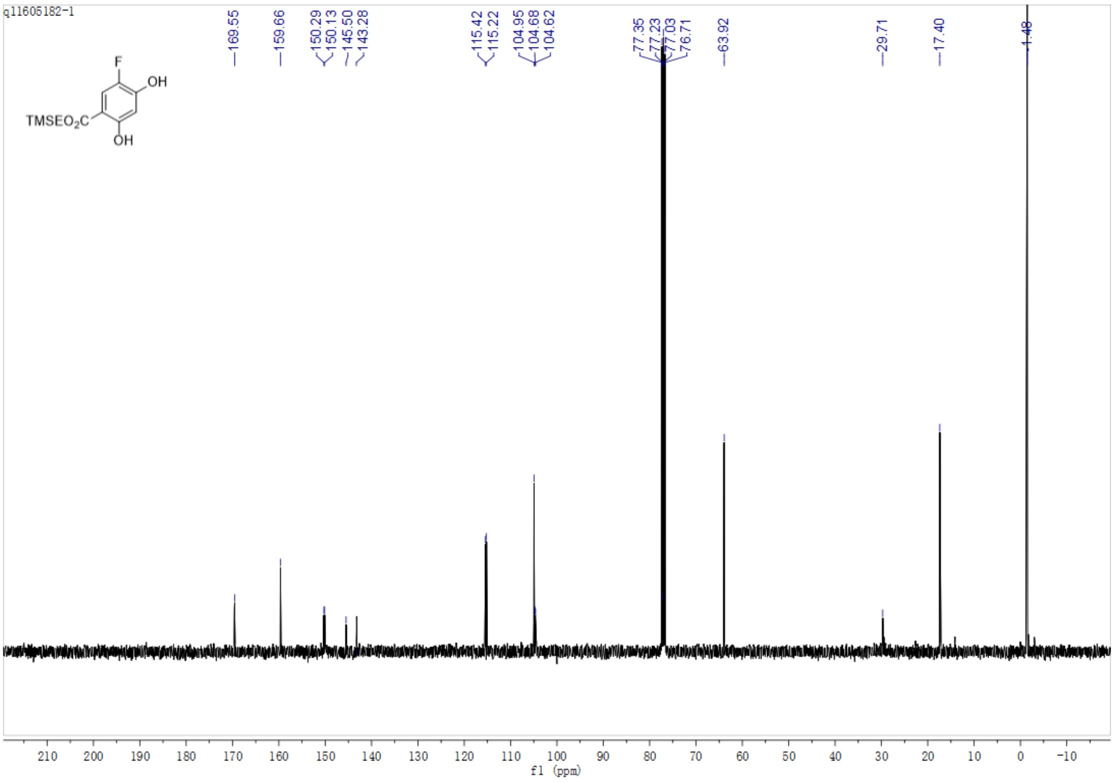


**Figure S43**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **S11** in CDCl$_3$.

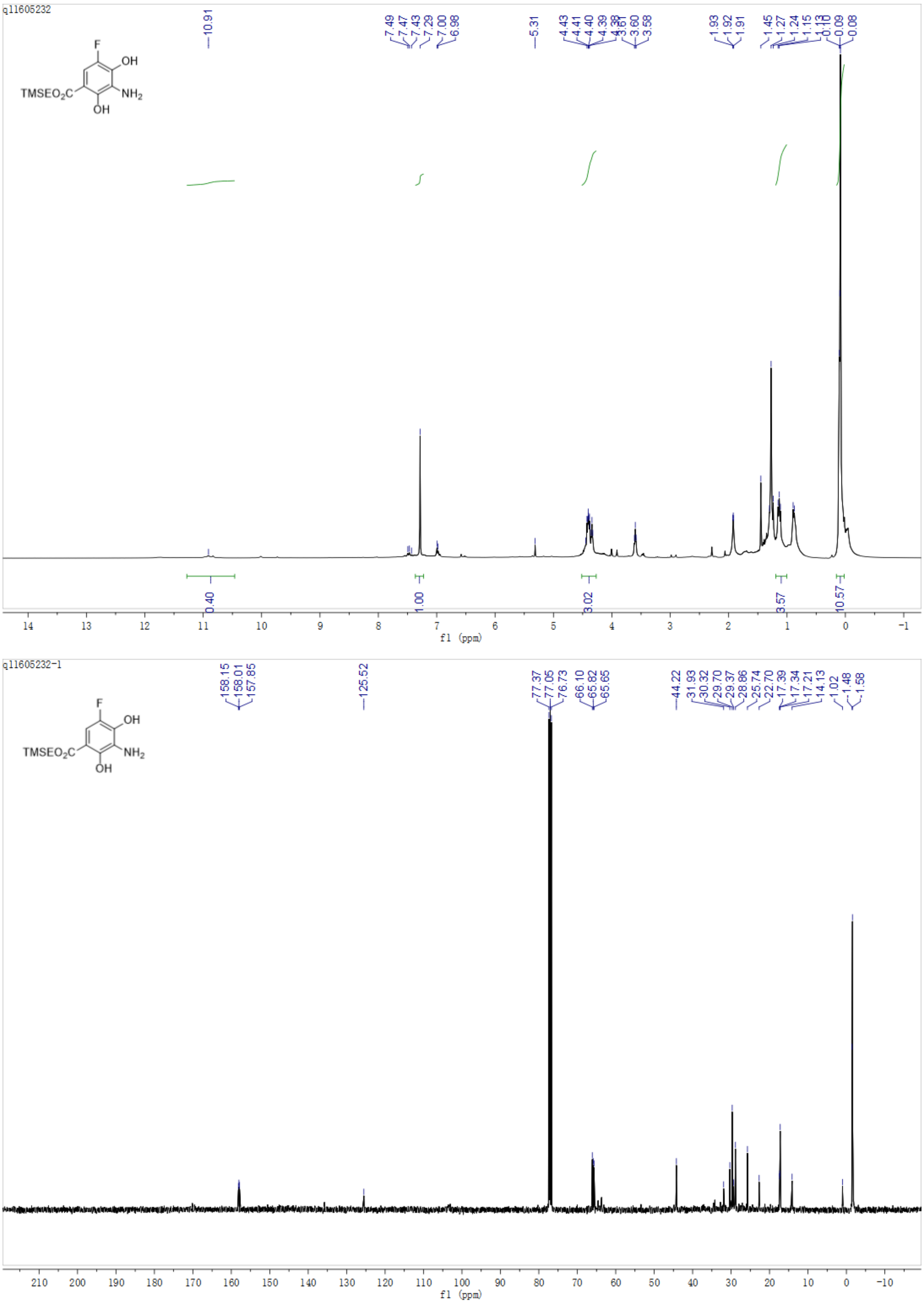


**Figure S44**. $^1$H NMR (400 MHz) and $^{13}$C NMR (126 MHz)spectrum of **18** in MeOD.

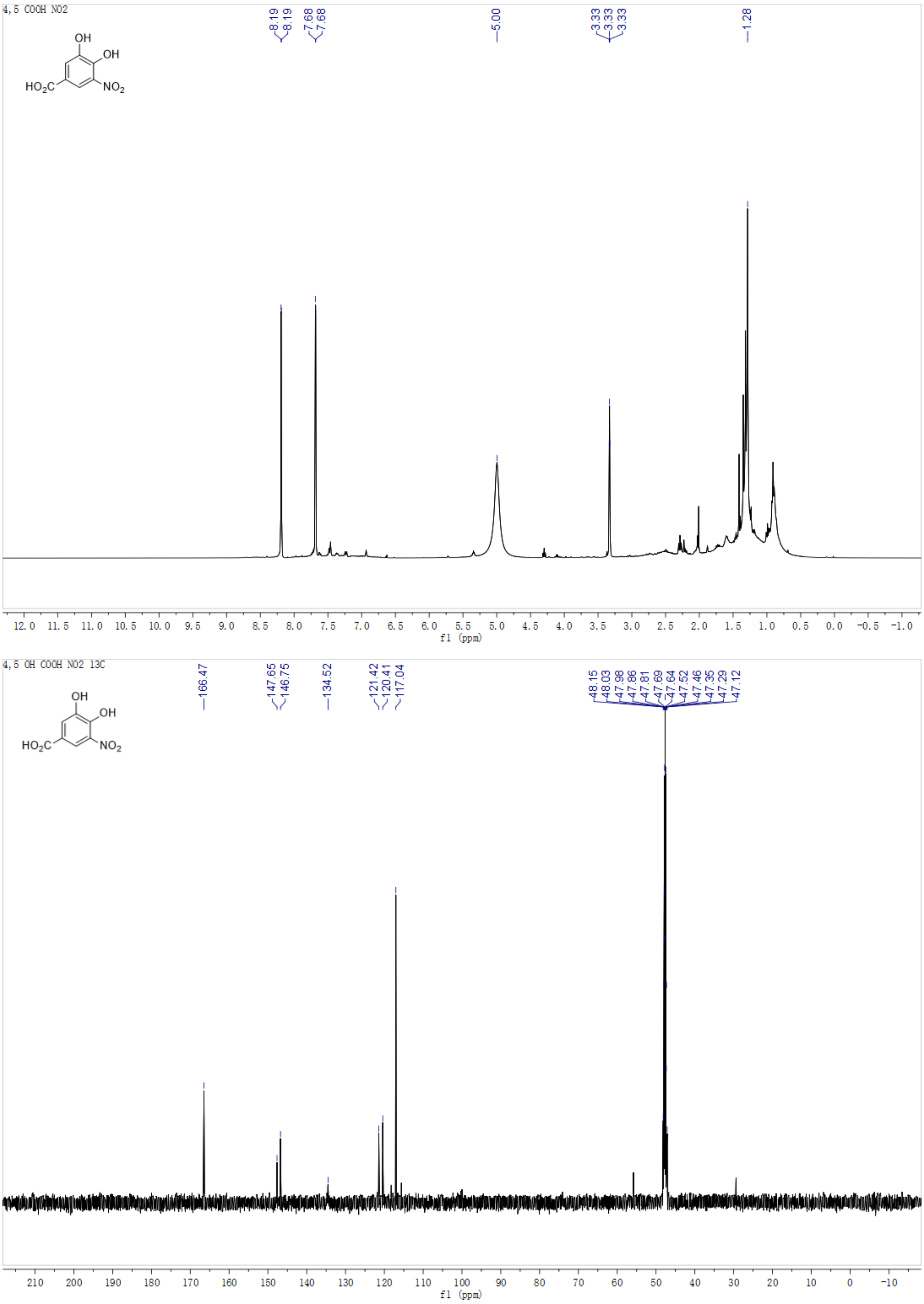


**Figure S45**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **S13** in $CDCl_3$.

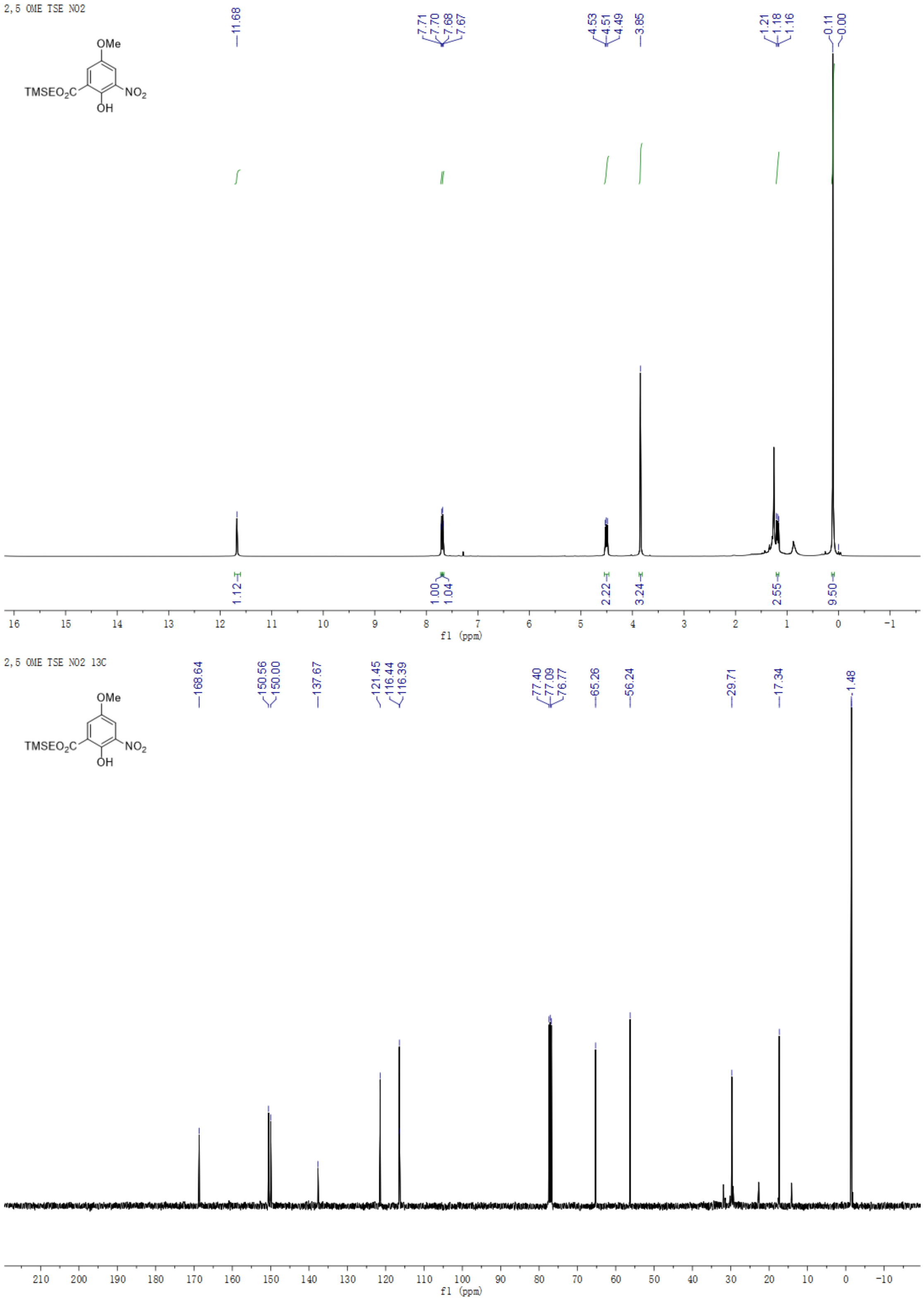


**Figure S46**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **S15** in DMSO-$d_6$

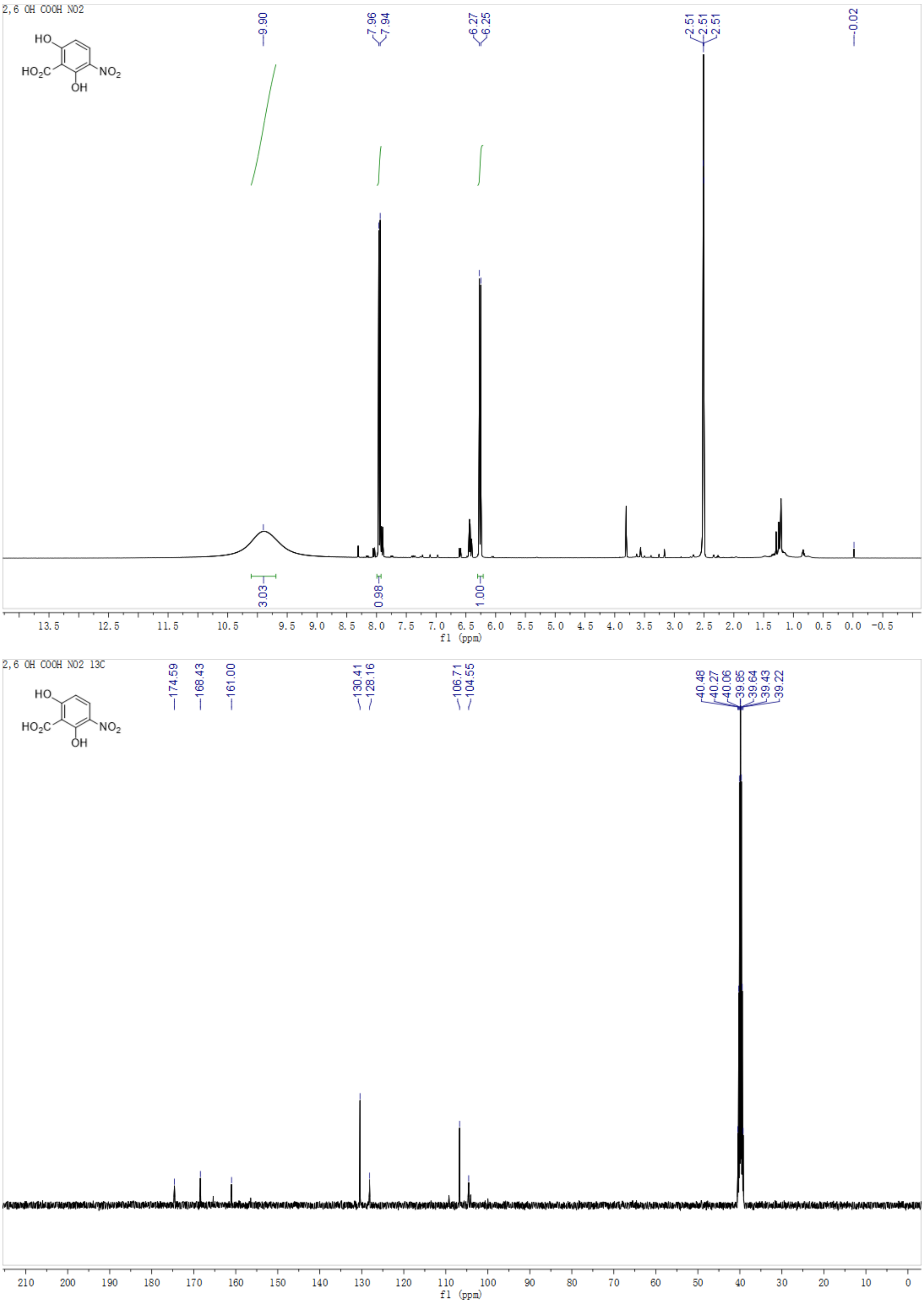


**Figure S47**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **S18** in $CDCl_3$.

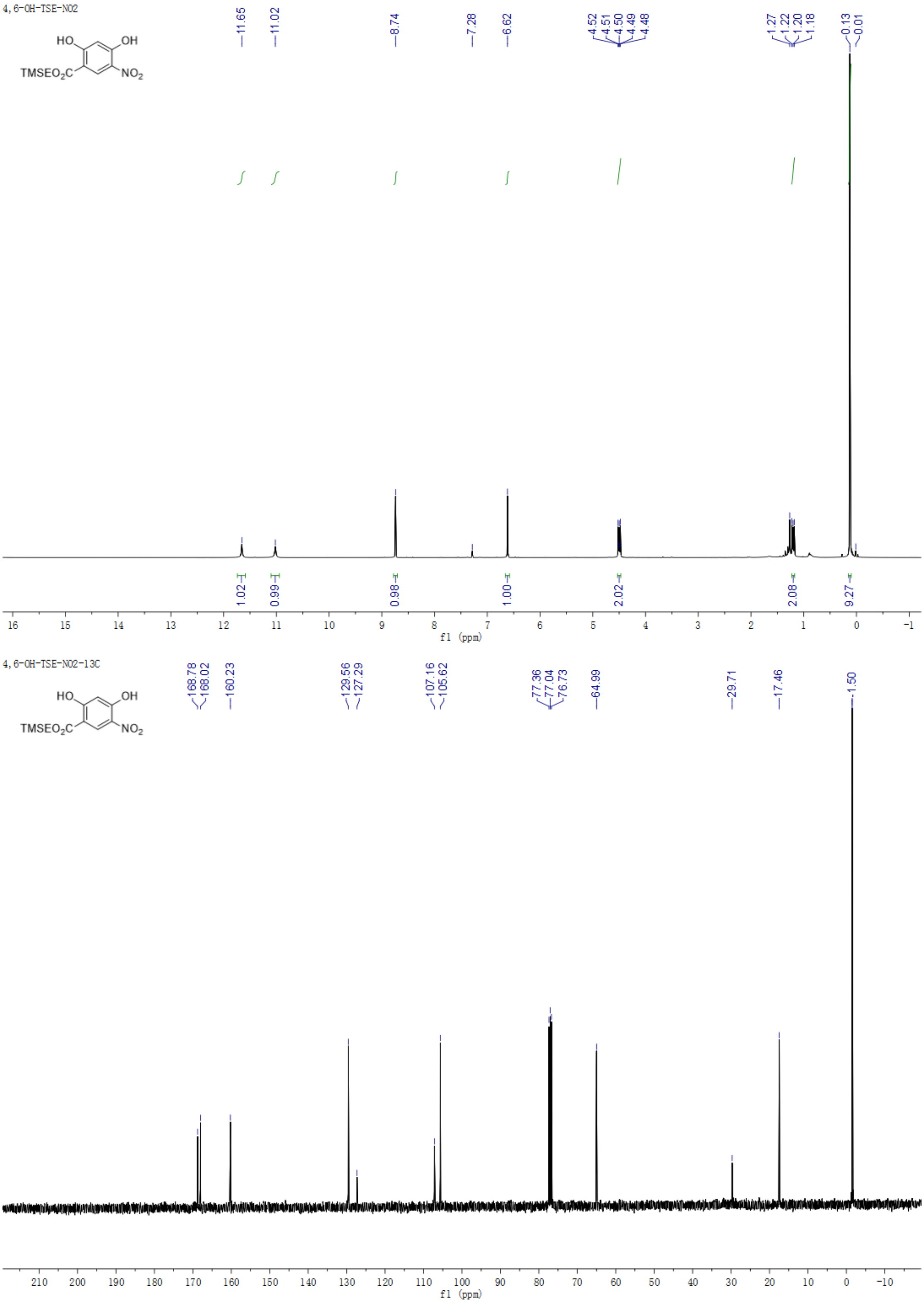
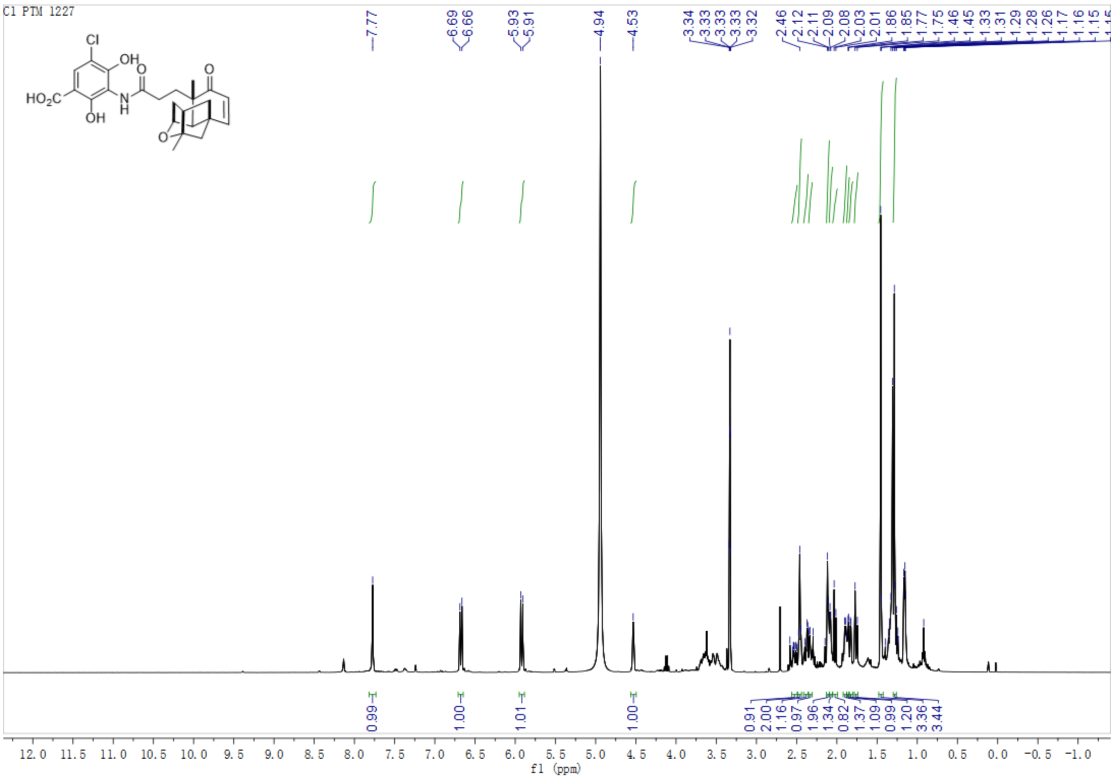


**Figure S48**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **s-4f** in MeOD.



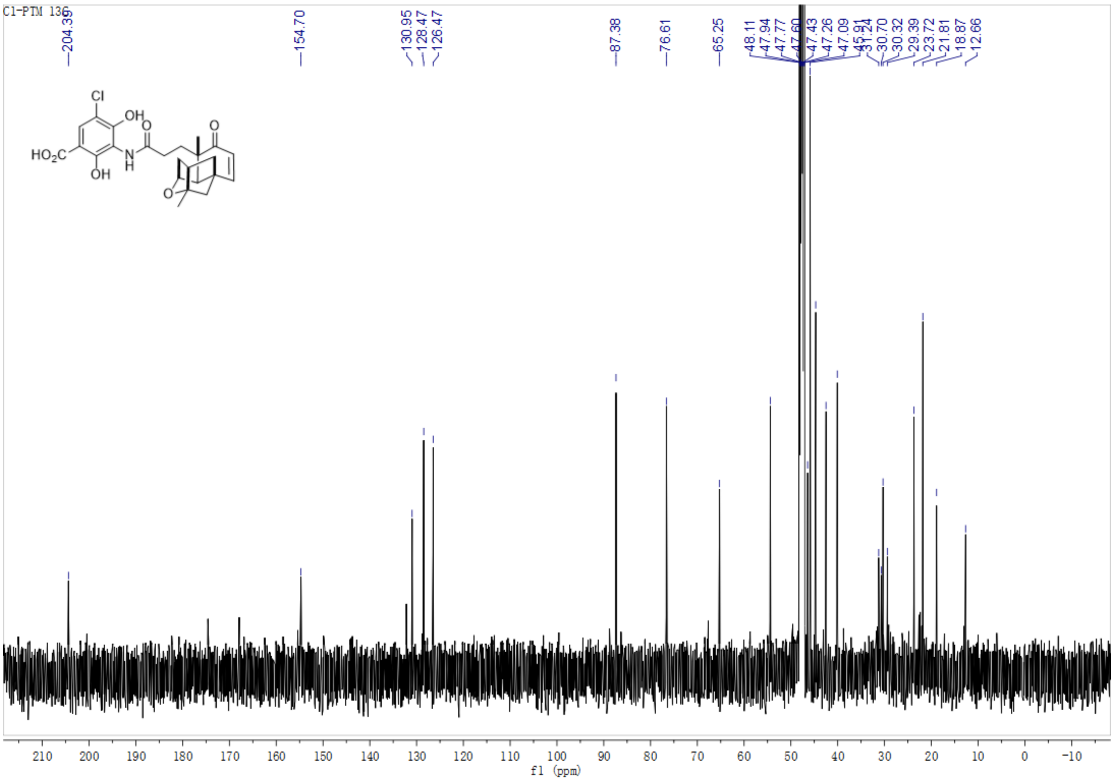


**Figure S49**. $^1$H–$^{13}$C HSQC spectrum of **s-4f** in MeOD

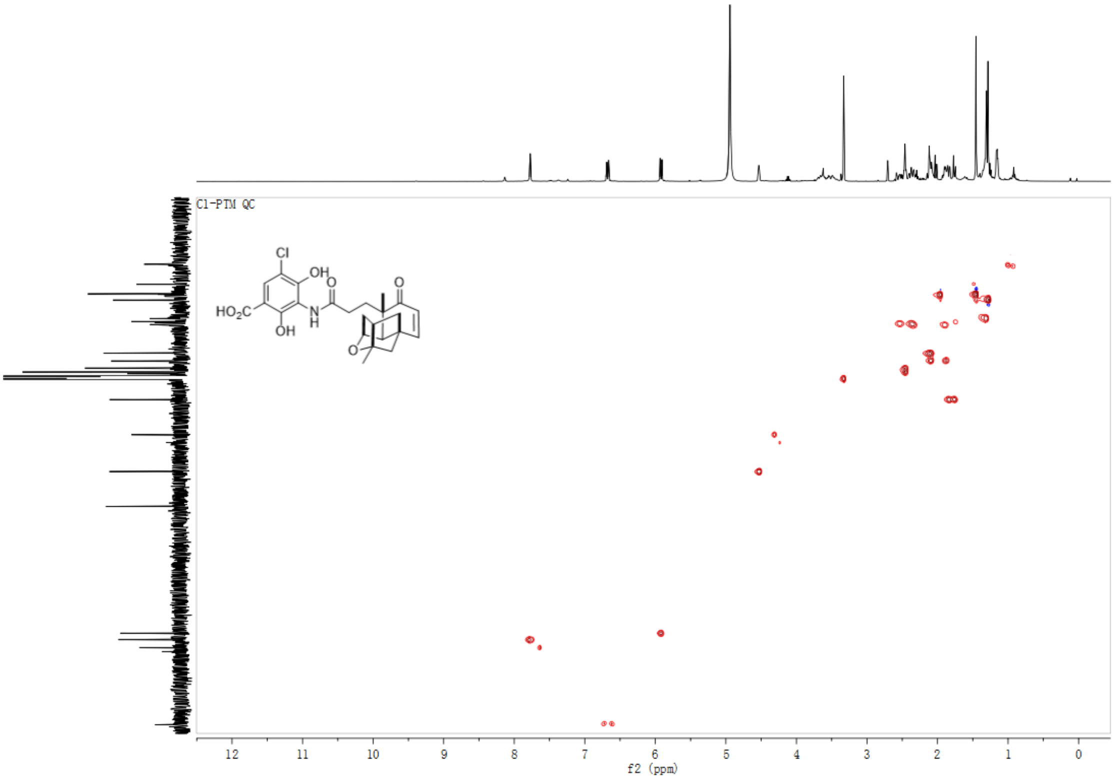
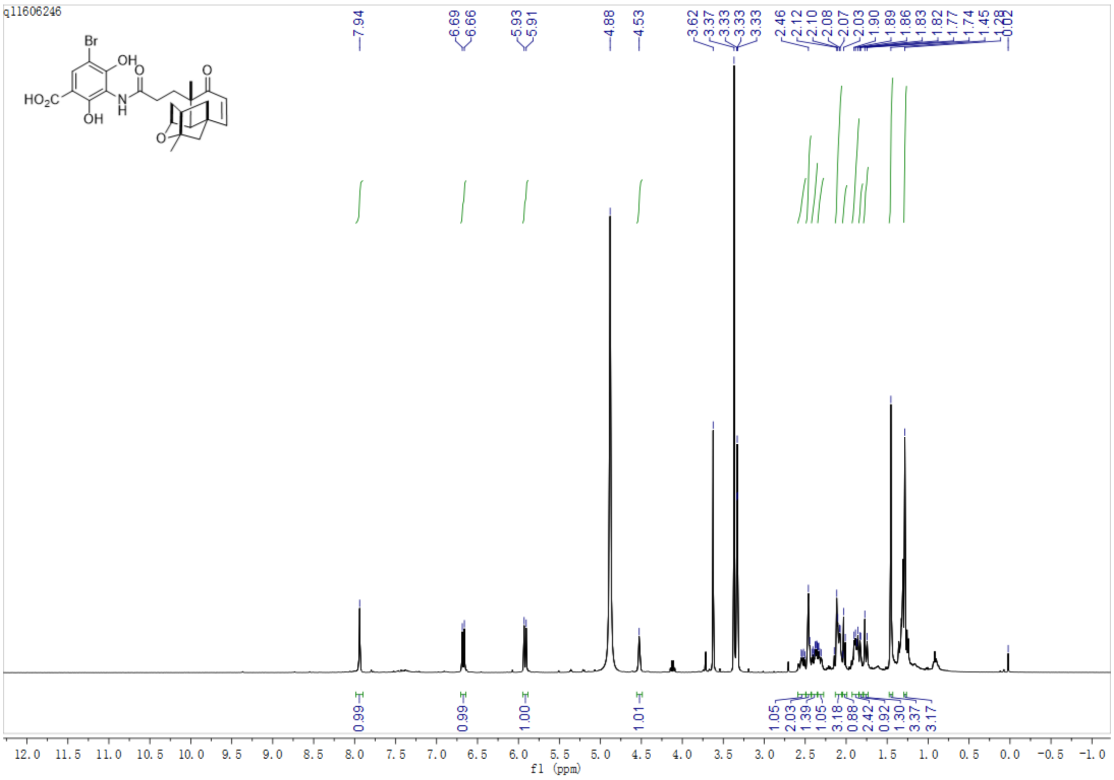


**Figure S50**. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectrum of **s-4h** in MeOD.



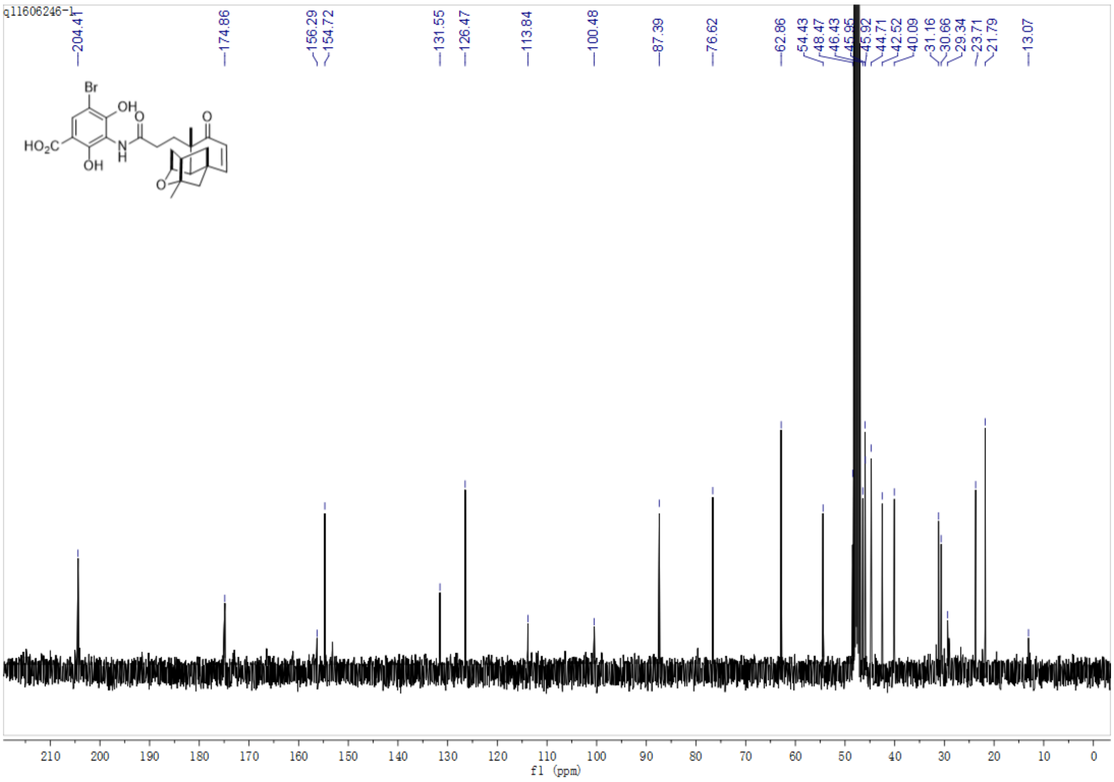


**Figure S51**. $^1$H–$^{13}$C HSQC spectrum of **s-4h** in MeOD

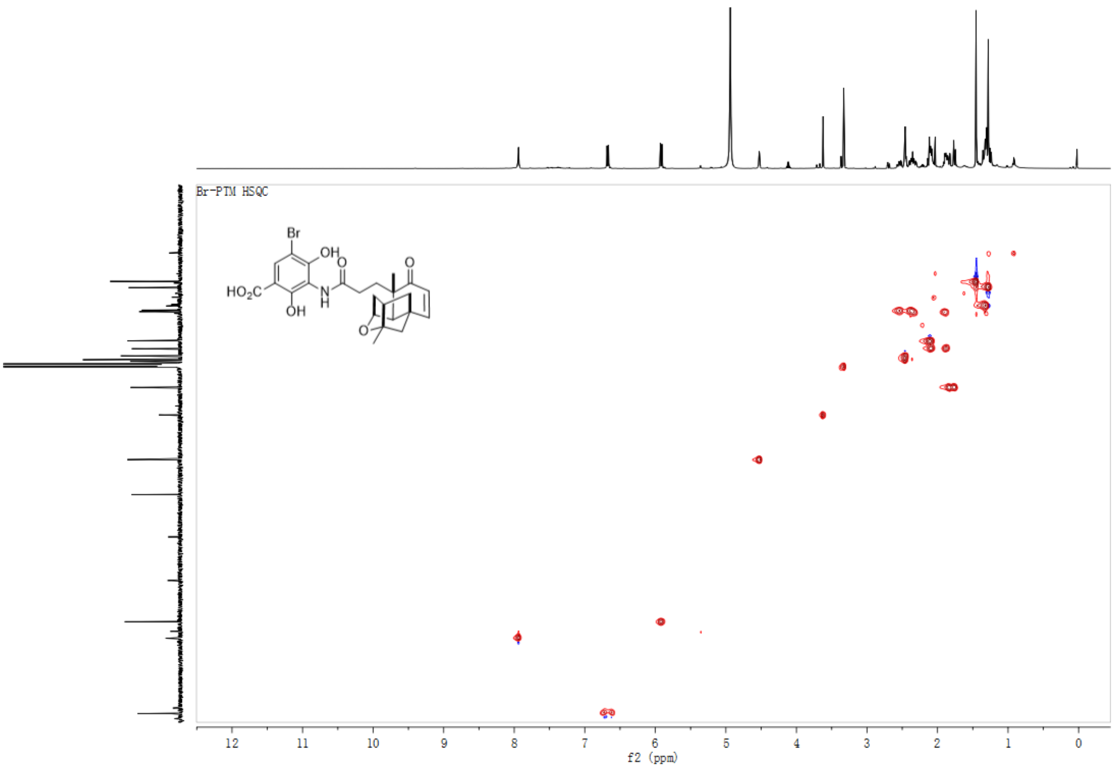
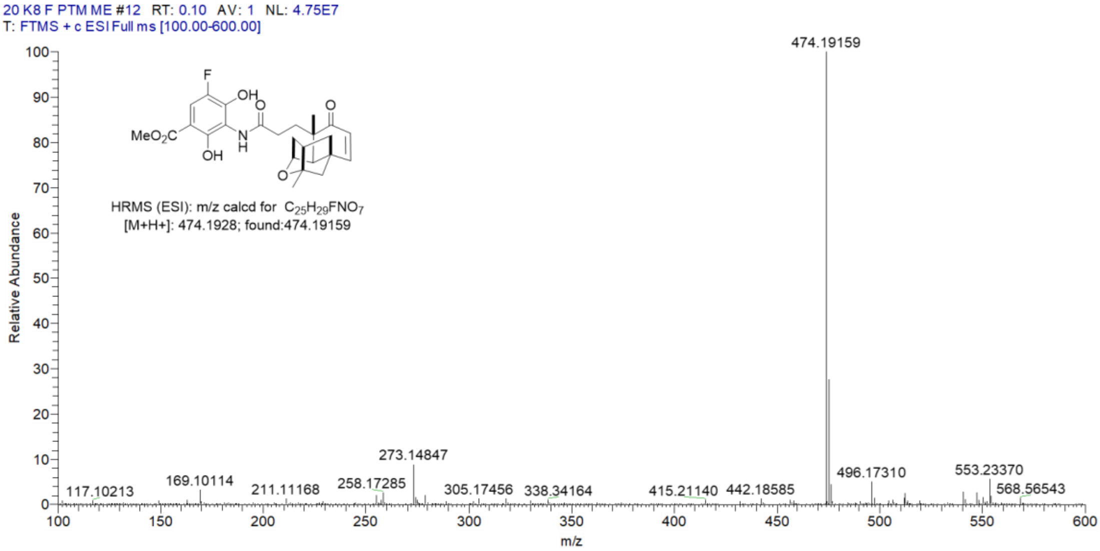
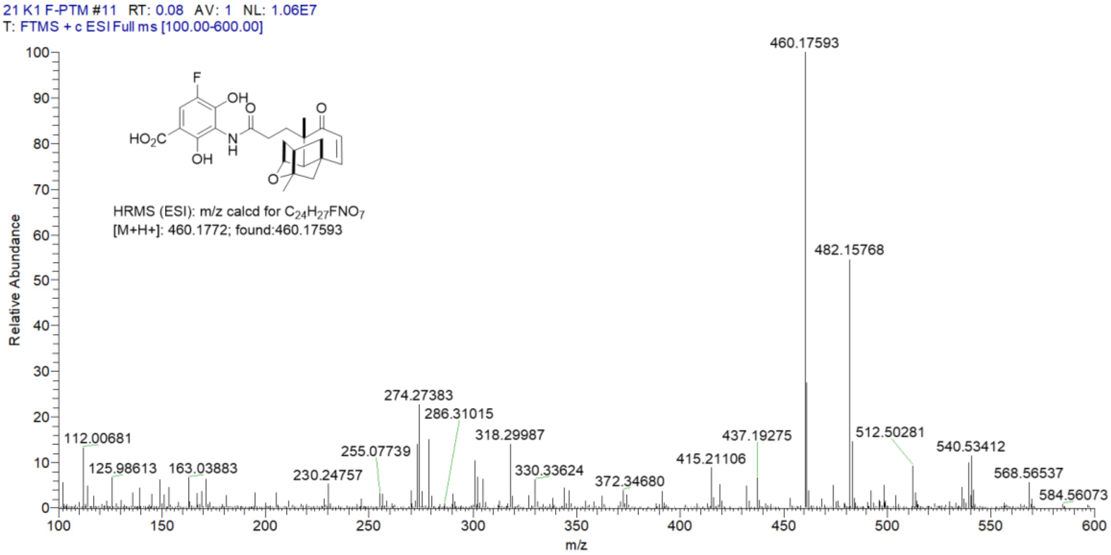


**Figure S52**. HRMS spectrum of **7a**



HRMS (ESI): m/z calcd for $C_{25}H_{29}FNO_7$ [M+H+]: 474.1928; found:474.19159

**Figure S53**. HRMS spectrum of **7b**



HRMS (ESI): m/z calcd for $C_{24}H_{27}FNO_7$ [M+H+]: 460.1772; found:460.17593

**Figure S54**. HRMS spectrum of **8**

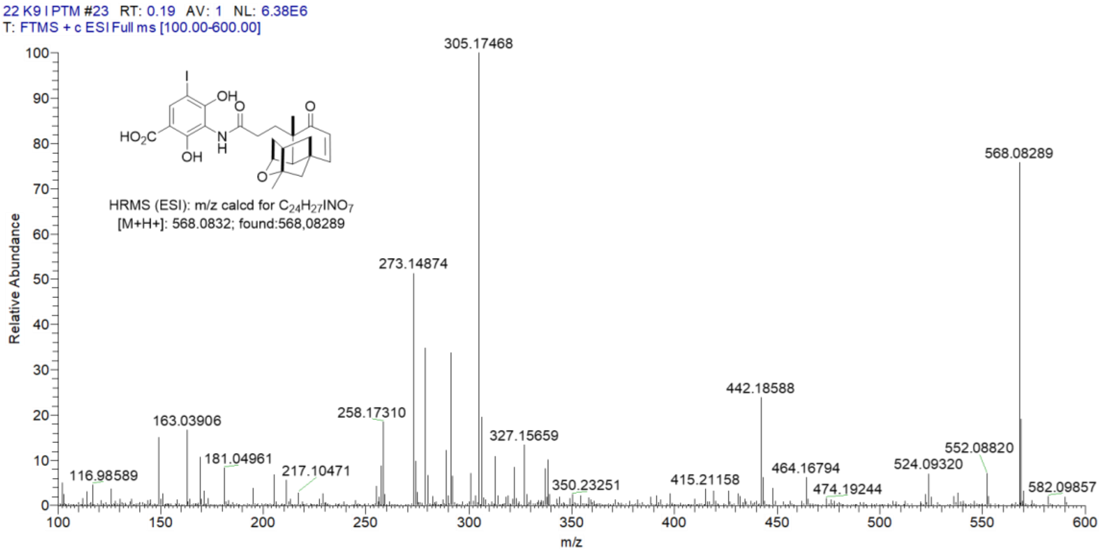


**Figure S55**. HRMS spectrum of **9**

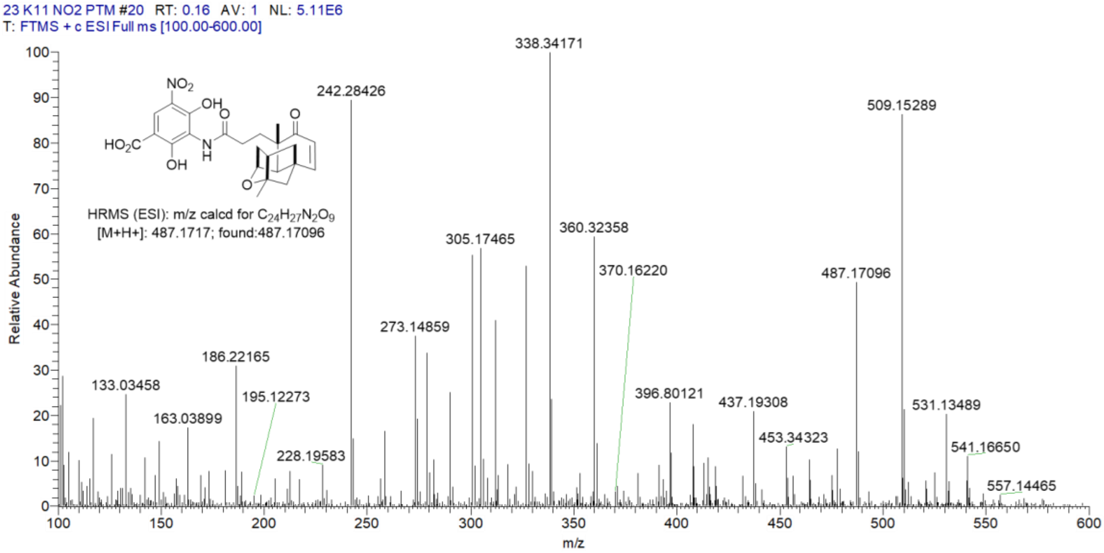


**Figure S56**. HRMS spectrum of **10a**

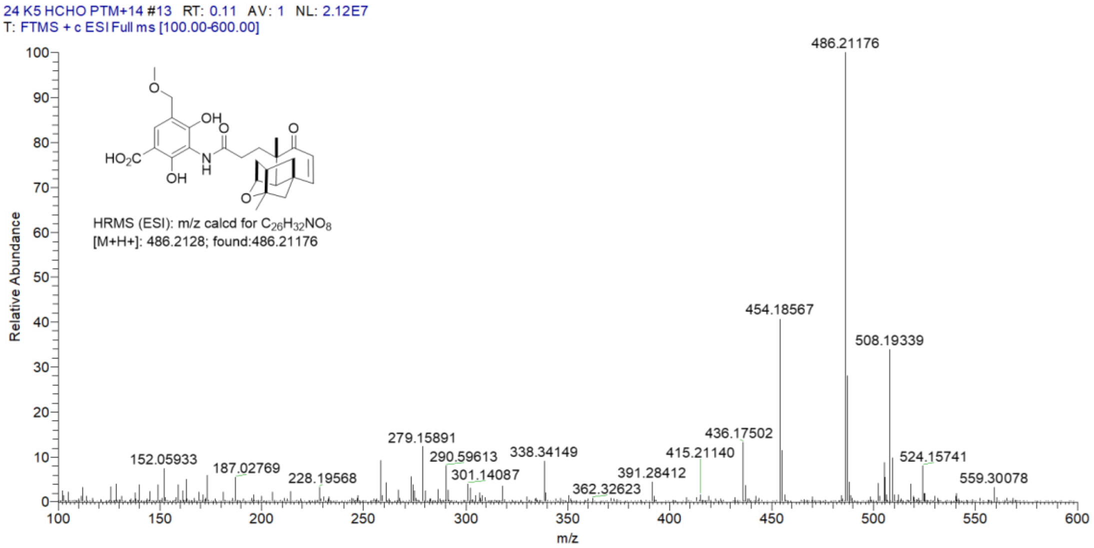


**Figure S57**. HRMS spectrum of **10b**

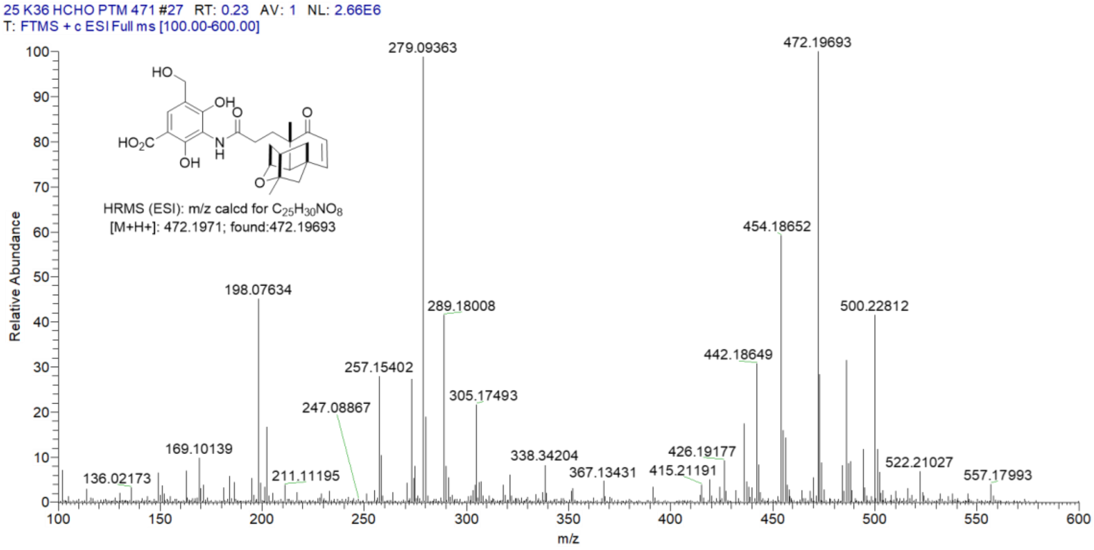


**Figure S58**. HRMS spectrum of **25a**

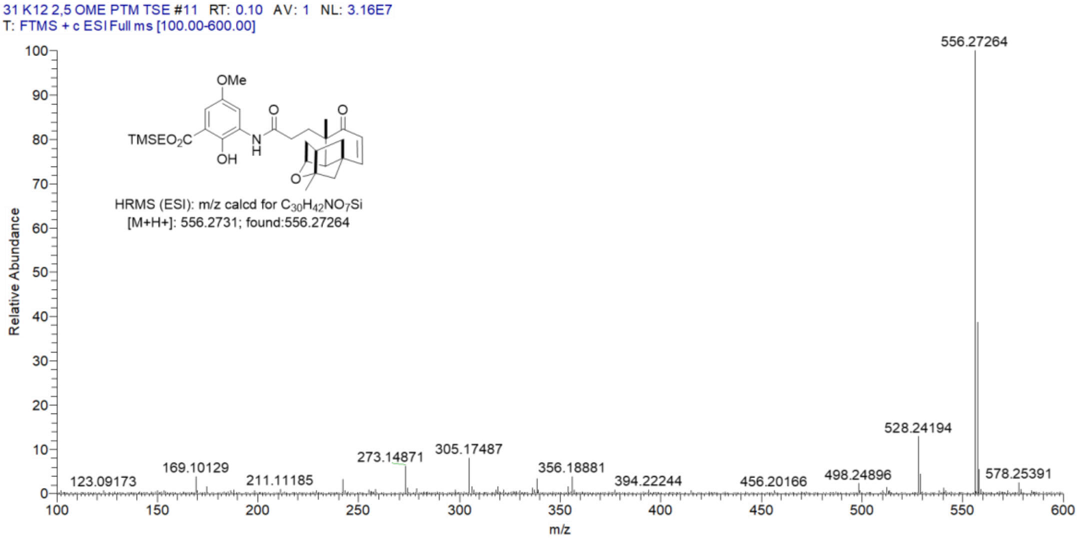


**Figure S59**. HRMS spectrum of **26a**

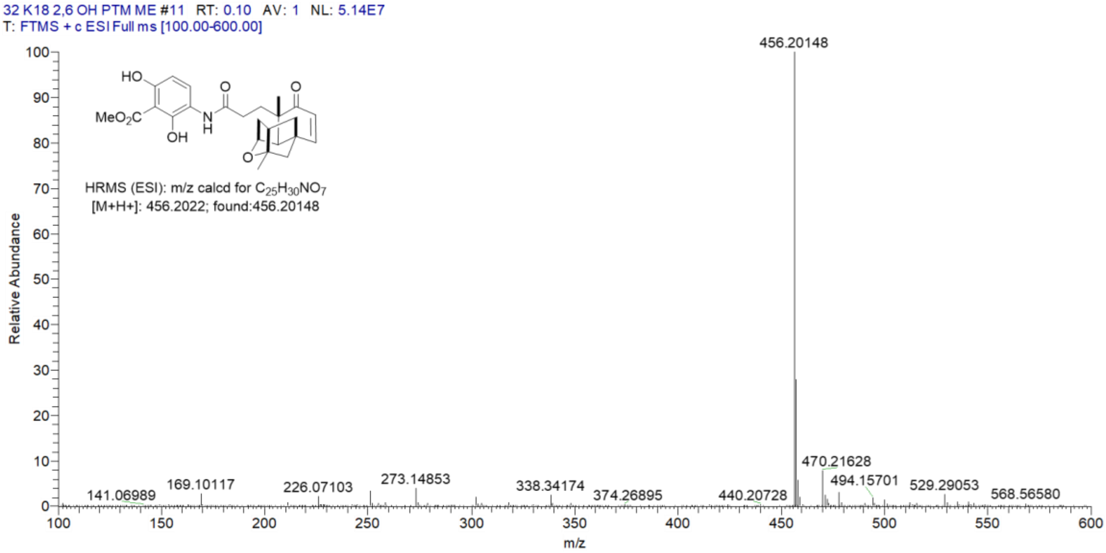
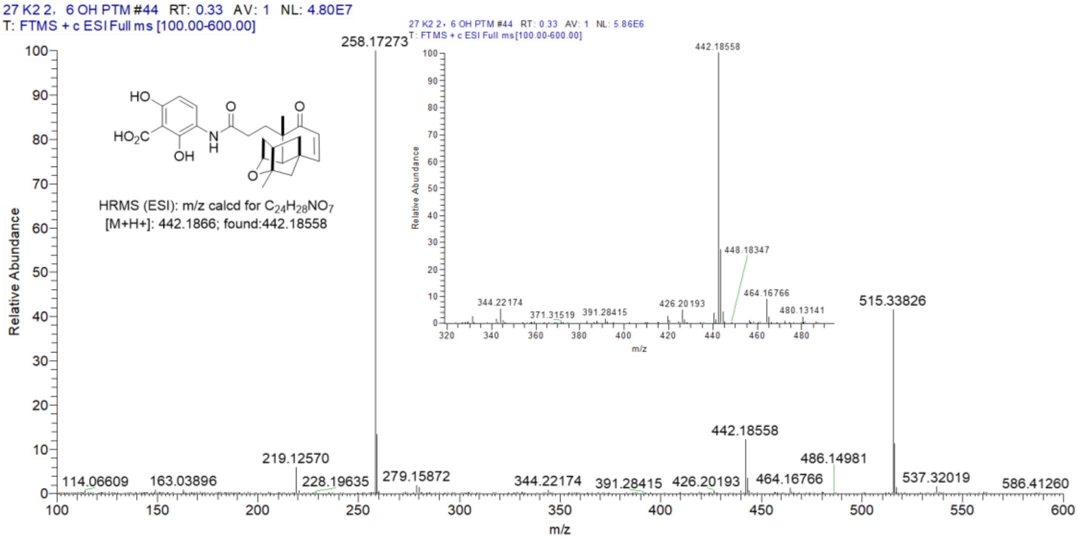
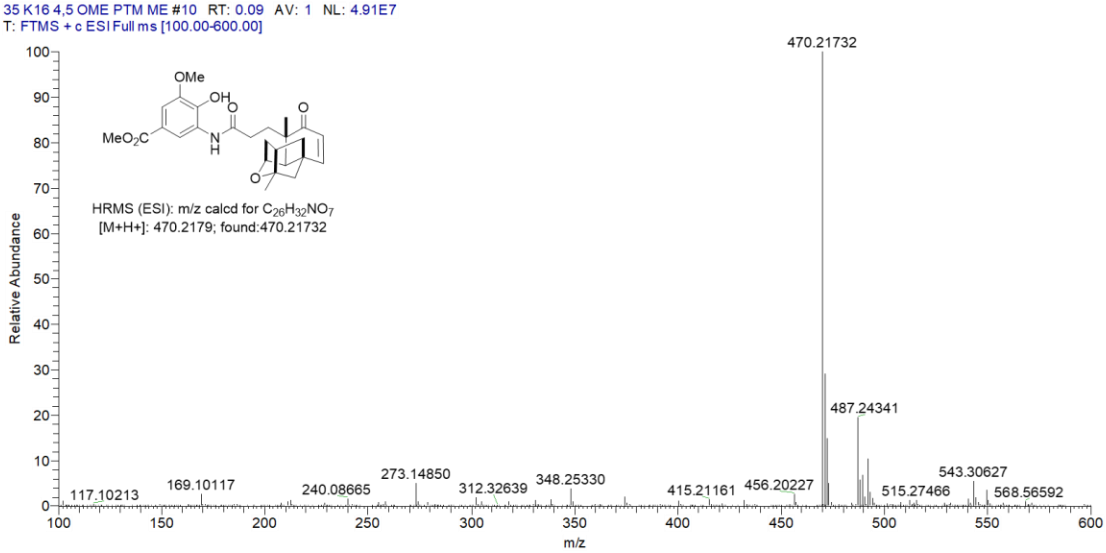


**Figure S60**. HRMS spectrum of **26b**



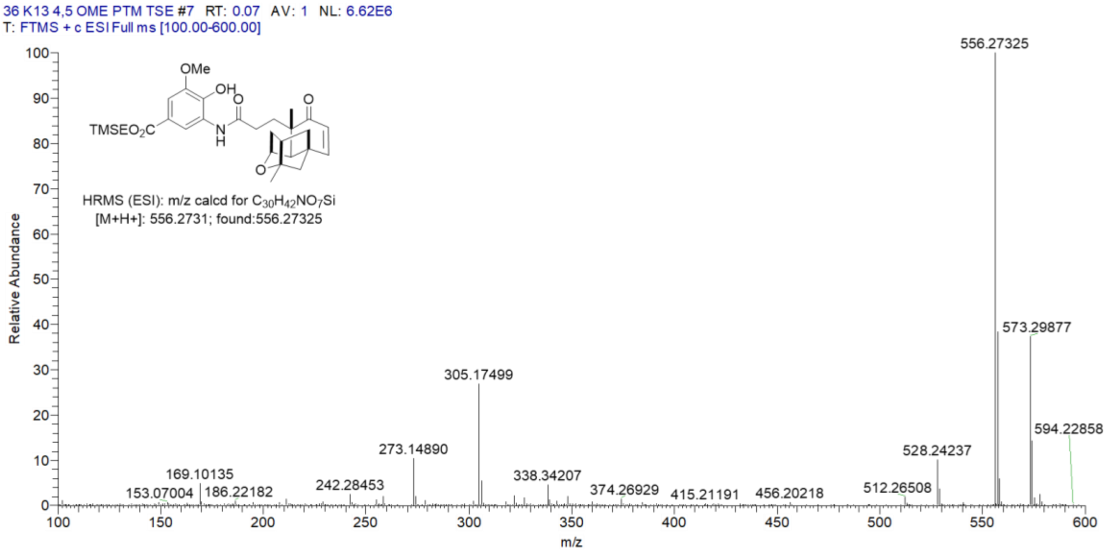
HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_7$ [M+H+]: 442.1866; found:442.18558

**Figure S61**. HRMS spectrum of **27a**



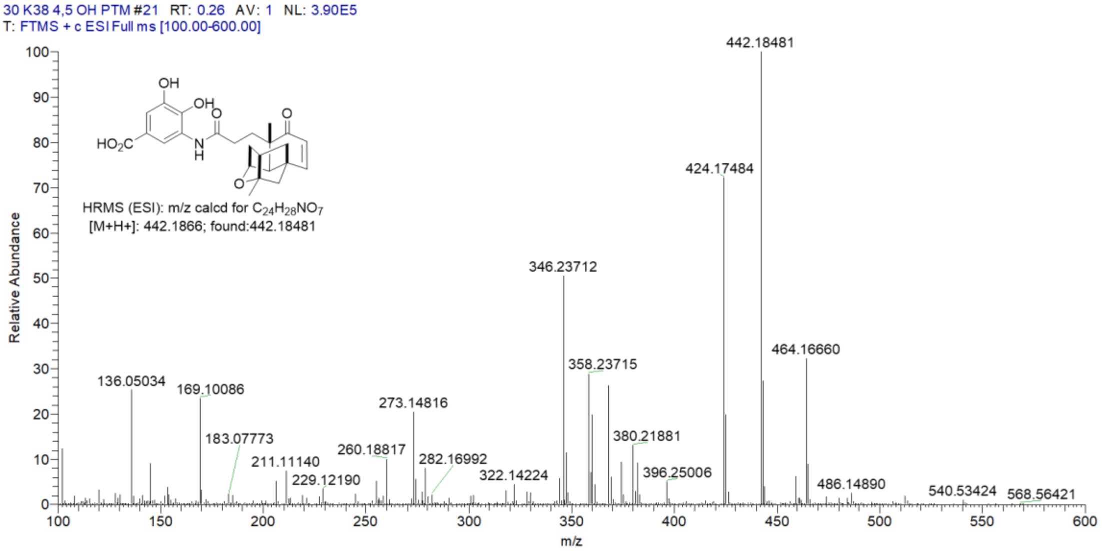
HRMS (ESI): m/z calcd for $C_{26}H_{32}NO_7$ [M+H+]: 470.2179; found:470.21732

**Figure S62**. HRMS spectrum of **27b**



HRMS (ESI): m/z calcd for $C_{30}H_{42}NO_7Si$ [M+H+]: 556.2731; found:556.27325

**Figure S63.** HRMS spectrum of **28**



HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_7$ [M+H+]: 442.1866; found:442.18481

**Figure S64**. HRMS spectrum of **29a**

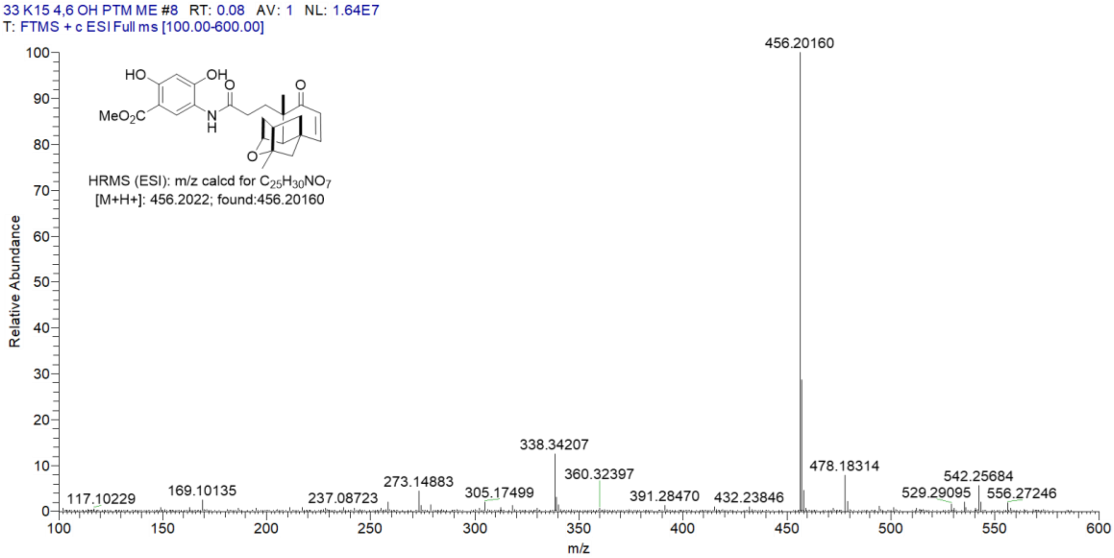


**Figure S65**. HRMS spectrum of **30**

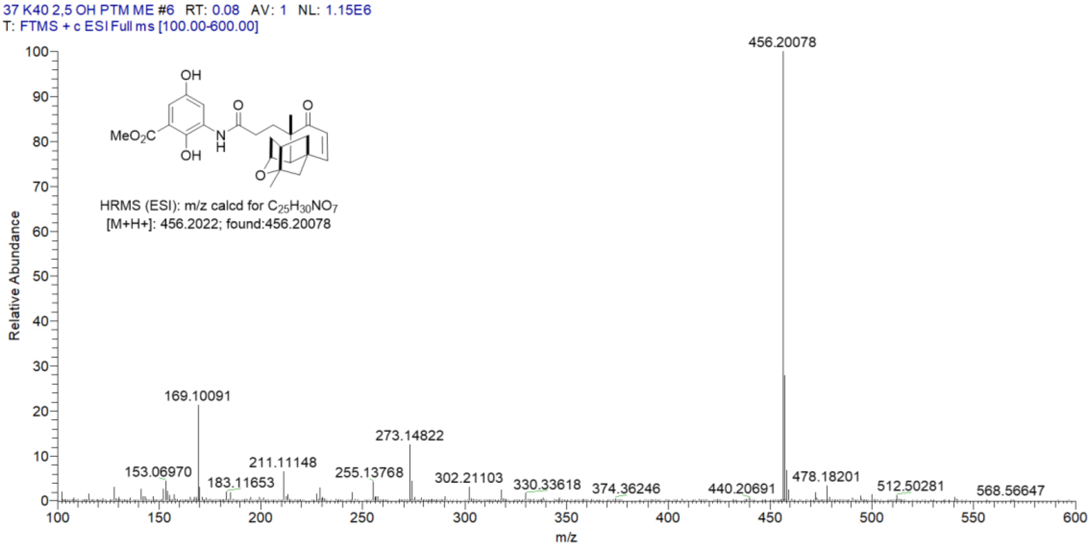
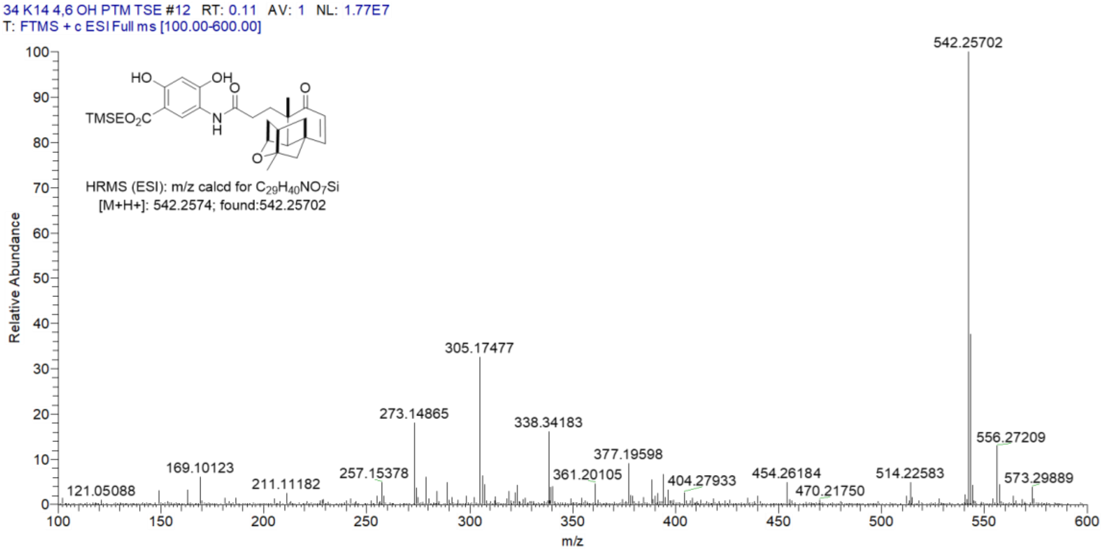


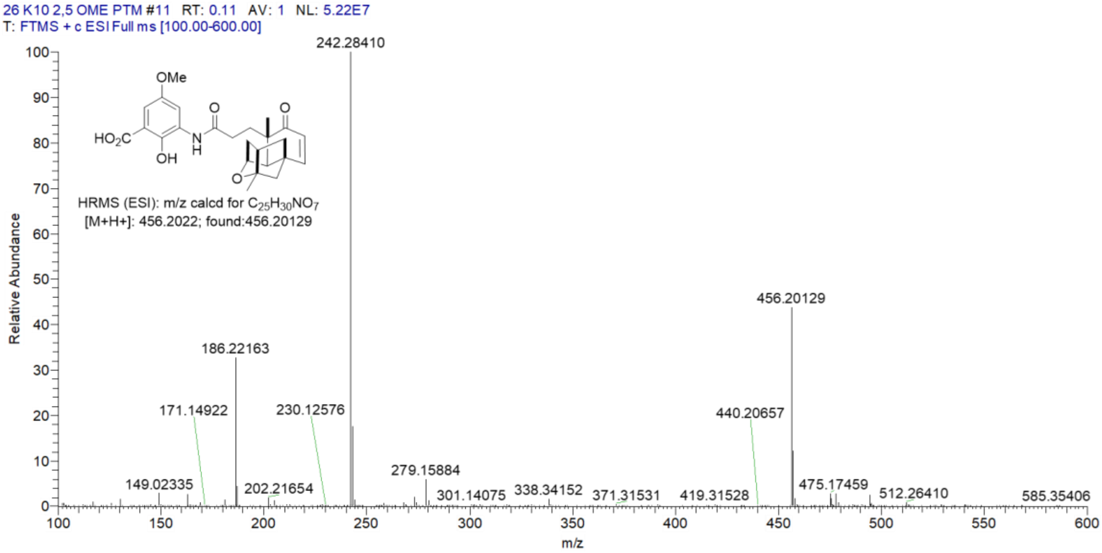
**Figure S66**. HRMS spectrum of **29b**



34 K14 4,6 OH PTM TSE #12 RT: 0.11 AV: 1 NL: 1.77E7
T: FTMS + c ESI Full ms [100.00-600.00]

HRMS (ESI): m/z calcd for $C_{29}H_{40}NO_7Si$ [M+H+]: 542.2574; found:542.25702

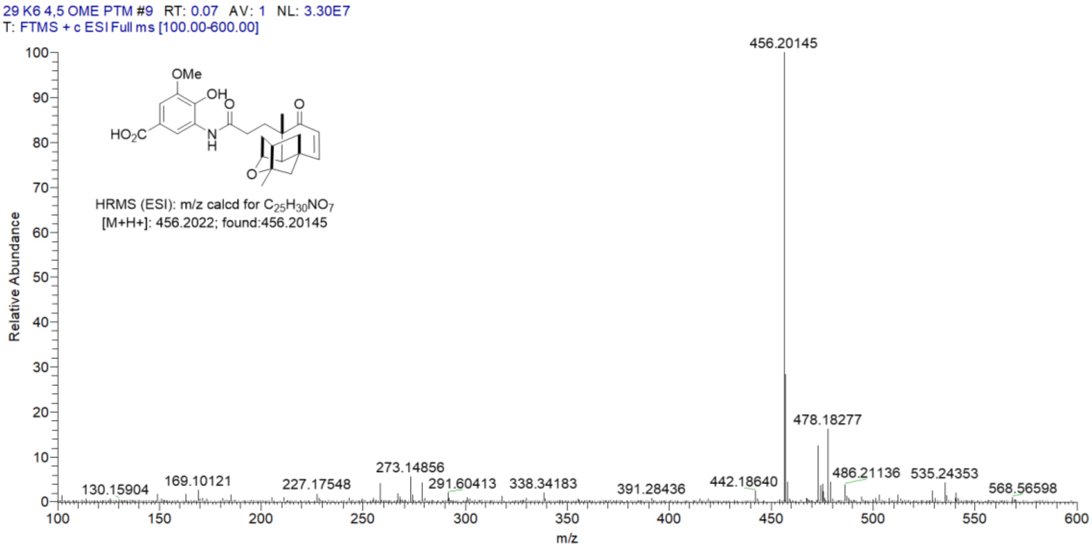
**Figure S67**. HRMS spectrum of **25b**



26 K10 2,5 OME PTM #11 RT: 0.11 AV: 1 NL: 5.22E7
T: FTMS + c ESI Full ms [100.00-600.00]

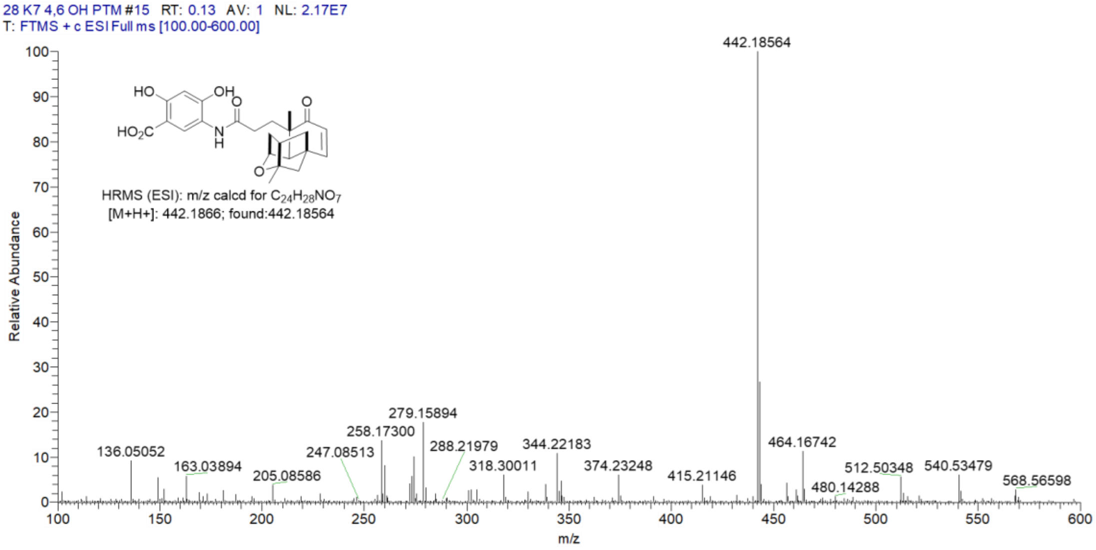
HRMS (ESI): m/z calcd for $C_{25}H_{30}NO_7$ [M+H+]: 456.2022; found:456.20129

**Figure S68**. HRMS spectrum of **27c**



HRMS (ESI): m/z calcd for $C_{25}H_{30}NO_7$ [M+H+]: 456.2022; found:456.20145

**Figure S69**. HRMS spectrum of **29c**



HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_7$ [M+H+]: 442.1866; found:442.18564

**Figure S70**. HRMS spectrum of **5**

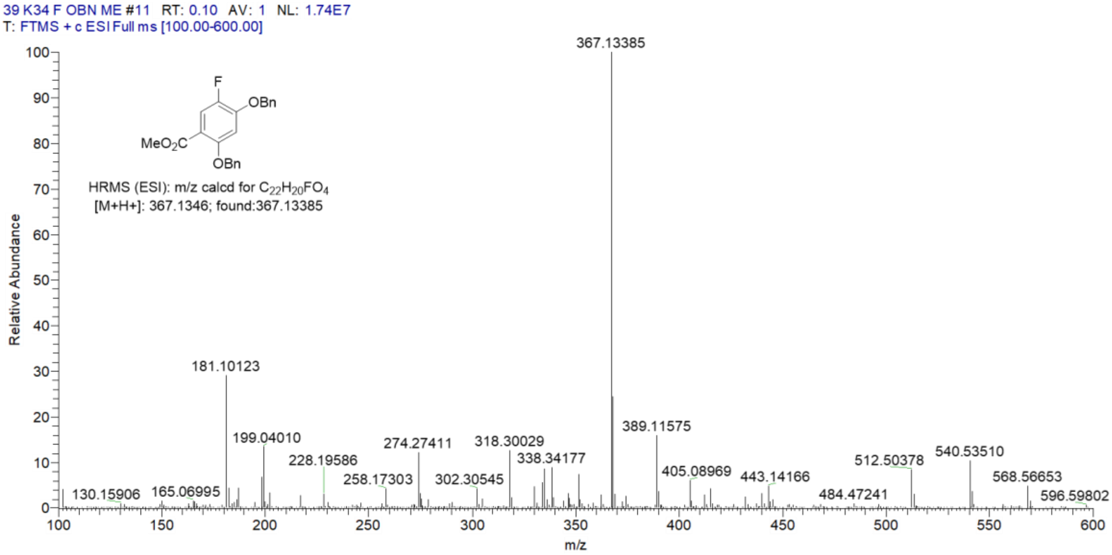


**Figure S71**. HRMS spectrum of **6**

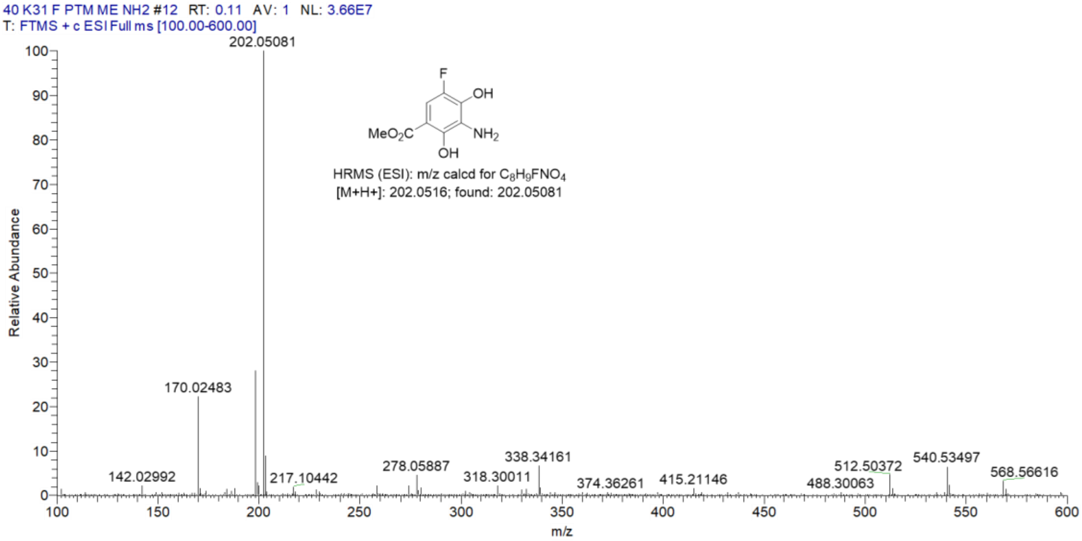


**Figure S72**. HRMS spectrum of **13**

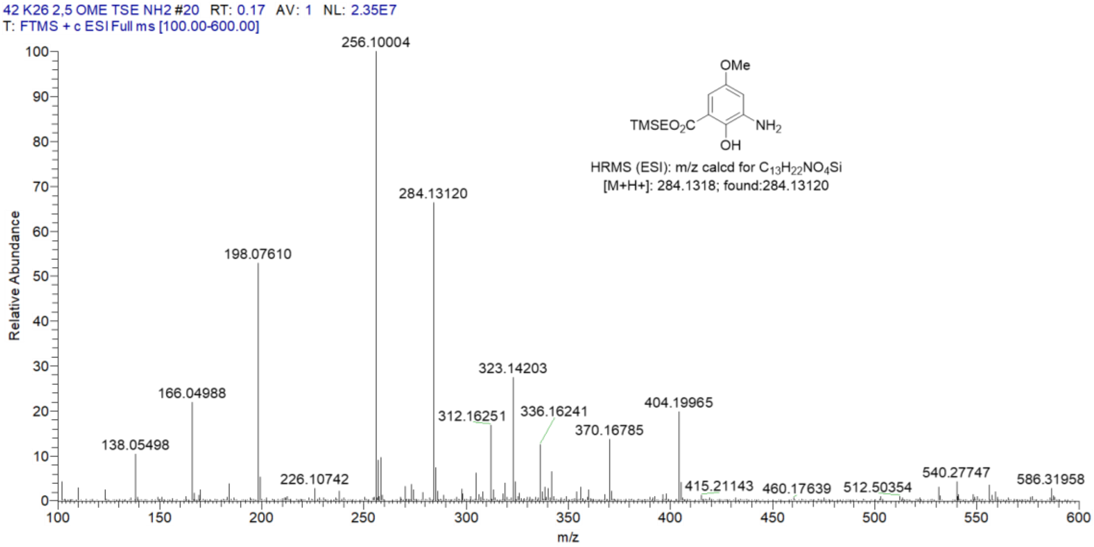


**Figure S73**. HRMS spectrum of **15a**

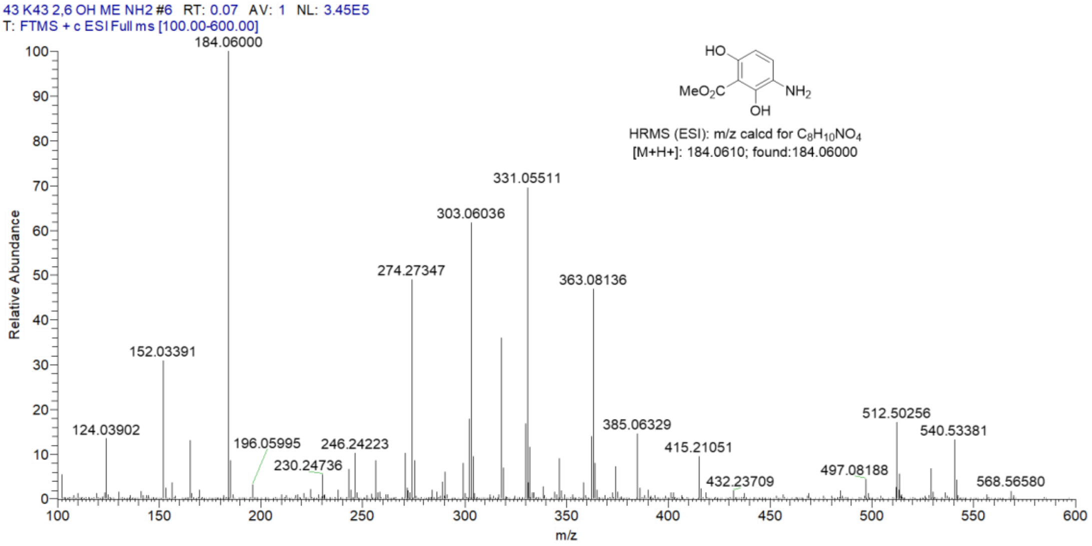


**Figure S74**. HRMS spectrum of **15b**

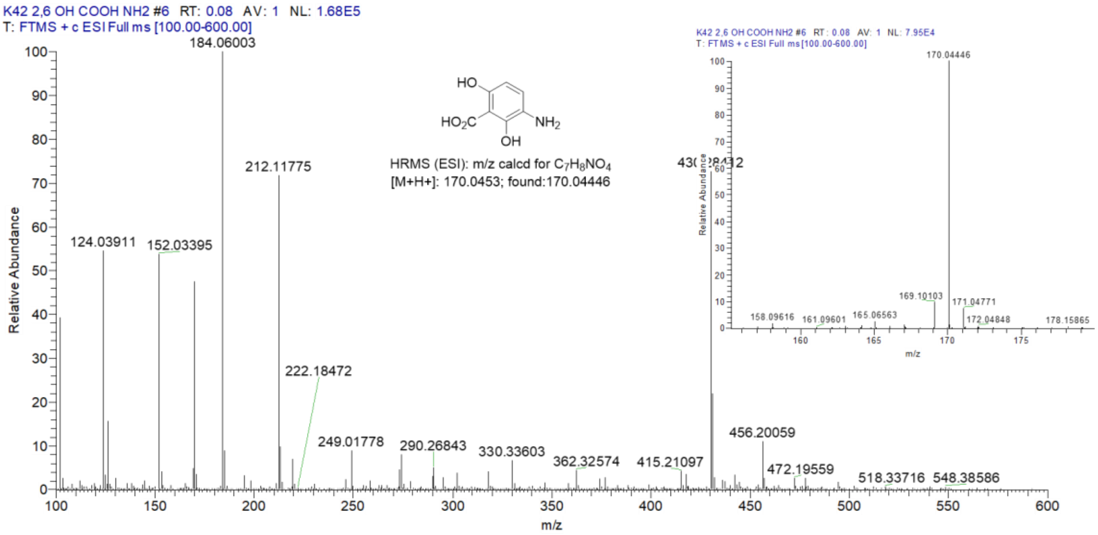


**Figure S75**. HRMS spectrum of **17a**

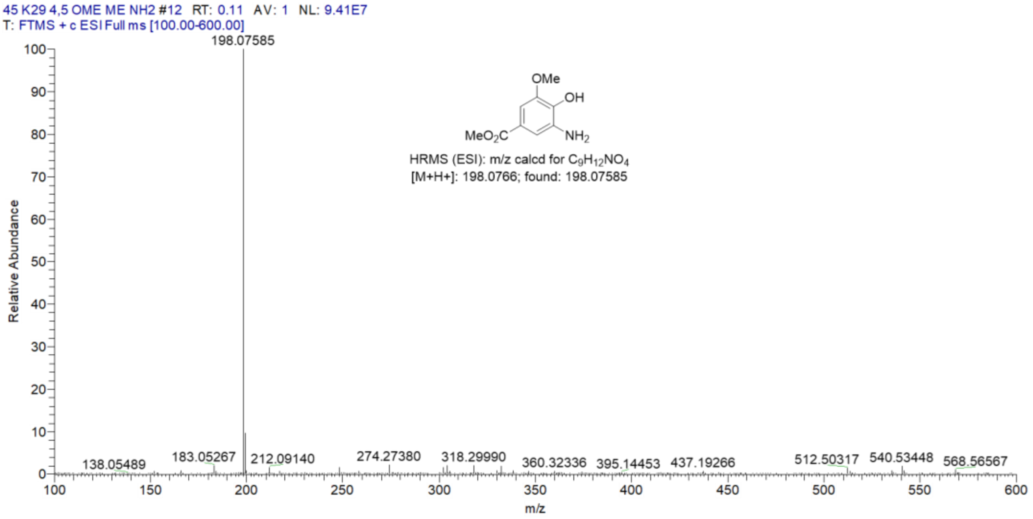
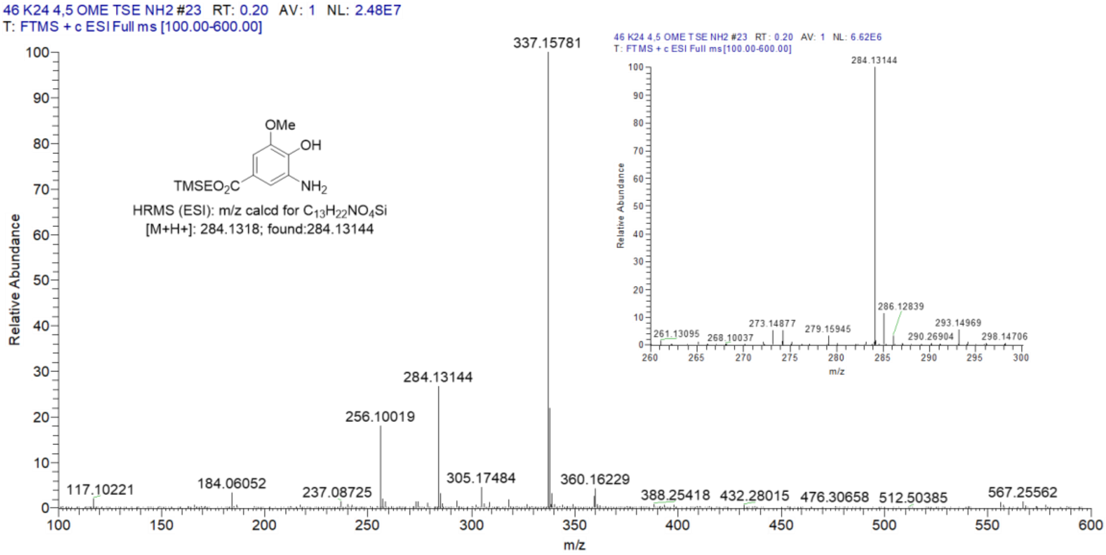
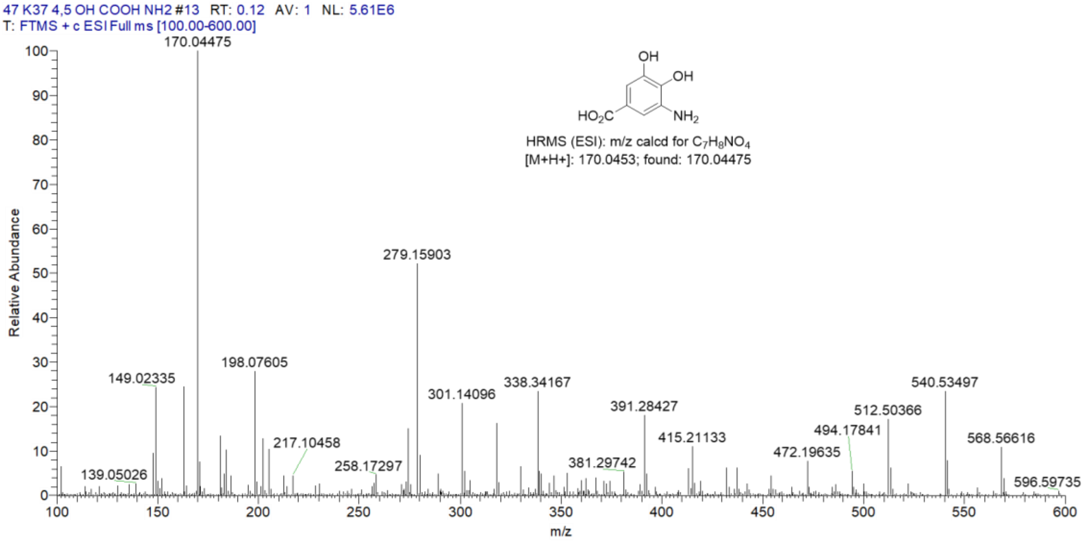


**Figure S76**. HRMS spectrum of **17b**



HRMS (ESI): m/z calcd for $C_{13}H_{22}NO_4Si$ [M+H+]: 284.1318; found:284.13144

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



HRMS (ESI): m/z calcd for $C_7H_8NO_4$ [M+H+]: 170.0453; found: 170.04475

**Figure S78**. HRMS spectrum of **21a**

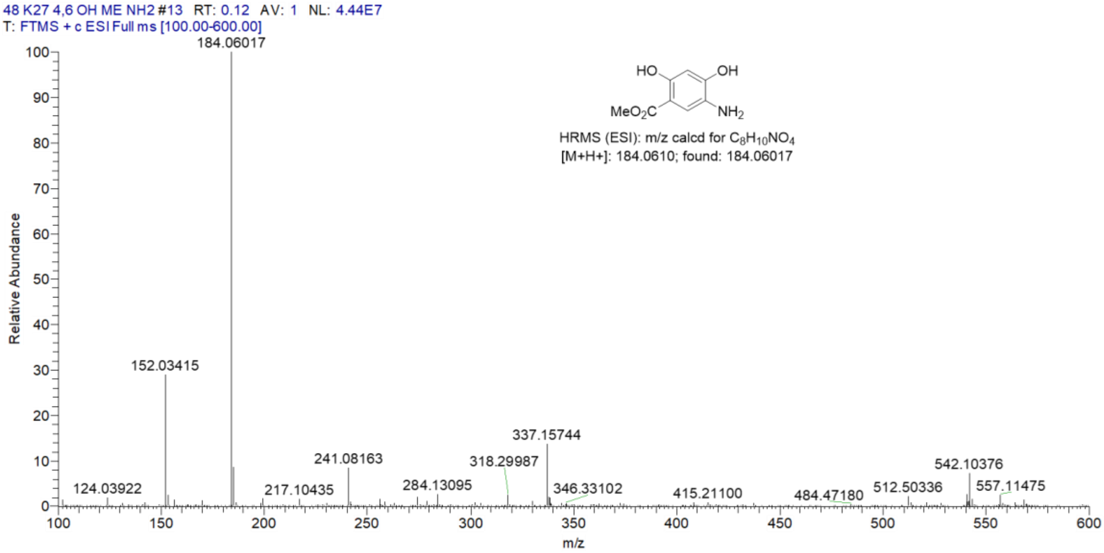


**Figure S79**. HRMS spectrum of **21b**

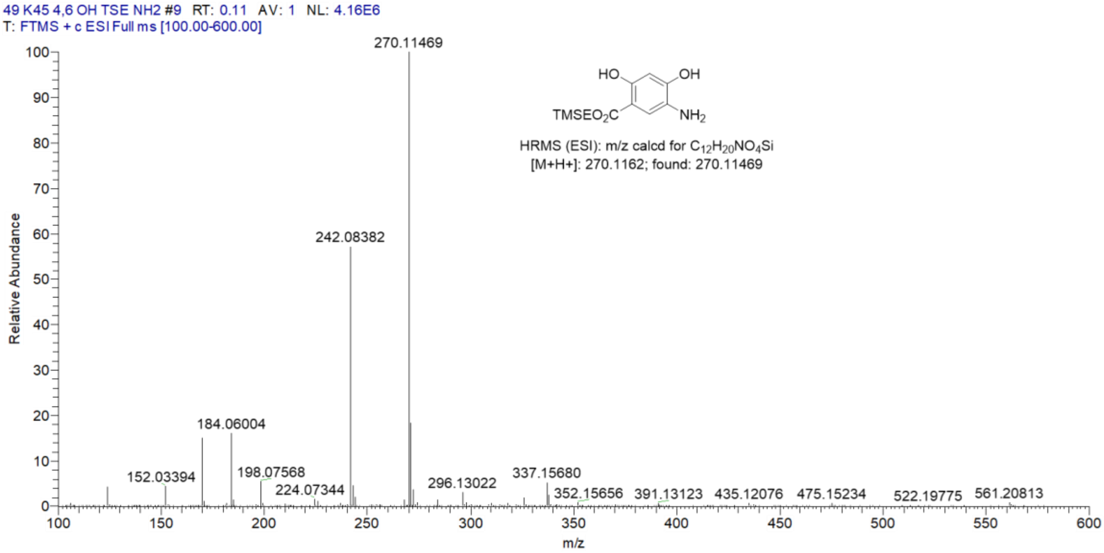
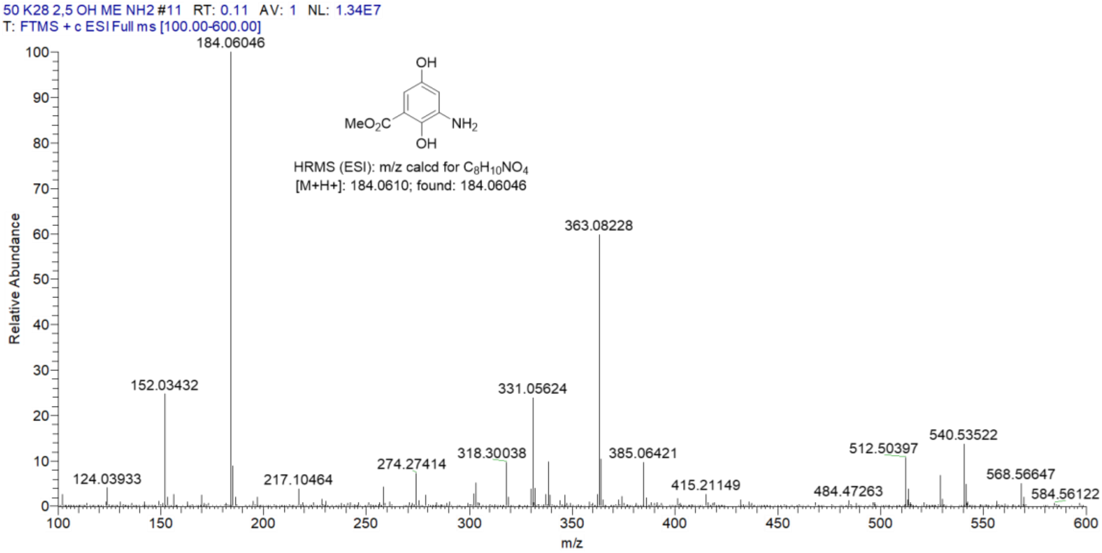
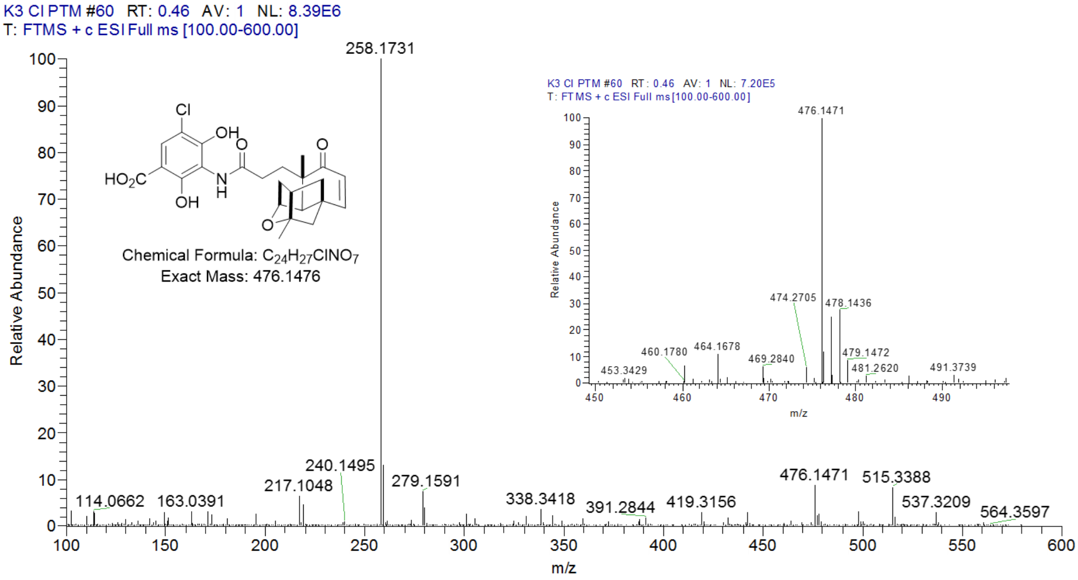


**Figure S80**. HRMS spectrum of **24**



HRMS (ESI): m/z calcd for $C_8H_{10}NO_4$ [M+H+]: 184.0610; found: 184.06046

**Figure S81**. HRMS spectrum of **s-4f**



Chemical Formula: $C_{24}H_{27}ClNO_7$
Exact Mass: 476.1476

**Figure S82**. HRMS spectrum of **s-4h**