# Supplementary Materials

## Anti-Multiple Myeloma Potential of Resynthesized Belinostat Derivatives: An Experimental Study on Cytotoxic Activity, Drug Combination and Docking Studies

Hong Phuong Nguyen,[a+] Quang De Tran,*[b+] Cuong Quoc Nguyen,[b] Tran Phuong Hoa,[a] Tran Duy Binh,[a] Huynh Nhu Thao,[b] Bui Thi Buu Hue,[b] Nguyen Trong Tuan,[b] Quang Le Dang,[cd] Nguyen Quoc Chau Thanh,[b] Nguyen Van Ky,[b] Minh Quan Pham,[de] and Su-Geun Yang,*[a]

[a.] Department of Biomedical Science, BK21 FOUR Program in Biomedical Science and Engineering, Inha University College of Medicine, Incheon 22212, South Korea.
[b.] Department of Chemistry, College of Natural Sciences, Can Tho University, Can Tho 90000, Vietnam.
[c.] Institute for Tropical Technology, Vietnam Academy of Science and Technology, Hanoi, 10000, Vietnam.
[d.] Graduate University of Science and Technology, Vietnam Academy of Science and Technology, Hanoi 100000, Vietnam
[e.] Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology, Hanoi 100000, Vietnam.

+ These authors contributed equally to this work.

* Correspondence:
**Quang De Tran**, PhD.
Department of Chemistry, College of Natural Sciences, Can Tho University, Can Tho 90000, Vietnam.
Tel: +84934527817; Email: tqde@ctu.edu.vn

**Su-Geun Yang**, PhD.
Department of Biomedical Science, Inha University College of Medicine, B-308, Chungsuk Bldg, 366, Seohae-Daero, Jung-Gu, Incheon 22332, Republic of Korea.
Tel: +82-32-890-2832, Fax: +82-32-890-1199, E-mail: sugeun.yang@inha.ac.kr

**S1. Detailed description for the synthesis of belinostat derivatives**

***Preparation of 3-nitrobenzaldehyde***

Potassium nitrate (3.0 g, 30 mmol) was dissolved in 12 mL concentrated sulfuric acid. This mixture was then cooled in the ice bath, adding benzaldehyde **1** (3.18 g, 30 mmol) while stirring. Continuing stirring for 2 hours, the temperature of the vessel should be maintained from 5 to 10 ℃. After the completion of the reaction, the crude product was poured slowly into the crushed ice while stirring vigorously. The yellow precipitate will be obtained. The precipitate was washed with saturated $Na_2CO_3$ solution until pH>7, with water (100 mL x 2) and then filted to get the pure product 3-nitrobenzaldehyde. Yellow solid (3.19 g). 70% yield.

$^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 10.12 (s, 1H, –C**H**O), 8.71 (dd, *J*= 1.8 Hz, 1H, >C**H**–), 8.47-8.71 (m, 1H, >C**H**–), 8.21-8.25 (m, 1H, >C**H**–), 7.76 (t, *J*= 7.95 Hz, 1H, >C**H**–).

***Preparation of (E)-3-(3-nitrophenyl)acrylic acid (3) using Knoevenagel reaction***

0.52 g Malonic acid and 0.25 mL pyridine were added into a round bottom flask and the mixture was vigorously stirred to dissolve malonic acid. Then 0.775 g of 3-nitrobenzaldehyde **2** was introduced into the flask. The mixture was stirred and heated under reflux for 2 hours. After the reaction was complete, the excess acid was neutralized by concentrated ammonium and 1N HCl, and a fine white precipitate will be obtained. The mixture was cooled for 1 hour for complete crystallization and filtered to get compound **3** in while white powder.

$^1$H NMR (300 MHz, $CDCl_3$, δ*ppm):* 12.63 (*s*, 1H, –COOH), 8.5 (*t*, *J*=1.8, 1H, =C**H**–), 8.24 (*q*, $J_1$ = 8.1 Hz, $J_2$ = 0.9 Hz, 1H, =C**H**–), 8.2 (*q*, $J_1$ = 6.9, $J_2$ = 0.6 Hz, 1H, =C**H**–), 7.7 (*q*, $J_1$ = 8.4 Hz, $J_2$ = 15.6 Hz, 2H, =C**H**–), 6.74 (*d*, *J* = 16.2, 1H, =C**H**–).

***Preparation of methyl (E)-3-(3-nitrophenyl)acrylate (4)***

Compound **3** (5.79 g, 30 mmol) and 150 mL $CH_3OH$ were added to a 250 mL flask, followed by the addition of concentrated sulfuric acid (0,5 mL). The mixture in the flask was agitated

heated under reflux. After 12 hours, the solvent was evaporated partly under reduced pressure, and then neutralized with solution $NaHCO_3$ 10% to get a white precipitate. It was then filtered by a vacuum, rinsed with 100 mL of $H_2O$ to obtain a fine white crystal **4** (5.5 g). 88.5% yield.

$^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 8.37 (d, *J*= 1.8 Hz, 1H, >C**H**–), 8.24 (dd, $J_1$= 1.5 Hz, $J_2$= 1.2 Hz, 1H, >C**H**–), 7.80 (d, *J*= 7.8 Hz, 1H, >C**H**–), 7.72 (d, *J*= 15.9 Hz, 1H, =C**H**–), 7.58 (t, *J*= 7.95 Hz, 1H, >C**H**–), 6.55 (d, *J*= 15.9 Hz, 1H, =C**H**–), 3.83 (s, 3H, –C**H**$_3$).

***Preparation of methyl (E)-3-(3-nitrophenyl)acrylate (4) using Wittig reaction:***

Triphenylphosphine (768 mg, 3 mmol) was dissolved in 12 mL $H_2O$ and then methyl 2-chloroacetate (405 mg, 3.3 mmol) was added to the solution. The mixture was stirred at 70 °C for 20 hour. The NaOH (264 mg, 6.6 mmol) was added portionwise, the mixture was stirred for 30 minutes at room temperature. After the completion of the reaction, the desired product was extracted by ethyl acetate and evaporated the solvent to obtain **3'** in white solid, the product is used directly for the next step without further purification.

The ylide intermediate **3'** (350 mg, 1 mmol) and **2** (300 mg, 1.0 mmol) in 5 mL $H_2O$ was refluxed for 2 hours. After being cooled down room temperature, the reaction mixture was extracted with EtOAc twice. Then combined organic phase was dried over $Na_2SO_4$, filtered, evaporated under vacuum system and purified by flash column chromatography, which gave the desired product **4** (243 mg). 64.3% yield.

***Preparation of methyl (E)-3-(3-aminophenyl)acrylate (5)***

$SnCl_2.2H_2O$ (7.9 g, 35 mmol) was dissolved in 300 mL EtOH in a 500 mL round bottom flask, then added **4** (2.07 g, 10 mmol), the mixture was heated at 90 °C for 3 hours. Allowing the mixture cooling to room temperature, then the solvent was evaporated. The residue was neutralized to pH = 7 with saturated $Na_2CO_3$ solution. The resulting mixture was extracted with EtOAc twice. The combined organic extract was washed again with brine, then dried by

anhydrous $Na_2SO_4$, evaporated. Purifying the product with column chromatography of the silica gel column to get **5** in luminous green (1.58 g, 89%).

$^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 7.60 (d, *J*= 15.9 Hz, 1H, =C**H**–), 7.17 (t, *J*= 7.65 Hz, 1H, >C**H**–), 6.92 (d, *J*= 7.8 Hz, 1H, >C**H**–) 6.81 (t, *J*= 1.8 Hz, 1H, >C**H**–), 6.68-6.72 (m, 1H, >C**H**–), 6.37 (d, *J*= 15.9 Hz, 1H, =C**H**–), 3.79 (s, 1H, –C**H**$_3$), 3.73 (s, 2H, –N**H**$_2$).

***Preparation of methyl (E)-3-(3-(chlorosulfonyl)phenyl)acrylate***

Concentrated hydrochloric acid (5 mL) is slowly added to **5** (885 mg, 5 mmol) while stiired (The reaction vessel should be kept under 5 °C during the addition). The resulting mixture is then cooled to 0 °C. $NaNO_2$ solution (345 mg, 5 mmol) in 1.48 mL $H_2O$ is added very slowly to the mixture. After that, the stirring was continued for 10 minutes to obtain diazonium salt of **5**.

In another flask, $SO_2$ gas is introduced into 50 mL AcOH, the reaction temperature of the reaction vessel should be lower than 5 °C until saturation. CuCl (250 mg, 2.5 mmol) was added to the reaction vessel, then continue adding $SO_2$ until the solution changing from green to yellow-green.

Diazonium salt was added slowly to the mixture and stirred at a temperature not exceeding 5 °C. After 2 hours, the reaction mixture was extracted with EtOAc, the organic extract was washed again with 5% $NaHCO_3$ and dried by anhydrous $Na_2SO_4$ and evaporated the solvent to obtain **5'** in black oil, the product is used directly for the next step without further purification. Compound **5'** is used directly for subsequent reactions without purification. (Note: **5'** decomposes at over 40 °C).

***General procedure for the synthesis of compound 6***

Amine (R-$NH_2$) (4 mmol) is added to $K_2CO_3$ in 1,4-dioxane (5 mL), which is continuously stirred at room temperature. Compound **5'** obtained from the above reaction is dissolved in 2

mL 1,4-dioxane and added slowly to the mixture while keeping the reaction at room temperature for 12 hour. The mixture after reaction was washed with HCl, extracted with EtOAc, brined and dried by anhydrous $Na_2SO_4$. The product was purified with silica gel column chromatography to obtain white crystals **6**.

**6a:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 8.19 (s, 1H, >N**H**), 8.00 (s, 1H, >C**H**–), 7.95 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.78 (d, *J*= 8 Hz, 1H, >C**H**–), 7.69 (d, *J*= 16.4 Hz, 1H, =C**H**–), 7.59 (t, *J*= 7.6 Hz, 1H, >C**H**–), 7.26-7.22 (m, 2H, >C**H**–), 7.04 (t, *J*= 8.6 Hz, 2H, >C**H**–), 6.69 (d, *J*= 16 Hz, 1H, =C**H**–), 4.02 (s, 2H, –C**H$_2$**–), 3.74 (s, 3H, –OC**H$_3$**).

**6b:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 8.10 (s, 1H, >N**H**), 7.95-7.93 (m, 2H, >C**H**–), 7.78 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.67 (d, *J*= 16 Hz, 1H, =C**H**–), 7.58 (t, *J*= 7.6 Hz, 1H, >C**H**–), 7.08-7.01 (m, 2H, >C**H**–), 6.67 (d, *J*= 16 Hz, 1H, =C**H**–), 3.97 (s, 2H, –C**H$_2$**–), 3.73 (s, 3H, –OC**H$_3$**), 2.20 (s, 3H, –C**H$_3$**).

**6c:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 8.10 (s, 1H, >N**H**), 8.03 (s, 1H, >C**H**–), 7.95 (d, *J*= 7.6 Hz, 1H, >C**H**–) 7.80 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.70 (d, *J*= 16 Hz, 1H, =C**H**–), 7.59 (t, *J*= 7.8 Hz, 1H, >C**H**–), 7.25-7.19 (m, 5H, >C**H**–), 6.69 (d, *J*= 16.4 Hz, 1H, =C**H**–), 4.03 (s, 2H, –C**H$_2$**–), 3.74 (s, 3H, –OC**H$_3$**).

**6d:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 8.09 (s, 1H, >C**H**–), 7.96 (d, *J*= 7.6 Hz, 1H, >C**H**–) 7.82 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.72 (d, *J*= 16 Hz, 1H, =C**H**–), 7.63 (s, 1H, >N**H**), 7.61-7.59 (m, 1H, >C**H**–), 6.70 (d, *J*= 16 Hz, 1H, =C**H**–), 3.72 (s, 3H, –OC**H$_3$**), 2.96 (s, 5H, >C**H**–), 1.55-1.40 (m, 5H, >C**H**–), 1.13-1.01 (m, 5H, >C**H**–).

**6e:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 9.81 (s, 1H, >N**H**), 8.00 (d, *J*= 8 Hz, 1H, >C**H**–), 7.95 (s, 1H, >C**H**–), 7.78 (d, *J*= 8 Hz, 1H, >C**H**–), 7.69 (d, *J*= 16 Hz, 1H, =C**H**–), 7.60 (t, *J*= 7.8 Hz, 1H, >C**H**–), 7.14 (t, *J*= 7.6 Hz, 1H, >C**H**–), 6.95-6.90 (m, 1H, >C**H**–), 6.81 (dd, $J_1$=

2.4 Hz, $J_2$= 10.4 Hz, 1H, >C**H**–), 6.64 (d, *J*= 16 Hz, 1H, =C**H**–), 3.72 (s, 3H, –OC**H$_3$**), 1.93 (s, 3H, –C**H$_3$**).

**6f:** $^1$H NMR (400 MHz, $CDCl_3$, δ ppm): 7.82 (s, 1H, >C**H**–), 7.70 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.64 (d, *J*= 7.2 Hz, 1H, >C**H**–), 7.61 (d, *J*= 16 Hz, 1H, =C**H**–), 7.44 (t, *J*= 7.8 Hz, 1H, >C**H**–), 7.25 (s, 1H, >N**H**), 7.97 (d, *J*= 8.8 Hz, 2H, >C**H**–), 6.76 (d, *J*= 8.8 Hz, 2H, >C**H**–), 6.40 (d, *J*= 16 Hz, 1H, =C**H**–), 3.80 (s, 3H, –OC**H$_3$**) 3.75 (s, 3H, –OC**H$_3$**).

**6g:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 10.09 (s, 1H, >N**H**), 7.98 (s, 1H, >C**H**–), 7.93 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.71 (d, *J*= 8 Hz, 1H, >C**H**–), 7.67 (d, *J*= 16 Hz, 1H, =C**H**–), 7.56 (t, *J*= 7.8 Hz, 1H, >C**H**–), 7.02-6.52 (m, 4H, >C**H**–), 6.62 (d, *J*= 16 Hz, 1H, =C**H**–), 3.73 (s, 3H, –OC**H$_3$**), 3.29 (s, 3H, –C**H$_3$**).

**6h:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 10.32 (s, 1H, >N**H**), 8.01-8.0 (m, 2H, >C**H**–), 7.73 (d, *J*= 6.8 Hz, 1H, >C**H**–), 7.70 (d, *J*= 16 Hz, 1H, =C**H**–), 7.60 (t, *J*= 8 Hz, 1H, >C**H**–), 7.39 (dd, $J_1$= 2.4 Hz „$J_2$= 10.2 Hz, 1H, >C**H**–), 7.28-7.2 (m, 2H, >C**H**–), 6.67 (d, *J*= 16 Hz, 1H, =C**H**–), 3.72 (s, 3H, –OC**H$_3$**).

**6i:** $^1$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 10.22 (s, 1H, >N**H**), 7.99 (s, 1H, >C**H**–), 7.95 (d, *J*= 8 Hz, 1H, >C**H**–), 7.70 (d, *J*= 7.2 Hz, 1H, >C**H**–), 7.67 (d, *J*= 15.6 Hz, 1H, =C**H**–), 7.57 (t, *J*= 7.8 Hz, 1H, >C**H**–), 7.08-7.03 (m, 4H, >C**H**–), 6.65 (d, *J*= 16 Hz, 1H, =C**H**–), 3.72 (s, 3H, –OC**H$_3$**).

**6j:** $^1$H NMR (400 MHz, DMSO, δ ppm): 10.15 (s, 1H, >N**H**), 8.00 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.97 (s, 1H, >C**H**–), 7.69 (d, *J*= 8 Hz, 1H, >C**H**–), 7.69 (d, *J*= 16 Hz, 1H, =C**H**–), 7.25-7.19 (m, 2H, >C**H**–), 7.02 (t, *J*= 8.6 Hz, 1H, >C**H**–), 6.66 (d, *J*= 16.4 Hz, 1H, =C**H**–), 3.72 (s, 3H, –OC**H$_3$**).

**6k**: $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 10.57 (s, 1H, >N**H**), 8.07 (s, 1H, >C**H**–), 7.98 (d, *J*= 7.6 Hz, 1H, >C**H**–), 7.78 (d, *J*= 8 Hz, 1H, >C**H**–), 7.70 (d, *J*= 16.4 Hz, 1H, =C**H**–), 7.60 (t, *J*= 7.8 Hz, 1H, >C**H**–), 7.26-7.22 (m, 1H, >C**H**–), 6.93-6.82 (m, 3H, >C**H**–), 6.68 (d, *J*= 16 Hz, 1H, =C**H**–), 3.72 (s, 3H, –OC**H$_3$**).

**6l:** $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ ppm): 10.86 (s, 1H, >N**H**), 8.12 (s, 1H, >C**H**–), 7.98 (d, *J*= 8 Hz, 1H, >C**H**–), 7.82 (d, *J*= 8.8 Hz, 3H, >C**H**–), 7.70 (d, *J*= 16 Hz, 1H, =C**H**–), 7.60 (t, *J*= 7.8 Hz, 1H, >C**H**–), 7.21 (d, *J*= 8.8 Hz, 2H, >C**H**–), 6.68 (d, *J*= 16 Hz, 1H, =C**H**–), 3.72 (s, 3H, –OC**H$_3$**), 2.44 (s, 3H, –C**H$_3$**).

***General procedure for the synthesis of compound 7***

KOH (784 mg, 14 mmol) was added to the hydroxylamine hydrochloride (973 mg, 14 mmol) in anhydrous EtOH (10 mL). The mixture was stirred and then cooled to 0 °C and filtered. The filtrate, KOH (135 mg, 2.4 mmol) and compound **6** (0.2 mmol) were added to a round bottom flask under agitation at 0 °C for 1 hour. After that, 10 mL $H_2O$ was added to quench the reaction. Then the neutralization was carried out by concentrated HCl solution until pH = 7, followed by the extraction with EtOAc. Purification of the product was carried out with silica gel column chromatography to obtain an off solid **7**.

**7a**: $^{1}$H-NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.81 (s, 1H, –O**H**), 9.11 (s, 1H, >N**H**), 8.23 (t, 1H, *J*= 6.5 Hz , >N**H**), 7.89 (s, 1H, >C**H**–), 7.78 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.75 (d, *J*= 8 Hz, 1H, >C**H**–), 7.59 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.50 (d, *J*= 15.5 Hz, 1H, =C**H**–), 7.27-7.24 (m, 2H, >C**H**–), 7.08-7.04 (m, 2H, >C**H**–), 6.54 (d, *J*= 16 Hz, 1H, =C**H**–), 4.02 (d, *J*= 6.5 Hz, 2H, –C**H$_2$**–). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 160.57, 140.04, 136.27, 131.94, 130.37, 130.12, 130.04, 125.02, 121.63, 115.49, 115.28, 45.88. MS (IDA) *m/z* 351.0808 $[M+H]^+$.

**7b**: $^{1}$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.81 (s, 1H, –O**H**), 9.11 (s, 1H, >N**H**), 8.14 (t, 1H, *J*= 6.25 Hz , >N**H**), 7.87 (s, 1H, >C**H**–), 7.76 (t, *J*= 8.75 Hz, 2H, 2 >C**H**–), 7.59 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.48 (d, *J*= 16 Hz, 1H, =C**H**–), 7.09 (d, *J*= 8 Hz, 2H, 2 >C**H**–), 7.04 (d, *J*= 8 Hz, 2H, 2 >C**H**–), 6.54 (d, *J*= 16 Hz, 1H, =C**H**–), 3.97 (d, *J*= 6.5 Hz, 1H, –C**H$_2$**–), 2.23 (s, 3H, –C**H$_3$**). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 160.86, 142.10, 136.75, 130.33, 129.19, 128.08, 125.02, 121.55, 117.42, 46.46, 21.10. MS (IDA) *m/z* 347.1060 $[M+H]^+$.

**7c**: $^{1}$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.78 (s, 1H, –OH), 9.13 (s, 1H, >NH), 8.20 (br, 1H, >NH), 7.92 (s, 1H, >CH–), 7.77 (t, *J*= 8.25 Hz, 2H, 2 >CH–). 7.59 (t, *J*= 7.75 Hz, 1H, >CH–), 7.49 (d, *J*= 15.5 Hz, 1H, =CH–), 7.28-7.18 (m, 5H, 5 >CH–), 6.55 (d, *J*= 16 Hz, 1H, =CH–), 4.02 (s, 2H, 2 –$CH_2$–). $^{13}$C NMR (100 MHz, $CD_3OD$, δ ppm): 164.14, 141.89, 138.26, 137.04, 135.95, 130.89, 129.42, 128.02, 127.55, 127.36, 125.47, 119.36, 46.56. MS (ESI) *m/z* 333.0920 $[M+H]^+$.

**7d**: $^{1}$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.80 (s, 1H, –O**H**), 9.12 (s, 1H, >N**H**), 7.97 (s, 1H, >C**H**–), 7.79 (dd, 2H, $J_1$= 1.5 Hz, $J_2$= 7.75 Hz, 2 >C**H**–), 7.68 (d, *J*= 7 Hz, 1H, >N**H**), 7.61 (t, *J* = 7.75 Hz, 1H, >C**H**–), 7.51 (d, *J* = 15.5 Hz, 1H, =C**H**–), 6.56 (d, *J* = 16 Hz, 1H, =C**H**–), 2.96-2.95 (m, 1H, >C**H**–), 1.56-1.55 (m, 5H, 5 –C**H$_2$**– ), 1.19-1.08 (m, 5H, 5 –C**H$_2$**–). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 143.56, 141.16, 136.27, 131.81, 130.39, 124.75, 121.59, 52.59, 33.68, 25.29, 24.77. MS (ESI) *m/z* 325.1228 $[M+H]^+$.

**7e**: $^{1}$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 9.81 (s, 1H, >N**H**), 7.99 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.92 (s, 1H, >C**H**–), 7.70-7.61 (m, 1H, >C**H**–), 7.61 (t, *J*= 8 Hz, 1H, >C**H**–), 7.61 (d, *J*= 15.5 Hz, 1H, =C**H**–), 7.18-7.15 (m, 1H, >C**H**–), 6.97-6.93 (m, 1H, 1 >C**H**–), 6.82-6.80 (m, 1H, 1 >C**H**–), 6.53 (d, *J*= 16 Hz, 1H, =C**H**–), 1.94 (s, 3H, –C**H$_3$**). $^{13}$C NMR (100 MHz, DMSO-$d_6$,

δ ppm): 178.983, 162.53, 161.73, 141.51, 137.07, 137.01, 136.38, 132.59, 132.53, 132.43, 130.56, 124.89, 120.93, 17.28. HRMS (ESI) *m/z* 351.0811 $[M+H]^+$.

**7f**: $^1$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.81 (s, 1H, –O**H**), 9.94 (s, 1H, >N**H**), 9.10 (s, 1H, >N**H**), 7.85 (s, 1H, >C**H**–), 7.76 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.62 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.56 (t, *J*= 7.5 Hz, 1H, >C**H**–), 7.46 (d, *J*= 16 Hz, 1H, =C**H**–), 6.97 (d, *J*= 9 Hz, 2H, 2 >C**H**–), 6.81-6.79 (m, 2H, 2 >C**H**–), 6.50 (d, *J*= 15.5 Hz, 1H, =C**H**–), 3.66 (s, 3H, –C**H**$_3$**)**. $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 162.54, 157.16, 140.69, 137.06, 136.22, 132.36, 130.35, 130.32, 127.61, 125.15, 124.15, 121.72, 114.82, 55.62. HRMS (ESI) *m/z* 349.0862 $[M+H]^+$.

**7g**: $^1$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.81 (s, 1H, –O**H)**, 10.13 (s, 1H, >N**H**), 9.11 (s, 1H, >N**H**), 7.88 (s, 1H, >C**H**–), 7.77 (d, *J*= 8 Hz, 1H, >C**H**–), 7.67 (d, *J*= 8 Hz, 1H, >C**H**–), 7.56 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.46 (d, *J*= 16 Hz, 1H, =C**H**–), 7.03 (d, *J*= 8.5 Hz, 2H, 2 >C**H**–), 6.97 (d, *J*= 8.5 Hz, 2H, 2 >C**H**–), 6.50 (d, *J*= 16 Hz, 1H, =C**H**–), 2.18 (s, 3H, –C**H**$_3$**)**. $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 140.78, 136.26, 135.31, 134.09, 132.38, 130.41, 130.08, 127.57, 125.18, 121.35, 20.76. HRMS (ESI) *m/z* 333.0893 $[M+H]^+$.

**7h**: $^1$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.81 (s, 1H, –O**H**), 10.34 (s, 1H, >N**H**), 9.11 (br, 1H, >N**H**), 7.89 (s, 1H, >C**H**–), 7.83 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.67 (d, *J*= 8 Hz, 1H, >C**H**–), 7.60 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.48 (d, *J*= 16 Hz, 1H, =C**H**–), 7.45-7.40 (m, 1H, >C**H**–), 7.27-7.22 (m, 2H, 2 >C**H**–), 6.51 (d, *J*= 16 Hz, 1H, =C**H**–). $^{13}$C NMR (100 MHz, $CD_3OD$, δ ppm): 164.11, 156.68, 154.20, 140.65, 138.12, 136.02, 131.53, 129.44, 127.49, 126.98, 125.56, 124.61, 124.56, 123.53, 119.59, 116.22, 115.98. HRMS (ESI) *m/z* 371.0266 $[M+H]^+$.

**7i**: $^1$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.81 (s, 1H, –O**H**), 10.25 (s, 1H, >N**H**), 9.12 (s, 1H, >N**H**), 7.88 (s, 1H, >C**H**–), 7.78 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.65 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.57 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.46 (d, *J*= 16 Hz, 1H, =C**H**–), 7.08 (d, *J*= 6.5 Hz, 4H, 4

>C**H**–), 6.50 (d, *J*= 16 Hz, 1H, =C**H**–). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 167.57, 160.86, 158.47, 142.32, 141.12, 140.45, 136.36, 134.14, 132.50, 130.49, 127.56, 125.19, 123.63, 123.55, 121.84, 116.52, 116.29, 113.20. HRMS (ESI) *m/z* 337.0660 $[M+H]^+$.

**7j**: $^1$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.80 (s, 1H, –O**H**), 10.17 (s, 1H, >N**H**), 9.10 (s, 1H, >N**H**), 7.85 (s, 1H, >C**H**–), 7.82 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.64 (d, *J*= 8 Hz, 1H, >C**H**–), 7.59 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.48 (d, *J*= 16 Hz, 1H, =C**H**–), 7.25-7.20 (m, 2H, 2 >C**H**–), 7.06-7.02 (m, 1H, 1 >C**H**–), 6.50 (d, *J*= 15.5 Hz, 1H, =C**H**–). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 162.54, 144.63, 141.12, 137.03, 136.29, 132.62, 130.43, 127.54, 124.96, 121.75, 112.32, 105.38. 105.14, 105.11, 104.88. HRMS (ESI) *m/z* 355.0566 $[M+H]^+$.

**7k**: $^1$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 10.81 (s, 2H, –O**H**, >N**H**), 9.12 (s, 1H, >N**H**), 7.95 (s, 1H, >C**H**–), 7.80 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.74 (d, *J*= 8 Hz, 1H, >C**H**–), 7.59 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.48 (d, *J*= 16 Hz, 1H, =C**H**–), 7.29-7.25 (m, 1H, >C**H**–), 6.94-6.83 (m, 3H, 3 >C**H**–), 6.52 (d, *J*= 16 Hz, 1H, =C**H**–). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ ppm): 163.90, 162.52, 161.48, 140.45, 139.95, 139.85, 136.48, 132.62, 131.54, 131.45, 130.64, 127.53, 125.27, 121.94, 116.08, 111.30, 107.17, 106.92. HRMS (ESI) *m/z* 337.0661 $[M+H]^+$.

**7l**: $^1$H NMR (500 MHz, DMSO-$d_6$, δ ppm): 11.06 (d, *J*= 1 Hz, 1H, –O**H**), 10.81 (s, 1H, –O**H)**, 10.46 (s, 1H, >N**H**), 9.11 (s, 1H, >N**H**), 7.95 (s, 1H, >C**H**–), 7.78 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.72 (d, *J*= 7.5 Hz, 1H, >C**H**–), 7.58 (t, *J*= 7.75 Hz, 1H, >C**H**–), 7.52 (d, *J*= 8 Hz, 2H, 2 >C**H**–), 7.47 (d, *J*= 15.5 Hz, 1H, =C**H**–), 7.11 (d, *J*= 8 Hz, 2H, 2 >C**H**–), 6.52 (d, *J*= 16 Hz, 1H, =C**H**–), 2.05 (d, *J*= 0.5 Hz 3H, –C**H**$_3$**).** HRMS (ESI) *m/z* 376.0974 $[M+H]^+$.

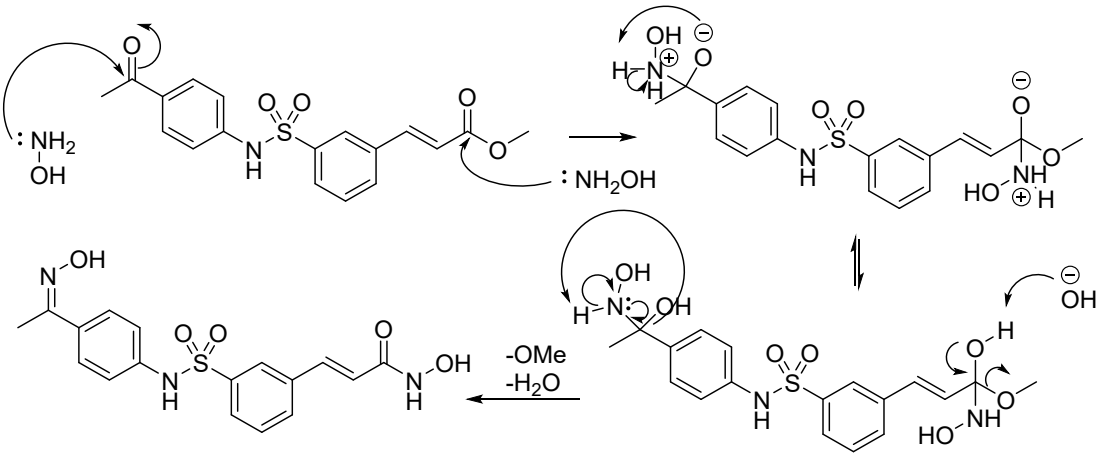
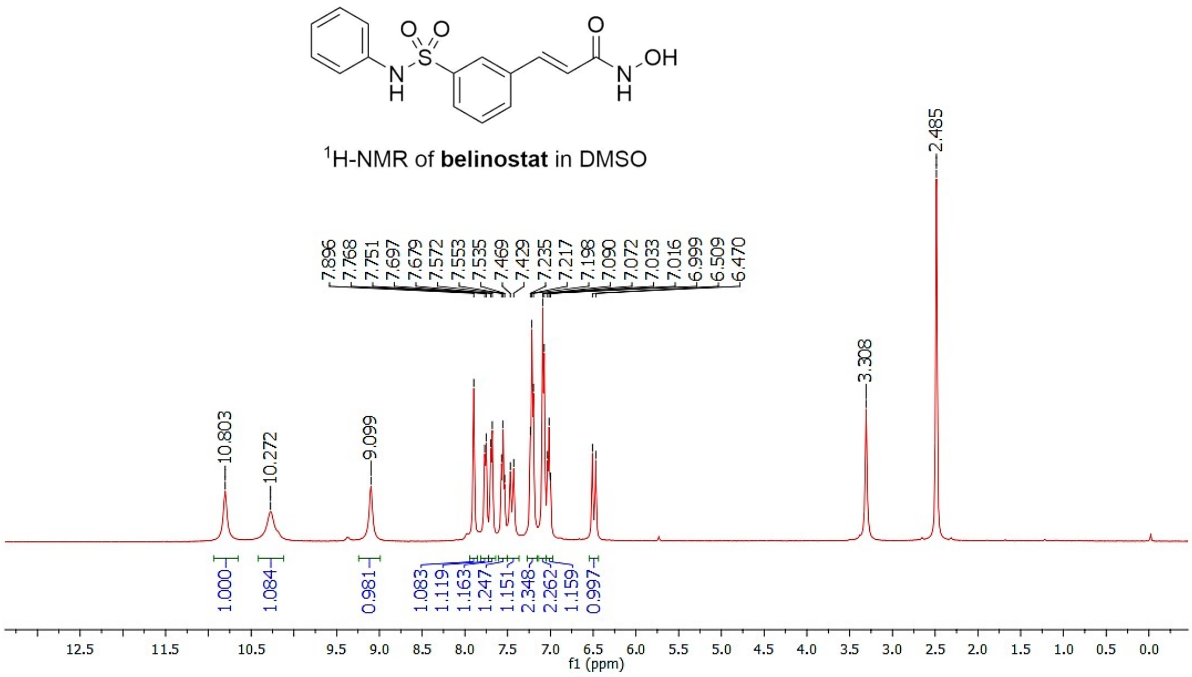
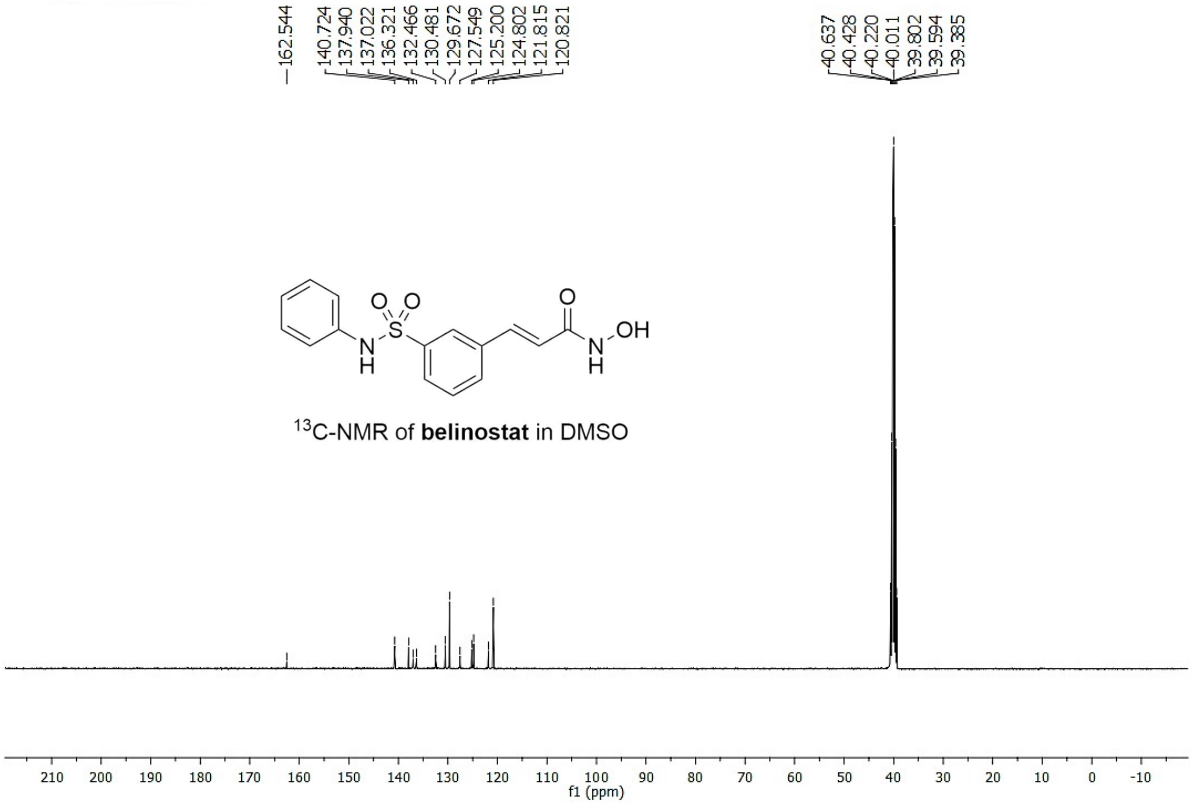
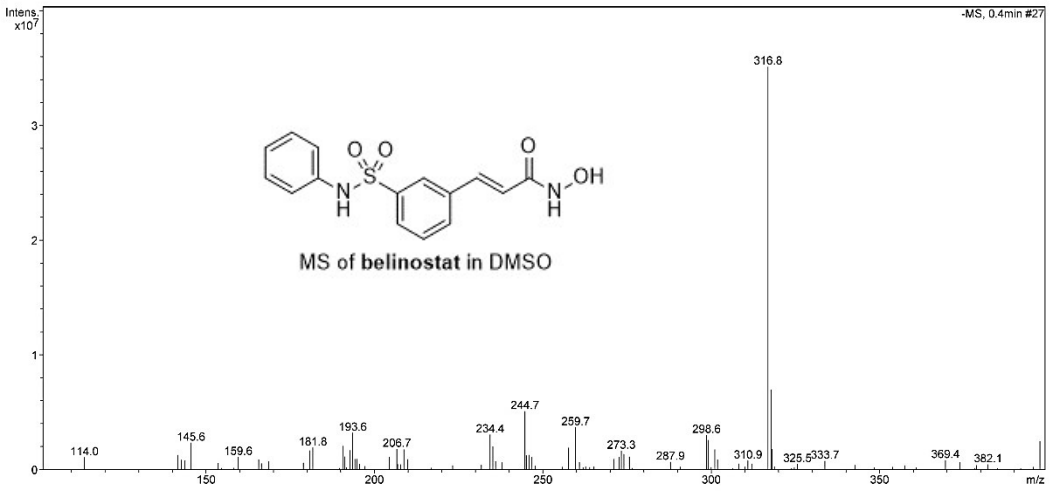


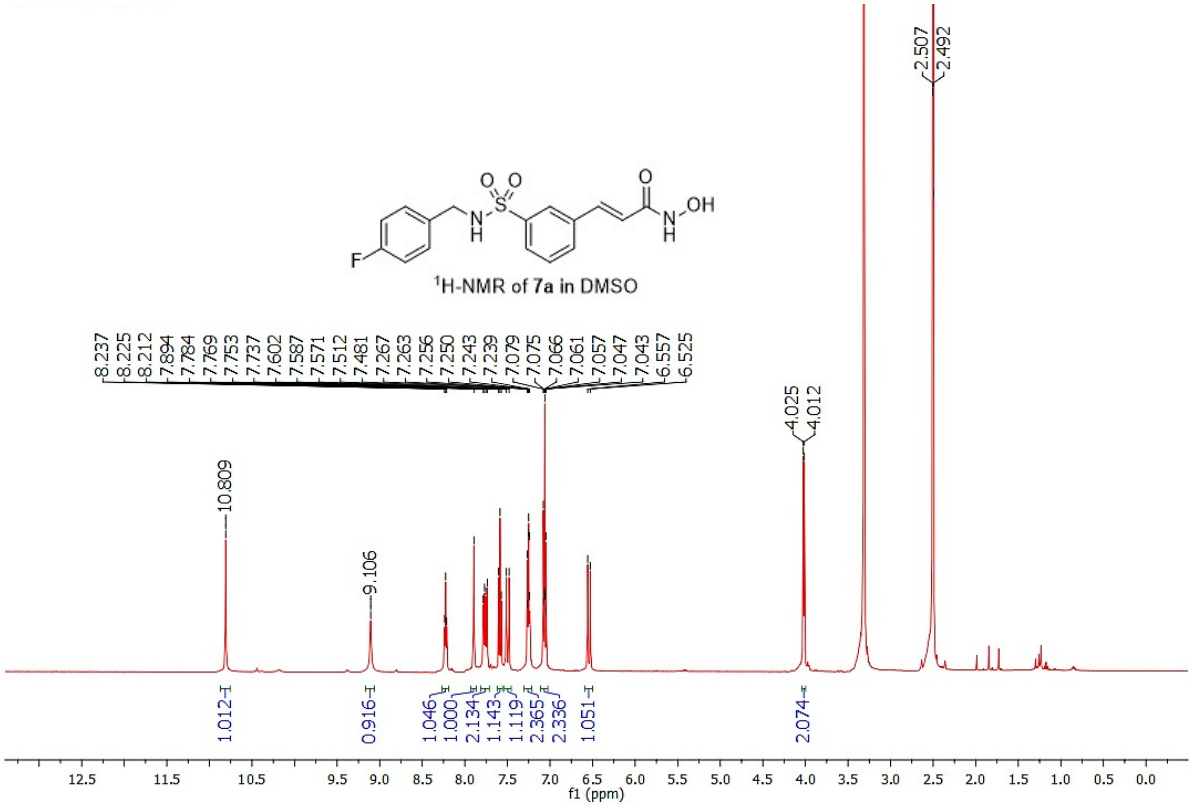

Fig S1. Reaction mechanisms to form ketoxime (**7l**)

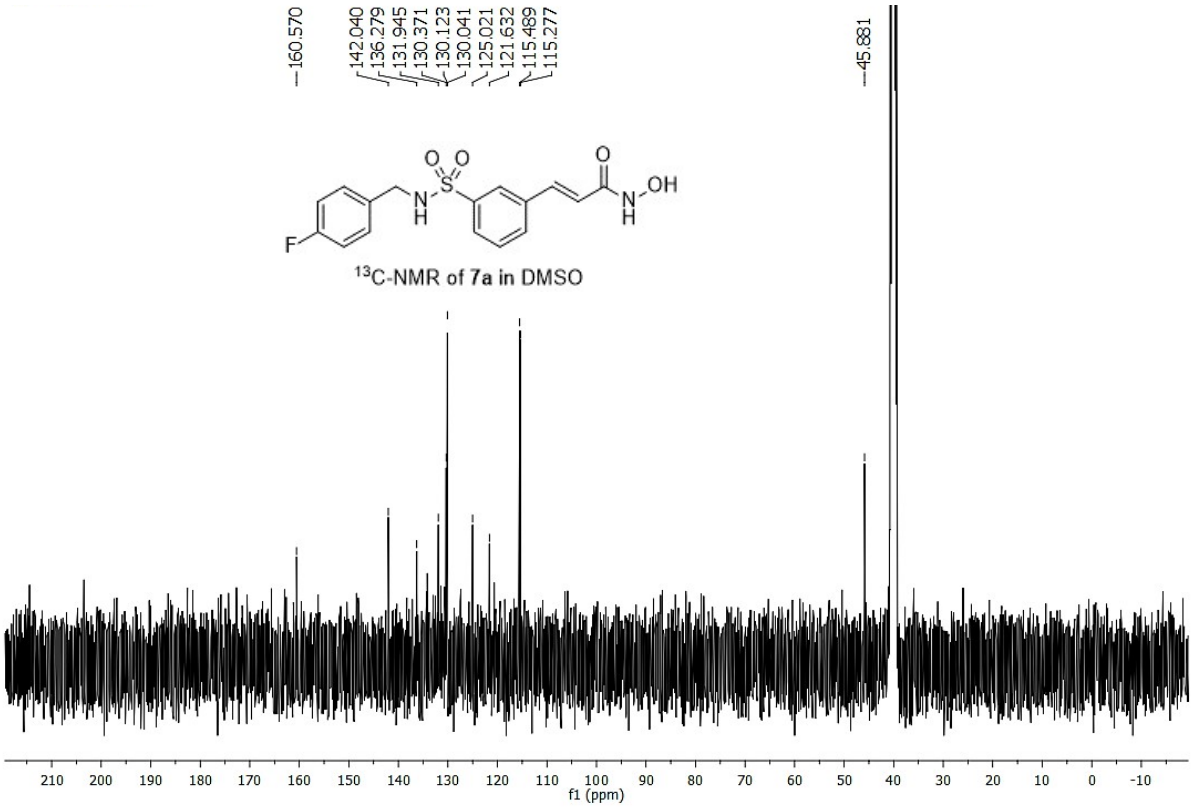
## S2. NMR and MS spectra of belinostat derivatives



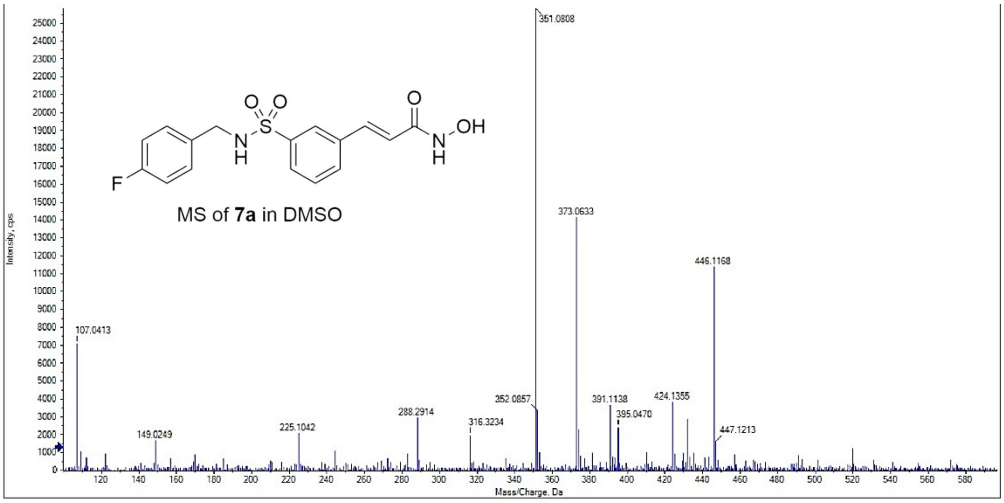




Intens.
x10^7
-MS, 0.4min #27
316.8
MS of belinostat in DMSO
244.7
259.7
193.6
234.4
298.6
145.6
206.7
273.3
114.0
159.6
181.8
287.9
310.9
325.5
333.7
369.4
382.1
m/z

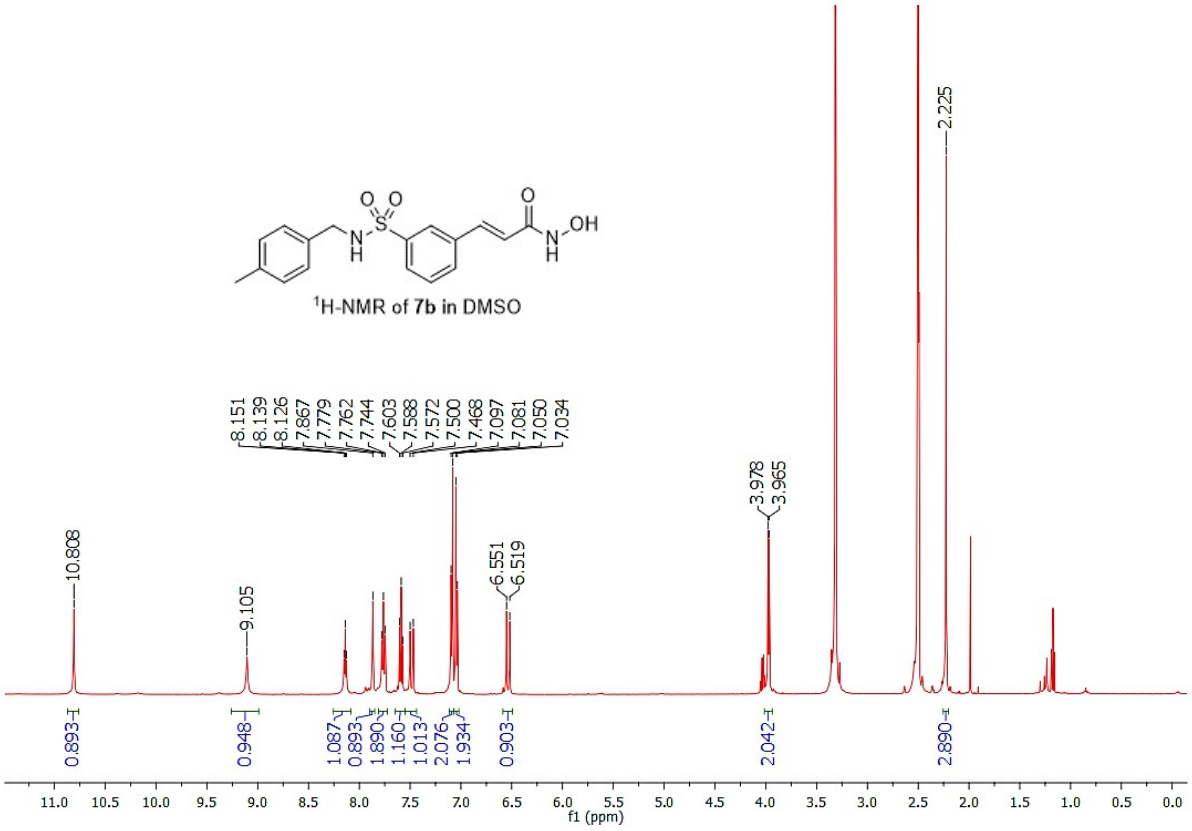

1H-NMR of 7a in DMSO
2.507
2.492
8.237
8.225
8.212
7.894
7.784
7.769
7.753
7.737
7.602
7.587
7.571
7.512
7.481
7.267
7.263
7.256
7.250
7.243
7.239
7.079
7.075
7.066
7.061
7.057
7.047
7.043
6.557
6.525
4.025
4.012
10.809
9.106
1.012
0.916
1.046
1.000
2.134
1.143
1.119
2.365
2.336
1.051
2.074
f1 (ppm)

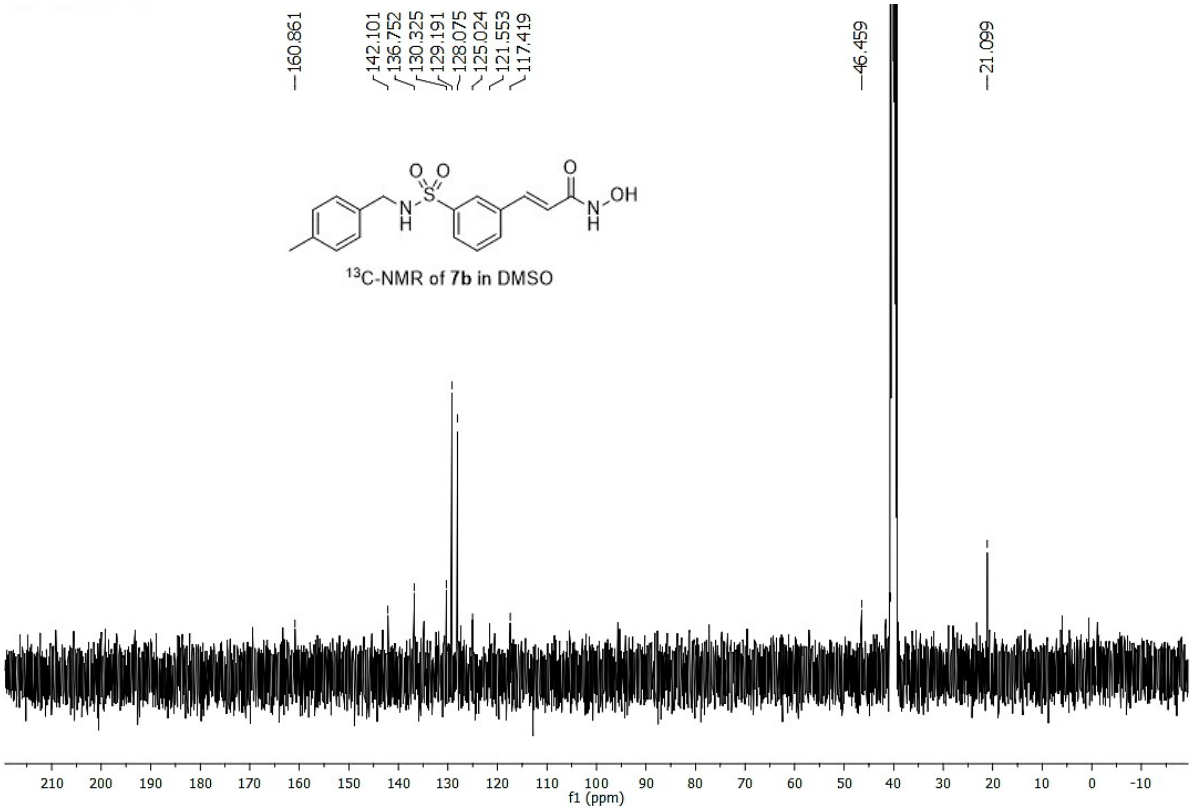


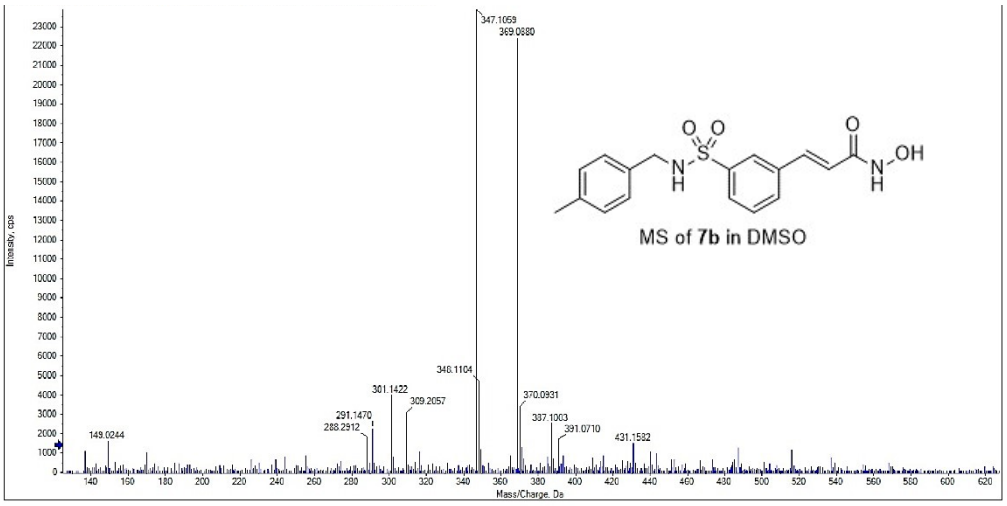

$^{13}$C-NMR of **7a** in DMSO

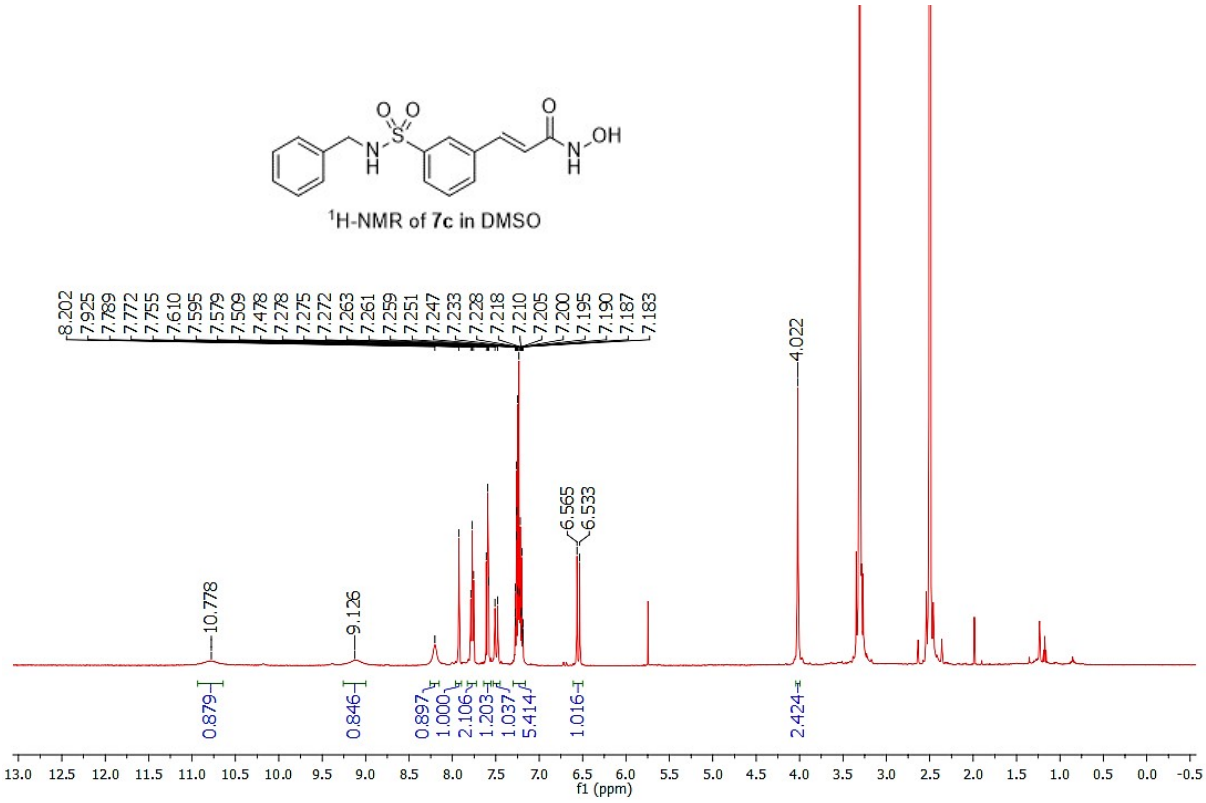


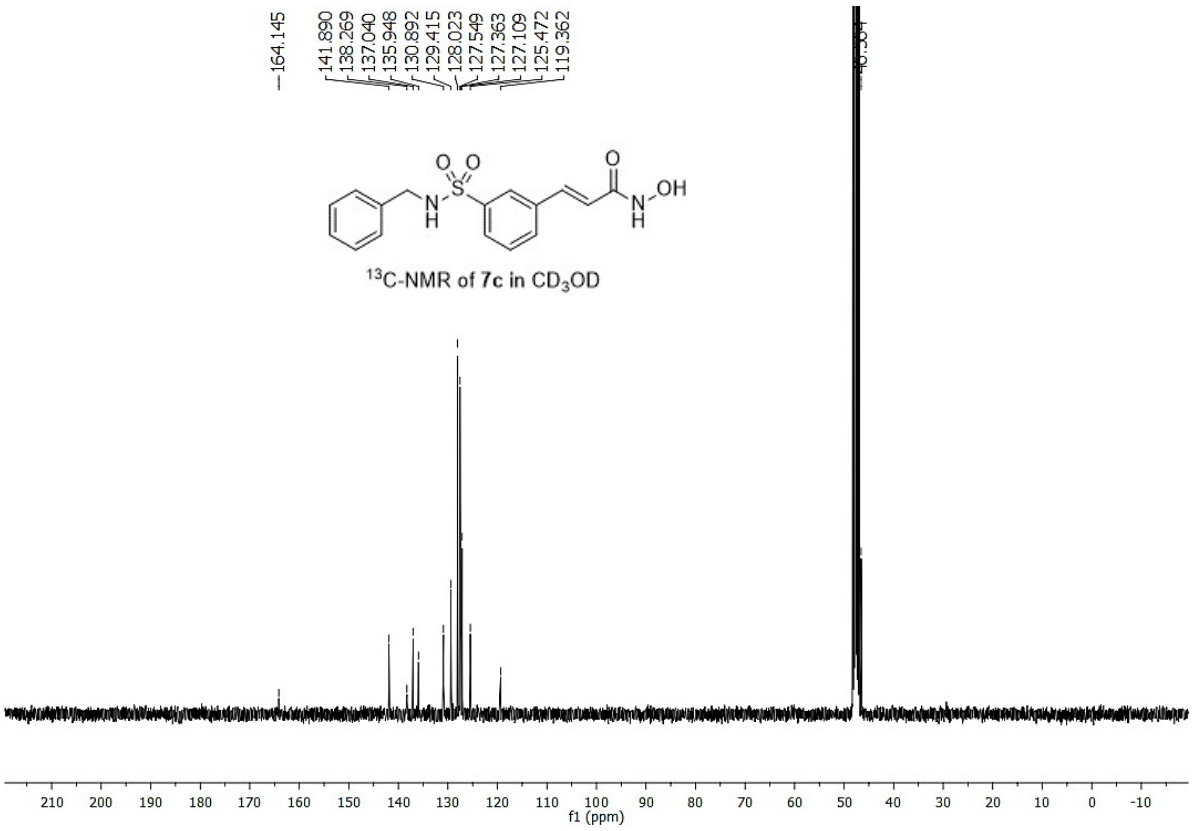

MS of **7a** in DMSO


$^1$H-NMR of 7b in DMSO
10.808
9.105
8.151
8.139
8.126
7.867
7.779
7.762
7.744
7.603
7.588
7.572
7.500
7.468
7.097
7.081
7.050
7.034
6.551
6.519
3.978
3.965
2.225
0.893
0.948
1.087
0.893
1.890
1.160
1.013
2.076
1.934
0.903
2.042
2.890
f1 (ppm)

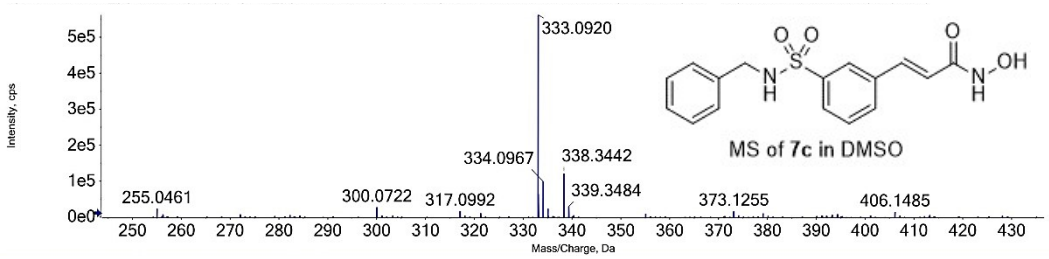

$^{13}$C-NMR of 7b in DMSO
160.861
142.101
136.752
130.325
129.191
128.075
125.024
121.553
117.419
46.459
21.099
f1 (ppm)


347.1059
369.0880
346.1104
301.1422
309.2057
370.0931
291.1470
288.2912
397.1003
391.0710
431.1582
149.0244
Intensity, cps
Mass/Charge, Da
MS of 7b in DMSO

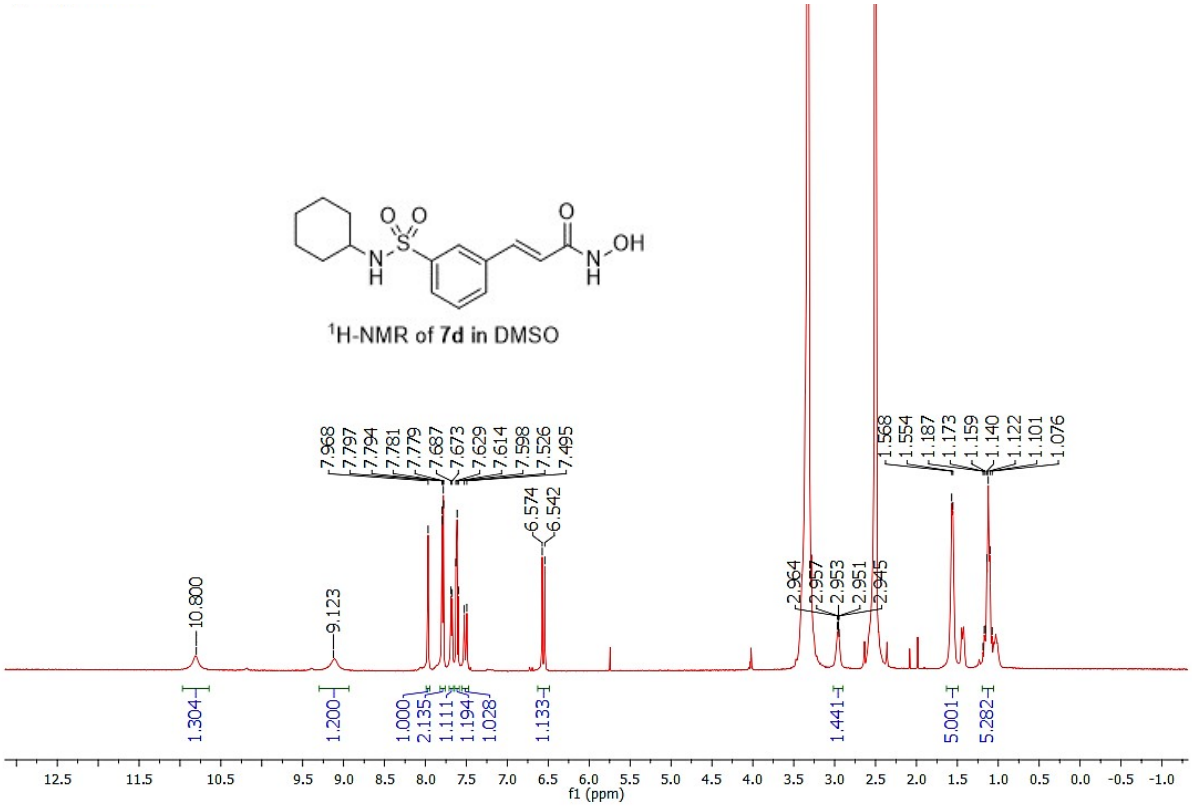

1H-NMR of 7c in DMSO
8.202
7.925
7.789
7.772
7.755
7.610
7.595
7.579
7.509
7.478
7.278
7.275
7.272
7.263
7.261
7.259
7.251
7.247
7.233
7.228
7.218
7.210
7.205
7.200
7.195
7.190
7.187
7.183
4.022
6.565
6.533
10.778
9.126
0.879
0.846
0.897
1.000
2.106
1.203
1.037
5.414
1.016
2.424
f1 (ppm)



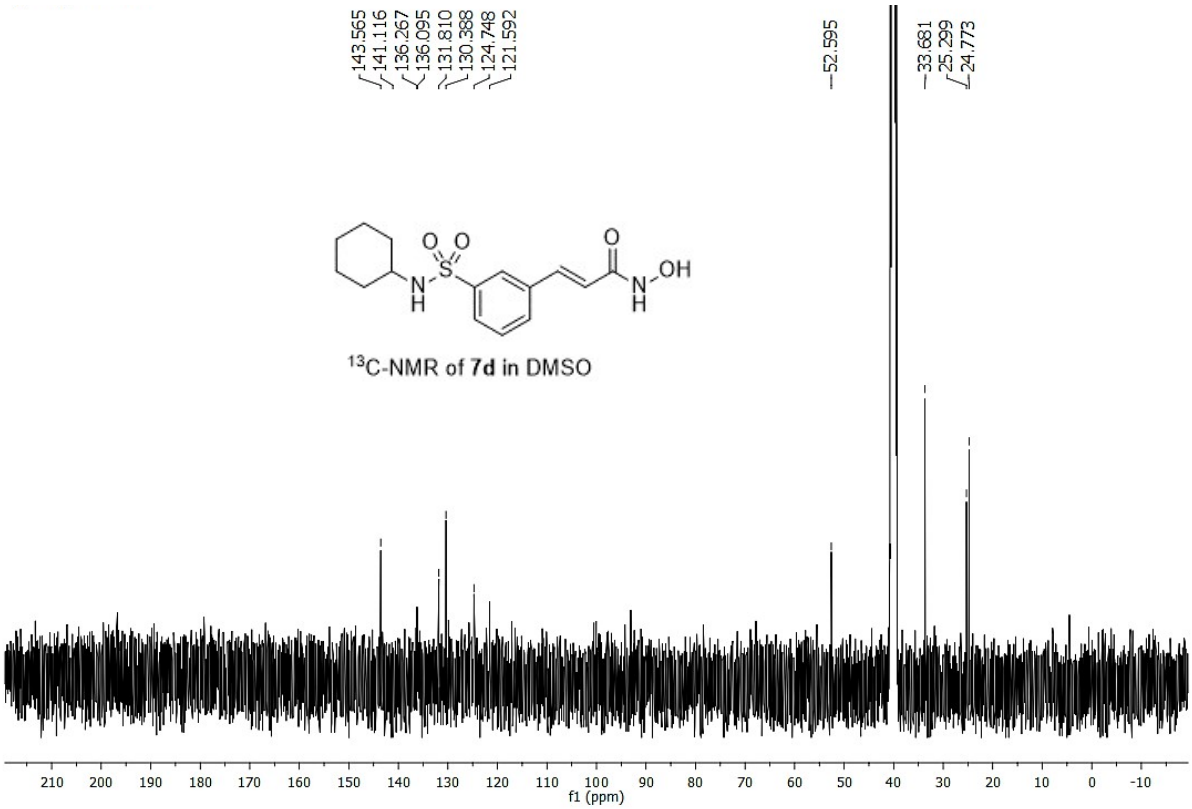

$^{13}$C-NMR of **7c** in $CD_3OD$



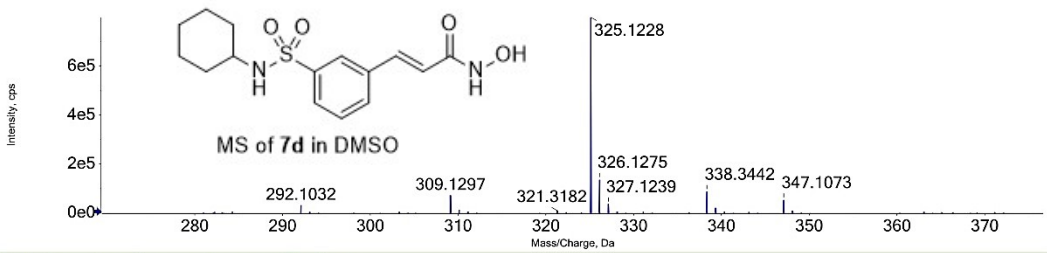

MS of **7c** in DMSO

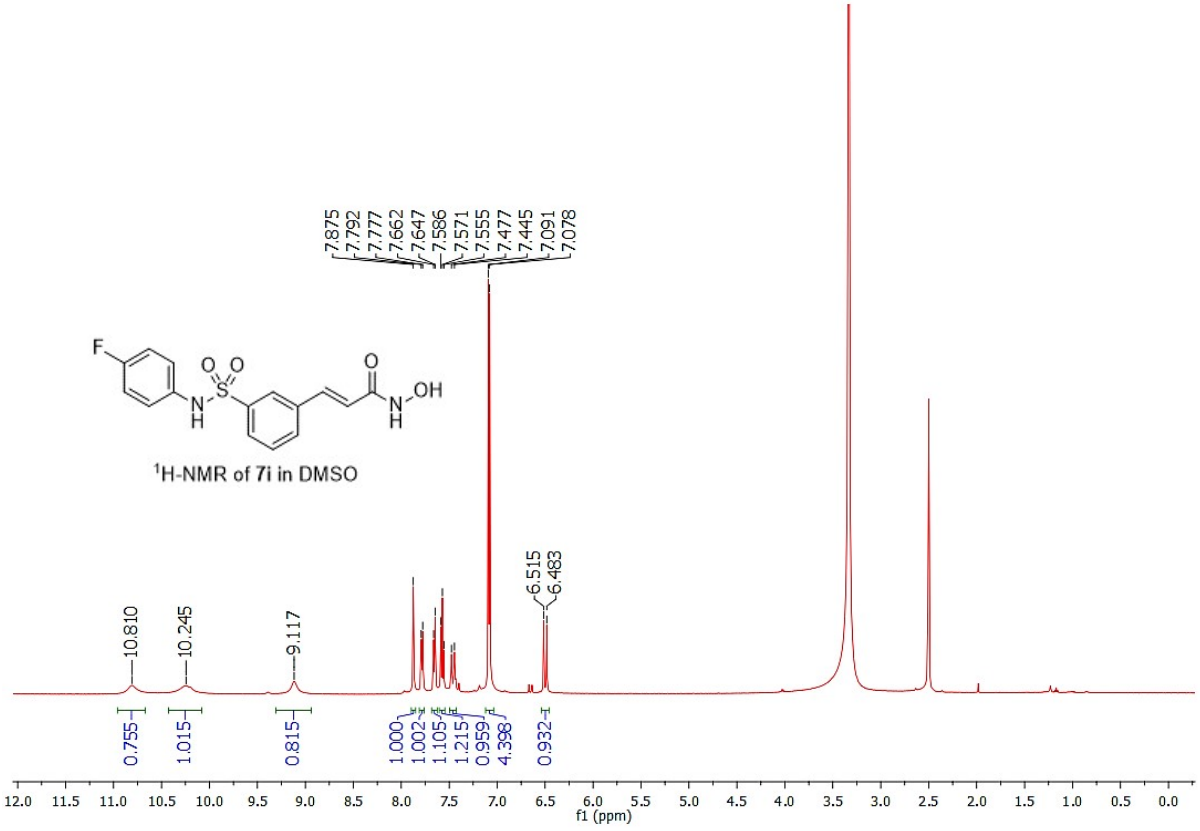


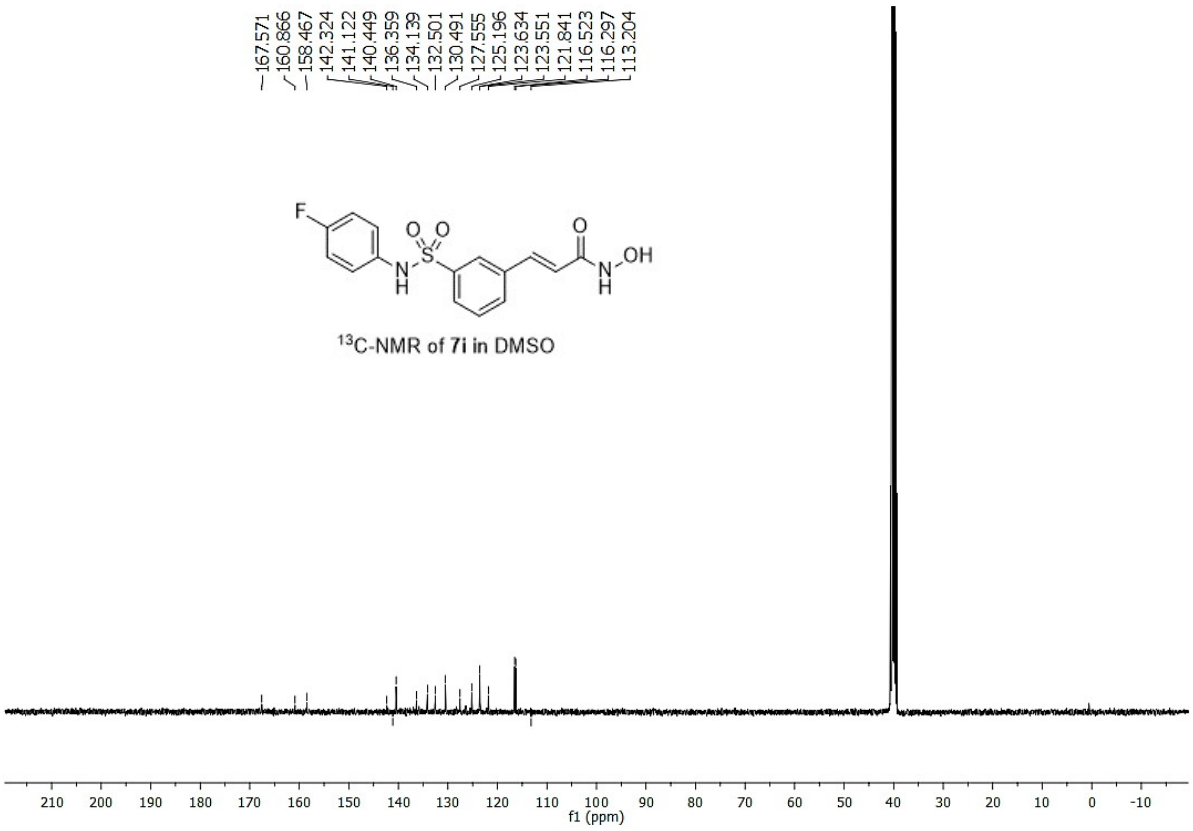

$^{1}$H-NMR of **7d** in DMSO



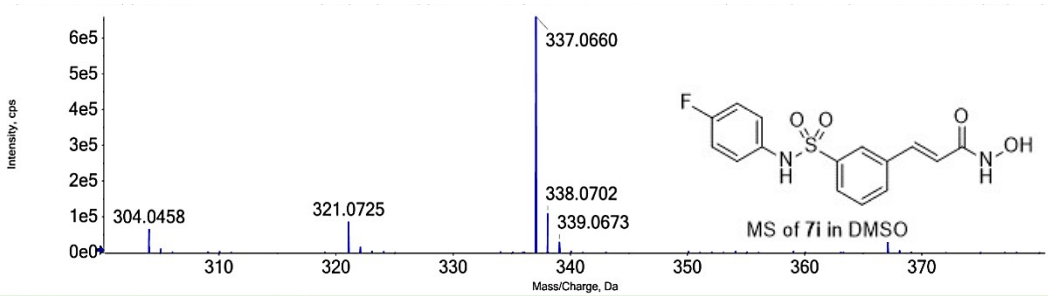

$^{13}$C-NMR of **7d** in DMSO


MS of 7d in DMSO
Intensity, cps
6e5
4e5
2e5
0e0
292.1032
309.1297
321.3182
325.1228
326.1275
327.1239
338.3442
347.1073
280
290
300
310
320
330
340
350
360
370
Mass/Charge, Da

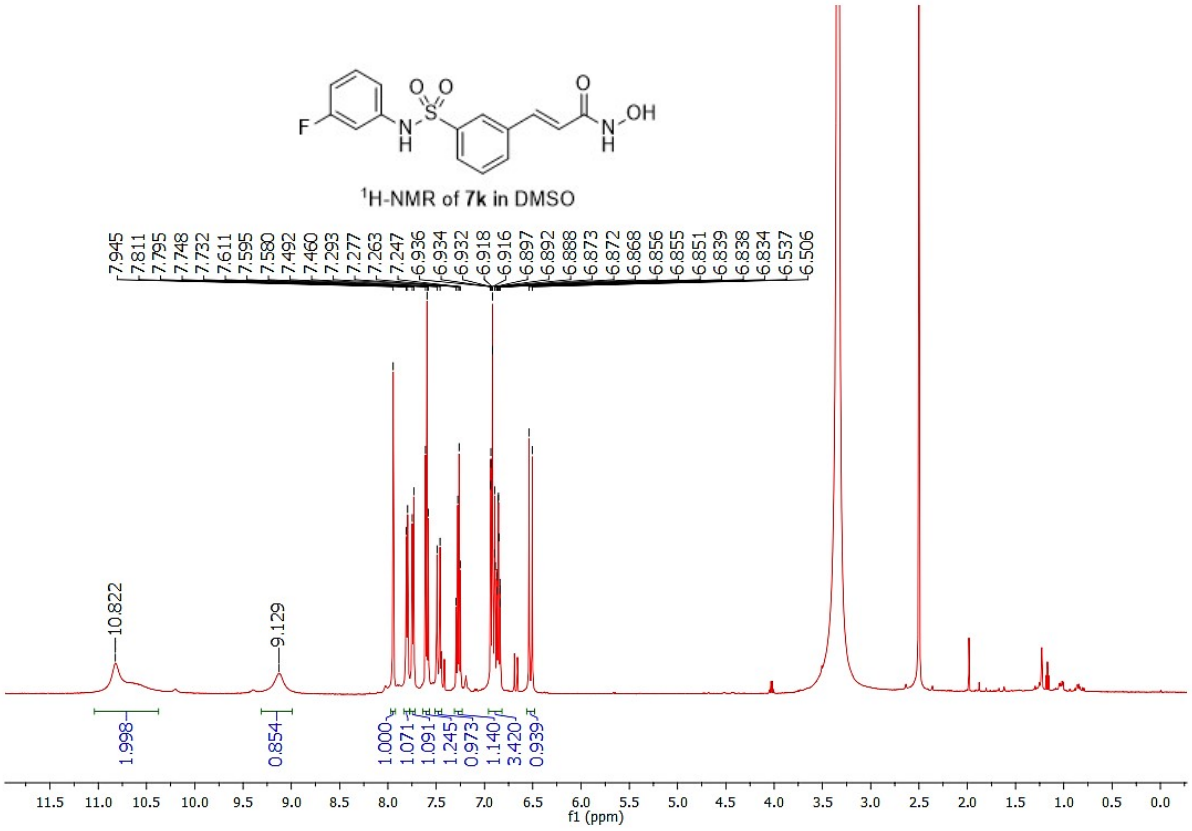

7.875
7.792
7.777
7.662
7.647
7.586
7.571
7.555
7.477
7.445
7.091
7.078
6.515
6.483
10.810
10.245
9.117
0.755
1.015
0.815
1.000
1.002
1.105
1.215
0.959
4.398
0.932
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

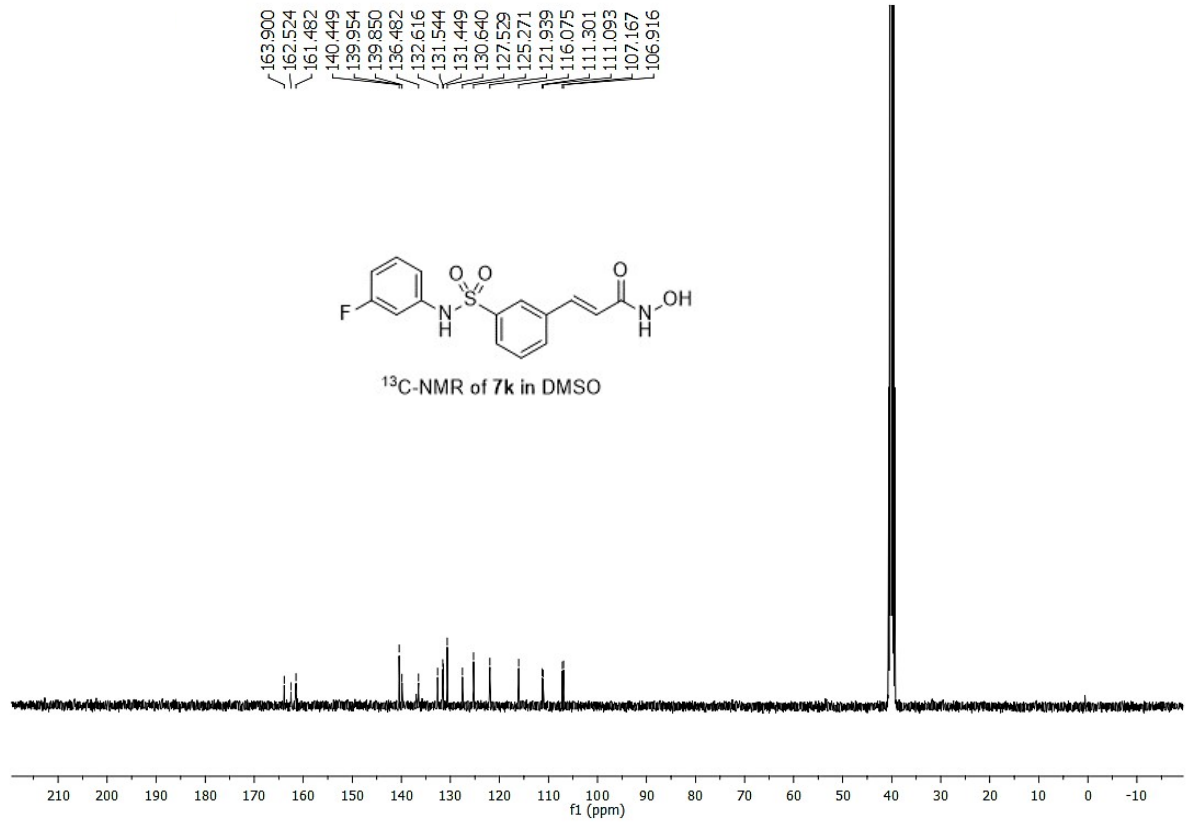


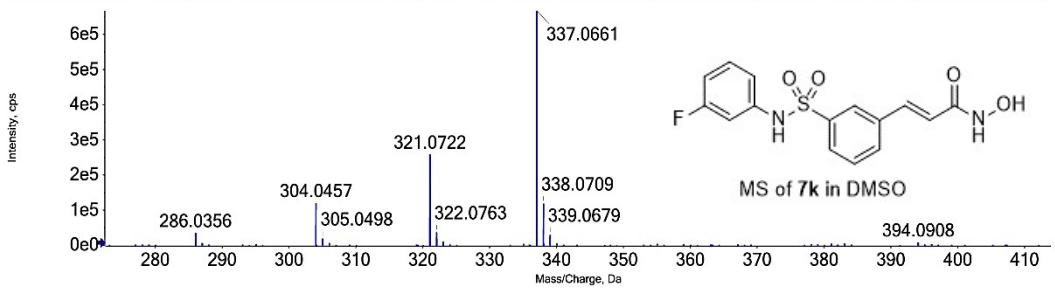

$^{13}$C-NMR of **7i** in DMSO

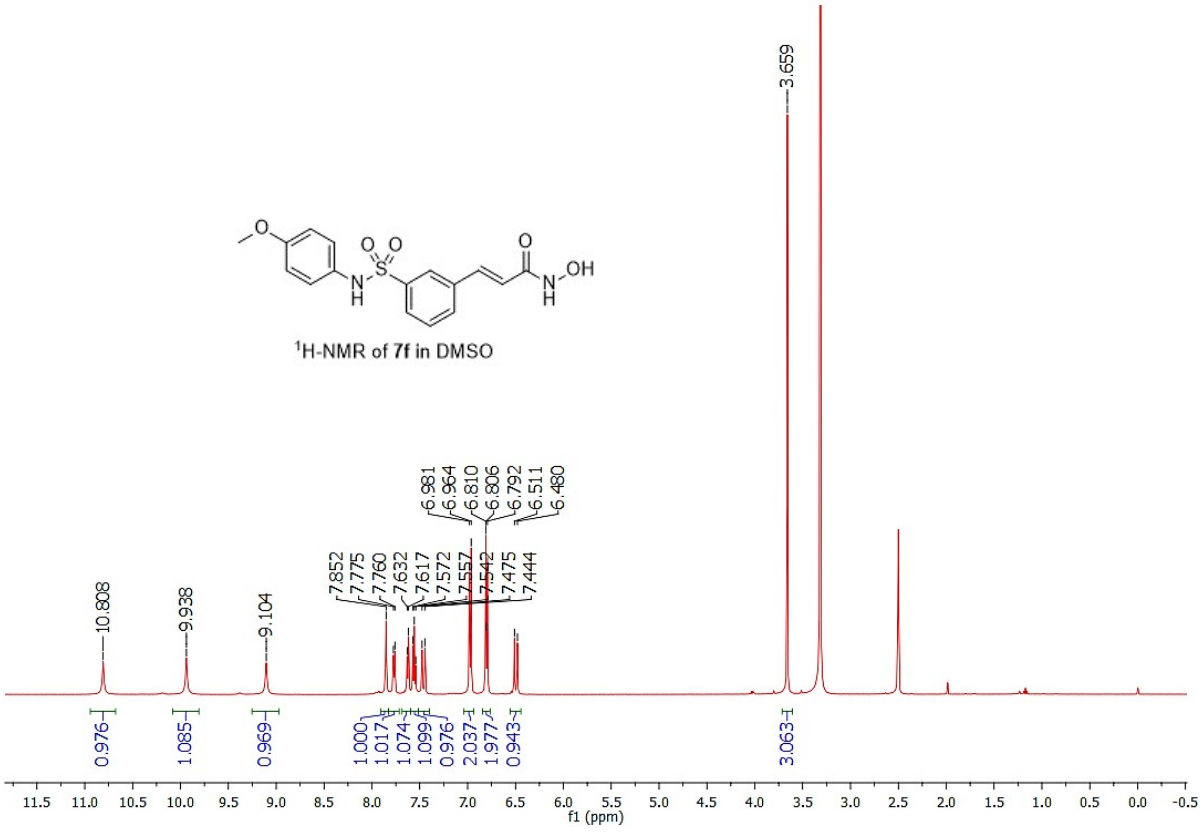


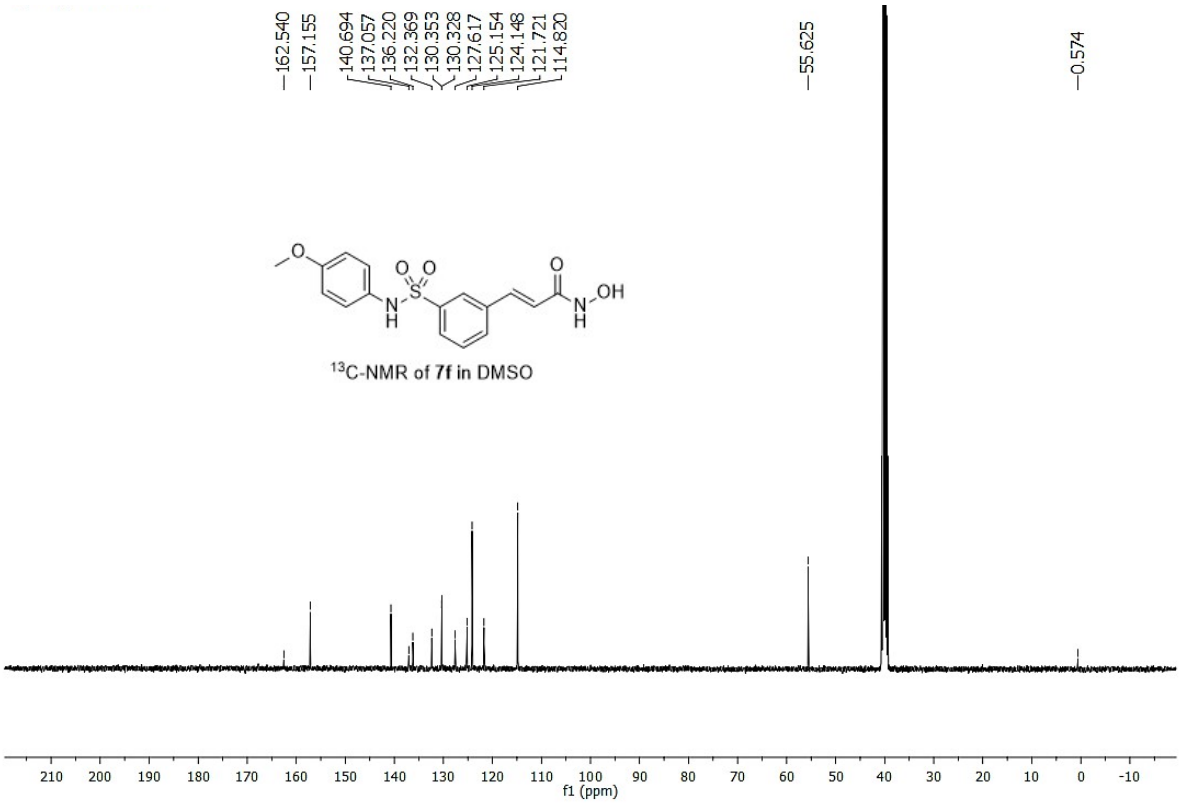

MS of **7i** in DMSO


F
N
H
O
O
S
O
N
H
OH
$^1$H-NMR of 7k in DMSO
7.945
7.811
7.795
7.748
7.732
7.611
7.595
7.580
7.492
7.460
7.293
7.277
7.263
7.247
6.936
6.934
6.932
6.918
6.916
6.897
6.892
6.888
6.873
6.872
6.868
6.856
6.855
6.851
6.839
6.838
6.834
6.537
6.506
10.822
9.129
1.998
0.854
1.000
1.071
1.091
1.245
0.973
1.140
3.420
0.939
f1 (ppm)

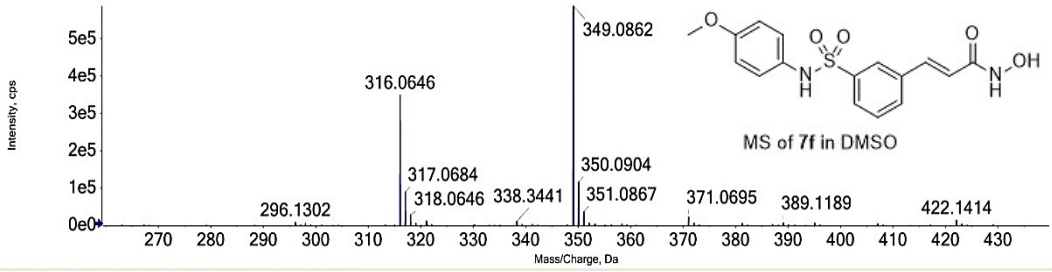

163.900
162.524
161.482
140.449
139.954
139.850
136.482
132.616
131.544
131.449
130.640
127.529
125.271
121.939
116.075
111.301
111.093
107.167
106.916
F
N
H
O
O
S
O
N
H
OH
$^{13}$C-NMR of 7k in DMSO
f1 (ppm)


Intensity, cps
6e5
5e5
4e5
3e5
2e5
1e5
0e0
337.0661
321.0722
304.0457
338.0709
286.0356
305.0498
322.0763
339.0679
394.0908
280
290
300
310
320
330
340
350
360
370
380
390
400
410
Mass/Charge, Da
MS of 7k in DMSO

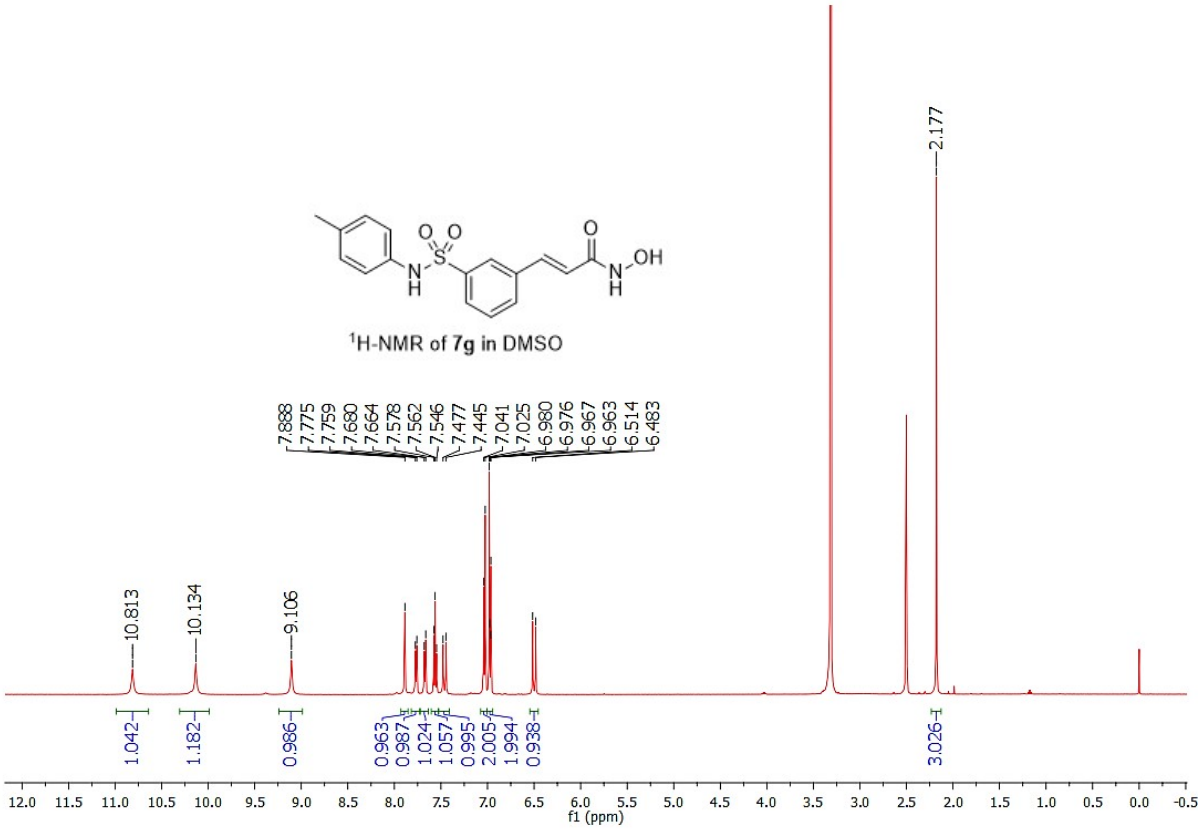

3.659
6.981
6.964
6.810
6.806
6.792
6.511
6.480
7.852
7.775
7.760
7.632
7.617
7.572
7.557
7.542
7.475
7.444
10.808
9.938
9.104
0.976
1.085
0.969
1.000
1.017
1.074
1.099
0.976
2.037
1.977
0.943
3.063
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
1H-NMR of 7f in DMSO



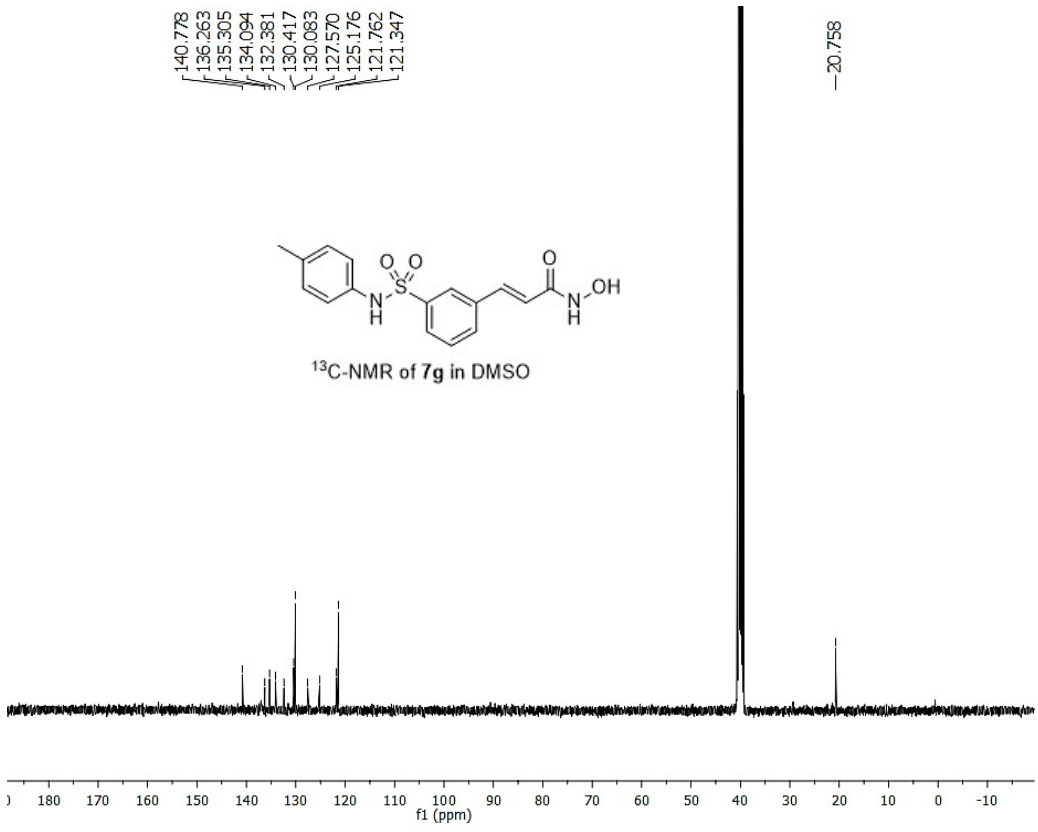

$^{13}$C-NMR of **7f** in DMSO



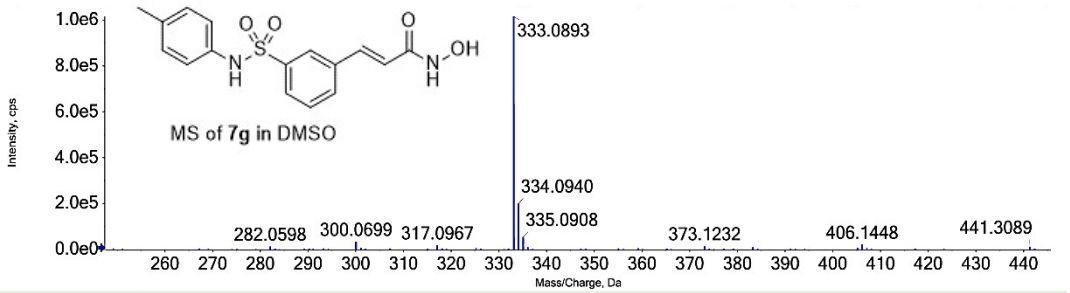

MS of **7f** in DMSO

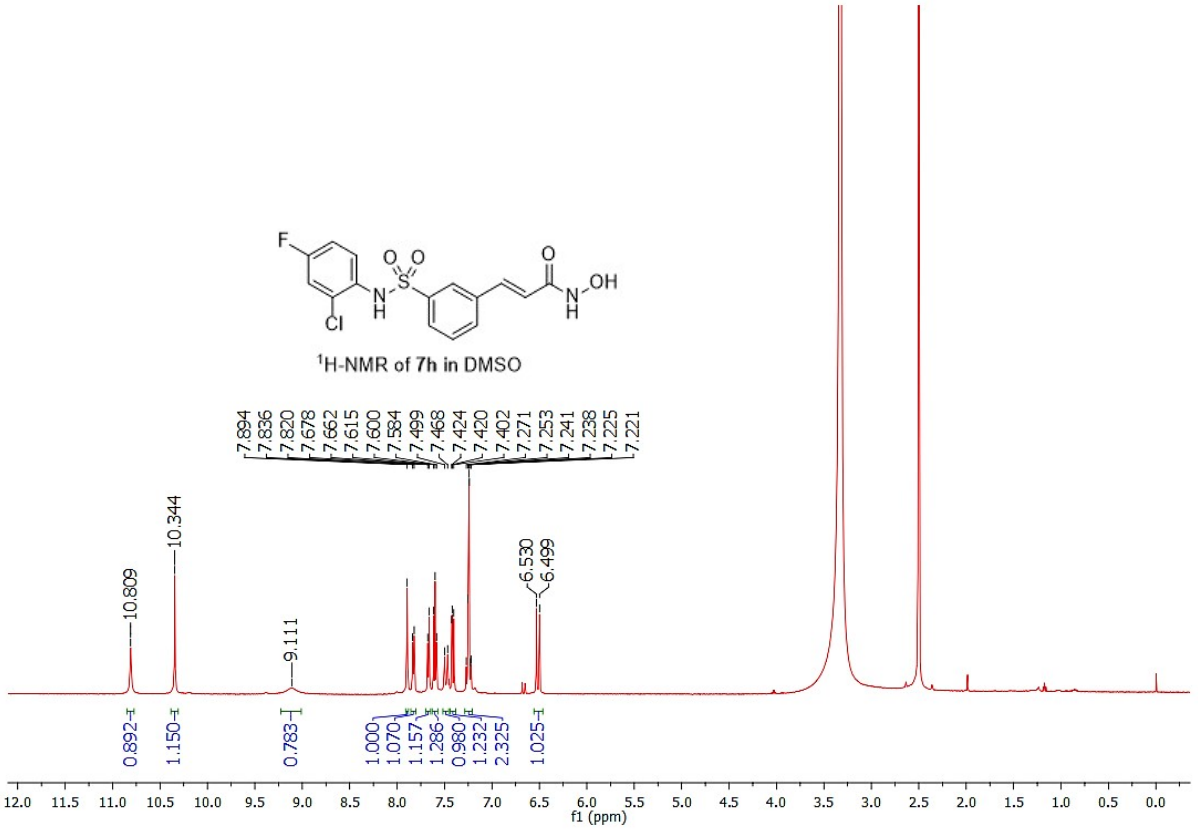


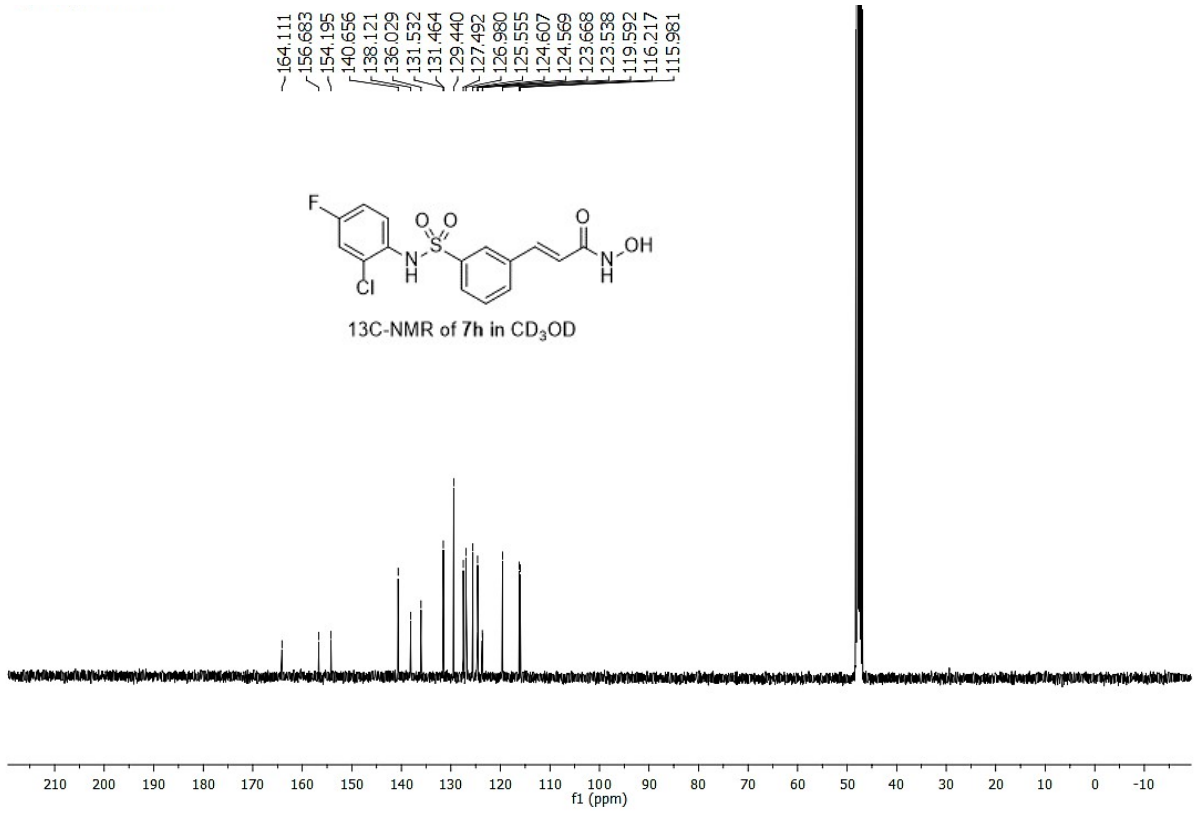

$^{1}$H-NMR of **7g** in DMSO

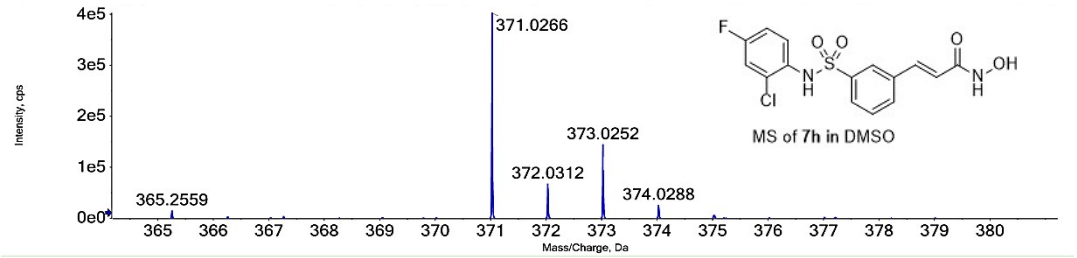


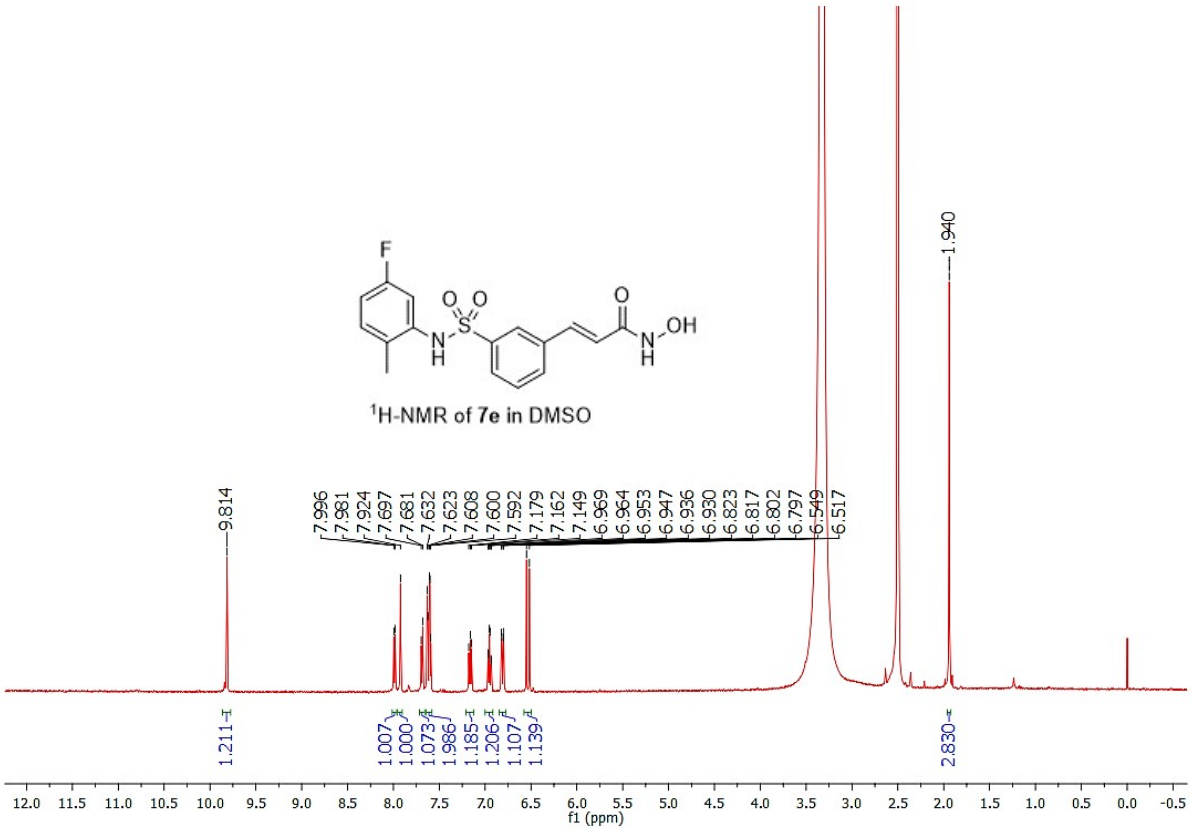

$^{13}$C-NMR of **7g** in DMSO

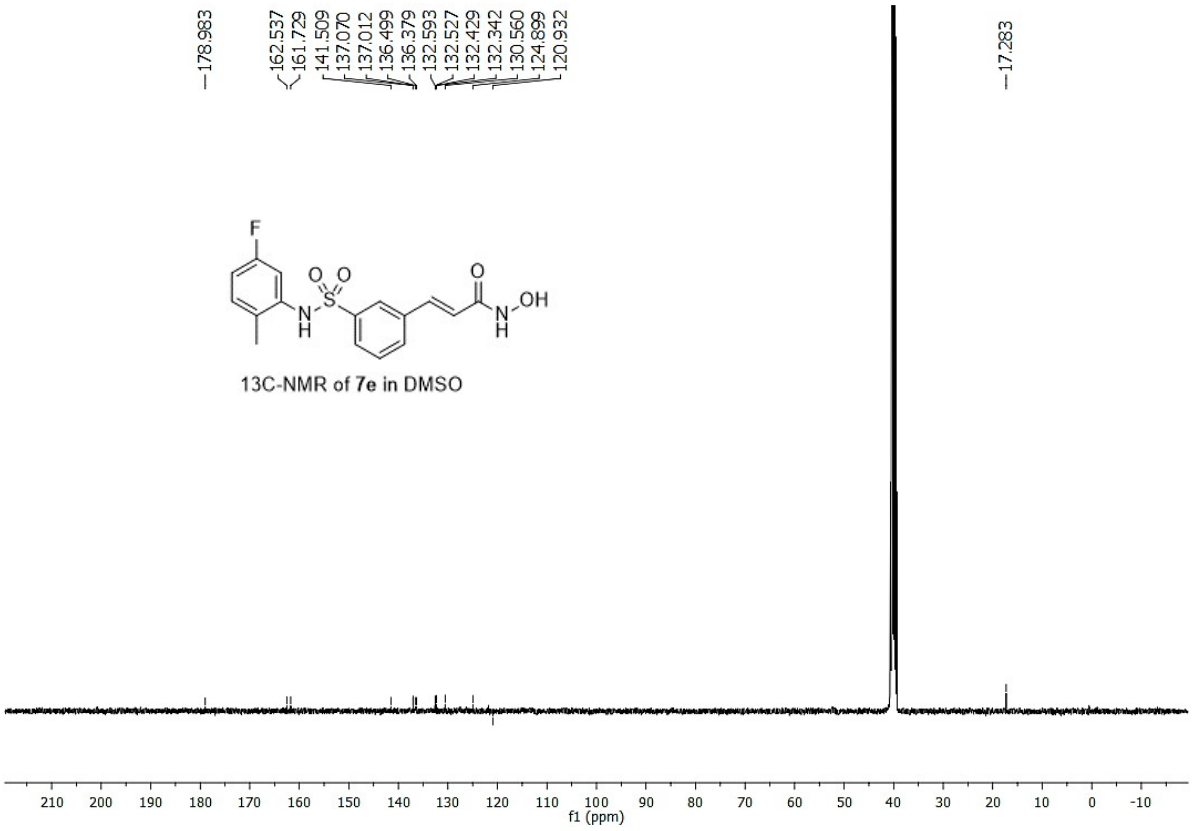

MS of 7g in DMSO
Intensity, cps
1.0e6
8.0e5
6.0e5
4.0e5
2.0e5
0.0e0
333.0893
334.0940
335.0908
282.0598
300.0699
317.0967
373.1232
406.1448
441.3089
260 270 280 290 300 310 320 330 340 350 360 370 380 390 400 410 420 430 440
Mass/Charge, Da


F
Cl
O
O
N
H
S
O
N
H
OH
1H-NMR of 7h in DMSO
7.894
7.836
7.820
7.678
7.662
7.615
7.600
7.584
7.499
7.468
7.424
7.420
7.402
7.271
7.253
7.241
7.238
7.225
7.221
10.809
10.344
9.111
6.530
6.499
0.892
1.150
0.783
1.000
1.070
1.157
1.286
0.980
1.232
2.325
1.025
f1 (ppm)

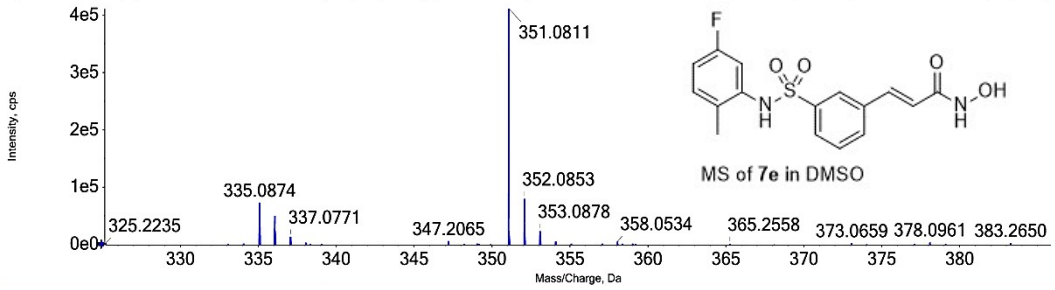

164.111
156.683
154.195
140.656
138.121
136.029
131.532
131.464
129.440
127.492
126.980
125.555
124.607
124.569
123.668
123.538
119.592
116.217
115.981
F
Cl
O
O
N
H
S
O
N
H
OH
13C-NMR of 7h in CD3OD
f1 (ppm)


4e5
3e5
2e5
1e5
0e0
Intensity, cps
371.0266
373.0252
372.0312
374.0288
365.2559
365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380
Mass/Charge, Da
F
Cl
O O
S
N H
O
N OH
H
MS of 7h in DMSO

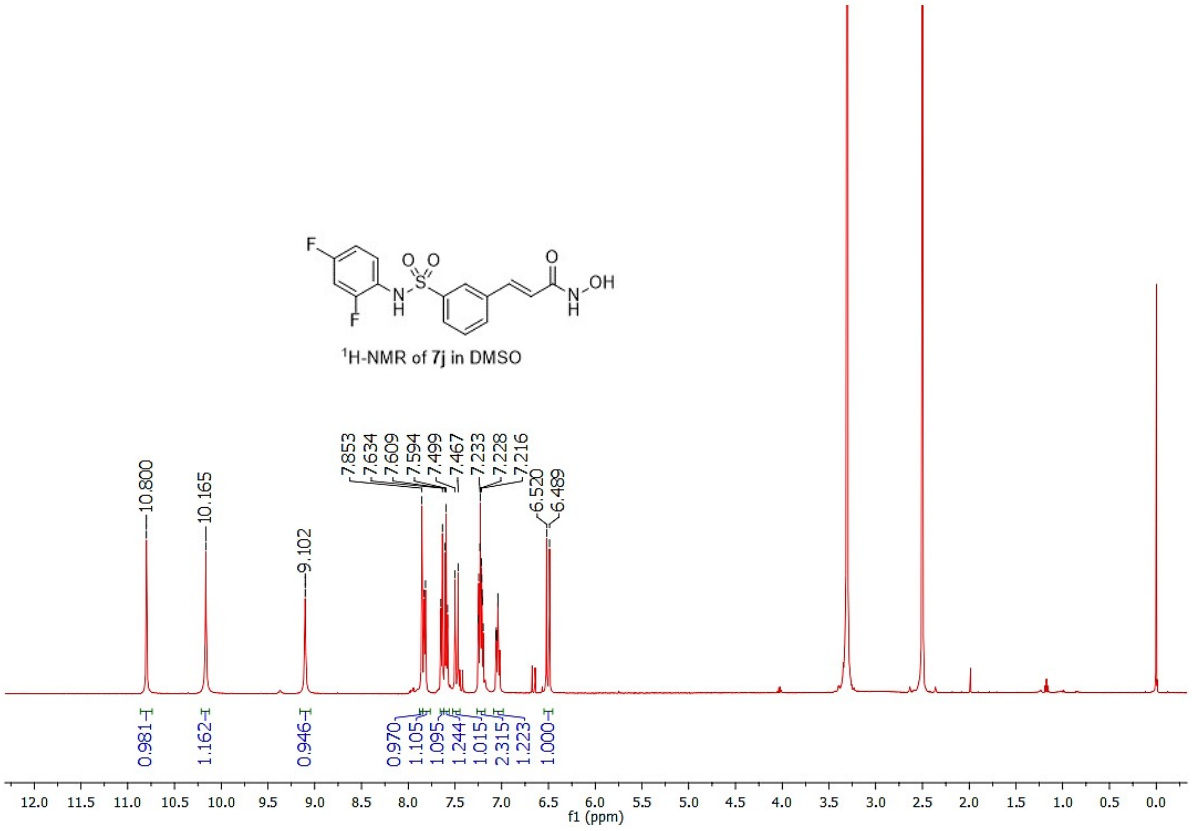

F
O O
S
N H
O
N OH
H
1H-NMR of 7e in DMSO
9.814
7.996
7.981
7.924
7.697
7.681
7.632
7.623
7.608
7.600
7.592
7.179
7.162
7.149
6.969
6.964
6.953
6.947
6.936
6.930
6.823
6.817
6.802
6.797
6.549
6.517
1.940
1.211
1.007
1.000
1.073
1.986
1.185
1.206
1.107
1.139
2.830
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



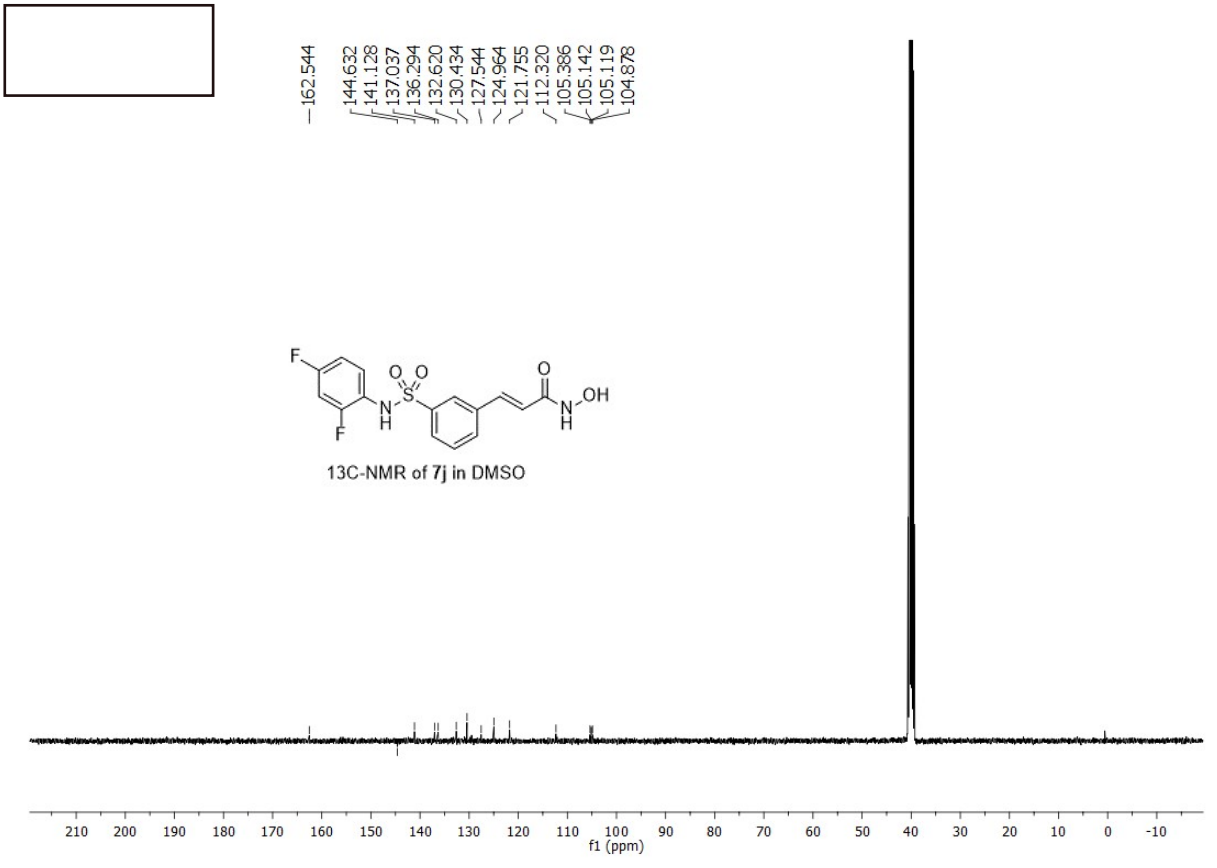

13C-NMR of **7e** in DMSO



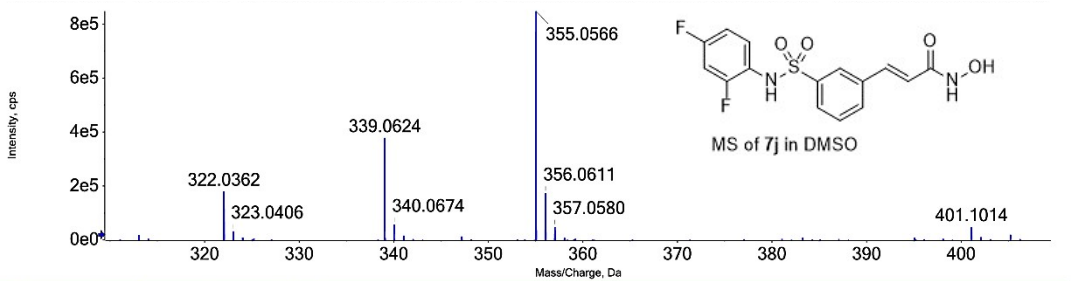

MS of **7e** in DMSO

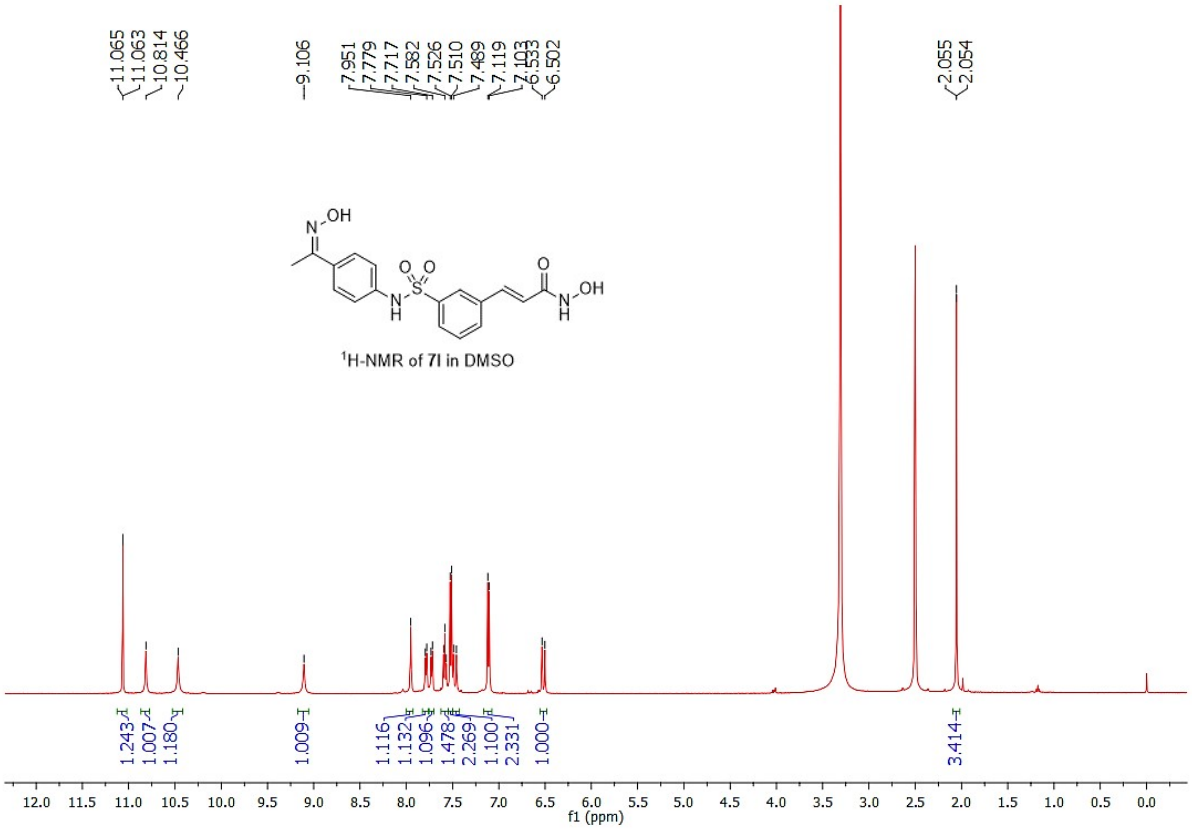


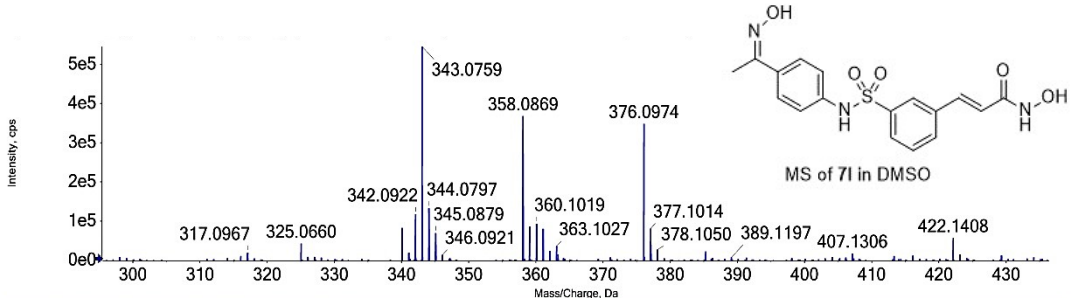

$^1$H-NMR of **7j** in DMSO




13C-NMR of **7j** in DMSO


Intensity, cps
Mass/Charge, Da
355.0566
339.0624
322.0362
323.0406
340.0674
356.0611
357.0580
401.1014
MS of 7j in DMSO


11.065
11.063
10.814
10.466
9.106
7.951
7.779
7.717
7.582
7.526
7.510
7.489
7.119
6.553
6.502
2.055
2.054
1.243
1.007
1.180
1.009
1.116
1.132
1.096
1.478
2.269
1.100
2.331
1.000
3.414
f1 (ppm)
¹H-NMR of 7l in DMSO


Intensity, cps
Mass/Charge, Da
343.0759
358.0869
376.0974
342.0922
344.0797
345.0879
346.0921
360.1019
363.1027
377.1014
378.1050
389.1197
407.1306
422.1408
317.0967
325.0660
MS of 7l in DMSO

## S3. Detailed description for docking studies

The molecular docking study utilizes AutoDock4Zn with Lamarckian genetic algorithm (LGA) for searching the optimum dock pose together with scoring function to calculate the binding affinity. AutoDock Tools (ADT) was employed to set up and performed docking calculation.
In this study, we performed the docking study assuming that having a rigid protein and consider the conformational space of the ligands to analyze the inductive effect of the hybrid compounds. To turn the protein molecule into a free receptor, the heteroatoms including water molecules were deleted and polar hydrogen atoms and Kollman charges were added. All other bonds were allowed to be rotatable. In the docking analysis, the binding site was enclosed in a box with the number of grid points in x × y × z directions (66 × 66 × 66) and a grid spacing of 0.375 Å. Initially, AutoGrid was run to generate the grid map of various atoms of the ligands and receptor. After the completion of the grid map, AutoDock was run by using autodock parameters as follows: GA population size, 150; maximum number of energy evaluations, 2 500 000; and the number of generations, 27 000. A maximum of 50 conformers were considered for each molecule, and the root-mean-square (RMS) cluster tolerance was set to 2.0 Å in each run. The redocking result is considered as reliable when the RMSD value does not exceed 2.0 Å.
The outputs from AutoDock modeling studies were analyzed using PyMOL, Discovery Studio Visualizer, LigPlus and Maestro (Schrödinger). PyMOL was used to calculate the distances of hydrogen bonds as measured between the hydrogen and its assumed binding partner.

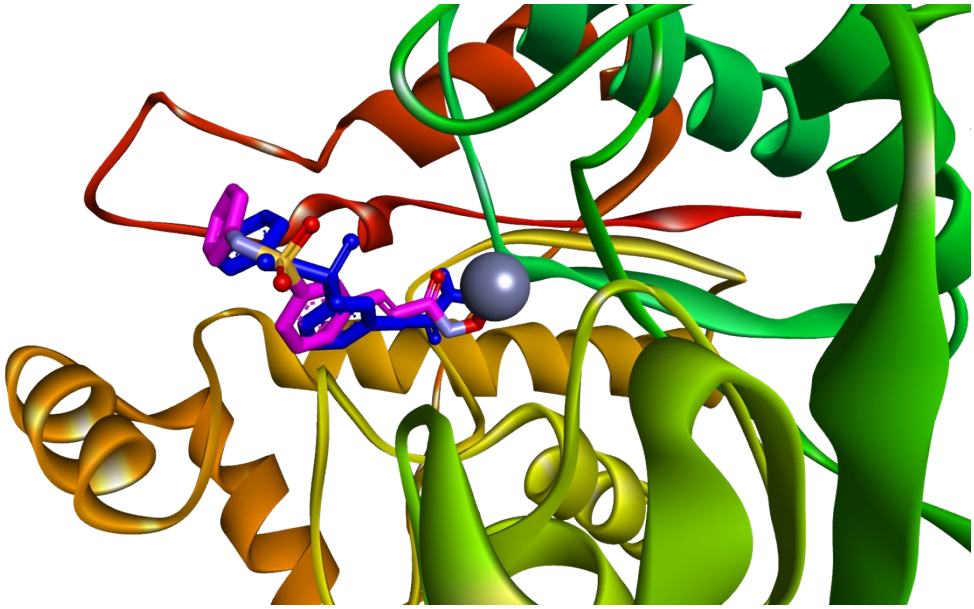


Fig S2: Redocking (blue) and co-crystallized belinostat (violet) in the HDAC6 binding site suggested. RMSD value of 1.4301 Å for backbone chain