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SUPPORTING INFORMATION

Novel Histone Deacetylase 6 Inhibitors Using Benzimidazole as Caps for Cancer Treatment

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Running title: Novel Histone Deacetylase 6 Inhibitors Using Benzimidazole as Caps for Cancer Treatment

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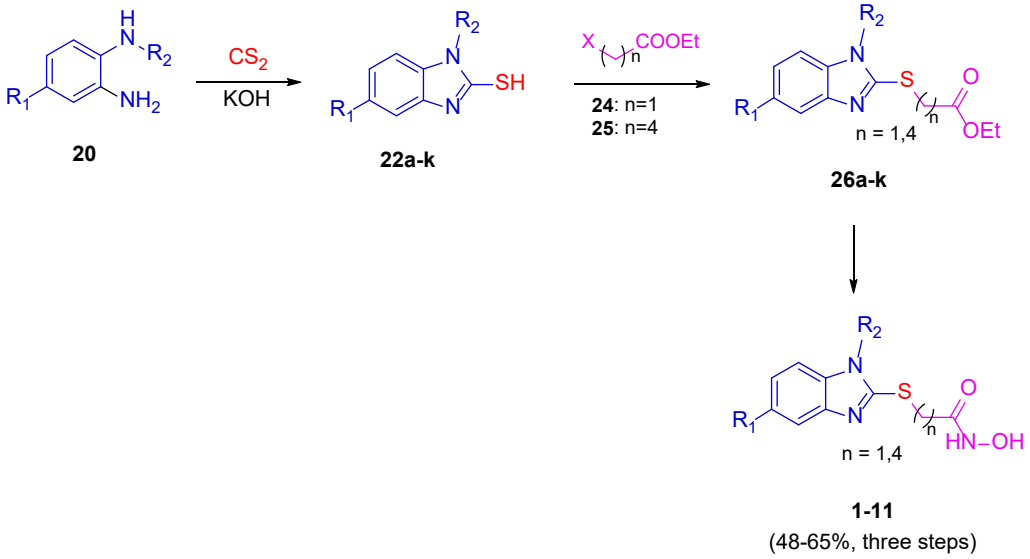
List of supplement material

S1. Chemistry

S1.1 General information

Reactions were monitored by thin-layer chromatography (TLC) on 0.2 mm pre-coated silica-gel 60 F254 plates (Merck). 1H NMR and 13C NMR spectra were measured with Bruker Avance 300 MHz, Bruker Avance 500 MHz and Bruker Avance 600 MHz spectrometers. Mass spectrometry (MS) data were recorded on an 1100 series LC-MSD-Trap-LS Agilent spectrometer and HRESI-MS observation was performed on a Bruker MicrOTOF-Q mass spectrometer. FT-IR was conducted using KBr pellet method on Thermo Nicolet 6700. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (Me4Si, $\delta = 0$); J values are given in Hertz.

S1.2 Preparation of benzimidazole based hydroxamates (1-11)



				Yield (%)			
	R_1	R_2	n	**22**	**26**	**1-11**	
a	H	H	4	85	75	79	**1**
b	Cl	H	4	91	83	81	**2**
c	OCH_3	H	4	87	85	65	**3**
d	H	Bn	4	90	86	78	**4**
e	CF_3	Bn	4	95	81	86	**5**
f	CF_3	*o*-Cl-Bn	4	92	83	76	**6**
g	H	*o*-Cl-Bn	4	89	89	72	**7**
h	H	Bn	1	90	89	73	**8**
i	CF_3	Bn	1	95	84	82	**9**
j	CF_3	*o*-Cl-Bn	1	92	87	74	**10**
k	H	*o*-Cl-Bn	1	89	91	70	**11**

Scheme S1. Synthesis of benzimidazole based hydroxamates

S1.2.1 General procedure for the synthesis of 2-mercaptobenzimidazoles (22a-k)

A mixture of **20** (5 mmol) and KOH (2 equiv) in ethanol (30 mL) was stirred at room temperature for 30 min, then CS_2 (2 equiv) was added and the resulting mixture was refluxed for 4-5 hrs. After

the reaction was finished (monitored by TLC), the solvent was removed under reduced pressure and 10 mL of water was added. Aqueous saturated solution of NH_4Cl was gradually added to adjust the pH to 7, which led to the formation of solid. The solid was filtered, washed with water and dried to give the corresponding 2-mercaptobenzimidazole derivatives **(22a-k)**, which were used for the next step without further purification.

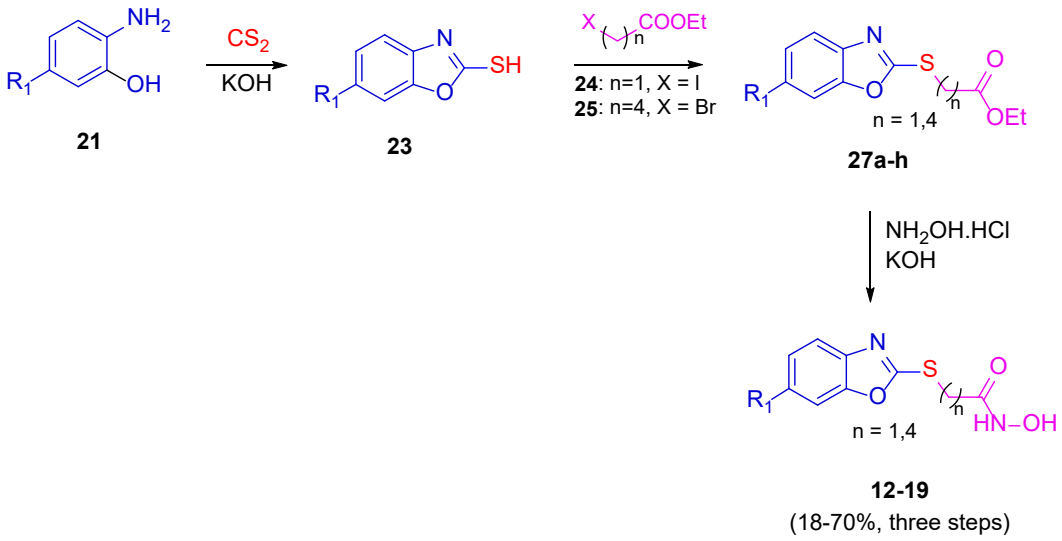
S1.2.2 General procedure for the synthesis of ester (26a-k)

A mixture of **(22a-k)** (2 mmol) and K_2CO_3 (3 equiv) in 10 mL acetone was stirred at room temperature for 30 min. Ester **24** or **25** (3 equiv) was added and the reaction mixture was stirred at 70℃ for 2-5 hrs. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water (10 mL), neutralised with aqueous saturated NH_4Cl solution and the organic layer was extracted by ethyl acetate (3×30 mL). The combined organic extracts were washed with a solution of saturated NaCl and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the corresponding intermediate esters (**26a-k**).

S1.2.3 General procedure for the synthesis of hydroxamates (1-11)

A solution of $NH_2OH.HCl$ (20 mmol) in ethanol (5 mL) was stirred at room temperature for 20 min and then at 0^{o}C for additional 10 min, then solution of KOH (20.5 mmol) in EtOH (6 mL) was added followed by solution of the intermediates **(26a-k)** (0.5 mmol) in ethanol (4 mL). The resulting mixture was stirred for 0.5-1 hrs. At the end of the reaction, the mixture was poured into water (50 mL), neutralised with a solution of HCl (1M) to pH 5-6 and extracted with ethyl acetacte (3×30 mL). The combined organic layers were washed with a solution of saturated NaCl, dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was recrystallized in (Hex:EtOAc = 1:2) to give the target compounds **(1-11)**.

S1.3 Preparation of benzoxazole based hydroxamates (12-19)



			Yield (%)			
	R_1	n	**23**	**27**	**12-19**	
a	H	1	84	86	65	**12**
b	CH_3	1	90	92	82	**13**
c	Cl	1	93	90	22	**14**
d	F	1	85	89	55	**15**
e	OCH_3	1	95	87	60	**16**
f	H	4	93	92	66	**17**
g	CH_3	4	98	94	76	**18**
h	OCH_3	4	95	89	68	**19**

Scheme S2. Synthesis of benzoxazole based hydroxamates

S1.3.1 General procedure for the synthesis of 2-mercaptobenzoxazoles (23a-h)

To a solution of KOH (1.5 mmol) in ethanol (10 mL) was added compound **21** (1.5 mmol) followed by carbon disulfide (3 mmol). The reaction mixture was stirred at 80°C for 2 hrs. After completion of the reaction (based on TLC), excess solvent was removed under reduced pressure and the

residue was dissolved in water (10 mL) and then acidified with dilute hydrochloric acid (10%) to pH 7, which led to the formation of solids. The solids were filtered off, washed with water and dried to give the corresponding 2-mercaptobenzoxazole derivatives **(23a-h)**, which was used for the next step without further purification.

S1.3.2 General procedure for the synthesis of esters (27a-h)

The intermediates 2-mercaptobenzoxazole (**23**) (0.8 mmol) was dissolved in 7 mL of acetone, then K_2CO_3 (1.2 mmol) was added and the mixture was stirred at room temperature for 15 min. Then ester (**24**) or (**25**) (0.96 mmol) was added slowly into the reaction mixture and the resulting mixture was stirred at 80℃ for 2 hrs. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the resulting mixture was poured into water (10 mL), neutralised with 5% HCl solution and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with a solution of saturated NaCl, dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the corresponding (**27a-h**).

S1.3.3 General procedure for the synthesis of benzoxazole based hydroxamates (12-19)

A solution of $NH_2OH.HCl$ (6 mmol) in ethanol (5 mL) was stirred at 0℃ for 15 min, then KOH (6.9 mmol) was added. The mixture was stirred for further 15 min then the solution of intermediates **(27a-h)** (0.3 mmol) in ethanol (2 mL) was added. The resulting mixture was stirred for 0.5-1 hrs. At the end of this reaction, excess solvent was removed under reduced pressure. The resulting mixture was poured into water (10 mL), neutralised with a 10% solution of HCl to pH~7, extracted with ethyl acetacte (3×10 mL). The combined organic layers were washed with a solution of saturated NaCl, dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to obtaine the products **(12-19)**.

S1.4 Spectral data

Spectral data of compounds **1** [1] and **8** [2] were previously described in literature.

5-((5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxypentanamide (2): Yield 61% as red solid. Mp 174-176°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3636, 3265, 2939, 2864, 2705, 1738, 1652, 1511, 1387, 1061, 808, 756, 434. HR-ESI-MS found *m/z* 300.0574 $[M+H]^+$ (calcd. 300.0495, $C_{12}H_{14}ClN_3O_2S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 12.68 (*d*, *J* = 13.0 Hz, 1H), 10.34 (*s*, 1H**)**, 8.66 (*s*, 1H), 7.55 (*s*, 0.55 H), 7.50 (*d*, *J* = 8.5 Hz, 0.55H), 7.33 (*s*, 0.46H), 7.35 (*d*, *J* = 8.5 Hz, 0.6H), 7.12 (*d*, *J* = 8.0 Hz, 1H), 3.27 (*t*, *J* = 6.5 Hz, 2H), 1.99 (*t*, *J* = 8.0 Hz, 2H), 1.66-1.71 (*m*, 4H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 168.8, 152.3, 151.8, 144.6, 142.5, 136.1, 134.2, 125.8, 125.5, 121.4, 121.3, 118.3, 116.7, 111.3, 110.0, 31.7, 30.7, 28.8, 24.2.

***N*-Hydroxy-5-((5-methoxy-1*H*-benzo[*d*]imidazol-2-yl)thio)pentanamide (3)**: Yield 48% as brown yellow solid. Mp 155-157°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3477, 3175, 2930, 2844, 2669, 2046, 1751, 1636, 1407, 1203, 756, 438. HR-ESI-MS found *m/z* 296.1070 $[M+H]^+$ (calcd. 296.0991, $C_{13}H_{17}N_3O_3S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 12.32 (*s*, 1H), 10.34 (*s*, 1H**)**, 8.66 (*s*, 1H), 7.38 (*d*, *J* = 8.5 Hz, 0.62H), 7.22 (*d*, *J* = 8.5 Hz, 0.49H), 7.07 (*s*, 0.48H), 6.86 (*d*, *J* = 2.0 Hz, 0.62H), 6.72-6.74 (*m*, 1H), 3.76 (*s*, 3H), 3.23 (*m*, 2H), 1.97 (*t*, *J* = 7.0 Hz, 2H), 1.63-1.65 (*m*, 4H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 168.8, 155.3, 155.0, 150.0, 148.2, 144.5, 138.2, 135.9, 129.8, 117.7, 110.5, 110.3, 109.9, 100.6, 94.1, 55.4, 31.7, 31.0, 28.9, 24.2.

5-((1-Benzyl-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxypentanamide (4): Yield 60% as white solid. Mp 165-167°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3430, 3244, 1643, 1620, 1421, 1384, 739, 728. HR-ESI-MS found *m/z* 356.1434 $[M+H]^+$ (calcd. 356.1354, $C_{19}H_{21}N_3O_2S$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 10.35 (*s*, 1H), 8.68 (*s*, 1H), 7.57-7.58 (*m*, 1H), 7.45-7.47 (*m*, 1H), 7.33 (*t*, *J* = 7.2 Hz, 2H), 7.27 (*t*, *J* = 7.2 Hz, 1H), 7.19 (*d*, *J* = 7.2 Hz, 2H), 7.13-7.17 (*m*, 2H), 5.39 (*s*, 2H), 3.33 (s, 2H), 1.97-1.99 (*m*, 2H), 1.69-1.72 (*m*, 2H), 1.61-1.65 (*m*, 2H). ^{13}C-NMR (150 MHz,

DMSO-d_6, δ ppm): 168.8, 151.6, 143.0, 136.4, 136.1, 128.7, 127.7, 127.0, 121.7, 121.6, 117.6, 109.7, 46.6, 31.7, 31.5, 28.6, 24.2.

5-((1-Benzyl-5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxypentanamide (5): Yield 66% as white solid. Mp 162-164°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3253, 3131, 2867, 1653, 1627, 1426, 1105, 729. HR-ESI-MS found *m/z* 424.1306 $[M+H]^+$ (calcd. 424.1228, $C_{20}H_{20}F_3N_3O_2S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.34 (*s*, 1H), 8.66 (*s*, 1H), 7.93 (*s*, 1H), 7.69 (*d*, *J* = 8.0 Hz, 1H), 7.49 (*d*, *J* = 8.5 Hz, 1H), 7.34 (*t*, *J* = 7.5 Hz, 2H), 7.28 (*t*, *J* = 7.5 Hz, 1H), 7.19 (*d*, *J* = 7.5 Hz, 2H), 5.46 (*s*, 2H), 3.34-3.39 (*m*, 2H), 1.99 (*t*, *J* = 9.0 Hz, 2H), 1.71-1.74 (*m*, 2H), 1.61-1.66 (*m*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 168.8, 154.9, 142.5, 138.5, 135.8, 128.8, 127.8, 126.9, 126.0, 123.9, 122.7, 122.5, 118.4, 114.8, 110.6, 46.9, 31.7, 31.5, 28.5, 24.1.

5-((1-(2-Chlorobenzyl)-5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxypentanamide (6): Yield 58% as white solid. Mp 166-168°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3407, 3242, 3074, 2928, 1629, 1331, 1102, 740. HR-ESI-MS found *m/z* 458.0916 $[M+H]^+$ (calcd. 458.0839, $C_{20}H_{19}ClF_3N_3O_2S$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 10.33 (*s*, 1H), 8.66 (*s*, 1H), 7.97 (*s*, 1H), 7.61 (*d*, *J* = 8.4 Hz, 1H), 7.54 (*dd*, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.49 (*dd*, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.34 (*td*, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.25 (*td*, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.61 (*d*, *J* = 7.2 Hz, 1H), 5.54 (*s*, 2H), 3.33 (s, 2H), 1.97 (*t*, *J* = 7.2 Hz, 2H), 1.67-1.71 (*m*, 2H), 1.58-1.62 (*m*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 168.8, 155.2, 142.5, 138.7, 132.9, 131.8, 129.7, 129.6, 127.8, 127.6, 126.0, 123.9, 122.9, 122.7, 118.7, 114.9, 110.5, 44.9, 31.7, 31.5, 28.5, 24.1.

5-((1-(2-Chlorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxypentanamide (7): Yield 57% as white solid. Mp 150-152°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3417, 3186, 2930, 1649, 1445, 1052, 745. HR-ESI-MS found *m/z* 390.1046 $[M+H]^+$ (calcd. 390.0965, $C_{19}H_{20}ClN_3O_2S$). ^{1}H-NMR (500

MHz, DMSO-d_6, δ ppm): 10.33 (*s*, 1H), 8.66 (*s*, 1H), 7.61 (*d*, J = 7.5 Hz, 1H), 7.53 (*dd*, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.37 (*d*, J = 7.5 Hz, 1H), 7.32 (*td*, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 7.23 (*t*, J = 7.5 Hz, 1H), 7.13-7.20 (*m*, 2H), 6.56 (*dd*, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 5.47 (*s*, 2H), 3.30-3.34 (*m*, 2H), 1.95-1.98 (*m*, 2H), 1.66-1.70 (*m*, 2H), 1.58-1.62 (*m*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 168.8, 151.9, 143.0, 136.3, 133.4, 131.6, 129.6, 129.4, 127.6, 127.4, 121.9, 121.8, 117.8, 109.6, 44.5, 31.7, 31.5, 28.6, 24.1.

2-((1-Benzyl-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxyacetamide (8): Yield 58% as white solid. Mp 177-179°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3251, 3035, 1663, 1420, 1382, 742, 727. HR-ESI-MS found *m/z* 314.0965 $[M+H]^+$ (calcd. 314.0885, $C_{16}H_{15}N_3O_2S$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 10.83 (*s*, 1H), 9.03 (*s*, 1H), 7.55-7.56 (*m*, 1H), 7.48-7.50 (*m*, 1H), 7.34 (*t*, J = 7.8 Hz, 2H), 7.28 (*t*, J = 7.8 Hz, 1H), 7.23 (*d*, J = 7.2 Hz, 2H), 7.16-7.18 (*m*, 2H), 5.42 (*s*, 2H), 4.02 (*s*, 2H). ^{13}C-NMR (150 MHz, DMSO-d_6, δ ppm): 163.9, 150.9, 142.8, 136.3, 136.2, 128.7, 127.7, 127.1, 121.9, 121.7, 117.7, 109.9, 46.7, 33.3.

2-((1-Benzyl-5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxyacetamide (9): Yield 65% as white solid. Mp 190-192°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3261, 3086, 2850, 1667, 1430, 1330, 1100, 723. HR-ESI-MS found *m/z* 382.0841 $[M+H]^+$ (calcd. 382.0759, $C_{17}H_{14}F_3N_3O_2S$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 10.83 (*s*, 1H), 9.05 (*s*, 1H), 7.89 (*s*, 1H), 7.72 (*d*, J = 8.4 Hz, 1H), 7.51 (*dd*, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.33-7.36 (*m*, 2H), 7.28-7.30 (*m*, 1H), 7.23 (*d*, J = 7.8 Hz, 2H), 5.49 (*s*, 2H), 4.06 (*s*, 2H). ^{13}C-NMR (150 MHz, DMSO-d_6, δ ppm): 163.7, 154.3, 142.3, 138.6, 135.7, 128.8, 127.9, 127.1, 125.8, 124.0, 122.6, 118.7, 114.8, 110.8, 47.1, 33.4.

2-((1-(2-Chlorobenzyl)-5-((difluoro-λ^3-methyl)-λ^2-fluoranyl)-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxyacetamide (10): Yield 59% as white solid. Mp 198-200°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3264, 3065, 2841, 1666, 1447, 1328, 1103, 808, 746. HR-ESI-MS found *m/z* 416.0446 $[M+H]^+$ (calcd. 416.0369, $C_{17}H_{13}ClF_3N_3O_2S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.82 (*s*,

1H), 9.04 (*s*, 1H), 7.93 (*s*, 1H), 7.64 (*d*, *J* = 8.5 Hz, 1H), 7.55 (*dd*, J_1 = 8.0 Hz, J_2 = 0.5 Hz, 1H), 7.51 (*dd*, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.36 (*td*, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.26 (*td*, J_1 = 7.5 Hz, J_2 = 0.5 Hz, 1H), 6.71 (*d*, *J* = 7.0 Hz, 1H), 5.58 (*s*, 2H), 4.04 (*s*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 163.6, 154.6, 142.2, 138.8, 132.8, 131.9, 129.8, 129.7, 127.9, 127.8, 126.0, 123.8, 123.0, 122.8, 118.9, 114.9, 110.7, 45.1, 33.4.

2-((1-(2-Chlorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*-hydroxyacetamide (11): Yield 57% as white solid. Mp 170-172°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3418, 3236, 2854, 1664, 1380, 1052, 741. HR-ESI-MS found *m/z* 348.0576 $[M+H]^+$ (calcd. 348.0495, $C_{16}H_{14}ClN_3O_2S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.80 (*s*, 1H), 9.02 (*s*, 1H), 7.59 (*d*, *J* = 7.5 Hz, 1H), 7.54 (*dd*, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.40 (*d*, *J* = 7.8 Hz, 1H), 7.34 (*td*, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.25 (*dd*, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.15-7.23 (*m*, 2H), 6.66 (*dd*, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 5.51 (*s*, 2H), 4.00 (*s*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 163.8, 151.2, 142.8, 136.3, 133.3, 131.7, 129.6, 129.5, 127.7, 127.6, 122.1, 121.9, 117.8, 109.7, 44.7, 33.4.

2-(Benzo[*d*]oxazol-2-ylthio)-*N*-hydroxyacetamide (12): Yield 43% as white solid. Mp 145-150°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3635, 3158, 2853, 1650, 1493, 1242, 1143, 1052, 743, 573. HR-ESI-MS found *m/z* 225.0332 $[M+H]^+$ (calcd. 225.0256, $C_9H_8N_2O_3S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.85 (*s*, 1H), 9.08 (*s*, 1H), 7.61-7.65 (*m*, 2H), 7.30-7.36 (*m*, 2H), 4.02 (*s*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 163.6, 163.2, 151.2, 141.1, 124.6, 124.3, 118.2, 110.2, 32.97.

2-((5-Methylbenzo[*d*]oxazol-2-yl)thio)-*N*-hydroxyacetamide (13): Yield 69% as white solid. Mp 135-140°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3472, 3174, 2979, 1651, 1482, 1161, 1042, 795, 550. HR-ESI-MS found *m/z* 239.045 $[M+H]^+$ (calcd. 239.0412, $C_{10}H_{10}N_2O_3S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.84 (*s*, 1H), 9.08 (*s*, 1H), 7.50 (*d*, *J* = 8.0 Hz, 1H), 7.42 (*s*, 1H), 7.13 (*dd, J_1*

= 8.0 Hz, J_2 = 0.5 Hz, 1H), 4.04 (*s*, 2H), 2.40 (*s*, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 163.4, 163.2, 149.5, 141.3, 134.0, 125.1, 118.1, 109.5, 32.9, 20.8.

2-((5-Chlorobenzo[*d*]oxazol-2-yl)thio)-*N*-hydroxyacetamide (14): Yield 18% as white solid. Mp 135-140°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3382, 3159, 2980, 2854, 1654, 1452, 1222, 1149, 802, 561. HR-ESI-MS found *m/z* 258.9943 $[M+H]^+$ (calcd. 258.9866, $C_9H_7ClN_2O_3S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.86 (*s*, 1H), 9.09 (*s*, 1H), 7.73 (*d*, *J* = 2.0 Hz, 1H), 7.68 (*d, J* = 8.5 Hz, 1H), 7.37 (*dd*, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 4.04 (*s*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 165.6, 163.0, 150.0, 142.4, 128.9, 124.2, 117.9, 111.4, 33.0.

(2-((5-Fluorobenzo[d]oxazol-2-yl)thio)-*N*-hydroxyacetamide (15): Yield 42% as white solid. Mp 136-139°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3303, 2945, 2915, 1630, 1500, 1476. HR-ESI-MS found m/z 243.0239 $[M+H]^+$ (calcd. 243.0161, $C_9H_7FN_2O_3S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.87 (*s*, 1H), 9.10 (*s*, 1H), 7.68 (*dd*, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 7.51 (*dd*, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 7.18 (*td*, J_1 = 9.5 Hz, J_2 = 2.5, 1H), 4.03 (*s*, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 165.9, 163.1, 160.4, 158.5, 147.8, 142.1, 142.0, 111.6, 111.4, 111.0, 110.9, 105.1, 104.8, 33.0.

***N*-Hydroxy-2-((5-methoxybenzo[*d*]oxazol-2-yl)thio)acetamide (16)**: Yield 50% as white solid. Mp 154-156°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3224, 2992, 2836, 1659, 1478, 1440. HR-ESI-MS found *m/z* 255.0438 $[M+H]^+$ (calcd. 255.0361, $C_{10}H_{10}N_2O_4S$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 10.85 (*s*, 1H), 9.09 (*s*, 1H), 7.52 (*d, J* = 9.0 Hz, 1H), 7.17 (*d*, *J* = 2.4 Hz, 1H), 6.89 (*dd*, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 3.99 (*s*, 2H), 3.79 (*s*, 3H). ^{13}C-NMR (150 MHz, DMSO-d_6, δ ppm): 164.1, 163.3, 157.0, 145.9, 142.2, 111.8, 110.3, 102.2, 55.8, 33.0.

5-(Benzo[*d*]oxazol-2-ylthio)-*N*-hydroxypentanamide (17): Yield 56% as white solid. Mp 115-116°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3458, 3247, 2905, 1721, 1649, 1494, 1458. HR-ESI-MS found *m/z* 267.0805 $[M+H]^+$ (calcd. 267.0725, $C_{12}H_{14}N_3O_2S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.35 (*s*, 1H), 8.67 (*s*, 1H), 7.63-7.65 (*m,* 2H), 7.29-7.35 (*m*, 2H), 3.33 (*s*, 2H), 2.01 (*t*, *J* = 7.5 Hz,

2H), 1.76 (quin, J = 7.5 Hz, 2H), 1.65 (*quin*, J = 7.5 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 168.7, 164.4, 151.2, 141.3, 124.5, 124.2, 118.2, 110.1, 31.6, 31.4, 28.5, 24.1.

***N*-Hydroxy-5-((5-methylbenzo[d]oxazol-2-yl)thio)pentanamide (18)**: Yield 70% as white solid. Mp 136-138°C; FT-IR (KBr) ν_{max} (cm^{-1}): 3428, 3221, 2920, 1655, 1484. HR-ESI-MS found *m/z* 281.9902 $[M+H]^+$ (calcd. 281.0882, $C_{13}H_{16}N_3O_2S$). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.35 (*s*, 1H), 8.67 (*d*, J = 1.0 Hz, 1H), 7.50 (*d*, J = 8.5 Hz, 1H), 7.44 (*s*, 1H), 7.12 (*dd*, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 3.30 (2H), 2.40 (s, 3H), 2.01 (*t*, J = 7.5 Hz, 2H), 1.76 (*quin*, J = 7.5 Hz, 2H), 1.65 (*quin*, J = 7.5 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 168.7, 164.2, 149.4, 141.5, 133.9, 124.9, 118.1, 109.5, 31.6, 31.3, 28.5, 24.0, 20.9.

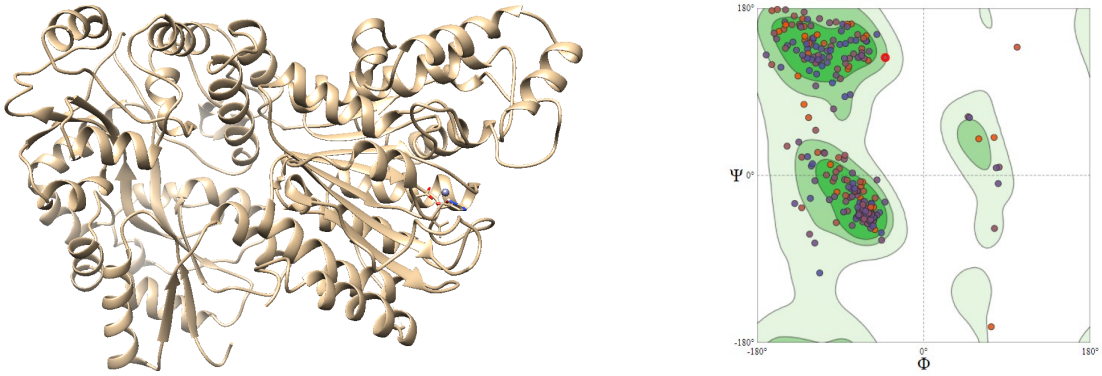
***N*-Hydroxy-5-((5-methoxybenzo[*d*]oxazol-2-yl)thio)pentanamide (19)**: Yield 57% as white solid. Mp 115-116°C. FT-IR (KBr) ν_{max} (cm^{-1}): 3458, 3247, 2905, 1721, 1649, 1494, 1458. HR-ESI-MS found *m/z* 297.0908 $[M+H]^+$ (calcd. 297.8331, $C_{13}H_{16}N_2O_4S$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 10.35 (*s*, 1H), 8.68 (*s*, 1H), 7.52 (*d, J* = 9.0 Hz, 1H), 7.22 (*d*, J = 2.4 Hz, 1H), 6.87 (*dd*, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 3.79 (*s*, 3H), 3.30 (*t*, J = 6.6 Hz, 2H), 2.00 (*t*, J = 7.2 Hz, 2H), 1.75 (*quin*, J = 7.8 Hz, 2H), 1.64 (*quin*, J = 7.8 Hz, 2H). ^{13}C-NMR (150 MHz, DMSO-d_6, δ ppm): 168.7, 164.9, 156.9, 145.7, 142.2, 111.6, 110.2, 102.1, 55.8, 31.6, 31.4, 28.5, 24.1.

S2. 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 (64 × 64 × 64) 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, 300; 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.

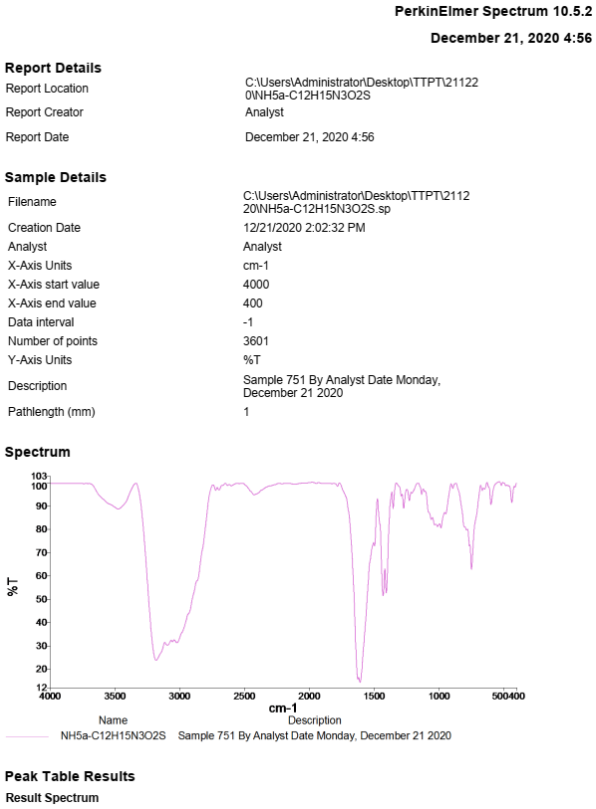
The outputs from AutoDock modeling studies were analyzed using PyMOL, Discovery Studio Visualizer. PyMOL was used to calculate the distances of hydrogen bonds as measured between the hydrogen and its assumed binding partner.



(A) (B)

Figure S2.1. (A) Swiss-Model of HDAC11; (B) Ramachandran plot analysis of the structure of HAC11 model

S3. Scanned NMR spectra of compounds (1-19)



PerkinElmer Spectrum 10.5.2

December 21, 2020 4:56

Report Details

Report Location	C:\Users\Administrator\Desktop\TTPT\211220\NH5a-C12H15N3O2S
Report Creator	Analyst
Report Date	December 21, 2020 4:56

Sample Details

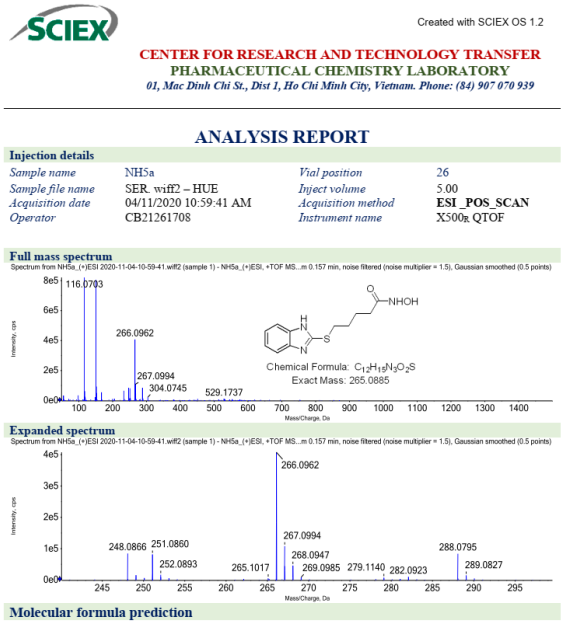
Filename	C:\Users\Administrator\Desktop\TTPT\211220\NH5a-C12H15N3O2S.sp
Creation Date	12/21/2020 2:02:32 PM
Analyst	Analyst
X-Axis Units	cm-1
X-Axis start value	4000
X-Axis end value	400
Data interval	-1
Number of points	3601
Y-Axis Units	%T
Description	Sample 751 By Analyst Date Monday, December 21 2020
Pathlength (mm)	1

Spectrum

Peak Table Results

Result Spectrum

Figure S3.1 IR spectrum of compound **1**



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01, Mac Dinh Chi St., Dist 1, Ho Chi Minh City, Vietnam. Phone: (84) 907 070 939

ANALYSIS REPORT

Injection details

Sample name	NH5a	*Vial position*	26
Sample file name	SER. wiff2 – HUE	*Inject volume*	5.00
Acquisition date	04/11/2020 10:59:41 AM	*Acquisition method*	**ESI_POS_SCAN**
Operator	CB21261708	*Instrument name*	X500B QTOF

Full mass spectrum

Expanded spectrum

Molecular formula prediction

Figure S3.2 MS spectrum of compound **1**

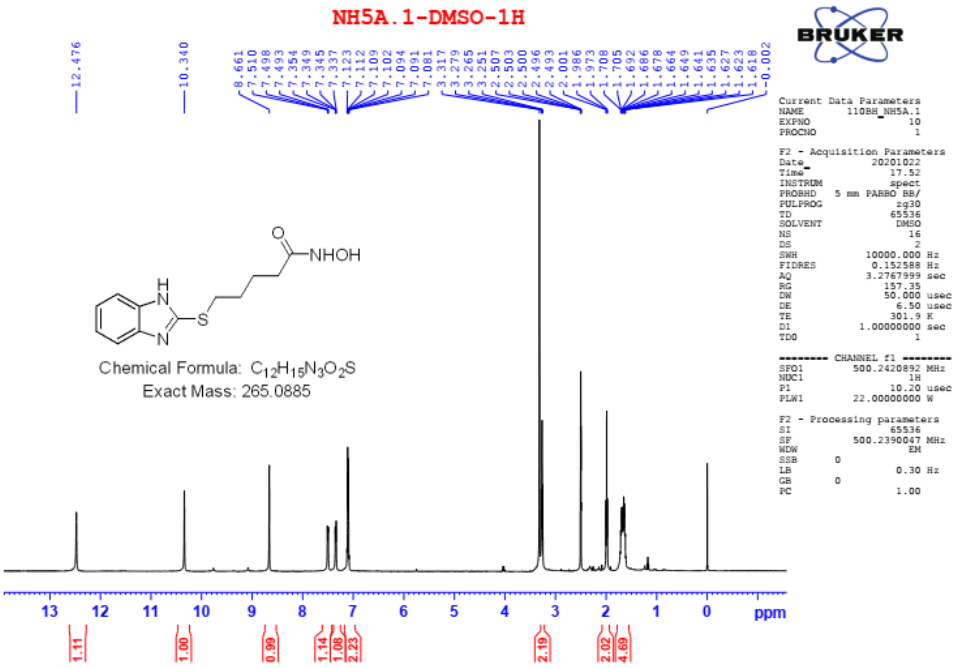

Figure S3.3 ^{1}H-NMR spectrum of compound **1**

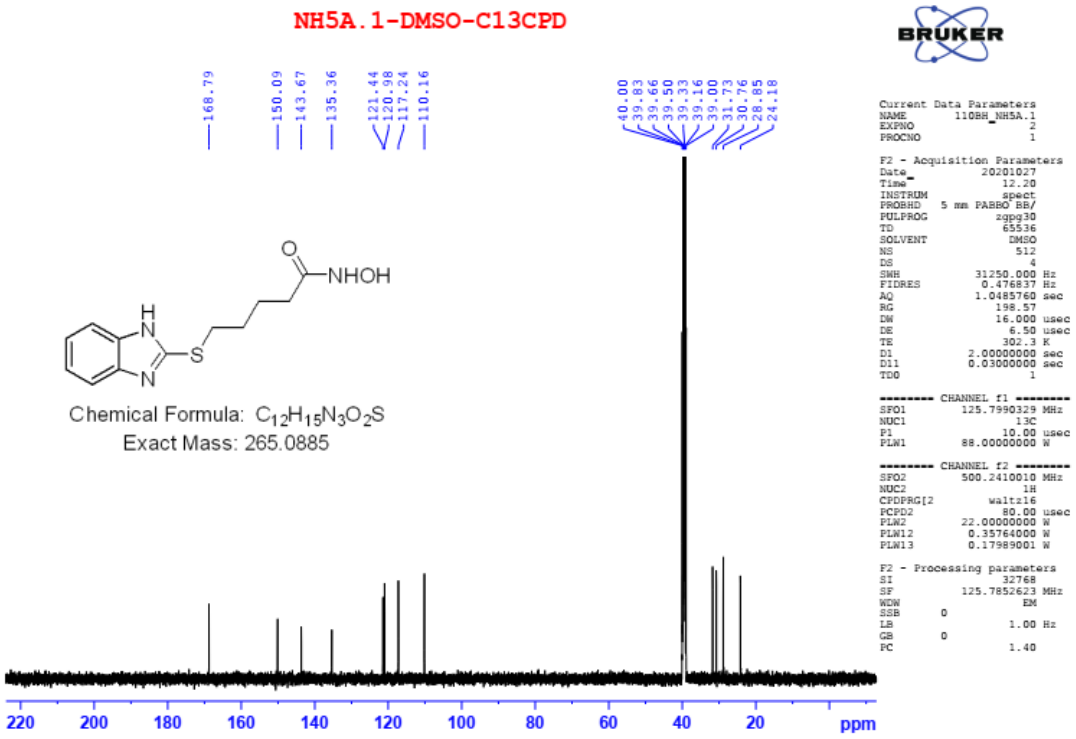

Figure S3.4 ^{13}C-NMR spectrum of compound **1**

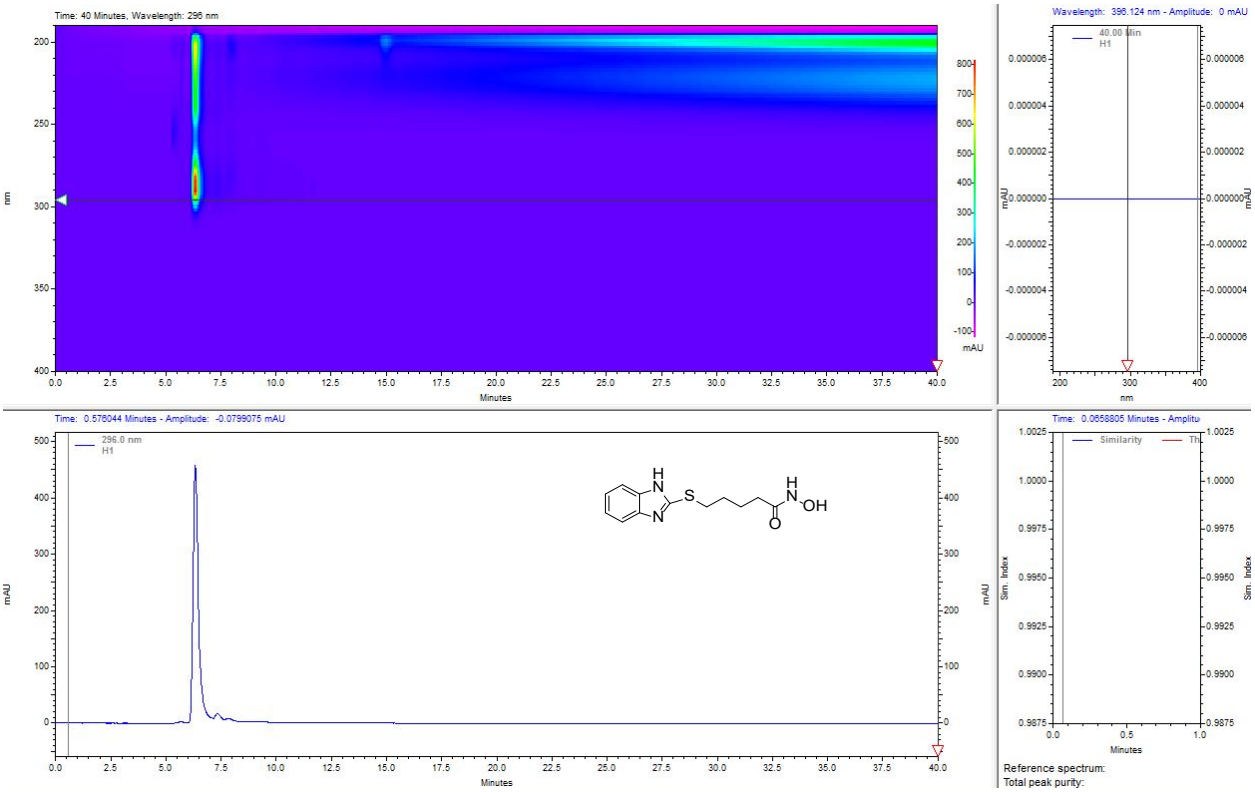

Figure S3.5 HPLC spectrum of compound **1**

PerkinElmer Spectrum 10.5.2

December 21, 2020 4:53

Report Details

Report Location	C:\Users\Administrator\Desktop\TTPT\21122 0\NH5b-C12H14ClPN3O2S
Report Creator	Analyst
Report Date	December 21, 2020 4:53

Sample Details

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Analyst	Analyst
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X-Axis start value	4000
X-Axis end value	400
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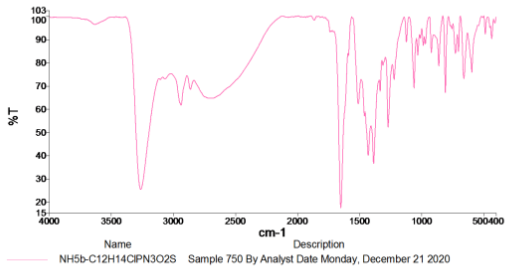
Number of points	3601
Y-Axis Units	%T
Description	Sample 750 By Analyst Date Monday, December 21 2020
Pathlength (mm)	1

Spectrum



Peak Table Results

Result Spectrum

Figure S3.6 IR spectrum of compund **2**

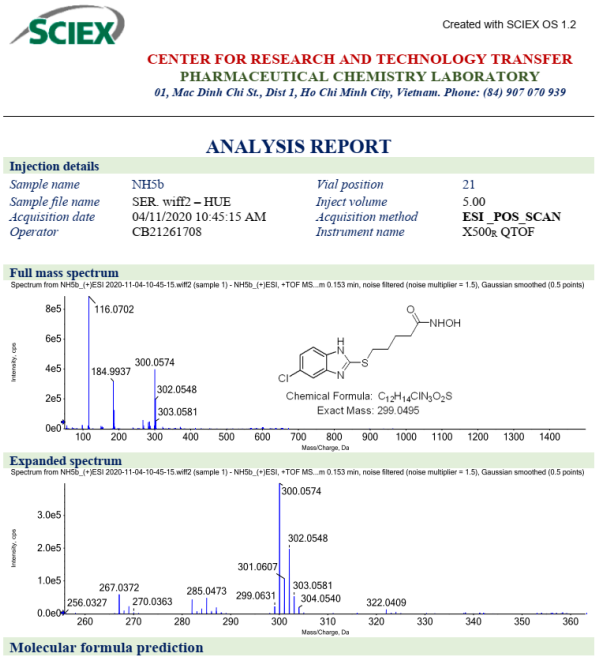


Figure S3.7 MS spectrum of compound **2**

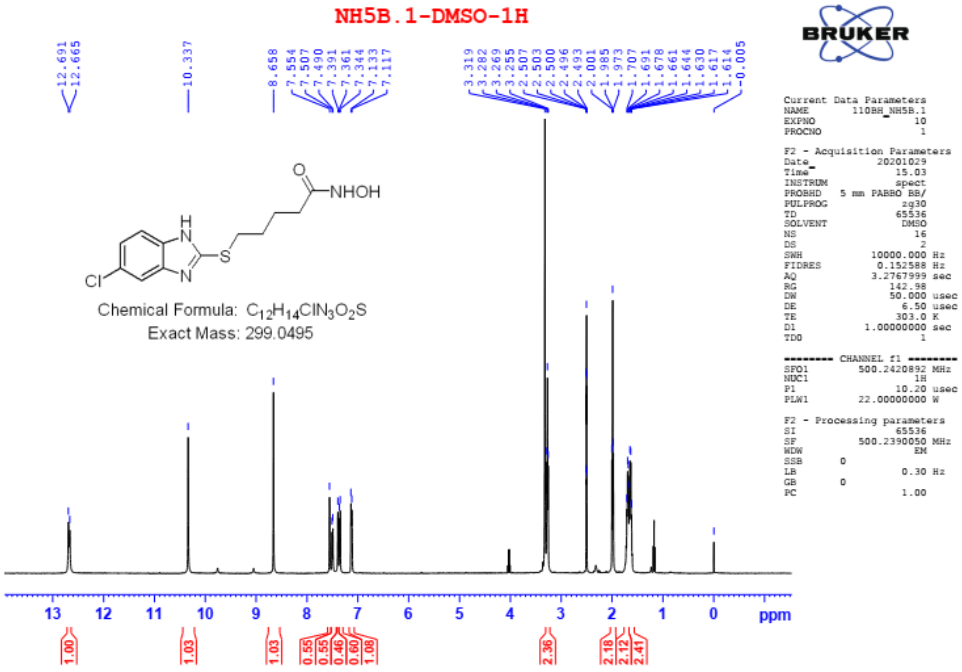


Figure S3.8 ^{1}H-NMR spectrum of compound **2**

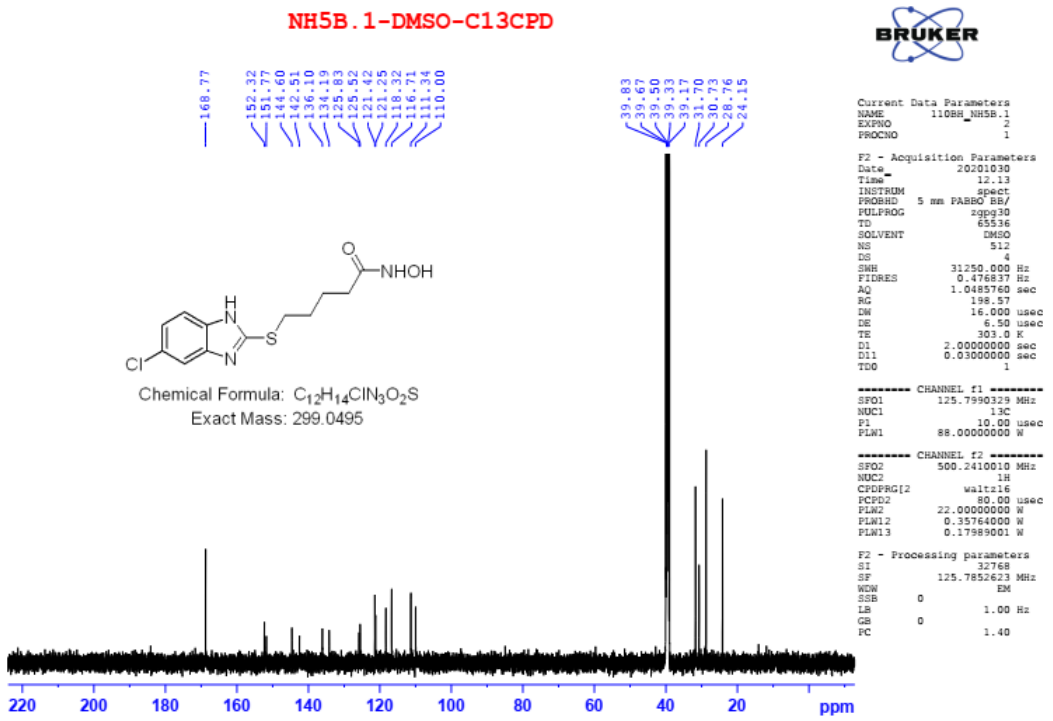


Figure S3.9 ^{13}C-NMR spectrum of compound **2**

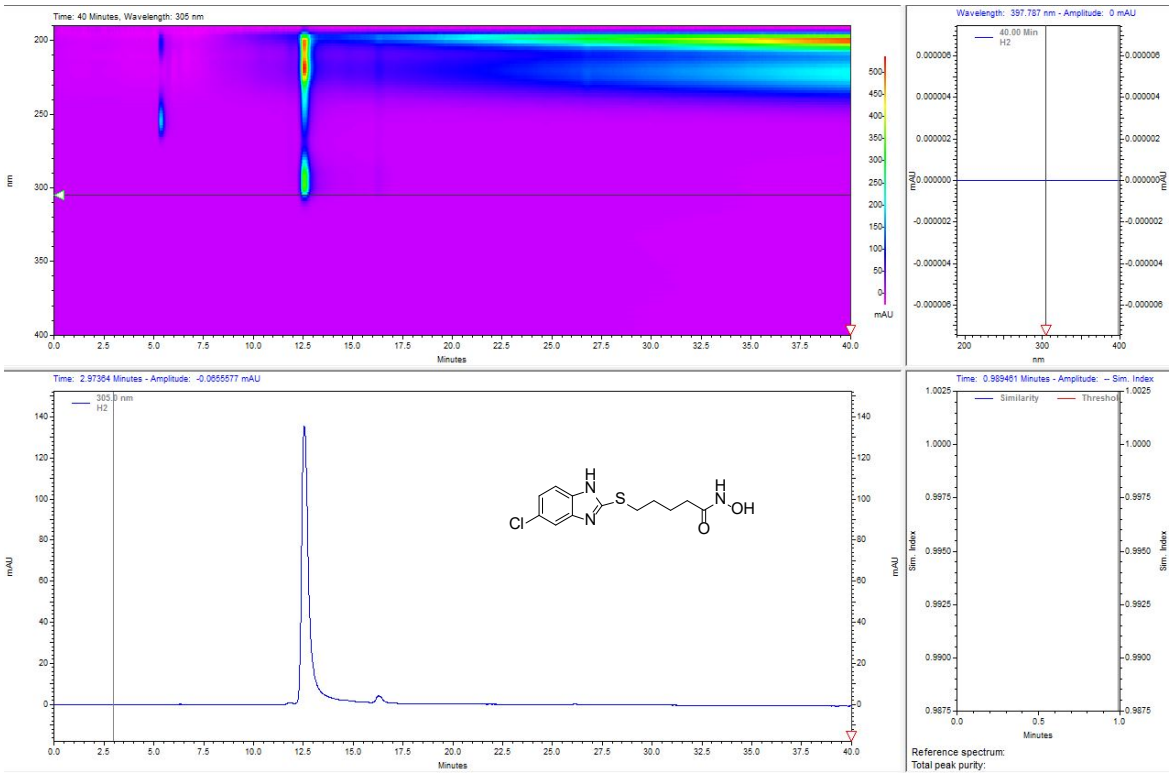


Figure S3.10 HPLC spectrum of compound **2**

PerkinElmer Spectrum 10.5.2

December 21, 2020 4:52

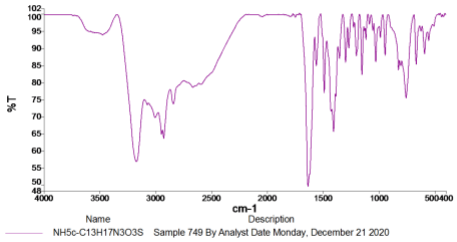
Report Details

Report Location	C:\Users\Administrator\Desktop\TTPT\21122 0\NH5c-C13H17N3O3S
Report Creator	Analyst
Report Date	December 21, 2020 4:52

Sample Details

Filename	C:\Users\Administrator\Desktop\TTPT\2112 20\NH5c-C13H17N3O3S.sp
Creation Date	12/21/2020 1:55:11 PM
Analyst	Analyst
X-Axis Units	cm-1
X-Axis start value	4000
X-Axis end value	400
Data interval	-1
Number of points	3601
Y-Axis Units	%T
Description	Sample 749 By Analyst Date Monday, December 21 2020
Pathlength (mm)	1

Spectrum



Peak Table Results

Result Spectrum

Figure S3.11 IR spectrum of compund **3**

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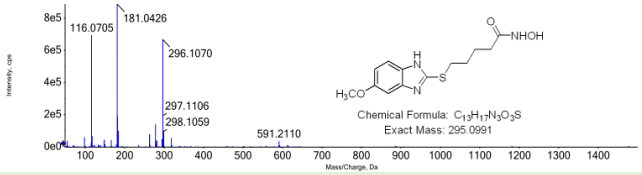
ANALYSIS REPORT

Injection details

Sample name	NH5c	*Vial position*	22
Sample file name	SER. wiff2 – HUE	*Inject volume*	5.00
Acquisition date	04/11/2020 10:48:30 AM	*Acquisition method*	**ESI _POS_SCAN**
Operator	CB21261708	*Instrument name*	X500R QTOF

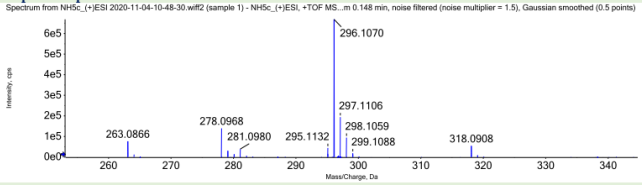
Full mass spectrum

Spectrum from NH5c_(+)ESI 2020-11-04-10-48-30.wiff2 (sample 1) - NH5c_(+)ESI, +TOF MS...m 0.148 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)



Expanded spectrum

Spectrum from NH5c_(+)ESI 2020-11-04-10-48-30.wiff2 (sample 1) - NH5c_(+)ESI, +TOF MS...m 0.148 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)



Molecular formula prediction

Figure S3.12 MS spectrum of compound **3**

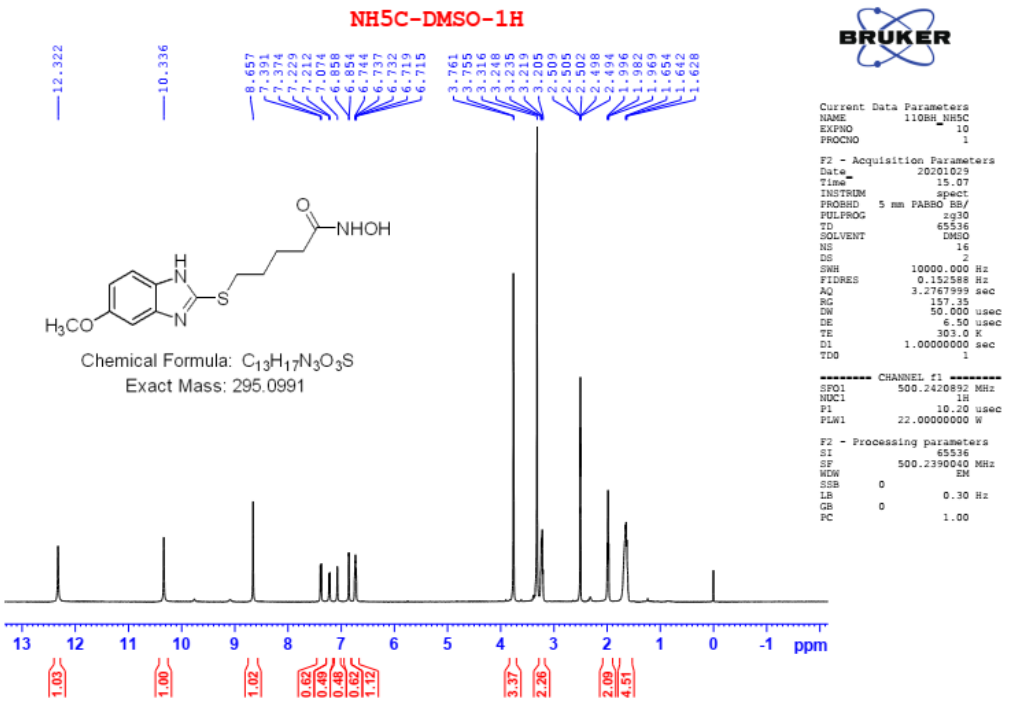


Figure S3.13 ^{1}H-NMR spectrum of compound **3**

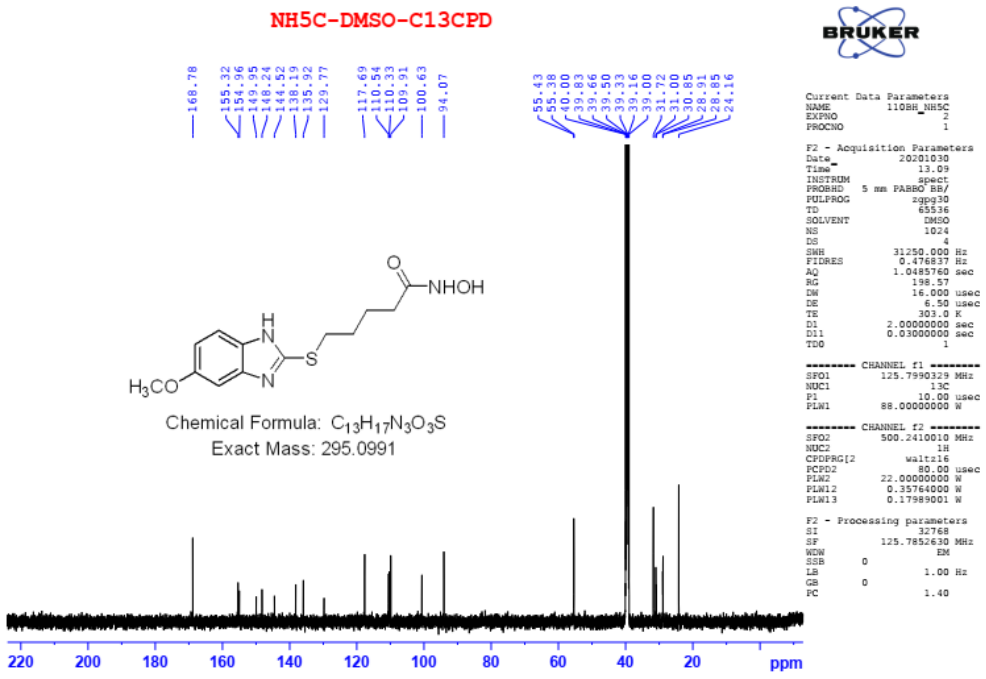


Figure S3.14 ^{13}C-NMR spectrum of compound **3**

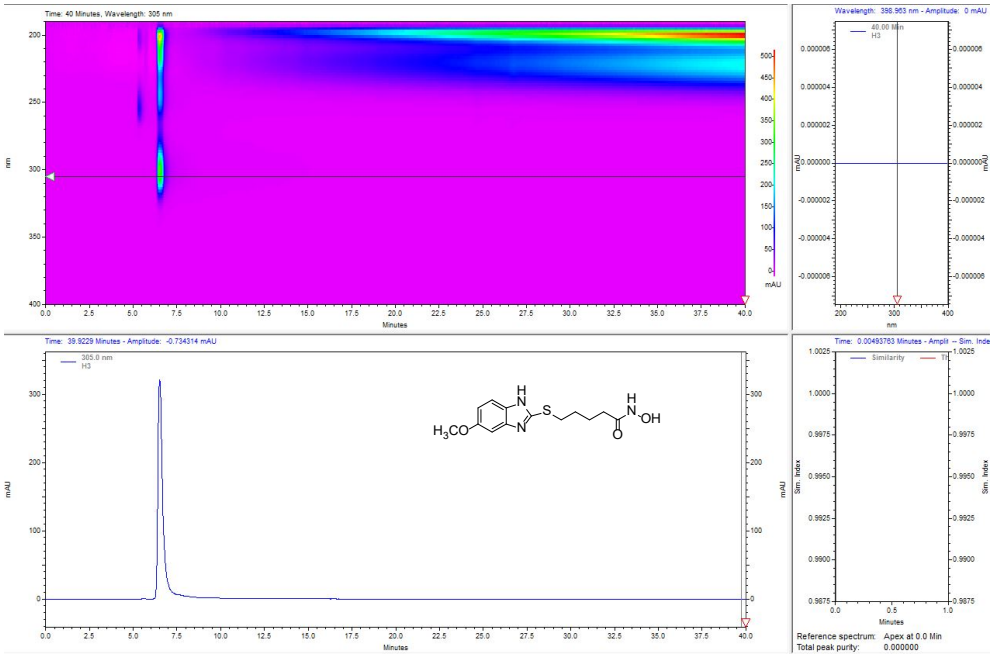


Figure S3.15 HPLC spectrum of compound **3**

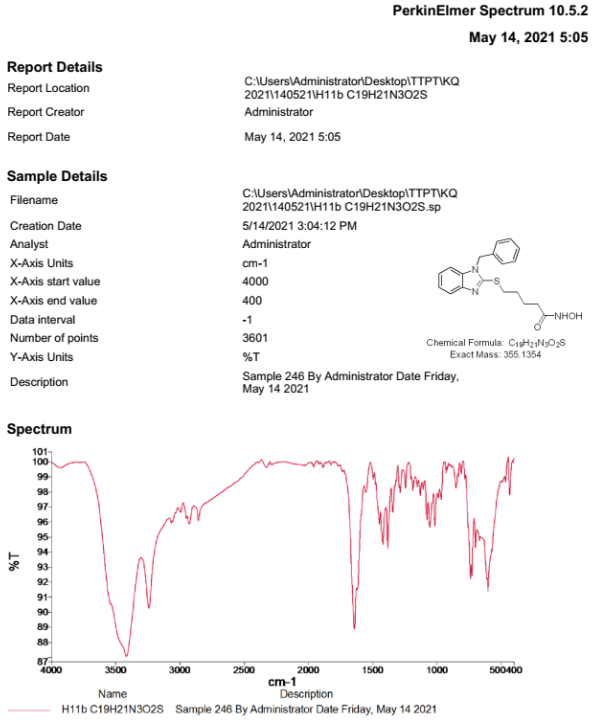


Figure S3.16 IR spectrum of compund **4**

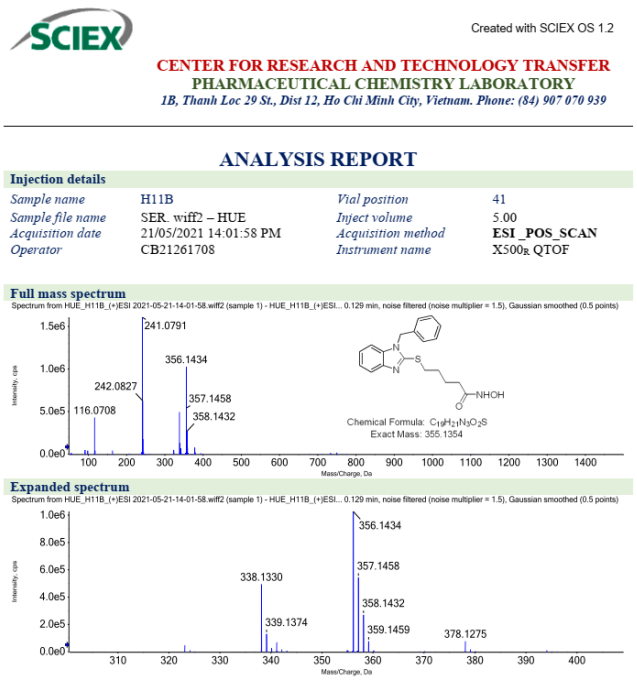


Figure S3.17 MS spectrum of compound **4**

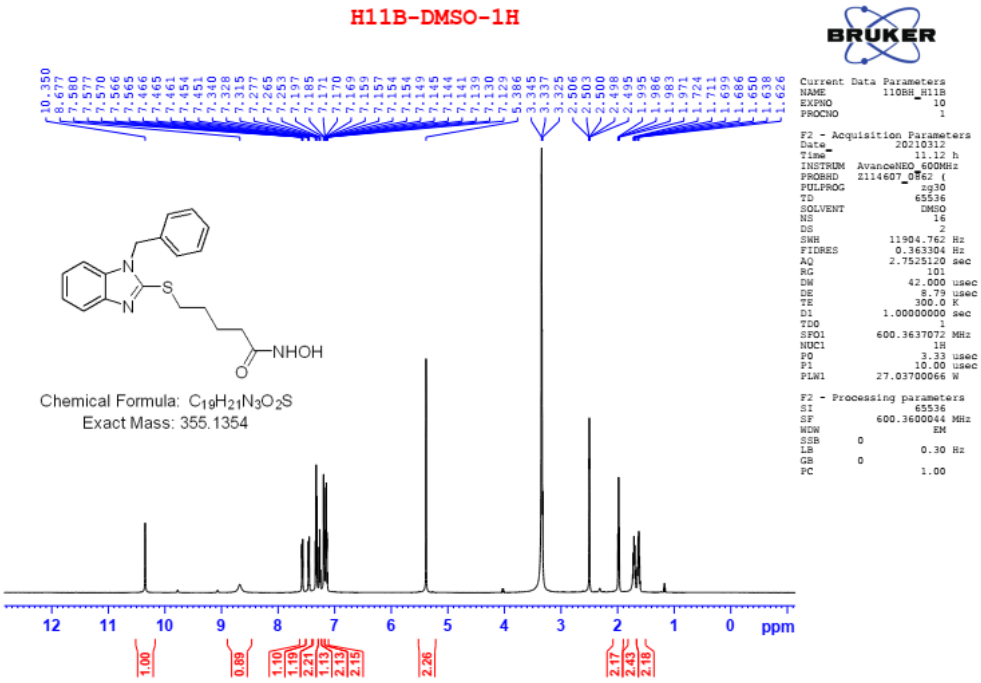


Figure S3.18 ^{1}H-NMR spectrum of compound **4**

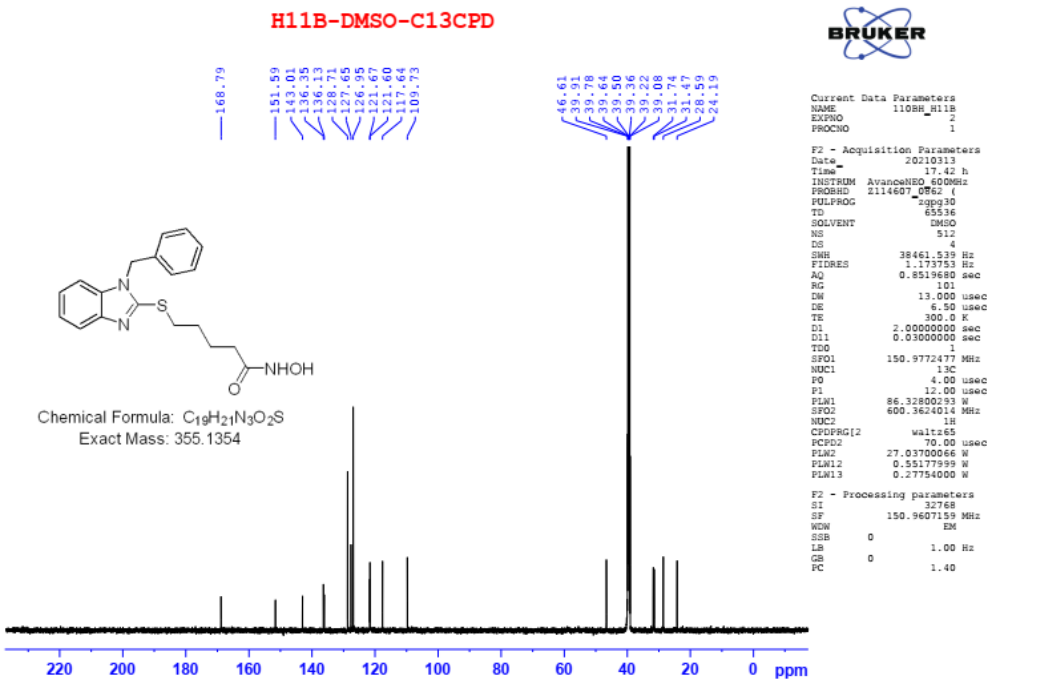


Figure S3.19 ^{13}C-NMR spectrum of compound **4**

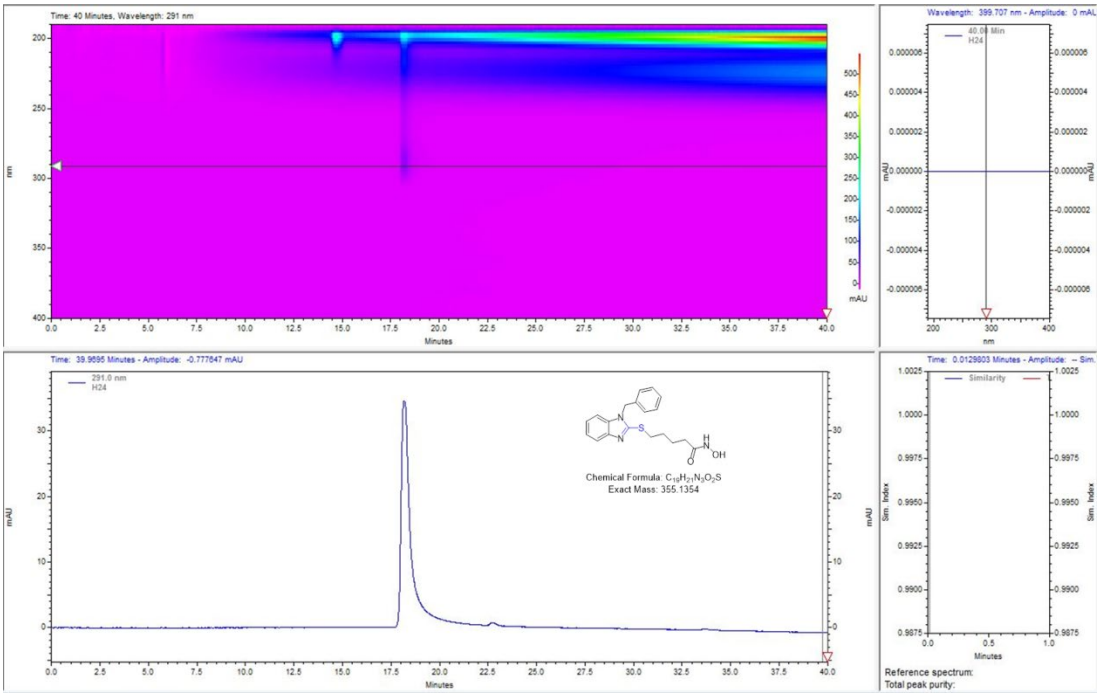


Figure S3.20 HPLC spectrum of compound **4**

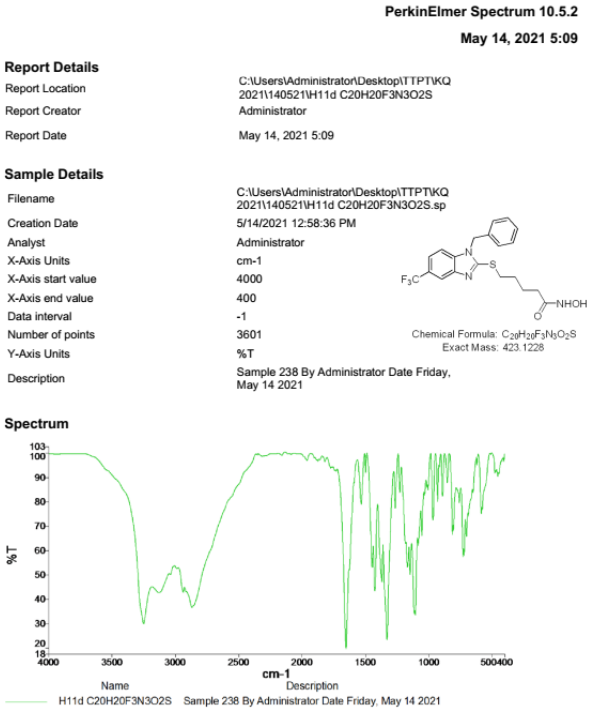


Figure S3.21 IR spectrum of compound **5**

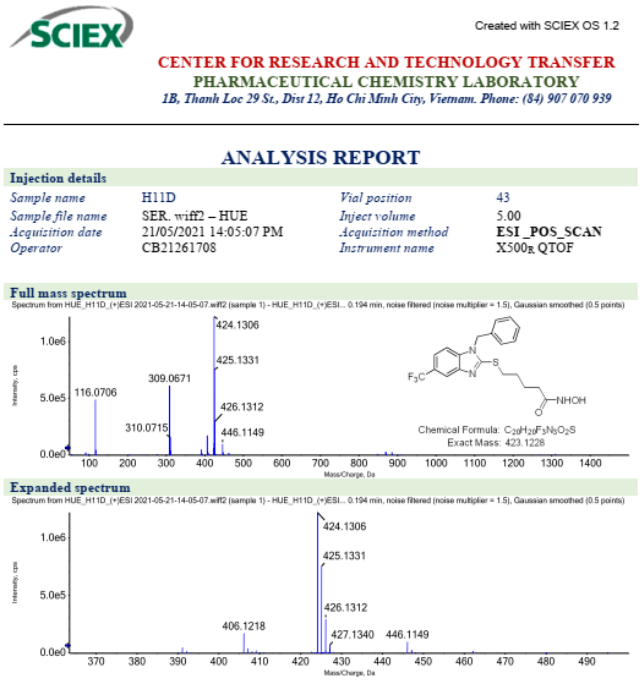


Figure S3.22 MS spectrum of compound **5**

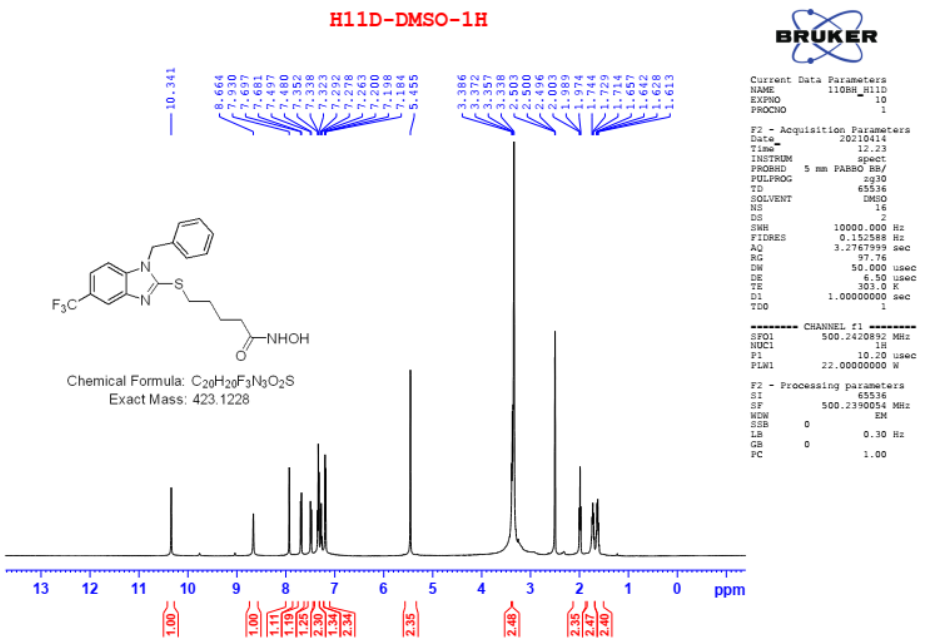


Figure S3.23 ^{1}H-NMR spectrum of compound **5**

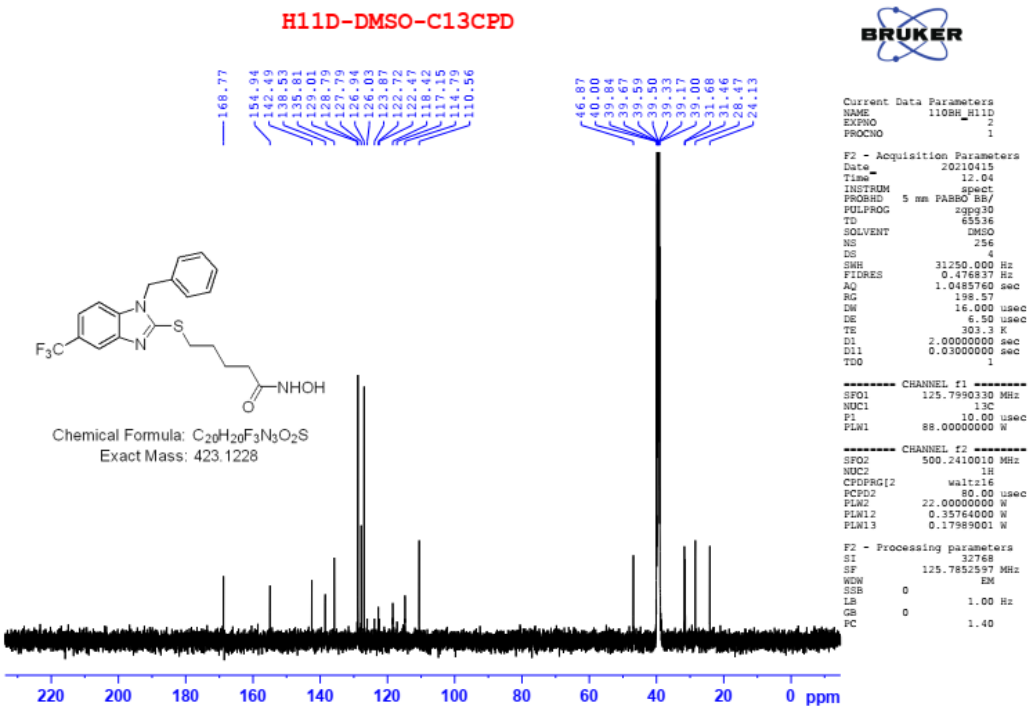


Figure S3.24 ^{13}C-NMR spectrum of compound **5**

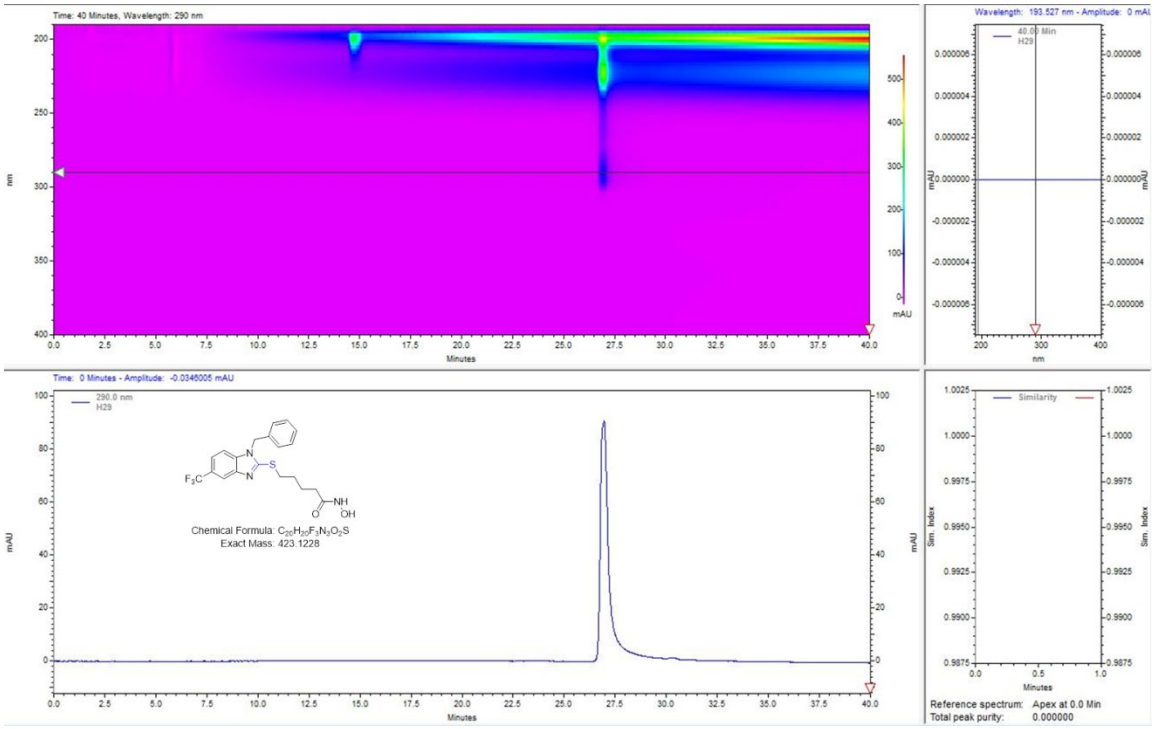


Figure S3.25 HPLC spectrum of compound **5**

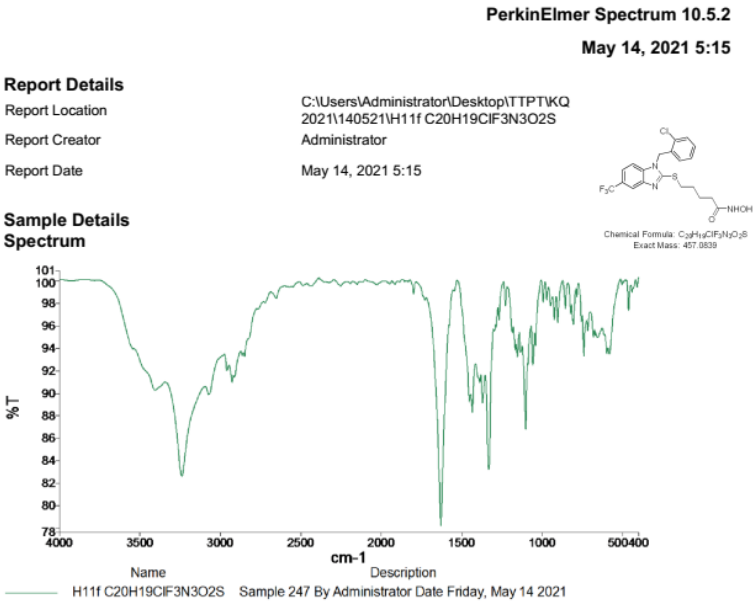


Figure S3.26 IR spectrum of compound **6**

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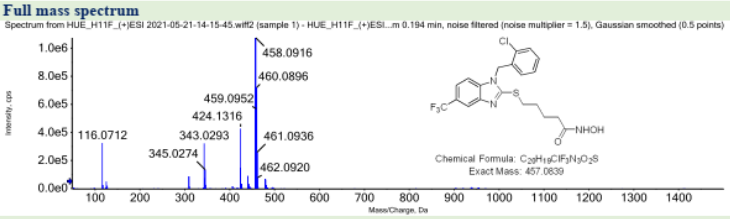
ANALYSIS REPORT

Injection details

Sample name	H11F	*Vial position*	45
Sample file name	SER. wiff2 – HUE	*Inject volume*	5.00
Acquisition date	21/05/2021 14:15:45 PM	*Acquisition method*	**ESI_POS_SCAN**
Operator	CB21261708	*Instrument name*	X500R QTOF

Full mass spectrum



Expanded spectrum

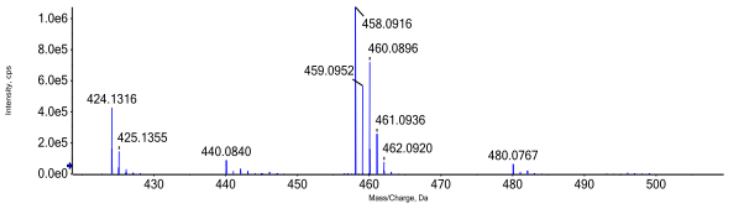


Figure S3.27 MS spectrum of compound **6**

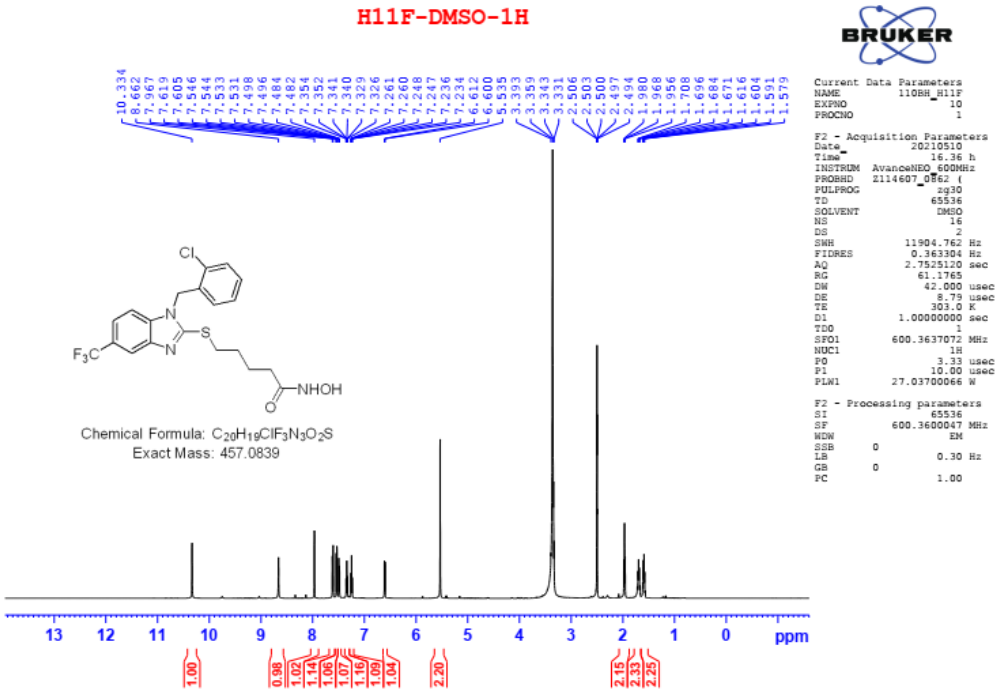


Figure S3.28 ^{1}H-NMR spectrum of compound **6**

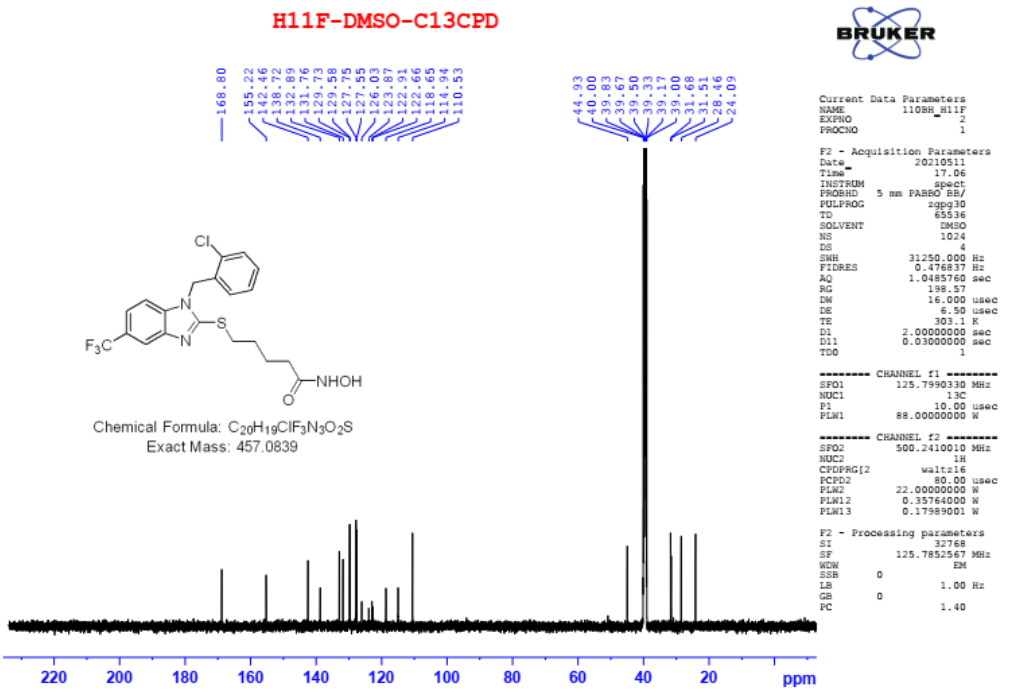


Figure S3.29 ^{13}C-NMR spectrum of compound **6**

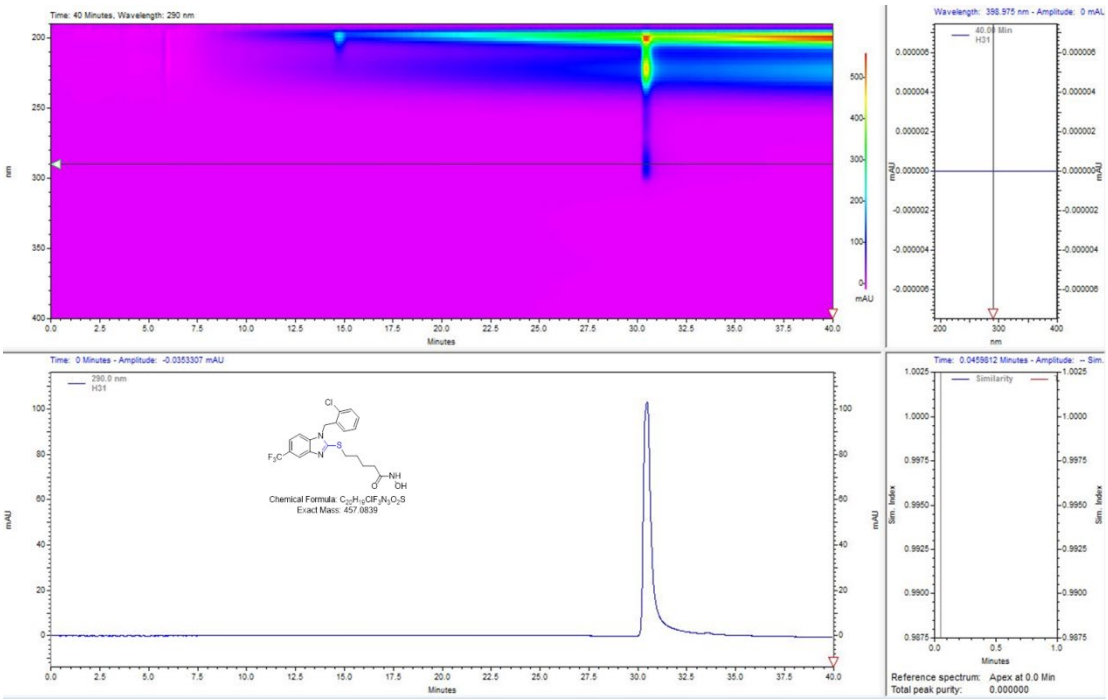


Figure S3.30 HPLC spectrum of compound **6**

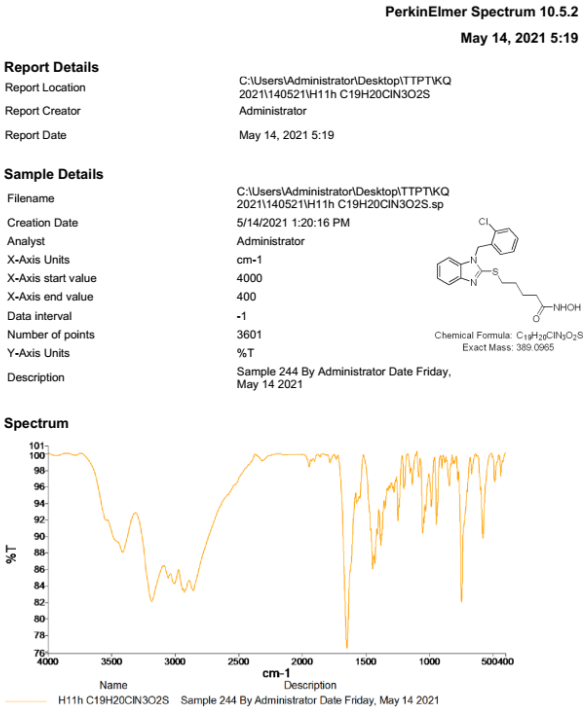


Figure S3.31 IR spectrum of compound **7**

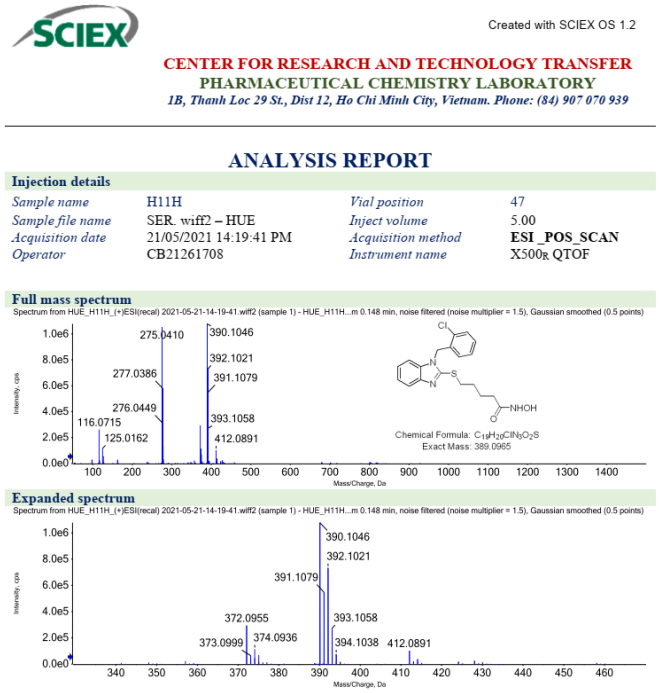


Figure S3.32 MS spectrum of compound **7**

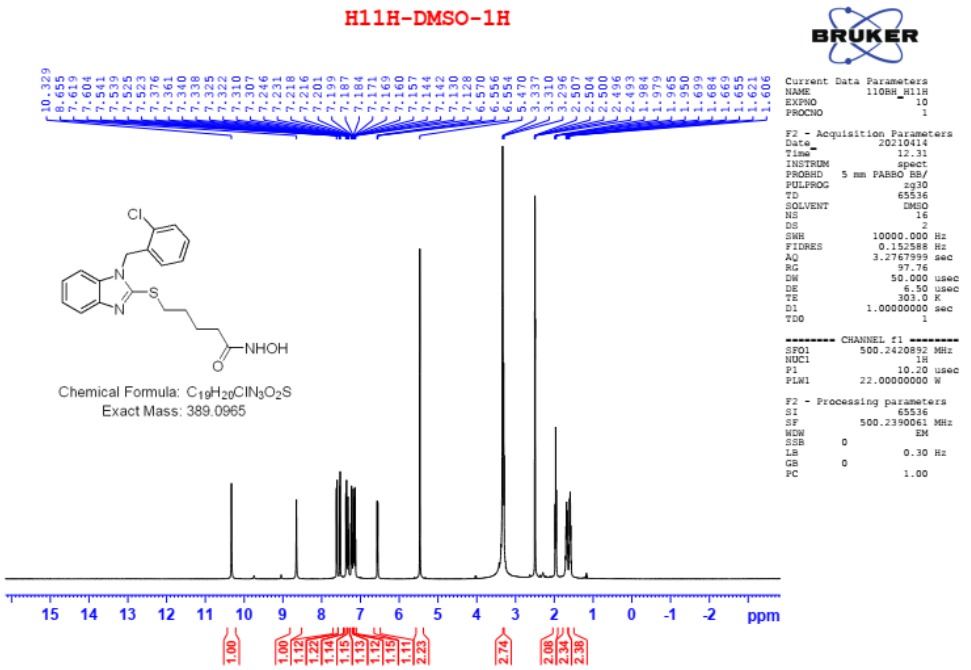


Figure S3.33 ^{1}H-NMR spectrum of compound **7**

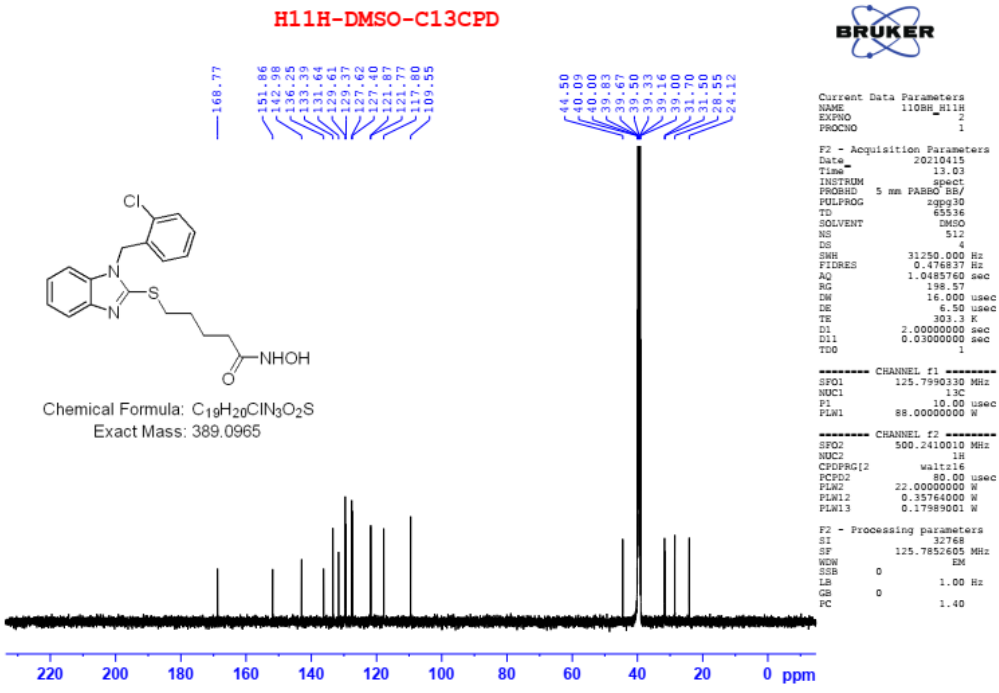


Figure S3.34 ^{13}C-NMR spectrum of compound **7**

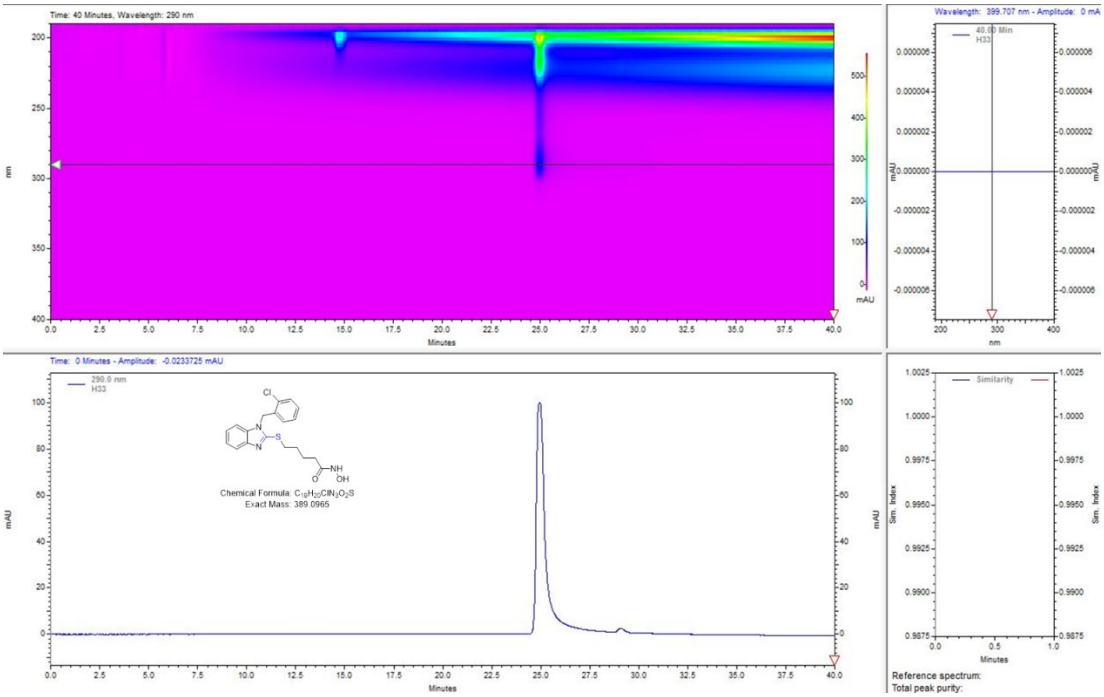


Figure S3.35 HPLC spectrum of compound **7**

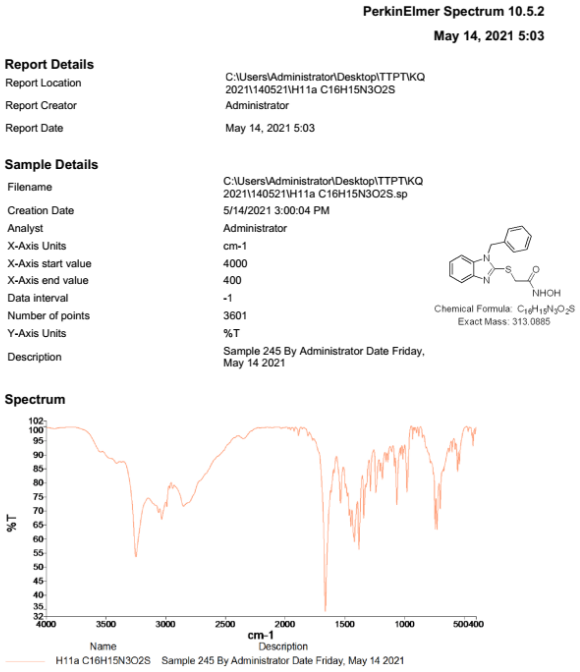


Figure S3.36 IR spectrum of compound **8**

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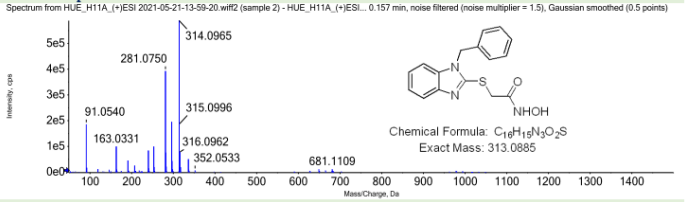
ANALYSIS REPORT

Injection details

Sample name	H11A	*Vial position*	40
Sample file name	SER. wiff2 – HUE	*Inject volume*	5.00
Acquisition date	21/05/2021 13:59:20 PM	*Acquisition method*	**ESI _POS_SCAN**
Operator	CB21261708	*Instrument name*	X500R QTOF

Full mass spectrum



Expanded spectrum

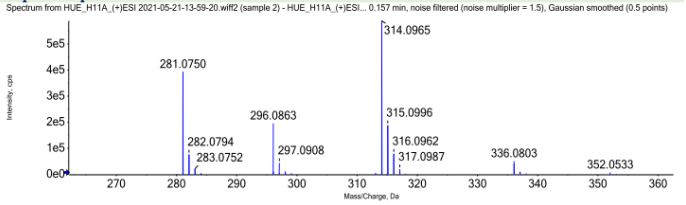


Figure S3.37 MS spectrum of compound **8**

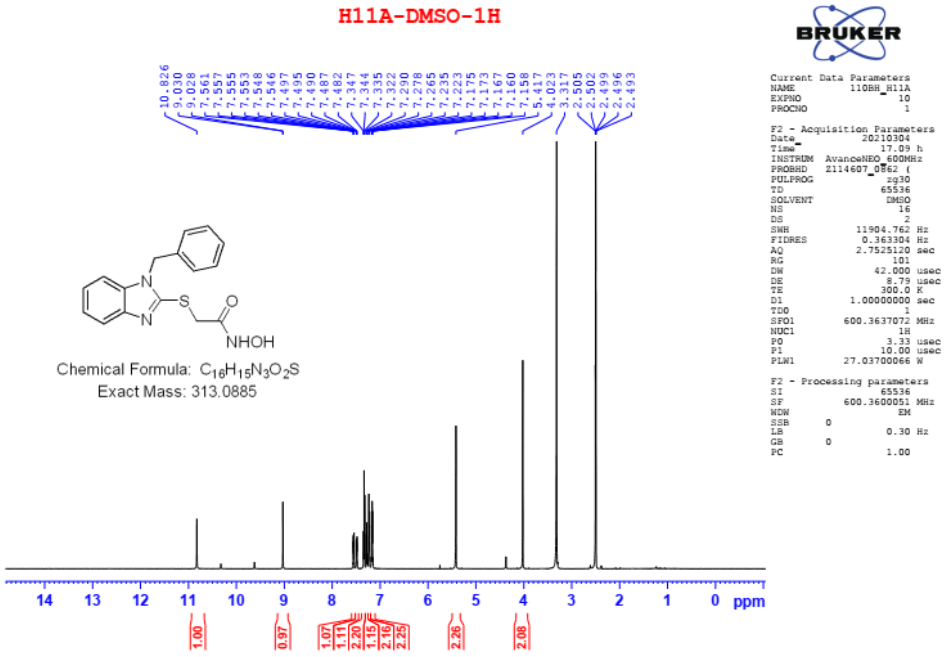


Figure S3.38 ^{1}H-NMR spectrum of compound **8**

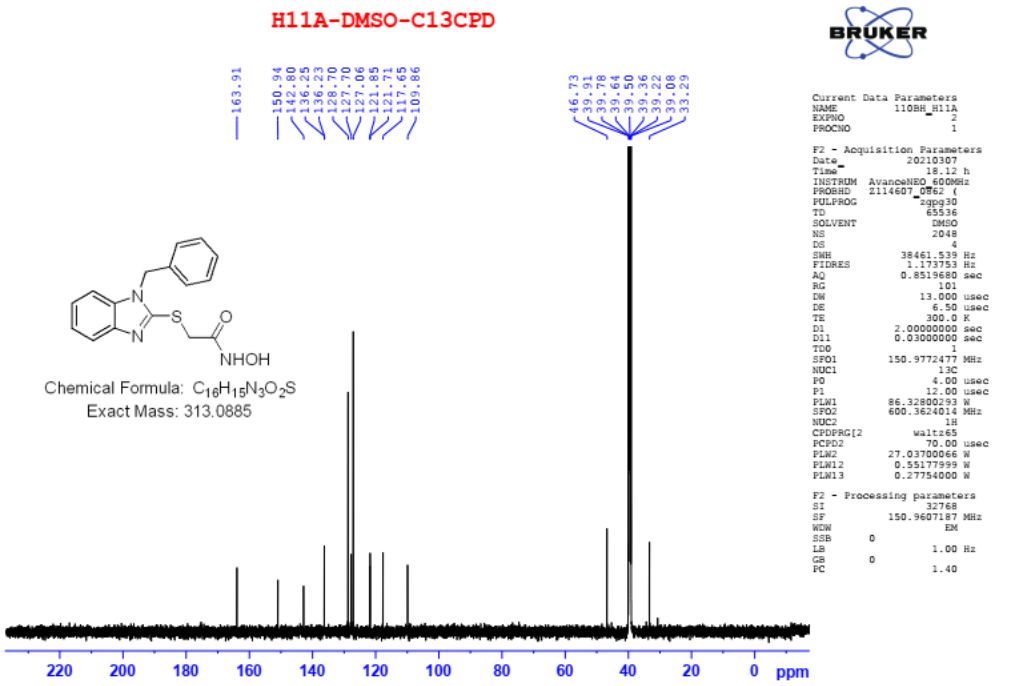


Figure S3.39 ^{13}C-NMR spectrum of compound **8**

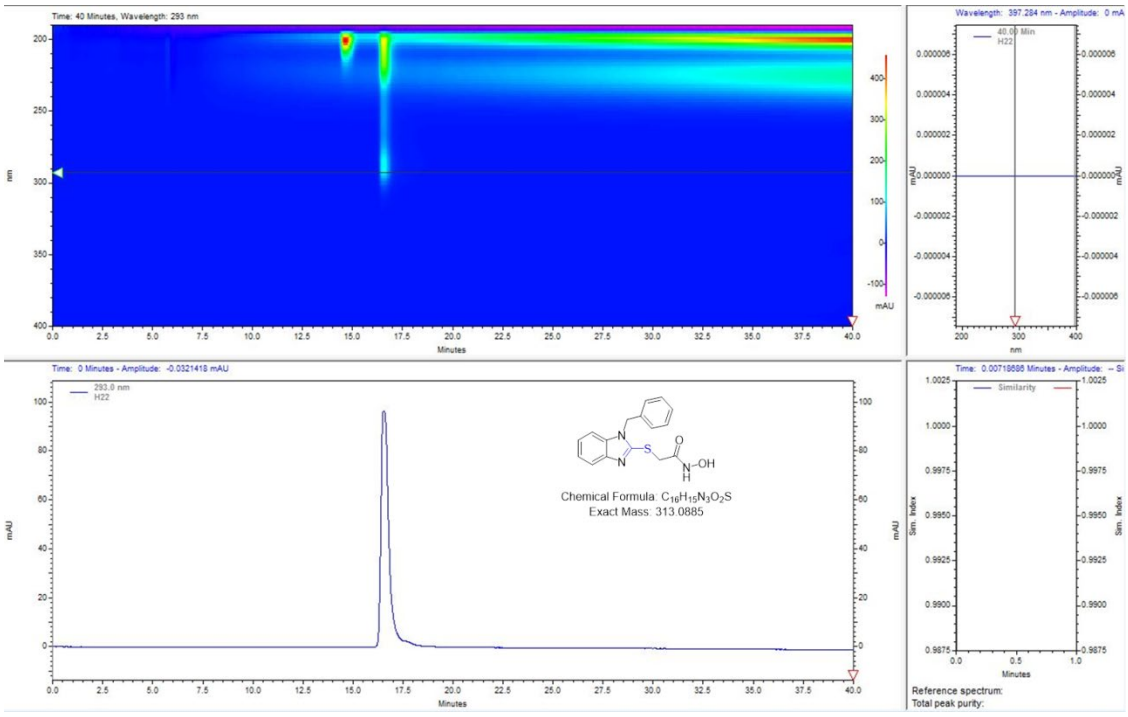


Figure S3.40 HPLC spectrum of compound **8**

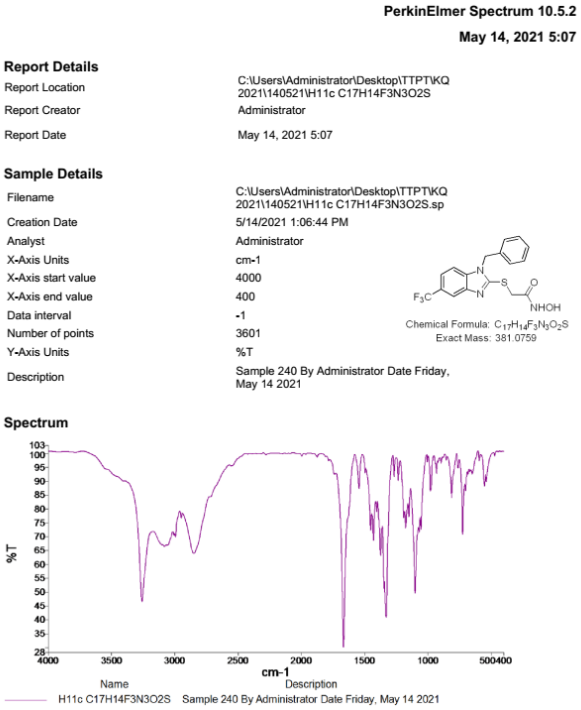


Figure S3.41 IR spectrum of compound **9**

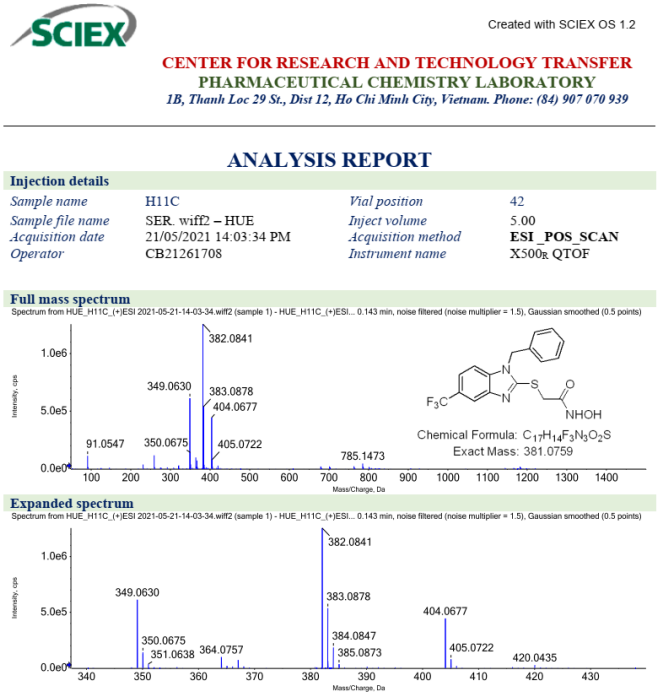


Figure S3.42 MS spectrum of compound **9**

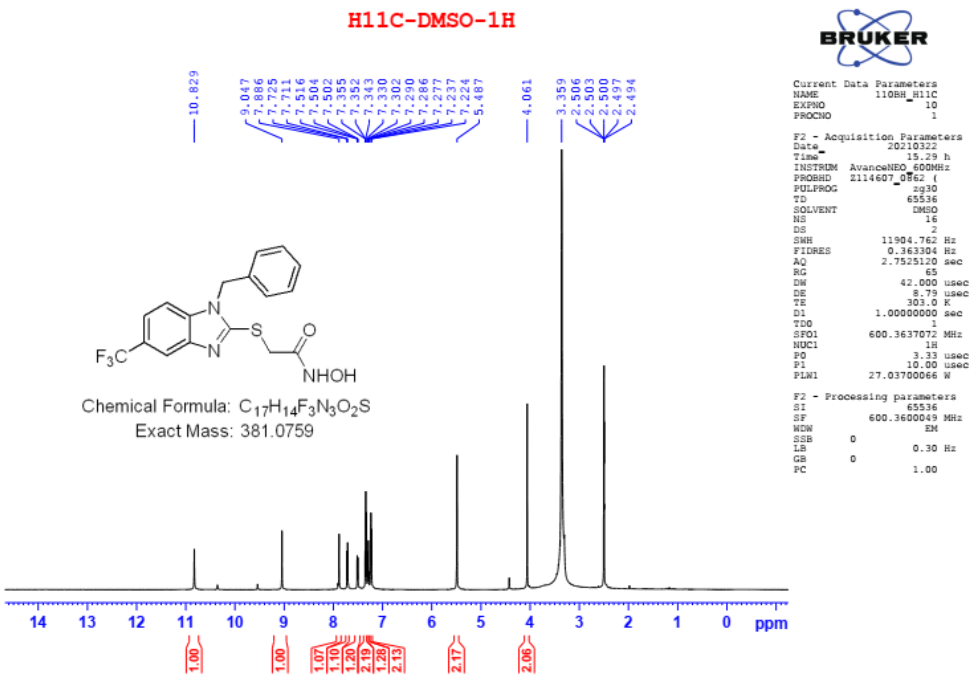


Figure S3.43 ^{1}H-NMR spectrum of compound **9**

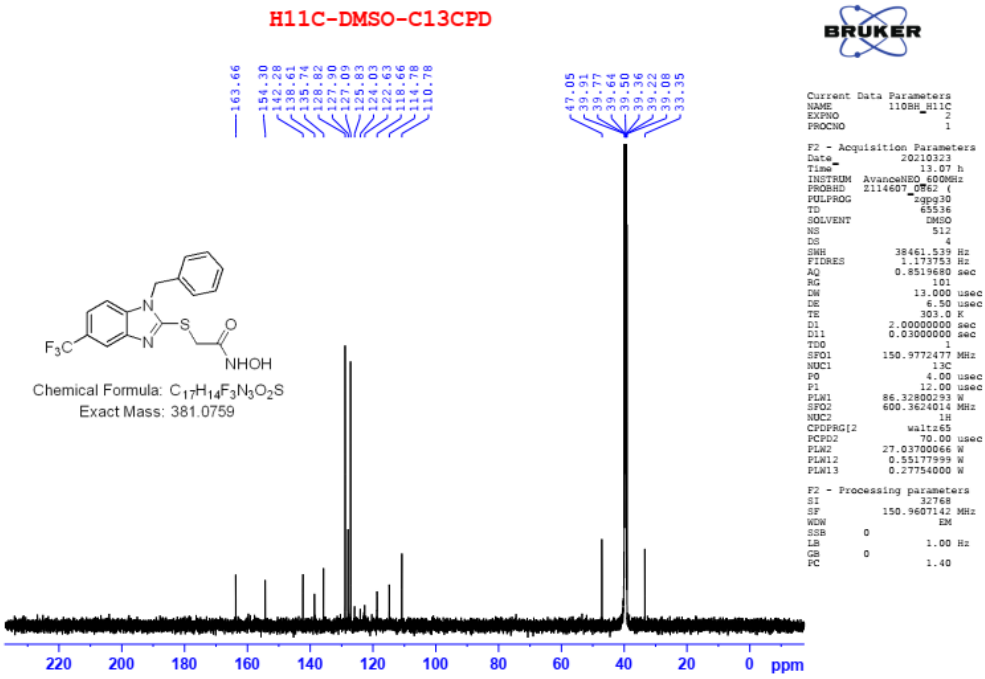


Figure S3.44 ^{13}C-NMR spectrum of compound **9**

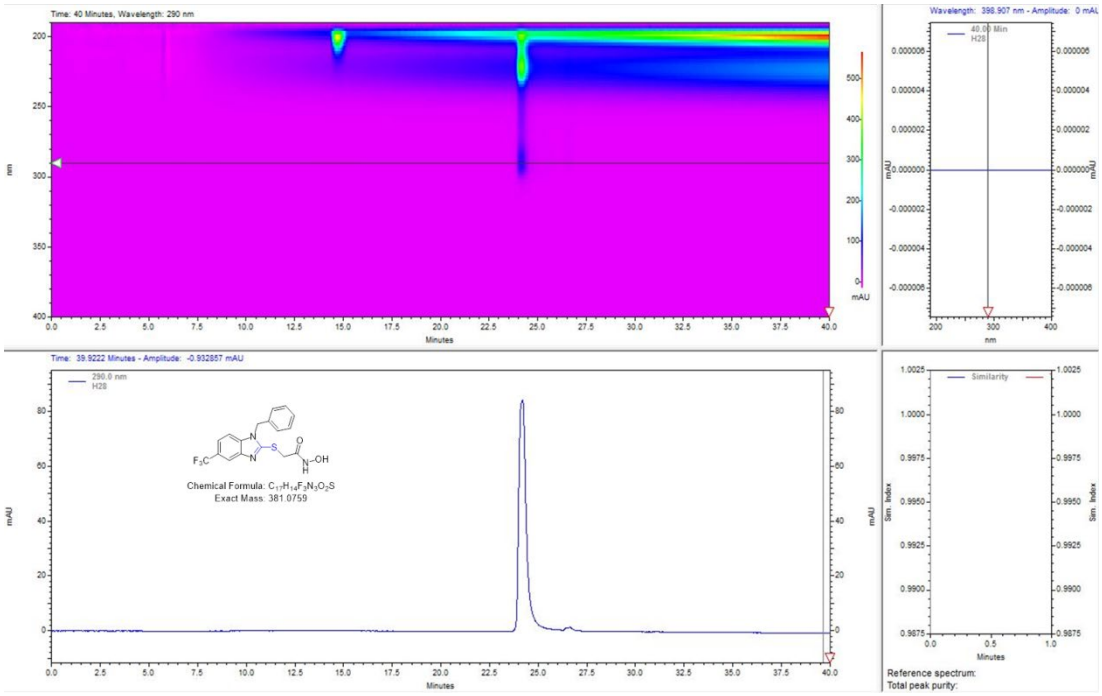


Figure S3.45 HPLC spectrum of compound **9**

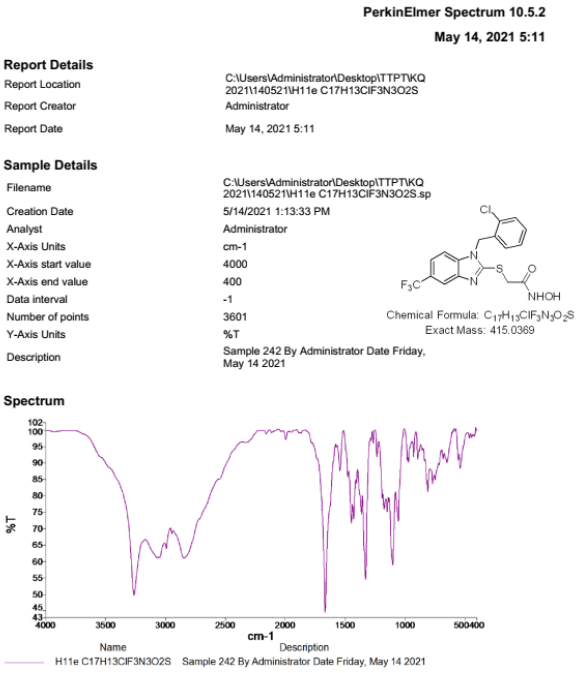


Figure S3.46 IR spectrum of compound **10**

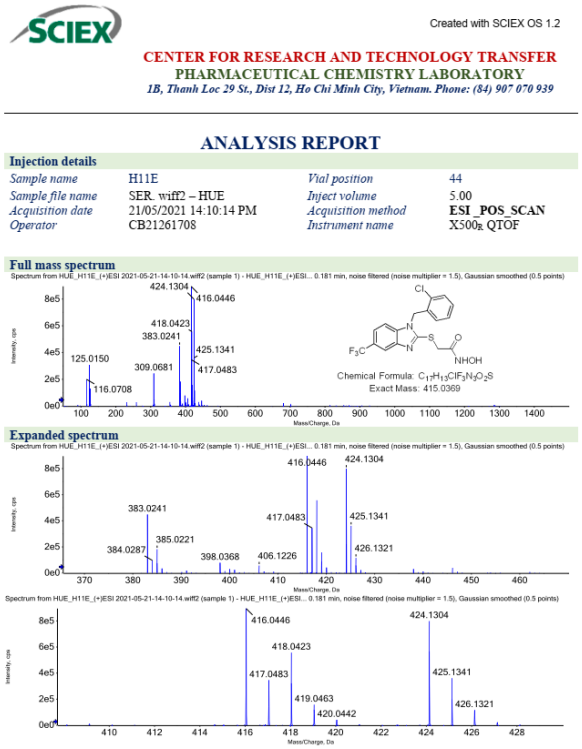


Figure S3.47 MS spectrum of compound **10**

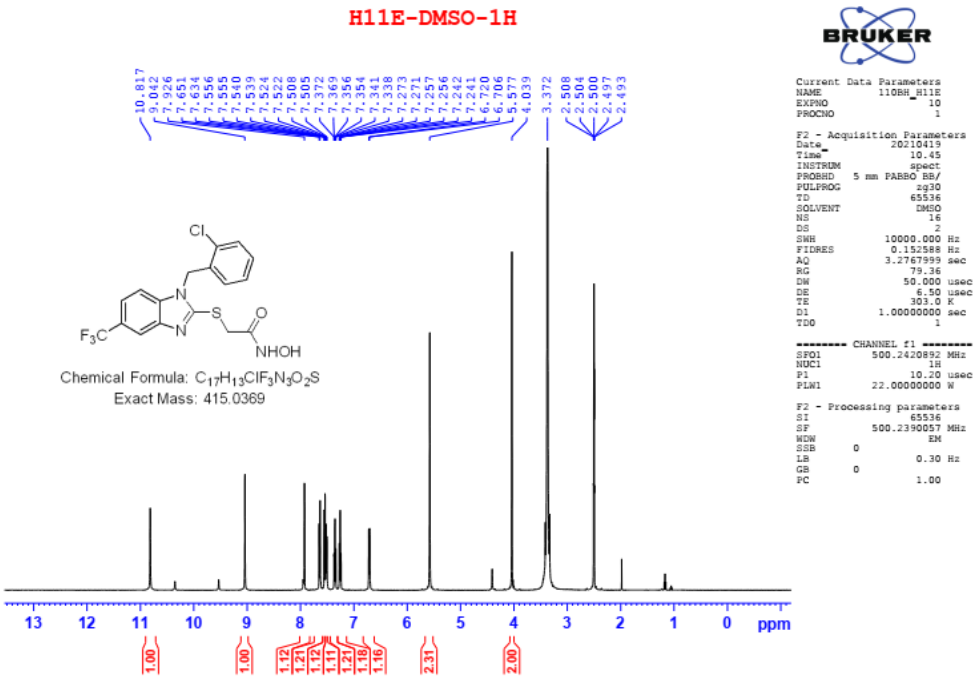


Figure S3.48 ^{1}H-NMR spectrum of compound **10**

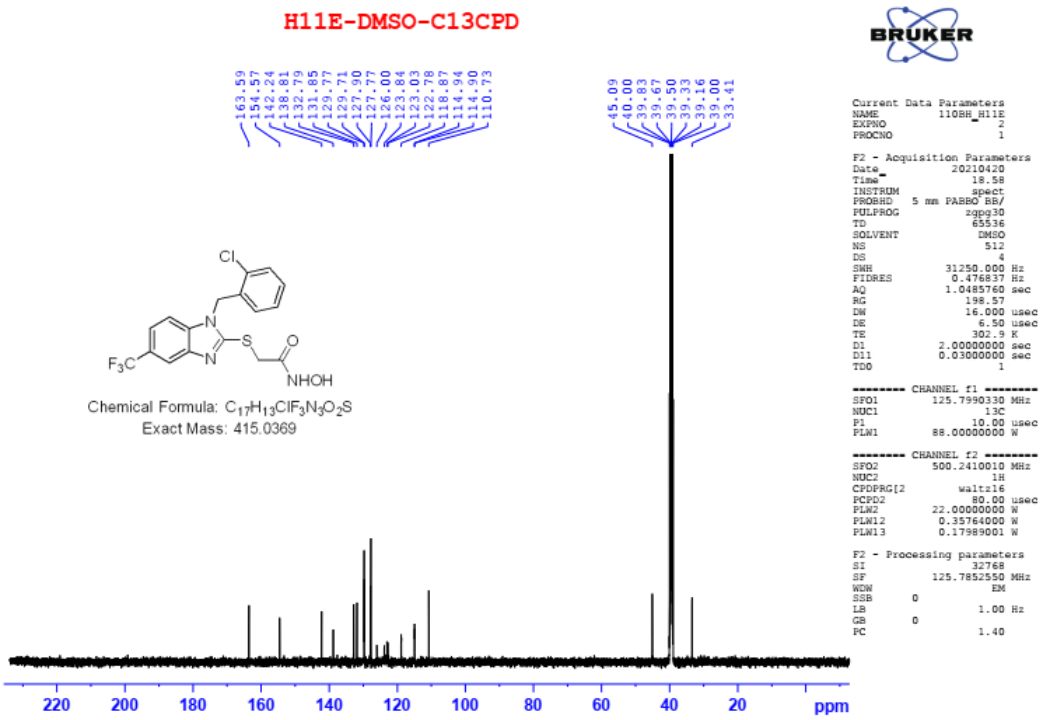


Figure S3.49 ^{13}C-NMR spectrum of compound **10**

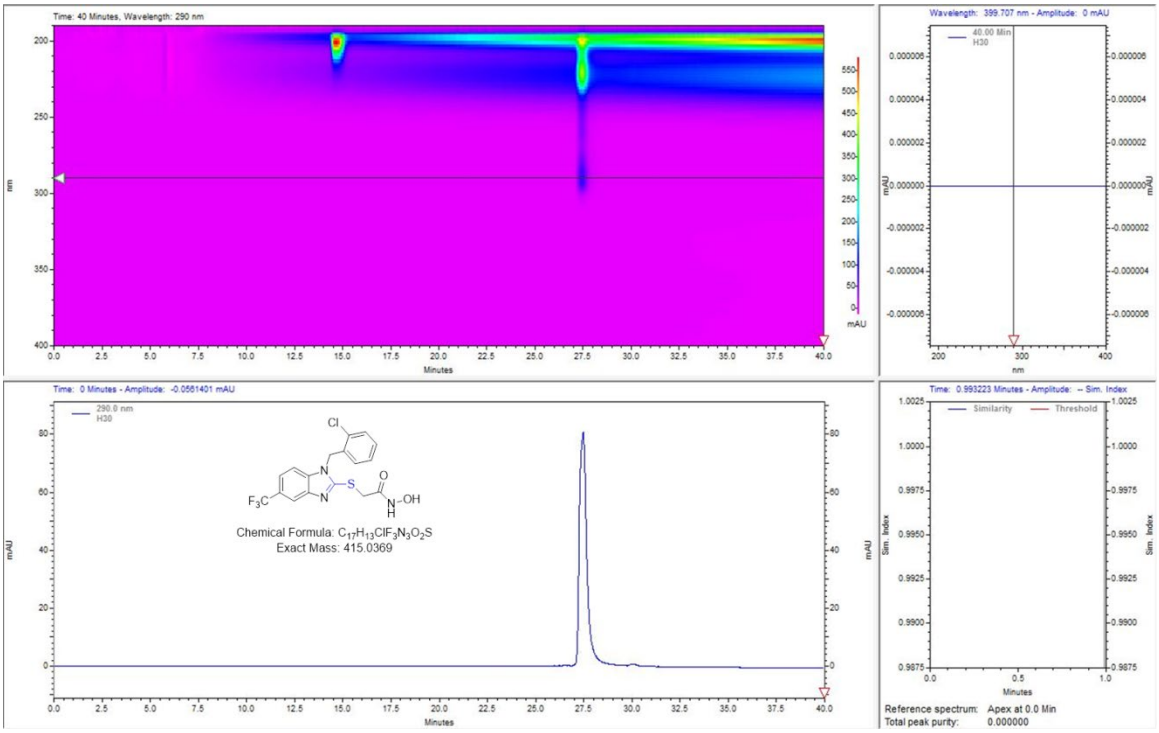


Figure S3.50 HPLC spectrum of compound **10**

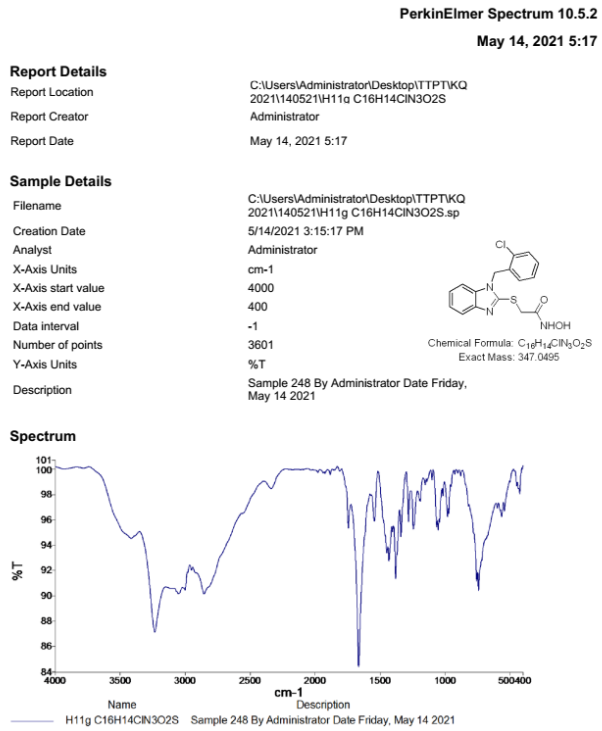


Figure S3.51 IR spectrum of compound **11**

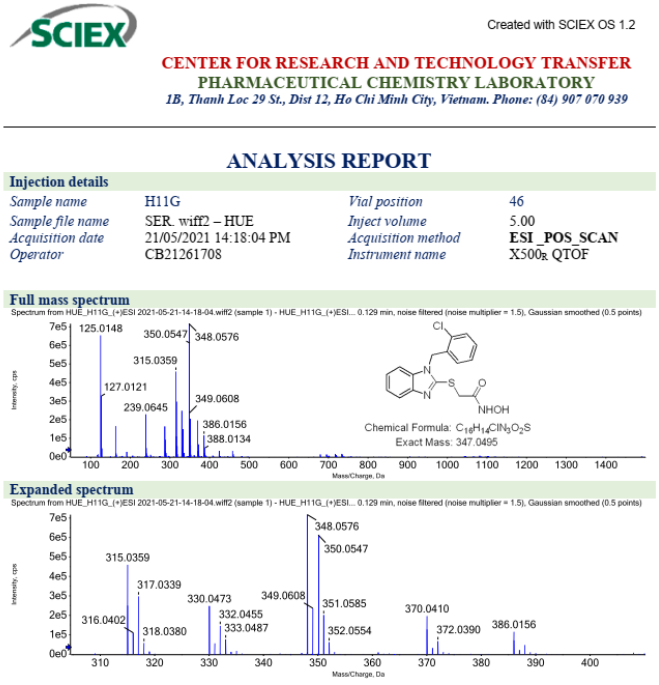


Figure S3.52 MS spectrum of compound **11**

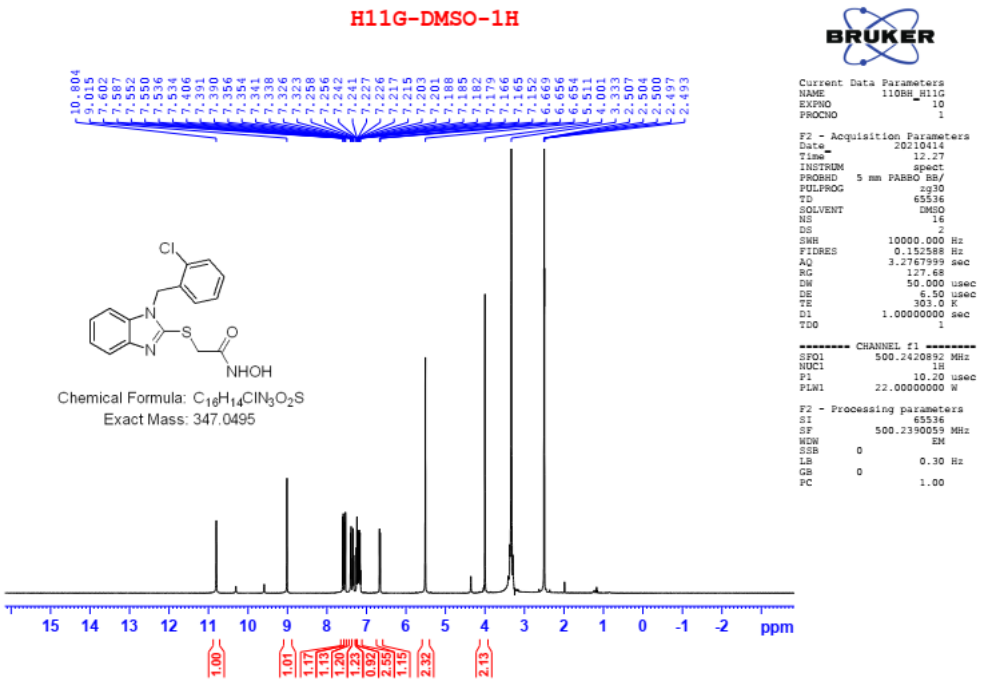


Figure S3.53 ^{1}H-NMR spectrum of compound **11**

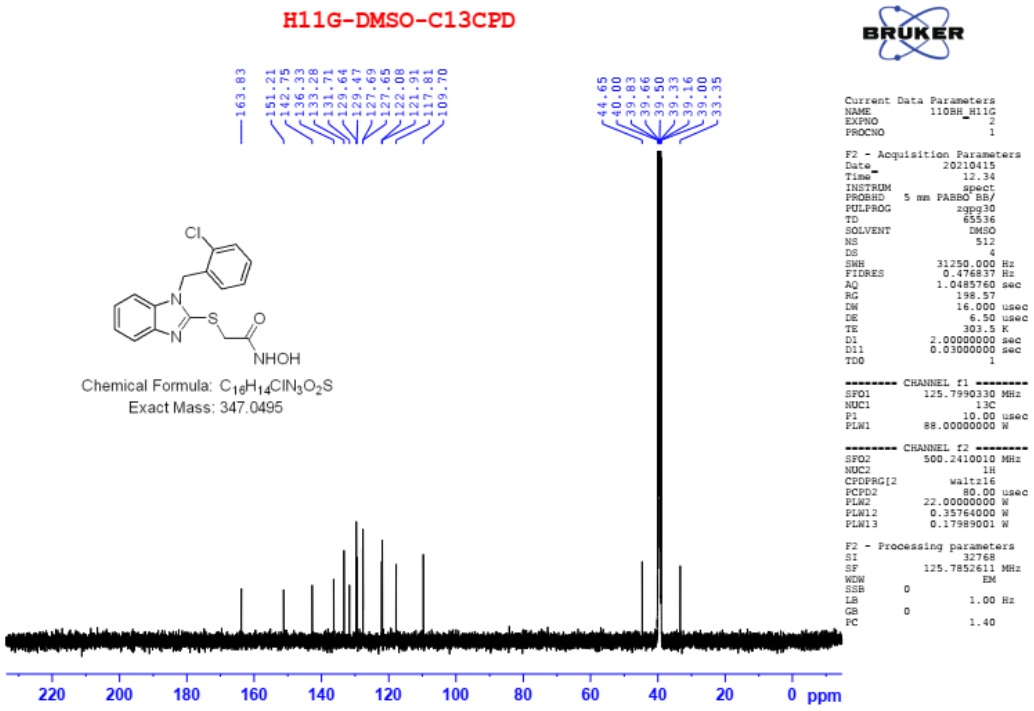


Figure S3.54 ^{13}C-NMR spectrum of compound **11**

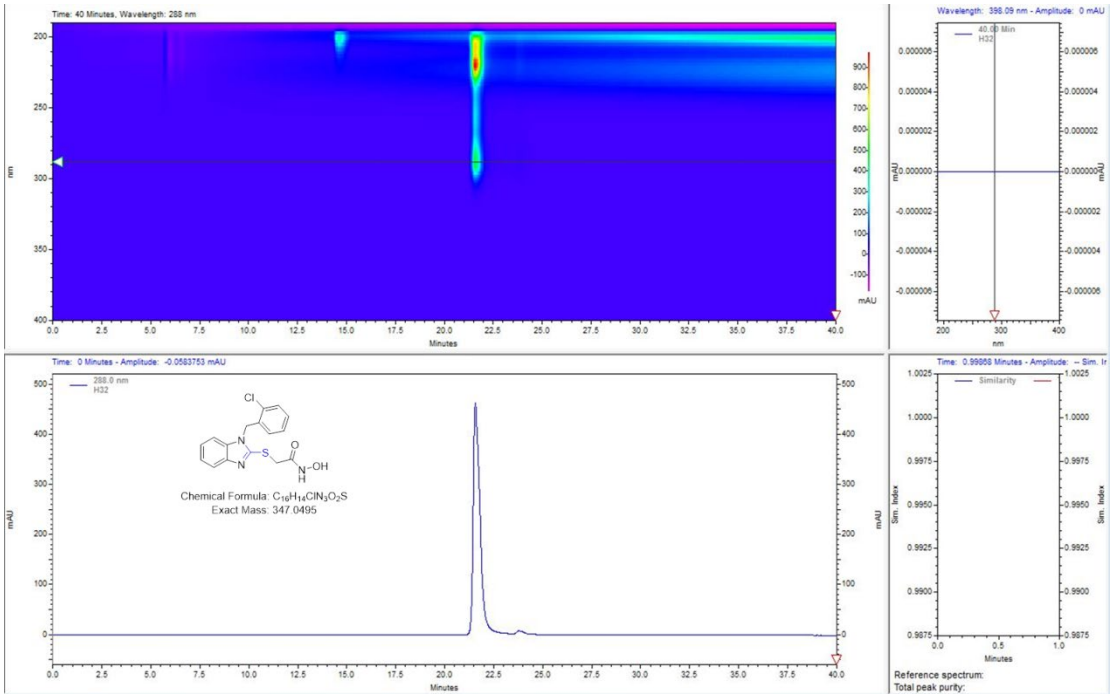


Figure S3.55 HPLC spectrum of compound **11**

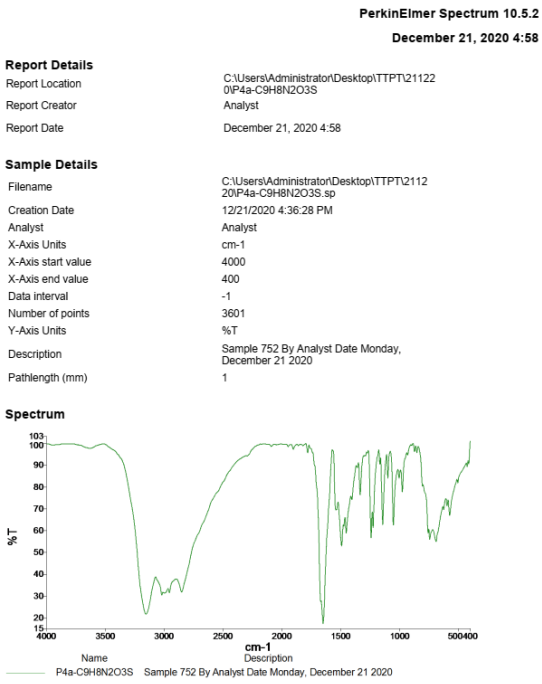


Figure S3.56 IR spectrum of compound **12**

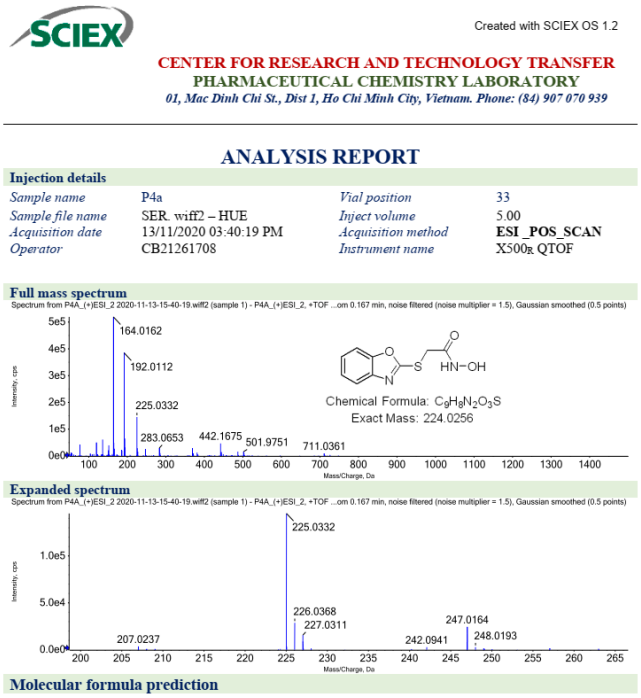


Figure S3.57 MS spectrum of compound **12**

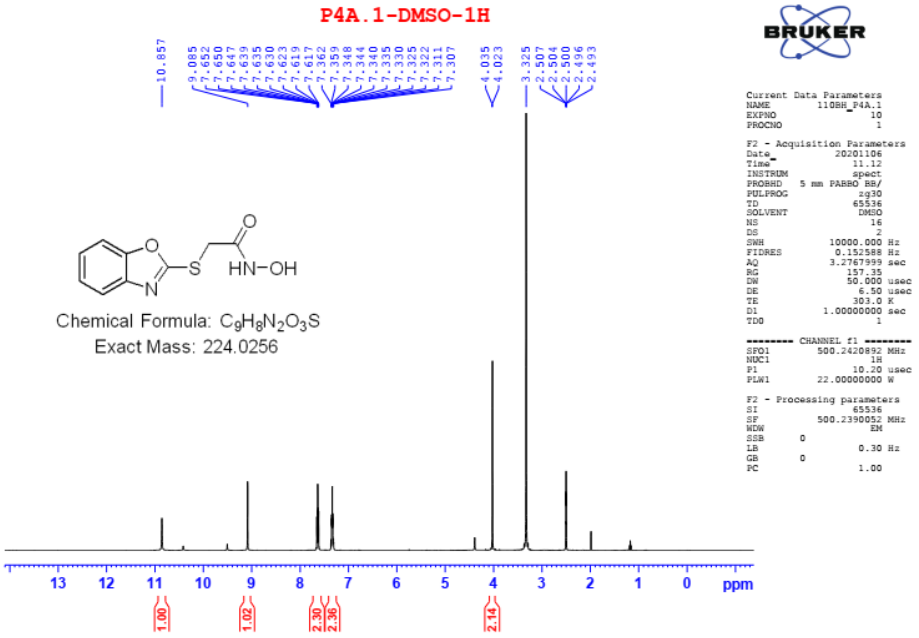


Figure S3.58 ^{1}H-NMR spectrum of compound **12**

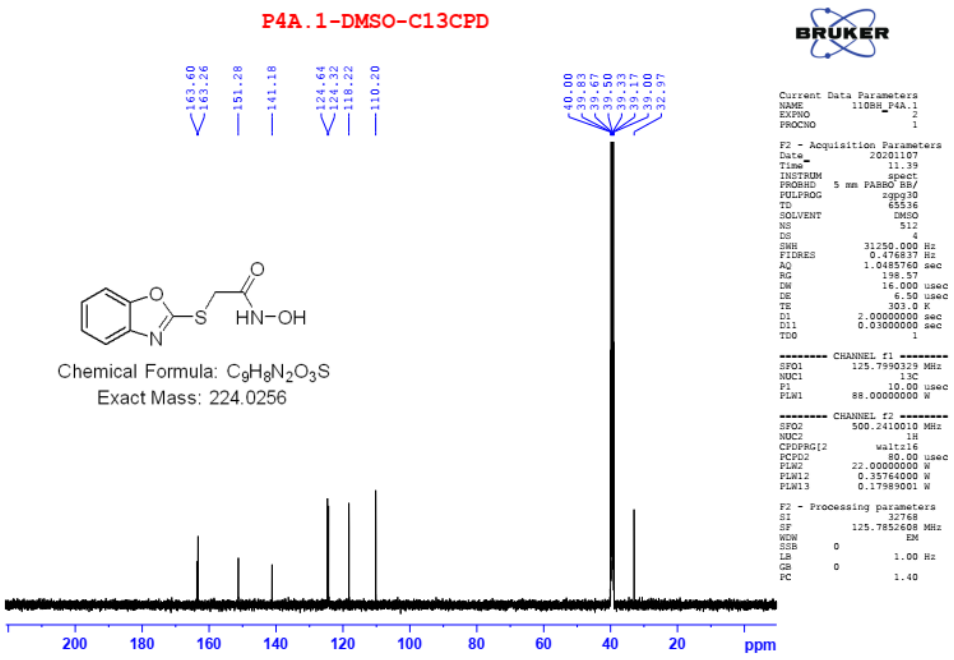


Figure S3.59 ^{13}C-NMR spectrum of compound **12**

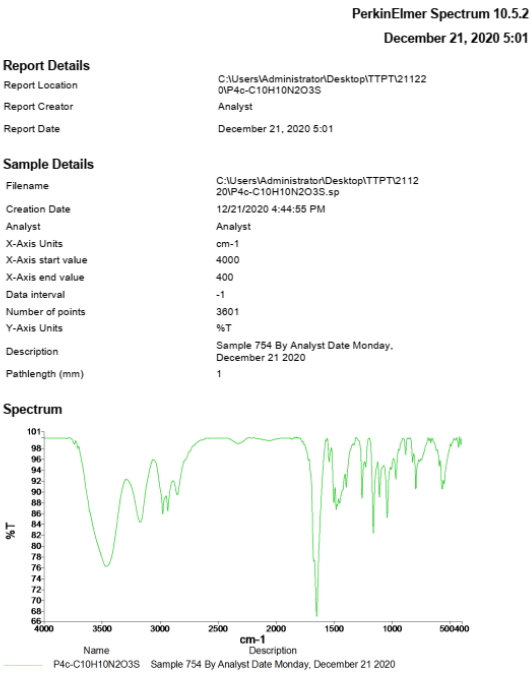


Figure S3.60 IR spectrum of compound **13**

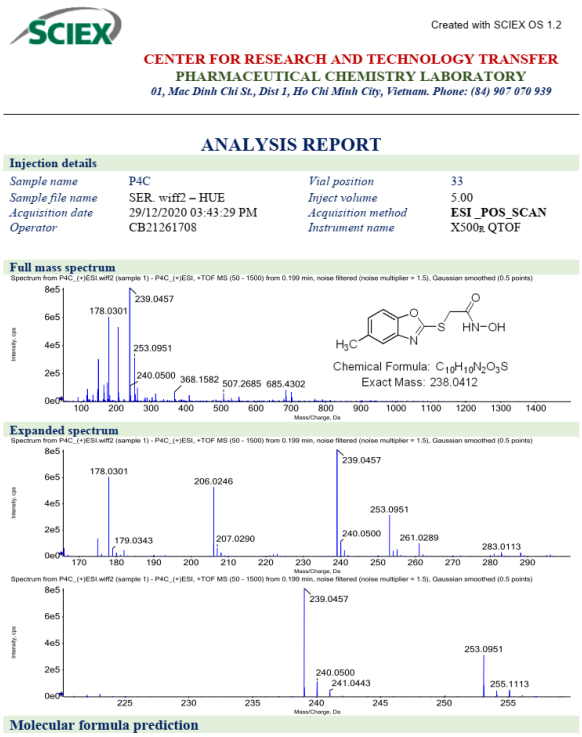


Figure S3.61 MS spectrum of compound **13**

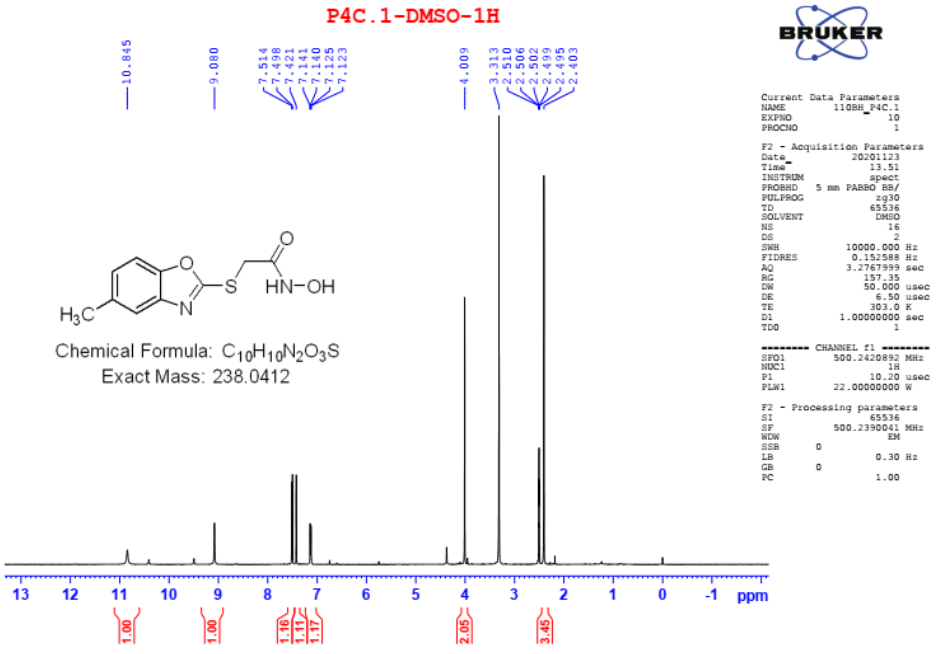


Figure S3.62 ^{1}H-NMR spectrum of compound **13**

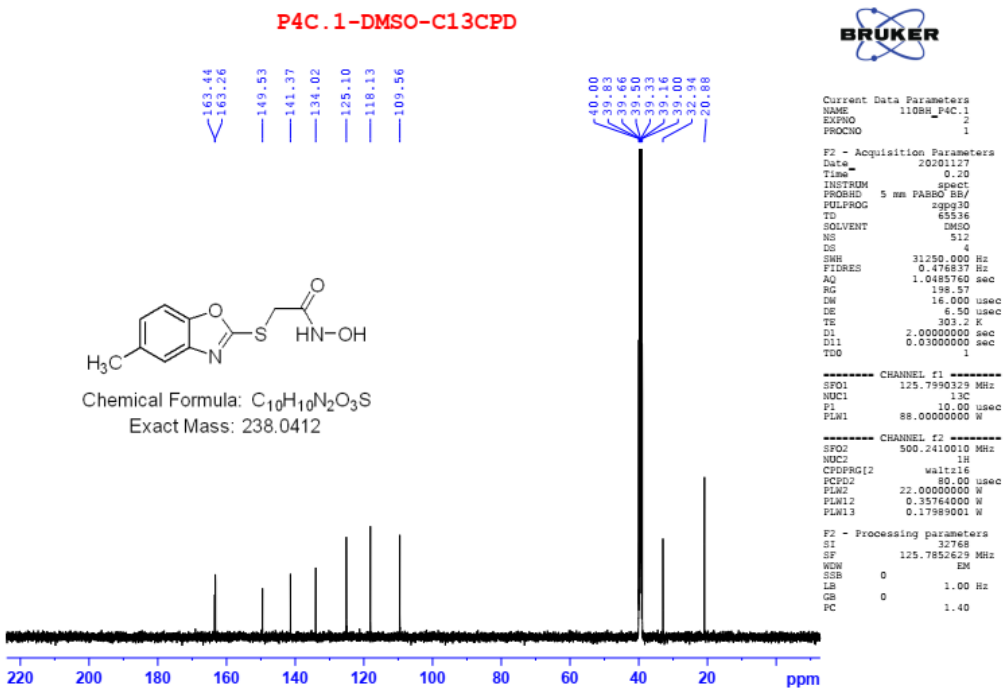


Figure S3.63 ^{13}C-NMR spectrum of compound **13**

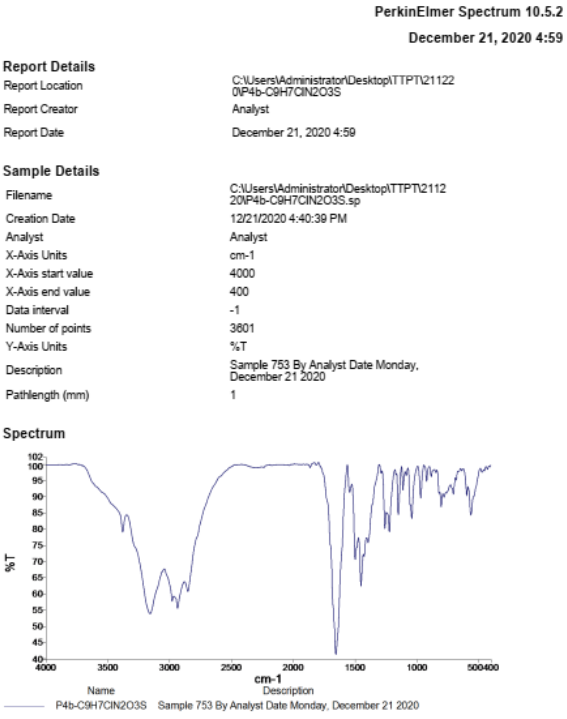


Figure S3.64 IR spectrum of compound **14**

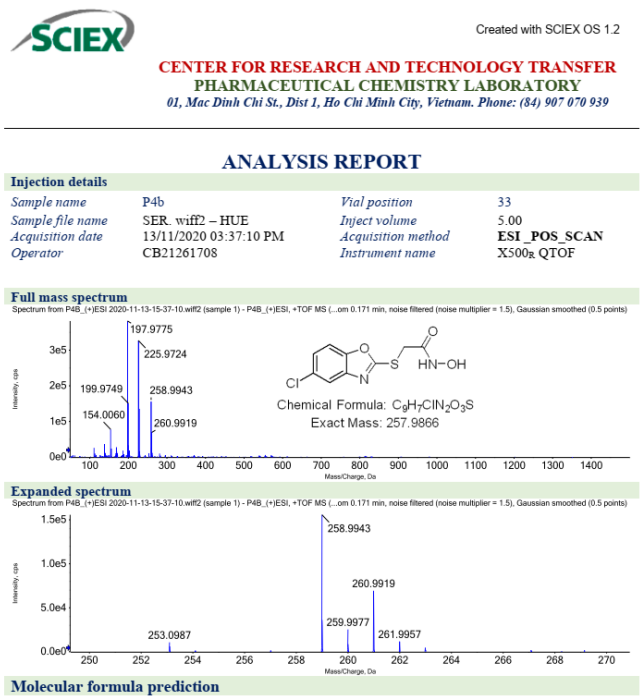


Figure S3.65 MS spectrum of compound **14**

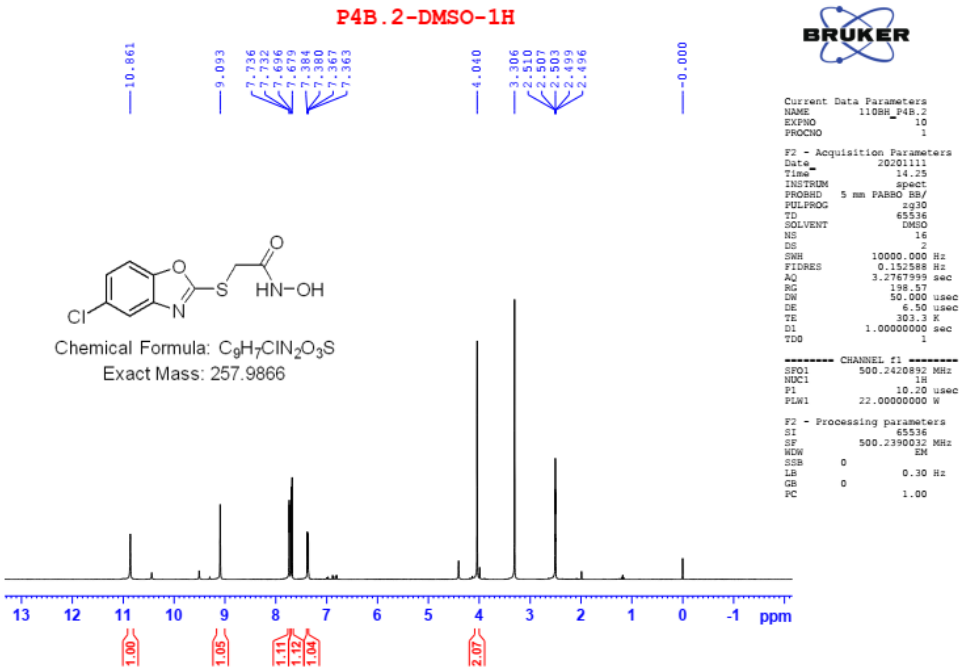


Figure S3.66 ^{1}H-NMR spectrum of compound **14**

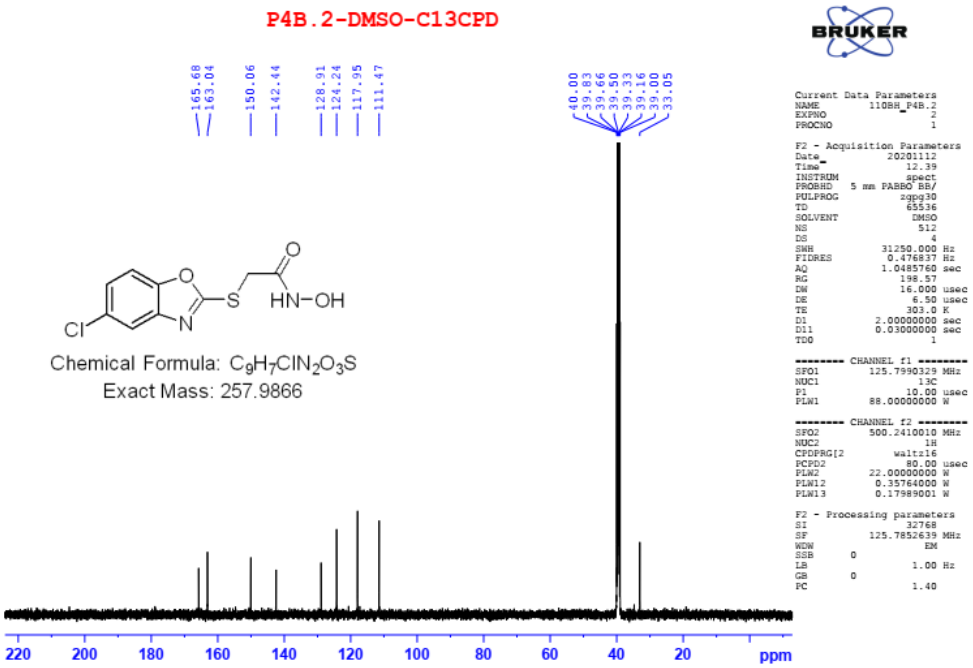


Figure S3.67 ^{13}C-NMR spectrum of compound **14**

Figure S3.68 IR spectrum of compound **15**

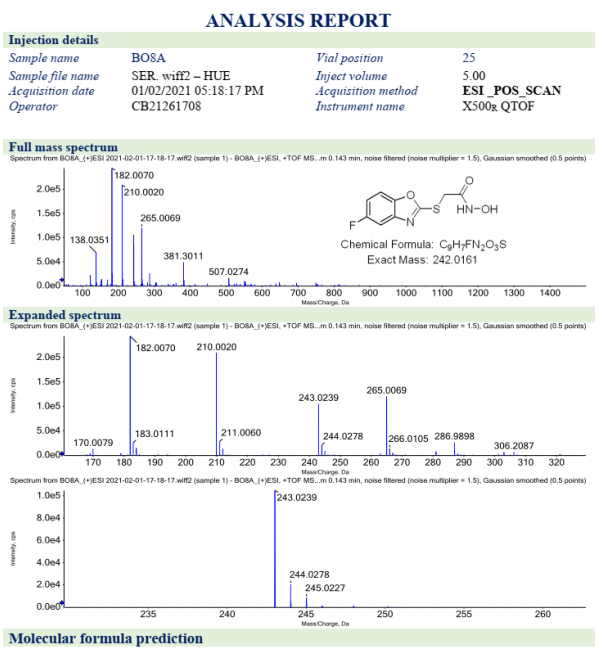


Figure S3.69 MS spectrum of compound **15**

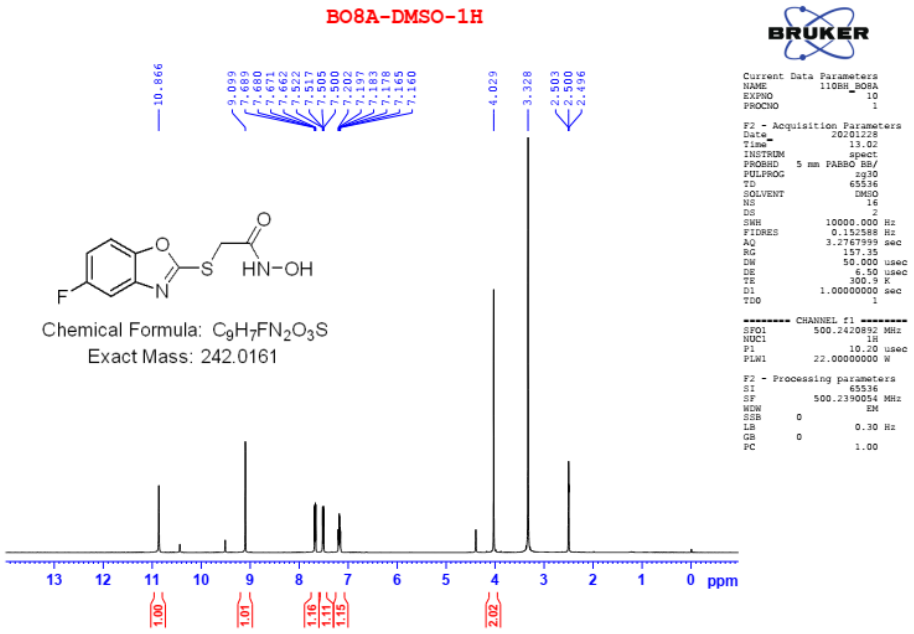


Figure S3.70 ^{1}H-NMR spectrum of compound **15**

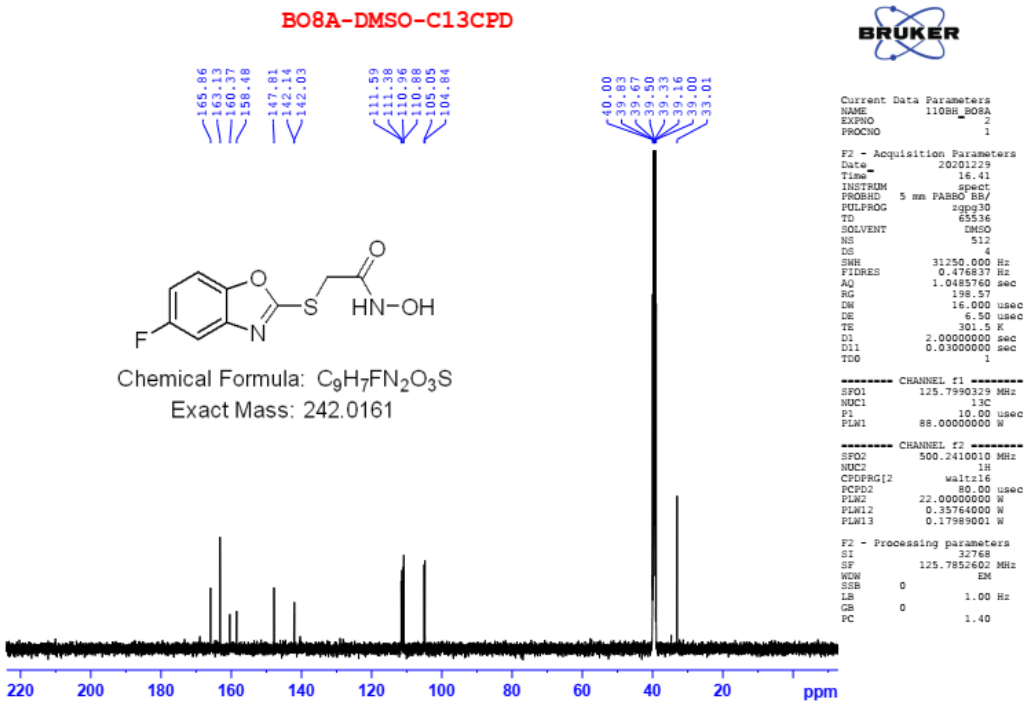


Figure S3.71 ^{13}C-NMR spectrum of compound **15**

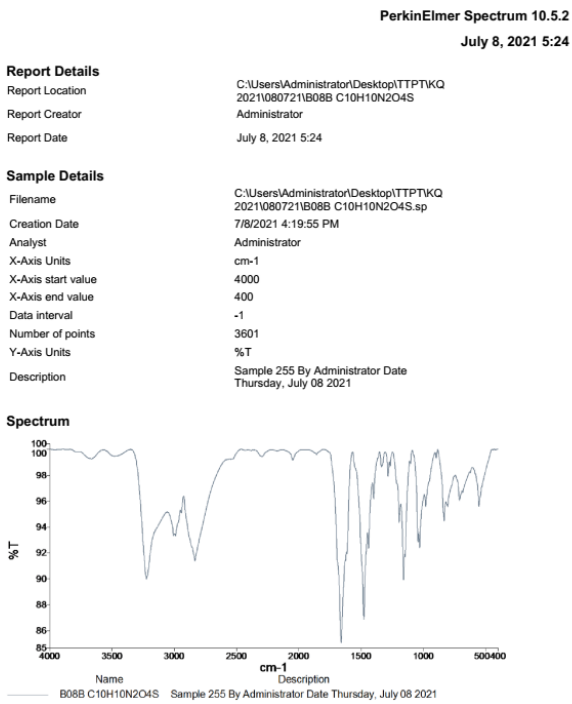


Figure S3.72 IR spectrum of compound **16**

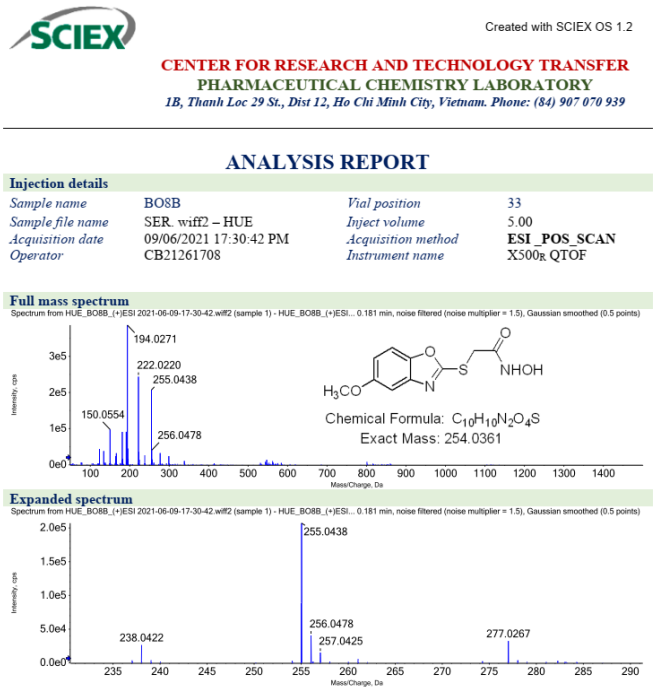


Figure S3.73 MS spectrum of compound **16**

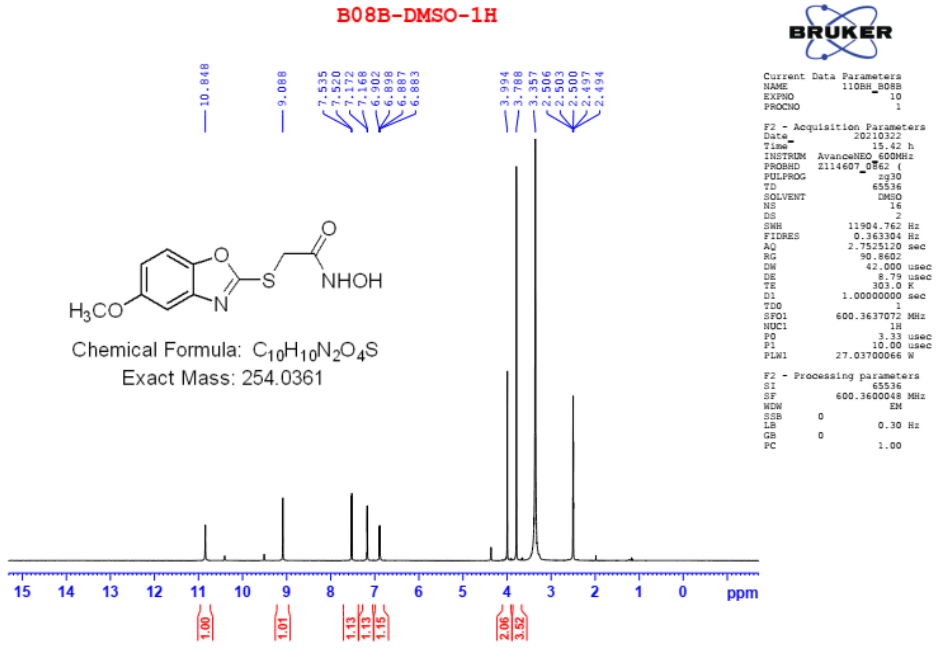


Figure S3.74 ^{1}H-NMR spectrum of compound **16**

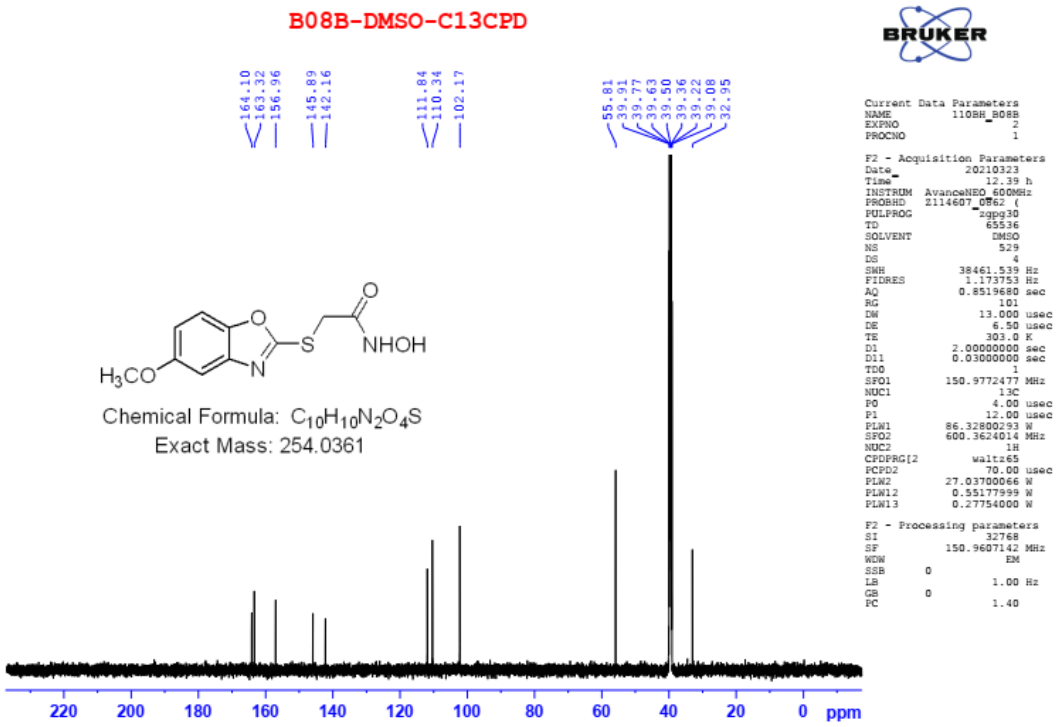


Figure S3.75 ^{13}C-NMR spectrum of compound **16**

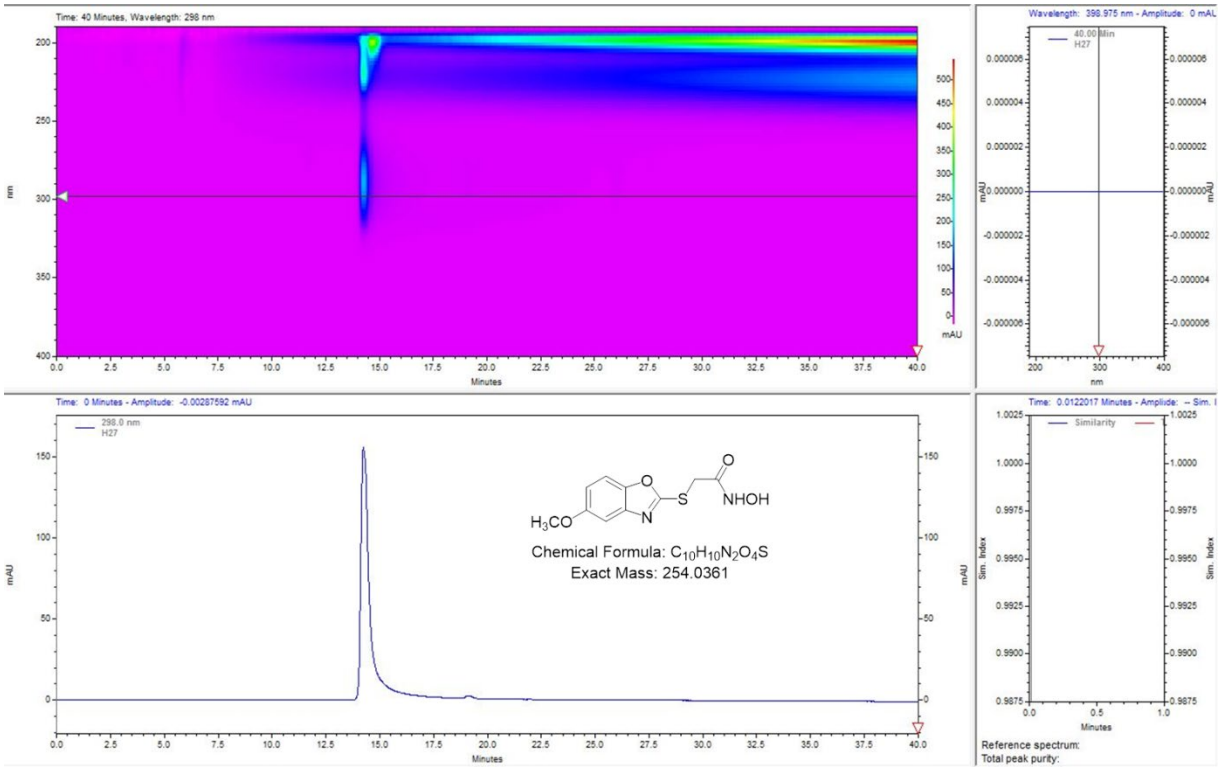


Figure S3.76 HPLC spectrum of compound **16**

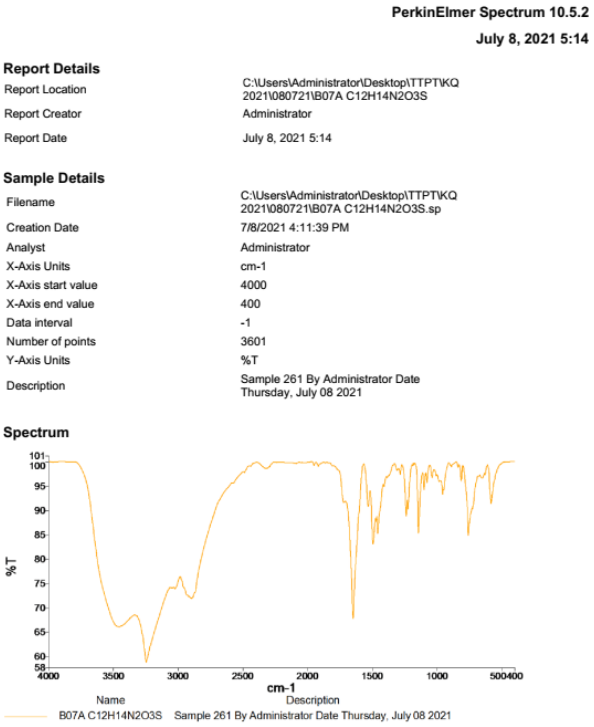


Figure S3.77 IR spectrum of compound **17**

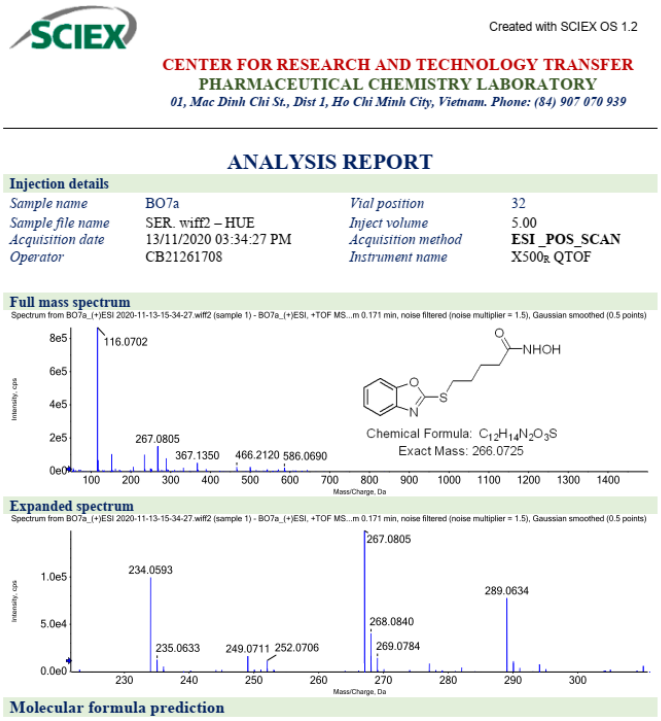


Figure S3.78 MS spectrum of compound **17**

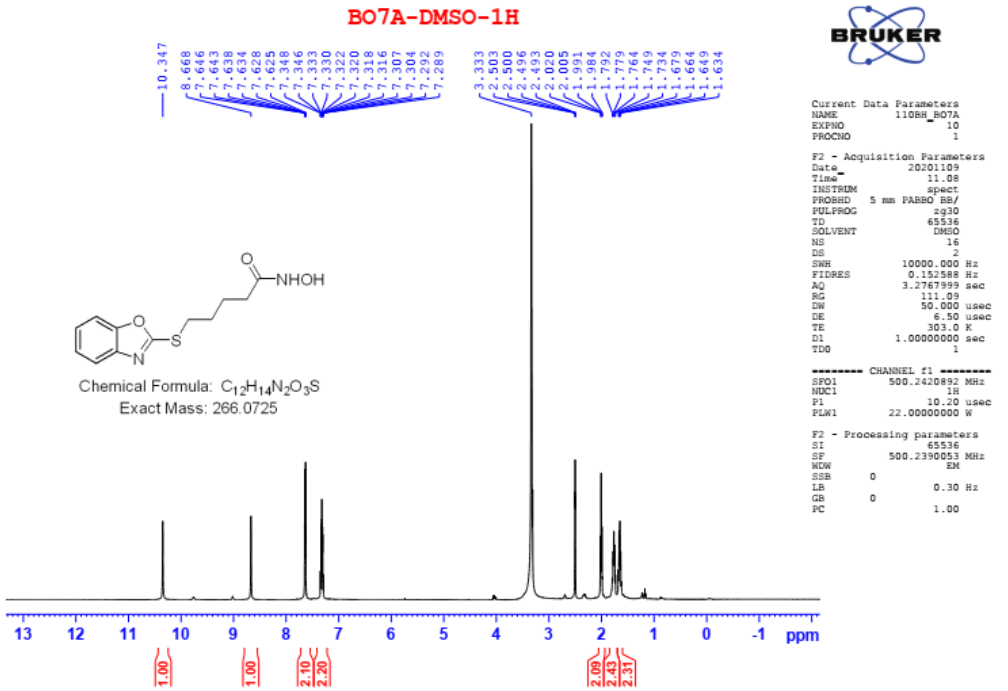


Figure S3.79 ^{1}H-NMR spectrum of compound **17**

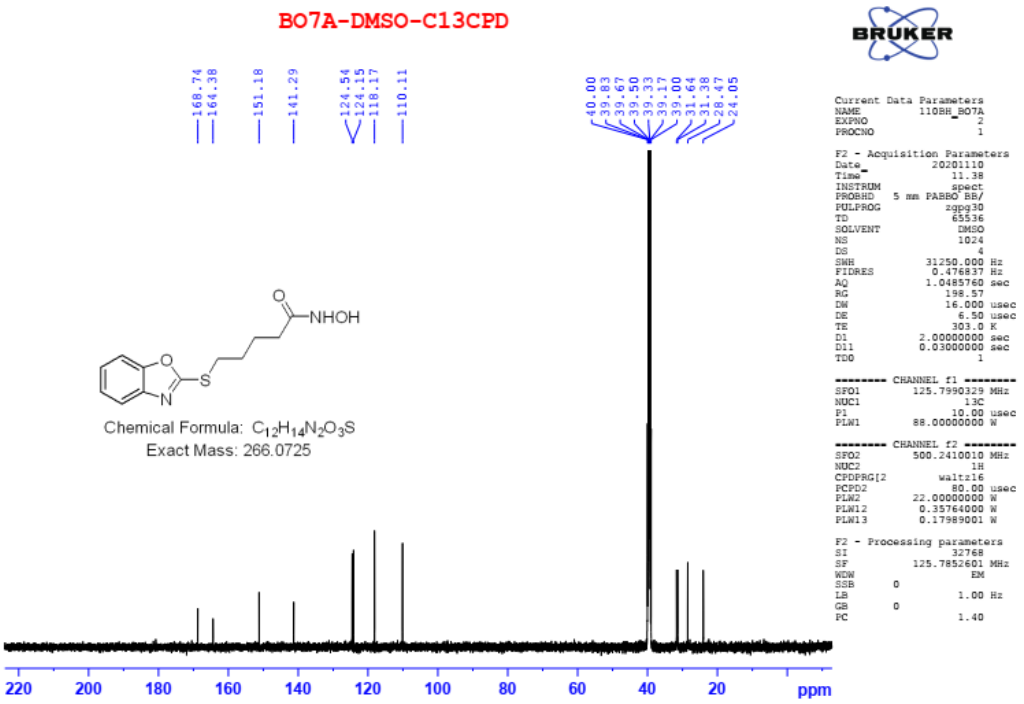


Figure S3.80 ^{13}C-NMR spectrum of compound **17**

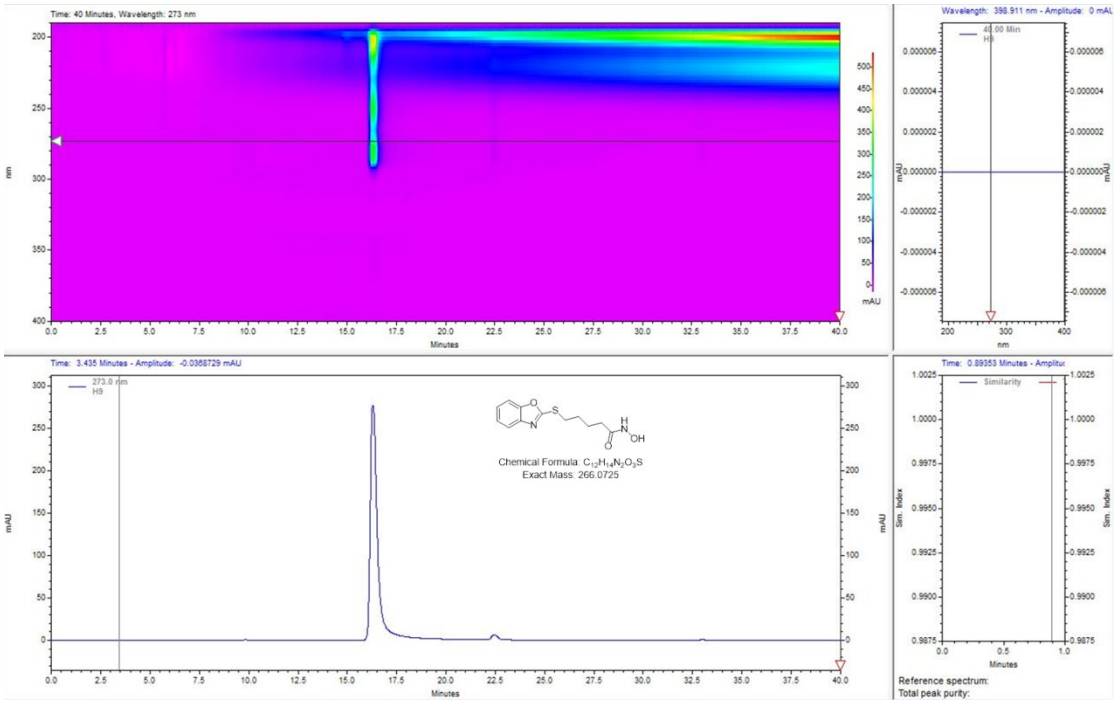


Figure S3.81 HPLC spectrum of compound **17**

PerkinElmer Spectrum 10.5.2

July 8, 2021 5:28

Report Details

Report Location	C:\Users\Administrator\Desktop\TTPT\KQ 2021\080721\B07D C13H16N2O3S
Report Creator	Administrator
Report Date	July 8, 2021 5:28

Sample Details

Filename	C:\Users\Administrator\Desktop\TTPT\KQ 2021\080721\B07D C13H16N2O3S.sp
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Analyst	Administrator
X-Axis Units	cm-1
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Data interval	-1
Number of points	3601
Y-Axis Units	%T
Description	Sample 255 By Administrator Date Thursday, July 08 2021

Spectrum

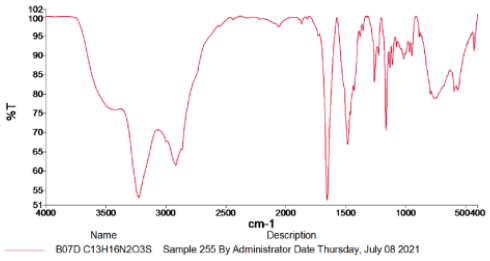

Figure S3.82 IR spectrum of compound **18**

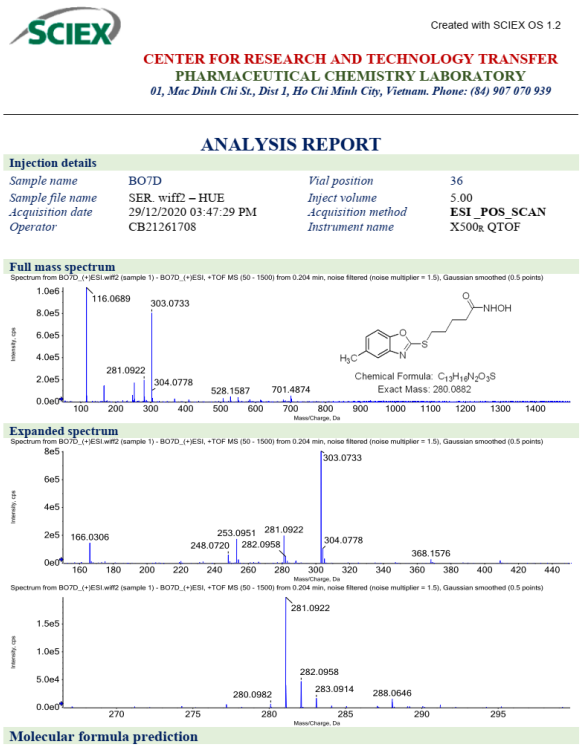

Figure S3.83 MS spectrum of compound **18**

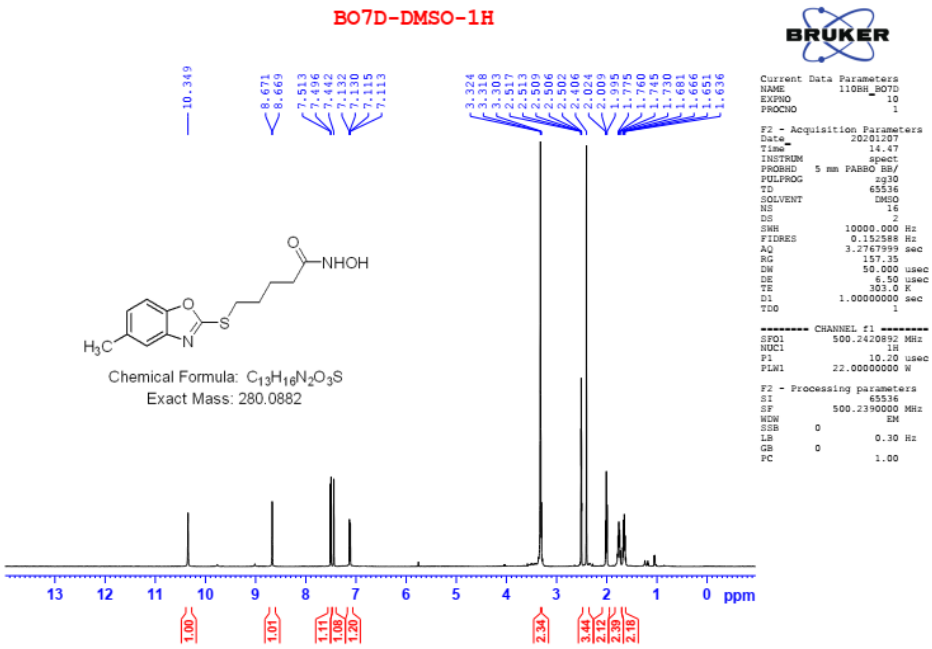

Figure S3.84 ^{1}H-NMR spectrum of compound **18**

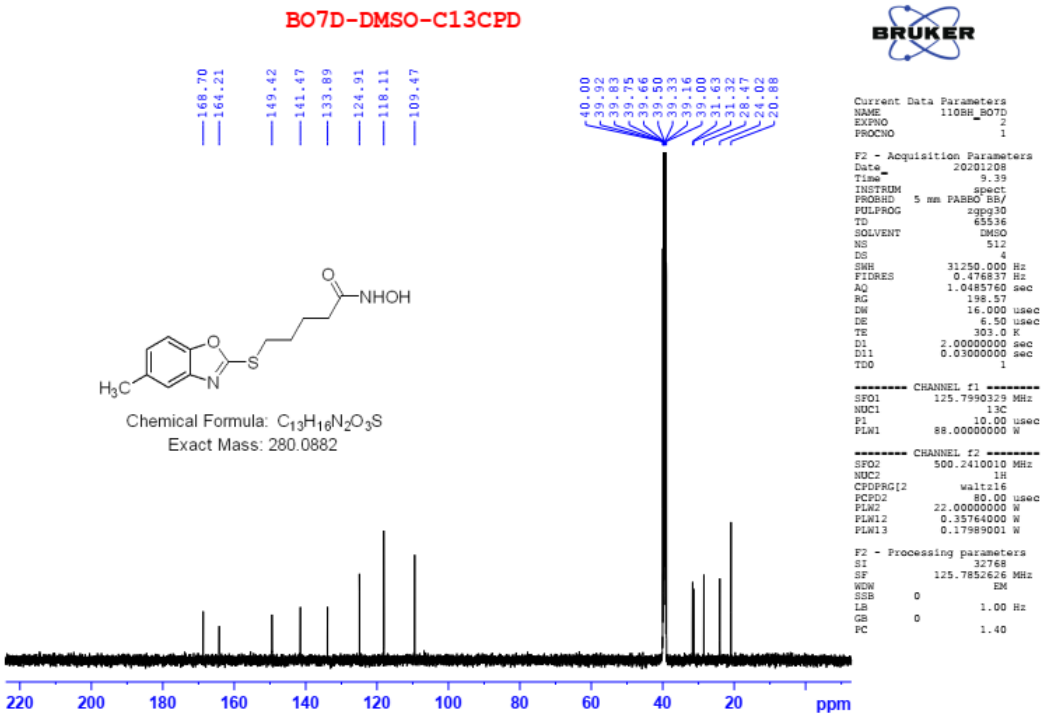

Figure S3.85 ^{13}C-NMR spectrum of compound **18**

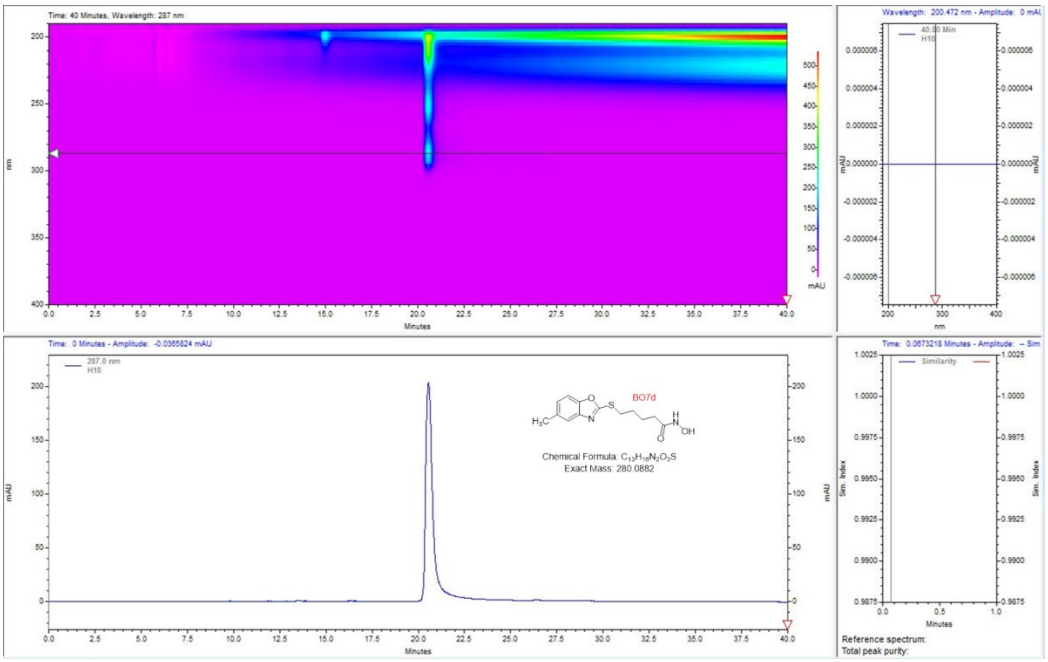

Figure S3.86 HPLC spectrum of compound **18**

PerkinElmer Spectrum 10.5.2

July 8, 2021 5:38

Report Details

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Report Creator	Administrator
Report Date	July 8, 2021 5:38

Sample Details

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Creation Date	7/8/2021 4:33:17 PM
Analyst	Administrator
X-Axis Units	cm-1
X-Axis start value	4000
X-Axis end value	400
Data interval	-1
Number of points	3601
Y-Axis Units	%T
Description	Sample 255 By Administrator Date Thursday, July 08 2021

Spectrum

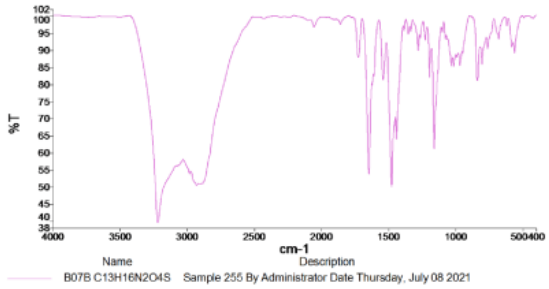

Figure S3.87 IR spectrum of compound **19**

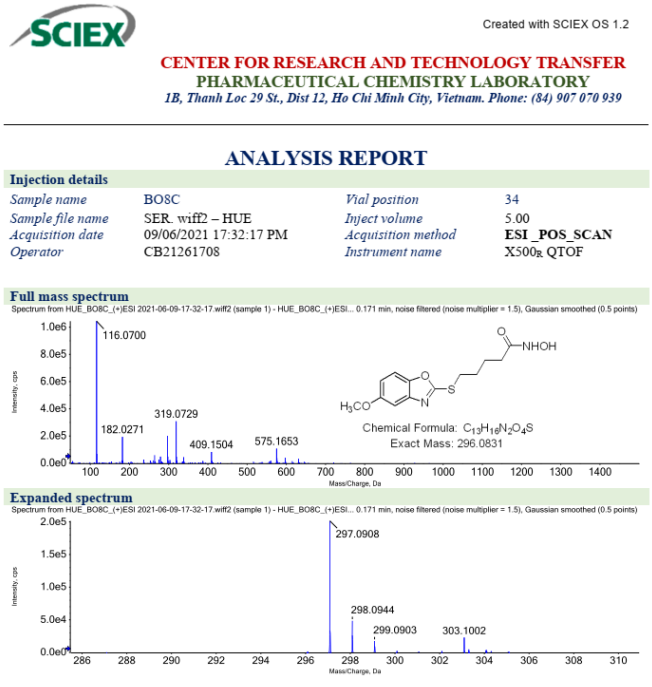

Figure S3.88 MS spectrum of compound **19**

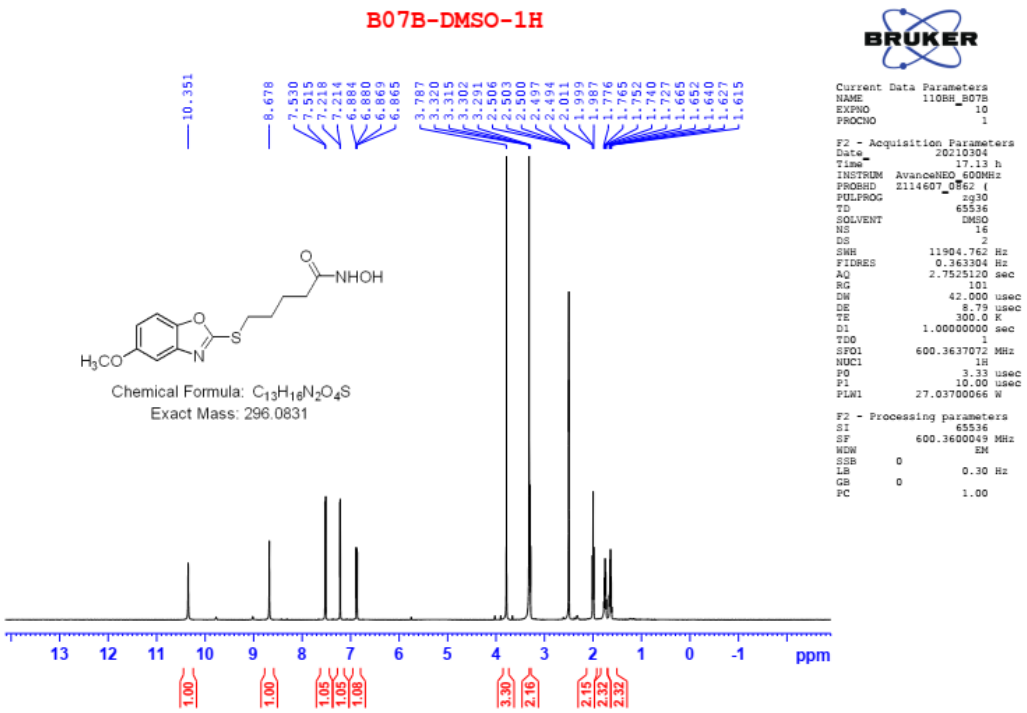

Figure S3.89 ^{1}H-NMR spectrum of compound **19**

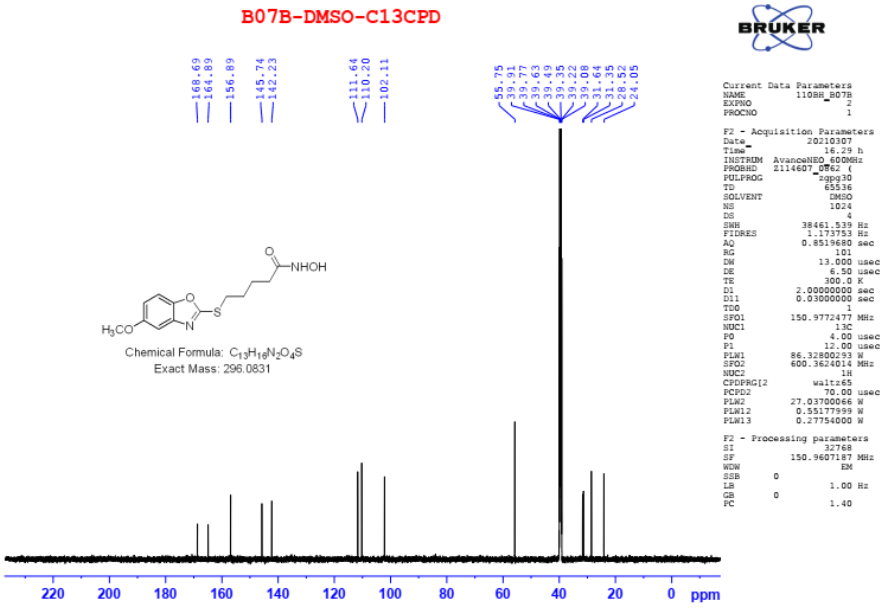

Figure S3.90 ^{13}C-NMR spectrum of compound **19**

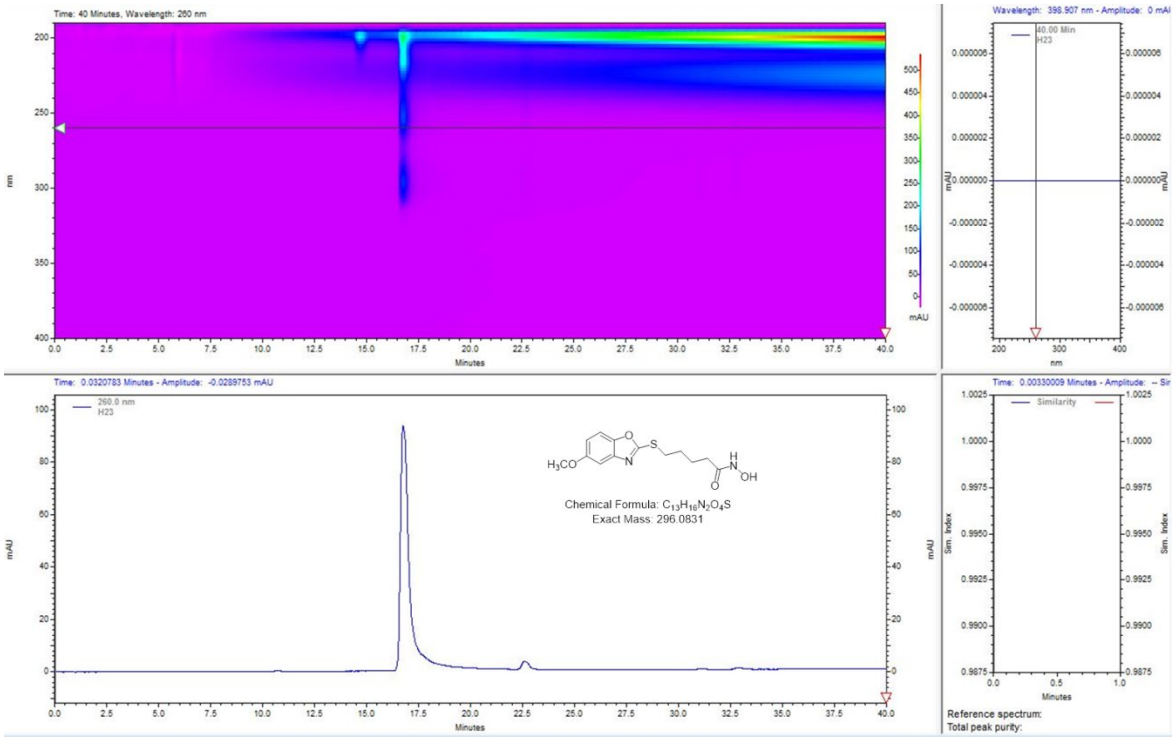

Figure S3.91 HPLC spectrum of compound **19**

References

[1] Guta R, Putinã G, Ilie C, Cristescu C, Caproiu MT, Ganea E, et al. New Benzimidazoles Derivates (Small Hydroxamates) Possible Inhibitors of the Matrix Metalloproteinase. Rev Chim. 2009;60:1146-9.

[2] Kassab SE, Mowafy S, Alserw AM, Seliem JA, El-Naggar SM, Omar NN, et al. Structure-based design generated novel hydroxamic acid based preferential HDAC6 lead inhibitor with on-target cytotoxic activity against primary choroid plexus carcinoma. Journal of enzyme inhibition and medicinal chemistry. 2019;34:1062-77.