Supporting Information for

Original Article

First small-molecule PROTACs for G protein-coupled receptors: inducing α_{1A}-adrenergic receptor degradation

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Table of contents

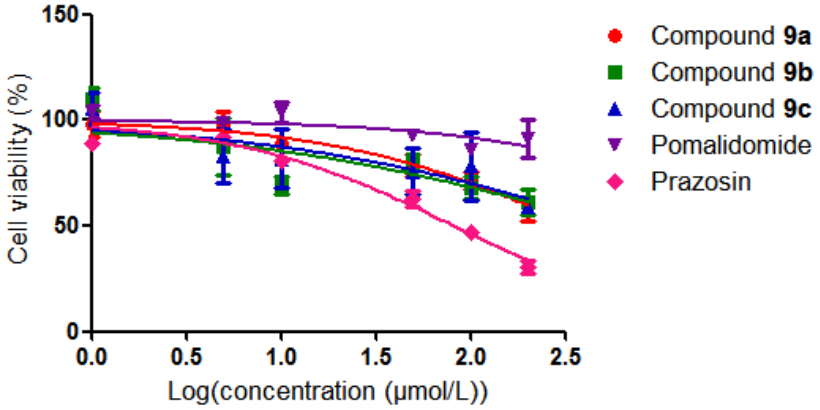


Figure S1 The cytotoxicity of compounds, 0–200 μmol/L.

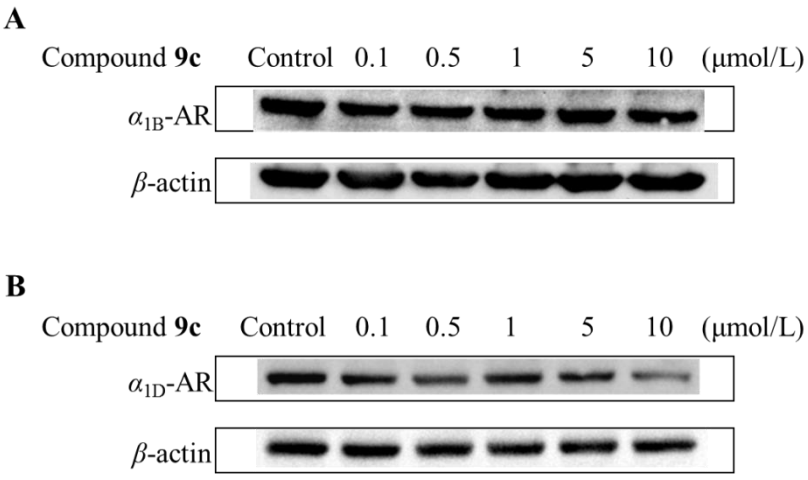


Figure S2 The effects of compound **9c** on the level of α_{1B}-AR and α_{1D}-AR. The cells were treated with compound **9c** as indicated for 12 h before harvesting and then analyzed by Western blotting.

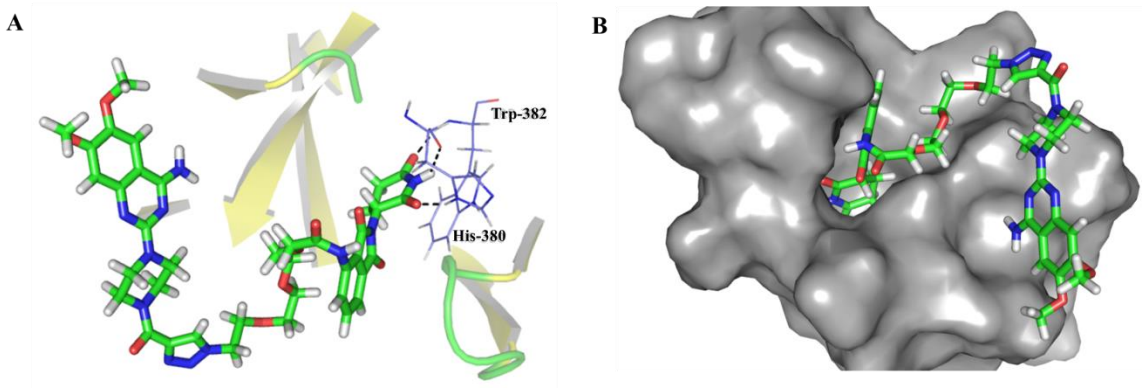


Figure S3 (A) Binding sites of the hydrogen bonds between compound **9c** and CRBN. Compound **9c** is highlighted in the green stick. The dimer forming the cap for the binding pocket is colored in light yellow. Black dash lines represent the key hydrogen bonds. (B) Docking model of the compound **9c** bound to DDB1-CRBN (PDB: 4CI3).

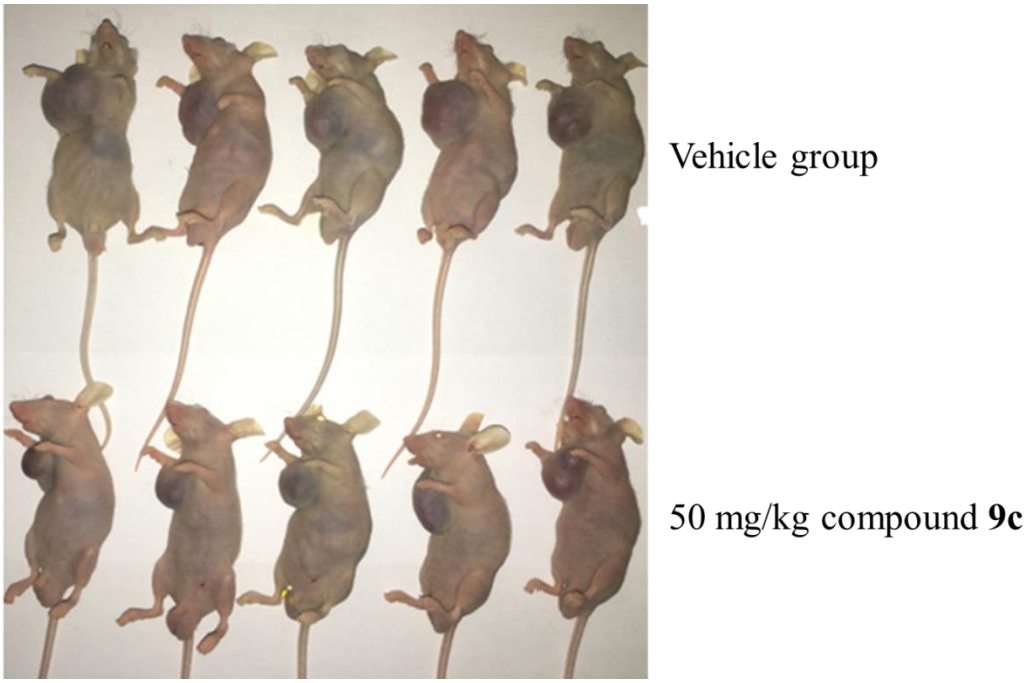
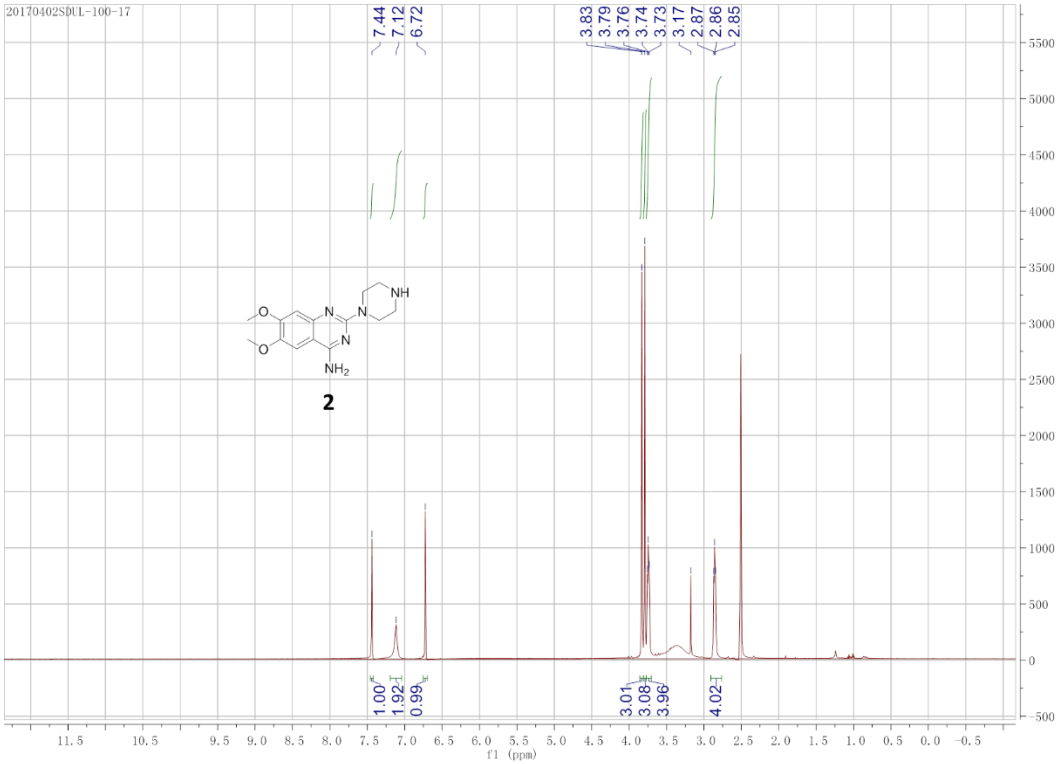


Figure S4 The nude mice with the PC-3 derived prostate cancer xenografts were photographed after two weeks of intraperitoneal administration.

NMR, MS and HRMS data of compounds



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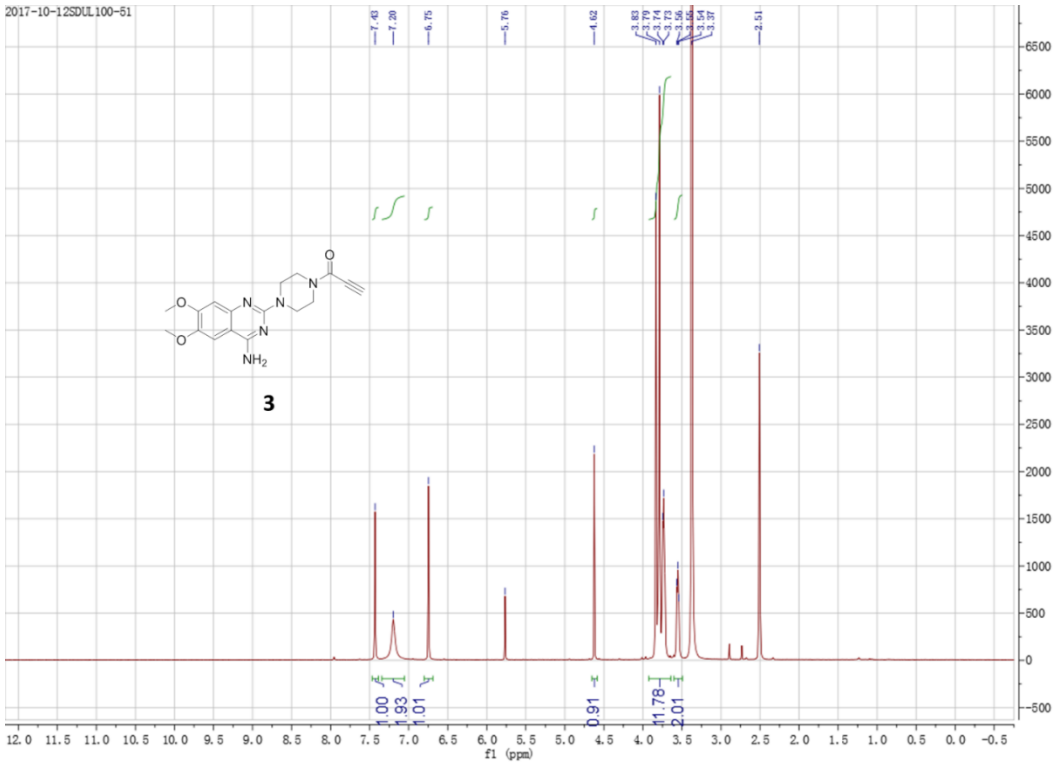

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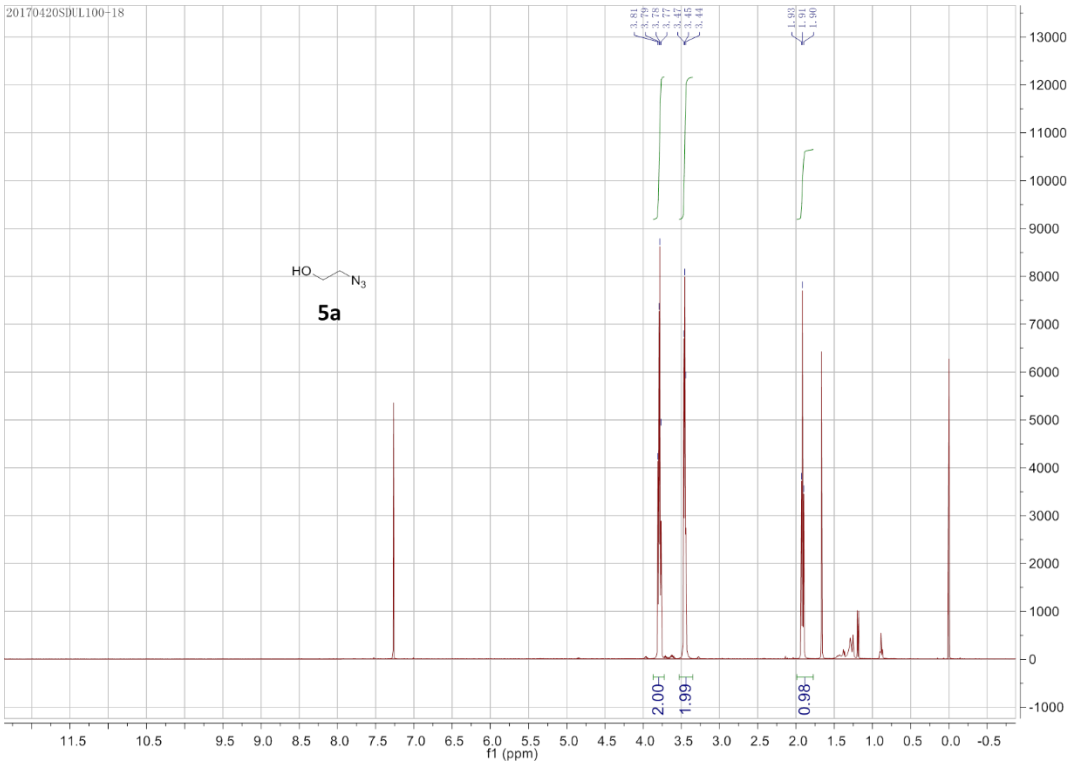
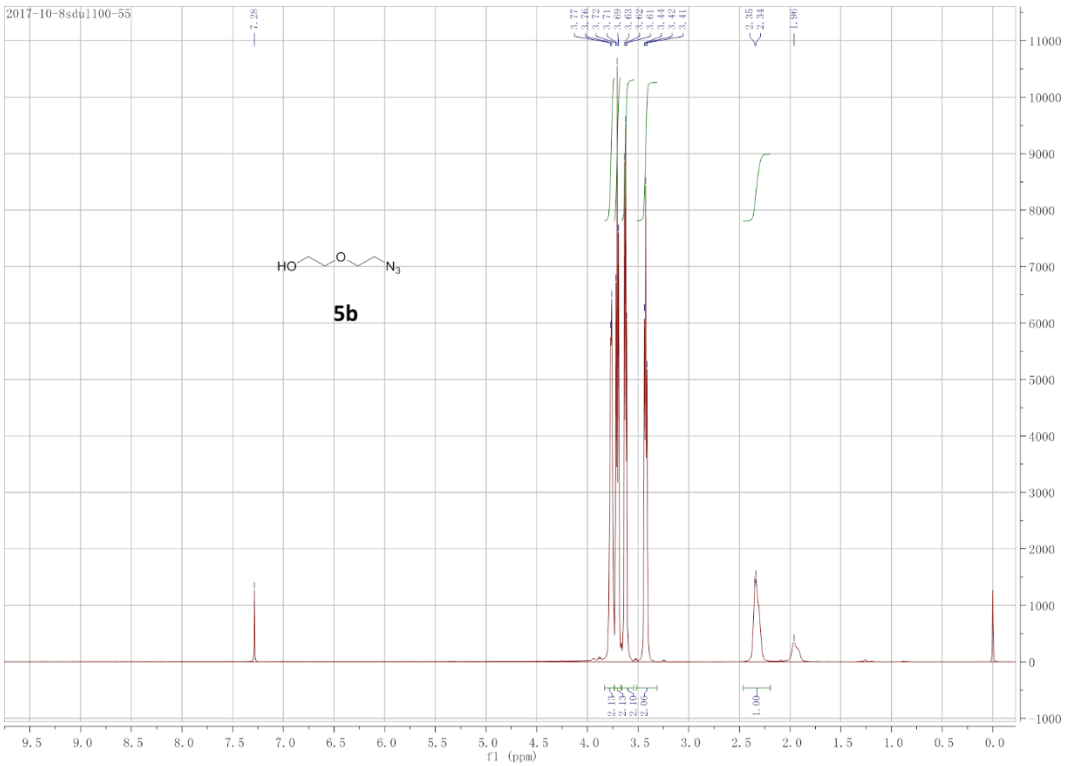
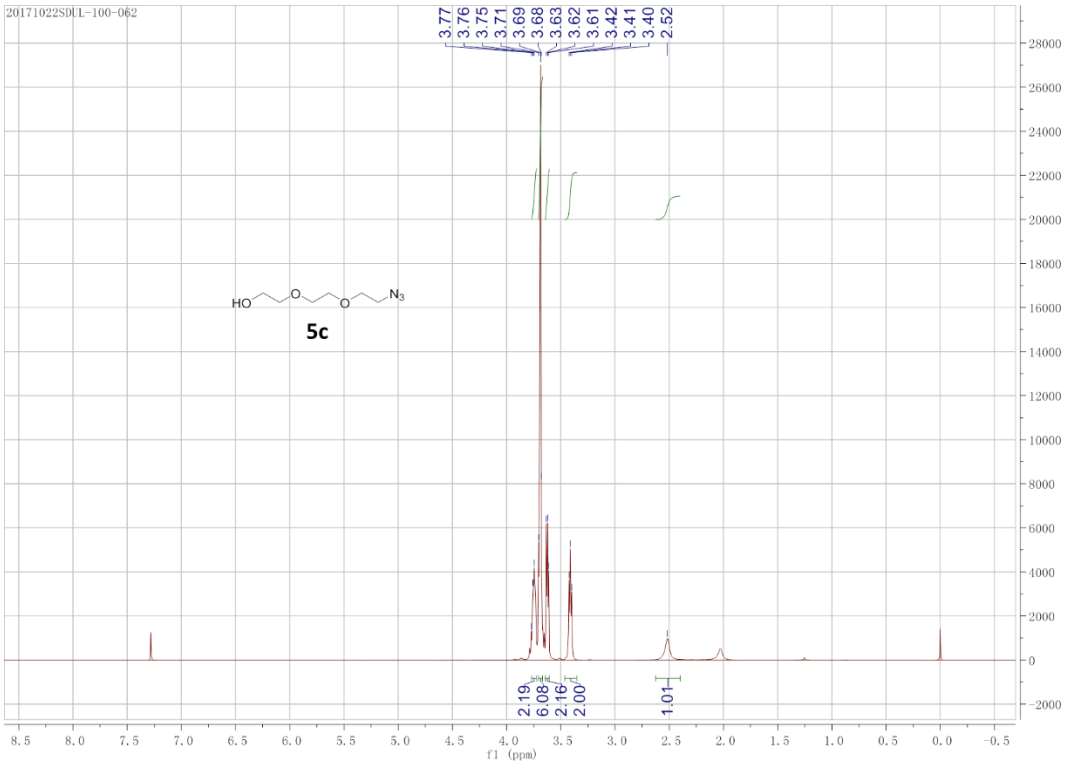

20170420SDUL100-18
HO
N3
5a
f1 (ppm)


2017-10-8sdu1100-55
HO
O
N3
5b
f1 (ppm)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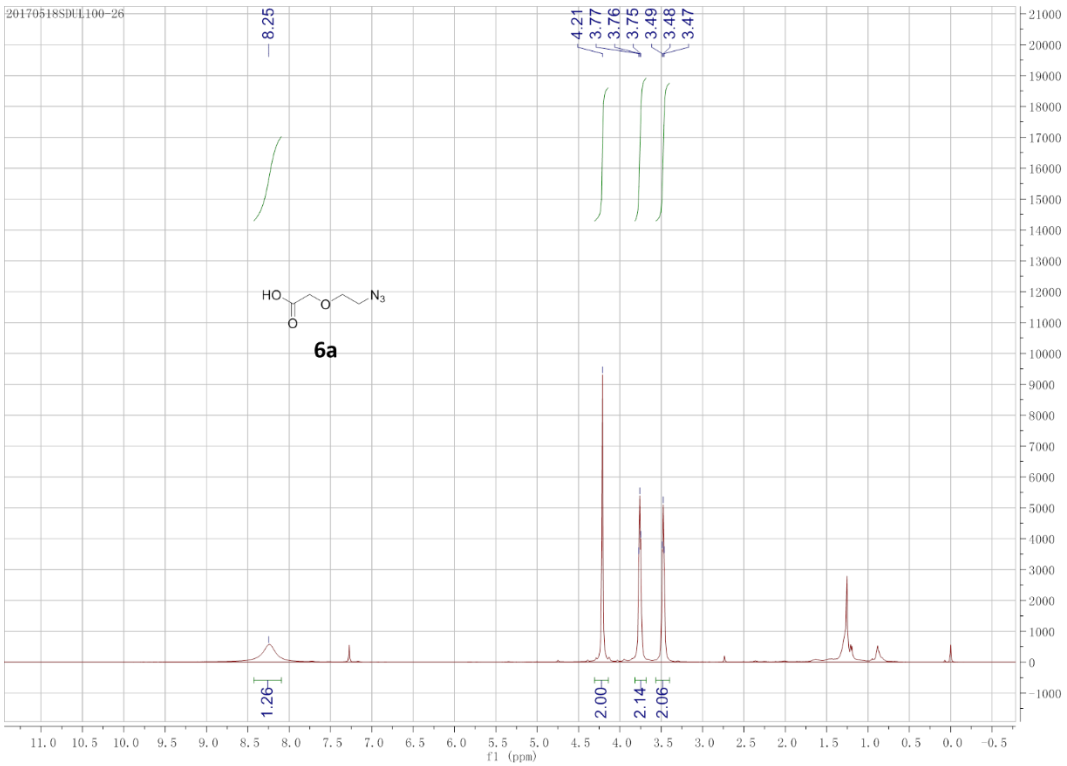
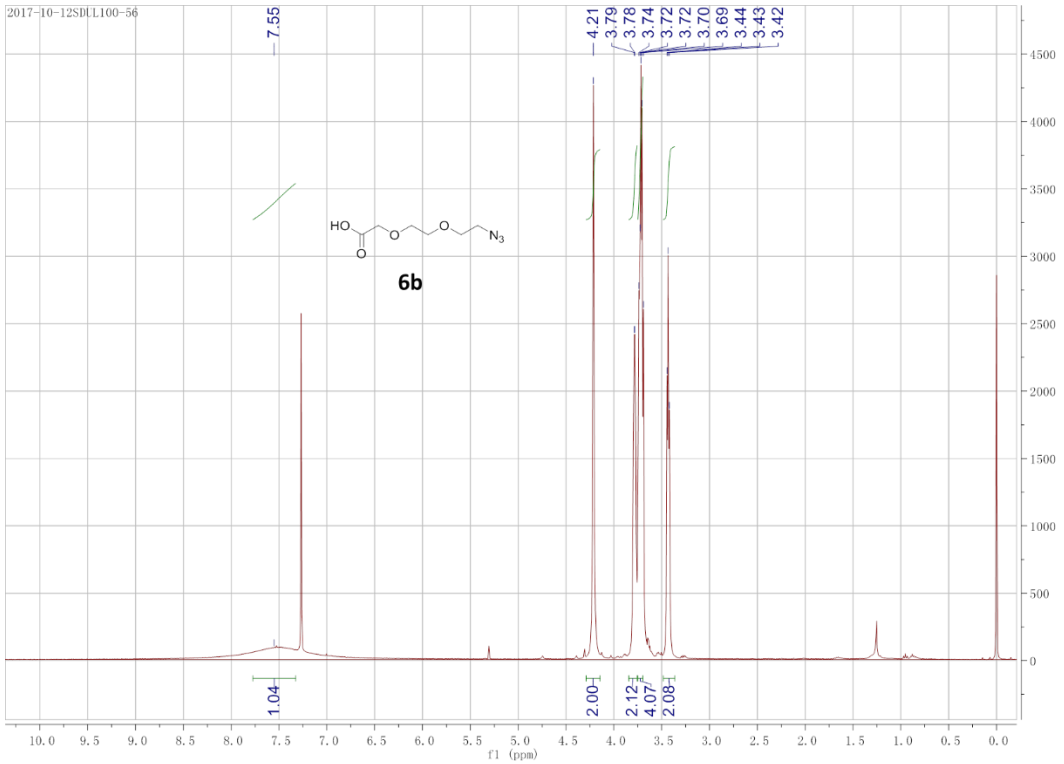
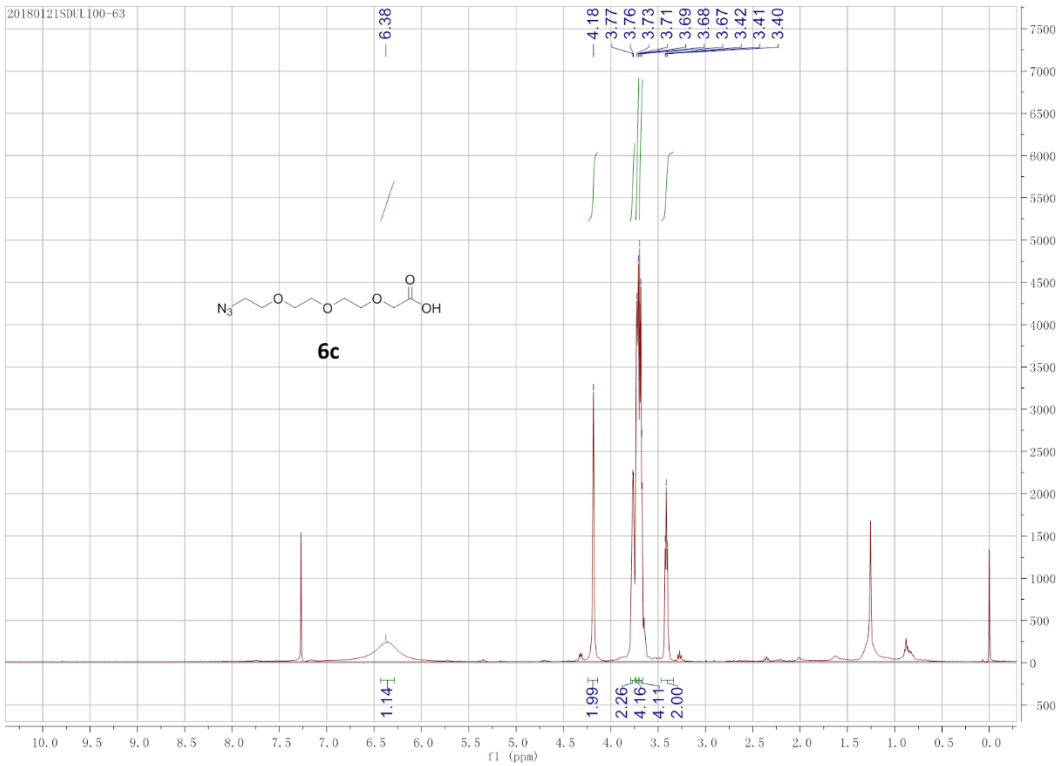
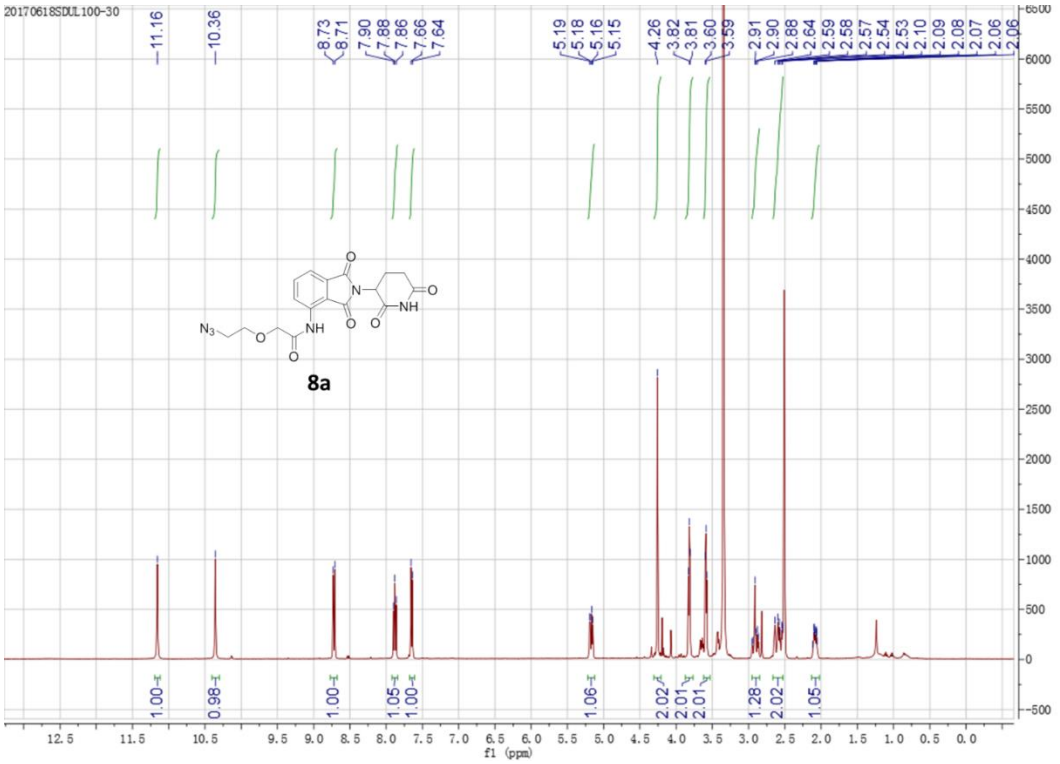
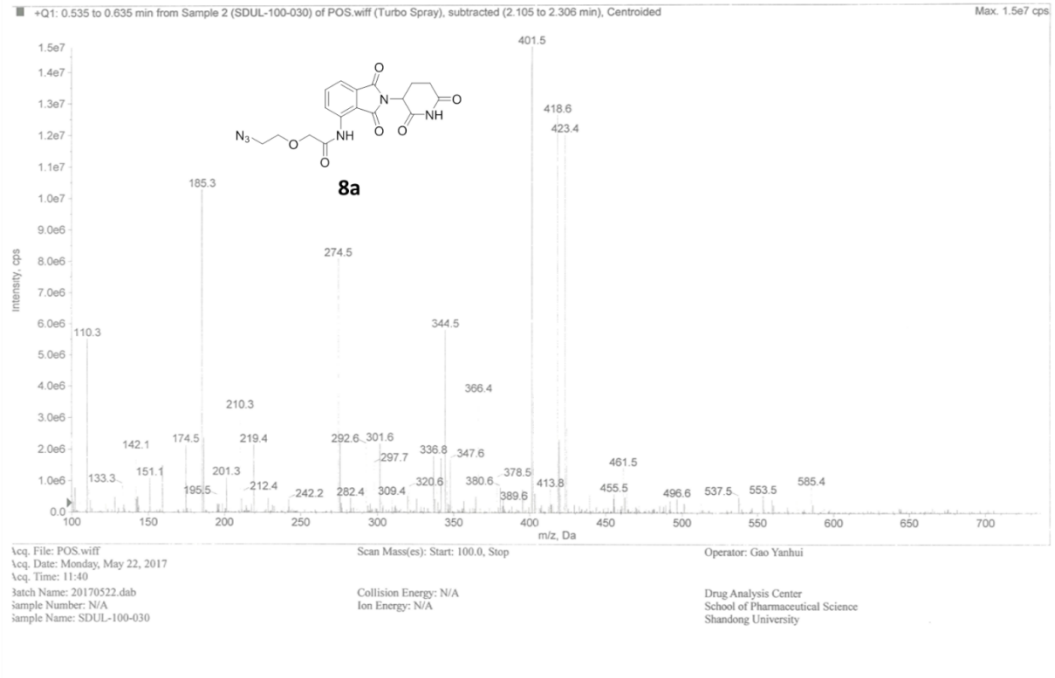
3.77
3.76
3.75
3.71
3.69
3.68
3.63
3.62
3.61
3.42
3.41
3.40
2.52
HO
O
O
N3
5c
2.19
6.08
2.16
2.00
1.01
f1 (ppm)

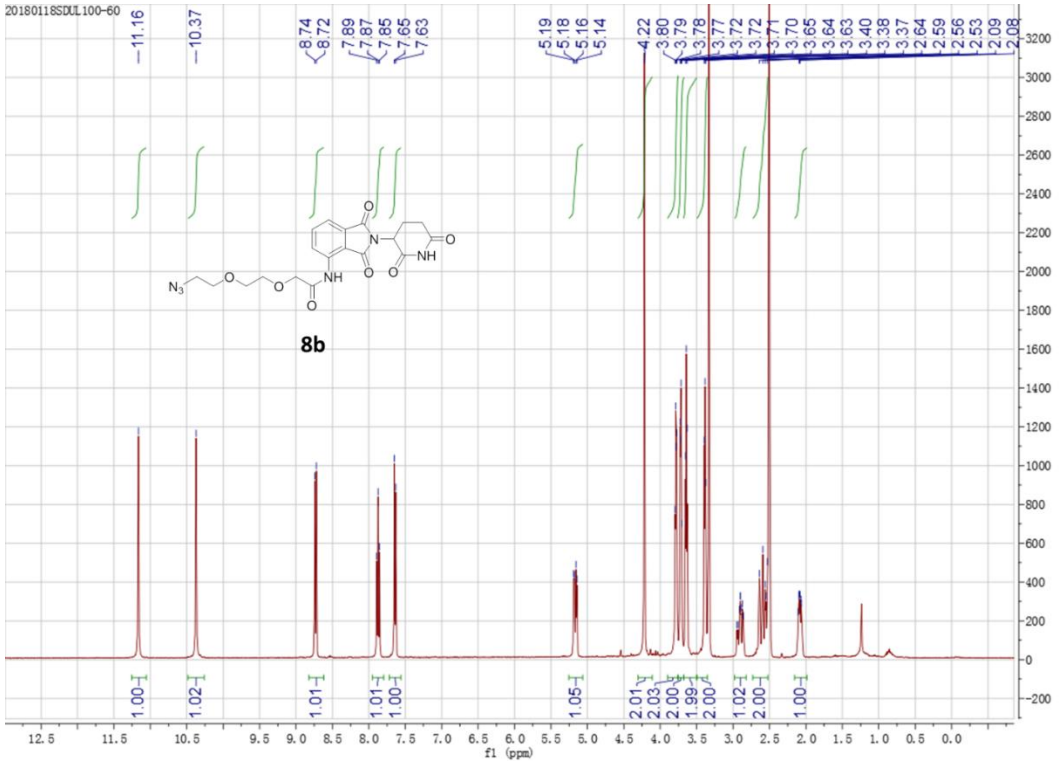

20170518SDLL100-26
8.25
4.21
3.77
3.76
3.75
3.49
3.48
3.47
HO
O
O
N3
6a
1.26
2.00
2.14
2.06
f1 (ppm)

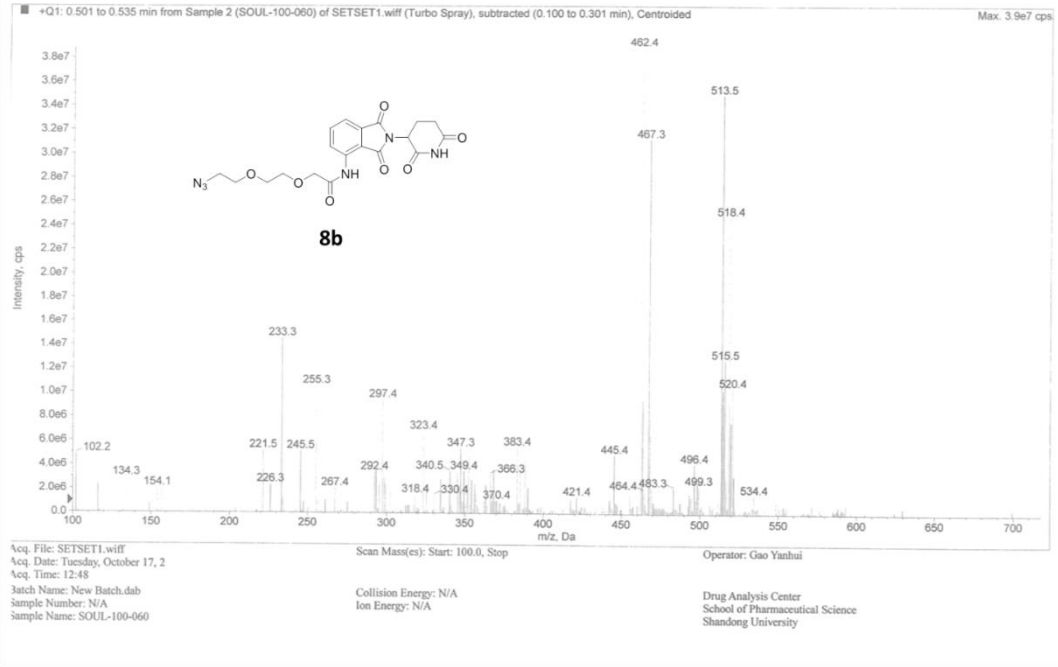

2017-10-12SDLL100-56
7.55
4.21
3.79
3.78
3.74
3.72
3.72
3.70
3.69
3.44
3.43
3.42
HO
O
O
O
N3
6b
1.04
2.00
2.12
4.07
2.08
f1 (ppm)

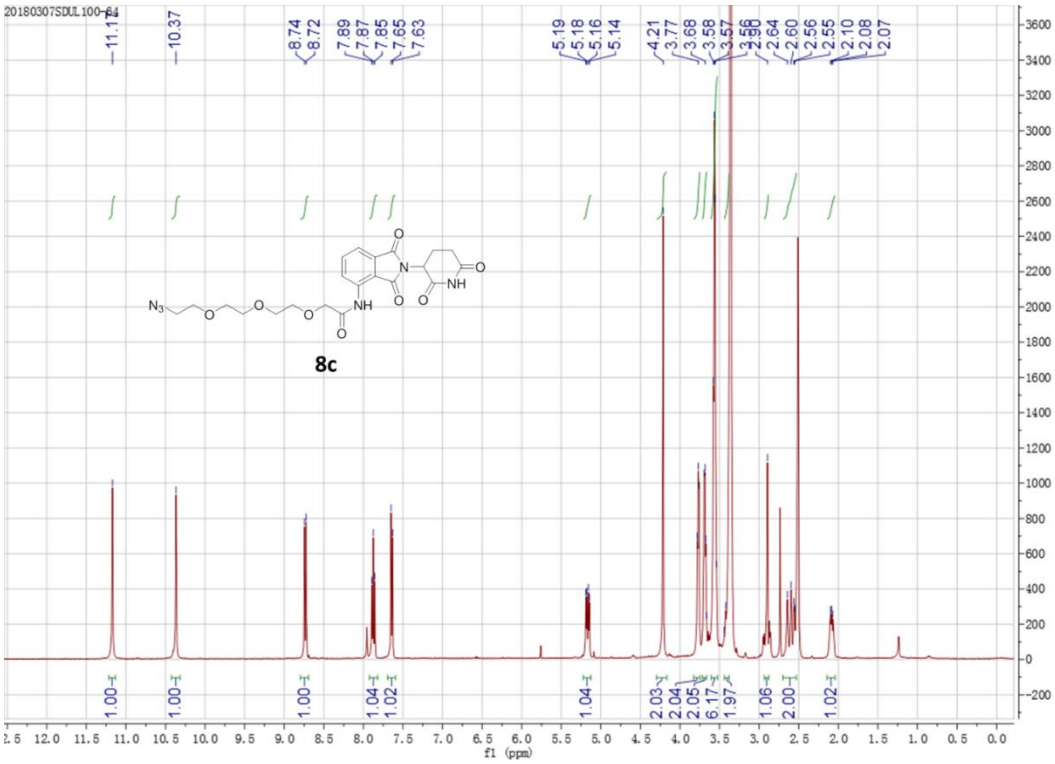

20180121SDLL100-63
6.38
4.18
3.77
3.76
3.73
3.71
3.69
3.68
3.67
3.42
3.41
3.40
N3
O
O
O
O
OH
6c
1.14
1.99
2.26
4.16
4.11
2.00
f1 (ppm)

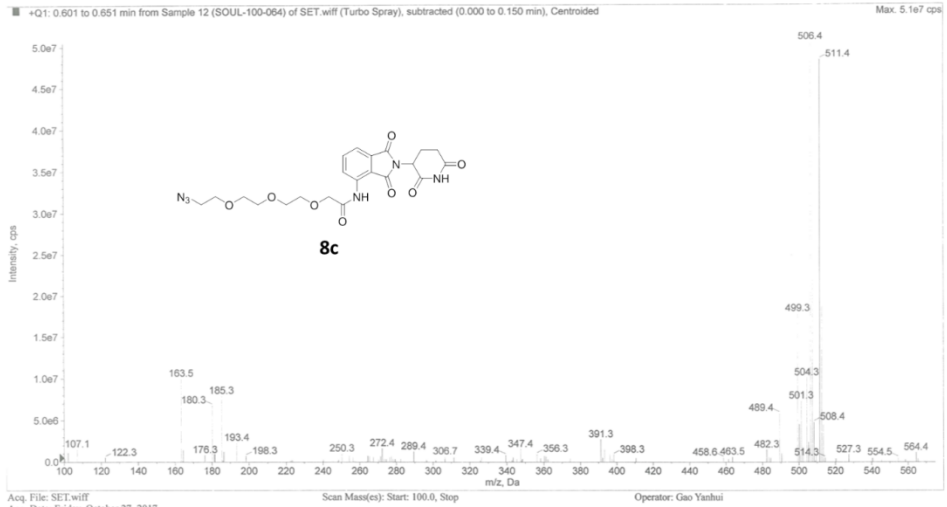

20170618SDUL100-30
11.16
10.36
8.73
8.71
7.90
7.88
7.86
7.66
7.64
5.19
5.18
5.16
5.15
4.26
3.82
3.81
3.60
3.59
2.91
2.90
2.88
2.64
2.59
2.58
2.57
2.54
2.53
2.10
2.09
2.08
2.07
2.06
2.06
1.00
0.98
1.00
1.05
1.00
1.06
2.02
2.01
2.01
1.28
2.02
1.05
f1 (ppm)
8a

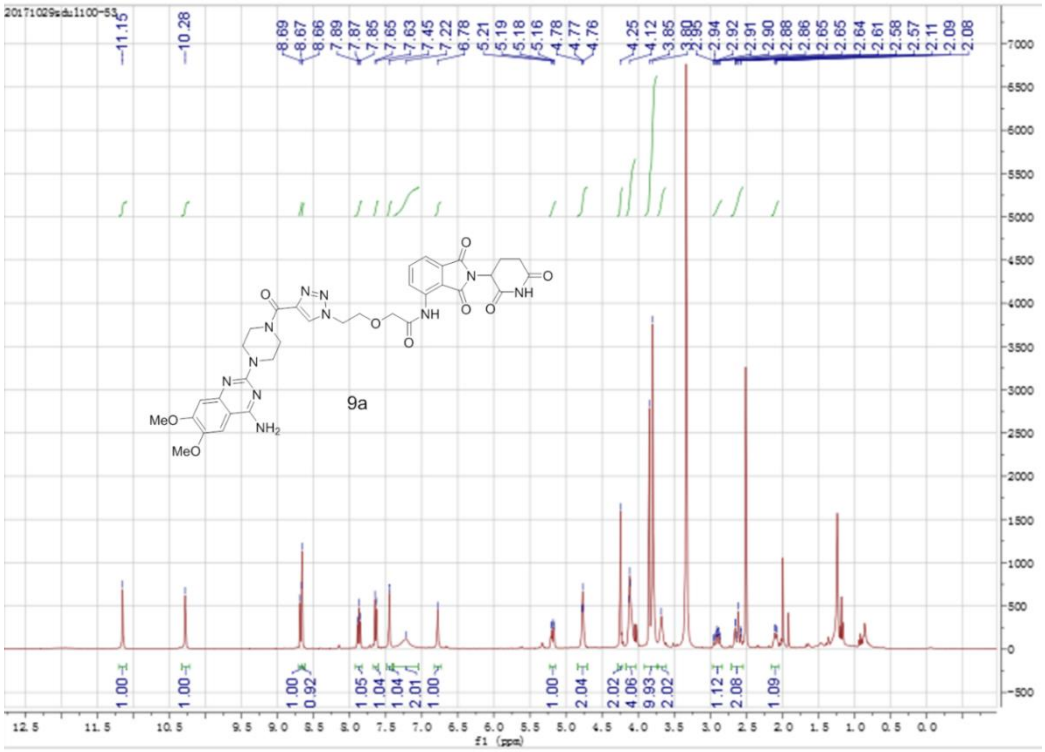

+Q1: 0.535 to 0.635 min from Sample 2 (SDUL-100-030) of POS.wiff (Turbo Spray), subtracted (2.105 to 2.306 min), Centroided
Max. 1.5e7 cps.
Intensity, cps
m/z, Da
401.5
418.6
423.4
185.3
274.5
344.5
110.3
366.4
210.3
8a
Acq. File: POS.wiff
Acq. Date: Monday, May 22, 2017
Acq. Time: 11:40
Batch Name: 20170522.dab
Sample Number: N/A
Sample Name: SDUL-100-030
Scan Mass(es): Start: 100.0, Stop
Collision Energy: N/A
Ion Energy: N/A
Operator: Gao Yanhui
Drug Analysis Center
School of Pharmaceutical Science
Shandong University

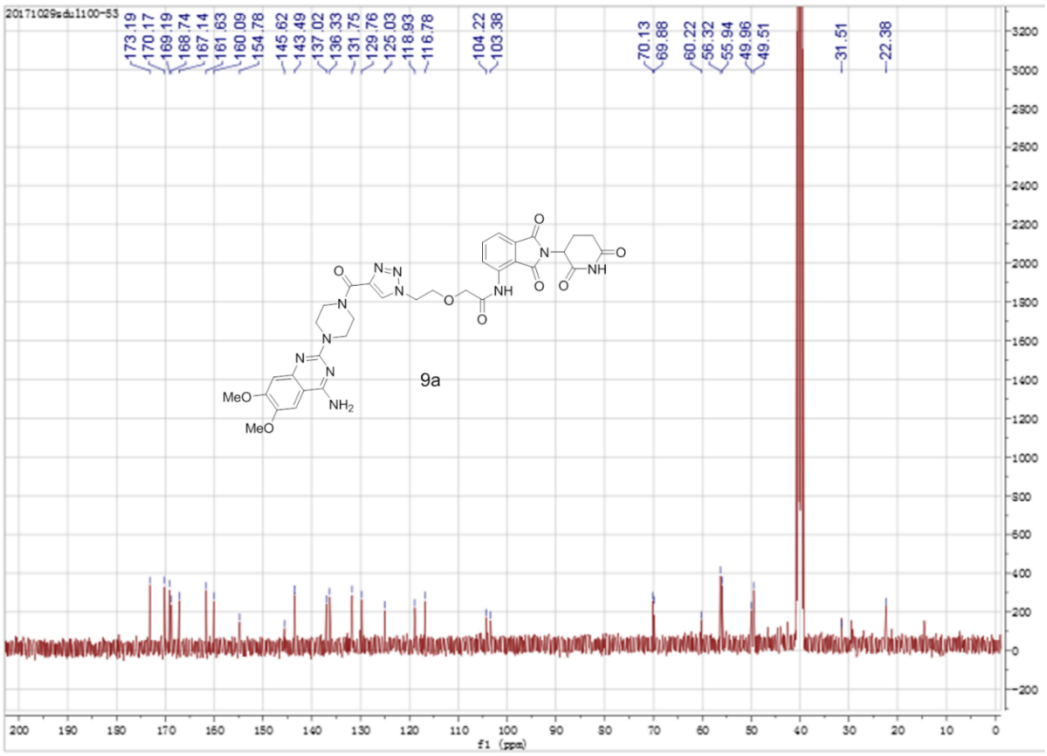

20180118SDUL100-60
8b
f1 (ppm)

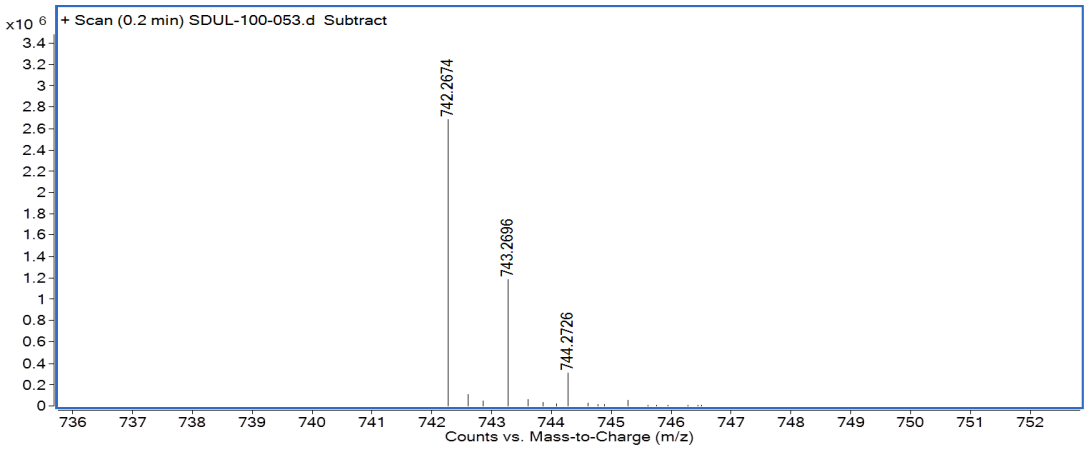

+Q1: 0.501 to 0.535 min from Sample 2 (SOUL-100-060) of SETSET1.wiff (Turbo Spray), subtracted (0.100 to 0.301 min), Centroided
Max. 3.9e7 cps.
8b
Intensity, cps
m/z, Da
Acq. File: SETSET1.wiff
Acq. Date: Tuesday, October 17, 2
Acq. Time: 12:48
Batch Name: New Batch.dab
Sample Number: N/A
Sample Name: SOUL-100-060
Scan Mass(es): Start: 100.0, Stop
Collision Energy: N/A
Ion Energy: N/A
Operator: Gao Yanhui
Drug Analysis Center
School of Pharmaceutical Science
Shandong University


20180307SDUL100-64
11.15
10.37
8.74
8.72
7.89
7.87
7.85
7.65
7.63
5.19
5.18
5.16
5.14
4.21
3.77
3.68
3.58
3.57
3.56
2.90
2.64
2.60
2.56
2.55
2.10
2.08
2.07
1.00
1.00
1.00
1.04
1.02
1.04
2.03
2.04
2.05
6.17
1.97
1.06
2.00
1.02
f1 (ppm)
8c


+Q1: 0.601 to 0.651 min from Sample 12 (SOUL-100-064) of SET.wiff (Turbo Spray), subtracted (0.000 to 0.150 min), Centroided
Max. 5.1e7 cps
Intensity, cps
m/z, Da
506.4
511.4
499.3
504.3
501.3
508.4
489.4
163.5
185.3
180.3
193.4
107.1
122.3
178.3
198.3
250.3
272.4
289.4
306.7
339.4
347.4
356.3
391.3
398.3
458.6
463.5
482.3
514.3
527.3
554.5
564.4
8c
Acq. File: SET.wiff
Acq. Date: Friday, October 27, 2017
Acq. Time: 17:59
Batch Name: 20171027.dab
Sample Number: N/A
Sample Name: SOUL-100-064
Scan Mass(es): Start: 100.0, Stop
Collision Energy: N/A
Ion Energy: N/A
Operator: Gao Yanhui
Drug Analysis Center
School of Pharmaceutical Science
Shandong University


20171029sdu1100-53
11.15
10.28
8.69
8.67
8.66
7.89
7.87
7.85
7.65
7.63
7.45
7.22
6.78
5.21
5.19
5.18
5.16
4.78
4.77
4.76
4.25
4.12
3.85
3.80
2.94
2.92
2.91
2.90
2.88
2.86
2.65
2.65
2.64
2.61
2.58
2.57
2.11
2.09
2.08
9a
MeO
MeO
NH2
NH
NH
1.00
1.00
1.00
0.92
1.05
1.04
1.04
2.01
1.00
1.00
2.04
2.02
4.06
9.93
2.02
1.12
2.08
1.09
f1 (ppm)


20171029sdu1100-53
173.19
170.17
169.19
168.74
167.14
161.63
160.09
154.78
145.62
143.49
137.02
136.33
131.75
129.76
125.03
118.93
116.78
104.22
103.38
70.13
69.88
60.22
56.32
55.94
49.96
49.51
31.51
22.38
9a
MeO
MeO
NH2
NH
NH
f1 (ppm)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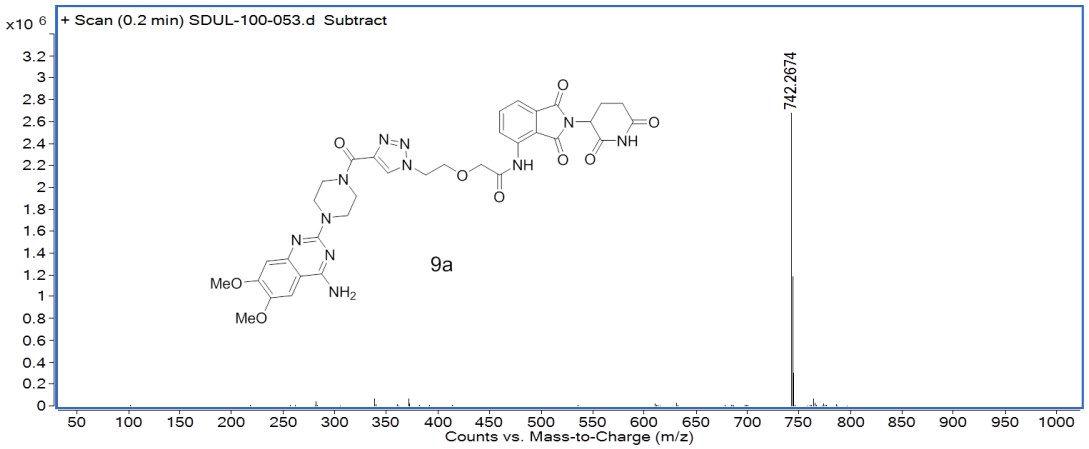
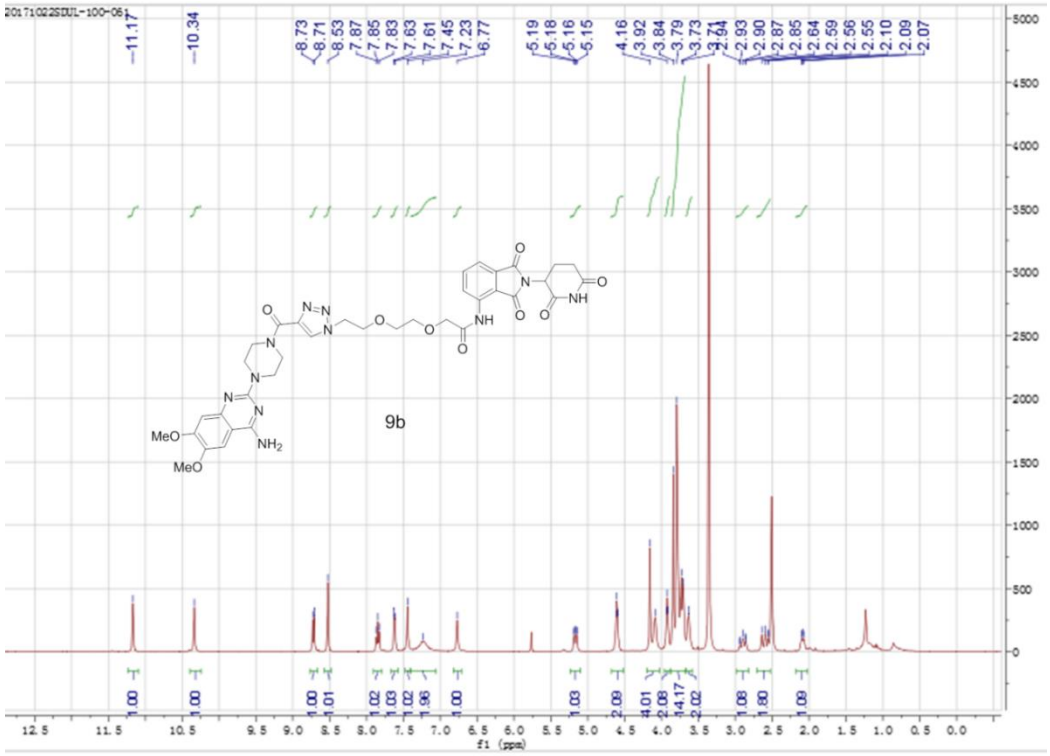
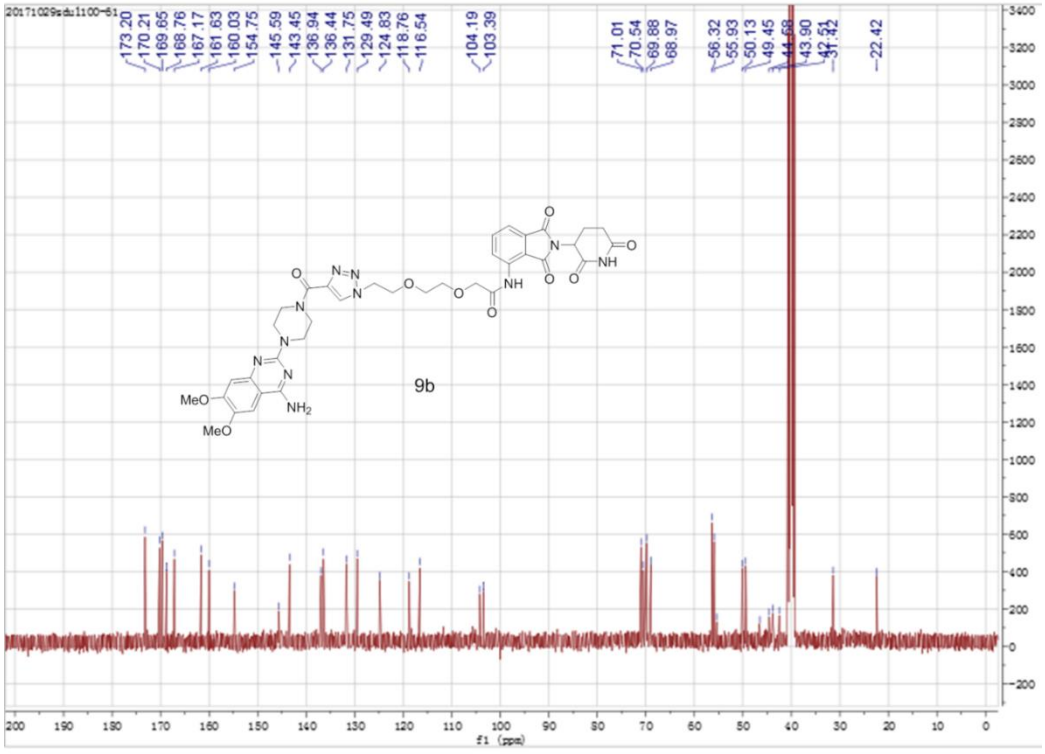
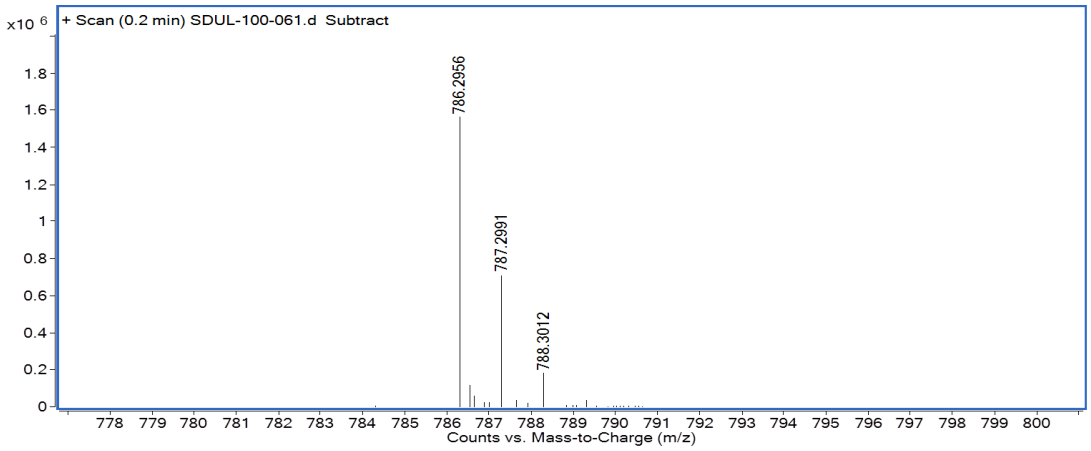
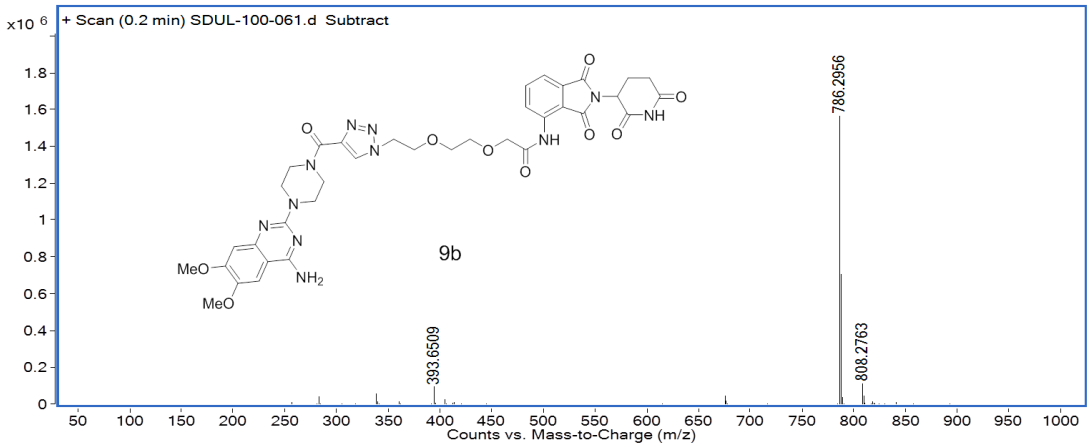
742.2674
743.2696
744.2726
Counts vs. Mass-to-Charge (m/z)

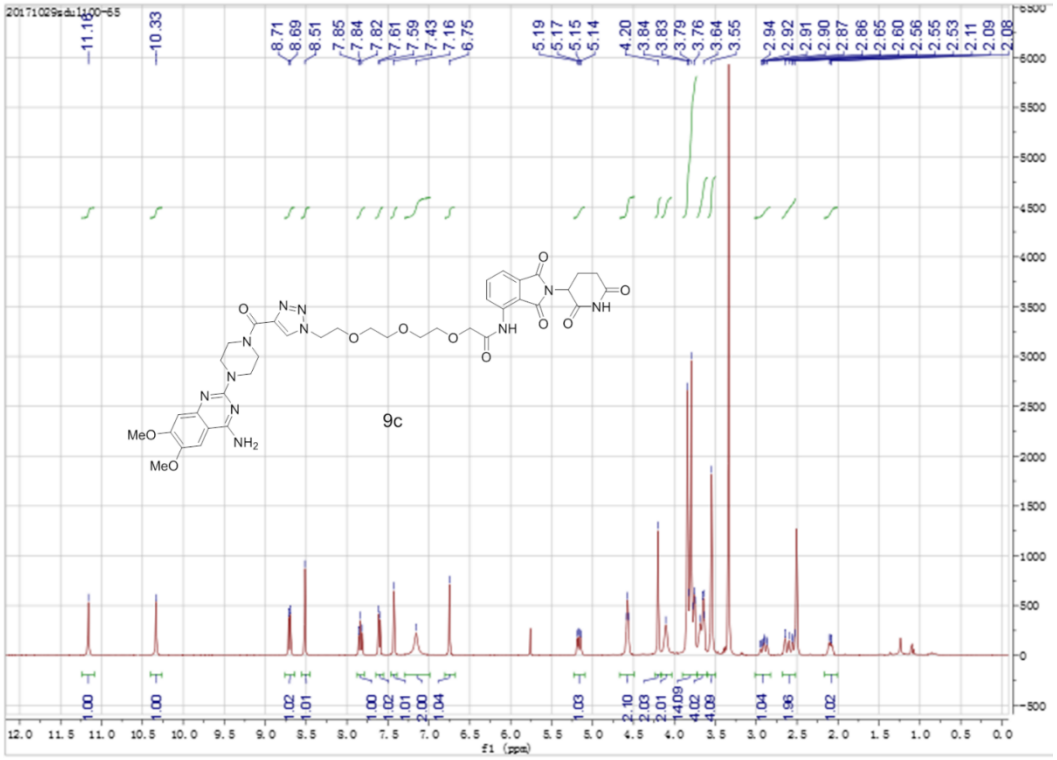

x10 6
+ Scan (0.2 min) SDUL-100-053.d Subtract
742.2674
9a
Counts vs. Mass-to-Charge (m/z)

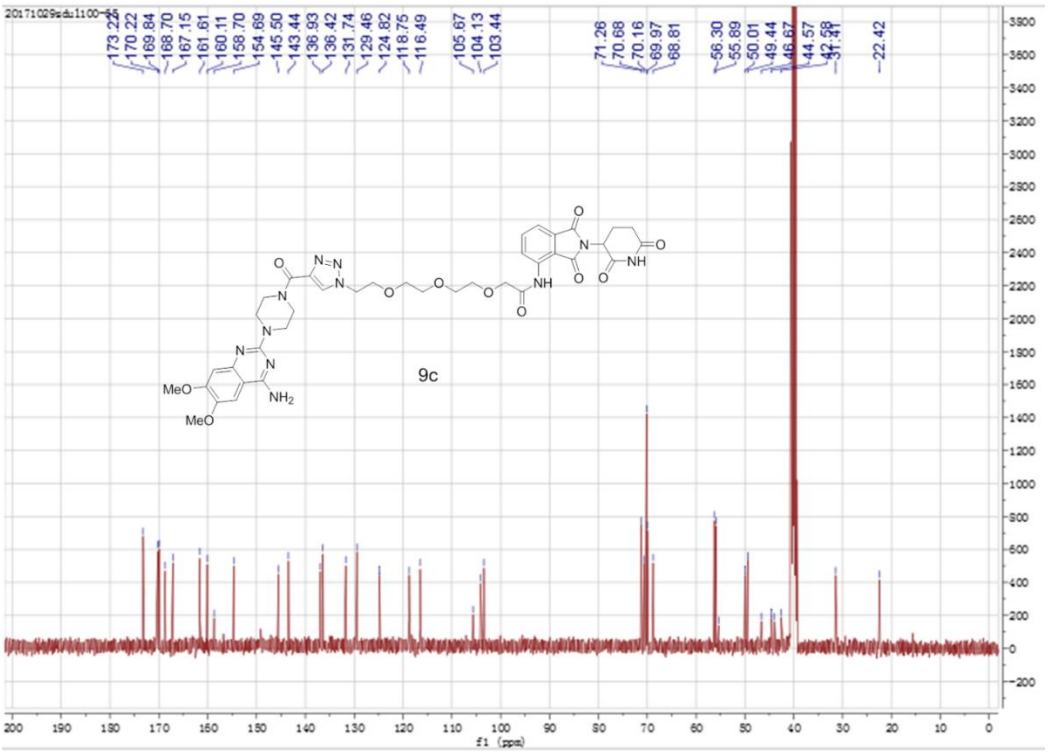

9b
MeO
MeO
NH2

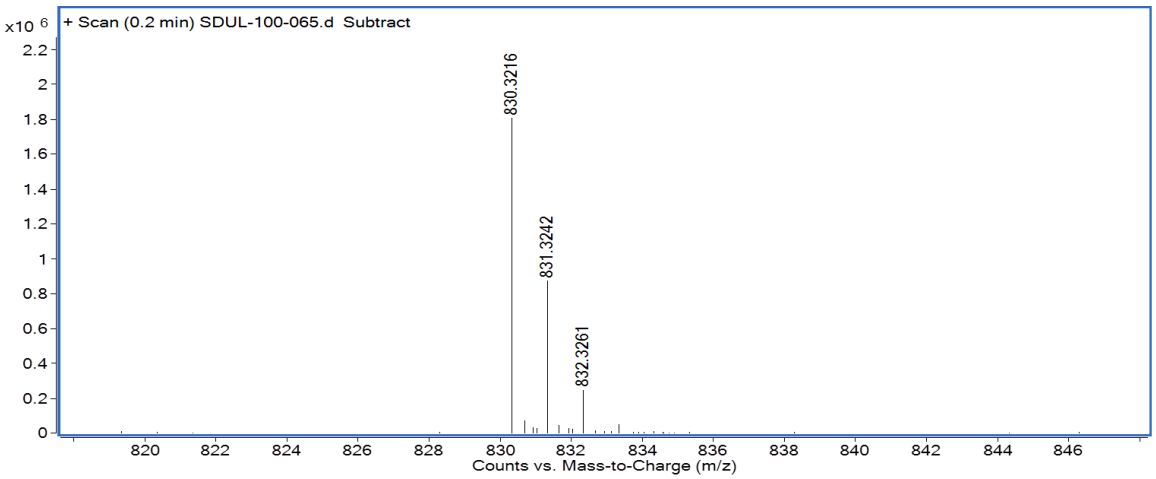

9b
MeO
MeO
NH2

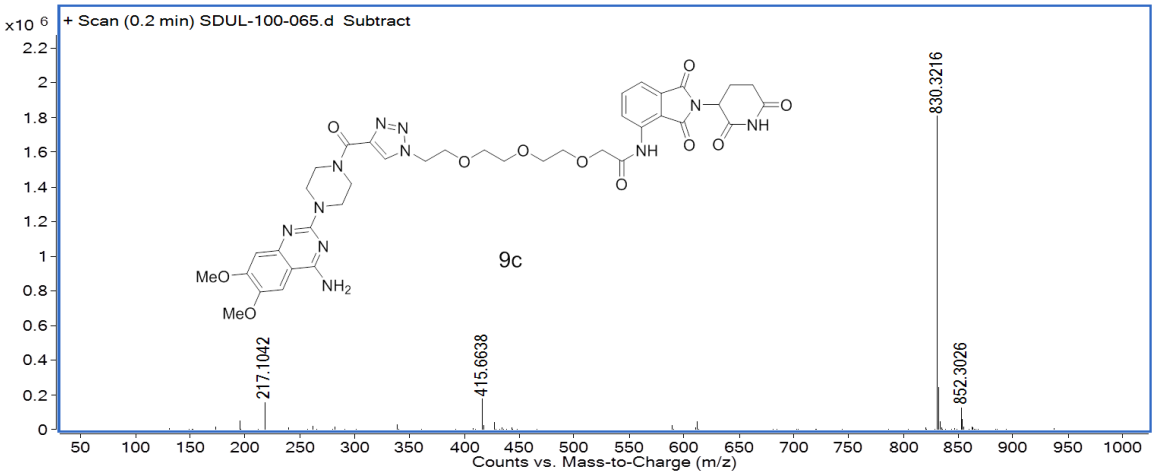

x10 6
+ Scan (0.2 min) SDUL-100-061.d Subtract
786.2956
787.2991
788.3012
Counts vs. Mass-to-Charge (m/z)


x10 6
+ Scan (0.2 min) SDUL-100-061.d Subtract
9b
MeO
MeO
NH2
786.2956
808.2763
393.6509
Counts vs. Mass-to-Charge (m/z)

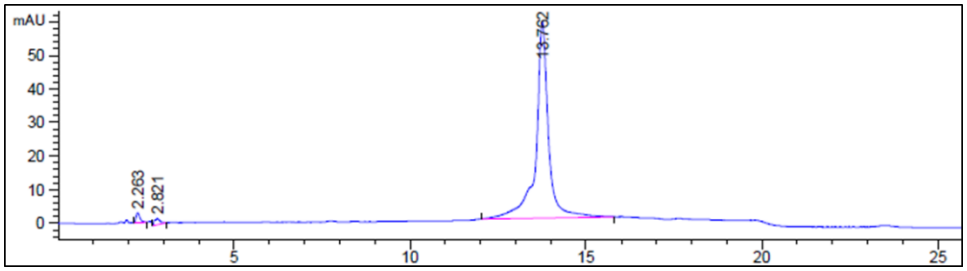

11.16
10.33
8.71
8.69
8.51
7.85
7.84
7.62
7.61
7.59
7.43
7.16
6.75
5.19
5.17
5.15
5.14
4.20
3.84
3.83
3.79
3.76
3.64
3.55
2.94
2.92
2.91
2.90
2.87
2.86
2.65
2.60
2.56
2.55
2.53
2.11
2.09
2.08
9c
MeO
MeO
NH2
NH
f1 (ppm)


173.22
170.22
169.84
168.70
167.15
161.61
160.11
158.70
154.69
145.50
143.44
136.93
136.42
131.74
129.46
124.82
118.75
116.49
105.67
104.13
103.44
71.26
70.68
70.16
69.97
68.81
56.30
55.89
50.01
49.44
46.67
44.57
42.58
31.47
22.42
9c
MeO
MeO
NH2
NH
f1 (ppm)


x10 6
+ Scan (0.2 min) SDUL-100-065.d Subtract
830.3216
831.3242
832.3261
Counts vs. Mass-to-Charge (m/z)

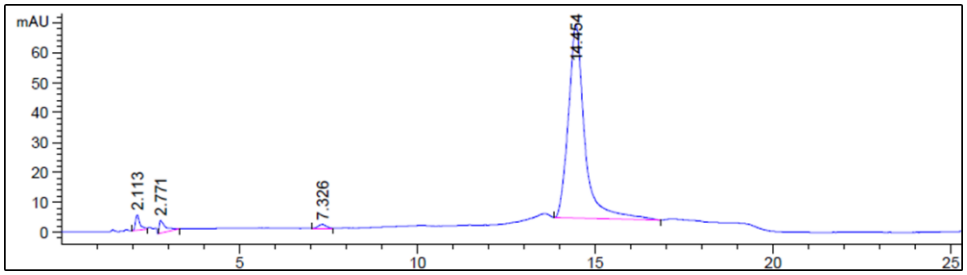

x10 6
+ Scan (0.2 min) SDUL-100-065.d Subtract
9c
MeO
MeO
NH2
217.1042
415.6638
830.3216
852.3026
Counts vs. Mass-to-Charge (m/z)

HPLC data of final compounds



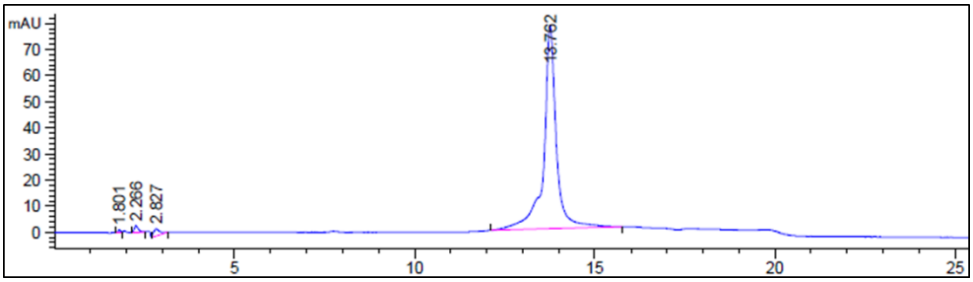
Peak	Retention time (min)	Peak types	Peak width	Peak area	Peak height	Peak area (%)
1	2.263	BB	0.1160	22.53704	2.98896	1.4953
2	2.821	BB	0.1452	19.77697	1.78535	1.3122
3	13.762	BB	0.3518	1464.83813	58.56503	97.1925

HPLC analysis of compound **9a**.



Peak	Retention time (min)	Peak types	Peak width	Peak area	Peak height	Peak area (%)
1	2.113	BV	0.1349	46.53817	5.17572	2.1330
2	2.771	BB	0.1574	50.87490	4.25820	1.3317
3	7.326	BB	0.2046	19.47536	1.23116	0.8926
4	14.454	BB	0.4568	2064.94604	64.96188	95.6427

HPLC analysis of compound **9b**.



Peak	Retention time (min)	Peak types	Peak width	Peak area	Peak height	Peak area (%)
1	1.801	BV	0.0785	6.08178	1.17374	0.3082
2	2.266	BB	0.1211	19.89354	2.49283	1.0083
3	2.827	BB	0.1618	33.25452	2.77606	1.6854
4	13.762	BB	0.3467	1913.82581	77.88319	96.9981

HPLC analysis of compound **9c**.