Supporting Information:

Targeting zoonotic viruses: structure-based inhibition of the 3C-like protease from bat coronavirus HKU4 – the likely reservoir host to the human coronavirus that causes Middle East Respiratory Syndrome.

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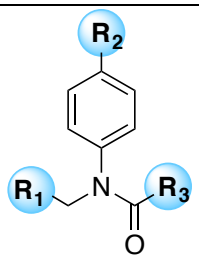
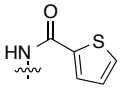
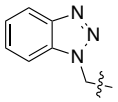
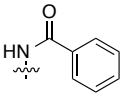
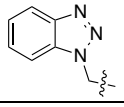
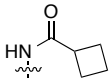
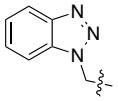
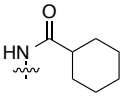
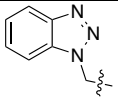
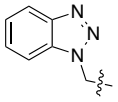
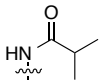
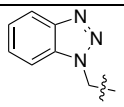
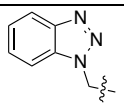
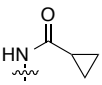
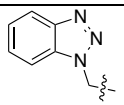
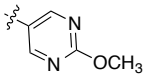
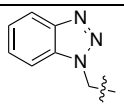
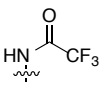
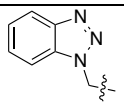
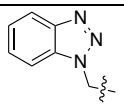
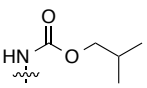
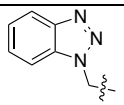
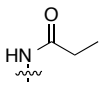
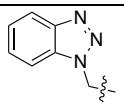
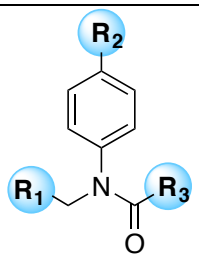
Supporting Spectra:

S1. Comprehensive Class A Peptidomimetic Library.

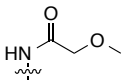
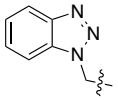
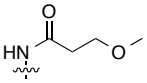
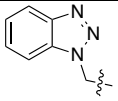
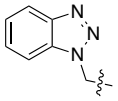
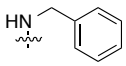
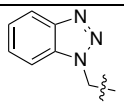
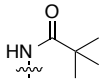
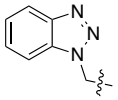
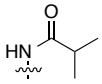
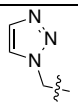
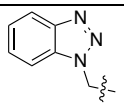
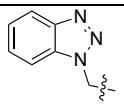
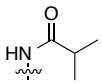
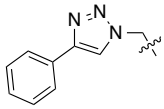
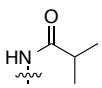
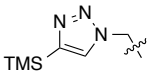


Peptidomimetic Backbone 1 (Class A)

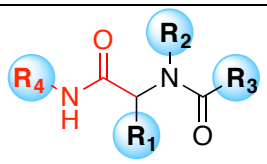
Cmpd.	R_1	R_2	R_3	% Inhib. at 100 μM	IC_{50} (μM)	% Max. Inhibition
1A				93%	0.33 ± 0.02	97.8 ± 0.6
2A				90%	0.41 ± 0.04	92.1 ±1.2
3A				94%	1.2 ± 0.2	92.7 ± 2.2
4A				88%	1.2 ± 0.06	92.5 ± 0.7
5A				98%	1.5 ± 0.1	93.9 ± 1.6
6A				92%	1.6 ± 0.09	97.5 ± 1.0
7A				90%	1.7 ± 0.2	90.4 ± 1.5
8A				89%	1.9 ± 0.09	92.7 ± 0.8
9A				83%	2.0 ± 0.2	84.8 ± 1.7
10A				92%	2.2 ± 0.2	87.4 ± 1.7
11A				90%	2.4 ± 0.3	92.6 ± 2.1
12A				75%	2.8 ± 0.4	69.0 ± 1.7
13A				92%	3.1 ± 0.3	95.7 ± 1.8



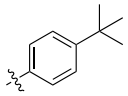
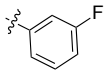
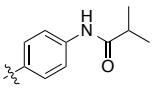
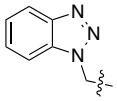
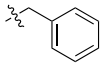
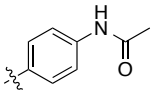
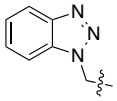
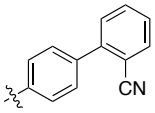
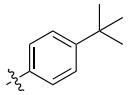
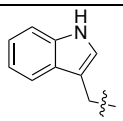
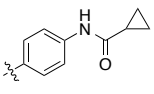
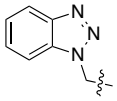
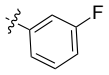
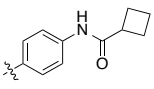
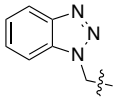
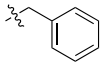
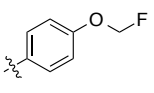
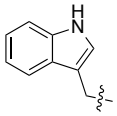
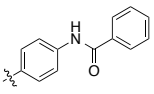
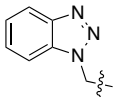
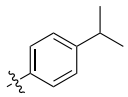
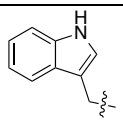
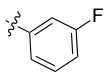
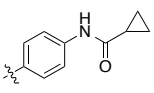
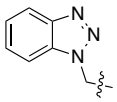
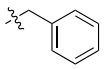
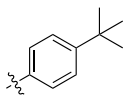
Peptidomimetic Backbone 1
(Class A)

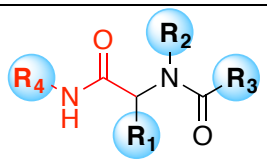
Cmpd.	R_1	R_2	R_3	% Inhib. at 100 μM	IC_{50} (μM)	% Max. Inhibition
14A				91%	3.1 ± 0.3	95.1 ± 1.5
15A				94%	3.7 ± 0.4	94.5 ± 2.0
16A				91%	4.8 ± 0.4	93.9 ± 1.7
17A				64%	5.3 ± 0.6	53.2 ± 1.2
18A				67%	8.8 ± 0.8	78.0 ± 1.6
19A				63%	16.0 ± 4.0	83.9 ± 5.5
20A				31%	n/t	n/t
21A				21%	n/t	n/t
22A				49%	n/t	n/t
23A				25%	n/t	n/t
24A				24%	n/t	n/t
25A				15%	n/t	n/t

S2. Comprehensive Class B Peptidomimetic Library.

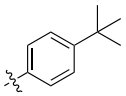
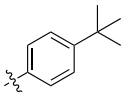
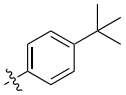
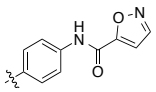
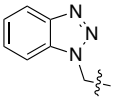
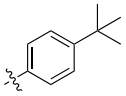
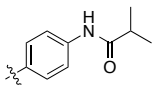
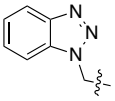
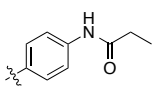
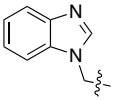
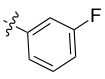
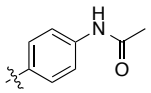
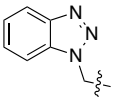
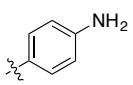
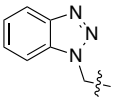
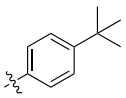
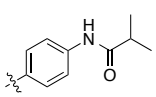
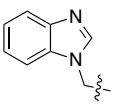
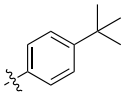


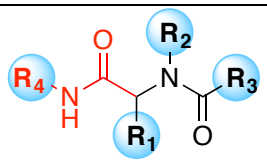
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 μM	IC_{50} (μM)	% Max. Inhibition
1B					60%	1.3 ± 0.3	50.4 ± 2.4
2B					62%	1.5 ± 0.3	53.1 ± 1.8
3B					53%	1.8 ± 0.5	36.4 ± 1.7
4B					62%	2.2 ± 0.6	56.6 ± 2.5
5B					79%	2.2 ± 0.4	79.2 ± 2.7
6B					85%	2.7 ± 0.4	82.6 ± 2.2
7B					74%	3.4 ± 0.4	78.1 ± 2.0
8B					52%	3.9 ± 0.7	56.2 ± 2.1
9B					79%	4.2 ± 0.2	91.3 ± 0.8
10B					78%	6.9 ± 0.7	78.2 ± 1.7
11B					71%	7.0 ± 1.2	76.1 ± 2.8
12B					96%	8.6 ± 0.9	107.2 ± 2.5

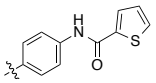
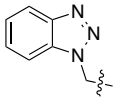
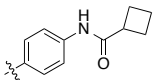
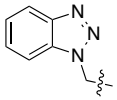
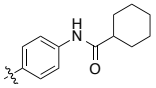
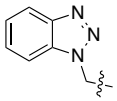
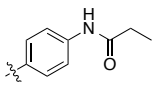
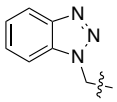
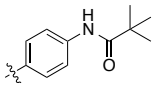
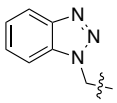
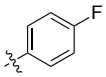
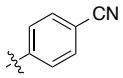
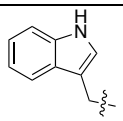
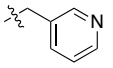
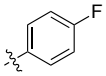
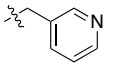
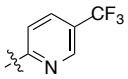
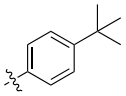


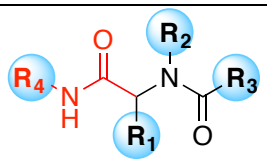
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
13B					93%	9.3 ± 0.5	100.9 ± 1.2
14B					78%	9.5 ± 2.0	86.9 ± 4.2
15B					94%	11.1 ± 0.6	100.2 ± 1.3
16B					76%	14.7 ± 1.1	92.1 ± 1.8
17B					84%	15.4 ± 2.1	94.2 ± 3.3
18B					76%	17.2 ± 2.8	89.0 ± 3.9
19B					68%	18.3 ± 4.7	65.4 ± 4.7
20B					71%	18.7 ± 2.6	85.4 ± 3.4
21B					64%	22.0 ± 7.4	53.7 ± 5.5
22B					65%	35.6 ± 5.2	96.5 ± 5.1
23B					56%	52.3 ± 21.2	63.2 ± 10.9
24B					58%	55.6 ± 14.3	58.6 ± 6.6

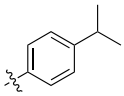
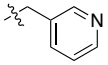
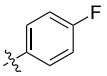
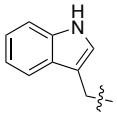
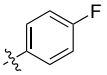
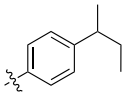
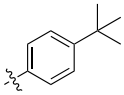
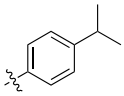
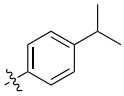
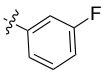
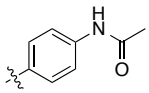
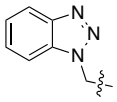
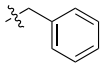
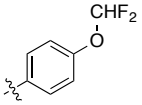
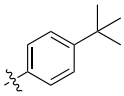
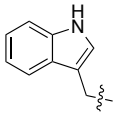
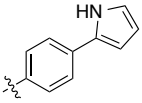
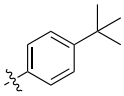


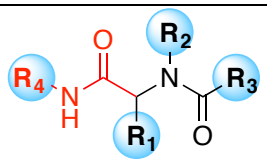
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
25B					26%	n/t	n/t
26B					20%	n/t	n/t
27B					21%	n/t	n/t
28B					34%	n/t	n/t
29B					18%	n/t	n/t
30B					53%	n/t	n/t
31B					49%	n/t	n/t
32B					48%	n/t	n/t
33B					47%	n/t	n/t
34B					43%	n/t	n/t
35B					42%	n/t	n/t
36B					41%	n/t	n/t

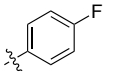
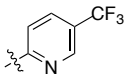
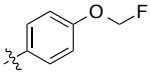
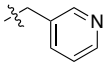
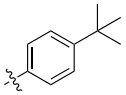
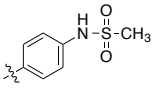
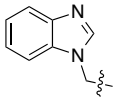
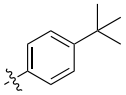
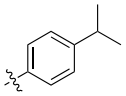
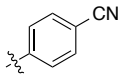
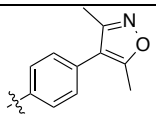
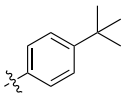
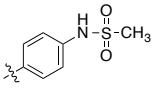
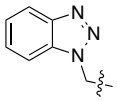
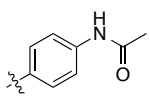
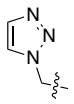
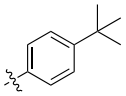
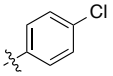
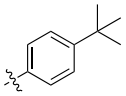
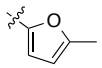


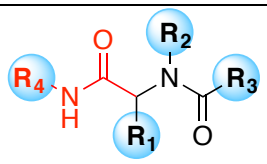
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
37B					41%	n/t	n/t
38B					41%	n/t	n/t
39B					41%	n/t	n/t
40B					39%	n/t	n/t
41B					35%	n/t	n/t
42B					36%	n/t	n/t
43B					34%	n/t	n/t
44B					32%	n/t	n/t
45B					31%	n/t	n/t
46B					31%	n/t	n/t
47B					31%	n/t	n/t
48B					30%	n/t	n/t

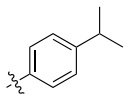
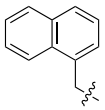
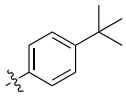
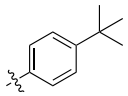
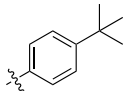
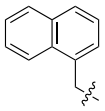
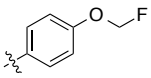
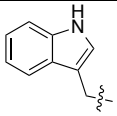
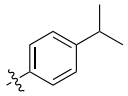
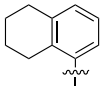
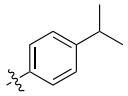
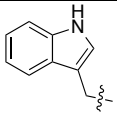
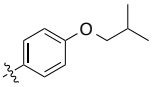
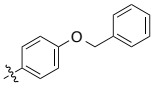
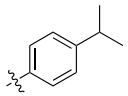
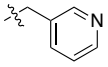
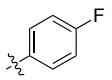
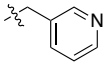
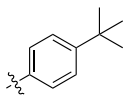
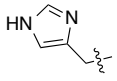
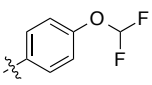
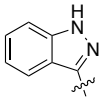


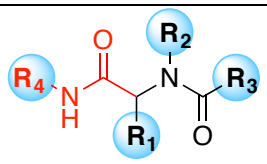
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
49B					29%	n/t	n/t
50B					29%	n/t	n/t
51B					29%	n/t	n/t
52B					28%	n/t	n/t
53B					28%	n/t	n/t
54B					28%	n/t	n/t
55B					28%	n/t	n/t
56B					28%	n/t	n/t
57B					27%	n/t	n/t
58B					27%	n/t	n/t
59B					27%	n/t	n/t
60B					26%	n/t	n/t

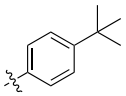
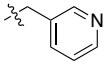
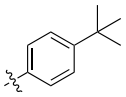
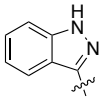
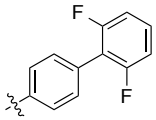
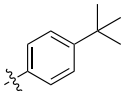
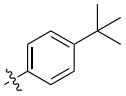
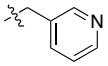
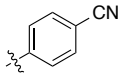
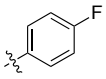
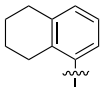
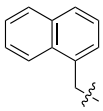
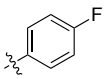
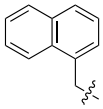
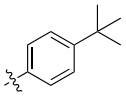
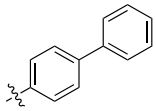
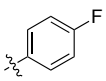
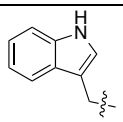


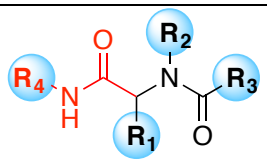
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
61B					26%	n/t	n/t
62B					26%	n/t	n/t
63B					26%	n/t	n/t
64B					25%	n/t	n/t
65B					25%	n/t	n/t
66B					25%	n/t	n/t
67B					25%	n/t	n/t
68B					25%	n/t	n/t
69B					24%	n/t	n/t
70B					24%	n/t	n/t
71B					24%	n/t	n/t
72B					24%	n/t	n/t

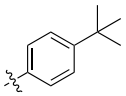
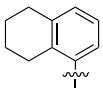
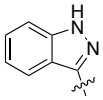
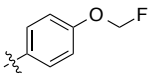
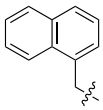
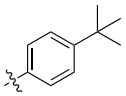
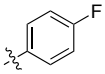
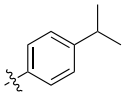
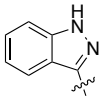
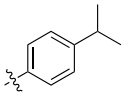
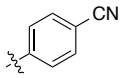
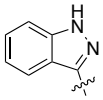
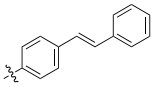
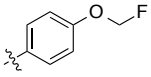
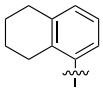
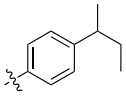
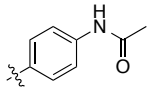
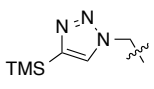
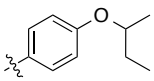


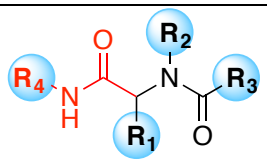
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
73B					23%	n/t	n/t
74B					23%	n/t	n/t
75B					23%	n/t	n/t
76B					23%	n/t	n/t
77B					23%	n/t	n/t
78B					23%	n/t	n/t
79B					22%	n/t	n/t
80B					22%	n/t	n/t
81B					22%	n/t	n/t
82B					22%	n/t	n/t
83B					22%	n/t	n/t
84B					22%	n/t	n/t

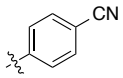
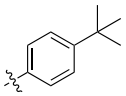
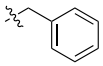
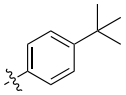
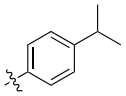
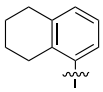
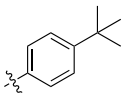
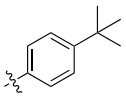
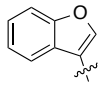
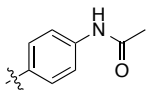
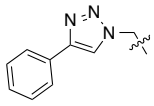
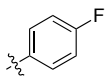
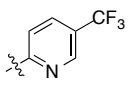
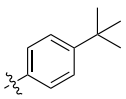
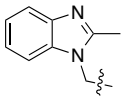
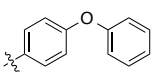
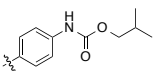
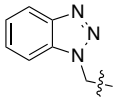
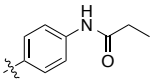
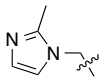


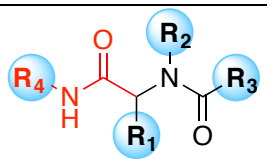
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
85B					21%	n/t	n/t
86B					21%	n/t	n/t
87B					21%	n/t	n/t
88B					21%	n/t	n/t
89B					21%	n/t	n/t
90B					21%	n/t	n/t
91B					21%	n/t	n/t
92B					21%	n/t	n/t
93B					21%	n/t	n/t
94B					20%	n/t	n/t
95B					20%	n/t	n/t
96B					20%	n/t	n/t

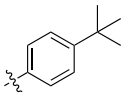
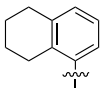
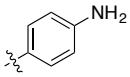
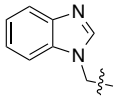
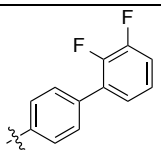
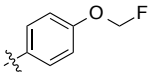
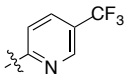
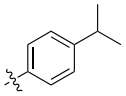
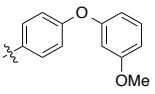
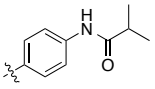
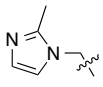
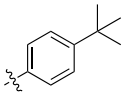
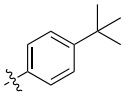
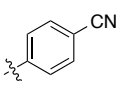
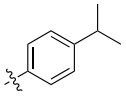
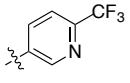


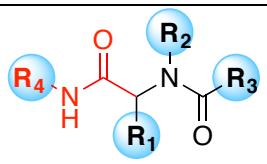
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
97B					20%	n/t	n/t
98B					20%	n/t	n/t
99B					20%	n/t	n/t
100B					20%	n/t	n/t
101B					19%	n/t	n/t
102B					19%	n/t	n/t
103B					19%	n/t	n/t
104B					19%	n/t	n/t
105B					19%	n/t	n/t
106B					19%	n/t	n/t
107B					19%	n/t	n/t
108B					19%	n/t	n/t

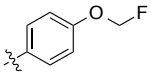
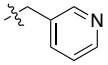
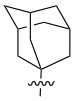
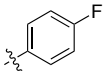
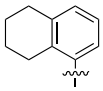
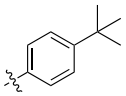
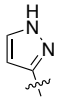
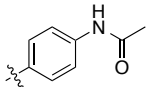
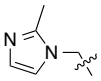
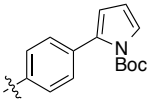
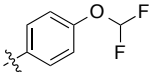
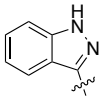
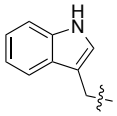
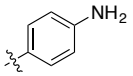
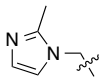
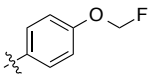
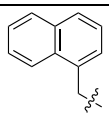
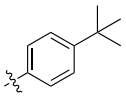
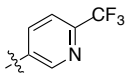
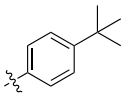
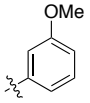


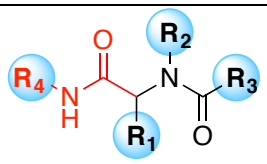
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 μM	IC_{50} (μM)	% Max. Inhibition
109B					18%	n/t	n/t
110B					18%	n/t	n/t
111B					18%	n/t	n/t
112B					18%	n/t	n/t
113B					18%	n/t	n/t
114B					18%	n/t	n/t
115B					18%	n/t	n/t
116B					18%	n/t	n/t
117B					18%	n/t	n/t
118B					18%	n/t	n/t
119B					18%	n/t	n/t
120B					18%	n/t	n/t

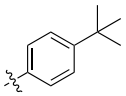
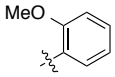
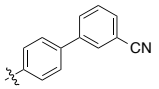
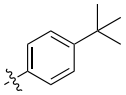
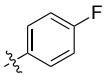
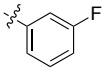
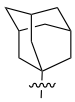
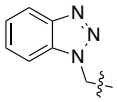
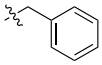
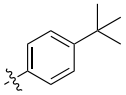
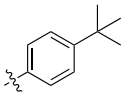
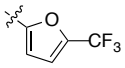
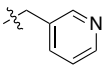
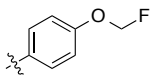
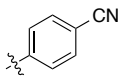
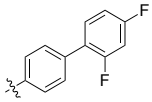
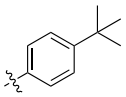
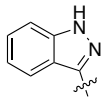
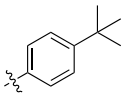


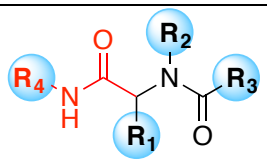
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
121B					18%	n/t	n/t
122B					18%	n/t	n/t
123B					17%	n/t	n/t
124B					17%	n/t	n/t
125B					17%	n/t	n/t
126B					17%	n/t	n/t
127B					17%	n/t	n/t
128B					17%	n/t	n/t
129B					17%	n/t	n/t
130B					17%	n/t	n/t
131B					17%	n/t	n/t
132B					17%	n/t	n/t

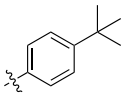
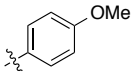
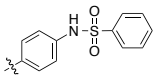
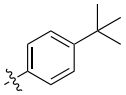
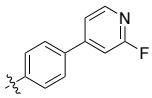
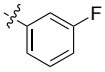
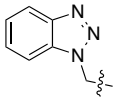
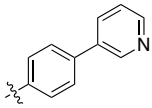
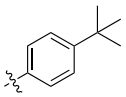
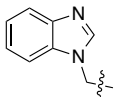
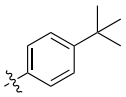
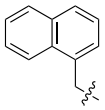
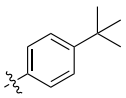
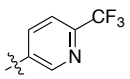
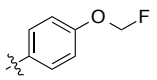
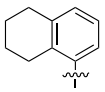
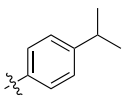
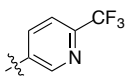


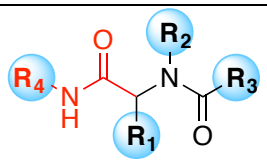
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 μM	IC_{50} (μM)	% Max. Inhibition
133B					17%	n/t	n/t
134B					16%	n/t	n/t
135B					16%	n/t	n/t
136B					16%	n/t	n/t
137B					16%	n/t	n/t
138B					16%	n/t	n/t
139B					16%	n/t	n/t
140B					16%	n/t	n/t
141B					16%	n/t	n/t
142B					16%	n/t	n/t
143B					16%	n/t	n/t
144B					16%	n/t	n/t

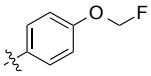
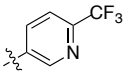
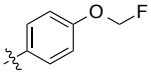
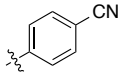
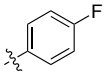
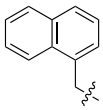
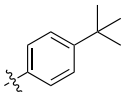
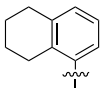
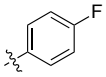
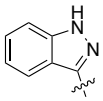
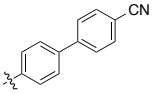
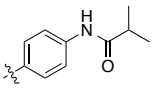
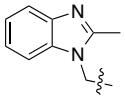
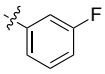
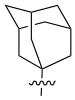
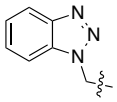
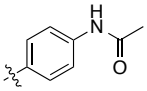
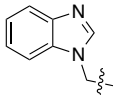
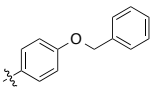
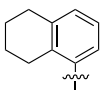
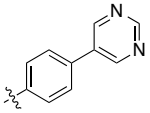


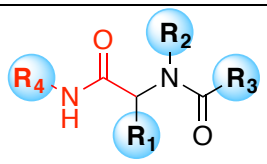
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 μM	IC_{50} (μM)	% Max. Inhibition
145B					16%	n/t	n/t
146B					16%	n/t	n/t
147B					16%	n/t	n/t
148B					16%	n/t	n/t
149B					16%	n/t	n/t
150B					15%	n/t	n/t
151B					15%	n/t	n/t
152B					15%	n/t	n/t
153B					15%	n/t	n/t
154B					15%	n/t	n/t
155B					15%	n/t	n/t
156B					15%	n/t	n/t

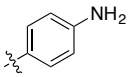
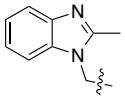
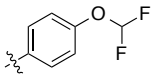
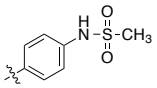
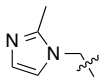
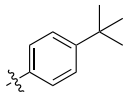
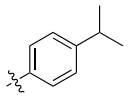
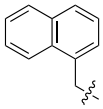
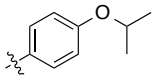
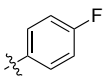
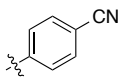
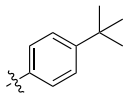
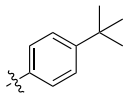
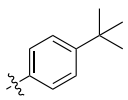
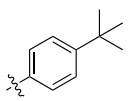
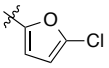
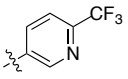


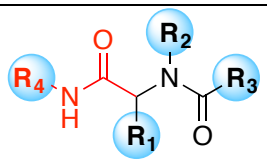
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 μM	IC_{50} (μM)	% Max. Inhibition
157B					15%	n/t	n/t
158B					15%	n/t	n/t
159B					15%	n/t	n/t
160B					14%	n/t	n/t
161B					14%	n/t	n/t
162B					14%	n/t	n/t
163B					14%	n/t	n/t
164B					14%	n/t	n/t
165B					14%	n/t	n/t
166B					14%	n/t	n/t
167B					14%	n/t	n/t
168B					14%	n/t	n/t

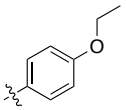
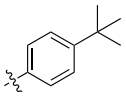
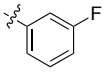
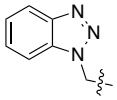
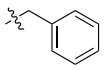
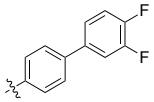
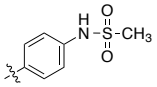
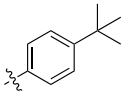
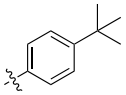
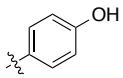
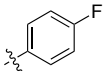
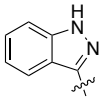
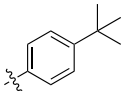
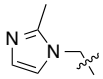
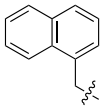
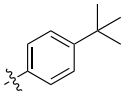
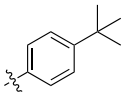
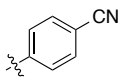


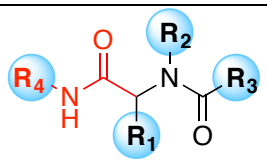
Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
169B					14%	n/t	n/t
170B					13%	n/t	n/t
171B					13%	n/t	n/t
172B					13%	n/t	n/t
173B					13%	n/t	n/t
174B					13%	n/t	n/t
175B					13%	n/t	n/t
176B					13%	n/t	n/t
177B					13%	n/t	n/t
178B					13%	n/t	n/t
180B					12%	n/t	n/t
181B					12%	n/t	n/t

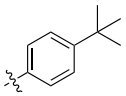
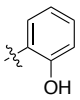
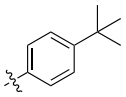
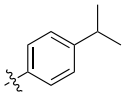
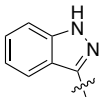
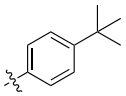
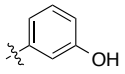
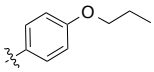
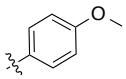
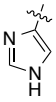
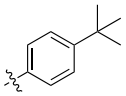
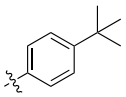
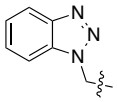
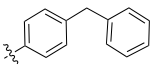
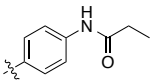
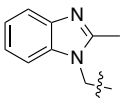
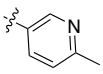
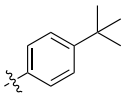


Peptidomimetic Backbone 2
(B Class)

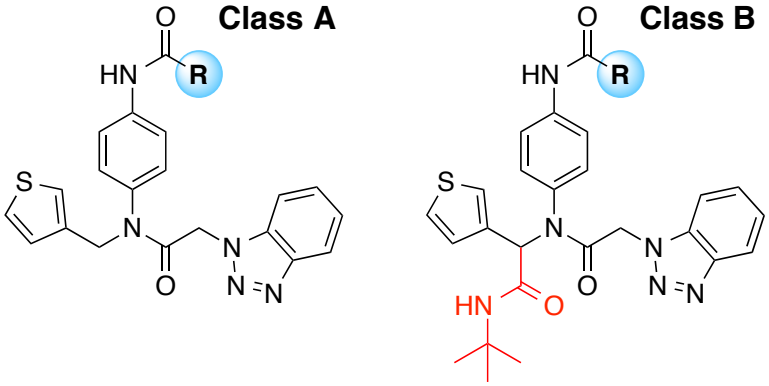
Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
182B					12%	n/t	n/t
183B					12%	n/t	n/t
184B					12%	n/t	n/t
185B					12%	n/t	n/t
186B					12%	n/t	n/t
187B					12%	n/t	n/t
188B					11%	n/t	n/t
189B					11%	n/t	n/t
190B					11%	n/t	n/t
191B					11%	n/t	n/t
192B					11%	n/t	n/t
193B					11%	n/t	n/t



Peptidomimetic Backbone 2
(B Class)

Cmpd.	R_1	R_2	R_3	R_4	% Inhib. at 100 µM	IC_{50} (µM)	% Max. Inhibition
194B					11%	n/t	n/t
195B					11%	n/t	n/t
196B					11%	n/t	n/t
197B					10%	n/t	n/t
198B					10%	n/t	n/t
199B					10%	n/t	n/t
200B					9%	n/t	n/t
201B					9%	n/t	n/t
202B					8%	n/t	n/t
203B					8%	n/t	n/t
204B					8%	n/t	n/t
205B					6%	n/t	n/t

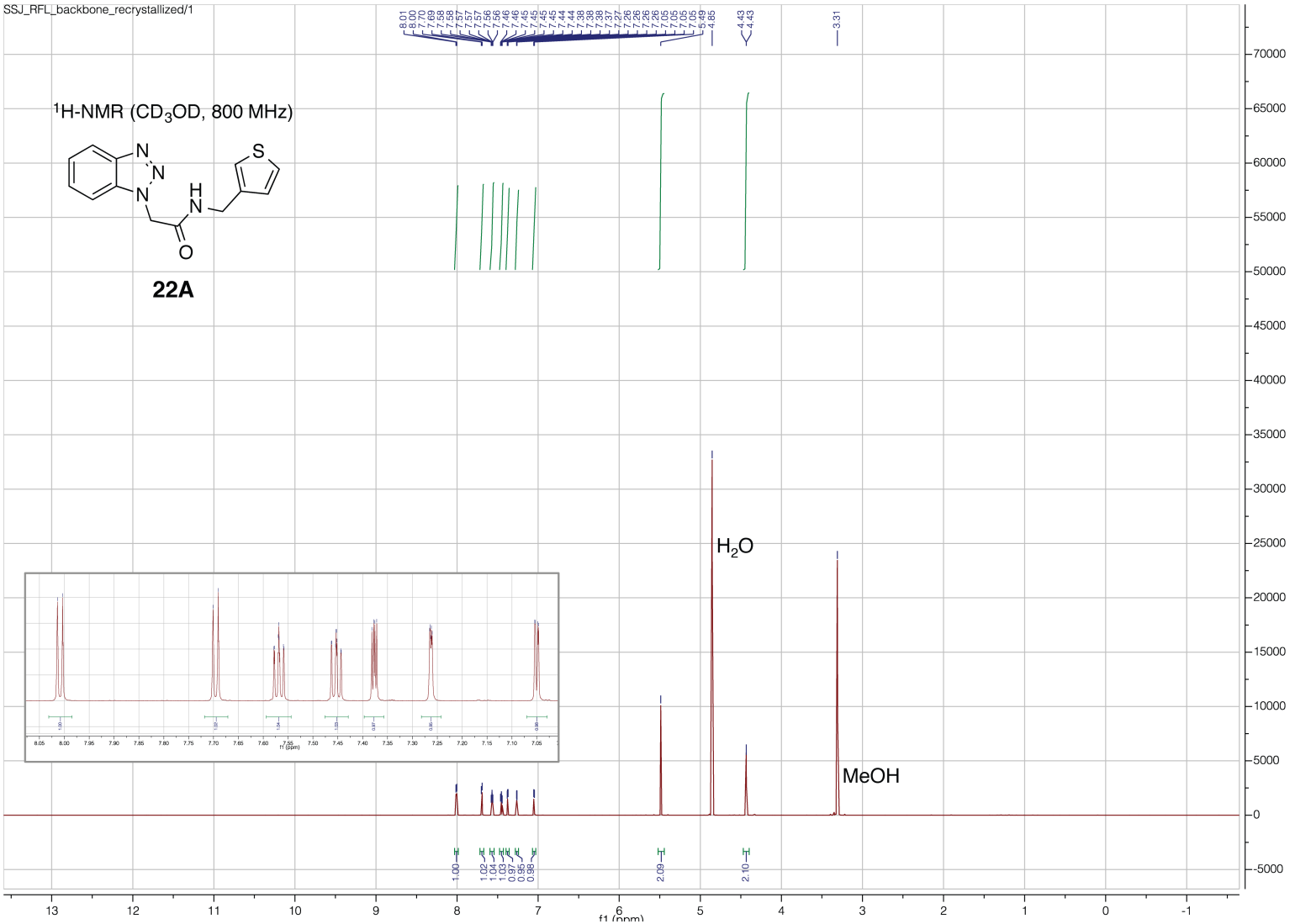
S3. Comparison of Class A and B Inhibitors.

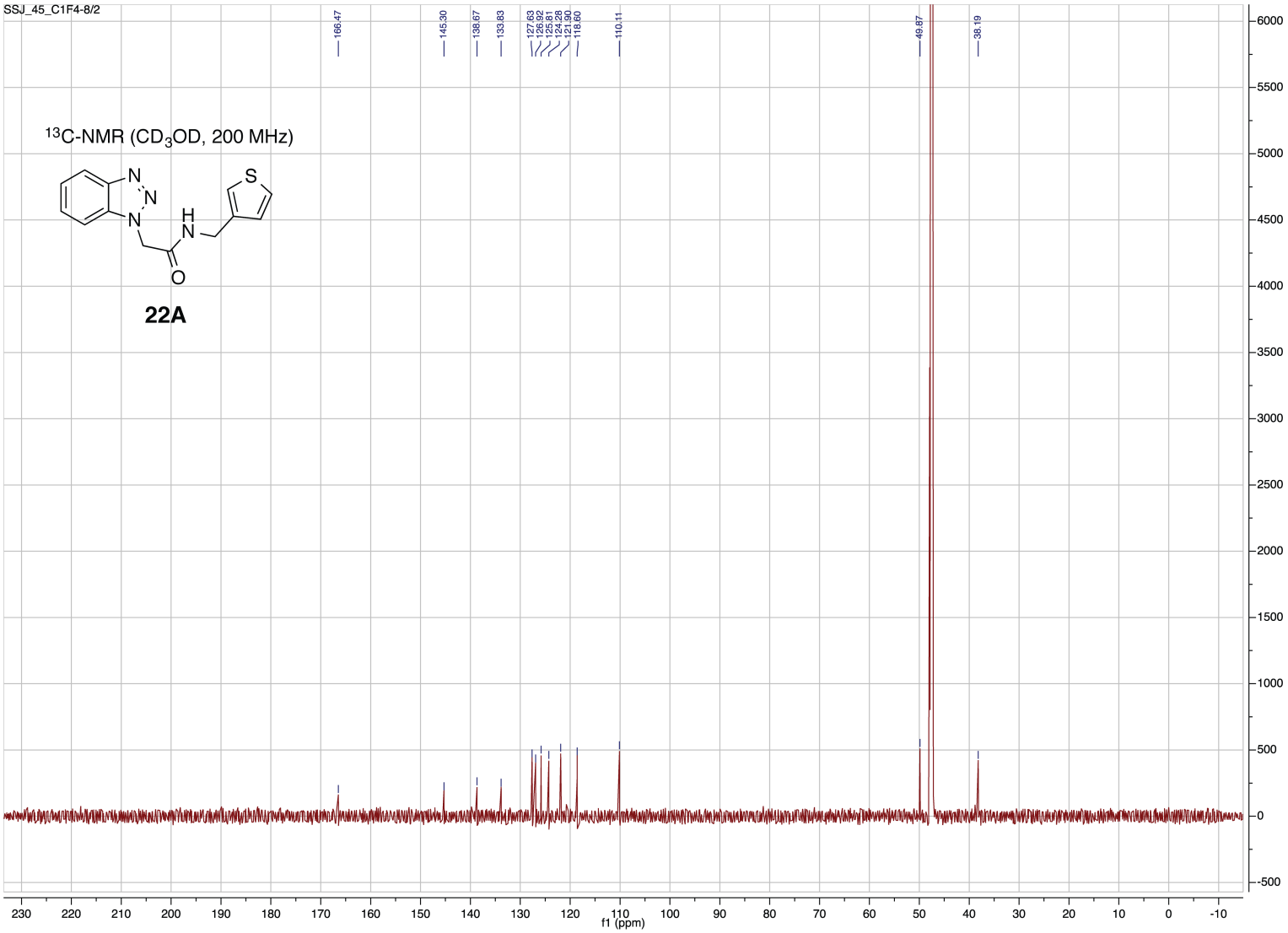


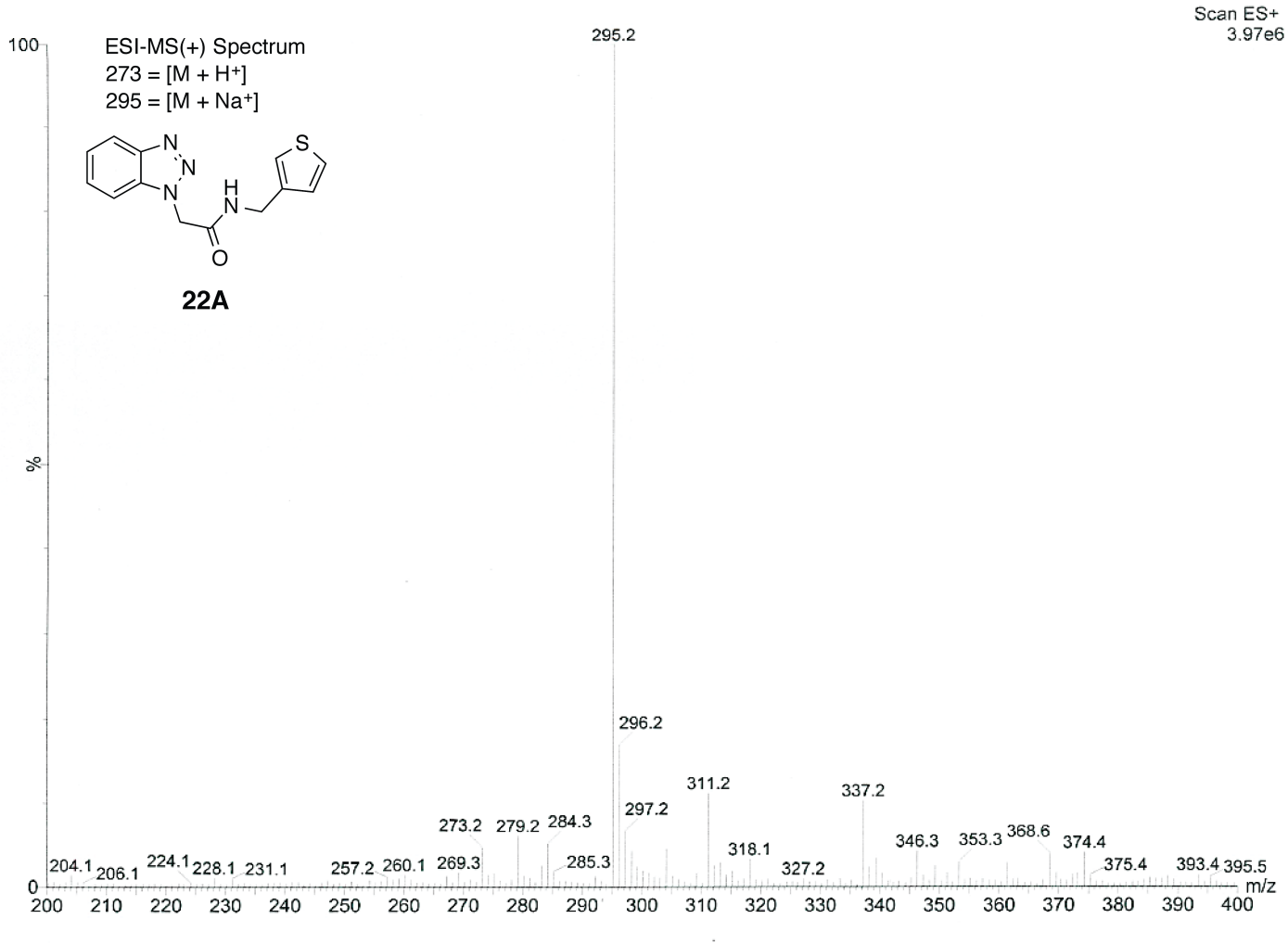
Class A Cmpd.	Class B Cmpd.	R	Class A % Inhibition at 100 µM	Class B % Inhibition at 100 µM	Class A IC_{50} (µM)	Class B IC_{50} (µM)
1A	25B		93%	26%	0.33 ± 0.02	n/t
2A	9B		90%	79%	0.41 ± 0.04	4.2 ± 0.9
3A	26B		94%	20%	1.2 ± 0.2	n/t
4A	27B		88%	21%	1.2 ± 0.06	n/t
6A	18B		92%	76%	1.6 ± 0.09	17.2 ± 2.8
8A	6B		89%	85%	1.9 ± 0.09	2.7 ± 0.4
13A	28B		92%	34%	3.1 ± 0.3	n/t
18A	29B		67%	18%	16.0 ± 4.2	n/t

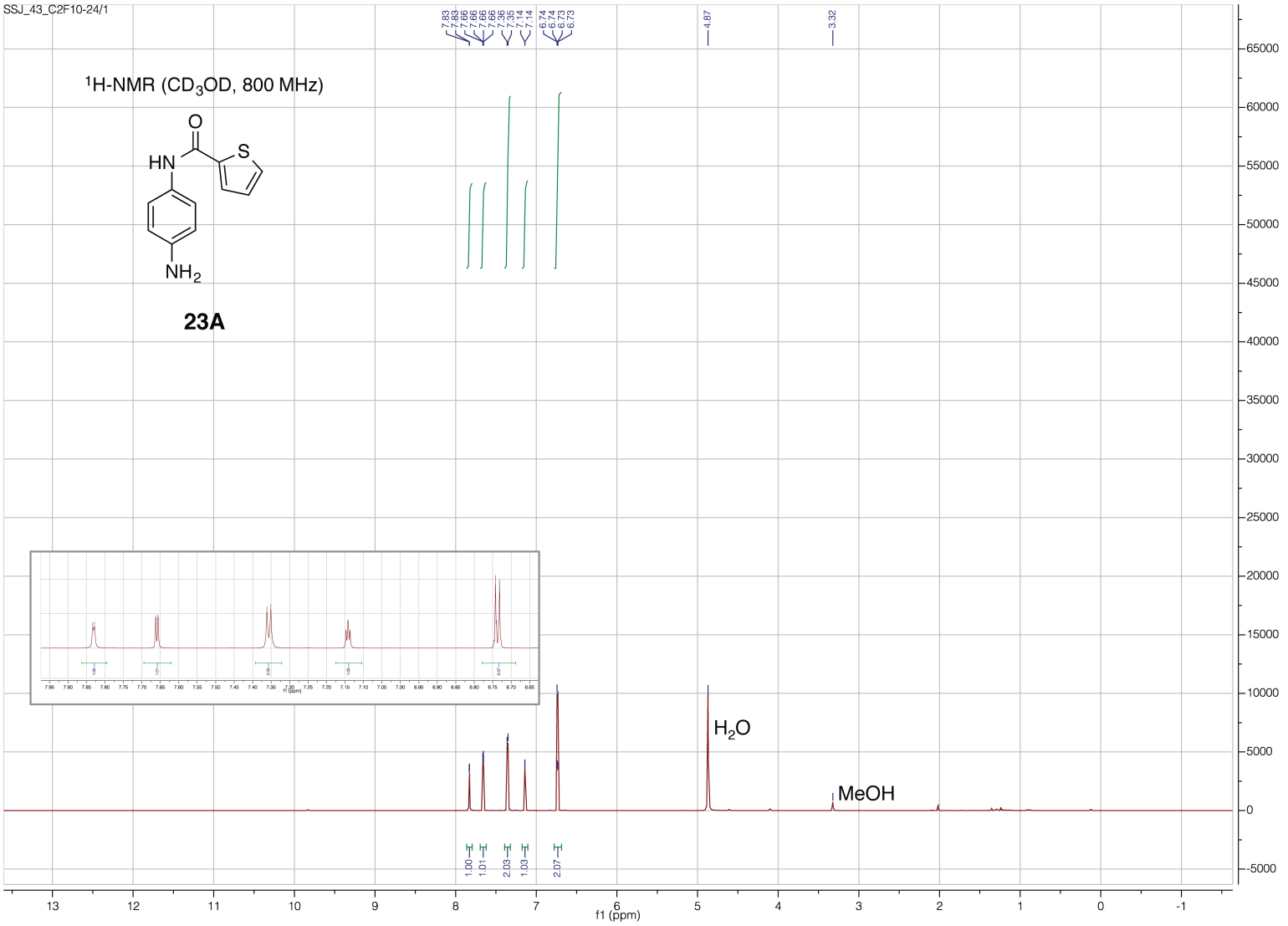
S4. X-Ray Data Collection and Refinement Statistics.

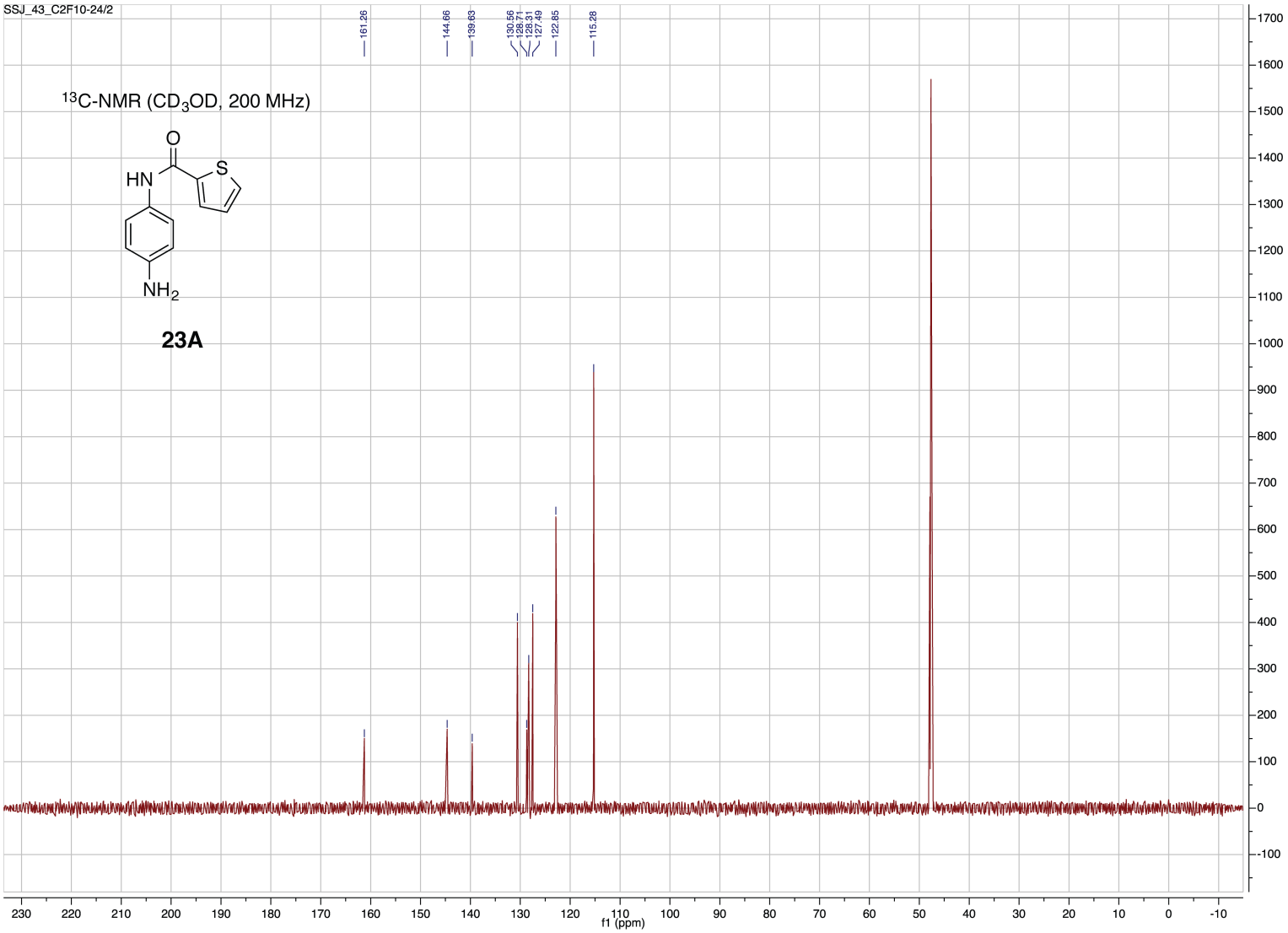
Data Collection	**HKU4-CoV 3CL^{pro}:1A(4YOI)**	**HKU4-CoV 3CL^{pro}:2A(4YOJ)**	**HKU4-CoV 3CL^{pro}:3B(4YOG)**	**HKU4-CoV 3CL^{pro}(4YO9)**
Space Group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P3_121$
a, b, c (Å)	57.81, 87.99, 113.96	57.93, 88.34, 112.88	57.80, 87.53, 112.99	a = b = 80.32, 179.54
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90	90, 90, 120
Resolution (Å)	1.82	1.90	2.00	2.30
Resolution range (Å)	29.9-1.82 (1.88-1.82)	26.3-1.90 (1.97-1.90)	28.6-2.00 (2.25-2.00)	26.3-2.30 (2.69-2.30)
Total reflections collected	931,692	1,439,677	1,035,166	1,168,282
Unique reflections	53,467	46,594	39,549	30,634
R_{merge} (%)	12.0 (72.9)	11.3 (85.3)	12.2 (87.4)	7.9 (97.6)
R_{pim} (%)	4.6 (29.1)	4.4 (34.6)	4.8 (39.4)	2.4 (28.4)
$I/\sigma I$	31.86 (3.0)	25.3 (3.5)	16.5 (1.7)	43.8 (3.0)
% Completeness	99.2 (94.1)	99.9 (100.0)	97.3 (95.2)	99.8 (99.9)
Refinement				
Reflections in working set	52,950	46,488	38,445	30,498
Reflections in test set	2,002	1,999	1,999	2,007
R_{work} (%)	17.35	16.03	16.97	19.28
R_{free} (%)	20.97	20.93	20.99	25.44
Wilson B factor (Å^2)	20.3	20.7	25.8	48.1

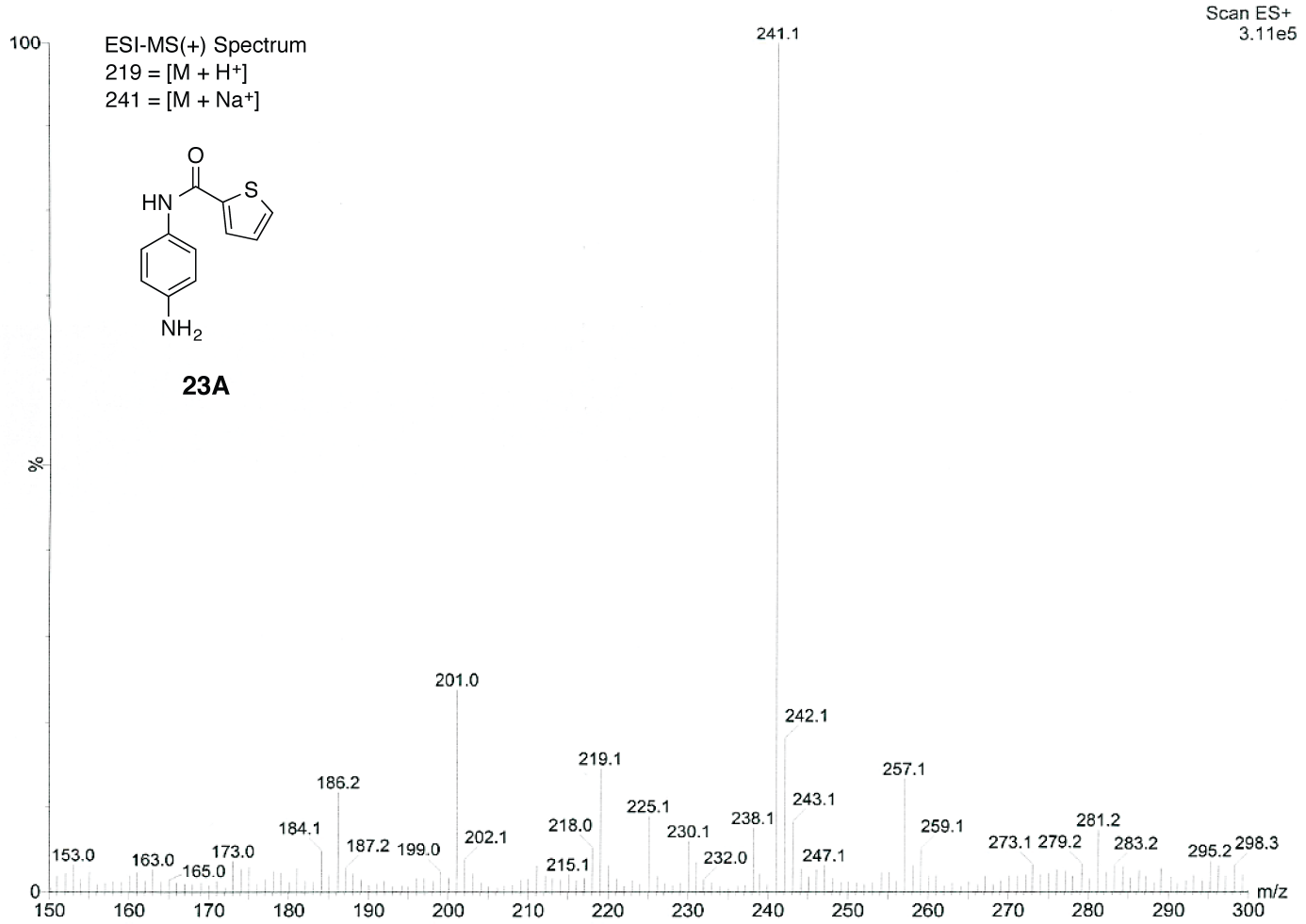

SSJ_RFL_backbone_recrystallized/1
1H-NMR (CD3OD, 800 MHz)
22A
H2O
MeOH
f1 (ppm)


SSJ_45_C1F4-8/2
166.47
145.30
138.67
133.83
127.63
125.92
125.61
124.28
121.90
118.60
110.11
49.87
38.19
^{13}C-NMR (CD_3OD, 200 MHz)
22A
f1 (ppm)

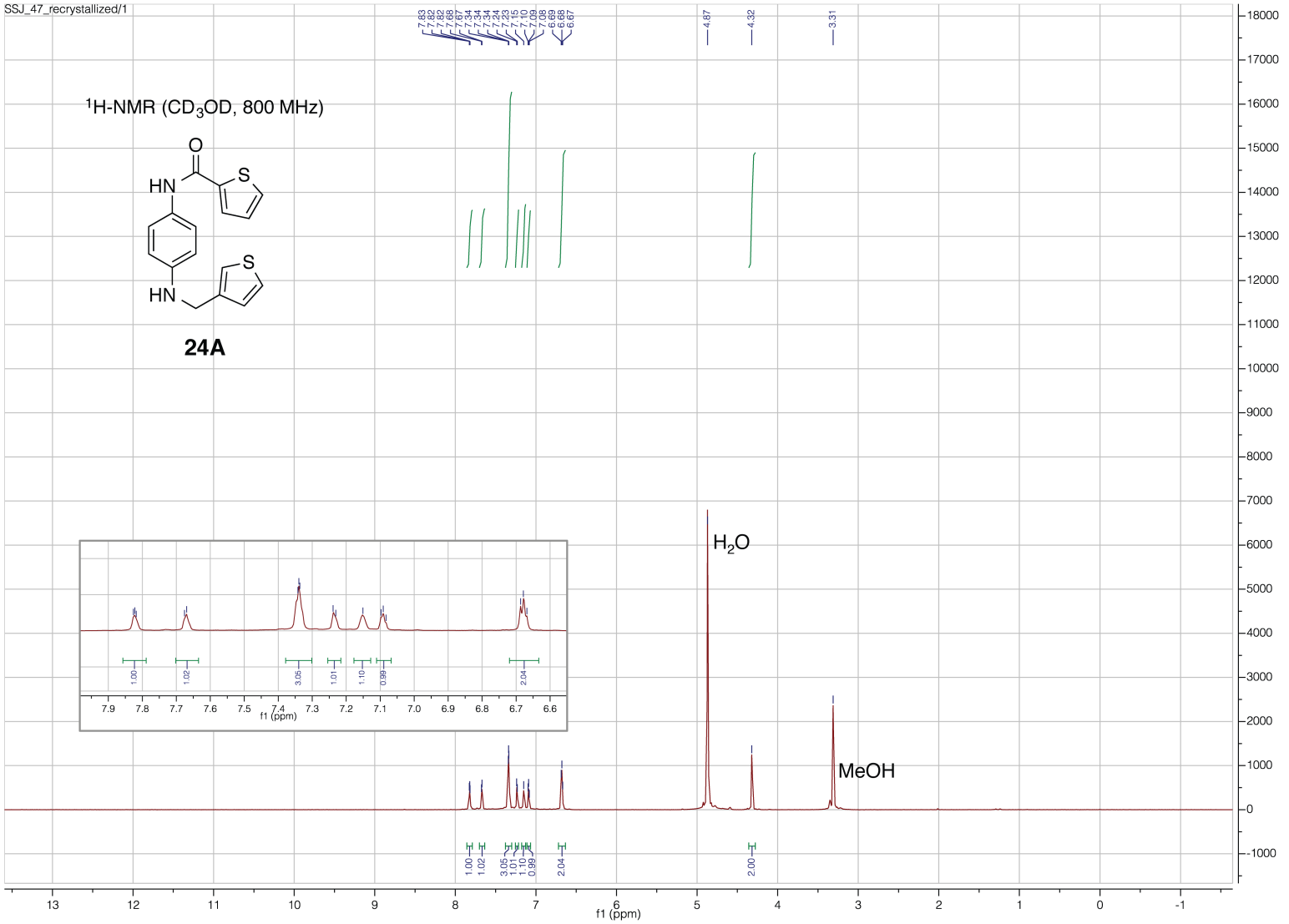

ESI-MS(+) Spectrum
273 = [M + H+]
295 = [M + Na+]
22A
Scan ES+
3.97e6
100
%
0
295.2
296.2
311.2
337.2
297.2
273.2
279.2
284.3
318.1
346.3
353.3
368.6
374.4
204.1
206.1
224.1
228.1
231.1
257.2
260.1
269.3
285.3
327.2
375.4
393.4
395.5
m/z
200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400

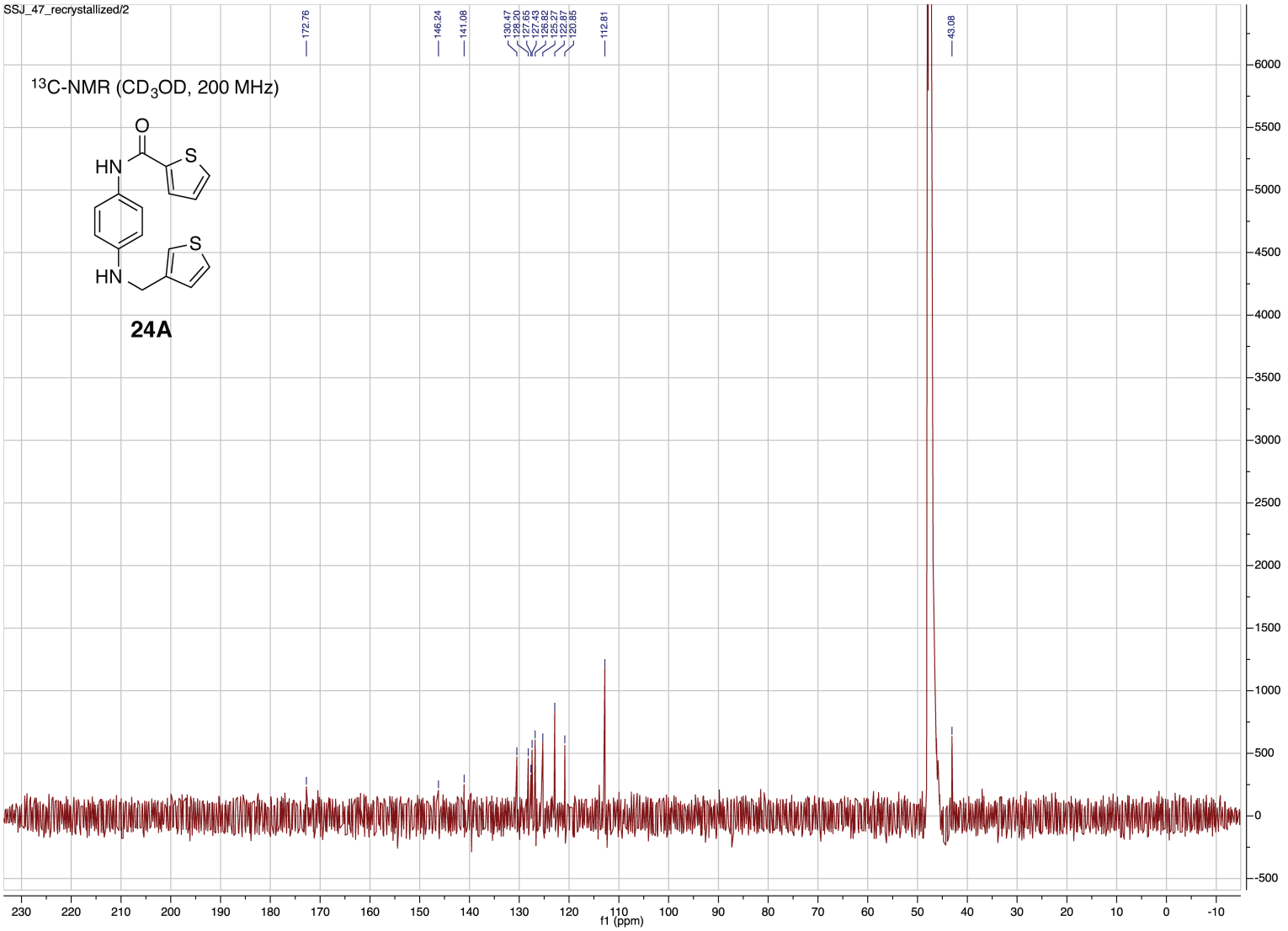

SSJ_43_C2F10-24/1
^{1}H-NMR (CD_3OD, 800 MHz)
HN
O
S
NH_2
23A
7.83
7.83
7.66
7.66
7.66
7.66
7.36
7.35
7.14
7.14
6.74
6.74
6.73
6.73
4.87
3.32
H_2O
MeOH
1.00
1.01
2.03
1.03
2.07
f1 (ppm)

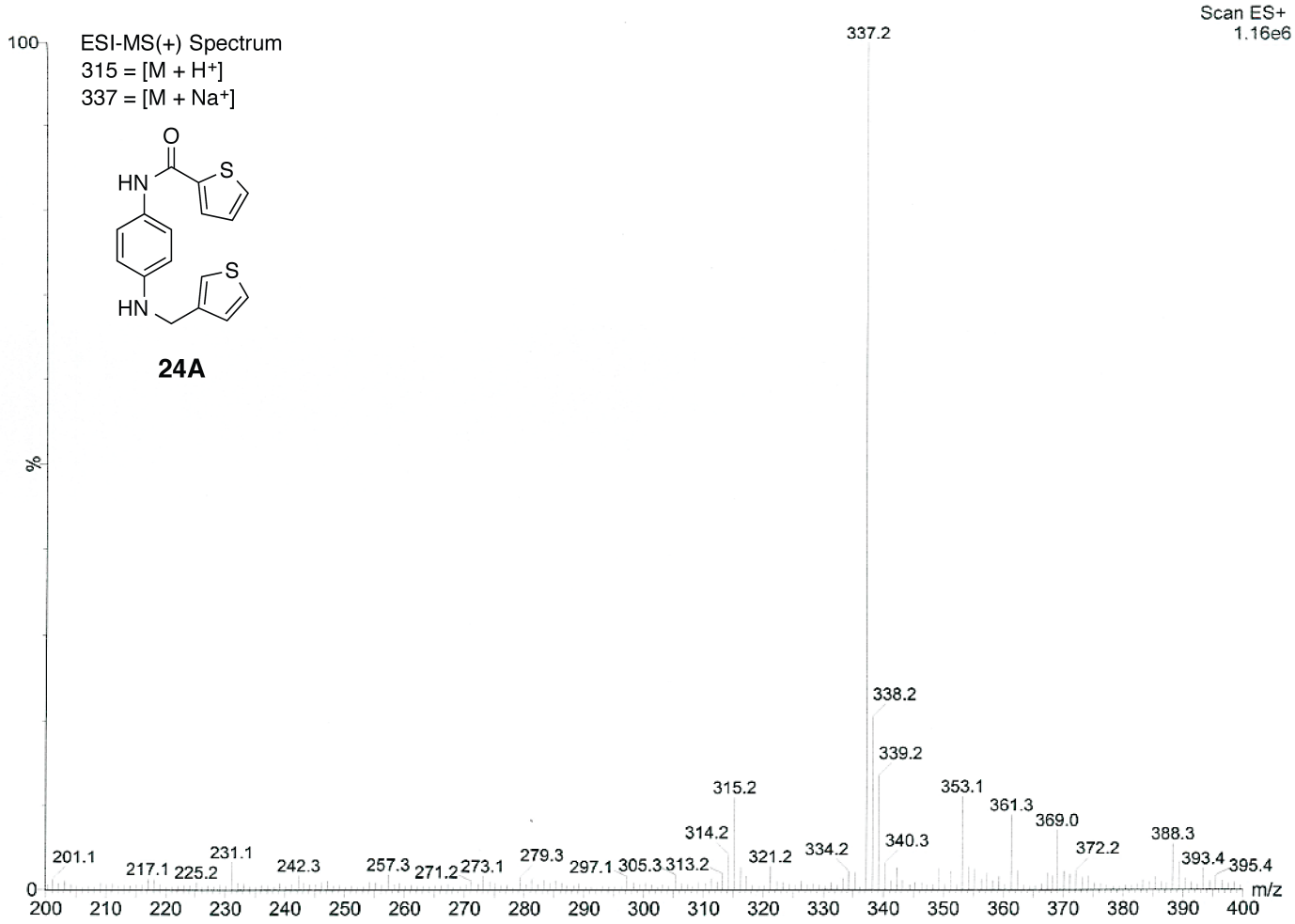

SSJ_43_C2F10-24/2
161.26
144.66
139.63
130.56
128.71
128.31
127.49
122.85
115.28
^{13}C-NMR (CD_3OD, 200 MHz)
O
HN
S
NH_2
23A
f1 (ppm)


ESI-MS(+) Spectrum
219 = [M + H+]
241 = [M + Na+]
Scan ES+
3.11e5
100
%
0
241.1
201.0
242.1
219.1
257.1
186.2
225.1
243.1
238.1
184.1
230.1
259.1
281.2
218.0
202.1
187.2
199.0
153.0
163.0
165.0
173.0
215.1
232.0
247.1
273.1
279.2
283.2
295.2
298.3
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
m/z

23A


SSJ_47_recrystallized/1
^{1}H-NMR (CD$_3$OD, 800 MHz)
24A
H$_2$O
MeOH
f1 (ppm)


SSJ_47_recrystallized/2
172.76
146.24
141.08
130.47
128.20
127.65
127.43
126.82
125.27
122.87
120.85
112.81
43.08
^{13}C-NMR (CD_3OD, 200 MHz)
O
HN
S
S
HN
24A
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


ESI-MS(+) Spectrum
315 = [M + H+]
337 = [M + Na+]
24A
Scan ES+
1.16e6
100
%
0
337.2
338.2
339.2
315.2
353.1
361.3
369.0
314.2
340.3
388.3
372.2
334.2
321.2
393.4
395.4
201.1
217.1
225.2
231.1
242.3
257.3
271.2
273.1
279.3
297.1
305.3
313.2
m/z
200
210
220
230
240
250
260
270
280
290
300
310
320
330
340
350
360
370
380
390
400