Supporting Information

Comprehensive Synthesis of Amino Acid-derived Thiazole Peptidomimetic Analogues to Understand Enigmatic Drug/Substrate-Binding Site of P-glycoprotein

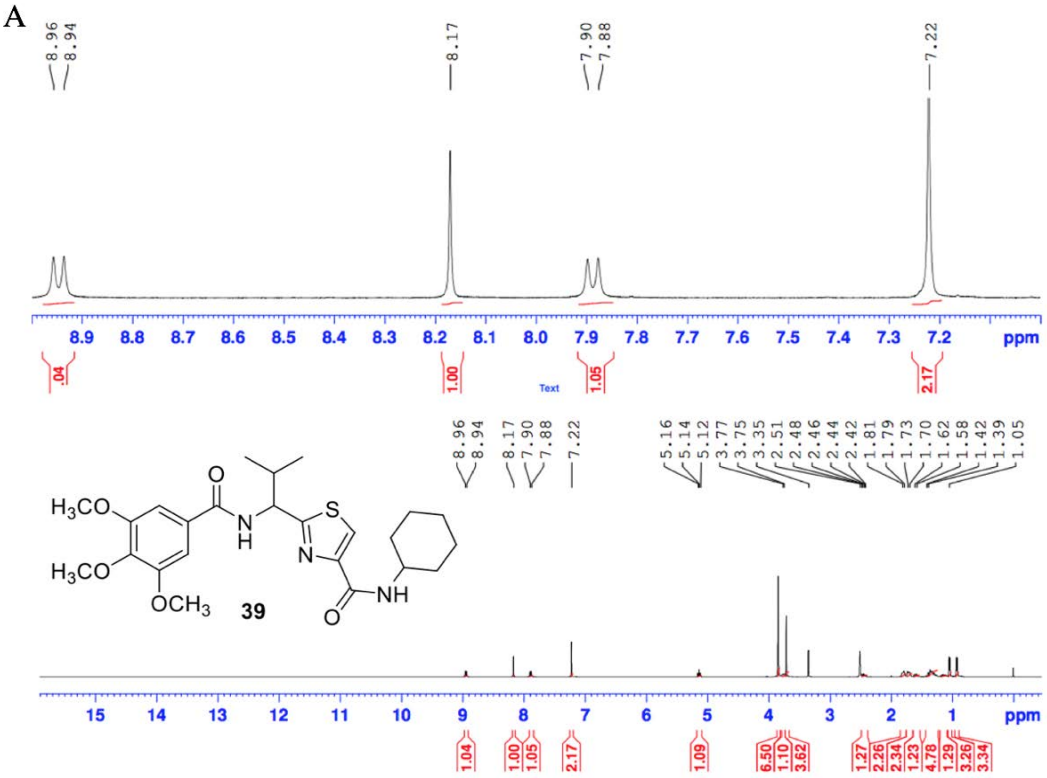
Bhargav A. Patel[†,§], Biebele Abel[‡], Anna Maria Barbuti[†], Uday Kiran Velagapudi[†], Zhe-Sheng Chen[†], Suresh V. Ambudkar[,‡], Tanaji T. Talele[*,†]*

[†]Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Queens, NY 11439, USA

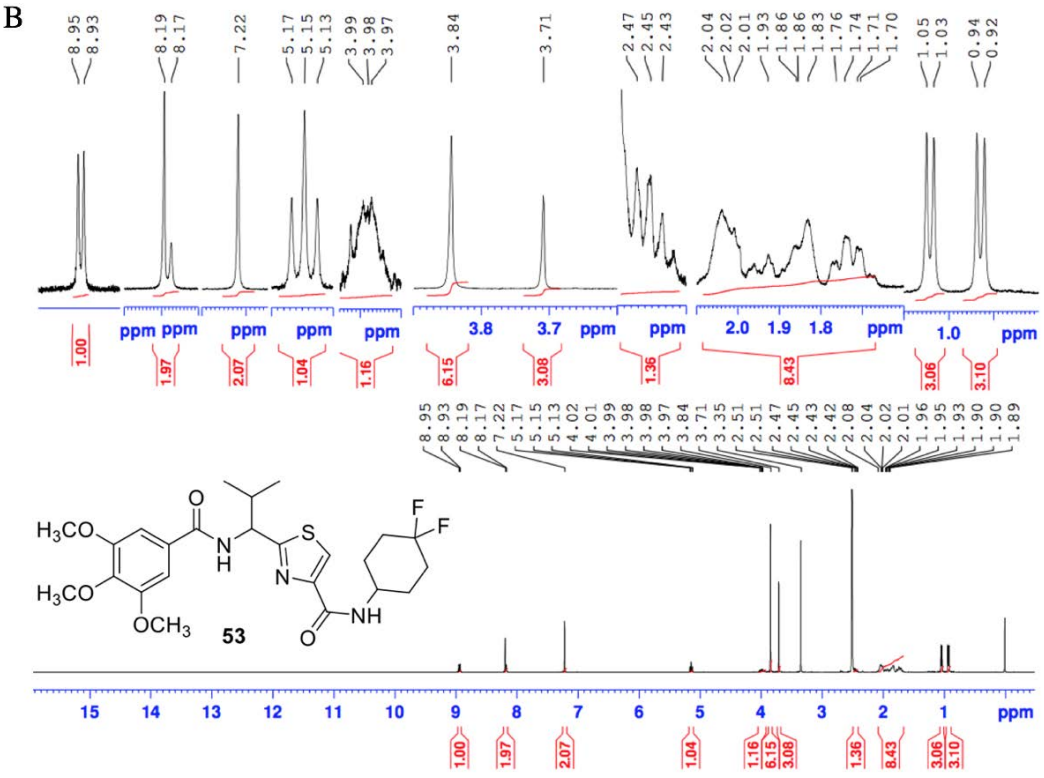
[‡]Laboratory of Cell Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

Contents of SI

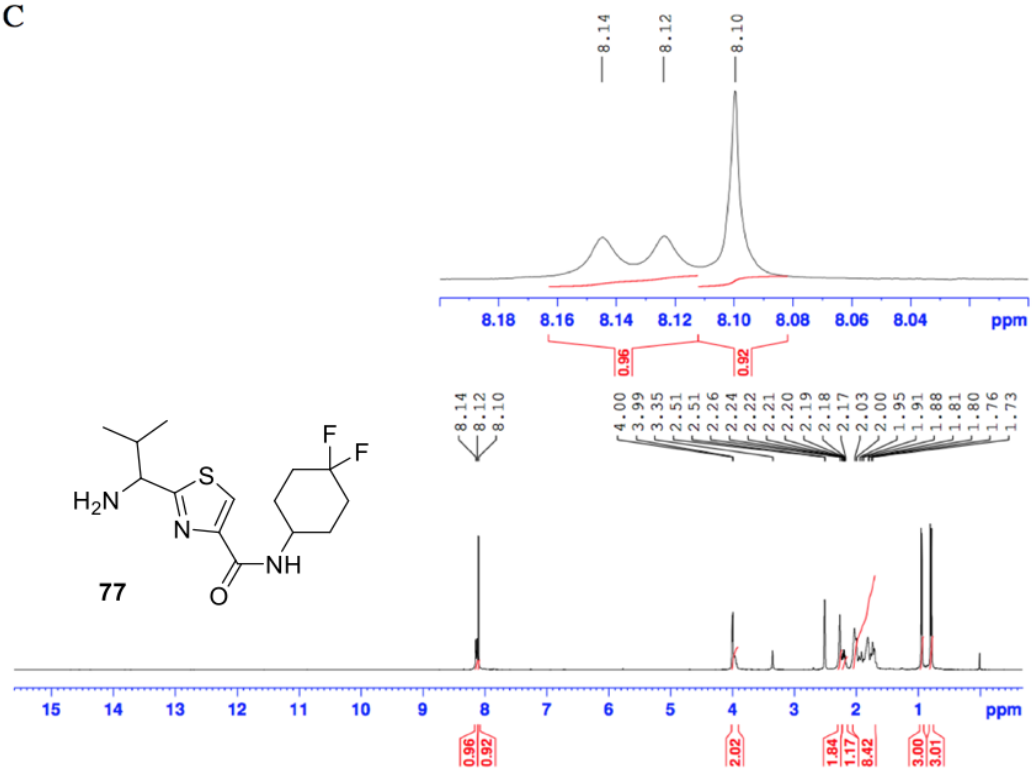
A


8.96
8.94
8.17
7.90
7.88
7.22
ppm
39

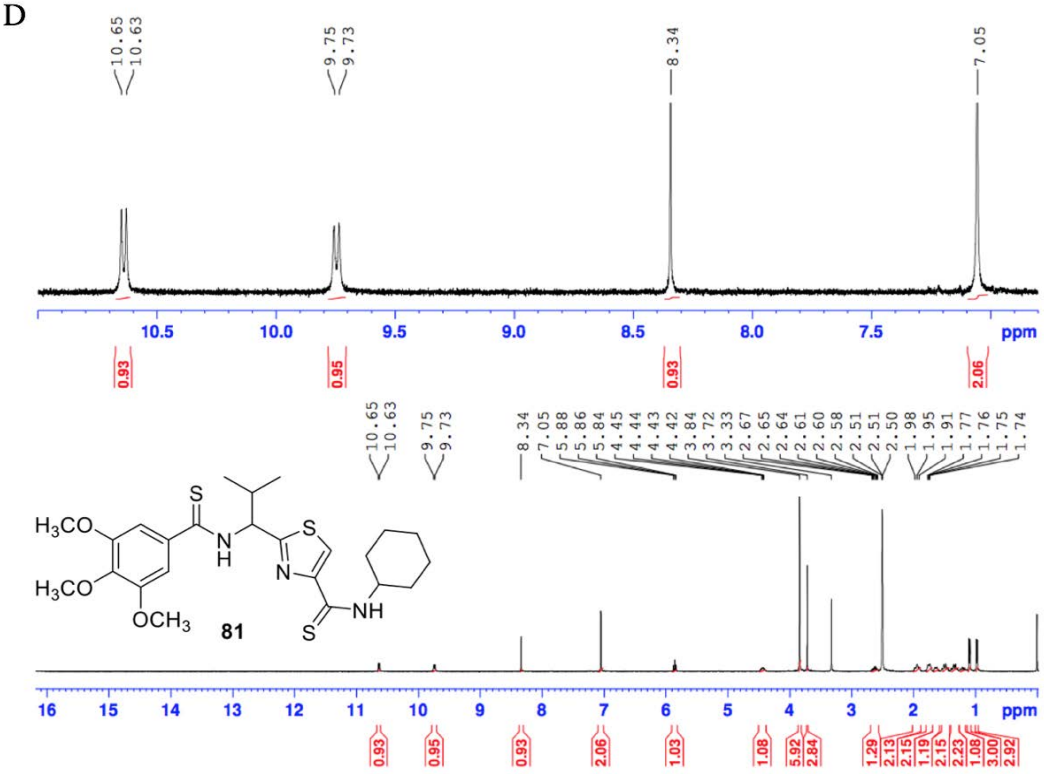
B


8.95
8.93
8.19
8.17
7.22
5.17
5.15
5.13
3.99
3.98
3.97
3.84
3.71
2.47
2.45
2.43
2.04
2.02
2.01
1.93
1.86
1.83
1.76
1.74
1.71
1.70
1.05
1.03
0.94
0.92
ppm
53

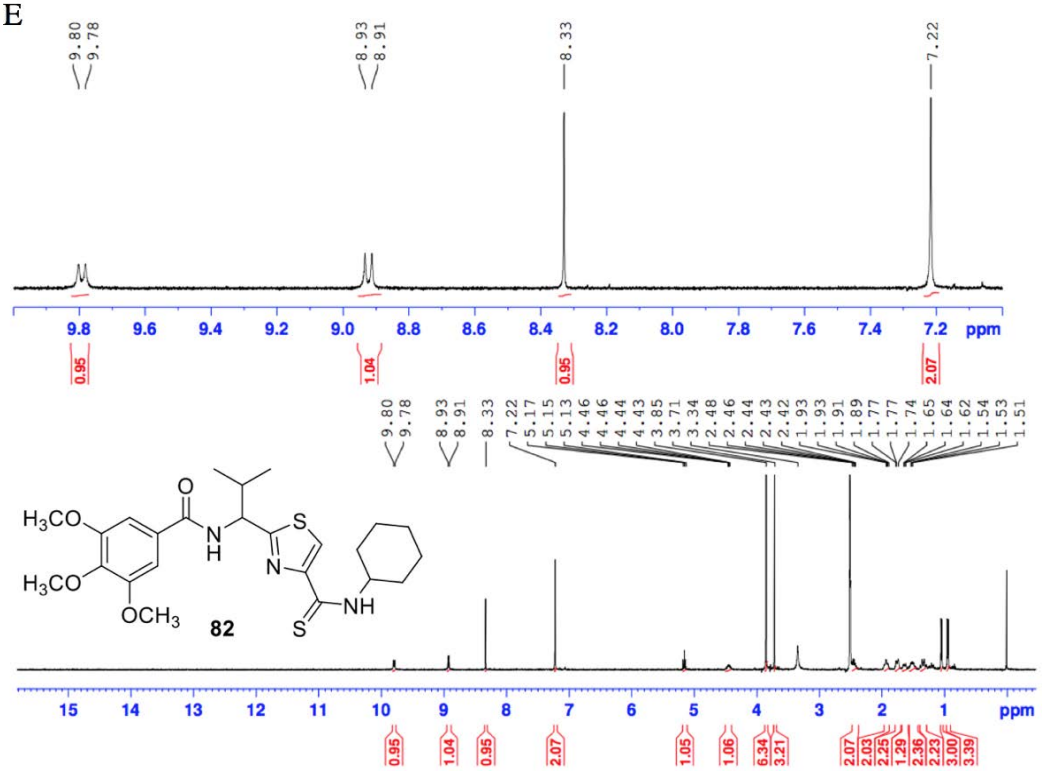
C


8.14
8.12
8.10
8.18 8.16 8.14 8.12 8.10 8.08 8.06 8.04 ppm
0.96
0.92
4.00 3.99 3.35 2.51 2.26 2.24 2.22 2.21 2.20 2.19 2.18 2.17 2.03 2.00 1.95 1.91 1.88 1.81 1.80 1.76 1.73
F
F
S
H_2N
N
NH
O
77
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.96 0.92 2.02 1.84 1.17 8.42 3.00 3.01

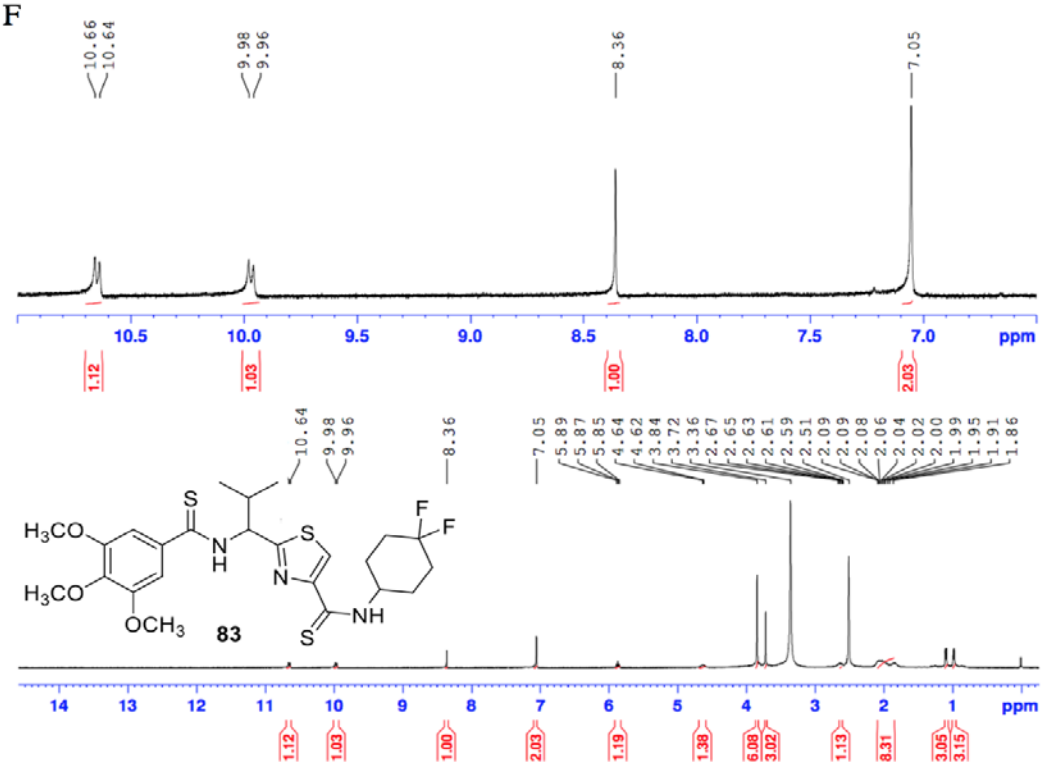
D


10.65
10.63
9.75
9.73
8.34
7.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 ppm
0.93 0.95 0.93 2.06
8.34 7.05 5.88 5.86 5.84 4.45 4.44 4.43 4.42 3.84 3.72 3.33 2.67 2.65 2.64 2.61 2.60 2.58 2.51 2.51 2.50 1.98 1.95 1.91 1.77 1.76 1.75 1.74
H_3CO
H_3CO
OCH_3
S
N
H
S
N
NH
S
81
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.93 0.95 0.93 2.06 1.03 1.08 5.92 2.84 1.29 2.13 2.15 1.19 2.15 2.23 1.08 3.00 2.92

E


9.80
9.78
8.93
8.91
8.33
7.22
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
ppm
0.95
1.04
0.95
2.07
5.17
5.15
5.13
4.46
4.44
4.43
3.85
3.71
3.34
2.48
2.46
2.44
2.43
2.42
1.93
1.91
1.89
1.77
1.74
1.65
1.64
1.62
1.54
1.53
1.51
H3CO
H3CO
OCH3
O
N
H
S
N
NH
S
82
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.95
1.04
0.95
2.07
1.05
1.06
6.34
3.21
2.07
2.03
2.25
1.29
2.36
2.23
3.00
3.39

F


10.66
10.64
9.98
9.96
8.36
7.05
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
ppm
1.12
1.03
1.00
2.03
5.89
5.87
5.85
4.64
4.62
3.84
3.72
3.36
2.67
2.65
2.63
2.61
2.59
2.51
2.09
2.09
2.08
2.06
2.04
2.02
2.00
1.99
1.95
1.91
1.86
H3CO
H3CO
OCH3
S
N
H
S
N
NH
S
F
F
83
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.12
1.03
1.00
2.03
1.19
1.38
6.08
3.02
1.13
8.31
3.05
3.15

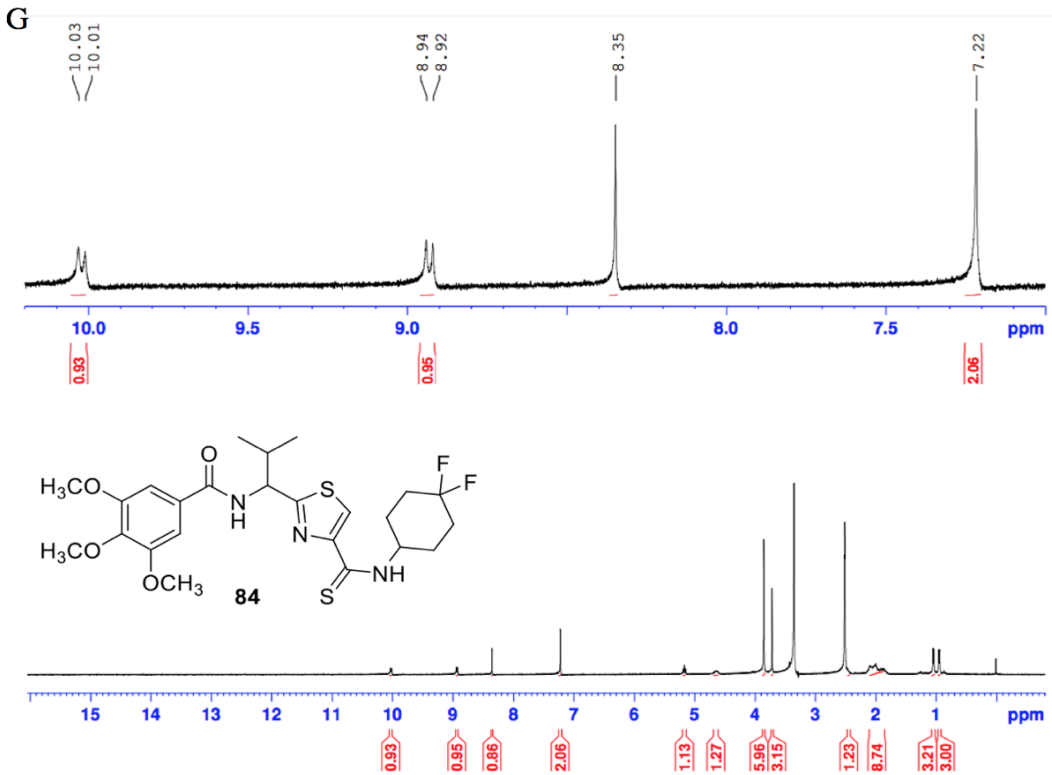


Figure S1. ^{1}H-NMR spectrums of compounds (A) **39**, (B) **53**, (C) **77**, (D) **81**, (E) **82**, (F) **83**, (G) **84** in DMSO-d_6.

Table S1. Calculated molecular descriptors for target compounds

Comp.	AlogP[a]	HBA[a]	HBD[a]	PSA[a]	Rotatable bonds[a]	Mol. Wt.[b]	No. of N and O[b]	Molar refractivity[c]	Molar volume[c]	A[d]	B[d]
1	4.98	7	2	144.09	11	573.67	9	159.10	452.80	-0.13	2.64
5	4.98	7	2	144.09	11	573.67	9	159.10	452.80	-0.16	2.65
7	4.98	7	2	144.09	11	573.67	9	159.10	452.80	-0.12	2.59
18	4.36	7	3	156.12	11	588.69	10	163.88	453.50	-0.11	2.87
19	4.36	7	3	156.12	11	588.69	10	163.88	453.50	-0.09	2.86
20	5.14	7	2	136.25	11	561.66	9	155.75	445.20	-0.48	2.45
21	5.55	6	2	127.02	11	559.69	8	158.62	454.10	-0.26	2.44
28	5.73	7	2	144.09	11	652.57	9	166.79	469.00	-0.11	2.63
29	3.81	7	2	156.45	12	614.69	12	NC[e]	NC	NC	NC
31	4.29	4	3	142.42	8	498.61	7	143.30	383.00	0.48	2.45
32	3.86	4	2	128.76	9	524.61	9	NC	NC	NC	NC
33	3.86	4	2	128.76	9	524.61	9	NC	NC	NC	NC
34	3.86	4	2	128.76	9	524.61	9	NC	NC	NC	NC
35	4.61	4	2	128.76	9	603.51	9	NC	NC	NC	NC
36	2.49	6	2	127.02	9	433.53	8	113.59	337.30	-0.13	2.17
37	2.95	6	2	127.02	9	447.56	8	118.22	353.40	-0.14	2.20
38	3.41	6	2	127.02	9	461.59	8	122.85	369.50	-0.17	2.22
39	3.86	6	2	127.02	9	475.61	8	127.48	385.60	-0.14	2.24
40	4.15	6	2	127.02	9	527.69	8	141.88	414.00	0.03	2.42
41	3.47	8	2	156.56	11	576.72	11	151.75	459.30	-0.20	2.97
42	1.58	6	2	139.05	9	476.60	9	126.50	377.00	-0.10	2.51
43	1.84	7	2	136.25	9	477.58	9	124.59	375.50	-0.29	2.41
44	1.83	7	1	135.30	8	475.57	9	124.88	377.40	0.09	2.44
46	2.16	6	2	139.05	10	490.63	9	132.77	414.60	-0.09	2.50
48	1.35	6	1	144.25	8	476.60	9	128.30	388.50	-0.14	2.52
50	2.67	6	2	153.04	10	504.65	9	137.59	426.20	-0.09	2.47
51	1.57	8	2	169.54	9	525.65	10	131.67	388.40	0.25	2.43
52	2.30	7	2	144.09	9	489.60	9	127.60	382.40	0.09	2.40
53	3.11	6	2	127.02	9	511.59	8	127.73	395.80	-0.13	2.29
54	4.32	6	2	127.02	9	503.67	8	136.75	418.20	-0.09	2.29
55	5.93	6	1	118.23	10	557.76	8	153.43	462.80	-0.12	2.62
56	3.24	6	1	121.47	9	544.72	9	149.42	452.10	-0.07	2.76
57	3.70	6	2	130.26	11	566.73	9	156.07	450.20	-0.12	2.71

58	2.53	8	2	156.04	10	554.67	11	147.04	419.90	-0.09	3.22
59	4.60	6	2	127.02	9	523.66	8	142.92	411.40	-0.21	2.40
60	4.60	6	2	127.02	9	523.66	8	142.92	411.40	-0.21	2.40
61	3.03	6	1	118.23	8	497.57	8	123.35	377.90	-0.14	2.34
62	3.73	6	1	118.23	9	529.58	8	129.53	414.00	-0.16	2.41
63	3.44	6	2	127.02	10	525.61	8	132.36	411.90	-0.10	2.29
64	4.47	6	2	127.02	10	543.61	8	132.45	417.40	-0.14	2.36
65	3.79	6	2	127.02	9	487.55	8	129.30	378.90	-0.17	2.23
66	4.20	6	2	127.02	9	523.54	8	129.29	387.30	-0.26	2.29
67	3.59	6	2	127.02	12	503.55	8	122.71	402.00	-0.03	2.26
69	1.86	4	2	140.46	6	428.53	6	104.57	314.10	0.59	2.11
70	1.38	5	2	125.11	6	423.49	7	104.23	316.60	0.63	2.43
71	3.34	4	2	112.22	6	472.56	6	123.99	356.50	0.47	2.27
72	1.85	4	2	108.56	6	429.53	6	106.75	340.80	0.41	2.04
73	2.87	3	2	99.33	6	463.54	5	109.89	361.10	0.58	1.93
74	3.13	5	2	117.79	8	481.57	7	121.36	374.20	0.09	2.13
75	3.14	4	2	108.56	7	451.54	6	115.00	352.60	0.32	1.98
76	3.16	3	2	99.33	6	421.51	5	108.63	330.90	0.52	1.88
77	1.47	2	1	96.25	4	317.40	4	79.14	254.90	0.36	1.45
78	3.77	3	2	99.33	6	475.48	5	108.97	344.20	0.47	1.94
79	3.14	6	2	127.02	10	525.62	8	132.36	411.90	-0.11	2.29
80	3.00	7	2	144.09	10	539.60	9	132.47	408.70	0.07	2.50
81	6.05	4	2	157.06	11	507.74	6	141.47	401.90	-0.49	2.03
82	4.96	5	2	142.04	10	491.68	7	134.48	393.80	-0.32	2.12
83	5.30	4	2	157.06	11	543.72	6	141.72	412.10	-0.48	2.08
84	4.20	5	2	142.04	10	527.66	7	134.72	403.90	-0.31	2.17
101	2.12	6	2	127.02	7	455.48	8	109.25	330.20	-0.16	2.08
107	1.78	6	2	127.02	8	469.51	8	113.88	346.30	-0.12	2.09
108	3.50	6	2	127.02	10	525.62	8	132.36	411.90	-0.11	2.32
109	3.82	6	2	127.02	10	559.64	8	143.2	421.30	-0.16	2.41
110	3.55	7	3	147.25	10	575.64	9	144.73	418.10	0.02	2.41
111	2.58	6	1	118.23	7	509.58	8	125.94	375.20	-0.15	2.38

Calculated using [a]calculate property functionality in Maestro v10.1 (Schrödinger, LLC, New York, NY, 2015), [b]Qikprop (Mol. Wt. and No. of N and O; QikProp, Schrödinger, LLC, New York, NY, 2015), [c]ACD/Chemsketch (Molar refractivity and Molar volume; ACD/Labs 2017.1.2, Advanced Chemistry Development Inc. Toronto, Ontario, Canada) and [d]Open Notebook Science Challenge (A and B; http://showme.physics.drexel.edu/onsc/models/AbrahamDescriptorsModel001.php), [e]Could not be calculated (NC) by ACD/Chemsketch program.

AlogP, Atom based logP; HBA, Hydrogen Bond Acceptors; HBD, Hydrogen Bond Donors; PSA, Polar Surface Area; Rotatable bonds, No. of rotatable bonds; No. of N and O, Number of nitrogen and oxygen atoms; A, Hydrogen bond acidity; B, Hydrogen bond basicity.