Structure–Activity Relationships in a Series of Dihydrouracil-JQ1 Conjugates: Discovery of Highly Potent BRD4 Degraders.

Supporting Information File 1

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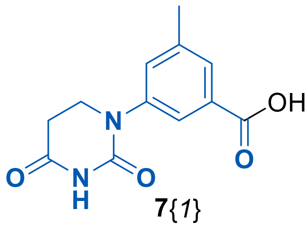
Table of Contents



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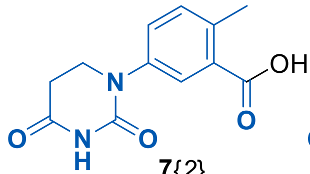

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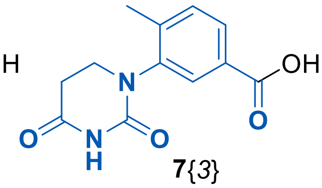

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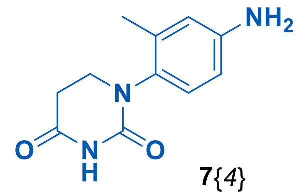

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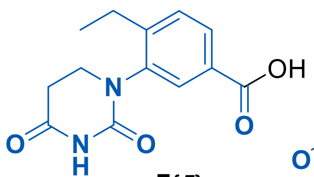

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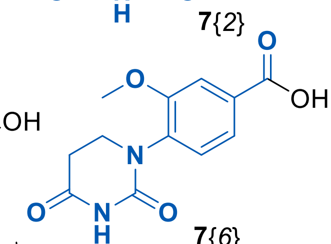

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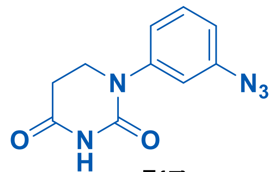

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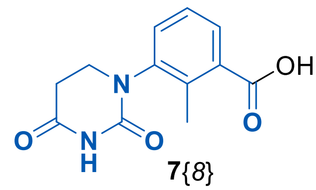

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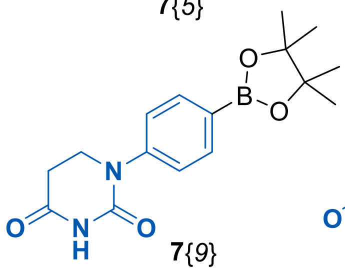

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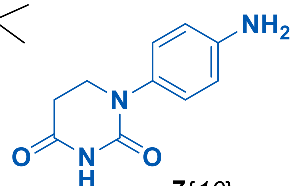

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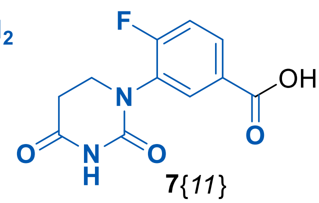

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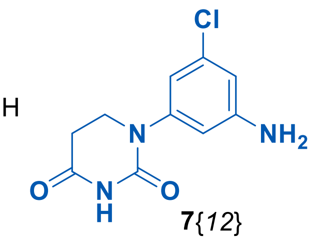

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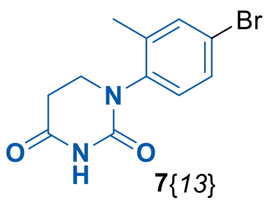

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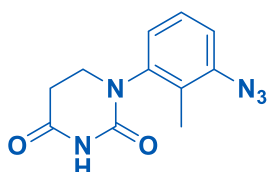

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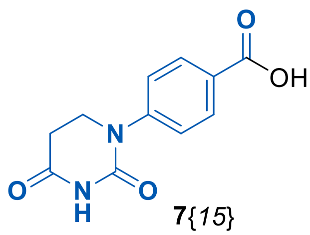

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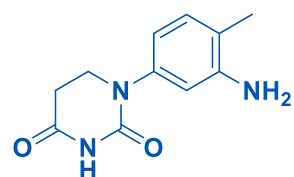

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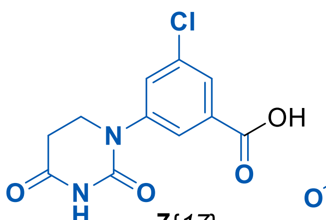

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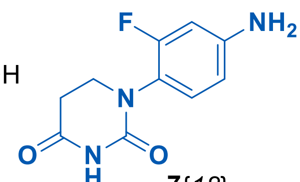

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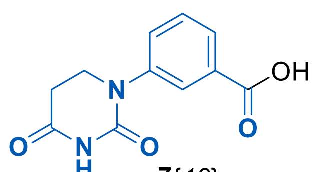

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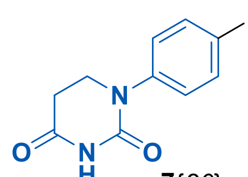

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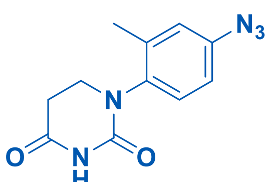

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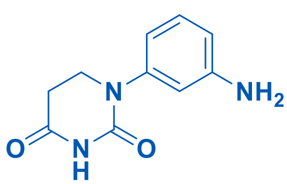

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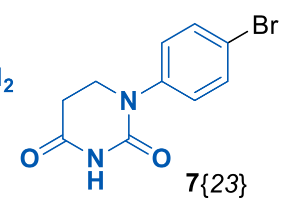

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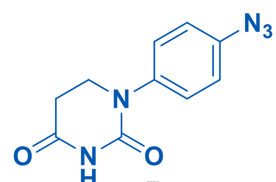

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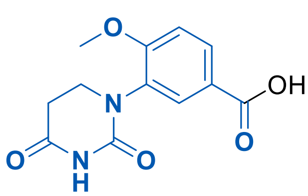

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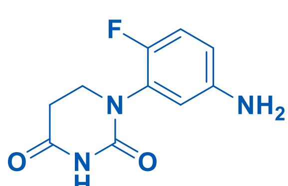

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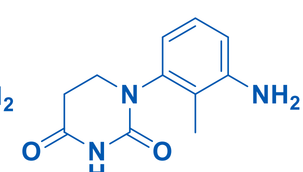

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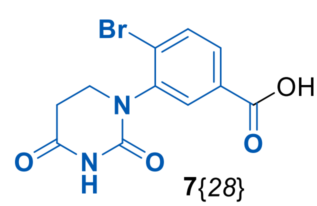

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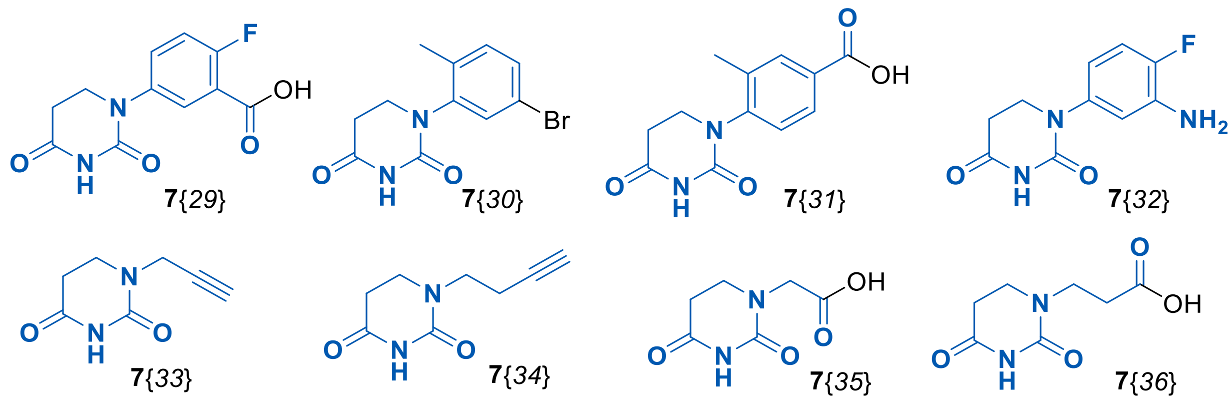


Figure S1. Structures of dihydrouracil-derived building blocks **7**{*1–36*}

Table S1. Displacement of Cy5-labeled thalidomide from DDB1 – CRBN complex by compounds **7**{*1–36*} and their simplest model derivatives in the FP assay at 10 μM

#	ID	SMILES	Displa-cement, %	RSD, %	SMILES	Displa-cement, %	RSD, %
1	**7**{*1*}	Cc1ccc(cc1N1CCC(=O)NC1=O)C(O)=O	83.3	1.6	CNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O	67.9	3.7
2	**7**{*2*}	Cc1cc(cc(c1)C(O)=O)N1CCC(=O)NC1=O	79.9	4.0	CNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O	57.6	1.7
3	**7**{*3*}	Cc1ccc(cc1C(O)=O)N1CCC(=O)NC1=O	99.5	1.9	CNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O	65.8	2.0
4	**7**{*4*}	Cl.Cc1cc(N)ccc1N1CCC(=O)NC1=O	77.3	3.7	CC(=O)Nc1ccc(N2CCC(=O)NC2=O)c(C)c1	59.6	5.3
5	**7**{*5*}	CCc1ccc(cc1N1CCC(=O)NC1=O)C(O)=O	65.7	3.4	CCc1ccc(cc1N1CCC(=O)NC1=O)C(=O)NC	58.1	10.0
6	**7**{*6*}	COc1cc(ccc1N1CCC(=O)NC1=O)C(O)=O	51.7	1.0	CNC(=O)c1ccc(N2CCC(=O)NC2=O)c(OC)c1	17.5	3.9
7	**7**{*7*}	[N-]=[N+]=Nc1cccc(c1)N1CCC(=O)NC1=O	45.5	4.4	COCc1cn(nn1)-c1cccc(c1)N1CCC(=O)NC1=O	35.6	5.3
8	**7**{*8*}	Cc1c(cccc1C(O)=O)N1CCC(=O)NC1=O	40.8	0.7	CNC(=O)c1cccc(N2CCC(=O)NC2=O)c1C	16.3	2.3
9	**7**{*9*}	CC1(C)OB(OC1(C)C)c1ccc(cc1)N1CCC(=O)NC1=O	94	7.1	–	–	–
10	**7**{*10*}	Cl.Nc1ccc(cc1)N1CCC(=O)NC1=O	65.9	4.6	CC(=O)Nc1ccc(cc1)N1CCC(=O)NC1=O	33.9	1.2
11	**7**{*11*}	OC(=O)c1ccc(F)c(c1)N1CCC(=O)NC1=O	43.3	3.9	CNC(=O)c1ccc(F)c(c1)N1CCC(=O)NC1=O	44.3	2.1
12	**7**{*12*}	Nc1cc(Cl)cc(c1)N1CCC(=O)NC1=O	77	1.7	CC(=O)Nc1cc(Cl)cc(c1)N1CCC(=O)NC1=O	48.7	2.7
13	**7**{*13*}	Cc1cc(Br)ccc1N1CCC(=O)NC1=O	62.7	3.2	–	–	–

14	**7**{*14*}	Cc1c(cccc1N1CCC(=O)NC1=O)N=[N+]=[N-]	61.1	1.4	COCc1cn(nn1)-c1cccc(N2CCC(=O)NC2=O)c1C	27.9	0.7
15	**7**{*15*}	OC(=O)c1ccc(cc1)N1CCC(=O)NC1=O	55.3	7.6	CNC(=O)c1ccc(cc1)N1CCC(=O)NC1=O	23.3	5.4
16	**7**{*16*}	Cl.Cc1ccc(cc1N)N1CCC(=O)NC1=O	83.4	4.7	CC(=O)Nc1cc(ccc1C)N1CCC(=O)NC1=O	48.1	11.5
17	**7**{*17*}	OC(=O)c1cc(Cl)cc(c1)N1CCC(=O)NC1=O	76.7	2.5	CNC(=O)c1cc(Cl)cc(c1)N1CCC(=O)NC1=O	43.2	2.6
18	**7**{*18*}	Cl.Nc1ccc(N2CCC(=O)NC2=O)c(F)c1	67.3	5.4	CC(=O)Nc1ccc(N2CCC(=O)NC2=O)c(F)c1	45.6	0.2
19	**7**{*19*}	OC(=O)c1cccc(c1)N1CCC(=O)NC1=O	67.1	4.5	CNC(=O)c1cccc(c1)N1CCC(=O)NC1=O	42.1	5.2
20	**7**{*20*}	Ic1ccc(cc1)N1CCC(=O)NC1=O	65.6	4.0	–	–	–
21	**7**{*21*}	Cc1cc(ccc1N1CCC(=O)NC1=O)N=[N+]=[N-]	59.4	2.9	COCc1cn(nn1)-c1ccc(N2CCC(=O)NC2=O)c(C)c1	55.6	13.4
22	**7**{*22*}	Nc1cccc(c1)N1CCC(=O)NC1=O	76.8	8.2	CC(=O)Nc1cccc(c1)N1CCC(=O)NC1=O	40.1	5.6
23	**7**{*23*}	Brc1ccc(cc1)N1CCC(=O)NC1=O	65.5	2.9	–	–	–
24	**7**{*24*}	[N-]=[N+]=Nc1ccc(cc1)N1CCC(=O)NC1=O	44.5	3.2	COCc1cn(nn1)-c1ccc(cc1)N1CCC(=O)NC1=O	34.3	1.3
25	**7**{*25*}	COc1ccc(cc1N1CCC(=O)NC1=O)C(O)=O	68.1	2.2	CNC(=O)c1ccc(OC)c(c1)N1CCC(=O)NC1=O	47.7	2.0
26	**7**{*26*}	Cl.Nc1ccc(F)c(c1)N1CCC(=O)NC1=O	65.1	2.8	CC(=O)Nc1cc(ccc1F)N1CCC(=O)NC1=O	32.7	4.9
27	**7**{*27*}	Cl.Cc1c(N)cccc1N1CCC(=O)NC1=O	70.2	5.8	CC(=O)Nc1cccc(N2CCC(=O)NC2=O)c1C	45.7	4.5
28	**7**{*28*}	OC(=O)c1ccc(Br)c(c1)N1CCC(=O)NC1=O	76.4	8.0	CNC(=O)c1ccc(Br)c(c1)N1CCC(=O)NC1=O	49.6	1.6
29	**7**{*29*}	OC(=O)c1cc(ccc1F)N1CCC(=O)NC1=O	79.3	3.4	CNC(=O)c1cc(ccc1F)N1CCC(=O)NC1=O	44	2.6
30	**7**{*30*}	Cc1ccc(Br)cc1N1CCC(=O)NC1=O	66.4	1.9	–	–	–
31	**7**{*31*}	Cc1cc(ccc1N1CCC(=O)NC1=O)C(O)=O	79.7	0.3	CNC(=O)c1ccc(N2CCC(=O)NC2=O)c(C)c1	38.6	1.4
32	**7**{*32*}	Cl.Nc1cc(ccc1F)N1CCC(=O)NC1=O	50.8	1.5	CC(=O)Nc1ccc(F)c(c1)N1CCC(=O)NC1=O	49.3	4.1
33	**7**{*33*}	O=C1CCN(CC#C)C(=O)N1	11.5	3.0	–	–	–
34	**7**{*34*}	O=C1CCN(CCC#C)C(=O)N1	15.2	5.5	–	–	–
35	**7**{*35*}	OC(=O)CN1CCC(=O)NC1=O	1.6	1.3	–	–	–
36	**7**{*36*}	OC(=O)CCN1CCC(=O)NC1=O	30.3	2.4	–	–	–

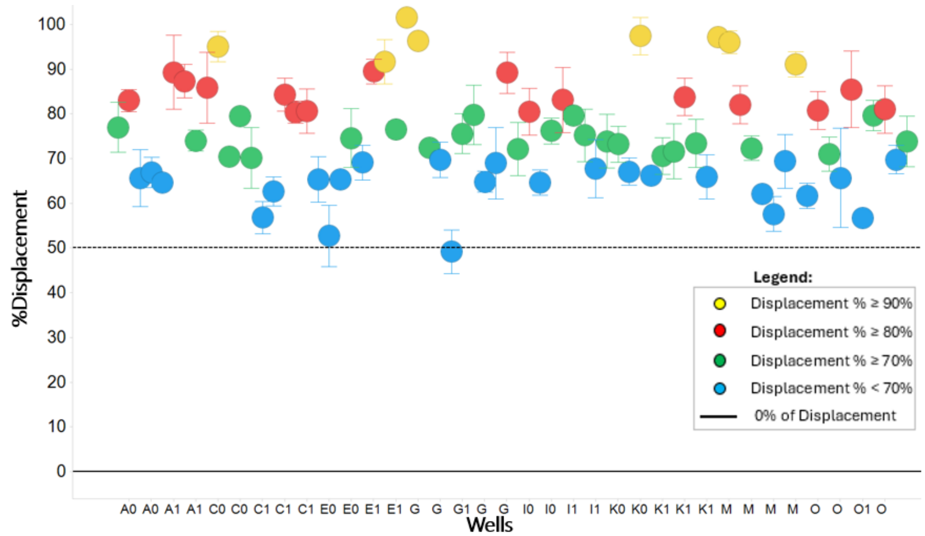


Figure S2. Labeled thalidomide probe displacement by compounds **6**{*1–4,1–20*} in TR-FRET assay. The compounds were tested at 1.11 µM in DMSO against the recombinant CRBN – DDB1 complex and thalidomide-red ligand to evaluate the level of probe displacement by detecting the change in the TR-FRET ratio. 47 compounds possess a displacement higher than 70% (green data points), 24 compounds – higher than 80% (red data points), and 8 – higher than 90% (yellow data points)

Table S2. Displacement of fluorescently-labeled thalidomide probe by compounds **6**{*1–4,1–20*} in the TR-FRET assay at 1.11 µM

#	Compound	SMILES	Displace-ment, %	RSD, %
1	**6**{*4,2*}	Cc1nnc2[C@H](CC(=O)NCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	77	5.59
2	**6**{*2,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	83	2.48
3	**6**{*1,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	65.6	6.38
4	**6**{*2,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	66.9	3.39
5	**6**{*2,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	64.6	1.13
6	**6**{*1,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	89.3	8.25

7	**6**{*4,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	87.3	3.72
8	**6**{*1,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	74	2.35
9	**6**{*4,10*}	Cc1nnc2[C@H](CC(=O)NCCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	85.9	7.93
10	**6**{*4,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	95	3.41
11	**6**{*3,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	70.4	1.29
12	**6**{*3,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	79.5	1.06
13	**6**{*3,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	70.1	6.79
14	**6**{*3,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	56.8	3.59
15	**6**{*3,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	62.7	3.24
16	**6**{*4,9*}	Cc1nnc2[C@H](CC(=O)NCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	84.3	3.68
17	**6**{*4,17*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	80.4	2.5
18	**6**{*4,15*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	80.6	4.91
19	**6**{*1,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	65.3	5.09
20	**6**{*3,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	52.7	6.84
21	**6**{*3,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	65.4	1.11
22	**6**{*1,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	74.6	6.55

23	**6**{*1,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	69.1	3.93
24	**6**{*4,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	89.5	2.79
25	**6**{*2,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	91.6	4.95
26	**6**{*1,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	76.5	1.84
27	**6**{*4,20*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	101.5	0.65
28	**6**{*4,6*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	96.3	1
29	**6**{*1,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	72.4	0.41
30	**6**{*3,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	69.7	3.98
31	**6**{*3,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	49.2	4.9
32	**6**{*4,7*}	Cc1nnc2[C@H](CC(=O)NCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	75.6	4.46
33	**6**{*4,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	79.8	6.61
34	**6**{*1,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	64.8	2.33
35	**6**{*2,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	69	8
36	**6**{*4,1*}	Cc1nnc2[C@H](CC(=O)NCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	89.2	4.56
37	**6**{*2,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	72.1	5.92
38	**6**{*3,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	80.5	5.28
39	**6**{*3,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	64.6	2.84

40	**6**{*1*,*7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	76.2	2.9
41	**6**{*4*,*16*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	83.1	7.31
42	**6**{*1*,*4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	79.6	1.9
43	**6**{*1*,*1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	75.2	5.85
44	**6**{*2*,*10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	67.8	6.51
45	**6**{*2*,*17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	73.9	5.97
46	**6**{*3*,*2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	73.2	4.09
47	**6**{*1*,*6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	67.1	2.99
48	**6**{*2*,*5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	97.4	4.14
49	**6**{*3*,*7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	66.2	0.92
50	**6**{*2*,*9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	70.6	4.08
51	**6**{*4*,*13*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	71.6	6.16
52	**6**{*2*,*16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	83.8	4.18
53	**6**{*1*,*2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	73.4	5.36
54	**6**{*1*,*15*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	65.9	4.96
55	**6**{*3*,*5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	97.2	0.9
56	**6**{*4*,*19*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	96.1	2.55

57	**6**{*2,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	82	4.22
58	**6**{*2,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	72.3	2.77
59	**6**{*2,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	62.1	0.82
60	**6**{*3,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	57.6	3.91
61	**6**{*3,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	69.4	6.04
62	**6**{*4,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	91.1	2.81
63	**6**{*1,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	61.7	2.8
64	**6**{*4,18*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	80.8	4.22
65	**6**{*2,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	71	3.88
66	**6**{*3,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	65.7	11.04
67	**6**{*4,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	85.5	8.6
68	**6**{*1,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	56.7	0.42
69	**6**{*1,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	79.6	3.4
70	**6**{*4,8*}	Cc1nnc2[C@H](CC(=O)NCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	81	5.31
71	**6**{*2,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	69.8	3.24
72	**6**{*2,18*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	73.8	5.63

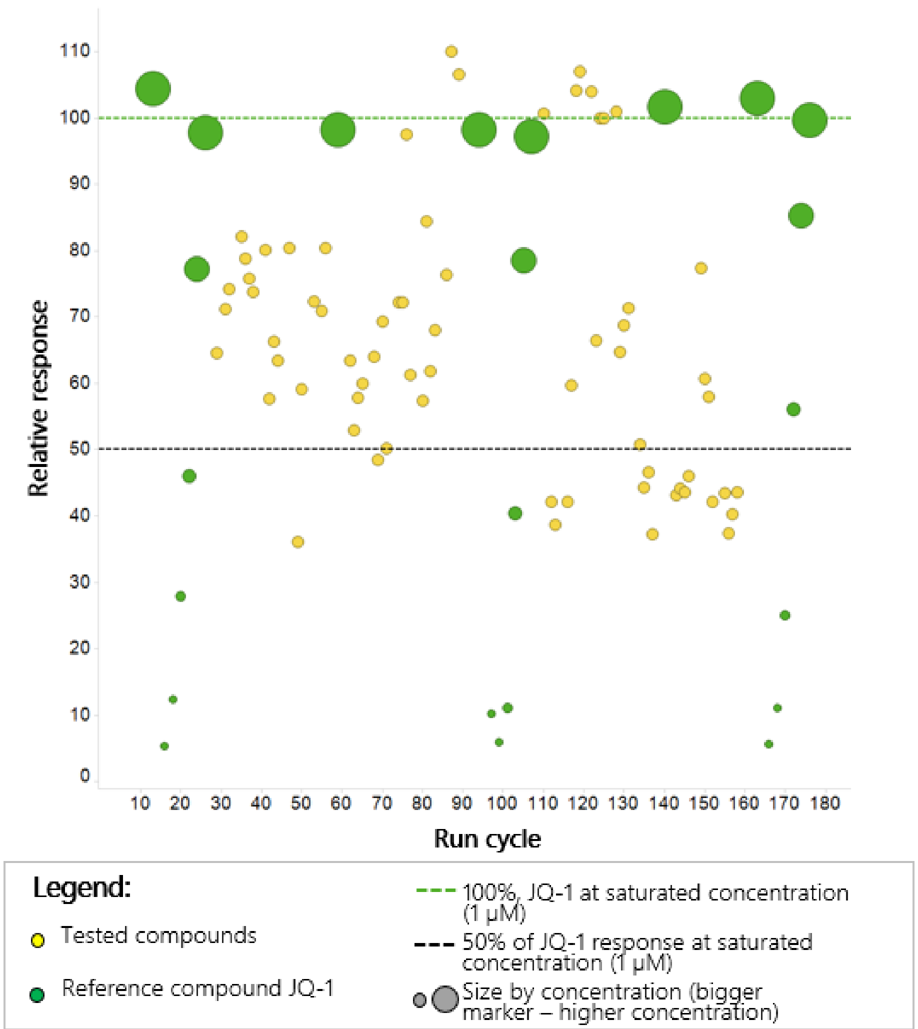


Figure S3. Binding screen for compounds **6**{*1–4*,*1–20*} in the SPR assay. The relative binding response of the compounds at 100 nM is shown.

Table S3. Relative binding response of compounds **6**{*1–4*,*1–20*} in the SPR assay at 100 nM

#	Compound	SMILES	Kinetic K_d, nM
1	**6**{*4*,*18*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.8
2	**6**{*1*,*17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	10.7
3	**6**{*3*,*17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	12.2

4	**6**{*3,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	13.1
5	**6**{*2,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	14.0
6	**6**{*2,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	14.8
7	**6**{*3,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	18.6
8	**6**{*1,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	19.4
9	**6**{*1,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	19.7
10	**6**{*2,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	20.3
11	**6**{*1,15*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	21.7
12	**6**{*4,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	30.6
13	**6**{*4,7*}	Cc1nnc2[C@H](CC(=O)NCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	34.2
14	**6**{*1,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	34.7
15	**6**{*4,2*}	Cc1nnc2[C@H](CC(=O)NCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	37.9
16	**6**{*4,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	41.3
17	**6**{*3,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	41.5
18	**6**{*2,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	42.7
19	**6**{*4,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	43.3
20	**6**{*3,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	43.5
21	**6**{*4,19*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	44.1
22	**6**{*1,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	46.4

23	**6**{*4,10*}	Cc1nnc2[C@H](CC(=O)NCCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	48.4
24	**6**{*4,1*}	Cc1nnc2[C@H](CC(=O)NCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	50.7
25	**6**{*4,8*}	Cc1nnc2[C@H](CC(=O)NCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	51.9
26	**6**{*4,9*}	Cc1nnc2[C@H](CC(=O)NCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	52.4
27	**6**{*4,20*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	52.7
28	**6**{*4,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	53.3
29	**6**{*1,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	54.5
30	**6**{*4,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	54.6
31	**6**{*2,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	55.3
32	**6**{*1,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	59.5
33	**6**{*3,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	59.9
34	**6**{*1,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	60.7
35	**6**{*3,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	61.4
36	**6**{*3,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	61.6
37	**6**{*2,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	62.8
38	**6**{*3,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	62.9
39	**6**{*4,6*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	63.1
40	**6**{*2,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	63.9
41	**6**{*3,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	65.5

42	**6**{*3,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	67.1
43	**6**{*3,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	69.4
44	**6**{*1,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	69.8
45	**6**{*1,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	72.1
46	**6**{*3,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	73.5
47	**6**{*2,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	76.6
48	**6**{*1,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	82.5
49	**6**{*1,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	86.6
50	**6**{*2,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	88.2
51	**6**{*2,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	88.4
52	**6**{*2,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	90.8
53	**6**{*4,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	91.9
54	**6**{*3,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	92.3
55	**6**{*2,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	93.7
56	**6**{*1,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	97.1
57	**6**{*1,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	100.0
58	**6**{*1,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	107.0
59	**6**{*3,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	108.0
60	**6**{*2,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	108.3

61	**6**{*2,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	111.6
62	**6**{*2,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	113.2
63	**6**{*4,17*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	113.3
64	**6**{*4,16*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	114.2
65	**6**{*1,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	115.8
66	**6**{*4,15*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	116.1
67	**6**{*4,13*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	127.1
68	**6**{*3,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	128.7
69	**6**{*2,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	129.7
70	**6**{*3,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	130.8
71	**6**{*2,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	136.8
72	**6**{*1,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	139.4

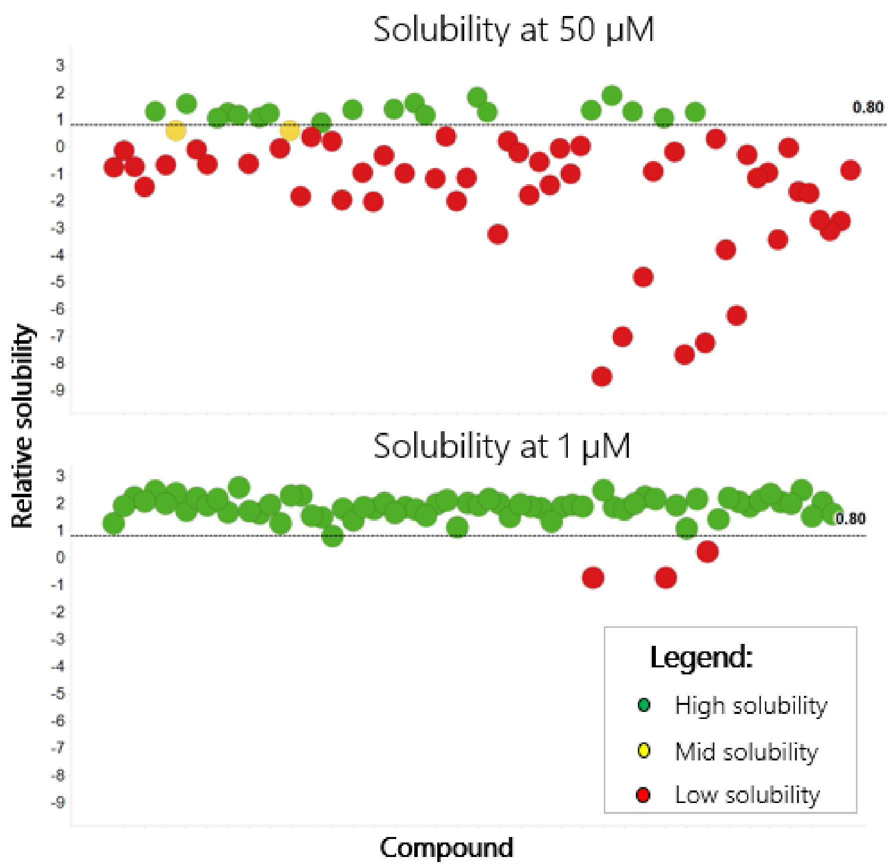


Figure S4. Nephelometry solubilities of compounds **6**{*1–4*,*1–20*} at 50 µM and 1 µM. Data point coloring corresponds to high (green), medium (yellow), and low (red) compound solubility

Table S4. Solubility grades for compounds **6**{*1–4*,*1–20*} at 50 µM and 1 µM

#	Compound	SMILES	Solubility grade at	
			50 µM	1 µM
1	**6**{*4,2*}	Cc1nnc2[C@H](CC(=O)NCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
2	**6**{*4,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
3	**6**{*1,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High

4	**6**{*4,6*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
5	**6**{*2,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
6	**6**{*3,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
7	**6**{*3,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	Low
8	**6**{*4,18*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
9	**6**{*2,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
10	**6**{*3,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
11	**6**{*3,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
12	**6**{*1,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
13	**6**{*3,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
14	**6**{*1,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
15	**6**{*4,19*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	Low
16	**6**{*2,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
17	**6**{*1,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
18	**6**{*3,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High

19	**6**{*3,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
20	**6**{*3,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
21	**6**{*3,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Medium	High
22	**6**{*2,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
23	**6**{*2,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
24	**6**{*3,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
25	**6**{*2,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
26	**6**{*3,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
27	**6**{*1,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
28	**6**{*3,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
29	**6**{*1,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
30	**6**{*3,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
31	**6**{*2,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
32	**6**{*4,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High

33	**6**{*2,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
34	**6**{*3,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
35	**6**{*1,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Medium	High
36	**6**{*4,7*}	Cc1nnc2[C@H](CC(=O)NCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
37	**6**{*4,16*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
38	**6**{*2,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
39	**6**{*2,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
40	**6**{*1,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High
41	**6**{*1,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
42	**6**{*3,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
43	**6**{*4,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
44	**6**{*4,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
45	**6**{*1,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
46	**6**{*4,13*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High

47	**6**{*3,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
48	**6**{*1,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
49	**6**{*4,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
50	**6**{*4,9*}	Cc1nnc2[C@H](CC(=O)NCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
51	**6**{*2,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
52	**6**{*1,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
53	**6**{*1,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
54	**6**{*2,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
55	**6**{*3,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
56	**6**{*4,8*}	Cc1nnc2[C@H](CC(=O)NCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
57	**6**{*1,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
58	**6**{*4,17*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
59	**6**{*1,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
60	**6**{*2,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High

61	**6**{*2,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
62	**6**{*1,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
63	**6**{*4,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
64	**6**{*2,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
65	**6**{*4,10*}	Cc1nnc2[C@H](CC(=O)NCCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
66	**6**{*4,15*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
67	**6**{*4,20*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	Low
68	**6**{*4,1*}	Cc1nnc2[C@H](CC(=O)NCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
69	**6**{*2,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
70	**6**{*1,15*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
71	**6**{*1,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	Low	High
72	**6**{*2,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	High	High

Table S5. The efficiency of (TCF) for 69 selected compounds **6**{*1–4*,*1–18*} with CRBN and BRD4 in the TCF TR-FRET assay

#	Com-pound	SMILES	EC_{50}, nM	EC_{max}, nM
1	**6**{*3,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.2	45.7
2	**6**{*4,6*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	4.96	51.7
3	**6**{*1,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	2.88	51.7
4	**6**{*4,18*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.94	58.4
5	**6**{*2,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	4.06	58.4
6	**6**{*4,1*}	Cc1nnc2[C@H](CC(=O)NCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.06	58.4
7	**6**{*4,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.34	65.9
8	**6**{*1,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.35	65.9
9	**6**{*4,10*}	Cc1nnc2[C@H](CC(=O)NCCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.02	65.9
10	**6**{*3,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	10.9	74.5
11	**6**{*4,7*}	Cc1nnc2[C@H](CC(=O)NCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.01	74.5
12	**6**{*4,9*}	Cc1nnc2[C@H](CC(=O)NCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.54	74.5
13	**6**{*1,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.35	74.5
14	**6**{*4,2*}	Cc1nnc2[C@H](CC(=O)NCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.29	84.2
15	**6**{*3,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.63	84.2
16	**6**{*2,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.87	84.2
17	**6**{*1,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.45	84.2

18	**6**{*4,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.74	84.2
19	**6**{*2,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.83	84.2
20	**6**{*4,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.62	84.2
21	**6**{*2,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.07	84.2
22	**6**{*1,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.77	95.1
23	**6**{*4,8*}	Cc1nnc2[C@H](CC(=O)NCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.73	95.1
24	**6**{*1,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	12.5	95.1
25	**6**{*1,15*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.5	95.1
26	**6**{*2,18*}	Cc1nnc2[C@H](CC(=O)NCCCCN(C)CCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	4.82	95.1
27	**6**{*2,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.08	107
28	**6**{*2,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	4.79	107
29	**6**{*3,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.77	107
30	**6**{*3,17*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.17	107
31	**6**{*2,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	4.5	107
32	**6**{*4,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.37	107
33	**6**{*1,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.61	107
34	**6**{*1,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.43	107
35	**6**{*2,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.17	107
36	**6**{*1,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	10.5	121

37	**6**{*2,2*}	Cc1nnc2[C@H](CC(=O)NCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.45	121
38	**6**{*4,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.33	121
39	**6**{*2,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.22	121
40	**6**{*3,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.81	121
41	**6**{*1,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.14	121
42	**6**{*3,1*}	Cc1nnc2[C@H](CC(=O)NCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	10.3	137
43	**6**{*1,16*}	Cc1nnc2[C@H](CC(=O)NCCCN(C)CCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.42	137
44	**6**{*3,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.35	137
45	**6**{*3,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.03	137
46	**6**{*1,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.75	137
47	**6**{*4,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.71	137
48	**6**{*1,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.52	137
49	**6**{*3,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.71	155
50	**6**{*3,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	11.5	155
51	**6**{*3,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.87	155
52	**6**{*4,17*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.91	155
53	**6**{*2,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.48	155
54	**6**{*4,15*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	10	155
55	**6**{*1,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	13.5	155

56	**6**{*3,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	10.5	175
57	**6**{*1,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.39	175
58	**6**{*1,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.6	175
59	**6**{*3,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	6.49	175
60	**6**{*2,7*}	Cc1nnc2[C@H](CC(=O)NCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.16	175
61	**6**{*2,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	11	175
62	**6**{*4,16*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	13.4	175
63	**6**{*2,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.38	175
64	**6**{*2,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.32	198
65	**6**{*2,8*}	Cc1nnc2[C@H](CC(=O)NCCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.18	198
66	**6**{*1,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	11.8	224
67	**6**{*4,13*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	12.5	224
68	**6**{*3,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	10.6	224
69	**6**{*3,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	8.22	253

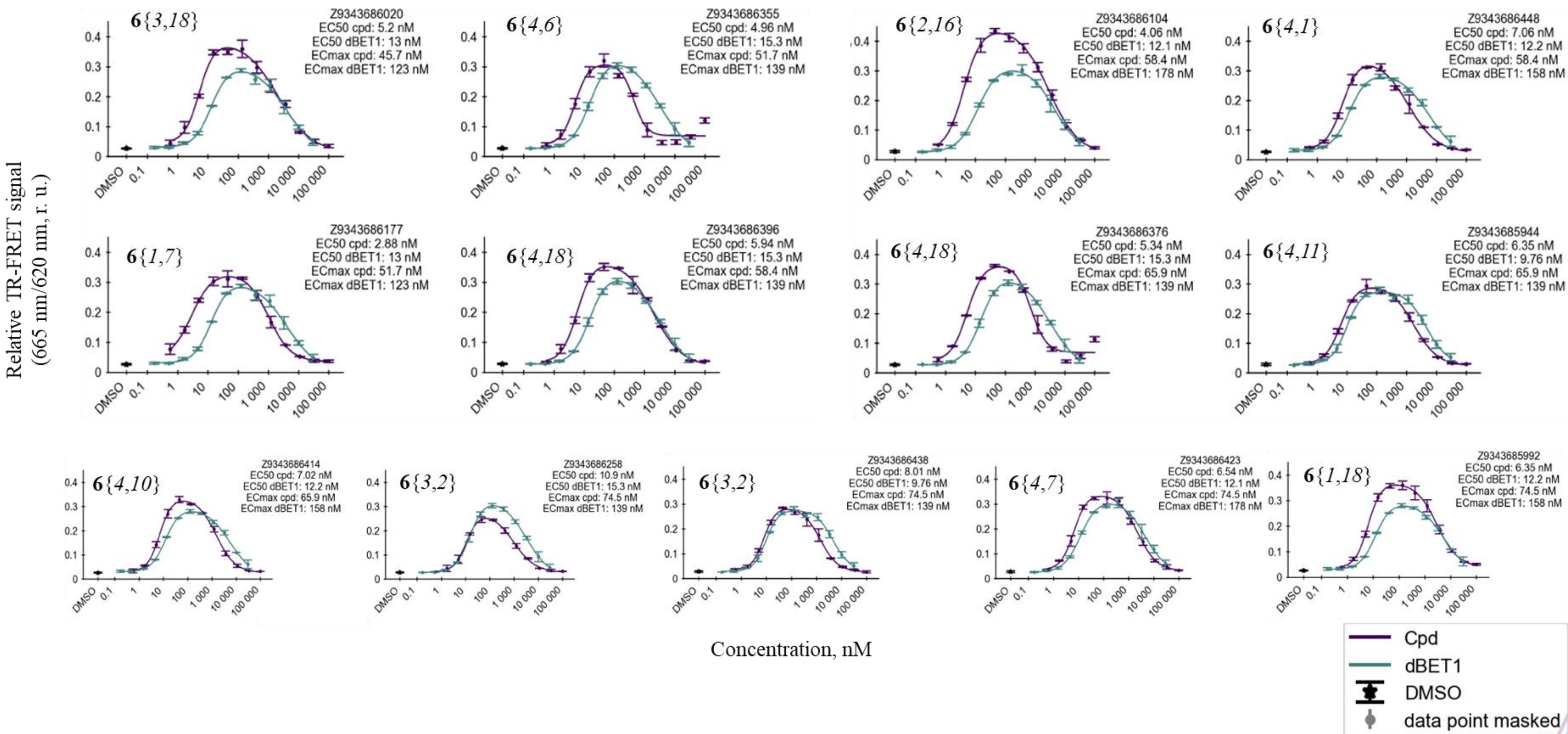
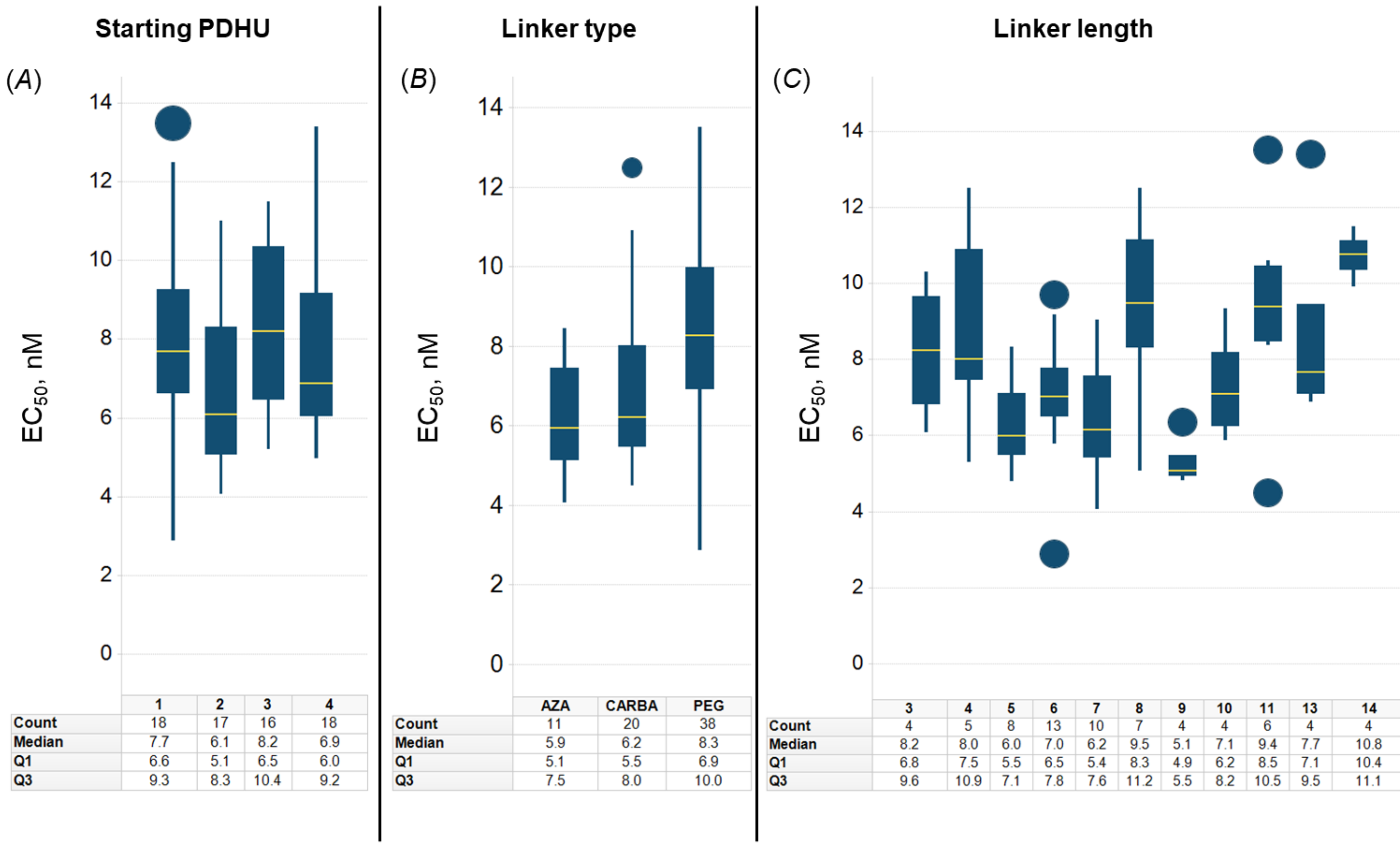


Figure S5. Curves for the ternary complex formation (TCF) induced by compounds **6**{*1–4*,*1–18*} with maximal ternary complex formation concentration (EC_{max}) below 80 nM. Fitting was performed using a Bell-shaped dose-response model.



	1	2	3	4
Count	18	17	16	18
Median	7.7	6.1	8.2	6.9
Q1	6.6	5.1	6.5	6.0
Q3	9.3	8.3	10.4	9.2

	AZA	CARBA	PEG
Count	11	20	38
Median	5.9	6.2	8.3
Q1	5.1	5.5	6.9
Q3	7.5	8.0	10.0

	3	4	5	6	7	8	9	10	11	13	14
Count	4	5	8	13	10	7	4	4	6	4	4
Median	8.2	8.0	6.0	7.0	6.2	9.5	5.1	7.1	9.4	7.7	10.8
Q1	6.8	7.5	5.5	6.5	5.4	8.3	4.9	6.2	8.5	7.1	10.4
Q3	9.6	10.9	7.1	7.8	7.6	11.2	5.5	8.2	10.5	9.5	11.1

Figure S6. SAR trends within the series of compounds **6**{*1–4*,*1–18*} regarding ternary complex formation (EC_{50}) shown as box-and-whiskers plots: (*A*) effect of starting PDHU **7**{*1–4*}; (*B*) effect of linker type (CARBA: olygomethylene linkers, PEG: oxygen-containing linkers, AZA: nitrogen-containing linkers); (*C*) effect of linker length (functional groups excluded). Yellow lines correspond to median average values within the subsets.

Table S6. BRD4 degradation by compounds **6**{*1–4*,*1–18*} in the HepG2 cell line at 30 μM

#	Compound	SMILES	Degradation, %	RSD, %
1	**6**{*1*,*1*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	68.8	6.0
2	**6**{*1*,*2*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	11.3	8.6
3	**6**{*1*,*3*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	97.4	1.5
4	**6**{*1*,*4*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	96.7	0.8
5	**6**{*1*,*5*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCCCCCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	97.0	2.2
6	**6**{*1*,*6*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	103.9	1.7
7	**6**{*1*,*7*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	51.8	5.2
8	**6**{*1*,*8*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	68.9	0.4
9	**6**{*1*,*9*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	91.1	1.1
10	**6**{*1*,*10*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	97.5	1.6
11	**6**{*1*,*11*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCOCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	75.3	3.8

12	**6**{*1,12*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	96.8	5.2
13	**6**{*1,13*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	99.5	0.5
14	**6**{*1,14*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	80.6	5.5
15	**6**{*1,15*}	CN(CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O |c:10|	–17.1	3.6
16	**6**{*1,16*}	CN(CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O |c:10|	–8.8	2.6
17	**6**{*1,17*}	CN(CCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O)CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1 |c:34|	3.0	4.9
18	**6**{*1,18*}	CN(CCCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCCCNC(=O)c1cc(C)cc(c1)N1CCC(=O)NC1=O |c:11|	–18.5	13.6
19	**6**{*2,1*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	37.7	10.8
20	**6**{*2,2*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	–14.2	2.1
21	**6**{*2,3*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	60.1	1.2
22	**6**{*2,4*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	96.8	3.6
23	**6**{*2,5*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCCCCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	94.9	2.3
24	**6**{*2,6*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	97.7	5.4

25	**6**{*2*,*7*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	85.0	0.9
26	**6**{*2*,*8*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	95.1	2.3
27	**6**{*2*,*9*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	89.6	3.4
28	**6**{*2*,*10*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	76.5	2.4
29	**6**{*2*,*11*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCOCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	91.2	2.8
30	**6**{*2*,*12*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	51.7	2.1
31	**6**{*2*,*13*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	95.9	0.6
32	**6**{*2*,*14*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	64.0	4.7
33	**6**{*2*,*16*}	CN(CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O |c:10|	2.6	6.2
34	**6**{*2*,*17*}	CN(CCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O)CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1 |c:34|	48.2	4.9
35	**6**{*2*,*18*}	CN(CCCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCCCNC(=O)c1cc(ccc1C)N1CCC(=O)NC1=O |c:11|	56.1	3.7
36	**6**{*3*,*1*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	–3.8	10.7
37	**6**{*3*,*2*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	3.7	9.1

38	**6**{*3,3*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	101.3	0.1
39	**6**{*3,4*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	103.2	0.1
40	**6**{*3,6*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	92.0	4.0
41	**6**{*3,7*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	90.1	1.1
42	**6**{*3,8*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	99.6	2.9
43	**6**{*3,9*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	99.7	0.5
44	**6**{*3,10*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	89.3	2.9
45	**6**{*3,11*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCOCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	98.6	3.1
46	**6**{*3,12*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	98.2	2.1
47	**6**{*3,13*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	99.1	2.3
48	**6**{*3,14*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	93.6	6.0
49	**6**{*3,16*}	CN(CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O |c:10|	–11.4	8.9

50	**6**{*3,17*}	CN(CCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1 |c:34|	20.8	3.1
51	**6**{*3,18*}	CN(CCCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O |c:11|	17.9	2.7
52	**6**{*4,1*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	47.9	1.3
53	**6**{*4,2*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	94.8	0.4
54	**6**{*4,3*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	76.7	6.7
55	**6**{*4,4*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	75.2	1.0
56	**6**{*4,5*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	77.8	2.3
57	**6**{*4,6*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	59.7	10.7
58	**6**{*4,7*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	75.3	2.9
59	**6**{*4,8*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	57.4	3.4
60	**6**{*4,9*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	62.9	6.7
61	**6**{*4,10*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	64.3	4.8
62	**6**{*4,11*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCOCCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	57.6	0.8

63	**6**{*4,12*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	29.8	4.9
64	**6**{*4,13*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	26.9	8.2
65	**6**{*4,14*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	7.2	8.7
66	**6**{*4,15*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	8.8	7.8
67	**6**{*4,16*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCOCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	13.7	8.0
68	**6**{*4,17*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCOCCOCCOCCOCCC(=O)Nc1ccc(N3CCC(=O)NC3=O)c(C)c1)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	24.1	4.9
69	**6**{*4,18*}	CN(CCCNC(=O)C[C@@H]1N=C(c2c(C)c(C)sc2-n2c(C)nnc12)c1ccc(Cl)cc1)CCCC(=O)Nc1ccc(N2CCC(=O)NC2=O)c(C)c1 |c:10|	58.6	1.9

Table S7. BRD4 degradation by compounds **6**{*1–4*,*1–18*} in the HepG2 cell line at 0.3 μM and at 30 nM

#	Compound	SMILES	At 30 nM		At 0.3 μM	
			Degradation, %	RSD, %	Degradation, %	RSD, %
1	**6**{*1,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	38.3	1.5	91.0	2.8
2	**6**{*1,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	17.1	2.5	73.9	6.7
3	**6**{*1,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	37.4	0.6	100.2	1.5
4	**6**{*1,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	14.6	5.0	77.2	4.3
5	**6**{*1,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	3.9	0.2	42.1	2.3
6	**6**{*1,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	7.1	2.0	39.9	3.8
7	**6**{*1,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	17.7	4.6	67.5	3.1
8	**6**{*1,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	18.0	11.1	54.3	4.8
9	**6**{*1,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	22.0	11.9	75.1	2.8
10	**6**{*1,14*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCOCCNC(=O)c3cc(C)cc(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	–2.0	11.1	32.5	0.5
11	**6**{*2,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.8	23.5	55.8	3.4
12	**6**{*2,4*}	Cc1nnc2[C@H](CC(=O)NCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	44.6	0.6	97.4	3.0
13	**6**{*2,5*}	Cc1nnc2[C@H](CC(=O)NCCCCCCCCCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	72.1	2.4	100.8	1.3
14	**6**{*2,6*}	Cc1nnc2[C@H](CC(=O)NCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	17.9	4.0	73.3	3.7
15	**6**{*2,9*}	Cc1nnc2[C@H](CC(=O)NCCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	15.4	9.6	75.6	3.4

16	**6**{*2,10*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	25.0	9.3	68.9	3.4
17	**6**{*2,11*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	18.2	6.5	81.8	1.9
18	**6**{*2,12*}	Cc1nnc2[C@H](CC(=O)NCCOCCOCCOCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	9.6	5.3	50.3	0.1
19	**6**{*2,13*}	Cc1nnc2[C@H](CC(=O)NCCCOCCOCCOCCCNC(=O)c3cc(ccc3C)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	21.3	1.8	81.9	5.3
20	**6**{*3,3*}	Cc1nnc2[C@H](CC(=O)NCCCCCNC(=O)c3ccc(C)c(c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	43.0	2.2	92.3	0.5
21	**6**{*3,4*}	Cc1sc-2c(c1C)C(=N[C@@H](CC(=O)NCCCCCCNC(=O)c1ccc(C)c(c1)N1CCC(=O)NC1=O)c1nnc(C)n-21)c1ccc(Cl)cc1 |c:8|	53.5	11.1	90.9	4.7
22	**6**{*4,2*}	Cc1nnc2[C@H](CC(=O)NCCCCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	3.3	8.2	51.9	3.8
23	**6**{*4,7*}	Cc1nnc2[C@H](CC(=O)NCCOCC(=O)Nc3ccc(c(C)c3)N3CCC(=O)NC3=O)N=C(c3ccc(Cl)cc3)c3c(C)c(C)sc3-n12	5.7	3.7	38.5	3.9

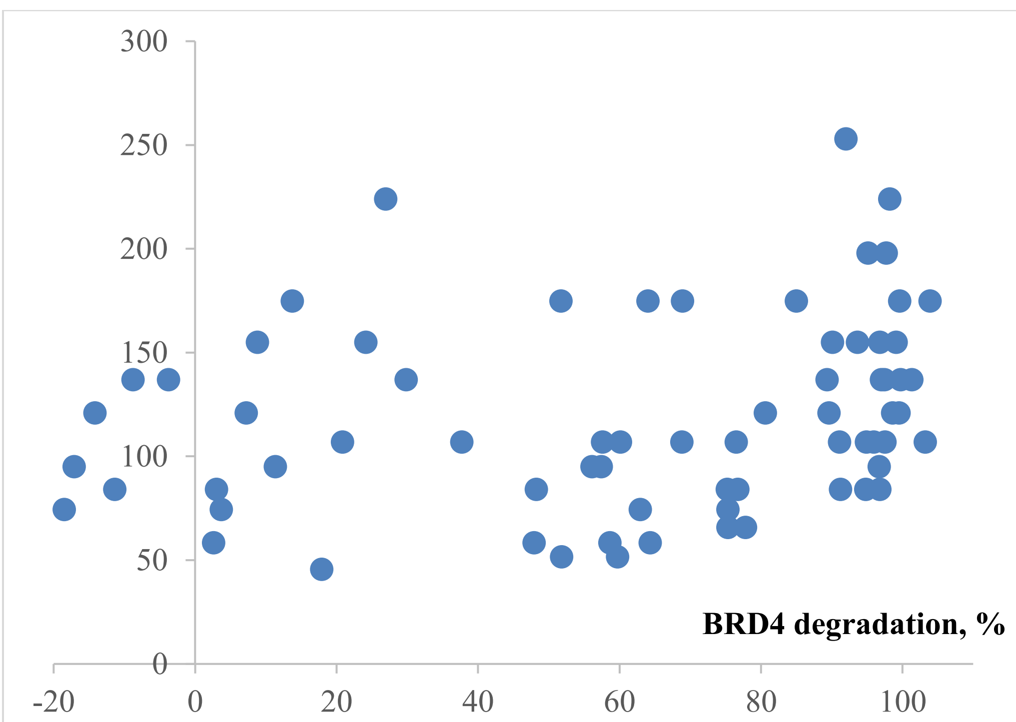
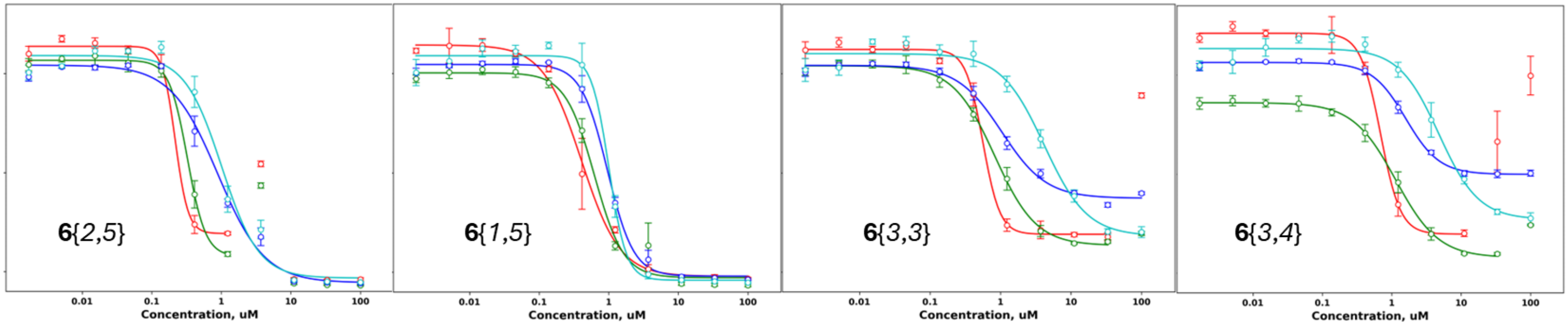


Figure S7. Absence of correlation between BRD4 degradation in the HepG2 cell line and maximal ternary complex formation concentration EC_{max} (the combined data from Tables S5 and S6)



6{2,5}

Cell line	EC50, uM	Slope	Color
HDF	0.217	-4.7	red
HepG2	0.326	-3.3	green
K562	0.890	-1.3	blue
U2-OS	1.0	-1.6	cyan

6{1,5}

Cell line	EC50, uM	Slope	Color
HDF	0.406	-1.6	red
HepG2	0.623	-2.1	green
K562	0.959	-2.3	blue
U2-OS	1.0	-3.5	cyan

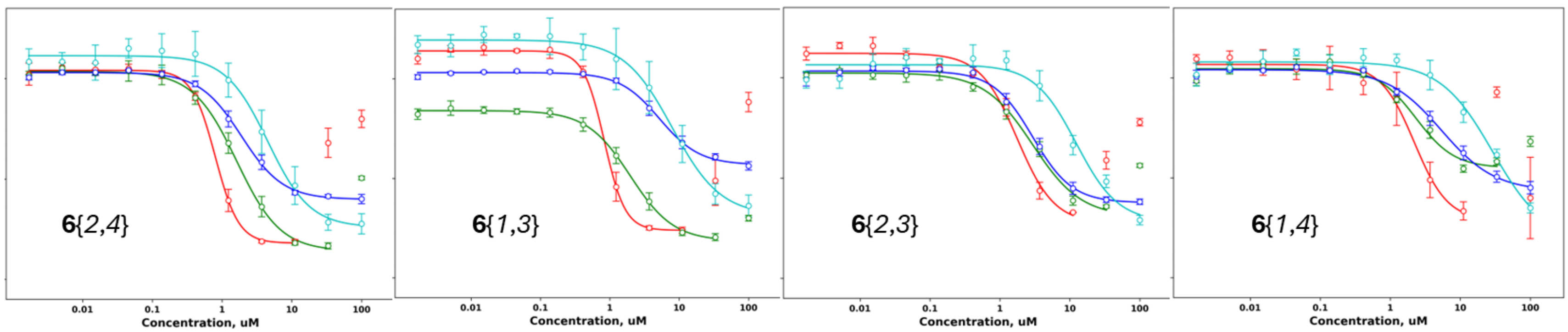
6{3,3}

Cell line	EC50, uM	Slope	Color
HDF	0.561	-3.6	red
HepG2	0.826	-1.5	green
K562	1.0	-1.4	blue
U2-OS	4.2	-1.4	cyan

6{3,4}

Cell line	EC50, uM	Slope	Color
HDF	0.690	-3.0	red
HepG2	1.1	-1.4	green
K562	N/D	-1.8	blue
U2-OS	4.8	-1.5	cyan

Viability, %



6{2,4}

Cell line	EC50, uM	Slope	Color
HDF	0.801	-2.6	red
HepG2	1.6	-1.4	green
K562	1.9	-1.5	blue
U2-OS	4.5	-1.4	cyan

6{1,3}

Cell line	EC50, uM	Slope	Color
HDF	0.832	-2.9	red
HepG2	2.0	-1.4	green
K562	N/D	-1.5	blue
U2-OS	8.0	-1.2	cyan

6{2,3}

Cell line	EC50, uM	Slope	Color
HDF	1.8	-1.6	red
HepG2	2.9	-1.3	green
K562	2.9	-1.5	blue
U2-OS	12.4	-1.5	cyan

6{1,4}

Cell line	EC50, uM	Slope	Color
HDF	2.2	-1.8	red
HepG2	N/D	-1.6	green
K562	5.4	-1.1	blue
U2-OS	29.1	-1.2	cyan

Concentration, µM

Figure S8. Dose-response curves obtained in cell viability assay.

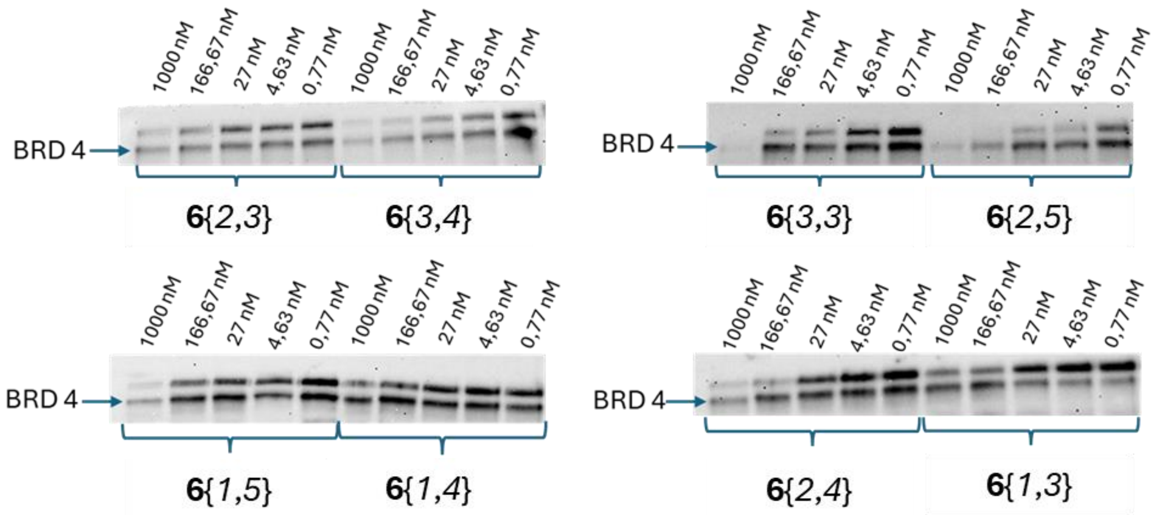


Figure S9. Western blot analysis of BRD4 degradation induced by tested PROTACS in HepG2 cells. The blotograms show dose-dependent degradation of BRD4 following treatment with the tested compounds.

EXPERIMENTAL SECTION

General (chemistry). The solvents were purified according to the standard procedures.[1] Compounds **7–9** were obtained from Enamine stock. All other starting materials were received from commercial sources. ^{1}H NMR spectra were recorded on an Agilent ProPulse 600 spectrometer at 600 MHz, a Bruker 170 Avance 500 spectrometer at 500 MHz, or a Varian Unity Plus 400 spectrometer at 400 MHz using DMSO-d_6, CD_3OD, or D_2O as solvents. ^{1}H NMR chemical shifts are reported in ppm (δ scale) downfield from TMS and are referenced using residual NMR solvent peaks at 2.50 in DMSO-d_6, 3.31 in CD_3OD, and 4.79 for ^{1}H in D_2O. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). HPLC purification was performed using Agilent 1260 Infinity systems equipped with DAD and mass-detector, Waters Sunfire C18 OBD Pre Column, 100 Å, 5 μm, 19 mm × 100 mm with SunFire C18 Prep Guard Cartridge, 100 Å, 10 μm, 19 mm × 10 mm, gradient deionized water – HPLC-grade acetonitrile or methanol with or without 0.1% formic acid as eluent.

Representative procedure for the synthesis of intermediates 10: *N*-(4-aminobutyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3*,*2*}·HCl). Carboxylic acid **7**{*3*} (1.0 g, 4.03 mmol) was dissolved in dry DMF (30 mL), and [(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylidene]dimethylazanium hexafluorophosphate (HATU, 1.99 g, 5.24 mmol) and iPr$_2$NEt (2.46 mL, 14.1 mmol, 3.5 equiv) were added to the resulting solution. After stirring at rt for 30 min, amine **8**{*2*} (758 mg, 4.03 mmol) was added. The reaction mixture was stirred at 60 °C for 16 h. After the reaction completion (according to LC-MS), the solvent was evaporated, water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (200 mL). The organic layer was washed with 10% aq citric acid (100 mL) and brine (100 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give corresponding crude *N*-Boc derivative (2.01 g, 75% purity) that was used in the next step without purification. It was dissolved in CH_3CN (50 mL), and 2 M HCl in 1,4-dioxane (5.02 mL, 10.0 mmol, 2.8

equiv) was added in one portion. The reaction mixture was stirred at rt for 16 h. After that, the precipitate formed was filtered, washed with CH_3CN and dried to give target product **10**{*3,2*}·HCl. Beige solid. Yield 0.084 g, 59%. ^{1}H NMR (500 MHz, CD_3OD) δ 7.81 – 7.63 (m, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.72 – 3.64 (m, 1H), 3.42 (s, 2H), 3.04 – 2.73 (m, 4H), 2.33 (s, 3H), 1.71 – 1.67 (m, 4H) ppm. MS (EI, m/z): 319.2 [M^++H].

***N*-(3-Aminopropyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,1*}·HCl).** Beige solid. Yield 0.416 g (9%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.70 (t, *J* = 5.6 Hz, 1H), 7.94 (br. s, 3H), 7.60 (s, 1H), 7.56 (s, 1H), 7.31 (s, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.31 (q, *J* = 6.2 Hz, 2H), 2.84 – 2.77 (m, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 1.80 (q, *J* = 7.0 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.02, 166.43, 152.60, 142.44, 138.52, 135.19, 129.20, 125.71, 121.84, 45.03, 37.18, 36.67, 31.55, 27.71, 21.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{15}H_{20}N_4O_3^+$: 305.1531; Found: 305.1604.

***N*-(4-Aminobutyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,2*}·HCl).** Colorless solid. Yield 0.617 g (15%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.50 (br. s, 1H), 7.69 (br. s, 3H), 7.56 (s, 1H), 7.52 (s, 1H), 7.30 (s, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.27 – 3.24 (m, 2H), 2.83 – 2.73 (m, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 1.54 (s, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.03, 166.14, 152.61, 142.40, 138.46, 135.48, 129.08, 125.71, 121.84, 45.05, 38.95, 38.90, 31.55, 26.54, 24.94, 21.33 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_3^+$: 319.1686; Found: 319.1759.

***N*-(5-Aminopentyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,3*}·HCl).** Colorless solid. Yield 0.453 g (29%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.52 (t, *J* = 5.2 Hz, 1H), 8.01 (br. s, 3H), 7.59 (s, 1H), 7.55 (s, 1H), 7.28 (s, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.23

(q, *J* = 6.3 Hz, 2H), 2.77 – 2.72 (m, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.33 (s, 3H), 1.54 (dp, *J* = 30.1, 7.3 Hz, 4H), 1.34 (p, *J* = 7.1 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.02, 166.08, 152.61, 142.38, 138.43, 135.59, 129.02, 125.71, 121.83, 45.05, 39.34, 39.07, 31.55, 28.95, 27.10, 23.74, 21.32 ppm. MS (EI, m/z): 333.2 [M$^+$+H]. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_3^+$: 333.1840; Found: 333.1914.

***N*-(6-Aminohexyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,4*}·HCl).** Beige solid. Yield 0.592 g (33%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.47 (br. s, 1H), 7.84 (s, 3H), 7.57 (s, 1H), 7.53 (s, 1H), 7.29 (s, 1H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.25 – 3.19 (m, 2H), 2.79 – 2.65 (m, 4H), 2.34 (s, 3H), 1.57 – 1.44 (m, 4H), 1.30 (s, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.03, 166.05, 152.61, 142.38, 138.44, 135.61, 128.98, 125.68, 121.80, 45.03, 39.08, 31.55, 29.36, 27.34, 26.41, 26.00, 21.33 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_3^+$: 347.1997; Found: 347.2071.

***N*-(11-Aminoundecyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,5*}·HCl).** Beige solid. Yield 0.539 g (30%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.42 (br. s, 1H), 7.75 (br. s, 3H), 7.55 (s, 1H), 7.51 (s, 1H), 7.28 (s, 1H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.24 – 3.19 (m, 2H), 2.77 – 2.65 (m, 4H), 2.34 (s, 3H), 1.50 (d, *J* = 13.6 Hz, 4H), 1.25 (d, *J* = 15.7 Hz, 14H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.02, 165.99, 152.60, 142.38, 138.42, 135.65, 128.96, 125.67, 121.77, 45.03, 39.65, 39.15, 31.55, 29.54, 29.40, 29.33, 29.26, 29.22, 28.96, 27.37, 26.93, 26.27, 21.33 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{23}H_{37}N_4O_3^+$: 417.2779; Found: 417.2851.

***N*-(2-(2-Aminoethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,6*}·HCl).** Yellowish solid. Yield 0.954 g (33%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.57 (br. s, 1H), 7.97 (br. s, 3H), 7.61 (s, 1H), 7.57 (s, 1H), 7.30 (s, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.64 – 3.54 (m, 4H), 3.45 (q, *J* = 5.5 Hz, 2H), 3.01 – 2.90 (m, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.07, 166.45, 152.64, 142.40, 138.49, 135.37, 129.25, 125.93, 121.98, 69.42, 66.65, 45.10, 39.04, 31.61, 21.34 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_4^+$: 335.1634; Found: 335.1707.

***N*-(3-(2-Aminoethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,7*}·HCl)**. Yellowish solid. Yield 0.953 g (31%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.58 (t, *J* = 5.4 Hz, 1H), 8.02 (br. s, 3H), 7.60 (s, 1H), 7.56 (s, 1H), 7.29 (s, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 3.45 (t, *J* = 6.2 Hz, 2H), 3.34 – 3.29 (m, 2H), 2.98 – 2.92 (m, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 1.76 (p, *J* = 6.3 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.05, 166.25, 152.61, 142.36, 138.45, 135.46, 129.10, 125.78, 121.83, 68.32, 66.76, 45.06, 38.90, 36.65, 31.55, 29.57, 21.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1788; Found: 349.1861.

***N*-(2-(3-Aminopropoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,8*}·HCl)**. Yellowish solid. Yield 0.584 g (19%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.54 (br. s, 1H), 7.76 (br. s, 3H), 7.58 (s, 1H), 7.54 (s, 1H), 7.30 (s, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.53 – 3.47 (m, 6H), 2.86 – 2.79 (m, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 1.77 (p, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 171.05, 166.34, 152.61, 142.34, 138.46, 135.28, 129.12, 125.76, 121.79, 69.19, 67.61, 45.01, 37.03, 31.53, 27.55, 21.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1790; Found: 349.1863.

***N*-(3-(3-Aminopropoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,9*}·HCl)**. Yellowish solid. Yield 0.327 g (9%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.57 (br. s, 1H), 8.01 (br. s, 3H), 7.59 (s, 1H), 7.55 (s, 1H), 7.29 (s, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.41 (dt, *J* = 12.9, 5.9 Hz, 4H), 3.29 (q, *J* = 6.2 Hz, 2H), 2.86 – 2.78 (m, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.33 (s, 3H), 1.76 (ddt, *J* = 30.7, 12.5, 6.2 Hz, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 171.07, 166.16, 152.63, 142.37, 138.46, 135.47, 129.06, 125.71, 121.80, 68.17, 67.43, 45.02, 37.02, 36.82, 31.54, 29.82, 27.65, 21.35 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_4^+$: 363.1945; Found: 363.2019.

***N*-(2-(2-(2-Aminoethoxy)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,10*}·HCl)**. Yellowish solid. Yield 0.490 g (29%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.51 (br. s, 1H), 7.80 (br. s, 3H), 7.57 (s, 1H), 7.53 (s, 1H), 7.30 (s, 1H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.60 – 3.54 (m, 6H), 3.52 (t, *J* = 6.0 Hz, 2H), 3.43 – 3.38 (m, 2H), 2.96 – 2.90 (m, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.04, 166.27, 152.62, 142.40, 138.50, 135.28, 129.15, 125.77, 121.88, 70.13, 69.90, 69.32, 67.06, 45.03, 38.93, 31.55, 21.31 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_5^+$: 379.1896; Found: 379.1970.

***N*-(3-(2-(3-Aminopropoxy)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,11*}·HCl)**. Yellow oil. Yield 0.557 g (30%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.47 (br. s, 1H), 7.78 (br. s, 3H), 7.56 (s, 1H), 7.52 (s, 1H), 7.29 (s, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.50 – 3.40 (m, 8H), 3.31 – 3.26 (m, 2H), 2.83 – 2.80 (m, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 3H), 1.75 (dt, *J* = 13.2, 6.7 Hz, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.02, 166.13, 152.61, 142.39, 138.46, 135.53, 129.03, 125.68, 121.80, 69.93, 69.89, 68.68, 67.78, 45.03, 37.10, 31.55, 29.84, 27.60, 21.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_5^+$: 407.2207; Found: 407.2280.

***N*-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,12*}·HCl).** Beige oil. Yield 0.88 g (25%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.53 (br. s, 1H), 7.88 (br. s, 3H), 7.58 (s, 1H), 7.54 (s, 1H), 7.30 (s, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.60 – 3.54 (m, 4H), 3.52 – 3.48 (m, 8H), 3.39 (q, *J* = 6.2 Hz, 2H), 2.94 – 2.90 (m, 2H), 2.70 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.03, 166.26, 152.61, 142.40, 138.49, 135.31, 129.13, 125.73, 121.84, 70.16, 70.11, 70.08, 70.02, 69.31, 67.05, 45.03, 38.93, 31.55, 21.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_6^+$: 423.2155; Found: 423.2229.

***N*-(3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,13*}·HCl)**. Yellow oil. Yield 0.477 g (30%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.44 (br. s, 1H), 7.66 (br. s, 3H), 7.55 (s, 1H), 7.51 (s, 1H), 7.29 (s, 1H), 3.78 (t, J = 6.6 Hz, 2H), 3.52 – 3.40 (m, 12H), 3.32 – 3.24 (m, 2H), 2.87 – 2.76 (m, 2H), 2.70 (t, J = 6.7 Hz, 2H), 2.34 (s, 3H), 1.78 – 1.70 (m, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.02, 166.12, 152.60, 142.39, 138.46, 135.50, 129.00, 125.62, 121.76, 70.19, 70.08, 69.97, 69.90, 68.68, 67.78, 44.99, 37.20, 37.10, 31.52, 29.79, 27.58, 21.31 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_6^+$: 451.2469; Found: 451.2542.

***N*-(14-Amino-3,6,9,12-tetraoxatetradecyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide hydrochloride (10{*1,14*}·HCl)**. Brownish oil. Yield 0.705 g (23%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.54 (t, J = 5.5 Hz, 1H), 7.94 (br. s, 3H), 7.58 (s, 1H), 7.54 (s, 1H), 7.30 (s, 1H), 3.78 (t, J = 6.6 Hz, 2H), 3.58 (t, J = 5.3 Hz, 2H), 3.52 – 3.47 (m, 14H), 3.39 (q, J = 5.7 Hz, 2H), 2.93 (t, J = 8.1 Hz, 2H), 2.70 (t, J = 6.6 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.04, 166.26, 152.60, 142.39, 138.48, 135.32, 129.13, 125.73, 121.81, 70.21, 70.19, 70.16, 70.09, 70.05, 70.04, 69.30, 67.04, 45.03, 38.94, 31.54, 21.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_7^+$: 467.2418; Found: 467.2491.

***N*-(2-((3-Aminopropyl)(methyl)amino)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide dihydrochloride (10{*1,15*}·2HCl)**. Yellowish solid. Yield 0.760 g (16%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.40 (s, 1H), 10.25 (br. s, 1H),8.83 (br. s, 1H), 7.90 (br. s, 3H), 7.64 (s, 1H), 7.60

(s, 1H), 7.34 (s, 1H), 3.79 (t, J = 6.7 Hz, 2H), 3.70 – 3.58 (m, 2H), 3.32 – 3.07 (m, 2H), 2.96 – 2.84 (m, 2H), 2.84 – 2.76 (m, 2H), 2.70 (t, J = 6.6 Hz, 2H), 2.35 (s, 3H), 2.06 (s, 3H), 2.02 – 1.91 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.04, 166.21, 152.62, 142.38, 138.47, 135.47, 129.10, 125.76, 121.86, 54.82, 54.41, 45.06, 38.47, 31.55, 26.66, 24.53, 21.33, 20.78 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{28}N_5O_3^+$: 362.2105; Found: 362.2180.

***N*-(3-((3-Aminopropyl)(methyl)amino)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide dihydrochloride (10{*1,16*}·2HCl)**. Yellow oil. Yield 0.658 g (12%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 10.32 (br. s, 1H), 8.67 (br. s, 1H), 7.95 (br. s, 3H), 7.60 (s, 1H), 7.56 (s, 1H), 7.31 (s, 1H), 3.79 (t, J = 6.8 Hz, 2H), 3.64 – 3.42 (m, 2H), 3.25 – 2.97 (m, 6H), 2.92 – 2.79 (m, 2H), 2.73 – 2.65 (m, 5H), 2.35 (s, 3H), 2.07 – 1.82 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.04, 166.34, 152.61, 142.41, 138.50, 135.17, 129.24, 125.79, 121.89, 53.55, 52.32, 45.06, 36.97, 36.63, 31.55, 24.12, 22.04, 21.33 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{19}H_{30}N_5O_3^+$: 376.2261; Found: 376.2335.

***N*-(4-((3-Aminopropyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide dihydrochloride (10{*1,17*}·2HCl)**. Yellowish oil. Yield 0.780 g (28%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.67 (br. s, 1H), 10.37 (s, 1H), 8.61 (t, J = 5.4 Hz, 1H), 8.17 (br. s, 3H), 7.61 (s, 1H), 7.57 (s, 1H), 7.29 (s, 1H), 3.79 (t, J = 6.6 Hz, 2H), 3.35 – 3.13 (m, 4H), 3.12 – 2.98 (m, 2H), 2.93 – 2.83 (m, 2H), 2.73 – 2.66 (m, 5H), 2.34 (s, 3H), 2.04 – 1.98 (m, 2H), 1.77 – 1.68 (m, 2H), 1.59 – 1.52 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.06, 166.23, 152.61, 142.37, 138.47, 135.45, 129.11, 125.77, 121.85, 54.98, 52.24, 45.05, 38.87, 36.64, 31.55, 26.62, 22.01, 21.33, 21.06 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{32}N_5O_3^+$: 390.2422; Found: 390.2494.

***N*-(4-((4-Aminobutyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide dihydrochloride (10{*1,18*}·2HCl)**. Brown oil. Yield 0.225 g (4%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.47 (s, 1H), 10.38 (s, 1H), 8.60 (s, 1H), 8.05 (s, 3H), 7.60 (s, 1H), 7.56 (s, 1H), 7.30 (s, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.29 – 3.24 (m, 2H), 3.14 – 2.89 (m, 4H), 2.82 – 2.75 (m, 2H), 2.73 – 2.65 (m, 5H), 2.34 (s, 3H), 1.77 – 1.68 (m, 4H), 1.59 – 1.53 (m, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.05, 166.22, 152.62, 142.38, 138.47, 135.47, 129.10, 125.76, 121.86, 54.82, 54.41, 45.06, 38.86, 38.47, 31.55, 26.66, 24.53, 21.33, 21.14, 20.78 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{21}H_{34}N_5O_3^+$: 404.2574; Found: 404.2648.

***N*-(3-Aminopropyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,1*}·HCl)**. Beige solid. Yield 0.542 g (14%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H), 8.45 (t, *J* = 5.7 Hz, 1H), 7.96 (br. s, 3H), 7.30 – 7.26 (m, 2H), 7.23 (d, *J* = 8.2 Hz, 1H), 3.77 (t, *J* = 6.7 Hz, 2H), 3.27 (q, *J* = 6.4 Hz, 2H), 2.92 – 2.78 (m, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.31 (s, 3H), 1.79 (p, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.06, 169.17, 152.61, 139.92, 137.64, 133.24, 131.13, 126.86, 124.31, 45.06, 37.22, 36.53, 31.56, 27.77, 19.47 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{15}H_{21}N_4O_3^+$: 305.1529; Found: 305.1601.

***N*-(4-Aminobutyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,2*}·HCl)**. Beige solid. Yield 0.469 g (6%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.33 (t, *J* = 5.5 Hz, 1H), 7.95 (br. s, 3H), 7.29 – 7.20 (m, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 3.21 (q, *J* = 6.1 Hz, 2H), 2.80 – 2.76 (m, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H), 1.56 (dt, *J* = 22.4, 6.8 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.04, 168.89, 152.57, 139.86, 137.97, 133.15, 131.04, 126.71, 124.21, 45.04, 38.92, 38.67, 31.53, 26.56, 24.97, 19.42 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_3^+$: 319.1687; Found: 319.1760.

***N*-(5-Aminopentyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,3*}·HCl)**. Beige solid. Yield 0.468 g (12%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.27 (s, 1H), 7.90 (br. s, 3H), 7.31 – 7.15 (m, 3H), 3.78 – 3.74 (m, 2H), 3.20 – 3.17 (m, 2H), 2.76 – 2.72 (m, 2H), 2.71 – 2.67 (m, 2H), 2.29 (s, 3H), 1.59 – 1.55 (m, 2H), 1.51 – 1.48 (m, 2H), 1.36 – 1.32 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.04, 168.79, 152.57, 139.82, 138.03, 133.05, 131.00, 126.59, 124.18, 45.00, 39.03, 31.51, 28.89, 27.00, 23.72, 19.36 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_3^+$: 333.1845; Found: 333.1919.

***N*-(6-Aminohexyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,4*}·HCl)**. Yellowish oil. Yield 0.141 g (11%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.27 (t, *J* = 5.5 Hz, 1H), 7.86 (br. s, 3H), 7.28 – 7.19 (m, 3H), 3.77 – 3.76 (m, 2H), 3.19 (q, *J* = 6.6 Hz, 2H), 2.77 – 2.66 (m, 4H), 2.29 (s, 3H), 1.56 – 1.45 (m, 4H), 1.37 – 1.26 (m, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.06, 168.77, 152.57, 139.82, 138.10, 132.96, 130.99, 126.50, 124.13, 44.96, 39.13, 39.04, 31.48, 29.30, 27.33, 26.38, 25.96, 19.33 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_3^+$: 347.1996; Found: 347.2069.

***N*-(11-Aminoundecyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,5*}·HCl)**. Yellowish solid. Yield 0.521 g (7%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.24 (t, *J* = 5.4 Hz, 1H), 7.84 (br. s, 3H), 7.28 – 7.19 (m, 3H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.20 – 3.14 (m, 2H), 2.73 – 2.66 (m, 4H), 2.28 (s, 3H), 1.53 – 1.46 (m, 4H), 1.29 – 1.23 (m, 14H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.02, 168.73, 152.56, 139.83, 138.17, 132.97, 130.97, 126.52, 124.12, 44.98, 39.25, 39.13, 31.50, 29.48, 29.42, 29.31, 29.26, 29.15, 28.98, 27.36, 26.86, 26.28, 19.29 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{23}H_{37}N_4O_3^+$: 417.2777; Found: 417.2850.

***N*-(2-(2-Aminoethoxy)ethyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,6*}·HCl)**. Beige solid. Yield 0.490 g (15%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.36 (t, *J* = 5.3 Hz, 1H), 8.02 (br. s, 3H), 7.29 – 7.20 (m, 3H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.61 (t, *J* = 5.1 Hz, 2H), 3.54 (t, *J* = 5.6 Hz, 2H), 3.41 (q, *J* = 5.4 Hz, 2H), 2.97 – 2.96 (m, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.06, 169.01, 152.59, 139.83, 137.67, 133.26, 131.04, 126.83, 124.37, 69.40, 66.61, 45.01, 39.08, 38.97, 31.54, 19.39 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_4^+$: 335.1633; Found: 335.1708.

***N*-(3-(2-Aminoethoxy)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,7*}·HCl)**. Yellowish solid. Yield 0.790 g (17%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.33 (t, *J* = 5.6 Hz, 1H), 7.96 (br. s, 3H), 7.29 – 7.20 (m, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 3.48 (t, *J* = 6.2 Hz, 2H), 3.29 (q, *J* = 6.5 Hz, 2H), 2.96 (p, *J* = 5.4 Hz, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H), 1.75 (p, *J* = 6.4 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.05, 168.95, 152.59, 139.85, 137.92, 133.10, 131.04, 126.64, 124.26, 68.34, 66.78, 45.01, 38.87, 36.39, 31.52, 29.60, 19.40 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1789; Found: 349.1862.

***N*-(2-(3-Aminopropoxy)ethyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,8*}·HCl)**. Yellowish oil. Yield 0.198 g (12%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H), 8.33 (br. s, 1H), 7.77 (br. s, 3H), 7.25 (q, *J* = 8.5 Hz, 3H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.52 – 3.51 (m, 4H), 3.39 – 3.36 (m, 2H), 2.86 – 2.81 (m, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.30 (s, 3H), 1.81 – 1.75 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.04, 169.06, 152.60, 139.85, 137.82, 133.12, 131.06, 126.61, 124.23, 69.25, 67.66, 44.99, 40.53, 39.24, 37.16, 31.52, 27.63, 19.33 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1791; Found: 349.1864.

***N*-(3-(3-Aminopropoxy)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,9*}·HCl).** Yellowish oil. Yield 0.455 g (19%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.29 (t, *J* = 5.6 Hz, 1H), 7.82 (br. s, 3H), 7.29 – 7.20 (m, 3H), 3.76 (t, *J* = 6.7 Hz, 2H), 3.42 (q, *J* = 6.2 Hz, 2H), 3.26 (q, *J* = 6.6 Hz, 2H), 2.86 – 2.81 (m, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 2H), 1.75 (dp, *J* = 31.2, 6.3 Hz, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.03, 168.92, 152.59, 139.88, 137.99, 133.07, 131.05, 126.60, 124.21, 68.13, 67.55, 45.00, 37.15, 36.50, 31.52, 29.80, 27.66, 19.35 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_4^+$: 363.1951; Found: 363.2022.

***N*-(2-(2-(2-Aminoethoxy)ethoxy)ethyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,10*}·HCl).** Yellowish oil. Yield 0.245 g (76%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H), 8.33 (t, *J* = 5.6 Hz, 1H), 7.96 (br. s, 3H), 7.29 – 7.20 (m, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 3.59 (t, *J* = 5.3 Hz, 2H), 3.56 (s, 4H), 3.51 (t, *J* = 6.0 Hz, 2H), 3.37 (q, *J* = 5.8 Hz, 2H), 2.92 (d, *J* = 5.4 Hz, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.03, 169.02, 152.59, 139.85, 137.78, 133.18, 131.08, 126.65, 124.26, 70.15, 69.84, 69.31, 67.08, 44.99, 39.22, 38.98, 31.52, 19.33 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_5^+$: 379.1896; Found: 379.1971.

***N*-(3-(2-(3-Aminopropoxy)ethoxy)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,11*}·HCl).** Beige solid. Yield 0.445 g (14%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H), 8.28 (br. s, 1H), 7.86 (br. s, 3H), 7.28 – 7.19 (m, 3H), 3.76 (t, *J* = 6.2 Hz, 2H), 3.50 – 3.42 (m, 8H), 3.29 – 3.17 (m, 2H), 2.82 – 2.79 (m, 2H), 2.69 (t, *J* = 6.3 Hz, 2H), 2.29 (s, 3H), 1.80 – 1.74 (m, 2H), 1.74 – 1.69 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.06, 168.86, 152.60, 139.87, 138.02, 133.10, 131.04, 126.63, 124.23, 69.94, 68.62, 67.78, 45.03, 37.01, 36.74, 31.54, 29.84, 27.61, 19.37 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_5^+$: 407.2205; Found: 407.2277.

***N*-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)ethyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,12*}·HCl).** Yellowish oil. Yield 0.299 g (12%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.29 (t, *J* = 5.5 Hz, 1H), 7.89 (br. s, 3H), 7.29 – 7.20 (m, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 3.58 (t, *J* = 5.3 Hz, 2H), 3.55 – 3.48 (m, 10H), 3.40 – 3.32 (m, 2H), 2.97 – 2.91 (m, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.03, 169.00, 152.58, 139.85, 137.81, 133.18, 131.07, 126.69, 124.23, 70.21, 70.12, 70.09, 69.97, 69.29, 67.09, 45.00, 40.53, 39.25, 38.99, 31.52, 19.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_6^+$: 423.2159; Found: 423.2231.

***N*-(3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,13*}·HCl).** Yellowish oil. Yield 0.351 g (11%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.26 (br. s, 1H), 7.81 (br. s, 3H), 7.28 – 7.21 (m, 3H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.51 – 3.45 (m, 12H), 3.29 – 3.20 (m, 2H), 2.85 – 2.78 (m, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.29 (s, 3H), 1.78 – 1.69 (m, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.03, 168.86, 152.58, 139.88, 133.06, 131.04, 126.60, 124.19, 70.20, 70.11, 70.02, 69.92, 68.64, 67.80, 45.01, 40.53, 37.18, 36.77, 31.51, 29.81, 27.60, 19.32 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_6^+$: 451.2471; Found: 451.2544.

***N*-(14-Amino-3,6,9,12-tetraoxatetradecyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide hydrochloride (10{*2,14*}·HCl).** Brown oil. Yield 0.340 g (10%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.29 (t, *J* = 5.5 Hz, 1H), 7.86 (s, 3H), 7.29 – 7.20 (m, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 3.58 (t, *J* = 5.2 Hz, 2H), 3.56 – 3.47 (m, 14H), 3.38 – 3.32 (m, 2H), 2.96 – 2.92 (m, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.03, 169.00, 152.58, 139.85, 137.82, 133.18, 131.06, 126.70, 124.21, 70.22, 70.20, 70.11, 70.07, 69.99, 69.29, 67.08, 45.00, 40.53, 39.25, 38.99, 31.52, 19.31 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_7^+$: 467.2423; Found: 467.2496.

***N*-(3-((3-Aminopropyl)(methyl)amino)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide dihydrochloride (10{*2,16*}·2HCl)**. Yellowish oil. Yield 0.1 g (5%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.71 (br. s, 1H), 10.37 (s, 1H), 8.46 (t, *J* = 5.5 Hz, 1H), 8.11 (br. s, 3H), 7.30 – 7.27 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 3.32 – 3.16 (m, 4H), 3.14 – 2.98 (m, 2H), 2.95 – 2.79 (m, 3H), 2.73 – 2.67 (m, 6H), 2.32 (s, 3H), 2.08 – 1.86 (m, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.04, 169.11, 152.59, 139.88, 137.53, 133.27, 126.83, 124.31, 53.59, 52.43, 45.02, 40.53, 36.68, 31.53, 22.16, 19.48 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{19}H_{30}N_5O_3^+$: 376.2261; Found: 376.2334.

***N*-(4-((3-Aminopropyl)(methyl)amino)butyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide dihydrochloride (10{*2,17*}·2HCl)**. Yellowish oil. Yield 0.077 g (2%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.63 (br. s, 1H), 10.35 (s, 1H), 8.36 (s, 1H), 8.07 (br. s, 3H), 7.29 – 7.20 (m, 3H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.25 – 3.19 (m, 4H), 3.13 – 2.96 (m, 2H), 2.95 – 2.79 (m, 2H), 2.73 – 2.67 (m, 5H), 2.30 (s, 3H), 2.07 – 1.91 (m, 2H), 1.79 – 1.64 (m, 2H), 1.60 – 1.46 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 171.05, 168.93, 152.57, 139.86, 137.89, 133.10, 131.04, 126.68, 124.24, 55.00, 52.26, 45.01, 38.58, 36.65, 31.50, 26.68, 22.05, 21.08, 19.38 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{32}N_5O_3^+$: 390.2425; Found: 390.2498.

***N*-(4-((4-Aminobutyl)(methyl)amino)butyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide dihydrochloride (10{*2,18*}·2HCl).** Beige solid. Yield 0.038 g (1%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.27 (br. s, 1H), 7.28 – 7.19 (m, 3H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.22 – 3.17 (m, 4H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.30 – 2.20 (m, 7H), 2.08 (s, 3H), 1.50 – 1.40 (m, 4H), 1.36 – 1.32 (m, 4H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.03, 168.81, 152.60, 139.90, 138.27, 133.02, 131.01, 126.53, 124.15, 57.42, 57.28, 45.04, 42.19, 40.47, 40.30, 40.13, 31.55, 27.51, 24.70, 24.59, 19.31 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{21}H_{34}N_5O_3^+$: 404.2574; Found: 404.2650.

***N*-(3-Aminopropyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,1*}·HCl).** Beige solid. Yield 0.860 g (31%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.74 (br. s, 1H), 7.99 (s, 3H), 7.86 – 7.66 (m, 2H), 7.36 (d, *J* = 7.1 Hz, 1H), 3.80 (br. s, 1H), 3.58 – 3.48 (br. m, 1H), 3.25 (br. s, 2H), 2.90 – 2.63 (m, 4H), 2.21 (s, 3H), 1.85 – 1.73 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.20, 166.04, 152.23, 141.27, 139.60, 133.53, 130.95, 126.80, 126.63, 45.08, 37.14, 36.63, 31.66, 27.67, 17.98 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{15}H_{21}N_4O_3^+$: 305.1527; Found: 305.1600.

***N*-(4-aminobutyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,2*}·HCl**). Beige solid. Yield 0.840 g (59%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.81 – 7.63 (m, 2H), 7.42 (d, J = 8.3 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.72 – 3.64 (m, 1H), 3.42 (s, 2H), 3.04 – 2.73 (m, 4H), 2.33 (s, 3H), 1.71 – 1.67 (m, 4H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.19, 165.79, 152.25, 141.23, 139.44, 133.79, 130.91, 126.73, 126.60, 45.05, 38.98, 38.88, 31.66, 26.59, 24.96, 17.96 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_3^+$: 319.1685; Found: 319.1758.

***N*-(5-Aminopentyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,3*}·HCl).** Beige solid. Yield 0.630 g (42%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.49 (br. s, 1H), 7.93 (s, 3H), 7.78 – 7.69 (m, 2H), 7.34 (d, *J* = 7.8 Hz, 1H), 3.86 – 3.72 (m, 1H), 3.55 – 3.49 (m, 1H), 3.36 – 3.27 (m, 2H), 3.30 – 3.17 (m, 2H), 2.83 – 2.65 (m, 2H), 2.20 (s, 3H), 1.66 – 1.44 (m, 4H), 1.33 (br. s, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.20, 165.69, 152.21, 141.15, 139.30, 133.83, 130.86, 126.72, 126.62, 45.06, 39.31, 39.03, 31.65, 28.94, 27.06, 23.77, 17.96 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_3^+$: 333.1845; Found: 333.1919.

***N*-(6-Aminohexyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,4*}·HCl).** Beige solid. Yield 0.660 g (43%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.49 (s, 1H), 7.90 (br. s, 3H), 7.77 – 7.69 (m, 2H), 7.34 (d, *J* = 7.8 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.56 – 3.48 (m, 1H), 3.29 – 3.17 (m, 2H), 2.83 – 2.65 (m, 4H), 2.20 (s, 3H), 1.51 (dd, *J* = 13.9, 6.8 Hz, 4H), 1.32 – 1.28 (m, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.19, 165.66, 152.23, 141.17, 139.30, 133.88, 130.87, 126.67, 126.54, 45.01, 39.07, 31.61, 29.39, 27.34, 26.41, 26.00, 17.92 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_3^+$: 347.19989; Found: 347.2071.

***N*-(11-Aminoundecyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,5*}·HCl).** Colorless solid. Yield 0.520 g (28%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.44 (s, 1H), 7.87 (br. s, 3H), 7.75 – 7.67 (m, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 3.88 – 3.72 (m, 1H), 3.53 (dd, *J* = 12.2, 6.0 Hz, 1H), 3.27 – 3.15 (m, 2H), 2.77 – 2.66 (m, 4H), 2.20 (s, 3H), 1.52 – 1.47 (m, 4H), 1.27 – 1.21 (m, 14H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.17, 165.61, 152.22, 141.17, 139.27, 133.92, 130.86, 126.64, 126.52, 45.01, 39.62, 39.14, 31.62, 29.57, 29.40, 29.32, 29.25, 29.23, 28.96, 27.35, 26.94, 26.28, 17.92 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{23}H_{37}N_4O_3^+$: 417.2776; Found: 417.2848.

***N*-(2-(2-Aminoethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,6*}·HCl).** Beige solid. Yield 0.280 g (19%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.62 (s, 1H), 8.03 (br. s, 3H), 7.83 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 3.86 – 3.77 (m, 1H), 3.64 – 3.49 (m, 5H), 3.47 – 3.42 (m, 2H), 3.00 – 2.91 (m, 2H), 2.83 – 2.67 (m, 2H), 2.21 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.24, 166.00, 152.19, 141.14, 139.49, 133.55, 130.85, 126.91, 126.79, 69.40, 66.56, 45.05, 39.35, 38.95, 31.63, 17.95 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_4^+$: 335.1634; Found: 335.1706.

***N*-(3-(2-Aminoethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,7*}·HCl).** Beige solid. Yield 0.464 g (26%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.58 (t, *J* = 5.6 Hz, 1H), 7.98 (br. s, 3H), 7.78 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.58 – 3.50 (m, 3H), 3.35 – 3.33 (m, 2H), 3.45 (t, *J* = 6.2 Hz, 2H), 2.96 – 2.93 (m, 2H), 2.83 – 2.66 (m, 2H), 2.21 (s, 3H), 1.77 (p, *J* = 6.4 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.21, 165.86, 152.21, 141.19, 139.40, 133.74, 130.87, 126.74, 126.62, 68.27, 66.76, 45.03, 38.88, 36.56, 31.62, 29.59, 17.93 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1790; Found: 349.18632.

***N*-(2-(3-Aminopropoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,8*}·HCl).** Beige solid. Yield 1.05 g (68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.60 (s, 1H), 7.88 (br. s, 3H), 7.78 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.57 – 3.43 (m, 5H), 3.44 – 3.36 (m, 2H), 2.87 – 2.65 (m, 4H), 2.21 (s, 3H), 1.81 – 1.75 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.21, 165.98, 152.23, 141.18, 139.46, 133.59, 130.91, 126.77, 126.65, 69.25, 67.63, 45.04, 37.02, 31.63, 27.56, 17.94 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1790; Found: 349.1863.

***N*-(3-(3-Aminopropoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,9*}·HCl).** Yellowish solid. Yield 0.498 g (21%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.50 (s, 1H), 7.82 (br. s, 3H), 7.77 – 7.69 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 3.84 – 3.73 (m, 1H), 3.56 – 3.50 (m, 1H), 3.44 – 3.42 (m, 4H), 3.34 – 3.26 (m, 2H), 2.86 – 2.81 (m, 2H), 2.80 – 2.73 (m, 1H), 2.72 – 2.65 (m, 1H), 2.21 (s, 3H), 1.75 (dt, *J* = 18.6, 6.4 Hz, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.20, 165.79, 152.22, 141.16, 139.39, 133.74, 130.89, 126.67, 126.54, 68.16, 67.41, 44.98, 37.02, 36.77, 31.59, 29.82, 27.62, 17.91 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_4^+$: 363.1946; Found: 363.2020.

***N*-(2-(2-(2-Aminoethoxy)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,10*}·HCl).** Beige solid. Yield 0.979 g (39%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.57 (t, *J* = 5.4 Hz, 1H), 7.85 (br. s, 3H), 7.76 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.60 – 3.50 (m, 9H), 3.45 – 3.36 (m, 2H), 2.90 (t, *J* = 5.2 Hz, 2H), 2.83 – 2.73 (m, 1H), 2.73 – 2.64 (m, 1H), 2.21 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d) δ 171.21, 165.89, 152.25, 141.19, 139.50, 133.56, 130.94, 126.74, 126.60, 70.12, 69.90, 69.35, 67.08, 44.99, 38.92, 31.61, 17.94 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_5^+$: 379.1893; Found: 379.1966.

***N*-(3-(2-(3-Aminopropoxy)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,11*}·HCl).** Yellowish oil. Yield 0.920 g (52%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.44 (s, 1H), 7.80 – 7.55 (m, 5H), 7.35 (d, *J* = 7.9 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.56 – 3.50 (m, 1H), 3.48 (s, 4H), 3.44 (dt, *J* = 11.4, 6.1 Hz, 4H), 3.32 – 3.25 (m, 2H), 2.84 – 2.74 (m, 3H), 2.72 – 2.66 (m, 1H), 2.21 (s, 3H), 1.74 (q, *J* = 6.8 Hz, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.17, 165.77, 152.24, 141.21, 139.41, 133.81, 130.92, 126.65, 126.49, 69.94, 69.89, 68.67, 67.80, 44.99, 37.23, 37.05, 31.61, 29.86, 27.62, 17.92 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_5^+$: 407.2213; Found: 407.2286.

***N*-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,12*}·HCl).** Yellowish oil. Yield 0.660 g (36%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.37 (br. s, 1H), 8.50 (s, 1H), 7.76 – 7.69 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 3.84 – 3.71 (m, 1H), 3.57 – 3.51 (m, 13H), 3.43 – 3.37 (m, 2H), 2.95 – 2.91 (m, 2H), 2.83 – 2.74 (m, 1H), 2.71 – 2.64 (m, 1H), 2.21 (s, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.74, 171.18, 165.87, 152.23, 141.19, 139.52, 133.55, 130.94, 126.69, 126.54, 70.13, 70.09, 70.05, 70.01, 69.32, 67.10, 44.97, 38.97, 31.58, 17.92 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_6^+$: 423.2155; Found: 423.2229.

***N*-(3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,13*}·HCl).** Yellowish oil. Yield 0.670 g (34%). ^{1}H NMR (500

MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.42 (br. s, 1H), 7.74 – 7.70 (m, 2H), 7.66 (br. s, 3H), 7.35 (d, J = 7.9 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.56 – 3.43 (m, 13H), 3.30 – 3.26 (m, 2H), 2.84 – 2.74 (m, 3H), 2.71 – 2.65 (m, 1H), 2.21 (s, 3H), 1.74 (dt, J = 6.7, 6.7 Hz, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.21, 165.78, 152.25, 141.21, 139.42, 133.80, 130.93, 126.64, 126.49, 70.20, 70.10, 69.99, 69.91, 68.69, 67.80, 44.98, 37.29, 37.08, 31.60, 29.84, 27.60, 17.92 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_6^+$: 451.2469; Found: 451.2542.

***N*-(14-Amino-3,6,9,12-tetraoxatetradecyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide hydrochloride (10{*3,14*}·HCl).** Yellowish solid. Yield 0.370 g (18%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.48 (br. s, 1H), 7.77 – 7.64 (m, 5H), 7.36 (d, J = 8.0 Hz, 1H), 3.83 – 3.72 (m, 1H), 3.59 – 3.47 (m, 17H), 3.40 (d, J = 5.4 Hz, 2H), 2.95 (br. s, 2H), 2.85 – 2.72 (m, 1H), 2.72 – 2.64 (m, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.17, 165.91, 152.25, 141.22, 139.54, 133.61, 130.96, 126.68, 126.53, 70.18, 70.12, 70.05, 69.37, 67.10, 44.98, 39.11, 31.60, 17.93 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_7^+$: 467.2419; Found: 467.2492.

***N*-(3-((3-Aminopropyl)(methyl)amino)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide dihydrochloride (10{*3,16*}·2HCl).** Yellowish oil. Yield 0.180 g (10%). ^{1}H NMR (500 MHz, D_2O) δ 7.62 – 7.55 (m, 2H), 7.39 (d, J = 7.9 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.64 (dt, J = 12.5, 6.2 Hz, 1H), 3.50 – 3.43 (m, 2H), 3.40 – 3.36 (m, 2H), 3.27 – 3.16 (m, 2H), 3.15 – 3.06 (m, 2H), 3.00 – 2.94 (m, 2H), 2.94 – 2.84 (m, 1H), 2.80 (s, 3H), 2.78 – 2.71 (m, 1H), 2.20 (s, 3H), 2.12 – 1.86 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.24, 165.96, 152.23, 141.22, 139.62, 133.43, 130.93, 126.80, 126.65, 53.53, 52.28, 45.02, 36.90, 36.61, 31.62, 24.15, 22.04, 17.98 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{19}H_{30}N_5O_3^+$: 376.2261; Found: 376.2333.

***N*-(4-((3-Aminopropyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide dihydrochloride (10{*3,17*}·2HCl).** Beige solid. Yield 1.036 g (45%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (br. s, 2H), 8.57 (s, 1H), 8.01 (br. s, 3H), 7.77 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.57 – 3.50 (m, 1H), 3.29 – 3.25 (m, 4H), 3.03 (br. s, 2H), 2.88 – 2.85 (m, 2H), 2.83 – 2.69 (m, 2H), 2.67 (s, 3H), 2.21 (s, 3H), 1.96 (t, *J* = 8.2 Hz, 2H), 1.70 (t, *J* = 7.7 Hz, 2H), 1.58 – 1.50 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.20, 165.84, 152.23, 141.19, 139.44, 133.74, 130.90, 126.75, 126.62, 55.03, 52.29, 45.02, 38.82, 36.65, 31.62, 26.65, 22.06, 21.12, 17.93 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{32}N_5O_3^+$: 390.2422; Found: 390.2495.

***N*-(4-((4-Aminobutyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide dihydrochloride (10{*3,18*}·2HCl).** Yellowish oil. Yield 0.170 g (9%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 10.26 (s, 1H), 8.58 (s, 1H), 7.96 (s, 3H), 7.77 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.56 – 3.54 (m, 1H), 3.29 – 3.25 (m, 2H), 3.12 – 3.02 (m, 2H), 3.01 – 2.94 (m, 2H), 2.80 – 2.75 (m, 2H), 2.73 – 2.66 (m, 5H), 2.21 (s, 3H), 1.74 – 1.67 (m, 4H), 1.59 – 1.50 (m, 4H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.22, 165.88, 152.28, 141.24, 139.52, 133.76, 130.97, 126.74, 126.60, 55.00, 54.58, 45.03, 40.44, 40.28, 38.85, 31.64, 26.73, 24.59, 21.28, 20.90, 17.96 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{21}H_{34}N_5O_3^+$: 404.2575; Found: 404.2647.

4-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide hydrochloride (10{*4,1*}·HCl). Colorless solid. Yield 0.643 g (33%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 10.09 (s, 1H), 7.87 (br. s, 3H), 7.48 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.49 – 3.43 (m, 1H), 2.87 – 2.60 (m, 4H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.87 – 1.81 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.21, 170.79, 152.30, 138.64, 136.33, 136.16, 127.88, 121.34, 117.99, 45.14, 38.78, 33.43, 31.59, 23.51, 18.14 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{15}H_{21}N_4O_3^+$: 305.1530; Found: 305.1602.

5-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)pentanamide hydrochloride (10{*4,2*}·HCl). Beige solid. Yield 0.614 g (44%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 10.08 (s, 1H), 7.90 (br. s, 3H), 7.50 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.51 – 3.41 (m, 2H), 2.79 – 2.61 (m, 2H), 2.33 (t, *J* = 6.7 Hz, 2H), 2.12 (s, 3H), 1.66 – 1.53 (m, 4H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.45, 171.25, 152.34, 138.84, 137.67, 136.15, 128.89, 127.88, 121.31, 117.96, 45.18, 38.93, 31.62, 26.95, 22.58, 18.17 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_3^+$: 319.1686; Found: 319.1759.

6-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)hexanamide hydrochloride (10{*4,3*}·HCl). Beige solid. Yield 0.580 g (35%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 10.00 (s, 1H), 7.87 (br. s, 3H), 7.50 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.52 – 3.45 (m, 1H), 2.83 – 2.58 (m, 4H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.59 – 1.51 (m, 4H), 1.35 – 1.29 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.58, 171.21, 152.31, 138.86, 136.17, 136.09, 127.82, 121.27, 117.92, 45.15, 39.04, 36.50, 31.59, 27.19, 25.91, 25.04, 18.14 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_3^+$: 333.1842; Found: 333.1915.

7-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)heptanamide hydrochloride (10{*4,4*}·HCl). Beige solid. Yield 0.573 g (43%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.98 (s, 1H), 7.86 (br. s, 3H), 7.49 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 3.68 – 3.63 (m, 1H), 3.50 – 3.43 (m, 1H), 2.75 – 2.72 (m, 3H), 2.68 – 2.61 (m, 1H), 2.29 (t, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 1.56 (dt, *J* = 17.3, 8.5 Hz, 4H), 1.32 – 1.28 (m, 5H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.73, 171.21, 152.31, 138.88, 136.09, 128.84, 127.83, 121.26, 117.91, 45.15, 44.99, 39.13, 36.59, 33.97, 31.59, 31.55, 28.45, 28.42, 27.20, 27.15, 26.00, 25.97, 25.31, 24.68, 18.13, 17.95 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_3^+$: 347.1999; Found: 347.2072.

8-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)octanamide hydrochloride (10{*4,5*}·HCl). Beige solid. Yield 0.710 g (49%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.99 (s, 1H), 7.89 (s, 3H), 7.50 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.49 – 3.43 (m, 1H), 2.73 (q, *J* = 7.4 Hz, 3H), 2.69 – 2.61 (m, 1H), 2.29 (t, *J* = 7.1 Hz, 2H), 2.12 (s, 3H), 1.54 (d, *J* = 23.5 Hz, 4H), 1.28 (br. s, 6H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 171.76, 171.21, 152.30, 138.87, 136.08, 127.81, 121.20, 117.86, 45.13, 39.12, 36.72, 31.57, 28.82, 28.72, 27.34, 26.16, 25.46, 18.12 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{19}H_{29}N_4O_3^+$: 361.2151; Found: 361.2224.

8-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)octanamide hydrochloride (10{*4,6*}·HCl). Beige solid. Yield 0.690 g (40%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.95 (s, 1H), 7.84 (br. s, 3H), 7.48 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.50 – 3.41 (m, 1H), 2.79 – 2.70 (m, 3H), 2.69 – 2.61 (m, 1H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 1.58 – 1.48 (m, 4H), 1.32 – 1.20 (m, 10H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.83, 171.25, 152.35, 138.92, 136.13, 127.86, 121.27, 117.91, 45.18, 40.43, 40.26, 39.20, 36.81, 31.62, 29.13, 29.06, 28.94, 27.38, 26.27, 25.60, 18.17 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{21}H_{33}N_4O_3^+$: 389.2464; Found: 389.2537.

2-(2-Aminoethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)acetamide hydrochloride (10{*4,7*}·HCl). Orange oil. Yield 0.850 g (19%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.30 (s, 1H), 9.82 (s, 1H), 8.09 (br. s, 3H), 7.59 – 7.50 (m, 2H), 7.19 (d, *J* = 8.1 Hz, 1H), 4.15 – 4.09 (m, 2H), 3.72 – 3.68 (br. m, 3H), 3.50 – 3.44 (m, 1H), 3.06 – 3.02 (m, 2H), 2.82 – 2.58 (m, 2H), 2.14 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.21, 168.22, 152.29, 137.65, 136.93, 136.10, 127.77, 122.49, 119.11, 70.52, 67.53, 45.13, 38.97, 31.59, 18.13 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{15}H_{21}N_4O_4^+$: 321.1478; Found: 321.1551.

3-(2-Aminoethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propanamide hydrochloride (10{*4,8*}·HCl). Yellowish oil. Yield 0.507 g (23%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 10.05 (s, 1H), 7.83 (s, 3H), 7.49 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 3.76 – 3.67 (m, 3H), 3.60 – 3.56 (m, 2H), 3.48 – 3.39 (m, 1H), 2.97 – 2.93 (m, 2H), 2.76 – 2.58 (m, 4H), 2.12 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.21, 169.76, 152.30, 138.71, 136.32, 136.12, 127.84, 121.38, 118.03, 66.92, 66.67, 45.14, 38.86, 37.20, 31.59, 18.14 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_4O_4^+$: 335.1634; Found: 335.1708.

4-(2-Aminoethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide hydrochloride (10{*4,9*}·HCl). Yellowish solid. Yield 0.705 g (18%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 10.05 (s, 1H), 7.92 (br. s, 3H), 7.50 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.56 – 3.52 (m, 3H), 3.45 (t, *J* = 6.3 Hz, 2H), 2.98 – 2.90 (m, 2H), 2.77 – 2.69 (m, 1H), 2.69 – 2.62 (m, 1H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.12 (s, 3H), 1.83 (p, *J* = 6.9 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.56, 171.21, 152.31, 138.86, 136.18, 136.09, 127.82, 121.28, 117.94, 69.91, 66.60, 45.15, 39.03, 33.28, 31.59, 25.52, 18.14 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1796; Found: 349.1869.

3-(3-Aminopropoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propanamide hydrochloride (10{*4,10*}·HCl). Yellowish oil. Yield 0.488 g (35%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 10.06 (s, 1H), 7.79 (br. s, 3H), 7.50 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 3.74 – 3.62 (m, 4H), 3.47 (t, *J* = 5.9 Hz, 2H), 2.79 – 2.61 (m, 4H), 2.55 (t, *J* = 5.9 Hz, 2H), 2.12 (s, 3H), 1.79 – 1.72 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.20, 169.84, 152.33, 138.69, 136.32, 136.19, 127.90, 121.33, 117.98, 67.59, 66.72, 45.14, 37.38, 37.10, 31.59, 27.51, 18.14 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_4^+$: 349.1794; Found: 349.1868.

4-(3-Aminopropoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide hydrochloride (10{*4,11*}·HCl). Yellowish oil. Yield 0.644 g (25%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 10.01 (s, 1H), 7.86 (br. s, 3H), 7.49 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 3.74 – 3.66 (m, 1H), 3.50 – 3.32 (m, 5H), 2.85 – 2.79 (m, 2H), 2.78 – 2.61 (m, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.12 (s, 3H), 1.84 – 1.73 (m, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d) δ 171.45, 171.20, 152.32, 136.17, 136.11, 127.84, 121.27, 117.91, 69.90, 67.44, 45.15, 37.01, 36.93, 33.50, 31.59, 27.69, 25.62, 18.14 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_4^+$: 363.1948; Found: 363.2020.

2-(2-(2-Aminoethoxy)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)acetamide hydrochloride (10{*4,12*}·HCl). Yellowish oil. Yield 0.196 g (4%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.30 (s, 1H), 9.76 (s, 1H), 7.88 (br. s, 3H), 7.52 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 4.10 (s, 2H), 3.72 – 3.59 (m, 6H), 3.50 – 3.43 (m, 2H), 2.99 – 2.95 (m, 2H), 2.80 – 2.61 (m, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 171.25, 168.75, 152.31, 137.86, 136.73, 136.23, 127.90, 121.89, 118.52, 70.59, 70.49, 69.98, 67.08, 45.11, 40.20, 38.89, 31.57, 18.15 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{25}N_4O_5^+$: 365.1745; Found: 365.1818.

3-(2-(2-Aminoethoxy)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propenamide hydrochloride (10{*4,13*}·HCl). Yellowish oil. Yield 0.559 g (25%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 10.01 (s, 1H), 7.81 (br. s, 3H), 7.49 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 3.69 (t, *J* = 12.1 Hz, 2H), 3.59 – 3.52 (m, 5H), 3.49 – 3.43 (m, 1H), 2.93 – 2.89 (m, 2H), 2.76 – 2.69 (m, 1H), 2.68 – 2.63 (m, 1H), 2.58 – 2.48 (m, 4H), 2.12 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.21, 169.78, 152.31, 138.75, 136.28, 136.16, 127.88, 121.24, 117.90, 70.06, 69.93, 67.09, 67.06, 45.15, 38.93, 37.53, 31.59, 18.15 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{27}N_4O_5^+$: 379.1893; Found: 379.1966.

2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)acetamide hydrochloride (10{*4,14*}·HCl). Yellowish oil. Yield 0.727 g (36%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.30 (s, 1H), 9.72 (s, 1H), 7.86 (br. s, 3H), 7.52 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 4.08 (s, 2H), 3.77 – 3.53 (m, 8H), 3.50 – 3.41 (m, 4H), 2.95 – 2.91 (m, 2H), 2.79 – 2.70 (m, 1H), 2.70 – 2.62 (m, 1H), 2.13 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.20, 168.78, 152.31, 137.80, 136.78, 136.25, 127.91, 121.92, 118.54, 70.72, 70.62 (2C), 70.08, 67.08, 45.13, 38.95, 38.87, 31.59, 18.13 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{19}H_{29}N_4O_6^+$: 409.1999; Found: 409.2073.

3-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propanamide hydrochloride (10{*4,15*}·HCl). Yellowish oil. Yield 0.714 g (20%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 10.03 (s, 1H), 7.87 (s, 3H), 7.49 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 3.67 – 3.69 (m, 2H), 3.60 – 3.41 (m, 12H), 2.95 – 2.88 (m, 2H), 2.77 – 2.69 (m, 1H), 2.69 – 2.63 (m, 1H), 2.54 (t, J = 6.2 Hz, 2H), 2.12 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.21, 169.76, 152.31, 138.74, 136.27, 136.15, 121.24, 117.89, 70.10, 70.07 (2C), 67.09, 67.04, 45.16, 38.94, 37.55, 35.21, 31.59, 18.14, 17.96 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_6^+$: 423.2160; Found: 423.2233.

14-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)-3,6,9,12-tetraoxatetradecanamide hydrochloride (10{*4,16*}·HCl). Yellowish oil. Yield 0.651 g (16%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.30 (s, 1H), 9.70 (s, 1H), 7.83 (br. s, 3H), 7.54 – 7.45 (m, 2H), 7.17 (d, J = 8.5 Hz, 1H), 4.08 (s, 2H), 3.74 – 3.45 (m, 16H), 2.97 – 2.91 (m, 2H), 2.80 – 2.70 (m, 1H), 2.70 – 2.59 (m, 1H), 2.13 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.21, 168.80, 152.31, 137.78, 136.79, 136.24, 127.91, 121.91, 118.52, 70.75, 70.58, 70.26, 70.21, 70.13, 70.06, 70.03, 67.04, 45.13, 38.95, 31.59, 18.12 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{21}H_{33}N_4O_7^+$: 453.2263; Found: 453.2336.

1-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)-3,6,9,12-tetraoxapentadecan-15-amide hydrochloride (10{*4,17*}·HCl). Yellowish oil. Yield 0.766 g (20%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.98 (s, 1H), 7.80 (br. s, 3H), 7.49 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 3.68 (t, *J* = 6.2 Hz, 2H), 3.59 – 3.48 (m, 16H), 2.96 – 2.92 (m, 2H), 2.80 – 2.69 (m, 1H), 2.69 – 2.62 (m, 1H), 2.54 (t, *J* = 6.0 Hz, 2H), 2.12 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.21, 169.73, 152.30, 138.71, 136.29, 136.16, 127.88, 121.24, 117.89, 70.19, 70.12, 70.09, 70.05, 67.08, 67.05, 45.16, 38.97, 38.89, 37.55, 31.59, 18.15, 17.96 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_7^+$: 467.2423; Found: 467.2500.

4-((3-Aminopropyl)(methyl)amino)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide dihydrochloride (10{*4,18*}·2HCl). Yellowish oil. Yield 0.670 g (21%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.58 (br. s, 1H), 10.29 (s, 1H), 10.15 (s, 1H), 8.03 (br. s, 3H), 7.50 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.50 – 3.40 (m, 2H), 3.24 – 3.19 (m, 1H), 3.16 – 2.96 (m, 2H), 2.93 – 2.82 (m, 1H), 2.79 – 2.70 (m, 5H), 2.69 – 2.63 (m, 1H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.12 (s, 3H), 2.00 – 1.96 (m, 4H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.22, 170.50, 152.31, 138.63, 136.35, 136.16, 127.87, 121.38, 118.03, 54.82, 52.20, 45.14, 36.63, 33.42, 31.58, 22.05, 19.66, 18.15, 17.95 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{19}H_{30}N_5O_3^+$: 376.2263; Found: 376.2336.

9-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)nonanamide hydrochloride (10{*4,19*}·HCl). Beige oil. Yield 0.563 g (42%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.93 (s, 1H), 7.79 (br. s, 3H), 7.48 (s, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.46 (p, *J* = 6.1 Hz, 1H), 2.77 – 2.70 (m, 3H), 2.69 – 2.64 (m, 1H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.61 – 1.46 (m, 4H), 1.27 (s, 8H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 171.78, 171.25, 152.32, 138.89, 136.10, 127.84, 121.21, 117.86, 45.15, 39.13, 36.76, 31.59, 29.04, 28.95, 28.85, 27.35, 26.24, 25.56, 18.16 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{20}H_{31}N_4O_3^+$: 375.2312; Found: 375.2385.

11-Amino-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)undecanamide hydrochloride (10{*4,20*}·HCl). Colorless solid. Yield 0.545 g (31%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.95 (s, 1H), 7.87 (br. s, 3H), 7.49 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.46 (dt, *J* = 12.1, 5.9 Hz, 1H), 2.79 – 2.69 (m, 3H), 2.69 – 2.61 (m, 1H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.57 – 1.48 (m, 4H), 1.24 (s, 12H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ 171.77, 171.20, 152.30, 138.88, 136.13, 136.09, 127.83, 121.24, 117.88, 45.15, 39.15, 36.80, 31.59, 29.23 (2C), 29.07, 28.94, 27.37, 26.26, 25.58, 18.14 ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{22}H_{35}N_4O_3^+$: 403.2620; Found: 403.2694.

Representative procedure for the synthesis of PROTACs 6: (*S*)-*N*-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,2*}). Dihydrochloride of (*S*)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetic acid (JQ-1 carboxylic acid, 50.0 mg, 0.106 mmol) was dissolved in dry DMF (5 mL). (3-[(Ethylimino)methylidene]aminopropyl)dimethylamine hydrochloride (EDC·HCl, 30.4 mg, 0.159 mmol), 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol (HOAt, 14.4 mg, 0.106 mmol), and *i*Pr$_2$NEt (100 µL, 0.582 mmol, 5.5 equiv) were added to the resulting solution. After stirring at rt for 30 min, intermediate **10**{*3,2*}·HCl (37.5 mg, 0.106 mmol) was added. The reaction mixture was stirred at 60°C for 16 h. After the reaction completion (according to LC-MS), the crude product (0.25 g, 60% purity by LC-MS) was subjected to HPLC purification (gradient H_2O– MeCN with 0.1% formic acid), which gave target compound **6**{*3,2*}. Beige solid. Yield 0.033 g (45%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.41 (t, *J* = 5.8 Hz, 1H), 8.18 (t, *J* = 5.8 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.83 – 3.71 (m, 1H), 3.55 – 3.50 (m, 1H), 3.24 – 3.06 (m, 6H), 2.79 – 2.72 (m, 1H), 2.70 – 2.63 (m, 1H), 2.57 (s, 3H), 2.39 (s, 3H), 2.21 (s, 3H), 1.59 (s, 3H), 1.56 –

1.51 (m, 2H), 1.50 – 1.45 (m, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_4S^+$: 701.2335; Found: 701.2411.

(*S*)-*N*-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,1*}). Colorless solid. Yield 0.042 g (58%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.43 (br. s, 1H), 8.25 (br. s, 1H), 7.55 (s, 1H), 7.51 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.30 (s, 1H), 4.49 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.28 – 3.09 (m, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 1.72 – 1.66 (m, 2H), 1.58 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{34}H_{36}ClN_8O_4S^+$: 687.2188; Found: 687.2264.

(*S*)-*N*-(4-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,2*}). Beige solid. Yield 0.046 g (62%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.43 (br. s, 1H), 8.19 (br. s, 1H), 7.56 (s, 1H), 7.52 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.29 (s, 1H), 4.48 (dd, *J* = 8.2, 5.8 Hz, 1H), 3.77 (t, *J* = 6.7 Hz, 2H), 3.28 – 3.03 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.58 (s, 3H), 1.56 – 1.51 (m, 2H), 1.50 – 1.45 (m, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_4S^+$: 701.2345; Found: 701.2416.

(*S*)-*N*-(5-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)pentyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,3*}). Beige solid. Yield 0.040 g (53%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.41 (br. s, 1H) 8.18 (br. s, 1H), 7.55 (s, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 1H), 4.48 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.27 – 2.99 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.60 (s, 3H), 1.57 – 1.41 (m, 4H), 1.33 (d, *J* = 6.5 Hz, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_4S^+$: 715.2502; Found: 715.2577.

(*S*)-*N*-(6-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)hexyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,4*}). Beige solid. Yield 0.056 g (73%). 1H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.41 (br. s, 1H), 8.16 (br. s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.28 (s, 1H), 4.52 – 4.44 (m, 1H), 3.77 (t, J = 6.6 Hz, 2H), 3.26 – 3.02 (m, 6H), 2.68 (t, J = 6.6 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 1.59 (s, 3H), 1.48 (br. s, 2H), 1.43 (br. s, 2H), 1.30 (br. s, 4H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_4S^+$: 729.2655; Found: 729.2730.

(*S*)-*N*-(11-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)undecyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,5*}). Yellowish solid. Yield 0.045 g (53%). 1H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.39 (br. s, 1H), 8.13 (br. s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.28 (s, 1H), 4.47 (dd, J = 8.3, 6.1 Hz, 1H), 3.78 (t, J = 6.6 Hz, 2H), 3.25 – 2.90 (m, 6H), 2.69 (t, J = 6.7 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.60 (s, 3H), 1.47 (s, 2H), 1.40 (s, 2H), 1.26 – 1.20 (m, 14H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{42}H_{52}ClN_8O_4S^+$: 799.34379; Found: 799.3511.

(*S*)-*N*-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,6*}). Beige solid. Yield 0.039 g (51%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.48 (br. s, 1H), 8.28 (br. s, 1H), 7.57 (s, 1H), 7.54 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 1H), 4.48 (dd, J = 8.2, 6.0 Hz, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.54 (br. s, 2H), 3.47 (br. s, 2H), 3.42 (br. s, 2H), 3.27 – 3.15 (m, 4H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_5S^+$: 717.2289; Found: 717.2359.

(*S*)-*N*-(3-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,7*}). Beige solid. Yield 0.020 g (25%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.43 (br. s, 1H), 8.26 (br. s, 1H), 7.55 (s, 1H), 7.52 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 1H), 4.49 (t, *J* = 7.0 Hz, 1H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.43 (dt, *J* = 12.1, 5.9 Hz, 6H), 3.26 – 3.17 (m, 4H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H), 1.77 – 1.71 (m, 2H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2442; Found: 731.2518.

(*S*)-*N*-(2-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,8*}). Colorless solid. Yield 0.029 g (38%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.45 (br. s, 1H), 8.19 (br. s, 1H), 7.56 (s, 1H), 7.53 (s, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 1H), 4.49 (t, *J* = 7.0 Hz, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.48 – 3.40 (m, 4H), 3.40 – 3.35 (m, 2H), 3.24 – 3.12 (m, 4H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H), 1.69 – 1.63 (m, 2H), 1.58 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2450; Found: 731.2526.

(*S*)-*N*-(3-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,9*}). Colorless solid. Yield 0.033 g (42%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.43 (br. s, 1H), 8.20 (br. s, 1H), 7.55 (s, 1H), 7.51 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 1H), 4.49 (t, *J* = 6.9 Hz, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.41 – 3.35 (m, 6H), 3.25 – 3.12

(m, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 1.69 (dt, *J* = 29.3, 6.2 Hz, 2H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_5S^+$: 745.2614; Found: 745.2687.

(*S*)-*N*-(2-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,10*}). Beige solid. Yield 0.049 g (51%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.49 (br. s, 1H), 8.25 (br. s, 1H), 7.56 (s, 1H), 7.53 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.29 (s, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.54 – 3.49 (m, 4H), 3.46 – 3.37 (m, 4H), 3.28 – 3.15 (m, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_6S^+$: 761.2549; Found: 761.2625.

(*S*)-*N*-(3-(2-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,11*}). Yellowish solid. Yield 0.038 g (46%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.41 (br. s, 1H), 8.17 (br. s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 1H), 4.48 (t, *J* = 7.1 Hz, 1H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.47 (br. s, 4H), 3.46 – 3.39 (m, 6H), 3.24 – 3.07 (m, 4H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.76 – 1.70 (m, 2H), 1.68 – 1.62 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_6S^+$: 789.2867; Found: 789.2943.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-6,9,12-trioxa-3-azatetradecan-14-yl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,12*}). Beige solid. Yield 0.047 g (55%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.49 (br. s, 1H), 8.26 (br. s, 1H), 7.56 (s, 1H), 7.52 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3

Hz, 2H), 7.29 (s, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.53 – 3.49 (m, 10H), 3.45 – 3.36 (m, 4H), 3.27 – 3.15 (m, 4H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_7S^+$: 805.2811; Found: 805.2887.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-7,10,13-trioxa-3-azahexadecan-16-yl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,13*}). Beige solid. Yield 0.036 g (41%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.41 (br. s, 1H), 8.17 (br. s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 1H), 4.47 (t, *J* = 7.5 Hz, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.52 – 3.39 (m, 14H), 3.23 – 3.06 (m, 4H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 1.75 – 1.69 (m, 2H), 1.68 – 1.62 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_7S^+$: 833.3129; Found: 833.3198.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-17-yl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,14*}). Beige solid. Yield 0.039 g (44%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 8.49 (br. s, 1H), 8.26 (br. s, 1H), 7.56 (s, 1H), 7.52 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.29 (s, 1H), 4.47 (t, *J* = 7.5 Hz, 1H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.52 – 3.47 (m, 14H), 3.45 – 3.36 (m, 4H), 3.28 – 3.14 (m, 4H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_8S^+$: 849.3081; Found: 849.3158.

(*S*)-*N*-(2-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,15*}). Beige solid. Yield 0.031 g (40%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.32 (br. s, 1H), 8.17 (br. s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.27 (s, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.23 – 3.07 (m, 4H), 2.67 (t, *J* = 6.7 Hz, 2H), 2.56 (s, 3H), 2.40 – 2.33 (m, 7H), 2.31 (s, 3H), 2.17 (s, 3H), 1.60 – 1.57 (m, 7H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{43}ClN_9O_4S^+$: 744.2760; Found: 744.2833.

(*S*)-*N*-(3-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,16*}). Beige solid. Yield 0.032 g (40%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.48 (br. s, 1H), 8.19 (br. s, 1H), 7.54 (s, 1H), 7.50 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.27 (s, 1H), 4.48 (t, *J* = 6.8 Hz, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.25 – 3.05 (m, 4H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.56 (s, 3H), 2.38 (s, 3H), 2.31 (br. s, 9H), 2.11 (s, 3H), 1.66 – 1.51 (m, 7H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{38}H_{45}ClN_9O_4S^+$: 758.2922; Found: 758.2999.

(*S*)-*N*-(4-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,17*}). Beige solid. Yield 0.025 g (31%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.42 (br. s, 1H), 8.16 (br. s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.28 (s, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.26 – 3.05 (m, 4H), 2.68 (t, *J* = 6.7 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.34 – 2.23 (m, 9H), 2.10 (s, 3H), 1.61 – 1.37 (m, 9H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{47}ClN_9O_4S^+$: 772.3082; Found: 772.3151.

(*S*)-*N*-(4-((4-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)butyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylbenzamide (6{*1,18*}). Beige solid. Yield 0.043 g (52%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.42 (br. s, 1H), 8.17 (br. s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.28 (s, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.24 – 2.99 (m, 8H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H), 2.28 – 2.22 (m, 5H), 2.07 (s, 3H), 1.60 (s, 3H), 1.55 – 1.33 (m, 5H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{40}H_{49}ClN_9O_4S^+$: 786.32359; Found: 786.3311.

(*S*)-*N*-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,1*}). Colorless solid. Yield 0.038 g (52%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.26 – 8.21 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.19 (m, 3H), 4.52 – 4.46 (m, 1H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.26 – 3.10 (m, 6H), 2.66 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.71 – 1.65 (m, 2H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{34}H_{36}ClN_8O_4S^+$: 687.2187; Found: 687.2264.

(*S*)-*N*-(4-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)butyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,2*}). Beige solid. Yield 0.023 g (31%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.31 – 8.13 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.18 (m, 3H), 4.48 (t, *J* = 7.1 Hz, 1H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.26 – 3.03 (m, 6H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.60 (s, 3H), 1.57 – 1.45 (m, 4H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_4S^+$: 701.2337; Found: 701.2414.

(*S*)-*N*-(5-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)pentyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,3*}). Yellowish solid. Yield 0.020 g (26%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.30 – 8.10 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.18 (m, 3H), 4.51 – 4.45 (m, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.27 – 3.03 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H), 1.54 – 1.42 (m, 4H), 1.34 (q, *J* = 8.4 Hz, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_4S^+$: 715.2501; Found: 715.2579.

(*S*)-*N*-(6-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)hexyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,4*}). Yellowish solid. Yield 0.043 g (56%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.24 (t, *J* = 5.6 Hz, 1H), 8.16 (t, *J* = 5.6 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.17 (m, 3H), 4.51 – 4.45 (m, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.25 – 3.02 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.60 (s, 3H), 1.55 – 1.37 (m, 4H), 1.33 – 1.29 (m, 4H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_4S^+$: 729.2657; Found: 729.2732.

(*S*)-*N*-(11-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)undecyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,5*}). Beige solid. Yield 0.044 g (52%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.34 (s, 1H), 8.26 – 8.09 (m, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.18 (m, 3H), 4.51 – 4.45 (m, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.24 – 2.97 (m, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.61 (s, 3H), 1.52 – 1.35 (m, 4H), 1.30 – 1.18 (m, 14H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{42}H_{52}ClN_8O_4S^+$: 799.3440; Found: 799.3512.

(*S*)-*N*-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,6*}). Beige solid. Yield 0.038 g (50%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.34 (s, 1H), 8.36 – 8.19 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.18 (m, 3H), 4.47 (t, *J* = 7.2 Hz, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.57 – 3.51 (m, 2H), 3.50 – 3.45 (m, 2H), 3.43 – 3.35 (m, 2H), 3.26

– 3.13 (m, 4H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_5S^+$: 717.2290; Found: 717.2367.

(*S*)-*N*-(3-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,7*}). Beige solid. Yield 0.043 g (56%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.31 – 8.22 (m, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.27 – 7.17 (m, 3H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.75 (t, *J* = 6.7 Hz, 2H), 3.49 – 3.39 (m, 4H), 3.28 – 3.18 (m, 6H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.56 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H), 1.73 (t, *J* = 6.8 Hz, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2450; Found: 731.2528.

(*S*)-*N*-(2-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)ethyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,8*}). Beige solid. Yield 0.047 g (60%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.34 (s, 1H), 8.27 (t, *J* = 5.6 Hz, 1H), 8.18 (t, *J* = 5.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.17 (m, 3H), 4.47 (t, *J* = 7.1 Hz, 1H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.48 – 3.41 (m, 4H), 3.37 – 3.33 (m, 2H), 3.26 – 3.08 (m, 4H), 2.66 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.69 – 1.63 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2446; Found: 731.2522.

(*S*)-*N*-(3-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,9*}). Beige solid. Yield 0.043 g (54%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.34 (s, 1H), 8.33 – 8.11 (m, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.17 (m, 3H), 4.47 (t, *J* = 6.9 Hz, 1H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.43 – 3.37 (m, 4H), 3.27 – 3.09 (m, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.76 – 1.62 (m, 4H), 1.61 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_5S^+$: 745.2611; Found: 745.2684.

(*S*)-*N*-(2-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethoxy)ethyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,10*}). Beige solid. Yield 0.043 g (53%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.30 – 8.23 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.18 (m, 3H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.75 (t, *J* = 6.7 Hz, 2H), 3.57 – 3.48 (m, 6H), 3.44 (t, *J* = 5.8 Hz, 2H), 3.38 – 3.34 (m, 2H), 3.27 – 3.17 (m, 4H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_6S^+$: 761.2553; Found: 761.2628.

(S)-*N*-(3-(2-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)ethoxy)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,11*}). Yellowish solid. Yield 0.042 g (50%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.30 – 8.11 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.18 (m, 3H), 4.51 – 4.45 (m, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.50 – 3.38 (m, 8H), 3.27 – 3.09 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.75 – 1.69 (m, 2H), 1.68 – 1.62 (m, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_6S^+$: 789.2863; Found: 789.2937.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-6,9,12-trioxa-3-azatetradecan-14-yl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,12*}). Beige solid. Yield 0.035 g (41%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.30 – 8.22 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.18 (m, 3H), 4.51 – 4.45 (m, 1H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.56 – 3.47 (m, 8H), 3.43 (t, *J* = 5.8 Hz, 2H), 3.38 – 3.33 (m, 2H), 3.27 – 3.14 (m, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_7S^+$: 805.2827; Found: 805.2891.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-7,10,13-trioxa-3-azahexadecan-16-yl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,13*}). Beige solid. Yield 0.046 g (52%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.26 – 8.11 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.18 (m, 3H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.75 (t, *J* = 6.7 Hz, 2H), 3.54 – 3.38 (m, 12H), 3.25 – 3.08 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.74 – 1.68 (m, 2H), 1.68 – 1.62 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_7S^+$: 833.3130; Found: 833.3208.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-17-yl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,14*}). Beige solid. Yield 0.048 g (54%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.28 – 8.23 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.18 (m, 3H), 4.51 – 4.45 (m, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.55 – 3.46 (m, 12H) 3.43 (t, *J* = 5.7 Hz, 2H), 3.35 (q, *J* = 5.7 Hz, 2H), 3.28 (s, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_8S^+$: 849.3087; Found: 849.3142.

(*S*)-*N*-(3-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)propyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,16*}). Beige solid. Yield 0.036 g (45%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.27 (t, *J* = 5.3 Hz, 1H), 8.17 (t, *J* = 5.3 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.26 – 7.17 (m, 3H), 4.47 (t, *J* = 7.0 Hz, 1H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.25 – 3.16 (m, 4H), 3.13 – 3.08 (m, 2H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.35 – 2.26 (m, 7H), 2.13 (s, 3H), 1.67 – 1.51 (m, 7H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{38}H_{45}ClN_9O_4S^+$: 758.2924; Found: 758.3002.

(*S*)-*N*-(4-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)butyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,17*}). Beige solid. Yield 0.014 g (18%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.35 (s, 1H), 8.26 (br. s, 1H), 8.16 (br. s, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.17 (m, 3H), 4.48 (t, *J* = 7.1 Hz, 1H), 3.75 (t, *J* = 6.7 Hz, 2H), 3.24 – 3.03 (m, 6H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.32 – 2.22 (m, 7H), 2.10 (s, 3H), 1.60 (s, 3H), 1.58 – 1.36 (m, 6H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{47}ClN_9O_4S^+$: 772.3075; Found: 772.3148.

(*S*)-*N*-(4-((4-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)butyl)(methyl)amino)butyl)-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylbenzamide (6{*2,18*}). Beige solid. Yield 0.009 g (10%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.25 (m, 3H), 4.69 – 4.56 (m, 1H), 3.85 (t, *J* = 6.7 Hz, 2H), 3.44 – 3.32 (m, 6H), 2.78 (t, *J* = 6.7 Hz, 2H), 2.69 (s, 3H), 2.62 – 2.50 (m, 5H), 2.44 (s, 3H), 2.42 – 2.28 (m, 5H), 1.69 (s, 3H), 1.66 – 1.54 (m, 8H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{40}H_{49}ClN_9O_4S^+$: 786.3231; Found: 786.3307.

(*S*)-*N*-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,1*}). Beige solid. Yield 0.038 g (52%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.41 (t, *J* = 5.4 Hz, 1H), 8.24 (t, *J* = 6.0 Hz, 1H), 7.72 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 4.49 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.55 – 3.48 (m, 1H), 3.28

– 3.09 (m, 6H), 2.82 – 2.63 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.21 (s, 3H), 1.70 (q, *J* = 6.8 Hz, 2H), 1.58 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{34}H_{36}ClN_8O_4S^+$: 687.2182; Found: 687.2259.

(*S*)-*N*-(5-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)pentyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,3*}). Beige solid. Yield 0.032 g (42%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.40 (br. s, 1H), 8.17 (br. s, 1H), 7.72 (s, 2H), 7.54 – 7.26 (m, 5H), 4.48 (br. s, 1H), 3.77 (br. s, 1H), 3.52 (br. s, 1H), 3.24 – 2.99 (m, 6H), 2.84 – 2.62 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.20 (s, 3H), 1.60 (s, 3H), 1.57 – 1.26 (br. m, 6H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_4S^+$: 715.2499; Found: 715.2570.

(*S*)-*N*-(6-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)hexyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,4*}). Beige solid. Yield 0.041 g (53%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.39 (s, br. 1H), 8.16 (br. s, 1H), 7.73 – 7.67 (m, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.78 (br. s, 1H), 3.52 (br. s, 1H), 3.25 – 3.01 (m, 6H), 2.75 (br. s, 1H), 2.68 (br. s, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H), 1.59 (s, 3H), 1.52 – 1.39 (m, 4H), 1.30 (br. s, 4H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_4S^+$: 729.2658; Found: 729.2727.

(*S*)-*N*-(11-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)undecyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,5*}). Beige solid. Yield 0.048 g (57%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.37 (t, *J* = 5.7 Hz, 1H), 8.12 (t, *J* = 5.7 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 1H), 4.51 – 4.44 (m, 1H), 3.82 – 3.73 (m, 1H), 3.56 – 3.49 (m, 1H), 3.27 – 2.97 (m, 6H), 2.83 – 2.72 (m, 1H), 2.72 – 2.64 (m, 1H), 2.57 (s, 3H), 2.39 (s, 3H), 2.20 (s, 3H), 1.61 (s, 3H), 1.53 – 1.35 (m, 2H), 1.31 – 1.17 (m, 16H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{42}H_{52}ClN_8O_4S^+$: 799.3442; Found: 799.3516.

(*S*)-*N*-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,6*}). Beige solid. Yield 0.036 g (48%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H), 8.46 (s, 1H), 8.28 (s, 1H), 7.78 – 7.67 (m, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 4.48 (t, *J* = 6.8 Hz, 1H), 3.84 – 3.71 (m, 1H), 3.59 – 3.39 (m, 7H), 3.30 – 3.15 (m, 4H), 2.81 – 2.72 (m, 1H), 2.69 – 2.61 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.19 (s, 3H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_5S^+$: 717.2306; Found: 717.2387.

(*S*)-*N*-(3-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,7*}). Beige solid. Yield 0.027 g (35%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H), 8.42 (br. s, 1H), 8.26 (br. s, 1H), 7.74 – 7.67 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 4.49 (t, *J* = 6.9 Hz, 1H), 3.86 – 3.69 (m, 1H), 3.57 – 3.37 (m, 5H), 3.27 – 3.17 (m, 4H), 2.81 – 2.70 (m, 1H), 2.70 – 2.60 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H), 1.78 – 1.71 (m, 4H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2447; Found: 731.2521.

(*S*)-*N*-(2-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,8*}). Beige solid. Yield 0.026 g (34%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.44 (br. s, 1H), 8.19 (br. s, 1H), 7.75 – 7.68 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 6.9 Hz, 1H), 4.49 (t, *J* = 7.0 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.55 – 3.34 (m, 6H), 3.24 – 3.09

(m, 3H), 2.82 – 2.70 (m, 1H), 2.69 – 2.62 (m, 1H), 2.57 (s, 3H), 2.37 (s, 3H), 2.19 (s, 3H), 1.69 – 1.59 (m, 4H), 1.58 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2443; Found: 731.2515.

(*S*)-*N*-(3-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,9*}). Beige solid. Yield 0.044 g (56%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.42 (br. s, 1H), 8.20 (br. s, 1H), 7.73 – 7.67 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 4.49 (t, *J* = 6.9 Hz, 1H), 3.82 – 3.71 (m, 1H), 3.56 – 3.47 (m, 1H), 3.42 – 3.35 (m, 4H), 3.25 – 3.10 (m, 6H), 2.82 – 2.71 (m, 1H), 2.70 – 2.62 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H), 1.75 – 1.69 (m, 2H), 1.69 – 1.62 (m, 2H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_5S^+$: 745.2603; Found: 745.2675.

(*S*)-*N*-(2-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethoxy)ethyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,10*}). Beige solid. Yield 0.040 g (49%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.48 (br. s, 1H), 8.25 (br. s, 1H), 7.75 – 7.68 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 4.48 (t, *J* = 6.9 Hz, 1H), 3.82 – 3.71 (m, 1H), 3.57 – 3.49 (m, 7H), 3.44 – 3.36 (m, 4H), 3.27 – 3.16 (m, 4H), 2.82 – 2.72 (m, 1H), 2.72 – 2.63 (m, 1H), 2.57 (s, 3H), 2.39 (s, 3H), 2.20 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_6S^+$: 761.2553; Found: 761.2627.

(*S*)-*N*-(3-(2-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)ethoxy)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,11*}). Beige solid. Yield 0.051 g (62%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38

(s, 1H), 8.41 (br. s, 1H), 8.18 (br. s, 1H), 7.73 – 7.66 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 1H), 4.53 – 4.36 (m, 1H), 3.85 – 3.71 (m, 1H), 3.56 – 3.45 (m, 5H), 3.45 – 3.39 (m, 6H), 3.25 – 3.07 (m, 4H), 2.84 – 2.61 (m, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H), 1.76 – 1.70 (m, 2H), 1.68 – 1.62 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_6S^+$: 789.28549; Found: 789.2942.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-6,9,12-trioxa-3-azatetradecan-14-yl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,12*}). Colorless solid. Yield 0.023 g (28%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.47 (br. s, 1H), 8.25 (br. s, 1H), 7.74 – 7.68 (m, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.84 – 3.71 (m, 1H), 3.53 – 3.49 (m, 17H), 3.44 – 3.36 (m, 2H), 3.27 – 3.15 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.20 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_7S^+$: 805.2814; Found: 805.2890.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-7,10,13-trioxa-3-azahexadecan-16-yl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,13*}). Beige solid. Yield 0.040 g (45%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.40 (t, *J* = 5.9 Hz, 1H), 8.17 (t, *J* = 5.9 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.82 – 3.73 (m, 1H), 3.55 – 3.38 (m, 15H), 3.28 – 3.08 (m, 4H), 2.82 – 2.72 (m, 1H), 2.71 – 2.63 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H), 1.72 (p, *J* = 6.9 Hz, 2H), 1.65 (p, *J* = 6.6 Hz, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_7S^+$: 833.3129; Found: 833.3197.

(*S*)-*N*-(1-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-17-yl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-

methylbenzamide (6{*3,14*}). Beige solid. Yield 0.044 g (50%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.47 (br. s, 1H), 8.25 (br. s, 1H), 7.74 – 7.68 (m, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.82 – 3.73 (m, 1H), 3.55 – 3.46 (m, 15H), 3.45 – 3.35 (m, 4H), 3.26 – 3.14 (m, 4H), 2.82 – 2.72 (m, 1H), 2.71 – 2.63 (m, 1H), 2.57 (s, 3H), 2.39 (s, 3H), 2.20 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_8S^+$: 849.3078; Found: 849.3153.

(*S*)-*N*-(3-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)propyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,16*}). Beige solid. Yield 0.043 g (54%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.45 (br. s, 1H), 8.18 (br. s, 1H), 7.72 – 7.65 (m, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 4.48 (t, *J* = 6.3 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.55 – 3.47 (m, 1H), 3.27 – 3.17 (m, 4H), 3.15 – 3.09 (m, 2H), 2.81 – 2.71 (m, 1H), 2.70 – 2.63 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.34 – 2.25 (m, 4H), 2.19 (s, 3H), 2.11 (s, 3H), 1.65 – 1.53 (m, 7H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{38}H_{45}ClN_9O_4S^+$: 758.2921; Found: 758.2990.

(*S*)-*N*-(4-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,17*}). Beige solid. Yield 0.040 g (49%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.40 (br. s, 1H), 8.16 (br. s, 1H), 7.73 – 7.66 (m, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.54 – 3.48 (m, 1H), 3.24 – 3.16 (m, 4H), 3.13 – 3.07 (m, 2H), 2.81 – 2.72 (m, 1H), 2.71 – 2.63 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.31 – 2.24 (m, 4H), 2.20 (s, 3H), 2.09 (s, 3H), 1.61 – 1.50 (m, 5H), 1.52 – 1.46 (m, 2H), 1.44 – 1.39 (m, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{47}ClN_9O_4S^+$: 772.3081; Found: 772.3154.

(*S*)-*N*-(4-((4-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)butyl)(methyl)amino)butyl)-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzamide (6{*3,18*}). Beige solid. Yield 0.021 g (25%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.37 (s, 1H), 8.40 (br. s, 1H), 8.16 (br. s, 1H), 7.72 – 7.66 (m, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.84 – 3.71 (m, 1H), 3.55 – 3.48 (m, 1H), 3.26 – 3.16 (m, 2H), 3.16 – 3.01 (m, 2H), 2.83 – 2.72 (m, 1H), 2.72 – 2.63 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.27 – 2.22 (m, 6H), 2.20 (s, 3H), 2.07 (s, 3H), 1.60 (s, 3H), 1.53 – 1.44 (m, 1H), 1.43 – 1.39 (m, 7H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{40}H_{49}ClN_9O_4S^+$: 786.3233; Found: 786.3311.

(*S*)-4-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide (6{*4,1*}). Beige solid. Yield 0.052 g (72%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.90 (s, 1H), 8.27 (t, *J* = 5.8 Hz, 1H), 7.50 – 7.37 (m, 6H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.53 – 4.46 (m, 1H), 3.75 – 3.65 (m, 1H), 3.49 – 3.43 (m, 1H), 3.28 – 3.08 (m, 4H), 2.77 – 2.69 (m, 1H), 2.68 – 2.63 (m, 1H), 2.58 (s, 3H), 2.39 (s, 3H), 2.36 – 2.31 (m, 2H), 2.12 (s, 3H), 1.79 – 1.71 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{34}H_{36}ClN_8O_4S^+$: 687.2179; Found: 687.2257.

(*S*)-5-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)pentanamide (6{*4,2*}). Brownish solid. Yield 0.026 g (35%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.88 (s, 1H), 8.20 (t, *J* = 5.6 Hz, 1H), 7.49 – 7.37 (m, 6H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.74 – 3.65 (m, 1H), 3.50 – 3.42 (m, 1H), 3.27 – 3.22 (m, 1H), 3.19 – 3.10 (m, 2H), 3.10 – 3.03 (m, 2H), 2.77 – 2.69 (m, 1H), 2.69 – 2.63 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.32 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 1.67 – 1.53 (m, 4H), 1.50 – 1.44 (m, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_4S^+$: 701.2345; Found: 701.2418.

(*S*)-6-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)hexanamide (6{*4,3*}). Beige solid. Yield 0.042 g (55%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.86 (s, 1H), 8.17 (t, *J* = 5.6 Hz, 1H), 7.50 – 7.45 (m, 3H), 7.44 – 7.37 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.74 – 3.64 (m, 1H), 3.50 – 3.41 (m, 1H), 3.26 – 3.04 (m, 4H), 2.75 – 2.68 (m, 1H), 2.68 – 2.63 (m, 1H), 2.57 (s, 3H), 2.39 (s, 3H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 1.62 – 1.56 (m, 5H), 1.49 – 1.42 (m, 2H), 1.37 – 1.30 (m, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_4S^+$: 715.2493; Found: 715.2564.

(*S*)-7-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)heptanamide (6{*4,4*}). Beige solid. Yield 0.023 g (30%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.87 (s, 1H), 8.15 (br. s, 1H), 7.49 – 7.38 (m, 6H), 7.13 (d, *J* = 8.4 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.74 – 3.62 (m, 1H), 3.51 – 3.38 (m, 1H), 3.27 – 3.03 (m, 4H), 2.77 – 2.63 (m, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.27 (br. t, *J* = 7.7 Hz, 2H), 2.11 (s, 3H), 1.60 (s, 3H), 1.58 – 1.50 (m, 2H), 1.48 – 1.37 (m, 2H), 1.33 – 1.23 (m, 4H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_4S^+$: 729.2660; Found: 729.2736.

(*S*)-8-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)octanamide (6{*4,5*}). Brownish solid. Yield 0.045 g (57%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.85 (s, 1H), 8.15 (t, *J* = 5.4 Hz, 1H), 7.49 – 7.44 (m, 3H), 7.43 – 7.37 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.73 – 3.64 (m, 1H), 3.50 – 3.41 (m, 1H), 3.27 – 3.02 (m, 4H), 2.78 – 2.60 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.26 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 1.60 (s, 3H), 1.59 – 1.51 (m, 2H), 1.44 – 1.40 (m, 2H), 1.30 – 1.26 (m, 6H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{38}H_{44}ClN_8O_4S^+$: 743.2813; Found: 743.2886.

(*S*)-10-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)decanamide (6{*4,6*}). Beige solid. Yield 0.044 g (54%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.84 (s, 1H), 8.14 (br. s, 1H), 7.49 – 7.43 (m, 3H), 7.43 – 7.38 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.73 – 3.64 (m, 1H), 3.50 – 3.42 (m, 1H), 3.26 – 2.99 (m, 4H), 2.77 – 2.62 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.26 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.41 (s, 1H), 1.25 (br. s, 10H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{40}H_{48}ClN_8O_4S^+$: 771.3138; Found: 771.3208.

(*S*)-2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(2-(2-((4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)amino)-2-oxoethoxy)ethyl)acetamide (6{*4,7*}). Yellowish solid. Yield 0.047 g (63%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.61 (s, 1H), 8.44 (br. s, 1H), 7.54 – 7.35 (m, 6H), 7.12 (d, *J* = 8.4 Hz, 1H), 4.51 (dd, *J* = 8.5, 5.8 Hz, 1H), 4.09 (s, 2H), 3.75 – 3.62 (m, 1H), 3.61 – 3.56 (m, 2H), 3.49 – 3.41 (m, 2H), 3.37 – 3.30 (m, 2H), 3.24 – 3.14 (m, 1H), 2.77 – 2.63 (m, 2H), 2.57 (s, 3H), 2.36 (s, 3H), 2.06 (d, *J* = 15.6 Hz, 3H), 1.53 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{34}H_{36}ClN_8O_5S^+$: 703.2131; Found: 703.2205.

(*S*)-3-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propanamide (6{*4,8*}). Colorless solid. Yield 0.033 g (44%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.96 (s, 1H), 8.26 (t, *J* = 5.9 Hz, 1H), 7.50 – 7.37 (m, 6H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.73 – 3.67 (m, 3H), 3.49 – 3.41 (m, 3H), 3.28 – 3.13 (m, 4H), 2.78 – 2.68 (m, 1H), 2.68 – 2.62 (m, 1H), 2.59 – 2.53 (m, 5H), 2.39 (s, 3H), 2.11 (d, *J* = 3.6 Hz, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{35}H_{38}ClN_8O_5S^+$: 717.2292; Found: 717.2367.

(*S*)-4-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide (6{*4,9*}). Beige solid. Yield 0.033 g (43%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.90 (s, 1H), 8.25 (br. s, 1H), 7.52 – 7.35 (m, 6H), 7.12 (d, *J* = 8.2 Hz, 1H), 4.51 – 4.47 (m, 1H), 3.73 – 3.62 (m, 2H), 3.51 – 3.35 (m, 4H), 3.28 – 3.16 (m, 6H), 2.76 – 2.63 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.11 (s, 3H), 1.86 – 1.74 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2448; Found: 731.2522.

(*S*)-3-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propanamide (6{*4,10*}). Beige solid. Yield 0.044 g (57%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.94 (s, 1H), 8.17 (br. s, 1H), 7.50 – 7.45 (m, 3H), 7.45 – 7.37 (m, 3H), 7.13 (d, *J* = 8.6 Hz, 1H), 4.49 (t, *J* = 7.1 Hz, 1H), 3.74 – 3.60 (m, 3H), 3.50 – 3.38 (m, 3H), 3.23 – 3.07 (m, 4H), 2.79 – 2.62 (m, 2H), 2.57 (s, 3H), 2.55 – 2.50 (m, 2H), 2.38 (s, 3H), 2.11 (s, 3H), 1.67 – 1.58 (m, 5H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_5S^+$: 731.2452; Found: 731.2532.

(*S*)-4-(3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide (6{*4,11*}). Beige solid. Yield 0.033 g (42%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.89 (s, 1H), 8.20 (br. s, 1H), 7.50 – 7.44 (m, 3H), 7.42 – 7.37 (m, 3H), 7.12 (d, *J* = 8.5 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.73 – 3.63 (m, 1H), 3.50 – 3.41 (m, 1H), 3.41 – 3.35 (m, 6H), 3.23 – 3.09 (m, 4H), 2.79 – 2.63 (m, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.10 (s, 3H), 1.82 – 1.71 (m, 2H), 1.68 – 1.62 (m, 2H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_5S^+$: 745.2597; Found: 745.2672.

(*S*)-2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(2-(2-(2-((4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)amino)-2-oxoethoxy)ethoxy)ethyl)acetamide (6{*4,12*}). Beige solid. Yield 0.042 g (54%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.30 (s, 1H), 9.62 (s, 1H), 8.30 (br. s, 1H), 7.54 – 7.44 (m, 4H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 1H), 4.52 – 4.45 (m, 1H), 4.07 (s, 2H), 3.73 – 3.60 (m, 6H), 3.51 – 3.41 (m, 4H), 3.27 – 3.16 (m, 2H), 2.78 – 2.63 (m, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.11 (s, 3H), 1.59 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{36}H_{40}ClN_8O_6S^+$: 747.2396; Found: 747.2468.

(*S*)-3-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propenamide (6{*4,13*}). Brownish solid. Yield 0.128 g (89%). 1H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.94 (s, 1H), 8.26 (br. s, 1H), 7.49 – 7.44 (m, 3H), 7.43 – 7.37 (m, 3H), 7.14 (d, J = 8.4 Hz, 1H), 4.52 – 4.43 (m, 1H), 3.70 – 3.65 (m, 3H), 3.51 (s, 4H), 3.48 – 3.39 (m, 3H), 3.26 – 3.15 (m, 4H), 2.74 – 2.63 (m, 2H), 2.57 (s, 3H), 2.55 – 2.51 (m, 2H), 2.39 (s, 3H), 2.11 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{37}H_{42}ClN_8O_6S^+$: 761.2547; Found: 761.2622.

(*S*)-2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(2-(2-(2-(2-((4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)amino)-2-oxoethoxy)ethoxy)ethoxy)ethyl)acetamide (6{*4,14*}). Brownish solid. Yield 0.041 g (49%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 9.60 (s, 1H), 8.25 (s, 1H), 7.55 – 7.44 (m, 4H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 1H), 4.48 (t, *J* = 6.9 Hz, 1H), 4.06 (s, 2H), 3.73 – 3.51 (m, 11H), 3.49 – 3.39 (m, 3H), 3.26 – 3.14 (m, 2H), 2.81 – 2.62 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.12 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{38}H_{44}ClN_8O_7S^+$: 791.2658; Found: 791.2738.

(*S*)-3-(2-(2-(2-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethoxy)ethoxy)ethoxy)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)propanamide (6{*4,15*}). Beige solid. Yield 0.037 g (44%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.92 (s, 1H), 8.25 (br. s, 1H), 7.49 – 7.37 (m, 6H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.55 – 4.38 (m, 1H), 3.73 – 3.62 (m, 4H), 3.55 – 3.38 (m, 10H), 3.30 – 3.13 (m, 4H), 2.79 – 2.63 (m, 2H), 2.57 (s, 3H), 2.55 – 2.50 (m, 2H), 2.39 (s, 3H), 2.12 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_7S^+$: 805.2816; Found: 805.2891.

(*S*)-14-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)-3,6,9,12-tetraoxatetradecanamide (6{*4,16*}). Yellowish solid. Yield 0.030 g (34%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 (s, 1H), 9.59 (s, 1H), 8.24 (br. s, 1H), 7.53 – 7.44 (m, 4H), 7.42 – 7.38 (m, 2H), 7.17 (d, *J* = 8.5 Hz, 1H), 4.51 – 4.45 (m, 1H), 4.05 (s, 2H), 3.74 – 3.57 (m, 4H), 3.56 – 3.49 (m, 11H), 3.48 – 3.38 (m, 3H), 3.26 – 3.15 (m, 2H), 2.79 – 2.63 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.13 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{40}H_{48}ClN_8O_8S^+$: 835.2926; Found: 835.3001.

(*S*)-1-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)-3,6,9,12-tetraoxapentadecan-15-amide (6{*4,17*}). Beige solid. Yield 0.030 g (34%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 (s, 1H), 9.93 (s, 1H), 8.27 (s, 1H), 7.49 – 7.44 (m, 3H), 7.43 – 7.37 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.69 – 3.63 (m, 3H), 3.53 – 3.46 (m, 15H), 3.45 – 3.39 (m, 2H), 3.26 – 3.16 (m, 2H), 2.76 – 2.62 (m, 2H), 2.57 (s, 3H), 2.54 – 2.51 (m, 2H), 2.39 (s, 3H), 2.12 (s, 3H), 1.60 (s, 3H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_8S^+$: 849.3076; Found: 849.3151.

(*S*)-4-((3-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)propyl)(methyl)amino)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)butanamide (6{*4,18*}). Beige solid. Yield 0.017 g (22%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.87 (s, 1H), 8.18 (t, *J* = 5.4 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.43 – 7.36 (m, 4H), 7.12 (d, *J* = 8.5 Hz, 1H), 4.49 (t, *J* = 7.1 Hz, 1H), 3.73 – 3.64 (m, 1H), 3.45 (dt, *J* = 12.1, 5.9 Hz, 2H), 3.27 – 3.14 (m, 2H), 3.16 – 3.07 (m, 1H), 2.79 – 2.58 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 2.33 – 2.26 (m, 8H), 2.14 – 2.08 (m, 5H), 1.72 – 1.66 (m, 2H), 1.60 (s, 3H), 1.58 – 1.53 (m, 2H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{38}H_{45}ClN_9O_4S^+$: 758.2921; Found: 758.2997.

(*S*)-11-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)undecanamide (6{*4,19*}). Beige solid. Yield 0.042 g (52%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.84 (s, 1H), 8.15 (br. s, 1H), 7.49 – 7.44 (m, 3H), 7.43 – 7.38 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.73 – 3.64 (m, 1H), 3.50 – 3.41 (m, 1H), 3.23 – 3.12 (m, 2H), 3.13 – 3.01 (m, 2H), 2.78 – 2.63 (m, 1H), 2.57 (s, 3H), 2.39 (s, 3H), 2.26 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 1.60 (s, 3H), 1.57 – 1.50 (m, 2H), 1.45 – 1.37 (m, 2H), 1.26 (br. s, 13H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{41}H_{50}ClN_8O_4S^+$: 785.3281; Found: 785.3357.

(*S*)-9-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)-*N*-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methylphenyl)nonanamide (6{*4,20*}). Beige solid. Yield 0.053 g (64%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 9.83 (s, 1H), 8.13 (br. s, 1H), 7.48 – 7.43 (m, 3H), 7.43 – 7.38 (m, 3H), 7.13 (d, *J* = 8.6 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.74 – 3.64 (m, 1H), 3.53 – 3.39 (m, 2H), 3.24 – 2.99 (m, 2H), 2.78 – 2.64 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.26 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 1.66 – 1.49 (m, 5H), 1.46 – 1.34 (m, 2H), 1.24 (br. s, 9H) ppm. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{39}H_{46}ClN_8O_4S^+$: 757.2967; Found: 757.3045.

FP displacement assay for dihydrouracil-derived building blocks 7{*1–36*}. 36 dihydrouracil-derived building blocks **7**{*1–36*} (Figure S1) and their 27 simplest derivatives (shown in Table S1) have been tested in the fluorescence polarization assay, where competitive binding with CRBN was observed between the Cy5-Thalidomide probe and compounds. The assay was performed in a black 384-well plate (Corning #4514) in quadruplicates with a reaction volume of 20 µL per well. Control wells with DMSO in the presence of all reaction components were used as 0% displacement control, and no protein control was utilized to imitate 100% displacement to allow for normalization of tested compounds. Reference compound Pomalidomide was added at an IC50 concentration (0.25 µM) to monitor the assay quality. Using an Echo 650 acoustic dispenser (Labcyte), samples as well as DMSO and Pomalidomide control, were transferred into the empty wells of 384-well assay plates to obtain a final 10 µM tested compound concentration, 0.25 µM Pomalidomide concentration, and 1% DMSO concentration. The final concentrations for DDB1/CRBN protein (R&D #E3-500-025) and Cy5-Thalidomide (Enamine) were 17 and 10 nM, respectively. Reaction components were diluted in 50 mM Tris-HCl (pH 7.5), 1 mM DTT, 0.01% BSA, 0.01% Triton X-100 assay buffer. The compounds were pre-incubated with CRBN/DDB1 for 1 hour at room temperature (RT). The complete reaction was incubated for 2.5 hours. The fluorescent signal was read with a BMG PHERAstar FSX (BMG LABTECH) plate reader. The percentage displacement of each PROTAC was calculated from the mP units normalized to the controls.

TR-FRET displacement assay. The assay was performed in a buffer containing 50 mM Tris-HCl (pH=7.5), 1 mM DTT, 0.01% Triton X-100, 0.01% BSA, and conducted in a 384-well plate (Corning #4513) in quadruplicates with a reaction volume of 9 µL per well. Control wells containing all assay components with no compound (0% displacement) and without protein (100% displacement) were included to allow for normalization of tested compounds. Also, reference compound Lenalidomide was added at an IC_{50} concentration (2 µM) to monitor the assay quality. Using an Echo 650 acoustic dispenser (Labcyte), 72 synthesized PROTACs, as well as DMSO and Lenalidomide control, were transferred into the empty wells of 384-well assay plates to obtain a final 1.11 µM tested compound concentration, 2 µM Lenalidomide concentration, and 0.5% DMSO concentration. The final concentrations of the reaction components were 5 nM for FLAG-CRBN/DDB1 (BPS #102166), 5 nM for Thalidomide-Red ligand (Revvity # 64BDCRBNRED), and 0.25 nM for LANCE Eu-W1024 Anti-FLAG Antibody (Revvity #AD0274). The compounds were pre-incubated with CRBN/DDB1 for 30 minutes at room temperature (RT). After 1 hour of incubation with detection reagents, the TR-FRET signal was recorded on a PHERAstar plate reader (BMG LABTECH) (ex=340 nm, em1=620 nm, em2=665 nm). The percentage displacement of each PROTAC was calculated from the TR-FRET ratio normalized to the controls.

SPR for binary complex formation study of BRD4 and PROTACs 6{*1–4*,*1–20*}. Surface plasmon resonance (SPR) experiments were performed on a Biacore T200 system (GE Healthcare) using NA Sensor Chip (Cytiva), that was preconditioned prior to immobilization according to the vendor's recommendations. Biotinylated Avi-tagged BrD4(BD1), produced at Enamine, was immobilized at 25 °C in 1× HBS-N buffer (Cytiva) to a target density of 1000 RU. Post-immobilization, both flow cells were blocked by injecting 10 µg/mL of Biocytin (Thermo Fisher Scientific) for 3 min at 10 µL/min to prevent nonspecific binding. The chip was then equilibrated in running buffer (1 x HBS-P+ buffer, 0.5 mM TCEP, 3% DMSO, pH 7.4). All procedures were conducted at 25 °C.

The reference compound JQ1 was assessed in a dose-response with the top concentration set to 1000 nM using a 3-fold serial dilution across five points. The dissociation time for JQ1 was 420 s, which enabled its assessment in Multi-Cycle Kinetics mode. The 1000 nM point (10×KD) was also injected separately every 30 cycles throughout the run. PROTACs were assessed at a single concentration (100 nM) in Multi-Cycle Kinetics mode, with a contact time of 60 s and a dissociation time of 420 s. The flow rate for all steps was set to 30 µL/min. Data was processed using Biacore Insight Evaluation Software (Cytiva). Binding Screen analysis included solvent correction, double referencing, molecular weight adjustment, and normalization to the saturated (+)-JQ1 response. All raw and corrected sensorgrams were visually inspected and manually verified.

High-throughput solubility threshold measurement for PROTACs 6{*1–4*,*1–20*}. DMSO stock solutions of 72 test compounds were prepared at 20 mM and 0.4 mM. Formazine at 5 and 10 NTU was prepared by diluting a 4000 NTU aqueous concentrate. To perform the screening, 0.5 µl concentration aliquots of DMSO stocks of test compounds were added to each well of the 96-well microplate with a clear flat bottom. Then, 200 µl of PBS was dispensed into each well using a Matrix Multichannel Electronic Pipette and mixed. After this, the samples were incubated for 5 minutes, after which the turbidity of the solutions was scanned for each well. The final concentration of compounds was 50 and 1 µM. The final concentration of DMSO was 0.25%.

Solubility for each compound, normalized to formazine 5 NTU (100% soluble) and formazine 10 NTU (low solubility), was calculated. Selected ranges of Relative Solubility allow dividing compounds into distinguishable groups according to their solubility thresholds: <0.6 µM – low, 0.6…0.8 µM – medium, and >0.8 µM – high solubility.

TR-FRET ternary complex formation assay. The assay was performed in a buffer containing 50 mM Tris-HCl (pH=7.5), 1 mM DTT, 0.01% Triton X-100, 0.01% BSA, and conducted in a 384-well plate (Corning #4513) with a reaction volume of 10 µL per well. Using a Labcyte Echo 650 acoustic dispenser, the 69 titrated PROTACs in DMSO were transferred into the empty wells of 384-well assay plates to obtain a preferred compound concentration (12-point, 3-fold serial dilution in duplicates from 100 µM) and 0.5% final DMSO concentration. The final concentrations of the reaction components were 75 nM for Biotin-Avi-BrD4 (BD1) (Enamine), 10 nM for Streptavidin-d2 (Revvity # 610SADLA/B), 5 nM for FLAG-

CRBN/DDB1 (BPS #102166), and 0.5 nM for LANCE Eu-W1024 Anti-FLAG Antibody (Revvity #AD0274). First, a mixture of Biotin-Avi-BrD4(BD1) and Streptavidin-d2 was added to the plate containing the compounds and preincubated for 30 minutes at room temperature (RT). Subsequently, a mixture of FLAG-CRBN/DDB1 and LANCE Eu-W1024 Anti-FLAG Antibody was added. Titrated dBET1 reference compound was utilized as assay control (12-point, 3-fold serial dilution in duplicates from 30 μM). After an additional 2 h of incubation, TR-FRET signal was recorded on a PHERAstar plate reader (BMG LABTECH) (ex=340 nm, em1=620 nm, em2=665 nm). The bell-shaped dose-response curves of each PROTAC, as well as the reference dBET1 compound, were created from the TR-FRET ratio using Prism software (GraphPad, v.10). The EC_{50} and EC_{max} values were calculated from the logistic model.

TR-FRET BrD4 degradation cell-based assay. The HepG2 cells (DSMZ #ACC180) were grown in medium containing MEM, 10% FBS, 1% pen/strep, and seeded 16 hours before compound dosing. The target cell density was estimated as 15000 cells per well. The assay was conducted in a 384-well, TC plate (Revvity #6008238) with a reaction volume of 20 μL per well. The assay medium consisted of MEM, 1% FBS, and 1% pen/strep. Control wells containing assay components and DMSO (0% degradation) and saturated concentration of dBET6 control (100% degradation) were included to allow for normalization of tested compounds. Using an Echo 650 acoustic dispenser (Labcyte), the selected PROTACs, as well as DMSO and dBET6 control, were transferred into the empty wells of 384-well assay plates to obtain a final desired compound concentration, saturated dBET6 concentration (100% degradation control), and 0.1% DMSO concentration. The compounds were pre-incubated with cells for 6 hours (12 μL) following the addition of 4× lysis buffer (4 μL). After additional incubation for 30 minutes, the BrD4 antibody mixed solution (Revvity #64BRD4TPEG) was added to all tested wells (4 μL). After overnight incubation with detection reagents, the TR-FRET signal was recorded on a SpectraMax Paradigm plate reader (Molecular

Devices) (ex=340 nm, em1=620 nm, em2=665 nm). The percentage degradation from each PROTAC was calculated from the TR-FRET ratio normalized to the controls.

Western blot analysis. The following antibodies were used: anti-BRD4 (Cell Signaling Technology, #13440) and HRP-conjugated anti-rabbit secondary antibody (Invitrogen, #65-6120). NuPAGE™ Sample Buffer (Invitrogen™, #NP0007) and NuPAGE™ Sample Reducing Reagent (Invitrogen™, #NP0009) were used for preparation of protein samples prior to electrophoresis. Chemiluminescent detection was performed using Pierce™ ECL Western Blotting Substrate (Thermo Scientific, #32109). PVDF membranes were used for protein transfer, and signal detection was performed using the iBright imaging system.

Human hepatocellular carcinoma cells HepG2 (DSMZ, #ACC-180) were cultured at 37 °C in a humidified atmosphere containing 5% CO_2 in the appropriate culture media: DMEM (Capricorn Scientific, #DMEM-HA-P50) supplemented with 10% FBS (Sigma, #F7524-500ML), 2 mM GlutaMAX (Gibco, #3505065), 1 mM Sodium pyruvate (Sigma-Aldrich, #S8636-100ML), 100 U/mL penicillin, and 100 µg/mL streptomycin (Gibco, Life Technologies).

For the experiment, cells were seeded in 6-well plates (Corning, #353046) at a density of 450,000 cells per well in 2 mL of DMEM supplemented with 1% FBS, 2mM GlutaMAX, 1 mM Sodium pyruvate, 100 U/mL penicillin, and 100 µg/mL streptomycin. Cells were incubated for 24 hours to allow cell attachment prior to compound treatment.

Test compounds were initially prepared as 20 mM stock solutions in DMSO. A six-fold serial dilution series was prepared in a 96-well plate to generate five concentration points. Intermediate dilutions were prepared in assay medium and corresponded to 11× the final working concentrations. After preparation, compound solutions were thoroughly mixed, and 200 µL of each dilution was transferred to plates containing HepG2 cells. The final compound concentrations in the wells consisted of five concentration points starting from 1000 nM, followed by a six-fold serial dilution.

Cells were incubated with compounds for 48 h under standard culture conditions. After compound incubation, cells were lysed using RIPA buffer supplemented with protease and phosphatase inhibitor cocktail to obtain whole-cell protein lysates. Protein concentration in the lysates was determined using a BCA protein assay according to the manufacturer's instructions. Lysates were subsequently normalized to equal protein concentration.

Equalized protein samples were mixed with NuPAGE™ Sample Buffer and NuPAGE™ Sample Reducing Reagent and incubated at 70 °C for 10 minutes to ensure protein denaturation and reduction prior to electrophoresis. Protein samples were separated by SDS-PAGE using 12% polyacrylamide resolving gels with a 4% stacking gel, prepared according to the Bio-Rad gel preparation protocol. Electrophoresis was performed using Tris-glycine running buffer. Each sample was loaded at a concentration of 12 μg of total protein per gel well.

Following electrophoresis, proteins were transferred onto PVDF membranes using the Trans-Blot® Turbo™ Transfer System (Bio-Rad). After transfer, membranes were blocked with 3% BSA in TBST to prevent nonspecific antibody binding. Membranes were incubated with primary antibody against BRD4 (Cell Signaling Technology, #13440) diluted 1:1500 overnight at 4 °C with gentle agitation. The following day, membranes were washed with TBST and incubated with HRP-conjugated anti-rabbit secondary antibody (Invitrogen, #65-6120) diluted 1:3000 for 1.5 hours at room temperature. After secondary antibody incubation, membranes were washed with TBST and developed using Pierce™ ECL Western Blotting Substrate. Chemiluminescent signals were detected using the iBright imaging system.

Competition experiments. The BET degrader dBET6 (Cat. No. HY-112588) was obtained from MedChemExpress (Monmouth Junction, NJ, USA). Lenalidomide (Cat. No. HY-A0003), JQ-1 (Cat. No. HY-13030), and Pevonedistat (Cat. No. HY-70062) were obtained from MedChemExpress (Monmouth Junction, NJ, USA). Test compounds were dissolved in DMSO to achieve a 20 mM stock concentration and were stored in 384-well low dead volume (LDV) microplates (LP-0200; Beckman Coulter Life Sciences). The HTRF Human and Mouse Total BRD4 Detection Kit (Cat. No. 64BRD4TPEG) was purchased from Revvity (Waltham, MA, USA).

HepG2 cells were maintained in Minimum Essential Medium (MEM) supplemented with GlutaMAX™ (Gibco, Life Technologies), 10% fetal bovine serum (FBS; Gibco, Life Technologies), 100 U/mL penicillin, and 100 µg/mL streptomycin (Gibco, Life Technologies). Cells were cultured at 37 °C in a humidified atmosphere containing 5% CO_2. For assay setup, cells were plated in assay medium consisting of MEM supplemented with GlutaMAX™, 1% FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin (Gibco, Life Technologies). Trypsin-EDTA solution (Sigma-Aldrich, Cat. No. T4049) was used for cell detachment.

Compounds were diluted in 100% DMSO to the desired concentrations. Using the Echo® 655 Liquid Handler (Beckman Coulter Life Sciences). 75 nL of each diluted compound was transferred to the intermediate compound plate. Following the addition of assay medium to the intermediate compound plate, compounds at 3x concentration were transferred to the assay plate using the Integra ViaFlo 384 electronic pipette (Integra Biosciences).

The HTRF assay was performed in white, small-volume 384-well plates (Revvity, Cat. No. 6008238), with a final reaction volume of 20 µL per well. Cells were seeded at a density of 15,000 cells per well in assay medium and incubated overnight at 37 °C in a humidified atmosphere containing 5% CO_2. Following a 6-hour incubation with test compounds, cells were lysed, and d_2- and Europium Cryptate-labeled antibodies were added to each well. The reaction mixture was then incubated overnight at 25 °C. The signal was monitored using a SpectraMax Paradigm multi-mode microplate reader (Molecular Devices) equipped with the 0200-7011 HTRF detection module, using excitation at 340 nm and dual emission at 665 and 620 nm, respectively. The HTRF signal was calculated as the ratio of fluorescence intensities at 665 nm and 620 nm (665/620) for each well. Raw values were normalized to the signals obtained from DMSO-treated (negative control) and 1 μM dBET6-treated (positive control) samples.

Cell viability assay. HepG2 cells (DSMZ #ACC-180) were grown in medium containing DMEM, 10% FBS, 1% GlutaMAX, 1% sodium pyruvate, 1% pen/strep; HDF cell line (PromoCell #C-12302) was grown in DMEM, 10% FBS, 1% GlutaMAX, 1ng/mL bFGF, 1% pen/strep; U2-OS cell line (ATCC #HTB-96) in DMEM, 10% FBS, 1% GlutaMAX, 1% pen/strep; and K562 (ATCC #CCL-243) - in RPMI, 10% FBS, and 1% pen/strep. All cells were seeded on plates 24 hours before compound dosing at the optimal cell densities of 5000, 2000, 1000, and 2500 cells per well, respectively. The assay was conducted in a white, 384-well plate (Greiner #781098), with a reaction volume of 50 μL per well. Control wells containing DMSO (100% viability) and saturated concentration of Doxorubicin (0% viability) were included to allow for normalization of tested compounds. Using an Echo 650 acoustic dispenser (Labcyte), the selected PROTACs, as well as DMSO, dBET1, and Doxorubicin, were transferred into the empty wells of 384-well assay plates to obtain a final desired compound concentration, saturated (100 μM) Doxorubicin concentration (0% cell viability control), and 0.5% DMSO concentration. The compounds were incubated with cells for 48 hours (10 μL) following the addition of CellTiter-Glo Reagent (10 μL) with a 30-minute pre-incubation of plates at room temperature. After that, plates were put on VibraTranslator (Union Scientific) for 15 min at 9A (~25°C, in the dark). The luminescent signal was recorded on a BMG PHERAstar plate reader (BMG LABTECH) right after a 25°C 3 min pre-incubation inside the reader. The percentage viability of each PROTAC was calculated based on the RLU data normalized to the controls.

Resulting IC_{50} values were determined using a 4PL logistic model. To assess for rank correlation between degradation and cytotoxicity results in the HepG2 cell line, Spearman's non-parametric correlation test was utilized.

References

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