Electronic Supplementary Information (ESI)

*"*Analysis of the Productivity of DNA Encoded Libraries*"*

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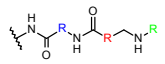
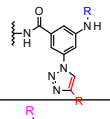
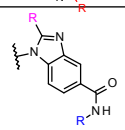
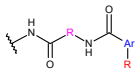
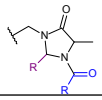
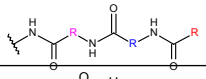
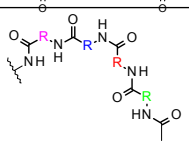
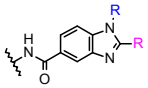
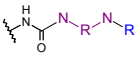
Table S1. Library Schemes for 16 DELs contained in library pool.

Lib ID	Scheme[a]	Lib ID	Scheme
1,3,10		**8**	
2		**9**	
4,15		**11**	
5, 14		**12**	
6		**13**	
7		**16**	

[a]General synthetic protocols have been previously reported by Satz A.L. *et al.*, 2015, *Bioconjugate Chem*. **26**, 1623–1632.

Table S2. List of DEL-derived small molecule compounds synthesized following screening of phosophodiesterase and kinase targets.

Cmpd ID	Cluster ID	pIC50	LIB_ID	cLogP	MW	Heavy Atoms	Rot Bond	Enrich[a]	BBs[b]	Target
1	1	0	4	4.4	376	27	4	55	2	phosphodiesterase
2	2	4.7	2	5.0	563	38	12	94	2	phosphodiesterase
3	1	8.7	4	3.6	386	29	5	144	2	phosphodiesterase
4	3	6.6	5	1.0	525	37	7	29	2	phosphodiesterase
5	4	9.0	5	3.2	579	40	8	17	3	phosphodiesterase
6	2	0	2	4.5	456	33	9	349	2	phosphodiesterase
7	2	5.2	2	4.1	492	36	10	138	2	phosphodiesterase
8	3	6.8	5	1.3	559	40	8	116	2	phosphodiesterase
9	4	6.1	5	3.7	316	23	8	90	2	phosphodiesterase
10	5	5.8	5	3.6	408	29	8	229	2	phosphodiesterase
11	6	7.2	4	2.5	244	18	3	84	2	phosphodiesterase
12	7	6.8	5	3.0	448	30	6	126	2	phosphodiesterase
13	8	4.0	4	2.3	452	33	9	17	2	phosphodiesterase
14	9	4.4	5	3.2	362	26	6	164	2	phosphodiesterase
15	10	5.5	1	3.3	447	25	7	111	2	phosphodiesterase
16	2	4.6	2	4.1	442	32	10	243	2	phosphodiesterase
17	11	7.3	4	3.2	329	24	6	21	2	phosphodiesterase
18	12	6.5	5	3.8	537	35	6	95	2	phosphodiesterase
19	13	7.6	1	2.9	526	33	10	44	3	phosphodiesterase
20	14	5.3	4	4.6	336	23	5	28	2	phosphodiesterase
21	15	6.2	5	3.1	469	33	10	120	2	phosphodiesterase
22	16	0	5	2.9	530	39	9	21	3	phosphodiesterase
23	12	0	5	4.3	521	38	7		2	phosphodiesterase

Cmpd ID	Cluster ID	pIC50	LIB_ID	cLogP	MW	Heavy Atoms	Rot Bond	Enrich[a]	BBs[b]	Target
24	12	4.0	5	4.5	495	37	7	16	2	phosphodiesterase
25	2	6.5	2	4.4	501	36	11	251	2	phosphodiesterase
26	12	7.0	5	3.5	447	33	7	145	2	phosphodiesterase
27	2	4.6	2	5.4	562	38	13	179	2	phosphodiesterase
28	10	5.4	1	3.5	400	25	7	90	2	phosphodiesterase
29	3	7.3	5	0.2	536	39	8		2	phosphodiesterase
30	17	0	6	2.6	415	31	5	48	2	kinase
31	18	4.3	5	1.1	308	23	4	21	2	kinase
32	19	0	3	4.0	393	28	3	21	2	kinase
33	20	5.6	7	5.4	437	33	5	303	2	kinase
34	21	0	16	3.3	565	37	8	119	2	kinase
35	22	0	11	5.4	467	33	4	38	2	kinase
36	20	0	7	4.7	446	34	4	45	2	kinase
37	23	5.6	16	4.8	608	44	8	35	2	kinase
38	24	0	5	3.2	354	26	4	20	2	kinase
39	21	7.2	16	3.0	509	33	7	65	2	kinase
40	18	5.7	5	1.5	308	23	3	30	2	kinase
41	25	5.2	16	3.4	505	35	5	12	2	kinase
42	26	6.6	16	4.2	506	35	7	30	2	kinase
43	22	5.6	11	6.5	561	42	6	136	2	kinase
44	27	0	1	2.4	462	34	7	63	2	kinase
45	28	5.4	7	6.4	606	45	9	182	2	kinase
46	21	5.9	16	3.2	594	38	8	15	2	kinase
47	29	6.7	5	1.7	594	44	8	9	3	kinase
48	18	5.6	5	3.8	410	31	5	48	2	kinase
49	30	6.1	5	1.5	544	31	9	81	2	kinase
50	31	0	2	4.7	478	35	10	567	2	kinase
51	32	5.4	16	4.5	551	40	8	12	2	kinase
52	29	5.9	5	0.9	447	33	4	65	2	kinase
53	33	0	9	4.9	535	40	10	30	2	kinase
54	34	6	14	2.8	459	34	9	39	2	kinase
55	25	6.1	16	4.2	458	33	6	71	2	kinase
56	31	0	2	4.0	486	34	11	548	2	kinase
57	30	0	5	3.9	516	33	7	18	2	kinase

[a]The extent to which the library member was enriched in a single screen above background (screen without protein present).

[b]Number of building blocks chemically joined together to produce the desired product.

Table S3. Tanimoto similarity based clustering of DEL-derived phosophodiesterase small molecule compounds results in 16 distinct clusters.[a]

Cluster ID	CMPD ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
1	1	1.00																												
2	2	0.26	1.00																											
1	3	0.68	0.31	1.00																										
3	4	0.19	0.31	0.13	1.00																									
4	5	0.25	0.27	0.20	0.34	1.00																								
2	6	0.19	0.56	0.29	0.24	0.27	1.00																							
2	7	0.19	0.59	0.29	0.24	0.25	0.67	1.00																						
3	8	0.14	0.24	0.13	0.84	0.34	0.24	0.24	1.00																					
16	9	0.19	0.23	0.20	0.23	0.25	0.30	0.22	0.23	1.00																				
5	10	0.23	0.27	0.24	0.19	0.30	0.31	0.30	0.19	0.29	1.00																			
6	11	0.28	0.18	0.27	0.17	0.25	0.26	0.22	0.17	0.31	0.32	1.00																		
7	12	0.23	0.36	0.15	0.41	0.43	0.25	0.23	0.32	0.29	0.30	0.18	1.00																	
8	13	0.10	0.10	0.12	0.21	0.21	0.13	0.16	0.21	0.11	0.12	0.15	0.16	1.00																
9	14	0.21	0.26	0.19	0.28	0.29	0.24	0.22	0.37	0.41	0.25	0.26	0.27	0.13	1.00															
10	15	0.36	0.34	0.26	0.30	0.26	0.27	0.27	0.23	0.26	0.28	0.22	0.34	0.12	0.27	1.00														
2	16	0.21	0.58	0.32	0.21	0.23	0.76	0.70	0.21	0.24	0.30	0.27	0.22	0.13	0.25	0.28	1.00													
11	17	0.33	0.28	0.50	0.17	0.23	0.34	0.30	0.17	0.24	0.26	0.34	0.17	0.15	0.16	0.24	0.33	1.00												
12	18	0.24	0.29	0.20	0.41	0.38	0.22	0.26	0.35	0.21	0.25	0.15	0.40	0.19	0.25	0.27	0.21	0.18	1.00											
13	19	0.24	0.31	0.17	0.41	0.31	0.24	0.26	0.35	0.21	0.21	0.18	0.35	0.19	0.33	0.35	0.25	0.17	0.33	1.00										
14	20	0.43	0.20	0.25	0.30	0.31	0.18	0.19	0.23	0.22	0.18	0.28	0.27	0.22	0.26	0.25	0.17	0.33	0.30	0.32	1.00									
15	21	0.23	0.18	0.26	0.19	0.30	0.21	0.23	0.19	0.19	0.28	0.24	0.28	0.24	0.22	0.18	0.20	0.24	0.29	0.21	0.32	1.00								
4	22	0.19	0.21	0.21	0.26	0.52	0.28	0.28	0.27	0.23	0.30	0.24	0.34	0.20	0.22	0.23	0.25	0.22	0.29	0.23	0.19	0.27	1.00							
12	23	0.17	0.21	0.17	0.35	0.35	0.21	0.23	0.44	0.30	0.21	0.19	0.31	0.19	0.48	0.21	0.20	0.16	0.66	0.28	0.24	0.25	0.28	1.00						
12	24	0.16	0.20	0.17	0.36	0.28	0.23	0.23	0.36	0.42	0.22	0.20	0.30	0.19	0.34	0.20	0.20	0.18	0.64	0.25	0.24	0.25	0.26	0.80	1.00					
2	25	0.21	0.68	0.33	0.23	0.22	0.65	0.60	0.23	0.26	0.27	0.24	0.22	0.13	0.26	0.27	0.85	0.33	0.21	0.26	0.17	0.20	0.23	0.19	0.20	1.00				
12	26	0.18	0.25	0.19	0.39	0.34	0.31	0.30	0.39	0.26	0.28	0.25	0.34	0.24	0.25	0.26	0.30	0.22	0.65	0.31	0.25	0.28	0.36	0.67	0.68	0.29	1.00			
2	27	0.26	0.67	0.29	0.29	0.27	0.64	0.65	0.24	0.22	0.27	0.22	0.32	0.12	0.24	0.32	0.67	0.30	0.29	0.29	0.22	0.18	0.23	0.23	0.21	0.57	0.27	1.00		
10	28	0.36	0.34	0.26	0.30	0.26	0.27	0.27	0.23	0.26	0.28	0.22	0.34	0.12	0.27	>.9	0.28	0.24	0.27	0.35	0.25	0.18	0.23	0.21	0.20	0.27	0.26	0.32	1.00	
3	29	0.14	0.36	0.22	0.75	0.27	0.35	0.34	0.75	0.22	0.20	0.16	0.29	0.21	0.24	0.20	0.32	0.27	0.35	0.29	0.20	0.21	0.26	0.33	0.36	0.37	0.38	0.32	0.20	1.00

[a]Compounds with similarity scores > 0.5 were grouped within the same cluster. Clusters possessing more than one compound have been color-coded. Calculations were determined using Pipeline Pilot with fingerprint property FCFP4.

Table S4. Tanimoto similarity clustering between DEL-derived kinase small molecule compounds results in 18 distinct clusters.[a]

Cluster ID	CMPD ID	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57
17	30	1.00																											
18	31	0.24	1.00																										
19	32	0.26	0.22	1.00																									
20	33	0.32	0.32	0.23	1.00																								
21	34	0.24	0.14	0.14	0.17	1.00																							
22	35	0.16	0.15	0.15	0.16	0.16	1.00																						
20	36	0.28	0.35	0.22	0.65	0.16	0.17	1.00																					
23	37	0.24	0.19	0.17	0.23	0.25	0.14	0.22	1.00																				
24	38	0.23	0.19	0.12	0.16	0.19	0.46	0.17	0.17	1.00																			
21	39	0.23	0.15	0.15	0.14	0.80	0.13	0.14	0.26	0.17	1.00																		
18	40	0.29	0.72	0.22	0.30	0.17	0.14	0.32	0.24	0.17	0.18	1.00																	
25	41	0.18	0.18	0.16	0.18	0.21	0.13	0.19	0.49	0.18	0.24	0.23	1.00																
26	42	0.25	0.22	0.19	0.20	0.34	0.13	0.19	0.24	0.14	0.41	0.29	0.31	1.00															
22	43	0.14	0.19	0.10	0.21	0.13	0.57	0.21	0.17	0.41	0.10	0.18	0.15	0.10	1.00														
27	44	0.26	0.22	0.21	0.17	0.16	0.18	0.17	0.22	0.23	0.17	0.21	0.17	0.14	0.21	1.00													
28	45	0.22	0.29	0.19	0.41	0.20	0.18	0.41	0.23	0.24	0.15	0.27	0.18	0.17	0.22	0.18	1.00												
21	46	0.18	0.13	0.11	0.12	0.58	0.17	0.12	0.23	0.25	0.62	0.15	0.23	0.24	0.21	0.17	0.13	1.00											
29	47	0.22	0.24	0.18	0.17	0.19	0.14	0.20	0.23	0.23	0.20	0.22	0.22	0.15	0.17	0.26	0.22	0.20	1.00										
35	48	0.28	0.39	0.22	0.27	0.21	0.14	0.28	0.22	0.17	0.23	0.46	0.32	0.33	0.14	0.25	0.25	0.19	0.17	1.00									
30	49	0.27	0.18	0.23	0.15	0.22	0.16	0.18	0.20	0.24	0.22	0.17	0.16	0.19	0.12	0.21	0.27	0.15	0.27	0.17	1.00								
31	50	0.24	0.24	0.16	0.20	0.22	0.14	0.21	0.16	0.21	0.16	0.22	0.18	0.18	0.15	0.18	0.19	0.15	0.23	0.20	0.21	1.00							
32	51	0.35	0.30	0.23	0.30	0.25	0.13	0.31	0.28	0.18	0.21	0.33	0.24	0.28	0.18	0.20	0.31	0.19	0.25	0.44	0.21	0.23	1.00						
29	52	0.23	0.23	0.18	0.19	0.21	0.14	0.20	0.26	0.24	0.22	0.23	0.24	0.15	0.17	0.26	0.24	0.20	0.86	0.19	0.27	0.21	0.21	1.00					
33	53	0.14	0.19	0.11	0.29	0.15	0.19	0.28	0.22	0.14	0.13	0.18	0.18	0.12	0.26	0.29	0.31	0.14	0.21	0.21	0.14	0.13	0.22	0.22	1.00				
34	54	0.28	0.22	0.24	0.20	0.13	0.12	0.23	0.21	0.17	0.14	0.21	0.19	0.14	0.20	0.26	0.19	0.17	0.27	0.19	0.28	0.24	0.24	0.26	0.21	1.00			
25	55	0.24	0.24	0.18	0.23	0.27	0.14	0.24	0.22	0.17	0.35	0.28	0.54	0.47	0.14	0.17	0.20	0.23	0.16	0.42	0.15	0.23	0.31	0.18	0.16	0.19	1.00		
31	56	0.21	0.17	0.24	0.18	0.20	0.14	0.16	0.24	0.17	0.19	0.18	0.22	0.16	0.13	0.20	0.17	0.20	0.23	0.18	0.29	0.59	0.20	0.23	0.16	0.23	0.21	1.00	
30	57	0.31	0.20	0.24	0.17	0.19	0.21	0.18	0.16	0.23	0.18	0.18	0.17	0.19	0.16	0.37	0.25	0.13	0.25	0.20	0.62	0.22	0.22	0.25	0.18	0.30	0.18	0.26	1.00

[a]Compounds with similarity scores > 0.5 were grouped within the same cluster. Clusters possessing more than one compound have been color-coded. Calculations were determined using Pipeline Pilot with fingerprint property FCFP4.

Table S5. For the kinase target, clusters were prioritzed which lacked enrichment in the counter-screen; many of the resulting molecules are selective in the biochemical assay.[a]

CMPD ID[b]	Selectivity (IC50 target/counter-target)[c]
31	3.27
33	71
37	>65
39	16
40	0.42
41	>25
42	192
43	8
46	8
47	124
48	17
49	8
51	20
52	>115
54	19

[a]DEL screen was run side-by-side against kinase target and a related kinase target.
[b]Physical property descriptors for compounds provided in Table S2.
[c]Activity measured in LanthaScreen kinase binding assays for both kinase target and related kinase counter-target.

Table S6. Table with the Tanimoto values for each investigated DEL-derived compound of the most similar compounds in three searched databases (HTS library, ChEMBL and SureChEMBL). None of the 57 DEL-derived compounds has an exact match. Two similarity metrics (ECFP4 and Accelrys Direct) were used.

Target	Cluster ID	CMPD ID	HTS_ECFP4_SIM	HTS_DIRECT_SIM	CHEMBL_ECFP4_SIM	CHEMBL_DIRECT_SIM	SURE_ECFP4_SIM	SureChEMBL_DIRECT_SIM
Phosphodiesterase	1	1	0.48	0.76	0.44	0.79	0.55	0.83
Phosphodiesterase	1	3	0.49	0.73	0.44	0.78	0.50	0.84
Phosphodiesterase	2	2	0.44	0.80	0.41	0.82	0.50	0.84
Phosphodiesterase	2	6	0.39	0.81	0.38	0.82	0.41	0.87
Phosphodiesterase	2	7	0.37	0.77	0.35	0.76	0.40	0.81
Phosphodiesterase	2	16	0.43	0.81	0.44	0.82	0.44	0.87
Phosphodiesterase	2	25	0.43	0.79	0.43	0.84	0.46	0.81
Phosphodiesterase	2	27	0.46	0.74	0.46	0.76	0.44	0.80
Phosphodiesterase	3	4	0.47	0.83	0.49	0.88	0.54	0.90
Phosphodiesterase	3	8	0.48	0.86	0.47	0.83	0.49	0.87
Phosphodiesterase	3	29	0.51	0.86	0.49	0.87	0.49	0.84
Phosphodiesterase	4	5	0.41	0.82	0.40	0.82	0.44	0.86
Phosphodiesterase	4	22	0.53	0.83	0.50	0.82	0.52	0.81
Phosphodiesterase	5	10	0.47	0.78	0.47	0.77	0.62	0.81
Phosphodiesterase	6	11	0.51	0.67	0.55	0.65	0.58	0.68
Phosphodiesterase	7	12	0.46	0.81	0.45	0.85	0.58	0.85
Phosphodiesterase	8	13	0.61	0.87	0.61	0.90	0.64	0.95
Phosphodiesterase	9	14	0.61	0.74	0.55	0.78	0.56	0.80
Phosphodiesterase	10	15	0.51	0.77	0.51	0.77	0.54	0.75
Phosphodiesterase	10	28	0.51	0.79	0.51	0.79	0.54	0.77
Phosphodiesterase	11	17	0.46	0.76	0.42	0.76	0.57	0.77
Phosphodiesterase	12	18	0.60	0.93	0.62	0.94	0.65	0.96
Phosphodiesterase	12	23	0.58	0.90	0.63	0.91	0.76	0.94
Phosphodiesterase	12	24	0.55	0.91	0.61	0.91	0.61	0.93
Phosphodiesterase	12	26	0.57	0.89	0.75	0.93	0.80	0.95
Phosphodiesterase	13	19	0.41	0.66	0.40	0.70	0.41	0.75
Phosphodiesterase	14	20	0.57	0.74	0.43	0.67	0.53	0.75
Phosphodiesterase	15	21	0.65	0.85	0.80	0.91	0.84	0.87
Phosphodiesterase	16	9	0.58	0.73	0.60	0.75	0.60	0.76
Kinase	17	30	0.47	0.73	0.46	0.75	0.50	0.76

Kinase	18	31	0.73	0.91	0.73	0.91	0.68	0.79
Kinase	18	40	0.76	0.92	0.76	0.92	0.68	0.84
Kinase	19	32	0.55	0.82	0.51	0.79	0.55	0.78
Kinase	20	33	0.42	0.82	0.43	0.83	0.49	0.81
Kinase	20	36	0.41	0.84	0.38	0.83	0.46	0.84
Kinase	21	34	0.47	0.70	0.37	0.73	0.39	0.74
Kinase	21	39	0.53	0.77	0.48	0.77	0.48	0.79
Kinase	21	46	0.41	0.78	0.34	0.79	0.38	0.75
Kinase	22	35	0.46	0.78	0.42	0.84	0.46	0.80
Kinase	22	43	0.41	0.80	0.40	0.80	0.43	0.80
Kinase	23	37	0.53	0.82	0.51	0.80	0.49	0.82
Kinase	24	38	0.51	0.87	0.48	0.85	0.60	0.90
Kinase	25	41	0.52	0.84	0.47	0.89	0.46	0.86
Kinase	25	55	0.55	0.84	0.51	0.81	0.54	0.85
Kinase	26	42	0.56	0.78	0.52	0.76	0.56	0.79
Kinase	27	44	0.56	0.82	0.55	0.81	0.44	0.82
Kinase	28	45	0.49	0.82	0.40	0.81	0.49	0.87
Kinase	29	47	0.49	0.88	0.55	0.88	0.52	0.92
Kinase	29	52	0.51	0.88	0.62	0.89	0.56	0.92
Kinase	30	49	0.52	0.80	0.46	0.81	0.61	0.84
Kinase	30	57	0.63	0.92	0.56	0.93	0.69	0.97
Kinase	31	50	0.45	0.80	0.52	0.83	0.43	0.84
Kinase	31	56	0.41	0.82	0.44	0.85	0.42	0.87
Kinase	32	51	0.58	0.77	0.44	0.72	0.58	0.72
Kinase	33	53	0.47	0.82	0.41	0.82	0.53	0.87
Kinase	34	54	0.46	0.72	0.48	0.76	0.52	0.80
Kinase	35	48	0.51	0.85	0.50	0.85	0.53	0.87

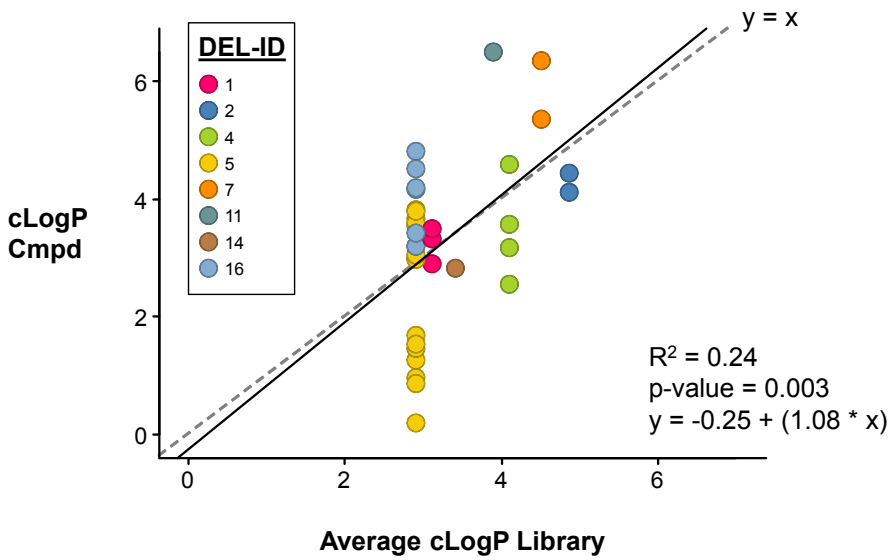


Figure S1. There is no clear relationship between cLogPs for DEL-derived compounds and the average library molecule. Ordinary least squares provides an R-squared value of 0.24. Only compounds with IC50 ≤ 10 μM in follow-up biochemical assay are shown (see supporting information Table S2). The average cLogP of library molecules was determined by enumerating 5000 randomly chosen potential small molecule moieties from each library (library schemes are provided in Table S1). The cLogP values were calculated using Pipeline Pilot (27).

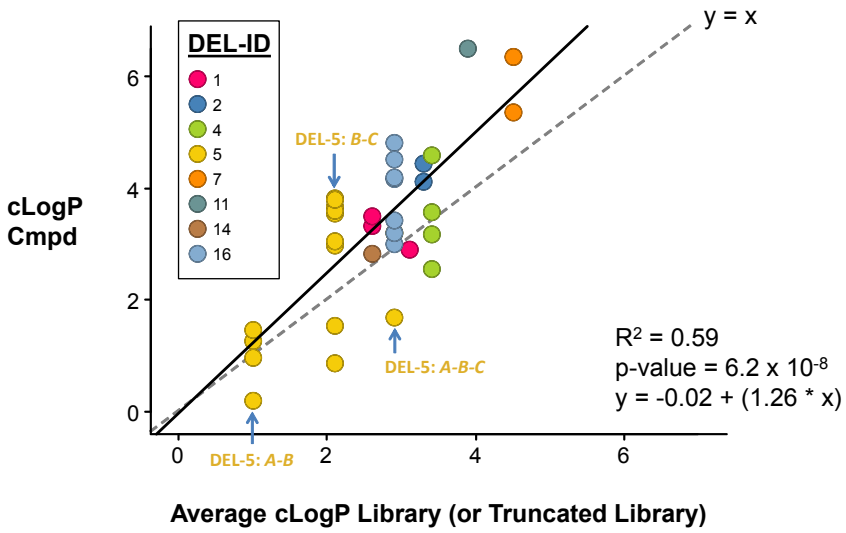


Figure S2. The relationship between cLogPs for DEL-derived compounds and the average library molecule is clearer after taking into account the presence of truncated sub-libraries. Ordinary least squares provides an R^2 value of 0.59; in comparison, the previous model which does not take into account the presence of truncated sub-libraries possesses an R^2 value of 0.24 (Figure S1). Only compounds with IC50 $\leq$ 10 μM in follow-up biochemical assay are shown (see supporting information Table S2). The average cLogP of library members was determined by enumerating 5000 randomly chosen potential small molecule moieties from each library (or truncated sub-library) (library schemes are provided in supporting information Table S1). See text for a discussion of fully enumerated and truncated sub-libraries. Three DEL-5 libraries are annotated; compounds were derived from the fully enumerated library (A-B-C) and both truncated sub-libraries (A-B and B-C). The average DEL-derived molecule has a cLogP value 0.66 log units greater than the average library member from which it is derived. This shift is significant (see Methods) and consistent with results reported for high-throughput screening (M. Hansson *et al.*, *J Biomol Screen*, 2013, **19**, 727-737).