Structure-activity relationship expansion and microsomal stability assessment of the 2-morpholinobenzoic acid scaffold as antiproliferative phosphatidylcholine-specific phospholipase C inhibitors

Supplementary Information Part 2: *In silico* experimental results

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Molecular modelling scores of synthesised compounds

Goldscore van der Waals (vdW) and hydrogen bonding (Hbond) scores are weighted terms in all tables.

Table S1. Docking scores of series **10** compounds (1,2,4-carboxylic esters) using genetic algorithms available in GOLD suite.

Compound	ChemPLP			Goldscore			Chemscore			ASP
	Fitness	Hbond	Metal	Fitness	vdW	Hbond	Fitness	ΔG	Hbond	Fitness
H (**a**)	74.97	1.00	1.00	60.99	45.69	19.83	32.73	-38.07	-2.11	42.09
2-F (**b**)	72.14	1.00	1.00	54.24	50.08	6.47	31.57	-33.37	-3.32	46.83
3-F (**c**)	79.13	0.00	1.74	56.51	54.47	4.79	30.87	-39.04	0.00	45.90
4-F (**d**)	78.56	0.00	1.73	55.83	53.40	4.85	33.17	-35.67	-2.14	45.70
2-Cl (**e**)	72.62	0.96	0.99	57.18	53.63	5.73	33.48	-34.59	-3.27	42.54
3-Cl (**f**)	74.65	0.00	1.85	58.10	54.56	5.24	33.06	-37.57	-2.21	44.13
4-Cl (**g**)	72.64	0.33	1.00	56.62	48.98	10.45	32.56	-39.50	0.00	44.45
2-Br (**h**)	74.46	0.98	1.00	58.44	50.04	12.68	31.44	-33.67	-2.83	41.53
3-Br (**i**)	80.33	0.00	1.93	57.92	49.98	11.30	33.71	-40.60	0.00	44.78
4-Br (**j**)	78.70	0.00	1.92	54.73	44.55	14.34	33.55	-40.50	0.00	43.92
2-OMe (**k**)	73.08	0.33	1.00	56.81	54.61	5.21	32.26	-33.26	-3.24	44.77
3-OMe (**l**)	79.88	0.00	1.89	59.14	53.73	10.70	34.12	-37.80	-4.09	46.00
4-OMe (**m**)	78.86	0.67	1.21	53.88	48.79	8.91	30.79	-38.72	0.00	46.93

Table S2. Docking scores of series **11** compounds (1,2,4-carboxylic acids) using genetic algorithms available in GOLD suite.

Compound	ChemPLP			Goldscore			Chemscore			ASP
	Fitness	Hbond	Metal	Fitness	vdW	Hbond	Fitness	ΔG	Hbond	Fitness
H (**a**)	115.92	1.00	7.81	83.69	41.16	46.32	44.44	-54.87	-3.33	49.05
2-F (**b**)	111.01	1.30	7.82	82.84	40.42	46.46	43.08	-53.62	-3.34	47.22
3-F (**c**)	115.55	1.00	7.82	82.99	40.67	46.68	42.62	-52.80	-3.34	48.88
4-F (**d**)	116.56	1.00	7.82	81.68	39.49	46.30	44.15	-53.47	-3.34	48.49
2-Cl (**e**)	116.76	1.00	7.87	82.09	41.02	46.03	45.81	-56.35	-5.28	50.01
3-Cl (**f**)	117.10	1.00	7.78	81.87	40.25	46.74	44.17	-54.76	-3.34	48.01
4-Cl (**g**)	117.63	1.00	7.86	81.98	42.48	45.57	43.40	-53.25	-3.71	47.92
2-Br (**h**)	114.26	1.00	7.82	83.13	44.35	47.86	45.38	-54.34	-3.34	42.07
3-Br (**i**)	116.05	1.00	7.84	85.50	43.23	46.45	44.55	-53.67	-3.34	48.43
4-Br (**j**)	117.80	1.00	7.78	80.36	40.57	46.99	43.82	-55.61	-3.28	46.94
2-OMe (**k**)	114.07	0.99	7.88	84.95	42.43	46.44	43.30	-53.15	-3.34	48.98
3-OMe (**l**)	114.35	1.00	7.87	84.76	41.54	47.04	43.29	-53.92	-3.32	51.02
4-OMe (**m**)	118.27	1.00	7.90	84.01	44.31	46.33	44.46	-54.53	-3.33	49.02

Table S3. Docking scores of series **12** compounds (1,2,4-hydroxamic acids) using genetic algorithms available in GOLD suite.

Compound	ChemPLP			Goldscore			Chemscore			ASP
	Fitness	Hbond	Metal	Fitness	vdW	Hbond	Fitness	ΔG	Hbond	Fitness
H (**a**)	89.82	0.02	2.95	81.08	53.98	29.15	48.25	-57.48	-9.56	64.73
2-F (**b**)	92.57	1.30	2.53	79.08	48.63	35.19	45.85	-54.78	-7.40	69.66
3-F (**c**)	89.90	0.75	2.62	80.03	48.82	35.56	45.69	-54.56	-6.46	69.79
4-F (**d**)	98.85	1.48	2.22	78.70	47.71	35.80	47.80	-55.66	-6.04	70.63
2-Cl (**e**)	95.69	1.00	2.72	81.31	54.15	30.88	48.34	-57.12	-8.75	68.99
3-Cl (**f**)	94.12	1.02	2.73	80.23	49.21	36.00	46.90	-56.24	-6.39	68.13
4-Cl (**g**)	94.47	0.81	2.64	80.60	49.19	35.87	48.56	-56.89	-7.73	67.72
2-Br (**h**)	89.84	1.15	2.94	79.18	48.98	34.50	47.55	-55.23	-6.76	68.17
3-Br (**i**)	95.56	1.01	2.63	80.24	50.68	34.38	45.55	-55.29	-6.43	67.65
4-Br (**j**)	95.56	1.01	2.63	80.24	50.68	34.38	45.55	-55.29	-6.43	67.65
2-OMe (**k**)	90.28	0.53	2.95	78.65	48.45	34.78	48.12	-55.81	-8.58	68.62
3-OMe (**l**)	97.35	1.33	2.42	81.27	50.27	35.35	46.07	-57.13	-8.84	68.87
4-OMe (**m**)	90.80	0.64	2.34	78.95	50.28	32.90	46.31	-56.26	-6.76	66.76

Table S4. Docking scores of series **19** compounds (THP esters) using genetic algorithms available in GOLD suite.

Compound	ChemPLP			Goldscore			Chemscore			ASP
	Fitness	Hbond	Metal	Fitness	vdW	Hbond	Fitness	ΔG	Hbond	Fitness
H (**a**)	72.05	1.00	0.00	60.74	52.59	11.99	30.71	-33.76	-3.31	46.01
2-F (**b**)	74.44	0.97	0.00	60.14	52.46	11.96	32.05	-34.01	-4.01	47.20
3-F (**c**)	75.46	1.00	0.00	61.19	54.27	10.67	32.08	-35.71	-2.18	46.11
4-F (**d**)	75.15	1.00	0.00	61.74	53.94	11.00	33.06	-34.85	-6.01	45.72
2-Cl (**e**)	71.96	0.00	1.97	62.90	56.40	11.23	34.90	-38.00	-3.88	41.91
3-Cl (**f**)	71.99	0.96	0.00	62.91	55.41	11.70	33.81	-38.73	-1.08	45.00
4-Cl (**g**)	72.64	1.00	0.00	58.46	52.25	11.12	34.40	-37.66	-4.01	46.84
2-Br (**h**)	71.20	0.00	1.93	62.81	59.92	8.54	34.44	-37.89	-3.98	40.59
3-Br (**i**)	74.62	1.00	0.00	62.26	54.72	12.21	33.70	-36.05	-4.65	45.67
4-Br (**j**)	73.57	1.00	0.00	64.29	54.86	12.88	33.70	-38.15	-1.11	45.26
2-OMe (**k**)	70.71	0.00	1.94	61.00	55.29	9.21	32.06	-33.62	-4.09	41.81
3-OMe (**l**)	73.37	0.95	0.00	61.13	55.09	11.31	34.45	-36.76	-5.73	47.93
4-OMe (**m**)	74.17	1.00	0.00	58.01	56.23	5.37	28.69	-30.01	-3.18	49.60

Table S5. Docking scores of series **20** compounds (THP carboxylic acids) using genetic algorithms available in GOLD suite.

Compound	ChemPLP			Goldscore			Chemscore			ASP
	Fitness	Hbond	Metal	Fitness	vdW	Hbond	Fitness	ΔG	Hbond	Fitness
H (**a**)	111.43	1.90	7.65	68.87	35.14	37.87	39.93	-52.65	-3.62	44.96
2-F (**b**)	109.20	1.72	6.93	77.08	41.89	39.39	40.40	-52.12	-4.29	49.11
3-F (**c**)	109.60	1.14	6.16	80.71	44.77	38.73	38.72	-49.49	-3.89	48.93
4-F (**d**)	111.92	1.78	6.93	71.14	38.99	36.40	40.25	-54.34	-3.88	48.81
2-Cl (**e**)	104.38	1.10	7.55	85.65	50.26	38.82	40.17	-52.50	-4.14	48.09
3-Cl (**f**)	111.47	1.84	5.79	78.60	44.72	37.58	43.12	-54.42	-4.84	48.53
4-Cl (**g**)	107.92	1.06	6.44	81.06	42.14	42.72	42.05	-55.77	-4.36	48.31
2-Br (**h**)	109.76	1.49	7.38	82.16	48.77	40.61	42.98	-57.16	-4.50	44.88
3-Br (**i**)	111.44	1.76	7.53	79.40	45.20	38.22	42.01	-55.03	-3.35	47.35
4-Br (**j**)	110.79	1.71	6.72	78.73	44.10	39.31	42.86	-57.49	-5.44	48.52
2-OMe (**k**)	105.31	1.53	6.28	83.75	44.70	40.83	38.22	-50.66	-5.49	46.66
3-OMe (**l**)	112.86	1.65	6.22	75.71	42.92	36.43	40.13	-52.39	-3.58	45.42
4-OMe (**m**)	107.64	1.38	5.71	83.21	46.04	39.63	40.19	-51.31	-5.90	49.35

Table S6. Docking scores of series **21** compounds (THP carboxylic acids) using genetic algorithms available in GOLD suite.

Compound	ChemPLP			Goldscore			Chemscore			ASP
	Fitness	Hbond	Metal	Fitness	vdW	Hbond	Fitness	ΔG	Hbond	Fitness
H (**a**)	102.01	1.42	2.79	71.65	46.93	29.56	50.37	-58.68	-8.82	70.54
2-F (**b**)	101.58	1.62	2.57	76.94	53.72	30.14	45.72	-56.61	-8.14	71.01
3-F (**c**)	102.03	1.52	2.84	76.48	53.24	29.41	46.55	-57.01	-7.72	71.74
4-F (**d**)	105.99	1.70	2.87	76.58	53.01	29.49	48.03	-56.65	-7.86	70.66
2-Cl (**e**)	99.21	1.87	2.54	79.16	55.64	25.89	51.31	-59.96	-9.00	68.16
3-Cl (**f**)	101.43	2.31	3.14	76.92	54.98	28.85	49.64	-57.25	-7.06	69.81
4-Cl (**g**)	102.00	1.56	2.77	86.72	53.84	35.90	51.58	-60.61	-9.16	71.34
2-Br (**h**)	99.38	1.80	2.74	79.17	52.64	31.10	47.80	-58.78	-7.66	69.55
3-Br (**i**)	103.02	1.58	2.84	76.22	50.63	29.99	48.24	-58.44	-8.41	70.13
4-Br (**j**)	102.11	1.63	2.72	84.94	53.34	36.42	50.62	-58.12	-7.21	70.24
2-OMe (**k**)	95.12	2.24	3.09	85.56	55.28	36.86	45.80	-57.31	-7.75	68.66
3-OMe (**l**)	98.99	1.63	2.91	91.78	57.95	36.38	47.37	-56.25	-6.78	69.24
4-OMe (**m**)	104.80	1.98	2.54	86.73	54.44	34.78	46.31	-56.26	-6.76	72.14

Table S7. Docking scores of *N*-methylated compounds and positive control D609 using genetic algorithms available in GOLD suite.

Compound	ChemPLP			Goldscore			Chemscore			ASP
	Fitness	H bond	Metal	Fitness	vdW	Hbond	Fitness	ΔG	H bond	Fitness
D609	63.46	0.97	3.85	89.34	41.56	49.73	35.11	-38.69	-3.32	27.55
CA (**24**)	108.74	1.87	7.23	81.98	49.95	37.71	42.60	-49.84	-18.96	46.20
Ester (**23**)	76.09	0.00	2.91	60.29	49.61	12.75	33.45	-42.93	0.00	41.53
HA (**25**)	97.14	2.00	2.48	73.20	50.25	27.16	47.59	-60.17	-9.00	67.76

CA = carboxylic acid, HA = hydroxamic acid

Binding poses of selected compounds 1a, 11e, and 20e within the active site of PC-PLC$_{BC}$

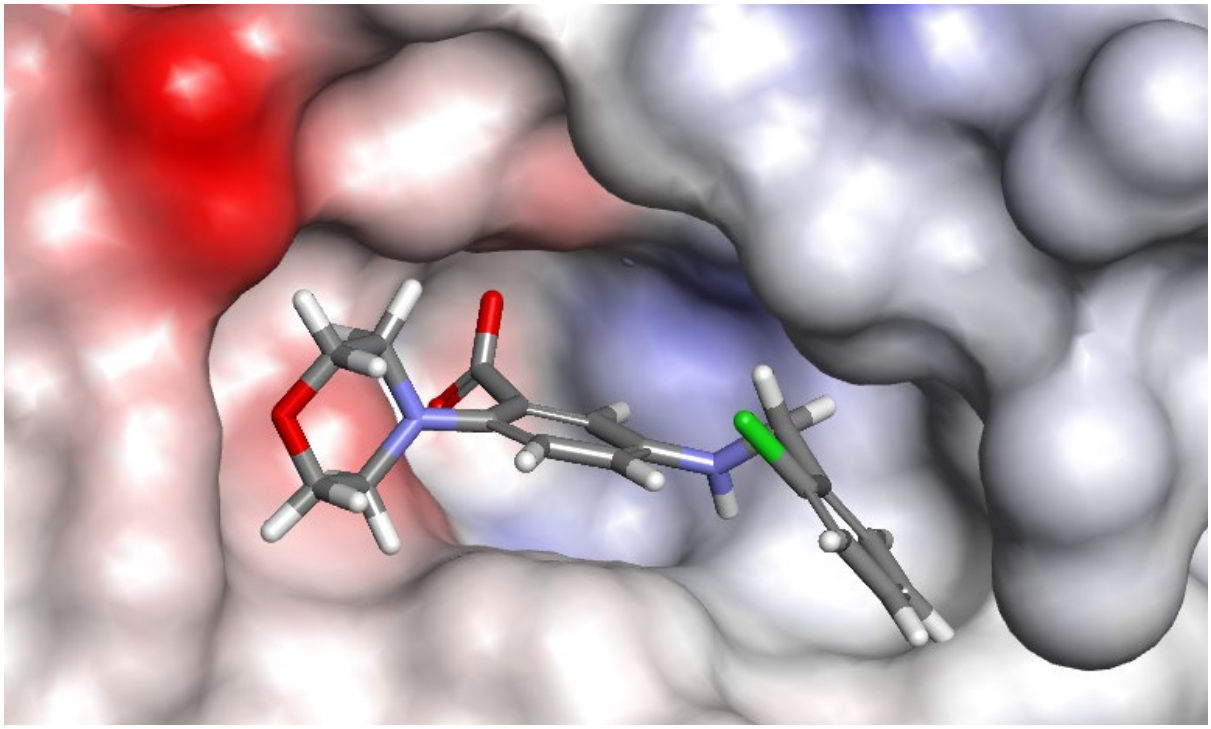

Figure S1. Predicted binding pose of compound **1a** within the active site of PC-PLC$_{BC}$ (PDB ID: 1AH7, 1.50 Å)[1] represented by a solvent ionizability surface. Blue areas represent basic residues, red areas represent acidic residues and white indicates neutral. Compound **1a** is represented by stick structure coloured by atom type.

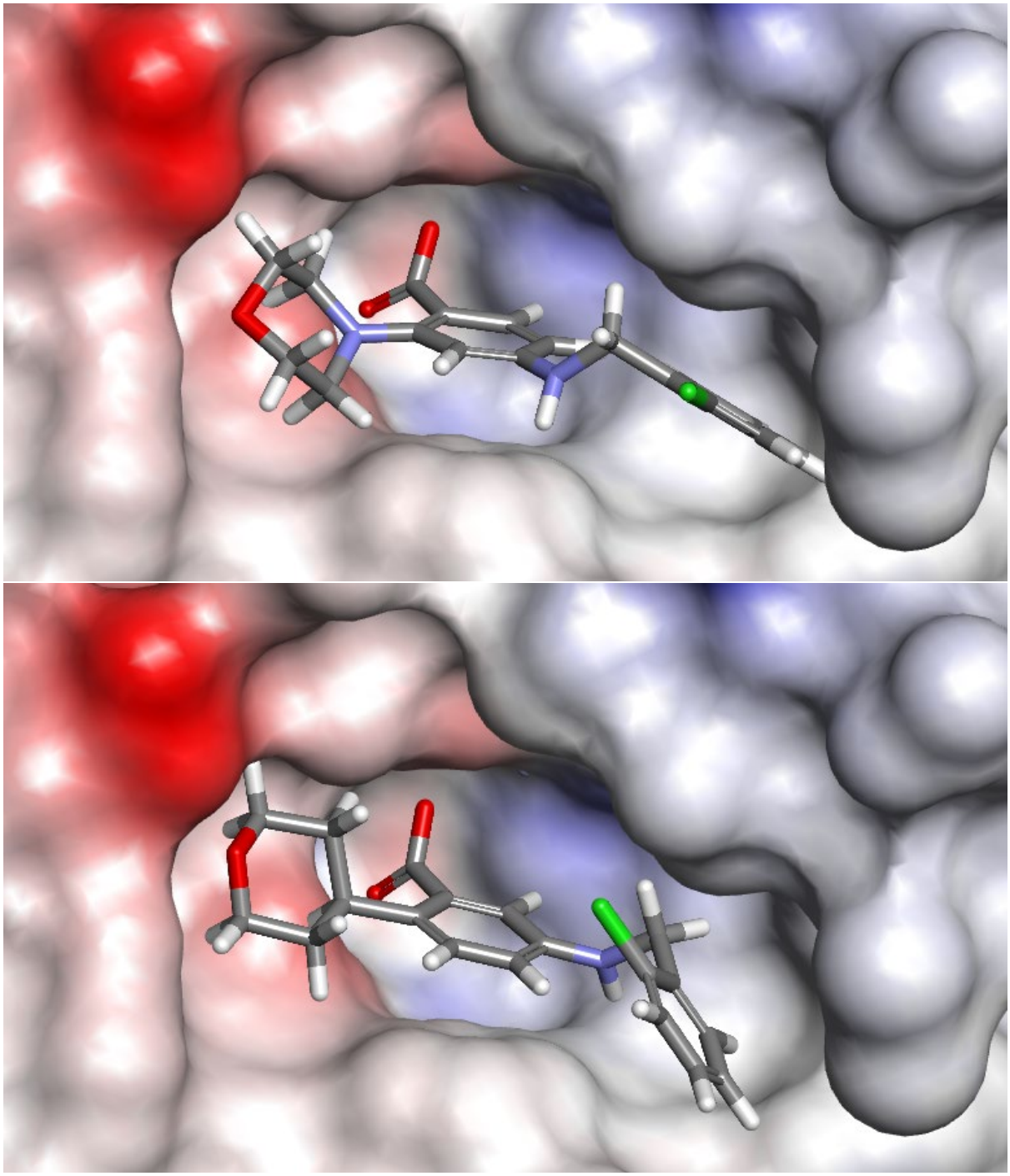

Figure S2. Predicted binding pose of 2-morpholinobenzoic acid derivatives within the active site of PC-PLC$_{BC}$ (PDB ID: 1AH7, 1.50 Å)[1] represented by a solvent ionizability surface. Blue areas represent basic residues, red areas represent acidic residues and white indicates neutral. *Top:* Compound **11e**; *bottom*: compound **20e**.

Tanimoto similarity coefficients of hydroxamic acid-containing compounds

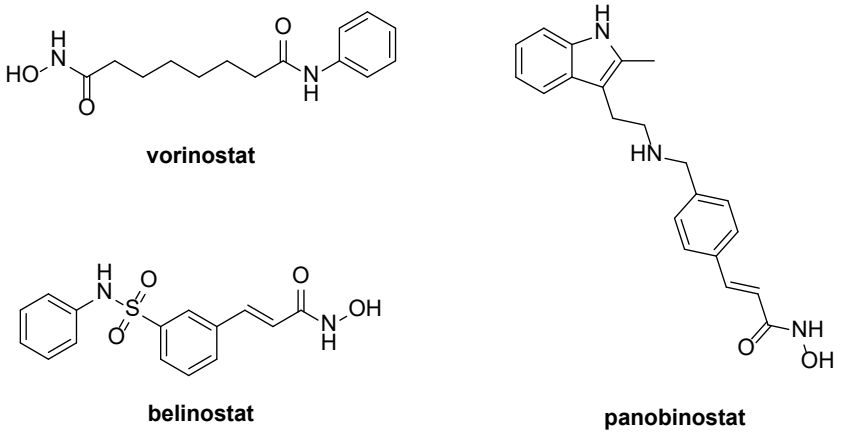

Figure S3. Structures of FDA-approved HDAC inhibitors.[2]

Table S8. Tanimoto scores of series **12** compounds compared to known HDAC inhibitors representing structural similarity. A score of 0 indicates no similarity and 1 indicates identical molecules. Values were calculated using R Statistical Software (v4.4.2) and the rcdk R package (v3.8.1).[3,4]

Compound	Tanimoto Score		
	Vorinostat	Belinostat	Panobinostat
12a	0.241	0.188	0.155
12b	0.202	0.170	0.130
12c	0.169	0.154	0.127
12d	0.163	0.137	0.152
12e	0.198	0.167	0.128
12f	0.182	0.154	0.127
12g	0.179	0.150	0.153
12h	0.188	0.182	0.130
12i	0.170	0.155	0.128
12j	0.163	0.137	0.142
12k	0.191	0.162	0.144
12l	0.187	0.159	0.132
12m	0.170	0.133	0.148
Summary statistics			
Min	0.163	0.133	0.127
1st Qu.	0.171	0.150	0.128
Median	0.182	0.155	0.132
Mean	0.185	0.158	0.138
3rd Qu.	0.191	0.167	0.148
Max	0.241	0.188	0.155

Table S9. Tanimoto scores of series **21** compounds compared to known HDAC inhibitors representing structural similarity. A score of 0 indicates no similarity and 1 indicates identical molecules. Values were calculated using R Statistical Software (v4.4.2) and the rcdk R package (v3.8.1).

Compound	Tanimoto Score		
	Vorinostat	Belinostat	Panobinostat
21a	0.188	0.186	0.143
21b	0.167	0.170	0.121
21c	0.161	0.152	0.117
21d	0.195	0.136	0.140
21e	0.182	0.165	0.118
21f	0.174	0.154	0.118
21g	0.184	0.147	0.140
21h	0.169	0.178	0.119
21i	0.161	0.154	0.118
21j	0.187	0.136	0.130
21k	0.185	0.159	0.132
21l	0.169	0.157	0.122
21m	0.169	0.132	0.137
Summary statistics			
Min	0.161	0.132	0.117
1st Qu.	0.169	0.147	0.118
Median	0.182	0.154	0.122
Mean	0.181	0.156	0.127
3rd Qu.	0.187	0.165	0.137
Max	0.238	0.186	0.143

ADMET data of all synthesised compounds

Physicochemical properties that have been linked to favourable drug profiles were calculated using ADMETlab 3.0[5] and the results are reported in table S6, SI part 2. All compounds satisfied Lipinski and Veber criteria of drug-likeness and no compounds were identified as pan-assay interference compounds (PAINS).[6–9] The criteria for drug-likeness required molecular weights of ≤ 500 Da, logP ≤ 5, hydrogen bond donors ≤ 5, and hydrogen bond acceptors ≤ 10 to satisfy Lipinski's rules.[7,8] Veber contributed new criteria of rotatable bonds ≤ 10, and polar surface area ≤ 140 Å^2.[9]

$LogD_{7.4}$ was included to represent distribution at physiological pH, which is particularly relevant for compounds containing carboxylic acid motifs. Calculations of pKa were first carried out and it was found that all of series **11** and **20** compounds values were < 7.4, indicating these compounds are in an ionised state under physiological conditions and therefore the logD value should be considered over logP when evaluating ADMET profiles.

All compounds satisfied lipophilicity criteria (all values <5) when considering both logP and logD. Additional criteria for logS and logD were considered from more literary references to define optimal space in these areas, being -1 to -5 for logS[10] and 1 to 3 for logD[11]. Compounds falling outside of these ranges are indicated by ^{a} in table S6. Violations of the range for logD was shown in series **10** and **19**, with values >3, but only to a maximum of 3.61 for compound **10e** and 3.79 for **19j**. None of these compounds had pKa values less than pH 7.4 so logD requirements are of lesser relevance in these cases but are lower, and therefore more favourable, than their logP values. LogS criteria were not met in **12j** and seven of the series **19** compounds (**19c**, **19e-j**), these results are more varied but mostly include THP methyl esters. The 4-bromo substituent also appears to be less favourable for drug-likeness owing to higher lipophilicity and lower aqueous solubility, but this was not the case in all of the synthesised series. It is worth noting that these ranges are considered optimal regions based off known drugs, and greater variability is tolerated for earlier stages in the drug development process.

Table S10. Computed physicochemical properties of all synthesised compounds which fall under Lipinski-Veber criteria of drug-like compounds.[8,9] Values were calculated using ADMETlab 3.0.[5]

Compound	MW (Da)	nHA	nHD	TPSA (Å^2)	nRot	logS	logD	logP
10a	326.16	5	1	50.8	6	-3.96	3.30[a]	3.34
10b	344.15	5	1	50.8	6	-4.44	3.54[a]	3.75
10c	344.15	5	1	50.8	6	-4.62	3.36[a]	3.68
10d	344.15	5	1	50.8	6	-4.55	3.33[a]	3.60
10e	360.12	5	1	50.8	6	-4.58	3.61[a]	3.89
10f	360.12	5	1	50.8	6	-4.81	3.54[a]	3.99
10g	360.12	5	1	50.8	6	-4.89	3.48[a]	4.03
10h	404.07	5	1	50.8	6	-4.38	3.54[a]	3.89
10i	404.07	5	1	50.8	6	-4.76	3.40[a]	3.97
10j	404.07	5	1	50.8	6	-4.97	3.36[a]	4.01
10k	356.17	6	1	60.03	7	-4.21	3.38[a]	3.38
10l	356.17	6	1	60.03	7	-4.14	3.22[a]	3.31
10m	356.17	6	1	60.03	7	-4.08	3.13[a]	3.26
11a	312.15	5	2	61.8	5	-3.35	2.32	3.12
11b	330.14	5	2	61.8	5	-3.90	2.64	3.28
11c	330.14	5	2	61.8	5	-3.92	2.70	3.39
11d	330.14	5	2	61.8	5	-3.94	2.64	3.24
11e	346.11	5	2	61.8	5	-3.86	2.60	3.79
11f	346.11	5	2	61.8	5	-3.88	2.60	3.89
11g	346.11	5	2	61.8	5	-3.96	2.52	3.91
11h	390.06	5	2	61.8	5	-3.80	2.56	3.76
11i	390.06	5	2	61.8	5	-3.76	2.53	3.90
11j	390.06	5	2	61.8	5	-3.86	2.52	3.98
11k	342.16	6	2	71.03	6	-3.46	2.29	2.88
11l	342.16	6	2	71.03	6	-3.92	2.42	3.02
11m	342.16	6	2	71.03	6	-3.56	2.29	2.70
12a	327.16	6	3	73.83	6	-3.54	1.81	1.59
12b	345.15	6	3	73.83	6	-3.98	2.09	1.99
12c	345.15	6	3	73.83	6	-3.94	2.09	1.85
12d	345.15	6	3	73.83	6	-3.78	1.95	1.68
12e	361.12	6	3	73.83	6	-4.63	2.41	2.59
12f	361.12	6	3	73.83	6	-4.86	2.38	2.63
12g	361.12	6	3	73.83	6	-4.91	2.33	2.61
12h	405.07	6	3	73.83	6	-4.59	2.27	2.42
12i	405.07	6	3	73.83	6	-4.92	2.24	2.48
12j	405.07	6	3	73.83	6	-5.05[a]	2.28	2.62
12k	357.17	7	3	83.06	7	-3.70	1.91	1.62
12l	357.17	7	3	83.06	7	-4.07	1.97	1.72
12m	357.17	7	3	83.06	7	-3.97	1.84	1.55
19a	325.17	4	1	47.56	6	-4.49	3.37[a]	3.58
19b	343.16	4	1	47.56	6	-4.66	3.46[a]	3.94

19c	343.16	4	1	47.56	6	-5.08[a]	3.51[a]	4.09
19d	343.16	4	1	47.56	6	-4.87	3.46[a]	3.90
19e	359.13	4	1	47.56	6	-5.19[a]	3.67[a]	4.23
19f	359.13	4	1	47.56	6	-5.40[a]	3.69[a]	4.37
19g	359.13	4	1	47.56	6	-5.39[a]	3.73[a]	4.40
19h	403.08	4	1	47.56	6	-5.04[a]	3.61[a]	4.16
19i	403.08	4	1	47.56	6	-5.40[a]	3.71[a]	4.38
19j	403.08	4	1	47.56	6	-5.53[a]	3.79[a]	4.41
19k	355.18	5	1	56.79	7	-4.61	3.38[a]	3.50
19l	355.18	5	1	56.79	7	-4.85	3.45[a]	3.64
19m	355.18	5	1	56.79	7	-4.72	3.40[a]	3.50
20a	311.15	4	2	58.56	5	-3.61	2.53	3.42
20b	329.14	4	2	58.56	5	-4.09	2.86	3.93
20c	329.14	4	2	58.56	5	-4.12	2.90	3.95
20d	329.14	4	2	58.56	5	-4.12	2.90	3.93
20e	345.11	4	2	58.56	5	-3.98	2.79	4.04
20f	345.11	4	2	58.56	5	-3.95	2.84	4.16
20g	345.11	4	2	58.56	5	-3.93	2.87	4.21
20h	389.06	4	2	58.56	5	-3.99	2.78	4.08
20i	389.06	4	2	58.56	5	-3.89	2.83	4.28
20j	389.06	4	2	58.56	5	-3.92	2.83	4.33
20k	341.16	5	2	67.79	6	-3.82	2.55	3.29
20l	341.16	5	2	67.79	6	-3.85	2.66	3.28
20m	341.16	5	2	67.79	6	-3.53	2.54	3.00
21a	326.16	5	3	70.59	6	-3.56	1.99	1.80
21b	344.15	5	3	70.59	6	-4.05	2.34	2.26
21c	344.15	5	3	70.59	6	-4.11	2.37	2.19
21d	344.15	5	3	70.59	6	-3.92	2.27	2.07
21e	360.12	5	3	70.59	6	-4.66	2.60	2.58
21f	360.12	5	3	70.59	6	-4.87	2.69	2.73
21g	360.12	5	3	70.59	6	-4.75	2.74	2.75
21h	404.07	5	3	70.59	6	-4.61	2.47	2.43
21i	404.07	5	3	70.59	6	-4.88	2.66	2.68
21j	404.07	5	3	70.59	6	-4.94	2.70	2.73
21k	356.17	6	3	79.82	7	-3.77	2.07	1.87
21l	356.17	6	3	79.82	7	-3.93	2.09	1.85
21m	356.17	6	3	79.82	7	-3.63	1.99	1.66
23	374.14	5	0	42.01	6	-4.70	3.76[a]	4.02
24	360.12	5	1	53.01	5	-4.28	2.66	3.73
25	375.13	6	2	65.04	6	-4.51	2.63	2.69

Heading abbreviations: MW = molecular weight; nHA = number of hydrogen bond acceptors; nHD = number of hydrogen bond donors; TPSA = topological polar surface area; nRot = number of rotatable bonds.

[a] Outside of optimal range (logS -1 to -5, logD 1 to 3)

Table S11. Scores of common ADMET properties calculated for all synthesised compounds. Data were calculated using ADMETlab 3.0.[5] Values of columns 3-6 are probability scores with a range from 0 to 1 on a probability scale; values of column 2 are on a logarithmic scale.

Compound	Caco-2[a]	Pgp inhibitor	Pgp substrate	hERG blocker[b]	Ames toxicity
10a	-5.11	0.45	0.03	0.57	0.59
10b	-5.31	0.52	0.01	0.48	0.67
10c	-4.98	0.70	0.02	0.56	0.64
10d	-4.94	0.86	0.02	0.58	0.63
10e	-4.96	0.70	0.00	0.55	0.53
10f	-4.81	0.50	0.02	0.68	0.46
10g	-4.78	0.75	0.01	0.72	0.42
10h	-5.12	0.90	0.00	0.37	0.53
10i	-4.90	0.73	0.01	0.56	0.43
10j	-4.92	0.78	0.01	0.62	0.36
10k	-5.07	0.77	0.02	0.51	0.57
10l	-4.94	0.58	0.02	0.59	0.64
10m	-4.92	0.34	0.04	0.58	0.64
11a	-5.10	0.00	0.03	0.38	0.48
11b	-5.36	0.00	0.01	0.30	0.57
11c	-5.25	0.01	0.03	0.37	0.53
11d	-5.20	0.01	0.02	0.39	0.53
11e	-5.13	0.00	0.00	0.36	0.43
11f	-5.06	0.00	0.02	0.49	0.36
11g	-5.01	0.01	0.01	0.54	0.32
11h	-5.59	0.02	0.00	0.21	0.42
11i	-5.32	0.01	0.01	0.37	0.33
11j	-5.36	0.01	0.01	0.43	0.26
11k	-5.09	0.01	0.02	0.32	0.47
11l	-5.11	0.00	0.03	0.40	0.53
11m	-5.14	0.00	0.04	0.39	0.54
12a	-5.07	0.11	0.16	0.71	0.99
12b	-5.24	0.14	0.04	0.63	0.99
12c	-5.07	0.26	0.15	0.70	0.99
12d	-5.09	0.45	0.13	0.71	0.99
12e	-5.21	0.27	0.01	0.69	0.99
12f	-4.99	0.13	0.11	0.80	0.98
12g	-5.02	0.30	0.07	0.82	0.98
12h	-5.23	0.60	0.00	0.52	0.99
12i	-4.97	0.29	0.09	0.70	0.98
12j	-4.99	0.39	0.06	0.75	0.97
12k	-5.43	0.31	0.10	0.66	0.99
12l	-5.13	0.17	0.15	0.73	0.99
12m	-5.17	0.07	0.23	0.72	0.99
19a	-4.98	0.88	0.02	0.49	0.49

19b	-5.09	0.90	0.00	0.41	0.58
19c	-4.92	0.95	0.02	0.48	0.54
19d	-4.91	0.98	0.01	0.50	0.53
19e	-4.91	0.94	0.00	0.47	0.43
19f	-4.82	0.90	0.01	0.61	0.36
19g	-4.81	0.96	0.01	0.65	0.32
19h	-5.07	0.98	0.00	0.30	0.43
19i	-4.85	0.96	0.01	0.48	0.33
19j	-4.85	0.97	0.01	0.54	0.27
19k	-4.97	0.96	0.01	0.43	0.47
19l	-4.86	0.90	0.02	0.52	0.54
19m	-4.86	0.79	0.02	0.51	0.54
20a	-5.01	0.02	0.01	0.32	0.37
20b	-5.19	0.03	0.00	0.25	0.46
20c	-5.12	0.06	0.01	0.31	0.42
20d	-5.10	0.12	0.00	0.33	0.41
20e	-5.04	0.05	0.00	0.30	0.32
20f	-4.96	0.03	0.01	0.43	0.26
20g	-4.95	0.06	0.00	0.47	0.23
20h	-5.42	0.16	0.00	0.17	0.32
20i	-5.22	0.06	0.00	0.31	0.24
20j	-5.28	0.10	0.00	0.36	0.18
20k	-5.00	0.07	0.00	0.26	0.35
20l	-5.08	0.03	0.01	0.34	0.42
20m	-5.10	0.01	0.01	0.33	0.43
21a	-5.09	0.76	0.03	0.53	0.98
21b	-5.19	0.80	0.01	0.44	0.99
21c	-5.11	0.90	0.03	0.51	0.99
21d	-5.11	0.95	0.02	0.54	0.99
21e	-5.28	0.90	0.00	0.51	0.98
21f	-5.06	0.78	0.02	0.64	0.97
21g	-5.08	0.90	0.01	0.68	0.97
21h	-5.23	0.97	0.00	0.33	0.98
21i	-5.02	0.90	0.02	0.52	0.97
21j	-5.05	0.93	0.01	0.58	0.96
21k	-5.35	0.91	0.01	0.46	0.98
21l	-5.06	0.82	0.03	0.55	0.99
21m	-5.04	0.61	0.04	0.54	0.99
23	-5.02	0.45	0.20	0.33	0.52
24	-5.17	0.00	0.06	0.16	0.42
25	-5.12	0.11	0.66	0.39	0.98

[a] Caco-2 values are log units; optimal results are >-5.15. [b] Values are probability of being hERG blockers where IC_{50} ≤10 μM.

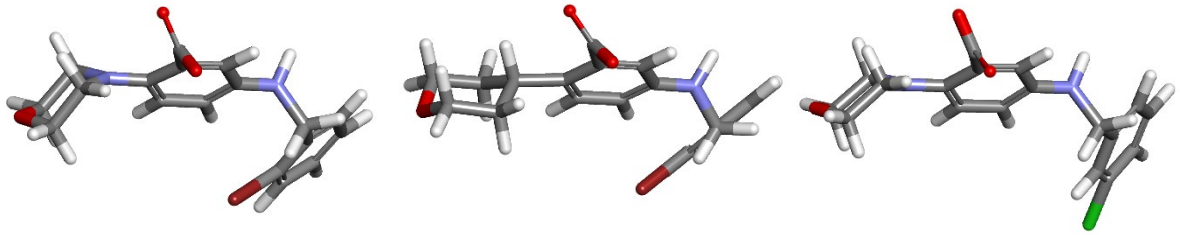

Figure S4. Comparison of binding conformations with alkyl ring modification. Left to right: compound **1c**, **20h**, **1b**. Between **20h** and the other compounds, being its corresponding morpholinyl analogue (**1c**) and most potent inhibitor **1b**, a chair flip of the alkyl ring can be seen. Between **1b** and the other two compounds, the carbonyl group has been rotated.

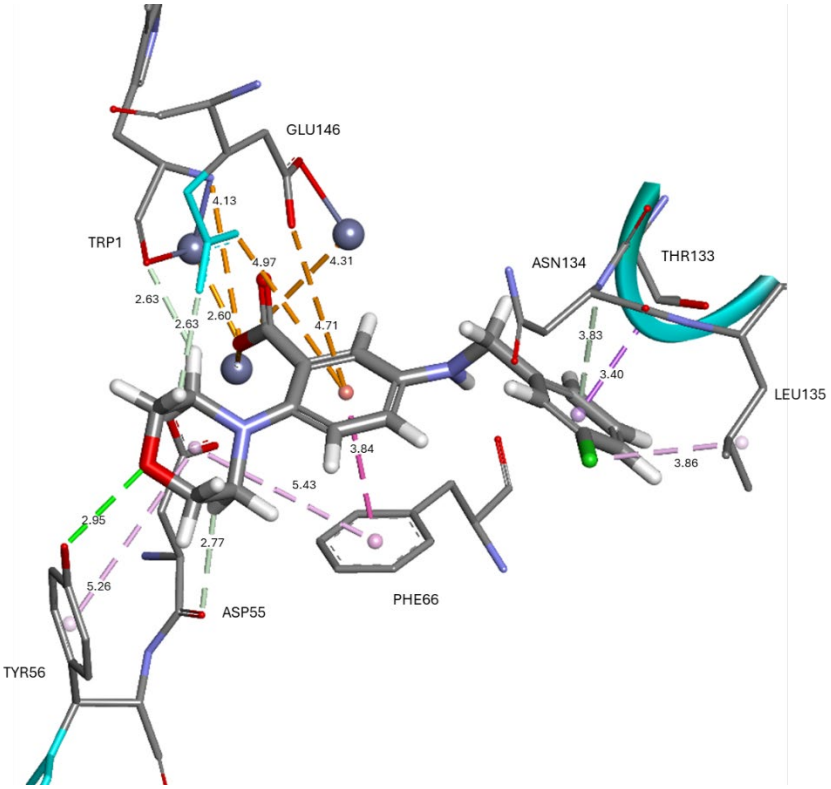

Figure S5. Interactions and distances between **1b** and PC-PLC$_{BC}$. Waters omitted for clarity.

Table S12. Interactions and distances between **1b** and PC-PLC$_{BC}$.

Protein Residue	Interaction Type	Distance (Å)
Leu135	π-alkyl	3.86
Asn134	π-donor H bond	3.85
Thr133	π-sigma	3.40
Phe66	π-alkyl and π- π	5.43 and 3.84
Zn247	Attractive charge	4.31
Zn246	Attractive charge	2.34
Zn248	Attractive charge	2.60
Glu146	C-H bond, π -anion bonds	2.63, 4.71, 4.97
Trp1	C-H bond	2.63
Tyr56	H bond	2.95

Table S13. Interactions and distances between **1b** and active waters of PC-PLC$_{BC}$.

Water molecule	Interaction type	Distance (Å)
HOH258	Unfavourable x 5	1.02 – 1.47
HOH341	Unfavourable x 2	1.58 and 1.86
HOH249	Favourable x 1, unfavourable x 1	2.82, 0.54
HOH250	Favourable, unfavourable x 2	2.74, 2.02 and 1.24
HOH452	Unfavourable x 3	1.55 – 1.91
HOH251	Unfavourable x 4	1.56 – 2.04
HOH254	Favourable	1.75
HOH256	Unfavourable x 6	1.20 – 1.78
HOH318	Unfavourable x 2	0.93 and 1.75

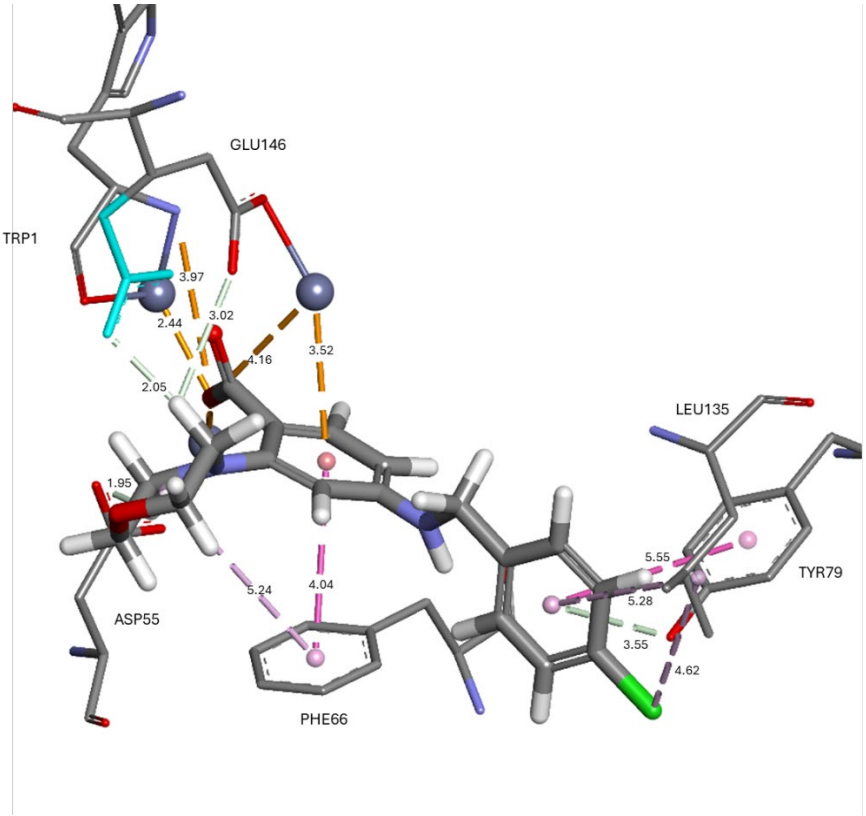

Figure S6. Interactions and distances between **20h** and PC-PLC$_{BC}$. Waters omitted for clarity.

Table S14. Interactions and distances between **20h** and PC-PLC$_{BC}$ as compared with **1b**.

Protein Residue	Interaction Type	Distance (Å)
Leu135	Absent	-
Asn134	Absent	-
Thr133	Absent	-
Phe66	π-alkyl and π-π	5.35 and 3.96
Zn247	Attractive charge	2.30
Zn246	Attractive charge	4.23
Zn248	Attractive charge	2.56
Glu146	C-H bond, π-anion bonds	3.08 and 4.64
Trp1	Absent	-
Tyr56	H bond	2.95
Ala3*	Alkyl	5.30

* interaction not observed in **1b**

Table S15. Interactions and distances between **20h** and active waters of PC-PLC$_{BC}$.

Water molecule	Interaction type (x quantity)	Distance (Å)
HOH258	Unfavourable x 3	1.02 – 2.0
HOH341	Unfavourable x 4	0.85 – 2.18
HOH249	Unfavourable x 2	0.58 and 1.66
HOH250	Unfavourable x 3	0.55 – 1.88
HOH452	Unfavourable x 2	1.74 – 1.87
HOH251	Unfavourable x 4	1.31 – 2.02
HOH254	Favourable x 1, unfavourable x 1	1.66 and 2.06
HOH256	Unfavourable x 4	0.92 – 1.58
HOH318	Unfavourable x 2	1.16 and 1.58

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