Supplementary Information

Table S1. Procurement details of SAMPL6 Part II Octanol-Water Partition Coefficient Challenge compounds. [1] Purities for these compounds were determined by LC-MS methods and reported elsewhere [29].

SAMPL6 Part II Molecule ID	Supplier	Lot no	Cat no	Supplier Reported Purity	Purity Detected by LC-MS	CAS no	eMolecules ID
SM02	ChemDiv	CM02432403	3232-0333		97.62%		1327907
SM04	ChemDiv		Z126957826		99.88%		30719859
SM07	Enamine	2017-0168841	Z57161635	95%	99.38%	100818-54-0	1327878
SM08	Enamine	2017-0168838	Z57157353	95%	99.24%	65418_08_8	1367649
SM09	Enamine	2017_0168839	Z220564816	95%	98.97%		1865544
SM11	Maybridge	142989	RJC00689SC	90%	98.02%	5334-30-5	719540
SM12	Maybridge	265423	DP00818SC		98.13%		1859493
SM13	Maybridge	248841	GK03474SC		97.51%		5828805
SM14	Enamine		Z57290870		96.48%		31653344
SM15	Enamine		Z1318268952		98.70%		37095168
SM16	VitaScreen		STK098832		97.73%		1284691

Table S2. Replicate potentiometric log *P* measurements performed with Sirius T3 for octanol and ISA water biphasic system. Three or four independent replicate experiments were performed starting from powder samples. Measurements were performed at 25.0 ± 0.5°C and in the presence of approximately 150 mM KCl to adjust ionic strength. A partitioning and ionization equilibrium model was fit to potentiometric measurements to estimate log *P* values of the neutral species and also the charged species. Experiments were optimizied to be able to determine log *P* of neutral species with good precision. log *P* estimates of charged species have high variance between replicates and is unreliable.

SAMPL6 Molecule ID	Experimental Molecule ID	log *P*, +1 charged	log *P*, neutral	log *P*, -1 charged	Experiment code	Target sample weight (mg)	Experiment ID	Experimental Report Filename in Supplementary Info
SM02	M02	1.32 +- 0.06	4.10 +- 0.03		EXP28-11	2 mg	18C-01011	SM02_18C-01011_M02_octanol_pH-metric high logP_report.pdf
SM02	M02	0.45 +- 0.04	4.08 +- 0.01		EXP29-11	2 mg	18C-03011	SM02_18C-03011_M02_octanol_pH-metric high logP_report.pdf
SM02	M02	0.59 +- 0.04	4.03 +- 0.01		EXP29-12	2 mg	18C-03012	SM02_18C-03012_M02_octanol_pH-metric high logP_report.pdf
SM02	M02	1.14 +- 0.04	4.16 +- 0.01		EXP30-15	2 mg	18C-06015	SM02_18C-06015_M02_octanol_pH-metric high logP_report.pdf
SM04	M04	0.82 +- 0.06	4.04 +- 0.02		EXP33-02	1.36 mg	18C-24002	SM04_18C-24002_M04_octanol_pH-metric high logP_report.pdf
SM04	M04	0.87 +- 0.03	3.95 +- 0.01		EXP33-03	1.36 mg	18C-24003	SM04_18C-24003_M04_octanol_pH-metric high logP_report.pdf
SM04	M04	0.77 +- 0.03	3.95 +- 0.02		EXP33-04	1.36 mg	18C-24004	SM04_18C-24004_M04_octanol_pH-metric high logP_report.pdf
SM07	M07	0.44 +- 0.03	3.29 +- 0.01		EXP28-11	1 mg	18B-28011	SM07_18B-28011_M07_octanol_pH-metric high logP_report.pdf
SM07	M07	-5.97 +- 0.89	3.14 +- 0.01		Exp28-012	1 mg	18B-28012	SM07_18B-28012_M07_octanol_pH-metric high logP_report.pdf
SM07	M07	0.31 +- 0.04	3.21 +- 0.01		Exp28-013	1 mg	18B-28013	SM07_18B-28013_M07_octanol_pH-metric high logP_report.pdf
SM08[1]	M08		3.05 +- 0.01	-0.40 +- 0.05	EXP29-07	1 mg	18C-02007	SM08_18C-02007_M08_octanol_pH-metric high logP_report.pdf
SM08[1]	M08		3.08 +- 0.01	-0.07 +- 0.05	EXP29-08	1 mg	18C-02008	SM08_18C-02008_M08_octanol_pH-metric high logP_report.pdf
SM08[1]	M08		3.16 +- 0.01	0.23 +- 0.03	EXP29-09	1 mg	18C-02009	SM08_18C-02009_M08_octanol_pH-metric high logP_report.pdf
SM09	M09	-9.50 +- 0.85	2.90 +- 0.01		EXP29-10	1 mg	18C-02010	SM09_18C-02010_M09_octanol_pH-metric high logP_report.pdf
SM09	M09	1.05 +- 0.04	3.14 +- 0.01		EXP29-01	1 mg	18C-03001	SM09_18C-03001_M09_octanol_pH-metric high logP_report.pdf
SM09	M09	0.91 +- 0.07	3.05 +- 0.02		EXP30-07	1 mg	18C-06007	SM09_18C-06007_M09_octanol_pH-metric high logP_report.pdf
SM11	M11	-5.60 +- 1.55	2.09 +- 0.01		EXP27-16	1 mg	18B-27016	SM11_18B-27016_M11_octanol_pH-metric high logP_report.pdf
SM11	M11	0.55 +- 0.07	2.19 +- 0.02		Exp28-01	1.1 mg	18C-01001	SM11_18C-01001_M11_octanol_pH-metric high logP_report.pdf
SM11	M11	-3.66 +- 2.11	2.01 +- 0.02		Exp28-02	1.1 mg	18C-01002	SM11_18C-01002_M11_octanol_pH-metric high logP_report.pdf
SM11	M11	-0.33 +- 0.82	2.12 +- 0.01		EXP31-10	1.5 mg	18C-09010	SM11_18C-09010_M11_octanol_pH-metric high logP_report.pdf
SM12	M12	1.02 +- 0.07	3.79 +- 0.02		EXP28-12	1.5 mg	18C-01012	SM12_18C-01012_M12_octanol_pH-metric high logP_report.pdf
SM12	M12	-4.20 +- 1.91	3.81 +- 0.01		EXP29-13	2 mg	18C-03013	SM12_18C-03013_M12_octanol_pH-metric high logP_report.pdf
SM12	M12	0.62 +- 0.05	3.91 +- 0.01		EXP29-14	2 mg	18C-03014	SM12_18C-03014_M12_octanol_pH-metric high logP_report.pdf
SM12	M12	0.40 +- 0.06	3.80 +- 0.01		EXP29-15	2 mg	18C-03015	SM12_18C-03015_M12_octanol_pH-metric high logP_report.pdf
SM13[2]	M13	-4.95 +- 1.76	2.87 +- 0.01		EXP31-11	1.5 mg	18C-09011	SM13_18C-09011_M13_octanol_pH-metric high logP_report.pdf
SM13[2]	M13	-7.57 +- 1.49	2.89 +- 0.02		EXP32-16	1.5 mg	18C-16016	SM13_18C-16016_M13_octanol_pH-metric high logP_report.pdf
SM13[3]	M13	0.09 +- 0.08	2.99 +- 0.03		EXP34-10	1 mg	18C-26010	SM13_18C-26010_M13_octanol_pH-metric high logP_report.pdf
SM14	M15	-4.96 +- 2.15	1.92 +- 0.01		EXP27-02	2 mg	18B-28002	SM14_18B-28002_M15_octanol_pH-metric high logP_report.pdf
SM14	M15	-0.11 +- 0.20	1.92 +- 0.01		Exp28-04	2 mg	18C-01004	SM14_18C-01004_M15_octanol_pH-metric high logP_report.pdf
SM14	M15	-0.05 +- 0.07	1.93 +- 0.01		EXP28-05	2 mg	18C-01005	SM14_18C-01005_M15_octanol_pH-metric high logP_report.pdf
SM14	M15	0.28 +- 0.16	2.04 +- 0.02		EXP29-06	2 mg	18C-03006	SM14_18C-03006_M15_octanol_pH-metric high logP_report.pdf
SM15	M16	1.38 +- 1.07	3.14 +- 0.01		EXP28-07	1.5 mg	18C-01007	SM15_18C-01007_M16_octanol_pH-metric high logP_report.pdf
SM15	M16	-1.34	3.04		EXP28-08	1.5 mg	18C-01008	SM15_18C-01008_M16_octanol_pH-metric high logP_report.pdf
SM15	M16	-0.17 +- 0.20	3.04 +- 0.01		EXP28-09	1.5 mg	18C-01009	SM15_18C-01009_M16_octanol_pH-metric high logP_report.pdf
SM16[2]	M18	-0.24 +- 0.09	2.63 +- 0.01		EXP31-14	1.5 mg	18C-09014	SM16_18C-09014_M18_octanol_pH-metric high logP_report.pdf
SM16[2]	M18	-0.73 +- 0.56	2.59 +- 0.01		EXP31-15	1.5 mg	18C-09015	SM16_18C-09015_M18_octanol_pH-metric high logP_report.pdf
SM16[2]	M18	-0.21 +- 0.12	2.63 +- 0.02		EXP31-16	1.5 mg	18C-09016	SM16_18C-09016_M18_octanol_pH-metric high logP_report.pdf

[1] Sample predosed with 80 uL octanol to help with kinetic solubility issues.
[2] Sample predosed with 100 uL octanol to help with kinetic solubility issues.
[3] Sample predosed with 200 uL octanol to help with kinetic solubility issues.

Table S3. SMILES and InChI identifiers of SAMPL6 log *P* Challenge molecules.

SAMPL6 Molecule ID	isomeric SMILES	InChI
SM02	c1ccc2c(c1)c(ncn2)Nc3cccc(c3)C(F)(F)F	InChI=1S/C15H10F3N3/c16-15(17,18)10-4-3-5-11(8-10)21-14-12-6-1-2-7-13(12)19-9-20-14/h1-9H,(H,19,20,21)
SM04	c1ccc2c(c1)c(ncn2)NCc3ccc(cc3)Cl	InChI=1S/C15H12ClN3/c16-12-7-5-11(6-8-12)9-17-15-13-3-1-2-4-14(13)18-10-19-15/h1-8,10H,9H2,(H,17,18,19)
SM07	c1ccc(cc1)CNc2c3ccccc3ncn2	InChI=1S/C15H13N3/c1-2-6-12(7-3-1)10-16-15-13-8-4-5-9-14(13)17-11-18-15/h1-9,11H,10H2,(H,16,17,18)
SM08	Cc1ccc2c(c1)c(c(c(=O)[nH]2)CC(=O)O)c3ccccc3	InChI=1S/C18H15NO3/c1-11-7-8-15-13(9-11)17(12-5-3-2-4-6-12)14(10-16(20)21)18(22)19-15/h2-9H,10H2,1H3,(H,19,22)(H,20,21)
SM09	COc1cccc(c1)Nc2c3ccccc3ncn2.Cl	InChI=1S/C15H13N3O.ClH/c1-19-12-6-4-5-11(9-12)18-15-13-7-2-3-8-14(13)16-10-17-15;/h2-10H,1H3,(H,16,17,18);1H
SM11	c1ccc(cc1)n2c3c(cn2)c(ncn3)N	InChI=1S/C11H9N5/c12-10-9-6-15-16(11(9)14-7-13-10)8-4-2-1-3-5-8/h1-7H,(H2,12,13,14)
SM12	c1ccc2c(c1)c(ncn2)Nc3cccc(c3)Cl.Cl	InChI=1S/C14H10ClN3.ClH/c15-10-4-3-5-11(8-10)18-14-12-6-1-2-7-13(12)16-9-17-14;/h1-9H,(H,16,17,18);1H
SM13	Cc1cccc(c1)Nc2c3cc(c(cc3ncn2)OC)OC	InChI=1S/C17H17N3O2/c1-11-5-4-6-12(7-11)20-17-13-8-15(21-2)16(22-3)9-14(13)18-10-19-17/h4-10H,1-3H3,(H,18,19,20)
SM14	c1ccc(cc1)n2cnc3c2ccc(c3)N	InChI=1S/C13H11N3/c14-10-6-7-13-12(8-10)15-9-16(13)11-4-2-1-3-5-11/h1-9H,14H2
SM15	c1ccc2c(c1)ncn2c3ccc(cc3)O	InChI=1S/C13H10N2O/c16-11-7-5-10(6-8-11)15-9-14-12-3-1-2-4-13(12)15/h1-9,16H
SM16	c1cc(c(c(c1)Cl)C(=O)Nc2ccncc2)Cl	InChI=1S/C12H8Cl2N2O/c13-9-2-1-3-10(14)11(9)12(17)16-8-4-6-15-7-5-8/h1-7H,(H,15,16,17)

Table S4. Molecules from SAMPL6 pK_a Challenge not included in SAMPL6 log *P* Challenge. These are molecules for which potentiometric log *P* experiments could not be optimized. Suspected reasons why good log *P* measurements could not be collected for these molecules are listed in the "Limitation for potentiometric log *P*" column. Limitation of pK_a value indicates that apparent pK_a shifts outside of measureable range in the presence of the octanol phase. Solubility limitation indicates that we could not find a potentiometric log *P* protocol that can avoid precipitation issues. Experimental pK_a values were originally reported elsewhere [29].

SAMPL6 Molecule ID	Limitation for potentiometric log *P*	Experimental pK_a	SMILES	Experimental Molecule ID
SM01	pK_a	9.53 (acid)	c1cc2c(cc1O)c3c(o2)C(=O)NCCC3	M01
SM03	solubility	7.02 (acid)	c1ccc(cc1)Cc2nnc(s2)NC(=O)c3cccs3	M03
SM05	solubility	4.59 (base)	c1ccc(c(c1)NC(=O)c2ccc(o2)Cl)N3CCCCC3	M05
SM06	solubility	3.03 (base), 11.74 (base)	c1cc2cccnc2c(c1)NC(=O)c3cc(cnc3)Br	M06
SM10	solubility	9.02 (base)	c1ccc(cc1)C(=O)NCC(=O)Nc2nc3ccccc3s2	M10
SM17	pK_a and solubility	3.16 (base)	c1ccc(cc1)CSc2nnc(o2)c3ccncc3	M19
SM18	pK_a and solubility	2.15 (base), 9.58 (acid), 11.02 (acid)	c1ccc2c(c1)c(=O)[nH]c(n2)CCC(=O)Nc3ncc(s3)Cc4ccc(c(c4)F)F	D01
SM19	pK_a and solubility	9.56 (acid)	CCOc1ccc2c(c1)sc(n2)NC(=O)Cc3ccc(c(c3)Cl)Cl	D02
SM20	solubility	5.70 (base)	c1cc(cc(c1)OCc2ccc(cc2Cl)Cl)/C=C/3\C(=O)NC(=O)S3	D05
SM21	solubility	4.10 (base)	c1cc(cc(c1)Br)Nc2c(cnc(n2)Nc3cccc(c3)Br)F	D06
SM22	solubility	2.40 (base), 7.43 (acid)	c1cc2c(cc(c(c2nc1O)I)I	D07
SM23	solubility	5.45 (base)	CCOC(=O)c1ccc(cc1)Nc2cc(nc(n2)Nc3ccc(cc3)C(=O)OCC)C	D08
SM24	pK_a	2.60 (base)	COc1ccc(cc1)c2c3c(ncnc3oc2c4ccc(cc4)OC)NCCO	D09

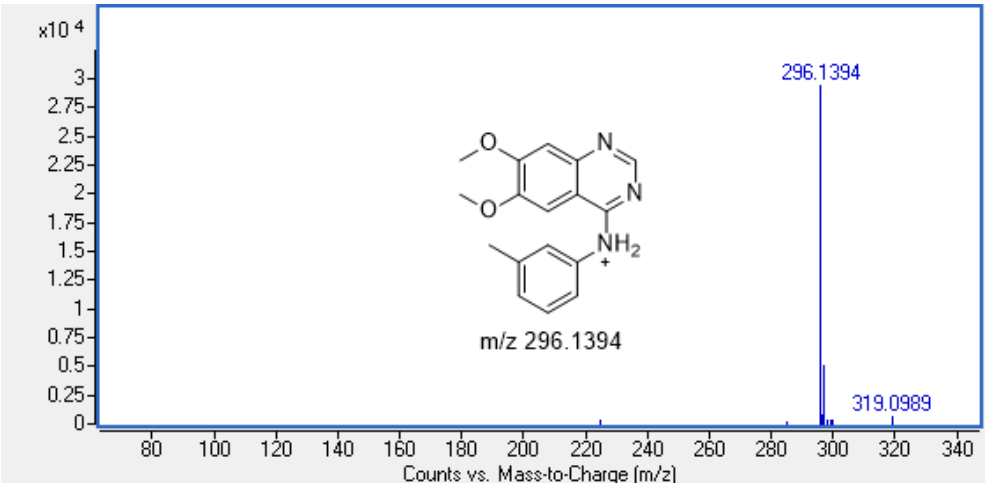

Figure S1. HRMS determination of SM13 molecular weight confirmed the supplier reported molecular weight.

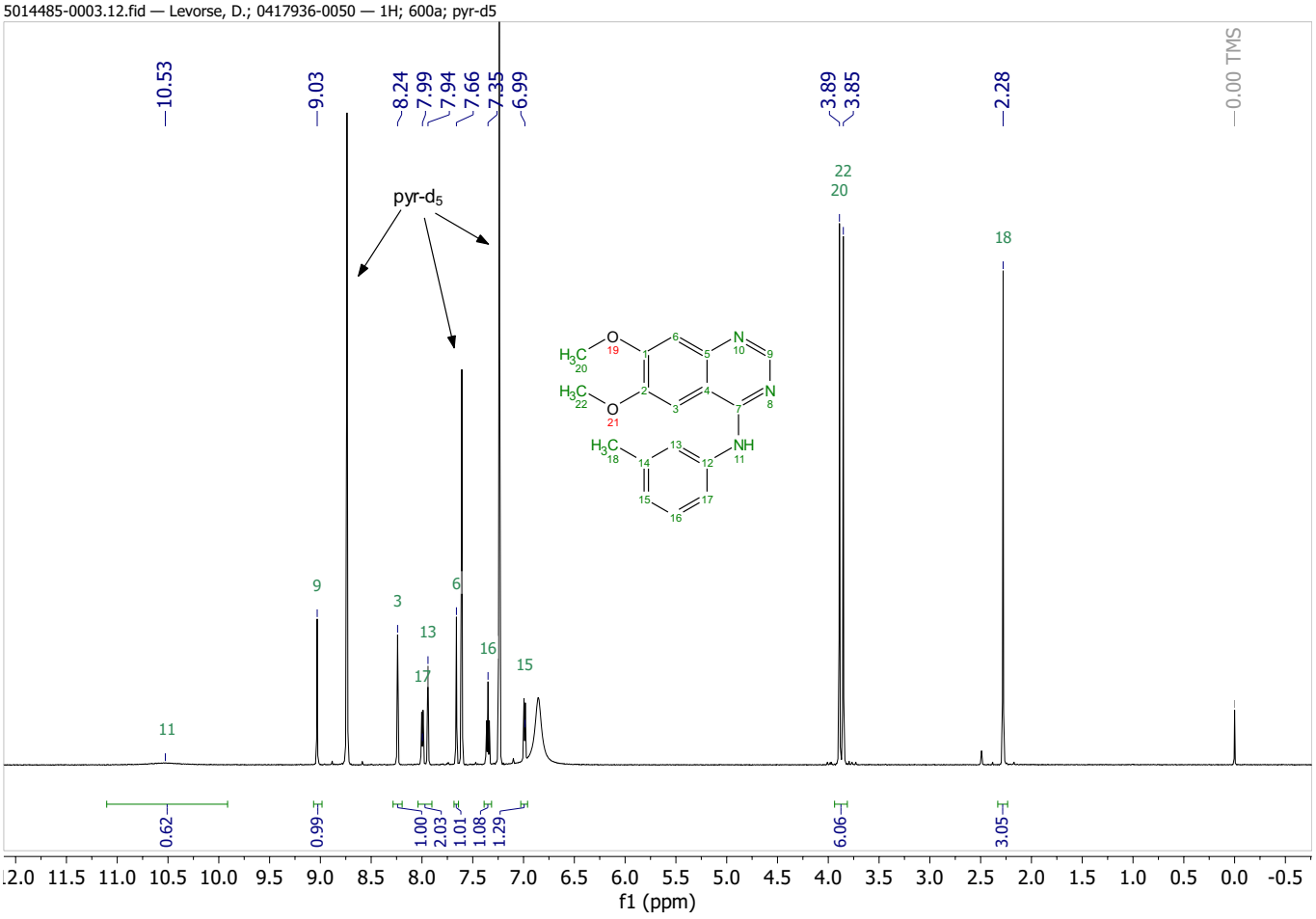

Figure S2. The ^{1}H 1D NMR spectrum of SM13 confirms compound identity and structure.