

## Statistics for CLND solubility changes upon N- and O-methylation

Methylation type	Class	SOL DIFF Count	SOL DIFF Avg	SOL DIFF StdDev	SOL DIFF StdErr	SOL DIFF Median	SOL DIFF Min	SOL DIFF Max	SOL DIFF L95	SOL DIFF U95	SOL %PAIRS > 0	Shapiro- Wilk test	Paired t test	Signed-rank test
Alk-CONH2	Amide	140	0.11	0.42	0.04	0.01	-1.2	1.18	0.04	0.18	52.1%	<0.0001*	0.0026*	NA
Alk-CONH-Alk	Amide	426	0.06	0.48	0.02	0.02	-2.52	2.65	0.01	0.1	53.1%	<0.0001*	0.0119*	NA
Alk-CONH-Ar	Amide	324	0.11	0.55	0.03	0.02	-2.57	2.49	0.05	0.17	54.6%	<0.0001*	0.0003*	NA
Ar-CONH2	Amide	410	0.07	0.51	0.03	0.02	-2.62	2.48	0.02	0.12	52.7%	<0.0001*	0.0082*	NA
Ar-CONH-Alk	Amide	517	0.25	0.58	0.03	0.08	-2.49	2.62	0.2	0.3	64.8%	<0.0001*	<0.0001*	NA
Ar-CONH-Ar	Amide	105	0.39	0.86	0.08	0.09	-1.71	2.64	0.22	0.55	59.0%	<0.0001*	<0.0001*	NA
Alk-NH-Alk	Amine	1121	-0.01	0.48	0.01	0.02	-2.62	3.02	-0.04	0.02	53.2%	<0.0001*	0.3869	NA
Ar-NH-Alk	Amine	604	-0.04	0.53	0.02	-0.03	-2.57	2.56	-0.08	0	41.1%	<0.0001*	0.0657	NA
Ar-NH-Ar	Amine	181	0.14	0.59	0.04	0.06	-1.62	2.38	0.05	0.22	56.4%	0.0198*	0.0026*	NA
Arom-NH	Amine	857	0.04	0.58	0.02	0.04	-2.49	2.12	0	0.08	54.7%	<0.0001*	0.0332*	NA
R-OCNH-R	Carbamate	50	-0.09	0.4	0.06	-0.02	-1.3	0.79	-0.2	0.02	40.0%	<0.0001*	0.1048	NA
Alk-COOH	Acid	349	-0.65	0.79	0.04	-0.41	-2.75	1.53	-0.72	-0.56	19.5%	<0.0001*	<0.0001*	NA
Alk-OH	Alcohol	610	-0.19	0.49	0.02	-0.07	-2.4	1.42	-0.23	-0.15	33.8%	<0.0001*	<0.0001*	NA
Ar-COOH	Acid	505	-0.94	0.86	0.04	-0.95	-2.83	2.65	-1	-0.85	13.5%	<0.0001*	<0.0001*	NA
Ar-OH	Phenol	964	-0.21	0.65	0.02	-0.07	-3.07	2.09	-0.25	-0.17	39.1%	<0.0001*	<0.0001*	NA
Alk-SO2-NH2	Sulfonamide	9	-0.09	0.35	0.12	0.05	-0.65	0.32	-0.32	0.14	55.6%	0.2146	NA	0.7344
Alk-SO2-NH-Alk	Sulfonamide	23	-0.33	0.43	0.09	-0.16	-1.26	0.31	-0.51	-0.16	8.7%	0.0177*	0.0011*	NA
Alk-SO2-NH-Ar	Sulfonamide	37	-0.22	0.48	0.08	-0.07	-1.61	0.68	-0.38	-0.07	29.7%	0.0009*	0.0076*	NA
Ar-SO2-NH2	Sulfonamide	65	-0.1	0.54	0.07	-0.03	-1.5	1.67	-0.24	0.03	43.1%	0.0006*	0.101	NA
Ar-SO2-NH-Alk	Sulfonamide	156	-0.23	0.53	0.04	-0.15	-1.84	1.28	-0.31	-0.14	32.7%	0.0331*	<0.0001*	NA
Ar-SO2-NH-Ar	Sulfonamide	60	-0.42	0.65	0.08	-0.31	-2.23	0.9	-0.58	-0.25	21.7%	0.0003*	<0.0001*	NA
Alk-NH-C(=O)-NH-Alk	Urea	18	0.36	0.46	0.11	0.15	-0.59	1.15	0.08	0.51	72.2%	0.094	NA	0.0030*
Alk-NR-C(=O)-NH-Alk	Urea	57	-0.02	0.45	0.06	-0.03	-1.3	1.83	-0.11	0.11	33.3%	<0.0001*	0.7608	NA
Ar-NH-C(=O)-NH-Ar	Urea	8	0.61	0.4	0.14	0.49	0.2	1.26	0.33	0.88	100.0%	0.3033	NA	0.0078*
Ar-NR-C(=O)-NH-Ar	Urea	5	0.94	0.99	0.44	0.66	0.14	2.63	0.07	1.8	100.0%	0.0976	NA	0.0625
[N;!H0]!@[c,CX3]@[c,CX3]!@C=O	Amide IMHB	12	0.36	1.02	0.3	0.46	-1.76	2.21	-0.22	0.94	66.7%	0.8235	NA	0.2036
[N;!H0]!@[c,CX3]!@[c,CX3]!@C=O	Amide IMHB	5	1.44	1.32	0.59	1.89	-0.01	2.63	0.29	2.6	80.0%	0.0891	NA	0.125
[N;!H0]!@C!@c[n;X2]	Amide IMHB	103	0.42	0.72	0.07	0.27	-1.33	2.6	0.3	0.58	70.9%	0.0013*	<0.0001*	NA
OccC(=O)[NH1][c,C]	Amide IMHB	44	0.22	0.6	0.09	0.02	-0.9	2.64	0.05	0.4	61.4%	<0.0001*	0.0177*	NA
[NH1]!@[c;X3]!@ccF	Amide IMHB	10	0.04	0.13	0.04	-0.01	-0.06	0.38	-0.04	0.13	50.0%	0.0032*	0.3191	NA
[c;C;X3]!@[NH1]!@ccF	Amide IMHB	2	-0.1	0.26	0.19	-0.1	-0.28	0.09	-0.46	0.27	50.0%	1	NA	1
No IMHBs	Amide IMHB	674	0.27	0.56	0.02	0.09	-1.45	2.51	0.22	0.31	65.0%	<0.0001*	<0.0001*	NA
Cyclic amides	Amide	169	-0.04	0.46	0.04	-0.03	-2.57	1.81	-0.11	0.03	43.2%	<0.0001*	0.2915	NA
Acyclic amides	Amide	778	0.28	0.62	0.02	0.08	-2.49	2.64	0.23	0.32	64.5%	<0.0001*	<0.0001*	NA

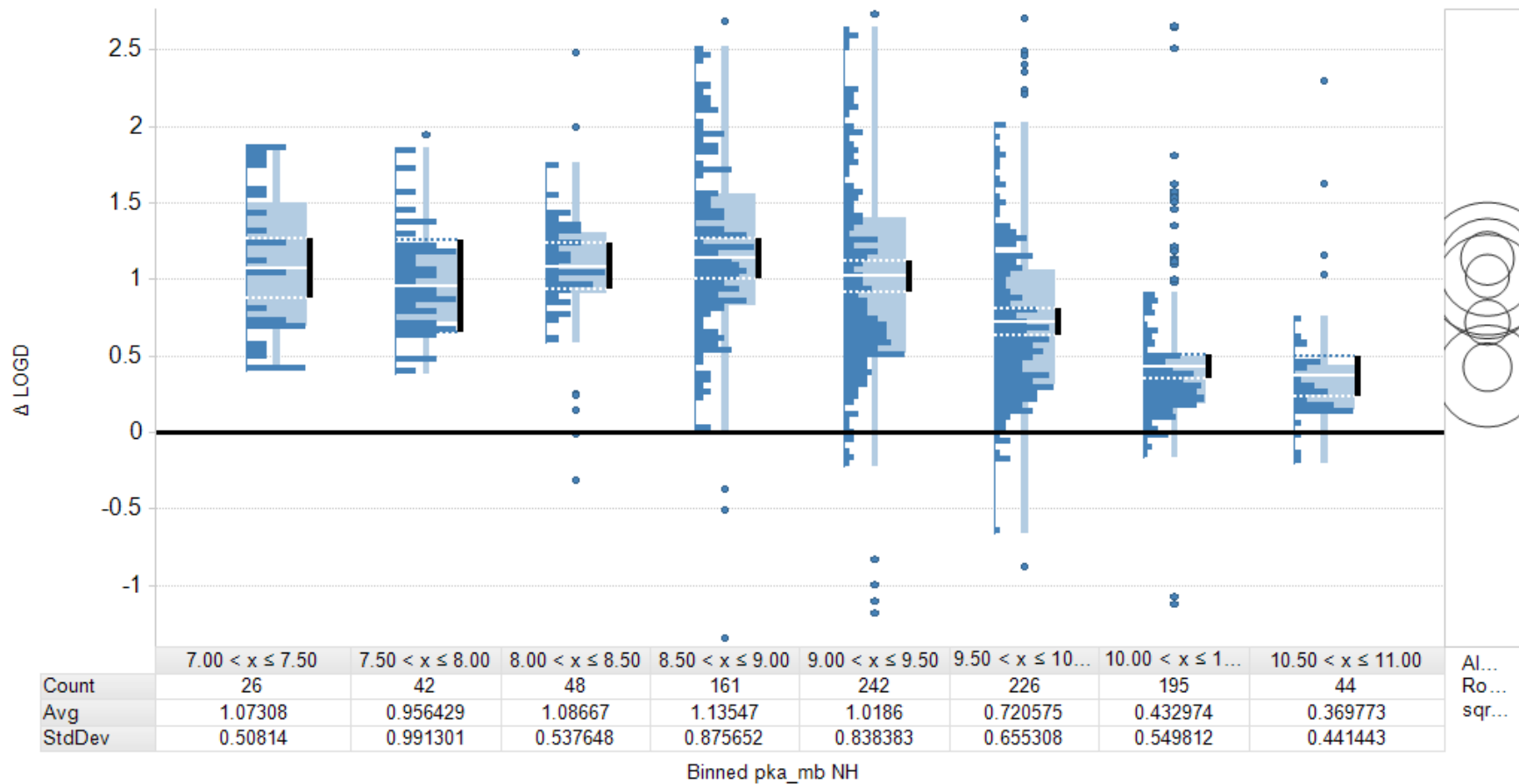
# Statistics for chromatographic log D changes upon N- and O-methylation

Methylation type	Class	LOGD DIFF Count	LOGD DIFF Avg	LOGD DIFF StdDev	LOGD DIFF StdErr	LOGD DIFF Median	LOGD DIFF Min	LOGD DIFF Max	LOGD DIFF L95	LOGD DIFF U95	LOGD %PAIRS > 0	Shapiro- Wilk test	Paired t test	Signed-rank test
Alk-CONH2	Amide	132	0.35	0.4	0.03	0.32	-1.98	2.22	0.29	0.42	95.5%	<0.0001*	<0.0001*	NA
Alk-CONH-Alk	Amide	386	0.54	0.51	0.03	0.53	-1.71	6.45	0.48	0.59	94.0%	<0.0001*	<0.0001*	NA
Alk-CONH-Ar	Amide	304	0.45	0.6	0.03	0.59	-4.57	1.77	0.38	0.52	86.5%	<0.0001*	<0.0001*	NA
Ar-CONH2	Amide	387	0.45	0.39	0.02	0.41	-1.75	4.67	0.41	0.49	97.9%	<0.0001*	<0.0001*	NA
Ar-CONH-Alk	Amide	482	0.14	0.66	0.03	0.25	-6.66	2.89	0.09	0.2	74.9%	<0.0001*	<0.0001*	NA
Ar-CONH-Ar	Amide	98	-0.42	1.3	0.13	-0.28	-7.08	2.98	-0.67	-0.16	31.6%	<0.0001*	0.002*	NA
Alk-NH-Alk	Amine	1011	0.83	0.78	0.02	0.7	-4.18	5.22	0.78	0.87	95.0%	<0.0001*	<0.0001*	NA
Ar-NH-Alk	Amine	571	0.78	0.69	0.03	0.75	-4.97	5.88	0.72	0.84	94.7%	<0.0001*	<0.0001*	NA
Ar-NH-Ar	Amine	158	0.54	0.51	0.04	0.55	-1.23	3.62	0.46	0.62	90.5%	<0.0001*	<0.0001*	NA
Arom-NH	Amine	810	0.6	0.54	0.02	0.6	-4.11	5.28	0.56	0.63	90.6%	<0.0001*	0.002*	NA
R-CONH-R	Carbamate	40	0.58	0.52	0.08	0.58	-1.23	1.82	0.42	0.74	95.0%	0.0003*	<0.0001*	NA
Alk-COOH	Acid	314	3.02	1.07	0.06	3.16	-3.65	6.65	2.9	3.14	99.0%	<0.0001*	<0.0001*	NA
Alk-OH	Alcohol	590	1.14	0.66	0.03	1.12	-8.61	3.25	1.08	1.19	98.3%	<0.0001*	<0.0001*	NA
Ar-COOH	Acid	475	3.36	0.97	0.04	3.49	-0.11	6.33	3.26	3.43	99.6%	<0.0001*	<0.0001*	NA
Ar-OH	Phenol	883	1.13	0.94	0.03	1.17	-4.28	5.63	1.06	1.19	91.1%	<0.0001*	<0.0001*	NA
Alk-SO2-NH2	Sulfonamide	5	0.28	0.45	0.2	0.45	-0.5	0.63	-0.11	0.67	80.0%	0.0413*	0.2368	NA
Alk-SO2-NH-Alk	Sulfonamide	17	0.68	0.24	0.06	0.65	0.33	1.13	0.56	0.79	100.0%	0.3354	NA	<0.0001*
Alk-SO2-NH-Ar	Sulfonamide	37	0.83	0.86	0.14	0.6	-0.68	2.94	0.55	1.1	91.9%	0.0003*	<0.0001*	NA
Ar-SO2-NH2	Sulfonamide	60	0.67	0.19	0.02	0.67	0.21	1.43	0.62	0.72	100.0%	0.0010*	<0.0001*	NA
Ar-SO2-NH-Alk	Sulfonamide	150	0.79	0.34	0.03	0.79	-1.14	1.71	0.74	0.84	97.3%	<0.0001*	<0.0001*	NA
Ar-SO2-NH-Ar	Sulfonamide	60	1.11	0.64	0.08	0.97	-0.04	2.88	0.95	1.27	98.3%	<0.0001*	<0.0001*	NA
Alk-NH-C(=O)-NH-Alk	Urea	17	0.62	0.35	0.08	0.53	0.14	1.28	0.47	0.77	100.0%	0.2068	NA	<0.0001*
Alk-NR-C(=O)-NH-Alk	Urea	55	0.69	0.31	0.04	0.65	0.05	1.87	0.62	0.77	100.0%	0.0002*	<0.0001*	NA
Ar-NH-C(=O)-NH-Ar	Urea	8	0.01	0.28	0.1	-0.01	-0.31	0.46	-0.19	0.2	50.0%	0.4199	NA	0.8672
Ar-NR-C(=O)-NH-Ar	Urea	5	-0.47	0.55	0.24	-0.22	-1.4	-0.03	-0.95	0.01	0.0%	0.0824	NA	0.1273
[N;!H0]!@[c,CX3]@[c,CX3]!@C=O	Amide IMHB	12	-1.71	1.23	0.35	-1.88	-3.21	0.01	-2.41	-1.02	8.3%	0.1352	NA	0.0010*
[N;!H0]!@[c,CX3]!@[c,CX3]!@[c,CX3]=O	Amide IMHB	4	-5.05	3.01	1.5	-6.26	-7.08	-0.61	-8	-2.11	0.0%	0.0637	NA	0.125
[N;!H0]!@C!@c[n;X2]	Amide IMHB	97	-0.27	0.63	0.06	-0.22	-2.53	2.08	-0.42	-0.16	37.9%	0.0006*	<0.0001*	NA
Occc(=O)[NH1][c,C]	Amide IMHB	43	-0.49	0.85	0.13	-0.25	-2.45	1.43	-0.74	-0.23	37.2%	0.0541	NA	0.0019*
[NH1]!@[C;X3]!@ccF	Amide IMHB	9	0.12	0.17	0.06	0.15	-0.25	0.36	0.01	0.23	88.9%	0.0853	NA	0.0898
[c,C;X3]!@[NH1]!@ccF	Amide IMHB	2	0.38	0.05	0.04	0.38	0.34	0.41	0.31	0.44	100.0%	1	NA	0.5
No IMHBs	Amide IMHB	618	0.22	0.51	0.02	0.28	-2.13	2.98	0.18	0.26	77.7%	<0.0001*	<0.0001*	NA
Cyclic amides	Amide	167	0.71	0.48	0.04	0.75	-4.57	1.77	0.64	0.78	98.2%	<0.0001*	0.0287*	NA
Acyclic amides	Amide	717	0.07	0.79	0.03	0.2	-7.08	2.98	0.01	0.12	68.5%	<0.0001*	<0.0001*	NA

## R<sup>2</sup> correlation coefficients between $\Delta\text{Log Sol}$ and $\Delta\text{Log D}$ for each *N*-methylation structural class

Methylation type	R2 Correlation between $\Delta\text{Log Sol}$ and $\Delta\text{Log D}$
Ar-SO <sub>2</sub> -NH-Ar	0.284
Ar-CONH-Ar	0.148
Ar-COOH	0.142
Alk-SO <sub>2</sub> -NH <sub>2</sub>	0.123
Alk-COOH	0.102
Ar-OH	0.102
Ar-SO <sub>2</sub> -NH-Alk	0.047
Arom-NH	0.045
Alk-NH-Alk	0.044
Ar-NH-Alk	0.044
Alk-CONH <sub>2</sub>	0.037
Alk-CONH-Ar	0.032
Ar-CONH-Alk	0.023
Alk-SO <sub>2</sub> -NH-Ar	0.021
Ar-NH-C(=O)-NH-Ar	0.019
Ar-NH-Ar	0.016
Alk-CONH-Alk	0.008
R-OCNH-R	0.007
Ar-NR-C(=O)-NH-Ar	0.007
Alk-OH	0.006
Alk-NH-C(=O)-NH-Alk	0.006
Alk-SO <sub>2</sub> -NH-Alk	0.003
Ar-SO <sub>2</sub> -NH <sub>2</sub>	0.002
Ar-CONH <sub>2</sub>	0.000
Alk-NR-C(=O)-NH-Alk	0.000

# Influence of $pK_a$ of aliphatic amine (Alk-NH-Alk) on change of $\log D$ upon *O*-methylation



# Influence of log *D* of aliphatic acid on change in solubility upon *O*-methylation

