Matched molecular pairs as a guide in the optimization of pharmaceutical properties; a study of aqueous solubility, plasma protein binding and oral exposure

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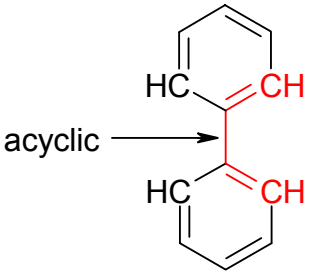
SUPPORTING INFORMATION

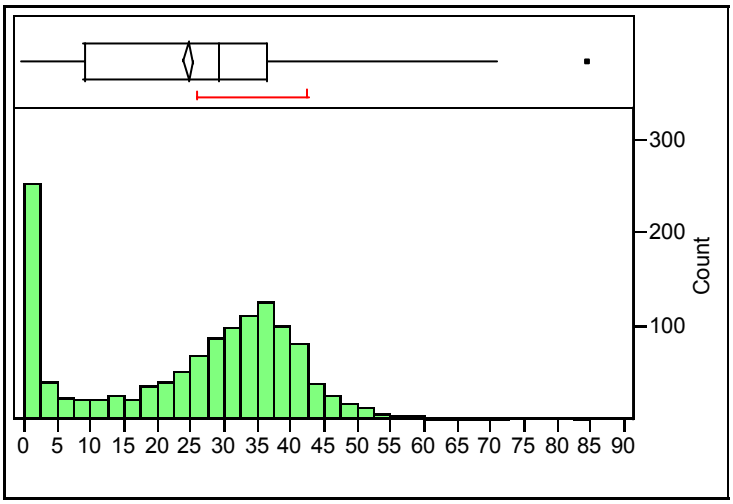
Contents:

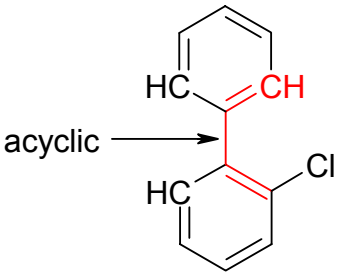
a) Interplane angle change in biphenyl compounds when ortho chlorine is added.
b) Matched molecular pairs analysis of human plasma protein binding
c) Conformational change for compounds 5 and 6
d) Pairwise comparisons of adding F and Cl to aromatic rings
e) Variation with lipophilicity of mean changes in solubility, plasma protein binding and AUC for methylations

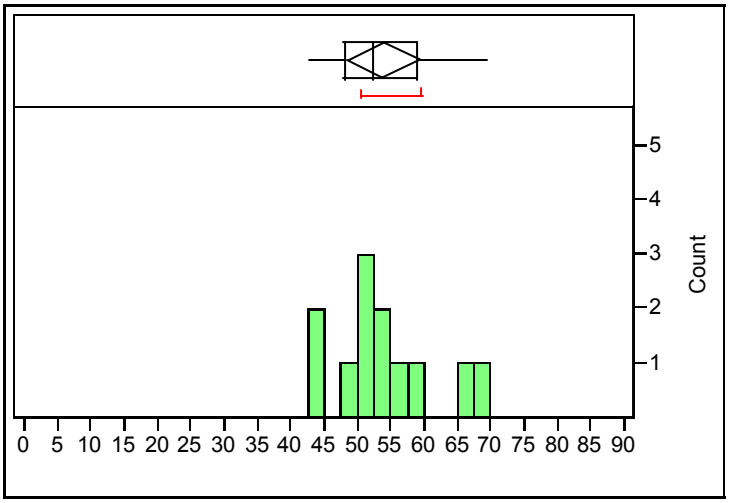
a) Interplane angle change in biphenyl compounds when ortho chlorine is added.

The Cambridge Crystallographic Database was searched for compounds with the following substructure and the values of the dihedral indicated in red were found. These were converted into interplane angles (the absolute magnitude of the dihedral angle was found and if >90 was substracted from 180). This yielded the two distributions below:









The full datasets of database entry code and plane angle can be provided.

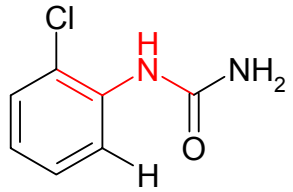
b) Matched molecular pairs analysis of human plasma protein binding

X	Mean change in $\log(K_1)$[a]	Standard deviation in change in $\log(K_1)$[b]	Standard error in the mean change[c]	Number of pairs	% of cases in which K_1 increases
F	+0.06	0.29	0.02	171	65
Cl	+0.58	0.32	0.04	68	96
Br	+0.66	0.37	0.10	15	87
CF_3	+0.60	0.41	0.10	18	94
Me	+0.31	0.18	0.03	36	100
OMe	+0.02	0.33	0.04	71	56
CN	-0.07	0.41	0.11	14	50

a) The mean value of $\log(K_1)$ for ArX minus $\log(K_1)$ for ArH where K_1 is the association constant for human plasma proteins, concentrations being measured in M. b) The standard deviation of the distribution of the values of $\log(K_1)$ for ArX minus $\log(K_1)$ for ArH. c) The standard error in the mean in column 2.

c) Conformational change for compounds 5 and 6

The geometries and energies of model compounds **7** and **8** obtained using constrained geometry optimizations in Gaussian03 at the B3LYP/6-31G* level (for citations see main text).



0º

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4	7	0	-1.000791	-1.086743	0.092673
5	6	0	0.337383	-0.660230	0.007272
6	6	0	0.837554	0.657505	-0.015392
7	17	0	-0.174767	2.072677	-0.232936
8	6	0	2.217870	0.890834	0.009208
9	6	0	3.132327	-0.154496	0.040968
10	6	0	2.656141	-1.466514	0.033773
11	6	0	1.289874	-1.702836	0.028972
12	1	0	-4.127066	-0.647757	-0.432214
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15º

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45º

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60º

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75º

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90º

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105º

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8	6	0	2.467357	0.152937	-0.205377
9	6	0	2.735504	-1.214298	-0.169429
10	6	0	1.698908	-2.113781	0.084828
11	6	0	0.403300	-1.659287	0.314477
12	1	0	-4.230897	0.138571	-0.513471
13	1	0	-3.301964	1.487235	-0.060868
14	1	0	-1.234951	1.177695	0.750960
15	1	0	3.253709	0.873509	-0.403196
16	1	0	3.747725	-1.568829	-0.339253
17	1	0	1.898583	-3.181012	0.114639
18	1	0	-0.406239	-2.350681	0.506542

150º

-915.9072714

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3	8	0	-2.530341	-1.481862	-0.297053
4	7	0	-1.179385	0.284707	0.343069
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6	6	0	1.209156	0.570823	-0.000411
7	17	0	0.981782	2.326586	-0.038543
8	6	0	2.498655	0.067963	-0.142348
9	6	0	2.705483	-1.310147	-0.122844
10	6	0	1.615632	-2.164356	0.049556
11	6	0	0.328188	-1.659253	0.209809
12	1	0	-4.289365	0.205887	-0.405645
13	1	0	-3.281621	1.562699	-0.250690
14	1	0	-1.188025	1.278624	0.529475
15	1	0	3.325660	0.757348	-0.274954
16	1	0	3.709410	-1.706674	-0.240425
17	1	0	1.764744	-3.240172	0.068585
18	1	0	-0.520168	-2.317024	0.338916

165º

-915.9081188

1	7	0	3.455321	0.651360	0.001807
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3	8	0	2.597372	-1.469210	0.113339
4	7	0	1.172568	0.333846	-0.177346
5	6	0	-0.090962	-0.265366	-0.094834
6	6	0	-1.233620	0.553235	-0.000546
7	17	0	-1.054289	2.315582	0.010813
8	6	0	-2.516432	0.021185	0.076797
9	6	0	-2.690126	-1.361557	0.073897
10	6	0	-1.570922	-2.189803	-0.013994
11	6	0	-0.287351	-1.657558	-0.102642
12	1	0	4.331767	0.234668	0.287340
13	1	0	3.295118	1.573592	0.387755
14	1	0	1.160697	1.335196	-0.317059
15	1	0	-3.365550	0.693064	0.143206
16	1	0	-3.689606	-1.780726	0.138308
17	1	0	-1.691972	-3.269357	-0.020304
18	1	0	0.581887	-2.296419	-0.171939

180º

-915.9084354

1	7	0	3.458615	0.669218	0.003976
2	6	0	2.419052	-0.254850	-0.013115
3	8	0	2.615955	-1.459128	-0.069723
4	7	0	1.170592	0.352541	-0.009948

5	6	0	-0.088022	-0.261686	-0.005844
6	6	0	-1.242017	0.547031	-0.003097
7	17	0	-1.080439	2.311150	-0.018970
8	6	0	-2.522483	0.004254	0.010944
9	6	0	-2.684631	-1.379714	0.025871
10	6	0	-1.554872	-2.198027	0.023933
11	6	0	-0.272526	-1.655776	0.006705
12	1	0	4.355615	0.232119	0.170291
13	1	0	3.326225	1.537235	0.508138
14	1	0	1.150346	1.358994	-0.106916
15	1	0	-3.379383	0.669528	0.011009
16	1	0	-3.682580	-1.807163	0.037514
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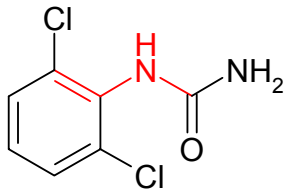

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4	7	0	0.768445	-0.995474	0.088656
5	6	0	-0.251802	-0.047307	-0.001193
6	6	0	-0.129976	1.362312	-0.014899
7	17	0	1.403496	2.175768	-0.248025
8	6	0	-1.254402	2.190640	0.023862
9	6	0	-2.538715	1.663207	0.053861
10	6	0	-2.704375	0.280976	0.025619
11	6	0	-1.585022	-0.537962	0.008915
12	17	0	-1.862611	-2.285376	0.005536
13	1	0	3.793406	-1.905301	-0.448655
14	1	0	2.413905	-2.215001	-1.392685
15	1	0	0.453846	-1.926975	-0.153513
16	1	0	-1.097534	3.263435	0.007746
17	1	0	-3.401962	2.320115	0.080549
18	1	0	-3.690795	-0.168905	0.030193

15º

-1375.484559

1	7	0	2.844005	-1.915258	-0.403407

2	6	0	2.117341	-0.929194	0.253610
3	8	0	2.596506	-0.175338	1.075580
4	7	0	0.748169	-1.023974	-0.048036
5	6	0	-0.257658	-0.057938	-0.055129
6	6	0	-0.085329	1.345120	-0.034153
7	17	0	1.462988	2.100818	-0.352719
8	6	0	-1.175809	2.209060	0.088669
9	6	0	-2.474051	1.719197	0.159540
10	6	0	-2.689973	0.344898	0.087141
11	6	0	-1.600736	-0.509715	-0.003701
12	17	0	-1.923581	-2.246226	-0.053139
13	1	0	3.838378	-1.844356	-0.228965
14	1	0	2.607135	-2.113187	-1.367604
15	1	0	0.453884	-1.929250	-0.391438
16	1	0	-0.985595	3.276548	0.098948
17	1	0	-3.312892	2.401804	0.249147
18	1	0	-3.690794	-0.070856	0.119103

30º

-1375.488209

1	7	0	2.884179	-1.894867	-0.298341
2	6	0	2.068817	-0.939162	0.296118
3	8	0	2.429060	-0.209721	1.197892
4	7	0	0.757162	-1.011282	-0.194923
5	6	0	-0.257063	-0.057542	-0.108207
6	6	0	-0.065086	1.340813	-0.059701
7	17	0	1.486040	2.070294	-0.420658
8	6	0	-1.136831	2.214041	0.133139
9	6	0	-2.436222	1.731809	0.243018
10	6	0	-2.672399	0.362335	0.142997
11	6	0	-1.597105	-0.501697	-0.013838
12	17	0	-1.931272	-2.232902	-0.097472
13	1	0	3.849126	-1.815105	-0.004094
14	1	0	2.768809	-2.057253	-1.291000
15	1	0	0.480590	-1.902715	-0.584723
16	1	0	-0.936129	3.279148	0.165527
17	1	0	-3.263567	2.419602	0.385589
18	1	0	-3.676423	-0.042118	0.205464

45º

-1375.491285

1	7	0	2.906520	-1.874539	-0.198308
2	6	0	2.027328	-0.935127	0.324375
3	8	0	2.275079	-0.235829	1.286137

4	7	0	0.793365	-0.959046	-0.344388
5	6	0	-0.249096	-0.046891	-0.158475
6	6	0	-0.070355	1.350715	-0.086852
7	17	0	1.474121	2.086631	-0.458702
8	6	0	-1.141713	2.207503	0.164941
9	6	0	-2.429885	1.701938	0.310432
10	6	0	-2.653746	0.331942	0.192916
11	6	0	-1.573771	-0.515211	-0.023247
12	17	0	-1.882868	-2.248436	-0.134498
13	1	0	3.833233	-1.801193	0.201234
14	1	0	2.899686	-2.012445	-1.201290
15	1	0	0.528634	-1.846785	-0.751080
16	1	0	-0.954672	3.274264	0.217232
17	1	0	-3.260584	2.374967	0.497819
18	1	0	-3.650007	-0.085615	0.285717

60º

-1375.493119

1	7	0	2.949009	-1.794432	-0.133774
2	6	0	2.006920	-0.893785	0.341583
3	8	0	2.133408	-0.255672	1.367370
4	7	0	0.867081	-0.850782	-0.483094
5	6	0	-0.233403	-0.026984	-0.201427
6	6	0	-0.126683	1.375023	-0.111692
7	17	0	1.389637	2.175420	-0.460961
8	6	0	-1.231630	2.171246	0.184481
9	6	0	-2.485119	1.590070	0.357703
10	6	0	-2.638247	0.211399	0.231045
11	6	0	-1.520667	-0.573093	-0.033556
12	17	0	-1.734541	-2.317579	-0.168510
13	1	0	3.828356	-1.736228	0.363206
14	1	0	3.046266	-1.880850	-1.137802
15	1	0	0.636984	-1.726049	-0.937822
16	1	0	-1.102044	3.245467	0.254081
17	1	0	-3.345929	2.213202	0.579371
18	1	0	-3.607187	-0.260225	0.350264

75º

-1375.493136

1	7	0	3.106918	-1.477801	-0.113639
2	6	0	2.052800	-0.705890	0.350465
3	8	0	2.023740	-0.181143	1.445974
4	7	0	1.006087	-0.620648	-0.589961
5	6	0	-0.211621	-0.005313	-0.232316

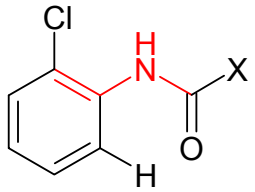
6	6	0	-0.322374	1.393249	-0.125609
7	17	0	1.071898	2.404786	-0.429783
8	6	0	-1.529963	2.007260	0.199938
9	6	0	-2.671963	1.231529	0.387299
10	6	0	-2.610080	-0.153441	0.252184
11	6	0	-1.389026	-0.751008	-0.047145
12	17	0	-1.327015	-2.503097	-0.209275
13	1	0	3.930079	-1.405753	0.470120
14	1	0	3.301069	-1.453696	-1.107023
15	1	0	0.894041	-1.454307	-1.156462
16	1	0	-1.569143	3.087338	0.286873
17	1	0	-3.615753	1.708917	0.632436
18	1	0	-3.490897	-0.771242	0.386561

90º

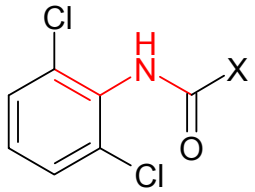
-1375.49167

1	7	0	-3.419468	0.301313	-0.142915
2	6	0	-2.157161	0.020664	0.358062
3	8	0	-1.927275	-0.220329	1.527247
4	7	0	-1.164807	0.056242	-0.640637
5	6	0	0.196163	0.009324	-0.249229
6	6	0	0.864283	-1.219844	-0.116060
7	17	0	-0.011960	-2.713424	-0.366833
8	6	0	2.214836	-1.286531	0.220903
9	6	0	2.936761	-0.108475	0.399924
10	6	0	2.316761	1.129644	0.247195
11	6	0	0.961751	1.173931	-0.071238
12	17	0	0.193635	2.741552	-0.273223
13	1	0	-4.156153	0.092325	0.518299
14	1	0	-3.620949	0.007668	-1.090752
15	1	0	-1.353423	0.725669	-1.379788
16	1	0	2.690521	-2.254778	0.328897
17	1	0	3.990862	-0.155385	0.656270
18	1	0	2.868427	2.053808	0.377568

The Cambridge Crystallographic Database compounds and their dihedral angles are:



BARPEQ	178.987
CFEACN	139.799
CLISLC	175.42
CLNACA10	-171.229
COMHUH	133.048
COMHUH	142.379
DALDOK	172.335
ETIDOA	-172.288
ETIDOA	-178.968
FAXWOR	-152.032
FETVUW	-173.556
HASDEK	159.861
IZAPOO	171.114
MOGKOI	178.481
MOGKOI	160.105
MPICAN	141.123
OBEQAN	173.937
OBEQER	178.802
OBEQIV	174.207
OBEQIV	179.467
OBIFAG	-135.169
PEFDUZ	-178.518
PIPACA	134.631
PIPACB	136.06
PIPACN	167.76
PIPANL	-134.234
QQQEKP10	-173.172
WUBGUV	140.977
XIHMEG	-134.861
XUXNOT	169.494
ZEDMOK	-65.416
CASRAQ	-177.397
CASRAQ	167.152
TAWNUB	-152.122
WALXIR	173.818
142388XX	180
574670XX	171.444
7545XX	-173.839



BIHXIA	117.581
BIHXIA	118.465
BOLFIR	113.103
FEFSAK	71.661
FEFSAK01	70.228
FEFSAK02	-71.242
FUWPIW	70.658
OBIBAC	-114.352
OBIBAC	117.796
OBIBEG	-117.874
OBIBIK	-78.805
OBIBIK	94.115
POBDEP	106.545
POBDEP01	104.703
POBDEP02	103.626
QIKNUT	-114.996
QIKPAB	-113.669
QIKPEF	99.494
QIKPIJ	-92.107
QIKPIJ	-85.987
SEDFIQ	62.001

d) Pairwise comparisons of adding F and Cl to aromatic rings

Solubility

Log(Solubility) for ArH	Log(Solubility) for ArF	Log(Solubility) for ArCl
-5.27	-5.24	-4.57
-4.89	-5.44	-5.59
-3.07	-3.16	-3.75
-3.77	-3.89	-4.37
-5.44	-4.74	-5.40
-5.82	-5.80	-6.43
-5.54	-6.37	-7.15
-3.17	-3.03	-4.06
-5.54	-5.96	-6.92
-3.77	-4.74	-4.30
-2.82	-3.32	-5.12
-4.94	-5.27	-6.31
-3.74	-3.64	-4.44
-3.43	-3.64	-4.44
-3.64	-3.64	-4.44
-3.74	-3.89	-4.38

-3.43	-3.89	-4.38
-3.64	-3.89	-4.38
-4.80	-4.92	-5.82
-4.72	-5.31	-5.23
-2.83	-2.71	-3.29
-3.74	-3.80	-4.92
-4.76	-3.39	-3.99
-4.11	-4.11	-5.82
-5.76	-5.28	-6.34
-5.36	-5.67	-4.36
-5.17	-5.67	-4.36
-4.54	-4.94	-4.39
-4.03	-4.55	-4.01
-4.10	-3.81	-4.69
-4.54	-4.93	-6.09
-4.07	-4.42	-5.42
-4.53	-5.19	-5.79
-3.37	-3.41	-4.15
-3.70	-4.51	-4.90
-3.63	-3.79	-3.57
-3.70	-4.52	-4.54
-4.51	-4.64	-4.75
-4.67	-4.26	-4.84
-3.84	-4.31	-3.83
-3.36	-2.86	-3.11
-4.48	-5.09	-5.21
-3.39	-3.28	-4.22
-3.36	-2.86	-2.93
-4.45	-3.97	-4.97
-4.18	-3.90	-5.14
-2.93	-3.08	-3.33
-3.19	-3.70	-4.53
-4.07	-3.84	-5.03
-3.02	-3.77	-4.85
-3.28	-3.87	-4.52
-4.54	-4.90	-5.79
-2.92	-3.02	-4.60
-3.85	-4.25	-4.90
-4.69	-5.31	-5.24
-4.54	-4.84	-5.11
-4.90	-4.99	-5.11
-4.54	-4.75	-6.09
-4.98	-4.84	-6.10
-2.83	-2.61	-3.33
-6.06	-5.18	-5.25
-3.11	-3.44	-3.33
-2.75	-3.47	-3.86

-5.36	-4.96	-4.36
-5.17	-4.96	-4.36
-3.72	-3.94	-5.76
-3.72	-3.94	-3.97
-4.40	-4.56	-5.20
-3.72	-3.84	-5.76
-3.72	-3.84	-3.97
-4.15	-5.22	-5.53
-4.20	-3.78	-4.56
-4.13	-4.47	-4.90
-3.85	-4.09	-4.75
-3.31	-3.65	-4.00
-5.04	-5.46	-6.00
-5.21	-5.28	-5.81
-3.44	-4.46	-4.58
-4.32	-4.94	-5.94
-3.90	-4.64	-4.50
-4.69	-5.84	-5.72
-3.49	-3.91	-4.33
-4.99	-5.51	-4.48
-3.23	-3.62	-3.53
-4.71	-4.93	-5.32
-3.41	-3.21	-4.02
-5.08	-4.90	-4.33
-4.23	-5.87	-4.97
-3.83	-4.73	-4.73
-2.93	-3.34	-3.50
-4.24	-3.89	-3.97
-3.33	-3.45	-3.78
-3.56	-3.70	-4.14
-4.25	-4.66	-5.51
-3.93	-4.82	-5.64
-3.80	-4.46	-4.06
-2.98	-3.47	-4.18
-3.66	-3.47	-4.18
-3.15	-4.97	-3.79
-3.37	-3.74	-3.99
-3.47	-3.56	-4.01
-3.81	-3.96	-4.01
-3.50	-3.96	-4.01
-2.63	-3.88	-3.67
-4.15	-4.86	-5.24
-4.80	-4.76	-4.33
-4.85	-5.39	-5.60
-4.44	-5.22	-5.35
-4.80	-4.98	-4.46
-4.21	-4.87	-5.63

-3.23	-3.19	-3.53
-3.41	-3.24	-3.64
-4.38	-2.73	-3.73
-3.03	-3.22	-3.92

Rat Plasma Protein Binding

Log(K_1) for ArH	Log(K_1) for ArF	Log(K_1) for ArCl
5.77	6.74	6.69
6.23	6.50	6.69
6.40	6.43	7.37
5.99	6.25	7.37
6.07	6.32	6.38
3.98	4.23	4.78
3.58	3.79	4.72
5.03	5.10	5.92
5.12	5.31	5.92
4.69	4.61	4.89
4.11	4.58	4.89
4.37	4.61	5.14
4.11	4.43	4.96
4.49	4.90	5.16
4.48	4.90	5.16
5.08	5.23	5.62
4.77	4.88	5.17
4.26	4.38	4.74
4.73	4.59	4.93
5.17	5.07	5.39
4.31	4.91	5.02
4.74	5.09	5.24
4.64	4.68	5.09
4.26	4.64	4.90
5.41	5.74	6.24
3.68	4.15	4.61
3.82	4.15	4.61
3.73	4.15	4.61
4.38	4.39	4.75
4.78	4.94	5.18
4.93	4.94	5.18
4.78	5.01	5.18
4.93	5.01	5.18
5.66	6.01	6.74
4.39	5.37	5.34
6.00	5.97	6.47
5.10	5.24	5.70
3.29	3.54	4.16
4.12	4.29	4.17

3.02	3.20	3.91
4.00	4.49	5.38
4.32	4.54	5.11
4.82	5.12	5.58
5.51	5.42	6.18
5.51	5.93	6.05
5.93	6.00	6.93
5.53	6.03	5.67
4.48	5.02	5.41
4.48	4.71	5.47
4.57	4.51	5.03
4.28	4.31	4.66
6.44	6.49	6.34
4.58	4.77	5.19
4.38	4.57	5.27
4.23	4.47	5.13
5.93	5.92	5.94
6.05	5.91	6.42
6.18	6.62	6.42
6.05	5.94	6.17
6.07	5.99	6.71
5.50	5.60	5.81
4.45	4.51	4.92
4.46	4.62	5.09
4.87	5.00	5.08
4.00	4.49	5.34
5.47	5.99	5.61
4.26	4.71	5.06
3.95	4.26	4.56
4.04	4.68	5.02
4.42	4.68	5.02
3.85	4.68	4.87
5.24	5.27	5.58
4.28	4.73	4.92
3.80	4.27	4.67
4.96	5.18	5.19
4.25	4.38	4.42
5.10	5.19	5.36
5.17	5.31	5.70
4.98	4.95	5.31
4.97	5.14	5.55

Rat Oral Exposure

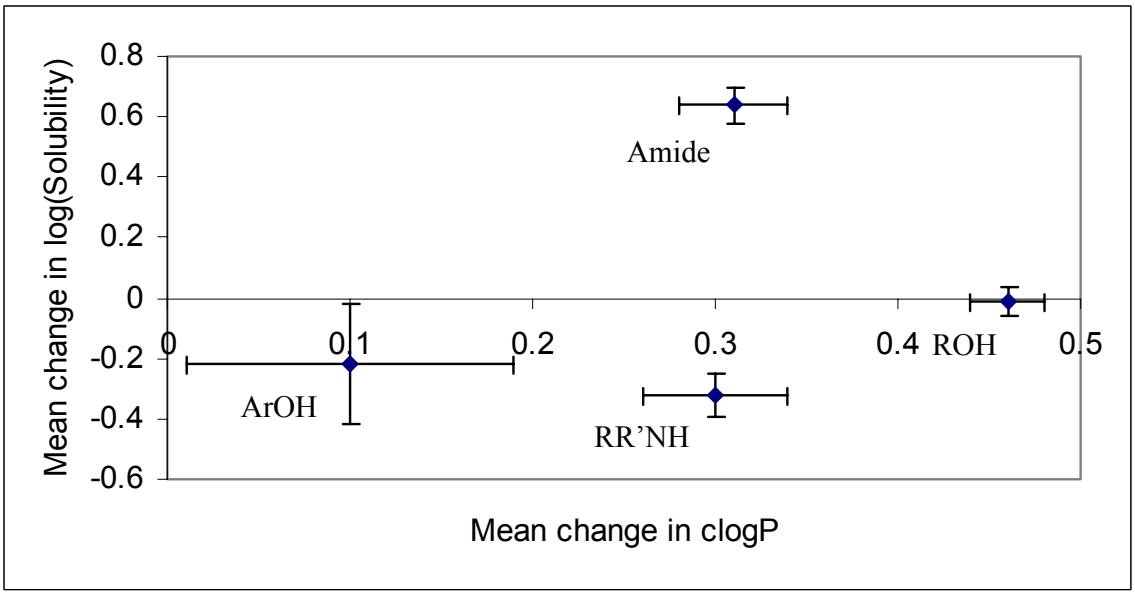
Log(AUC) for ArH	Log(AUC) for ArF	Log(AUC) for ArCl
0.56	0.18	-0.11
1.00	1.28	0.99
0.38	0.46	1.00

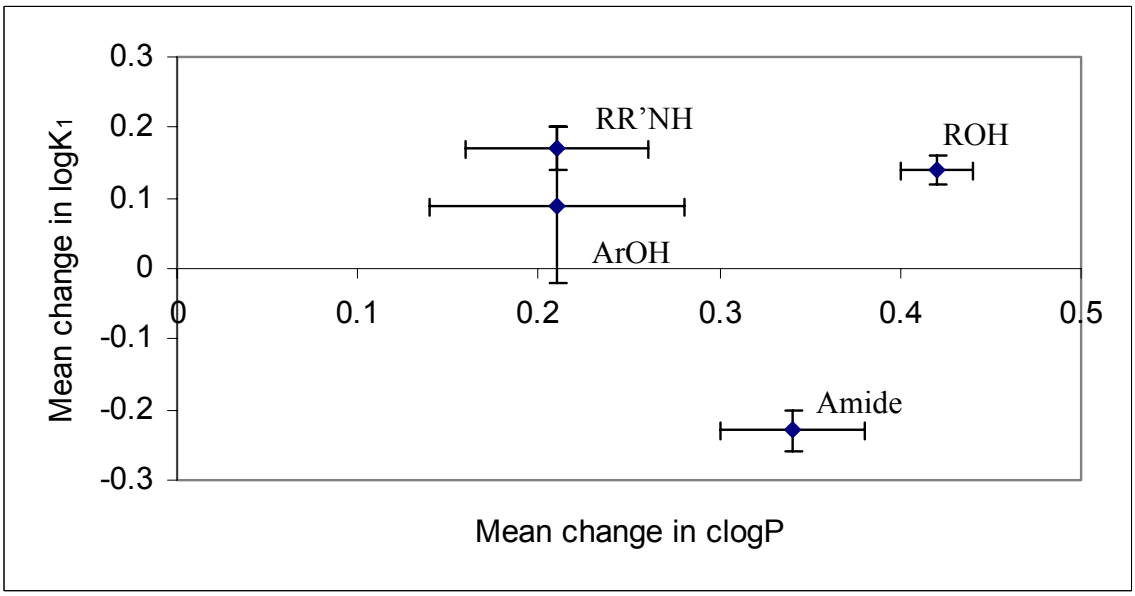
0.91	1.11	1.00
1.15	1.32	0.38
1.00	0.84	0.60
0.40	0.41	0.26
0.11	-0.11	0.26
0.40	0.01	-0.18
0.76	0.86	1.15
0.75	0.52	0.49
0.90	0.52	0.49
0.41	-0.02	0.41
0.40	-0.03	0.41
0.74	0.29	-0.11
0.18	0.23	-0.12
1.15	1.20	1.26
1.26	1.20	0.23
-1.07	-0.42	-0.57
1.31	0.92	1.06
-1.07	-1.03	-1.05
0.31	0.39	0.95
-2.20	0.23	-1.38
0.26	0.29	1.00
-0.40	-0.85	-0.66
-0.96	-1.68	-1.05
-1.72	-1.68	-1.05
-0.99	0.49	1.04
-0.59	-0.99	-0.92
0.38	0.34	-0.04
-0.96	-0.07	-0.28
-1.85	-3.00	-1.38
-0.38	-1.12	-1.22
0.40	-0.18	-0.40
-0.28	-0.24	-1.41
-0.55	0.35	-0.24
-0.96	-0.55	0.60
0.00	0.04	-0.02
-0.07	0.26	-0.40
-0.32	0.04	-0.03
-0.61	-0.21	-0.11
1.31	1.57	1.10
0.27	0.74	0.40
0.26	0.22	0.27
0.31	0.99	0.89
-0.55	-1.08	-0.88
0.40	0.60	0.47
0.13	1.22	1.29
0.34	-0.55	-0.28
0.34	-0.19	-0.35

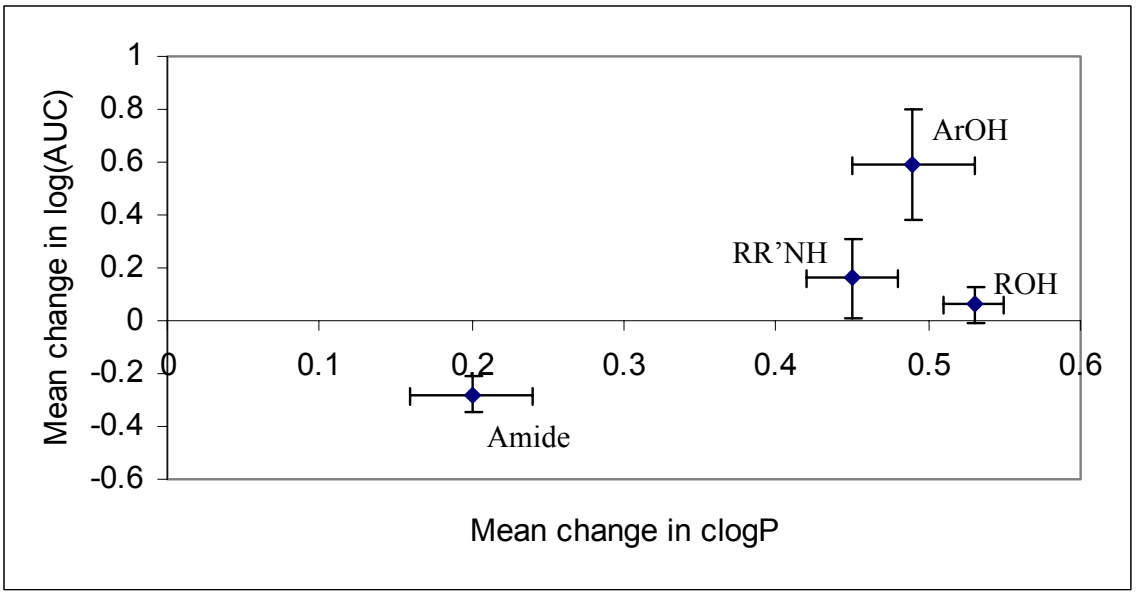
-0.88	-1.12	0.00
-1.29	-1.35	-0.83
-1.19	-1.35	-0.83
-0.94	-0.80	-0.15
-0.94	-0.77	-0.15
-2.47	-1.44	-1.04
-2.38	-0.40	-0.47
0.40	0.01	-0.11
-0.56	-0.44	-0.40
0.86	0.77	0.59
0.86	0.76	0.63
1.02	0.31	1.01
-1.97	-1.60	-1.45
-0.57	-1.24	-0.85
-1.35	-0.66	-0.61
-2.57	-2.28	-2.27
-2.57	-1.52	-1.97
-1.79	-2.42	-1.10
-0.37	-0.23	0.15
-2.15	-0.69	-1.08
-0.67	-0.48	-0.60
-2.25	-0.37	0.47
-1.18	-0.89	-0.92
-1.36	-0.89	-0.92
-1.25	-1.17	-1.20
-0.31	0.25	-0.48
0.20	-0.23	0.24
0.76	0.91	0.51
0.76	0.80	0.51
0.47	0.39	0.72
-3.30	0.15	0.72
0.63	0.15	-0.21
0.59	0.73	-0.21
0.63	0.51	0.39
-0.02	-0.59	0.51
-0.79	-0.41	-0.66
-0.03	-0.04	-1.23
-0.52	-0.06	-0.56
-2.75	-3.37	-2.73
-0.66	-0.96	-1.03
-2.17	-1.25	-1.55
-0.94	-0.80	-0.55
-0.94	-0.77	-0.55
-0.17	-0.25	-0.36
0.09	-0.33	-0.75
-0.86	-0.55	-0.48
-0.68	-0.48	-0.93

-0.37	-0.25	-0.14
-0.39	-0.39	-0.21
-1.43	-1.29	-1.73
-0.48	-0.23	-1.66
-0.56	-0.83	-1.61
-0.42	0.25	-0.24
-0.22	-0.59	-0.94
-0.18	-0.40	-0.90
-0.17	-0.10	-0.44
-0.17	0.20	-0.44
-0.65	-0.83	-0.74
-0.34	0.25	0.33
-0.38	-0.69	-1.30
-1.02	-0.42	-0.84
-0.31	-0.42	-0.84
-0.77	-0.45	-1.52
0.15	0.14	0.19
-1.05	-1.90	-2.04
-0.71	-1.47	-1.84
-0.80	-1.95	-1.52
-0.83	-0.88	-1.09
-0.92	0.47	0.36
0.04	0.03	0.13
-1.77	-1.62	-1.26
-0.86	-0.96	-1.04
0.16	1.00	0.92
-0.52	-0.04	-0.21
-0.75	-0.04	-0.21
-0.78	0.01	0.16
-1.08	-0.78	-1.28
-0.58	-0.85	-1.27
-0.22	-0.69	-0.84
0.11	-0.47	-0.20
-0.22	0.37	-0.20
-0.49	-0.27	-0.68
0.47	-0.17	0.28
-0.73	-1.25	-1.00
-1.43	-1.80	-1.18
-0.07	-0.68	-0.53
-1.03	-0.35	-0.77
0.34	0.38	-0.27
0.34	-0.10	-0.35
-0.10	-1.04	-0.74
0.20	-1.04	-0.74
-1.53	-1.41	-0.98
-0.86	-0.99	-0.99
-1.14	-3.02	-3.02

e) Variation with lipophilicity of mean changes in solubility, plasma protein binding and AUC for methylations






Mean change in log(AUC)
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
0
0.1
0.2
0.3
0.4
0.5
0.6
ArOH
RR'NH
ROH
Amide
Mean change in clogP