Electronic Supplementary Material (ESI) for Green Chemistry.

Redesigning hazardous chemicals by learning from structure-based drug discovery

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SUPPLEMENTARY INFORMATION

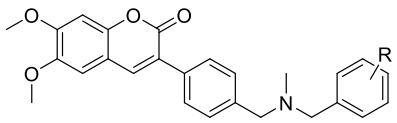


Figure S1. 3-(4[Benzylmethylamino)methyl]phenyl)-6,7-dimethoxy-2H-2chromenone scaffold used in modification perturbations to validate current MC/FEP approach against human AChE. R = *o*-NO_2, *m*-NO_2, *p*-NO_2, *o*-OCH_3, *m*-OCH_3, *p*-OCH_3, *o*-CH_3, *m*-OCH_3.

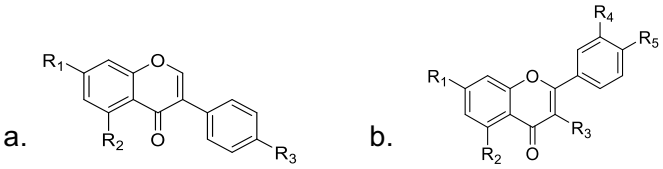


Figure S2. Validation dataset for ERα. **a.** Genistein (R_1 = OH, R_2 = OH, R_3 = OH), Daidzen (R_1 = OH, R_2 = H, R_3 = OH), Formononetin (R_1 = OH, R_2 = H, R_3 = OCH_3), Biochanin A (R_1 = OH, R_2 = OH, R_3 = OCH_3). **b.** Quercetin (R_1 = OH, R_2 = OH, R_3 = OH, R_4 = OH, R_5 = OH), Luteolin (R_1 = OH, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OH), Apigenin (R_1 = OH, R_2 = OH, R_3 = H, R_4 = H, R_5 = OH), Kaempferol (R_1 = OH, R_2 = OH, R_3 = OH, R_4 = H, R_5 = OH), Chrysin (R_1 = OH, R_2 = OH, R_3 = H, R_4 = H, R_5 = H).

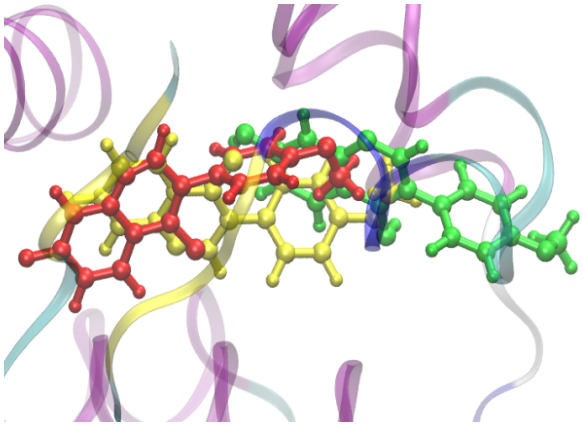


Figure S3. Top 3 poses of Formononentin in the binding pocket of ERα; Vina's predicted binding affinities were within 3 kcal/mol.

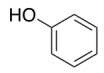
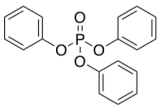
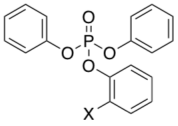
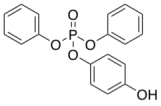
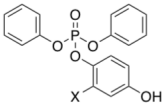
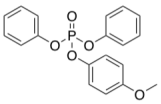
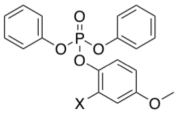
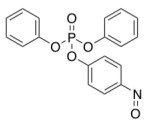
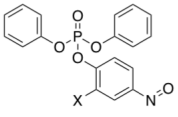
Table S1. Free energy perturbation results for chlorine and methyl scans of triphenyl phosphate (TPP). All values are in kcal/mol.

Acetylcholinesterase						
Chlorine Scan						
ortho						
position	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
2	17.54	0.10	18.40	0.10	-0.86	0.14
2’	14.16	0.07	18.40	0.10	-4.23	0.12
2”	12.09	0.09	18.40	0.10	-6.30	0.13
6	13.22	0.14	18.40	0.10	-5.18	0.17
6’	9.88	0.11	18.40	0.10	-8.52	0.15
6”	11.26	0.08	18.40	0.10	-7.13	0.13
$\Delta\Delta G_{corr}$ = -2.32 σ = 0.14						
meta						
position	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
3	-5.67	0.09	-0.04	0.09	-5.63	0.13
3’	-3.03	0.05	-0.04	0.09	-2.98	0.10
3”	2.97	0.08	-0.04	0.09	3.01	0.12
5	-0.17	0.06	-0.04	0.09	-0.12	0.11
5	-1.74	0.11	-0.04	0.09	-1.70	0.14
5”	2.09	0.10	-0.04	0.09	2.14	0.13
$\Delta\Delta G_{corr}$ = -1.10 σ = 0.12						
para						
position	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
4	-5.13	0.09	2.22	0.07	-7.35	0.12
4’	5.23	0.05	2.22	0.07	3.01	0.09
4”	4.86	0.05	2.22	0.07	2.64	0.09
$\Delta\Delta G_{corr}$ = -1.93 σ = 0.10						
Methyl Scan						
ortho						
position	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
2	15.94	0.17	18.01	0.10	-2.08	0.20
2’	16.56	0.13	18.01	0.10	-1.45	0.16
2”	18.41	0.12	18.01	0.10	0.40	0.16
6	20.55	0.10	18.01	0.10	2.53	0.14
6’	14.86	0.13	18.01	0.10	-3.16	0.16
6”	14.27	0.18	18.01	0.10	-3.74	0.21
$\Delta\Delta G_{corr}$ = -0.78 σ = 0.17						
meta						
position	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
3	3.27	0.05	4.05	0.08	-0.77	0.10
3’	-1.30	0.12	4.05	0.08	-5.35	0.15
3”	-1.88	0.08	4.05	0.08	-5.93	0.11
5	-2.51	0.11	4.05	0.08	-6.56	0.14
5’	-0.67	0.07	4.05	0.08	-4.71	0.11
5”	-4.67	0.12	4.05	0.08	-8.71	0.15
$\Delta\Delta G_{corr}$ = -2.31 σ = 0.13						
para						
position	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ

4	-0.71	0.14	3.41	0.11	-4.12	0.18
4’	-0.28	0.11	3.41	0.11	-3.69	0.16
4”	-5.17	0.12	3.41	0.11	-8.59	0.16
$\Delta\Delta G_{corr}$ = -2.43 σ = 0.17						
Estrogen Receptor						
Chlorine Scan						
ortho						
docking pose	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
2	11.06	0.07	10.71	0.13	0.35	0.15
3	11.35	0.09	11.15	0.09	0.21	0.13
5	10.63	0.06	13.79	0.09	-3.16	0.11
6	8.34	0.09	12.94	0.10	-4.60	0.14
7	13.37	0.07	12.51	0.11	0.87	0.14
8	13.73	0.07	12.68	0.08	1.05	0.11
9	12.27	0.08	11.86	0.11	0.41	0.14
$\Delta\Delta G_{corr}$ = -0.86 σ = 0.13						
meta						
docking pose	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
1	-2.36	0.08	-2.22	0.07	-0.15	0.11
2	-1.21	0.05	-3.66	0.08	2.44	0.09
3	-3.28	0.08	-2.51	0.07	-0.77	0.11
4	-0.82	0.06	-2.03	0.07	1.21	0.09
5	-2.16	0.06	-2.70	0.09	0.53	0.11
6	2.08	0.06	-2.29	0.07	4.37	0.10
8	-2.08	0.09	-1.47	0.08	-0.62	0.12
9	-1.35	0.06	-2.15	0.07	0.80	0.09
$\Delta\Delta G_{corr}$ = 0.15 σ = 0.10						
para						
docking pose	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
1	2.03	0.08	3.03	0.08	-0.99	0.11
2	3.01	0.03	3.59	0.08	-0.58	0.08
3	4.71	0.07	3.00	0.08	1.71	0.11
4	0.08	0.07	3.01	0.08	-2.93	0.10
5	7.89	0.05	3.20	0.09	4.69	0.10
6	2.00	0.08	2.87	0.08	-0.87	0.12
7	1.42	0.08	3.39	0.09	-1.98	0.12
8	4.24	0.06	3.30	0.09	0.94	0.10
9	2.68	0.05	3.50	0.07	-0.82	0.09
$\Delta\Delta G_{corr}$ = -0.36 σ = 0.10						
Methyl Scan						
ortho						
docking pose	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
1	23.08	0.15	24.69	0.25	-1.62	0.29
2	25.60	0.14	21.94	0.26	3.66	0.29
3	23.32	0.16	25.42	0.21	-2.10	0.26

4	24.85	0.16	25.16	0.28	-0.32	0.33
5	25.06	0.15	24.02	0.23	1.04	0.28
6	25.38	0.18	26.38	0.27	-1.00	0.32
7	23.48	0.17	23.94	0.22	-0.46	0.28
8	25.35	0.14	24.33	0.20	1.02	0.24
9	21.88	0.17	23.52	0.23	-1.64	0.29
$\Delta\Delta G_{corr}$ = -0.27 σ = 0.29						
meta						
docking pose	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
1	-0.66	0.07	-1.13	0.09	0.47	0.11
2	0.17	0.04	-0.61	0.09	0.79	0.10
3	-4.18	0.09	-0.30	0.10	-3.88	0.13
4	-1.33	0.07	-0.75	0.09	-0.58	0.11
5	-1.28	0.08	-1.41	0.09	0.13	0.12
6	-2.79	0.05	-1.86	0.09	-0.93	0.10
7	-3.65	0.09	-1.69	0.09	-1.96	0.12
8	-1.74	0.06	-1.53	0.10	-0.21	0.11
9	-3.11	0.09	-0.75	0.09	-2.36	0.13
$\Delta\Delta G_{corr}$ = -0.58 σ = 0.12						
para						
docking pose	ΔG_{bound}	σ_{bound}	$\Delta G_{unbound}$	$\sigma_{unbound}$	$\Delta\Delta G$	σ
1	12.97	0.17	3.53	0.10	9.44	0.20
2	9.56	0.19	3.77	0.10	5.80	0.21
5	8.34	0.17	4.71	0.10	3.63	0.20
6	8.84	0.17	4.46	0.10	4.38	0.20
8	6.99	0.18	3.92	0.10	3.07	0.20
9	8.48	0.17	3.83	0.11	4.65	0.20
$\Delta\Delta G_{corr}$ = 1.53 σ = 0.20						

Table S2. Metabolites of TPP and its *ortho*-halogenated analogs and corresponding properties and environmental-fate metrics as estimated using the EPI Suite™ Progam. X represents the halogen substituent (in this case Cl); "Log$K_{o/w}$" is the partition coefficient between octanol and water (experimental values provided in ellipses); "Biodeg" is a biodegradation metric predicted using the BIOWIN v4.10 model (>0.50 Likely to biodegrade rapidly); "Anaerobic" is a metric of anaerobic degradation (>0.50 Likely to biodegrade rapidly); "Atm pesist" is the half-life (in hrs) in the atmosphere predicted based on reactivity with hydroxyl radicals using the AOPWIN v1.92 model; Log BCF is a predicted bioconcentration value (L/kg wet-wt).

	Log$K_{o/w}$ = 1.51 (1.46) Biodeg = 0.95 Anaerobic = 0.66 Atm persist = 3.8 hrs Log BCF = 0.63		Log$K_{o/w}$ = 2.16 (2.15) Biodeg = 0.62 Anaerobic = 0.13 Atm persist = 13 hrs Log BCF = 1.1
	Log$K_{o/w}$ = 4.70 (4.59) Biodeg = 1.29 Anaerobic = 0.59 Atm persist = 11.8 hrs Log BCF = 1.9		Log$K_{o/w}$ = 5.35 Biodeg = 0.96 Anaerobic = 0.06 Atm persist = 15.5 hrs Log BCF = 2.4
	Log$K_{o/w}$ = 4.22 Biodeg = 1.27 Anaerobic = 0.54 Atm persist = 4.0 hrs Log BCF = 1.6		Log$K_{o/w}$ = 4.86 Biodeg = 1.07 Anaerobic = 0.24 Atm persist = 5.2 hrs Log BCF = 2.1
	Log$K_{o/w}$ = 4.78 Biodeg = 1.28 Anaerobic = 0.56 Atm persist = 5.4 hrs Log BCF = 2.0		Log$K_{o/w}$ = 5.43 Biodeg = 1.08 Anaerobic = 0.26 Atm persist = 6.7 hrs Log BCF = 2.4
	Log$K_{o/w}$ = 3.74 Biodeg = 1.15 Anaerobic = 0.46 Atm persist = 3.3 hrs Log BCF = 1.3		Log$K_{o/w}$ = 4.39 Biodeg = 0.95 Anaerobic = 0.17 Atm persist = 4.4 hrs Log BCF = 1.7