Electronic Supplementary Information (ESI)

Experiment stands corrected: accurate prediction of the aqueous pK_a values of sulfonamide drugs using equilibrium bond lengths

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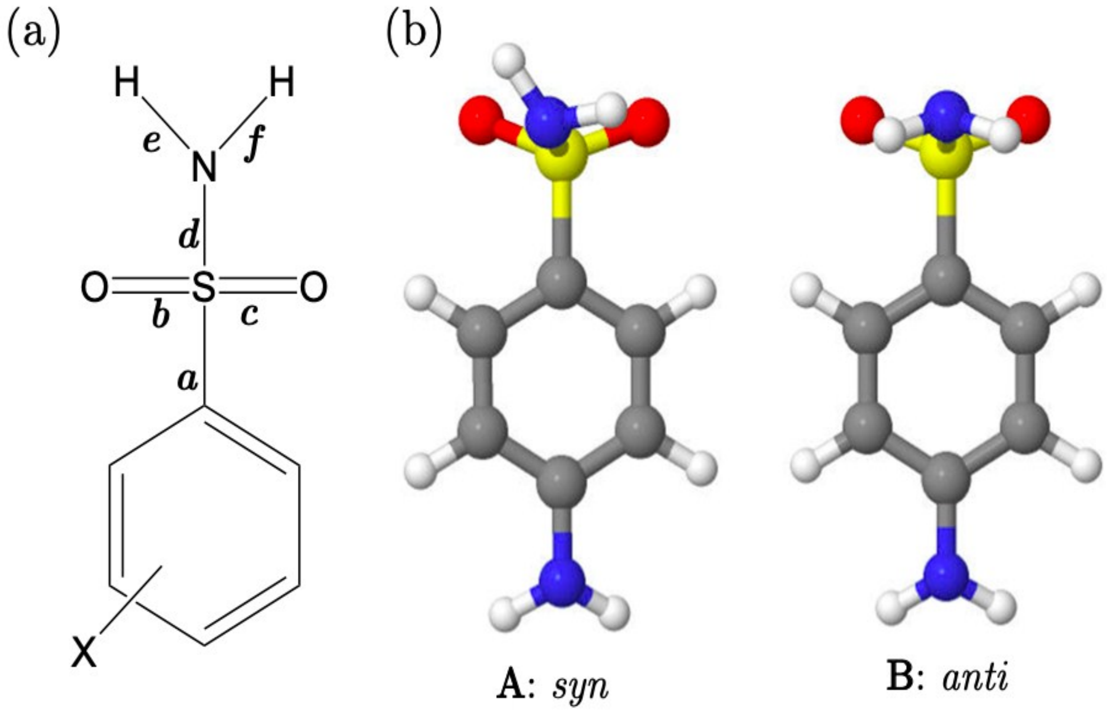
Figure S1. (a) The common fragment of the Pr-BSA series, where bond lengths under investigation for their relationship with pK_a are labelled ***a*-*f***. (b) The dominant (*anti*) conformation of the sulfonamide group in the presence of CPCM, labelled **B** for sulfanilamide, i.e. X = NH_2.



A: *syn*

B: *anti*

Table S1. Energies (kJ mol^{-1}), bond lengths (Å) B3LYP/6-311G(d,p) (gas-phase) optimized geometries of compounds **S1-1** to **S1-22,** when the sulfonamide group is in the *anti* conformation, **A**, and *experimental* pK$_a$ values.

ID	U	sub	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK$_a$
S1-1	-2195751.89	H	1.79757	1.45945	1.45945	1.69036	1.01411	1.01411	10.10[a]
S1-2	-2341142.75	4-NH_2	1.78163	1.46212	1.46055	1.69665	1.01510	1.01546	10.65[b]
S1-3	-2299008.50	4-CH_3	1.79345	1.46019	1.45965	1.69223	1.01435	1.01453	10.11[c]
S1-4	-2444366.27	4-$NHCH_3$	1.77949	1.46082	1.46246	1.69781	1.01561	1.01523	11.00[d*]
S1-5	-2496516.71	4-OMe	1.78686	1.45978	1.46127	1.69426	1.01515	1.01483	10.22[e*]
S1-6	-2444357.15	4-CH_2NH_2	1.79373	1.45997	1.46021	1.69260	1.01450	1.01434	10.08[f**]
S1-7	-3402485.26	4-Cl	1.79674	1.45875	1.45875	1.68806	1.01408	1.01408	9.77[e*]
S1-8	-2732803.19	3-NO_2	1.80312	1.45684	1.45781	1.68397	1.01412	1.01402	9.19[e*]
S1-9	-2732803.25	4-NO_2	1.80420	1.45737	1.45737	1.68337	1.01398	1.01398	9.14[e*]
S1-10	-2456368.57	4-F	1.79453	1.45913	1.45910	1.68950	1.01414	1.01415	10.00[a]
S1-11	-2437983.70	4-CN	1.80257	1.45770	1.45770	1.68440	1.01401	1.01401	9.26[d*]
S1-12	-3402483.31	3-Cl	1.80113	1.45834	1.45829	1.68676	1.01404	1.01404	9.80[c]
S1-13	-3939500.60	3-NO_2,4-Cl	1.80126	1.45666	1.45724	1.68236	1.01413	1.01408	9.18[d*]
S1-14	-2299007.78	3-CH_3	1.79722	1.45968	1.45988	1.69156	1.01439	1.01426	10.06[c]
S1-15	-2596627.33	4-$COCH_3$	1.80054	1.45831	1.45879	1.68711	1.01404	1.01400	9.66[d*]
S1-16	-2456365.69	3-F	1.80051	1.45848	1.45840	1.68732	1.01404	1.01401	9.70[a]
S1-17	-2716976.87	3,5-F_2	1.80316	1.45748	1.45748	1.68436	1.01394	1.01394	9.40[a]
S1-18	-2716948.73	2,6-F_2	1.80828	1.45223	1.45514	1.68137	1.01406	1.01367	9.10[a]
S1-19	-3498702.61	penta-F	1.81497	1.45034	1.45276	1.67542	1.01378	1.01358	8.20[a]
S1-20	-2456359.42	2-F	1.79709	1.45629	1.45863	1.68266	1.01397	1.01403	9.60[a]
S1-21	-3402467.67	2-Cl	1.80916	1.45904	1.45551	1.68117	1.01391	1.01359	9.58[d*]
S1-22	-2299041.15	2-Me	1.80282	1.46055	1.46019	1.69536	1.01526	1.01566	9.93[d*]

[a] Krishnamurthy, V. M.; Bohall, B. R.; Kim, C-Y.; Moustakas, D. T.; Christianson, D. W.; Whitesides, G. M. *Chem. Asian J.* **2007**, 2, 94–105

[b] Elofsson, R; Nilsson, S. O.; Agren, A. *Acta. Pharm. Suec.* **1970**, 7, 473-482

[c] Ludwig, M; Pytela, O.; Kalfus, K.; Vecera, M. *Collect. Czech. Chem. Commun.* **1984,** 49, 1182.

[d] Kakeya, N.; Aoki, M.; Kamada, A.; Yata, N. *Chem. Pharm. Bull.* **1969**, 17, 1010-1018

[e] Willi, A. V. *Helv. Chim. Acta*. **1956**, 39, 46-53

[f] Angyal, S. J. Aust. *J. Sci. Res. A*. **1950**, 3, 463-465

*Reported as measured at 20 degrees.
**Reported as measured at 21 degrees.

Table S2. Energies (kJ mol^{-1}), bond lengths (Å) for B3LYP/6-311G(d,p) (gas-phase) optimized geometries of compounds **S1-1** to **S1-22,** when the sulfonamide group is in the *syn* conformation, **B**, and *experimental* pK$_a$ values.

ID	U	sub	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK$_a$
S1-1	-2195748.60	H	1.80442	1.45526	1.45526	1.67619	1.01257	1.01257	10.10[a]
S1-2	-2341139.73	4-NH$_2$	1.79032	1.45673	1.45673	1.68218	1.01303	1.01303	10.65[b]
S1-3	-2299005.31	4-CH$_3$	1.80069	1.45562	1.45562	1.67779	1.01269	1.01269	10.11[c]
S1-4	-2444363.07	4-NHCH$_3$	1.78852	1.45704	1.45695	1.68352	1.01313	1.01311	11.00[d*]
S1-5	-2496513.22	4-OMe	1.79511	1.45616	1.45595	1.67946	1.01279	1.01280	10.22[e*]
S1-6	-2444354.26	4-CH$_2$NH$_2$	1.80084	1.45564	1.45591	1.67851	1.01278	1.01279	10.08[f**]
S1-7	-3402481.40	4-Cl	1.80368	1.45470	1.45470	1.67292	1.01227	1.01227	9.77[e*]
S1-8	-2732798.50	3-NO$_2$	1.81016	1.45305	1.45401	1.66688	1.01170	1.01178	9.19[e*]
S1-9	-2732798.74	4-NO$_2$	1.81042	1.45357	1.45357	1.66695	1.01173	1.01173	9.14[e*]
S1-10	-2456364.70	4-F	1.80184	1.45499	1.45499	1.67431	1.01236	1.01236	10.00[a]
S1-11	-2437979.30	4-CN	1.80891	1.45385	1.45385	1.66827	1.01184	1.01184	9.26[d*]
S1-12	-3402479.70	3-Cl	1.80801	1.45427	1.45434	1.67179	1.01222	1.01228	9.80[c]
S1-13	-3939496.02	3-NO$_2$,4-Cl	1.80845	1.45284	1.45363	1.66480	1.01172	1.01156	9.18[d*]
S1-14	-2299004.71	3-CH$_3$	1.80423	1.45564	1.45539	1.67737	1.01269	1.01268	10.06[c]
S1-15	-2596623.61	4-COCH$_3$	1.80680	1.45433	1.45475	1.67236	1.01223	1.01225	9.66[d*]
S1-16	-2456362.21	3-F	1.80733	1.45444	1.45436	1.67257	1.01233	1.01229	9.70[a]
S1-17	-2716973.20	3,5-F$_2$	1.81002	1.45357	1.45357	1.66904	1.01207	1.01207	9.40[a]
S1-18	-2716947.55	2,6-F$_2$	1.82154	1.45069	1.44890	1.66366	1.01206	1.01231	9.10[a]
S1-19	-3498700.59	penta-F	1.82879	1.44893	1.44715	1.65643	1.01162	1.01181	8.20[a]
S1-20	-2456358.15	2-F	1.80713	1.45186	1.45497	1.66745	1.01305	1.01274	9.60[a]
S1-21	-3402465.99	2-Cl	1.81947	1.45530	1.45119	1.66601	1.01246	1.01242	9.58[d*]
S1-22	-2299041.08	2-Me	1.81393	1.45534	1.45664	1.67518	1.01165	1.01252	9.93[d*]

Table S3. Energies (kJ mol^{-1}), bond lengths (Å) for B3LYP/6-311G(d,p)/CPCM optimized geometries of compounds **S1-1** to **S1-22,** when the sulfonamide group is in the *syn* conformation, **A**, and *experimental* pK$_a$ values.

ID	U	sub	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK$_a$
S1-1	-2195790.21	H	1.79274	1.46705	1.46608	1.67770	1.01674	1.01717	10.10[a]
S1-2	-2341195.64	4-NH$_2$	1.77164	1.47000	1.46865	1.68358	1.01704	1.01770	10.65[b]
S1-3	-2299047.80	4-CH$_3$	1.78785	1.46674	1.46773	1.67890	1.01731	1.01684	10.11[c]
S1-4	-2444417.31	4-NHCH$_3$	1.76811	1.46900	1.47052	1.68524	1.01789	1.01722	11.00[d*]
S1-5	-2496560.97	4-OMe	1.78041	1.46710	1.46843	1.68075	1.01758	1.01710	10.22[e*]
S1-6	-2444403.41	4-CH$_2$NH$_2$	1.78791	1.46782	1.46701	1.67882	1.01684	1.01729	10.08[f**]
S1-7	-3402522.82	4-Cl	1.79302	1.46597	1.46510	1.67532	1.01663	1.01702	9.77[e*]
S1-8	-2732849.98	3-NO$_2$	1.79926	1.46456	1.46368	1.67141	1.01652	1.01679	9.19[e*]
S1-9	-2732848.64	4-NO$_2$	1.80215	1.46398	1.46344	1.67036	1.01618	1.01650	9.14[e*]
S1-10	-2456406.56	4-F	1.79000	1.46664	1.46566	1.67661	1.01676	1.01717	10.00[a]
S1-11	-2438031.55	4-CN	1.80042	1.46449	1.46388	1.67171	1.01629	1.01664	9.26[d*]
S1-12	-3402520.75	3-Cl	1.79723	1.46572	1.46453	1.67439	1.01674	1.01700	9.80[c]
S1-13	-3939548.00	3-NO$_2$,4-Cl	1.79842	1.46381	1.46288	1.66970	1.01647	1.01669	9.18[d*]
S1-14	-2299046.48	3-CH$_3$	1.79250	1.46754	1.46634	1.67890	1.01689	1.01730	10.06[c]
S1-15	-2596673.63	4-COCH$_3$	1.79733	1.46555	1.46488	1.67415	1.01645	1.01682	9.66[d*]
S1-16	-2456403.09	3-F	1.79657	1.46593	1.46474	1.67515	1.01675	1.01703	9.70[a]
S1-17	-2717012.39	3,5-F$_2$	1.79995	1.46430	1.46354	1.67160	1.01629	1.01667	9.40[a]
S1-18	-2716988.60	2,6-F$_2$	1.80251	1.45815	1.46251	1.66826	1.01557	1.01498	9.10[a]
S1-19	-3498739.15	penta-F	1.81114	1.45549	1.45861	1.65790	1.01432	1.01419	8.20[a]
S1-20	-2456396.11	2-F	1.79230	1.46447	1.46346	1.67035	1.01578	1.01586	9.60[a]
S1-21	-3402504.26	2-Cl	1.80553	1.46309	1.46308	1.66838	1.01501	1.01455	9.58[d*]
S1-22	-2299041.15	2-Me	1.79947	1.46735	1.46700	1.67757	1.01653	1.01682	9.93[d*]

Table S4. Energies (kJ mol^{-1}), bond lengths (Å) for B3LYP/6-311G(d,p)/CPCM optimized geometries of compounds **S1-1** to **S1-22,** where the sulfonamide group is in the *anti* conformation, **B**, and *experimental* pK$_a$ values.

ID	U	sub	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK$_a$
S1-1	-2195794.59	H	1.79798	1.46297	1.46297	1.66888	1.01550	1.01550	10.10[a]
S1-2	-2341199.16	4-NH$_2$	1.77837	1.46526	1.46526	1.67684	1.01578	1.01578	10.65[b]
S1-3	-2299051.99	4-CH$_3$	1.79344	1.46348	1.46348	1.67050	1.01553	1.01553	10.11[c]
S1-4	-2444420.43	4-NHCH$_3$	1.77524	1.46560	1.46583	1.67853	1.01590	1.01589	11.00[d*]
S1-5	-2496564.60	4-OMe	1.78693	1.46383	1.46404	1.67243	1.01566	1.01564	10.22[e*]
S1-6	-2444407.59	4-CH$_2$NH$_2$	1.79350	1.46345	1.46357	1.67101	1.01559	1.01566	10.08[f**]
S1-7	-3402527.26	4-Cl	1.79848	1.46211	1.46211	1.66587	1.01533	1.01533	9.77[e*]
S1-8	-2732854.09	3-NO$_2$	1.80444	1.46080	1.46067	1.66095	1.01510	1.01496	9.19[e*]
S1-9	-2732853.41	4-NO$_2$	1.80675	1.46065	1.46065	1.66057	1.01510	1.01510	9.14[e*]
S1-10	-2456410.83	4-F	1.79573	1.46254	1.46254	1.66749	1.01542	1.01542	10.00[a]
S1-11	-2438036.26	4-CN	1.80516	1.46105	1.46105	1.66199	1.01516	1.01516	9.26[d*]
S1-12	-3402525.09	3-Cl	1.80252	1.46178	1.46153	1.66416	1.01514	1.01508	9.80[c]
S1-13	-3939552.22	3-NO$_2$,4-Cl	1.80354	1.46011	1.45997	1.65902	1.01514	1.01493	9.18[d*]
S1-14	-2299050.85	3-CH$_3$	1.79757	1.46335	1.46316	1.66970	1.01543	1.01540	10.06[c]
S1-15	-2596678.21	4-COCH$_3$	1.80214	1.46194	1.46187	1.66490	1.01524	1.01527	9.66[d*]
S1-16	-2456407.55	3-F	1.80109	1.46187	1.46169	1.66523	1.01531	1.01519	9.70[a]
S1-17	-2717017.22	3,5-F$_2$	1.80479	1.46073	1.46073	1.66175	1.01520	1.01520	9.40[a]
S1-18	-2716989.07	2,6-F$_2$	1.81238	1.45662	1.45662	1.65971	1.01526	1.01526	9.10[a]
S1-19	-3498740.92	penta-F	1.82179	1.45433	1.45433	1.65169	1.01498	1.01498	8.20[a]
S1-20	-2456401.79	2-F	1.79722	1.46117	1.46046	1.66210	1.01554	1.01568	9.60[a]
S1-21	-3402509.34	2-Cl	1.81042	1.46066	1.46048	1.66089	1.01547	1.01506	9.58[d*]
S1-22	-2299041.08	2-Me	1.80740	1.46266	1.46483	1.66782	1.01538	1.01433	9.93[d*]

Table S5. Bond lengths (Å) for B3LYP/6-311G(d,p) gas-phase optimized geometries of compounds **S2-1** to **S2-38**, and *experimental* pK_a values.

ID	**sub**	(*i*) C-S	(*ii*) S=O	(*iii*) S=O	(*iv*) S-N	(*v*) N-H	(*vi*) N-C	**pK_a**
S2-1	H	1.78430	1.45653	1.45785	1.70160	1.01269	1.42077	8.97[a]
S2-2	4-NO_2	1.77857	1.45546	1.45574	1.71000	1.01207	1.40288	6.80[b]
S2-3	4-H_2N-SO_2	1.77970	1.45589	1.45635	1.70913	1.01238	1.40875	7.85[b]
S2-4	4-Cl	1.78285	1.45645	1.45707	1.70518	1.01260	1.41791	8.56[a]
S2-5	3-CH_3	1.78467	1.45671	1.45809	1.70050	1.01267	1.42164	9.05[a]
S2-6	2-CH_3	1.78520	1.45652	1.45854	1.69901	1.01135	1.42253	9.34[a]
S2-7	4-NH_2	1.78630	1.45728	1.45909	1.69985	1.01279	1.42671	10.22[b]
S2-8	4-$N(CH_3)_2$	1.78690	1.45735	1.45929	1.69869	1.01280	1.42673	9.46[a]
S2-9	4-CH_3	1.78499	1.45672	1.45813	1.70098	1.01277	1.42238	9.25[a]
S2-10	4-OC_2H_5	1.78571	1.45718	1.45856	1.70012	1.01273	1.42546	9.21[a]
S2-11	3-OC_2H_5	1.78437	1.45750	1.45795	1.70089	1.01272	1.42221	8.46[a]
S2-12	3-OCH_3	1.78428	1.45758	1.45788	1.70091	1.01269	1.42183	8.72[a]
S2-13	2-OCH_3	1.78609	1.45730	1.45782	1.69933	1.01410	1.41719	9.43[a]
S2-14	2-OC_2H_5	1.78626	1.45724	1.45788	1.69918	1.01412	1.41771	9.60[a]
S2-15	4-OCH_3	1.78566	1.45717	1.45851	1.70031	1.01273	1.42537	9.34[a]
S2-16	4-Br	1.78276	1.45643	1.45705	1.70529	1.01262	1.41760	8.24[a]
S2-17	2-Br	1.78206	1.45686	1.45646	1.70522	1.01394	1.40814	8.02[a]
S2-18	3-Cl	1.78209	1.45622	1.45693	1.70591	1.01255	1.41626	8.28[a]
S2-19	3-Br	1.78219	1.45625	1.45696	1.70585	1.01258	1.41645	8.31[a]
S2-20	3-NO_2	1.78053	1.45647	1.45581	1.70960	1.01270	1.41354	7.67[a]
S2-21	3-CF_3	1.78172	1.45640	1.45654	1.70685	1.01268	1.41603	7.98[a]
S2-22	4-CF_3	1.78117	1.45601	1.45651	1.70643	1.01239	1.41143	7.80[a]
S2-23	4-CN	1.77979	1.45578	1.45601	1.70884	1.01226	1.40703	7.36[a]
S2-24	4-$COCH_3$	1.78124	1.45612	1.45666	1.70513	1.01240	1.40984	7.52[a]
S2-25	4-SO2CH_3	1.77893	1.45588	1.4562	1.71004	1.01232	1.40745	7.30[a]
S2-26	2,3-CH_3	1.78687	1.45697	1.45886	1.70292	1.01360	1.43571	9.72[a]
S2-27	2-CH_3, 5-Cl	1.78287	1.45607	1.45771	1.70270	1.01093	1.41630	9.00[a]
S2-28	2-CH_3, 6-Cl	1.78287	1.45693	1.45738	1.71493	1.01433	1.42318	8.78[a]
S2-29	3,5-Cl_2	1.78002	1.45580	1.4562	1.70884	1.01220	1.41060	7.62[a]
S2-30	2-Cl, 4-OCH_3	1.78336	1.45724	1.45717	1.70602	1.01319	1.41418	8.81[a]
S2-31	2-OCH_3, 4-Cl	1.78464	1.45719	1.4571	1.70284	1.01399	1.41459	8.67[a]
S2-32	2-C1, 4-NO_2	1.77652	1.45556	1.45435	1.71402	1.01289	1.39185	6.17[a]
S2-33	2-CH_3, 4-NO_2	1.77911	1.45547	1.45644	1.70820	1.01051	1.40395	6.98[a]
S2-34	2-NO_2, 4-Cl	1.77875	1.45720	1.45349	1.71264	1.01739	1.39082	6.79[a]
S2-35	2-Br, 4-NO_2	1.77678	1.45569	1.45447	1.71368	1.01379	1.39161	5.70[a]
S2-36	2-NO_2, 4-CF_3	1.77672	1.45662	1.45293	1.71524	1.01810	1.38284	6.10[a]
S2-37	4-NO_2, 2-CF_3	1.77556	1.45594	1.45463	1.71656	1.01133	1.39414	5.90[a]
S2-38	2-Cl	1.78188	1.45672	1.45639	1.70596	1.01319	1.40878	8.08[a]

Table S6. Bond lengths (Å) for B3LYP/6-311G(d,p)//CPCM optimized geometries of compounds **S2-1** to **S2-38,** and *experimental* pK_a values.

ID	sub	(*i*) C-S	(*ii*) S=O	(*iii*) S=O	(*iv*) S-N	(*v*) N-H	(*vi*) N-C	pK_a
S2-1	H	1.77340	1.46351	1.46503	1.70092	1.01505	1.42849	8.97[a]
S2-2	4-NO_2	1.76711	1.46212	1.46200	1.70587	1.01389	1.40217	6.80[b]
S2-3	4-H_2N-SO_2	1.76880	1.46272	1.46283	1.70353	1.01408	1.40907	7.85[b]
S2-4	4-Cl	1.77224	1.46324	1.46420	1.70306	1.01485	1.42357	8.56[a]
S2-5	3-CH_3	1.77376	1.46365	1.46522	1.69987	1.01509	1.42837	9.05[a]
S2-6	2-CH_3	1.77396	1.46377	1.46554	1.69804	1.01348	1.42861	9.34[a]
S2-7	4-NH_2	1.77587	1.46466	1.46683	1.69864	1.0152	1.43395	10.22[b]
S2-8	4-$N(CH_3)_2$	1.77610	1.46487	1.46712	1.69845	1.01524	1.43393	9.46[a]
S2-9	4-CH_3	1.77421	1.46379	1.46562	1.70029	1.01509	1.43019	9.25[a]
S2-10	4-OC_2H_5	1.77493	1.46424	1.46600	1.70000	1.01516	1.43206	9.21[a]
S2-11	3-OC_2H_5	1.77310	1.46382	1.46513	1.70084	1.01500	1.42786	8.46[a]
S2-12	3-OCH_3	1.77296	1.46391	1.46504	1.69988	1.01475	1.42628	8.72[a]
S2-13	2-OCH_3	1.77424	1.46392	1.46553	1.70088	1.01675	1.42565	9.43[a]
S2-14	2-OC_2H_5	1.77439	1.46392	1.46549	1.70031	1.01677	1.42575	9.60[a]
S2-15	4-OCH_3	1.77472	1.46417	1.46595	1.70030	1.01516	1.43174	9.34[a]
S2-16	4-Br	1.77233	1.46326	1.46419	1.70355	1.01497	1.42366	8.24[a]
S2-17	2-Br	1.77056	1.46299	1.46375	1.70531	1.01583	1.41528	8.02[a]
S2-18	3-Cl	1.77148	1.46329	1.46379	1.70358	1.01481	1.42160	8.28[a]
S2-19	3-Br	1.77161	1.46329	1.46377	1.70335	1.01472	1.42190	8.31[a]
S2-20	3-NO_2	1.76956	1.46316	1.46276	1.70456	1.01441	1.41598	7.67[a]
S2-21	3-CF_3	1.77089	1.46342	1.46356	1.70354	1.01459	1.42019	7.98[a]
S2-22	4-CF_3	1.77020	1.46290	1.46336	1.70332	1.01453	1.41587	7.80[a]
S2-23	4-CN	1.76882	1.46256	1.46277	1.70457	1.01421	1.40898	7.36[a]
S2-24	4-$COCH_3$	1.76961	1.46285	1.46332	1.70207	1.01424	1.41194	7.52[a]
S2-25	4-SO_2CH_3	1.76910	1.46263	1.46284	1.70413	1.01423	1.41037	7.30[a]
S2-26	2,3-CH_3	1.77643	1.46378	1.46644	1.69763	1.01549	1.44103	9.72[a]
S2-27	2-CH_3, 5-Cl	1.77185	1.46349	1.46423	1.70170	1.01336	1.42238	9.00[a]
S2-28	2-CH_3, 6-Cl	1.77321	1.46285	1.46461	1.70796	1.01544	1.42719	8.78[a]
S2-29	3,5-Cl_2	1.76907	1.46279	1.46281	1.70615	1.01429	1.41526	7.62[a]
S2-30	2-Cl, 4-OCH_3	1.77243	1.46342	1.46449	1.70651	1.01509	1.42144	8.81[a]
S2-31	2-OCH_3, 4-Cl	1.77316	1.46362	1.46474	1.70359	1.01641	1.42222	8.67[a]
S2-32	2-Cl, 4-NO_2	1.76447	1.46134	1.46074	1.71188	1.01435	1.39154	6.17[a]
S2-33	2-CH_3, 4-NO_2	1.76715	1.46229	1.46249	1.70468	1.01233	1.40230	6.98[a]
S2-34	2-NO_2, 4-Cl	1.76623	1.46247	1.46152	1.70807	1.01794	1.39156	6.79[a]
S2-35	2-Br, 4-NO_2	1.76482	1.46147	1.46085	1.71103	1.01523	1.39139	5.70[a]
S2-36	2-NO_2, 4-CF_3	1.76428	1.46185	1.46074	1.71030	1.01824	1.38279	6.10[a]
S2-37	4-NO_2, 2-CF_3	1.76393	1.46118	1.46115	1.71483	1.01227	1.39460	5.90[a]
S2-38	2-Cl	1.77105	1.46280	1.46366	1.70645	1.01512	1.41630	8.08[a]

[a] Seydel, J. K. *J. Med. Chem.* **1971**, 14, 724-729

[b] Cammarata, A.; Allen R. C. Observations Concerning the Correlation of In Vitro Sulfonamide Activity with pK_a and the Hammett Values. *J. Pharm. Sci.* **1967**, 56, 640-64.

Table S7. Identity of R1 and R2 groups of compounds **SU-1** to **SU-30**, with common skeleton shown in Figure 7 of the main text.

ID	R1	R2
SU-1	H	N1-But
SU-2	4-Et	N1-But
SU-3	4-OMe	N1-But
SU-4	4-OEt	N1-But
SU-5	4-NMe_2	N1-But
SU-6	4-OCOEt	N1-But
SU-7	4-NHCOMe	N1-But
SU-8	4-COMe	N1-But
SU-9	3-NO_2	N1-But
SU-10	4-NO_2	N1-But
SU-11	4-Cl	N1-But
SU-12	4-Br	N1-But
SU-13	4-CH_2NH_2	N1-But
SU-14	3,4-Me_2	N1-But
SU-15	3-NO_2, 4-Me	N1-But
SU-16	3-NO_2, 4-OMe	N1-But
SU-17	3-NO_2, 4-Cl	N1-But
SU-18	3,4-Cl_2	N1-But
SU-19	H	iso-C3H7
SU-20	H	iso-C4H9
SU-21	H	X-CH3
SU-22	4-Cl	n-CH3
SU-23	4-Cl	n-C2H5
SU-24	4-Cl	n-C4H9
SU-25	4-Cl	iso-C3H7
SU-26	H	N1-cyclohexane
SU-27	3-NO_2	N1-cyclohexane
SU-28	4-NO_2	N1-cyclohexane
SU-29	4-Cl	N1-cyclohexane
SU-30	4-Me	N1-cyclohexane

Table S8. Calculated bond lengths (Å) for B3LYP/6-311G(d,p) gas-phase optimized geometries of compounds **SU-1** to **SU-30** (the identity of which is given in Table S7), and *experimental* pK_a values.

ID	C-S (A)	S=O (B)	S=O (C)	S-N (D)	N-H (E)	N-C (F)	C=O (G)	C-N (H)	N-H (I)	pK_a
SU-1	1.79152	1.45839	1.46475	1.68789	1.01446	1.42975	1.22075	1.34672	1.01173	5.02[i]
SU-2	1.79265	1.45355	1.46169	1.68899	1.01275	1.42848	1.21468	1.35508	1.01229	5.24[i]
SU-3	1.78576	1.45384	1.46227	1.69119	1.01272	1.42716	1.21493	1.35575	1.01233	5.28[i]
SU-4	1.78537	1.45391	1.46232	1.69150	1.01271	1.42701	1.21502	1.35570	1.01232	5.33[i]
SU-5	1.77694	1.45491	1.46331	1.69587	1.01256	1.42461	1.21590	1.35626	1.01246	5.85[i]
SU-6	1.79796	1.45333	1.46074	1.68437	1.01282	1.43131	1.21374	1.35429	1.01220	4.38[i]
SU-7	1.79214	1.45320	1.46155	1.68760	1.01286	1.42915	1.21425	1.35534	1.01231	5.03[i]
SU-8	1.79949	1.45245	1.46081	1.68434	1.01297	1.43128	1.21363	1.35466	1.01223	4.35[i]
SU-9	1.80304	1.45239	1.45887	1.67995	1.01308	1.43485	1.21282	1.35344	1.01211	3.92[i]
SU-10	1.80374	1.45193	1.45949	1.67984	1.01311	1.43433	1.21262	1.35406	1.01217	3.95[i]
SU-11	1.79590	1.45286	1.46066	1.68483	1.01291	1.43100	1.21367	1.35485	1.01224	4.67[i]
SU-12	1.79613	1.45286	1.46070	1.68471	1.01289	1.43098	1.21368	1.35485	1.01227	4.74[i]
SU-13	1.79255	1.45377	1.46173	1.68978	1.01277	1.42817	1.21494	1.35487	1.01227	5.38[i]
SU-14	1.79233	1.45387	1.46185	1.68980	1.01270	1.42808	1.21490	1.35497	1.01226	5.33[i]
SU-15	1.79878	1.45270	1.45914	1.68146	1.01300	1.43358	1.21318	1.35385	1.01222	4.22[i]
SU-16	1.79219	1.45334	1.45954	1.68366	1.01290	1.43223	1.21354	1.35438	1.01229	4.38[i]
SU-17	1.80130	1.45215	1.45861	1.67869	1.01316	1.43607	1.21244	1.35301	1.01192	4.03[i]
SU-18	1.79908	1.45234	1.45982	1.68186	1.01302	1.43320	1.21311	1.35406	1.01209	4.21[i]
SU-19	1.79183	1.45853	1.46475	1.68716	1.01425	1.43018	1.22101	1.34633	1.01288	4.99[ii]
SU-20	1.79172	1.45869	1.46509	1.68676	1.01458	1.43518	1.22107	1.34539	1.01224	4.94[ii]
SU-21	1.79093	1.45826	1.46475	1.68780	1.01445	1.42953	1.22027	1.34615	1.01110	5.14[ii]
SU-22	1.79131	1.45754	1.46398	1.68439	1.01432	1.43037	1.21979	1.34602	1.01106	4.52[ii]
SU-23	1.79154	1.45761	1.46389	1.68500	1.01447	1.43099	1.22019	1.34662	1.01174	4.84[ii]
SU-24	1.79169	1.45760	1.46392	1.68516	1.01450	1.43092	1.22029	1.34654	1.01168	4.75[ii]
SU-25	1.79182	1.45772	1.46395	1.68404	1.01434	1.43138	1.22053	1.34609	1.01276	4.54[ii]
SU-26	1.79145	1.46477	1.45857	1.68681	1.01422	1.43018	1.22100	1.34672	1.01285	5.00[i]
SU-27	1.79797	1.46258	1.45626	1.68071	1.01478	1.43441	1.21958	1.34601	1.01254	4.11[i]
SU-28	1.80070	1.46251	1.45632	1.67851	1.01448	1.43447	1.21974	1.34529	1.01265	4.00[i]
SU-29	1.79190	1.46397	1.45771	1.68425	1.01436	1.43172	1.22051	1.34631	1.01276	4.61[i]
SU-30	1.78649	1.46532	1.45908	1.68858	1.01411	1.42930	1.22131	1.34699	1.01285	5.50

Table S9. Calculated bond lengths (Å) for B3LYP/6-311G(d,p) CPCM optimized geometries of compounds SU-1 to SU-30 (the identity of which is given in Table S7) and *experimental* pK_a values.

ID	C-S (A)	S=O (B)	S=O (C)	S-N (D)	N-H (E)	N-C (F)	C=O (G)	C-N (H)	N-H (I)	pK_a
SU-1	1.79673	1.45325	1.46131	1.68730	1.01281	1.42953	1.21432	1.35484	1.01225	5.02[i]
SU-2	1.79265	1.45355	1.46169	1.68899	1.01275	1.42848	1.21468	1.35508	1.01229	5.24[i]
SU-3	1.78603	1.45411	1.46199	1.69067	1.01268	1.42749	1.21495	1.35550	1.01238	5.28[i]
SU-4	1.78563	1.45415	1.46211	1.69093	1.01266	1.42728	1.21500	1.35560	1.01242	5.33[i]
SU-5	1.77694	1.45491	1.46331	1.69587	1.01256	1.42461	1.21590	1.35626	1.01246	5.85[i]
SU-6	1.79188	1.45358	1.46124	1.68770	1.01277	1.42941	1.21440	1.35475	1.01222	4.38[i]
SU-7	1.79796	1.45333	1.46074	1.68437	1.01282	1.43131	1.21374	1.35429	1.01220	5.03[i]
SU-8	1.79972	1.45294	1.46041	1.68383	1.01288	1.43184	1.21366	1.35411	1.01220	4.35[i]
SU-9	1.80304	1.45239	1.45887	1.67996	1.01308	1.43485	1.21282	1.35344	1.01211	3.92[i]
SU-10	1.80374	1.45193	1.45949	1.67984	1.01311	1.43433	1.21262	1.35406	1.01217	3.95[i]
SU-11	1.79590	1.45286	1.46066	1.68483	1.01292	1.43100	1.21367	1.35485	1.01224	4.67[i]
SU-12	1.79613	1.45286	1.46070	1.68471	1.01289	1.43098	1.21368	1.35485	1.01227	4.74[i]
SU-13	1.79255	1.45377	1.46173	1.68978	1.01271	1.42817	1.21494	1.35487	1.01229	5.38[i]
SU-14	1.79233	1.45387	1.46185	1.68980	1.01270	1.42808	1.21490	1.35497	1.01226	5.33[i]
SU-15	1.79878	1.45270	1.45914	1.68146	1.01300	1.43358	1.21319	1.35385	1.01222	4.22[i]
SU-16	1.79219	1.45334	1.45954	1.68366	1.01290	1.43223	1.21354	1.35438	1.01229	4.38[i]
SU-17	1.80130	1.45216	1.45861	1.67869	1.01316	1.43607	1.21244	1.35301	1.01193	4.03[i]
SU-18	1.79908	1.45234	1.45982	1.68186	1.01302	1.43320	1.21311	1.35406	1.01210	4.21[i]
SU-19	1.79181	1.45866	1.46508	1.68653	1.01447	1.43427	1.22103	1.34507	1.01131	4.99[ii]
SU-20	1.79137	1.45823	1.46499	1.68751	1.01428	1.42984	1.22079	1.34651	1.01117	4.94[ii]
SU-21	1.79093	1.46475	1.45826	1.68780	1.01445	1.42954	1.22027	1.34615	1.01110	5.14[ii]
SU-22	1.79131	1.45754	1.46398	1.68439	1.01432	1.43037	1.21979	1.34602	1.01106	4.52[ii]
SU-23	1.79154	1.45761	1.46389	1.68500	1.01447	1.43099	1.22019	1.34663	1.01174	4.84[ii]
SU-24	1.79169	1.45760	1.46392	1.68516	1.01450	1.43092	1.22029	1.34654	1.01168	4.75[ii]
SU-25	1.79182	1.45772	1.46395	1.68404	1.01434	1.43138	1.22053	1.34609	1.01276	4.54[ii]
SU-26	1.79690	1.46133	1.45341	1.68632	1.01276	1.43040	1.21457	1.35437	1.01323	5.00[i]
SU-27	1.80322	1.45866	1.45258	1.68005	1.01320	1.43636	1.21313	1.35276	1.01295	4.11[i]
SU-28	1.80392	1.45948	1.45211	1.67892	1.01307	1.43548	1.21291	1.35330	1.01309	4.00[i]
SU-29	1.79606	1.46062	1.45303	1.68407	1.01289	1.43206	1.21397	1.35413	1.01316	4.61[i]
SU-30	1.79266	1.45372	1.46167	1.68804	1.01272	1.42937	1.21494	1.35462	1.01326	5.50

[I] Asada, S.; Nakasato, T.; Takino, S. Physicochemical Properties of Medicinal Agents. II. Relationship between Acid Dissociation Constants of Arylsulfonylurea Derivatives and the Hammett Equation. *YAKUGAKU ZASSHI*, **1973**, 93, 1647-1654.

[II] Asada, S.; Fujita, R.; Shirakura, Y. Physicochemical Properties of Medicinal Agents. III. Partition Coefficients and Acid Dissociation Constants of N_2-Substituted-N_1-arylsulfonylurea Derivatives. *YAKUGAKU ZASSHI*. **1974**, 94, 80-84.

Table S10. Bond lengths (Å) for B3LYP/6-311G(d,p) CPCM optimized geometries of compounds **TS1-1** to **TS1-6.** The bond lengths shown are extracted from the most stable geometry of an ensemble of 25 conformations. In each case, the sulfonamide group is in the *anti* conformation, **B**. *Experimental* pK_a values are also shown, for which references are given in the main text.

ID	Compound	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK_a
TS1-1	methyclothiazide	1.80040	1.46099	1.46024	1.66085	1.01542	1.01503	9.40[1]
TS1-2	chlorthalidone	1.81148	1.46002	1.46052	1.65980	1.01504	1.01549	9.35[2]
TS1-3	sulpiride	1.78844	1.46350	1.46327	1.67018	1.01543	1.01545	10.21[3]
TS1-4	celecoxib	1.78343	1.46416	1.46428	1.67352	1.01563	1.01571	11.10[4]
TS1-5	metolazone	1.79629	1.46184	1.46428	1.66554	1.01572	1.01523	9.70[5]
TS1-6	polythiazide	1.80025	1.46110	1.46428	1.66138	1.01551	1.01506	9.10[6]

1. J. A. Raihle, Methyclothiazide, APDS, 1976. 5, 307–326.

2. A. L. J. Fleurren, C. A. M. van Ginneken, J. M. van Rossum, Differential potentiometric method for determining dissociation constants of very slightly water soluble drugs applied to the sulfonamide diuretic chlorthalidone. *J. Pharm. Sci.* 1979, 68, 1056–1058

3. D. Pitre, R. Stradi, G. Nathansohn, Sulpiride. In Analytical Profiles of Drug Substances, Florey, K., Ed. Academic Press: San Diego, California, **1988**; Vol. 17.

4. S. K. Paulson, M. B. Vaughn, S. M. Jessen, Y. Lawal, C. J. Gresk, B. Yan, T. J. Maziasz, C. S. Cook, A. Karim, A., Pharmacokinetics of Celecoxib after Oral Administration in Dogs and Humans: Effect of Food and Site of Absorption. *J. Pharmacol. Exp. Ther.* **2001**, 297, 638-645. (Also: http://www.pfizer.com.au/sites/g/files/g10005016/f/201311/PI_Celebrex_242.pdf)

5. F. T. Manallack, The pK(a) Distribution of Drugs: Application to Drug Discovery. Perspect. Medicin. Chem., **2007**, 1, 25-38. (Also: http://products.sanofi.ca/en/zaroxolyn.pdf)

6. U. G. Hennig, L. G. Chatten, R. E. Moskalyk, C. Ediss, Benzothiadiazine dissociation constants. Part 1. Ultraviolet spectrophotometric pKa determinations. *Analyst,* **1981**, 106, 557–564.

Table S11. Bond lengths (Å) for test compounds **TS1-7** to **TS1-14** in their neutral form. The bond lengths shown are extracted from the most stable geometry identified in the gas-phase at the B3LYP/6-311G(d,p) level. In each case, the sulfonamide group is in the *anti* conformation, **B**. *Experimental* pK$_a$ values are also shown, for which references are given below.

ID	Compound	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK$_a$
TS1-7	hydroflumethiazide	1.80879	1.45930	1.46185	1.66313	1.01453	1.01546	10.70[1]
TS1-8	chlorothiazide	1.79738	1.46064	1.46141	1.66234	1.01512	1.01554	9.70[2]
TS1-9	hydrochlorothiazide	1.79809	1.46131	1.46066	1.66200	1.01546	1.01509	10.39[3]
TS1-10	trichloromethiazide	1.80158	1.46085	1.45994	1.66020	1.01544	1.01495	10.30[1]
TS1-11	penflutizide	1.80786	1.45930	1.46192	1.66338	1.01458	1.01549	10.39[4]
TS1-12	bumetanide	1.80317	1.46193	1.46166	1.66457	1.01593	1.01679	10.37[5]
TS1-13	furosemide	1.81609	1.45990	1.46032	1.66049	1.01501	1.01564	10.60[6]
TS1-14	piretanide	1.80540	1.46221	1.46185	1.66481	1.01602	1.01667	10.00[7]

[1] S. Goto, Y. Odawara, M. Nakano, Y. Araki, Stability and Serum Albumin Binding of Diuretics in Aqueous Solution. *YUKUGAKU ZASSHI* **1978,** *98*, 236-241.

[2] U. G. Hennig; L. G. Chatten; R. E. Moskalyk; Ediss, C., Benzothiadiazine dissociation constants. Part 1. Ultraviolet spectrophotometric pK$_a$ determinations, *Analyst,* **1981,** *106*, 557–564.

[3] T.Takayangi, M. Isoda, D. Itoh, H. Mizuguchi, Determination of Acid Dissociation Constants of Hydrochlorothiazide and Its Degradant through Measurement of the Effective Electrophoretic Mobilities in CZE. *BUNSEKI KAGAK,* **2017,** *66*, 509-514

[4] M. Yamazaki; T. Suzuka; Y. Ito; S. Itoh; M. Kitamura; K. Ohashi; Y. Takeda; A. Kamada; Y. Orita; Nakahama, H., Biopharmaceutical Studies of Thiazide Diuretics. I. Determination of pK$_a$ Values and Partition Coefficients of Thiazide Diuretics. *Chem. Pharm. Bull.* **1984,** *32*, 2380-2386.

[5] B. Song; A. K. Galande, K. Kodukula, W. H. Moos, S. M. Miller, Evaluation of the pK$_a$ Values and Ionization Sequence of Bumetanide Using 1H and 13C NMR and UV Spectroscopy. *Drug Development Research,* **2011,** *72*, 416-426

[6] H. Wan, A. G. Holman, Y. Wang, W. Lindberg, M. Englund, M. B. Nagard, R. A. Thompson, High-throughput screening of pK$_a$ values of pharmaceuticals by pressure-assisted capillary electrophoresis and mass spectrometry. *Rapid Commun. Mass Spectrom.* **2003,** *17*, 2639-2648.

Table S12. Bond lengths (Å) for test compounds **TS1-7** to **TS1-14** in their neutral form. The bond lengths shown are extracted from the most stable geometry identified in the gas-phase at the B3LYP/6-311+G(d,p) level. In each case, the sulfonamide group is in the *anti* conformation, **B**. *Experimental* pK$_a$ values are also shown, for which references are given in Table S11.

ID	Compound	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK$_a$
TS1-7	hydroflumethiazide	1.81065	1.46085	1.46345	1.66728	1.01551	1.01653	10.70[1]
TS1-8	chlorothiazide	1.81305	1.46046	1.46118	1.65934	1.01590	1.01636	9.70[2]
TS1-9	hydrochlorothiazide	1.81135	1.45310	1.45621	1.67199	1.01369	1.01393	10.39[3]
TS1-10	trichloromethiazide	1.80226	1.46284	1.46207	1.66450	1.01661	1.01611	10.30[1]
TS1-11	penflutizide	1.80995	1.46082	1.46351	1.66743	1.01556	1.01662	10.39[4]
TS1-12	bumetanide	1.80781	1.46424	1.46348	1.66798	1.01701	1.01755	10.37[5]
TS1-13	furosemide	1.81758	1.46185	1.46217	1.66437	1.01607	1.01673	10.60[6]
TS1-14	piretanide	1.80556	1.46385	1.46324	1.66769	1.01690	1.01766	10.00[7]

Table S13. Bond lengths (Å) for test compounds **TS1-7** to **TS1-14** in their anionic form. The bond lengths shown are extracted from the most stable geometry identified in the solution phase at the B3LYP/6-311G(d,p) level with CPCM. In each case, the sulfonamide group is in the *anti* conformation, **B**. *Experimental* pK$_a$ values are also shown, for which references are given in Table S11.

ID	Compound	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK$_a$
TS1-7	hydroflumethiazide	1.79784	1.46183	1.46381	1.67104	1.01486	1.01573	10.70[1]
TS1-8	chlorothiazide	1.79788	1.46147	1.46183	1.66433	1.01528	1.01562	9.70[2]
TS1-9	hydrochlorothiazide	1.78788	1.46321	1.46327	1.66980	1.01577	1.01551	10.39[3]
TS1-10	trichloromethiazide	1.79231	1.46255	1.46237	1.66721	1.01566	1.01532	10.30[1]
TS1-11	penflutizide	1.79875	1.46170	1.46377	1.67070	1.01488	1.01567	10.39[4]
TS1-12	bumetanide	1.79786	1.46346	1.46408	1.67094	1.01618	1.01723	10.37[5]
TS1-13	furosemide	1.80951	1.46238	1.46174	1.66720	1.01538	1.01586	10.60[6]
TS1-14	piretanide	1.79974	1.46390	1.46435	1.67133	1.01626	1.01718	10.00[7]

Table S14. Bond lengths (Å) for test compounds **TS1-7** to **TS1-14** in their anionic form. The bond lengths shown are extracted from the most stable geometry identified in the solution phase at the B3LYP/6-311+G(d,p) level with CPCM. In each case, the sulfonamide group is in the *anti* conformation, **B**. *Experimental* pK_a values are also shown, for which references are given in Table S11.

ID	Compound	***a*** C-S	***b*** S=O	***c*** S=O	***d*** S-N	***e*** N-H	***f*** N-H	pK_a
TS1-7	hydroflumethiazide	1.80052	1.46327	1.46537	1.67453	1.01575	1.01675	10.70[1]
TS1-8	chlorothiazide	1.79972	1.46342	1.46371	1.66789	1.01638	1.01668	9.70[2]
TS1-9	hydrochlorothiazide	1.78992	1.46517	1.46524	1.67329	1.01683	1.01658	10.39[3]
TS1-10	trichloromethiazide	1.79364	1.46454	1.46449	1.67102	1.01672	1.01647	10.30[1]
TS1-11	penflutizide	1.80120	1.46316	1.46534	1.67449	1.01583	1.01676	10.39[4]
TS1-12	bumetanide	1.80294	1.46579	1.46570	1.67357	1.01719	1.01795	10.37[5]
TS1-13	furosemide	1.81208	1.46406	1.46351	1.67008	1.01637	1.01689	10.60[6]
TS1-14	piretanide	1.80100	1.46524	1.46546	1.67313	1.01712	1.01799	10.00[7]

Table S15. Bond lengths (Å) for B3LYP/6-311G(d,p) CPCM optimized geometries of compounds **TS2-1** to **TS2-10.** *Experimental* pK_a values are also shown, for which references are given in the main text.

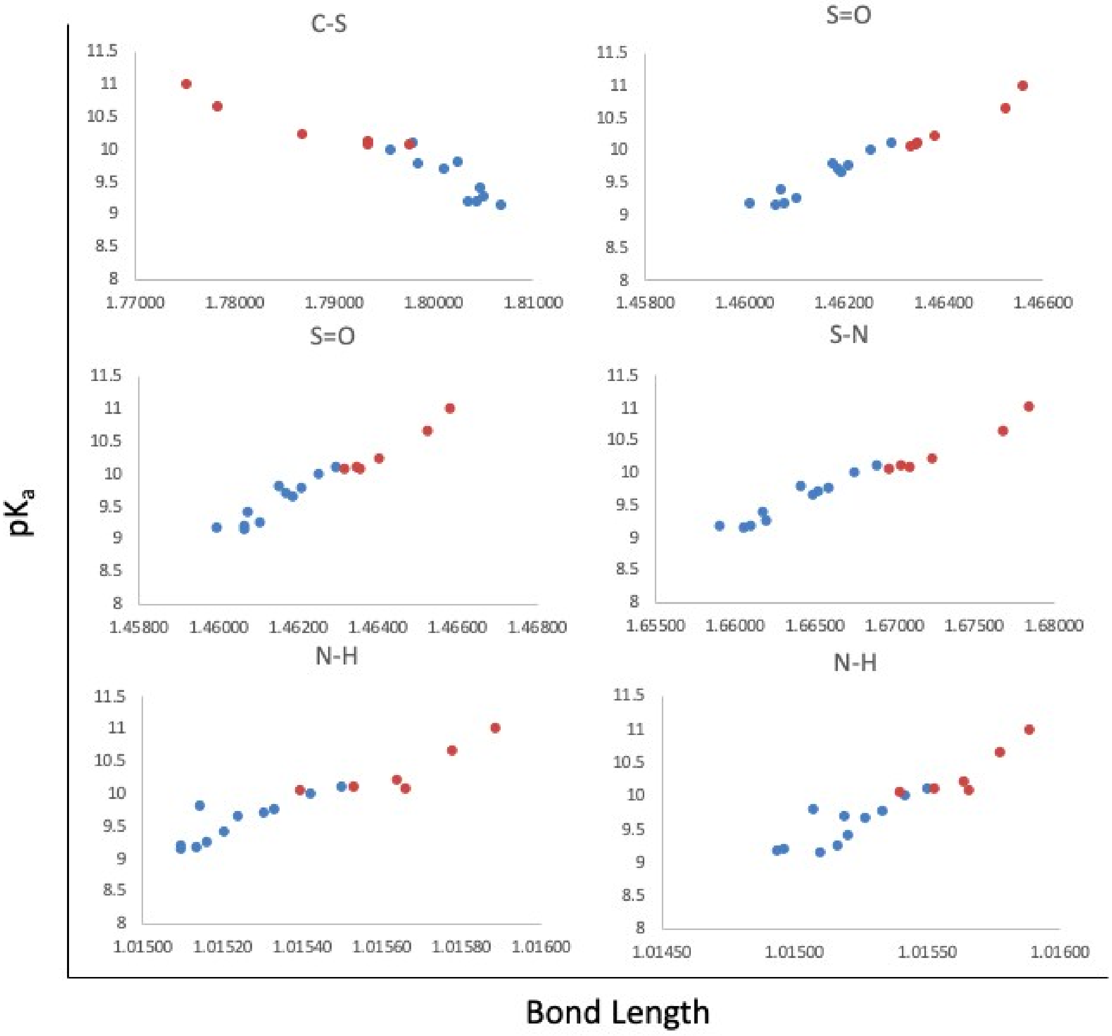
		(*i*)	(*ii*)	(*iii*)	(*iv*)	(*v*)	(*vi*)	
ID	Compound	C-S	S=O	S=O	S-N	N-H	N-C	pK_a
TS2-1	sulfadiazine	1.76742	1.45934	1.46495	1.69798	1.01269	1.39168	6.52
TS2-2	sulfamerazine	1.76800	1.45950	1.46530	1.69653	1.01274	1.39417	7.06
TS2-3	sulfamonomethoxine	1.76760	1.46205	1.46156	1.69982	1.01489	1.39754	6.22
TS2-4	sulfamethoxypyridazine	1.76853	1.46521	1.46561	1.70788	1.01731	1.41190	7.17
TS2-5	sulfadimethoxine	1.76841	1.46203	1.46192	1.69890	1.01496	1.39941	7.02
TS2-6	5-phenyl-4-sulfa-pyrimidine	1.76604	1.45875	1.46483	1.70592	1.01290	1.38457	6.04
TS2-7	sulfamethoxydiazine	1.76823	1.46291	1.46670	1.69527	1.01350	1.40167	6.63
TS2-8	sulfisomidine	1.76828	1.46207	1.46169	1.70028	1.01537	1.39916	7.40
TS2-9	sulfamethazine	1.76884	1.45973	1.46569	1.69528	1.01286	1.39681	7.37
TS2-10	sulfapyridine	1.77119	1.46330	1.46314	1.69819	1.01611	1.41594	8.43

Table S16. Bond lengths (Å) for B3LYP/6-311G(d,p) CPCM optimized geometries of compounds **TSU-1** to **TSU-6**. *Experimental* pK_a values are also shown, for which references are given in the main text.

		C-S	S=O	S=O	S-N	N-H	N-C	C=O	C-N	N-H	pK_a
ID	compound name	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	
TSU-1	Chlorpropramide	1.79168	1.45756	1.46397	1.68513	1.01448	1.43079	1.22021	1.34674	1.01172	4.75
TSU-2	Carbutamide	1.78003	1.45460	1.46289	1.69367	1.01262	1.42571	1.21542	1.35611	1.01242	5.79
TSU-3	Acetohexamide	1.79593	1.46374	1.45756	1.68266	1.01435	1.43225	1.22047	1.34586	1.01272	4.31
TSU-4	Glibenclamide	1.78698	1.46495	1.45843	1.6898	1.01454	1.43113	1.22244	1.34541	1.01285	5.30
TSU-5	Glipizide	1.78794	1.46505	1.45887	1.68822	1.01433	1.42994	1.22119	1.34675	1.01278	5.07*
TSU-6	Glimepiride	1.78658	1.46470	1.45883	1.69235	1.01452	1.43048	1.22384	1.34436	1.01280	5.32*

*Measured in this work via the method detailed in **S1.**

Figure S2. The relationship between each bond length (Å) of the SO_2NH_2 fragment in the *anti* (B) conformation, and aqueous pK_a values, for compounds **S1-1** to **S1-17**. This demonstrates an increase in bond order for all bonds except C-S for more acidic compounds. Red data points denote electron donating groups and blue denotes electron withdrawing.



Technical Section 1: details of experimental measurement of pK_a values for glimepiride, glipizide and celecoxib.

Experimental pK_a measurements were collected using the SiriusT3 instrument (Sirius Analytical Instruments, East Sussex, Great Britain), an automatic titration system incorporating *in situ* UV spectroscopy. The Sirius T3 is equipped with an Ag/AgCl double-junction reference electrode to monitor pH, a dip probe attached to UV spectrophotometer, a stirrer, and automated volumetric titration capability. The Sirius T3 UV-metric pK_a measurement protocol measures the change in multi-wavelength absorbance in the UV region of the absorbance spectrum while the pH is titrated. Measurements were carried out at 25°C and constant ionic strength (0.01 M KCl), UV absorbance data are collected from 160–760 nm while the 250–450 nm region is typically used for pK_a determinations. Because of the low water solubility of the tested compounds, the titrations were carried out in a co-solvent (methanol). The method involves the compound titration with three different methanol concentrations and the calculation of the pK_a in aqueous conditions by extrapolation using the Yasuda–Shedlovsky[1,2] equation. Two Sirius T3 computer programs (Sirius T3 Control v1.1.3.0 and Sirius T3 Refine v1.1.3.0) were used to execute measurement protocols and analyse pH-dependent multi-wavelength spectra, respectively.

[1] Shedlovsky, T. In *Electrolytes; Peace, B., Ed.; Pergamon Press:* New York, **1962**; 146-151.

[2] Yasuda, M. *Bull. Chem. Soc. Jpn.* **1959**, 32, 429-432.

Technical Section 2: Model Validation Metrics.

The q^2 value that we calculate to assess model predictability is produced via k-fold cross validation, where k=7. Hence, a seventh of the dataset is removed, and the remaining 6/7^{ths} of the input features and observables are used to form the predictive equation. Predictions are then made for the seventh that was removed. The second seventh is then removed, and the first seventh joins the remaining 5/7 to make up the 6/7 training set. When all 7 cycles are complete and all compounds have been predicted once, the following equation is used to obtain to the q^2 value:

$$q^2 = 1 - \frac{\sum_{i}^{N}(y_{i,obs} - y_{i,\,pred})^2}{\sum_{i}^{N}(y_{i,obs} - \bar{y})^2} \qquad (1)$$

where $y_{i,obs}$ and $y_{i,pred}$ correspond to the observed and predicted values for each of the training set compounds, and $\bar{y}$ is the mean value of the observed values for the training set. The RMSEE values that we quote are derived from the following equation:

$$RMSEE = \sqrt{\frac{\sum_{i}^{N}(y_{i,obs} - y_{i,\,pred})^2}{N}} \qquad (2)$$

where $y_{i,obs}$ and $y_{i,pred}$ are defined as above and N is the number of compounds of the training set.

External validation is performed by calculation of the Mean Absolute Error (MAE) and by employing Roy's MAE evaluation criteria[1]. The mean absolute error is defined as:

$$MAE = \frac{\sum_{i}^{N_{ext}}|y_{i,obs} - y_{i,\,pred}|}{N_{ext}} \qquad (3)$$

where $y_{i,obs} - y_{i,pred}$ is the residual error, and where i is now the test set compound and N_{ext} denotes the number of compounds in the external test set. According to Roy, The two criteria that must be met by a "good" model are that:

1) The MAE must be less than 10% of the training set range, and

2) The MAE+3σ must be less than 20% of the training set range.

Here σ denotes the standard deviation of the absolute errors. If the model does not fit the above criteria then it can be deemed "moderate", that is, if for the second criterion 25% is used in place of 20%, or "poor" if it does not obey either criterion. The Root-Mean-Squared-Error of Prediction (RMSEP) calculated for the test set is also used to evaluate model prediction accuracy, the formalism for which can again be found in Technical Section 2.

[1] Roy, K.; Das, N.; Ambure, P.; Aher, R. B., *Chemo. Intell. Lab. Syst.,* **2016**, 152, 18-33.

Technical Section 3: IQA Analysis Using AIMAll.

The extent of electronic delocalization between two atoms can be calculated within the context of a quantum topological energy decomposition framework called Interacting Quantum Atoms (IQA)[1]. Originating from the Quantum Theory of Atoms in Molecules (QTAIM)[2,3], IQA has been used to analyse a large variety of chemical phenomena[4-7]. By decomposing the total energy of a system into intra- and interatomic terms, we may derive the exchange-correlation potential energy $\mathrm{V}_{\mathrm{xc}}^{\mathrm{AB}}$, which is the sum of the exchange energy $\mathrm{V}_{\mathrm{x}}^{\mathrm{AB}}$, and the correlation energy $\mathrm{V}_{\mathrm{c}}^{\mathrm{AB}}$. The former term usually dominates $\mathrm{V}_{\mathrm{xc}}^{\mathrm{AB}}$, and denotes the Fock-Dirac exchange, which describes the ever-reducing probability of finding two electrons of the same spin close to one another (i.e. the Fermi hole). The latter term $\mathrm{V}_{\mathrm{c}}^{\mathrm{AB}}$, is associated with the Coulomb hole and the electrostatic repulsion between electrons. The absolute value of $\mathrm{V}_{\mathrm{xc}}^{\mathrm{AB}}$ evaluated between two atoms can be taken as the extent delocalization of electrons between them, and so can be interpreted as a measure of covalency. Finally, $\mathrm{V}_{\mathrm{cl}}^{\mathrm{AB}}$ denotes the classical potential energy between two topological atoms, which accounts for the electrostatic component of the interaction energy. These values were obtained by the AIMAll[8] program (version 17), using DFT-compatible IQA partitioning[7] with default parameters on wavefunctions obtained at the B3LYP/6-311G(d,p) level.

[1] Blanco, M. A.; Pendás, A. M.; Francisco, E. *J.Chem.Theor.Comput.*, **2005**, 1, 1096-1109.

[2] Popelier, P. L. A. *Atoms in Molecules. An Introduction*, Pearson Education, London, Great Britain, **2000**.

[3] Bader, R. F. W. *Atoms in Molecules. A Quantum Theory*, Oxford Univ. Press, Oxford, Great Britain **1990**.

[4] Wilson, A. L.; Popelier, P. L. A. *J. Phys. Chem. A*, **2016**, 120, 9647-9659.

[5] Thacker, J. C. R.; Popelier, P. L. A. *J. Phys. Chem. A.*, **2018**, 122, 1439-1450.

[6] Thacker, J. C. R.; Popelier, P. L. A. *Theor. Chem. Acc.*, **2017**, 136, 86.

[7] Maxwell, P.; Pendás, A. M.; Popelier, P. L. A. *Phys. Chem. Chem. Phys.*, **2016**, 18, 20986.

[8] Keith, T. A. *AIMAll*, TL Gristmill Software: Overland Park, KS, USA.

Table S17. r^2, RMSEE, leave-one-seventh-out cross validation q^2 values for the linear fit between gas-phase and solvent-phase (obtained via inclusion of the CPCM implicit solvation) bond lengths ***a*-*f*** *versus* aqueous pK_a values for a set of 22 primary benzene sulfonamides. Bond lengths are listed in Tables S1-S4, and are taken from compounds with the sulfonamide group either in the *syn* (**A**) or *anti* (**B**) conformations.

Conformer	Metric	***a*** (C-S)	***b*** (S=O)	***c*** (S=O)	***d*** (S-N)	***e*** (N-H)	***f*** (N-H)
A ***gas***	r^2	0.804	0.771	0.840	0.860	0.559	0.526
	RMSEE	0.267	0.288	0.241	0.226	0.400	0.415
	q^2	0.789	0.767	0.823	0.832	0.505	0.359
A ***CPCM***	r^2	0.792	0.799	0.925	0.928	0.686	0.500
	RMSEE	0.275	0.270	0.165	0.162	0.338	0.426
	q^2	0.773	0.795	0.920	0.915	0.631	0.381
B ***gas***	r^2	0.754	0.837	0.724	0.933	0.610	0.713
	RMSEE	0.282	0.230	0.299	0.146	0.355	0.305
	q^2	0.729	0.826	0.706	0.921	0.506	0.652
B ***CPCM***	r^2	0.821	0.881	0.858	0.949	0.787	0.356
	RMSEE	0.255	0.208	0.228	0.136	0.278	0.484
	q^2	0.809	0.875	0.854	0.941	0.777	0.031
	Slope (+/-)	-	+	+	+	+	+

Table S17 lists the r^2, RMSEE and q^2 and values calculated for the linear regression of each bond length against each compound's pK_a value for both gas and solvent phase. Internal energies, bond lengths and pK_a values for each training set compound **S1-1** to **S1-22** are listed in Tables S1-S4. Table 1 shows that the internal validation criteria generally improve when the CPCM is used to model the solvent. This effect is most pronounced for bonds ***b***, ***c*** and ***d*** (i.e. both S=O bonds and S-N). However, the S-N bond (***d***) is most highly correlated to the pK_a values in both gas and solvent phase, for both conformations **A** and **B**. We therefore denote S-N the "active bond", for which there is a strong positive correlation with pK_a.

Table S18. S-N bond lengths, experimental pK_a values and AIBL predictions for 6 thiazide drugs. The absolute error (AE), mean absolute error (MAE), standard deviation of error (σ) and Root Mean Squared Error of Prediction (RMSEP) are also shown, corresponding to the inclusion of the newest pK_a measurement for celecoxib. Predictions are made via insertion of the relevant bond length into the equation pK_a = 92.95*r(S-N) - 145.10. $^+$Measured in this work. All bond lengths for **TS1-1** to **TS1-6** are shown in Table S10. Experimental pK_a values are referenced in Table S11.

ID	Compound	r(S-N) (Å)	Exp pK_a	AIBL pK_a	AE	Marvin	AE
TS1-1	methyclothiazide	1.66085	9.40	9.28	0.12	9.29	0.11
TS1-2	chlorthalidone	1.65980	9.35	9.18	0.17	9.03	0.32
TS1-3	sulpiride	1.67018	10.21	10.14	0.06	10.24	0.03
TS1-4	celecoxib	1.66561	11.10/9.52$^+$	9.72	1.38/0.20	10.70	0.40/1.18
TS1-5	metolazone	1.66554	9.70	9.71	0.01	9.54	0.16
TS1-6	polythiazide	1.66138	9.10	9.33	0.23	9.31	0.21
MAE					0.13		0.34
σ					0.08		0.43
RMSEP					0.15		0.51

Table S19. Experimental pK_a values and AIBL predictions for 6 thiazide drugs that were calculated using the predictive equation pK_a = 92.95*r(S-N) - 145.10. Bond lengths were extracted from geometries optimized at the B3LYP/6-311G(d,p) level in the neutral state, the anionic state and then once more in the anionic state with the 6-311+G(d,p) basis set. The absolute error (AE), mean absolute error (MAE), standard deviation of error (σ) and Root Mean Squared Error of Prediction (RMSEP) are also given, which show a marked improvement between the results obtained with the neutral molecules compared to predictions made using B3LYP/6-311+G(d,p). All bond lengths for **TS1-7** to **TS1-14** are shown in Tables S11-S14.

		neutral 6-311G(d,p)		neutral 6-311+G(d,p)		anionic 6-311G(d,p)		anionic 6-311+G(d,p)			
ID	Exp pK$_a$	Calc pK$_a$	AE	Calc pK$_a$	AE	Calc pK$_a$	AE	Calc pK$_a$	AE	Marvin	AE
TS1-7	10.70	9.49	1.21	9.87	0.83	10.22	0.48	10.55	0.15	9.07	1.63
TS1-8	9.70	9.41	0.29	9.14	0.56	9.60	0.10	9.93	0.23	9.10	0.60
TS1-9	10.39	9.38	1.01	10.31	0.08	10.11	0.28	10.43	0.04	9.09	1.30
TS1-10	10.30	9.22	1.08	9.62	0.68	9.87	0.43	10.22	0.08	9.53	0.77
TS1-11	10.39	9.51	0.88	9.89	0.50	10.19	0.20	10.54	0.15	9.05	1.34
TS1-12	10.37	9.62	0.75	9.94	0.43	10.21	0.16	10.46	0.09	9.61	0.76
TS1-13	10.60	9.24	1.36	9.60	1.00	9.87	0.73	10.13	0.47	9.62	0.98
TS1-14	10.00	9.64	0.36	9.91	0.09	10.25	0.25	10.42	0.42	9.83	0.17
MAE			0.87		0.52		0.33		0.20		0.94
σ			0.39		0.33		0.57		0.16		0.47
RMSEP			0.94		0.60		0.38		0.25		1.04

Technical Section 4: MAE-based Model Evaluation for Pr-BSA

The range of the 22 training set compounds is 2.8. Roy[1] recommends that his criteria based on MAE evaluation be performed on a test set of at least 10 compounds, and that there must be no ‘systematic error’ in the model predictions. Our set of residuals is indicative of negligible bias. Our Pr-BSA model passes the first of Roy’s criteria (10% of the training set range is 0.28, which is larger than the MAE of 0.16). It also passes the second criterion, given that 20% of the training set range is 0.57, and 0.16 + (3*0.08)=0.40 is indeed smaller than 0.57. Therefore, we may class the Pr-BSA model as good.

Table S20. r^2, RMSEE, leave-one-seventh-out cross validation q^2 values for the linear fit between gas-phase and solvent-phase (obtained via inclusion of the CPCM implicit solvation) bond lengths ***i*-*vi*** vs aqueous pK_a values for a set of 38 4-amino-N-phenylbenzenesulfonamide derivatives. All bond lengths are given Tables S5 and S6.

	Metric	(***i***) C-S	(***ii***) S=O	(***iii***) S=O	(***iv***) S-N	(***v***) N-H	(***vi***) N-C
gas	r^2	0.947	0.449	0.868	0.757	0.023	0.852
	RMSEE	0.258	0.848	0.418	0.567	1.137	0.443
	q^2	0.943	0.417	0.835	0.751	-0.100	0.838
CPCM	r^2	0.959	0.884	0.941	0.747	0.025	0.901
	RMSEE	0.231	0.392	0.280	0.578	1.135	0.362
	q^2	0.953	0.877	0.930	0.738	-0.100	0.899
	Slope (+/-)	+	+	+	-	N/A	+

Table S21. Predictions for both the aniline group and the secondary sulfonamide group present in NHAS compounds **TS2-1** to **TS2-10**. Predictions for the sulfonamide groups were made using C-S equilibrium bond lengths of neutral structures optimized with CPCM solvation, and inserted into the equation: pK_a = 323.08*r(C-S) - 564.02. Predictions for anilines were made using the C-N equilibrium bond lengths, extracted from neutral structures optimized in the gas-phase, and inserted into the equation: pK_a =141.57*r(C-N) - 193.51. All bond lengths for **TS1-1** to **TS2-10** are given in Table S15.

ID	Compound	Exp pK_a Aniline	AIBL-pK_a Predicted	AE	Exp pK_a AP-BSA	AIBL-pK_a Predicted	AE
TS2-1	Sulfadiazine	2.21[1]	2.13	0.08	6.33[2] 6.52[3]	7.00	0.66 0.48
TS2-2	Sulfamerazine	2.27[2]	2.20	0.07	6.71[2] 7.01[4]* 7.06[5]	7.19	0.48 0.18 0.13
TS2-3	Sulfamonomethoxine	1.73[2]	1.76	0.03	6.22[2]	7.06	0.84
TS2-4	Sulfamethoxypyridazine	2.09[2]	1.85	0.24	6.83[2] 7.17[6] 7.20[7]	7.36	0.53 0.19 0.16
TS2-5	Sulfadimethoxine	1.84 - 1.95[9]	1.89	0.01	5.83[2] 6.17[6] 6.70[8]	7.32	1.49 1.15 0.62
TS2-6	5-phenyl-4-sulfa-pyrimidine	-	1.96	-	6.04[10]	6.55	0.51
TS2-7	Sulfamethoxydiazine	-	2.26	-	6.63[10] 7.00[7]	7.26	0.63 0.26
TS2-8	Sulfasomidine	-	1.74	-	7.40[10]	7.28	0.12
TS2-9	Sulfamethazine	2.65[12]	2.26	0.39	7.37[11] 7.40[7]	7.46	0.09 0.06
TS2-10	Sulfapyridine	-	1.98	-	8.43[11]	8.22	0.21
	min AE			0.14			0.34
	max AE						0.56

*Measured at 23 °C. There are no values reported for the aniline group in the case of compounds **TS2-6**, **TS2-7**, **TS2-8** and **TS2-10**.

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[1] Stober, H.; DeWitte, W., Sulfadiazine. In *Analytical Profilcs of Drug Subrtances*, K, F., Ed. Academic Press In: New York, 1982; Vol. 11, pp 523-551.

[2] Şanli, S.; Altun, Y.; Şanli, N.; Alsancak, G.; Beltran, J. L., Solvent Effects on pKa values of Some Substituted Sulfonamides in Acetonitrile-Water Binary Mixtures by the UV-Spectroscopy Method. *J. Chem. Eng. Data* **2009,** *54*, 3014-3021.

[3] Rieder, J., Physicalisch-chemische und biologische untersuchungen an sulfonamiden. *Arzneim-Forsch.* **1963,** *13*, 81-88.

[4] Brent, D. A.; Sabatka, J. J.; Minick, J.; Henry, D. W., A simplified high-pressure liquid chromatography method for determining lipophilicity for structure-activity relationships. *J. Med. Chem.* **1983,** *26*, 1014-1020.

[5] Bell, P. H.; Roblin, R. O., Studies in Chemotherapy. VII. A Theory of the Relation of Structure to Activity of Sulfanilamide Type Compounds. *J. Am. Chem. Soc.* **1942,** *64*, 2905-2917.

[6] Yoshioka, M.; Hamamoto, K.; Kubota, T., Dissociation Constants of Sulfanilamides and Substituent Effect on the Constant. *YUKUGAKU ZASSHI* **1963,** *84*, 90-93.

[7] Soriano-Correa, C.; Barrientos-Salcedo, C.; Francisco-Márquez, M.; Sainz-Diaz, C. I., Computational Study of substituent effects on the acidity, toxicity and chemical reactivity of bacteriostatic sulfonamides. *J. Mol. Graph. Model.* **2018,** *81* (116-124).

[8] James, M. O.; Kleinow, K. M., Trophic Transfer of Chemicals in the Aquatic Environment. In *Aquatic Toxicology: Molecular, Biochemical, and Cellular Perspectives*, D. C. Malins; Ostrander, G. K., Eds. CRC Press: Boca Raton, FL, 2018; p 6.

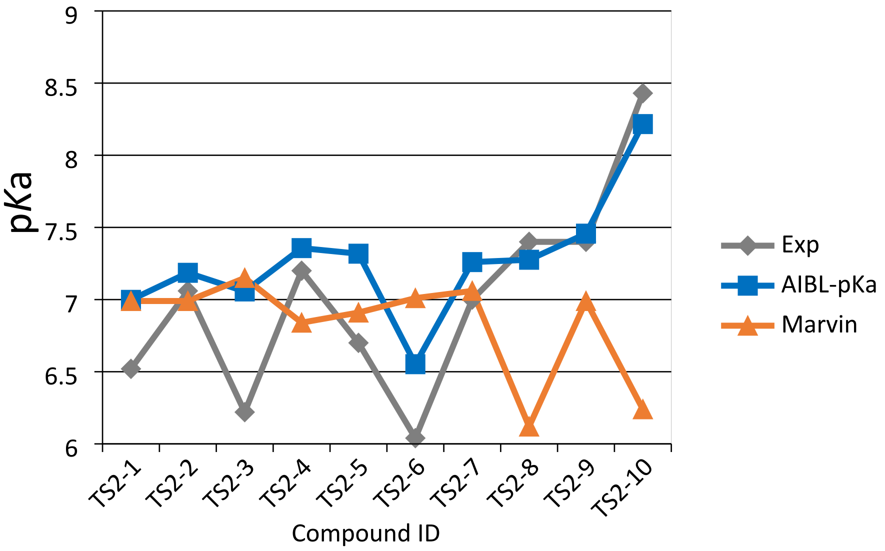
[9] Shoghi, E. F., Elisabet; Bosch, Elisabeth; Rafols, Clara, Solubility–pH profiles of some acidic, basic and amphoteric drugs. *European Journal of Pharmaceutical Sciences* **2013,** *48*, 291 - 300.

[10] Cammarata, A.; Allen , R. C., Observations Concerning the Correlation of In Vitro Sulfonamide Activity with pKa and the Hammett Values. *J. Pharm. Sci.* **1967,** *56*, 640-642.

[11] Bell, P. H.; Roblin, R. O., Studies in Chemotherapy. VII. A Theory of the Relation of Structure to Activity of Sulfanilamide Type Compounds. *J. Am. Chem. Soc.* **1942,** *64*, 2905-2917.

[12] Papastephanou, C.; Frantz, M., Sulfamethazine. In *Analytical Profiles of Drug Sunstances*, Florey, K., Ed. Academic Press, Inc: San Diego, California, 1978; Vol. 7, pp 401–422.

Figure S3. Plot showing relative pK_a values for the series **TS2-1** to **TS2-10.** Marvin's overall performance in terms of mean absolute error evaluation is below 1 pK_a unit. AIBL-pK_a performs marginally better in terms predicting the overall trend in the magnitude of pK_a values across the series.



Technical Section 5: MAE-based Model Evaluation for AP-BSA

The pK_a range of the 39 training set compounds is 4.52. As removal of an outlier would mean that the test set would contain less than 10 data points, this was not performed in order to maximize statistical reliability. The model passes the first of Roy's criteria (10% of the training set range is 0.45, which is larger than the MAE of 0.34). However, it does not pass the second criterion, given that 20% of the training set range is 0.90, and 0.34 + (3*0.23) = 1.03 is larger than 0.90. There also appears to be is also some systematic bias, as 8/10 of the predictions are higher than the reported experimental values.

Figure S4. The optimized geometry of N$_1$-methylphenylsulfonamide. This is the most stable conformation of the phenylsulfonylurea fragment used as the 3D skeleton for all sulfonylureas of the training set, listed in **Table S12.** There appears to be an intramolecular hydrogen bonding interaction between an oxygen atom and the N-H moiety of the urea group.

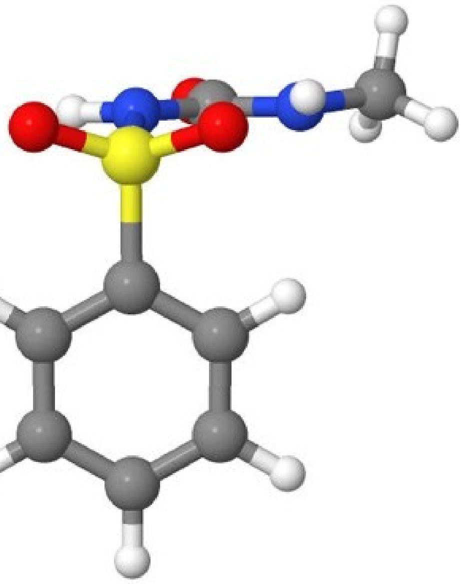


Figure S5. Plot showing relative pK_a values for the series **SU-1** to **SU-6.** AIBL-pK_a performs very well in terms prediction accuracy and in predicting the overall trend in the magnitude of pK_a values across the series.

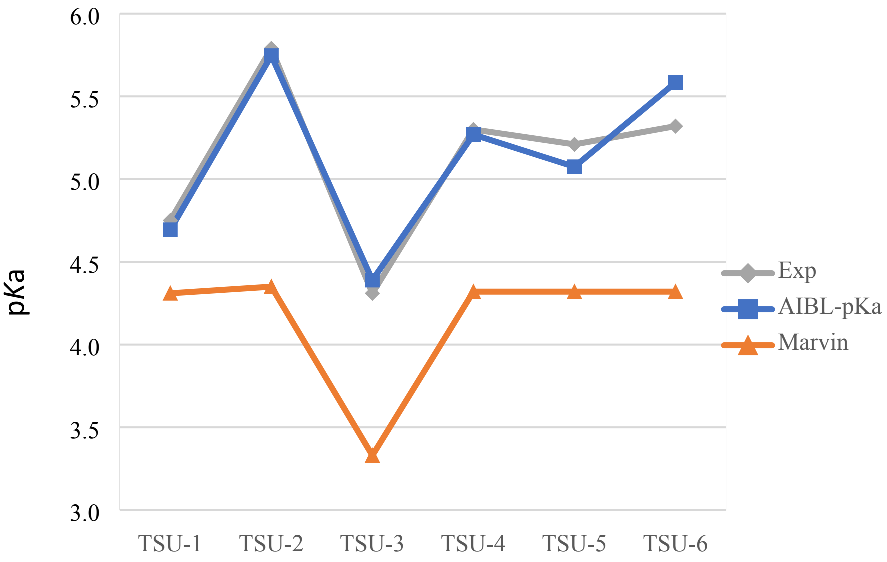


Table S22. Statistics for linear regression of bond lengths **A**-**I** *vs* pK_a for compounds **SU-1** to **SU-30**.

	Metric	C-S (A)	S=O (B)	S=O (C)	S-N (D)	N-H (E)	N-C (F)	C=O (G)	C-N (H)	N-H (I)
gas	r^2	0.78	0.63	0.19	0.86	0.01	0.76	0.12	0.01	0.00
	RMSEE	0.25	0.32	0.47	0.19	0.52	0.26	0.50	0.53	-
	q^2	0.76	0.62	0.17	0.86	0.01	0.74	0.10	0.00	-
CPCM	r^2	0.78	0.02	0.29	0.93	0.02	0.78	0.07	0.01	0.01
	RMSEE	0.25	0.52	0.44	0.14	0.52	0.25	0.51	0.53	0.53
	q^2	0.77	-0.09	0.27	0.93	-0.03	0.76	0.02	-0.04	-0.08

Table S23. Exchange-correlation energy V_{xc}(A,B) (top) and Coulombic interaction energies V_{cl}(A,B) (bottom) between two topological atoms (A and B) corresponding to bonded atoms of the sulfonamide ionizable group. Values obtained using the program AIMAll (v.17) are shown in kJ mol^{-1}.

V_{XC}	ID	C-S	S=O	S=O	S-N	N-H	N-H	pK_a
S1-9	4-NO_2	-322.7	-444.4	-444.7	-329.2	-329.4	-329.4	9.14
S1-1	unsub	-326.8	-443.8	-443.9	-328.7	-331.9	-331.9	10.10
S1-4	4-$NHCH_3$	-336.9	-442.7	-442.6	-328.1	-333.9	-334.0	11.00
	r^2	0.93	0.97	0.97	1.00	1.00	1.00	
	slope(+/-)	-	+	+	+	-	-	

V_{Cl}	ID	C-S	S=O	S=O	S-N	N-H	N-H	pK_a
S1-9	4-NO_2	-110.6	-2194.9	-2194.6	-1548.3	-228.2	-228.2	9.14
S1-1	unsub	-110.5	-2172.4	-2172.2	-1454.7	-216.2	-216.2	10.10
S1-4	4-$NHCH_3$	-114.1	-2156.1	-2155.8	-1377.4	-206.3	-206.2	11.00
	r^2	0.70	0.99	1.00	1.00	1.00	1.00	
	slope(+/-)	-	+	+	+	+	+	

Table S24. Statistics for regression of bond lengths **A**-**I** *vs* pK_a for compounds **SU-1** to **SU-18**, all of which possess an *n*-butyl group.

Metric	**C-S (A)**	**S=O (B)**	**S=O (C)**	**S-N (D)**	**N-H (E)**	**N-C (F)**	**C=O (G)**	**C-N (H)**	**N-H (I)**
r^2	0.81	0.85	0.90	0.96	0.89	0.95	0.96	0.81	0.64
slope (+/-)	-	+	+	+	-	-	+	+	+