Table S1 The tests using the proton exchange scheme via higher level model chemistries for solvation free energies.

Tests	Model Chemistry	Results
3[i]	B3LYP/6-311++G(3df,3pd)/CPCM(UFF radii, water as solvent)//B3LYP/6-31+G(d)	There are no significant improvements compared to Test 2.
4	B971/6-311++G(3df,3pd)/CPCM(UFF radii, water as solvent)//B3LYP/6-31+G(d)	There are no significant improvements compared to Test 2.
5	CBS-4M/CPCM(UFF radii, water as solvent)//B3LYP/6-31+G(d)	Some of the compounds could not be modelled using the Windows Gaussian 09 system owing to computer resource limitations.
6	CBS-4Q/CPCM(UFF radii, water as solvent)//B3LYP/6-31+G(d)	Some of the compounds could not be modelled using the Windows Gaussian 09 system owing to computer resource limitations.
7	Gaussian-4/CPCM(UFF radii, water as solvent)//B3LYP/6-31+G(d)	Some of the compounds could not be modelled using the Windows Gaussian 09 system owing to computer resource limitations.

[i] B3LYP/6-311++G(3df,3pd)/CPCM(UFF radii, water as solvent)//B3LYP/6-31+G(d) means that the single-point energy calculation at B3LYP/6-311++G(3df,3pd)/CPCM(UFF radii, water as solvent) based on the optimised structure at B3LYP/6-31+G(d) in vacuum.

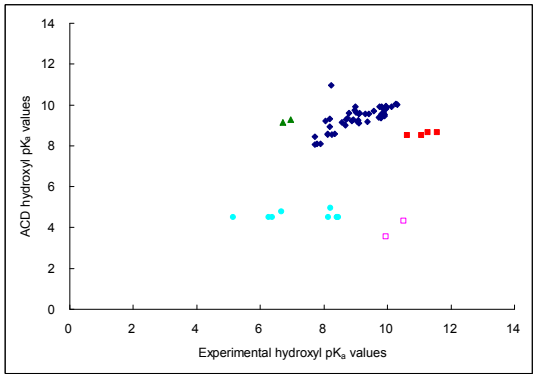

Fig. S1 ACD predictions for hydroxyl pK_a values.

▲ 2-(piperidin-1-ylmethyl)-HPOs.

■ 2-fluoro-HPOs.

● 2-amido-HPOs.

□ 2,6-difluoro-HPOs.

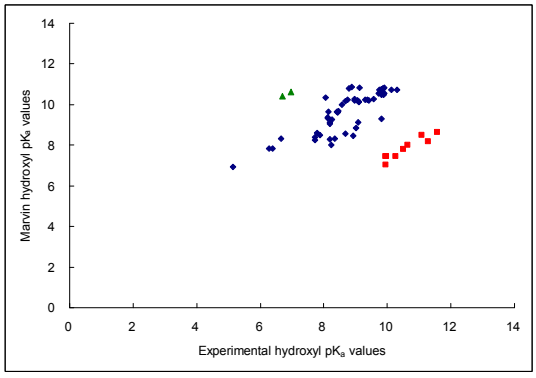

Fig. S2 Marvin predictions for hydroxyl pK_a values.

▲ 2-(piperidin-1-ylmethyl)-HPOs.

■ 2-fluoro-HPOs.