Comment on "Towards rational molecular design: derivation of property guidelines for reduced acute aquatic toxicity [Voutchkova et al., *Green Chem.*, 2011, 13, 2373]"

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In their article, Voutchkova et al.[1] "derive property guidelines for the design of chemicals with reduced acute aquatic toxicity to multiple species" using properties such as "chemical solubilities, size, shape and molecular orbital energies." The authors claim to use a dataset of "865 neutral organic compounds," and then proceed to "predict 36 physicochemical properties" such as "molecular weight, number of freely rotatable bonds, partition coefficients for octanol/water ($logP_{o/w}$), water/gas ($logP_{w/g}$), and octanol/gas ($logP_{o/g}$), aqueous solubility, solvent accessible surface area (SASA), polar surface area (PSA), globularity, molecular volume, number of H-bonds, and others" using QikProp. Furthermore, Voutchkova et al.[1] also state that "HOMO and LUMO energy values for all compounds were calculated using the AM1 semiempirical molecular orbital method on fully optimized geometries."

Voutchkova et al.[1] do not list all 865 purportedly "neutral organic compounds" that they conducted their molecular modeling exercises on, but their supporting information appears to provide a small subset of CAS # molecular identifiers for some of the compounds they considered. A large number of the compounds examined by these authors are not "neutral organic compounds" as the authors claim, but rather have basic and/or acidic ionizable functionalities (such as aliphatic and aromatic amines, phenols, etc.) with pK_a values such that these molecules would be substantially or, in many cases, effectively entirely ionized in aqueous solutions at the pH values relevant to the aquatic toxicity endpoints being modeled against. For example, in the supporting information of Voutchkova et al.,[1] the small subset of CAS # identifiers they list yields the following compounds with toxicologically and environmentally relevant experimental or estimated pK_a values: hexamethylenetetramine (CAS 100970), 6.2;[2] 5,5-dimethyl-2,4-imidazolidinedione (CAS 77714), 8.88;[3] 2,2',2"-nitrilotrisethanol (CAS 102716), 7.76-7.92;[4] 1-piperazineethanol (CAS 103764), 9.57;[3] 2,2'-iminobisethanol (CAS 111422), 9.37;[3] 1,4-bis(3-aminopropyl)piperazine (CAS 7209383), 10.17;[3] 4-morpholine ethanol (CAS 622402), 6.91;[3] 1-amino-2-propanol (CAS 78966), 9.81;[3] 1-methylpiperazine (CAS 109013), 9.14;[5] 2-methylpiperazine (CAS 109079), 9.57;[5] N-(2-aminoethyl)piperazine (CAS 140318), 9.89;[3] 2-aminoethanol (CAS 141435), 9.62;[6] 2-(diethylamino)ethanol (CAS 100378), 9.87;[7] triethylenediamine (CAS 280579), 8.92;[8] 2-(ethylamino)ethanol (CAS 110736), 10.24;[3] 1,3-propanediamine (CAS 109762), 10.6;[9] 5-chlor-2-pyridinol (CAS 4214793), 9.51;[3] N-(3-hydroxyphenyl)acetamide (CAS 621421), 9.36;[3] 1,2-propanediamine (CAS 78900), 9.82;[10] 5,6-dimethyl-1,2,4-triazin-3-amine (CAS 17584122), 4.90;[3] 2-methylpyridine (CAS 109068), 6.00;[10] N-ethylethanamine (CAS 109897), 10.85;[3] N-(4-hydroxyphenyl)acetamide (CAS 103902), 9.48;[3] 2,2'-(phenylimino)bisethanol (CAS 120070), 4.36;[3] N,N-bis(2,2-diethoxyethyl)methylamine (CAS 6948863), 6.09;[3] 2-chlor-3-pyridinol (CAS 6636788), 6.97;[3] 1,1-dimethylhydrazine (CAS 57147), 7.21;[11] 2-hydroxybenzaldehyde (CAS 90028), 8.28;[12] 1-octanamine (CAS 111864), 10.65;[10] 1-nonanamine (CAS 112209), 10.64;[10] 2-octanamine (CAS 693163), 10.37;[3] and 4-hydroxy-3,5-diiodobenzonitrile (CAS 1689834), 3.9.[13]

Because a substantial proportion of the compounds that Voutchkova et al.[1] do provide molecular identifiers for in their supporting information are not "neutral organic compounds" as the authors claim, one must reasonably conclude that the true set of ionizable compounds among the total dataset of 865 molecules is likely larger than presented herein. Properties such as the molecular weight, partitioning coefficients between various matrices (where at least one of the matrices is water), aqueous solubility, solvent accessible surface area, polar surface area, molecular volume, number of H-bonds, HOMO/LUMO energies, etc., are all pH dependent (i.e., speciation dependent) for ionizable compounds. Since Voutchkova et al.[1] appear to have conducted all their molecular modeling efforts on the neutral forms of all compounds, the authors appear to have obtained molecular descriptors for speciations of the compounds that are not relevant for the toxicological properties being modeled against.

Notes and references

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