Testing a Computation Workflow for Drug Design: pKa and logP from the SAMPL7 Blind Challenge

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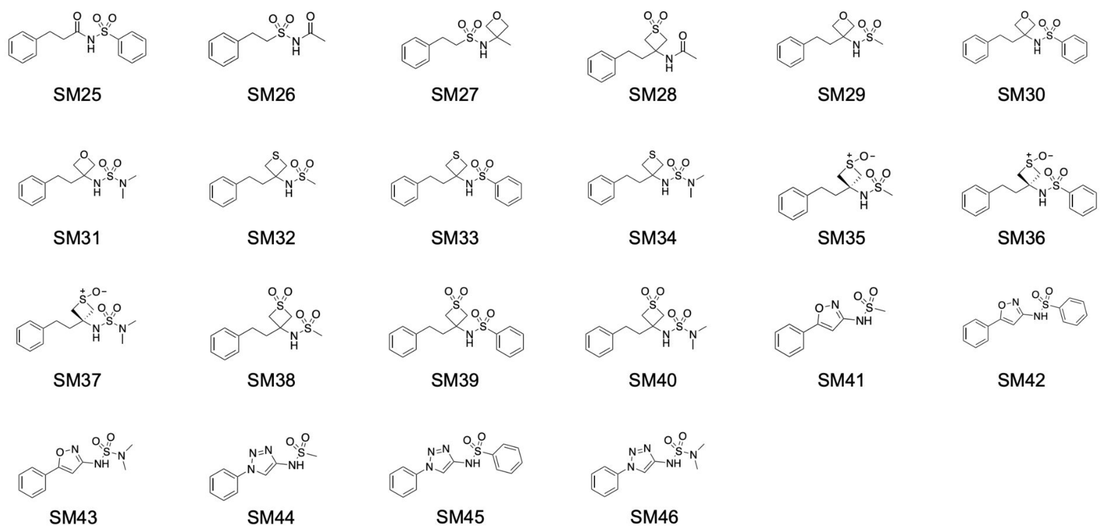
Introduction

Being able to produce accurate predictions of pKa for various molecules is an ongoing effort in computational chemistry. Drug companies and industries are constantly seeking accurate predictions of pKa and lipophilicity for molecules that are possible drug candidates. Accurate predictions of these values means that time, money, and effort won't be wasted synthesizing molecules that aren't going to be effective drugs. The Janesko group has developed a workflow that uses CREST for conformational analysis and (M11plus/def2TZVP/SMD) DFT calculations to identify a molecule's pKa. The DFT calculations process and refine the relative energies of the stable conformations.

Purpose

The goal of this project is to benchmark the current workflow against the Statistical Assessment of Modeling of Proteins and Ligands 7 (SAMPL7) challenge, which will test the workflow's outperformance of the best quantum-mechanical methods from 2021. The SAMPL challenge is a competition that asks participants to predict the properties of molecules that have never been synthesized. These molecules will then be created in labs and their properties will be accurately tested. Comparison of the competitor's predicted properties to the true values measured will assess the accuracy of the competitor's predictions. If the prediction of pKa using the current workflow is accurate based off the benchmark against the SAMPL7 challenge, then the workflow could be entered into the next SAMPL Blind challenge.

SAMPL 7 Blind Challenge Molecules



Bergazin TD, Tielker N, Zhang Y, Mao J, Gunner MR, francisco karol, et al. Evaluation of Log P, pKa and Log D Predictions from the SAMPL7 Blind Challenge. *ChemRxiv. 2021*; doi:10.26434/chemrxiv.14461962.v1

Results

Conclusion

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References

Casey J. Patterson-Gardner, Gretchen M. Pavelich, April T. Cannon, Alexander J. Menke, and Eric E. Simanek, (2023). Adaptation of Empirical Methods to Predict the LogD of Triazine Macrocycles. *ACS Medicinal Chemistry Letters 2023 14 (10)*, 1378-1382. DOI: 10.1021/acsmedchemlett.3c00290

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