Contribution ID : **124** Type : **Oral Presentation**

Automated atropisomer predictions via a web app

Atropisomerism is a form of stereoisomerism caused by restricted rotation about hindered single bonds.1,2 Atropisomerism plays a critical role in pharmaceutical drug development, where the stereochemical properties of a molecule can significantly impact its function. Approximately 30% of recently approved FDA drugs possess potential atropisomeric axes,3 highlighting the significance of accurately predicting and characterizing these features.

We have developed an automated workflow that efficiently identifies bonds within molecules that could lead to atropisomerism and calculates their rotational barrier, atropisomer class, and half-life of interconversion via a thorough conformational searching and optimization procedure using density functional theory (DFT). Our workflow is benchmarked against an experimental dataset of 155 known rotational barriers and demonstrates a high degree of accuracy, achieving a correlation coefficient (r2) of 0.97 and a root mean square error (RMSE) of 1.6 kcal/mol. To facilitate user interaction and data exploration, we have developed a web application with streamlit (python) that allows non-experts to submit atropisomer screens, view results, and explore the effects of temperature on the half-life of interconversion, offering valuable insights into the dynamic behavior of atropisomers under different conditions. Additionally, this web application is part of a larger platform aimed at democratizing internal reactivity prediction workflows and computational databasing.

This work has a significant impact on pharmaceutical drug development, allowing for the rapid and detailed stereochemical classification of compounds at an early stage of development. By providing highly accurate insights into atropisomeric behaviours, our approach aids in the effective management of these compounds, boosting the efficacy of drug discovery and ensuring a safer therapeutic profile for novel pharmaceuticals.

[1] LaPlante, S. R., Fader, L. D., Fandrick, K. R., Fandrick, D. R., Hucke, O., Kemper, R., Miller, S. P. F., & Edwards, P. J. J. Med. Chem. 2022, 54(20), 7005-7022. [2] LaPlante, S. R., Edwards, P. J., Fader, L. D., Jakalian, A., & Hucke, O. ChemMedChem. 2011, 6(3), 505-513. [3] Basilaia, M., Chen, M. H., Secka, J., & Gustafson, J. L. Acc. Chem. Res. 2022, 55(12), 2904-2919.

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