Poster 6

Tri-Cyclic Sulfonamides in the Spotlight: Synthetic Strategies, Molecular Docking, and Bioactivity

Mohammed Aber[1,3], Khaled Elokely[2], Wayne Childers[3], Magid Abou-Gharbia[3], Zine Regainia[1]

[1]Laboratory of Aquatic and Terrestrial Ecosystem, School of Technology and Science, Chemistry Department, University of Souk Ahras, Algeria
[2] Division of Pharmaceutical Sciences, School of Pharmacy, University of Wyoming, USA
[3] Moulder Center for Drug Discovery Research, Department of Pharmaceutical Sciences, School of Pharmacy, Temple University, USA

We present a comprehensive study on the synthesis and evaluation of two novel tri-ring cyclosulfonamide analogues, one featuring a flexible 7-membered ring and the other a rigid 6-membered ring, to explore how ring size influences binding interactions with biological targets. Advanced computational modeling, utilizing MM/GBSA calculations, was employed to assess the interactions of these compounds with various biological targets. The 7-membered ring analogue consistently demonstrated superior binding affinities, with average binding free energies ranging from -25.84 to -34.29 kcal/mol across different targets, reflecting its conformational flexibility and ability to adapt to diverse binding pockets. In contrast, the 6-membered ring analogue exhibited variable performance, achieving a favorable average of -18.30 kcal/mol against one target but weaker or unfavorable binding (up to 9.14 kcal/mol) elsewhere, underscoring the limitations imposed by its structural rigidity.

To further evaluate these compounds, we conducted a series of biological assays against relevant bacterial strains. These experiments aimed to probe the pharmacological potential of the analogues, complementing the computational findings. This study highlights distinct structure-activity relationships, with the 7-membered ring's flexibility enhancing binding efficiency and the 6-membered ring's rigidity constraining adaptability. By elucidating the role of ring size in molecular interactions, this work advances our understanding of cyclosulfonamide derivatives in drug design and provides a foundation for future optimization of ring-based scaffolds in medicinal chemistry.