

ABSTRACT

The discovery of new small-molecule therapeutics remains one of the major challenges in modern medicine. Although advances in medicinal chemistry have expanded the number of biologically active compounds, only a small fraction of accessible chemical space has been explored. Traditional lead optimization is highly effective within individual analogue series but provides only limited insight into the broader structure–activity landscape. As a result, many promising regions of chemical space remain unexplored.

Among privileged heterocyclic scaffolds, 4-thiazolidinones have attracted considerable attention because of their broad biological activity and exceptional structural versatility. Hundreds of derivatives have been reported with anticancer, antibacterial and other pharmacological properties. However, knowledge of their structure–activity relationship remains fragmented across independent studies. This limits the identification of general design principles and hinders the rational exploration of new regions of thiazolidinone chemical space.

The aim of this doctoral thesis was to develop an integrated framework for the discovery and optimization of biologically active 4-thiazolidinone derivatives by combining medicinal chemistry with modern computational approaches. Local structure-activity relationship discontinuities and activity cliffs were treated as sources of design information and ultimately incorporated into *de novo* molecular generation.

The work combined compound design, organic synthesis, biological evaluation and computational modelling. Novel 4-thiazolidinone derivatives were synthesized and evaluated for anticancer and antibacterial activity, leading to the identification of promising lead compounds. Molecular docking and molecular dynamics simulations were used to investigate ligand–target interactions and support the interpretation of experimental results. Quantitative structure–activity relationship (QSAR) models were developed to characterize structure–activity relationships and predict biological activity across thiazolidinone chemical space.

The thesis then extended beyond conventional SAR analysis. Activity cliffs were investigated as local regions of the structure–activity landscape where small structural modifications produce large changes in biological activity. These regions represent highly informative molecular events but also remain one of the greatest challenges for modern machine learning models. Rather than treating activity cliffs as prediction errors, this work explored their

potential as sources of medicinal chemistry knowledge. Their role was analyzed across the AI pipeline, from molecular representation and model evaluation to generative molecular design.

Building on these findings, an activity cliff-informed *de novo* design strategy was developed for the rational generation of novel 4-thiazolidinone derivatives. The proposed framework integrates experimental data, predictive modelling and local SAR knowledge to prioritize compounds with improved biological potential. This work demonstrates that combining medicinal chemistry with artificial intelligence enables a more efficient exploration of thiazolidinone chemical space than conventional analogue-based optimization alone. More broadly, it highlights activity cliffs as actionable design principles for next generation drug discovery.

Keywords: 4-thiazolidinones; Medicinal Chemistry; Activity Cliffs; Artificial Intelligence

A handwritten signature in blue ink, appearing to read 'James S. ...', is positioned below the keywords section.