

Developing new chemical tools to understand the biology of fatty acid binding protein 4

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Abstract

Fatty acid-binding proteins (FABPs) are a family of small, soluble proteins involved in diverse physiological processes, including lipid transport and cellular signalling. FABPs have been implicated in diseases associated with disrupted lipid metabolism. Among them, FABP4 is highly expressed in adipocytes and macrophages. Genetic studies have shown that loss of FABP4 function can ameliorate metabolic and inflammatory conditions such as diabetes and atherosclerosis, highlighting FABP4 as a potential therapeutic target. Despite this, the molecular mechanisms through which FABP4 contributes to these disease pathways are still not well understood. Existing high-affinity FABP4 ligands often suffer from poor physicochemical properties, including excessive lipophilicity, limited aqueous solubility and non-specific binding, restricting their utility as chemical probes.

This research focuses on the development of selective, high-affinity FABP4 ligands with improved drug-like properties using an integrated fragment- and structure-based drug discovery approach. Fragment screening identified promising chemical starting points, which were subsequently optimised through iterative compound design and synthesis, incorporating microscale parallel chemistry. Binding kinetics were assessed using off-rate screening by surface plasmon resonance (SPR), enabling rapid prioritisation of promising compounds for further investigation. Prioritised compounds were resynthesised and further characterised using complementary biophysical and structural techniques, including SPR, isothermal titration calorimetry, NMR spectroscopy and X-ray crystallography, to validate binding and guide optimisation. This approach led to the identification of several ligands with improved binding affinity, including submicromolar binders. Selected ligands were also evaluated in cellular assays as an initial assessment of their activity in a cellular context. Overall, this work has generated diverse FABP4 ligand series, including compounds with improved binding affinity and selectivity, and provides a foundation for the continued development of chemical tools to investigate FABP4 biology.

Biography

Imesha Hettige obtained a BSc (Honours) in Chemistry at the University of Sri Jayewardenepura and a Graduateship in Chemistry at the Institute of Chemistry Ceylon, Sri Lanka. In 2022, she commenced her PhD in Medicinal Chemistry at the Monash Institute of Pharmaceutical Sciences (MIPS), Monash University, under the supervision of Prof. Martin Scanlon, A/Prof. Ben Capuano and Dr Indu Chandrashekar. Her research focuses on developing new chemical tools to investigate the biology of fatty acid-binding protein 4 (FABP4), integrating fragment- and structure-based drug design, medicinal chemistry and biophysical approaches. Her work has been recognised through several poster presentation awards, including a Best Poster Prize at the 2025 EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry in Porto, Portugal, which featured over 440 poster presentations, and Best Poster Presentation at Fragment-Based Drug Discovery Down Under 2024.

