

# SELECTIVE INHIBITION OF ATP-SENSITIVE POTASSIUM CHANNELS: ADVANCES IN TARGETING KIR6.1/SUR2B FOR THERAPEUTIC APPLICATIONS

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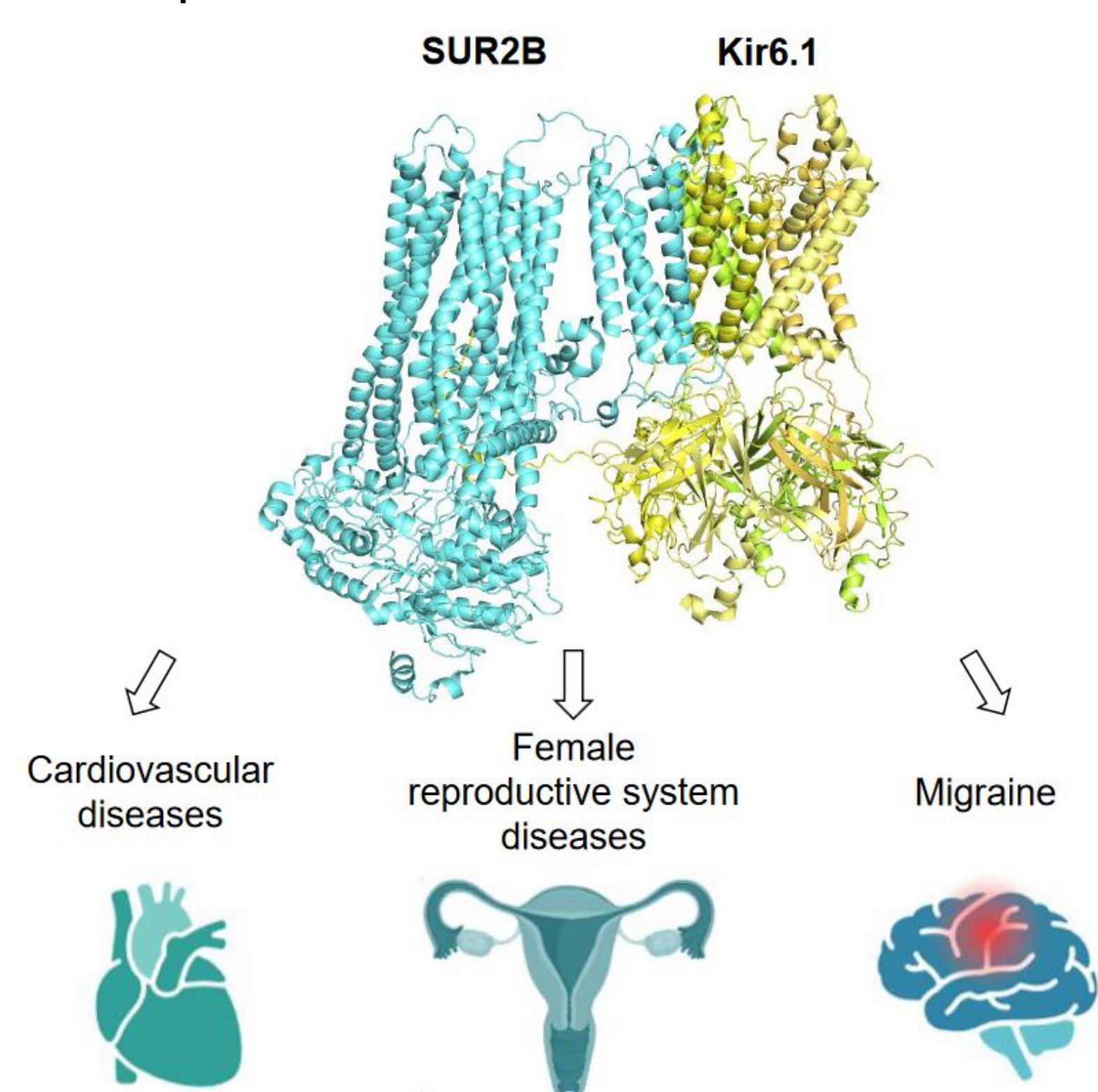
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## Introduction

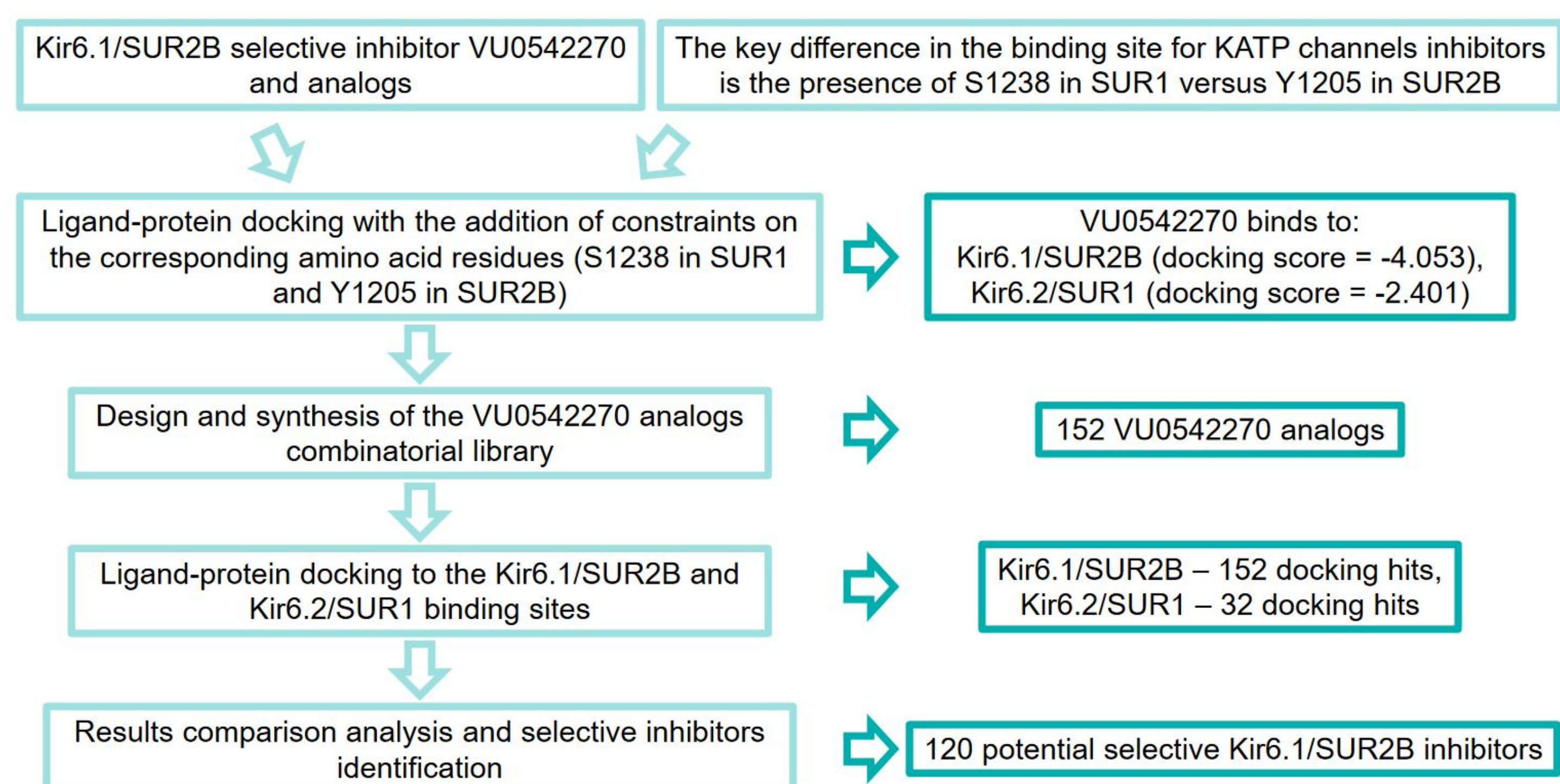
ATP-sensitive potassium (KATP) channels link cellular energy status to membrane excitability in various cell types, regulating numerous physiological processes. These channels consist of eight subunits: four pore-forming potassium inwardly rectifying (Kir) subunits (Kir6.1 or Kir6.2) and four regulatory sulfonylurea receptor (SUR) subunits (SUR1, SUR2A, or SUR2B).

While Kir6.1 and SUR2 subunits are found in multiple tissues and contribute to different physiological functions, Kir6.1/SUR2B channels are primarily expressed in vascular smooth muscle cells, where they regulate vascular tone, blood flow, and blood pressure.

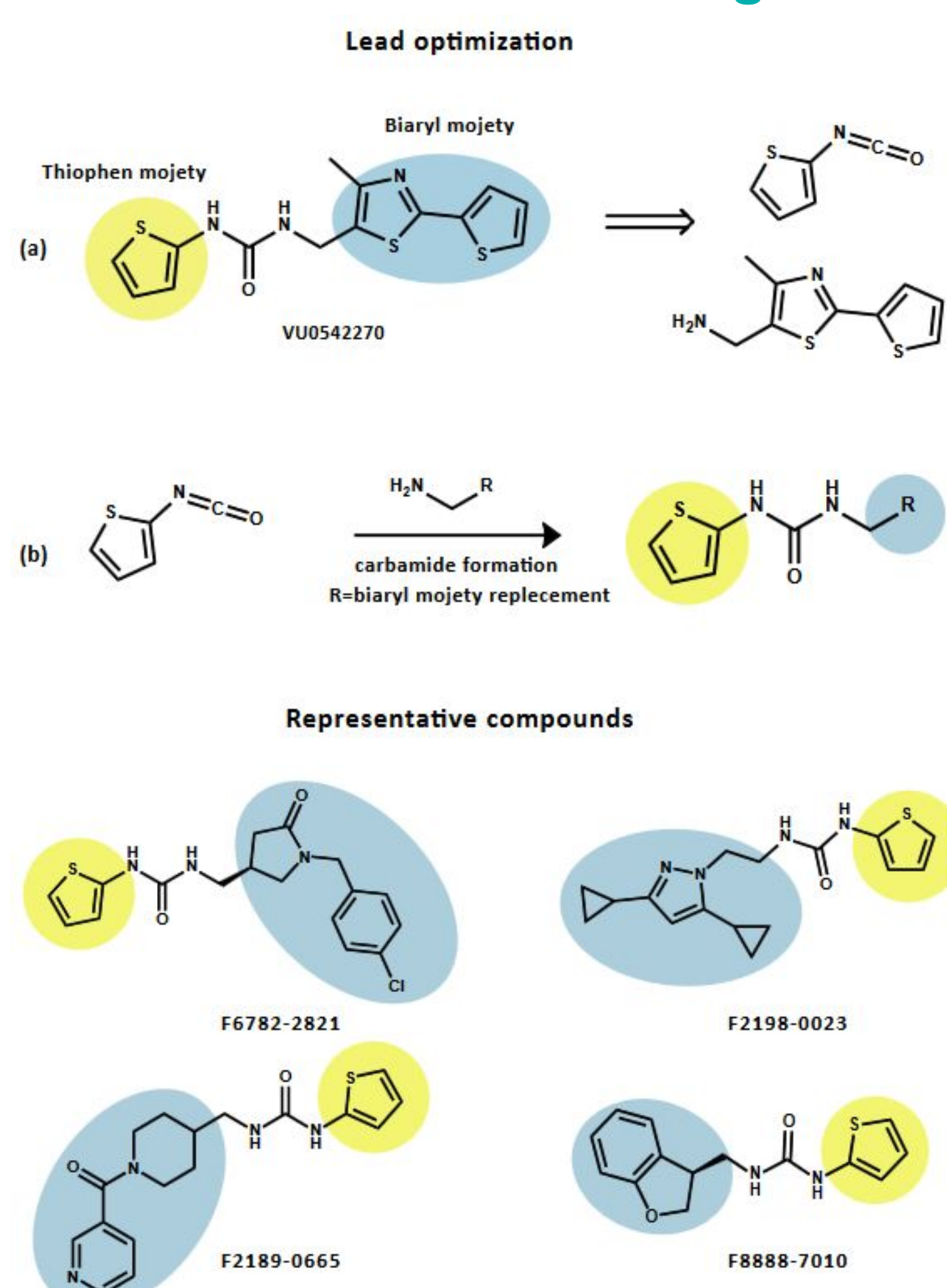


Due to their critical role in cardiovascular function, **Kir6.1/SUR2B channels** are a promising therapeutic target for **cardiovascular disease** drug discovery. Additionally, emerging evidence suggests their potential in treating **Cantú syndrome, migraines, and disorders of the female reproductive system.**

## Methodology and Result



## VU0542270 Analog Combinatorial Library: Design and Synthesis



To identify **selective Kir6.1/SUR2B inhibitors**, we designed a combinatorial library of **VU0542270 analogs**. Structural modifications on the **left-side urea linkage** were well-tolerated, allowing variations without loss of activity. However, modifications to the **right-side thiophene group** often led to inactivity, except when replaced by other aryl groups, which preserved activity.

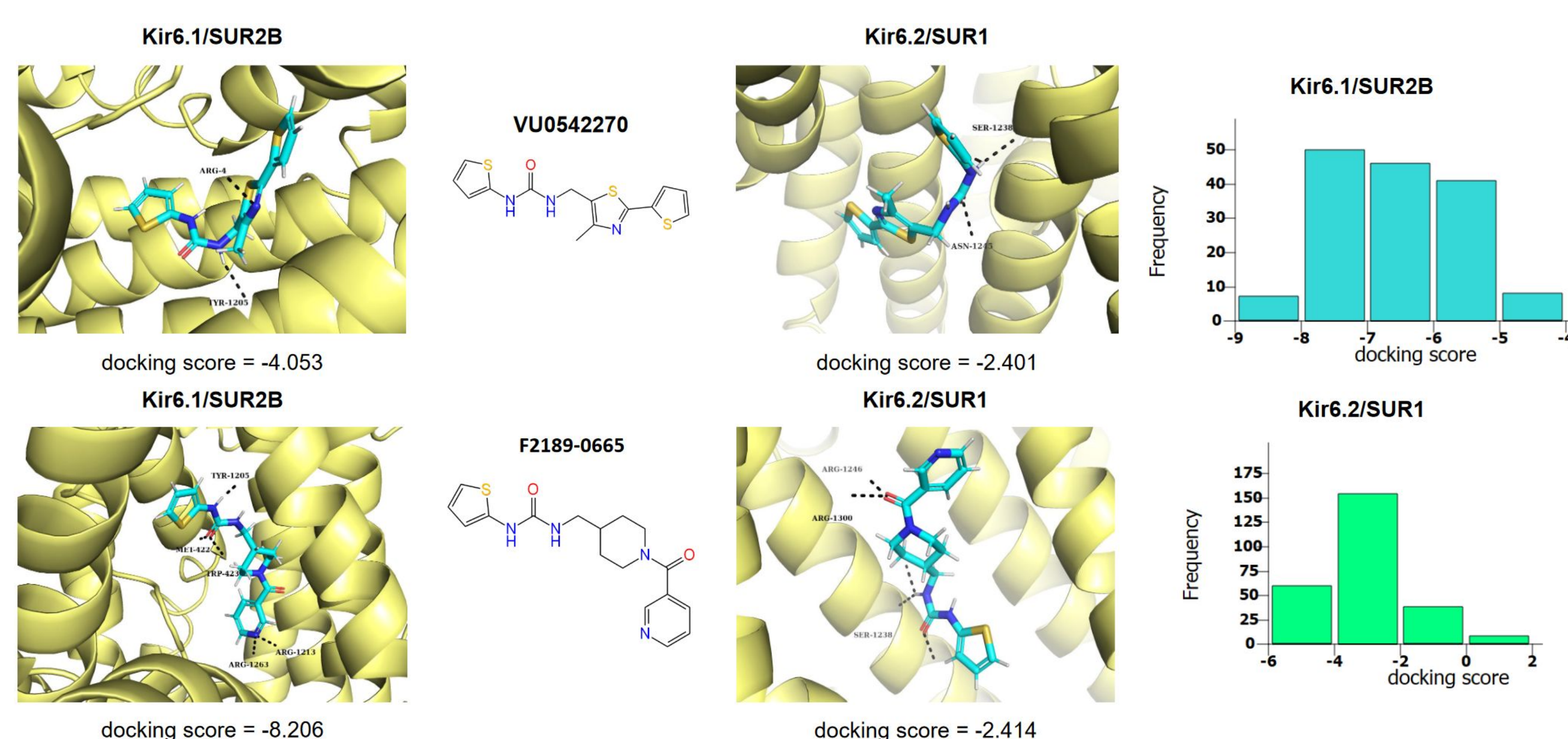
Our library design prioritized **left-side modifications** while maintaining key right-side features, using commercially available **2-thienyl isocyanate** and in-stock **aromatic amines** as core building blocks.

## Ligand-Protein Docking and Selective Inhibitor Identification

Docking studies with Kir6.1/SUR2B showed that all **152 VU0542270 analogs** had docking scores better than -4.105, outperforming the reference compound. In contrast, only 32 compounds bound to Kir6.2/SUR1 with docking scores below -4. To ensure selectivity, these 32 compounds were excluded from further analysis.

Next, we assessed the **QikProp properties and ADMET descriptors** of the reference inhibitor VU0542270, confirming compliance with all recommended parameters.

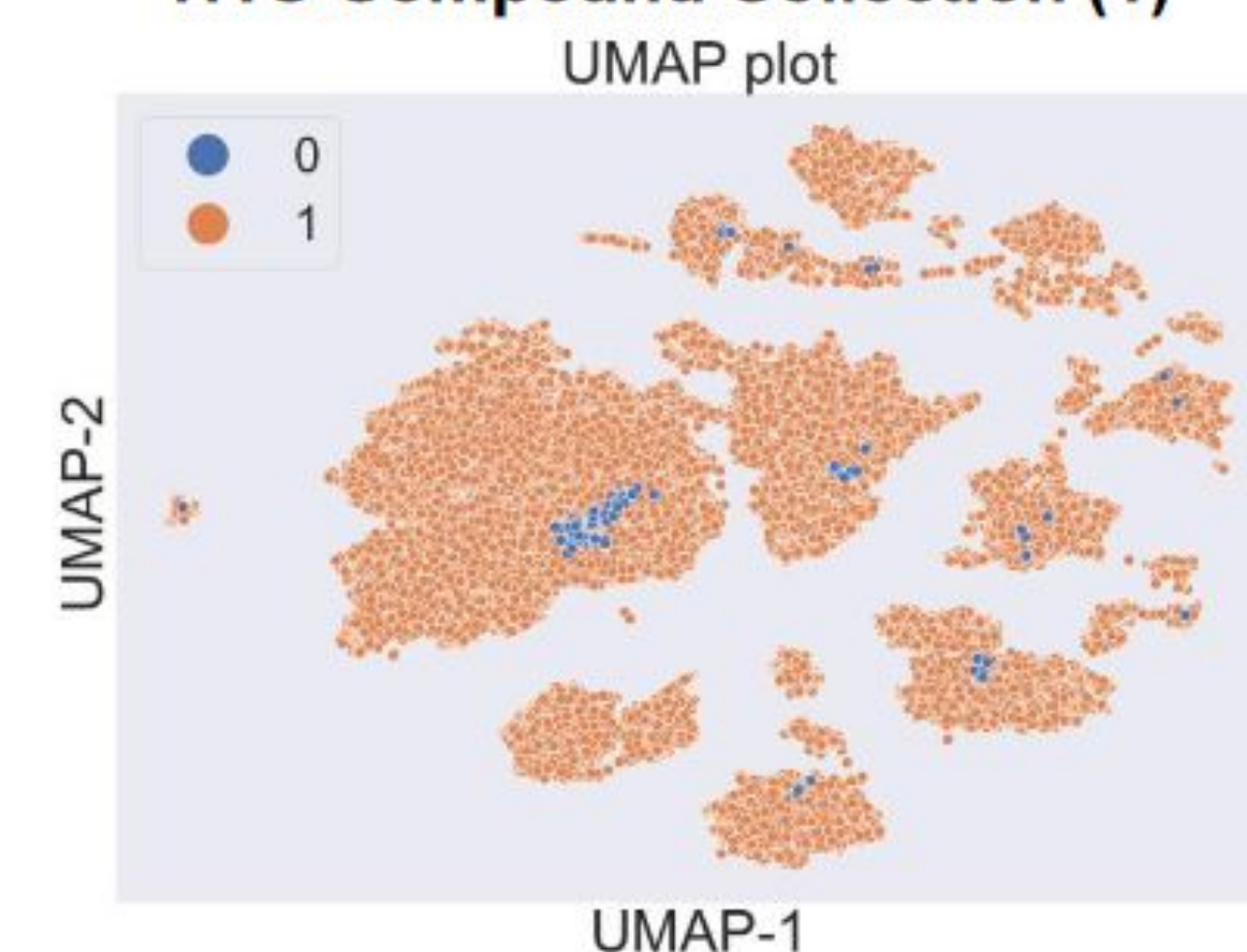
After evaluating **120 remaining potential selective Kir6.1/SUR2B inhibitors** synthesized by us, it was established that **70 compounds** met all QikProp criteria. Moreover, all of them have a better docking score than VU0542270, and 40 have a docking score below -6, indicating strong binding affinity.



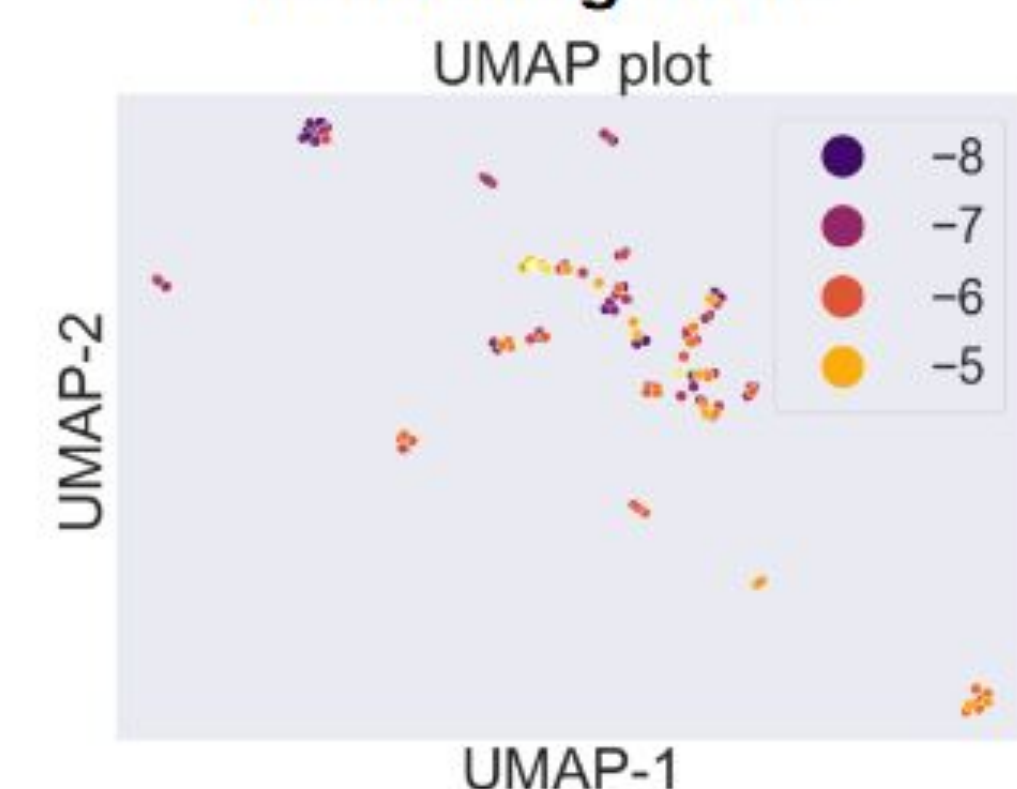
## Key docking findings

- **Best interactions** were observed for analogs featuring a **substituted pyrrolidine-2-one moiety** on the left side.
- **R-configuration** of this substituent showed **superior binding affinity**, suggesting a stereochemical preference in the target interaction.
- **Chemical space visualization** identified a sparse central cluster and two peripheral clusters of compounds, with nearly identical structures, suggesting high selectivity and strong therapeutic potential of the designed compounds.

## Visualisation of chemical space of selected compounds (0), compared to HTS Compound Collection (1)



## Visualisation of chemical space tailored to docking score



## Compound distribution by the key physicochemical descriptors

