Myocardial infarction

Introduction

Myocardial ischemia (or cardiac ischemia) means your heart muscle is not getting enough blood (which contains oxygen and nutrients) to work as it should. If this lack of blood from your coronary arteries is severe or lasts for more than a few minutes, it can damage your heart muscle. Then, it becomes a myocardial infarction (heart attack). Due to the stagnant process of prevention, morbidity, and mortality from ischemic heart disease in developing countries are increasing.

Treatment involves a mix of lifestyle changes and medication furthermore if necessary surgery and cardiac devices. Recently studies link air pollution with cardiac diseases. Medications such as beta-blockers, calcium channel blockers, aspirin, or statins are prescribed.

Problem Statement

To identify an efficient drug for myocardial ischemia in comparison with existing drugs.

Materials and Method

Data collection through PubChem

Data integration through Knime

Data collection

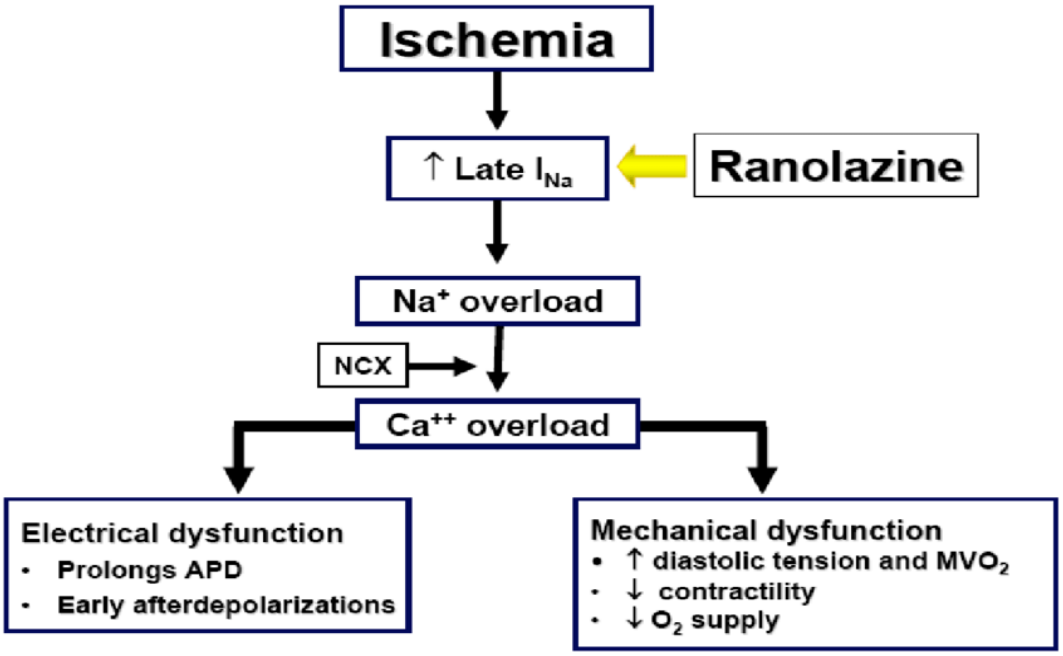
Drug Selection

Primary drug: Ranolazine is the most effective drug for myocardial ischemia so far. It is in a class of medications called anti-anginal.

Mechanism of Action

- Ranolazine inhibits sodium and potassium ion channel currents. It has been shown to exert weak activity on L-type calcium channels making it a weak direct vasodilator and exerts minimal direct effects on atrioventricular nodal conduction. Some additional mechanisms

have been elucidated. Ranolazine exerts antagonistic activity towards the alpha 1 and beta 1 adrenergic receptors and inhibition of fatty acid oxidation.



Drug Library: Calcium channel blockers inhibit Ca^{2+} channels in the myocardium or vascular smooth muscle cells, inhibit myocardium contraction, inhibit the impulse conduction system (anti-arrhythmias), and cause vasodilation. New classifications based on subtypes of Ca channels and α1 subunits have been proposed.

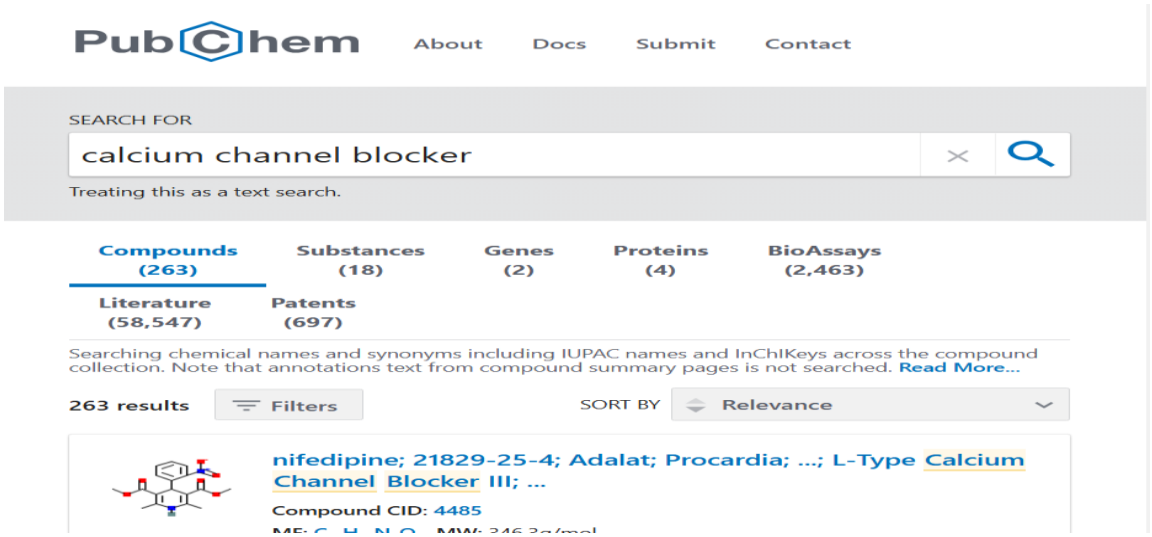
Data collection

1. Ranolazine Structure:

   PubChem was used to source the 2D and 3D structures of Ranolazine in SDF format, providing information on molecular structure and atomic connections.

2. Calcium Channel blockers

   The existing Calcium channel blocker dataset has been sourced from PubChem as Calcium channel blockers (CCBs) inhibit Ca^{2+} channels in the myocardium or vascular smooth muscle cells, inhibit myocardium contraction, inhibit the impulse conduction system (anti-arrhythmias) and cause vasodilation.

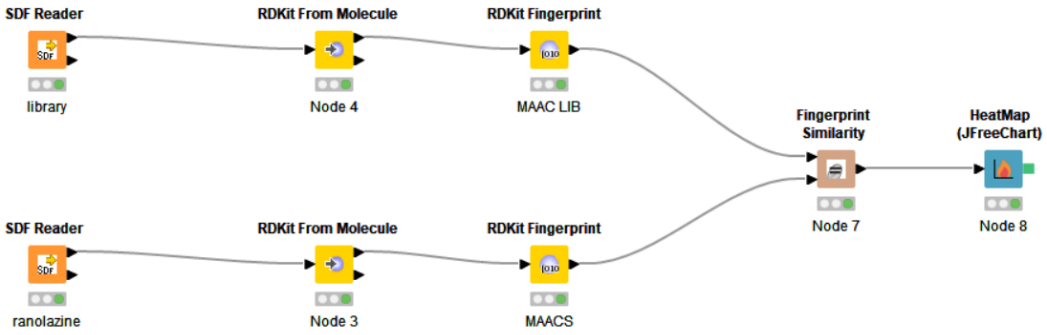


Data Integration

Here we use the KNIME open-source data science platform that allows users to analyze, report, and integrate data.

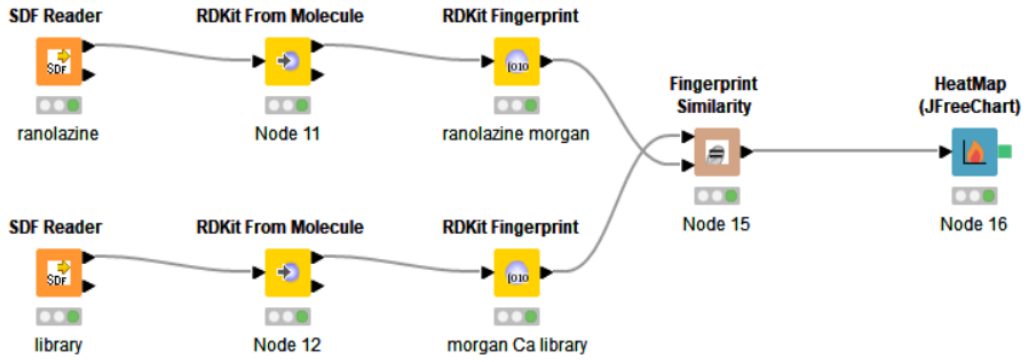
2D Fingerprint Analysis:

- **IMPORTING SDF DATA INTO KNIME**: To import the retrieved SDF data into KNIME, the **"SDF Reader"** node is used. This node is configured to load the downloaded SDF files. The outcome would be A table containing molecular structure information for Ranolazine and CCBs prepared within KNIME.
- **GENERATING MOLECULAR FINGERPRINTS:** For molecular comparison, fingerprints are generated using the **"RDKit Fingerprint"** node (or the **"CDK Fingerprint"** node as an alternative). This step selects the desired fingerprint type, such as Morgan, MACCS keys, or RDKit Standard. Once configured, the node generates fingerprint representations for each compound.
- **CALCULATING TANIMOTO SIMILARITY:** To measure the structural similarity between Ranolazine and the CCB compounds, the "Similarity Search" node is used. The Tanimoto similarity metric is selected, with Ranolazine's fingerprint acting as the reference against which the CCB fingerprints are compared.
- **VISUALIZING DATA WITH A HEATMAP:** To visualize the similarity data, the **"Heatmap"** node is employed. The node is configured to display the similarity matrix, with a suitable color gradient to represent the similarity scores (e.g., green for high similarity and red for low similarity). Rows and columns are labeled8 with compound names for easier interpretation. The heatmap can then be explored interactively within KNIME.

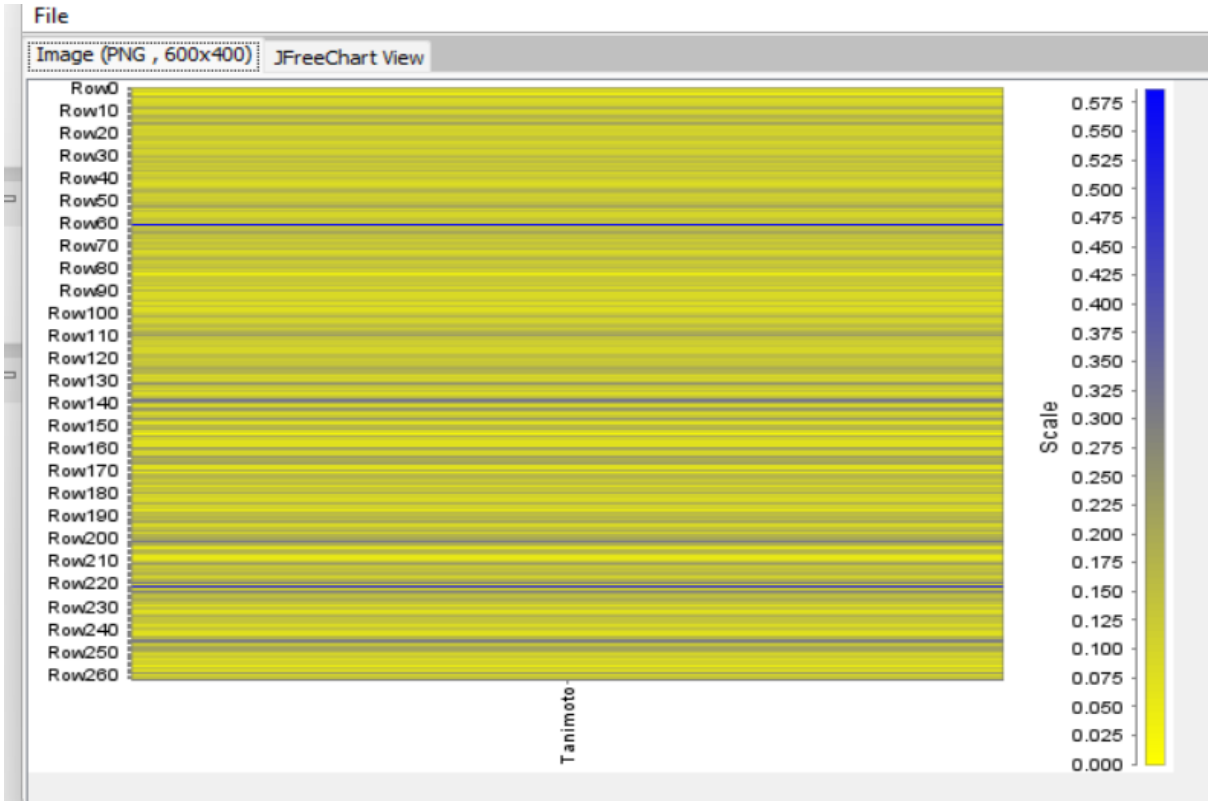


The above picture represents a MAAC fingerprint, they are individual keys were empirically defined by medical chemists.

The same steps are repeated to create Morgan fingerprint: It encodes the atom groups of a chemical into a binary vector with length and radius as its two parameters. The radius of the circular can be set/ length of the bit string also can be defined.



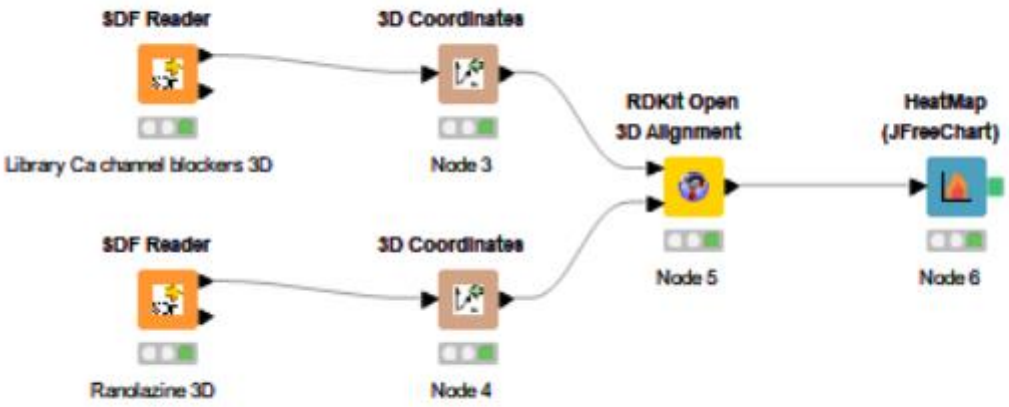
The heatmap created to visualize Tanimoto similarity scores using JFreeChart provides a graphical representation of the compounds most structurally similar to Ranolazine.



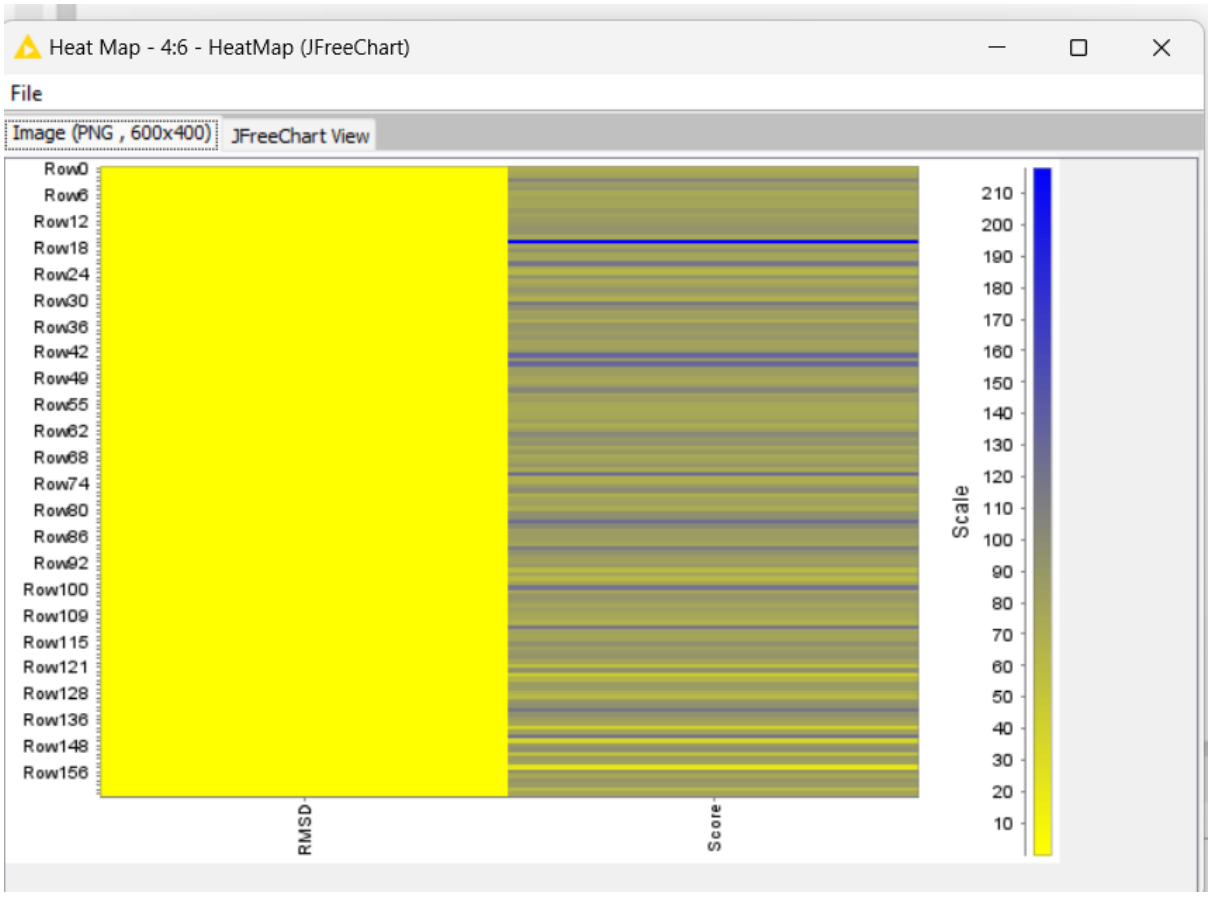
3D Fingerprint Analysis:

- Importing data is the same as in 2D then **"RDKit Generate 3D Coordinates"** node is applied. This node computes and assigns 3D coordinates to each molecule.The outcome would be that aTo compare the 3D conformations of Ranolazine with CCB molecules, the **"RDKit Open3D Alignment"** node is used. This node aligns molecules based on their 3D spatial orientation.
- Ranolazine serves as the **reference molecule** for alignment.The CCB molecules are aligned to this reference structureThe molecules are confirmed to have appropriate 3D coordinates for

alignment.



- The **Root Mean Square Deviation (RMSD)**, which quantifies the structural differences between aligned molecules, is calculated using the **"RDKit RMSD"** node.
    - **Reference Input**: Aligned Ranolazine molecule.
    - **Target Input**: Aligned CCB molecules.
    - Output: Pairwise RMSD values for Ranolazine compared to each CCB.
- The **"Heatmap"** node is employed to generate a visual representation of the RMSD values. A heatmap showing the RMSD-based structural similarity between Ranolazine and CCB molecules is generated.



Integration of 2D and 3D Analysis

By integrating the results from both the 2D and 3D analyses, the study provides a more complete understanding of the structural similarities between ranolazine and the Calcium channel blockers. This integrated approach combines the speed of 2D similarity screening with the depth provided by 3D spatial analysis.

Result and Interpretations

2D Analysis

The Tanimoto coefficient is a ratio that measures how similar two compounds are by comparing the number of chemical features they share to the total number of features. Its range varies from 0 to 1 which means higher values indicate greater similarity.

The Tanimoto coefficient ranges from 0.2 to 0.8 .The highest value being 0.75 exhibited in row 35 marking them as promising candidates for further research.

The discovered analogs may be useful looking for new drugs and improving existing ones.

3D Analysis

RMSD values indicate the root mean square deviation between molecules, where lower values suggest higher structural similarity.

The RMSD results highlight that rows 46 and 86 align most closely to Ranolazine in 3D space, possibly sharing structural motifs or orientations important for molecular interactions. The higher RMSD values for other CCBs emphasize the distinct conformations relative to Ranolazine, aligning with their differing pharmacological targets.

3D Similarity: Minor variations in the spatial arrangement of functional groups were identified using 3D shape and field-based similarity analysis, which could have an effect on binding affinities and selectivity.

Designing new compounds with enhanced potency and specificity can be influenced by the identification of common characteristics.

We can better understand the structure-activity correlations of ursodiol and its analogs by integrating computational and experimental methods, which will eventually result in the creation of new medicinal medicines.