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Abstract

Application of PASS Algorithm for the Discovery of New Trpa1 Antagonists †

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TRPA1 is a calcium ion channel found on the plasma membrane of many animal cells and it is involved in the cellular response to endogenous inflammatory mediators as well as a plethora of volatile irritants [1,2]. It istherefore a promising therapeutic target for the discovery of new treatments that relate to pain, irritationand sensory hypersensitivity [3–5]. PASS (Prediction of Activity Spectra for Substances) is a software used for predicting the biological activity profile of given molecules based on their chemical structure. The current study seeks to validate the use of PASS for the discovery of new therapeutic agents that act as TRPA1 antagonists.

The molecular structures of inhibitors with known IC50 values were searched and downloaded from the ChEMBL database. With the use of PASS, we calculated "Pa" (the probability of a compound being active) and "Pi" (the probability of a compound being inactive). We evaluated the sensitivity of the method based on these values.

A number of 371 small molecules retrieved from ChEMBL database and their predicted activity spectra were analyzed. We identified the optimal threshold for finding new TRPA1 antagonists. The method was used to confirm new inhibitory structures based on previous repurposing studies.

The PASS software can be used for further studies regarding the discovery of new TRPA1 inhibitors.

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