IDENTIFICATION OF NOVEL POTENTIAL ECTO-5'-NUCLEOTIDASE INHIBITORS BY PHARMACOPHORE-BASED SCREENING AND MOLECULAR SHAPE MATCHING

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Introduction: Ecto-5'-nucleotidase (e5NT) hydrolyzes extracellular AMP to adenosine, acting as a key-enzyme in the control of purinergic signaling.1 Recent studies have shown that high expression levels of e5NT are associated with changes in the course of several pathophysiological events, such as cancer, AIDS, autoimmune diseases, infections and atherosclerosis.1 In spite of its potential relevance as a biological target, so far only few e5NT inhibitors have been reported. Objective: The aim of this study was to search for novel potential human e5NT inhibitors, using two different virtual screening (VS) approaches: (1) pharmacophore-based screening2 and (2) molecular shape matching.

Materials and methods: Crystal structure of e5NT in complex with PSB11552 inhibitor was used to generate a chemical feature-based pharmacophore model, using LIGANDSCOUT3 program v.3.1. Additionally, a set of 11 sulfonamide e5NT inhibitors4 was used as template for a VS model based on molecular shape matching, using ROC5 program v.3.2.0.4. The pharmacophore model and the generated shape query were applied to the ZINC database (release 12; ~23x106 structures, conformers generated by OMEGA6), respectively, and some of the selected compounds are being tested in in vitro enzymatic assays.

Results: The generated pharmacophore model selected 58 compounds from the ZINC database. Six of them were purchased and are being tested as e5NT inhibitors. So far, two of the tested compounds showed moderate inhibition against e5NT at 200 µM. Furthermore, the best-ranked 400 compounds (according to the Tanimoto combo score), reported by the ROC5 search, were selected using the shape matching approach. These compounds were further analyzed by docking, and those that best fit into e5NT catalytic site will be purchased and submitted to inhibition assays for the experimental validation of the model.

Conclusions: Pharmacophore-based and molecular shape matching approaches, applied to the ZINC database, selected 58 and 400 compounds, respectively. So far, two of the tested compounds showed moderate inhibition against e5NT at 200 µM.

References:

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