Ultra-large virtual screens using fuzzy similarity, QSAR, docking, and molecular dynamics for multi-target anti-Alzheimer's agents

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Alzheimer's disease (AD) represents a severe problem to current society that still has not an effective and safe therapeutic treatment available. Its multi factorial nature and the existence of several pathophysiologically related targets opens paths to explore approaches such as multi-target virtual screening (MTVS)[1]. In order to improve the outcome of MTVS, here, we employ an ensemble of computational methods as shown in Figure 1. Initial screening was caried out using FTrees (BioSolveIT)[2] considering 8 known AD drugs as queries to build a small library out from the 23 billion-compound REAL chemical space. This library was sequentially submitted to predictions by robust QSAR machine learning models with regard to their potential to act, simultaneously, as inhibitors of two AD targets: AChE and GSK-3β. These models were developed using Random Forest, Morgan molecular fingerprints, 5-fold external cross-validation, Y-randomization, and considering respective applicability domains[3]. They showed correct classification rates (CCR) of 84 and 78%, respectively. Furthermore, remaining compounds were submitted to consensus docking (GlideSP and HYBRID), considering the conservation of same key interactions observed to known ligands for each target as well as visual inspection. We thus selected four compounds that, so far, have been validated through 150 ns molecular dynamics simulations. Results indicate that our screening campaign culminated in compounds with potential to act as inhibitors of studied targets and as promising hits that shall be validated and further optimized to drug candidates acting as multi-target anti-AD agents.

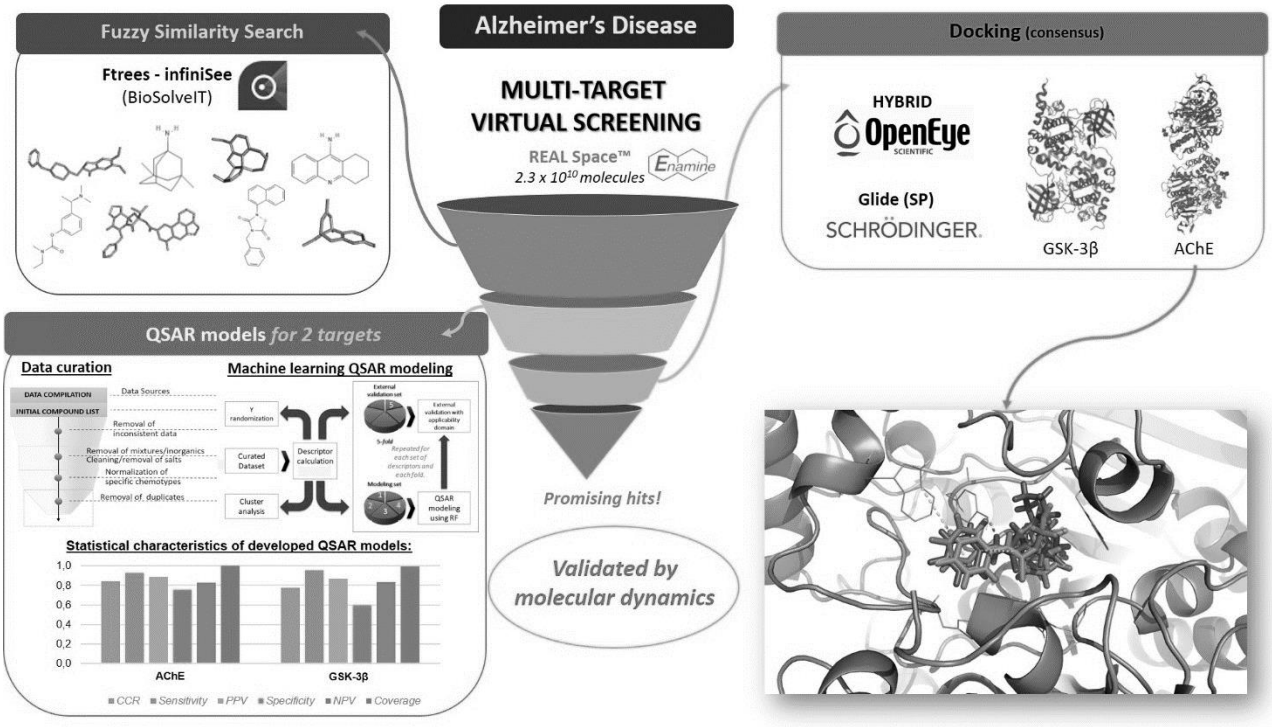

Figure 1. Workflow of ultra-large virtual screening for multi-target anti-Alzheimer's agents.

Bibliography:

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[2] BioSolveIT GmbH, Sankt Augustin, Germany (2022) - www.biosolveit.de/
[3] Tropsha, A. *Molecular Informatics*. 29 (2010) 476–488.