P25 LIGAND AND STRUCTURE-BASED VIRTUAL SCREENING TOWARD IDENTIFYING NEW POTENT INHIBITORS AGAINST SGK1

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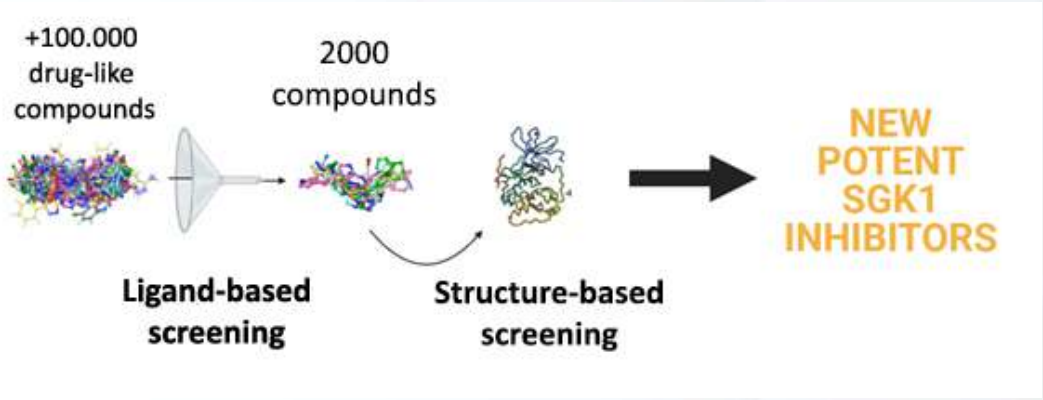
Alzheimer´s Disease (AD) is a devastating neurodegenerative disease characterized by memory impairment and cognitive defects which are typically caused by the loss of cortical and hippocampal neurons [1]. As for other neurodegenerative disorders, there is no current effective treatment, and the etiology is far from being deciphered despite the increasing efforts over the last decades. AD main features are (i) the deposit of β-amyloid in the extracellular space and (ii) the formation of neurofibrillary tangles inside neurons due to the abnormal aggregation of tau protein [2]. Since tau hyper-phosphorylation and its consequent imbalance are clearly involved in its aggregation, protein kinases represent new targets of great interest against this disease. Among them, serum and glucocorticoid-regulated kinase 1 (SGK1) is a novel kinase that may be involved in several neurodegeneration-related pathways such as neuro-inflammation, autophagy and apoptosis [3,4]. In this work, a high-throughput virtual screening of structurally diverse compounds whitin a library of more than 100,000 drug-like ligands was performed. The successful combination of both ligand and structure-based methods led to the discovery of several potent and structurally diverse SGK1 inhibitors with IC50 values ranging from low micromolar to low nanomolar. These compounds are currently being tested in several *in vitro* AD models and preliminary results reveal that SGK1 inhibitors are able to recover the cell viability from the toxic effect of okadaic acid, a widely used AD *in vitro* model.



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