Natural compounds as potential PI3K-AKT1 signaling pathway inhibitors by means of pharmacophore modeling

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MOTIVATION

AKT1, a modulator of PI3K-AKT1 pathway, is dysregulated in several human diseases, and understanding deeper its role in the complexity of biological systems remains an important goal. The research has been focused on development and study of potential synthetic-natural allosteric inhibitors for AKT1, and recent studies have shown how some natural compounds may play this role (1). We are interested in a screening of small bioactive molecules, in order to identify the potential “lead compounds”, for next experimental assays, searching those potentially able to inhibit AKT1 and its signaling mechanisms, trying to re-establish the normal balance and safeguarding of human health.

METHODS

The workflow executed is the following: 1) search in PDB database of a model structure for AKT1 (comparing different structures and choosing the most suitable for our purposes), through algorithm BLAST. 2) pharmacophore modeling by means of ZINCpharmer web-server, to investigate all purchasable compounds of the ZINC database, using the Pharmer as efficient and exact pharmacophore search technology (2). 3) screening of possible natural AKT1 inhibitors, using the pharmacophore generated by ZINCpharmer, choosing only the best candidates for next steps. 4) molecular validation of selected compounds, to analyze the ligand-protein interactions. 5) study of physical-chemical properties of selected compounds to trace their origin. 6) prediction of their biosynthetic pathways and Pharmacokinetics/Pharmacodynamics models, by means of ADMET/toxicity predictor server in order to direct the design of next experimental assays.

RESULTS

Our attention is focused on the study of natural compounds that can show many health benefits, through the realization and analysis of “pharmacophore modeling”, essential step in drug discovery (3). We selected the PDB structure 3O96 as the reference complex (protein-ligand), and we analyzed it by means of ZINCpharmer, to generate three different “pharmacophore models” with three different list of natural compounds. It is performed a thorough screening of compounds applying other filters, to find some good candidates as possible natural AKT1 allosteric inhibitors. The compounds that match a well-defined pharmacophore have been analyzed through direct molecular docking, for selecting only the best candidates and studying the protein-ligand interactions. Selected compounds have been investigated in more details, to trace their origin, by their chemical-physical properties. This information can help us to predict some plausible enzyme-catalyzed reaction pathways, investigated with PathPred server and KEGG compound database, in order to highlight the most important reactions for biosynthesis of compounds and obtain Pharmacokinetics/Pharmacodynamics (PK/PD) models through ADME predictor server and to realize of next experimental assays.

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REFERENCES

