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An in silico analysis of docking protocols used to identify a small-molecule inhibitor of PDZ1-SR-B1 interaction

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Inhibitors of PDZ domains have important implications in a variety of biological processes including treatment of cancer and Parkinson's disease. PDZ domains have been considered difficult to target with small molecule inhibitors because of the shallow and elongated binding pocket. It was aimed to inhibit PDZK1, a 519 amino acids protein with four PDZ (1-4) domains, activity. PDZ1 domain was reported to bind the C terminus of the HDL-receptor scavenger receptor class B, type 1(SR-B1). It was demonstrated that SB-R1 binding increases when it binds to the backbone of Y20 and to a conserved water molecules network that exists in many other PDZ domains. A set of 'known actives' (26) with a larger database of molecular decoy (10K) and the X-Ray structure of PDZ1 bound to SR-BI (3NGH) were used to find the best docking protocol. 'Known actives' are compounds that were known to bind other PDZ domains and are relevant due to the high degree of sequence similarity and almost identical binding pocket residues of this domain. Four different docking protocols were examined; dehydrated with constraints, dehydrated without constraints, hydrate with constraints and hydrated without constraints were tested in a preliminary study. The results showed that 50% of the 'known actives' were found within the 1%, 2%, 2% and 4% of the ranked library accordingly. Since all protocol showed similar results we selected the dehydrated + constraints to avoid possibly making the error of including high energy water or water with wrong angles, both of which could hinder the screening results. Following the screen of 1.5 M compounds, 200 diverse compounds were selected, 50 were purchased, 30 were tested and 1 active probe was found so far.

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