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Development of a novel filtered-based pharmacophore for the identification of human equilibrative nucleoside transporter 1 inhibitors

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Statement of the Problem: The human equilibrative nucleoside transporters (hENTs) are important transporters that allow nucleosides and nucleobases permeation into the cell. hENT 1 is a promising target against heart and Huntington's diseases as its inhibition mediates cardiac- and neural protection effects, respectively. However, the current hENT1 inhibitors have significant off-target effects and poor pharmacological profile. Hence there is a need for new novel inhibitors.

Methodology: Therefore, we developed a computational protocol for developing ligand-based pharmacophores that identify and select inhibitors of hENT1 in an efficient and specific manner. To examine the efficacy of the pharmacophore and its application later on in the drug discovery of new hENT1 inhibitors, we used this pharmacophore as a filter prior to a small-scale virtual screening (VS) of a drug-like ligand library. The library consisted of 5000 compounds; 56 of which were known hENT1 inhibitors.

Findings: First, several pharmacophores were created using a set of known inhibitors. Among the several created pharmacophores, the best inhibitor pharmacophore exhibited high selectivity and specificity rates of 92% and 88%, respectively. Furthermore, another pharmacophore was validated for the oppositely acting type of the hENT1 molecules (i.e. permeants) to act as an extra refinement step in our search for hENT1 inhibitors. Interestingly, employing the inhibitor pharmacophore as a filter-in along with the permeant pharmacophore as a filter-out resulted in up to twofold enhancement of docking-based virtual screening results (see Table 1).

Conclusion & Significance: This in silico approach can prove very useful in the discovery of new cardio- and neuroprotective hENT1 inhibitors.

Table 1. Retrieved rate of hENT1 inhibitors at various portions of the sorted docked ligands from filter-based and non-filtered-based virtual screening

Output percentage of the top-ranked docked 5000-ligand library	The rate of retrieved inhibitors		
	No-filter	One filter	Two filters
1	12.5	19.6	21.27
3	17.8	35.29	34.04
5	26.78	49.02	48.93
10	42.85	80.39	80.85
20	57.14	98.04	100

Biography

Azza Ramadan is a molecular biologist and currently an Assistant Professor at Al Ain University in the United Arab Emirates. She obtained her PhD from the University of Toronto in Canada with a specialization in biomedical sciences. Among her areas of research, is investigating the role of the human equilibration nucleoside membrane transporter hENT1 in cardio and neuroprotection. Her research interest stems from her work during her graduate studies that shed light on ENT1 central role in purinergic s signalling in the cardiovascular system. Her research was supervised by the internationally renowned expert in membrane transport proteins, Prof Imogen Coe.

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