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Designing of multi-targeted molecules using combination of molecular screening and *in silico* drug cardiotoxicity prediction approaches

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ABSTRACT

We have previously investigated and reported a set of phenol- and indole-based derivatives at the binding pockets of carbonic anhydrase isoenzymes using *in silico* and *in vitro* analyses. In this study, we extended our analysis to explore multi-targeted molecules from this set of compounds. Thus, 26 ligands are screened at the binding sites of 229 proteins from 5 main enzyme family classes using molecular docking algorithms. Derived docking scores are compared with reported results of ligands at carbonic anhydrase I and II isoenzymes. Results showed potency of multi-targeted drugs of a few compounds from investigated ligand set. These promising ligands are then tested *in silico* for their cardiotoxicity risks. Results of this work can be used to improve the desired effects of these compounds by molecular engineering studies. In addition these results may lead to further investigation of studied molecules by medicinal chemists to explore different therapeutic aims.

1. Introduction

The rational drug design strategy for screening single-targeted and highly specific ligands was widely investigated in last decade [1,2]. In spite of appealing simplicity of the approach, there are large number of complex diseases (*i.e.*, cancer, cardiovascular diseases, neurodegenerative diseases, rheumatoid arthritis) where single-target strategy fails. For example, many high affinity agonists or antagonists of specific receptors are known for altering cell function by simultaneous binding to number of other targets. Systems biology and network control analysis have shown that complex diseases are solid against perturbations and are always controlled by more than one biochemical pathways and processes in cells [2]. Although poly-pharmacology is naturally associated with drug toxicity and off-target side effects, especially when rationally designed, they can have larger therapeutic window [1,2]. For example, patients with mild cognitive disorders and risk of Alzheimer's disease dementia are often considered for the treatment using anti-hypertensive drugs. Angiotensin II (Ang II) type 1 (AT1) blockers are used for patients with intolerance for ACE inhibitors or if these inhibitors do not provide the desired effects [3–5].

We have previously investigated a set of phenol- and indole-based derivatives for their effect to inhibit carbonic anhydrase (CA) targets with *in silico* and *in vitro* approaches [6,7]. These compounds showed sub-micromolar to low micromolar affinity to the CA isoenzymes. In this study, our main goal was to investigate multi-target interactions and multi-functional potentials of these compounds. For this aim, molecular docking of 26 ligands into binding sites of 229 proteins from different classes were performed to determine potential interactions of these ligands with the active site residues.

The 2D structures for ligands considered in this study are collected in Table 1. The target enzymes used in this study are classified according to the reactions they catalyze (see Section 2 for selection of target enzymes). The five classes that screened in this study are: transferases (Class-II), hydrolases (Class-III), lyases (Class-IV), isomerases (Class-V), and ligases (Class-VI) [8–10]. Transferases (Class-II) catalyze transfer (*i.e.*, movement) of a functional group from one molecule to the other. A broad variety of functional groups are targeted by the corresponding transferases, which include phosphate, glycosyl and methyl groups. The corresponding

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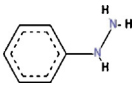
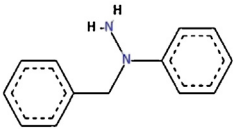
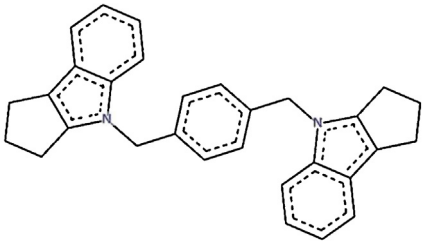
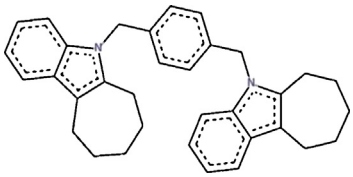
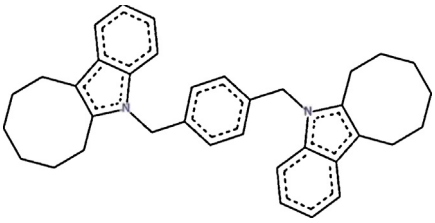
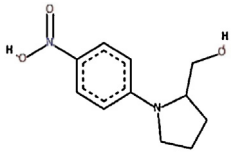
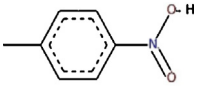
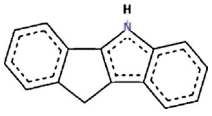
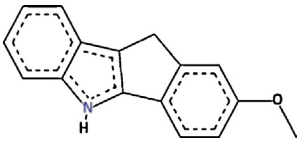
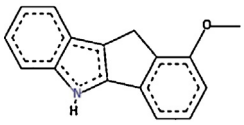
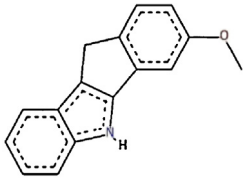
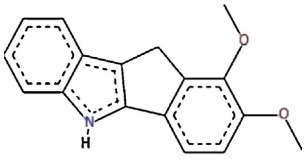
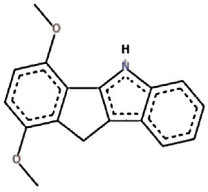
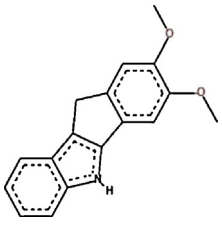
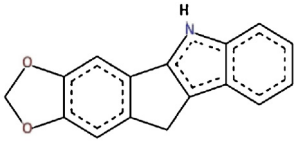
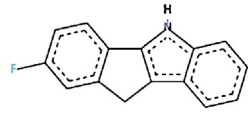
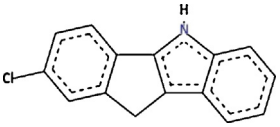
1093-3263/

Table 1
Molecular structures of the tested (docked) compounds [6,7].

Comp. no.	2D structures	Comp. no.	2D structures
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	
17		18