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Molecular docking studies on fluoro-substituted chalcones as potential DprE1 enzyme inhibitors

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ABSTRACT

In this study, docking studies were performed on a series of fluoro-substituted chalcones (**E1**–**E7, Z1-Z7, H1**–**H7**) with DprE1 enzyme inhibition activities. The results showed that both the positions of the substituents and the type of chalcones seemed to be critical for their inhibition against DprE1. Chalcone derivatives exhibited binding affinity values of < −8.0 kcal/mol. The compounds **E6**, **E7**, and **Z7** having a double bond in the linker group were effective inhibitors and it were found that this structural motif had an influence on the binding profile of molecules. The best docking results were detected for **Z7**, which is the *cis*-isomer of **E7** from the E group. The SAR results of the novel DprE1 inhibitors were revealed in this study and the inhibitors were predicted to have excellent potencies from the developed models. The results could greatly contribute toward designing potential new DprE1 inhibitors with better activities.

1. Introduction

Mycobacterium tuberculosis (MTB), an infectious bacillus, is the causative agent of many cases of tuberculosis and is the second largest cause of mortality due to infectious diseases. Given the increase in drug-resistant strains of MTB, the design of novel antitubercular molecules is urgent. Research groups have to find new targets with attractive microbiological properties for tackling tuberculosis. One such target is decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1), which is the key enzyme involved in the arabinogalactan biosynthesis of mycobacterium cell walls [1]. Following the discovery of nitrobenzothiazinone, which binds covalently to the DprE1 enzyme [2], there has been a growing interest in this target.

Our ongoing studies focus on the development of novel antimycobacterial lead molecules. For this purpose, we have focused on molecular docking studies into the active site of the DprE1 enzyme as an essential aspect of MTB survival and as a novel mechanism of antitubercular activity. In addition, new molecular structures are being developed for treating tuberculosis. Chalcones, a sub-group of flavonoids, comprise open chain flavonoids in which the two aromatic rings are linked by three carbons and have α,β-unsaturated/saturated carbonyl systems in their open chains. Chalcones have been reported to have a range of pharmacological properties including anti-inflammatory, antifungal, antioxidant, antibacterial, antitumor, and anticancer activities [3]. A number of natural and synthetic chalcones have also been identified as exhibiting antimycobacterial activity [4]. *In vitro* and *in silico* studies of their activities have revealed that a number of chalcones have a high inhibition activity against MTB at low concentrations [5]. The simplicity, speed, and low cost of their synthesis along with other important features of chalcones mean that they have huge potential as future anti-tuberculosis agents. Considering these advantages, our research group carries out molecular docking studies of chalcone derivatives with DprE1 enzyme inhibitors and for antitubercular drug design. These molecular docking studies were performed with 21 molecules including chalcone derivatives containing fluorine in the B ring, which increased the DprE1 enzyme activity. Of all the fluoro-substituted chalcone compounds were investigated in this study.

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Any computational studies between DprE1 enzyme and fluoro-substituted chalcones couldn't find literature. In only one study; Prasath et al. [6] were studied with three chalcone derivatives, except our molecules, experimentally and theoretically. Our work is also important for the effect of fluorine in chalcones.

2. Materials and methods

2.1. Chemistry

Fluoro- and non-fluoro-substituted chalcone compounds (**E1**−**E7, Z1-Z7, H1**−**H7**) (Table 1) were synthesized and showed antiproliferative and antitubercular activity as described previously [7,8]. The structures of all compounds were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

2.2. Receptor and ligand preparation

DprE1 from MTB crystallized with co-factor flavin adenine dinucleotide (FAD) and {(4s)-2-[7-(hydroxyamino)-6-methyl-5-(trifluoromethyl)-1,3-benzothiazol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}(pyrolidin-1-yl)methanone (O95), which is an inhibitor that acts as an antitubercular agent and was used as a receptor for the docking protocol. The crystal structure (PDB ID: 4P8H [9]) was obtained from the Protein Data Bank (www.rcsb.org) [10] (Fig. 1). DprE1 enzyme in 3D structure was isolated from Mycobacterium tuberculosis (strain ATCC 25618/H37Rv) as organism with Escherichia coli BL21 (DE3) expression system. X-RAY Diffraction Crystallography Method was used to determine tertiary protein structure with 3 Å resolution value [9]. The receptor was in dimer form, so first one of the subunits, B, was removed, and then the receptor was prepared by the cleaning of all the heteroatoms except FAD molecules (i.e., nonreceptor atoms such as water, ions, and co-crystallized ligands). Co-factor FAD was not removed owing to its close proximity to the active site [11]. After that Gasteiger charges and polar hydrogens were assigned, and the receptor input file was prepared in PDBQT format for AutoDock Vina by using the AutoDock Tools package [12].

Ligands given in Table 1 were drawn with Discovery Studio Client 3.5 [13]. The conformations were fixed with the “clean geometry” option of this package. Clean Geometry tool uses a fast, DREIDING-like force field to optimize the structure geometry. The tool improves the geometry of the molecule and results in an approximate 3D structure. For all ligands, including O95, the non-polar hydrogen atoms were merged, and the Gasteiger charges were assigned. Later, ligand input files were also arranged in PDBQT format using the AutoDock Tools package.

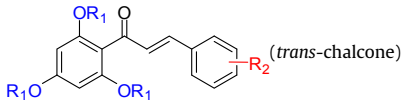
2.3. Docking protocol

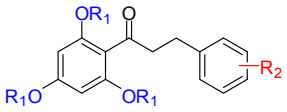
The docking area was defined around the O95 binding site by Chimera [14] (Fig. 3), which was determined in the crystal structure, by a grid box of $25 \times 25 \times 25$ Å using a 0.375 Å grid point spacing in AutoGrid. The docking grid box was defined with the x, y, and z centers as −19.957, −21.982, and 0.829, respectively. AutoDock Vina uses a global heuristic optimizer algorithm, Iterated Local Search, with a local optimization algorithm called Broyed-Fletcher-Goldfarb-Shanno (BFGS) [12]. The docking conformations of ligands in the binding sites of the receptor were searched with this İterated Local Search Global Optimizer algorithm with a Monte Carlo sampling technique as a molecular mechanic method. Semi-flexible algorithm was used in docking protocol. AutoDock Vina considered the target conformation (receptor) as a rigid unit, where as the ligands were allowed to be flexible and adaptable to the target. This algorithm applies some flexibilities in the ligand's bonds [15,16]. All docking results were superposed, and the flexibility was shown by different conformations of ligand in Figure S1 and S2 (for detailed information see the supplementary data).

All docking results were ranked according to their binding affinity (kcal/mol) and inhibitory constant, K_i, (molar) after the docking process was completed. The inhibitory constant, K_i ($K_i = K_d$ (dissociation constant) $= 1/K_b$ (binding constant)) was calculated by using binding affinity values with Equation (1), as given below.

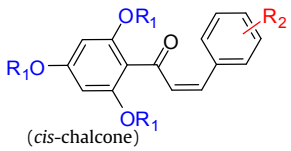
An equilibrium constant is related to the standard Gibbs free energy (ΔG) change for the reaction.

Table 1
Ligands with their functional groups that were thought to be effective for the inhibition of DprE1.





Comp.	R_1	R_2	Comp.	R_1	R_2	Comp.	R_1	R_2	Comp.	R_1	R_2
E1	$-CH_3$	H	E5	$-CH_3$	4-F	**H1**	$-CH_3$	H	**H5**	$-CH_3$	4-F
E2	$-CH_3$	2-F	E6	−H	2-F	**H2**	$-CH_3$	2-F	**H6**	−H	2-F
E3	$-CH_3$	3-F	E7	−H	2,5-diF	**H3**	$-CH_3$	3-F	**H7**	−H	2,5-diF
E4	$-CH_3$	2,5-diF				**H4**	$-CH_3$	2,5-diF			



Comp.	**R_1**	**R_2**	**Comp.**	**R_1**	**R_2**
Z1	$-CH_3$	H	Z5	$-CH_3$	4-F
Z2	$-CH_3$	2-F	Z6	−H	2-F
Z3	$-CH_3$	3-F	Z7	−H	2,5-diF
Z4	$-CH_3$	2,5-diF	Comp.		