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RESEARCH ARTICLE

De novo designing of novel drug-like inhibitors of aldose reductase

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ABSTRACT

Aldose reductase (AR, ALR2) is a member of the aldo-keto reductase superfamily. It is the first and rate-limiting enzyme of the polyol pathway. AR plays an essential role in the development of diabetic complications. It is designated as the most legitimate target for managing diabetic complications. One of the key challenges to the successful development of target-specific AR inhibitors is target selectivity. In this research, target-specific drug-like ALR2 inhibitors have been designed using the *de novo* technique and are present for further synthesis and development.

KEY WORDS: Aldose reductase, *De novo* designing, Diabetic complications, Polyol pathway

INTRODUCTION

Diabetes is a group of multifactorial diseases characterized by hyperglycemia. There are two major types of diabetes: type 1 and type 2. Type 1 diabetes occurs when the β-cells of the pancreas cannot produce sufficient insulin.[1] In contrast, type 2 diabetes arises when the body tissues become resistant to the insulin produced by the pancreatic cells. Long-term persistence of diabetes results in diabetic complications such as cardiac problems, vasculopathy, neuropathy, nephropathy, retinopathy, cataracts, periodontitis, foot ulceration, and amputation. These are the foremost causes of morbidity and mortality in people with diabetes in most countries. Regardless of advances in the treatment of diabetes, it is still challenging to reduce the development and evolution of various disabling complications.[2] Aldose reductase (AR, ALR2), a key member of the aldo-keto reductase superfamily, is the first and rate-limiting enzyme of the polyol pathway, its overexpression in the hyperglycemic state is the basis of diabetic complications. Aldose reductase (ALR2) converts glucose into sorbitol using the cofactor NADPH in the polyol pathway. In the next step of the polyol pathway, sorbitol is converted into fructose *via* the sorbitol dehydrogenase enzyme. The overexpression of ALR2 in diabetic patients leads to the accumulation of sorbitol, further leading to the development of micro- and macro-vascular diabetic complications.[3] Several drug molecules, including epalrestat, fidarestat, ranirestat, sorbinil, tolrestat, and zopolrestat, have been developed so far as aldose reductase inhibitors (ARIs) for the treatment of long-term diabetic complications; however, Epalrestat bearing rhodanine scaffold is only available commercially for the treatment of diabetic neuropathy, and others have been cast-off due to either intolerable adverse effects or inadequate efficacy.[4] Here, we have designed novel ARIs using *de novo* design within the pocket of the enzyme.

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COMPUTATIONAL METHODOLOGY

Preparation of target structure

The three-dimensional (3D) crystal structure of the target having 1.08 Å resolution was saved from the research collaboratory for the structural bioinformatics protein data bank (PDB ID: 2FZD). It was co-crystallized

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with *N*-{[6-methoxy-5-(trifluoromethyl)-1-naphthyl] carbothioyl}-*N*-methylglycine, having a total structure weight of 37 kDa and atom count of 2975. The target structure was prepared and optimized using Molegro Virtual Docker (MVD). The target structure was imported into the workspace of MVD by taking care of neglecting the water molecules attached to it. In the next step, the 3D target structure in the workspace was prepared using the option "prepare molecules" present in the preparation tab. The molecular preparation assigns missing bonds, bond order, hybridization, tripos atom types, and charges, creates explicit hydrogen, and detects flexible torsions in the ligand and the target structure that undergoes this step.[5]

Detection of potential binding cavities

The potential binding sites were mapped within the target by choosing the option "detect cavities" present in the preparation window of MVD, which is a grid-based cavity prediction algorithm. For the execution of this computational algorithm, the parameters were set as follows: the maximum number of cavities as 5, the minimum cavity volume as 10 Å, the maximum cavity volume as 10000 Å, the probe size as 12 Å, the maximum number of ray checks as 16, the minimum number of ray hits as 12, and the grid resolution as 0.[6]

De Novo designing using LEA3D

The *de novo* design of ALR2 inhibitors was performed using the LEA3D engine. It provides an opportunity to create small molecular architects as target-specific compounds. LEA3D creates novel compounds that require the optimization of their substituents either from scratch or using a user-defined framework.[7] A genetic algorithm is used to optimize the arrangement of fragments during *de novo* molecular synthesis in LEA3D. With the help of a USAN (Comprehensive Medicinal Chemistry, Symyx Solutions, Inc.), LEA3D breaks down the molecular components, rings, and acyclic fragments from authorized and experimental drugs for the *de novo* molecular production process. Each fragment has one or more "X" dummy atoms that can recall the stereochemistry and the fragment's initial substitution pattern. When a fragment has multiple substitution sites, one is chosen randomly to be joined. Finally, the constructed molecule's 3D conformation is produced using the Frog program. The docking affinity was evaluated in terms of the PLANT score.[8]

The PDB structure of AR (Id.: 2FZD) was uploaded to the LEA3D web server. The coordinates of the center of the binding site were set as similar to predicted cavity 1 (X: 19.9126 Å, Y: -7.44146 Å, Z: 21.6251 Å), corresponding to the co-crystallized ligand. The weight in final scores was set as 1. The molecular properties for the generating compounds were set as follows: the maximum molecular weight of compounds is 499 Da, the minimum molecular weight is 300 Da, the value of log *P* is 4.8, the number of atoms is 10–70, the number of hydrogen bond donors is ≤3, the number of hydrogen bond acceptors is ≤3, the polar solvent accessible surface area is 140, fsp^3 is 0.3, the number of rotatable bonds is 2–8, the number of rings is 1–8, and the number of aromatic rings is 3.[9,10]

In Silico drug likeness/ADMET screening

The *de novo*-produced compounds were subjected to TSAR drug-likeness/ADMET screening. Lipinski's criteria were used, which state that a molecule should only have one violation of each of the following standards to qualify as an orally active drug-like molecule: molecular weight ≤500, cLog *P* ≤5, numbers of hydrogen bond donors ≤5, numbers of hydrogen bond acceptors ≤10.[11]

RESULTS AND DISCUSSION

De novo drug design is a computer-aided approach to designing new molecules using the receptor's 3D structure. In this research article, we have used LEA3D Server for the *de novo* design of new ARIs. A total of 7 molecules [Figure 1] were generated within the active pocket of the aldose reductase enzyme.

The complexes of *de novo*-generated molecules with aldose reductase are shown in Figure 2. The designed molecules showed good target affinity regarding the PLANTS score [Table 1]. All the compounds were further

Table 1: Docking score and *in silico* ADME properties of *de novo* generated molecules

Comp. No.	PLANTS score (Kcal/mol)	Molecular weight	H-Bond donor	H-Bond acceptor	QPlogPo/w	PSA	Rule of five
1	−106.730	276.353	1	5	2.177	73.579	0
2	−120.340	365.425	1	7.4	3.146	103.683	0
3	−133.890	669.857	4.5	16.4	0.852	231.757	3
4	−142.870	596.679	1	9.7	5.685	148.476	2
5	−143.530	697.868	4.25	16.75	0.659	275.437	3
6	−141.810	602.816	4.75	12.95	1.191	181.552	3
7	−153.680	744.881	5.5	18.2	0.331	306.029	3

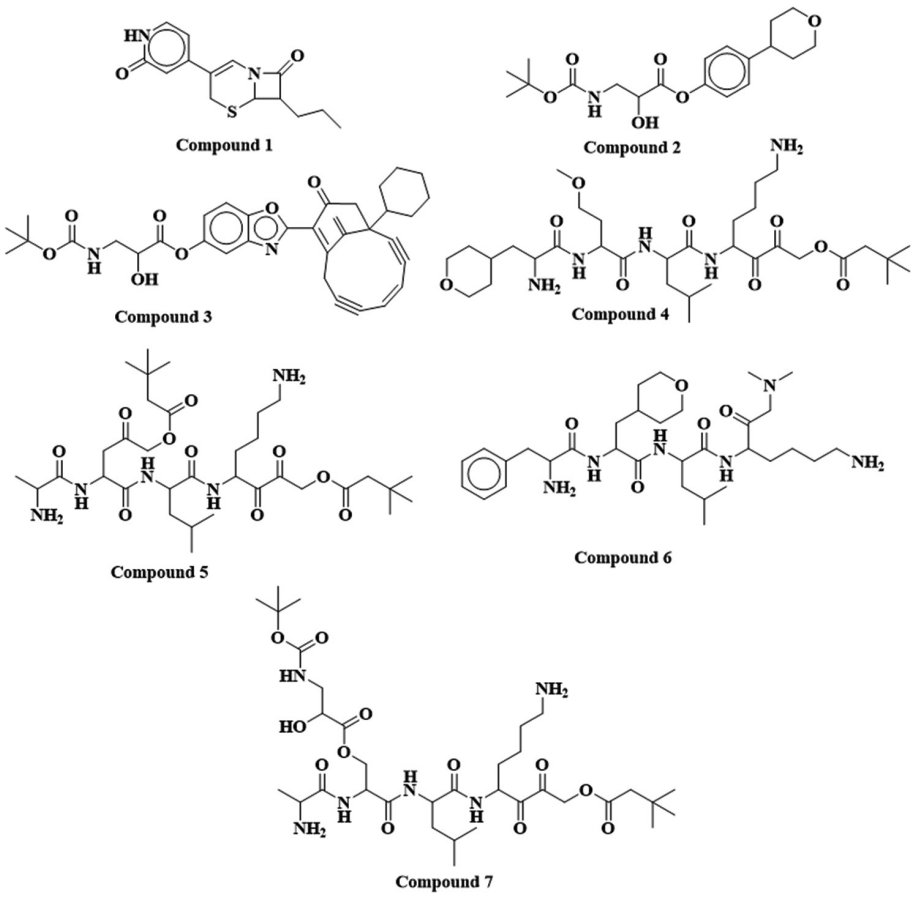

Figure 1: Chemical structures of de novo generated molecules

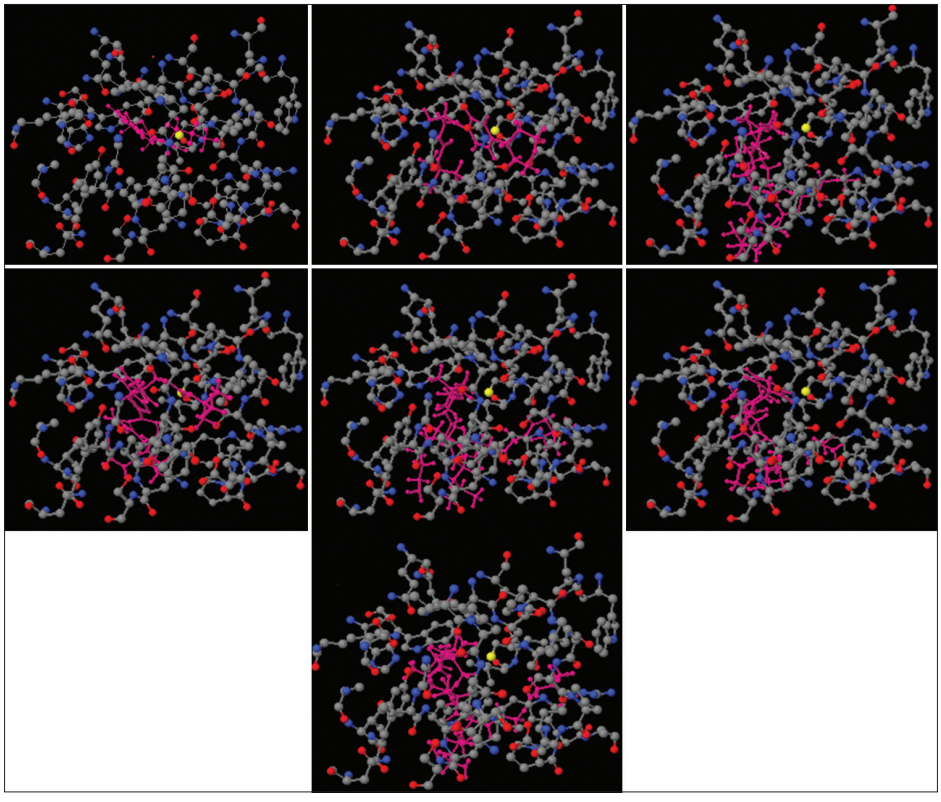

Figure 2: Complexes of *de novo* generated molecules (compound 1–7) with aldose reductase

screened for drug-likeness and ADMET using TSAR [Table 1]. However, only molecules 1 and 2 fit the *in silico* drug-likeness standards or ADMET screening based on "Lipinski's rule of five." These two molecules can be further synthesized and developed as new ARIs.

CONCLUSION

In silico de novo molecular design is a consistent and expeditious combined annotation-dependent depletion tool to create novel target-specific leads from scratch with pre-defined molecular constraints. Here, seven molecules were generated in the core of the aldose reductase enzyme (ALR2) (PDB Id. 2FZD) using the LEA3D *de novo* designing server. Out of which, two molecules (Compounds 1 and 2) have shown zero Lipinski rule violations and can be synthesized in the lab to further develop new ARIs.

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