

# Benzothiazole Analogues: As Aldose Reductase Inhibitor (ARIs) for the Management of Diabetic Neuropathy and Cardiomyopathy

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**Abstract:** Currently, 463 million people are suffering from diabetes globally, which is about 9.3% and it will be supposed to be increased to 578 million by 2030. Long-term suffering leads to other different complications associated with diabetes, among them diabetic polyneuropathy and cardiomyopathy are the most common. However, only one drug till now has passed phase-III clinical trials for the treatment of diabetic complications, namely Epalrestat, an aldose reductase inhibitor (ARIs) that is manufactured and marketed by Alfresa Pharma Corporation, Japan. So, research is going on for the finding of new drugs. ARIs can be the potent drug of choice for diabetic complications. The 3D structure of the aldose reductase enzyme was predicted by X-ray crystallography and the binding affinity towards the various new ARIs has been studied through molecular modeling and docking. The ARIs with a carboxylic group and a benzothiazole moiety always had shown better activity than the other derivatives. Lidorestat and zopalrestat are two ARIs currently in clinical trials.

**Keywords:** Diabetes, epalrestat, ARIs, carboxylic group, benzothiazole

## 1. Introduction

Aldose reductase is an enzyme, which helps our body by converting glucose into fructose by forming sorbitol as an intermediate product, following the polyol pathway. In the case of diabetes, the activity of aldose reductase increases as the concentration of glucose rises, and it especially affects those tissues of the body that are not sensitive to insulin. As

through the cell membrane sorbitol cannot diffuse, so it accumulates in the tissues which lead to the damage of different nerves and muscles of the body and it creates neuropathy or cardiomyopathy. Single nucleotide polymorphisms (SNPs) of the ALD2 (human AR gene) are associated with diabetic complications, including cardio, and renal complications, and that has been revealed by genetic studies.

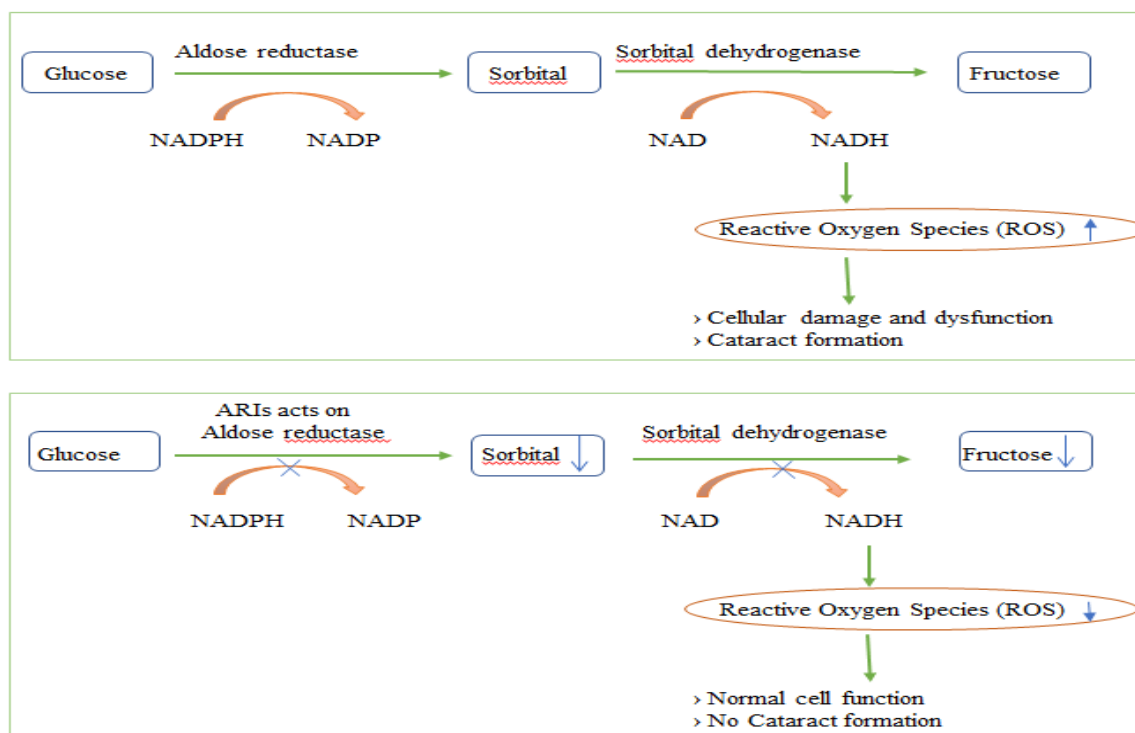
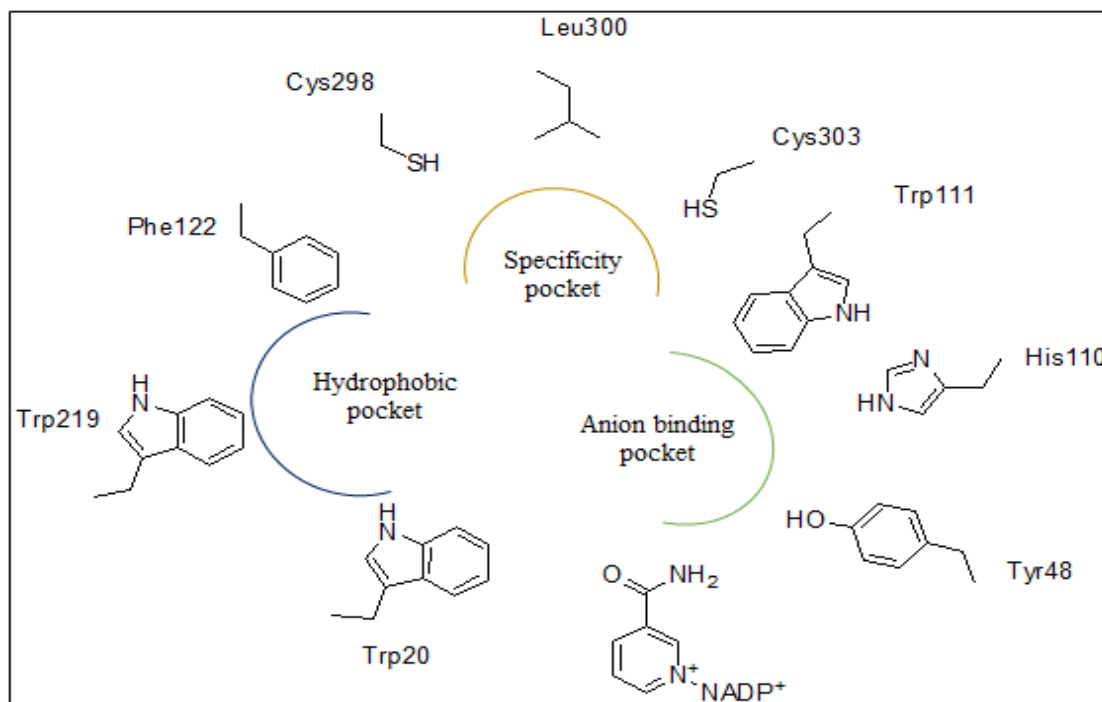


Figure 1: Polyol pathway



**Figure 2:** Schematic diagram of AR with ligand binding site

Aldose reductase inhibitors (ARIs) act by reducing the formation of sorbitol from glucose and manage secondary complications in diabetes like neuropathy or cardiomyopathy. As benzothiazole became a lead molecule in recent drug discovery and developments for its wide range of pharmacological activity, it also attracts researchers for its activity in diabetes management by blocking the aldose reductase enzyme. [1-4]

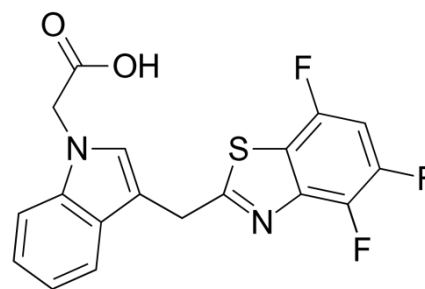
### Early Work

In the year 1987 Sorbinil was discovered by Pfizer for the treatment of diabetic neuropathy as a hydantoin aldose reductase inhibitor. However, it shows the hypersensitivity reaction in the patients, including fever and myalgia. It was confirmed by performing the assay that sorbinil oxidatively metabolized to a toxic intermediate. The structural similarities between Sorbinil and phenytoin may cause a similar type of adverse reaction to appear, which underlying hypersensitivity reactions for both drugs. [5] To reduce these side effects the lead molecule spirohydantoin was avoided and several other drugs were synthesized keeping the carboxylic acid group in their structure as being a first active drug sorbinil contains a carboxylic group and a carboxylic acid group is a desired group for the proper functioning of an aldose reductase inhibitor. That carboxylic group terminus binds to the NADPH and changes the conformation of the enzyme first and the enzyme oxidized NADPH to  $\text{NADP}^+$ . Among the carboxylic group containing analogous, only the benzothiazole-containing drugs show the most potent activity.

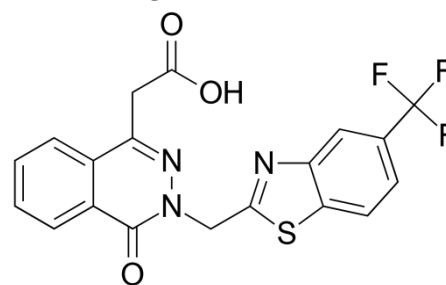
### ARIs in Clinical Trials

The Institute for Diabetes Discovery LLC and Pfizer recently discovered 2 benzothiazole-containing ARIs which are currently under clinical trials namely lidorestat and

zopolrestat. Both drugs is having a benzothiazole ring with three fluorine atoms and a carboxylic group.



**Figure 3:** Lidorestat



**Figure 4:** Zopolrestat

Lidorestat is currently under phase-II clinical trials for diabetic polyneuropathy and Zopolrestat is currently under phase-III clinical trials for diabetic cardiomyopathy and it has shown very impressive result in phase-II clinical trials, its developments for diabetic neuropathy is currently being prohibited for its minimum dose per day is 250-500mg was not so effective as on phase III clinical trials results, though in phase II clinical trials the dose 1000mg/kg was effective. [6-8]

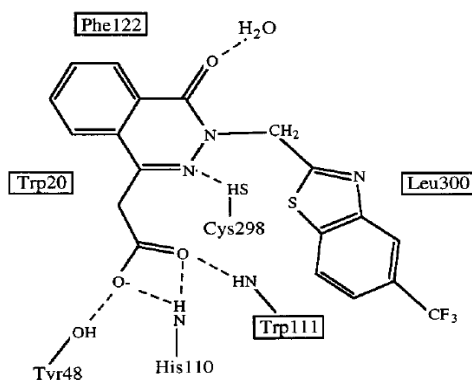


Figure 5: Schematic diagrams of the interactions between Zopolrestat and ALR2 in the crystal structure of the complex

Drug Information:

Table 1

Name of the drug	Information about drug
<p>Lidorestat</p>	<p>Originator-Institute for Diabetes Discovery LLC                      Study type-Interventional                      Purpose-Treatment for diabetic polyneuropathy                      Study ID number-676/US/2-01                      Clinical trial phase-Phase-II</p>
<p>Zopolrestat</p>	<p>Originator-Pfizer                      Mass-419.0551                      Class-Aldose reductase inhibitor                      Target pathway-Fructose and mannose metabolism                      Clinical trial phase-Phase-III</p>

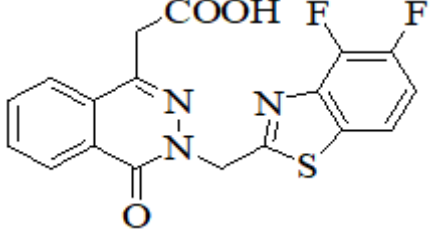
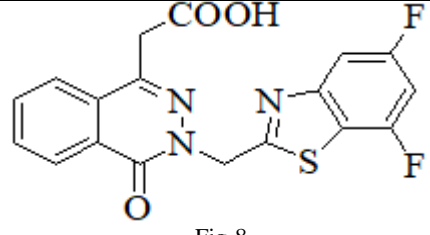
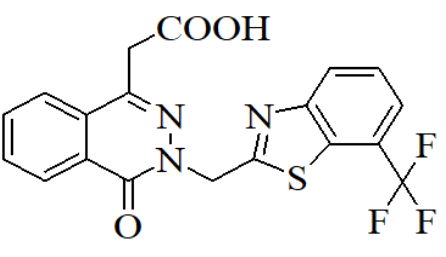
Recent Advances

A series of different congeners of Zopolrestat had been synthesized by Fizer in search of new benzothiazole derivatives with potent aldose reductase inhibitor activity compare to sorbinil. Benzothiazole moiety was chosen as a lead molecule as Sorbinil has a side effect of hypersensitivity and it belongs to the class spirohydantoin.

From the structure-activity relationship, it has been already discovered that spirohydantoin or carboxylic acids are the two most important classes of aldose reductase enzyme inhibition. The percentage of inhibition of sorbitol had been checked using all the synthesized compounds and some of the compound showed an excellent percent of inhibition, the structure of those compounds are given below. [9]

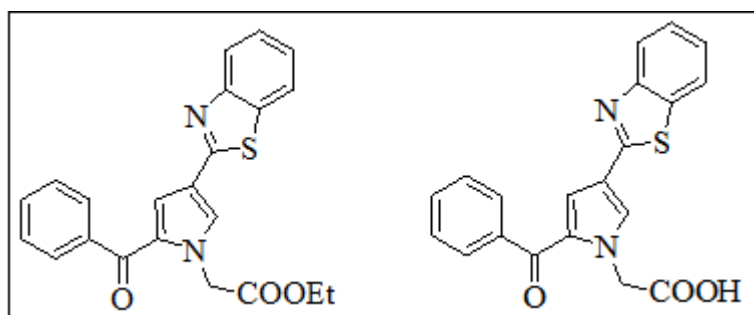
Table 2: Different congeners of Zopolrestat

Compounds	% Inhibition of Sorbitol
<p>Fig-6</p>	87%

 <p style="text-align: center;">Fig-7</p>	82%
 <p style="text-align: center;">Fig-8</p>	80%
 <p style="text-align: center;">Fig-9</p>	80%

The followings are two synthesized benzothiazole derivatives intended for aldose reductase inhibition. As there is a sequence similarity of around 85% between rats lenses with humans, to check the activity of the synthesized compound the assay was performed by

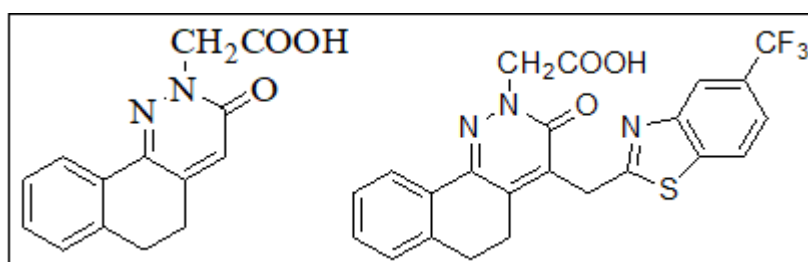
spectrophotometric monitoring of the NADPH oxidation method using a rat's lens. Both compounds had shown comparatively better activity with a reference drug Sorbinil. [10]



**Figure 10:** New benzothiazole derivatives

A structure-based drug design of aldose reductase inhibitor had shown the comparative study of two model structures obtained by docking or molecular modeling, where the compound substituted with a benzothiazole moiety shows

better activity concerning non-substituted compound. Both drugs belong to the class carboxylic acid inhibitors as most of the active ARIs developed till now are from this class. [11]



**Figure 11:** New benzothiazole derivatives

Carboxylic acid containing different compounds is currently in the clinical trial phase as an aldose reductase inhibitor; among them the most active compound was found to be

zopolrestat. These findings help us to know about the interaction between the zopolrestat and the enzyme ARI2 by the resolution of crystal structure. After this study and the

evidence different compounds containing both a carboxylic group and a benzothiazole moiety are currently being prepared and studied by the researchers. In this paper, some new benzothiazole-containing compounds had been synthesized and evaluated. From them, one benzothiazole-containing compound showed the most potent activity as compared to zenarestat. The structure of the compound is bellowed. [12]

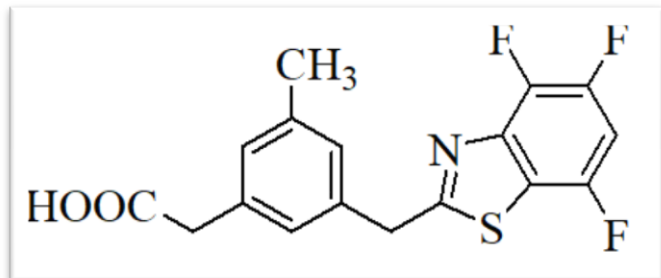


Figure 12: Benzothiazole derivative with ARI activity

By X-ray crystallography, it has been proven that the benzothiazole moiety of zopolrestat fits into the hydrophobic pockets of the aldose reductase enzyme. These pockets of the binding site are developed after changing the conformation of the enzyme, and it shows the ligand specificity towards the aldose reductase enzyme. The

compounds with a benzothiazole moiety bind to these specific pockets and show higher selective aldose reductase inhibition activity. Following is a new ARI with a carboxylic group. [13]

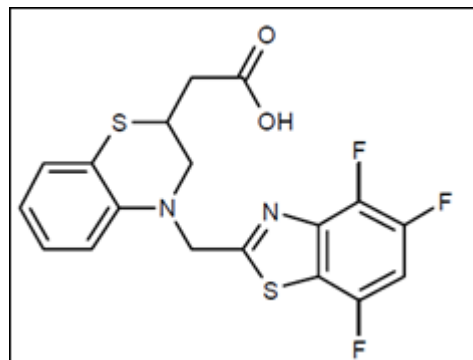


Figure 13: New benzothiazole derivative with ARI activity

Inst. Pharm. Discovery has recently patented two acetic acid analogs with benzothiazole moiety one is showing excellent activity on AR selectively over aldehyde reductase and another one is having activity on both AR as well as aldehyde reductase. The followings are the structure of newly patented compounds. [13]

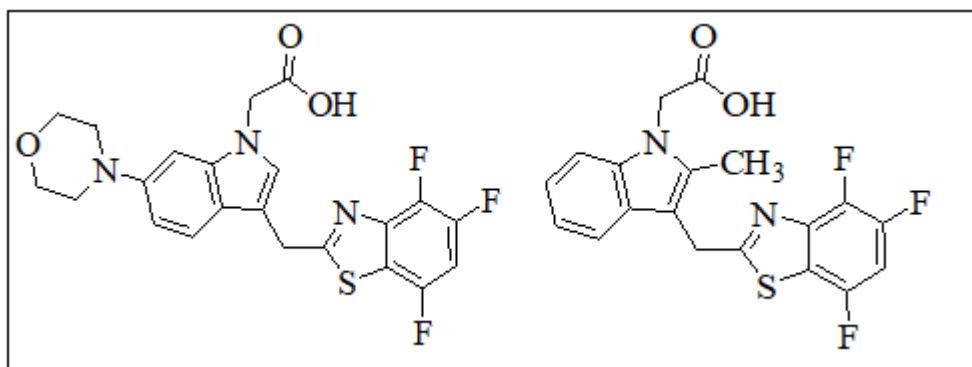


Figure 14: Newly patented benzothiazole derivative with ARI activity

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