DESIGN OF NEW ALDOSE-REDUCTASE-INHIBITORS – A STRUCTURE BASED APPROACH

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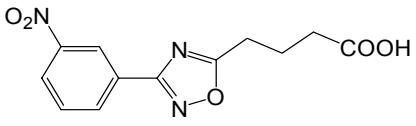
Diabetes mellitus is a universal health problem. The WHO estimates that 150 million people suffer from diabetes mellitus worldwide in 2005. A serious problem in the treatment of diabetes are the so-called long-term complications as neuropathy, retinopathy, nephropathy or cataract. The sorbitol accumulation has been proposed to be an important factor in their development. Catalyzing the NADPH-dependent reduction of glucose to sorbitol, aldose reductase is an important target for preventing these complications. Therefore, new aldose reductase inhibitors are strongly needed.

A structure-based design approach is an efficient way to create new aldose reductase inhibitors. Virtual screening based on the ultrahigh resolution crystal structure of the inhibitor IDD594 in complex with human AR, identified two compounds (**1,2**) with IC_{50} values in the micromolar range, serving us as lead structures [1]. Based on the known interactions between the ligand and its binding pocket, we reduced the lead structures on the minimal structural requirements and developed practical synthetic pathways from commercially available compounds (**3**). The new synthesized compounds were assayed for their inhibition of AR, showing inhibitory activities in a low micromolar range. Additionally, based on flexible docking results, the alkylcarboxylic acid moiety was replaced by phenylacetic acid (**4**), improving the inhibitory activity.



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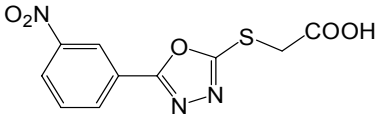

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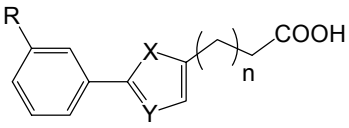

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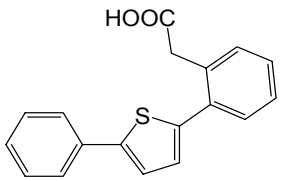

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[1] Kraemer, O. *et al*., *Proteins: Struct., Funct., Bioinf.* **2004**, *55*, 814-823.