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Synthesis, α-glucosidase inhibition, and molecular docking studies of novel *N*-substituted hydrazide derivatives of atranorin as antidiabetic agents

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ABSTRACT

A series of novel *N*-substituted hydrazide derivatives were synthesized by reacting atranorin, a compound with a natural depside structure (**1**), with a range of hydrazines. The natural product and 12 new analogues (**2–13**) were investigated for inhibition of α-glucosidase. The *N*-substituted hydrazide derivatives showed more potent inhibition than the original. The experimental results were confirmed by docking analysis. This study suggests that these compounds are promising molecules for diabetes therapy. Molecular dynamics simulations were carried out with compound **2** demonstrating the best docking model using Gromac during simulation up to 20 ns to explore the stability of the complex ligand-protein. Furthermore, the activity of all synthetic compounds **2–13** against a normal cell line HEK293, used for assessing their cytotoxicity, was evaluated.

Type 2 diabetes mellitus (T2DM) affects a large population worldwide. It is a serious and common chronic disease resulting from a complex inheritance-environment interaction along with other risk factors such as obesity and sedentary lifestyle. There are several classes of antidiabetic drugs to treat this disease include insulin, metformin, thiazolinediones, sulfonylureas, DPPIV inhibitors, and α-glucosidase inhibitors. However, it is difficult to effectively treat T2DM by single treatment option in the long term. Therefore, there is a significant unmet medical need for the development of new, long term safety and highly effective antidiabetic therapies with novel and multiple mode of action[1]

α-Glucosidase is the enzyme that catalyzes the breakage of the α-1,4-glycosidic bonds of polysaccharides with concomitant conversion into glucose.[2] α-Glucosidase inhibitors are therapeutic agents that can reduce the level of glucose in type 2 diabetes (T2DM) by preventing the hydrolysis of glucose by α-glucosidase, a carbohydrate metabolizing enzyme. Acarbose is an antidiabetic drug used to treat T2DM that causes various side effects including abdominal discomfort, diarrhea, bloating, pain, and flatulence. Previous studies have shown that α-glucosidase can be related to diseases such as cancer and viral infections.[3] Therefore, α-glucosidase is an attractive target for developing drugs to treat T2DM and several α-glucosidase inhibitors are already in the market or in clinical trial.

Atranorin, a biologically active lichen metabolite, exhibits a wide range of biological activities, being antimicrobial, antiviral, anti-inflammatory, analgesic, and cytotoxic at levels from moderate to high.[4–6] Interestingly, it is able to inhibit enzymes involved in human diseases, including tyrosinase, glucosidase, acetylcholinesterase, and xanthine oxidase.[7–12] Atranorin is present in large amounts in the *Parmotrema* lichens.[7,13] The preparation of atranorin derivatives is

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