3 Biotech (2025) 15:5
https://doi.org/10.1007/s13205-024-04178-1

ORIGINAL ARTICLE

Exploration of leads from bis-indole based triazine derivatives targeting human aldose reductase in diabetic type 2: in-silico approaches

Miah Roney[1,2] · Abdul Rashid Issahaku[3] · Md. Nazim Uddin[4] · Anke Wilhelm[3] · Mohd Fadhlizil Fasihi Mohd Aluwi[1,2]

Received: 21 June 2024 / Accepted: 26 November 2024 / Published online: 11 December 2024

Abstract

Diabetes mellitus (DM) poses a major global healthcare challenge, highlighting the need for new treatments beyond current options. Currently available drugs have side effects including weight gain, nausea, vomiting, diarrhea, insulin resistance etc. Therefore, given the benefits of indole derivatives in diabetes and the lack of computational studies on bis-indole-based triazine derivatives with aldose reductase (AR), this study employs in-silico analysis to explore their potential as type-2 diabetes treatments. Based on the Differential Expression analysis, the human aldose reductase (HAR) encoding gene AKR1B1 showed overexpression in GSE30122 diabetes patients (Log2FC = 0.62, $P < 0.01$). Moreover, the compounds 2-((5,6-di(1H-indol-3-yl)-1,2,4-triazin-3-yl)thio)-1-(3-hydroxy-5-methylphenyl)ethan-1-one (4) and 2-((5,6-di(1H-indol-3-yl)-1,2,4-triazin-3-yl)thio)-1-(4-nitrophenyl)ethan-1-one (8) were identified as leading candidates, showing binding energies of − 62.12, − 81.73 kcal/mol and − 57.19, − 85.97 kcal/mol, respectively. Docking, MM/GBSA screening, molecular dynamics (MD) simulations, PCA, and post-MM/GBSA analysis confirmed their stability and favorable binding compared to the apo protein and control. Further in-vitro, in-vivo, and clinical studies are required to validate their therapeutic potential.

Keywords Anti-diabetic · In-silico · Human aldose reductase · Bis-indole based triazine derivatives · Docking · MD Simulation

Introduction

Diabetes mellitus (DM) is a chronic and progressive disease which is typified by disruptions in the metabolism of fat, protein, and carbohydrates (Amin et al. 2023; Wang et al. 2023). According to data that is currently available, 403 million individuals globally were diagnosed with diabetes in 2019, and it is projected that by 2045, this figure would have increased to 700 million people (Wang et al. 2023). The two primary causes of type-2 diabetes (T2D) are inadequate pancreatic manufacture of insulin (type-2) or inefficient insulin utilization by the body (type-1). Of all cases of DM, 90–95% are caused by type 2 diabetes, often known as non-insulin dependent diabetes (Hussain et al. 2023). However, the current anti-diabetic type 2 drugs either increase insulin production or change glucose excretion and absorption without reducing insulin resistance (Amin et al. 2023). In addition, there are a few drawbacks and possible side effects of these medications, such as hypoglycemia, insulin resistance, nausea, vomiting, diarrhea, and the need for many daily prescriptions or repeated injections, which can be costly and inconvenient. Therefore, it is imperative to keep looking for novel therapeutic drug candidates that have fewer side effects and may successfully prevent and treat diabetes.

Chronic retinopathy, malignancy, neuropathy, mental problems, nephropathy, and other consequences are the main types of diabetic sequelae linked to hyperglycemia (Alexiou et al. 2009). Insulin-dependent glucose absorption and the

✉ Mohd Fadhlizil Fasihi Mohd Aluwi
fasihi@umpsa.edu.my

1 Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Tun Razak, Gambang, 26300 Kuantan, Pahang, Malaysia

2 Centre for Bio-Aromatic Research, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Tun Razak, Gambang, 26300 Kuantan, Pahang, Malaysia

3 Department of Chemistry, University of the Free State, 205 Nelson Mandela Avenue, Bloemfontein 9301, South Africa

4 Institute of Food Science and Technology, Bangladesh Council of Scientific and Industrial Research, Dhaka 1205, Bangladesh