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RESEARCH ARTICLE

GLP-1 Targeted Novel 3-phenyl-7-hydroxy Substituted Coumarins Mitigate STZ-induced Pancreatic Damage and Improve Glucose Homeostasis in OGTT Method

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Abstract: *Background*: Worldwide, type 2 diabetes mellitus accounts for a considerable burden of disease, with an estimated global cost of >300 billion USD annually. For this reason, the search for more effective and efficient therapeutic anti-diabetic agents is continuing. Recent studies support the search for coumarins or related compounds with potential blood glucose-lowering properties.

Aim: The study aims to design, synthesize and evaluate the hypoglycemic activity of a new class of 7-hydroxy coumarin derivatives.

Objective: To explore and establish the *in-silico*-driven pharmacological role of a new class of 7-hydroxy coumarin derivatives as the therapeutic strategies against type 2 diabetes mellitus.

Methods: A new class of 7-hydroxy coumarin derivatives was designed by assessment of their physicochemical properties and molecular docking against the Glucagon-like peptide-1 (GLP-1) receptor. Two novel series of 30 compounds were synthesized. The chemical structures of all the synthesized analogues have been elucidated by spectral studies of IR, ^{1}H-NMR, and mass spectroscopy. After considering the molecular docking score and their physicochemical properties, the compounds were screened out for the evaluation of their hypoglycemic potential. The compounds were investigated for their hypoglycemic activity using a streptozotocin (STZ) induced diabetic model and an oral glucose tolerance test (OGTT) method at different dose levels.

Results: The molecular docking studies of synthesized derivatives reveal significant molecular interaction with the various amino acid residues of the GLP-1 receptor. IR spectra analysis revealed a strong band of -NH stretching in the range of 3406.7-3201.61 cm^{-1} and one strong band for the lactone carbonyl group of the coumarin ring in the range of 1722.0-1703.5 cm^{-1}, confirming the chemical structure of all produced compounds. The synthesized coumarin analogues with the best docking score exhibited remarkable hypoglycemic potential as assessed by the STZ model and the OGTT method.

Conclusion: Coumarin derivatives explored a good structure-activity relationship (SAR) and produced significant hypoglycemic potential.

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1. INTRODUCTION

Nature has shown an ability to synthesize unique and novel chemical moieties with effective therapeutic potential, with various structure-activity correlations. Anti-diabetic medications are still difficult to find, despite improvements in contemporary medicine and the creation of new therapeutic agents [1]. Most commonly, coumarins are utilized in anticoagulation and antithrombotic therapy because of their widespread distribution in natural plants. As coumarins and their derivatives have become more well studied, so has their impact on diabetes and its consequences [2]. However, in drug development, combinatorial chemistry and high-throughput screening pose a barrier to research targeted at discovering new natural therapeutic compounds. New coumarin compounds, either extracted from traditional medicine or chemically synthesized, are continually being sought in the search for new diabetes-fighting agents [3].

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