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Synthesis of 2-phenyl-3*H*-quinazolin-4-one derivatives and *in vitro* and *in silico* evaluation as potential antidiabetic agents *via* α-amylase inhibition and glucose uptake in yeast cells

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Diabetes mellitus is a common endocrine disorder characterized by hyperglycemia, which is increasing steadily all over the world. Current medications have limitations due to lower efficacy and side effects. Thus, the introduction of novel compounds is crucial. The main objective of this study is to synthesize 2-phenyl-3*H*-quinazolin-4-one and its derivatives (4-OH, 3-OH, 2-OH, 4-F, 4-Cl, 4-OCH_3, 2-OCH_3, 4-NO_2, 3-NO_2, 2-NO_2, 2.4-diOCH_3, 2.5-diOCH_3, 3,4,5-triOCH_3, and 3-OCH_3-4-OH) and evaluate their alpha amylase inhibitory activities and glucose uptake across the cell membrane in the yeast cell *in vitro* and *in silico*. The synthesis was carried out by oxidative cyclocondensation of 2-aminobenzamide with the corresponding benzaldehyde in an iron (III) chloride solution. The structures of the derivatives were confirmed by spectroscopic techniques, including FTIR, NMR, and HRMS. The quinazolinone core structure possesses multiple pharmacological properties, such as antioxidant, anti-inflammatory, antimicrobial, antifungal, anticancer, and antidiabetic properties. The similarity of the structure to that of other known antidiabetic drugs due to the presence of carbonyl, amine, and amide groups enhances its anti-diabetic properties. Results from glucose uptake by yeast showed that 2-(4-methoxyphenyl)-3*H*-quinazolin-4-one had the lowest 50% uptake value of 24.02 ± 0.96 mM, compared with the standard drug metformin (25.99 ± 2.41 mM). The alpha-amylase inhibitory assay showed that 2-(2-methoxyphenyl)-3*H*-quinazolin-4-one exhibited potent inhibition, with an IC_{50} of 0.42 ± 0.05 mM, compared with the standard drug acarbose (0.53 ± 0.05 mM). Docking results revealed that 2-(4-nitrophenyl)-3*H*-quinazolin-4-one has a stronger binding affinity to the GLUT2 protein with a binding energy of -9.6 kcal/mol. The compounds 2-(4-hydroxyphenyl)-3*H*-quinazolin-4-one and 2-(3-nitrophenyl)-3*H*-quinazolin-4-one have the highest binding affinity for the amylase enzyme, with -8.2 kcal/mol among the synthesized derivatives. These findings suggest that synthesized 2-phenyl-3*H*-quinazolin-4-one derivatives are promising candidates for diabetes mellitus. Further, it suggests that more research is required to validate the efficacy, toxicity, and mechanisms of action of these compounds.

Keywords:

Diabetes mellitus, 2-phenyl-3*H*-quinazolin-4-one, Glucose uptake by yeast, alpha amylase