Effect of 4-oxoquinoline-3-acyl-hydrazone ribonucleosides on diabetes-related α-glycosidase activities

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Introduction

Quinolone-based drugs are widely prescribed in clinics due to their broad-spectrum antimicrobial activity and high oral bioavailability. One side effect of these drugs is severe hypoglycemia, especially in patients under sulfonylureas treatment. The exact mechanism by which this event occurs is still unclear, but some studies suggest that it is due to an increase of insulin secretion and GLUT-1 modulation¹.

The hypoglycemic effect of quinolone compounds suggests a new therapeutic application as oral antihyperglycemic agents. Combined with α-glycosidase inhibitory activity these compounds may act as multi-target drugs helping in the treatment of diabetes mellitus by avoiding post-prandial hyperglycemia, a potential harmful event.

In this study, we evaluated the effect of seven new 4-oxoquinoline-3-acyl-hydrazone ribonucleosides² (Fig. 1) on the activity of α-glycosidases used as models for the development of oral antihyperglycemic drugs. The carbohydrate moiety resembles the structure of potent α-glycosidases inhibitors previously identified by our group³.

![Figure 1. Acyl-hydrazone ribonucleoside 1.](image)

Results discussion

Initial screening at 100 μM showed that compounds 1a (R1 = hydrogen; R2 and R3 = chloro) and 1g (R1 = bromine; R2 = hydrogen; R3 = chloro) inhibited near 40% of yeast maltase activity while 1a inhibited 60% of porcine pancreatic α-amylase activity (Fig. 2). A curve with variable inhibitor concentrations was obtained in order to determine IC₅₀ for each of these compounds (Fig. 3).

![Figure 2. Screening of title compounds (100 µM) against yeast maltase and porcine pancreatic α–amylase activities. The commercial inhibitor acarbose is included as a reference. Bars represent mean ± standard deviation (n=3).](image)

![Figure 3. Inhibition curves and IC₅₀ values for 1a (A and B) and 1g (C) against diabetes-related α-glycosidase activities. Data expressed as mean ± standard deviation (n=3).](image)

These results indicate that 1a was the most potent compound of this series since it showed the lowest IC₅₀ and inhibited both enzymes.

Conclusions

Compound 1a was the most active on both α-glycosidases tested. These results suggest that 1a may serve as a scaffold for the development of new antihyperglycemic drugs. Further experiments will evaluate the inhibition mode of this compound and its hypoglycemic effect in vivo.

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² Forezi, L. S. M. 2014. Tese de doutorado, Instituto de Química, Programa de Pós-Graduação em Química, UFF.