

## Effect of 4-oxoquinoline-3-acyl-hydrazone ribonucleosides on diabetes-related $\alpha$ -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 modulation<sup>1</sup>.

The hypoglycemic effect of quinolone compounds suggests a new therapeutic application as oral antihyperglycemic agents. Combined with  $\alpha$ -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 ribonucleosides<sup>2</sup> (Fig. 1) on the activity of  $\alpha$ -glycosidases used as models for the development of oral antihyperglycemic drugs. The carbohydrate moiety resembles the structure of potent  $\alpha$ -glycosidase inhibitors previously identified by our group<sup>3</sup>.

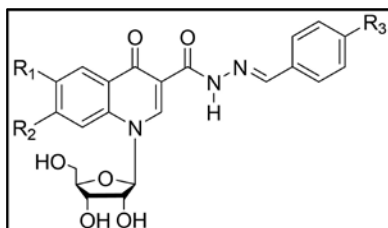


Figure 1. Acyl-hydrazone ribonucleoside 1.

### Results discussion

Initial screening at 100  $\mu$ M showed that compounds **1a** ( $R_1$  = hydrogen;  $R_2$  and  $R_3$  = chloro) and **1g** ( $R_1$  = bromine;  $R_2$  = hydrogen;  $R_3$  = chloro) inhibited near 40% of yeast maltase activity while **1a** inhibited 60% of porcine pancreatic  $\alpha$ -amylase activity (Fig. 2). A curve with variable inhibitor concentrations was obtained in order to determine  $IC_{50}$  for each of these compounds (Fig. 3).

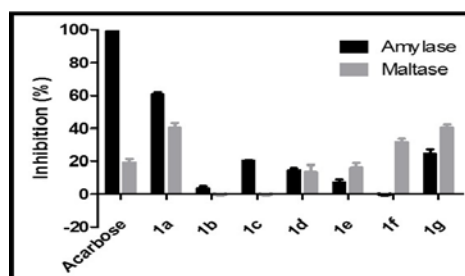


Figure 2. Screening of title compounds (100  $\mu$ M) against yeast maltase and porcine pancreatic  $\alpha$ -amylase activities. The commercial inhibitor acarbose is included as a reference. Bars represent mean  $\pm$  standard deviation ( $n=3$ ).

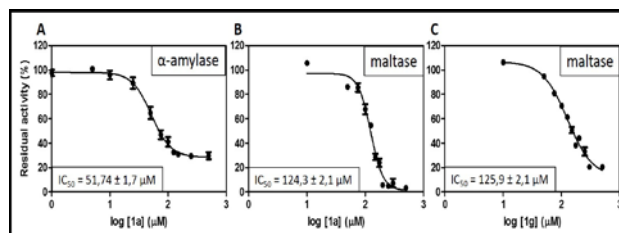


Figure 3. Inhibition curves and  $IC_{50}$  values for **1a** (A and B) and **1g** (C) against diabetes-related  $\alpha$ -glycosidase activities. Data expressed as mean  $\pm$  standard deviation ( $n=3$ ).

These results indicate that **1a** was the most potent compound of this series since it showed the lowest  $IC_{50}$  and inhibited both enzymes.

### Conclusions

Compound **1a** was the most active on both  $\alpha$ -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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