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Design, synthesis, and docking of highly hypolipidemic agents: *Schizosaccharomyces pombe* as a new model for evaluating α -asarone-based HMG-CoA reductase inhibitors

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ABSTRACT

A series of α -asarone-based analogues was designed by conducting docking experiments with published crystal structures of human HMG-CoA reductase. Indeed, synthesis and evaluation of this series showed a highly hypocholesterolemic *in vivo* activity in a murine model, as predicted by previous docking studies. In agreement with this model, the polar groups attached to the benzene ring could play a key role in the enzyme binding and probably also in its biological activity, mimicking the HMG-moiety of the natural substrate. The hypolipidemic action mechanism of these compounds was investigated by developing a simple, efficient, and novel model for determining HMG-CoA reductase inhibition. The partial purification of the enzyme from *Schizosaccharomyces pombe* allowed for testing of α -asarone- and fibrate-based analogues, resulting in positive and significant inhibitory activity.

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1. Introduction

It is generally recognized that hypercholesterolemia and high levels of serum LDL-cholesterol contribute significantly to the progression of atherosclerosis,^{1,2} which is the leading cause of cardiovascular diseases.^{3,4} Liver enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMGR) catalyzes the formation of mevalonate, the key step in the biosynthesis of cholesterol and isoprenoids.⁵ Therefore, inhibition of this enzyme has proven to be the most efficient therapy for hyperlipidemia.⁶

Statins, which possess an HMG-like moiety linked to a hydrophobic decalin core, are the most effective hypocholesterolemic drugs for clinical use today.⁷ Synthetic statin-like compounds that include an HMG-like moiety have shown significant hypocholesterolemic activity.⁸ There are other agents without a structural HMG-like moiety that are known to inhibit HMGR, such as cholestin,⁹

diosgenin,¹⁰ ketanserine tartrate,¹¹ lanosterol analogues,¹² β -sitosterols,¹³ and tunicamycin,¹⁴ among many others.¹⁵ This is also the case of α -asarone (**1**) (Fig. 1), which is the active metabolite of the Yucatan peninsula tree called Elemuy (*Mosannonna depressa* (Baill.) Chatrou).^{16,17} It has exhibited a potent *in vivo* hypolipidemic activity,¹⁸ and inhibits hepatic HMGR.¹⁹ By using an automated docking approach, we have reported a binding model of **1** with HMGR, concluding that the three methoxy groups of the substituted benzene bind to the enzyme active site like an HMG-moiety.²⁰

In order to determine the pharmacophoric groups that give rise to the activity of **1**, and also to improve the latter and its pharmacological profile, numerous synthetic analogues have been prepared,²¹ revealing the importance of the polar oxygen atoms and the hydrocarbon side-chain. Among the most active analogues are two series of compounds, one carrying a polar substituent in the C-4 carbon of the benzene ring, such as halogens, an amino or a nitro group, **2a–d** (Fig. 1),^{21a} and the other in which the position of the double bond of the side-chain is changed.^{21b} The series of hydroxyl analogues **3a–c**, which are the synthetic precursors of compounds **1** and **2**, exhibited significant hypocholesterolemic activity.^{21a} Those compounds in which the characteristic three

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