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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.

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] ketanserin 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 (*Mosannona 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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