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Research Article

Hypolipidemic Activity of New Phenoxyacetic Derivatives Related to α-Asarone with Minimal Pharmacophore Features

María del Carmen Cruz,[1] María Salazar,[2] Yésica Garciafigueroa,[2] Dolores Hernández,[2] Francisco Díaz,[1] Germán Chamorro,[2]* and Joaquín Tamariz[1]*

[1]*Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n, 11340 México, D.F., México*

[2]*Departamento de Farmacia, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n, 11340 México, D.F., México*

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ABSTRACT Five new series of potential hypolipidemic agents **3–7** were synthesized, in order to establish the minimal pharmacophore features associated to the potent hypocholesterolemic activity of natural α-asarone (**1**) and synthetic clofibrate mimetic derivatives **2**. The compounds were examined in hyperlipidemic male mice after oral administration of 25, 50, and 100 mg/Kg for 6 days. The isomeric series of acids and esters **3a–3c** and **4a–4c** were unexpectedly less active than the most simple structural isomeric compounds **5–7**. This reveals that the phenoxyacetic acid scaffold carrying a hydrocarbon side chain, also found in derivatives **2**, seems to be the most favorable lead for further development of potent hypolipidemic drugs. Drug Dev. Res. 60:186–195, 2003.

Key words: α-asarone; hypocholesterolemia; minimal pharmacophores; phenoxyacetic scaffold

INTRODUCTION

Hypocholesterolemic drugs are in urgent demand since a strong relationship between hypercholesterolemia and atherosclerosis has been established through epidemiological, experimental, and clinical data [Vogel et al., 1998]. α-Asarone (**1**) has attracted widespread interest in view of its hypolipidemic activity [Chamorro et al., 1993; Garduño et al., 1994], and more recently as a potential antithrombotic [Poplawski et al., 2000], antimicrobial, insecticidal, nematicidal, and antifeedant agent [Momin et al., 2002]. As part of our ongoing pharmacological studies in this field, various analogues of **1** have been prepared and evaluated, exhibiting in vivo hypocholesterolemic activity [Díaz et al., 1993]. In this series, some nitrogenated groups and halogens were introduced in the aromatic ring of **1**, replacing the C-4 methoxy group. We have also evaluated the perturbation on the activity of **1** associated with its propenyl side chain, by unconjugating the double bond to the aryl ring [Chamorro et al., 1998], by reducing or increasing its length [Cruz et al., 2001a], and by

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*Correspondence to: Joaquín Tamariz, Escuela Nacional de Ciencias Biológicas, IPN, Prol. Carpio y Plan de Ayala s/n, 11340 México, D.F., México. E-mail: jtamariz@woodward.encb.ipn.mx

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