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

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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 hypcholesterolemic 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. © 2003 Wiley-Liss, Inc.

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

INTRODUCTION Hypcholesterolemic 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, nematocidal, 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 hypcholesterolemic 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 unconjugatig the double bond to the aryl ring [Chamorro et al., 1998], by reducing or increasing its length [Cruz et al., 2001a], and by

Contract grant sponsor: Consejo Nacional de Ciencia y Tecnología (CONACYT); Contract grant number: 38431N; Contract grant sponsor: Coordinación General de Posgrado e Investigación (CGPII), Instituto Politécnico Nacional; Contract grant numbers: 990175 and 20021247.

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Received 18 February 2003; accepted 3 May 2003
Published online in Wiley Interscience (www.interscience.wiley.com) DOI: 10.1002/ddr.10281