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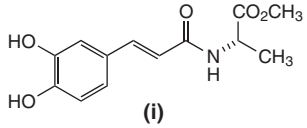
monitor

MOLECULES

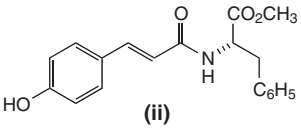
Cinnamic acid derivatives as novel antihypercholesterolemic agents

Low-density lipoprotein (LDL) is a major carrier of cholesterol and there is a correlation between LDL-cholesterol concentration and the incidence of coronary heart disease [1,2]. Acyl-CoA:cholesterol acyltransferase (ACAT; EC 2.3.1.26) catalyzes the esterification of cholesterol with an acyl group from fatty acyl-CoA and thus participates in the regulation of intracellular storage and intercellular circulation of cholesterol [3]. Research indicates that ACAT might affect the development of atherosclerosis via foam cell formation [4,5]. In mammals, two isoforms of ACAT have been identified – ACAT-1 and ACAT-2. It is generally accepted that compounds that inhibit both isotypes will have a significant therapeutic effect [6]. Research performed by Lee *et al.* [7] indicated that 3,4-dihydroxycinnamic acid (L-alanine methyl ester) amide (**i**) is a potent antiatherogenic agent. Continuing on from this research, Lee and co-workers [8] recently described a series of derivatives structurally related to **i**. In particular, compounds **ii** and **iii** were selected for several biological assays, including ACAT inhibition, antioxidant activity and high-density lipoprotein (HDL)-particle rearrangement [8].

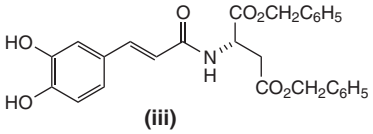
When tested for antioxidant activity using the thiobarbituric acid reactive substances assay [extent of inhibition determined by measuring malondialdehyde (MDA) generation], compounds **i**, **ii** and **iii** showed inhibition levels of 75%, 28% and 91%, respectively, at a final compound concentration of 10 μM [8]. In the ACAT-inhibition assay, compound **ii** showed comparable inhibition (IC_{50} of 60 μM) of ACAT-1 and ACAT-2, whereas **iii** was slightly more potent towards ACAT-1 (IC_{50} of 81 μM) than ACAT-2 (IC_{50} of 95 μM). By contrast, compound **i** was inactive in this test. With respect to the HDL-particle rearrangement assay, compound **ii** maintained the original size of reconstituted HDL (96 Å), whereas addition of compound **iii** led to a reduction in size (83 Å). These results suggest that **ii** could interact with apolipoprotein A-I to regulate the particle rearrangement activity. Finally, **ii** and **iii** showed no toxicity when tested on mouse RAW264.7 macrophage cell (1×10^5 cell/100 μl) at concentrations in the range 50–100 μM/1×10^5 cell. Cell viability was reduced by <10% at the lower concentration and by ~20% at the higher concentration in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and lactate dehydrogenase-release assays. These results suggest that the compounds could be promising substrates for the development of novel antihypercholesterolemic agents.



(i)



(ii)



(iii)

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