Design, synthesis and hypolipidemic activity of novel 2-(naphthalen-2-yloxy)propionic acid derivatives as desmethyl fibrate analogs

Gamal A. Idrees, Omar M. Aly*, Gamal El-Din A.A. Abuo-Rahma, M.F. Radwan

Department of Medicinal Chemistry, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt

ABSTRACT

A series of 2-(naphthalen-2-yloxy)propionic acid derivatives were prepared. The hypolipidemic activity of the new compounds as well as the intermediate acid 2 was evaluated in the high cholesterol diet (HCD) fed hyperlipidemic rat model. Interestingly, the S-allylated mercaaptoprazole 8b and the 1,3,4-oxadiazole 9 produced striking reduction of serum levels of total cholesterol (TC), triglycerides (TGs) and low-density lipoproteins (LDLs) and elevation of serum high-density lipoproteins (HDLs) being more active than the reference gemfibrozil. In addition, the 1,2,4-triazole 7a, the hydroxypropazoline 10 and the pyrazoline derivative 11 exhibited good hypolipidemic activity on different lipid parameters.

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1. Introduction

Hypolipidemia is the major risk factor for atherosclerosis and atherosclerosis-associated conditions such as coronary heart diseases (CHD), ischemic cerebrovascular diseases, and peripheral vascular diseases. A 1% drop in serum cholesterol level was reported to reduce the risk for CHD by 2% [1]. The search for effective and safe hypolipidemic agents has engaged the interests of medicinal chemists, biochemists, pharmacologists and clinicians. Fibrin acid derivatives (fibrates) represent an important class of lipid modifying agents. The discovery of the biological target of fibrates, peroxisome proliferator-activated receptors (PPARs) specifically the alpha isotype, enabled to explain the diverse lipid and non-lipid effects of fibrates which contribute in their hypolipidemic and antatherosclerotic benefits [2–4]. Literature references to SAR for this class of drugs are sparse [5]. In order to define the structural requirements for the maximal hypolipidemic properties related to fibrates, several modifications of the fibrate moiety were reported and their biological activities were investigated. From the literature, it is evident that the high lipophilicity is required for the optimal antihyperlipidemic effects of fibrates. Although most active fibrates contain a phenoxysobutyrate moiety [5], it was proven that the desmethyl fibrate analogs (2-phenoxypropionic acid derivatives) e.g. desmethylclofibrin acid retained the hypolipidemic activity with fewer side effects [6]. The presence of the acidic functionality is critical for the hypolipidemic action of fibrates [5]. Unfortunately, the free carboxylic group is responsible for the potential unwanted gastrointestinal discomfort which is a frequent side effect associated with fibrate therapy [7,8]. Modification of the carboxylic group to less acidic functions as amides, hydrazides and cyclic derivatives may help to minimize the gastrointestinal upset [9]. Moreover, several compounds containing the 1,2,4-triazole and pyrazole moieties were found to be of value in the management of hypolipidemia [10,11]. Motivated by these findings, the present work aims at the design, synthesis and hypolipidemic study of novel 2-(naphthalen-2-yloxy)propionic acid derivatives as desmethyl fibrate analogs. The new analogs are designed to be prepared by replacement of the p-chlorophenyl moiety in clofibrin acid by the lipophilic 2-naphthyl moiety and the carboxyl function by selected carboxylic acid derivatives like amide, hydrazide and some cyclic derivatives (pyrazole, 1,2,4-triazole and their isosteric 1,3,4-oxadiazole) with the aim of exploring the impact of such modifications on the hypolipidemic profile.

* Corresponding author. Tel.: +20106007771; fax: +2062369075.
E-mail addresses: emaarokan@yahoo.com (O.M. Aly).

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