



Design and microwave facilitated green synthesis of 2-[4-(3-carboxymethyl, methoxy carbonylmethyl-2,4-dioxo and 4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-2 and 3-methyl propionic acid ethyl ester derivatives: a novel structural class of antidyslipidemic agents

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Abstract An interesting hybrid molecular framework comprising of benzylidenethiazolidin-4-one, chalcone and fibrate was designed and synthesized (**BRF1–12**) in order to develop safe and efficacious compounds for the treatment of dyslipidemia, and related complications such as atherosclerosis. The synthesized derivatives were characterized by Fourier transform infrared spectroscopy, mass, and nuclear magnetic resonance spectral studies and evaluated for their antihyperlipidemic potential, using in vivo and in silico methods. All the synthesized compounds exhibited promising antidyslipidemic activity comparable to, and sometimes better than that of, the standard drug-fenofibrate at the tested dose of 30 mg/kg body weight. The most active compounds of the series, **BRF4** and **BRF6**, demonstrated significant antidyslipidemic profile by lowering low density lipoprotein cholesterol, very low density lipoprotein cholesterol, and triglyceride and increasing the level of high density lipoprotein cholesterol, thereby decreasing the atherogenic index. Overall, these effects of **BRF4** and **BRF6** were found to be more potent than fenofibrate, in lipid lowering activity and reducing atherogenic index. Structure–activity relationship studies conclusively established that the presence of N-acetic acid methyl ester at 3rd position of the thiazolidin-4-one nucleus, and a C-3 fibric acid moiety at benzene nucleus were instrumental for enhanced biological activity. The binding mode of benzylidenethiazolidin-4-one fibrate class of compounds, showing crucial hydrogen bonds and pi–pi stacking

interactions with the key amino acid residues Phe118, His440, and Tyr464 at the active site of PPAR α receptor, was assessed by molecular docking studies.

Keywords Anti-hyperlipidemic · Rhodanine · Microwave assisted synthesis · Molecular docking · Benzylidenethiazolidin-4-one · Fibrates

Introduction

Dyslipidemia, a common metabolic syndrome, remains one of the leading causes of many pathological conditions related to insulin resistance, type 2 diabetes, obesity, atherosclerosis and thereby enhanced risk of coronary heart disease (CHD) (Sashidhara et al. 2013). Several studies have demonstrated the relationship between plasma cholesterol levels and the development of CHD (Tiwari et al. 2006). A 1% drop in serum cholesterol reduces the risk of CHD by 2% (Mc Gill 1985). Currently, the most common method to treat dyslipidemia is the use of statins, a HMG-CoA reductase inhibitor. The widespread clinical use of the statins is accompanied by potential dose-limiting hepatotoxicity and myotoxicity, which may be due to the reduced levels of essential isoprenoid precursors, the antioxidant ubiquinone, or dolichols (Sashidhara et al. 2014). Moreover, statins can hardly normalize the high density lipoprotein (HDL) abnormality and significant residual cardiovascular risk remains in many patients despite statins therapy. In view of the recent warning by the US-FDA that statins may enhance the risk of diabetes mellitus (Graham et al. 2004; US Food and Drug Administration 2012),

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