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Original article

2,5,6-Trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles: Search for antihyperlipidemic agents

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ABSTRACT

A novel series of 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles **4**(**a**–**d**) and **7**(**a**–**i**) were rationally designed through QSAR based pharmacophore approach and synthesized from 5-(1,3-benzodioxol-5-yl)-[1,3,4]thiadiazol-2-amine (**1**). The structures of these compounds were established by IR, ^{1}H NMR, ^{13}C NMR, HRMS technique. All the compounds were evaluated for their in vitro antihyperlipidemic activity using trition induced hyperlipidemic model. The newly synthesized title compound **7d**, **7e** and **7h** showed a significant decrease in the serum, TCH, TG LDL and VLDL values along with an increase in serum HDL levels as compared to standard drug Fenofibrate. The treated groups also showed significant decrease in the atherogenic index, LDL:HDL risk ratios and the level of SGOT, SGPT and ALP activities compared to cholesterol induced hyperlipidemic control group.

1. Introduction

Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions such as coronary heart disease, ischemic cerebrovascular disease, and peripheral vascular disease [1]. A causal relationship between the elevated plasma lipids and the development of atherosclerotic plaques has been well established. Hyperlipidemia is an elevation of lipids in the bloodstream and these lipids include fats, fatty acids, cholesterol, cholesterol esters, phospholipids, and triglycerides [2,3]. Therefore, agents that increase HDL cholesterol concentration in the blood and thereby ratio of HDL cholesterol to total cholesterol (H/C) would have promising therapeutic utility as antihyperlipidemic agents [4,5]. Despite significant medical advances, heart attacks due to coronary artery disease (due to atherosclerosis that affects the arteries supplying blood to the heart) and stroke (due to atherosclerosis that affects the arteries supplying blood to the brain) are responsible for more deaths than all other causes combined. In addition to this; different cholesterol lowering drugs or non-pharmacological treatments can significantly reduce morbidity from CHD, thus providing a causal role for cholesterol in coronary events. During recent years, there have been intense investigations on thiadiazole and imidazo[2,1-*b*][1,3,4]thiadiazole compounds carried out, many of which are known to possess interesting biological properties such as antimicrobial [6,7], antitubercular [8,9], anti-inflammatory [10,11], anticonvulsant [12,13], antihypertensive [14,15], and anticancer activities [16].

In view of the above facts and in continuation of our research for various biologically active molecules [9,17–19] and encouraging QSAR and docking study reported in the literature by Kathia M. Honorio et al. [20,21] has prompted us to synthesize novel molecules of fused imidazo[2,1-*b*][1,3,4]thiadiazole and screen for their in vitro antihyperlipidemic activity (Fig. 1).

2. Rationale and designing

The Farnesoid-X-Receptor (FXR) is an attractive drug target for the development of novel therapeutic agents for the treatment of dyslipidemia and cholestasis. Hologram Quantitative Structure Activity Relationship (HQSAR) studies were conducted on a series of potent FXR activators originated from natural product-like libraries by Kathia M. Honorio et al. [21]. In HQSAR, it is possible to visualize the individual contribution to activity of each atom in a

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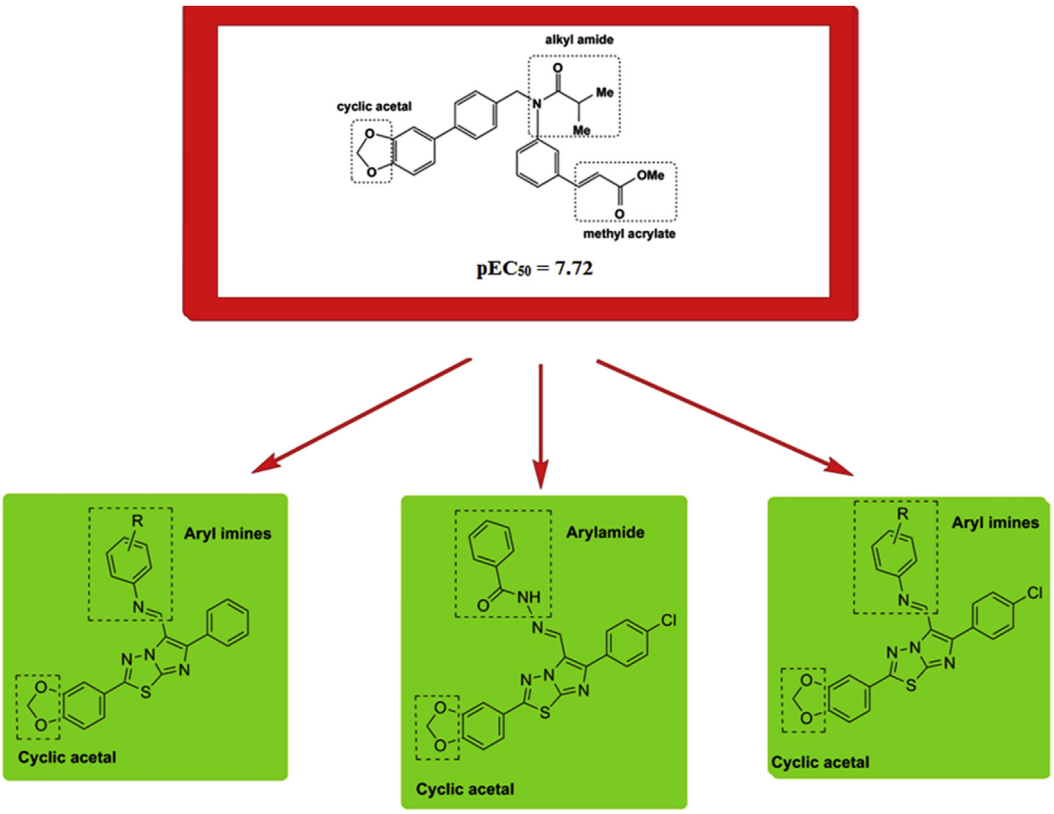

Fig. 1. Synthesized fused imidazo[2,1-*b*][1,3,4]thiadiazoles based upon QSAR model proposed by Kathia M. Honorio et al. [21].

given molecule of the data set through the generation of contribution maps. They suggested that one fragment of the molecular structure, represented by the 1,3-benzodioxol moiety, is strongly related to the biological activity having $pEC_{50} = 7.72$ as shown in Fig. 1. An important role of a QSAR model, besides predicting the activities of untested molecules, is to provide hints about what molecular fragments are directly related to biological activity. This information, combined with knowledge of synthetic chemistry, promoted us to the synthesis new 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles containing 1,3-benzodioxol moiety as novel FXR ligands having improved potency.

3. Chemistry

Synthesis of fused imidazo[2,1-*b*][1,3,4]thiadiazole **4**(**a**–**d**) and **7**(**a**–**i**) is outlined in Scheme 1. 5-(Benzo[*d*][1,3]dioxol-5-yl)-[1,3,4]thiadiazol-2-amine **1** is prepared as per the reported method [22]. Condensation of **1** with respective bromoacetyl compound in ethanol and dimethylformamide yields imidazo thiadiazole **2** and **5** in good yields [23]. Vilsmeier–Hack reaction of imidazo thiadiazole **2** and **5**, in DMF and $POCl_3$ provided respective 5-formyl derivatives **3** and **6** [23]. The aldehyde functional group when treated with amines gave the corresponding imine derivatives **4**(**a**–**d**) and **7**(**a**–**i**). The detail reaction mechanism is depicted in physical data is given in Table 1.

4. Pharmacology

4.1. Experimental animals

Wistar albino adult male rats weighing 200–250 g were obtained from the animal house department of pharmacology, Sree Siddagang College of Pharmacy, Tumkur (Karnataka) India. The animal were grouped and housed in polyacrylic cages (38 × 23 × 10 cm) with not more than six animals per cage and maintained under standard laboratory conditions (temperature 25 ± 2 °C) with dark and light cycle (14/10 h). They were allowed free access to standard dry pellet diet and water ad libitum. The mice were acclimatized to laboratory condition for 10 days before commencement of experiment. The experimental protocol was approved by Institutional Animal Ethical Committee (IAEC No. SSCP/IAEC/2010-11/52) constituted under CPCSEA.

4.2. Induction of hyperlipidemia

Hyperlipidemia was induced in Wistar albino rats by single intraperitoneal injection of freshly prepared solution of Triton-X-100 (100 mg/kg) in physiological saline solution after overnight fasting for 18 h. The animals were divided into four groups of six rats each. The first group was given standard pellet diet, water and orally administered with 5% CMC. The second group was given a single dose of triton administered at a dose of 100 mg/kg, i.p. After 72 h of triton injection, this group received a daily dose of 5% CMC (p.o.) for 7 days. The third group was administered a daily dose of synthesized compounds 250 mg/kg suspended in 5% CMC (p.o.) for 7 days, after inducing hyperlipidemia. Fourth group was administered with the standard Fenofibrate 250 mg/kg (p.o.) for 7 days [24].

4.3. Collection of blood

At the end of experimental period, blood was collected by retro orbital sinus puncture, under mild ether anesthesia. The serum was separated by centrifugation at 2500× *g* for 15 min at 4 °C. Then serum samples were collected and assayed for total cholesterol,