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Hypolipidemic effect of dihydroisoquinoline oxaziridine in high-fat diet-fed rats

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ABSTRACT

Obesity is a serious health problem that increases the risk of many complications, including diabetes and cardiovascular disease. This study aims to evaluate, for the first time, the effects of oxaziridine **3** on lipoprotein lipase activity in the serum of rats fed with a high-fat diet (HFD) on body weight, lipid profile and liver-kidney functions. The administration of oxaziridine **3** to HFD-rats lowered body weight and inhibited the lipase activity of obese rats leading to notable decrease of T-Ch, TGs and LDL-Ch levels accompanied with an increase in HDL-Ch concentration in serum. Moreover, the findings of this study revealed that oxaziridine **3** helped to protect liver tissue from the appearance of fatty cysts. Additionally, oxaziridine **3** administration to HFD-rats induces antioxidant activity proven by the increase of superoxide dismutase (SOD) and catalase (CAT) activities and the decrease in Thiobarbituric acid reactive substances (TBARS) levels. It also induces the protection of liver-kidney functions confirmed by a decrease in the levels of toxicity parameters in blood.

1. Introduction

Obesity can be defined as an excess of body fat. In clinical terms, a surrogate decision- maker for body fat content is the body mass index (BMI), which exceeds 30 kg/m^2 called obesity [1–4].

It is well-known that obesity is associated with many chronic diseases. In fact, it is a major risk factor for developing hyperlipidaemia [5], hypertension [6], type 2 diabetes [7], cardiovascular diseases [8,9] and certain cancers [10,11].

Many synthetic drugs such as Orilistat and Lorcaserin [12,13] are available for the treatment of hyperlipidemia, but all of them have serious side effects [14,15]. Thus, there is a need to develop new synthetic hypolipidemic agents with fewer or no side effects.

Organic compounds incorporating heterocyclic ring systems continue to attract considerable interest due to their wide range of biological activities. From these classes of heterocyclic compounds, oxaziridine has attracted considerable attention due to various biological properties such as anti-tumor agent [16], anti-malaria [17], and antifungal [18] to analogues of penicillin [19]. Furthermore, they are widely used as reagents and intermediates in the preparation of biologically active molecules [20–22]. In this study, oxaziridine **3** was tested for anti-obesity activity in vivo.

2. Materials and methods

2.1. Chemistry

The oxaziridine **3** was previously reported in our earlier research work to be an agent for the transfer of oxygen on organosulfides [23]. The oxaziridine **3** used in the current study was synthesized starting from the commercial tertiary alcohol **1** (Scheme 1). The imine **2** from step (a) was obtained by cyclisation of the tertiary alcohol **1** by a Ritter-type procedure. The peracidic oxidation of imine **2** led to oxaziridine **3** in 62% yield (Scheme 1).

The structure of compound **3** was confirmed by single-crystal x-ray structure determination. The experimental details of data collection and structure refinement are summarized in the

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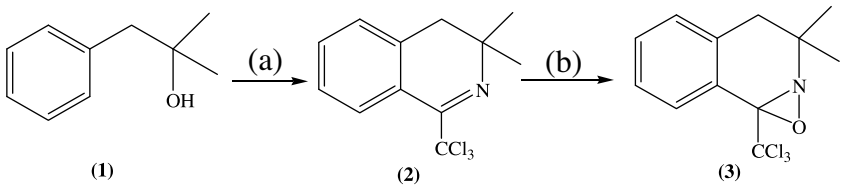

(a) H_2SO_4, CCl_3CN, hexane; 68°C, 2h. 30 min.
(b) *m-CPBA* (2 eq), MeOH, 3h.

Scheme 1. Synthesis of Oxaziridine **3**.

experimental section. An ORTEP diagram of the molecular structure of oxaziridine **3** in the crystal form is shown in Fig. 1.

2.2. Animals

The assays of the present study were conducted on adult male Wistar rats (180± 20 g), obtained from the local Central Pharmacy, Tunisia. All rats were kept in an environmentally controlled breeding room (temperature: 20 ± 2 °C; humidity: 60 ± 5%; 12 h dark/light cycle) where they had standard diets and free access to tap water. The experimental protocols were conducted in accordance with the guide for the care and use of laboratory animals issued by the University of Sfax, Tunisia, and approved by the Committee of Animal Ethics.

2.3. Experimental design

The rats were randomly divided into four groups of six animals each.

Group I: (Cont) Normal rats which were fed a standard laboratory diet.

Group II: (HFD) Rats which were fed a high-fat diet (normal diet supplemented with 1% of fats and 0.25% of bile salts).

Group III: (HFD + Flu) Rats which received high-fat diet and treated with fluvastatin (2 mg/kg, body weight/daily) for 6 weeks. Fluvastatin (trade names Lescol, Canef, and Vastin) is a member of the drug class of statins, used to treat hypercholesterolemia and prevent cardiovascular disease [24].

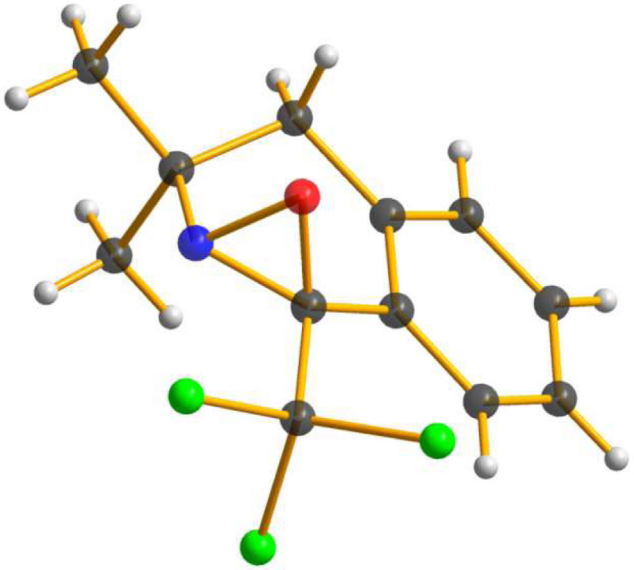

Fig. 1. Molecular structure of the Oxaziridine **3**.

Group IV: (HFD + oxaziridine **3**) Rats which received high-fat diet and treated with oxaziridine **3** by gastric gavages route (200 mg/kg of body weight/daily) for 6 weeks.

After 6 weeks of induction, the animals were sacrificed by decapitation in order to minimize the handling stress, and the trunk blood collected. The serum was prepared by centrifugation (1500*g*, 15 min, 4 °C), frozen, and stored at −20 °C until analysis. The kidney and liver were removed and cleaned of fat. All samples were stored at −80 °C until used.

2.4. Biochemical variables

The liver of each rat was excised and homogenized in Tris-Buffered Saline (TBS), pH 7.6 and centrifuged (5000*g*, 20 min). The supernatant of liver homogenate was frozen and stored for further use for the essay of lipid profile. The analyses of serum lipase and serum lipid levels of triglycerides (TG), total cholesterol (T-Ch), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) were measured using the corresponding commercial kits (Biolabo, France) on an automatic biochemistry analyzer (BS 300, China) at the biochemical laboratory of Hedi Chaker Hospital of Sfax. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (T-bilirubin), Creatine phosphokinase (CPK) activities and creatinine, uric acid and urea rates were measured in frozen aliquots of serum by standardized enzymatic procedures using commercial kits from Biolabo, France, on an automatic biochemistry analyzer (Vitalab Flexor E, USA) at the biochemical laboratory of Hedi Chaker Hospital of Sfax.

The antioxidant activities were measured after the homogenization of the liver and kidney in a phosphate buffer. The lipid peroxidation in the liver and kidney of control group and all treated groups of animals was measured by the quantification of thiobarbituric acid reactive substances (TBARS) by the method of Yoshioka et al. [25]. The activity of SOD was assayed by the spectrophotometric method of Marklund and Marklund [26] and expressed as U/mg protein. The CAT activity was assayed by the calorimetric methods at 240 nm and expressed as μmoles of H_2O_2 consumed/(min × mg protein) as described by Abei [27,28]. The level of total protein was determined by the method of Lowry et al. [29] using bovine serum albumin as the standard at 660 nm.

2.5. Histopathological analysis

For histological studies, pieces of liver and kidney tissues were removed and fixed in 10% formaldehyde solution. The washed tissues were dehydrated in increasing gradient of ethanol and finally cleared in toluene. The tissues were then embedded in molten paraffin wax, and the sections were cut at 5 mm thickness and stained with haematoxylin and eosin.