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Original article

Synthesis of novel triterpene and *N*-allylated/*N*-alkylated niacin hybrids as α-glucosidase inhibitors

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia. α-Glucosidase (EC 3.2.1.20) inhibitors interfere with enzymatic action to slow down the liberation of D-glucose from oligosaccharides and disaccharides, resulting in delayed glucose absorption and decreased postprandial plasma glucose levels. In continuation of our drug discovery program on antidiabetic agents, we synthesized novel *N*-allylated/*N*-alkylated niacin and α-amyrin (**4**–**9**) and lupeol (**12**–**16**) hybrids and tested for their α-glucosidase inhibiting activity. Compounds **4**–**9** showed better activity profile than the marketed α-glucosidase inhibitor i.e. acarbose. Compound **4** possess the highest inhibitory action with IC_{50} of 5 μM. Kinetic and CD studies revealed that **4** inhibited the α-glucosidase in a noncompetitive manner and caused conformational changes in secondary structure of the enzyme protein.

1. Introduction

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion (Type 1 diabetes), insulin action (Type 2 diabetes) or both. As a consequence, raised blood sugar leads to common effect of uncontrolled diabetes with serious damage to many of the body's systems, especially the nerves and blood vessels. Type 2 diabetes mellitus (T2DM) accounts for approximately 80–90% of all cases of diabetes and it is the fastest growing global threat to public health [1]. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [2]. It is usually associated with older age, obesity, family history, impaired glucose metabolism, physical inactivity, and race or ethnicity.

Plants have always been an ideal source of drugs and many of the currently available drugs have been derived directly or developed from plants. The ethnobotanical information reports that about 800 plants may possess anti-diabetic potential [3]. Plant-derived active chemical compounds like terpenoids, flavonoids, alkaloids, guanidines, steroids, carbohydrates and amino acids exhibit activity against T2DM. Metformin is currently used as antidiabetic agent in the treatment of type-2 diabetes. Metformin and its analogs [4,5] were synthesized on the basis of a natural product lead, galegine, which was isolated from the seeds of *Galega officinali* [6]. The unusual amino acid hypoglycin B isolated from *Blighia sapid* possesses antihyperglycemic activity [7]. Trigonelline (*N*-methylniacin or *N*-methyl nicotinic acid) isolated from seeds of *Trigonella foenumgraecum* was reported as hypoglycemic agents in alloxan induced diabetic mice [8].

Ficus racemosa Linn. (Moraceae) commonly known as Gular [9] has traditionally been used for the treatment of diabetes [10]. The hypoglycemic potential of its leaf extract was demonstrated in streptozotocin-induced diabetic rats [11]. Glucose lowering efficacy of the stem bark in normal as well as alloxan-induced diabetic rats was also reported [12]. As a part of our drug discovery program, we identified α-amyrin acetate **1** as antihyperglycemic principle from the fruits of *F. racemosa* [13] for the first time.

Lupeol and its derivatives hold the promising antiprotozoal, anti-inflammatory, antitumor, cardioprotective, hepatoprotective, antimicrobial activities [14]. Recently we reported antihyperglycemic activity in hybrids prepared from these triterpenoids (α-amyrin and lupeol) and niacin (nicotinic acid) [13,15]. *N*-methylated niacin also known as trigonelline isolated from the seeds of *T. foenumgraecum*

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seeds has been reported for its antihyperglycemic activity [8]. We therefore planned and prepared *N*-allylated/N-alkylated derivatives of α-amyrin/lupeol and niacin hybrids [14,15] and screened for their PTPase, glucose-6-phosphatase, glycogen phosphorylase and α-glucosidase activity. Interestingly *N*-allylated/*N*-alkylated niacin and amyrin hybrids showed strong α-glucosidase inhibitory activity in our studies. α-Glucosidase inhibitors are one of the alternative therapeutic approaches for T2DM. The digestion and absorption of carbohydrate would be delayed by the inhibition of intestinal α-glucosidase (Fig. 1) resulting in decreased postprandial hyperglycemia [16]. In addition, α-glucosidase inhibitors have also been reported for other biological activities such as reducing triglycerides [17] and anti-HIV activity [18]. Thus, during the past few decades, considerable attention has been paid on designing potent α-glucosidase inhibitors in the chemical and medical research. Few α-glucosidase inhibiting drugs from natural sources, such as plants, foodstuffs and microbes have also been identified [19–21] (Fig. 1). We here report on the synthesis of hybrids of triterpenes viz. α-amyrin/lupeol and *N*-allylated/*N*-alkylated niacin [15,22] and their α-glucosidase inhibiting activity.

2. Results and discussion

2.1. Synthesis

The synthesis of α-amyrin–niacin hybrids having *N*-alkylated or *N*-allylated chain was accomplished by subjecting the α-amyrin acetate **1** to deacetylation by freshly prepared sodium methoxide in dry methanol. α-Amyrin **2** thus, obtained was esterified using niacin employing DCC–DMAP (Steglich esterification) protocol in dry DCM to afford non-natural α-amyrin–niacin hybrid **3**. This was then subjected to *N*-allylation using prenyl bromide (3,3-dimethylallyl bromide) in dry diethyl ether at room temperature to afford *N*-prenylated α-amyrin–niacin hybrid **4** and *N*-alkylation using appropriate alkyl bromides in dry toluene at reflux condition to afford α-amyrin–*N*-alkylated niacin hybrids **5**–**9** (Scheme 1).

The similar protocol was used to prepare derivatives **12**–**16** from lupeol (**10**) (Scheme 2).

2.2. In vitro α-glucosidase inhibition and structure activity relationship

The parent compounds **3** and **11** were not soluble; therefore their α-glucosidase inhibiting activity has not been done. Compounds **4**–**9** and **12**–**16** prepared from **3** and **11** respectively have been tested for their α-glucosidase inhibiting activity. The results are summarized in Table 1. As evident from the results, most of the amyrin

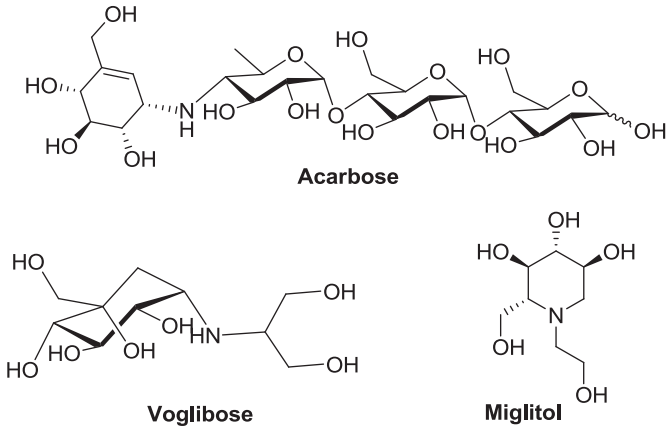
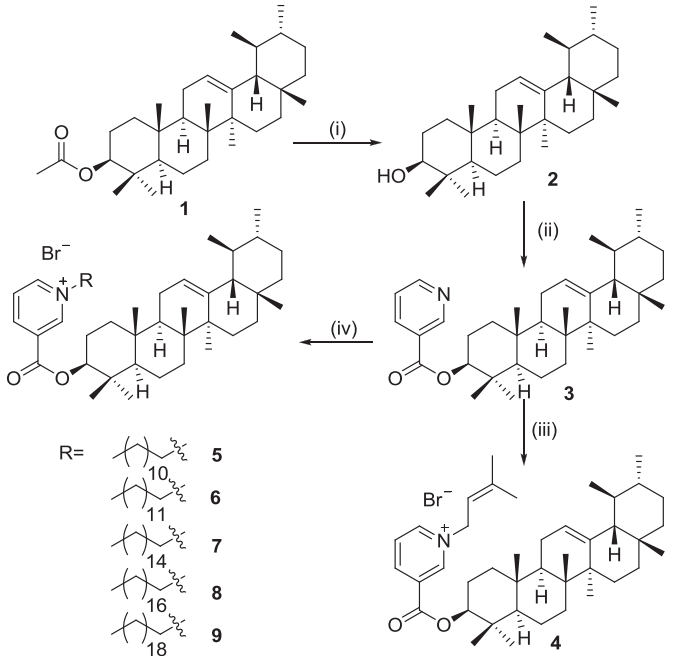
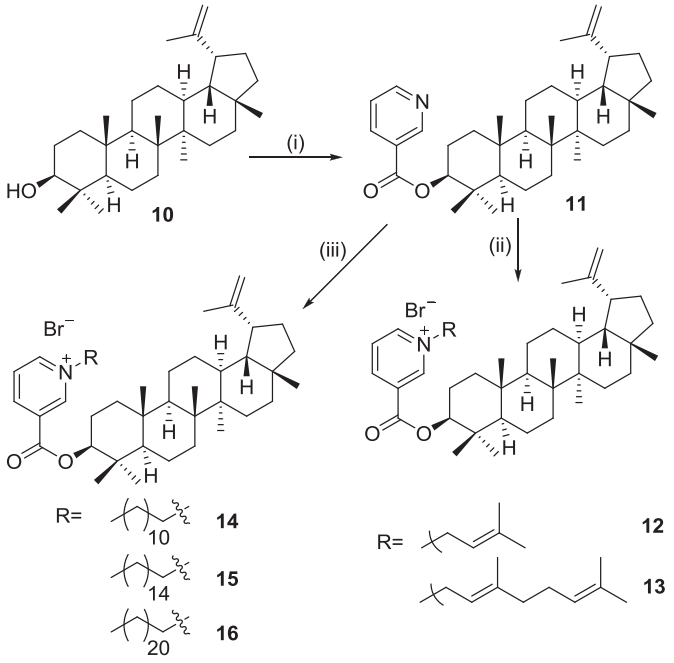


Fig. 1. α-Glucosidase inhibiting drugs available in the market.



Scheme 1. Synthesis of α-amyrin and *N*-allylated/*N*-alkylated niacin hybrids. Reagents and conditions: (i) Sodium methoxide, methanol, r.t., 2 h, (ii) Nicotinic acid, DCC-DMAP, DCM, r.t., 6 h, (iii) 3,3-Dimethylallyl bromide, Diethyl ether, r.t., 6-7 h, (iv) Appropriate alkyl bromide, toluene, reflux, 36 h.

hybrids showed significant inhibitory activity against α-glucosidase. In the current series, compound **4** was found to be the most active, showing concentration-dependent inhibition of α-glucosidase activity with 95% inhibition at 10 μM concentration ($p < 0.001$). From the dose–response curve, IC_{50} value of **4** was calculated as 5 μM (Fig. 2). Acarbose (marketed α-glucosidase inhibitor), showed 70.9% inhibitory activity at 100 μM concentration under similar assay conditions ($p < 0.001$). It is noteworthy to mention here that



Scheme 2. Synthesis of lupeol and *N*-allylated/*N*-alkylated niacin hybrids. Reagents and conditions: (i) Nicotinic acid, DCC-DMAP, DCM, r.t., 6 h, (ii) Appropriate allyl bromide, Diethyl ether, r.t., 6-7 h. (iii) Appropriate alkyl bromide, reflux, 36 h.