

## Synthesis of novel imbricatolic acid analogues via insertion of N-substituted piperazine at C-15/C-19 positions, displaying glucose uptake stimulation in L6 skeletal muscle cells

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### ABSTRACT

A new class of N-substituted piperazine analogues of imbricatolic acid have been designed and synthesized by using the appropriate synthetic routes in excellent yield. All synthesised compounds were screened for their in vitro glucose uptake stimulatory activity. Among them compounds **4b**, **4e**, **8b**, and **8e** triggered L6 skeletal muscle cells for glucose uptake at 54.73%, 40.79%, 40.90%, and 39.55% stimulation, respectively. Compound **4b** has emerged as important lead compound showing potential antidiabetic activity. Illustration about their synthesis and in vitro glucose uptake activity is described.

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Type 2 diabetes mellitus is a currently rising problem, affecting approximately 194 million people all over world according to World Health Organisation, and this number is projected to be 366 million by 2030.<sup>1</sup> Over the last 30 years, an enormous number of studies have been dedicated to unraveling the pathophysiology of type 2 diabetes mellitus.<sup>2</sup> A major pathogenic defect in the disease is insulin resistance, which is characterized by the impeded capacity of peripheral tissues, most notably in skeletal muscle to utilize glucose effectively in face of hyperinsulinemia.<sup>3</sup> This leads to a concomitant rise in blood glucose level and ends up with diabetes. To date, some antidiabetic drugs like pioglitazone and rosiglitazone (Fig. 1) are in markets which were approved by the US FDA for the treatment of type 2 diabetes in 1999.<sup>4</sup> However, therefore, development of newer and safer drugs is urgently needed to overcome some factors like weight gain, congestive heart failure etc., that limit the use of these drugs.<sup>5</sup>

Labdane-type terpenes are excellent example of natural products with important pharmaceutical potentials. They make a large family of bicyclic diterpenes, mainly isolated from plant sources and characterized by the presence of 4,10-dimethyl substituted decalin system with exomethylene group at C-8 position.

They have been reported to exhibit a wide range of potent biological activities including antitubercular,<sup>6</sup> antibacterial,<sup>7</sup>

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antiplasmodial,<sup>8</sup> antiproliferative,<sup>9</sup> antiviral,<sup>10</sup> neuroprotective,<sup>11</sup> trypanocidal,<sup>12</sup> and cytotoxic.<sup>13</sup> Some easily isolated labdane diterpenes such as labdanolic acid, ozic acid and isocupressic acids are common starting materials for synthesis of other natural products and numerous diterpene derivatives with privileged motifs for further modification and structure–activity relationship analyses.<sup>14</sup>

Among labdane-type diterpenes, the most relevant molecule having bicyclic framework is the imbricatolic acid as a

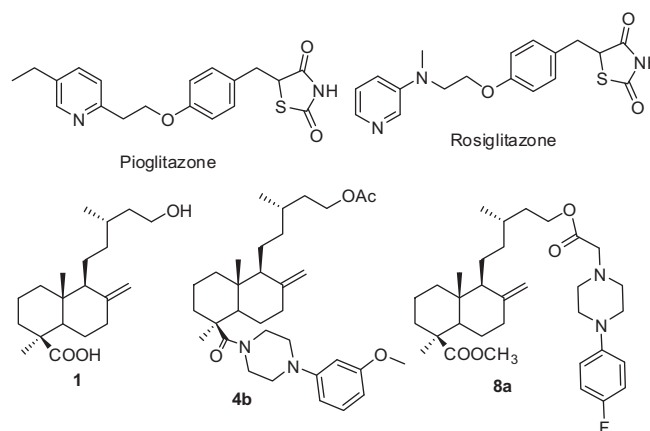


Figure 1. Structures of representative glucose uptake stimulators.

representative compound **1** because of its abundance and widespread occurrence.<sup>15</sup> An initial literature survey revealed that it possesses cytotoxic<sup>16</sup> and gastroprotective effect.<sup>17</sup> Korey Sakar et. al. isolated **1** from the acidic fraction of the petroleum ether extract of *Juniperus nana* Willd unripe berries which showed strong cytotoxic activity according to Brine Shrimp bioassay (LD<sub>50</sub> 0.16 µg/mL).<sup>16</sup> Despite the many studies on the chemical modification of this class of molecules, only few studies have been reported for imbricatolic acid. In a recent progress, a study has shown that imbricatolic acid and its amide derivative showed gastroprotective effect in ethanol/HCl induced gastric lesions model in mice and found to be cytotoxic against MRC-5, AGS and Hep G2 cell lines.<sup>18</sup> Due to rarity and paucity of information in the literature concerning chemical modification, this frameworks draw attention as synthetic targets to realize a thoroughly examination of their pharmacological properties. Hence, we are keenly interested to explore it chemically with convenient synthetic pathways.

In continuation of our research into the chemical modification of natural products in the treatment of type 2 diabetes mellitus, as well as keeping the structural features of imbricatolic acid in mind, we planned to synthesized analogues of **1** with insertion of N-substituted piperazine moieties which were available commercially. All the modified compounds were evaluated against type 2 diabetes mellitus via stimulating glucose uptake in L6 skeletal muscle cells. In order to understand chemical as well as biological properties of imbricatolic acid, we now report herein the results of this effort.

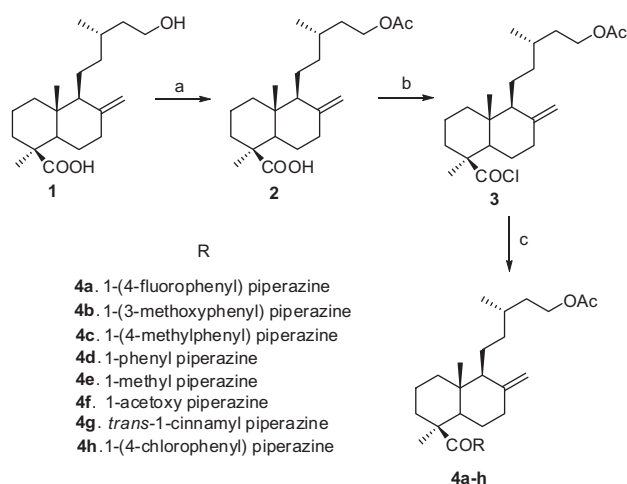
We have isolated imbricatolic acid **1** as starting compound from chloroform fraction of *Cupressus sempervirens* fruits by using extensive column chromatography.<sup>19</sup> The purity of starting compound was proven on the basis of NMR spectral data which were also accordance with published data in literature.<sup>20</sup> To explore the glucose uptake activity, the carboxylic acid at C-19 and hydroxyl group at C-15 position of **1** was transformed into their amides and esters analogues respectively. The reactions sequence to introduce the N-substituted piperazine is shown in the Scheme 1 and 2.

Compound **1** was acetylated at C-15 in anhydrous pyridine with addition of 1.1 equivalent of acetic anhydride and yielded compound **2** (Scheme 1). Acid chloride **3** was obtained from **2** via reaction of oxalyl chloride in dry CH<sub>2</sub>Cl<sub>2</sub> at 0 °C according to literature.<sup>21</sup> Good yield of **2** was achieved by addition of dry DMF in catalytic amount. This step was preferred in situ in terms of

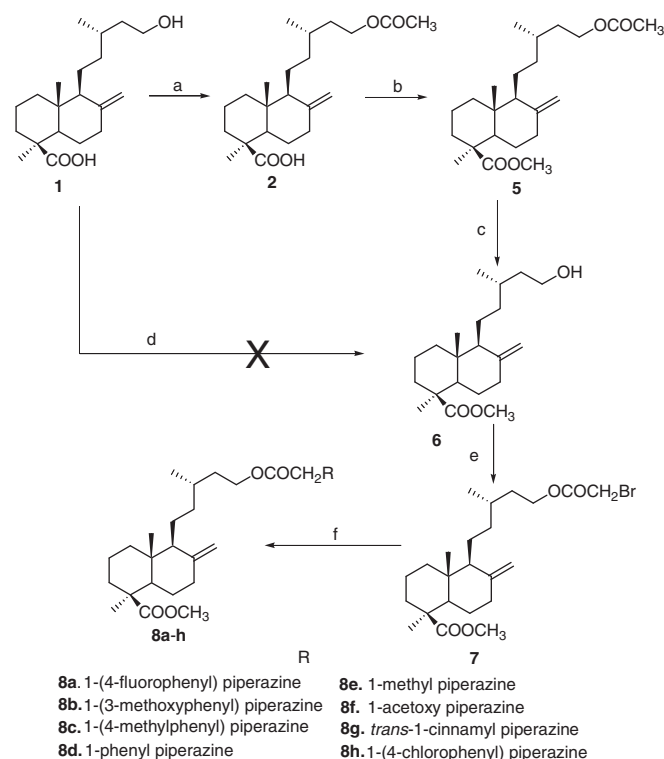
yield. Corresponding amide derivatives **4a–h** resulted from amidation of carboxylic acid by the reaction of N-substituted piperazine in the presence of dry CH<sub>2</sub>Cl<sub>2</sub> and (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N at room temperature within two hours, on the basis of the published procedure.<sup>22</sup>

Similar optimized synthetic route was also used to obtain second series of N-substituted piperazine with methylene linker as outlined in Scheme 2. Reaction of **2** with CH<sub>3</sub>I and anhydrous K<sub>2</sub>CO<sub>3</sub> in appropriate solvent at 0 °C upto room temperature to yielded compound **5** as described previously.<sup>23</sup> Compound **6** was synthesized in two different synthetic routes, by the direct methylation of carboxylic acid of C-19 used methyl iodide in basic medium of anhydrous K<sub>2</sub>CO<sub>3</sub> or by the estrification of hydroxyl group of C-15 in alkyl chain followed by deprotection of hydroxyl group in 10% methanolic KOH at room temperature. It was found that protection of the hydroxyl groups as esters was very convenient and necessary, since direct methylation of acid was low yielding with the formation of undesired by products due to the interaction of OH group. According to literature<sup>24</sup> procedure slow addition of bromo acetyl bromide at 0 °C in solution of **6** with dry CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>3</sub>N and stirred at room temperature, after 30 min compound **7** was obtained in good yield. Correspondingly, following the reaction sequence as shown in Scheme 1 treatment of **7** with N-substituted piperazine in dry CH<sub>2</sub>Cl<sub>2</sub> and (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N at room temperature for 1 hour yielded compounds **8a–h** in almost quantitative yield. All the synthesised compounds were analyzed by using IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and ESIMS analytical methods.

The biological scope of **1** and its synthetic analogues were examined and summarised in Table 1 and 2. Each compound was screened at 10 µM concentration for *in vitro* glucose uptake stimulatory effect in L6 skeletal muscle cells by using previously described method.<sup>25</sup> All tested samples were dissolved in DMSO (0.1%). Twelve out of tested synthetic analogues along with



**Scheme 1.** Reagents and conditions: (a) C<sub>6</sub>H<sub>5</sub>N (ca. 1.1 equiv), Ac<sub>2</sub>O (ca. 1.1 equiv), rt, 1 h, (b) CH<sub>2</sub>Cl<sub>2</sub>, (COCl)<sub>2</sub> (ca. 1.1 equiv), 0 °C, 4 h (c) CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, substituted piperazine (1.0 equiv), 0 °C to rt, 1.5 h.



**Scheme 2.** Reagents and conditions: (a) C<sub>6</sub>H<sub>5</sub>N, Ac<sub>2</sub>O, rt, 1 h (b) CH<sub>2</sub>Cl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>I (5.0 equiv), 0 °C, 6 h (c) 10% KOH, MeOH, rt, 1 h (d) CH<sub>2</sub>Cl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>I (5.0 equiv), 0 °C, 6 h (e) CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, BrCOCH<sub>2</sub>Br (1.1 equiv), 0 °C, 1.5 h (f) CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, substituted piperazine (1.0 equiv), rt, 2 h.

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