Isoferulic Acid 類似物之合成及其降血糖作用之研究

Studies on the Synthesis and Hypoglycemic Activity of Isoferulic Acid Analogues

中文摘要

最近，本學系實驗室發現由中藥北升麻（Cimicjfuga dahurica）分離出成分之 isoferulic acid（1）具有降血糖的活性，其活性對於第一型糖尿病（IDDM）較第二型糖尿病（NIDDM）顯著；且 isoferulic acid 對於健康老鼠的血糖不會影響。其降血糖作用之機轉係由於增加體內骨骼肌對葡萄糖之利用以及降低肝臟對肝醣之分解所致。今擬以 isoferulic acid 爲先導化合物進行化學構造修飾，合成一系列 isoferulic acid 衍生物，並研討其化學構造變化對降血糖藥效之影響，以期作爲設計新型降血糖前導藥物之重要參考。

Isoferulic acid（1）及其第三位氧烷基取代之類似物是由 Knoevenagel 縮合反應製備而得，將 malonic acid 及不同的第三位氧烷基取代之 benzaldehydes（例如 isovanillin、veratraldehyde、piperonal 及化合物 5、7、9），在 pyridine 及少許 piperidine 的環境下進行縮合反應，可得一系列第三位氧烷基取代之類似物 1、3、4、6、8 及 10。第三位氧 acyl 基團取代之類似物 11 及 12 是將 isoferulic acid 於酸性下與無水酸酐反應而得。第四位氧烷基取代之類似物 14 及 16 是將各種不同的第四位氧烷基取代之 benzaldehydes（13 及 15）與 malonic acid 進行縮合反應而得。酯類類似物 17?19 則是由 isoferulic acid 與不同的醇類進行酯化反應而得。

3-Hydroxy-4-methoxycinnamoyl chloride 與不同的一級或二級胺類進行縮合反應，可得到醯類類似物 20?25。直接將反式 isoferulic acid 以紫外光照射，進行光化學反應，則可得順式類似物 26。將 isoferulic acid 進行氫化反應可得到飽和類似物 27。若將 isoferulic acid methyl ester（17）與 diazomethane 及 palladium (II) acetate 進行環化反應，再將酯類水解即得環丙烷類似物 29。α-甲基類似物 30 可由 methyl malonic acid 與 3-hydroxy-4-methoxy benzaldehyde 進行縮合反應而得。以上共合成 1、3、4、6、8、10?12、14、16?27、29 及 30 等共 23 個類似物，各別之化學構造均經融點測定、紅外光譜、氫譜、質譜、碳譜及元素分析確認其化學構造。

本研究初步選擇 1?4、6、11、17、20、22、24、25、27、29 及 30 等共 15 個化合物進行降血糖活性試驗。經由 streptozotocin 誘導糖尿病鼠的離體肌母細胞對葡萄糖吸回作用的結果顯示，化合物 6、11、16、22 及 24 的作用較 isoferulic acid（1）爲佳，其中又以化合物 6 及 11 對降血糖活性的提升最爲顯著。由化學結構與活性關係部分之結果來看，苯環上第四位-OCH3 及不飽和雙鍵乃活性所必需，而三級醯胺、第三位氧乙基取代或第三位氧 acyl 基團所取代之類似物亦能增強其降血糖活性。

英文摘要

Recently, isoferulic acid isolated from the rhizome of Cimicjfuga dahurica Maxim.(Ranunculaceae) has been identified to have in vivo antihyperglycemic activity in our laboratory. The effect for lowering of plasma glucose by isoferulic acid in IDDM rats is more active than that in NIDDM rats. Furthermore, the plasma glucose in normal rats is not markedly influenced by isoferulic acid under similar treatment. The antihyperglycemic mechanism is through the enhancement of glucose utilization in peripheral tissues and a reduction of hepatic gluconeogenesis. In order to study the structure and activity relationship (SAR) of isoferulic acid (1), a series of isoferulic acid analogues are prepared and their antidiabetic activities are evaluated. Isoferulic acid (1) and its 3-O-alkyl analogues are prepared by Knoevenagel condensation. Condensation of malonic acid with various 3-O-alkyl benzaldehydes (e.g. isovanillin, veratraldehyde, piperonal, compound 5, 7, and 9) in the presence of pyridine and a trace of piperidine gave the 3-O-alkyl analogues 1, 3, 4, 6, 8, and 10. The 3-O-acyl analogues, 11 and 12, are prepared by isoferulic acid and anhydrides in acid medium. The 4-O-alkyl analogues 14 and 16 are prepared by condensation of various 4-O-alkyl benzaldehydes (13 and 15) and malonic acid. The ester analogues 17?19 are prepared by esterification of isoferulic acid with various alcohols. Condensation of 3-hydroxy-4-methoxycinnamoyl chloride with various primary and secondary amines gave the amide analogues 20?25. The cis-form analogue 26 is generated by photochemical reaction with direct UV irradiation of the trans-isoferulic acid. Catalytic hydrogenation of isoferulic acid gave the dihydroisoferulic acid 27. Cyclopropane analogue 29 was prepared by treated isoferulic acid methyl ester (17) with diazomethane and palladium (II) acetate followed with hydrolysis. The α-methyl analogue 30 is prepared by the condensation of methyl malonic acid and 3-hydroxy-4-methoxybenzaldehyde. Twenty three products were prepared including 1, 3, 4, 6, 8, 10?12, 14, 16?27, 29, and 30. All these analogues were characterized by M.P., IR, 1H-NMR, mass spectrometry, 13C-NMR and element analysis.
Initially, 15 analogues including 1?4, 6, 11, 16, 17, 20, 22, 24, 25, 27, 29, and 30 were selected to evaluate their antidiabetic activities. The glucose uptake study of soleus muscle cells from streptozotocin induced diabetic rats shows that 6, 11, 16, 22, and 24 were more active than that of isoferulic acid (1). Among these compounds, 6 and 11 have the most remarkable antidiabetic activities. The preliminary results of structure and activity relationships show that the 4-OCH3 on aromatic ring and the unsaturated double bond are essential for antidiabetic activities. The tertiary amides, the 3-O-ethyl or 3-O-acetyl substitutions also enhance the activity.