Xanthone Glucosides

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Xanthones are secondary metabolites found in plants, fungi, lichens, and bacteria froma variety of families and genera, with the majority found in the Gentianaceae, Polygalaceae, and Clusiaceae. They have a diverse range of bioactivities, including anti-oxidant, anti-bacterial, antimalarial, anti-tuberculosis, and cytotoxic properties. Xanthone glucosides are a significant branch of xanthones. After glycosylation, xanthones may have improved characteristics (such as solubility and pharmacological activity). Currently, no critical review of xanthone glucosides has been published.

Keywords: xanthone glucosides ; chemical synthesis ; pharmacological activity ; 9H-xanthen-9-one

1. Introduction

In natural product chemistry, xanthones are one of the most abundant types of chemicals. They are secondary metabolites found in higher plant families, fungi, lichen, and bacteria, and are primarily found in Gentianaceae, Polygalaceae, Clusiaceae, and others [1][2][3]. They have a variety of health-promoting properties, including anti-bacterial, anti-carcinogenic, anti-oxidant, and anti-diabetic properties [4][5][6][7][8].

The structure of xanthone determines its bioactivity, and different substitutions might result in a variable bioactivity [9][10][11]. The chemical formula of xanthone is C13H8O2. Its main structure is 9H-xanthen-9-one with a dibenzo-γ-pirone scaffold. Research on xanthones has received much attention in recent years [12][13][14][15]. In general, xanthones are categorized into six classes based on substitutions on the basic structure of xanthones: simple xanthones, xanthone glucosides (or glycosylated xanthones), prenylated xanthones, xanthonolignoids, bis-xanthones, and miscellaneous xanthones [16][17]. The main distribution of these xanthones varies, as prenylated xanthones are widely distributed in the Clusiaceae and most compounds of simple xanthones and xanthone glucosides are from the Gentianaceae. These primary groupings are further subdivided into non, mono-, di-, tri-, tetra-, penta-, hexa-, and hepta-oxygenated xanthones based on the degree of oxygenation [18][19][20].

More recently, xanthone glucosides have been explored, and the mutation of these glycosyl groups can change the biological activity of xanthone, which has a wide range of clinical applications [21][22]. However, xanthones usually have poor solubility; herein, many studies are being devoted to the synthesis of glycosylated xanthones to improve their solubility and activity and minimize their toxicity [23][24]. Xanthone glucosides are an important class of xanthones that are extensively dispersed in the plant families Gentianaceae and Polygalaceae. For natural xanthone glucosides, each xanthone site can be connected to a sugar group, which can be either monosaccharide or disaccharide. Recent research has revealed that xanthone glucosides have anti-oxidant [25], anti-inflammatory [26], anti-cancer [21][27], and other pharmacological properties. We separated xanthone glucosides into xanthone C-glucoside and xanthone O-glucoside and classified the substances accordingly. C–C bonds connect the sugar moiety to the xanthone nucleus in C-glucosides, which are usually resistant to acidic and enzymatic hydrolysis, whereas O-glucosides have normal glycosidic linkages. In glucosides whose glycosyl group is disaccharide, the second sugar residue is often glucose, xylose, or rhamnose and is usually associated with C-6 of the first glucose unit. However, when the second residue is rhamnose, it is linked to the C-2 of the first residue. The structures and connection site of sugars to the xanthone core that may be used in their full names are shown below.

2. Structure, Isolation and Bioactivity of Xanthone Glucoside

This class of xanthone glucosides is composed of xanthone and sugar groups that are linked together by carbon atoms in the structure. D-glucose is a sugar group that is commonly found in these compounds. The majority of the sugar binding sites are located at position 2, and glycosylation can often boost the activity to a certain amount [28]. All of the xanthones have hydroxyl substitutions on their skeletons, and some of them have methoxy groups. The scavenging of free radicals and the anti-oxidant activity of these compounds are their most notable impacts. We will classify these compounds by distinct genera in the order in which they were discovered, followed by a description of their biological activity.

Dhasmana and Garg isolated 2,3,7-trimethoxyxanthone-1-O-glucoside(48) and 2,3,5-trimethoxyxanthone-1-O-glucoside (49) from Halenia elliptrca D. Don. in 1989, and parts from an alcoholic plant extract containing these two compounds showed anti-amoebic activity. The structural difference between these two compounds is that the methoxy groups are at sites 2, 3, and 7 in 48 and 2,3, and 5 in 49 [29].

In 2013, Luo's group isolated 7-hydroxy-3,4,8-trimethoxyxanthone-1-O-(β-d-glucoside) (87), 6-hydroxy-3,5-dimethoxyxanthone-1-O-(β-d-glucoside) (88), and 3,4,7,8-tetramethoxyxanthone-1-O-(β-d-glucoside) (89) from Swertia mussotii. These three compounds were found to have moderate anti-oxidant activity. Their oxygen radical absorbance capacity (ORAC) values at a concentration of 3.1 μM were 30.2 ± 0.2, 33.1 ± 0.2 and 33.2 ± 0.7, respectively. The experiment in this study also showed that the bio-activity of glycosylated xanthones was higher than that of xanthones without glycosylation [30].

An and coworkers separated 1-hydroxy-3,5-dimethoxy-xanthone-6-O-β-d-glucoside (128) from Iris minutiaurea Makino in 2016. To assess the anti-inflammatory activity of this compound, they measured its inhibitory rate of it on nitric oxide (NO) production, and tumor necrosis factor-α (TNF-α), interleukin-1 β (IL-1β), and IL-6 release by LPS-induced RAW 264.7 macrophage cells. The results showed that the compound could exert an anti-inflammatory effect by inhibiting the production of the pro-inflammatory cytokine NO [31].

3. NMR Difference of Xanthone Glucosides

After investigation on the NMR data of xanthone C-glucosides and xanthone O-glucosides reported in the literature, it was discovered that there was no significant difference in the chemical shift of protons in 1H NMR spectrum. However, the 13C NMR data showed regular difference in the chemical shifts of C-1 of sugars which connected to the xanthone structures.

Generally, the chemical shifts of the sugar group appear among the range of δ 60–110 (13C NMR). It was found that the chemical shift of C-1 on the sugar group in xanthone C-glucosides is obviously smaller than that of xanthone O-glucosides. The chemical shift value of the former is basically distributed around δ 74, while that of the latter is mainly distributed between δ 100–110. Conversely, for the chemical shifts of C-3 and C-5 of sugar group, xanthone C-glucosides is slightly greater than xanthone O-glucosides. For example, neomangiferin is a compound bearing both C- and O-glycosides. The chemical shifts of C-1, C -3, and C-5 of the sugar group via O -linker are 103.1, 76.5, and 77.2, respectively, while the chemical shifts of C-1, C-3, and C-5 via C-linker are 73.2, 79.1, and 81.4, respectively [32].

4. Synthesis of Xanthone Glucosides or Derivatives

The structure of mangiferin (1) is 2-(β-d-glucosyloxy)-1,3,6,7-tetrahydroxyxanthone, which is distributed in a variety of plants and has demonstrated many biological activities. To improve the solubility of 1, several mangiferin derivatives were synthesized by Wu and coworkers (Scheme 2). They used nucleophilic substitution to add alkyl or benzyl groups to the skeleton of mangiferin and nine derivatives 168– 176 were obtained [33].

Neomangiferin (4) is a derivative of 1. Li and coworkers solved the problem of hydroxyl selectivity and realized the semi-synthesis of 4 from 1 in 2014 (Scheme 3). First, compound 177 was synthesized by acylation in high yield, which is a suitable intermediate for selective benzylation at the 1-, 3- and 6-positions. After de-acylation, only the remaining 7-OH can be coupled with α - d -glucopyranosyl bromide under optimized conditions to give the corresponding product 4 after the removal of all the protective groups [34].

As a continuing work, the Li group completed the total synthesis of three xanthone glucosides including 1, homomangiferin (2) and 4 using an alternative method in 2016. They chose tetrabenzylglucose (181), phloroglucinol derivatives (182–183) and bromobenzene derivatives (184) as the starting materials. Compounds 1 and 2 were synthesized by a series of steps, including glycosylation, Vilsmeier formylation, de-protection, selective reprotection, and ring formation reactions. Then, according to the research in 2014, the construction of 4 was completed (Scheme 4) [35].

In addition to chemical methods, enzyme catalysis can also be used to synthesize xanthone glucosides. For example, Zarena et al. used enzyme catalysis to achieve glycosylation of α−mangostin (193) in a supercritical carbon dioxide system [36], and Sohng completed the diversified glycosylation of 193 by a one-pot enzymatic catalysis [37]. In addition, Kim and coworkers modified 1 with glucansucrase to obtain the disglycation product mangiferin-(1→6)-α-d-glucopyranoside (194), thus improving the activity and solubility of mangiferin [24].

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