SYNTHESIS OF NATURAL ARYL GLYCOSIDES, VANILLYL AND 3,4-DIHYDROXYBEZOYL ALCOHOLS DERIVATIVES

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СИНТЕЗ ПРИРОДНЫХ АРИЛГЛИКОЗИДОВ, ПРОИЗВОДНЫХ ВАНИЛИНОВОГО И 3,4-ДИГИДРОКСИБЕНЗИЛОВОГО СПИРТОВ

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Аннотация. *Как известно, медицинские препараты, полученные из природных источников, представляют из себя композицию соединений с различными свойствами, в которой необходимо определить наиболее полезный компонент и выделить его отдельно от остальных, либо получить его синтетический аналог. К таким веществам относятся арилгликозиды, обладающие противовоспалительными, антиоксидантными и другими полезными свойствами. Именно поэтому, в представленной работе нами была разработана схема синтеза и впервые проведён полный синтез природных арилгликозидов, производных ванилинового и 3,4-дигидроксибензилового спиртов (**1**, **2**) и их сложных эфиров с остатками кофейной, ванилиновой и бензойной кислот (**3**-**7**).*

Natural glycosides vanillyl and 3,4-dihidroxybenzyl alcohols derivatives, such as vanilloloside **1** and calleryanin **2** were isolated from *Nelumbo nucifera* stamens [1] and *Pyrus Calleryana* leaves [2] respectively. In addition, vanilloloside along with its derivative 7-*O*-*trans*-caffeoylvanilloloside **3** were isolated from *Strychnos axillaris* Colebr. [3]; 7-*O*-*trans*-caffeoylcalleryanin **4**, derivative of calleryanin, was isolated from *P. Calleryana* [4]. Another derivative of vanilloloside, 7-*O*-vanilloylvanilloloside **5** was isolated from *Ilex litseaefolia* stems [5].

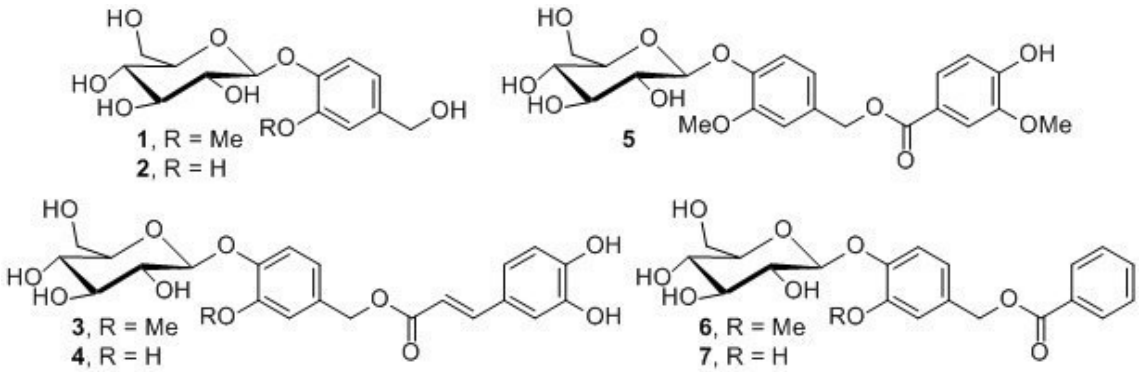

Fig. 1. Desired aryl glycosides

All these compounds have specific biological activity. Studies of vanilloloside **1** reveal that it has specific activity against cancer cells, such as HeLa (cervix cancer) and MCF-7 (breast cancer) [6], and is extremely efficient at inhibiting fermentative activity of acetylcholinesterase and, thereby, could potentially be utilized to cure Alzheimer [1]. Additionally, 7-*O*-*trans*-caffeoylvanilloloside **3** and 7-*O*-vanilloylvanilloloside **4** may have similar medical activity and show a specific activity related to residues of caffeic and vanillic acids respectively. Furthermore, calleryanin **2** shows an antioxidant and scavenging activity [2] and may have anti-inflammatory activity [4]. Moreover, its derivative **5** may have the similar activity and in analogy to the compound **3** it may show a specific activity related to caffeic acid residue.

All these aryl glycosides occur in a number of different plants and can be isolated by means of known and commonly accepted methods, for instance, extraction followed by chromatographic separation. However, isolation of separated compounds from plants is disadvantageous, because it requires high expenses of natural and often inaccessible raw materials and specific technologies of their processing and gives the yields of few milligrams. Whilst that, chemical synthesis gives an opportunity to utilize common substrates, which are cheaper than plants, and get the higher yields.

Based on this assumption and the fact that none of these glycosides was previously mentioned as synthesised, it was decided to develop a scheme of synthesis of natural aryl glycosides vanillyl and 3,4-dihidroxybenzyl alcohols derivatives and their esters with residues of caffeic and vanillic acids. In addition, it was decided to synthesise their benzoic acid esters which isolation from plants was not mentioned before.

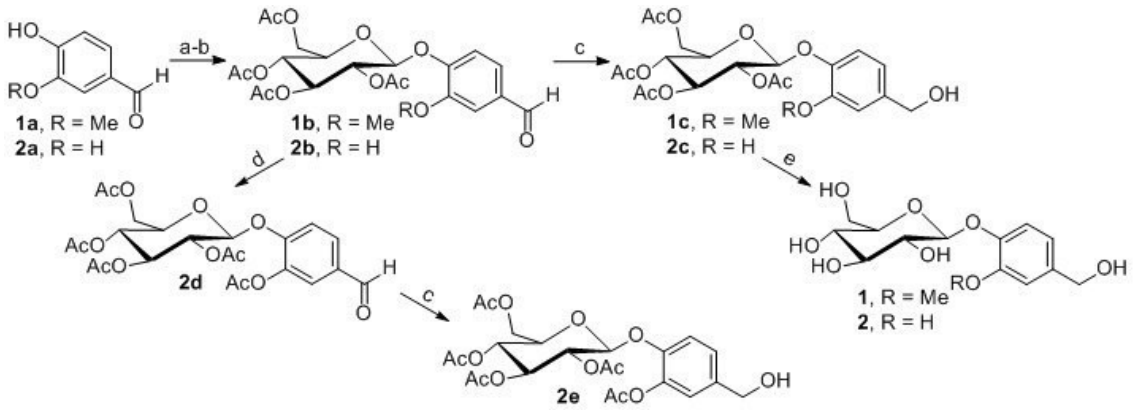

*Fig. 2. Synthesis of desired aryl glycosides **1**, **2**: **a** – Ag_2O, ABG, quinolone, 2h; **b** – ABG, KOH, MeOH, CH_3Cl, 78°C, 3h; **c** – $NaBH_4$, CTMAB, $CHCl_3$, H_2O, RT, 3-6h; **d** – 2 eq. Ac_2O, Py, RT, 24h; **e** – MeOH, MeONa, RT, 10 min*

On the first step of the synthesis we performed glycosylations of vanillin **1a** and protocatechuic aldehyde **2a** with acetobromoglucose (ABG) in two different systems. Vanillin was glycosylated in a suspension of silver oxide and quinolone to give a glycoside **1b**; and protocatechuic aldehyde was glycosylated in a solution of dry MeOH and dry $CHCl_3$ in the presence of KOH to give a glycoside **2b**. The yield in the first reaction was higher (60%) than in the second one (25%). Obtained glycosides **1b** and **2b** were subjected to selective reduction of aldehyde group with $NaBH_4$ in conditions of interphase catalysis with CTMAB [7] (cetyltrimethylammonium bromide) to give tetraacetates of vanilloloside **1c** and calleryanin **2c** respectively. Then the last glycosides were deacetylated in the presence of MeONa [8] to give desired vanilloloside **1** and calleryanin **2**.

Glycoside **2b** was acetylated to protect hydroxyl of the aglycon in further synthesis. Obtained pentaacetate of aldehyde **2d** was also reduced with $NaBH_4$ to give glycoside **2e** (pentaacetate of calleryanin).

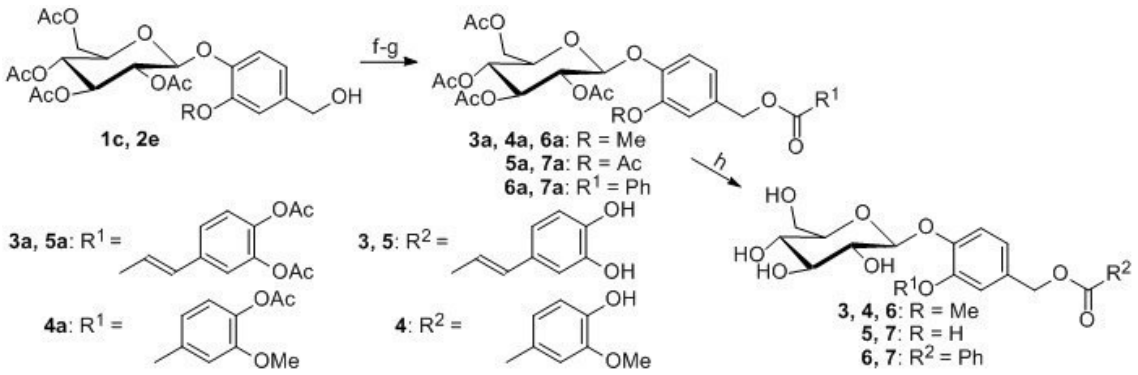

*Fig. 3. Synthesis of desired aryl glycosides **3-7**: **f** – R^1OCl, 2 eq. Py, $CHCl_3$, RT, 24h; **g** –vanillic acid acetate, DMAP, DCC, CH_2Cl_2, RT, 24h; **h** – HCl/EtOH/$CHCl_3$ (1:3:1)*

Then we preformed esterification of glycosides **1c** and **2e** with chlorides of diacetate of caffeic acid and benzoic acid in the chloroform in the presence of the 2 equivalents of pyridine. Furthermore, we performed esterification of vanilloloside tetraacetate **1c** with acetate of vanillic acid in methylene chloride with DMAP (dimethylaminopyridine) and DCC (*N,N'*-dicyclohexylcarbodiimide). Obtained glycosides **3-7a** were subjected to deacetylation in the system HCl/EtOH/$CHCl_3$ (1:3:1) [9] to give desired aryl glycosides **3-7**.

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