Transformations of Phytogenous Glycosides as a New Scientific Field

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Abstract

Selective transformations of a triterpene glycoside (glycyrrhizic acid), the main biologically active component of licorice roots (*Glycyrrhiza glabra* L., *Gl. uralensis* Fisher) with respect to the carbohydrate chain and/or aglycon have been performed. Novel groups of biologically active substances valuable for medical purposes are obtained (amides, glycopeptides, pyrazoles, conjugates with amino sugars, triterpene glycosides) those exhibit high anti-inflammatory, anti-ulcer, immunostimulating and antiviral activities. It is established that chemical modifying of glycyrrhizic acid via introduction of amino acids, dipeptides and amino sugars in the carbohydrate part of the molecule offers considerable scope for obtaining novel stimulants of the humoral immune response, as well as anti-HIV-1, anti-SARS CoV and anti-EBV agents.

Key words: glycyrrhizic acid, transformations, derivatives, analogues, activity

INTRODUCTION

The problem of the synthesis of novel biologically active substances as well as the creation of new pharmaceutical preparations on their basis for the treatment and prophylaxis of viral infections and immunodeficiency with various etiology is still remaining one of the major problems in the field of medical and organic chemistry. It is caused by an increasingly wider circulation of a number of socially hazardous viral infections (HIV, hepatitis B and C) as well as by the occurrence of new respiratory viral infections, such as the atypical pneumonia (Severe acute respiratory syndrome, SARS), the bird's flu (avian influenza), *etc*.

One of economically and socially important directions in order to solve the problem under consideration consists in the development of biologically active preparations of medical purpose based on individual natural compounds isolated from available plant raw material. Natural compounds are taking root with especial intensity in the field of oncology, immunodeficiency and metabolic diseases. They play an important role in the development of antibacterial and antifungal preparations [1–7].

Synthetic transformations of biologically active natural compounds represent one of prospective ways to obtain novel leading compounds with improved pharmacological properties. The effective strategy of searching for such compounds and their modifiers is based on the knowledge obtained from chemoinformatics, scientific and folk medicine, pharmacology as well as virtual in vitro and in vivo screening [10–15].

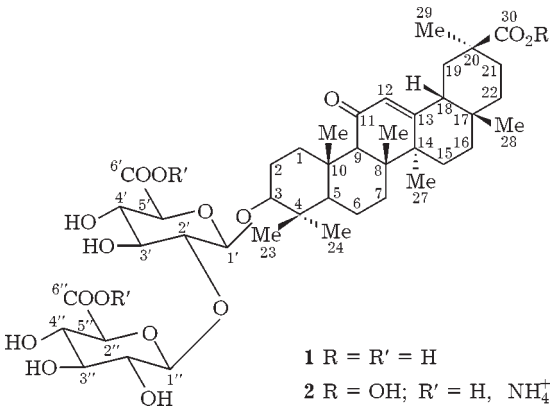
One could consider available biologically active phytogenous glycosides or saponines to be among the natural compounds of a great medical importance as template structures for the creation of novel antineoplastic, immunomodulating and anti-infectious preparations [16, 17]. Recent achievements in the field of glycobiology have confirmed the important role of various glycosides in the immune processes, viral and bacterial infections, inflammations and many other inter- and intracellular transformations. In addition, molecular mechanisms for most kinds of biological activity of these substances are still not completely studied, whereas

studies concerning the structure-activity relationship were carried out to a scarce extent in the world. Synthetic approaches those allow one to obtain structurally similar compounds and chemical compound libraries are considered to be preferred in order to perform systematic studies on this relationship.

Glycyrrhizic acid (GA) **1**, the main biologically active triterpene glycoside from the roots of licorice species (*Glycyrrhiza glabra* L. and *Gl. uralensis* Fisher) known to exhibit high anti-inflammatory, anti-ulcer, antiallergenic, antioxidative, hepatoprotective and antiviral activities, is of a special interest as a basis for the creation of novel highly efficient pharmaceutical preparations [18–20]. Glycyrrhizic acid represents one of the leading natural compounds suitable for treatment of HIV infection at early stages of the virus replication cycle [21, 22]. Preparation SNMC (Stronger Neo-Minophagen Co.) containing GA is successfully applied in the form of intravenous injections for the treatment of chronic viral hepatitis B, C and hepatocirrhosis in Japan [23, 24]. Communications have appeared concerning the licorice glycoside ability to inhibit the replication of new coronavirus species (CoV) bringing on atypical pneumonia (SARS), Epstein Barr virus, EBV (the promoter of skin tumors), as well as 6 and 7 types herpes viruses, influenza virus, cytomegaloviruses, *etc.* [25–30].

The unique properties of GA include the ability to inhibit viruses at the initial stages of the replication cycle, in particular at the stages of adsorption of virus adsorption by cells and at the stage of virus-membrane fusion [22, 31, 32]. Similar compounds influencing the duplication cycle of viruses at the initial stages, do not influence directly the processes of viral genetic information coding and realization, do not cause the development of any drug resistance.

Due to this fact they are rather prospective for the further promotion as pharmaceutical preparations suitable for long-term therapy of HIV infections, hepatitis B and C, herpes and coronaviral infections, particularly in the cases of combined therapy [33–38.] Russia nowadays has no efficient antiviral preparations obtained basing on GA, with the exception of Glitsiram (monoammonium salt of GA) **2**, allowed for application in medicine as an anti-inflammatory remedy, as well as Fosfogliv recommended as a hepatoprotective agent [39–41].



A preparation Niglzin have been synthesized at the Institute of Organic Chemistry of the Ufa Scientific Centre of the RAS (Ufa) representing a semisynthetic GA derivative which exhibits considerable activity with respect to mutant HIV species resistant against the action of Azidothymidine (AZT) [42, 43]. Thus, chemical modifying of GA offers inexhaustible potentialities for obtaining novel compounds with improved pharmacological properties and preset biological activity. Due to the availability, low toxicity as well as to the presence of a plant raw-material base, the search for new highly effective pharmaceutical substances among GA derivatives becomes one of the promising directions in the creation of remedies for viral diseases treatment and prophylaxis including new and socially hazardous viral infections [44].

The present work has been performed within the framework of the program for the studies on synthetic transformations of low-molecular plant metabolites as a scientific basis for the creation of pharmaceutical preparations of high social importance formulated within Academician G. A. Tolstikov's scientific school. Prospective methods have been developed for industrial-scale obtaining pharmacopeial Glitsiram and GA of high purity level from commercial licorice root extracts as well as from the Ural licorice roots of Russian origin [45–51].

Selective GA transformations with respect to the carbohydrate chain and/or aglycon have been performed to result in obtaining novel groups of biologically active substances valuable for medicine (amides, glycopeptides, pyra-

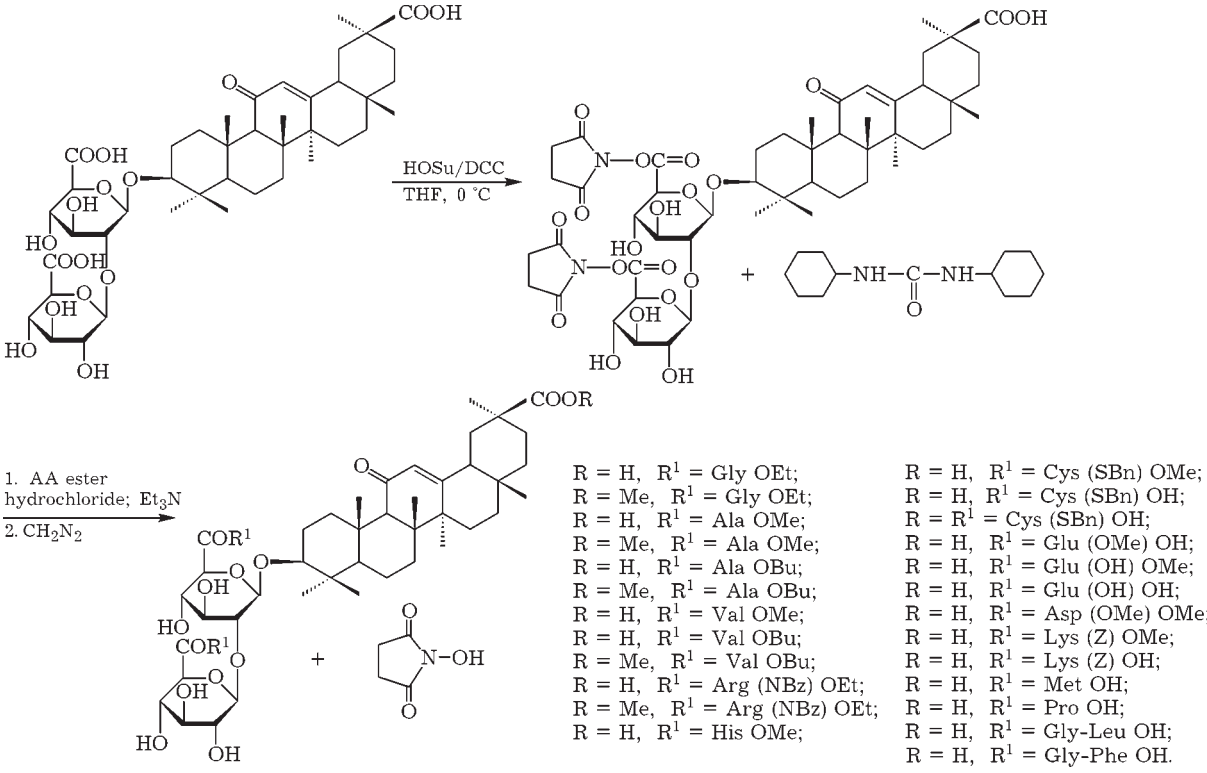
zoles, conjugates with amino sugars, triterpene glycosides) those exhibit high anti-inflammatory, anti-ulcer, immunostimulating and antiviral activity [45–57].

SYNTHESIS OF NOVEL BIOACTIVE GLYCYRRHIZIC ACID DERIVATIVES

The synthesis has been performed of a new group of aromatic heterocyclic and carbocyclic GA di- and triamides containing the fragments of uracils, biogenic amines and sulphanylamides among those potential anti-HIV-1 agents were revealed [58–61].

Throughout the works on searching new immune active derivatives of GA we have developed a selective method for the synthesis of GA glycopeptides (Scheme 1) containing the fragments of amino acids and amino acid esters only within the carbohydrate part of the molecule via the activation of GA carboxylic groups with the help of HOSu-DCC. Such an approach has allowed us to synthesize novel GA conjugates with amino acids and amino acid esters including *L*-cysteine, *L*-lysine, dicarbonic (glutamic and aspartic) acids and dipeptides among those we revealed effective anti-inflammatory and anti-ulcer agents, stimulants of humoral immune (antibody) response as well as anti-HIV-1 agents [62–73].

In order to increase hydrophilic properties of the GA molecule we have for the first time performed the modification of GA carbohydrate chain through the introduction of amino sugar molecules and other monosaccharides. We have synthesized GA conjugates of the oligosaccharide type, each containing two α-*D*-glucosamine or β-glycosylamine residues, linked with COOH groups of the carbohydrate part of the molecule by CONH bond [74]. We have realized a partial synthesis of novel triterpene saponines of glycyrrhetic acids (GLA) with the ester bond type via the glycosylation of pentaacetyl-GA or its 30-methyl ester using α-bromo-2,3,4,6-tetra-O-acetyl-*D*-gluco- and galactopyranose in dichloroethane medium in the presence of the Fetison reagent [75, 76].



Scheme 1.

SYNTHESIS OF GLYCYRRHIZIC ACID ANALOGUES

Synthetic analogues of bioactive natural triterpene glycosides are of interest from the standpoint of the studies on the structure–activity relationship. For the purpose of obtaining the analogues of GA with modified aglycon and/or the carbohydrate part we carried out reductive transformations of glycoside **1** and its trimethyl ester by means of $NaBH_4$ ($LiAlH_4$) with the obtaining of novel triterpene glycosides [77].

It has been established that the composition of reduction products varies depending on the reaction conditions. We have revealed the conditions for selective reduction of C^{11}=O an Azidothymidine glycon group and COOH ($COOCH_3$) groups of the carbohydrate chain. Preparative methods have been proposed for obtaining β-*D*-sophoroside analogue of GA and glycoside containing oleane-9(11),12(13)-diene system in the agycon, the modified analogue of a minor saponine of the Ural licorice roots (licorice saponine B_2) [78].

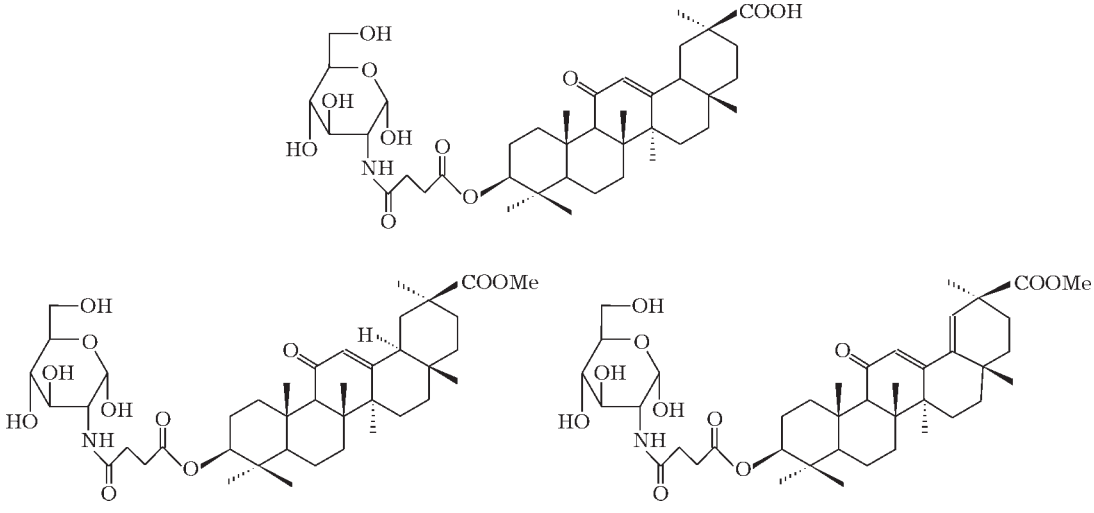
We have synthesized new esters of β-sophoroside analogue of GA and 18α-GA (*D/E trans*-isomer), the analogues of GA penta-O-nicotinate (Niglizin) and sodium GA penta-O-sulphonate those a high anti-HIV activity (sulphonates, nicotinates, methoxycinnamated) [78]. We have for the first time synthesized conjugates and N-glycoconjugates of triterpene acids such as 18β- and 18α-GLA, 11-deoxo- and 18,19-dehydro-GLA of spacer type with *D*-glucosamine and β-glycosylamines resulting in the obtaining of new modified GA analogues with the carbohydrate chain replaced by the residues of these amino sugars (Scheme 2) [79–81].

BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY OF GLYCYRRHIZIC ACID

There have been substances found among novel GA derivatives and analogues those exhibit a high anti-inflammatory, anti-ulcer and antiviral activity [44–46, 52–55, 57, 58, 67, 68, 74–76, 82–87]. Pharmacological studies carried out at the Bashkiria State Medical University have demonstrated that the GA glycopeptides synthesized represent efficient stimulants of the primary immune (nonboosted) response, whereas their immunotropic activity depends on the structure of the amino acid bound with the carboxylic groups of the carbohydrate part of GA, as well as on the method of administration and doze [62–64, 66, 69, 72].

GA derivative such as Niglizin being in the pelletized form appeared efficient for the treatment of digestive system diseases as well as for the combined therapy of patients seeking with hemorrhagic fever accompanied by the renal syndrome [88, 89]. Also hepatoprotective properties and pharmacokinetics of the preparation were investigated in rats [90].

Anti-HIV-1 activity for a number of novel GA derivatives and analogues have been studied at the State Research Center of Virology and Biotechnology Vector (Prof. A. G. Pokrovsky and O. A. Plyasunova) for MT-4 cell culture



Scheme 2.

within the framework of traditional model of primarily HIV-infected lymphoid MT-4 cells with the use of HIV-1/EVC strain as compared to GA at the concentration of 100 μg/mL and AZT facilitating AIDS clinical course [44–46, 59–61, 70, 71, 73, 74, 81, 85–87]. It has been established that the introduction of 5-aminouracil and *L*-cysteine molecules as well as dipeptides into GA molecule results a considerable enhancing the anti-HIV-1 activity of compounds in the culture of MT-4 cells as compared to the naturally occurring glycoside.

The substitution of GA carbohydrate chain by α-*D*-glucosamine residue also results in a considerable (10-fold) increase in the anti-HIV activity level [71, 73, 82]. This fact indicates that GA chemical modifying via the introduction of amino acids and dipeptides into the carbohydrate part represents a promising way to design novel anti-HIV agents surpassing the natural glycoside in antiviral activity.

The anti-SARS-CoV activity of a number of novel GA derivatives has been investigated at the Institute of Medical Virology, J. W. Goethe University Hospital (Prof. J. Cinatl, Frankfurt am Main, Germany) for the of VERO cellular culture comparing to GA with the use of SARS-CoV strain FFM1 [91.] N-glycoconjugate of GA with 2-acetamido-β-*D*-glucosamine is of interest as a low-toxic inhibitor of SARS virus. It is established that the manifestation of the mentioned kind of antiviral activity requires the presence of the diglucouronide chain, 18β-configuration and a free 30-COOH group of aglycon. We hypothesize that the penetration of viruses into cells could be inhibited by binding GA and its derivatives with carbohydrates of corona strain viral S-proteins.

The experts of the Institute of Microbiology, Immunology and Molecular Medicine, Tzu Chi University (Prof. J.-Ch. Lin, Taiwan) have appraised the antiviral activity level for a number of GA derivatives and analogues with respect to EBV virus, the promoter of skin tumours *in vitro* [92]. The authors have revealed the substances those inhibit the EBV viral antigen expression, and for the first time established some laws for the relationship between the structure and antiviral activity in the series of novel GA derivatives and analogues.

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