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Glycyrrhizic acid derivatives as Dengue virus inhibitors

Lidia A. Baltina^{a,*}, Yan-Ting Tasi^{b,c}, Su-Hua Huang^c, Hsueh-Chou Lai^{d,e}, Baltina Lia A.^a, Svetlana F. Petrova^a, Marat S. Yunusov^a, Cheng-Wen Lin^{b,c,f,*}^a Ufa Institute of Chemistry, Ufa Federal Research Centre of RAS, 71, Prospect Oktyabrya, Ufa 450054, Russian Federation^b Department of Medical Laboratory Science and Biotechnology, China Medical University, 91, Hsueh-Shih Rd., Taichung 40402, Taiwan, ROC^c Department of Biotechnology, Asia University, 500, Lioufeng Rd., Wufeng, Taichung 41354, Taiwan, ROC^d School of Chinese Medicine, China Medical University, 91, Hsueh-Shih Rd., Taichung 40402, Taiwan, ROC^e Division of Hepato-gastroenterology, Department of Internal Medicine, China Medical University Hospital, 2, Yude Rd., Taichung 40447, Taiwan, ROC^f Chinese Medicine Research Center, China Medical University, 91, Hsueh-Shih Rd., Taichung 40402, Taiwan, ROC

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ABSTRACT

Dengue virus (DENV) is one of the most geographically distributed pathogenic flaviviruses transmitted by mosquitoes *Aedes* spp. In this study, the structure-antiviral activity relationships of Glycyrrhizic acid (GL) derivatives was evaluated by the inhibitory assays on the cytopathic effect (CPE) and viral infectivity of DENV type 2 (DENV2) in Vero E6 cells. GL (96% purity) had a low cytotoxicity to Vero E6 cells, inhibited DENV2-induced CPE, and reduced the DENV-2 infectivity with the IC₅₀ of 8.1 μM. Conjugation of GL with amino acids or their methyl esters and the introduction of aromatic acylhydrazide residues into the carbohydrate part strongly influenced on the antiviral activity. Among compounds tested GL conjugates with isoleucine **13** and 11-aminoundecanoic acid **17** were found as potent anti-DENV2 inhibitors (IC₅₀ 1.2–1.3 μM). Therefore, modification of GL is a perspective way in the search of new antivirals against DENV2 infection.

Dengue virus (DENV) is one of the most geographically distributed pathogenic flaviviruses transmitted by mosquitoes *Aedes* spp. DENV re-emerges in recent years and poses a threat to the health of the population of more than 100 countries around the world, as considered one of the greatest virus threats to mankind.^{1,2} Over the past 50 years, the incidence of Dengue fever has increased 30-fold as a result of its expansion into new countries. The number of cases of infection with DENV in the world is 50–100 million people annually, including 250,000–500,000 cases of Dengue hemorrhagic fever and 24,000 deaths. The Dengue fever epidemic is a serious public health problem in Indonesia, Malaysia, Myanmar, Sri Lanka, Thailand, Cambodia, the Philippines, Laos, Vietnam, and India, where DENV infection is one of the leading causes of hospitalization and death in children.^{3–5}

Due to the expanding geographic expansion of DENV and the mosquitoes carrying *Aedes* spp., an increase in the frequency of epidemics, and the emergence of Dengue fever in new areas, WHO declares DENV the main virus threat to humanity.⁶ According to the antigenic structure, DENV is close to the yellow fever virus and is divided into four serotypes (DENV1–DENV4) that cause Dengue fever, Dengue hemorrhagic fever and Dengue shock syndrome, which leads to death. Infection with a one serotype of the virus provides long-term resistance

to this serotype, but does not lead to the development of immunity from other serotypes.⁷ DENV2 infection manifests itself as a hemorrhagic fever, which is characterized by increased viremia, vascular permeability and is characterized by high blood plasma levels of TNF, TNFR1, TNFR2, IFN, CXCL8, CXCL9, CXCL10, CXCL11, CCL5, VEGFA and IL-10.^{8,9} Despite the increasing number of outbreaks of Dengue fever in the last decade, there are currently no licensed vaccines and specific chemotherapy against this infection.¹⁰ Thus, the search of new antiviral agents against DENV is one of urgent problems of medicinal chemistry and virology.

One of the priority areas in the development of antiviral drugs is the use as scaffolds plant's derived natural compounds with established antiviral activity and a new mechanism of antiviral action.^{11,12} The chemical modification of available plant metabolites, the screening of antiviral activity of modifiers, the study of the structure-activity relationships and the choice of lead compounds are a necessary stage and scientific basis for the creation of new effective antiviral agents for the treatment and prevention of viral infections caused by pathogenic viruses.

Glycyrrhizic acid (GL) (**1**) is the leading natural triterpene glycoside, promising as a basis for the development of new antiviral

* Corresponding authors at: Ufa Institute of Chemistry, Ufa Federal Research Centre of RAS, 71, Prospect Oktyabrya, Ufa 450054, Russian Federation (L.A. Baltina). Department of Medical Laboratory Science and Biotechnology, China Medical University, 91, Hsueh-Shih Rd., Taichung 40402, Taiwan, ROC (C.-W. Lin).

E-mail addresses: baltina@anrb.ru (L.A. Baltina), cwlin@mail.cmu.edu.tw (C.-W. Lin).

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agents.^{13,14} GL inhibits a number of DNA and RNA viruses (Vaccinia, New Castle, Vesicular stomatitis, varicella-zoster, Herpes simplex type 1, Herpes B), influenza viruses, cytomegaloviruses, hepatitis B and C. GL is used clinically for the treatment of chronic viral hepatitis B and C in Japan and China (SNMC preparations, Compound Glycyrrhizin Ingepcion Injection, Compound Glycyrrhizin Ingepcion Tablets).^{15,16} GL inhibits the reproduction of HIV-1 in the culture of MT-4 cells and is suggested for long-term therapy for HIV-infected patients in combination with other anti-HIV drugs.^{14,17} GL also affects other cellular factors, such as protein kinase II, casein kinase II and transcription factors (activating protein I and nuclear factor kB).¹⁷

Chemical modification of GL is a promising way of obtaining new immune modulators and antiviral agents. Early we synthesized a series of amides, amino acid and dipeptide conjugates, which exceed the natural glycoside by anti-HIV activity.^{18,19} GL and its derivatives constitute the first group of substances that inhibit the Marburg virus, which causes acute hemorrhagic fever with a high level of lethality.²⁰ The inhibitory effect has been found for GL derivatives *in vitro* against SARS-associated coronaviruses.²¹ Among GL derivatives inhibitors of the Epstein-Barr virus were found.²² Most recently, we detected inhibitory effects of GL derivatives *in vitro* against influenza A/H1N1 virus.^{23,24}

GL is also of interest as a scaffold for the preparation of potential inhibitors of pathogenic flaviviruses like DENV, since it is reported about the GL ability to inhibit DENV and yellow fever viruses at high non-toxic concentrations.²⁵ The antiviral activity of GL and its derivatives is associated with the ability to potentiate γ -interferon production *in vitro* and *in vivo*. The stimulating effect of GL was noted on the secretion of IL-2, inducing the production of interferon by peripheral lymphocytes.^{13,14} The antiviral activity of GL derivatives against DENV was not studied else.

In this study, we report firstly about the antiviral activity of GL derivatives (2–21) (Fig. 1) to be conjugates with L- and D-amino acids and their methyl esters and aromatic acylhydrazides against DENV2 and

the structure-antiviral activity regularities for those compounds.

GL derivatives used in the study were divided into 3 groups. Group I (compounds 3–15) are GL conjugates containing three free amino acids or their methyl esters residues. Group II (compounds 16, 17) is presented by GL conjugates containing amino components in the carbohydrate part of glycoside. Group III includes acyl hydrazide (18–21) with C30-methyl ester at the R position and residues at the R' position in GL derivatives.

GL was produced from its mono ammonium salt according to Refs.^{26,27} and had a purity $96.0 \pm 1.0\%$ (HPLC). Trimethyl ester (2) was produced from GL by using diazometane.²⁸ GL conjugates with amino acids esters (3–12) were prepared by using *N*-hydroxybenzotriazole (HOBt), *N,N'*-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC) as we described previously.^{29–31} GL conjugates (10–12), containing D-amino acids methyl esters, were synthesized according to Ref.²⁴, conjugates (13–14) with free amino acids according to Refs.^{32,33}. Compounds (16, 17) containing the residues of aspartic and 11-amino undecanoic acid methyl esters in the carbohydrate part of GL were produced by using *N*-hydroxysuccinimide (HOSu) and DCC.^{34,35} The analytical and spectral data of GL derivatives 2–17 were identical to the literature data, the purity of compounds was monitored by thin layer chromatography and high pressure liquid chromatography (HPLC) ($\sim 95\%$ of purity) (in the [Supplementary Material, Supplemental Figs. 1–3](#)).

To expand the library of GL derivatives for testing GL derivatives 18–21 were produced by the modification of GL with the introduction of aromatic acyl hydrazide residues in the carbohydrate part. General experimental details, analytical and spectral data (IR and ¹³C) for new compounds (18–21) are given in the [Supplemental data](#). Bis-hydrazide of GL 18 was obtained from GL trimethyl ester 2 by reflux with hydrazine hydrate in methanol with 77% yield. The ester methyl group in the aglycone of compound 18 is retained, it was confirmed by the presence of C-30 and OCH₃ shifts at 177.1 and 51.9 ppm in the ¹³C NMR spectrum. Aromatic acyl-hydrazides (19–21) were produced by the reaction of 18 with aromatic aldehydes in ethanol at reflux for 3 h and target compounds were isolated by column chromatography (CC) on silica gel (SG) with 72–74% yields. The structures of compounds 18–21 were confirmed by IR and ¹³C NMR spectrum. In the ¹³C NMR spectrum of compounds 18–21 the carbon atoms of the new CH=N bonds are detected at 146.2–148.6 ppm, and a set of signals of aromatic carbon atoms appears in the weak field region (131.9–115.5 ppm). ¹³C NMR spectrum of bis-(pyridine-4-carbal)-hydrazide 21 contains shifts of carbon atoms of pyridine residues in the weak field region (142.7–121.4 ppm). The elemental analysis of all compounds corresponded to the calculated data (see the [Supplementary material](#)).

The primary screening of cytotoxicity and antiviral activity of GL and a number of its derivatives (compounds 3–21) was performed *in vitro* against DENV2 (the strain 16681). Cytotoxicity and antiviral activity were investigated in Vero E6 cell culture in supporting Dulbecco modified medium (DMEM). An MTT cytotoxicity test for each compound was performed in a Vero E6 cell culture in 96-well plates, as described in our previous report.³⁶ The cytotoxic (50%) concentration (CC50) was calculated according to cell survival rate of treated cells compared to mock cells using a computer program (John Spouge, NCBI, NIH). GL (96% purity) was used in the study of antiviral activity as a reference sample. It was established that for GL and its derivatives, the CC50 exceeded 100 μ M (Table 1).

To determine the antiviral activity, a screening study of the cytopathic effect (CPE) reduction was initially conducted in Vero E6 cells infected with the DENV2 virus (MOI of 0.01) in the presence of 10 μ M of the test compound. After 96 h of incubation, infected cells were photographed using reverse phase contrast microscopy. Microscopic photographs showed that GL and some of its derivatives at a concentration of 10 μ M significantly reduce CPE in cells infected with DENV2. GL had low cytotoxicity to Vero E6 cells,^{1–36} concentration-dependently inhibited CPE and NS4B positive cells (70.5% inhibition)

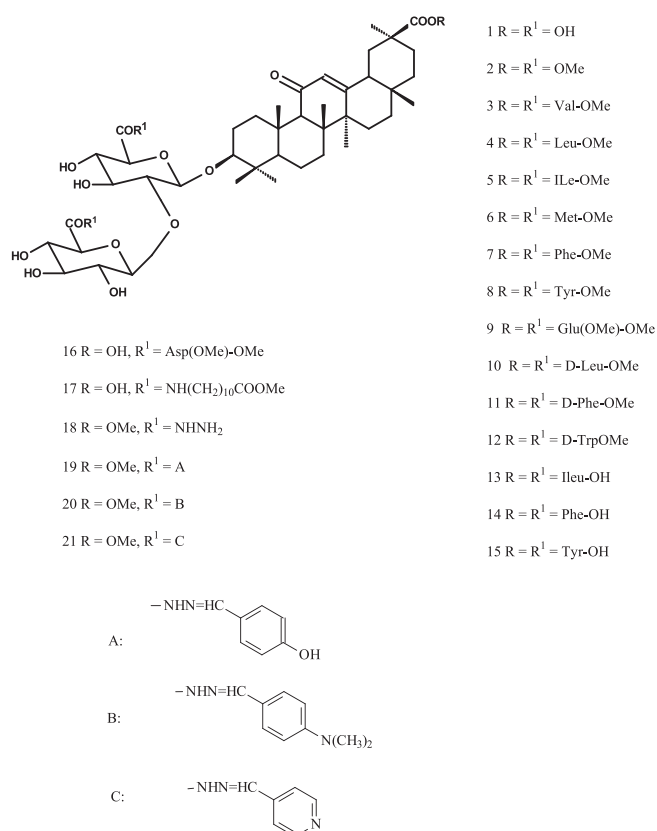


Fig. 1. Structure of GL and its derivatives (Compounds 2–21).

Table 1
Antiviral activity of GL derivatives against DENV2 in *Vero* E6 cells.

Compounds	CPE reduction at 10 μ M	Inhibition of NS4B-positive cells (%) at 10 μ M ^a	Cytotoxicity to <i>Vero</i> cells (CC50, μ M) ^b	Reduction in virus-infected cells (IC50, μ M) ^c	TI (CC50/IC50)
1	++	70.5	>100	8.1	>12.3
3	–	–	ND	ND	ND
4	–	–	ND	ND	ND
5	–	–	ND	ND	ND
6	++	66.3	>100	4.5	>22.2
7	–	–	ND	ND	ND
8	–	–	ND	ND	ND
9	–	–	ND	ND	ND
10	+	53.1	ND	ND	ND
11	–	–	ND	ND	ND
12	–	–	ND	ND	ND
13	+++	95.7	>100	1.3	>76.3
14	–	–	ND	ND	ND
15	++	68.5	>100	2.2	>46.5
16	+	35.8	ND	ND	ND
17	+++	79.5	>100	1.2	>80
18	–	–	ND	ND	ND
19	+	32.5	ND	ND	ND
20	–	–	ND	ND	ND
21	–	–	ND	ND	ND

ND – not detected.

^a Inhibitory rate = $(1 - \text{NS4B positive percentage in treated infected cells} / \text{NS4B positive percentage in mock-treated infected cells}) \times 100$.

^b CC50, 50% cytotoxic concentration determined by the survival rate of treated cells at different concentrations of each compound.

^c IC50, 50% inhibitory concentration calculated according to NS4B positive percentage in the presence of different concentrations of each compound.

post DENV-2 infection. The most active GL conjugates **6**, **13**, **15**, and **17** (Table 1) proved the significant CPE reduction in the infected cells, representing greater than 50% inhibition on the ratio of DENV2 NS4B-positive cells of infected cells treated with 10 μ M indicated derivatives. The antiviral activity of GL and its active derivatives to reduce DENV2 CPE and infectivity was studied in a concentration-dependent manner (0, 0.1, 1, 10 μ M). GL and its active derivatives dose-dependently inhibited DENV2-induced CPE in *Vero* E6 cells. GL conjugate with isoleucine (compound **13**) showed the highest inhibitory activity on DENV2-induced CPE at the concentration of 10 μ M (Fig. 2).

To assess the values of 50% inhibitory concentration (IC50), a quantitative analysis of the inhibitory effect of GL and its active derivatives on the infectivity of DENV2 was carried out *in vitro* by the immunofluorescence method.³⁶ The infectivity of virus was determined as the ratio of NS4B-positive cells to the total number of cells stained with DAPI (4',6-diamidino-2-phenylindole). This analysis has demonstrated that GL and its active derivatives (**6**, **13**, **15**, and **17**) reduced the number of infected DENV-2 cells (viral NS4B-positive cells) in a dose-dependent form. For example, the rates of NS4B-positive cells were 36.9%, 37.2%, 29.4%, and 1.6% in 0.1, 1 and 10 μ M compound **13**-treated infected cells, respectively (Fig. 3). Meanwhile, the inhibitory rate on DENV2 was 20.2%, and 95.7% by 1 and 10 μ M compound **13**, respectively. In addition, human lung epithelial A549 cells were used to

examine the antiviral activity of GL derivative **13** against DENV2 (Supplemental Fig. 4), in which GL derivative **13** exhibited the potent anti-DENV2 activity in a cell-type independent manner. GL derivatives **13** and **15**, containing free amino acids residues (Ile-OH) and (Tyr-OH), and **17** with two long chain amino acid fragments, were found as highly active against anti-DENV2 (IC50 values of 1.3–2.2 μ M), as significantly more potent than GL (IC50 of 8.1 μ M) (Table 1). In addition, compounds **13** and **17** exhibited the higher therapeutic index (TI, TI = CC50/IC50) than 70, which was 6-fold greater than that of GL. Tyrosine containing conjugate **15** was less active than **13** and **17**.

Among group I GL derivatives, conjugates **3–5** and **7–12** with amino acid methyl esters at the R and R' positions were less active than GL against DENV2. Only conjugate **6** containing Met-OMe fragments showed a significant inhibition on the *in vitro* replication of DENV2 and its IC50 (4.5 μ M) was less than for GL. The anti-DENV activity of conjugate **6** could be linked with the introduction of Met-OMe at the R position of triterpene part, in which an S-methyl thioether side chain of methionine might form NH...S H-bonds with the residues of DENV2 target protein. Conjugates **13** and **15** containing Ile-OH and Tyr-OH at the R and R' positions refined anti-DENV activity (IC50 of 1.3–2.2 μ M), but conjugate **14** with Phe-OH dropped the anti-DENV activity. The finding inferred that the –OH group of tyrosine plays the important role in donating or accepting a hydrogen bond with the residues of viral target protein. A weak inhibitory activity on CPE test and NS4B-positive cells was found for compound **16** with a free triterpene COOH group and Asp(OMe)-OMe in the carbohydrate portion of GL. However, compound **17** containing 11-amino undecanoic acid methyl ester exhibited the potent efficacy on inhibiting the DENV2 replication (IC50 of 1.2 μ M). Those results indicated that 11-amino undecanoic acid methyl ester at the R' position in the carbohydrate part of GL had a more effective interaction with the antiviral target(s) than conjugate **16**. GL derivatives of group III (**18–21**) lost the antiviral activity against DENV2. A weak inhibition (32.5%) of NS4B in DENV2-infected cells was found for compound **19** containing aromatic hydroxyl group. Therefore, the structure-antiviral activity study indicated that GL conjugates with three free amino acids (compounds **13**, **15**) and long chain amino acid residue in the carbohydrate part (compound **15**) exhibited higher anti-DENV activity compared to group III derivatives. Thus, the presence of hydroxyl group at the R position of triterpene part or free carboxyl groups of amino acids are important for interacting with antiviral target(s). Meanwhile, GL derivatives **13**, **15**, and **17** are compounds with the significantly improved antiviral activity against DENV2 infection, suggesting that isoleucine, tyrosine, or 11-amino undecanoic acid methyl ester at the R' position of the carbohydrate part also interconnected with the other part of active side of antiviral target(s).

We concluded that this study was the first report to display structure-anti-DENV activity relationships of GL derivatives, revealing that the modification of GL by the conjugation with amino acids and the introduction of aromatic acyl hydrazide residues into the carbohydrate part strongly influenced on the antiviral activity of GL against DENV2. Among GL derivatives tested, GL compounds **13**³² and **17**³⁵ have been identified as potent DENV2 inhibitors. Thus, the conjugation of GL derivatives with amino acids is a perspective way to produce potent DENV2 inhibitors. The second way to potentiate GL activity is its modification with the introducing of long chain amino acids in the

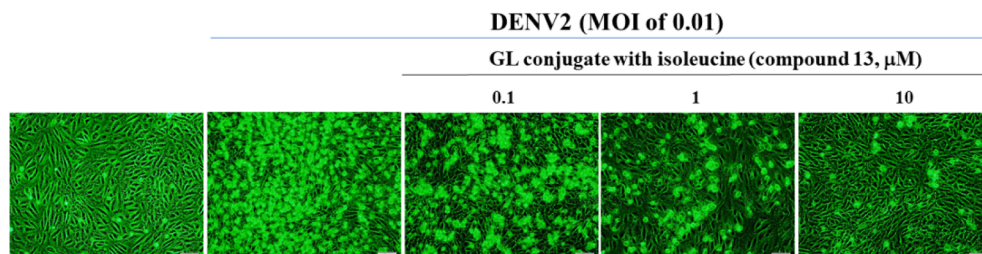


Fig. 2. Inhibition of DENV2-induced cytopathic effects by GL conjugate with isoleucine (Compound **13**). *Vero* E6 cells were infected with DENV2 at a MOI of 0.01 and immediately treated with the indicated concentrations of compound **13**. Images of DENV2-induced cytopathic effect were photographed 96 h post infection by phase-contrast microscopy.

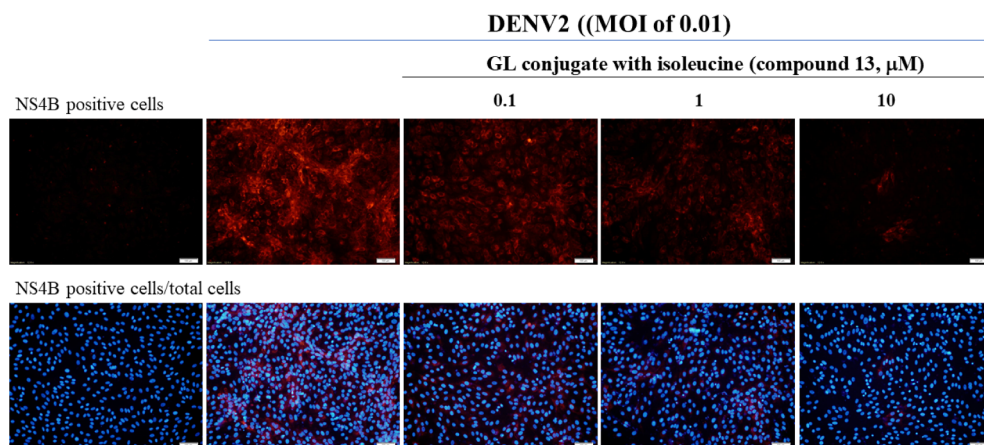


Fig. 3. Inhibition of DENV2 infectivity by GL conjugate with isoleucine (Compound 13). Vero E6 cells infected with DENV2 (MOI of 0.01) were analyzed using immunofluorescence staining with anti-DENV2 NS4B antibodies after a 96-h treatment with the indicated concentrations of compound 13. ZENV2 infectivity was discovered by the ratio of DENV2 NS4B positive cells (top) to total cells stained with DAPI.

carbohydrate part of the molecule keeping triterpene COOH group free. Highly active GL derivatives will be the subject of extensive research on antiviral activity and the study of the mechanisms of antiviral action against DENV2 by using docking studies and their interaction with DENV2 targets like NS2B-NS3 protease, NS3 helicase, and NS5 RNA-dependent RNA polymerase.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bmcl.2019.126645>.

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