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Synthesis of Cyclohexane Containing 5′-O-Glycine Derivatives of Uridine as Potential Inhibitors of *UDP*-glucuronosyltransferase

Dimitar K. Alargov[1,*], **Roumyana G. Gugova**[1], **Pavleta S. Denkova**[2], **Gunther Müller**[3], and **Evgeny V. Golovinsky**[1]

[1] Institute of Molecular Biology, Bulgarian Academy of Sciences, BG-1113 Sofia, Bulgaria
[2] Institute of Organic Chemistry, Bulgarian Academy of Sciences, BG-1113 Sofia, Bulgaria
[3] Institut für Hygiene und Arbeitsmedizin, Universität Essen, D-45122 Essen, Germany

Summary. In order to design potential inhibitors of *UDP*-glucuronosyltransferase, two different pathways for the synthesis of cyclohexane containing 5′-O-glycine derivatives of uridine were developed, one starting with the cyclohexyl moiety, and a second one beginning with the uridine moiety. Thus, 5′-O-(cyclohexylcarboxyl-glycyl)-2′,3′-O-isopropylideneuridine and 5′-O-(cyclohexylpropionyl-glycyl)-2′,3′-O-isopropylideneuridine were obtained. According to the results, the second approach is more convenient.

Keywords. Uridine; 5′-O-Amino acid derivatives; Cyclohexanecarboxylic acid; Cyclohexylpropionic acid; *UDP*-Glucuronosyltransferase.

Synthese von cyclohexylsubstituierten 5′-O-Glycin-uridinderivaten als potentielle Inhibitoren der *UDP*-Glukuronosyltransferase

Zusammenfassung. Mit dem Ziel, potentielle Inhibitoren der *UDP*-Glukuronosyltransferase herzustellen, wurden zwei verschiedene Synthesewege für 5′-O-Glycinderivate entwickelt. Der erste Syntheseweg beginnt mit dem Cyclohexylfragment, der zweite mit dem Uridinest. Es wurden 5′-O-(Cyclohexylcarboxyl-glycyl)-2′,3′-O-isopropylidenuridin und 5′-O-(Cyclohexylpropionyl-glycyl)-2′,3′-O-isopropylidenuridin hergestellt. Entsprechend den Ergebnissen ist die zweite Methode besser geeignet.

Introduction

UDP-Glucuronosyltransferase (*UGT*, EC 2.4.1.17) is a multigenic family of membrane-bound isoenzymes involved in the biotransformation and detoxication of various exogenous and endogenous compounds [1]. These enzymes catalyze the transfer of glucuronic acid from *UDP*-glucuronic acid (*UDP-GlcA*) to the

* Corresponding author

respective aglycones (*RX*H) containing hydroxyl, amino, carboxyl, or sulfhydryl groups, forming water soluble β-(*D*)-glucuronides which are readily excreted due to the hydrophilicity of the glucuronic acid moiety.

Enzymatic glucuronidation also plays a pivotal role in the biotransformation of drugs. Various drugs, including the anti-HIV agent *AZT* (3′-azido-3′-deoxythymidine) are extensively converted to their inactive glucuronides and excreted from the organism [2,3]. Thus, the inhibition of *UGT* could increase the plasma level and therapeutic efficacy of a number of drugs. Simultaneously, the development of selective inhibitors of *UGT* could also provide a useful approach in studying the active sites of different *UGT* isoforms.

In the last years, several classes of *UGT* inhibitors have been developed [4–7]. According to the current concepts, the *UDP* part or the uridine moiety is thought to provide most of the free binding energy of the ligand-enzyme complex [8]. Linkage of lipophilic aryl or arylalkyl residues to *UDP* and uridine have led to powerful *UGT* inhibitors considered as possible transition state analogs [9–13].

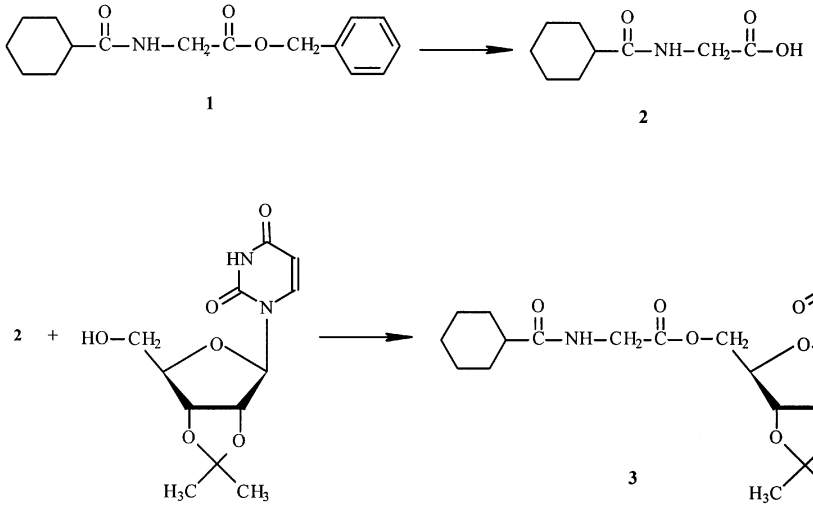
Recently, we have synthesized novel uridinyl analogs modified at the 5′-O-position by protected and unprotected amino acids [14] and oligopeptides [15]. The inhibitory potency of these compounds on the glucuronidation of 4-nitrophenol (4-*NP*) and phenolphthalein (*PPh*) by rat liver microsomes has also been tested. Some of them have been found to be inhibitors of both 4-*NP* and *PPh*-glucuronidation [16]. To estimate the contribution of the different parts of the inhibitors to the active site binding, a quantitative structure-activity relationship (QSAR) study was also performed [17].

Continuing our studies on the design and the structure-activity relationships of effective *UGT* inhibitors, we decided to synthesize a series of compounds containing lipophilic residues attached to amino acid derivatives of uridine. Here we report the synthesis of cyclohexane containing 5′-O-glycine derivatives of uridine as potential inhibitors of *UDP*-glucuronosyltransferase.

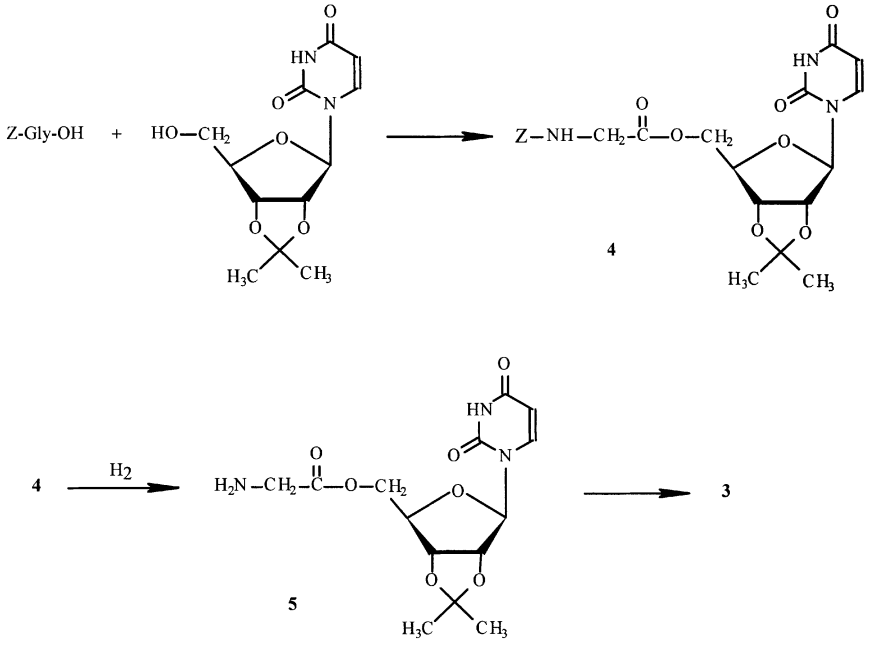
Results and Discussion

For the synthesis of the compounds, two different pathways were tried, one starting with the cyclohexyl moiety and a second one beginning with the uridine residue. According to the first approach (Scheme 1), cyclohexanecarboxyl glycine benzyl ester (**1**) was prepared from cyclohexanecarboxylic acid and glycine benzyl ester using the *DCC* (dicyclohexylcarbodiimide) method [18] in 94% yield after recrystallisation from EtOAc/*PE*. The benzyl group of **1** was then deprotected by catalytic hydrogenolysis over 10% Pd/C/ammonium formate [19] to yield cyclohexanecarboxyl glycine (**2**). Then, **2** was esterified with 2′,3′-O-isopropylideneuridine to provide **3** using 4-dimethylaminopyridine as the catalyst [20]. The rather low yield of **3** (20%, 15% overall yield based on 2′,3′-O-isopropylideneuridine) was due to the poor solubility of **2** in solvents like *DMF* or *DMSO*. To avoid this problem, we decided to try another approach.

According to the second approach (Scheme 2), **3** was prepared by a three-step synthesis starting from 5′-O-(N-benzyloxycarbonyl-glycyl)-2-′,3′-O-isopropylideneuridine (**4**). The latter was prepared from N-benzyloxycarbonyl glycine and 2′,3′-O-isopropylideneuridine in analogy to **3** in 94% yield. In the next step, the



Scheme 1



Scheme 2

benzyloxycarbonyl group (*Z*) of **4** was deprotected by catalytic hydrogenolysis in the same way as for **2** to give 5′-O-glycyl-2′,3′-O-isopropylideneuridine (**5**) which was used in the next step without further purification. A 76% yield of **3** was obtained after esterification of **5** with cyclohexanecarboxylic acid. The overall yield based on 2′,3′-O-isopropylideneuridine was 71%. In a similar way as described above, cyclohexylpropionyl glycine benzyl ester (**6**), cyclohexylpropionyl glycine (**7**), and 5′-O-(cyclohexylpropionyl-glycyl)-2′,3′-O-isopropylideneuridine

(**8**) were prepared. The new derivatives were TLC pure and were characterized by ^{1}H NMR, MS, and elemental analyses.

Conclusions

In order to design potential inhibitors of *UDP*-glucuronosyltransferase, two different pathways for the synthesis of cyclohexane containing 5′-O-glycine derivatives of uridine were developped. According to the results, the second approach (Scheme 2) is more convenient and should therefore be used for the synthesis of similar compounds.

Experimental

The amino acid derivatives were purchased from Bachem Biochemica GmbH (Heidelberg). 2′,3′-O-Isopropylideneuridine was obtained from Sigma. All other chemicals were of analytical grade. Melting points were measured with a Büchi 535 apparatus. TLC analysis was performed on aluminium sheets Silica gel 60 F_{254} (Merck) using the following chromatographic systems: A: BuOH:AcOH:H_2O (3:1:1), B: $CHCl_3$:MeOH (9:1); the spots were visualized by UV light or by spraying with the appropriate reagents (*Reindel* [21], ninhydrin). For column chromatography, Merck Kieselgel 60 (76–230mesh ASTM) was used. Optical rotation was determined with a Polamat A Carl-Zeiss instrument. The ^{1}H NMR spectra were obtained on a Bruker DRX-250 instrument (250 MHz). Elemental analyses were performed with a Perkin-Elmer M 240 apparatus; the results were in good agriment with the calculated values. Mass spectra were recorded with a Jeol JMS D100 spectrometer.

Cyclohexylcarboxyl glycine benzyl ester (**1**; $C_{16}H_{21}NO_3$)

2.28 g Cyclohexanecarboxylic acid (17.8 mmol) and 1.48 g *DCC* (8.9 mmol) were stirred in 10 cm^3 *DMF* for 30 min at 0°C. Then, 2.0 g glycine benzyl ester *p*-tosylate (5.9 mmol) and 0.82 cm^3 Et_3N (5.9 mmol) were added, and stirring was continued for 24 h at room temperature. The N,N′-dicyclohexyl urea was removed by filtration. EtOAc was added to the filtrate, and the organic phase was washed with a 5% solution of $NaHCO_3$ and H_2O. The EtOAc solution was dried over anhydrous Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from EtOAc/*PE* to give 1.52 g pure **1** (94%) as white crystals.

M.p.: 90.5–104°C; R_f (A) = 0.86, R_f (B) = 0.87; ^{1}H NMR ($(CD_3)_2SO$, δ, 250 MHz): 8.17 (bt, 1H, NH), 7.35 (s, 5H, H-arom), 5.1 (s, 2H, CH_2-benzl), 3.84 (d, 2H, H-α (Gly), $J_{\alpha,NH} = 5.96$ Hz), 2.14 (m, 1H, H-α (Ch ring), 1.69–1.58 (m, 5H, 2×CH_2-β and H-δ (Ch ring)), 1.36–1.04 (m, 5H, 2×CH_2-γ and H-δ (Ch ring)) ppm; MS: $m/z = 275$ (M^+), 253, 220, 209, 184, 168, 154, 141, 111, 91 ($C_6H_5CH_2^+$), 83 (100%), 76, 67, 55.

Cyclohexylcarboxyl glycine (**2**; $C_9H_{15}NO_3$)

0.5 g Cyclohexylcarboxyl glycine benzyl ester (**1**, 1.7 mmol) was dissolved in 20 cm^3 absolute MeOH. Then, 10% Pd/C and 0.32 g ammonium formate (5.0 mmol) were added. The reaction mixture was stirred at room temperature for 10 min. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The raw product was recrystallized from EtOAc/*PE* to give 0.25 g **2** (81%) as chromatographically pure crystals.

M.p.: 66.7–67°C; R_f (A) = 0.73; ^{1}H NMR ($(CD_3)_2SO$, δ , 250 MHz): 7.22 (bt, 1H, NH), 3.38 (d, 2H, H-α(Gly), $J_{\alpha,NH} = 3.76$ Hz), 2.11 (m, 1H, H-α (Ch ring)), 1.68–1.56 (m, 5H, 2×CH_2-β and H-δ

(Ch ring)), 1.33–1.07 (m, 5H, 2×CH_2-γ and H-δ (Ch ring)) ppm; MS: $m/z = 185$ (M^+), 167, 141, 130, 117, 112, 110, 83, 76, 73, 73, 67, 60, 55 (100%).

5′-O-(Cyclohexylcarboxyl-glycyl)-2′,3′-O-isopropylideneuridine (**3**; $C_{21}H_{29}N_3O_8$)

2.07 g cyclohexylcarboxyl glycine (7.0 mmol) and 0.77 g *DCC* (3.7 mmol) were stirred in 10 cm^3 *DMF* for 30 min at 0°C. Then, 0.7 g 2′,3′-O-isopropylideneuridine (2.5 mmol) and 0.035 g 4-dimethylaminopyridine (0.25 mmol) were added, and stirring was continued for 48 h at room temperature. N,N′-Dicyclohexyl urea was removed by filtration. EtOAc was added to the filtrate, and the organic phase was washed with a 5% solution of $NaHCO_3$ and H_2O. The EtOAc solution was dried over anhydrous Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from EtOAc/*PE* to give chromatographically pure 0.23 g **3** (20%).

M.p.: 147.5°C; $[\alpha]_D^{20} = -10.7$ ($c = 1.0$, CH_3OH); R_f (A) = 0.76; ^{1}H NMR ($(CD_3)_2SO$, δ, 250 MHz): 11.37 (s, 1H, NH-*U*), 7.78 (d, 1H, H-6, $J_{6,5} = 8.07$ Hz), 5.82 (d, 1H, H-1′, $J_{1',2'} = 2.70$ Hz), 5.63 (d, 1H, H-5, $J_{5,6} = 8.07$ Hz), 5.10 (t, 1H, H-5′, $J_{5',5''} = 10.55$ Hz), $J_{5',4'} = 5.28$ Hz), 4.88 (dd, 1H, H-2′, $J_{2',1'} = 2.70$ Hz, $J_{2',3'} = 6.35$ Hz), 4.74 (dd, 1H, H-3′, $J_{3',4'} = 3.53$ Hz, $J_{3',2'} = 6.35$ Hz), 4.06 (m, 1H, H-4′), 3.62–3.51 (m, 3H, H-α(Gly) and H-5), 2.14 (m, 1H, H-α (Ch ring)), 1.70–1.58 (m, 4H, 2×CH_2-β (Ch ring)), 1.48 (s, 3H, CH_3-isopropylidene), 1.37–1.14 (m, 6H, 2×CH_2-γ and CH_2-δ (Ch ring)), 1.27 (s, 3H, CH_3-isopropylidene) ppm; MS: $m/z = 451$ (M^+), 436, 340, 326, 269, 209, 186, 168, 137, 113 (B+2H), 111 (B^+), 99, 83 (100%), 75, 69, 55.

5′-O-(N-Benzyloxycarbonyl-glycyl)-2′,3′-O-isopropylideneuridine (**4**; $C_{22}H_{25}N_3O_9$)

The title compound was prepared from 1.55 g N-benzyloxycarbonyl glycine (7.4 mmol), 0.76 g *DCC* (3.7 mmol), 0.7 g 2′,3′-O-isopropylideneuridine (2.5 mmol), and 0.03 g 4-dimethylaminopyridine (0.25 mmol) as described for **7** in 94% (1.12 g) yield.

M.p.: 101.6°C; $[\alpha]_D^{20} = -1.5$ ($c = 1.0$, CH_3OH); R_f (A) = 0.73, R_f (B) = 0.76; ^{1}H NMR ($(CD_3)_2SO$, δ, 250 MHz): 11.40 (s, 1H, NH-*U*), 7.68 (t, 1H, NH (Gly), $J_{NH,\alpha} = 6.40$ Hz), 7.65 (d, 1H, H-6, $J_{6,5} = 8.09$ Hz), 7.37–7.29 (m, 5H, H-arom), 5.80 (d, 1H, H-1′, $J_{1',2'} = 2.14$ Hz), 5.64 (d, 1H, H-5, $J_{5,6} = 8.09$ Hz), 5.03 (s, 2H, CH_2-benzl), 5.00 (dd, 1H, H-2′, $J_{2',1'} = 2.14$ Hz, $J_{2',3'} = 6.50$ Hz), 4.77 (dd, 1H, H-3′, $J_{3',4'} = 3.43$ Hz, $J_{3',2'} = 6.50$ Hz), 4.32–4.17 (m, 3H, 2H-5′, H-4′), 3.79 (d, 2H, H-α(Gly), $J_{\alpha,NH} = 6.40$ Hz), 1.48 (s, 3H, CH_3-isopropylidene), 1.28 (s, 3H, CH_3-isopropylidene) ppm; MS: $m/z = 475$ (M^+), 460, 417, 352, 256, 198, 167, 137, 113 (B+2H), 107, 91 ($C_6H_5CH_2^+$, 100%), 79, 69, 55.

Cyclohexylpropionyl glycine benzyl ester (**6**; $C_{18}H_{25}NO_3$)

6 was prepared from 5.64 g cyclohexylpropionic acid (36.0 mmol), 3.7 g *DCC* (18.0 mmol), 4.05 g glycine benzyl ester *p*-tosylate (12.0 mmol), and 1.66 cm^3 Et_3N (12.0 mmol) in accordance with the procedure described for **1** in 90% (3.28 g) yield.

M.p.: 166°C; R_f (A) = 0.93, R_f (B) = 0.87; ^{1}H NMR ($(CD_3)_2SO$, δ , 250 MHz): 8.28 (bt, 1H, NH), 7.30–7.35 (m, 5H, H-arom), 5.11 (s, 2H, CH_2-benzl), 3.89 (d, 2H, H-α(Gly), $J_{\alpha,NH} = 5.90$ Hz), 2.15–2.09 (m, 2H, H-2 (Chpr)), 1.66–1.62 (m, 5H, 2×CH_2-β and H-α (Ch ring)), 1.42–1.33 (m, 2H, H-3 (Chpr)), 1.16–1.09 (m, 4H, 2×CH_2-γ (Ch ring)), 0.88–0.79 (m, 2H, 2×H-δ (Ch ring)) ppm; Ms: $m/z = 304$ (M^+), 220, 207, 196, 169, 148, 139, 132, 121, 106, 91 ($C_6H_5CH_2^+$, 100%), 83, 69, 55.

Cyclohexylpropionyl glycine (**7**; $C_{11}H_{19}NO_3$)

1.0 g cyclohexylpropionyl glycine benzyl ester (3.1 mmol) was dissolved in 20 cm^3 absolute MeOH. Then, 10% Pd/C and 0.59 g ammonium formate (9.4 mmol) were added. The reaction mixture was stirred at room temperature for 10 min and treated as described for **2** to give 0.61 g **4** (92%).

M.p.: 153°C; R_f (A) = 0.79; ^{1}H NMR ($(CD_3)_2SO$, δ, 250 MHz): 7.38 (bt, 1H, NH), 5.12 (bs, 1H, COOH), 3.41 (d, 2H, H-α(Gly), $J_{\alpha,NH}$ = 5.06 Hz), 2.08 (m, 2H, H-2 (Chpr)), 1.66–1.62 (m, 5H, 2×CH_2-β and H-α (Ch ring)), 1.35 (m, 2H, 2H, H-3 (Chpr)), 1.17 (m, 4H, 2×CH_2-γ (Ch ring)), 0.80 (m, 2H, 2×H-δ (Ch ring)) ppm; MS: m/z = 214 (M^+), 196, 184, 168, 139, 130, 121, 117 (100%), 109, 95, 89, 83, 76, 69, 55.

5′-O-(Cyclohexylpropionyl-glycyl)-2′,3′-O-isopropylideneuridine (**8**; $C_{23}H_{33}N_3O_8$)

Prepared from 1.58 g cyclohexylpropionyl glycine (7.4 mmol), 0.76 g *DCC* (3.7 mmol), 0.7 g 2′,3′-O-isopropylideneuridine (2.5 mmol) and 0.03 g 4-dimethylaminopyridine (0.25 mmol) as described for **6** in 30% (0.36 g) yield.

M.p.: 140.8°C; $[\alpha]_D^{20} = -6.9$ (c = 1.0, CH_3OH); R_f (A) = 0.82; ^{1}H NMR ($(CD_3)_2SO$, δ, 250 MHz): 11.42 (s, 1H, NH-*U*), 7.80 (d, 1H, H-6, $J_{6,5}$ = 8.05 Hz), 5.78 (d, 1H, H-1′, $J_{1',2'}$ = 2.05 Hz), 5.63 (d, 1H, H-5, $J_{5,6}$ = 8.00 Hz), 5.8 (dd, 1H, H-2′, $J_{2',1'}$ = 2.06 Hz, $J_{2',3'}$ = 6.40 Hz), 4.92 (dd, 1H, H-3′, $J_{3',4'}$ = 2.06 Hz, $J_{3',2'}$ = 6.40 Hz), 4.66 (m, 1H, H-4′), 4.25 (m, 4H, H-α(Gly) and H-5′), 2.27 (m, 2H, H-2 (Chpr)), 1.67 (m, 5H, 2×CH_2-β and H-α (Ch ring)), 1.48 (s, 3H, CH_3-isopropylidene), 1.42 (m, 2H, 2H, H-3 (Chpr)), 1.28 (s, 3H, CH_3-isopropylidene), 1.18 (m, 4H, 2×CH_2-γ (Ch ring)), 0.83 (m, 2H, 2×H-δ (Ch ring)) ppm; MS: m/z = 480 (M^+), 466, 368, 326, 214, 168, 139 (100%), 137, 121, 113 (B+2H), 97, 83, 69, 55.

5′-O-(Cyclohexylcarboxyl-glycyl)-2′,3′-O-isopropylideneuridine (**3**; $C_{21}H_{29}N_3O_8$) (*second approach*)

3 was prepared from 1.51 g cyclohexanecarboxylic acid (7.5 mmol), 0.78 g *DCC* (3.8 mmol), and 1.19 g 5′-O-(N-benzyloxycarbonyl-glycyl)-2′-3′-O-isopropylideneuridine (2.5 mmol) as described for **2** and 0.35 cm^3 Et_3N (2.5 mmol) as described for **1** in 76% (1.13 g) yield.

5′-O-(Cyclohexylpropionyl-glycyl)-2′,3′-O-isopropylideneuridine (**6**; $C_{23}H_{33}N_3O_8$) (*second approach*)

The title compound was prepared from 1.17 cm^3 cyclohexylpropionic acid (7.5 mmol), 0.78 g *DCC* (3.8 mmol), and 1.19 g 5′-O-(N-benzyloxycarbonyl-glycyl)-2′,3′-O-isopropylideneuridine (2.5 mmol) which were treated as described for **2** and 0.35 cm^3 Et_3N (2.5 mmol) as described for **1** in 78% (1.20 g) yield.

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