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Process Development of 4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline Dihydrochloride: A Key Intermediate for TAK-779, a Small-Molecule Nonpeptide CCR5 Antagonist

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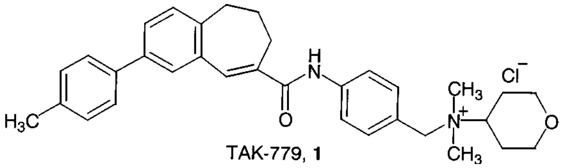
Abstract:

A new and efficient synthesis of 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline dihydrochloride, a key intermediate for the CCR5 antagonist TAK-779, is described. Reductive alkylation of methylamine with tetrahydro-4*H*-pyran-4-one followed by alkylation of *N*-methyl-*N*-(tetrahydropyran-4-yl)amine with 4-nitrobenzylbromide and reduction of *N*-(4-nitrobenzyl)-*N*-(tetrahydropyran-4-yl)amine results in a 78% isolated yield from the starting materials by a scalable method, using only commercially available reagents.

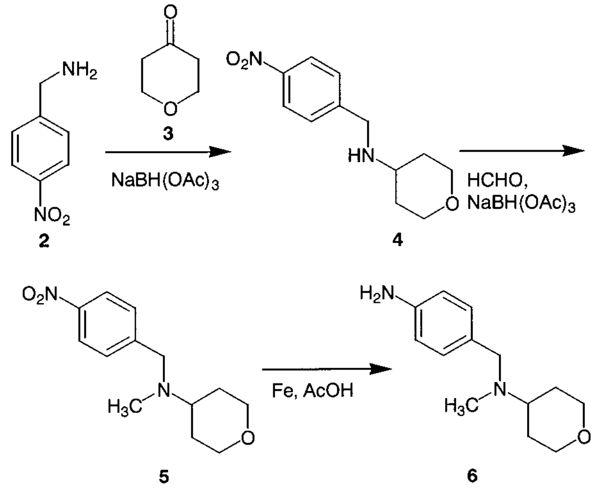
Results and Discussion

Recently, the β-chemokine receptor CCR5 has been reported to act as a major coreceptor for fusion and entry of macrophage-tropic HIV-1 into the host cell.[1] CCR5 antagonists are attractive as candidates for HIV-1 therapy, having a new mechanism of action in comparison with that of well-known chemotherapy represented by HIV-1 reverse transcriptase and protease inhibitors.[2,3] During our intensive research of many derivatives, *N*,*N*-dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]-amino]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride (**1**, TAK-779) was identified as a small-molecule nonpeptide CCR5 antagonist.[4]



TAK-779, **1**

Scheme 1. **Reported synthesis of 6**



This compound inhibits the replication of macrophage (M)-tropic HIV-1 in both MAGI-CCR5 cells and peripheral blood mononuclear cells (PBMCs). Synthesis of **1** was accomplished by amidation followed by methylation and anion exchange from two key intermediates, 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline (**6**) and 2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-carboxylic acid.[5] In the initial screening stage, key intermediate **6** was synthesized by reductive alkylation of 4-nitrobenzylamine (**2**) followed by a second reductive alkylation and reduction (Scheme 1). **6** was prepared in gram quantities via this Scheme for initial pharmacological screening.[6] However, the reported methods involved the following shortcomings from the viewpoint of large-scale manufacturability: use in bulk of starting material **2** with limited availability, separation of a large amount of solid waste including reducing reagents, and use of an environmentally unfriendly solvent, 1,2-dichloroethane. In particular, the difficulty of purchasing the starting materials was a serious problem in manufacturing **6**

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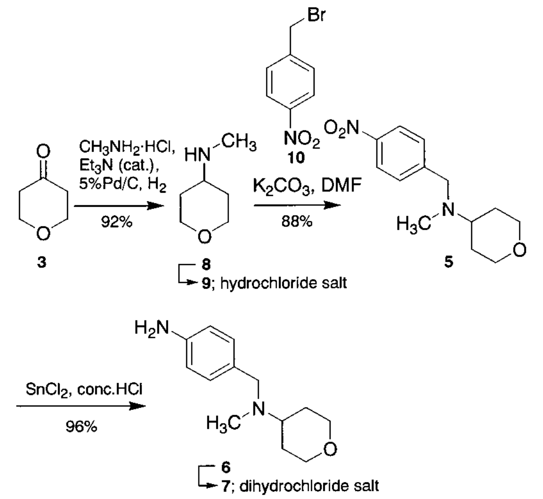
Scheme 2



for toxicological studies. Herein, we wish to report new and efficient methods amenable to a large-scale synthesis of **6**.

We focused on a synthetic route using 4-nitrobenzylbromide (**10**) and tetrahydro-4*H*-pyran-4-one (**3**) as a suitable process for large-scale synthesis (Scheme 2) since both are commercially available in large quantities. The synthesis of **6** was initiated by reductive alkylation of methylamine with **3**, followed by alkylation of *N*-methyl-*N*-(tetrahydropyran-4-yl)amine (**8**) with **10**, and reduction of *N*-(4-nitrobenzyl)-*N*-(tetrahydropyran-4-yl)methylamine (**5**).

Synthesis of *N*-Methyl-*N*-(tetrahydropyran-4-yl)amine Hydrochloride (9). Synthetic methods avoiding the use of sodium triacetoxyborohydride were first investigated to avoid the tedious removal of the catalyst and 1,2-dichloroethane for environmental considerations.[7] Thus, reductive alkylation of methylamine and **3** in the presence of Pd−C under hydrogen atmosphere in methanol as solvent proceeded almost quantitatively to give **8** in 69% isolated yield after distillation (95% purity).[8,9] However, further studies indicated that the yield is not consistent, presumably due to the low boiling point of **8** (72 °C/28 mmHg) or to its high solubility in water. To overcome this problem, crystallization of the product as its hydrochloride salt was developed.

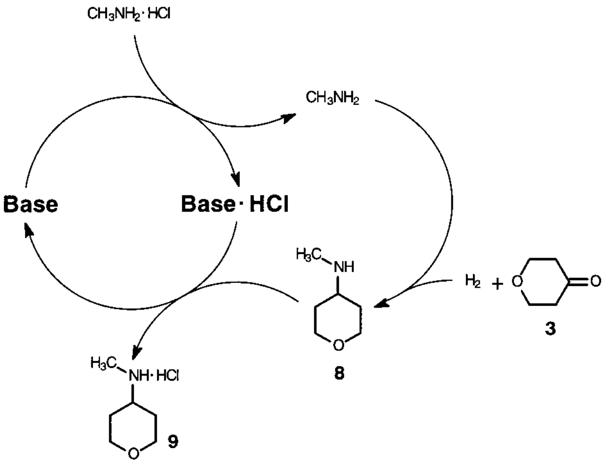
Although the isolated yield was improved in this way, we still continued our efforts to improve the process. One of the most significant issues on scale is the use of methylamine gas. In our early studies, methylamine gas was first dissolved in methanol; however, the quantity of methylamine absorbed was quite inconsistent and difficult to control. Furthermore, excess methylamine led to a large amount of by-products, whilst a lack of methylamine resulted in giving other by-products, including *N*-methyl-*N*,*N*-bis(tetrahydropyran-4-yl)amine. We investigated solid methylamine hydrochloride as an alternative agent, expecting to control the quantity of methylamine more easily. We envisaged that the reductive alkylation of methylamine with **3** would proceed in the presence of 1 equiv of a strong enough base to neutralize methylamine hydrochloride. **8** was prepared in 96.1% yield in the presence of 1 equiv of triethylamine as expected (Table 1, entry 1). However, a considerable amount of triethylamine hydrochloride was involved. Although extraction of the product into an organic solvent and washing with water is a well-known method to remove salts, this procedure markedly decreased the yield due to solubility of **8** that was too high in water. To overcome this problem, we investigated the new process which does not require the neutralization procedure, allowing isolation of **8** as hydrochloride salt.

Table 1. **Reductive alkylation of methylamine hydrochloride with 3**[a]

entry	base	equiv	K_b	time (h)	yield of **8**[b] (%)	recovery of **3**[b] (%)	yield of by-product[b] (%)
1	Et_3N	1.00	5.5×10^{-4}	2	96.1	0	0.5
2	Et_3N	0.03	5.5×10^{-4}	2	96.2 (91.6)	0	0.4
3	Et_3N	0.01	5.5×10^{-4}	3	96.1 (91.9)	0	1.0
4	Bu_3N	0.03	7.8×10^{-4}	3	97.0	0.5	1.5
5	Pr_3N	0.03	4.5×10^{-4}	3	90.9	0.8	1.4
6	Me_3N	0.03	0.6×10^{-4}	3	89.5	0	9.9
7	aniline	0.03	4.2×10^{-10}	3	88.1	0	7.9
8	none			10	84.8	6.1	9.0

[a] The reaction was carried out in methanol at 60 °C under the condition of 5 kgf/cm^2 hydrogen atmosphere. [CH_3NH_2·HCl]:[**3**]:[5%Pd/C] = 1:1:0.002. [b] Yield and recovery based on initial quantity of CH_3NH_2·HCl charged were determined by GC analysis. The value in parentheses indicates the isolated yield of **9**.

Scheme 3. **Hypothetical catalytic cycle for the synthesis of 9**



Reaction in the presence of trimethylamine as base involved a considerable amount of a by-product due to too low basicity ($K_b = 0.6 \times 10^{-4}$, entry 6). Aniline ($K_b = 4.2 \times 10^{-10}$) also failed to give satisfactory results. The by-product was assumed to be *N*-methyl-*N*,*N*-bis(tetrahydropyran-4-yl)amine. When weak amines represented by trimethylamine and aniline were used, methylamine did not sufficiently generate (Scheme 3). Thus, the catalytic cycle did not work well, resulting in by-products formed by the reaction of **8** with **3**. The reaction proceeded sluggishly in the absence of amines, involving a large amount of the by-product (entry 8). K_b of methylamine is 4.4×10^{-4}, and that of **8** is 9.5×10^{-4}. We speculated that **8** could be isolated as the hydrochloride salt via a hydrochloride salt of a base for which the K_b is 4.4×10^{-4} to 9.5×10^{-4} (Scheme 3). Amongst various tertiary amines of suitable basicity, we

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Table 2. **Alkylation of 9 with 10**[a]

entry	K_2CO_3 (equiv)	conditions	yield (%) of **5**[b]
1	2	25 °C, 5 h	82.3
2	1.05	25 °C, 5 h	95.4
3	1	25 °C, 6 h	90.4
4	1	60 °C, 2 h	97.4

[a] The reaction was carried out in *N*,*N*-dimethylformamide. [**9**]:[**10**] = 1:1. [b] Yield based on initial quantity of **9** charged were determined by HPLC analysis.

Table 3. **Reduction of 5**

entry	reducing agent	yield (%) of **6**[a]
1	Pd/C, H_2	trace
2	Raney-Ni, H_2	trace
3	Raney-Ni, $NH_2NH_2 \cdot H_2O$	81
4	Pd/C, $NH_2NH_2 \cdot H_2O$	76
5	$FeCl_3$, C, $NH_2NH_2 \cdot H_2O$	94
6	NaSH, H_2O	92.8 (65.4)
7	$SnCl_2$, H_2O	99.6 (56.8)
8	$SnCl_2$, hydrochloric acid	99.5 (96.0)
9	Sn, hydrochloric acid	98.8 (86.2)

[a] Yield based on initial quantity of **5** charged were determined by HPLC analysis. The value in parentheses indicates the isolated yield of **7**.

selected triethylamine ($K_b = 5.5 \times 10^{-4}$), and satisfactory results were realized (entries 2, 3). Several other tertiary amines also gave good results (entries 4, 5). On the other hand, we selected the reaction conditions of entry 2 as the most suitable for large-scale synthesis after consideration of the yield and the amount of by-products involved. The hydrochloride salt of **8** was crystallized and isolated (in 2-propanol as solvent) in high quality (99.0% purity) and high isolated yield (91.6%).

Synthesis of *N*-(4-Nitrobenzyl)-*N*-(tetrahydropyran-4-yl)methylamine (5). *N*-(4-Nitrobenzyl)-*N*-(tetrahydropyran-4-yl)methylamine (**5**) was synthesized in 82.3% yield by the reaction of **10** and the hydrochloride salt of **8** in the presence of K_2CO_3 (2 equiv) at room temperature (Table 2, entry 1). When an optimized amount of K_2CO_3 was applied, the yield was improved (entries 2, 3). The reaction temperature also played an important role to ensure the high yield of **5** (entry 4). We observed that a large excess of K_2CO_3 led to the further reaction of **5** with **10**, resulting in an inferior yield. The reaction condition of entry 4 was selected as the most suitable condition for large-scale synthesis from the viewpoint of the yield. **5** was isolated in high quality (99.5% purity) and in 88.0% isolated yield.

Synthesis of 4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)-aminomethyl]aniline Dihydrochloride (7). **6** was crystallized by completely evaporating the solvent to prevent decreasing the yield of **6** in the original synthesis because the solubility of **6** is too high in various solvents. However, this procedure is not suitable for large-scale synthesis. To overcome this problem, crystallization of the product as its hydrochloride salt from a solution was developed.

Although the method of crystallization was improved in this way, we still continued our efforts to improve the process. The synthesis of **6** was initially conducted by the reduction of **5** using the methods of the original synthesis. However, Fe/AcOH as the reducing reagent involved tedious work-up procedures including removal of the reagent from the system after the reaction. Thus, we investigated alternative reducing reagents more suitable for large-scale synthesis. The hydrogenation of **5** in the presence of metal catalysts produced 4-aminotoluene and *N*-methyl-*N*-(tetrahydropyran-4-yl)amine instead of **6** (Table 3, entries 1, 2). These by-products were presumably produced by using hydrogen gas as the hydrogen source, resulting in the hydrogenolysis of **6**.[12] On the other hand, the reduction using hydrazine as the reducing reagent in the presence of metal catalysts gave **6** in good yields (entries 3, 4).[13] Further studies indicated that the product was cleanly prepared in excellent yield in the presence of $FeCl_3$ and activated charcoal (entry 5). Despite these results, we continued our efforts, centering on other reducing agents because of the carcinogenicity of hydrazine. When NaSH/H_2O or $SnCl_2$/H_2O were used as reducing reagents, the reaction proceeded almost quantitatively. However, the isolated yield of 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline dihydrochloride (**7**) was only about 60% (entries 6, 7). These decreased isolated yields were caused by difficulties in separating a large amount of reagents generated during extraction. On the other hand, SnC1$_2$/HCl or Sn/HCl proceeded almost quantitatively to give **7** in excellent isolated yield (entries 8, 9).[14] In these cases, the catalysts were easily removed by extraction. **6** was isolated as its hydrogen chloride salt by extraction followed by crystallization in the presence of HCl in excellent quality (99.6% purity) and in high yield (96.0% isolated yield, entry 8).

In conclusion, we demonstrated a new and efficient synthesis of **7**, a key intermediate for the CCR5 antagonist TAK-779. These methods required only commercially available reagents and were applied on multikilogram scale to give **7** in 78% yield suitable for toxicological studies.

Experimental Section

All reagents and solvents were commercially available. Melting points were determined on a Büchi B-540 micromelting apparatus and are uncorrected. IR spectra were recorded with a Horiba FT-210 spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. HPLC analysis was performed with a Hitachi L-7000, and GC analysis, with a Shimadzu GC-17A. Elemental analysis was carried out by Takeda Analytical Research Laboratories, Ltd.

***N*-Methyl-*N*-(tetrahydropyran-4-yl)amine Hydrochloride (9).** A mixture of methylamine hydrochloride (540 g, 8.0 mol), tetrahydro-4*H*-pyran-4-one (**3**; 800 g, 8.0 mol), triethylamine (24 g, 240 mmol), 5% palladium on carbon

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(wet type, 40 g, 19 mmol), and methanol (5.6 L) was stirred at 60 °C for 3 h under a 5 kgf/cm^2 hydrogen atmosphere. The palladium on carbon was filtered off and washed with methanol (800 mL). The filtrate and washings were combined and concentrated to about 190 mL at about 40 °C under reduced pressure. After addition of 2-propanol (5.6 L) to the residue, the mixture was concentrated to about 1.9 L at about 40 °C under reduced pressure. After addition of isopropyl ether (1.7 L) to the residue, the mixture was stirred at 0−10 °C for 1 h. The resulting crystals were collected by filtration, washed with a mixture of 2-propanol (200 mL) and isopropyl ether (600 mL) and dried at about 40 °C under reduced pressure to give 1.11 kg (91.6%) of **9** as colorless crystals; mp 216 °C (dec).

^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.3-1.5$ (m, 3H), 1.7−1.9 (m, 2H), 2.42 (s, 3H), 2.5−2.6 (m, 1H), 3.3−3.5 (m, 2H), 3.8−4.0 (m, 2H) ppm.

***N*-(4-Nitrobenzyl)-*N*-(tetrahydropyran-4-yl)methylamine (5).** **9** (1.15 kg, 7.58 mol), potassium carbonate (1.05 kg, 7.60 mol), 4-nitrobenzylbromide (**10**; 1.64 kg, 7.6 mol), and *N*,*N*-dimethylformamide (4.5 L) were mixed at 0−10 °C, and the resulting mixture was stirred at room temperature for 3 h. After addition of ethyl acetate (27 L) to the reaction, the resulting mixture was washed successively with 5% brine (9 L) and water (9 L). After addition of 1 N hydrochloric acid (18 L) to the organic layer, the layers were separated. The resulting aqueous layer was washed with ethyl acetate (18 L). After addition of ethyl acetate (18 L) and saturated aqueous sodium hydrogen carbonate (27 L) to the aqueous layer, the layers were separated. The resulting organic layer was washed three times with water (9 L portions) and concentrated under reduced pressure to give 1.674 kg (87.8%) of **5** as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.5-1.8$ (m, 4H), 2.21 (s, 3H), 2.5−2.7 (m, 1H), 3.38 (dt, $J = 11.5$, 2.5 Hz, 2H), 3.68 (s, 2H), 4.0−4.1 (m, 2H), 7.51 (d, $J = 8.8$ Hz, 2H), 8.18 (d, $J = 8.8$ Hz, 2H) ppm.

IR (neat): $\nu = 2928$, 2846, 1517, 1446, 1380, 1344, 1141, 856 cm^{-1}.

4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline Dihydrochloride (7). *Synthesis of **7** with Pd/C from **5** (Refer to Table 3).* A solution of **5** (10 g, 40 mmol) in tetrahydrofuran (50 mL) was added dropwise to a mixture of 5% palladium on carbon (wet type, 1 g), hydrazine monohydrate (9.7 mL, 200 mmol), and methanol (50 mL) at 0−10 °C under nitrogen. The mixture was stirred for 1 h at 30 °C. The insoluble matter was filtered off, and then the filtrate was concentrated under reduced pressure. Tetrahydrofuran (50 mL) and concentrated hydrochloric acid (8.1 mL) were added to the residue, and the mixture was stirred for 1 h at room temperature. The resulting crystals were collected by filtration, washed with 2-propanol, and dried under reduced pressure to give 8.9 g (76%) of **7** as yellow crystals.

*Synthesis of **7** with Raney-Nickel from **5** (Refer to Table 3).* Hydrazine monohydrate (0.97 mL, 20.0 mol) was added dropwise to a suspension of Raney-nickel (0.2 g) in methanol (5 mL) at 0−10 °C. A solution of **5** (1.0 g, 4.0 mmol) in tetrahydrofuran (5 mL) was added dropwise to the suspension at the same temperature. The resulting mixture was stirred at 25 °C. After reaction, the insoluble matter was filtered off and washed with tetrahydrofuran. The filtrate and washings were combined and concentrated under reduced pressure. Ethyl acetate (20 mL) and tetrahydrofuran (10 mL) were added to the residue, and then the resulting solution was washed with brine. Concentrated hydrochloric acid (0.81 mL) was added to the organic layer. The resulting crystals were collected by filtration, washed with 2-propanol, and dried under reduced pressure to give 0.95 g (81.1%) of **7** as yellow crystals.

*Synthesis of **7** with $FeCl_3/NH_2NH_2{\cdot}H_2O$ from **5** (Refer to Table 3).* **5** (185.2 g, 740 mmol), iron (III) chloride (1.8 g, 11.1 mmol), activated charcoal (18.5 g), and tetrahydrofuran (1.8 L) were mixed, and then hydrazine monohydrate (126 mL, 2600 mol) was added dropwise to the mixture to keep the temperature at 60−65 °C. The mixture was stirred at the same temperature for 4 h. After cooling, the insoluble matter was filtered off and washed with tetrahydrofuran (1.8 L). The filtrate and washings were combined and concentrated under reduced pressure. After addition of ethyl acetate (3.6 L) to the residue, the resulting solution was washed twice with brine (1.8 L portions). The organic layer was concentrated under reduced pressure. 2-Propanol (2.7 L) was added to the residue to make a solution. Concentrated hydrochloric acid (150 mL) was added dropwise to the solution, and then the resulting mixture was stirred at 0−5 °C. The resulting crystals were collected by filtration, washed with 2-propanol (1.8 L), and dried at about 40 °C under reduced pressure to give 204 g (94%) of **7** as yellow crystals.

*Synthesis of **7** with $SnCl_2/HCl$ from **5** (Refer to Table 3).* A solution of tin (II) chloride dihydrate (1.235 kg, 5.47 mol) in concentrated hydrochloric acid (1.08 L) was added dropwise to a solution of **5** (425 g, 1.70 mol) in tetrahydrofuran (500 mL) at 20−40 °C. The resulting mixture was stirred for 1 h at the same temperature. Tetrahydrofuran (1.5 L) and water (1.2 L) were added to the reaction mixture. The mixture was made basic with 30% aqueous sodium hydroxide solution. The layers were separated, and the resulting aqueous layer was extracted with tetrahydrofuran (1.5 L). The organic layers were combined and concentrated to about 900 mL under reduced pressure. After addition of 2-propanol (1.5 L) to the residue, the resulting solution was concentrated to about 900 mL under reduced pressure. After addition of 2-propanol (3.9 L), concentrated hydrochloric acid (350 mL) was added dropwise to the solution at 20−40 °C. The resulting mixture was stirred for 1 h at 0−10 °C. The crystals were collected by filtration, washed with 2-propanol (1.5 L), and dried at about 40 °C under reduced pressure to give 478 g (96.0%) of **7** as yellow crystals.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.5-1.9$ (m, 4H), 2.45 (s, 3H), 3.22 (t, $J = 11.6$ Hz, 2H), 3.3−3.4 (m, 1H), 3.84 (d, $J = 11.6$ Hz, 2H), 3.95 (d, $J = 13.0$ Hz, 1H), 4.31 (d, $J = 13.0$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H) ppm.

IR (KBr): $\nu = 2856$, 1519, 1463, 1012 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}N_2OCl_2$ (293.2): C 53.25, H 7.56, N 9.53, Cl 24.18; found C 53.21, H 7.54, N 9.53, Cl 24.16.

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