Synthesis, Crystal Structure and Insecticidal Activities of (4a*R*,7a*S*)-6-Benzyl-1-((*R*)-2-(2-chlorophenyl)-4,5-dihydrothiazole-4-carbonyl)hexahydro-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione①

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ABSTRACT The title compound (4a*R*,7a*S*)-6-benzyl-1-((*R*)-2-(2-chlorophenyl)-4,5-dihydrothiazole-4-carbonyl)-hexahydro-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione ($C_{24}H_{22}ClN_3O_3S$) was synthesized, and its chemical structure was confirmed by ^{1}H NMR, ^{13}C NMR and single-crystal X-ray diffraction. The crystal of the title compound belongs to monoclinic system, space group *C*2/*c* with *a* = 28.929(6), *b* = 7.858(16), *c* = 22.936(5) Å, β = 125.20(3)°, *V* = 4221.4(15) Å^3, *Z* = 8, D_c = 1.473 g/cm^3, μ(Mo*Ka*) = 0.314 mm^{-1}, the final *R* = 0.0629 and *wR* = 0.1708 for 2812 observed reflections with $I > 2\sigma(I)$. The preliminary insecticidal activity indicated that the title compound exhibited good and promising insecticidal activities against *Mythimna separata*, *Plutella xylostella* and *Culex pipiens pallens*. Moreover, the calcium imaging experiment indicated that the title compound can activate intracellular calcium channels to release the stored calcium ion from endoplasmic reticulum (ER) to cytoplasm of *Mythimna separata*.

Keywords: synthesis, crystal structure, insecticidal activity, calcium imaging;
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1 INTRODUCTION

In the past decades, natural products (NPs) play an important role in the agrochemical design and development process owing to their various bioactivities, potential target sites, unique structures, and environment-friendly characteristics[1-4]. Although diverse natural products are obtained by extraction and separation, their bioactivities are generally too low to develop as agrochemicals. It is one of the most effective and promising ways to discover natural privileged active structures and improve their bioactivities by structural optimization on the basis of pharmacological skeletons from natural products[5-7].

(*R*)-2-(2-Hydroxyphenyl)-4,5-dihydrothiazole-4-carboxylic acid is a class of natural privileged active structure, and can bind to a variety of receptors, which makes them attractive scaffolds for drug discovery. Pyochelin and (−)-(*R*)-dihydroaeruginoic acid are two representative derivatives of 2-aryl-4,5-dihydrothiazole-4-carboxylic acid, which exhibit unique microbial siderophore and antiproliferative activity, respectively[8, 9]. In the past years, studies have found that 2-aryl-4,5-dihydrothiazole-4-carboxylic acid derivatives have a variety of medicinal properties such as anticancer[10], antiproliferative[11], anti-HIV[12], antibiotic[13], and metallo-β-lactamase inhibiting activity[14]. Recently, our research group found that 2-aryl-4,5-dihydrothiazole-4-carboxylic acid derivatives containing amide or ester group displayed potential antifungal and insecticidal activities in the field of agriculture[15-18]. Additionally, introducing heterocycle structures into bioactive molecules for the development of agrochemicals has attracted much attention[19-23].

Inspired by the above descriptions, to discover potent agrochemical candidates, herein the title compound (4a*R*,7a*S*)-6-benzyl-1-((*R*)-2-(2-chlorophenyl)-4,5-dihydro-thiazole-4-

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carbonyl)hexahydro-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione was designed and synthesized, and its chemical structure was confirmed by ^{1}H NMR, ^{13}C NMR and X-ray diffraction. The insecticidal activity of the title compound was evaluated accordingly. Furthermore, the preliminary insecticidal mechanism of the title compound was investigated by calcium imaging technique.

2 EXPERIMENTAL

2. 1 Instruments and reagents

Melting points were confirmed on an X-4 binocular microscope melting point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on 400 MHz using a Bruker AV 400 spectrometer using $CDCl_3$ as solvent with tetramethylsilane (TMS) as the internal standard. Elemental Analysis (EA) was detected by using a Vario EL elemental analyzer. The crystal structure was recorded by a Rigaku Saturn 724 CCD diffractometer. Column chromatography purification was carried out using silica gel (200～300 mesh). 6-Benzyl-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (**1**) and (*R*)-2-(2-chlorophenyl)-4,5-dihydrothiazole-4-carboxylic acid (**4**) were synthesized according to our previous work[8]. Reagents were all analytically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use.

2. 2 Synthetic procedure

2. 2. 1 Synthesis of (4a*R*,7a*S*)-6-benzylhexahydro-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (**3**)[8]

1 (2.384 g, 10.0 mmol) and Pd/C (0.184 g, 5.0 *wt*%) were added in a 50 mL reaction kettle, followed by the addition of 20 mL anhydrous methanol. Then the reaction was heated to 90 ℃ under 4.0 MPa hydrogen atmosphere, which was detected by TLC. After completion, the resulting mixture was filtered and the filtrate was collected and evaporated to obtain 6-benzyltetrahydro-1*H*-pyrrolo[3,4-*b*]-pyridine-5,7(6*H*)-dione (**2**). Then **2** (1.221 g, 5.0 mmol) was added in 10 mL ethanol (90%), and D(−)-tartaric acid (0.755 g, 5 mmol) was added to the above solution in batches. The reaction was stirred at 50 ℃ for 30 min, then cooled to 20 ℃ slowly, and a large amount of white solid appeared. This solid was filtered, washed with anhydrous ethanol, and dried. The obtained solid was dissolved in 10 mL water, basified to pH 11 with 1 mol/L sodium hydroxide, and extracted with ethyl acetate. The organic layer was collected and evaporated to afford (4a*R*,7a*S*)-6-benzyltetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (**3**): white solid, yield 43.9%, m.p. 74～75 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38～7.34 (m, 2H, Ph-H), 7.33～7.29 (m, 2H, Ph-H), 7.28～7.25 (m, 1H, Ph-H), 4.65 (s, 2H, Ph$\underline{CH_2}$), 3.84 (d, J = 7.1 Hz, 1H, NH$\underline{CH}$CO), 2.86 (q, J = 7.1 Hz, 1H, $CH_2\underline{CH}$CO), 2.79 (dt, J = 10.7, 5.3 Hz, 1H, 1/2NH$\underline{CH_2}CH_2$), 2.67 (dt, J = 11.7, 5.9 Hz, 1H, 1/2NH$\underline{CH_2}CH_2$), 1.97 (m, 2H, NH and 1/2$\underline{CH_2}$CHCO), 1.66 (dt, J = 13.7, 6.9 Hz, 1H, 1/2$\underline{CH_2}$CHCO), 1.56～1.39 (m, 2H, $CH_2\underline{CH_2}CH_2$).

2. 2. 2 Synthesis of (4a*R*,7a*S*)-6-benzyl-1-((*R*)-2-(2-chlorophenyl)-4,5-dihydrothiazole-4-carbonyl)hexahydro-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (**5**)

(*R*)-2-(2-Chlorophenyl)-4,5-dihydrothiazole-4-carboxylic acid (0.241 g, 1.0 mmol) was dissolved in 5 mL anhydrous dichloromethane, followed by successively adding 1-hydroxy-1*H*-benzotriazole (HOBt, 0.143 g, 1.0 mmol) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimidehydrochloride (EDCI, 0.230 g, 1.05 mmol). The mixture was stirred for 30 min, and 1.1 mmol *N*,*N*-diisopropylethylenediamine was added to the above mixture. After 10 min, (4a*R*,7a*S*)-6-benzylhexahydro-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (0.244 g, 1.0 mmol) dissolved in 5 mL dichloromethane was added to the reaction mixture. Then the reaction was stirred at room temperature and detected by TLC. After completion, 10 mL dichloromethane was added to the mixture which was then washed with water, 1 mol/L hydrochloric acid, and saturated sodium bicarbonate solution successively. The organic layer was collected and purified by chromatography on silica gel to afford the title compound: white solid, yield 75.5%, m.p. 110～111 °C, ^{1}H NMR (400 MHz, $DCCl_3$), δ: 7.65 (dd, J = 7.6, 1.6 Hz, 1H, Ph-H), 7.43 (d, J = 7.9, 1.0 Hz, 1H, Ph-H), 7.41～7.36 (m, 2H, Ph-H), 7.36～7.27 (m, 5H, Ph-H), 5.82 (d, J = 8.5 Hz, 1H, $CH_2N\underline{CH}$), 5.50 (t, J = 9.1 Hz, 1H, $SCH_2\underline{CH}$), 4.69 (s, 2H, Ph$\underline{CH_2}$), 4.64～4.55 (m, 1H, NCH$\underline{CH}$), 4.24 (dd, J = 11.1, 9.1 Hz, 1H, 1/2S$\underline{CH_2}$), 3.52 (dd, J = 11.1, 9.2 Hz, 1H, 1/2S$\underline{CH_2}$), 3.16～3.01 (m, 2H, $\underline{CH_2}$NCH), 2.11 (ddd, J = 10.8, 8.7, 5.4 Hz, 1H, 1/2CHCH$\underline{CH_2}$), 1.70 (ddd, J = 16.0, 11.0, 7.3 Hz, 1H, 1/2CHCH$\underline{CH_2}$), 1.58～1.45 (m, 2H, $CH_2\underline{CH_2}CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.95, 174.63, 169.21, 167.83, 135.49, 132.65, 132.06, 131.40, 131.14, 130.78, 128.85, 128.78, 128.15, 126.74, 77.48, 51.66, 42.92, 42.57, 38.98, 34.64, 24.24, 21.02. EA calculated for $C_{24}H_{22}ClN_3O_3S$: C, 61.60; H, 4.74; N, 8.98. Found: C, 61.65; H, 4.75; N, 8.90.

2. 3 Crystal structure determination

The single crystal of the title compound suitable for X-ray diffraction study was cultivated from dichloromethane and *n*-hexane (volume ratio 3:10) by self-volatilization, and the white block crystal with dimensions of 0.20mm × 0.18mm × 0.12mm was mounted on a Rigaku Saturn 724 CCD diffractometer Mo*Kα* radiation (λ = 0.71073 Å), and the absolute chiral configuration of the title compound was confirmed C9 (*R*), C14 (*R*) and C15 (*S*). Intensity data were collected at 113(2) K by using a multi-scan mode in the range of $1.72 \leqslant \theta \leqslant 25.02°$ (index ranges: $-34 \leqslant h \leqslant 22$, $-9 \leqslant k \leqslant 9$, $-24 \leqslant l \leqslant 27$). A total of 12974 reflections were collected with 3720 unique ones (R_{int} = 0.0650), of which 2812 were observed with $I > 2\sigma(I)$. The crystal structure was solved by direct methods with SHELXS-97 program[24] and refined by full-matrix least-squares on F^2 with SHELXL-97[25]. All non-hydrogen atoms were located with successive difference Fourier syntheses and refined by using anisotropic thermal parameters. All hydrogen atoms were located in the calculated positions and refined according to theoretical models. The final full-matrix least-squares refinement converged at R = 0.0629 and wR = 0.1708 ($w = 1/[\sigma^2(F_o^2) + (0.0883P)^2 + 0.7616P]$, where $P = (F_o^2 + 2F_c^2)/3$) with $(\Delta/\sigma)_{max}$ = 0.000 and S = 1.056.

2. 4 Insecticidal screening

Insecticidal assays of the title compound against *Mythimna separata*, *Plutella xylostella*, and *Culex pipiens pallens* were conducted in the greenhouse according to the reported method[26-28] with chlorantraniliprole used as the positive control. The bioassay was replicated at 25 ± 1 ℃ according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected by applying Abbott's formula[29]. Evaluation was based on a percentage scale of 0～100, in which 0 equals no activity and 100 equals total kill. The standard deviations of the tested biological values were ±5%.

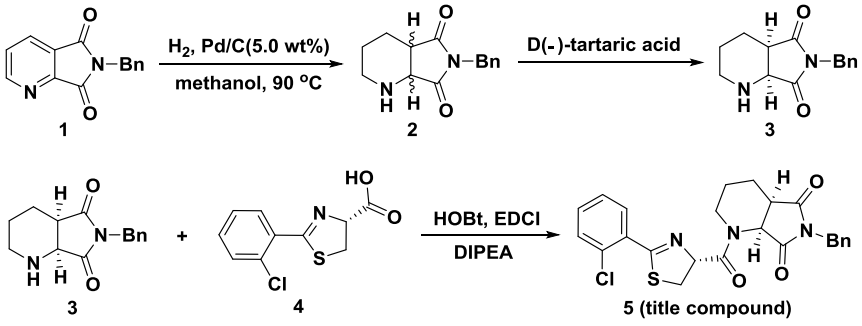
2. 5 Calcium imaging experiment

The preliminary insecticidal mechanism of the title compound was explored by calcium imaging technique according to our previous method[30].

3 RESULTS AND DISCUSSION

3. 1 Synthesis and spectra analysis

The synthetic route of the title compound is shown in Scheme 1. Intermediates 6-benzyl-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione **1** and (*R*)-2-(2-chlorophenyl)-4,5-dihydrothiazole-4-carboxylic acid **4** were prepared by referring to our previous work[8]. Compound **1** was reduced by hydrogen to prepare compound **2** optical isomers, and then the optical isomers were separated by using D(−)-tartaric acid. During separation, temperature had a great impact on the resolution of optical isomers. Thus we applied the programmed temperature control method to optimize the resolution conditions. Finally, the title compound was synthesized by a convenient one-step condensation reaction with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxy-1*H*-benzotriazole (HOBT) as condensation agents. The structure of the pure title compound was confirmed by ^{1}H NMR, ^{13}C NMR and elemental analysis (EA). As shown in Fig. 1S (in Supporting information), the doublet signal at 5.82 ppm is the proton on carbon atom C(**g**), and the triplet signal at 5.50 ppm belongs to the proton on carbon atom C(**b**). Due to the effect of the chiral carbon atom C(**b**), the two protons on carbon atom C(**a**) appear at around 4.24 and 3.52 ppm with double of doublet signals. Similarly, the two protons on carbon atom C(**e**) are found at around 2.11 and 1.70 ppm with triple doublet signals. The signals at around 4.69, 4.60, 3.08 and 1.51 ppm belong to the protons on carbon atoms C(**h**), C(**f**), C(**c**) and C(**d**), respectively.



Scheme 1. Synthetic route of the title compound

3. 2 Crystal structure

The molecular structure of the title compound is shown in Fig. 1 and the crystal packing in Fig. 2. The selected bond lengths, bond angles and torsion angles are listed in Table 1.

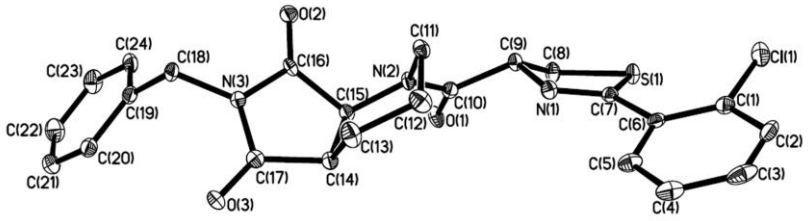


Fig. 1. Molecular structure of the title compound

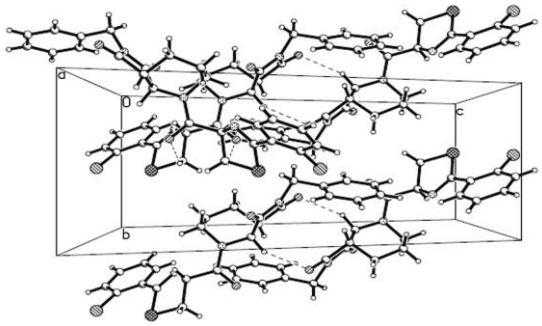


Fig. 2. Crystal packing of the title compound

Generally, the average bond lengths and bond angles of phenyl ring system are in normal ranges[31]. The bond lengths of N(2)–C(10) (1.354(5) Å), N(3)–C(16) (1.388(4) Å) and N(3)–C(17) (1.382(5) Å) are much shorter than the normal bond length of N–C (1.47 Å), but close to the normal bond length of N=C (1.33 Å), which is owing to the *p*-π conjugate effect[32]. The bond angles of C(10)–N(2)–C(11), C(10)–N(2)–C(15) and C(15)–N(2)–C(11) are 125.8(3)°, 119.0(3)° and 114.3(3)°, respectively, with their sum to be 359.1° (approximately 360°), implying that N(2) atom is the sp^2 hybridization state. The sum of C(17)–N(3)–C(16) (112.4(3)°), C(17)–N(3)–C(18) (122.8(3)°) and C(15)–N(3)–C(18) (124.2(3)°) bond angles is 359.4° (approximately 360°), indicating that N(3) atom is also the sp^2 hybridization state. The torsion angle of S(1)–C(8)–C(9)–N(1) is –29.5(3)°, which means that the dihydrothiazole ring is nonplanar, and the torsion angles of C(12)–C(13)–C(14)–C(15), C(15)–N(2)–C(11)–C(12), C(11)–C(12)–C(13)–C(14) and N(2)–C(11)–C(12)–C(13) are –60.6(4), –42.3(5)°, 60.1(4)°, and 52.9(5)°, respectively, suggesting that the piperidine ring is also not in the same plane and exhibits a chair conformation. The pyrrole ring is also nonplanar as the torsion angle of C(14)–C(15)–C(16)–N(3) is –23.9(4)°. The torsion angles of C(18)–N(3)–C(16)–O(2) and C(18)–N(3)–C(17)–O(3) are –0.7(5)° and 13.6(5)°, respectively, which implied that the two carbonyl groups are opposite. The intermolecular interactions are shown in Fig. 2, and two non-classical intermolecular hydrogen bonds (C(8)–H(8B)···O(1) and C(15)–H(15)···O(3)) exist in the structure. The intermolecular interactions strengthen the integration of the 3D network, and play an important role in stabilizing the crystal structure.

Table 1. Selected Bond Lengths (Å), Bond Angles (°), and Torsion Angles (°) for the Title Compound

Bond	Dist.	Bond	Dist.	Bond	Dist.
N(2)–C(10)	1.354(5)	N(3)–C(16)	1.388(4)	N(3)–C(17)	1.382(5)
N(1)–C(7)	1.282(4)	C(9)–C(10)	1.530(5)	S(1)–C(8)	1.809(4)
Angle	(°)	Angle	(°)	Angle	(°)
C(10)–N(2)–C(11)	125.8(3)°	C(10)–N(2)–C(15)	119.0(3)°	C(15)–N(2)–C(11)	114.3(3)°
C(17)–N(3)–C(16)	112.4(3)°	C(17)–N(3)–C(18)	122.8(3)°	C(15)–N(3)–C(18)	124.2(3)°
Torsion angle	(°)	Torsion angle	(°)	Torsion angle	(°)
S(1)–C(8)–C(9)–N(1)	–29.5(3)°	C(12)–C(13)–C(14)–C(15)	–60.6(4)	C(15)–N(2)–C(11)–C(12)	–42.3(5)°
N(2)–C(11)–C(12)–C(13)	52.9(5)°	C(18)–N(3)–C(16)–O(2)	–0.7(5)°	C(11)–C(12)–C(13)–C(14)	60.1(4)°
C(14)–C(15)–C(16)–N(3)	–23.9(4)°	C(18)–N(3)–C(17)–O(3)	13.6(5)°		

Table 2. Hydrogen Bond Lengths (Å) and Bond Angles (°)

Compound	D–H···A	d(D–H)	d(H···A)	d(D···A)	∠DHA
5	C(8)–H(8B)···O(1)$^{\#1}$	0.95	2.45	3.232(4)	154
	C(15)–H(15)···O(3)$^{\#2}$	0.98	2.35	3.328(5)	147

Symmetry transformations used to generate the equivalent atoms: $^{\#1}$ –*x*, –*y*, –*z*+1, $^{\#2}$ –*x*, –*y*+1, –*z*+1

3. 3 Insecticidal activity

Insecticidal activities of the title compound against *Mythimna separata*, *Plutella xylostella* and *Culex pipiens pallens* are listed in Table 3. The preliminary bioassay results indicated that the title compound exhibited good and promising insecticidal activities. The title compound displayed 100% larvicidal activity against *Mythimna separata* and *Plutella xylostella* at 100 mg/L, equivalent to that of chlorantraniliprole (100%). Moreover, even at 10 mg/L, the title compound exhibited 73% larvicidal activity against *Plutella xylostella*, which was a little weaker than that of chlorantraniliprole (100%). More impressively, for *Culex pipiens pallens*, the insecticidal activity of the title compound (100%) was the same with chlorantraniliprole (100%) even at 2 mg/L. Furthermore, the title compound exhibited more than 90% insecticidal efficacy, which was comparable to that of chlorantraniliprole (100%).

Table 3. Insecticidal Activity of the Title Compound

Compound	Larvicidal activity (%)										
	Mythimna separata (mg/L)			*Plutella xylostella* (mg/L)				*Culex pipiens pallens* (mg/L)			
	200	100	50	200	100	50	10	10	5	2	1
Title compound (**5**)	100	100	57	100	100	95	73	100	100	100	92
Chlorantraniliprole	100	100	100	100	100	100	100	100	100	100	100

3. 4 Calcium imaging

To explore the preliminary insecticidal mechanism of the title compound, we investigated the influence on calcium signaling in the central neurons isolated from the third instar of *Mythimna separata* by calcium imaging technique. The isolated central neurons were loaded with fluo-3 AM. As shown in Fig. 3, when the isolated central neurons were treated with the title compound (100 mg/L) and chlorantraniliprole (100 mg/L) in the absence of extracellular calcium, respectively, the cytosolic calcium concentrations were increased differently, compared to the initial values. The result was similar to our previous research[22, 30]. Owing to the absence of extracellular calcium in bathing solution, the result implied that the title compound, similar to chlorantraniliprole, can activate intracellular calcium channels to release the stockpiled [Ca^{2+}]i from endoplasmic reticulum (ER) to cytoplasm of *Mythimna separata*. Therefore, the insecticidal mechanism of the title compound was related to calcium homeostasis modulation in insects.

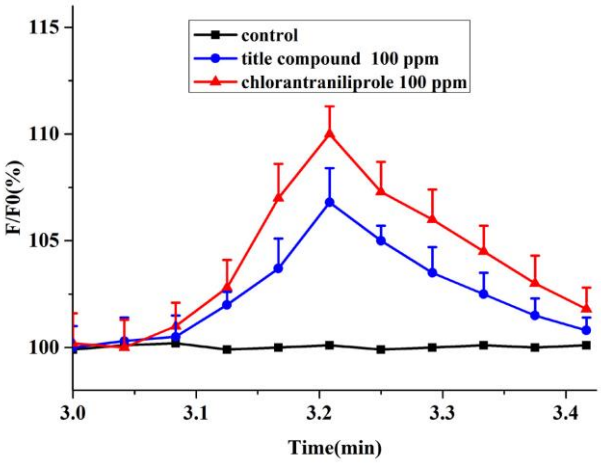


Fig. 3. Change of [Ca^{2+}]i versus recording time when the neurons of *Mythimna separata* third-instar larvae were treated with the title compound (100 ppm) and chlorantraniliprole (100 ppm). The central neurons were dyed by loading with fluo-3 AM

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