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Research Article

Synthesis of Phenylpiperazine Derivatives of 1,4-Benzodioxan as Selective Tyrosyl-Trna Synthetase Inhibitors

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Keywords

- Phenylpiperazine
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- Tyrosyl-TRNA synthetase
- Antibacterial activities
- Molecular docking

Abstract

Five phenylpiperazine derivatives of 1,4-benzodioxan have been designed, and evaluated for antimicrobial activities. Docking simulations have been performed to position compounds into the Tyrosyl-tRNA synthetase active site to determine their probable binding models. All of the compounds exhibited better antibacterial activities against Gram-positive strains. Interestingly, compound 3c exhibited better antibacterial activities with IC50 values of 0.03 μg/mL against *Staphylococcus aureus*.

INTRODUCTION

Aminoacyl-tRNA synthetases (aaRSs) are a kind of key enzymes which catalyze the transfer of amino acids to their cognate tRNAs during protein synthesis [1-3]. AaRSs have been proved to be antimicrobial targets [4], and they have been interesting targets in antibacterial drug design [5-7]. As a member of aaRS family, Tyrosyl-tRNA synthetase (TyrRS) are found in all living organisms and plays an important role in protein synthesis [8-12]. TyrRS belong to the class I tRNA synthetase family, which has two highly conserved sequence motifs at the active site, HIGH and KMSKS [13,14]. There are several distinctive differences between bacterial and human TyrRS. These properties suggest that small-molecule inhibitors of TyrRS could be promising drug candidates leading to high selectivity and broad-spectrum antibacterial agents [15,16]. Phenylpiperazine derivatives have showed broad varieties of biological activities especially antimicrobial activity. As a continuous work of our previous work [17], we have researched a series of phenylpiperazine derivatives as potential TyrRS inhibitors. Besides, it is reported that 1,4-benzodioxan afforded a new scaffold for small molecular antibacterial activity [18,19]. Thus our main objective is to design novel phenylpiperazine derivatives of 1,4-benzodioxan as specific inhibitors of TyrRS in the hope that these molecules may be further explored as powerful and novel antibacterial lead-candidates. Our strategy is intended to obtain potent antibacterial activity with selective inhibition of TyrRS using traditional medicinal chemistry techniques motivated by the comparative modeling of TyrRS complexed with **A** in the available pharmacophore (Figure 1). Therefore, we combined two scaffolds and made the molecular docking (Figure 2). In the binding model, compounds **3a-3e** were bound to the TyrRS with hydrogen interaction bonds, π-cation bonds and π-π bonds. Therefore, these preliminary analysis served as a stimulant to synthesize these phenylpiperazine derivatives containing 1,4-benzodioxan skeleton **3a-3e**. (Scheme 1).

RESULTS

Antibacterial activities

The IC_{50} of compounds **3a-3e** against these bacterial strains are tested by MTT method. Based on the data obtained (Table 1), we found that Compounds **3a-3e** possess high selectivity to exhibit better antibacterial activity against Gram-positive bacteria; compound **3c** exhibited better antibacterial activities with IC_{50} values of 0.03 μg/mL against *Staphylococcus aureus*. Compound **3d** displays antibacterial activity with IC_{50} values of 0.07μg /mL against *Bacillus subtilis*. Based on the data, we can concluded that the substituent at different positions led to different activity, and *para*-substituted compounds have the best activities.

Crystal structures of compounds 3a-3e

Crystals of five compounds were obtained from methanol solution. Figure (3) shows a perspective view of the monomeric unit with the atomic numbering scheme, Figure (4) depicts the intra-molecular and inter-molecular hydrogen bonds. Crystallographic data, details of data collection and structure refinement parameters are listed in Table (2). Single crystals of **3a** (0.21 mm×0.21 mm×0.18 mm), **3b** (0.21 mm×0.21 mm×0.18

mm), **3c** (0.21 mm×0.21 mm×0.19 mm), **3d** (0.21 mm×0.21 mm×0.18 mm), **3e** (0.21 mm×0.21 mm×0.19 mm), were mounted on a D-8 venture diffractometer equipped with graphite-monochromated MoKα (k = 0.71073 Å) radiation.

For **3a**, a total of 16,546 reflections were collected, of which 3229 were unique with R_{int} = 0.054 and 1947 observed reflections with $I > 2\sigma(I)$ were used in the succeeding structure calculations. The final cycle of refinement of full matrix least-squares was converged to R = 0.0593 and wR = 0.1649. The highest and lowest residual peaks in the final difference Fourier map are 0.40 and -0.32 e/Å^3, respectively. For **3b**, a total of 15,962 reflections were collected, of which 3076 were unique with R_{int} = 0.060 and 1669 observed reflections with $I > 2\sigma(I)$ were used in the succeeding structure calculations. The final cycle of refinement of full matrix least-squares was converged to R = 0.0537 and wR = 0.1416. The highest and lowest residual peaks in the final difference Fourier map are 0.24 and -0.17 e/Å^3, respectively. For **3c**, a total of 30,921 reflections were collected, of which 6622 were unique with R_{int} = 0.045 and 4026 observed reflections with $I > 2\sigma(I)$ were used in the succeeding structure calculations. The final cycle of refinement of full matrix least-squares was converged to R = 0.0557 and wR = 0.1497. The highest and lowest residual peaks in the final difference Fourier map are 0.29 and -0.25 e/Å^3, respectively. For **3d**, a total of 16,425 reflections were collected, of which 3163 were unique with R_{int} = 0.029 and 2693 observed reflections with $I > 2\sigma(I)$ were used in the succeeding structure calculations. The final cycle of refinement of full matrix least-squares was converged to R = 0.0417 and wR = 0.1089. The highest and lowest residual peaks in the final difference Fourier map are 0.22 and -0.27 e/Å^3, respectively. For **3e**, a total of 17,610 reflections were collected, of which 3469 were unique with R_{int} = 0.027 and 2781 observed reflections with $I > 2\sigma(I)$ were used in the succeeding structure calculations. The final cycle of refinement of full matrix least-squares was converged to R = 0.0411 and wR = 0.1146. The highest and lowest residual peaks in the final difference Fourier map are 0.35 and -0.20 e/Å^3, respectively.

Molecular docking study

Automated docking studies were carried out using Discovery Studio (version 3.5) as implemented through the graphical user interface DS-CDocker protocol.

The results have been plotted as a line-scatter graph and presented in Figure 5. We could see that compound **3d** and **3e** have the lower interaction energy than the others, which is consistent with the antibacterial activities.

Table 1: Inhibitory activity (IC_{50}) of the synthetic compounds against bacteria.

Compound	IC_{50} (μg/mL)			
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	1.78	14.22	>50	>50
3b	2.15	11.18	>50	>50
3c	0.03	0.28	>50	>50
3d	0.17	0.07	>50	>50
3e	3.58	5.12	>50	>50

Table 2: Crystallographic data, details of data collection and structure refinement parameters.

Compound	3a	3b	3c	3d	3e
Empirical formula	$C_{19}H_{21}ClN_2O_2$	$C_{19}H_{22}N_2O_2$	$C_{19}H_{21}N_3O_4$	$C_{19}H_{21}FN_2O_2$	$C_{19}H_{20}Cl_2N_2O_2$
Formula weight	344.83	310.39	355.39	328.38	379.27
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	*P*21/c	*P*21/c	*P*21/n	*P*212121	*P*21/n
a (Å)	8.9539(16)	8.9980(7)	10.0927(5)	9.7090(11)	9.6197(6)
b (Å)	17.099(3)	16.4968(12)	9.9642(6)	11.1305(13)	14.5024(9)
c (Å)	11.0759(19)	11.0039(9)	34.6853(18)	15.4361(18)	13.7924(8)
α(º)	90	90	90	90	90
β(º)	94.156(6)	94.406(3)	94.073(2)	90	109.369(2)
γ(º)	90	90	90	90	90
V(Å)	1691.3(5)	1628.6(2)	3479.3(3)	1668.1(3)	1815.26(19)
Z	4	4	8	4	4
D calc/g cm $^{-3}$	1.354	1.266	1.357	1.308	1.388
θRange(º)	2.2, 25.8	2.2, 25.7	2.1, 25.7	2.3, 25.7	2.1, 25.8
F(000)	728	664	1504	696	792
Reflections collected/unique	16,546/3229	15,962/3076	30,921/ 6622	16,425/3163	17,610/ 3469
Data/restraints/parameters	1947/0/ 217	1669/0/ 208	4026/0/ 469	2693/0/ 217	2781/0/ 226
Absorption coefficient (mm^{-1})	0.240	0.083	0.097	0.093	0.373
$R_1/_wR_2[I > 2\sigma(I)]$	0.054 /0.1649	0.060/ 0.1416	0.045/ 0.1497	0.029 /0.1089	0.027/ 0.1146
$R_1/_wR_2$ (all date)	0.0593/0.1649	0.0537/ 0.1416	0.0557/0.1497	0.0417/0.1089	0.0411/ 0.1146
GOOF	1.041	1.014	1.022	1.052	1.049

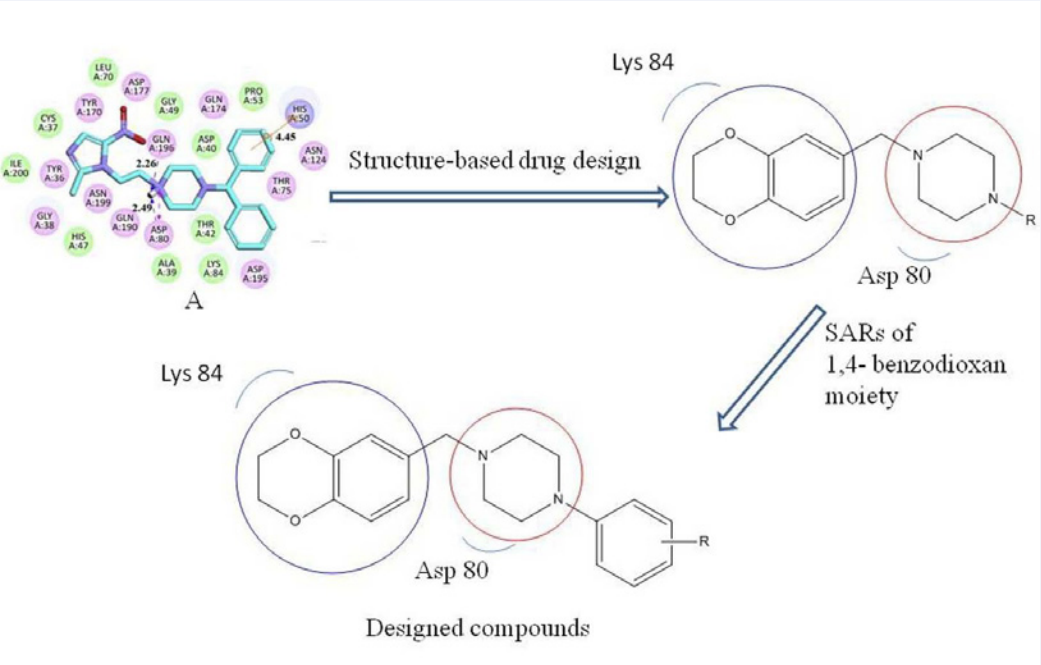


Figure 1 Design strategy of the target compounds.

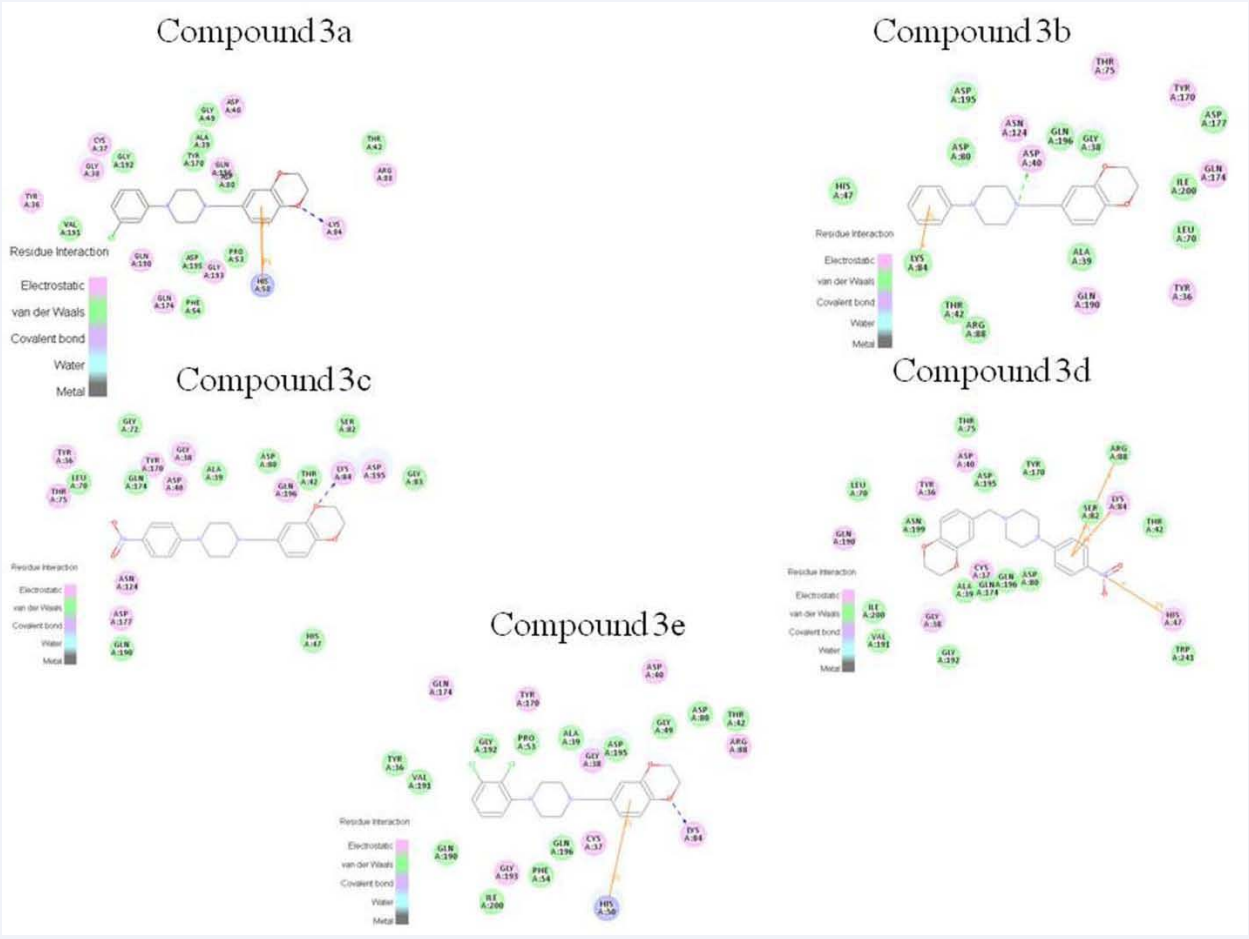


Figure 2 2D molecular docking modeling with 1JIJ.

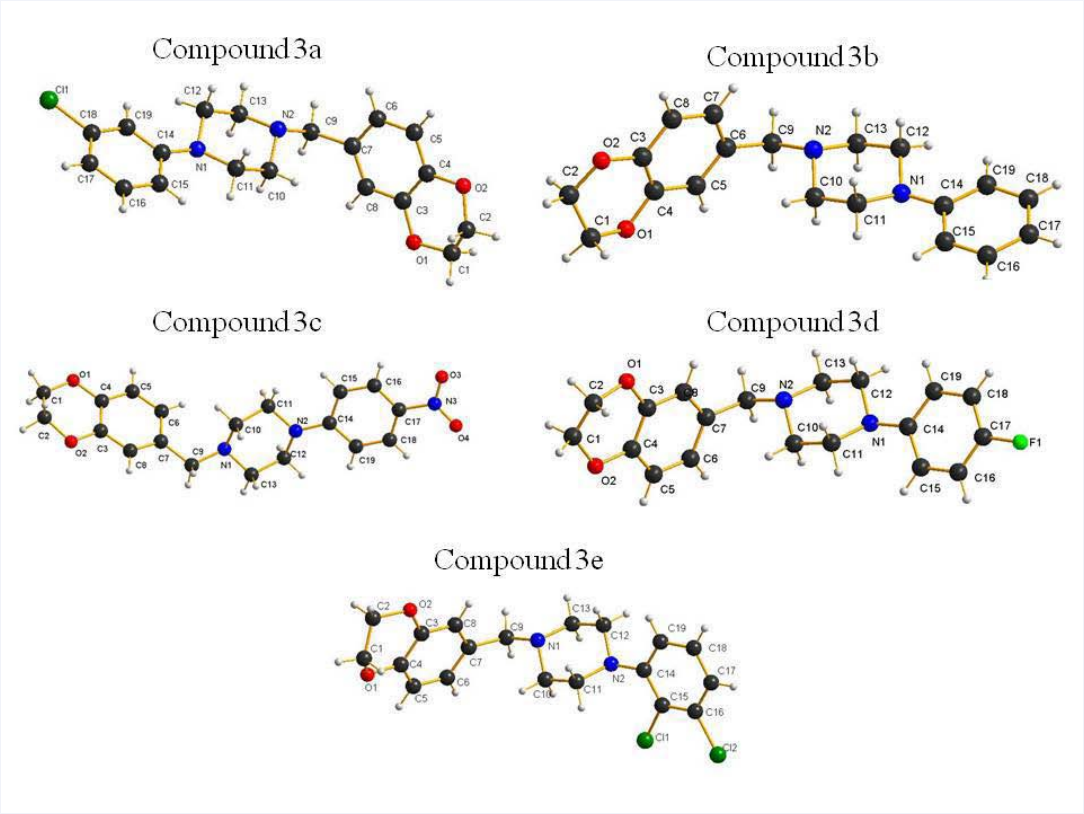


Figure 3 Molecular structures of the title compounds with atomic numbering scheme.

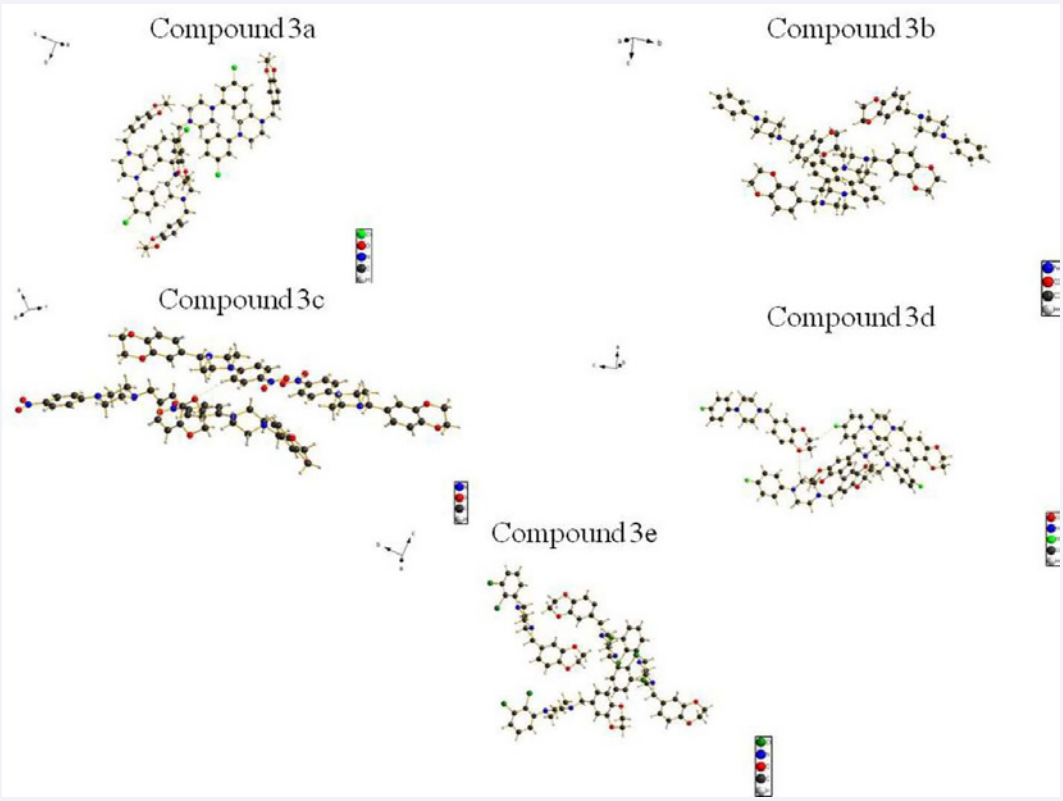


Figure 4 Crystal packing of the title compounds.

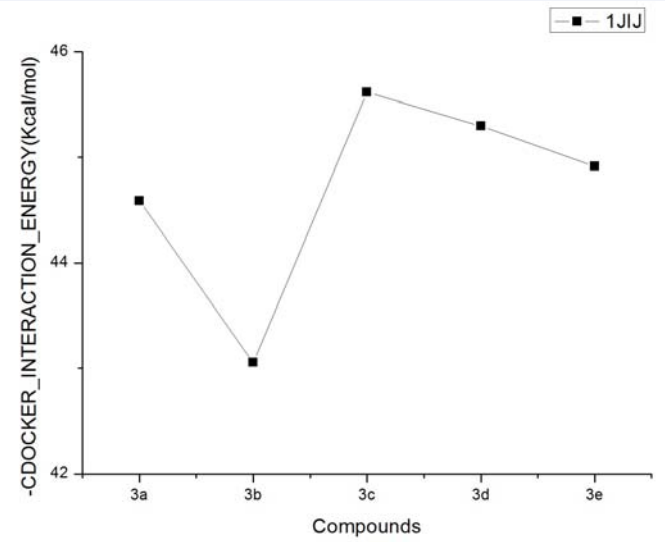
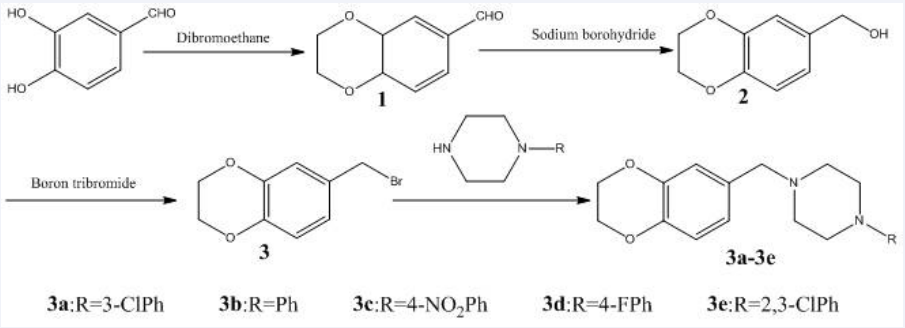


Figure 5 The CDOCKER_INTERACTION_ENERGY (kcal/mol) obtained from the docking study of all synthesized compounds by the CDOCKER protocol (DS 3.5, Accelrys, Co. Ltd).



Scheme 1 General synthesis of compounds 3a–3e.

CONCLUSION

In conclusion, a series of phenylpiperazine derivatives of 1,4-benzodioxan **3a-3e** were synthesized, structure characterization, molecular docked and tested for their inhibitory activities against *E. coli, P. aeruginosa, B. subtilis* and *S. aureus*. According to the data presented in Figure 2, the compounds were nicely bound to the TyrRS with hydrogen interaction bonds, π-π bonds and π-cation interactions. Especially, compound **3a** and **3e** were primely bound to LYS 84 with H-bond interaction, and bound to the HIS 50 with π-π interaction. Compound **3b** were bound to ASP 40 with H-bond interaction, and bound to the LYS 84 with π-cation interactions. Furthermore, the docking studies of compounds reveals that 1,4-benzodioxan as one scaffolds was primely bound to the LYS 84. Thus, the introduction of hydrogen bonds makes the corresponding compounds possess high selectivity antibacterial activities. From the theoretical perspective, we could conclude that the target compounds were appropriately positioned into the TyrRS active site.

However, according to the data presented in Table (1), compounds **3a-3e** possess high selectivity to exhibit better antibacterial activities against two Gram-positive strains. Besides, compound **3c** displays antibacterial activity against *S. aureus* from the close inspection of the data, the activities of the target compounds are consistent with the theoretical results.

SUPPLEMENT FILES

Experimental protocol is in the supplement files.

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