



MOLECULAR INTERACTION AND COMPUTATIONAL EVALUATION OF ANLE138B AS AN INHIBITOR OF α -SYNUCLEIN AGGREGATION IN PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disorder strongly associated with the misfolding and aggregation of α -synuclein, making this protein an important target for disease-modifying therapeutic strategies. This study computationally evaluated Anle138b as a potential α -synuclein-targeting compound using molecular docking, interaction analysis, physicochemical profiling, ADME prediction, and toxicity assessment. Molecular docking identified a best-ranked binding pose with an affinity of -9.456 kcal/mol, supported by multiple non-covalent interactions, including aromatic, electrostatic, and hydrogen-bond-associated contacts. Physicochemical analysis showed a molecular weight of 342.00 g/mol, TPSA of 47.14 Å², logP of 4.44 , and limited molecular flexibility. ADME prediction indicated a high blood–brain barrier probability of 0.987 , supporting potential central nervous system accessibility. However, toxicity prediction revealed comparatively high probabilities for drug-induced liver injury, carcinogenicity, neurotoxicity, and respiratory toxicity. Overall, Anle138b demonstrated favorable predicted binding and CNS-relevant pharmacokinetic characteristics, but its potential safety liabilities require further investigation. Molecular dynamics simulations, free-energy calculations, aggregation assays, neuronal toxicity studies, and in vivo validation are recommended to confirm its therapeutic potential against α -synuclein-associated pathology in Parkinson's disease.

Keywords: Parkinson's disease; α -synuclein; Anle138b; molecular docking; ADMET



1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that involves the loss of function of dopaminergic neurons and the buildup of abnormal proteinaceous aggregates in areas of the brain. Protein misfolding, misregulated proteostasis, mitochondrial dysfunction, neuroinflammation, and defective degradation pathways are all molecular processes that play a role in PD and lead to neuronal vulnerability. Protein aggregation is especially relevant due to the fact that the disruption of protein homeostasis in the cellular systems may lead to accumulation of structurally abnormal proteins and to an increase of the neurodegenerative processes (Rissardo & Caprara, 2025). SNCA encodes alpha-synuclein (α -synuclein) which is a neuronal protein that is closely linked to the molecular pathology of PD. In pathological conditions, α -synuclein undergoes conformational changes that allow α -syn to oligomerize and further assemble into amyloid-like β -sheet rich aggregates (Gul, 2025). The conformational state plays an important role in the amyloid aggregation of α -synuclein, as shown by computational investigation which revealed that structural changes between α -strand and β -sheet conformations are a significant factor in the aggregation of α -synuclein (Balupuri et al., 2019). Proteins are also directly linked to PD-associated neuropathology via the misfolded form of α -synuclein, which is a major component of Lewy pathology.

Pathological α -synuclein has been shown to be clinically relevant. A Lewy-fold specific α -synuclein seed amplification assay was highly sensitive and specific for Lewy-fold α -synucleinopathies and showed that quantitative α -synuclein seeding measures were correlated with clinical severity, suggesting that pathological α -synuclein is a disease-associated molecule and may be a biomarker for α -synucleinopathy (Bernhardt et al., 2025). This connection between α -synuclein abnormalities, cell-cell interactions and PD-related neurodegeneration was further supported by experiments showing that disease-associated microglia can drive endogenous α -synuclein pathology in midbrain organoids (Zuccoli et al., 2025).

Therefore, inhibition of α -synuclein misfolding and aggregation has been identified as a promising disease-modifying approach. The current strategies involve small molecules, peptides, proteins, molecular chaperones and aggregation interfering compounds which can stabilize non-amyloidogenic states or disrupt pathological assemblies (Galkin et al., 2024). Another mechanistic approach involves the use of molecular tweezers which obstruct the folding and self-assembly of α -synuclein (Devi & Paul, 2026). Experimental and computational studies indicating that intermolecular contacts between γ -synuclein and α -synuclein could affect aggregation further support the importance of using intermolecular contacts to manipulate the aggregation behavior (Sanjeev & Mattaparthi, 2019).

Thus, structure-based and computational drug-discovery strategies have become an increasing part of the search for molecules that can modify the disease process, specifically molecules that target α -synuclein. These strategies allow for fast screening of ligand-binding configuration, interaction residues, physicochemical properties and pharmacokinetic liabilities prior to experimental validation. This approach was complementary to general computational and synthetic strategies for the discovery of drugs for neurodegenerative diseases (Bucolo, 2023). In PD, molecular imaging and biomarker studies are ongoing to better elucidate brain pathways involved in disease and to identify biomarkers that warrant development of therapeutics that target the underpinning disease mechanisms rather than just symptoms (Haas, 2024). Identification of compounds that prevent the aggregation of α -synuclein continues to be a strategy for the development of potential compounds that modify the disease (Peña Díaz, 2022).

The present study thus sought to computationally assess the potential of Anle138b as an α -synuclein-targeting drug for Parkinson's disease. The scope consisted of in silico molecular docking, characterization of the protein–ligand interactions, physicochemical characterization, blood–brain barrier assessment, transporter assessment, and in silico prediction of toxicity. The aim was to define the preferred binding conformation and binding affinity, to characterize important molecular interactions, to assess the drug-likeness and central nervous system relevant pharmacokinetic properties and to identify potential unwanted effects to consider for further development of the



compound.

2. Methodology

2.1 Molecular Structure Preparation and Ligand Processing

The computational workflow aimed to assess the molecular interaction, physicochemical properties, pharmacokinetic behavior and predicted toxicity profile of Anle138b. The structure of the ligand was created in three dimensional format for molecular docking. The docking geometry of the ligand was verified for connectivity of its atoms and molecular representation before docking. To create the receptor structure, unwanted non-receptor elements were removed and only the structural part necessary for interaction analysis with the ligand was kept. Receptor and ligand were prepared with addition of polar hydrogen atoms and the necessary atomic charges to make docking ready structures. No experimental biological data set was analysed, no observations on the level of the patients was made, nor clinical outcome variables were used, so accordingly sample-size denominators and subject-level covariates were not relevant.

2.2 Molecular Docking Using AutoDock Vina

The molecular docking was carried out with AutoDock Vina (Trott & Olson, 2010), which uses the empirical scoring function and efficient conformational search procedure to determine the orientation and binding affinity of the ligand in the most favorable binding conformation in the receptor. Finally, the prepared Anle138b ligand was searched using the 3D search space of $20 \times 20 \times 20$ Å, within the selected receptor structure. The position of the grid center was around $x = -23.0$ Å, $y = -11.0$ Å, and $z = 4.0$ Å, and exhaustiveness was fixed to 4. The predicted Vina binding affinity (kcal/mol) was used to rank multiple ligand conformations. The more negative the values were, the more favorable the predicted binding was. The RMSD lower-bound and upper-bound were used to numerically quantify the positional difference between the top-ranked pose and the other poses. These were algorithmic molecular scores and not replicated experimental measurements, so there was no inferential statistical test, confidence interval, hypothesis test, correlation analysis or regression model applied.

2.3 Protein–Ligand Interaction Visualization

Molecular interaction analysis was used in BIOVIA Discovery Studio Visualizer (DSV) to the highest ranked docked complex. Two and three dimensional representations were analyzed to detect residues in the environment of binding and to characterize the main classes of non-covalent interactions between the ligand and the receptor. C-H bonds, π -cation interactions, π -anion interactions, π - π stacked interactions, π - π T-shaped interactions and π -alkyl interactions were the interaction categories analyzed. The following residues were displayed in the final docked interaction environment: GLU46, ALA64, ARG67, GLU154, PRO155, TYR156, PHE157, TRP231, TRP341, and ARG345. For interaction assignments, the maps of ligand interaction were taken at face value. There was no frequency denominator or significance testing since one best rank docking conformation was structurally interpreted.

2.4 Physicochemical and ADME Prediction Using ADMETlab 3.0

The physicochemical, drug-likeness, absorption, distribution, transporter-associated, and related pharmacokinetic properties were predicted by ADMETlab 3.0 (Fu et al., 2024). The molecular weight (MW), hydrogen-bond acceptors (nHA), hydrogen-bond donors (nHD), topological polar surface area (TPSA), rotatable bonds (nRot), rings (nRing), maximum ring size (MaxRing), heteroatoms (nHet), formal charge (fChar), rigid bonds (nRig), logP, logD, logS, quantitative estimate of drug-likeness (QED), and fraction of sp^3 carbon atoms (Fsp3) were included as variables. The blood-brain barrier (BBB) penetration, PAMPA, P-glycoprotein inhibition and substrate status, MRP1, OATP1B1, OATP1B3, BCRP and BSEP were selected as ADME endpoints that were retained for interpretation. The model outputs were considered as prediction probabilities or scores on a 0–1 scale instead of rates that were measured in the experiment.



2.5 Toxicity Assessment and Data Interpretation

Ames mutagenicity, carcinogenicity, drug-induced liver injury (DILI), human hepatotoxicity (H-HT), hERG-associated cardiotoxicity, nephrotoxicity, neurotoxicity, ototoxicity, and respiratory toxicity were assessed as toxicological endpoints. The interpretation of each endpoint was made independently on the probability scale of the model. Higher values denoted greater model support for the toxicity classification and were not interpreted as "observed" incidences. No t-test, ANOVA, chi-square test, non-parametric test, correlation coefficient, logistic regression, linear regression or multivariable regression was performed as one of the ligands was estimated computationally. Docking was performed using AutoDock Vina, structural interaction visualization was carried out using BIOVIA Discovery Studio Visualizer, and physicochemical, ADME, transporter and toxicity predictions were done using ADMETlab 3.0.

3. Results

3.1 Molecular Docking Performance and Binding Interactions

A total of three binding conformations were obtained for Anle138b by AutoDock Vina. The highest affinity (most favorable) predicted pose was the top ranked one at -9.456 kcal/mol, followed by -7.527 and -6.541 kcal/mol. The first was used as the RMSD reference while the second was left relatively near to the RMSD reference and the third was significantly different. The docking results are summarized in Table 1.

Table 1. Molecular docking scores and RMSD values for Anle138b

Pose	Affinity (kcal/mol)	RMSD lower bound (Å)	RMSD upper bound (Å)
1	-9.456	0.000	0.000
2	-7.527	1.591	2.192
3	-6.541	12.626	13.512

The best ranked complex was determined to be a heterogeneous interaction environment including GLU46, ALA64, ARG67, GLU154, PRO155, TYR156, PHE157, TRP231, TRP341 and ARG345. The following interaction map was obtained and is summarized in the table (Table 2), it depicted aromatic, electrostatic, hydrophobic and carbon-hydrogen-associated contacts (Figure 1). As shown in Figure 2, the docking poses exhibited binding affinities ranging from -6.541 to -9.456 kcal/mol. Pose 1 demonstrated the most favorable binding affinity (-9.456 kcal/mol), followed by Pose 2 (-7.527 kcal/mol) and Pose 3 (-6.541 kcal/mol), indicating that Pose 1 represents the most energetically favorable docking configuration among the three evaluated poses.

Table 2. Principal residues and interaction classes in the selected Anle138b complex

Residue(s)	Predominant interaction class	Structural interpretation
GLU46, GLU154	π -anion / electrostatic	Electrostatic stabilization
ARG67, ARG345	π -cation / electrostatic	Cation–aromatic stabilization
TYR156, PHE157, TRP231, TRP341	π - π stacked / π - π T-shaped	Aromatic stabilization
ALA64, PRO155	π -alkyl / hydrophobic	Hydrophobic stabilization
Selected local contacts	Carbon-hydrogen bond	Directional local stabilization

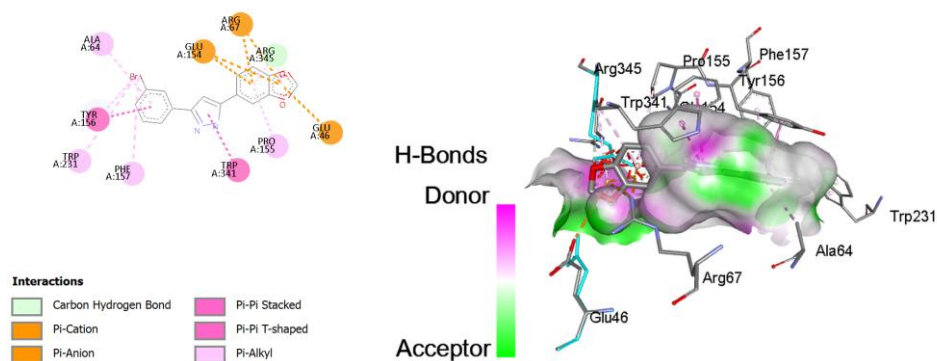


Figure 1. Two-dimensional and three-dimensional representation of the predicted Anle138b binding interactions within the selected α -synuclein-associated receptor environment

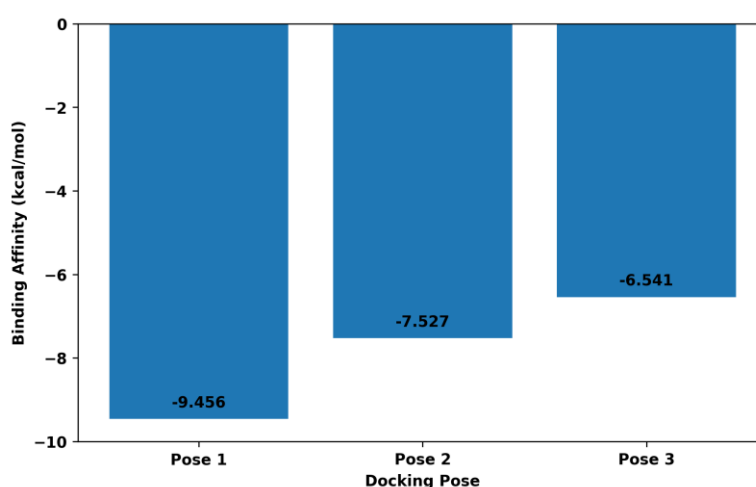


Figure 2. Binding affinity of the three retained Anle138b docking conformations obtained using AutoDock Vina

3.2 Physicochemical and Drug-Likeness Characteristics

Anle138b had a molecular weight of 342.00 g/mol, and TPSA of 47.14 Å², four hydrogen-bond acceptors, one hydrogen-bond donor, two rotatable bonds, and four rings. The predicted logP and logD values were 4.436 and 3.794 respectively and logS was -5.168. The QED value was 0.757 and Fsp3 was 0.062. The physicochemical descriptors selected are presented in Table 3.

Table 3. Selected physicochemical and drug-likeness properties of Anle138b

Property	Predicted value
Molecular weight	342.00 g/mol
H-bond acceptors (nHA)	4
H-bond donors (nHD)	1
TPSA	47.14 Å ²
Rotatable bonds (nRot)	2
Number of rings (nRing)	4
Maximum ring size (MaxRing)	9
Heteroatoms (nHet)	5
Formal charge (fChar)	0
Rigid bonds (nRig)	21
logP	4.436
logD	3.794
logS	-5.168



QED	0.757
Fsp3	0.062

3.3 ADME and Toxicity Profile

The predicted probability of BBB was very high according to the ADME profile as 0.987. High model scores were obtained by OATP1B1, OATP1B3 and BSEP while low model scores were obtained by P-gp substrate and BCRP. Intermediate were PAMPA, P-gp inhibition and MRP1 predictions. These values are shown in Figure 3. The probability of toxicity in the various endpoints through the toxicity screen were relatively high for DILI, carcinogenicity, neurotoxicity and respiratory toxicity and lower for hERG and ototoxicity. The principal ADME and toxicity predictions are integrated into a single table (Table 4), and the toxicity probability profile is shown in Figure 4.

Table 4. Selected ADME and toxicity predictions for Anle138b

Category	Endpoint	Predicted value / probability
ADME	BBB	0.987
ADME	PAMPA	0.345
ADME	P-gp inhibitor	0.630
ADME	P-gp substrate	0.001
ADME	MRP1	0.576
ADME	OATP1B1	0.948
ADME	OATP1B3	0.978
ADME	BCRP	0.243
ADME	BSEP	1.000
Toxicity	Ames	0.563
Toxicity	Carcinogenicity	0.846
Toxicity	DILI	0.963
Toxicity	H-HT	0.530
Toxicity	hERG	0.380
Toxicity	Nephrotoxicity	0.604
Toxicity	Neurotoxicity	0.818
Toxicity	Ototoxicity	0.267
Toxicity	Respiratory toxicity	0.733

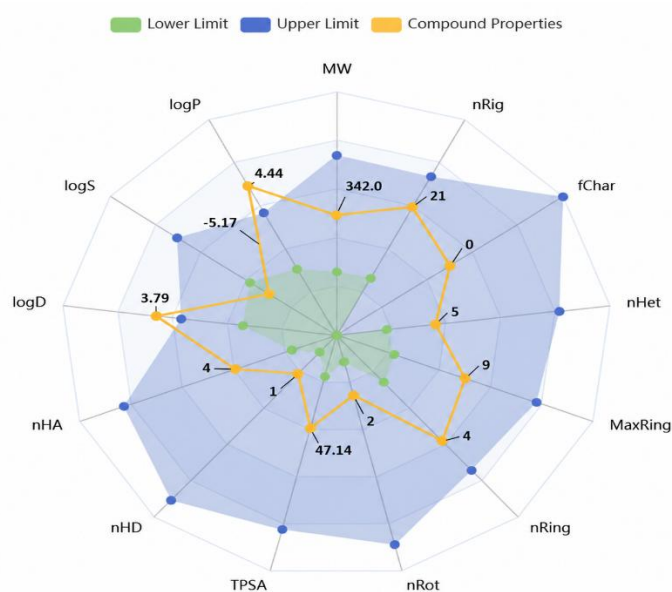


Figure 3. Selected absorption, distribution, and transporter-associated predictions for Anle138b obtained from ADMET profiling

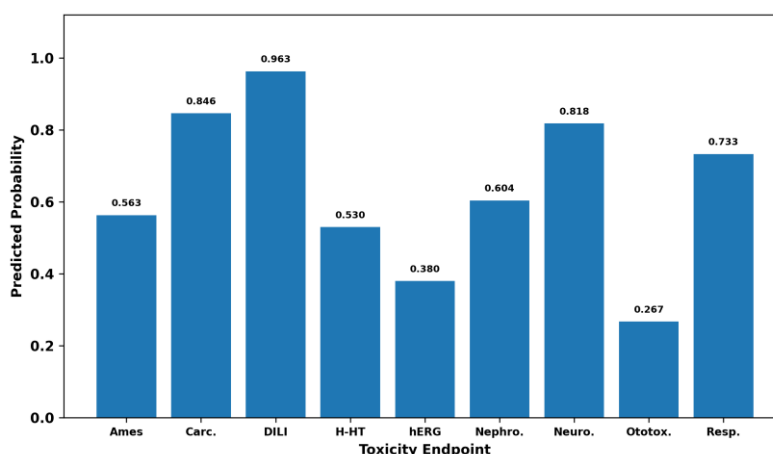


Figure 4. Selected toxicity probability predictions for Anle138b obtained from ADMET profiling

4. Discussion

A favorable binding orientation for Anle138b was identified during this computational investigation and the best ranked pose was found to have a predicted binding affinity of -9.456 kcal/mol, and those for the following poses were -7.527 and -6.541 kcal/mol, respectively. A particularly active separation of the leading pose favours a favored predicted binding conformation in the explored receptor environment. The use of integrated docking-based prioritization of compounds that form favorable interactions with α -synuclein aggregation-prone structural regions has also been shown to be useful in the computational identification of inhibitors against this protein (Siddiqui et al., 2025).

The interaction profile showed several non-covalent interaction classes such as π -cation, π -anion, π - π , π -alkyl, and carbon-hydrogen contacts. This kind of interaction diversity could be important, as the stabilization of ligands around aggregation-prone parts of proteins is often carried out by a combination of aromatic, hydrophobic, electrostatic, and hydrogen-bonding interactions. In fact, studies conducted within the polyphenols have demonstrated that α -synuclein aggregation inhibition occurs through several modes of interaction at the molecular level instead of one predominant type of interaction (Martins et al., 2023). Similar computational screening of plant metabolites has also



shown that ligand binding, molecular dynamics, and pharmacokinetic evaluation can provide complementary information to aid in prioritization of potential α -synuclein aggregation inhibitors (Bhattacharya et al., 2025).

Previous experimental-computational studies support targeting α -synuclein conformational behavior. Crocin was found to disrupt the amyloid formation of E46K α -synuclein and thereby provide a proof that small molecules can regulate aggregation-associated processes (Ghasemi Tigan et al., 2019). Similarly, the computational analysis of the complexes of β -cyclodextrin-EGCG with aggregated α -synuclein showed hydrophobic interactions, suggesting a potential role for aromatic and hydrophobic contacts in the stabilization of inhibitory complexes (Srinivasan & Rajasekaran, 2019). Earlier structure-based screening has also identified candidate molecules that could interfere with α -synuclein aggregation, and given in vivo support for the computationally selected inhibitors (Jayaraj & Elangovan, 2014).

The observed docking performance is also encouraging for the overall potential of the structural diversity of the molecules to target α -synuclein. The interaction-site chemistry of peptides was found to be important in their ability to inhibit fibrillization of α -synuclein, as revealed by recent peptide screening. Recent peptide screening showed that specific amino-acid composition can lead to strong α -synuclein binding and stabilization, with interaction-site chemistry being an important factor in inhibiting fibrillization. Protein-protein interaction studies with 14-3-3 and α -synuclein also suggest that certain interaction interfaces can be used to develop modulators of pathological behavior of α -synuclein (Chakraborty & Patra, 2024). Further, molecular docking and dynamics studies have revealed direct structural interactions between α -synuclein and P2RX7, suggesting that α -synuclein may interact with inflammatory signaling pathways associated with neurodegeneration (Kumar et al., 2025).

Here, we present the physicochemical profile of Anle138b, which revealed properties of MW 342.00 g/mol, TPSA 47.14 Å², logP 4.44, logD 3.79, four hydrogen-bond acceptors, one hydrogen-bond donor, and two rotatable bonds. These properties suggest a fairly lipophilic, conformationally restricted compound. Notably, the forecast of BBB probability 0.987 enables favourable computational CNS exposure which is critical for drugs targeting brain α -synuclein. The utility of the combination of the structural screening and the ADMET assessment has also been shown in the drug discovery processes related to other disease proteins like Parkin (Naha et al., 2022).

But this does not mean that docking and BBB predictions are not to be taken out of the context of safety. The present analysis yielded high model probabilities for DILI (0.963), carcinogenicity (0.846), neurotoxicity (0.818), and respiratory toxicity (0.733). A recent computational investigation of hesperidin against α -synuclein also used binding analysis, MM-PBSA and ADMET profiling to demonstrate the need for docking affinity and pharmacokinetic and toxicity evaluation (Waheed et al., 2025). In this way, the present results confirm that Anle138b is a structurally interesting compound that selectively targets α -synuclein, but also indicate some predicted safety concerns that must be carefully considered. These docking scores are affinity (computational) values only and the predicted ADMET endpoints should be experimentally verified. Therefore, additional molecular-dynamics studies, binding free-energy calculations, aggregation assays, neuronal toxicity assays, and in vivo validation studies should be carried out before therapeutic significance can be confirmed.

5. Conclusion

This study computationally assessed Anle138b as a potential compound for the treatment of Parkinson's disease due to its ability to target α -synuclein. Molecular docking revealed a preferred conformation with a binding score of -9.456 kcal/mol, characterized by several non-covalent interactions, including aromatic and electrostatic contacts, and hydrogen bonding. The physicochemical profile yielded a molecular weight of 342.00 g/mol, a TPSA of 47.14 Å² and a logP of 4.44, suggesting characteristics appropriate for a small lipophilic ligand, while the limited flexibility of the molecule was confirmed by the physicochemical profile. The likelihood of crossing the blood-brain barrier of 0.987, which was predicted by BBDO, further confirmed its relevance to a



central nervous system target. The in silico toxicity profile, however, showed significant potential adverse effects, including drug induced liver injury, carcinogenicity, neurotoxicity and respiratory toxicity. These results suggest that Anle138b exhibits potential structural and pharmacokinetic properties to interact with α -synuclein, but cannot be regarded as a therapeutic candidate based on docking results alone. Additional studies that include molecular dynamics simulation, binding free-energy calculations, aggregation-inhibition assays, neuronal toxicity testing, and in vivo validation are necessary to validate the binding stability, biological efficacy, and safety. In general, the integrated computational approach offers a valuable framework for prioritizing and optimizing compounds targeting α -synuclein for Parkinson's disease research.

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