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Research Article

Insilco design, synthesis and computational study of novel 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

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ABSTRACT: 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide was synthesized through specification and transamidation of ester functionalized pyrazoles. This synthetic protocol on the Pyrazole scaffold was adjusted to optimize inhibition of protein kinases. Computational design and study of novel 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide is reported. The computational prediction aims at the understanding of candidate drugs in identifying their properties and effects on the human body. Simulation analysis of candidate drugs is carried out for providing clues about regulatory mechanisms, biochemical pathways and broader drug functions. The tested compound was free of gastrointestinal toxicity which is a common dangerous side effect.

INTRODUCTION

Pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, anti-arrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant, monoamine oxidase inhibiting and antidiabetic. The dihydropyrazoles are important in the treatment and prophylaxis of anemia associated with kidney disease, as a combination therapy with chemotherapy, in preparation for autologous blood donation, and other cases of chronic anemia . These molecules can also be important for the treatment of ischemic heart disease, for treating peripheral vascular disease and for the enhancement of wound healing. These carboxamides stimulate the Erythropoietin production (EPO) using own blood donors [1].

The design processes of drugs can be streamlined by focusing on “drug-like” molecules. As a first step, it is necessary to identify biologically and pharmacologically relevant properties which are easily computable from the structure. Hence, it will be instructive to analyze the physicochemical, topological, and electronic properties of all known drugs and compare the properties of different classes of drugs

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[2]. The results of large-scale theoretical calculation used for the study of the lipophilicity, solubility, absorption, polar surface area, solubility, bioavailability, partition coefficient, volume of distribution, gastro intestinal absorption, clearance and toxicity are reported. Drug plasma-protein binding which is one of the many factors influencing bioavailability of a drug has been calculated and P-glycoprotein which plays a role in the protection of the organism against potentially toxic substances has also been calculated.

MATERIALS AND METHODS

The compound was built with standard bond lengths and angles using the PC SPARTAN Pro Version 1.08 molecular modeling program. The molecular mechanical methods followed by the Hartree-Fock method at 6-31G** level were used to minimize energy of candidate compound. Molecular modeling and determination of molecular properties of drug structures were accomplished by Chem-Sketch [3], Molinspiration [4] and MolSoft [5]. Drug-likeness was determined by methods of Actelion and MolSoft [6].

Molecular Modeling: In order to obtain the most stable conformation, a combination of molecular mechanics and quantum chemical calculations at the semi-empirical level was used. Structure of the molecule (Fig. 1) was built by HyperChem [7] Release 8 for Windows using a molecular mechanics procedure under MM+ (Molecular mechanics) [8]. The geometry was optimized to an rms (root mean square) gradient of 0.001 in vacuo (Polak-Ribière method). Then a molecular dynamics program was run for 1 ps, with 0.001 ps steps and a relaxation time of 0.1 ps, at a simulation temperature of 300 K. This was followed by MM+ geometry optimization to an rms gradient of 0.2. The molecular dynamics run was repeated and a further MM+ protocol was carried out to a gradient of an rms 0.004 on the selected drug. Angles and bond-lengths were measured on the models. This method was employed to determine structural and electronic parameters, which were to be correlated with the psychoactivity. These parameters include bond distances, torsion angles, bond orders, ionization potential, energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) frontier orbital, etc. [9].

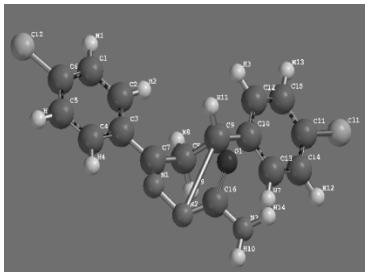

Figure 1. Structure of 3,5-bis(4-chlorophenyl)- 4,5-dihydro- H-pyrazole-1-carboxamide.

RESULTS

Molecular mechanics and Infrared spectrum: The calculated FTIR spectra (Fig. 2) exhibit a great number of bands, which are mainly due to the low symmetry

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of this molecule. Bands of greater intensity were observed between 1750-1100 cm^{-1} range which is the usual region of stretching vibrations. Theoretical calculations indicate that candidate molecule has a planar structure of the point group symmetry (Cs). The observed FT-IR is shown in Fig. 3. Comparison of the frequencies graph at the MM+ and B3LYP levels (Fig. 2) with experimental graph (Fig. 3) reveals the over estimation of the calculated vibrational modes due to neglect of anharmonicity in the real system. Inclusion of electron correlation in density functional theory, to a certain extent, makes the frequency values smaller in comparison with the MM+ frequency data. Notwithstanding the level of calculations, it is customary to scale down the calculated harmonic frequencies in order to improve the agreement with the experiment. In this study, vibrational frequencies calculated at the B3LYP/6-31G**level were scaled by 0.97, Comparing the B3LYP and MM+ methods, above 3000 cm^{-1}, the predicted frequencies by B3LYP are larger than those by MM+; whereas under 3000 cm^{-1}, most of calculated frequencies by MM+ are larger than those by B3LYP.

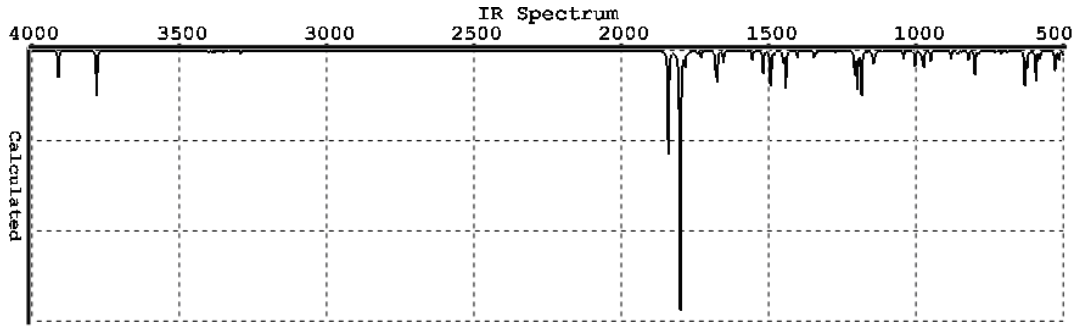

Figure 2. Theoretical Infra Red (IR) spectra of 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. {wavenumber (X-axis) vs percent transmittance (Y-axis)}.

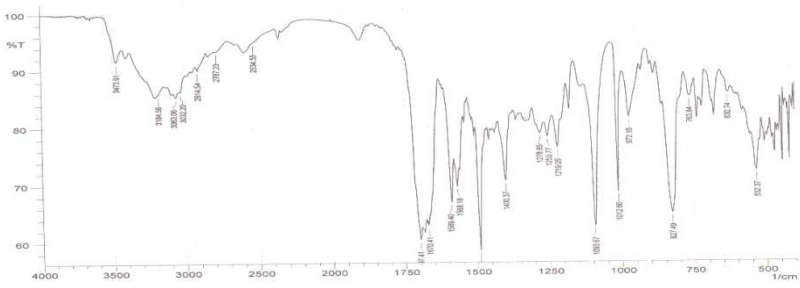

Figure 3. Experimental Infra Red (IR) spectra of 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. {(wavenumber (X-axis) vs percent transmittance (Y-axis)}.

Structural results: The calculated geometrical parameters (bonds lengths and valence angles) obtained by different calculations are given in Table1. The bond angles for the Density Functional Theory (DFT)- B3LYP method [10] are slightly better than MM+ compared to experimental results of similar molecules [11]. Based on the above comparison; although there are some differences

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between the theoretical values and the experimental values, the optimized structural parameters can well reproduce the experimental ones [11] and they are the basis for thereafter discussions.

The optimized bond lengths of C-C in the phenyl ring fall in the range from 1.389 to 1.488 A° for the MM+ method and 1.394 to 1.489 A° for the B3LYP method which are in good agreement with those of experimentally reported values for the C-C bond length of the phenyl ring of similar molecules[11]. The results also show that for all the calculations performed in the present work, there is a correlation between both N-C and C=O bond lengths. The C=O bond length is greater than that of the N-C. The N-N bond length is nearly equal to the C- C bond length and both are greater than the C-N bond length. The optimized C-Cl wavelengths by the two methods are 1.747 for the MM+ method and 1.648 for the B3LYP method, which are also in good agreement with the reported value.

Table 1. Optimized bond lengths and angles of 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

Parameters	MM+	B3LYP (6-31G**)
Bond length		
Cl12-C6	1.747	1.648
C7-N1	1.265	1.289
C16-N3	1.360	1.347
N1-N2	1.421	1.422
C3-C7	1.488	1.489
C9-C10	1.389	1.394
C11-Cl1	1.747	1.782
N2-C16	1.660	1.570
N-H	1.008	1.012
N3-C16	1.362	1.570
C-H	1.070	1.070
C16-O1	1.378	1.386
Bond angles		
C1-C2-C3	120.92	120.87
C4-C5-C6	119.52	119.46
C15-C11-C14	120.79	120.81
C13-C10-C12	119.23	119.23
Cl2-C6-C5	119.66	119.54
C3-C7-N1	117.39	117.37

Lipinski's rule of five: The molecule of this study fulfills all the requirements of Lipinski's rule of five [12], hence it can be used as an oral drug.

H-Bond donors and acceptors: The candidate drug has 3 H-bond donors and 4 H-bond acceptors; hence it has remarkable absorption capability [13].

Lipophilicity and partition coefficient (log P): An important consideration for

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the predictive design of drugs, is their Lipophilicity [14].

Partition or distribution coefficients are critical elements in efforts designed to describe the uptake, distribution, biotransformation, and excretion of organic chemicals in biological systems [15]. High log P values imply high solubility and good penetration of lipid membranes. Log P value predicted in this study for the target drug is 3.48. Log P value thus satisfies all the desirable criteria for the drug to be used orally.

Blood brain barrier: The blood-brain barrier (BBB) is of pivotal importance in maintaining homeostasis of the central nervous system (CNS), as it closely regulates the composition of the interstitial fluid in the brain [16].

The log BB value for the target drug was calculated from the formula [17], LogBB = -0.0148 (PSA, Polar Surface Area) + 0.152 log P + 0.139, and was found to be 0.037852 which is feasible.

Drug dissolution (log S): The solubility of drugs in water is of central importance because oral absorption is dependent on the compound dissolving in the aqueous of the gastrointestinal tract (dissolution) and then traversing the actual barrier of the gastrointestinal tract to reach the blood [18]. Log S correlates well with log P [19], but with an additional term involving the melting point (mp) for the crystalline solute, it is given as:

Log S = 0.8 - log P - 0.01(mp-25)

Virtually all drugs have aqueous solubilities of log S > -6.

Table 2: Solubility in buffer (log S) at different constituents of body 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1- carboxamide

S.N	Part of body	pH	Log S
1	Stomach	1.7	-4.29
2	Duodenum	4.6	-4.29
3	Jejunum and Ileum	6.5	-4.29
4	Blood	7.4	-4.29
5	Colon	8.0	-4.29

Solubility of the candidate drug at different constituents of the body (at different pHs) is shown in Table 2, which obtains a desirable value Log s = - 4.29.

Drug permeability and transport: Most drugs used to treat the CNS are lipid-soluble (lipophilic) and are able to diffuse through the endothelial membranes [20]. The physic-chemistry of different drugs suggests that molecular weight and lipophilicity should be around MW ~280 amu, LogP octanol ~2.0 [20] . Calculated values for this compound are as follows; MW = 333.04 amu and Log P octanol = 3.48), hence the designed drug can penetrate the BBB and will show activity at the target site of action.

As log P for the candidate drug is a low value of 3.48, the candidate drug is thus not lipophilic, hence the above discussed transporters can transport the candidate drug.

Electrostatic potential maps: The electrostatic potential map shows the value of the electrostatic potential onto an electron

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density surface to get a description of the electrostatic characteristics of the target drug [21]. By convention, colors toward red depict negative potential, while colors toward blue depict positive potential and colors in between depict intermediate values of the potential. Thus, this drug has both, negative and positive well defined regions, which increase the interaction possibilities from an electrostatic point of view. Thus, especially when H- bonding (electrostatic in nature) is involved, the calculation of the electrostatic surfaces can be very useful in visualization of the sites of interaction in both hosts and guests to predict their affinities [22]. In the present work, electrostatic potential maps were constructed for the candidate drug to analyze the characteristics of the electrostatic potential. Thus, in this context, molecular electrostatic potential (MEP) maps were generated based on the density functional theory by the B3LYP/6-31G** method for the lowest minimum energy conformations. The map is shown in Figure 4.

Electrostatic potential map reveals that candidate molecule has two negative regions. One is closer to the oxygen atom of the C=O and the other one is closer to the oxygen atom of the O-H group. This region is nucleophilic and tends to form hydrogen bond interactions by accepting hydrogen from a donor counterpart. Electrostatic potential also shows three positive regions. Out of these, one is closer to the hydrogen atoms of the napthelene ring, another is closer to the hydrogen atom of the O-H group and the third one is nearer to hydrogen atoms of the amide group.

The candidate drug is a good drug, which can be encapsulated in hosts cells and the kind of drug whose electrostatic surface potential shows fair 'variety of region' to interact.

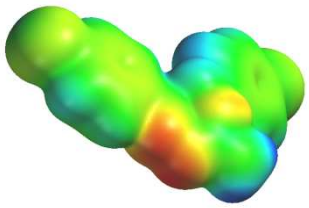

Figure 4. A 3D-view of electrostatic potential map of 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

Aqueous solubility (log W): Estimated aqueous solubility of drug-like molecules with the quantitative structure-property relationship (QSPR) approach is found to be between -5.16 to 0.92 [23]. The molecule of this study has log w of - 4.39, so it is well within the range [24].

Polar surface area (PSA): Molecular polar surface area (PSA) has been shown to correlate very well with human intestinal absorption, cell line for monolayer absorption (Caco-2) monolayer's permeability and blood-brain barrier penetration [18]. The PSA of the investigated molecule is 47.69 A^2, as predicted by MolSoft. It used 6K compounds from the WDI database and were used to find a PLS regression model. The best model was found with Q2=0.99 and Rmse=1.56.

P-Glycoprotein: The results of several studies suggest that P-glycoprotein plays a role in the protection of the organism against potentially toxic substances [25].

For the candidate drug molecule, P-glycoprotin substrate has a weak H

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acceptor and Abraham's beta is less than 1.5. Probability of drug to be a P-gp substrate is 0.089. High affinity P-gp substrate probability is 0.046.

Plasma protein binding (PPB): The PPB is normally recognized as an important factor in assessing drug disposition, efficacy and safety [26].

The strength of an interaction between plasma proteins and a drug is usually expressed as a %PPB value. This value for the target molecule is 95.02%. Similarly, the ability of a drug to bind to albumin, which is the most abundant carrier protein in human plasma, is represented by an HSA (Human serum albumin). This value for the candidate drug is 4.60. As the drug under investigation is an acidic compound, in plasma, such drugs predominantly bind to human serum albumin.

Volume of distribution (V_d): Volume of distribution (V_d), an important parameter for characterizing drug disposition, is a measure of relative partitioning of drugs between plasma and the tissues. V_d is necessary for simulating plasma concentration of a drug (C_p) and is a composite parameter, which depends on many chemical and biological factors. For of this parameter, software developed by ap-algorithms was used. This value for the target molecule was calculated to be 2.28 l/kg.

Gastro-intestinal (GI) absorption: Drugs are categorized based on permeability, aqueous solubility and elimination mechanisms to improve the ability to anticipate transporter effects and food and drug-drug interactions [27, 28]. Watari *et al*. [29] evaluated the pharmacokinetics of barbiturates in rabbits and found a linear relationship between the logarithms of k_a (drug absorption) and log P, as in equation:

$\text{Log } K_a$: 0.193 log P + 0.0148

The value for the target drug molecule, calculated with the above equation, is 0.6844.

Clearance (Log CL_R): Mayer *et al*.[30] demonstrate the relation between renal clearance values and log D as in equation:

$\text{Log } CL_R = -0.22 \text{ Log D } -0.84$

Thus, there is a simple linear relationship between log D of barbiturates and the logarithm of intrinsic clearance. For the molecule of this study, this value is : - 1.698.

Toxicity and organ specific health effects: The Ames test, which is used worldwide as an initial screen to determine genotoxic properties of new chemical entities (NCEs) for the pharma and chemical industry was used in this study. Ames genotoxicity is predicted from structure using the software developed by pharma-algorithms. Calculated probability of positive Ames test for the candidate drug is 0.204.

Predictions are displayed, in Table 3, in terms of color coded atomic/fragmental contributions ("color coded potentials"). This allows identifying and visualizing specific structural toxicophores: genotoxicity potential in the Ames test (green part is not involved in genotoxic activity, red part is associated with genotoxic properties).

Hansch and Clayton[31] modeled the acute toxicity of barbiturates to the mouse using only the octanol-water partition coefficient (P), a measure of hydrophobicity:

$\log 1/LD50 = 1.02\log P - 0.27(\log P)^2 + 1.86$ n = 13 $r^2 = 0.852$ s = 0.113

Where LD50 = dose to kill 50% of mice, n = number of compounds used in developing

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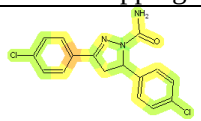
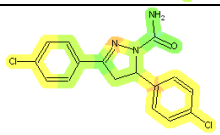
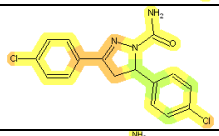
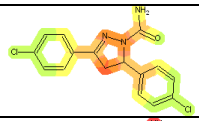
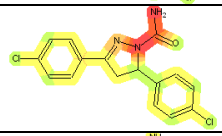
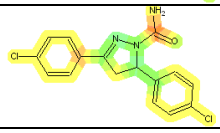
the QSAR (the train- ing set), r = correlation coefficient, and s = standard error of the estimate.

Table 3. Probability of health effect due to toxicity on various parts of the body and color mapping highlighting structural features contributing to an adverse health effect of 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

S.N.	Part of Body	Probability	Color Mapping
1	Blood	0.44	
2.	Cardiovascular System	0.75	
3.	Gastrointestinal System	0.48	
4.	Kidney	0.74	
5.	Liver	0.12	
6.	Lungs	0.27	

Calculated values of LD50 and pLD50 (predicted LD) for mouse and rat are shown in Table 4 and 5, respectively. All the values for the drug taken through various routes are well in the range. The drug of this study can be used as intraperitoneal, oral and subcutaneous, since the value of LD50 is between 500-1000, so it is slightly toxic. This cannot be taken intravenously because the value of LD50 is 73 mg/kg, which shows that this drug is moderately toxic. According to Gosselin *et al*. [32], if drug is slightly toxic, then the probable oral lethal dose for humans can be 5-15 gm/kg.

In this study, a model of the hERG force field, developed by quantum pharmaceuticals, for predicting a molecular structure with respect to its inhibition constant for the hERG channels was used. This model is very useful for molecular acido-toxicity prediction. The value of hERG for the target drug is 5.8, which is slightly greater than 5.5; hence this compound is slightly toxic [33].

The organ specific health effects were predicted using the software ToxBoxes V1.1[34]. This software uses health effects predictive algorithms based on long term toxicity studies with adverse effects reported on particular organs or

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organ systems.

Table 4. Acute toxicity LD5O for mouse.of 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

LD50 (mg/kg)		pLD50	Lower limit	Upper limit
Intraperitoneal	580	-0.23	-0.90	0.34
Oral	950	-0.44	-1.76	-0.08
Intravenous	96	0.56	-0.21	0.56
Subcutaneous	520	-0.18	-1.59	1.01

Table 5. Acute toxicity LD5O for rat of 3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

LD50 (mg/kg)		pLD50	Lower limit	Upper limit
Intraperitoneal	370	-0.04	-0.88	0.94
Oral	1100	-0.53	-2.10	-0.22

Data has been incorporated from chronic, subchronic, acute and carcinogenicity studies encompassing various species and routes of administration.

The structural features contributing to the adverse health effect are identified and highlighted using color mapping as shown in Table 3. Red sections are associated with the toxic action of the compound on a particular organ, while green sections of the molecule are not related to the health effect under investigation.

Bioavailability: Bioavailability values for drugs can be predicted by:

Bioavailability (%) = -45.20 + 5.08 (electron affinity) + 4.09 (aromatic ring count) -15.83 (HOMO) -3.34 (log *F*) -0.09 (molar volume) -0.72 (volumetric HLB (Hydrophile-Lipophile Balance)) - 4.75 × 10 (water solubility) + 1.18 (Hansen's hydrogen-bonding solubility parameter).

Predicted bioavailability of the drugs in the test set was used to evaluate the best overall predictive optimum performance model.

The linear correlation between predicted and observed values is an indication of the quality of the model predictions. Calculated bioavailability for the target drug molecule is above 82%. Probabilities of %F (Bioavailability) (Oral) > 30% is 0.811 and %F (Oral) > 70% is 0.756.

Druglikeness: The presence of structural fragments typically found in drug molecules with scores between 2 and 7 are classified as drugs; otherwise they are classified as non-drugs [35] in the present study, the candidate drug has a C=O functional group whose score is 3.4, hence it can be used as a drug. As this drug contains a single pharmacophoric group, it can attack the CNS.

A more recent example of the functional approach to identify drug-like molecules is the work of Muegge *et al*. [36]. Compounds containing specific single pharmacophoric groups can be classified as drugs. One such group is the amine group

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and does not have a nitro group, it can safely be classified as a drug. For calculation of the drug-likeness score towards GPCR (G protein-coupled receptors); ligands, ion channel modulators, kinase inhibitors and nuclear receptor ligands based on Molinspiration technology was carried out. The score came out as 1.67.

DISCUSSION

Lipinski parameters for the target drug are within the general limit found for clinical uses. The theoretical study of the candidate drug carried out to determine stable conformation, pK_a, lipophilicity, solubility, absorption, blood brain barrier, hydrogen bond donors, hydrogen bond acceptors, drug dissolution, drug permeability, electrostatic potential map, p-glycoprotein, plasma protein binding, volume of distribution, gastrointestinal absorption, drug clearance, toxicity, bioavailability, drug-likeness and polar surface area. The tested compound was free of gastro-intestinal toxicity which is a common and dangerous side effect. As the calculation in the present study yield satisfactory results for the target drug molecule, the candidate molecule is suitable for more future work to confirm its uses for analgesic, antinflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant and antidiabetic applications.

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