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# INSILICO DESIGNING AND SYNTHESIS OF IMIDAZOLE DERIVATIVES AS ANTIMICROBIAL AGENT

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## ABSTRACT

To emphasis the designing of drug molecule for increased the potency to recovery the infectious diseases by developing interaction of ligands with target proteins in insilico method , provided for selecting a new series of title compounds for synthesis. Title compounds 3-chloro-1-[1-(2-hydroxyethyl)-2-methyl-1*H*-imidazol-5-yl]-4-substituted phenylazetidin-2-one ($3a_{1-5}$) were synthesized by reaction of 2-(2-methyl-5-{[(substituted)phenylmethylidene]amino}-1*H*-imidazol-1-yl)ethanol ($2a_{1-5}$) and triethanolamine in the presence of chloro acetyl chloride with constant stirring for 7hrs. The compounds were established on the basis of their elemental analysis, FT-IR, $^1$HNMR and MS spectral data. The lipophilicity (logP) and ADME toxicity study was proven the drug likeness properties as in compounds $3a_{1-5}$ and activity efficacy of the $3a_{1-5}$ were typical which predicted by the best free energy poses interaction of target protein as compared to standard drugs. Thus it was observed that, both insilico and in vitro studies were parallely indicated the activities and identified the imidazole derivatives acted as an antimicrobial agent.

**KEYWORDS:Docking energies, Imidazole derivatives, ADME and Antimicrobial activity**.

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# INTRODUCTION

The microbes can be *saprophytes* (living on dead so causing the decay of foods, fabrics and timber etc). First fatality infection in human of fungal was documented by Hippocrates (460-377 B.C.) ,named as oral candidiasis - known as 'thrush' from around the time of Samuel Pepys. Normally *Escherichia coli* (gram-ve) is remarkable for urinary tract infection (UTI) and Various type conterminous infection diseases caused by *Staphylococcus aureus* (gram+ve ). While the main causative agent of typhoid is *Salmonella typhi*. Generally the fungal infection was occurred by the regulation and controlled expression of secreted aspartic proteinases (Saps). So it was worthwhile to developed the drug designed of imidazole derivatives towards the strength of antimicrobial by using of enzymatic key. The different constituents of many bioactive heterocyclic compounds consisted imidazole nucleus that are of wide interest because of their diverse biological and clinical applications including analgesic, antipyretic, anti-inflammatory and antimicrobial activities.[6-11] . The enzymatic key as receptors like antibacterial ( *E.coli*-3GI9[12], *S.aureus*-3FHU[13] and *S.typhi*-4AE5[14]) and antifungal (C.*albicans*-AI9, *A.nigers*-1KS5) were derived from protein data bank (RCBS). The interaction designing of receptors and ADME toxicity studies of selected compound $3a_{1-5}$ by insilico method was furnished novel series of 3-Chloro-1-[1-(2-hydroxy ethyl)-2-methyl-1H-imidazol-4-yl]-4-substituted phenyl azetidin-2-ones ($3a_{1-6}$). The *E. coli* (3GI9) receptor acts as Amino acid, polyamine, and organocation (APC) transporters which recycling the neurotransmitter to uptake of nutrient and regulate the ionic homeostasis. The *S. aureus (*4AE5) was contained fibrogen –binding clumping factor (ClfB) as like as dermokine peptide binding mode of (ClfB) ( glycine-serine-rich, GSR ) which binds with the imidazole derivatives and exert the antibacterial activity by blocking DNA replication . The 3FHUpdb was extracted from native PilS protein (DeltaPilS or IVb pilin) of *S.typhi*. The Delta pilS was interacted with extracellular domain of cystic fibrosis transmembrane conductance regulator (CFTR) and forming active site insight on the amino acids for binding. The pilus functions was helped to designing the suitable antibacterial analogs. The *C. albicans* (AI9) acts as oxidoreductase inhibitor when the dehydrofolate reductase binds with the compounds and exerted antifungal effect. The *A. nigers* (1KS5) contains the most active site of β-1,4-endoglucanase (EglA) which is the major source for spreading and regulating the infection. The active site of EglA was blocked or bound with compounds ($3a_{1-5}$) as a result the enzyme EglA totally inactive but the conformation of the enzyme was not changed and exerted antifungal effect.

# MATERIALS AND METHODS

- Drawing of these structures, energy minimization and docking of imidazole derivatives were done by using Chem schetch, MVD .
- The entire chemicals were supplied by S. D. Fine Chem. (Mumbai), Finar Chem. Ltd (Ahmedabad) and Loba Chemie. Pvt. Ltd. (Mumbai).
- Melting points were determined by open tube capillary method and were uncorrected.
- Purity of compounds were checked by thin layer chromatography (TLC) on silicagel-G in solvent system benzene: ethanol (8:4) and the spots were located under UV light.
- IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr.
- $^1$H NMR were recorded on Bruker DPX-300 MHz spectrometer in deuteriochloroform with trimethylsilane as internal standard (chemical shift in $\delta$ ppm).
- Mass spectra were obtained using Perkin-Elmer Hitachi RMU-6L MS-30 spectrometer at 70 ev and a 90 $^0$C inlet temperature.

### *Experimental works*

**Computational (Insilico) Method**

Computational methods are now a ubiquitous part of modern drug design. Being able to predict and visualize drug candidates and their interactions with the target receptor makes it possible to rationally optimize the potential drugs is an important advantage in a competitive area of researched field. Molegro virtual Docker is a highly accuracy molecular docking software which predicted the small flexible of ligands ($3a_{1-5}$) interaction with protein receptors (3GI9, 4AE5, 3FHU,1AI9 and 1KS5) by inter or intra hydrogen bonding during the docking time. The maximum and minimum docking energies poses of taget proteins-Ligands were shown in the tables- 1, 2, 3, 4 & 5.

### *ADME & Toxicity analysis*

Lipinski's Rule of Five is a rule to evaluate drug likeness which says that, in general, an orally active drug has no more than one violation of the following criteria: Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms), Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms), a molecular weight under 500 daltons and an octanol-water partition coefficient log P of less than 5. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME). The compounds ($3a_{1-5}$) used in this study satisfy the rule (see Table 6 ) and are efficient in analysis. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bonds, and a higher lipophilicity.

### *Chemical synthesis*

#### *2-(5-amino-2-methyl-1H-imidazol-1-yl) ethanol (1a)[1]*

Equimolar (0.01) mixture of 2-(5-nitro -2-methyl-1H-imidazol-1-yl) ethanol and tin was refluxed in ethanol for 10-15 minutes and 0.01 mole conc.HCl (20ml) was added drop wise during the refluxing. The reaction mixture was cooled, diluted with 15-20ml of water and add enough 20% sodium hydroxide solution to neutralize the tin hydroxide. Then the mixture was extracted in ether, washed the ethereal solution with water and filtered it. The filtrate was distilled up under reduced pressure and solid crude mass of 1a was separated out, dried it and recrystallized from dilute alcohol. The 90% yield, 185-187$^{o}$c was found in compound 1a.

IR (KBr, cm-1): 3408.3(OH), 3311.8(NH2), 2916.4(CH3), 2895.2(CH2)1591.3 (C=N). 1H NMR (400 MHz, DMSO-d6, $\delta$ ppm): 4.89(s,1H,OH),4.88(s,1H,NH),3.94(s,IH,=CH), 3.32 (s, 3H, CH3). MS (ESI): m/z 141,124,100,97,44,18.

#### *2-(2-methyl-5-{[(substituted)phenylmethylidene]amino}-1H-imidazol-1-yl)ethanol[2]*

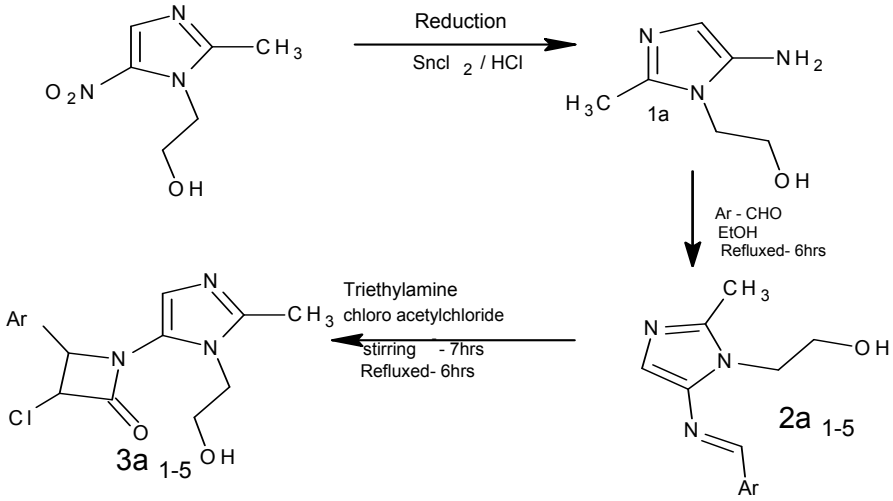
An equimolar (0.02mole) mixture of aromatic primary amines and aromatic aldehydes were refluxed in 40ml of dry ethanol for 18 hours. The excess of ethanol was then distilled off under reduced pressure and the resulting solid were washed with ethanol, followed by dry ether. The compounds ($2a_{1-5}$ ) were dried and recrystallized from benzene. The yield of the compounds were found 75-80 % and the sharp melting point were obtained from all the compounds. 2a. IR (KBr, cm-1): 3408.3(OH),3010(ArH), 2916.4(CH3), 2895.2(CH2)1670,1591.3 (C=N) 1H NMR (400 MHz, DMSO-d6, $\delta$ ppm): 7.80-6.66 (m, Ar-H), 5.89(s, H, OH). 3.85(s,IH,=CH), 3.14 (s, 3H, CH3). MS (ESI): m/z 229,203,185,124,100,52,44,18.

#### *3-chloro-1-[1-(2-hydroxyethyl)-2-methyl-1H-imidazol-5-yl]-4-phenylazetidin-2-one ($3a_1$)[3]*

Equimolar (0.001) solution of compound $2a_1$ in ethanol and triethanolamine was mixed with continuous stirring. After stirring the total mixture was cooled at 0-5$^{0}$ c a few drops of chloro acetyl chloride was added drop by drop. Then the whole mixture was stirred for 5-7 hrs and filtered. The filtrate was refluxed for 6hrs and cooled. On cooling the solid crude product of $3a_1$ was separated out, filtered, dried and recrystallized from ethanol. The 68% yield and

melt point-210-212$^{O}$c was found in compound $3a_1$. IR (KBr, cm-1): 3524.0(OH),2966.6(ArH), 2864.2(CH2),1708(C=O)1554.6 (C=N) 709(C-Cl),1H NMR (400 MHz, DMSO-d6, *δ* ppm): 7.27-5.55 (m, Ar-H), 5.13(s, H, OH). 3.26 (s, 3H, CH3).2.17(d,1H,CH of lactum) MS (ESI): m/z 305,287,277,264,193,179,124,100,52,44.18. Similarly compounds $3a_{2-5}$ were prepared and physical data was shown in table-02.

***SCHEME***




***(2,3) Ar:- $a_1$=$C_6H_5$, $a_2$= $C_6H_4Br(p)$, $a_3$ = $C_6H_4Cl(p)$, $a_4$= $C_6H_4NO_2(p)$ $a_5$= $C_6H_4OH(o)$ .***

***Antibacterial activity***

All the synthesized compounds were screened for antibacterial activity by cup plat method. The concentration100µg / ml of the compounds were prepared as a stock solution by using DMF solution. The standard drug coprafloxacin of concentration 20 µg /ml was prepared in distill water and determined the zone of inhibition. As compared to the standard, the synthesized compounds were shown promising inhibition activity against *E. coli, S. aureus and S. typhi*. Then it was observed that the antibacterial activity was determined by both Invitro and Insilco methods parallel. The result revealed that the imidazole derivatives can be used as an antimicrobial agent. The zone of inhibition of the compounds was shown in table-8.

## RESULTS AND DISCUSSION

Interestingly, docking results reveal that all the selected title compounds inside target proteins (three bacterial and two fungal ) were outlined by different amino acids and the hydrophobic pockets. Small ligand molecules were bound to 3GI9, 4AE5, 3FHU, 1AI9 and 1KS5 by four binding modes such as hydrogen bonds, Vander Waals, electrostatic and hydrophobic interactions. The total energy of four binding modes and different energies, interacting surfaces between designed compounds comparison with standard drugs were given in Tables-01-05. Calculated free energy of binding for compounds $3a_{1-5}$ and ciprofloxacin, miconazole in the binding sites were -153.264, -143.985, -148.386, -148.103,-138.869 and -154.046,-124.161 kcal/mol respectively in their best pose. The highest free energy of binding and lowest interactive surface is observed with Compound $3a_4$ and $3a_5$ than other docked molecules ($3a_1$,$3a_2$, $3a_3$). Therefore, among all docked molecules, $3a_{4-5}$ possess highest probability of interaction with binding site of target proteins and it is comparable with that of standard antagonist. Furthermore, the present data showed that the substituent like Cl, Br present in lactum ring resulted in improvement ability of binding was increased. The physical properties yield, sharp melting point of final compounds and established structural feature

by FT-IR,1HNMR,MS spectra were shown in tables-7& 8 respectively. The in vitro screening such as anti-bacterial and antifungal activities of synthesized compounds $3a_{1-5}$ were done by cup plat method and shown that the compounds $3a_4$ and $3a_5$ have best percentage of inhibition while compounds ($3a_1$,$3a_2$, $3a_3$) were shown significant activities as compared to standards. Therefore it was observed that the both in vitro and insilico methods parallely determined the anti inflammatory and antibacterial activities which revealed that the synthesized compounds imidazole derivatives acted as a anti antibacterial as well as antifungal agents.

**Table 1**
***Docking score of $3a_1$-$a_5$ against E .coli (3GI9)***

| Compound code | Mol. docking score | | RMSD | Torsion |
|---|---|---|---|---|
| | Max[m] | Min[m] | | |
| $3a_1$ | -138.303 | -126.399 | 65.418 /65.436 | 04 |
| $3a_2$ | -134.411 | -127.226 | 64.659/ 64.727 | 04 |
| $3a_3$ | -139.670 | -131.849 | 65.415/ 65.554 | 04 |
| $3a_4$ | -153.264 | -142.743 | 65.443/65.607 | 05 |
| $3a_5$ | -144.399 | -135.898 | 65.905/65.036 | 04 |
| ciprofloxacin | -94.489 | -90.744 | 69.579/68.039 | 04 |

**Table 2**
***Docking score of $3a_1$-$a_5$ against S. aureus (4AE5 )***

| Compound code | Mol. docking score | | RMSD | Torsion |
|---|---|---|---|---|
| | Max[m] | Min[m] | | |
| $3a_1$ | -131.512 | -121.329 | 60.365 /60.176 | 04 |
| $3a_2$ | -133.726 | -126.414 | 60.916/ 62.041 | 04 |
| $3a_3$ | -135.14 | -129.798 | 61.203/ 62.614 | 04 |
| $3a_4$ | -143.985 | -137.751 | 59.101/61.203 | 05 |
| $3a_5$ | -129.178 | -125.984 | 60.752/62.971 | 04 |
| ciprofloxacin | -71.919 | -57.574 | 46.437/46.301 | 04 |

**Table 3**
***Docking score of $3a_1$-$a_5$ against S. typhi (3FHU)***

| Compound code | Mol. docking score | | RMSD | Torsion |
|---|---|---|---|---|
| | Max[m] | Min[m] | | |
| $3a_1$ | -93.901 | -88.216 | 54.391 /60.026 | 04 |
| $3a_2$ | -137.314 | -126.708 | 54.505/ 57.695 | 04 |
| $3a_3$ | -137.296 | -127.786 | 54.476/ 53.767 | 04 |
| $3a_4$ | -148.386 | -136.896 | 37.132/39.179 | 04 |
| $3a_5$ | -138.873 | -132.109 | 52.959/53.618 | 04 |
| ciprofloxacin | -92.613 | -78.883 | 52.040/51.963 | 04 |

**Table 4**
***Docking score of $3a_1$-$a_5$ against C.albican (1AI9)***

| Compound code | Mol. docking score | | RMSD | Torsion |
|---|---|---|---|---|
| | Max[m] | Min[m] | | |
| $3a_1$ | -131.759 | -118.709 | 16.508 /14.878 | 04 |
| $3a_2$ | -140.855 | -125.609 | 20.412/ 17.020 | 04 |
| $3a_3$ | -131.241 | -122.139 | 16.770/17.613 | 04 |
| $3a_4$ | -148.103 | -139.147 | 16.433/15.584 | 05 |
| $3a_5$ | -140.227 | -123.366 | 16.244/15.768 | 04 |
| Miconazole | -154.046 | -139.668 | 18.553/17.824 | 04 |

**Table 5**
***Docking score of $3a_1$-$a_5$ against A.nigar (1KS5)***

| Compound code | Mol. docking score | | RMSD | Torsion |
|---|---|---|---|---|
| | Max[m] | Min[m] | | |
| $3a_1$ | -127.032 | -116.461 | 126.135 /124.861 | 04 |
| $3a_2$ | -131.321 | -122.225 | 125.783/124.49 | 04 |
| $3a_3$ | -134.670 | -118.05 | 125.956/125.304 | 04 |
| $3a_4$ | -138.869 | -126.5 | 123.97/123.312 | 05 |
| $3a_5$ | -124.846 | -121.904 | 125.545/124.661 | 04 |
| Miconazole | -124.161 | -118.935 | 124.959/121.439 | 04 |

**Table 6**
***Absorption and Permeability study of compounds ($3a_{1-5}$).***

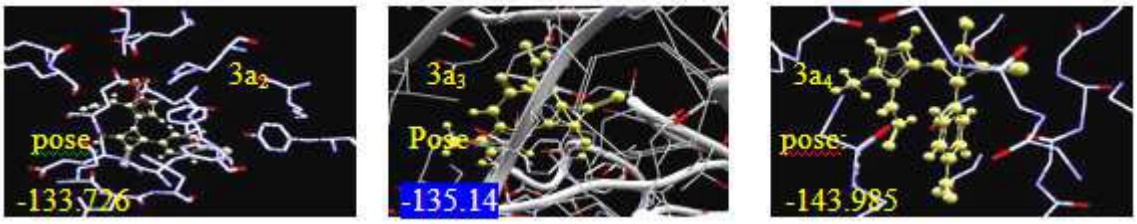
| Compounds Code | Molecular weight | S+logP | S+logD | M logP | HONH | NO | Alert |
|---|---|---|---|---|---|---|---|
| $3a_1$ | 305.766 | 1.241 | 1.234 | 2.455 | 01 | 05 | 0 |
| $3a_2$ | 385.667 | 2.067 | 2.062 | 3.086 | 01 | 05 | 0 |
| $3a_3$ | 340.211 | 1.949 | 1.944 | 2.966 | 01 | 05 | 0 |
| $3a_4$ | 351.771 | 0.884 | 0.177 | 1.988 | 02 | 08 | 0 |
| $3a_5$ | 321.765 | 0.918 | 0.909 | 2.462 | 02 | 06 | 0 |

***a) Sum of OH and NH H-bond Donors, b) Sum of N and O H-bond acceptors, c)Computational alert (Toxic) according to the rule of 5: 0, d)No problem detected; 1, poor absorption or permeation are more likely to the Molecular weight.***

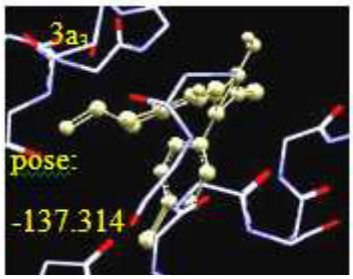
***Best docking figure poses of target proteins – Ligands***

***3GI9 pdb***


***4AE5 pdb***

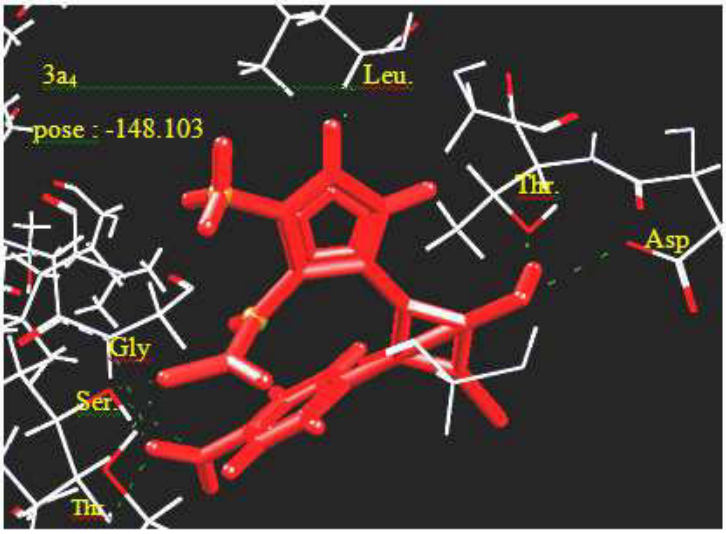


***3FHUpdb***






***1AI9 pdb***




***1KS5 pdb***

**Table 7**
***Physico-chemical data of compounds 3a$_{1-5}$***

| Compound Code | Molecular formula | Molar Volume in $cm^3$ | Melting Point ($0^0$c) | % of yield | % of elemental Analysis calculated(Found) | | | Rf values |
|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | |
| $3a_1$ | $C_{15}H_{16}ClN_3O_2$ | 217.8 | 210-212 | 68 | 58.27<br>56.32 | 5.27<br>4.70 | 13.74<br>13.78 | 0.78 |
| $3a_2$ | $C_{15}H_{15}BrClN_3O_2$ | 230.4 | 221-222 | 70 | 46.84<br>46.88 | 3.93<br>3.87 | 10.92<br>10.95 | 0.86 |
| $3a_3$ | $C_{15}H_{15}Cl_2N_3O_2$ | 227.1 | 230-232 | 72 | 52.96<br>52.94 | 4.44<br>4.42 | 12.35<br>12.38 | 0.75 |
| $3a_4$ | $C_{15}H_{15}ClN_4O_4$ | 223.0 | 234-236 | 75 | 51.36<br>51.40 | 4.31<br>4.28 | 15.97<br>15.99 | 0.65 |
| $3a_5$ | $C_{15}H_{16}ClN_3O_3$ | 215.1 | 212-214 | 70 | 55.99<br>55.97 | 5.01<br>5.03 | 13.06<br>13.09 | 0.79 |

**Table 8**
***Antimicrobial screening of compounds 3(a$_{1-5}$) by cup plate method.***

| **Compound Code** | **Zone of inhibition in mm (100µg / ml).** | | | | |
|---|---|---|---|---|---|
| | ***E. coli*** | ***S. aureus*** | ***S. typhi*** | ***C. albicans*** | ***A. nigar*** |
| $3a_1$ | 22 | 17 | 11 | 19 | 17 |
| $3a_2$ | 19 | 19 | 20 | 23 | 19 |
| $3a_3$ | 24 | 21 | 19 | 17 | 21 |
| $3a_4$ | 29 | 27 | 26 | 29 | 23 |
| $3a_5$ | 26 | 15 | 25 | 22 | 13 |
| Ciprofloxacin | 30 | 29 | 27 | _____ | _____ |
| Miconazole | _____ | _____ | _____ | 28 | 30 |
| DMF | 00 | 00 | 00 | 00 | 00 |

**# 6mm diameter, *E.coli- Escheria coli, S.aureus- Staphylococcus aureus* and *S.typhi -Salmonella typhi***
***C. albicans- Candida albicans, A. nigar- Aspergillus nigar.***

# CONCLUSION

In conclusion the synthesized title compounds resulted in good yields. The molecular docking study of the title compounds reveals better activity. Indicating the imidazole ring scaffold influences the pharmacological activity. From the best posed energy and activity data, the compounds having electronegative group such as halogens are found to be more activity as compared to others. It is observed that the chloro at 3 position on beta lactum ring increases the activity. However, the difference in activity profile with structural modifications provides further scope to explore these compounds for better bioactivity.

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