Design of novel JAK3 Inhibitors towards Rheumatoid Arthritis using molecular docking analysis

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Abstract:
Multiple cytokines play a pivotal role in the pathogenesis of Rheumatoid Arthritis by inducing intracellular signaling and it is known that the members of the Janus kinase (JAK) family are essential for such signal transduction. Janus kinase 3 is a tyrosine kinase that belongs to the Janus family of kinases. Drugs targeting JAK3 in the treatment of Rheumatoid arthritis are relevant. Therefore, it is of interest to design suitable inhibitors for JAK3 dimer using molecular docking with Molegro Virtual Docker. The compound possessing the highest affinity score is subjected to virtual screening to retrieve inhibitors. The compound SCHEMBL19100243 (PubChem CID- 76749591) displays a high affinity with the target protein. The affinity scores of this compound are more than known drugs. ADMET analysis and BOILED Egg plot provide insights into this compound as a potent inhibitor of JAK3.

Keywords: Rheumatoid Arthritis, JAK 3 inhibitor, Molecular docking, Virtual screening, BOILED-Egg plot, ADMET

Background:
Rheumatoid arthritis (RA) is defined as a chronic inflammatory disorder that primarily affects joints but can spread to other body systems, including the skin, eyes, lungs, heart and blood vessels. An autoimmune disorder, rheumatoid arthritis occurs when your immune system mistakenly attacks self-tissues and starts attacking the lining of your joints, causing a painful swelling that can eventually result in bone erosion and joint deformity. The multiple cytokines play pivotal roles in RA pathogenesis by inducing intracellular signaling, and members of the Janus kinase (JAK) family are essential for such signal transduction [1]. JAK3 is an intracytoplasmic tyrosine kinase that is physically and practically coupled to gamma chain permitting cytokine subordinate flag transduction. Janus Kinase (JAKs) assumes a fundamental job in cytokine receptor motioning since they phosphorylate and enact flag transducer and activator of translation (STAT) protein. A few of these JAK controlled cytokine receptor pathways are personally engaged with the intention and movement of Rheumatoid Arthritis sickness pathogenesis. The JAK/STAT pathway is generally communicated intracellular flag transduction pathway, on a very basic level essential for T lymphocyte separation and capacity.

Selective inhibition of JAK3 has been identified as an important strategy for the treatment of autoimmune disorders [3]. Based on the unique Cys909 of JAK3 at the gatekeeper position, a new irreversible covalent inhibitor (III-4) which is highly potent and
selective in targeting JAK3 [2]. Tofacitinib is a disease-modifying antirheumatic drug (DMARD) which was recently approved by the US Food and Drug Administration (FDA). There are several randomized clinical trials (RCTs) that have investigated the efficacy and safety of tofacitinib in adult patients with rheumatoid arthritis (RA). A systematic review with a meta-analysis of RCTs was undertaken to determine the efficacy and safety of tofacitinib in treating patients with RA [3]. The efficacy, safety and dose response of an oral Janus kinase inhibitor named peficitinib (ASP015K) as a mono therapy in Japanese patients with moderate to severe rheumatoid arthritis (RA). Peficitinib 50, 100 and 150 mg each showed statistically significantly higher ACR20 response rates compared with placebo, and response rates increased up to 150 mg with a statistically significant dose-response is known [4]. Decernotinib (VX-509), an oral selective inhibitor of JAK-3, was also tested in patients with rheumatoid arthritis (RA) in whom the response to methotrexate treatment was inadequate. VX-509 significantly improved the signs and symptoms of RA at weeks 12 and 24 compared with the placebo group when it was administered in combination with methotrexate [5]. Moreover, (JAK3) is expressed in lymphoid cells and is involved in the signaling of T cell functions. The development of a selective JAK3 inhibitor has been shown to have a potential benefit in the treatment of autoimmune disorders [6]. PF-06651600, a newly discovered potent JAK3-selective inhibitor, is highly efficacious at inhibiting γc cytokine signaling, which is dependent on both JAK1 and JAK3. PF-06651600 allowed the comparison of JAK3-selective inhibition to pan-JAK or JAK1-selective inhibition, in relevant immune cells to a level that could not be achieved previously without such potency and selectivity [7]. Therefore, it is of interest to design inhibitors against JAK3 dimeric structure using molecular docking and virtual screening.

Materials and Methodology:
Selection of JAK3 inhibitors:
Literature findings were conducted to find pre-established inhibitors of JAK-3 which were adept to binding and hence for restraining the activity of the protein. The aggregate number of established inhibitors was found to be 17, which were chosen for further analysis. The structures of 12 were available in the PubChem database from which these were directly downloaded while the 3D structures (Table 1) of remaining compounds were built using MarvinSketch and were saved in the 3D.sdf format (Figure 1).

Protein and ligand preparation:
The crystal structure of the target protein JAK3 was obtained from Protein Data Bank (PDB) with PBD ID: 3LXK [21] as shown in Figure 2. Ligand preparation was carried out by taking the 3D structures of retrieved as well as constructed ligands and processing them using the LigPrep module of Schrodinger suite, 2013 (Schrodinger. LLC, New York, NY) where, these were optimized through OPLS 2005 force field algorithm [22-26]. This preparation resulted in all the ligand structures in a single file, which was saved with a .sdf extension for docking with the target protein [27-29].
the pre-existing ligand from the protein structure [34-36]. Cavity one was witnessed to possess the largest volume and the ligand structure docked within it and was thence utilized for docking of the prepared ligands [37-41]. The single .sdf file created in the previous step was taken for loading all the ligand structures in the docker. Docking procedure-holding parameter of maximum iteration of 1500, grid solution 0.2 having a binding affinity, maximum population size 50, the protein and ligands were assessed on the subsequent confirmation of the Internal Electrostatic interaction (Internal ES), sp2-sp2 torsions, and internal hydrogen bond interaction [42-46]. Energy minimization and H-bond optimization were carried out after docking. Placing of Simplex Evolution at max steps 300 and neighbor distance faster 1.00. After docking to minimize the complex energy of ligand-receptor interaction the Nelder Mead Simplex Minimization (using non-grid force field and H-bond directionality) was used [47-52].

**Virtual screening:**
The compound, which showed the highest re-rank score value in the docking table was considered as the best-established drug. Similarity search was carried out against this best-established compound to get a superior compound possessing a larger binding affinity to the 3D crystal structure, other than any previously established drugs [53-57]. This similarity searching was carried out against PubChem database developed by NIH, one of the public chemical repositories, which contain structures of 93 million chemical compounds [58-61]. The filtration property parameter set by component rule of Lipinski’s rule of five was set at threshold >=95. These compounds were downloaded in sdf format and docked using the identical procedure with the crystal structure of JAK3 protein to find the compound showing a higher affinity towards the target protein than the best-established drug.

![Figure 2: Protein 3D structure of JAK3 obtained from PDB (PDB ID: 3LXK)](image)

**Table 1:** Established Inhibitors of JAK3 with PubChem ID (if structures are present in PubChem) with properties.

| SNo | Inhibitor           | Pub Id   | M. W     | HBA | HBD | Ref   |
|-----|---------------------|----------|----------|-----|-----|-------|
| 1.  | tofacitinib         | 9926791  | 312.377  g/mol | 1   | 5   | [8-10] |
| 2.  | peficitinib (ASP015K) | 57928403 | 326.4  g/mol | 4   | 4   | [11-13]|
| 3.  | Decernotinib (VX-509)| 59422203 | 392.386 g/mol | 3   | 8   | [14, 15]|
| 4.  | RB1                 | 9602155  | 271.32   | 2   | 3   | [16, 17]|
| 5.  | Oxindole inhibitor  | 321710   | 133.15 g/mol | 1   | 1   | [18]   |
| 6.  | PF-06651600         | 118115473| 285.351 g/mol | 2   | 4   | [7, 19]|
| 7.  | Tricyclic 1         |          | 263.38   | 2   | 3   | [19]   |
| 8.  | Tricyclic2          | 4592     | 298.34   | 2   | 4   | [19]   |
| 9.  | Tricyclic3          | 5325595  | 241.25   | 2   | 3   | [19]   |
| 10. | Tricyclic4          | 356.38   | 2        | 4   |     | [19]   |
| 11. | Tricyclic5          | 25180101 | 312.37   | 1   | 4   | [19]   |
| 12. | Tricyclic6          | 5494425  | 309.34   | 2   | 3   | [19]   |
ADMET studies:

Drug-Drug Comparative Study:

Docking of established drugs with the help of Molegro Virtual Docker led to the creation of a docking folder. An “unnamed complex” structure file was created in this folder. This structure file was opened with the help of Molegro and all constraints, cavities, and ligands in the structure were removed to obtain only the protein structure [62-63]. The best pose of the drug was tallied from the result generated and was then imported. The resultant structure generated was saved as the best-pose drug and was stored in PDB format. Similarly, the “unnamed complex” structure file resulting from the docking of virtually screened compounds was retrieved from its respective folder and the steps were reiterated to obtain the best virtually screened drug pose. An excel sheet was organized to check and compare all the affinities, hydrogen interaction, steric energy and high re-rank score to draw out a comparison between the two drugs [40, 44].

The admetSAR database provides a free and open web resource, which gives an estimation of the biological and chemical profile of the compound entered. The resource is available at http://lmmd.ecust.edu.cn:8000/ . Properties stated in the ADMET profile include digestion, adsorption, metabolism, toxicity, excretion and so on. These give us in-depth information regarding the development and discovery of drug in question. The database is divided into 22 qualitative classifications and 5 quantitative regression models, which aim to provide a comprehensive outcome with high precision based on estimation. Hence, this database was used to estimate the properties of the inhibitors under study. The analysis was made for the best-established compound to facitinib and the best virtual screened compound with PubChem CID: 76749591 to predict the bioactivity properties and toxicity using admetSAR [44].

Boiled-egg plot

A BOILED-Egg plot lends reassuring assistance and provides a unique statistical plot to support the two passive predictions made,
which is gastrointestinal absorption and brain penetration of small molecules, which is essential for discovery, and development of drugs. Both the parameters are represented on a cartesian plane in the shape of eclipses and include other important parameters such as MW, TPSA, MLOGP, GI, and BBB to recondition the BOILED-Egg plot. Accordingly, in the cartesian plane, if our compounds rest in the yolk region represented by the yellow ellipse, the probability of BBB (Blood Brain Barrier) is escalated whereas if the compounds rest under white areas, the conjecture of gastrointestinal absorption is amplified. Beside these regions, if the compounds rest in gray areas excluding the “egg” or are out of range of the graph, the compounds are non-absorptive even non-brain penetration and hence it contemplated as a remarked box. The regions are not exclusive of each other [40, 44, 48].

Software, Suites and Web servers Used:
Retrieval of inhibitor structures was done from NCBI’s PubChem database in 3DSDF format. The inhibitors which lacked PubChem CID or the 3D structure was absent in PubChem were drawn using MarvinSketch5.6.0.2, (1998-2011, Copyright ChemAxon Ltd.). Ligand optimization was done using Schrodinger suite (Schrodinger, LLC, 2009, New York, NY). Molegro Virtual Docker 2010.4.0.0 was used for flexible docking of receptor protein structure and all ligand structures. Molecular Visualization was conducted with the support of Accelrys Discovery Studio® Visualizer 3.5.0.12158 (Copyright © 2005-12, Accelrys Software Inc.). ADMET profiles were predicted and organized using admetSAR (Laboratory of Molecular Modeling and Design. Copyright (2012) East China University of Science and Technology, Shanghai Key Laboratory for New Drug-Drug Design).

Results and discussion:
The docking results of all pre-established drugs, when docked in the cavity 1 of the JAK3 protein structure show that Tofacitinib (CP 690,550) represented in the table as Cmpd5 displays the best interaction (Table 2). Some of the properties of this compound include a molecular weight of 312.37 and a measured logP value of 1.24. The compound has 1 hydrogen bond donor and 5 hydrogen bond acceptors. The IUPAC name of the compound is 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile.

Virtual Screening Results:
Similarity searching for this inhibitor against the PubChem database resulted in 314 compounds, which show a very similar structure to the best-established drug. Table 3 lists the top 10 docking results of these virtually screened compounds. The table establishes compound SCHEMBL19100243 (PubChem CID-76749591) as the best virtual docked compound. The compound displays physical properties such as a molecular weight of 380.444g/mol, 3 hydrogen bond donors, and 5 hydrogen bond acceptors. It is also clear from the table that the re-rank score of this compound (-134.539) is lower than the re-rank score of the best-established drug that is CP690,550 which indicates its greater affinity to the target protein.

Figure 3: The compound SCHEMBL19100243 (PubChem CID-76749591), the most effective virtual screen drug shows ligand-receptor interactions.

Table 4 compares the interaction energies of the best-established compound CP 690,550 (tofacitinib) with the best virtual screened compound PubChem CID: 76749591. The re-rank scores of both the compounds show that the virtual screened compound binds with far more affinity to JAK 3 receptor when compared to the best-established drug. The MolDock scores of these drugs show an even more superiority of the virtual screened drug. The same trend is mimicked in all the descriptors, with the virtual screened drug surpassing the established drug by large margins. External Ligand interactions, protein-ligand interactions, and steric interactions replicate these results. The hydrogen bond energies of both the compounds are relatively the same. Based on this table it can be concluded that the best virtual screened drug has the potential to bind with greater affinity and can hence be used with a superior effect in the treatment of Rheumatoid Arthritis.
Pharmacophore mapping provides us with tools for spatial systematic topographies of molecular interaction with a specific target protein receptor and serves as an alternative to the procedure of molecular docking. These studies help convey a precise query on the finest interface of the inhibitor with its target protein, aided by annotations and represent the aligned poses of the molecule and help to search for high interactions between the target protein and the inhibitor under study. The interaction of the receptor protein JAK3 is found to be quite effective with the drug SCHEMBL19100243 (PubChem CID - 76749591), pharmacophore studies are held to further understand different interactions that are present in the complex so formed. The interactions carried out for the purpose of this study include hydrogen bond interactions, van der walls interaction, aromatic interactions and ligand interactions.

Figure 3 displays receptor-ligand interaction shown by the virtual screened compound SCHEMBL19100243 (PubChem CID- 76749591) in the cavity of JAK-3 protein structure. Primary interaction between Leu 905 and the N5 of the ligand and Glu 903 and N4 of the ligand can be seen to provide affinity to keep the structure intact. Figure 4 highlights the best-virtual screened compound SCHEMBL19100243 (PubChem CID- 76749591) showing aromatic interaction in the binding cavity of protein JAK3. The protein cavity can be seen to be shaded in two different colors, with surfaces portraying blue color signifying the edges and while the shade surfaces displaying dull orange color signifying the face.

Table 5 summarizes the ADMET prediction of both the best-docked compound Tofacitinib (CP 690,550) and PubChem CID 76749591. It can be seen that the BBB (Blood Brain Barrier) values of both these compounds are almost equivalent, while the virtual screened compound shows better value for Human Intestinal Absorption (HIA), which is the prediction of absorption of the drug.
in the intestine. All other absorption criteria favor the virtual screened drug as better figures are presented in that column. Metabolism criteria of both these compounds are again almost equivalent, with some properties favoring the best-virtual screened drug. Both these compounds are non-carcinogens. When comparing the toxicity criteria, it can again be said that the virtual screened drug edges over the best-established drug. Both these compounds are also shown to be not easily biodegradable. **Table 6** summarizes the comparison of the regression prediction of ADMET analysis of the two drugs under consideration. The regression model shows that the virtual screened drug has a higher CaCo2 permeability in regression studies. Toxicity studies the virtual screened drug shows lower levels of rat acute toxicity as well as fish toxicity when compared to the best-established drug.

![Figure 6](image-url)  
**Figure 6:** Comparative ADMET studies of BBB, HIA, AMES toxicity and LD50 of the Established compounds against Virtual screened compounds. Expand abbreviations used in this Figure

A relative ADMET profile comparison was carried out for selected inhibitors. Predictions were based on parameters such as the Blood-Brain Barrier (BBB), Human Intestinal Absorption (HIA), AMES Toxicity, and LD50 rat toxicity. The established inhibitor CP 690,550 (Tofacitinib) and Cmpd 4, the virtual screened drugs PubChem CID 76749591 and PubChem CID 123462422 were taken up for comparison according to ADMET studies. These four inhibitors were graphically represented using R-programming as highlighted in **Figure 6** and **Table 7**. The parameters, BBB, HIA, AMES Toxicity, and LD50 acquired from the admetSAR database and were tabulated according to their estimated values. The best virtual screened compound PubChem CID 7674959 is seen to have the lowest AMES toxicity levels in mice among all the drugs. Also, this inhibitor shows the lowest levels of the Blood-Brain Barrier (BBB). The virtual screened compound shows Human Intestinal absorption values more than that compared to the best-established drug CP 690,550.

![Figure 7](image-url)  
**Figure 7:** Boiled-egg Plot

The compounds: CP 690,550 (Tofacitinib) and Cmpd 4, and the top two virtually screened compounds (PubChem CID76749591 and PubChem CID123462422) were plotted in the BOILED-Egg plot. **Table 8** summarizes the results of the plot. Observations indicate that all four drugs show high GI absorption and a negative result for Blood-Brain permeation. This observation justifies the placement of all the four compounds in the white region of the BOILED-Egg plot. The virtual screened drug with PubChemCID76749591 shows the highest value for TPSA and lies almost in the center of the white region. None of the compounds fall in the grey region of the plot, which confirms that all these compounds display high GI absorption and are all BBB permeable (**Figure 7**).
Table 4: Drug-Drug Comparative study

| Energy overview:                | Best Established compound: CP 690, 550 (Tofacitinib) | Best Virtual Screened compound: PubChem CID 76749591 |
|--------------------------------|----------------------------------------------------|---------------------------------------------------|
| Descriptors                    | MolDock Score Rerank Score                          | MolDock Score Rerank Score                          |
| Total Energy                   | -139.749 -118.272                                  | -163.788 -134.546                                  |
| External Ligand interactions   | -139.575 -117.041                                  | -170.157 -146.483                                  |
| Steric (by LJ12-6)             | -17.359                                            |                                                   |
| Hydrogen bonds                 | -4.752                                             |                                                   |
| Internal Ligand interactions   | 14.826                                             |                                                   |
| Torsional strain               | 7.222                                              |                                                   |
| Torsional strain (sp2-sp2)     | 2.796                                              |                                                   |
| Hydrogen bonds                 | 0                                                  |                                                   |
| Steric (by PLP)                | 7.604                                              | 5.891                                              |
| Steric (by LJ12-6)             | 1.308                                              | 4.202                                              |

Table 5: ADMET Predicted Profile and Classification

| Model                          | Result     | Probability | Result     | Probability |
|--------------------------------|------------|-------------|------------|-------------|
| Blood-Brain Barrier            | BBB+       | 0.9598      | BBB+       | 0.9568      |
| Human Intestinal Absorption    | HIA+       | 0.9956      | HIA+       | 0.9897      |
| Caco-2 Permeability            | Caco2-     | 0.5686      | Caco2+     | 0.5154      |
| P-glycoprotein Substrate       | Substrate  | 0.6712      | Substrate  | 0.6524      |
| P-glycoprotein Inhibitor       | Inhibitor  | 0.9773      | Inhibitor  | 0.8898      |
| Renal Organic Cation Transporter| Inhibitor | 0.5956      | Inhibitor  | 0.6368      |
| Subcellular localization       | Mitochondria| 0.3864      | Mitochondria| 0.37        |
| CYP450 2C9 Substrate           | Non-substrate | 0.8175      | Non-substrate | 0.8246   |
| CYP450 2D6 Substrate           | Non-substrate | 0.7281      | Non-substrate | 0.723     |
| CYP450 3A4 Substrate           | Substrate  | 0.6923      | Substrate  | 0.7649      |
| CYP450 1A2 Inhibitor           | Non-inhibitor | 0.7134      | Non-inhibitor | 0.734   |
| CYP450 2C9 Inhibitor           | Inhibitor  | 0.5072      | Non-inhibitor | 0.8014   |
| CYP450 2D6 Inhibitor           | Non-inhibitor | 0.9081      | Non-inhibitor | 0.9537   |
| CYP450 2C19 Inhibitor          | Non-inhibitor | 0.5384      | Non-inhibitor | 0.8036   |
| CYP450 3A4 Inhibitor           | Non-inhibitor | 0.6549      | Non-inhibitor | 0.9307   |
| CYP Inhibitory Promiscuity     | High CYP Inhibitory | 0.5527      | Low CYP Inhibitory | 0.7937 |
| Toxicity                       |            |             |            |             |
| Human Ether-a-go-go-Related Gene| Strong inhibitor | 0.6427      | Weak inhibitor | 0.5995    |
Inhibition

|                      | Inhibitor |       | Inhibitor |       |
|----------------------|-----------|-------|-----------|-------|
| AMES Toxicity        | Non AMES toxic | 0.5407 | Non AMES toxic | 0.5492 |
| Carcinogens          | Non-carcinogens | 0.8741 | Non-carcinogens | 0.9032 |
| Fish Toxicity        | High FHMT | 0.9553 | High FHMT | 0.7677 |
| Tetrahymena Pyriformis Toxicity | High TPT | 0.9269 | High TPT | 0.8348 |
| Honey Bee Toxicity   | Low HBT | 0.8765 | Low HBT | 0.8848 |
| Biodegradation       | Not ready biodegradable | 0.9934 | Not ready biodegradable | 0.9956 |
| Acute Oral Toxicity  | III | 0.6154 | III | 0.6845 |
| Carcinogenicity (Three-class) | Non-required | 0.5991 | Non-required | 0.6912 |

Table 6: ADMET Predicted Profile and Regression

| Model                    | Value   | Unit     | Value   | Unit     |
|--------------------------|---------|----------|---------|----------|
| Absorption               |         |          |         |          |
| Aqueous solubility       | -3.6174 | LogS     | -2.9488 | LogS     |
| Caco-2 Permeability      | 0.8086  | LogPapp, cm/s | 0.5977 | LogPapp, cm/s |
| Toxicity                 |         |          |         |          |
| Rat Acute Toxicity       | 2.7101  | LD50, mol/kg | 2.7249 | LD50, mol/kg |
| Fish Toxicity            | 1.1207  | pLC50, mg/L | 1.3125 | pLC50, mg/L |
| Tetrahymena Pyriformis Toxicity | 0.562 | pIGC50, ug/L | 0.5293 | pIGC50, ug/L |

Table 7: Comparative ADMET profile of the test ligands and the control

|                     | Blood-Brain Barrier | Human Intestinal Absorption | AMES Toxicity | Carcinogenicity | LD50 in rats |
|---------------------|---------------------|-----------------------------|---------------|-----------------|--------------|
| CP 690,550 (Tofacitinib) | 0.9568              | 0.9897                      | 0.5492        | Non- carcinogenic | 2.7249       |
| Cmpd 4              | 0.9806              | 0.9958                      | 0.584         | Non- carcinogenic | 2.5278       |
| PubChem CID 76749591 | 0.9598              | 0.9956                      | 0.5407        | Non- carcinogenic | 2.7101       |
| PubChem CID 123462422 | 0.9631           | 0.9973                      | 0.5608        | Non- carcinogenic | 2.7365       |

Table 8: Boiled egg parameters

| Molecule              | MW     | TPSA  | XLOGP 3 | MLOGP  | GI absorption | BBB permeant |
|-----------------------|--------|-------|---------|--------|---------------|--------------|
| Cmpd5                 | 312.37 | 88.91 | 1.5     | 0.7    | High          | No           |
| Cmpd4                 | 356.38 | 84.73 | 2.93    | 2.01   | High          | No           |
| CID76749591           | 380.44 | 105.98| 1.74    | 0.7    | High          | No           |
| CID123462422          | 380.49 | 88.91 | 3.19    | 1.79   | High          | No           |

Conclusion:
The known drug CP690,550 (Tofacitinib) shows a high degree of binding to the JAK 3 receptor. We describe a compound SCHEML19100243 (PubChem CID-76749591) that surpasses the affinity scores of CP690,550. The drug-drug comparison scores highlight the supremacy of this drug over all the previously established drugs, evident by comparing the re-rank scores. The pharmacophore mapping of the molecule shows the efficiency with which it binds to the receptor structure. The ADMET profile of this ligand is highly favorable, which predicts the ligand would give positive results when in vitro and in vivo studies are conducted. Furthermore, the boiled-egg plot confirms the ADMET results, adding weight to the potential for the virtual-screened ligand as a JAK3 inhibitor towards rheumatoid arthritis.

Conflict of Interest:
The authors declare no conflict of interest, financial or otherwise.
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