

## Bioinformatics study of the potential of JAK/STAT pathway inhibition as a new treatment strategy to control cytokine release syndrome in COVID-19

Bahareh Farasati Far<sup>a</sup>, Ali Aghajani Shahrivar<sup>b</sup>, Hazha Omar Othman<sup>c</sup>, Mehdi Shafiee Ardestani<sup>d</sup>, Hamidreza Pazoki-Toroudi<sup>e\*</sup>

<sup>a</sup> Department of Chemistry, Iran University of Science and Technology, Tehran, Iran

<sup>b</sup> Chemistry Department, Central Tehran Branch, Islamic Azad University, Tehran, Iran

<sup>c</sup> Chemistry Department, College of Science, Salahaddin University, Erbil, Iraq.

<sup>d</sup> Department of Radiopharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

<sup>e</sup> Department of Physiology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran

Correspondence to: Hamidreza Pazoki-Toroudi, aPostal code and address: Iran University of Medical Sciences, Hemmat Highway, next to Milad Tower, Tehran, Iran, 14496114535.

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\*Corresponding E-mail  
[pazoki1970@gmail.com](mailto:pazoki1970@gmail.com)

### ABSTRACT

COVID-19, a pandemic affecting virus, which is caused by the current SARS-CoV2 coronavirus. The present research is performed on anti-virus and immune-modulating therapies. Cytokine storms are the toxic drivers and mortality caused by various human viral infections. In addition, the intensity was linked to an elevated risk of acute respiratory failure, myocardial injury, and mortality in SARS-CoV-2-infected patients. The Janus kinase (JAK) therapeutic inhibitor class showed significant clinical benefits in anti-inflammatory and anti-viral effects. Among them, filgotinib has been approved as an active JAK inhibitor by decreasing biomarkers with main immune reaction functions and markers supporting matrix-degradation, angiogenesis, leukocyte adhesion, and recruitment in both research trials. In this study, we tried to get an insight into the choice of this drug in controlling the jack to treat COVID-19 using drug design methods.

### Keywords

COVID-19, JAK inhibitors, filgotinib, cytokine release syndrome, immune modulation



## INTRODUCTION

A new coronavirus disease with high mortality, emerging as pandemic disease, is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite many public health initiatives, pharmacological therapies remain desperately required to treat patients affected, decrease mortality, and limit virus shedding and eventual transmission optimally. The infection with SARS-CoV-2 pushes the host to a deep cytokine response, which involves various mediators aimed at Immune-mediated inflammatory diseases (IMIDs). No specific therapy for COVID-19 is available up to now cause many of the current treatments are symptomatic. (1) , (2)

Efficient prevention and care products are an immediate imperative, in particular in difficult, life-threatening situations. Pathogen infection with coronavirus (e.g., SARS, SARS-CoV-2) also contributes to the development of acute respiratory distress syndrome (ARDS) through severe cytokine and chemokine activity. Anti-viral cytokine signaling develops like a secondary haemophagocytic lymphohistiocytosis in some patients with moderate to severe COVID-19, hyper inflammatory status triggered by viral infections. Maintains the unacceptable levels of acute lung injury, chronic interferon activation, and deteriorate resistance to T cells and antibodies, perhaps for inadequate viral clearance. While the inflammation must mount most cytokines induced by SARS-CoV-2 infection and those attacked in some IMIDs, they do not regulate the virus clearance. The role of

immunosuppressive drugs widely used in immune-mediated diseases in the susceptibility and natural history of COVID-19 can be appropriately taken and concern expressed. (3-5)

The cytokine excess associated with the SARS-CoV-2 reaction may also affect both viral clearance and defensive immune responses. Patients with autoimmune disorders have a high risk of infection as a result of endogenous and external factors such as immunosuppressants (dysfunctional immune systems). One of the primary deficiencies of COVID-19 infection is the control of the cytokine storm. (6) , (7)

As described above, current COVID-19 management is primarily positive, and medically validated therapies are not available. ARDS and cytokine storms are the leading causes of death. In addition, 50% of cytokine storm syndrome patients suffer from ARDS. Considering the exceptionally rapid progression of systemic and pulmonary inflammation in a subset of COVID-19 patients, it is essential to recognize and control the immune reactions disrupted at an early stage. However, this must be checked, and other biomarkers that are more sensitive and more precise can be identified. (8) , (9)

Several explosive cytokines that include automatic diseases associated with their receptors have activated a JAK-based phosphorylation cascade, which constitutes signals of gene transcription. Thus, medications block signals of cytokine that impede the action of JAK. These antagonists target medical treatment to HIV, RA,

Psoriasis, Psoriatics, and inflammatory bowel diseases. (10)

Signal transduction plays a significant role in blocking the cytokine releases of the JAK family of enzymes and JAK inhibitors. Inhibitors of JAK can handle a cytokine storm by the induction of many inflammatory cytokines. Most inhibitors for JAK 1, JAK 2, less JAK 3, and the Tyrosine kinase 2 (TYK 2) are immensely successful for inhibition of Interleukin 6 (IL-6) and interferon, but also inhibit the signal cascade of both Interleukin 2 (IL-2) and Interferon alfa or beta (IFN- $\alpha$  /  $\beta$ ). JAK inhibitors have been efficient in inhibition. (11)

Inhibitions of small molecules in JAK are quite a recent concept for systemic autoimmune/inflammatory conditions. JAK Inhibitors are biological inhibitors that interact with the Adenosine triphosphate (ATP) binding domain by inhibiting type I / II cytokine receptors. Jak inhibitors have targeted synthetic immunosuppressant products that interfere with JAK Signal transducer and activator of transcription (JAK-STAT) signaling by inhibiting one or more members of the JAK family (JAK1, JAK2, JAK3, TYK2). These molecules mediate the transcription factors of the STAT family, which contribute to pro-inflammatory cytokine release. Thus, cytokine expression can be decreased by them and help regulate cytokine storms. Additional inhibition of JAK by small modules can also be detrimental as they further restrict the isolation and clearance of the pathogen and can cause unexpected complications. (12)

On the other hand, these compounds are provided as medications orally, with highly trained pharmacodynamics and pharmacokinetics. They can provide a more practical approach to calm down the cytokine storm transiently to avoid ARDS and fulminating myocarditis. In addition to blocking IL-6, JAK1 inhibitors not only block inflammatory pathways in a cytokine storm. (13)

The aims of JAK1 and JAK3 affect some cytokines involved in anti-viral reactions such as interferons, IL-2, IL-15, IL-21, and IFN $\beta$ . Thus, potentially, JAK1 inhibitors can inhibit SARS-CoV-2 clearance. Inhibition of the SARS-CoV-2 or the IL-17-induced cytokine inhibits viral induction. In particular, it seems to be very promising to apply interleukin 6 (IL-6) and GM-CSF blockers to manage the massive cytokine storm linked to the development of lung damage typically and resulting ARDS in the most attacking patterns of SAR S-CoV disease. Both of whom rely on SARS-CoV-2 signaling in part or entirely (Figure 1). (14)

Therefore, clinical trials have been JAK1 inhibitors are also suggested as a safe treatment in hospitalized patients with COVID-19. Based on recent analyzes of the COVID-19 inflammatory markers and previous knowledge of inflammatory responses in other mortal lung infections, the potential strategy for anti-ARDS, brilliant myocarditis, organ failure, and mortality at an advanced stage of the condition has been assessed. (15)

One of the significant challenges in this regard is the replacement of more effective

drugs. It has been indicated to be given to patients with COVID-19 in the late inflammatory process by baricitinib or other JAK inhibitors. Using different anti-viral medications, as a result of a growing understanding of infection pathophysiology, other drugs widely used in RA diagnosis have been proposed as alternative therapies for COVID-19. Baricitinib were tested for their anti-cytokine and anti-inflammatory function. Baricitinib induces cytokines with a lower IC<sub>50</sub> value, which indicates that cytokine-induced JAK1 / STAT signaling becomes more impaired in the dosing period. It implies a more potent overall inhibition of cytokine-induced JAK1 / STAT signaling during dosing. However, finding a drug with better therapeutic properties can help in the treatment of this disease. (16)

Finding new drugs is challenging, expensive, and time-consuming because there is no structured way to immediately discover a drug even though the drug activity's disorder, targets, and molecular mechanisms are well understood. There are millions of candidate molecules, and because of prohibitive costs, both in terms of time and energy, individual tests cannot be performed on any candidate. Reasonable drug design strategies have been introduced in recent months, particularly for In silico-based solutions, and this strategy has been backed by a recent study as a promising substitute or complementary method for efficient screening of potential drugs. Here, we used a bioinformatics approach to repurpose medication to classify the active

antagonists of SARS-CoV2 Key Jak1-inhibitors. (17) , (18)

## METHODS

In this study, the three-dimensional structures of ligand and proteins were obtained from PubChem and PDB database, respectively. Density functional theory at B3LYP/631+G (d, p) level implemented was used for 3D and geometry optimizations with energy minimization of each molecule. The protein-ligand interaction calculations were done by Autodock 4.2, and 2D ligand-protein interaction was calculated by Ligplot software. DRAGON software was used for molecular descriptors calculation. Genetic Algorithm and Partial least squares regression were used for feature selection. Computed Atlas evaluated the active site, surface, and volume of protein for Surface Topography of Proteins (CASTp). Swiss ADME and target prediction were used to determine the pharmacokinetic properties and target analysis of molecules. GROMACS-2019 version using OPLS force field during was used for Molecular dynamic simulations during 20 ns by selecting periodic boundary conditions and the TIP3P water model for solvating complexes, followed by addition of ions to neutralize. Energy minimization was Tolerance for energy minimization was 1000 kJ/mol/nm. (19-21)

## RESULTS AND DISCUSSION

The interaction of the JAK1 inhibitor drugs (clinical and pre-clinical) using Autodock software was studied, and the results are given in Table 1.

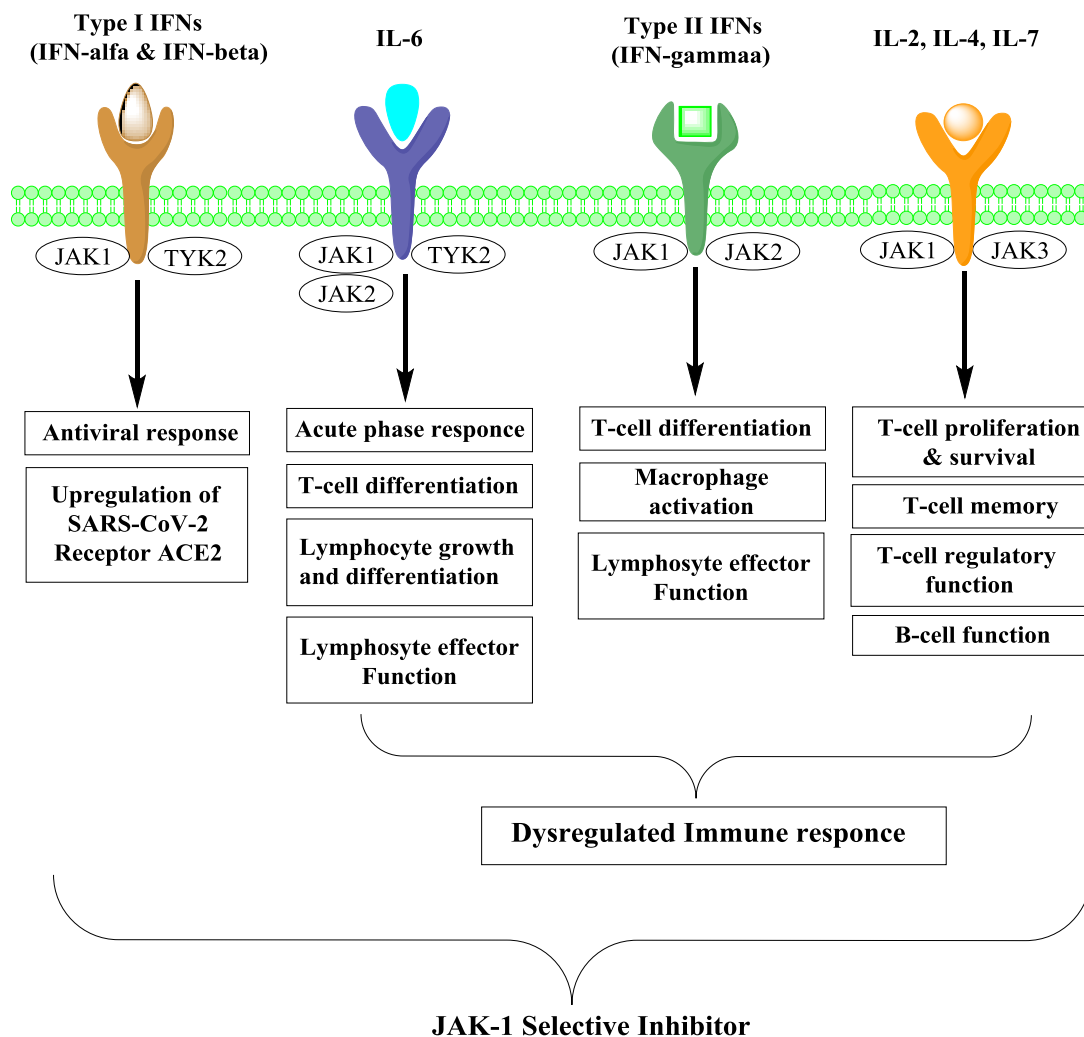
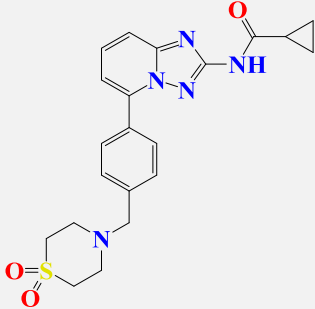
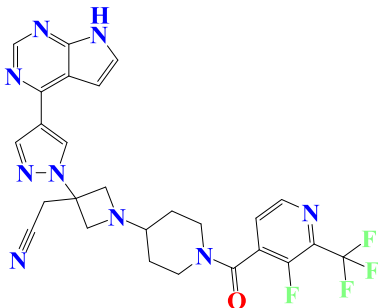
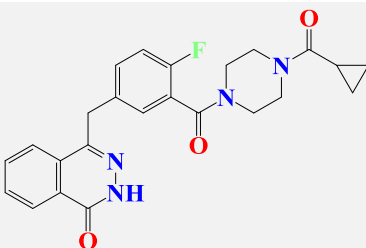
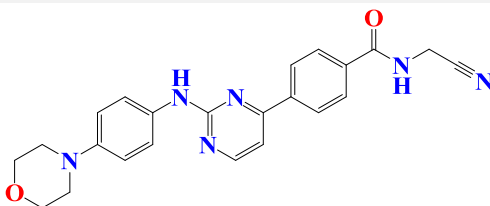
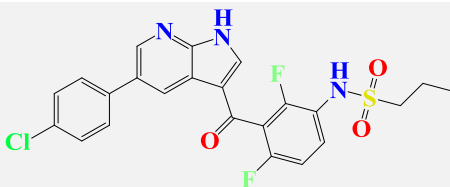
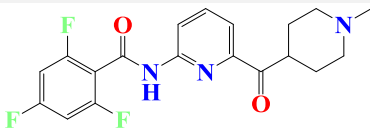


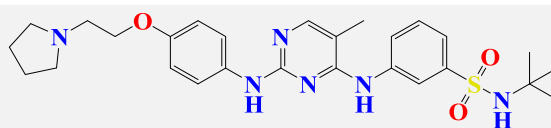
Figure 1- Inhibition mechanism of JAK-1 selective inhibitor

Table1. Estimated  $\Delta G$  for filgotinib derivatives using Autodock software

Name	Structure	Estimated $\Delta G(\text{Kcal/mol})$
<b>Filgotinib</b>		-9.54
<b>Itacitinib</b>		-9.43
<b>Olaparib</b>		-9.22
<b>Momelotinib</b>		-9.19
<b>Vemurafenib</b>		-9.17
<b>lasmiditan</b>		-8.89

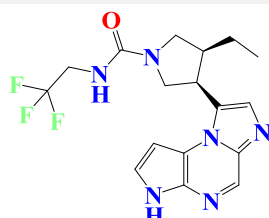


**Fedratinib**



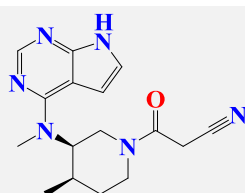
-8.84

**Upadacitinib**



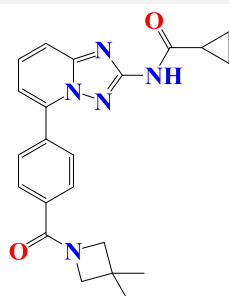
-8.7

**Tofacitinib**



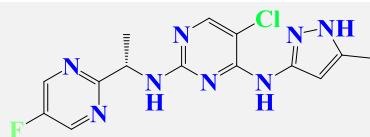
-8.7

**Solcitinib**



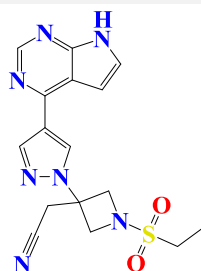
-8.33

**Azd-1480**



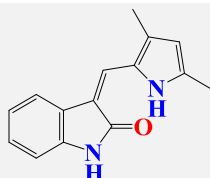
-8.3

**Baricitinib**



-8.19

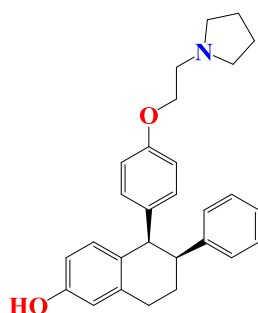
**Semaxanib**



-8.15

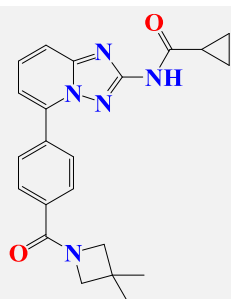
**Lasofexifene**

-8



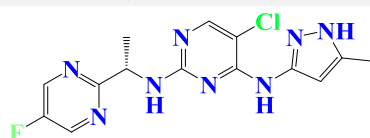
**Mirogabalin**

-6.75



**Fadrozole**

-6.67



The binding force of molecular docking demonstrates the affinity of a specific ligand and energy, by which a compound interacts and binds to the pocket of a target protein. As a potential drug choice, a compound with fewer binding energy is favored. The results showed that the drug filgotinib is more stable with Jack1.

Filgotinib (GLPG0634/GS-6034) is an active and selective inhibitor of JAK1 under investigation in the treatment of RAs and inflammatory bowel disease. Filgotinib has demonstrated promising efficacy and is well tolerated for the treatment of rheumatoid arthritis. It is an orally delivered, potent, and selective seed inhibitor of JAK1. The pharmacokinetics and active metabolite of filgotinib in safe volunteers and the usage and analysis of pharmacokinetics–

pharmaceutical models to help design the dosage for Phase IIB for patients with rheumatoid arthritis were addressed here. Two-phase II tests of another treatment for JAK1–filgotinib in 2018 showed effectiveness in both patients with psoriatic arthritis<sup>1</sup> and ankylosing spondylitis in patients<sup>2</sup>. Compared to upadacitinib 3,4, filgotinib therapy provided a mean improvement in hemoglobin and platelet counts.

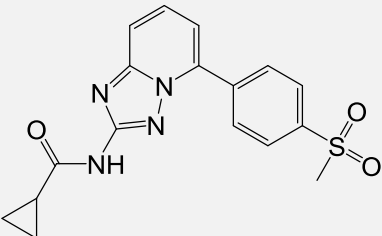
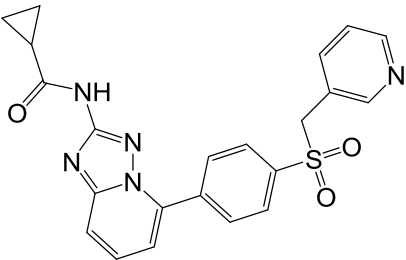
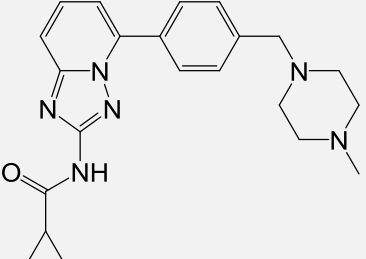
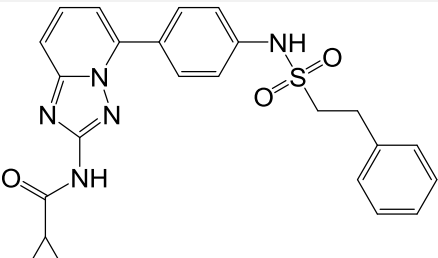
A study of the interaction of 33 derivatives of this drug using Autodock software showed that compared to the drugs studied in the previous section,  $\Delta G$  shifted to more stable values (Table 2) (Figure -2). QSAR calculations performed using algorithm-PLS genetics showed that the number of benzene rings and polarity is an essential factor in molecule-JAK1 interaction (Figure-2). Also, compared to filgotinib, only entry five has

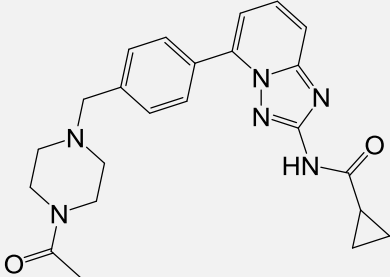
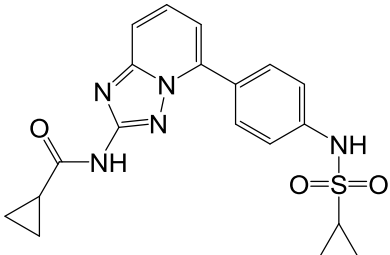
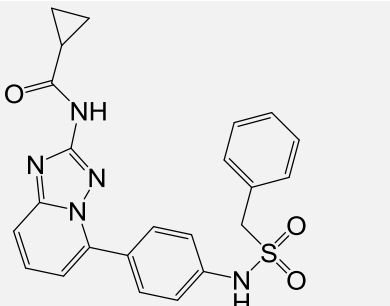
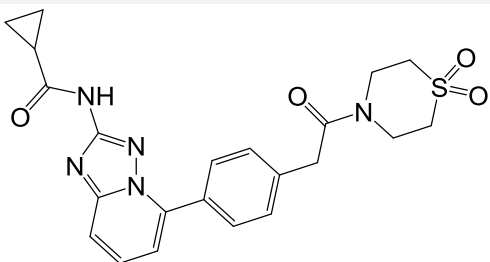
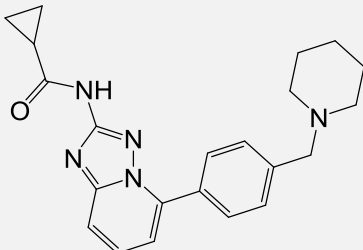


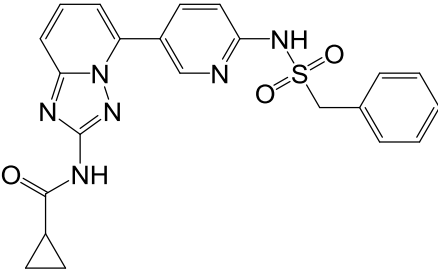
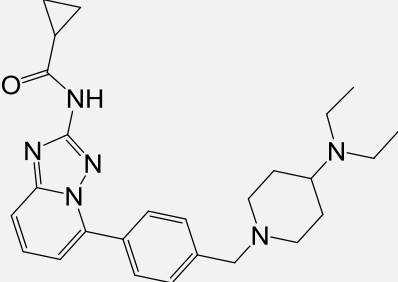
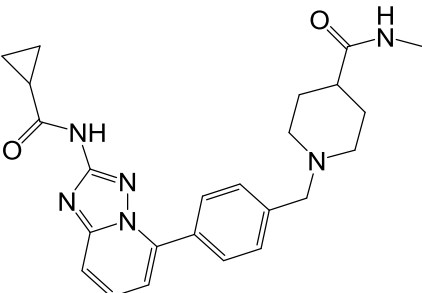
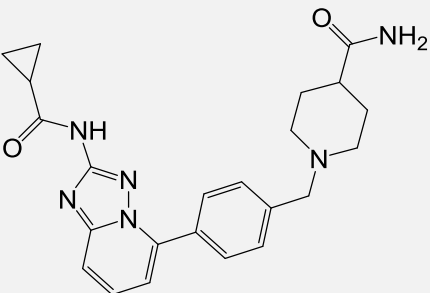
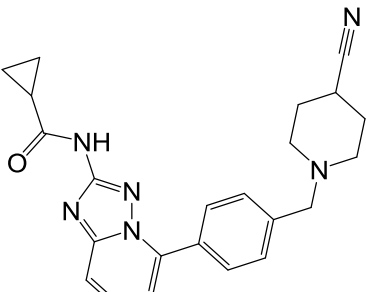
created a more stable complex. Pharmacophore analysis showed that the behavior of this substance is similar to that of filgotinib, and changes in volume and area are similar (Table-3) (Figure 4) (Figure-5). However, the 2D interaction result showed more hydrophobic interaction with amino acids (Table-4) (Figure-6). Target prediction results show that the A 93% composition targets the LAK, while the B

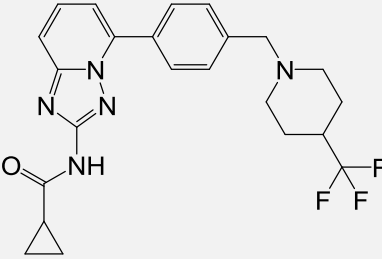
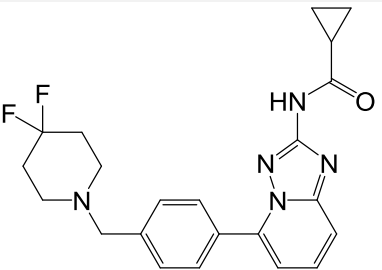
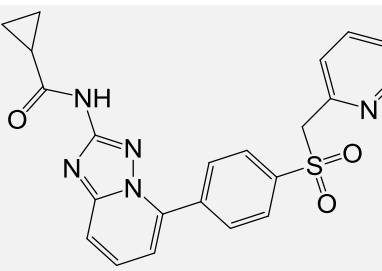
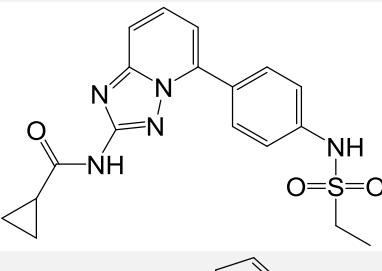
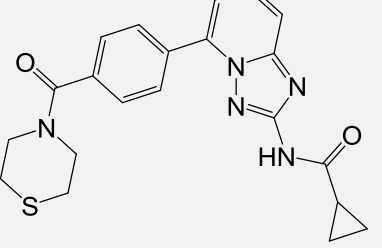
73.3% composition interacts (Figure-7). ADME studies also showed similar behavioral similarities to filgotinib (Table-5). As a result of these two compounds can be the alternative to barticinib drug.

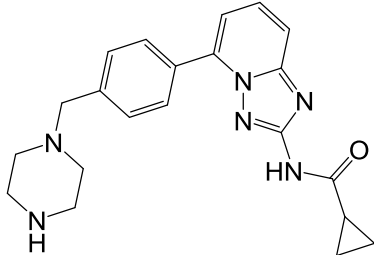
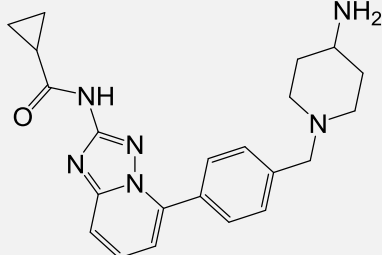
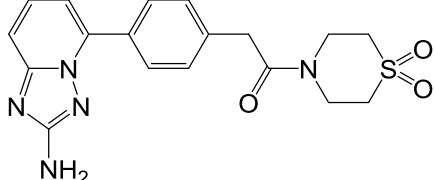
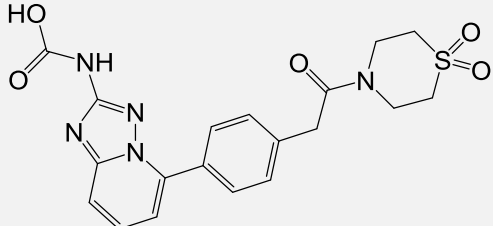
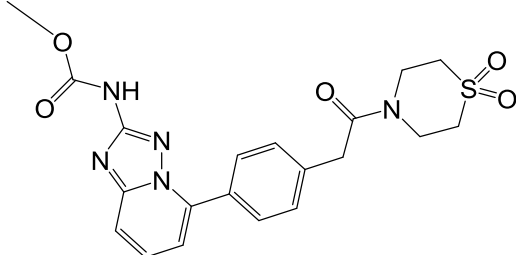
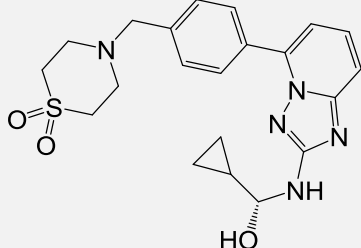
Table 2. Estimated  $\Delta G$  for filgotinib derivatives.

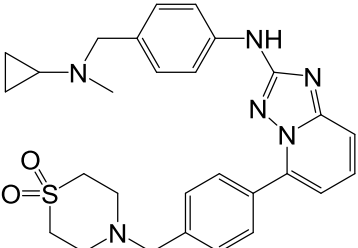
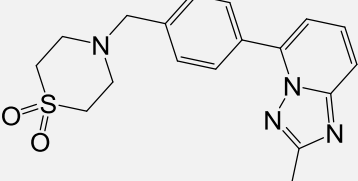
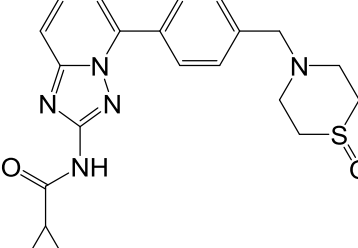
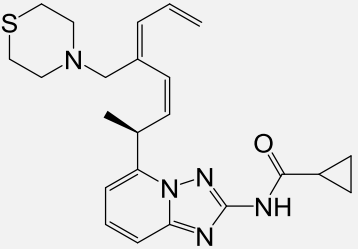
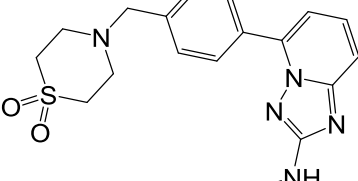
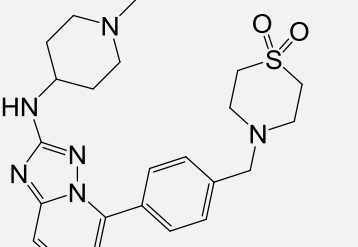
Structure	Measured	Predicted	Type
	-8.66	-8.72	Test
	-8.89	-9.14	Train
	-9.02	-9.2	Train
	-9.56	-9.67	Train

	-9.6	-9.83	Train
	-9.33	-9.42	Test
	-9.4	-9.5	Train
	-9.26	-9.18	Test
	-8.73	-8.98	Train

	-9.07	-9.23	Train
	-8.59	-8.64	Test
	-9.06	-9.23	Test
	-9.05	-9.11	Train
	-9.47	-9.56	Train

	-9.03	-9.16	Train
	-8.94	-9.01	Train
	-8.94	-9.18	Train
	-9.11	-9.07	Train
	-9.39	-9.45	Train

	-9.11	-9.09	Test
	-9.06	-9.13	Train
	-8.68	-8.8	Train
	-8.63	-8.72	Train
	-9.27	-9.53	Train
	-8.79	-8.91	Train

	-9.02	-9.07	Train
	-8.61	-8.87	Train
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	-8.95	-8.98	Train
	-8.74	-8.81	Train



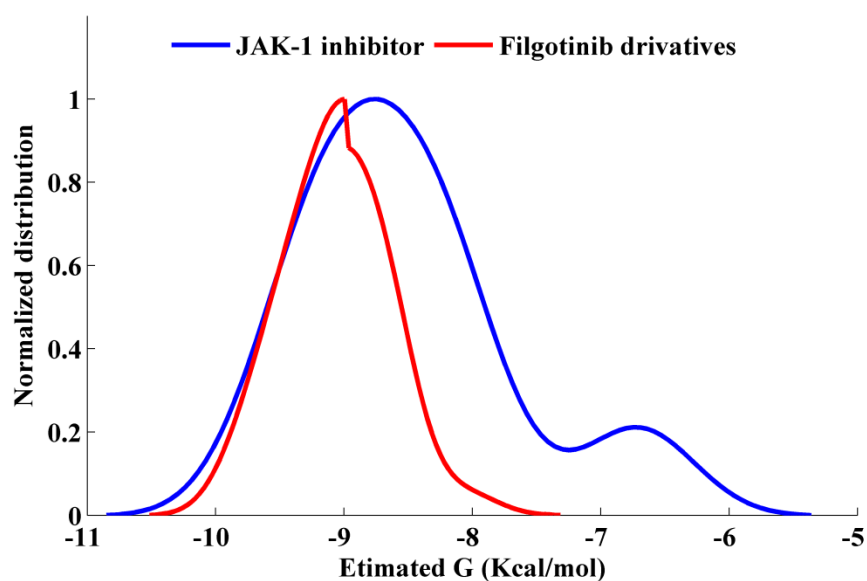
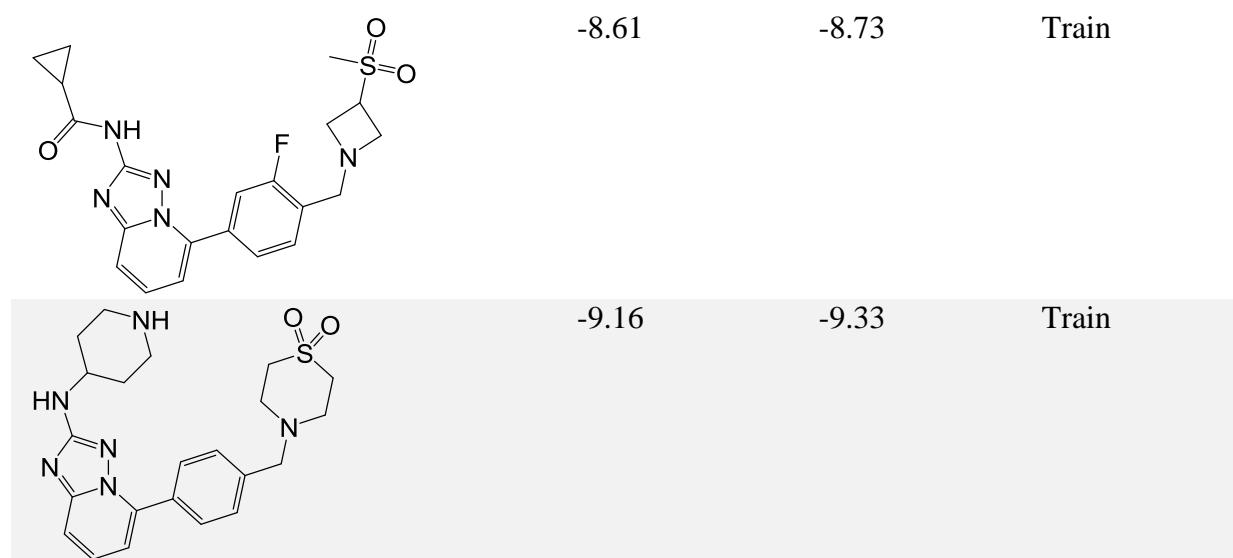


Figure 2. Estimated  $\Delta G$  distribution filgotinib derivatives (red) and JAK-1 inhibitors drug (blue)

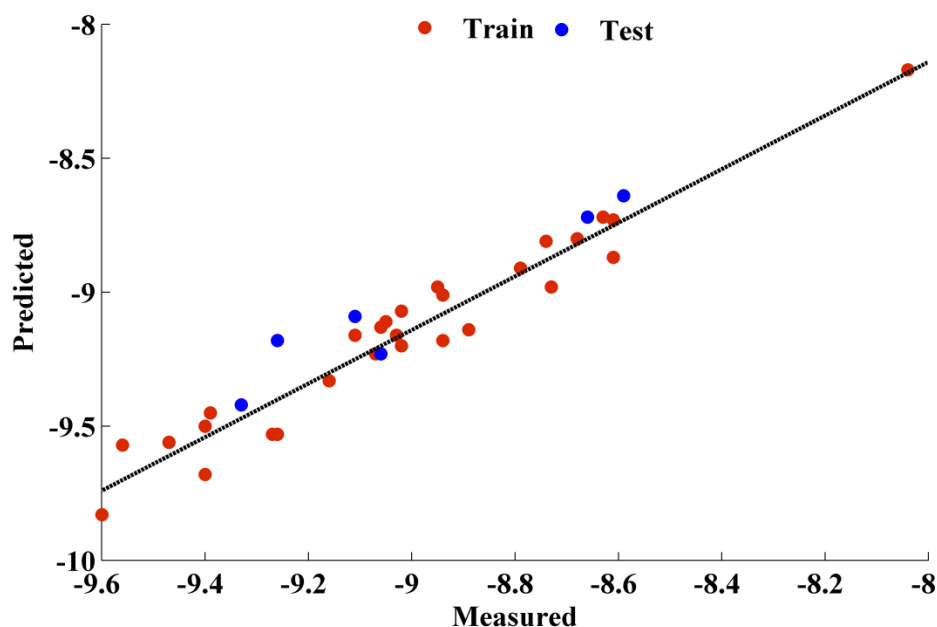


Figure 3. Measured and predicted results obtained from QSAR study

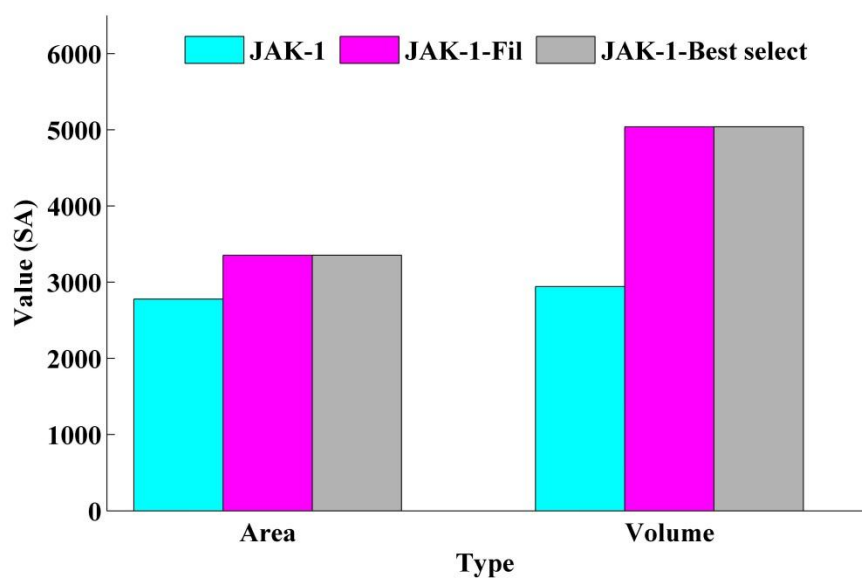


Figure 4. Comparison of the area and volume for filgotinib-JAK-1 (pink) and Best selected-JAK-1 (grey) complexes with JAK-1 (cyan)

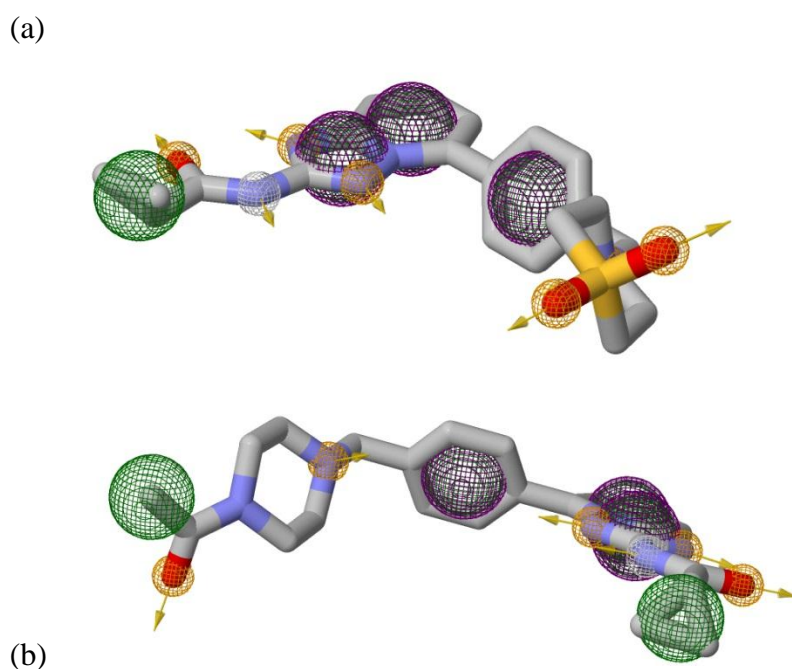


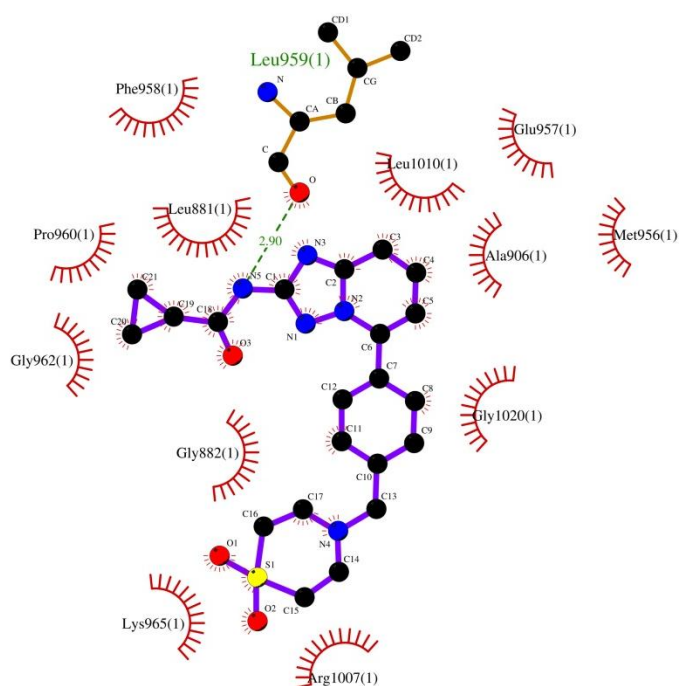
Figure 5. Pharmacophore study of (a) filgotinib and (b) best selected

Table 3. Results obtained from pharmacophore study of filgotinib and best selected

Bonding Type	Filgotinib				C <sub>23</sub> H <sub>26</sub> N <sub>6</sub> O <sub>2</sub>			
Pharmacophore	x	y	z	Radius	x	y	z	Radius
Aromatic	3.4	2.56	-0.38	1.1	2.9	-2.71	0.3	1.1
Aromatic	-0.83	2.25	0.24	1.1	-1.3	-2.04	-0.23	1.1
Aromatic	3.63	0.5	-0.03	1.1	3.29	-0.67	0	1.1
HydrogenAcceptor	-4.14	0.64	0.59	0.5	3.75	1.72	-0.34	0.5
HydrogenAcceptor	2.54	0.05	0.18	0.5	-4.49	-0.17	-0.48	0.5
HydrogenAcceptor	4.79	0.25	-0.13	0.5	2.23	-0.12	-0.19	0.5
HydrogenAcceptor	6.24	-2.21	0.13	0.5	4.47	-0.51	0.08	0.5
HydrogenAcceptor	-7.26	-2.26	-1.87	0.5	6.1	1.84	-0.14	0.5

<b>HydrogenDonor</b>	3.91	-1.9	0.36	0.5	-6.09	3.74	0.28	0.5
<b>Hydrophobic</b>	3.4	2.56	-0.38	1	-7.28	1.7	1.15	0.5
<b>Hydrophobic</b>	-0.83	2.25	0.24	1	2.9	-2.71	0.3	1
<b>Hydrophobic</b>	3.63	0.5	-0.03	1	-1.3	-2.04	-0.23	1
<b>Hydrophobic</b>	-7.85	-2.99	0.3	1	3.29	-0.67	0	1
<b>Hydrophobic</b>	4.8	-4.7	0.01	1	4.86	4.43	0.06	1

(a)



(b)

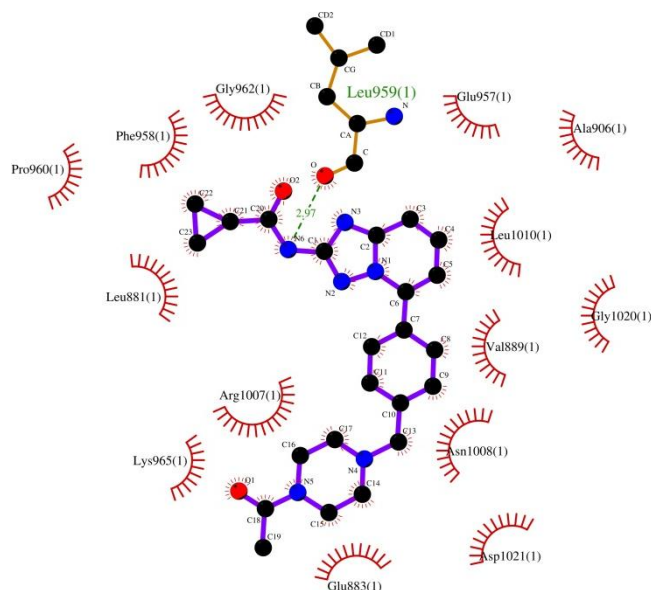
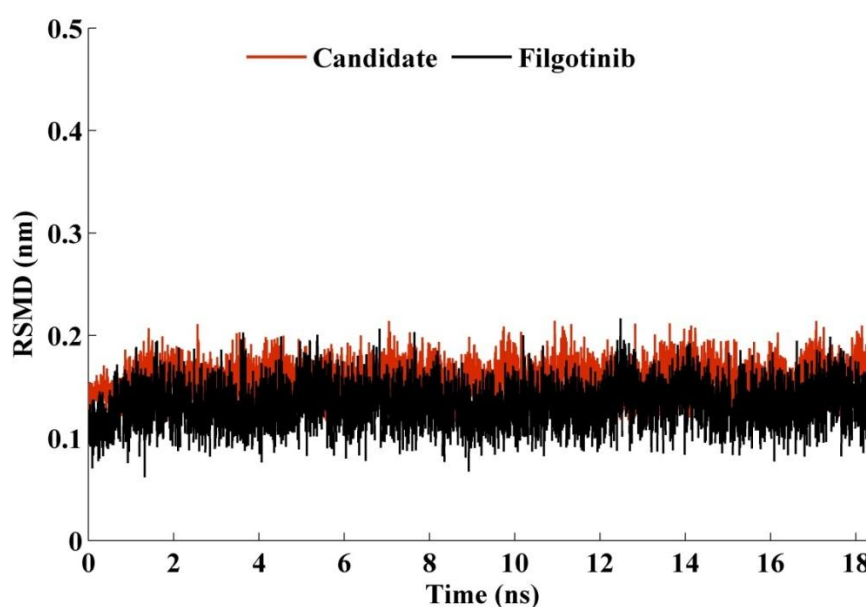


Figure 6. 2D interaction of (a) filgotinib-JAK-1 and (b) best selected-JAK-1

The molecular dynamics studies of Root mean square deviation (RMSD), Root means, and Radius of gyration values are

shown in Figure 8. The RMSD results, after 1.8 ns, the structure reached stability where the mean values for entry five were 0.37 nm. The RSMF results of these compounds represent less fluctuation with the average values of 0.34 nm.

(a)



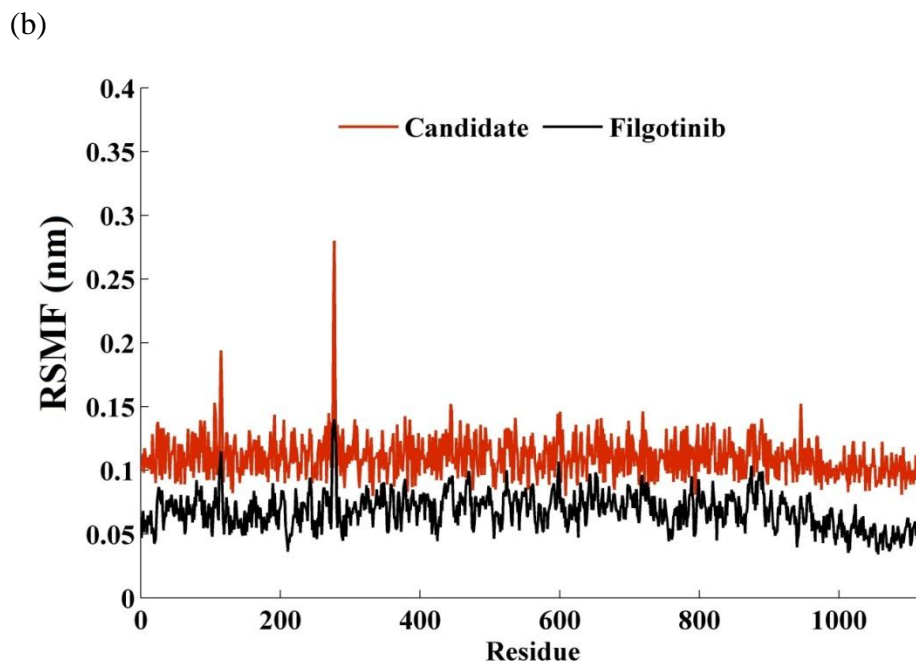


Figure 8. (a) Root mean square deviation (RMSD), (b) Root mean square fluctuation (RMSF) values for Entry 5



Table 4. Comparison of hydrogen and hydrophobic bond obtained from filgotinib-JAK-1 and best selected-JAK-1 interaction

Drug	Hydrogen Bond	Hydrophobic Bond
Filgotinib	Leu959	Leu881, Gly882, Pro960, Gly962, Lys965, Phe958, Ala906, Met956, Gly1020, Glu957, Leu1010
C <sub>23</sub> H <sub>26</sub> N <sub>6</sub> O <sub>2</sub>	Leu959	Leu881, Phe958, Pro960, Gly962, Lys965, Arg1007, Glu883, Asp1021, Asn1008, Val889, Gly1020, Leu1010, Ala906, Glu957

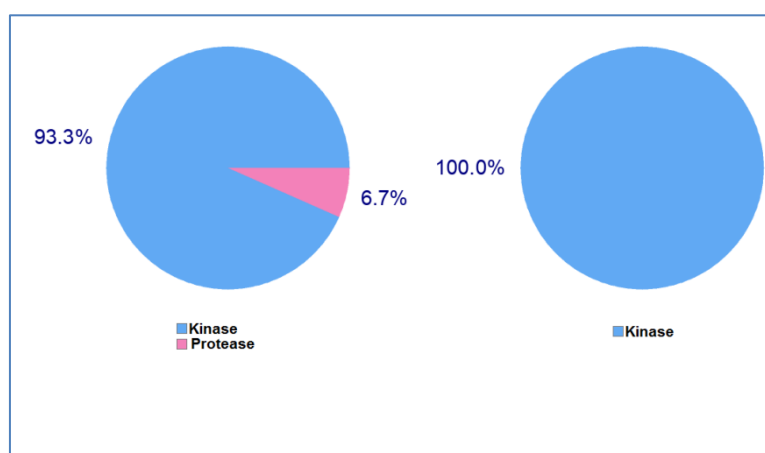


Figure 7. Target analysis of best selected (left) and filgotinib (right)

Table 5. ADME study of best selected and filgotinib

Pharmacokinetics			Druglikeness		
Parameter	Filgotinib	best selected	Parameter	Filgotinib	best selected
GI absorption	High	High	Lipinski	Yes	Yes
BBB permeant	No	No	Ghose	Yes	Yes
P-GP substrate	Yes	Yes	Veber	Yes	Yes
CYP1A2 inhibitor	No	No	Egan	Yes	Yes
CYP2C19 inhibitor	No	No	Muegge	Yes	Yes
CYP2C9 inhibitor	Yes	Yes	Bioavailability Score	0.55	0.55
CYP2D6 inhibitor	Yes	No			
CYP3A4 inhibitor	Yes	Yes			
Log Kp (skin permeation)	-7.80 cm/s	-7.93 cm/s			

Filgotinib and its derivatives were also screened via docking and QSAR; a concept of "multi compounds-multi proteins" interaction, although the present screening focused on identifying the lead hit molecules against COVID-19. In addition, the outcome of this study was based on knowledge-based regressions. Conversely, during COVID-19 infection, the dysregulated immune system may play an essential role in spreading COVID-19 virus into the host system; the main concept of this study is that it could be maintained via the JAK-STAT signaling pathway. Furthermore, identifying homologous proteins may also play a critical role in identifying new drug molecules that inspired our in-silico studies of targets based on the amino acid sequences of individual proteins. (22)

### Conclusion

Due to the lack of a definitive drug to treat COVID-19, Selective inhibition of JAK-1 is one of the suggested treatments. The obtained results from this study suggest new alternatives to treat JAK1 kinase that may reduce livery pathology, blocks both the human immune phenotype and related cytokine wind. These results have possible far-reaching importance to treat COVID-19. Still, need supports a more in-depth study on JAK-1 inhibits as the mechanism for therapeutic prevention of a cytokine storm and the downstream organ failure under this situation.

### Compliance with ethical guidelines

The authors have no financial or non-financial conflict of interest to declare. For this article, no studies with human participants or animals were performed by

any of the authors. All studies conducted were under the ethical standards indicated in each case.

### Conflict of interest

The authors declares that he has no conflict of interest.

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### Author contribution

Conception or design of the work: Hamidreza Pazoki-Toroudi

Data collection: Ali Aghajani Shahrivar

Data analysis and interpretation. Hazha Omar Othman, Hamidreza Pazoki-Toroudi

Drafting the article. Bahareh Farasati Far, Mehdi Shafiee Ardestani

Critical revision of the article. Bahareh Farasati Far

Final approval of the version to be published. Bahareh Farasati Far, Hamidreza Pazoki-Toroudi

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