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Crystal Oximes vs. JAKs Alternative Cancer Therapies: an *in silico* study

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Abstract: A main challenge in health is the development of selective treatments against cancer related to a wide variety of proteins, where Janus kinases are a family of proteins of interest involved in cell growth, differentiation, and proliferation. Molecular docking is a very useful tool in drug design, allowing the evaluation of the potential for interaction between protein and ligands studied whose activity can be used in diseases related to the target but limited at obtention by synthesis; alternatives can be the use of crystal database with molecules previously synthesized. In this work, energetic and interactional analysis were determined to predict the potential activity as a specific or combined JAKs inhibitor (JAK1, JAK2, JAK3) from a database of 3928 crystalized oximes obtained from Cambridge Structural Database to evaluate them through molecular docking with Schrödinger Suite. 362 oximes exceeded commercial inhibitors' reference binding coupling energy, showing selective, dual and/or PanJak activity. ICENAF oxime is presented as a potential selective inhibitor of JAK3, which is important for future evaluations since this enzyme lacks a specific inhibitor. The potential use as administered drugs was supported by the ADMET analysis, which showed that the oximes selected for each case meet the criteria of bioavailability.

Keywords: Molecular docking; ADMETx; Oximes; JAK Inhibitors; Cancer.

1. Introduction

Oximes are organic compounds with the general structure R1, R2-C=N-OH, where R1 and R2 could be an alkyl, aryl group, or hydrogen. These molecules are obtained by condensation between hydroxylamine and aldehyde or ketone. At present, the synthesis of many oximes has been reported [1–5], and a kind of classification of these is related to the substituents (R1 and R2). Some representative compounds were observed in Figure 1. The continuous search for new oximes synthesis is encouraged due to the great and various biological activity that these presents as antioxidant, antimicrobial, antiinflammatory, and antitumor activity [6–10].

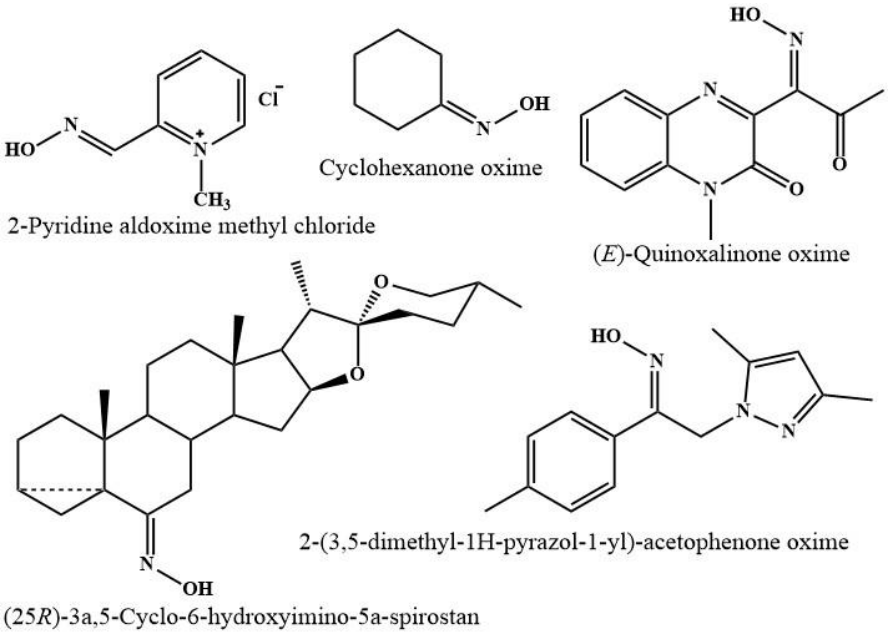

Figure 1. Representative oximes at present.

In the development of antitumoral drugs is important to know the activation pathway of the cancer to treat. One of great importance is the inhibition of Janus Kinases, but these are not widely studied [11–13]. Janus Kinases (JAK1, JAK2, JAK3) belongs to the family of non-receptor tyrosine kinases that catalyze the transfer of phosphate from ATP to tyrosine residues in proteins with essential roles in cell growth, differentiation, and proliferation. When activated, they phosphorylate signal transducers and activators of transcription (STATS) that translocate to the nucleus and induce transcription of proteins related in immunosuppressive networks that enhance tumor survival and converge on multiple oncogenic signaling pathways involving the combination of four JAK isoforms (JAK1, JAK2, JAK3), more than 50 cytokines binding to their receptors and seven STAT proteins exerting their effects on the cell [9–14].

Table 1. Diseases and related JAK enzymes.

Disease	Type	JAK1	JAK2	JAK3	References
Polycythemia vera	N		⊗		[15]
Acute myeloid leukemia	N	⊗	⊗		[16]
Acute lymphoblastic leukemia	N		⊗	⊗	[17,18]
Prostate cancer	N		⊗		[19]
Rheumatoid arthritis	A	⊗	⊗		[20]
Psoriasis	A	⊗	⊗		[21]
Bladder cancer	N	⊗	⊗		[22]
Breast cancer	N	⊗			[23]
Colorectal cancer	N	⊗	⊗		[24]
Ankylosing spondylitis	A	⊗		⊗	[25]
Atopic dermatitis	I	⊗	⊗		[26,27]
Lung cancer	N	⊗	⊗		[28,29]
Myelofibrosis	N		⊗		[30]
Hepatocellular carcinoma	N		⊗		[31]
T-Cell Lymphoma	N		⊗		[32]

N: Neoplasm, A: Autoimmune, I: Inflammatory

Current JAK inhibitors are called type I kinase inhibitors (JAKi), and they bind to the active conformation site of the enzyme and block the ATP binding pocket in the catalytic domain; currently, only 5 drugs are approved for treating autoimmune diseases. This sort of

inhibitor has different affinities to JAK due to high structural conservation amongst them [33]. Ruxolitinib is the first JAKi FDA-approved against JAK1 and JAK2 for the treatment of neoplasms like primary myelofibrosis, polycythemia vera, and essential thrombocythaemia and recently against COVID-19 [34,35]. Tofacitinib, approved in 2012 as a potent and selective JAKi that inhibits preferentially JAK1 and JAK3, is indicated for the treatment of moderate to severe rheumatoid arthritis (RA) and lately approved for the treatment of psoriatic arthritis, ulcerative colitis and ankylosing spondylitis [36–38]. Baricitinib, a JAK1 and JAK2 inhibitor, is also indicated in the treatment of RA and recently for severe alopecia areata and COVID-19 [39–41]. Fedranitib, a selective JAK2 inhibitor, is indicated for treating high-risk myelofibrosis [42]. Upadacitinib, a selective JAK1 inhibitor, was first approved for the treatment of RA, and like tofacitinib, got recent approval for psoriatic arthritis, atopic dermatitis, ulcerative colitis, and ankylosing spondylitis [43–45] Only these 5 inhibitors have been approved; nevertheless all of them presents black-box warnings due to their serious safety risks like heart-related events, cancer, blood clots and increased risk of death [46].

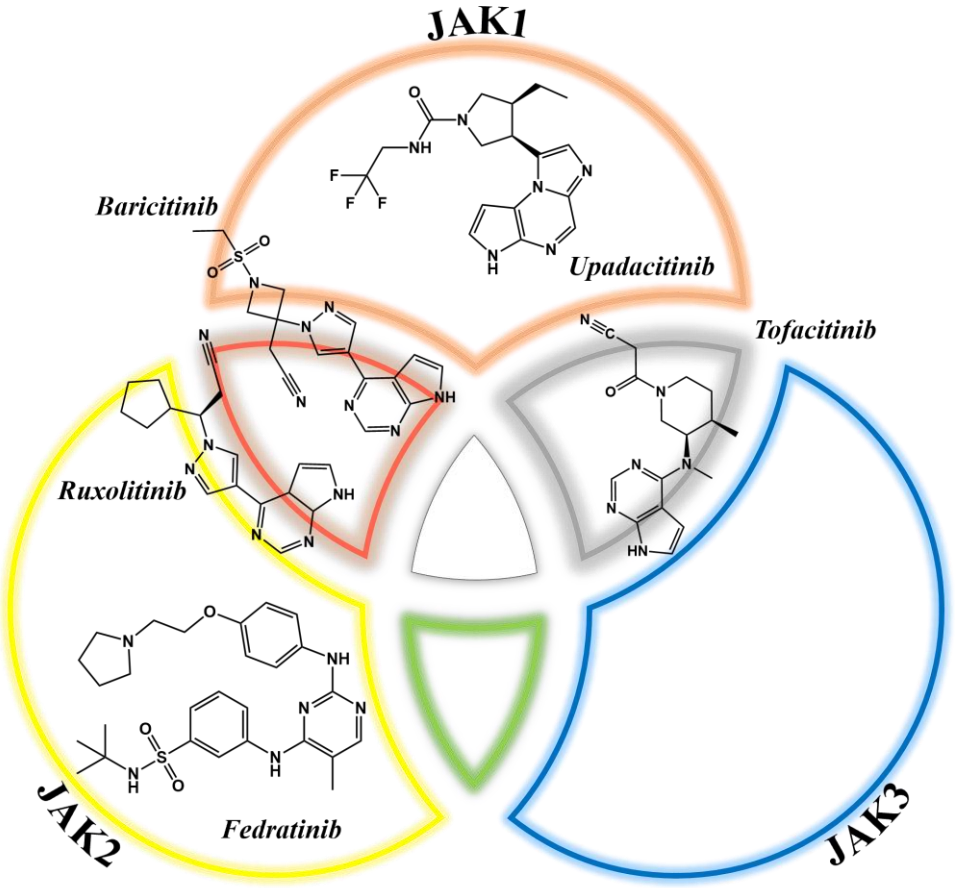

Figure 2. Commercial inhibitors of JAKs and their selectivity.

2. Materials and Methods

2.1. Ligand acquisition and preparation.

The drug references obtained for DrugBank: ruxolitinib (DB08877), tofacitinib (DB08895), baricitinib (DB11817), fedranitib (DB12500), Upadacitinib (DB15091) [47]. The crystal oximes were obtained in the Cambridge Structural Database [48] using an oxime group by filter in ConQuest and Mercury software [49,50]. All ligands were prepared in LigPrep [51] at physiological conditions with protocol previously reported [52].

2.2. Protein preparation.

All JAKs were obtained from RSCB PDB with identification codes for JAK1 (4EHZ), JAK2 (3KRR), and JAK3 (1YVJ) [53–55] (Fig.2). They were prepared in the protein preparation wizard of Schrödinger [51] at pH 7.4 [52].

2.3. Molecular docking and ADMET.

Drug references and oxime crystals were docked with glide with a protocol previously reported [51,52]**.** The redocking was realized with a co-crystal in each protein and obtained, in all cases, a RMSD < 1.0 Å. ADMET properties for Lipinski's Rule of Five were predicted using the Schrödinger QikProp module [56]**.**

3. Results and Discussion

The binding coupling energy (BCE) presented between each JAK and commercial inhibitors (Table 2) allows the establishment of energy levels necessary for the design of new inhibitors, as well as explaining the dual inhibitors or PanJak inhibitors (tri-JAK inhibitors), such as the case of Baricitinib and Ruxolitinib, which are inhibitors of JAK1, but also of JAK2 who is inhibited by Fedratinib specifically, agreeing that Fedratinib and Baricitinib have lower energy than Tofacitinib, an inhibitor of JAK3, with this, Baricitinib, Fedretanib and Tofacitinib of JAK1, JAK2, and JAK3, respectively, were established as the limit of inhibition, as well as these energy values for determining multiple inhibition effects according to the oxime studied.

Table 2. Reference binding coupling energies of approved JAKi.

Inhibitor	JAK1	JAK2	JAK3
Ruxolitinib	-7.773	-6.153	-7.756
Baricitinib	**-7.344**	-7.491	-8.966
Upadacitinib	-9.188	-8.065	-8.827
Tofacitinib	-8.521	-6.075	**-7.785**
Fedretanib	-3.988	**-5.344**	-8.114

When analyzing the evaluation with the entire database of previously prepared oxime crystals, several inhibition groups were obtained. As selective inhibitors for each JAK or with dual activity where 20 of the total crystal oximes present this characteristic, 3 against JAK1-2, 1 against JAK1-3, and 16 for JAK2-3; while 2 molecules of the total database resulted PanJak inhibitors, demonstrating the potential of this functional group against the activity of these enzymes.

3.1. Selective inhibitors.

Depending on the pathology studied, the desired inhibition of a JAK can be single or multiple, as discussed in Table 1, there is somewhere a completely selective inhibition is sought not to alter other metabolic processes and generate adverse effects outside the treatment of the chosen pathology. The best oxime for each JAK was selected (Figure 3), as confirmed by the interactional and energetic analysis of the possible interaction in the active site. For JAK1, a single oxime with the possibility of selective effect was found ,which can highlight a hydrogen bond between α, β unsaturated ketone, and LEU 959, which is an interaction residue in its reference (Upadacitinib). In general, the hydrophobic interactions were the most prevalent for this oxime.

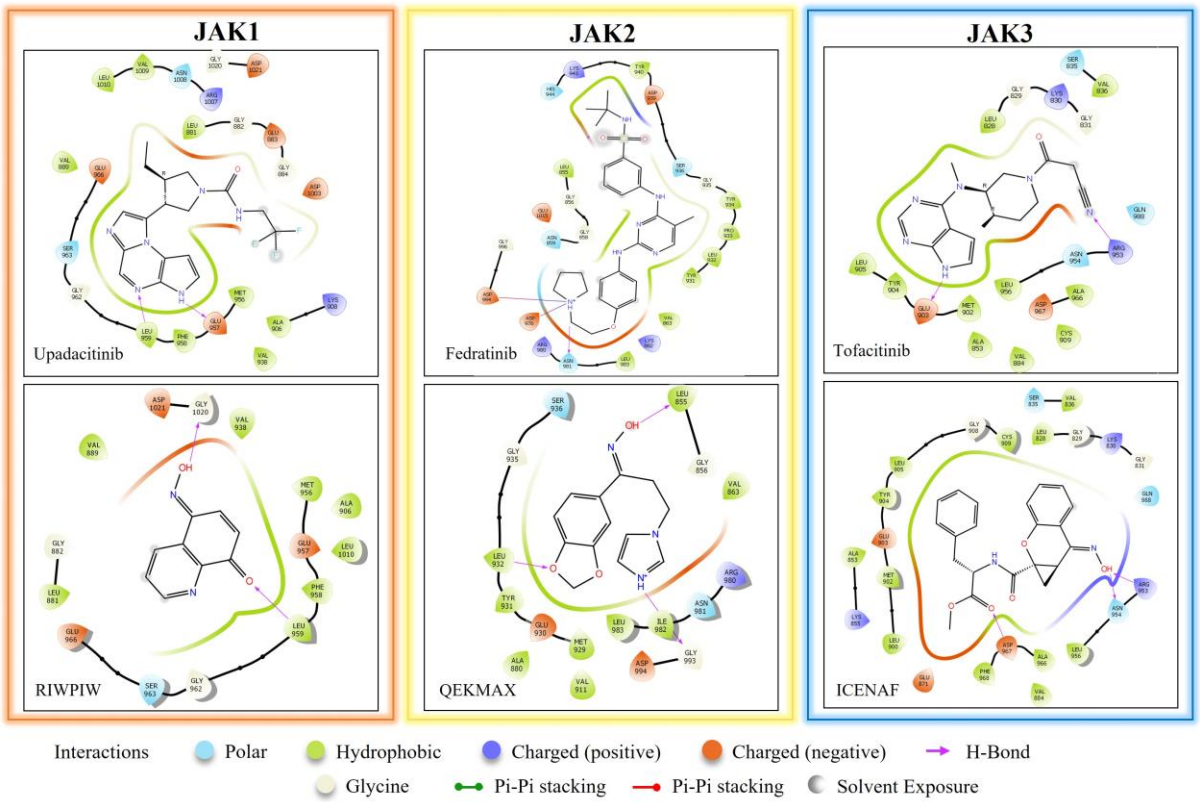

Figure 3. 2D interaction diagrams for the best molecules in JAKs.

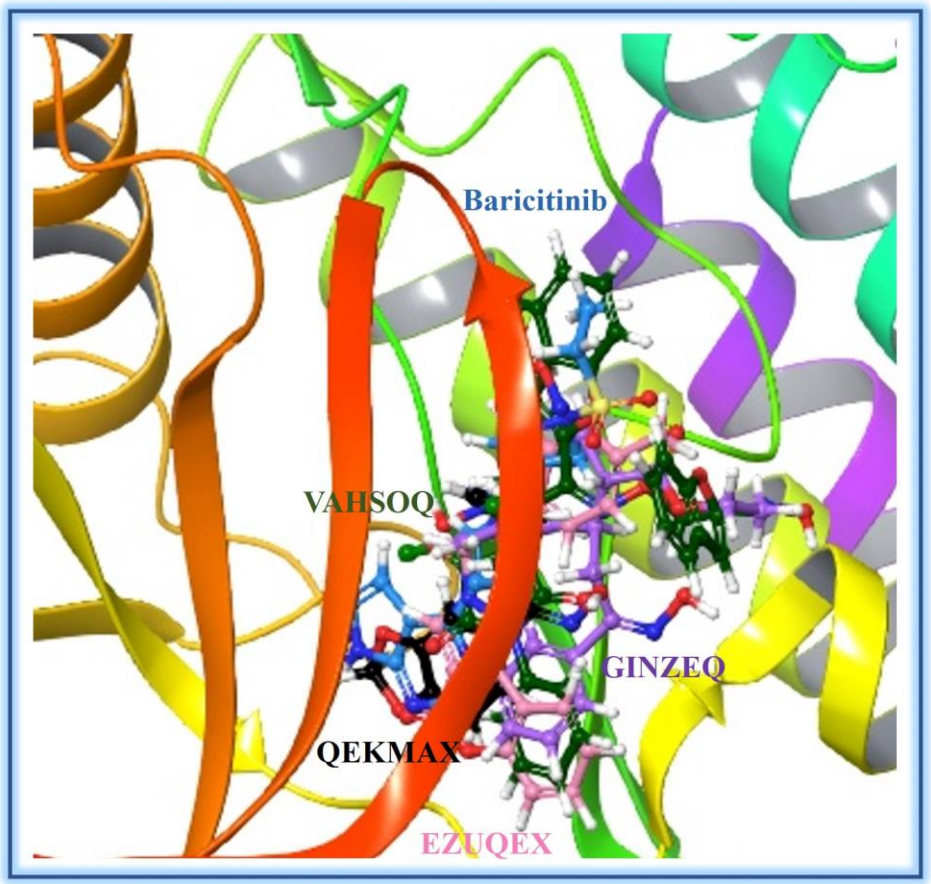

Figure 4. 3D interaction for JAK2-specific inhibitor oximes.

Something similar occurs for JAK3, which presents only one selected inhibitor. In this case, three hydrogen bonds were predicted, two between the oxime and the residues ASN 954

and ARG 953. Even though this oxime does not share important residues with its reference, it was confirmed its interaction in the active site with the other amino acids. The absence of repeatability of key interactions is attributed to the large size of the reference molecule, thus including a greater number of residues and leaving the interactions in the extreme zones. Due to its small size, the oxime is placed in the center of the active site of Fedratinib, leaving the interaction zones by hydrogen bond out of its reach.

In the case of JAK2, this presents a big number of oximes with the minimum energy for inhibition, in the next phase to select the best candidates, the Lipinski criteria were used, reducing it to 302 oximes; for a more specific selection, an energetic comparison between the BCEs of a commercial inhibitor and oximes was realized, in Table 2 the energies of interaction was present, Upadacitinib is the best, nevertheless, this is not reported like JAK2 inhibitor, for that reason the energy reference used was of Baricitinib, and 4 molecules were highlighted with better energy and securing the interaction in the active site (Figure 4).

3.2. Dual inhibitors.

3.2.1. JAK1-JAK2.

Three oximes can present a dual inhibition for JAK1 and JAK2. Analyzing each one with the JAKs, there is a big difference between the BCE, but in the analysis of each oxime with both JAKs, the BCE is closer, and the inhibition site was the same, the most relevant interactions, hydrogen bonds formed between GLU 966 and the oxime group and another one between GLY 1020 and an amino group for the oxime with better energy with JAK1, the first residue is present in the second oxime interactions with the oxime too, and glycine interaction is formed with the oxime group for the one with worse energy. In the case of interactions with JAK2, the inhibition site is the same for three oximes, and the residue SER 936 is key in binding (Table 3). Considering inhibitor references, the previously described oximes exceed the BCE of Fedretanib with JAK2 and Baricitinib with JAK1 but not with JAK2. Despite not exceeding the energy for the dual reference in JAK2, this probability increases since it exceeds the minimum energy for its specific inhibitor.

Table 3. Key amino acid residues for hydrogen bonding in dual inhibitors against JAK1-JAK2.

Reference drug/Oxime	JAK1	JAK2
Baricitinib BCE_{JAK1}= -7.344 kcal/mol BCE_{JAK2}= -7.491 kcal/mol	ARG 1007 GLU 957	LYS 857 ARG 980 LEU 932 GLU 930
Fedretanib BCE_{JAK2}= -5.344 kcal/mol	No inhibitor	ASN 981
JIJHUI BCE_{JAK1}= -8.339 kcal/mol BCE_{JAK2}= -7.073 kcal/mol	GLU 966 GLY 1020	SER 936
HAKJUA BCE_{JAK1}= -7.45 kcal/mol BCE_{JAK2}= -5.797 kcal/mol	GLU 996 PHE 886 HIS 885 LYS 908 ARG 1007	SER 936 ASP 976 ASN 981
GAVWOT BCE_{JAK1}= -7.431 kcal/mol BCE_{JAK2}= -5.779 kcal/mol	GLY 1020 LEU 959	SER 936 ASP 939

Interaction type: Positive charged, Negative charged, Hydrophobic, Glycine, Polar

3.2.2. JAK1-JAK3.

A dual inhibitor for JAK1 and JAK3 was predicted with just one oxime, RIGTEG, their BCE is very close between them, and the value of Tofacitinib with JAK3 is exceeded but not for JAK1. However, when analyzing the interactions, the prediction of hydrogen bonds was observed with ARG 1007 and LEU 959 in oxime and in reference for JAK1 (Figure 5). Specifically for the interactions with JAK3, we see that the energy of the RIGTEG exceeds that of the reference, it is found in the same place and without coincidence with its relevant residues (ARG 953 and GLU 903) with what could be considered as one of the best candidates as a dual inhibitor.

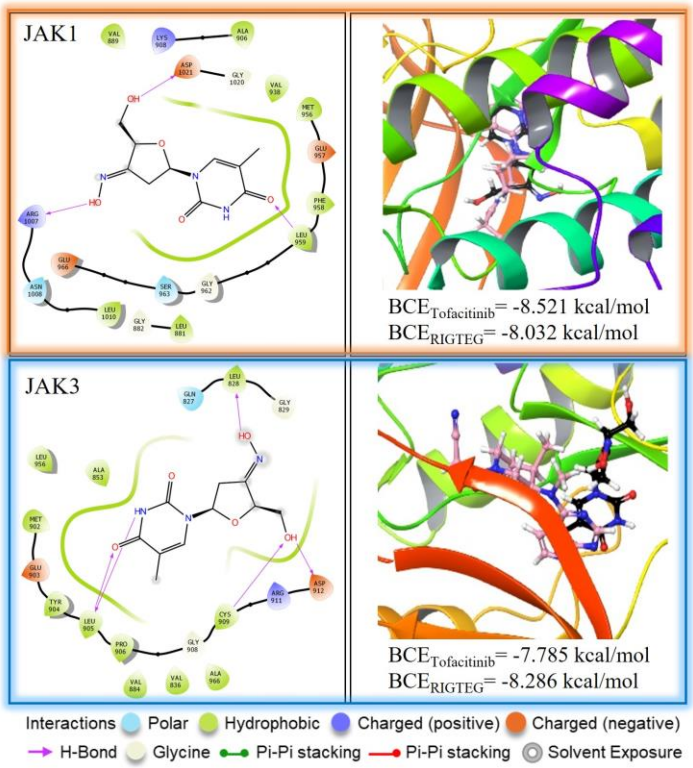

Figure 5. Dual inhibitor oxime for JAK1-JAK3

3.2.3. JAK2-JAK3.

From the first analysis, 16 oximes were found as dual inhibitors of JAK2-JAK3; using the Lipinski criteria, one of them was eliminated; in order to carry out a detailed study, the coupling energies of the commercial inhibitor with the best energy were taken into account for the case of JAK2 (Baricitinib) and thus improve the possibilities of activity, for JAK3 Tofacitinib was used since it is the only reference for this, with this consideration the list was reduced to only 2 oximes. Evaluating the active site of the references used, it was found that both oximes meet this requirement in terms of the most relevant interactions, hydrogen bonds; they coincide with their references, and the oxime that presents the best energy with JAK2 shares the interaction with ARG 980, the oxime with the best energy with JAK3, coincide in LEU 932, and between them there is in common the interaction with LEU 905 in the oxime group.

3.2.4 PanJAK.

Two PanJAK oximes were identified from the database due to the theoretical multifunctionality that they show, and the interest arises in determining what the interactions

in common that they present between them and with the reference inhibitors, which in this case will be different for each one due to the ECBs they present are. To compare the interaction with JAK1, the energy of the first oxime does not exceed that of the selective inhibitor Upadacitinib, but if that of Ruxolitinib, the second oxime does not exceed it either, it does exceed Baricitinib, so the comparison is at this value. With respect to JAK2, oxime 1 exceeds the ECB of the inhibitor with the best coupling, Baricitinib, the opposite case for oxime 2 whose reference was Ruxolitinib, and finally, in the case of JAK3, both oximes have energies higher than those of Tofacitinib, once the interaction is assured of both oximes at the site of their respective references in each enzyme, a comparison of the interaction residues was made, of which LEU 932 and GLU 930 stand out in JAK2, the hydrogen bond interactions that are predicted with the oxime group of the molecules is condensed in Table 4.

Table 4. Key amino acid interactions as an oxime inhibitor.

Inhibition type	JAK1	JAK2	JAK3
JAK1-JAK2	GLU 966 GLY 1020 PHE 886 HIS 885	SER 936 ASP 976	NI
JAK1-JAK3	ARG 1007	NI	LEU 828
JAK2-JAK3	NI	LEU 855 GLY 993 ASN 981 SER 936 ASP 939	ASN 954 ARG 953 ASP 912 ASP 967
PanJak	LEU 881 GLU 966	LEU 855	LEU 828

Interaction type: Positive charged, Negatively charged, Hydrophobic, Glycine, Polar

4.1. ADMET analysis.

Oral administration is, by far, the most preferred route for drug administration due to its good tolerability and ease of dose. For that, optimum intestinal absorption is a pivotal criterion to be considered, and Lipinski's rule of five indicates related absorption properties such as lipophilicity (Log P), Molecular Weight (MW), polar surface area (PSA), number of hydrogen bond acceptors (HBA) and number of hydrogen bond donors (HBD).

The best oximes for each JAK presented favorable predicted properties, indicating their potential to be well absorbed. All compounds have a molecular weight that does not surpass the limit of 500 g/mol, indicating an easier transport, and PSA of the molecules is in the range of well bioavailability for drug molecules as for LogP, HBD, and HBA for a relevant rate of potential intestinal absorption.

Table 5. Lipinski's criteria of selected oxime inhibitors.

Criteria	LogP	MW	PSA	HBD	HBA	Specificity
Molecule	<5	<500 g/mol	<140 Å	<5	<10	
RIWPIW	0.86	225.04	63.08	1	4.2	JAK1
QEKMAX	1.82	213.24	52.3	1	4.7	JAK2
ICENAF	-0.31	162.15	85.17	2	4.9	JAK3
JIJHUI	-0.39	193.16	96.38	1	6.1	JAK1-JAK2
HAKJUA	5.50	414.34	56.50	3	2.7	JAK1-2
GAVWOT	4.26	416.52	70.42	2	5.7	JAK1-2

Criteria	LogP	MW	PSA	HBD	HBA	Specificity
Molecule	<5	<500 g/mol	<140 Å	<5	<10	
RIGTEG	3.06	324.42	54.22	1	6.2	JAK1-3
NIVZUP	0.44	279.68	95.49	0	7.7	JAK2-3
ENUFUR	2.00	387.43	92.13	2	11.2	PanJAK
TUNQAU	3.25	377.52	81.13	2	6.4	PanJAK

For dual inhibitors, HAKJUA presented a higher LogP than the recommended, compromising its bioavailability with high chances of being sequestered in fatty tissue and reducing its plasma levels. ENUFUR also presents a violation of Lipinski's rule of five with 11.2 hydrogen bond acceptors, 1.2 higher than the optimal; this represents a potential reduction in the permeability of the oxime into cell membranes by favorable interactions with classical hydrogen bonding solvents like water.

4. Conclusion

Hydrogen bond resulted as key interaction type for oximes with each evaluated JAK where the bond was generated principally between the hydroxyl group from oximes and glutamate, serine, leucine, and aspartate residues; many oximes showed potential inhibition activity in JAKs, specifically some selected as candidates for treatment that require the selective inhibition of JAK1, JAK2 and/or JAK3. When it is necessary for the triple inhibition of the JAKs, the use of oxime with code TUNQAU was promising; it is required, the inhibition of JAK2 and JAK3, the use of oximes with code NIVZUP and XADJET showed great potential, and when treatment with greater selectivity is required, such as the inhibition of only JAK3, the oxime with code ICENAF is a great field of research since this enzyme is the only one that does not present a selectivity report.

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Conflicts of Interest

The authors declare no conflict of interest.

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