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In Silico Docking of Imidazopyridinyl Acrylonitrile Derivatives to Identify Potential SARS-Cov-2 Inhibitors

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Abstract

The infectious disease caused by COVID-19 was caused by a strain of coronavirus (SARS-CoV-2). It was declared a pandemic in March 2020, leading to 777 millions million cases and 7 millions deaths worldwide. The main protease (MPro) of SARS-CoV-2, a key protease of the virus, mediates viral replication and transcription. SARS-CoV-2 MPro has proven to be an important target for the design and development of drugs against SARS-CoV-2. The aim of this study is to propose a new chemical profile that could be used as an alternative in case of a coronavirus crisis. A literature review revealed that structure-activity relationship studies of MPro protease inhibitors helped identify the key structural features necessary for binding to SARS-CoV-2 MPro through interactions. Based on this, we proposed a series of imidazopyridinyl-acrylonitriles as potential inhibitors of SARS-CoV-2 MPro. Molecular docking studies were conducted on the MPro protein (PDB ID: 5R81) using Schrödinger software. Finally, ADME prediction was used to explore the pharmacokinetic properties. The results of the docking studies showed that imidazopyridinyl acrylonitrile derivatives with a chlorine atom at position 6 showed the best affinities for the target MPro protein (PDB ID: 5R81) and demonstrated favorable ADME characteristics. Furthermore, the trans configuration of the molecules, pi-pi interactions with the nitrogen heterocycle, hydrogen bonding with the pyridinic nitrogen of the imidazopyridine core, and hydrophobic interactions between the chlorine atom and threonine would promote the inhibitory activity of acrylonitrile hybrids on MPro. 6-Chloro-imidazopyridinylacrylonitriles have proven to be promising agents as inhibitors of SARS-CoV-2 MPro, showing significant interactions compared to N-methylpiperazine derivatives.

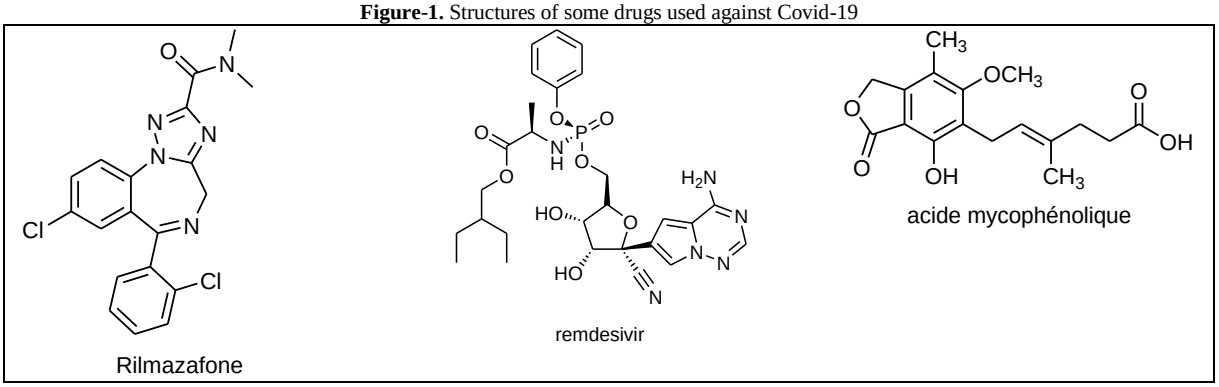
Keywords: Imidazopyridine ; Acrylonitrile ; SARS-CoV-2 MPro ; COVID-19 ; Coronavirus.

1. Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has had a major global impact between 2019 and 2023, with more than 777 million confirmed cases and 7 millions deaths worldwide [1]. Despite the progress made through vaccination programs, their variable efficacy and the emergence of new virus variants continue to pose serious challenges. This situation highlights the urgent need to develop new antiviral drugs, including through innovative strategic approaches such as *in silico* research, which allows the rapid identification of promising molecules.

To address this challenge, two main approaches are used. The first is drug repurposing, an effective strategy to identify drug candidates with a shorter clinical trial cycle. Drugs already in development or prescribed off-label for COVID-19 include mycophenolic acid, lopinavir, itacitinib, rilmazafone, and remdesivir [2-4]. Among these, hydroxychloroquine, an approved antimalarial drug, as well as two known antivirals, ritonavir and remdesivir, have been shown to be effective against SARS-CoV-2 *in vitro* [5]. However, recent studies have reported harmful side effects of chloroquine and hydroxychloroquine. These drugs can inhibit autophagy, inducing tissue injury and worsening organ damage in COVID-19 patients [6] (Figure 1).

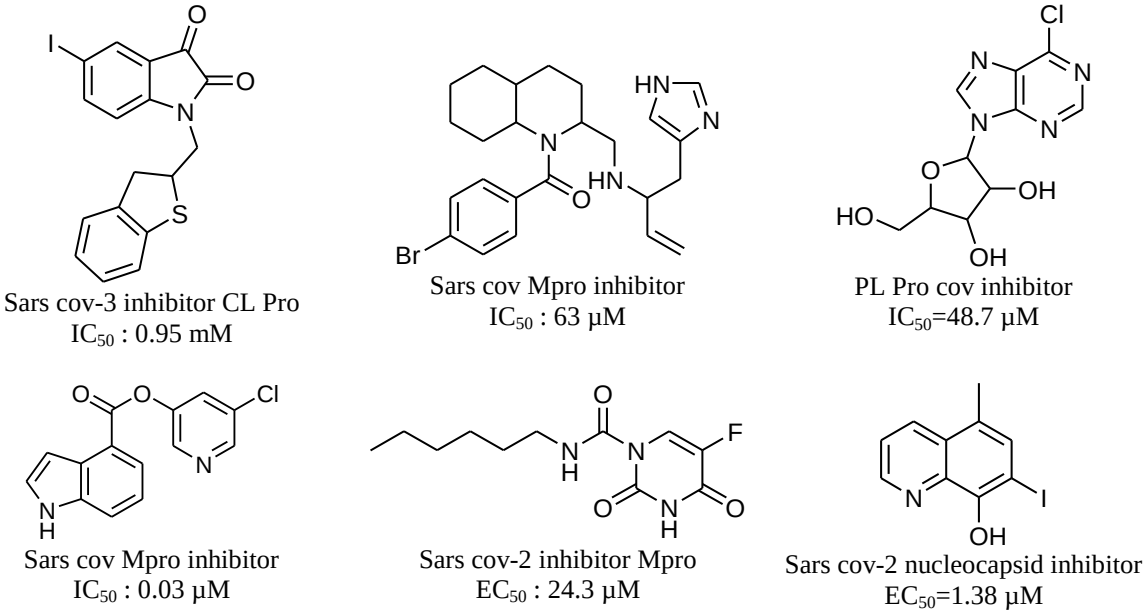
Figure-1. Structures of some drugs used against Covid-19



As a result, thanks to this strategy, the 2 drugs used to date in the management of COVID-19 are the combination nirmatrelvir/ritonavir (PAXLOVID), recommended as first-line treatment in adults at risk of developing a severe form, and remdesivir (VEKLURY) used in case of contraindication to the use of PAXLOVID [7, 8].

In a second approach, a large number of computer studies have been conducted to reuse existing drugs against COVID-19. These investigations have targeted various viral and cellular proteins, such as the host cell protease TMPRSS2 [9, 10], envelope (E) protein and ion channel [11], as well as immune evasion molecules such as 20-O-ribosemethyltransferase [12], nucleocapsid protein [13] and RNA-dependent RNA polymerase (RdRp) [14]. These *in silico* approaches have identified several promising candidates against the virus. In addition, heterocyclic compounds have attracted increasing interest due to their involvement in the treatment of diseases such as viral infections and cancer. Numerous studies have demonstrated that some halogenated heterocyclic derivatives possess variable efficacy against viruses of the genus Coronavirus, including SARS-CoV and SARS-CoV-2 [15] (Figure 2).

Figure-2. Some heterocyclic compounds with anti-coronavirus activity



These compounds are widely recognized in the field of medicinal chemistry for their efficient binding capacity to biological targets. For example, a recent study showed that halogenated thieno[2,3-*g*]chromene derivatives had a high binding affinity to SARS-CoV-2 MPro, with a higher inhibition percentage than Nelfinavir [16].

In this context, our approach focuses on the development of novel molecules with anti-SARS-CoV-2 potential. Specifically, we propose to design halogenated imidazo[1,2-*a*]pyridinyl acrylonitrile derivatives, inspired by hydroxychloroquine, an antimalarial drug whose efficacy has been explored against COVID-19.

SARS-CoV-2 is a coronavirus, and one of its main targets for drug development is the main proteinase (MPro). This protease is essential for viral replication and transcription, making it a prime target for therapeutic strategies against the virus. Thus, MPro has become a major target for the design of new antiviral drugs, and several studies have demonstrated that some chemical entities, such as the nitrile function (in remdesivir) and diazotized heteroaryls, show promising affinity for this protein, thus validating their potential against SARS-CoV-2 [13, 14].

In response to this urgent need for new treatments, we propose an innovative approach that combines interesting chemical structures: on the one hand, an imidazopyridine core (a diazotized heteroaryl) and, on the other hand, an acrylonitrile function. This combination could give rise to new imidazo[1,2-*a*]pyridinyl acrylonitrile derivatives, hybrid molecules with the potential to act effectively against SARS-CoV-2.

In this perspective, the main objective of our study is to propose a new chemical profile that could serve as an alternative in the event of a coronavirus crisis. We thus propose to develop imidazo[1,2-*a*]pyridine-supported acrylonitrile hybrid molecules, capable of targeting the main proteinase of SARS-CoV-2.

We have two specific objectives in this project:

- Evaluate the degree of affinity of imidazo[1,2-*a*]pyridinyl acrylonitrile hybrids for the main proteinase of SARS-CoV-2 (MPro), in order to determine their potential as viral inhibitors.

- Establish the predictive pharmacokinetic profile (ADME) of this series of compounds, by analyzing their absorption, distribution, metabolism and excretion, to assess their viability as therapeutic candidates.

2. Materials and Methods

The design of the hybrid molecules involved the hybridization of two chemical series of imidazo[1,2-*a*]pyridinyl acrylonitriles. The association of these two chemical structures could confer interesting antiviral properties.

2.1. Material of Docking Study

16 imidazo[1,2-*a*]pyridinyl-arylacrylonitriles derivatives (table 1) were tested, targeting the SARS-CoV-2 MPro protein (figure 3).

Compound 1: (Z)-2- 6-chloroimidazo[1,2-*a*]pyridin-2-yl)-3-(2,4-dichlorophenyl)acrylonitrile

Compound 2: (Z)-2-(6-chloroimidazo[1,2-*a*]pyridin-2-yl)-3-(2-chlorophenyl)acrylonitrile

Compound 3: (Z)-2-(2-chlorophenyl)-3-(6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)acrylonitrile

Compound 4: (Z)-2-(6-chloroimidazo[1,2-*a*]pyridin-2-yl)-3-(4-chlorophenyl)acrylonitrile

Compound 5: (Z)-3-(4-fluorophenyl)-2-(6-(4-methylpiperazin-1-yl)imidazo[1,2-*a]*pyridin-2-yl)acrylonitrile

Compound 6: (Z)-2-(5-chloro-6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-3-(4-fluorophenyl)acrylonitrile

Compound 7: (Z)-2-(5-chloro-6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-3-(4-chlorophenyl)acrylonitrile

Compound 8: (Z)-3-(4-fluorophenyl)-2-(3-iodo-6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)acrylonitrile

Compound 9: (Z)-2-(6-chloroimidazo[1,2-*a*]pyridin-2-yl)-3-phenylacrylonitrile

Compound 10: (Z)-2-(6-bromoimidazo[1,2-*a*]pyridin-2-yl)-3-(4-methoxyphenyl)acrylonitrile

Compound 11 : (Z)-2-(6-bromoimidazo[1,2-*a*]pyridin-2-yl)-3-phenylacrylonitrile

Compound 12: (Z)-2-(2,4-dichlorophenyl)-3-(6-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyridin-2-yl)acrylonitrile

Compound 13: (Z)-2-(3,5-dibromo-6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-3-(4-fluorophenyl)acrylonitrile

Compound 14: (Z)-3-(5-chloro-6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-2-(4-chlorophenyl)acrylonitrile

Compound 15: (Z)-3-(5-bromo-6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-2-(4-chlorophenyl)acrylonitrile

Compound 16: (Z)-2-(4-chlorophenyl)-3-(3-iodo-6-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridin-2-yl)acrylonitrile.

Table-1. Structures of 16 compounds used in the study

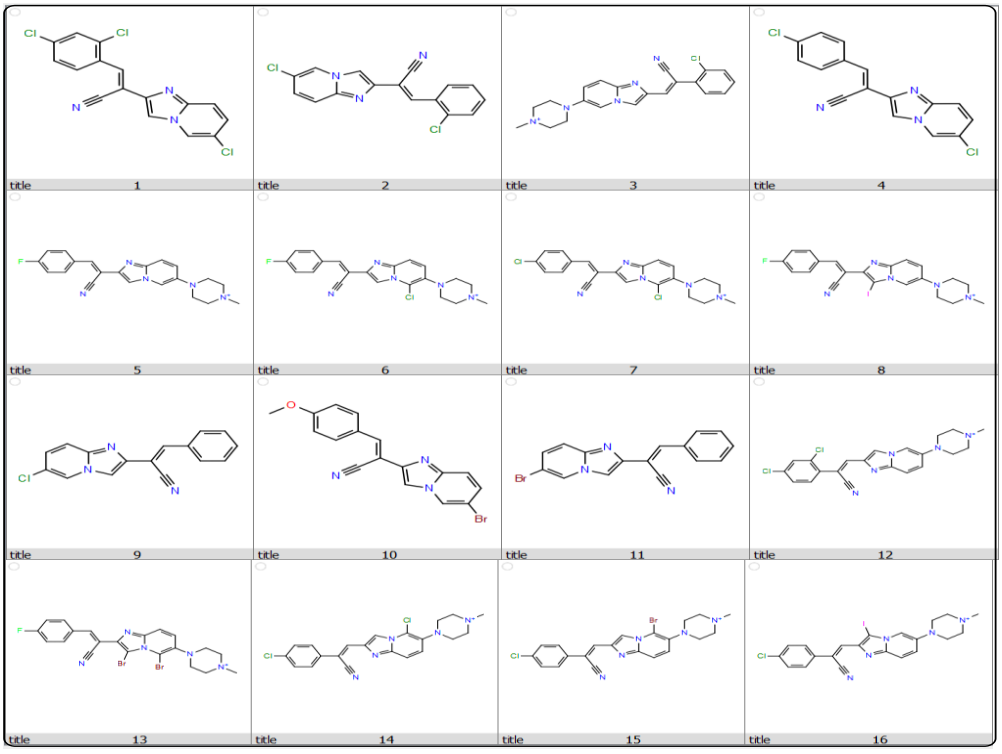
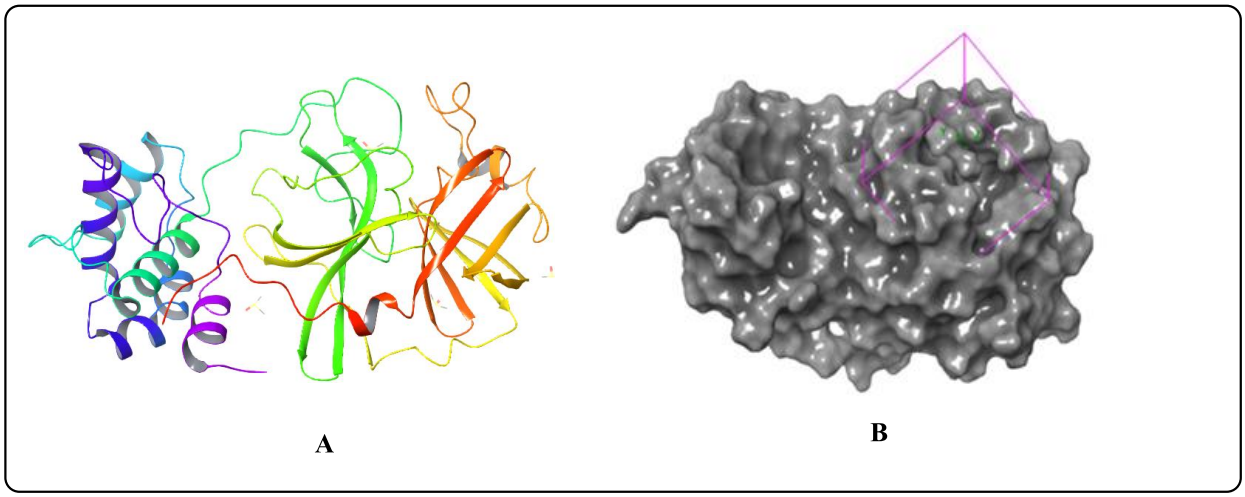


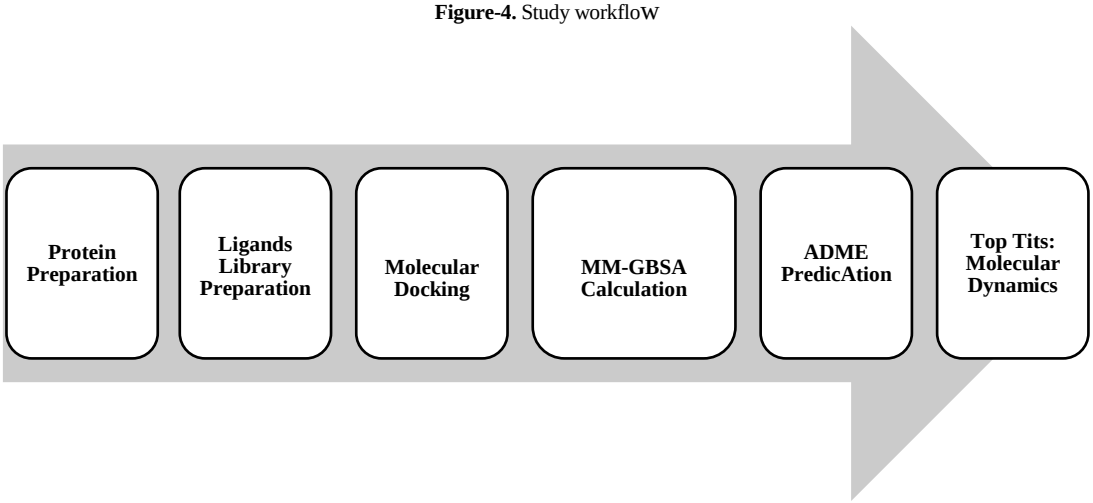
Figure-3. Structure of Mpro (PDB ID: 5R81) (A) and its binding site (B)



2.2. Methods of Docking Study

Compound docking was performed using Glide's standard precision (SP) method to simulate ligand-receptor interaction. Binding free energy was calculated using MM-GBSA to determine the strength of interaction between ligands and their target (figure 4).

Figure-4. Study workflow



2.2.1. Computational Studies

Docking and MM-GBSA studies were performed to explore protein-ligand interactions. Crystal structures of MPro (PDB ID: 5R81) were obtained from the Protein Database (RCSB). Compound interaction was simulated using Schrodinger suite software, and binding free energies were calculated.

2.2.2. Predictive ADME Studies

Pharmacokinetic properties of compounds were predicted using Schrodinger's QikProp tool, which allows estimation of criteria such as permeability, solubility, and percent oral absorption in humans. Analysis of the results showed that imidazo[1,2-*a*]pyridinyl acrylonitrile derivatives, especially those bearing a 7-chloro group, exhibit high lipophilicity and good permeability for the intestinal and blood barriers, as well as high oral absorption.

2.2.3. Determination of Drug Ability Properties

The druggability properties of imidazo[1,2-*a*]pyridinyl acrylonitrile derivatives were assessed using several pharmacokinetic descriptors and applying the famous Lipinski Rule of Five, which is a basic criterion in the selection of drug candidates. This rule states that a compound is more likely to have good oral bioavailability if its physicochemical properties meet the following criteria:

- LogP (log octanol-water partition coefficient): It measures the lipophilicity of a compound. Compounds must have a LogP between -2 and 6.5 to be considered as having a good potential to cross cell membranes.
- Aqueous solubility (QlogS): The solubility in water must be between -6.5 and 0.5 to ensure good absorption.
- Permeability through the intestinal and blood barrier: The permeability coefficient should be greater than 500 to ensure good systemic absorption.
- Permeability through the blood-brain barrier (QlogBB): This property indicates whether the compound can penetrate the central nervous system. Predicted values should be between -3 and 1.2.

- Percentage of oral absorption: An absorption percentage greater than 80% is ideal to ensure the efficacy of the drug after oral administration.

3. Results

3.1. Docking Study Results

The docking study simulated the interactions between imidazo[1,2-*a*]pyridinyl acrylonitrile derivatives and the SARS-CoV-2 MPro protein (Table 2).

Table-2. SP docking score, MM-GBSA bind free energies, and ADME properties of 15 compounds with Mpro protein (PDB ID: 5R81).

Title	docking score	MMGBSA dG Bind	QPlogPo/w[a]	QPlogS[b]	QPPCaco[c]	QPlogBB[d]	QPPMDCK[e]	Percent Human Oral Absorption[f]	RoF[g]
1	-7.065	-43.87	4.808	-6.73	2151.421	0.146	10000	100	0
2	-6.59	-40.85	4.361	-6.174	1998.982	-0.06	5667.716	100	0
3	-6.555	-43.3	3.626	-5.224	405.963	0.005	403.94	94.861	0
4	-6.475	-36.31	4.356	-6.21	1873.514	-0.066	5921.16	100	0
5	-6.474	-43.26	3.502	-4.989	443.094	0.038	408.79	94.818	0
6	-6.466	-39.95	3.842	-5.62	406.109	0.064	601.624	96.133	0
7	-6.351	-41.62	4.115	-5.991	415.431	0.127	842.661	100	0
8	-6.308	-41.62	4.109	-5.926	508.65	0.226	1050.686	100	0
9	-6.269	-32.91	3.845	-5.43	1853.52	-0.227	2381.317	100	0
10	-6.22	-32.09	4.075	-5.786	2162.642	-0.234	3027.556	100	0
11	-6.091	-32.05	3.924	-5.548	1856.91	-0.216	2566.104	100	0
12	-6.013	-47.54	4.123	-6.156	350.335	0.082	881.383	96.63	0
13	-6.006	-43.68	4.348	-6.029	499.124	0.32	1559.007	87.737	1
14	-5.629	-44.54	4.262	-6.154	504.863	0.228	1125.497	100	0
15	-5.398	-43.64	4.336	-6.25	506.186	0.241	1210.806	100	0
16	-5.261	-43.98	4.468	-6.442	486.109	0.275	1532.382	88.237	1

[a] Predicted octanol/water partition coefficient log P (acceptable range -2.0–6.5).
[b] Predicted aqueous solubility in mol/L (acceptable range -6.5–0.5).
[c] Predicted caco cell permeability in nm/s (acceptable range: <25 is poor and >500 is great).
[d] Predicted blood brain barrier permeability (acceptable range -3–1.2).
[e] Predicted apparent MDCK cell permeability in nm/s (acceptable range in nm/s (acceptable range: <25 is poor and >500 is great).
[f] Percentage of human oral absorption (acceptable range: <25 is poor and >80% is high.
[g] Lipinski rule of five.

4. Discussion

4.1. Docking Score and MMGBSA dG Bind

• Docking Score: This score reflects the binding affinity between the ligand and the target. The lower the score (more negative), the better the predicted binding between the compound and the target. For example, compound 1 has a score of -7.065, indicating a strong binding affinity. In contrast, compound 14 has a score of -5.629, indicating a weaker interaction.

• MMGBSA dG Bind: This parameter provides an estimate of the free energy of binding, and as with the docking score, more negative values are better. Compound 12 has a particularly low score (-47.54 kcal/mol), suggesting a strong binding affinity.

4.2. Physicochemical Properties

• QPlogPo/wa: This is the log octanol/water partition coefficient, a measure of lipophilicity. A log P between 2 and 5 is generally considered optimal for cell permeability and oral absorption. Compounds 1, 2, and 4 have high values, around 4.808 to 4.356, suggesting that they are moderately lipophilic and therefore potentially well absorbed orally.

• QPlogSb: Water solubility is a critical factor for bioavailability. Negative values are more favorable for good solubility. Compounds 3 and 16, for example, have values of -5.224 and -6.442, which put them in a favorable range for solubility, while values like -4.989 for compound 5 are somewhat higher but still acceptable.

• QPPCacoc: Permeability through Caco-2 cells, indicated by this value, is critical for predicting intestinal absorption. Compounds with permeability greater than 500 nm/s (such as compound 9 with 1853.52 nm/s) are promising candidates for good intestinal absorption. Compounds with values close to 400-600 nm/s are also favorable, e.g. compounds 3 and 6.

• QPlogBBd: This parameter predicts the ability of compounds to cross the blood-brain barrier (BBB). Values closer to zero are better for brain permeability. None of the compounds here appear to have high BBB permeability, except perhaps compound 16 with a value of 0.275, suggesting potential for BBB crossing.

• QPPMDCKe: MDCK cell permeability is also an indicator of systemic absorption. Compounds with high values (>500 nm/s) like compound 9 (2381.317 nm/s) are ideal candidates for good absorption.

4.3. Human Oral Absorption (% Human Oral Absorption)

Human oral absorption is an important criterion in the selection of drug candidates. An absorption percentage greater than 80% is desirable for oral efficacy. Most compounds (like compound 1, 2, 4, etc.) show 100% oral absorption, making them good candidates for oral administration. Some compounds, like compound 16, have slightly lower absorption (88.237%), but are still in a favorable range.

4.4. Lipinski's Rule (RoFg)

Lipinski's Rule indicates the ability of a compound to be an effective oral drug. In general, for a compound to meet Lipinski's rule, it should not violate more than 1-2 of the following rules:

• Number of donating hydrogen atoms: ≤ 5

• Number of accepting oxygen and nitrogen atoms: ≤ 10

• Molecular weight: ≤ 500 Da

• Log P: ≤ 5

A "RoFg" of 0 means that the compound meets Lipinski's rules. The majority of compounds here meet this rule, suggesting that they have a good probability of success as oral medications.

The following observations emerge from the above:

- Compounds with good potential for strong binding:

o Compound 1: Docking score of -7.065, excellent oral absorption (100%) and high permeability to Caco-2 (2151.421 nm/s).

o Compound 16: Very good binding affinity (MMGBSA dG Bind of -47.54 kcal/mol) and high oral absorption (88.237%). Although it has relatively high permeability to the BBB, it remains a good candidate due to its other properties.

- Compounds to monitor for adjustments:

o Compound 14: Although its docking score is moderate (-5.629), it has good oral absorption (100%) but relatively lower solubility and lower permeability to Caco-2.

- Compounds with a good balance between affinity and absorption:

o Compounds 2, 3, 4, 5 also show favorable docking and MMGBSA scores, with high oral absorption. However, some, like compound 5, may have slightly lower solubility and require adjustments.

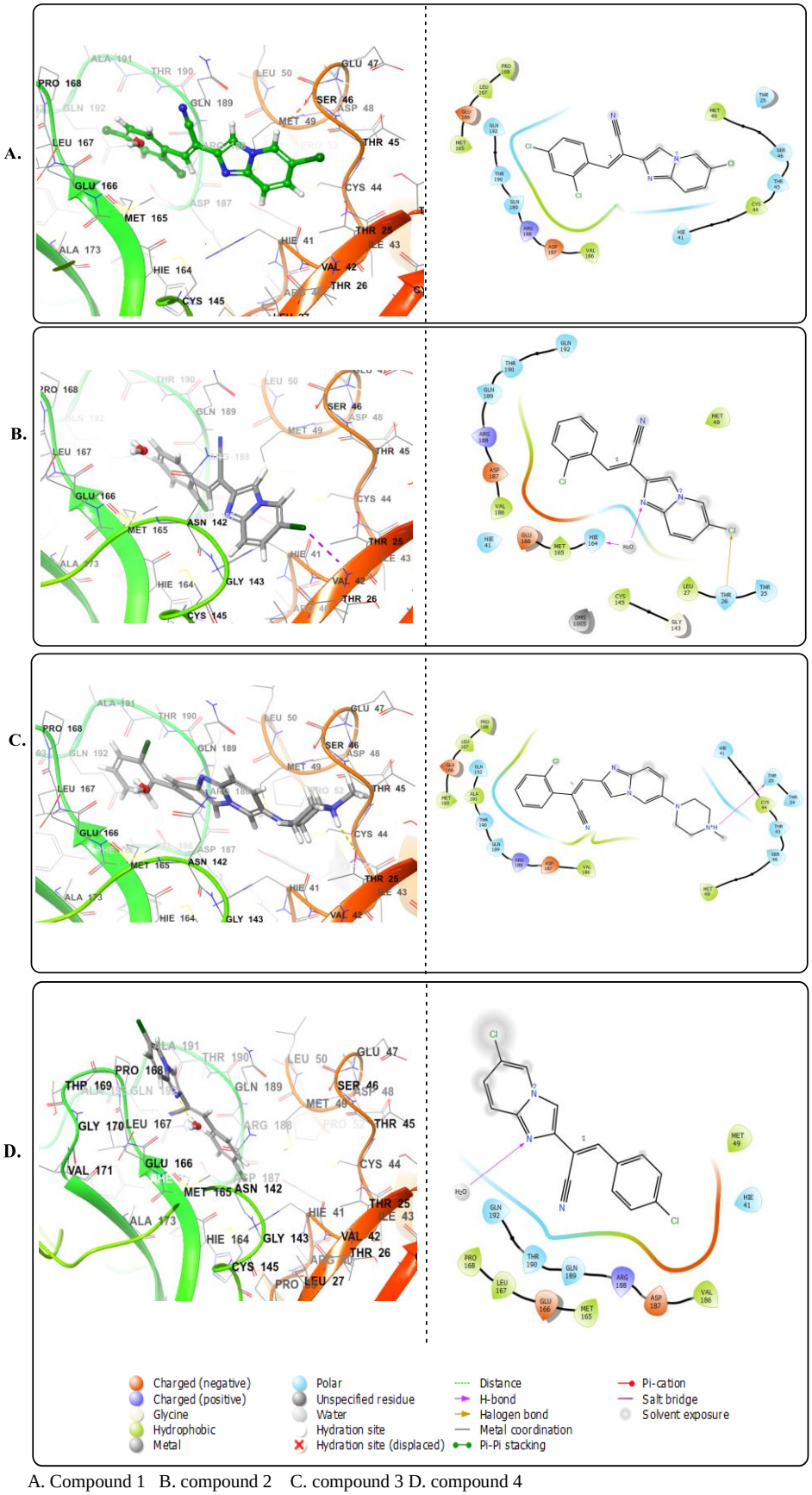
In summary

Compounds 1 to 4 stand out for their favorable docking scores and pharmacokinetic properties (oral absorption, cell permeability). These compounds deserve special attention for further development. The other compounds, although having reasonable affinities and good oral absorption, may benefit from improvements in areas such as solubility or permeability to maximize their clinical potential.

Four compounds were selected as having the best affinities for the viral target, based on their docking scores and calculated binding energies.

The docking scores are particularly interesting, as a lower value indicates a better affinity of the ligand for the target protein. Typically, a score close to -10 Kcal/mol indicates a strong interaction. After analysing the docking scores (in Kcal/mol) and docking interaction obtained for the top four compounds (table 2 and figure 5), the values observed for compounds 1 to 4 show strong interactions between the ligands and the SARS-CoV-2 MPro protein, confirming the relevance of these candidates for antiviral activity.

Figure-5. The 2D and 3D interactions with Mpro protein



A. Compound 1 B. compound 2 C. compound 3 D. compound 4

4.5. Key interactions of the compounds with MPro

For example, examination of the interaction of compound 2 with MPro revealed several key interactions:

• Trans configuration: This geometric configuration is favorable for the optimal alignment of the ligand in the active site of the protein.

• Pi-pi interactions: Pi-pi type interactions were observed between the imidazopyridine nitrogen heterocycle and MPro, which stabilizes the binding.

• Hydrogen bonds: A hydrogen bond was identified between the pyridine nitrogen and a residue of the protein, which improves the specificity of the binding.

• Hydrophobic interactions: The chlorine group of the compound interacts hydrophobically with a threonine residue, further enhancing the stability of the bond.

These interactions demonstrate a significant affinity between compound 2 and MPro, suggesting an effective inhibition of the viral enzyme, essential for virus replication.

4.6. Interpretation of the Predictive ADME Parameters

In silico pharmacokinetic studies were used to evaluate the ADME properties of the compounds using specific descriptors (table 2).

Here are the results for the four best compounds:

4.6.1. Lipophilicity

The results of the QPlogPo/wa descriptor show that all the derivatives have scores above 4, which means that they are lipophilic, i.e. they have a good affinity for cell membranes and can easily cross biological membranes.

4.6.2. Solubility

The results for QPlogS indicate that the compounds have low to moderate solubility in water, with values ranging from -6.73 to -5.22. This means that they are relatively poorly soluble in water, but this characteristic is often found in compounds with high lipophilicity.

4.6.3. Intestinal-Blood Permeability

QPPCaco values show that three of the derivatives (compounds 1, 2, 3) have high permeability to the intestinal barrier, with values ranging from 2151.421 to 1998.982, which is higher than the threshold value of 500. This suggests that these compounds have good intestinal absorption capacity.

4.6.4. Blood-Brain Barrier Permeability

QPlogBB descriptor results show that all four compounds have good permeability to the blood-brain barrier with values ranging from 0.146 to -0.066. This indicates that these compounds have the low ability to cross the blood-brain barrier, which is particularly important if one seeks to target the virus in the central nervous system.

4.6.5. Oral absorption percentage

The estimated oral absorption percentages for the 7-chlorinated derivatives are 100%, indicating excellent oral bioavailability. The 6-N-methylpiperazine derivative also shows an absorption percentage greater than 90%, which is also favorable for effective oral administration.

4.6.6. Lipinski Rule

Finally, all the derivatives meet the five criteria of Lipinski rule, meaning that they possess the necessary physicochemical properties to be good drug candidates with potentially high oral bioavailability.

The top four selected compounds showed docking scores (Kcal/mol) of -7.065, -6.59, -6.555, and -6.475, respectively, and MM-GBSA binding free energies of -43.87, -40.85, -43.3, and -36.31, respectively. These results indicate a high affinity of the compounds for their target. The analysis of the interaction of compound 2 with MPro revealed several key interactions, such as pi-pi interactions with the nitrogen heterocycle and hydrogen bonds with the pyridine nitrogen.

The results of docking studies and predicted pharmacokinetic properties show that imidazo[1,2-a]pyridinyl acrylonitrile derivatives, especially those bearing a 7-chloro and 6-N-methylpiperazine group, are good candidates for the development of anticoronavirus drugs. These compounds exhibit high affinities for SARS-CoV-2 MPro, good lipophilicity, high oral absorption, significant intestinal and blood permeability, and the ability to cross the blood-brain barrier. In addition, they comply with Lipinski's rule, making them promising as oral drugs.

5. Conclusion

This work is part of an approach aimed at identifying new anti-SARS-CoV-2 molecules using an in silico approach, by combining innovative chemical structures. These new molecules could contribute to the fight against the current pandemic and serve as alternative treatments for future health crises caused by coronaviruses.

The results of our in silico studies show that the hybrid compounds 7-chloro-imidazopyridinyl acrylonitriles and 6-N-methylpiperazine have interesting properties as new anticoronavirus drug candidates. These molecules not only have a high affinity for the MPro of SARS-CoV-2, but they also exhibit good pharmacokinetic properties, including excellent oral absorption and promising bioavailability. These results pave the way for the development of new therapeutic strategies against COVID-19 and other potentially emerging coronaviruses.

Competing Interests

Authors have declared that no competing interests exist concerning this manuscript.

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