Journal of Medicinal and Chemical Sciences 6 (2023) 2056-2084

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Rigidity and Flexibility of Pyrazole, s-Triazole, and v-Triazole Derivative of Chloroquine as Potential Therapeutic against COVID-19

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ARTICLE INFO

Article history

Receive: 2023-01-16
Received in revised: 2023-02-06
Accepted: 2023-03-07
Manuscript ID: JMCS-2302-1962
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Gholamabbas Chehardoli

DOI:10.26655/JMCHEMSCI.2023.9.14

KEYWORDS

COVID-19
Pryazole
1,2,4-Triazole
1,2,3-Triazole
Hydroxychloroquine
DFT
Molecular Docking
Drugs design

ABSTRACT

Based on the core unit of chloroquine, new types of N-heterocyclic compounds that are fused together have been made. The compounds were put into two groups. In series A, the five-member hetero-rings were directly connected to the core unit, while in series B, the CH_2 group was used to make the five-member ring more flexible (series B). Using the Gaussian 09 programme, the DFT method with hybrid correlation functional (B3LYP) and 6-311 (d, p) basis sets were used to figure out how to optimize and measure the quantum chemical properties of molecules. The molecular overeating environment (MOE) programme is used to study molecular docking. The binding of flexible compounds shows that AC8, AC10, AC3, and AC5 have the strongest binding affinities compared to the other candidates, while the rigid molecules ARC10 and ARC6 have the lowest binding affinities. In general, the results of the binding affinity showed that the drugs and receptors being studied might have anti-Covid-19 properties. Likewise, the flexible compounds AC8, AC10, AC3, and AC5 had the lowest Ki values of those made and could be used as a treatment. Our virtual physicochemical evaluation of all compounds in series A and B showed that all of them met the limits for molecular weight, lipophilicity (MLogP 4.15, the octanol-water partition coefficient), and water solubility. In addition to MR, the number of H-bond acceptors and the PSA were both within the acceptable range. It seems that the number of rotatable bonds is the only physicochemical property that separates the compounds in series B. The scores of compounds AC3, AC4, AC7, AC8, AC11, and AC12 are outside the acceptable range when compared to the results of chloroquine as the parent compound.

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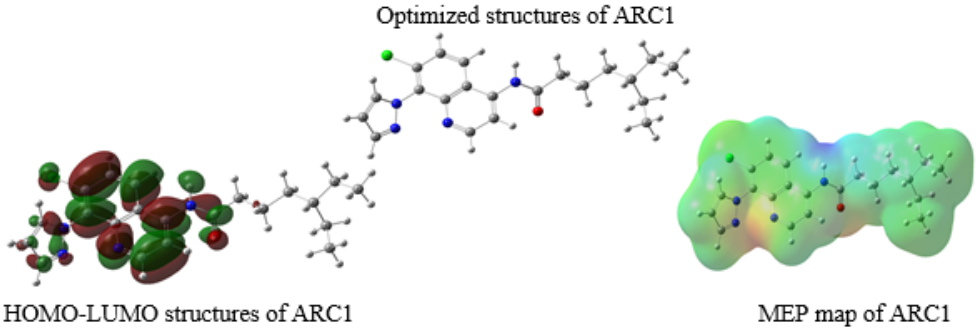
GRAPHICAL ABSTRACT



Introduction

We [1, 2] and others [3-5] have been interested in designing and making new molecules that have biological activities, medicinal uses, coordination behaviors [6-8] and studying their properties computationally. However, it is very important to find effective and safe drugs that can target the virus and/or change how the immune system responds [9]. Pyrazole is an example of an N-heterocyclic molecule with two N-atoms and a five-member ring. It has a wide range of biological and pharmacological activities. The connections between pyrazole and other five-membered N-heterocyclic molecules could lead to the creation of new molecules that move in different ways and have new biological properties. The biological activity of designed molecules 13 may be affected by how rigid or flexible a compound is. But molecules with more than one rotated bond can have very different shapes. Some of these shapes are good because they have low internal energies, while others are not. Therefore, when we made compounds, we thought about a few things to get them close to chloroquine both biologically and electronically. In fact, we focused on fused molecules that have more than one biologically active part. This was a continuation of our research interest in designing, making, and looking into the similarities between molecules of new fused molecules. Aromatic ring systems, especially five-membered heterocyclic ring systems, can be added to make derivatives with the best size, but the aromaticity of these rings can have an unpredictable effect on the affinity of the binding site [10]. In addition, the stacking formation between the aromatic rings may make molecules that are stacked more stable.

Materials and Methods

Structural design and modification

To change the structure of the parent compound, CQ (see Figure 1), we added three different "substituents" [11]. The main aromatic heterocyclic quinoline ring is kept, which is of great biological importance. Hence, the top 24 derivatives of 4-amino-7-chloroquinoline scaffold were made with a change at the 8th position of the quinoline ring and at the 10th and 15th positions of the 4-amino side chain, as displayed in Scheme 1.

In position 8, a 5-membered heterocyclic ring was added in place of a hydrogen atom in CQ. This was the first structural change. When a ring system is added to the main skeleton of an analogue, the size or surface area of the original molecule can change in ways that are hard to predict. The shape of the original molecule can also change depending on how the lead compound as a whole need to be changed, adding a ring system may bring about the desired molecular properties. Aromatic ring systems, especially five-membered heterocyclic ring systems, can be added to make derivatives with the best size, but the aromaticity of these rings can have an unpredictable effect on the affinity of the binding site [12].

Four of the 12 compounds in a series all have the same heterocyclic ring at position 8. As depicted in Scheme 1, the first four compounds in series A and B (set1) have a pyrazole ring, the second four compounds in series A and B (set 2) have a 1,2,4-triazole ring, and the last four compounds in series A and B (set 3) have a 1,2,3-triazole ring. Pyrazole (1*H*-pyrazole; 1,2-diazole) is a five-membered heterocyclic with two nitrogen atoms next to each other (Figure 2a).

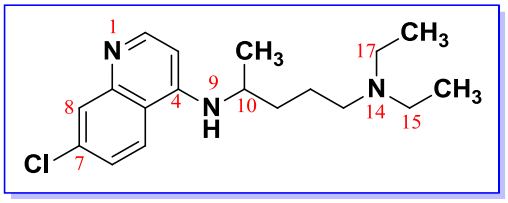
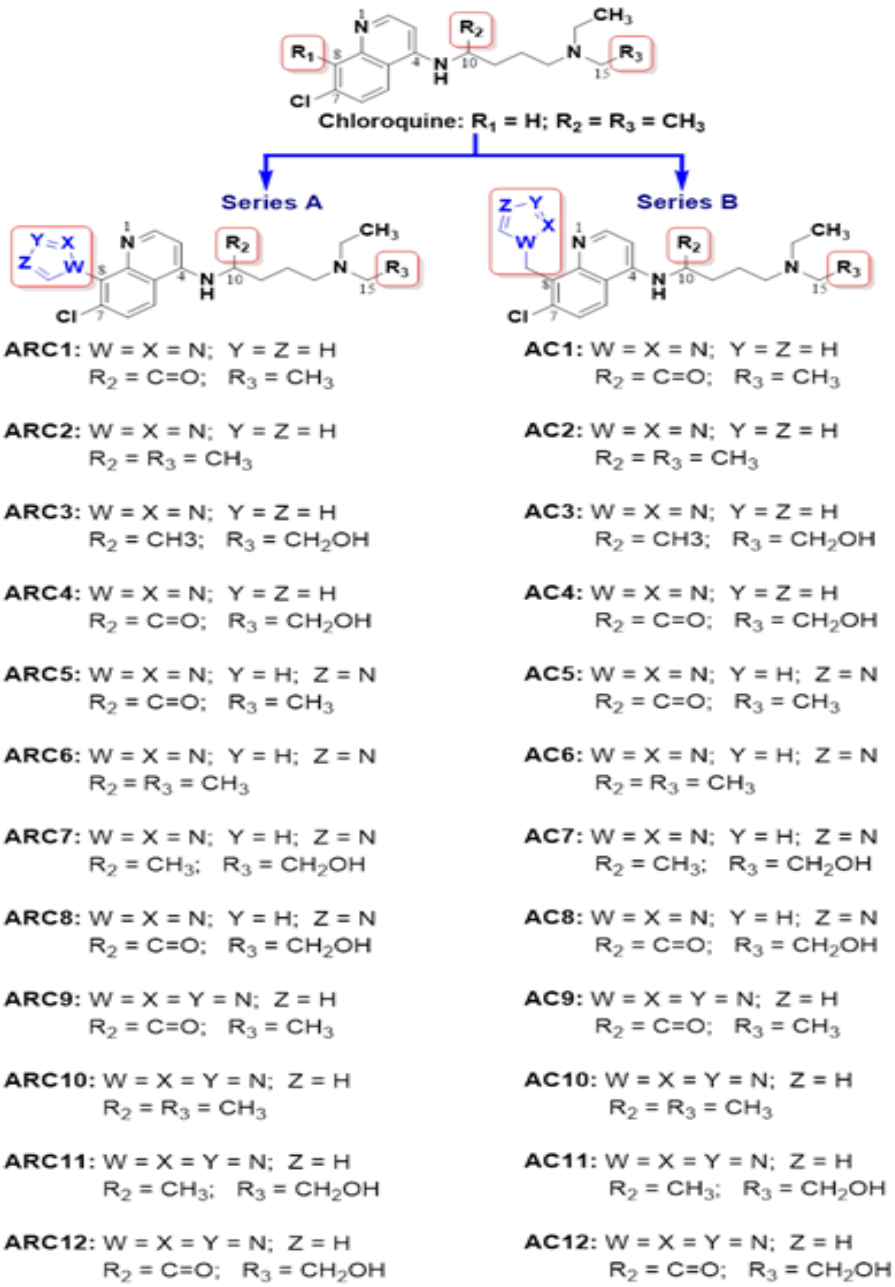


Figure 1: Chemical structure of Chloroquine



Scheme 1: Structural manipulation of chloroquine generating 24 derivatives divided as 12 per series

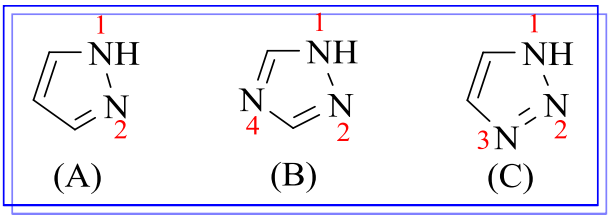


Figure 2: Structure of pyrazole (A), 1,2,4-triazole (B), and 1,2,3-triazole (C)

It is a stable aromatic ring with a pKa of 2.49, according to Van Nostrand (2006) and Slide (2007). The two nitrogen atoms at the ends of the pyrazole ring seem to be made of different chemicals. At position 1, there is acidic pyrrole-like nitrogen with a partial positive charge and a lone pair of electrons linked to ring aromaticity. This nitrogen can act as a hydrogen bond donor. Giller *et al.* (1965) called the other nitrogen a sp2-hybridized pyridine-like basic nitrogen with a partial negative charge at position 2, a lone pair of electrons that do not contribute to the aromaticity of the ring, and the ability to accept hydrogen bonds [13]. Substitutions on the ring seem to change how both nitrogen atoms act, and groups that give up electrons make the pyrrole-like nitrogen more acidic. As a chemical entity, the pyrazole ring shows a wide range of interesting physical and chemical phenomena. One of the most interesting is its ability to show tautomerism of the planar protopic type, in which the hydrogen atom seems to switch places between the two nitrogens next to it. This is followed by a change in the way the ring system works as a whole 14. 1,2,4-Triazole, also called "s-triazole," is a 5-membered heterocyclic ring system isomer with three nitrogen atoms at the 1, 2, and 4 positions (Figure 2b). The ring system is made up of one nitrogen atom like pyrole and two nitrogen atoms like pyridine. This is similar to v-trizole [15]. The acidity and basicity of this aromatic isomer and its counterpart, 1,2,3 trizole, are a little different, with a pKa of 2.19. Un-substituted 1,2,4 trizole can be made in three different tautomeric forms. 1,2,3-Triazole, also called v-triazole, is a five-membered heterocyclic ring with three nitrogen atoms in positions 1, 2, and 3 that are called vicinal nitrogen atoms (Figure 2c). A nitrogen atom that is similar to pyrrole in position 1 and two nitrogen atoms that are similar to pyridine in positions 2 and 3, whose electrons strongly contribute to the aromaticity of the ring system [16]. 1,2,3-triazole has a pKa of 1.17 and comes in two different forms called tautomers [17]. This aromatic ring can be used as a bioisosteric substitute for a wide range of chemical groups in medicinal chemistry, which is one of its best uses [18]. This is because it can act as both a hydrogen bond acceptor and a donor, and it is rigid, polar, and very stable.

All 12 CQ-derivatives of series B have a methylene group that acts as a bridge between the main structural skeleton and the lateral heterocyclic extension at position 8. This is one of the most important differences between the 12 derivatives of series A and those of series B. Methylene bridging and/or increasing the number of methylene groups in a side chain or ring system can hurt the size of molecule or its surface area and its ability to stick to fat. Within a certain compound, methylene bridging can either increase or decrease activity, depending on how a change in numbering affects the lipophilic nature of the compound of interest. This change in the number of methylene groups could affect the lipophilicity, water solubility, biological distribution and absorption, binding site affinity, and target site interaction in the long run. Thomas (2007) found the second changed position is 10 with a methyl group in the original structure of the parent compound CQ. In compounds ARC1, AC1, ARC4, AC4, ARC5, AC5, ARC8, AC8, ARC9, AC9, ARC12, and AC12, this methyl group has been replaced with a carbonyl group, which is important for a compound's ability to form hydrogen bonds in general [19]. In compounds ARC2, AC2, ARC3, AC3, ARC6, position 15 is the last part of the parent compound to be changed. As displayed in Figure 1, a methyl group is added to this spot. In this

spot, our virtual design was meant to add a bio-isosteric hydroxyl group to replace one of the native hydrogen atoms in the methyl group. Only the compounds ARC3, AC3, ARC4, AC4, ARC7, AC7, ARC8, AC8, ARC11, AC11, ARC12, and AC12 go through this process.

When a methyl group is added to the structure of a compound being studied, there will be a positive shift toward lipophilicity, a decrease in water solubility, and an improvement in the ease of absorption, as well as a slow tendency for the compound to move around in the body. With steric restriction generation, this small group may also change the size of the compound, making it easier for the compound to interact with a specific target. This is a very important effect. On the other hand, it seems that adding such a small group to any analogue can have unpredictable effects on the way it is metabolised. It was found that such a group can speed up the rate of metabolism by oxidation or demethylation, or it can slow down the rate of metabolism by hiding the active group of the enzyme that is doing the metabolising, leading to a slower rate of metabolism. In the end, it seems that adding a methyl group is the best way to increase lipophilicity without affecting solubility in water. On the opposite end of the spectrum from adding a methyl group, adding a hydroxyl group seems to increase the compound's hydrophilicity and decrease its lipophilicity. It further gives the compound another chance to strengthen its binding site interactions with a specific target by making hydrogen bonds stronger. In addition, the presence of such a group seems to change the way the analogue is metabolised, which affects how long it stays in the body after it is taken in. This is because the analogue is more likely to undergo metabolic conversion or detoxification [20]. Since the parent compound, chloroquine, and all 24 derivatives have a chlorine atom at position 7, the presence of halogens in the structure of any lead compound seems to have a positive additive effect on the lipohilic nature of the compound of interest with a decrease in water solubility. This means that the incorporation of halogens seems to help biological barriers penetrate and accumulate in fatty tissues. Aromatic halogens are less reactive than aliphatic halogens, and fluorine and chlorine groups in aromatic halogens are the most stable [21].

DFT calculations

The geometry of the study compounds was optimized using the hybrid correlation functional (B3LYP) and 6-311 (d, p) basis sets in the Gaussian 09 programme [22-25]. Using the HOMO and LUMO energy values of the named compounds [26-29], quantum chemical properties like ionization potential, electron affinity, energy gap, electronegativity, chemical potential, chemical hardness, chemical softness, electrophilicity index, and nucleophilicity index.

Drug-likeness and pharmacokinetics properties

To come up with a good method for predicting the pharmacokinetics of all 24 CQ-derivatives, a set of parameters for each derivative and its parent compound, chloroquine, were compared (CQ). The first thing to examine is the physicochemical properties of all of our derivatives. This includes the molecular weight (MW), polar surface area (PSA), the number of rotatable bonds, molar refractivity (MR), lipophilicity, water solubility, and number of hydrogen bond acceptor atoms in each derivative. The most important thing about this set of criteria is that it can show the size, polarity, lipophilicity, insolubility, and overall flexibility of the compounds of interest [18-30]. This helps a lot with the idea of the bioavailability radar [31], the degree of drug-likeness, the estimated oral bioavailability, and virtual structural optimization of all derivative

The MW is an important factor to consider when figuring out how much a compound is like a drug [32]. It also has the ability to change the pharmacokinetics and dynamics of the compounds being studied, which affects their bioavailability [33]. Another thing to study is the molecular PSA, which is the sum of the surfaces of polar atoms in a compound. This shows how likely it is for molecules to pass through cell membranes, how easy it will be for them to be absorbed, and if they can cross the blood-brain

barrier (BBB). Another important parameter is the number of rotatable bonds, which is a key indicator of oral bioavailability. This parameter, along with the total number of hydrogen bonds and a low PSA, shows how flexible a molecule is. It seems that a total of 10 or fewer rotatable bonds and a PSA score of 140 2 or less with 12 or fewer total hydrogen bonds is a good predictor of oral bioavailability in rats [34]. However, this parameter is not always a good predictor of molecular flexibility due to several limitations [35]. The tendency of a compound to crystallise is another important property that this variable may be able to predict early on [36]. As a predictor of steric factors, which can affect how well a compound interacts with a potential binding site, MR is a measure of the volume occupied by atoms. This gives an idea of steric properties and how they relate to biological activity and binding site affinity [37].

The level of lipophilicity of a molecular entity is a key parameter that needs to be looked into in depth to understand the ADME of any compound being studied [38]. Mannhold *et al.* (2009) found that the fact that a compound is lipophilic can hurt its overall suitability as a drug candidate, as well as its kinetics, dynamics, toxicological profile, and metabolic fate [39]. Lipophilicity is the most useful physicochemical parameter in medicinal chemistry for designing new drug candidates because it can predict molecular interactions and forces and, as a result, is a good predictor of the structure-activity relationship (SAR) of compounds [40]. Also, the lipophilic nature of a compound is what allows it to cross intestinal membranes and be absorbed by the gastro-intestinal tract (GIT). A compound's ability to move around in a biological system depends on its ability to cross cellular membranes and reach its target site. Being able to cross cellular membranes is another requirement for getting to metabolic enzymes and being able to do their job. Lipophilicity further controls the ability of any molecule to be reabsorbed after glomerular filtration and active secretion [41]. It also affects the ability of any compound to pass through the blood-brain barrier [42]. SWISSADME [43] adds a number of guesswork methods for lipophilicity to improve the accuracy of predictions. Moriguchi logP (MLOGP) is the method of choice in our study because it is easy to use and has a high level of reliability [44, 45] .

The solubility of a compound is a key parameter for successful formulation and administration of a drug [46]. It also has a huge effect on the kinetics and distribution of any compound that is being tested as a candidate for drug development. In biopharmaceutics, the rate and amount of drug absorption are controlled by how well the drug dissolves and how well it can cross biological barriers. Amidon *et al.* suggest that there is a link between *in vitro* drug dissolution and *in vivo* bioavailability [47]. The way the structure of a candidate is changed affects many of its properties, such as its lipophilicity, ability to form hydrogen bonds, surface area, and ability to be ionised [48]. Solubility is the most important thing in drug formulation and parenteral preparation because it is a prerequisite for achieving predictable drug levels in living organisms. For oral bioavailability, which is the main indicator of how easily a medicine can be absorbed by a living system when taken by mouth, aqueous solubility is more important than lipophilicity. This kind of parameter can have an effect on the pharmacological response of any compound under study [49]. Log S, as a predictor of aqueous solubility, uses the characteristic PSA score and the lipophilicity score of log P to make a first guess about the aqueous solubility of any virtual compound of interest [50]. This is why we chose log S as the solubility prediction method for our study. The number of hydrogen bond acceptors and donors is the last physicochemical factor used to predict how well a drug can be made. A compound's polarity can be determined by how many atoms in its structure accept hydrogen bonds and how many atoms give hydrogen bonds [51]. The ability of a molecule to form hydrogen bonds with other molecules in its environment is essential for making drugs and figuring out how well they will bind. For a medicinal chemist to change a parent compound and cause bio-isosteric substitutions, he or she should keep the parent molecule's original ability to form hydrogen bonds and, if possible, improve

it [52]. In our sturdy, each of our derivatives is judged based on a number of pharmacokinetic parameters. The first is whether or not the compound of interest can get past the GIT barriers and into the bloodstream. The extent of absorption should be carefully considered because it has a big effect on how well it works when taken by mouth. The tendency of the compound of interest to pass BBB can suggest that it plays a role in the central nervous system. This gives a first indication of the lipophilic profile that the compound(s) being studied will show [53]. It seems that for a molecular entity to be able to pass the BBB, it needs to have a low PSA score, a high log P value, a low number of HBDs, and a limited amount of flexibility [54, 55]. Therefore, a PSA value of 60-70 2 or less, balanced lipophilic and hydrogen bonding properties, and a molecular weight of 400 or less are the most important factors in a medicine's ability to pass the BBB [56, 57]. Another important kinetic parameter is how the compound under study interacts with P-glycoprotein (P-gp). Being a substrate or not can give a first idea of the metabolic and distribution profile, as well as how likely the compound of interest is to be taken up or thrown out of the cell [58-60]. This can give the first idea of how medicines work in physiological systems and on specific biological targets. A P-gp substrate has a big effect on how a drug is absorbed, where it goes, how it gets rid of itself, and what its pharmaceutical profile looks like [61]. The role that this efflux protein plays can be of the utmost importance, affecting both how candidate compounds move around and how well they pass through the BBB, as well as how well they are absorbed in the gut and how well they work when taken by mouth. Adding alcohols and N-heterocycles with uncapped NH groups seems to make molecules more likely to be P-gp substrates. This suggests that the ability of a candidate to donate hydrogen bonds is an important part of being a P-gp substrate. A good way to stop P-gp from recognising something is to keep the number of hydrogen bond donors (HBDs) below 2, and to limit the value of PSA to 90 2, or if possible 70 2 or less, without affecting the overall biological activity [62]. Four physicochemical parameters, the molecular weight, logS, logP, and MR should be taken into account for a compound to be a P-gp substrate [63]. In another study, the link between P-gp affinity and molecular size was stressed. It was shown that a bulkier compound with more hydrophobic interactions would have a higher affinity for P-gp [64]. N-heterocyclic moieties play a key role in determining the interaction level between a molecule with such groups and P-gp [65]. On the other hand, the susceptibility of the compounds under study to the cytochrome-P450 family of enzymes [66] is another important factor that needs to be carefully thought through. Since enzymes are a big family [67, 68], we only looked at five iso-enzymes that were the most important in drug metabolism [69]. This family of enzymes plays a very important role in drug metabolism and interactions [70]. Kirchmair *et al.* (2015) found that the way a compound is broken down in the body can make derivatives with more or less biological activity, different kinetic and dynamic behaviour, and different toxicological properties compared to the parent compound [71]. Lipophilic profiling of any compound is necessary to make a first guess about how likely it is to be a substrate for cytochromes. This is because lipophilicity, which is written as log P, is a complex indicator of both hydrophobicity, which is based on the size and surface area of the molecule, and polarity, which is based on the number of hydrogen bond donors and acceptors on the molecule. CYP1A2's substrates and inhibitors can be neutral or basic, and the lipophilicity of the compound does not have much to do with how well it binds. It has been said that CYP1A2 binding affinity and inhibition are mostly caused by - interactions with aromatic residues at the open active site. On the other hand, CYP2C9 substrates are acidic and ionised at physiological pH. They can form hydrogen bonds and are not water-loving. CYP2C19, on the other hand, does not seem to have a preference for basic or acidic molecules when it comes to its inhibitors. Still, substrates for CYP2D6 seem to hold basic nitrogen that becomes ionised when the pH is neutral. In

addition, substrates for this isoform have some hydrophobic interactions at the active site region. Long and Walker (2003) found that CYP3A4, which is the main cytochrome in drug metabolism and the most widely expressed isoenzyme, seems to attract inhibitors with a high lipophilic character, even though there are other ways for them to interact [72]. This is because the active site pocket of CYP3A4 can change its shape. Lipinski *et al.* (2001)'s "rule of five" was carefully taken into account when we tried to figure out how much our derivatives were like drugs [73]. The rule of five is a way to figure out if a compound is safe to take by mouth. It is based on several physicochemical criteria that need to be carefully watched. These physicochemical parameters are the molecular weight of the compound being studied, the number of hydrogen bond acceptors and donors, and the score of Moriguchi *et al.* (1992) [74]. lipophilicity predictor M logP. Thus, for a compound to be good enough to take by mouth, the number of hydrogen bond donors should not be more than 5, the molecular weight should not be more than 500, the number of hydrogen bond acceptors should not be more than 10, and the calculated MlogP should not be more than 4.15 [75]. To figure out how friendly the medicinal chemistry of a compound is, you have to look at several important criteria, such as the PAINS alert, the Brenk alert, and how easy it is to make [76]. Screening for Pan Assay Interference Compounds (PAINS) is the most important part of making sure a compound is safe and does not cause false positive biological responses. These compounds have what are called "promiscuous" functions, which means that they can interact in sneaky ways to produce results that are not specific to a particular target. This can waste a lot of time and resources for medicinal chemists who are looking for target-specific entities [77]. The idea of synthetic accessibility (SA) is important for finding new drugs and making them better. This is because SA can be a bad thing when figuring out which compounds are most likely to work after virtual screening and optimization [78].

Molecular docking

COVID-19, the main protease protein of SARS-COV-2, was the focus of molecular docking research to find out how the drugs under study might bind to it [PDB ID: 6LU7] [79]. From the RCSB PDB database at http://www.rcsb.org/, it was possible to get the 3D structure of the target receptor. The optimized structures of the compounds that had been researched were used as the substrate. The molecular overeating environment (MOE) programme is used to study molecular docking. The binding affinities of the studied drugs for the target receptor were put in order by the score function (S, kcal/mol).

Results and Discussion

DFT calculations

Geometry optimization

The named compounds' fully optimized geometries were displayed in Figure 3. The molecules have different dihedral angles and are not planar.

Frontier molecular orbital (FMO) and Global reactivity descriptors

The values of the Highest Occupied Molecular Orbital (HOMO), the Lowest Unoccupied Molecular Orbital (LUMO), and the HOMO-LUMO energy gap can be used to figure out if a molecule can give or take electrons [80]. These molecular orbitals are very important for understanding biological mechanisms, electrical and optical properties, luminescence, photochemical reactions, UV-Vis, quantum chemistry, and pharmacological research [81].

Quantum chemical computations were used to find the global reactivity electronic descriptors [82]. These calculations were based on the well-known Koopmans approximation. The approximation says that the electron affinity and the ionization potential are both about the same as the negative of the HOMO and LUMO energies. Therefore, using formulas from the literature, the global reactivity descriptors of chemical potential, electronegativity, chemical hardness, electrophilicity, and chemical softness could be calculated [83].

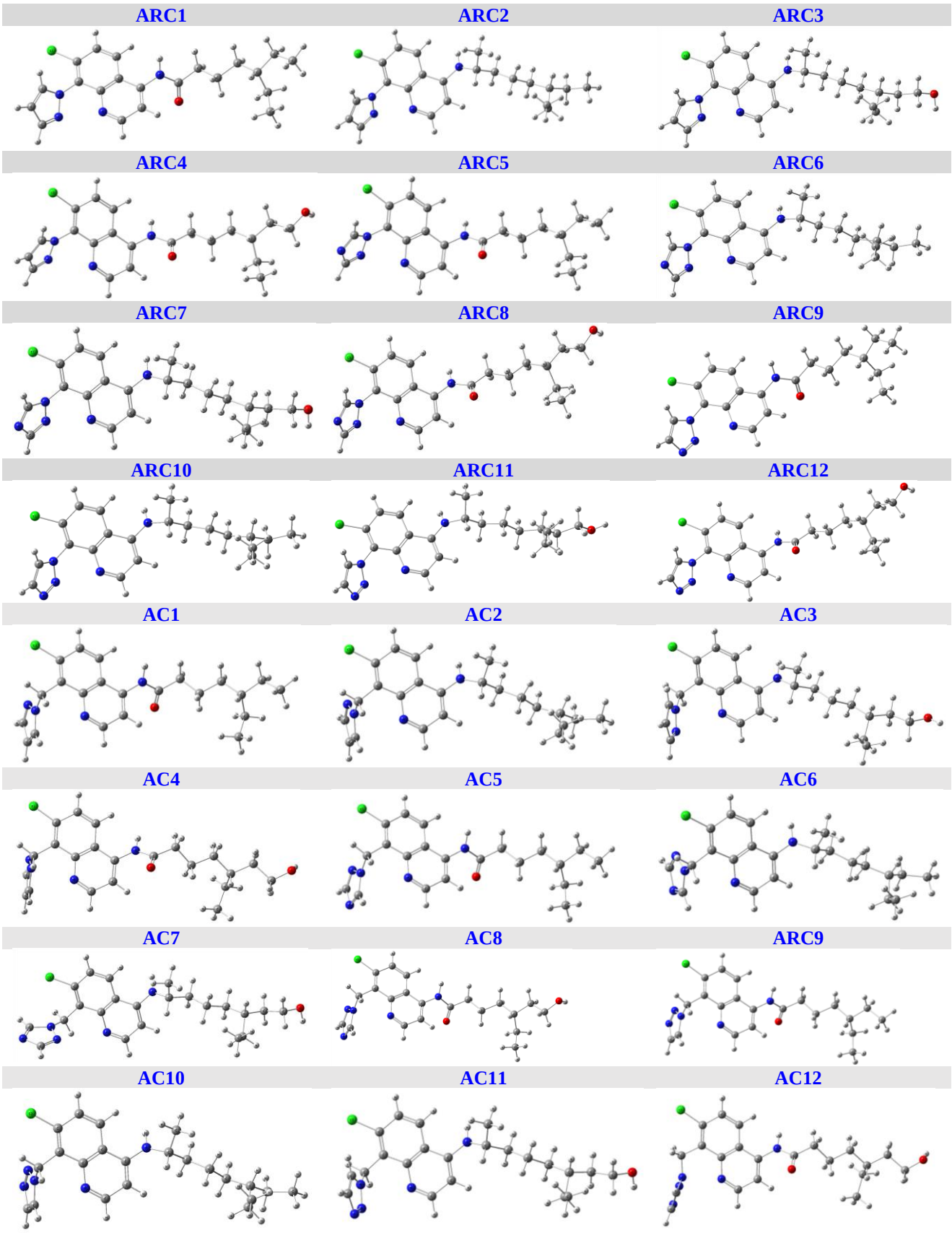


Figure 3: Optimized structures of the studied compounds

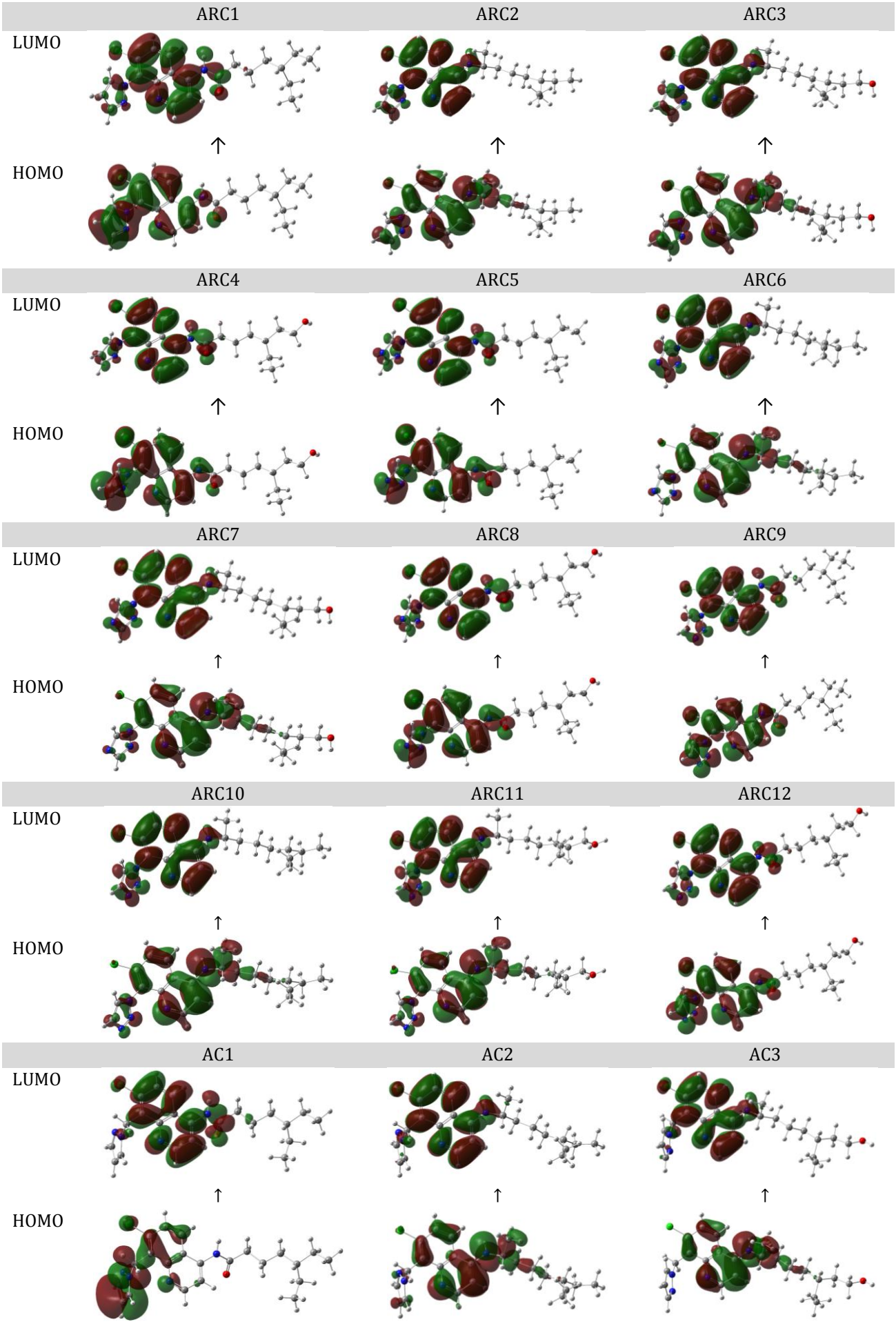
Table 1 lists the HOMO-LUMO energy parameters of the compounds, such as their hardness, softness, chemical potential, and electrophilicity index. Figure 1 depicts the 3D HOMO and LUMO plots of the compounds. The hardest molecules are AC5, AC8, and AC9, which have the biggest energy gaps. The fact that ARC11, ARC10, ARC7, and ARC6 have the smallest energy gaps shows that these ARCs are the softest and most reactive. Soft molecules have a low LUMO-HOMO energy gap, which makes them more chemically reactive [84]. Compared to hard molecules, soft molecules have more electron changes than hard molecules. The electrophilicity index says that ARC5, ARC12, AR9, and ARC8 are the compounds with the most electrophilicity.

Molecular electrostatic potential (MEP)

The molecular electrostatic potential is a well-known way to figure out how different chemical systems react in electrophilic and nucleophilic reactions, biological recognition, and hydrogen bonding interactions [84]. For the molecule under study, the MEP at the DFT-optimized geometry was used to predict where electrophilic and nucleophilic attacks would happen, as demonstrated in Figure 5. Different colors show how electrostatically charged the surface is. Possible increases are: red, orange, yellow, green, and blue. Electrophilic reactivity is linked to the negative parts of the MEP, which are red, orange, and yellow [85].

Table 1: Calculated chemical parameters of the studied compounds

	E_{HOMO}	E_{LUMO}	ΔE	I	A	χ	CP	η	σ	ω	Nu	ΔNmax
ARC1	-6.44	-1.86	4.57	6.44	1.86	4.15	-4.15	2.29	0.22	3.76	0.27	1.81
ARC2	-5.89	-1.48	4.41	5.89	1.48	3.69	-3.69	2.20	0.23	3.09	0.32	1.67
ARC3	-5.91	-1.50	4.41	5.91	1.50	3.71	-3.71	2.21	0.23	3.11	0.32	1.68
ARC4	-6.39	-1.83	4.55	6.39	1.83	4.11	-4.11	2.28	0.22	3.71	0.27	1.80
ARC5	-6.72	-2.04	4.68	6.72	2.04	4.38	-4.38	2.34	0.21	4.10	0.24	1.87
ARC6	-6.05	-1.67	4.38	6.05	1.67	3.86	-3.86	2.19	0.23	3.40	0.29	1.76
ARC7	-6.07	-1.69	4.38	6.07	1.69	3.88	-3.88	2.19	0.23	3.43	0.29	1.77
ARC8	-6.68	-2.01	4.67	6.68	2.01	4.35	-4.35	2.34	0.21	4.04	0.25	1.86
ARC9	-6.68	-2.03	4.66	6.68	2.03	4.36	-4.36	2.33	0.21	4.07	0.25	1.87
ARC10	-6.05	-1.71	4.34	6.05	1.71	3.88	-3.88	2.17	0.23	3.47	0.29	1.79
ARC11	-6.05	-1.71	4.34	6.05	1.71	3.88	-3.88	2.17	0.23	3.47	0.29	1.79
ARC12	-6.67	-2.03	4.64	6.67	2.03	4.35	-4.35	2.32	0.22	4.08	0.25	1.87
	E_{HOMO}	E_{LUMO}	ΔE	I	A	χ	CP	η	σ	ω	Nu	ΔNmax
AC1	-6.31	-1.83	4.48	6.31	1.83	4.07	-4.07	2.24	0.22	3.69	0.27	1.82
AC2	-5.97	-1.45	4.52	5.97	1.45	3.71	-3.71	2.26	0.22	3.05	0.33	1.64
AC3	-5.97	-1.49	4.48	5.97	1.49	3.73	-3.73	2.24	0.22	3.11	0.32	1.66
AC4	-6.36	-1.85	4.51	6.36	1.85	4.11	-4.11	2.26	0.22	3.74	0.27	1.82
AC5	-6.77	-1.95	4.82	6.77	1.95	4.36	-4.36	2.41	0.21	3.94	0.25	1.81
AC6	-6.07	-1.58	4.49	6.07	1.58	3.83	-3.83	2.24	0.22	3.27	0.31	1.71
AC7	-6.05	-1.55	4.49	6.05	1.55	3.80	-3.80	2.25	0.22	3.21	0.31	1.69
AC8	-6.78	-1.96	4.82	6.78	1.96	4.37	-4.37	2.41	0.21	3.97	0.25	1.82
AC9	-6.73	-1.96	4.77	6.73	1.96	4.35	-4.35	2.38	0.21	3.96	0.25	1.82
AC10	-6.08	-1.60	4.48	6.08	1.60	3.84	-3.84	2.24	0.22	3.29	0.30	1.71
AC11	-6.09	-1.65	4.44	6.09	1.65	3.87	-3.87	2.22	0.23	3.37	0.30	1.74
AC12	-6.51	-1.88	4.62	6.51	1.88	4.19	-4.19	2.31	0.22	3.81	0.26	1.82


ARC1
ARC2
ARC3
LUMO
HOMO
ARC4
ARC5
ARC6
LUMO
HOMO
ARC7
ARC8
ARC9
LUMO
HOMO
ARC10
ARC11
ARC12
LUMO
HOMO
AC1
AC2
AC3
LUMO
HOMO

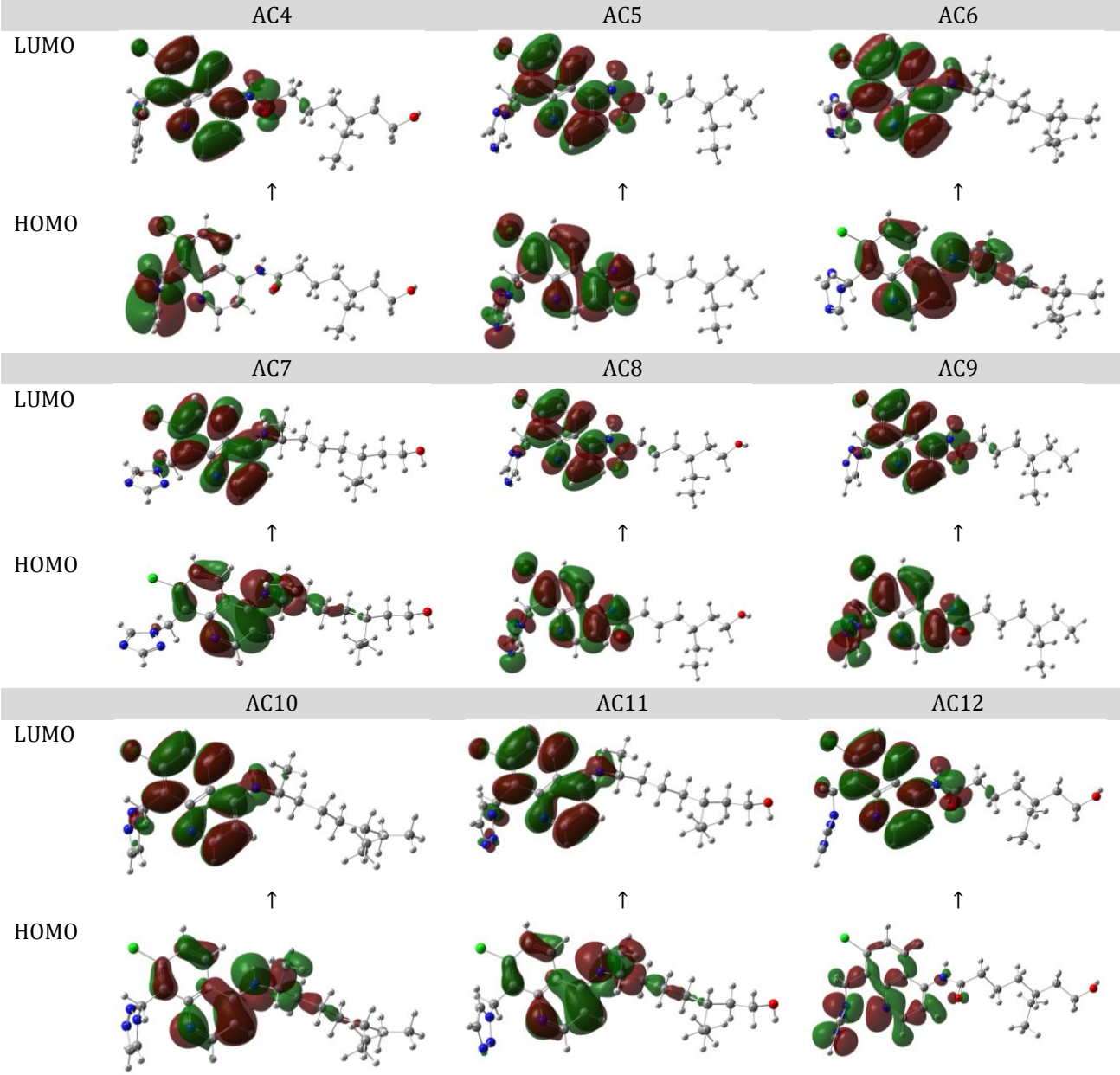
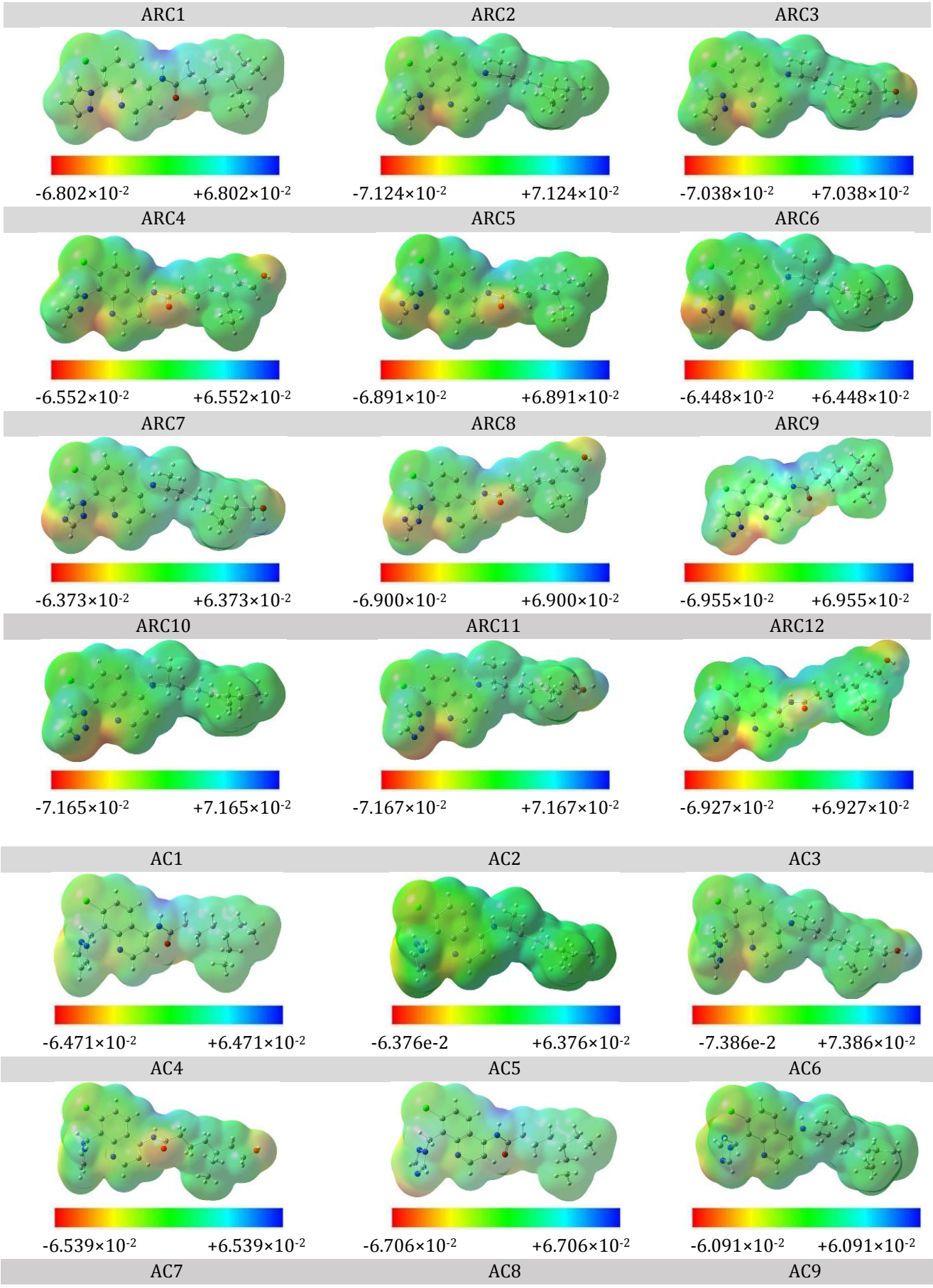


Figure 4: HOMO-LUMO structures of the studied compounds

The concentration of the most negative area in the hetero O- and N-regions and the most positive area in the hydrogen regions shows where a nucleophilic attack could happen. These websites give information about the part of the chemical where possible interactions between molecules can happen. This showed where attacks that were both electrophilic and nucleophilic would be most likely to happen.

Drug-likeness and pharmacokinetics properties

Using the free, comprehensive web tool SWISSADME, we did a virtual physicochemical evaluation of all 24 CQ-derivatives of series A and B. This gave us a thorough look at how drug-like our newly designed derivatives are compared to the parent compound chloroquine. All 24 compounds met the limits for molecular weight, lipophilicity (octanol-water partition coefficient MLogP 4.15), and water solubility. Along with MR, the number of hydrogen bond acceptors and the PSA were both within the acceptable range. It looks like the number of bonds that can be rotated is the only physicochemical property that separates the compounds in series B. The scores of compounds AC3, AC4, AC7, AC8, AC11, and AC12 are outside of the acceptable range, as shown in Tables 2 and 3.


ARC1
-6.802×10-2 +6.802×10-2
ARC2
-7.124×10-2 +7.124×10-2
ARC3
-7.038×10-2 +7.038×10-2
ARC4
-6.552×10-2 +6.552×10-2
ARC5
-6.891×10-2 +6.891×10-2
ARC6
-6.448×10-2 +6.448×10-2
ARC7
-6.373×10-2 +6.373×10-2
ARC8
-6.900×10-2 +6.900×10-2
ARC9
-6.955×10-2 +6.955×10-2
ARC10
-7.165×10-2 +7.165×10-2
ARC11
-7.167×10-2 +7.167×10-2
ARC12
-6.927×10-2 +6.927×10-2
AC1
-6.471×10-2 +6.471×10-2
AC2
-6.376e-2 +6.376×10-2
AC3
-7.386e-2 +7.386×10-2
AC4
-6.539×10-2 +6.539×10-2
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AC7
AC8
AC9

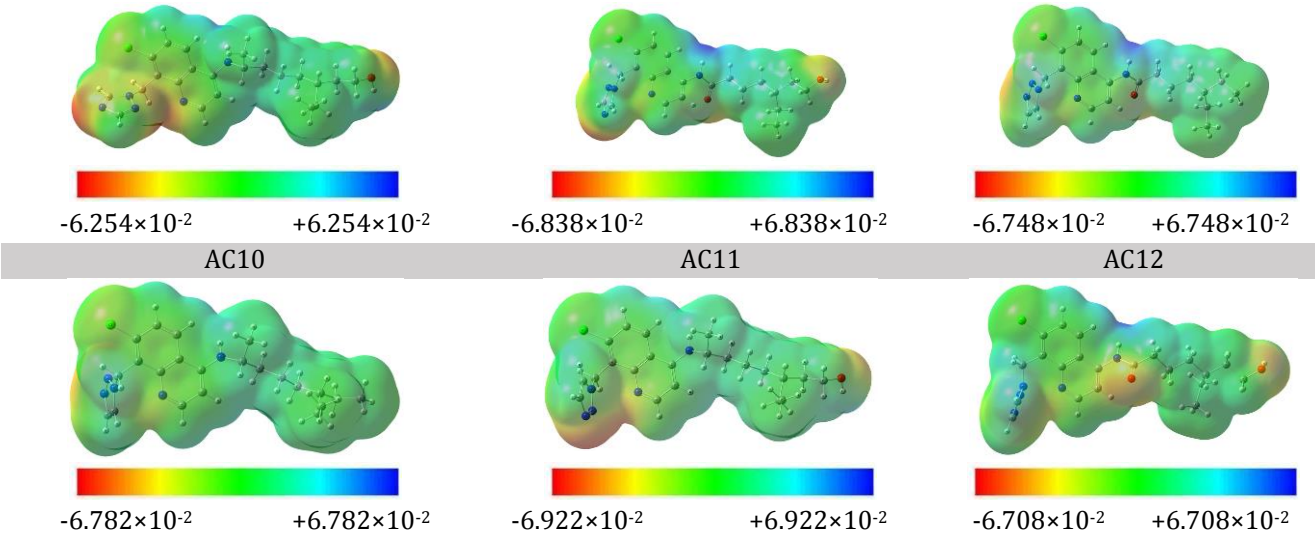


Figure 5: MEP map of the title compounds

Table 2: SWISSADME-computed physicochemical properties of series A derivatives

Compound	Mwt (g/mol)	nRot	HBA	TPSA (Å²)	M LogP	Ali Log S	MR
ARC1	385.89	9	4	63.05	2.37	-4.02	109.93
ARC2	385.93	9	3	45.98	3.08	-5.38	114.53
ARC3	401.93	10	4	66.21	2.26	-4.72	115.69
ARC4	401.89	10	5	83.28	1.57	-3.34	111.09
ARC5	386.88	9	5	75.94	2.16	-4.05	107.72
ARC6	386.92	9	4	58.87	2.86	-5.42	112.33
ARC7	402.92	10	5	79.10	2.06	-4.75	113.49
ARC8	402.88	10	6	96.17	1.38	-3.39	108.88
ARC9	386.88	9	5	75.94	2.16	-3.72	107.72
ARC10	386.92	9	4	58.87	2.86	-5.09	112.33
ARC11	402.92	10	5	79.10	2.06	-4.42	113.49
ARC12	402.88	10	6	96.17	1.38	-3.05	108.88

MW: Molecular weight; nRot: Number of rotatable bonds; HBA: Hydrogen-bonded acceptor; TPSA: Topological polar surface area; M log P: Lipophilicity log or Moriguchi octanol-water partition coefficient; Ali log S: Aqueous solubility descriptor; and MR: Molar refractivity.

All 24 of the compounds show excellent passive gastrointestinal absorption in the pharmacokinetic analysis. All of the interesting cytochrome p450 isoenzymes tend to be blocked by these derivatives, and P-gp and BBB permeability seem to be different factors that affect their metabolic fates and distribution patterns. Tables 4 and 5 present the results.

SWISSADME-integrated drug-likeness assessment using Lipinski-rule of five as a reference shows that all 24 compounds have the potential to be considered drugs, meeting all the limits set by Lipinski *et al.* [77], as provided in Tables 4 and 5. In Tables 4 and 5, you can see how friendly each of the 24 compounds is to medicinal chemistry. All of the 24 compounds being studied have structures that are similar to the parent compound CQ. None of the 24 compounds have PAINS or Brenk alerts that indicate they might be unstable or dangerous, and it is easy to make all of them. However, it seems clear that none of the 24 derivatives have the right physicochemical properties to be considered lead-like, as indicated in Tables 6 and 7.

Comparing the physiochemical, kinetic and medicinal chemistry friendliness of the parent compound CQ (Table 8), with our derivatives show numerous promising results.

Optimal range: molecular weight (MW) ≤ 600; Lipophilicity log or Moriguchi octanol-water partition coefficient (M log P) ≤ 5; Aqueous solubility descriptor (Ali log S) ≤ 0; Hydrogen-bonded acceptor (HBA) ≤ 10; Topological polar surface area (TPSA) ≤ 150 Å2; Number of rotatable bonds (nRot) ≤ 10; Molar refractivity (MR) ≤ 155. CYP*: Cytochromes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4); and *XLOGP3: An atomistic lipophilicity prediction method. All of the derivatives have a higher molecular weight than CQ, and their MR values are much higher than CQ's. This means that the compounds are bigger and heavier than CQ. The lipophilic profile of CQ seems to be the same as that of compounds ARC2 and AC2 because the methyl groups at positions 10 and 15 are still there. The pyrazole ring at position 8 does not seem to have any effect on the lipophilic profile, and all other compounds are less lipophilic than CQ.

The aqueous solubility descriptor of CQ shows that it dissolves well in water. This is based on the scores of compounds ARC3, AC3, ARC7, AC7, and ARC11, AC11, which show a similar solubility profile to the parent compound. All 24 CQ-derivatives have a much higher number of HBA than CQ, so it is expected that they will have stronger binding sites with their intended targets.

Table 3: SWISSADME-computed physicochemical properties results of series B derivatives

Compound	Mwt (g/mol)	nRot	HBA	TPSA (Å^2)	M LogP	Ali Log S	MR
AC1	399.92	10	4	63.05	2.32	-3.95	114.34
AC2	399.96	10	3	45.98	3.02	-5.32	118.94
AC3	415.96	11	4	66.21	2.21	-4.65	120.11
AC4	415.92	11	5	83.28	1.53	-3.28	115.50
AC5	400.91	10	5	75.94	2.12	-3.98	112.13
AC6	400.95	10	4	58.87	2.81	-5.35	116.74
AC7	416.95	11	5	79.10	2.01	-4.69	117.90
AC8	416.90	11	6	96.17	1.33	-3.31	113.29
AC9	400.91	10	5	75.94	2.12	-3.66	112.13
AC10	400.95	10	4	58.87	2.81	-5.02	116.74
AC11	416.95	11	5	79.10	2.01	-4.36	117.90
AC12	416.90	11	6	96.17	1.33	-2.99	113.29

MW: Molecular weight; nRot: Number of rotatable bonds; HBA: Hydrogen-bonded acceptor; TPSA: Topological polar surface area; M log P: Lipophilicity log or Moriguchi octanol-water partition coefficient; Ali log S: Aqueous solubility descriptor; and MR: Molar refractivity.

Table 4: SWISSADME-pharmacokinetic analysis results of series A derivatives

Compounds	GI absorption	BBB permeant	P-gp Substrate	CYP* Inhibition
ARC1	High	Yes	No	Yes
ARC2	High	Yes	No	Yes
ARC3	High	Yes	No	Yes except 2C9
ARC4	High	No	Yes	Yes except 1A2 & 2C9
ARC5	High	Yes	No	Yes except 1A2
ARC6	High	Yes	No	Yes
ARC7	High	Yes	No	Yes
ARC8	High	No	Yes	Yes except 1A2 & 2C9
ARC9	High	Yes	Yes	Yes except 1A2
ARC10	High	Yes	No	Yes
ARC11	High	Yes	Yes	Yes except 2C9
ARC12	High	No	Yes	Yes except 1A2, 2C19 & 2C9

GI: gastro-intestinal absorption; BBB: blood brain barrier; P-gp: P-glycoprotein; and CYP: Cytochromes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4).*

Table 5. SWISSADME-pharmacokinetic analysis results of series B derivatives

Compounds	GI absorption	BBB permeant	P-gp Substrate	CYP* Inhibition
AC1	High	Yes	Yes	Yes except 1A2
AC2	High	Yes	No	Yes
AC3	High	Yes	No	Yes except 2C9
AC4	High	No	Yes	Yes except 1A2 & 2C9
AC5	High	Yes	No	Yes except 1A2
AC6	High	Yes	No	Yes
AC7	High	No	No	Yes except 2C9
AC8	High	No	Yes	Yes except 1A2 & 2C9
AC9	High	Yes	Yes	Yes except 1A2
AC10	High	Yes	No	Yes
AC11	High	No	Yes	Yes except 1A2 & 2C9
AC12	High	No	Yes	Yes except 1A2, 2C19 & 2C9

GI: gastro-intestinal absorption; BBB: blood brain barrier; P-gp: P-glycoprotein; and CYP: Cytochromes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4).*

Table 6: SWISSADME-computed medicinal chemistry friendliness results of series A derivatives

Compounds	PAINS alert	Brenk alert	Lead likeness	Synthetic accessibility
ARC1	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.88
ARC2	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.49
ARC3	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.55
ARC4	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.93
ARC5	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.83
ARC6	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.43
ARC7	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	3.48
ARC8	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.92
ARC9	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.92
ARC10	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.54
ARC11	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	3.60
ARC12	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.98

**XLOGP3: An atomistic lipophilicity prediction method.*

Table 7: SWISSADME-computed medicinal chemistry friendliness results of series B derivatives

Compound	PAINS alert	Brenk alert	Lead likeness	Synthetic accessibility
AC1	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.88
AC2	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.51
AC3	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.56
AC4	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.94
AC5	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.86
AC6	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.48
AC7	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	3.53
AC8	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.91

AC9	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	2.96
AC10	0 alert	0 alert	No; 3 violations: MW>350, Rotors>7, XLOGP3*>3.5	3.59
AC11	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	3.64
AC12	0 alert	0 alert	No; 2 violations: MW>350, Rotors>7	3.01

**XLOGP3: An atomistic lipophilicity prediction method.*

Table 8: SWISSADME-mediated analysis of the physicochemical, pharmacokinetic and medicinal chemistry friendliness of chloroquine

MW	319.87 g/mol
M log P	3.20
Ali log S	-4.95
HBA	2
TPSA	28.16 $Å^2$
nRot	8
MR	97.41
PAINS alert	0
Brenk alert	0
Lead likeness	No; 2 violations: Rotors>7, XLOGP3*>3.5
Synthetic accessibility	2.76
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP* inhibition	Yes except 2C19 & 2C9
Lipinski rule of five	Yes; 0 violation

Another important factor is that the PSA values of all derivatives are very different from those of CQ. This shows that CQ is very good at getting through cell membranes and the blood-brain barrier (BBB), which greatly increases the risk of toxic side effects from CQ. When it comes to adaptability, CQ is in line with all derivatives. Another set of parameters that CQ shares with all of its derivatives is that it does not cause PAINS or Brenk alerts, is not compatible with being lead-like, and has a good synthetic score and good oral bioavailability. Based on a drug-likeness evaluation, all of our derivatives are excellent drug candidates, just like CQ. CQ can get through the BBB and does not tend to be a substrate for P-gp. It also blocks all P-450 isoenzymes except 2C19 and 2C9, just like most of the compounds we have made.

Set 1 of series A and B has different groups at positions 10 and 15, but they both have the same heterocyclic part at position 8 that looks like an aromatic pyrazole ring. Compounds ARC1 and AC1 have a carbonyl group and a methyl group. Compounds ARC2 and AC2 have two methyl groups. Compounds ARC3, AC3, ARC4, and AC4 have methyl, hydroxymethyl, carbonyl, and hydroxymethyl groups, respectively. As indicated in Table 1, different R2 and R3 groups lead to different physicochemical properties. The addition of the hydroxymethyl group at position 15 in ARC3 and ARC4, compared to ARC1 and ARC2, and in AC3 and AC4, compared to AC1 and AC2, seems to be the cause of the increase in the number of rotatable bonds and the noticeable increase in the molecular weight, as listed in Table 1. The number of hydrogen bond acceptors (HBA) in ARC1 and AC1 is the same as in ARC3 and AC3, with a methyl group in common but different oxygen-bearing groups at positions 10 and 15. ARC2 and AC2 have a low number of hydrogen bond acceptors (HBA) compared to other pyrazole-containing compounds in series A and series B. This is because they have methyl groups at positions 10 and 15, while ARC4 and AC4 have carbonyl and hydroxymethyl groups with oxygen atoms that can accept hydrogen bonds. Changes in R2 and R3 have a big effect on other physical and chemical properties, such as

solubility in water, lipophilicity, and PSA. In terms of PSA, the scores for the four compounds in set 1 of both series depend on how polar the newly added side groups make each derivative. As shown in Table 1, the order of increasing PSA within set 1 of series A and series B is 2134. The reason for this order is that AC2 and ARC2 have two methyl groups at positions 10 and 15, which makes them less polar than the other three derivatives in each series. ARC1 and AC1 derivatives have a carbonyl group, while ARC3 and AC3 derivatives have a hydroxymethyl group. There is a slight difference in PSA between ARC1 and ARC3 and AC1 and AC3. Even though each pair has a polar oxygen atom at positions 10 and 15, it seems that the hydroxyl oxygen contributes more to the total polar surface area than the carbonyl group. The highest score went to ARC4 and AC4 derivatives because they have two oxygen-containing groups at positions 10 and 15.

The side groups also change MR, which is an interesting parameter. As presented in Table 1, the order of increasing MR in set1 of both series is 1423. The MR of a compound depends on its density and molecular weight, as well as its polarisability, or its ability to be affected by a magnetic field from the outside. In general, MR is directly proportional to molecular weight, but our results don't show this. The reason for this disagreement is that the methyl group takes up more space than the carbonyl group, as in the case of ARC1, ARC3, AC1, and AC3. When ARC4, ARC1, AC4, and AC1 are compared, there does not seem to be much difference in their scores. However, replacing one of the methyl hydrogen atoms with a hydroxyl group seems to have a compensating effect on atomic occupancy. There is also a clear difference in score between compounds 2 and 3 of set 1 in each series. Each of the four compounds' lipophilicity is strongly affected by the groups on the side that are either hydrophobic or hydrophilic. In the opposite direction of PSA, the order of the least lipophilic to the most lipophilic derivatives in each set 1 series is 4312 (see Table 1). ARC4 and AC4 have polar groups at positions 10 and 15, which are carbonyl and hydroxymethyl, respectively. ARC3, ARC1, AC3, and AC1 seem to have slightly different scores, but the main difference is that ARC1 and AC1 have a carbonyl group at position 10, while ARC3 and AC3 have a hydroxymethyl group. This gives ARC1 and AC1 a more lipophilic effect because the carbonyl oxygen interacts less with the solvent than the at positions 10 and 15, ARC2 and AC2 derivatives have two methyl groups. This makes them very lipophilic. In terms of how well they dissolve in water, the order of increasing hydrophilicity within set 1 of both series is 2134, which is the same as the order of PSA. When you look at the pharmacokinetic assessment of set 1, you get a wide range of results, except for passive GI absorption, which is a criterion that all of the corresponding compounds meet, as shown in Tables 2 and 3. Inhibitors of cytochrome P450 iso-enzymes can be very different, and they can pass through the blood-brain barrier (BBB) and be substrates for P-gp in different ways. This suggests that there are many structural differences that come from alternating groups at positions 10 and 15, with PSA values playing a key role.

Set 2 compounds from both series have a 1,2,4-triazole ring at position 8 instead of a pyrazole ring. This is the main difference between set 2 and set 1. In terms of physicochemical parameters, there is a general increase in molecular weight, PSA, and HBA values because there is an extra nitrogen atom at position 4 of the five-membered ring. There is also a noticeable decrease in MlogP values, which shows that the lipophilicity of the molecule is decreasing overall. The scores of water solubility indicator, log S, show results that are almost the same. The number of bonds that can be rotated is the same in both set 1 and set 2 of series A and set 1 and set 2 of series B, but the MR decreases in both cases. As in set 1 of both sets, set 2 compounds are not lead-like enough to work together. All of the compounds are free of PAINS and Brenk alerts and are easy to make in general. The results are shown in Table 1. The results of the pharmacokinetic evaluation, which are shown in Tables 2 and 3, show that oral bioavailability is very good, but that BBB permeability and P450 inhibitory activity vary. Being a substrate for P-gp seems to be different for the compounds in set 2

of series A and set 2 of series B. The same is true for set 2 of series B.

Set 3 of both series A and B show 1,2,3-Triazole at position 8. The position of three nitrogen atoms in the five-membered ring seems to have no effect on the difference between set 2 of series A and B and set 3 of both series in terms of physiochemical properties and how well they work in medicinal chemistry. It seems that the difference in the number of atoms in heterocyclic ring has the most effect on how the drug moves through the body. In set 2 of series A and B, the derivatives ARC5, AC5, ARC6, AC6, and ARC7, AC7, but not ARC8 and AC8, are not likely to be substrates for P-gp, as depicted in Tables 2A and 2B. Even though ARC5, AC5, and ARC7, AC7 are the same as ARC9, AC9, and ARC11, AC11 in terms of the R2 and R3 substituents, the numbering of the heterocyclic rings seems to have a bad effect. As shown in Tables 2 and 3, a change in the position of the nitrogen atom seems to also affect how P450 enzymes are stopped from working.

Heterocyclic substitution at position 8 in the main core causes a number of physical and chemical changes, one of which is the difference between set 1 and its counterparts in sets 2 and 3. When compared to set 1 of series A and B, sets 2 and 3 have higher molecular weight values, a higher number of HBA, a noticeable rise in PSA, and a drop in MR. Ali logS values are about the same, and MLogP values are lower. The supposed differences in physicochemical and kinetic properties between the four compounds in sets 2 and 3 of series A and series B will follow the same pattern as in set 1, which is caused by a fixed lateral heterocyclic ring with alternating side groups at positions 10 and 15. The physicochemical properties of all three sets of series B at positions 8, 10, and 15 are mostly the same as those of series A, even though the structures have been changed. One difference between series A and series B is that all derivatives of series B have a methylene bridge at position 8 that connects the heterocyclic ring to the quinoline nucleolus of CQ. When a linker methylene group is added to all three sets of series B, compared to all three sets of series A, there is a noticeable increase in molecular weight and molar refractivity, as well as an increase in the number of rotatable bonds, a slight increase in water solubility, and a slight decrease in lipophilicity, which can be attributed to a larger volume of space being occupied or an increase in overall sphericity. Because of the methylene bridge, there was no difference between the two sets in terms of how well they worked with medicinal chemistry and how much they looked like drugs. Comparing the pharmacokinetics of all three sets of both series had no effect on the fact that all 24 derivatives had a high rate of absorption through the gastrointestinal tract. When set 1 of series A's BBB permeability is compared to set 1 of series B's BBB permeability, it shows that all compounds can pass through BBB. When set 2 of series A is compared to set 2 of series B, you can see that derivative ARC7 can cross, but AC7 cannot. The same thing was shown between ARC11 and AC11. In set 1, the susceptibility to P-gp is also changed, but in sets 2 and 3, the results are the same. When you compare compounds 1, 7, and 11 in series A to their counterparts in series B, you can see that their effects on cytochrome enzymes are not the same.

Molecular docking

Molecular docking is a computer technique that is used a lot in computer-aided drug design [86]. Elkanzi *et al.* (2023) gives us a useful tool for figuring out where a small molecule will bind to its target protein most effectively [87]. The main goal of molecular docking is to find the best shape for each drug and protein and the best orientation between them. This lowers the free energy of the whole system. It is a way to predict and figure out if the chemicals being looked into are good candidates for new medicines. It is a method that looks at the position and shape of molecules in the binding site of a macromolecular target. Comparative molecular docking was used to look at how the target compounds could deliver drugs as a possible anti-Covid-19 therapy candidate. This was done to reach the goal. The 3D crystallographic structures of the receptor molecules chosen for docking experiments were

found in the Protein Data Bank (PDB). In order to make the receptor proteins, water molecules had to be taken out, explicit hydrogens, charges, and distorted amino acid sequences had to be fixed. Based on how the crystallographic ligands interacted with the receptor molecules, which could be seen with the MOE, the active sites of the receptor protein were predicted and defined. The target substances docked with the SARS-COV-2 major protease viral protein receptor COVID-19 (PDB ID: 6LU7).

The docking results show that the compounds that were looked at have other types of bonds besides hydrogen bonds. These include donor-donor bonds, pi cations, pi sigmas, pi alkyls, salt bridges, and others. Table 9 and Figure 6 can be used to show the bond distances for these interactions (6). The docking results showed the following order of binding affinity: AC8> AC10> AC3> AC5> ARC7> AC2> AC7> AC11> AC9> ARC8> AC12> ARC4> ARC12> AC6> ARC2> ARC1> ARC3> AC4> ARC5> ARC9> AC1> ARC11 ARC10> ARC6.

Based on these binding results, AC8, AC10, AC3, and AC5 have the strongest binding affinities compared to the other compounds, while ARC10 and ARC6 have the lowest binding affinities. In general, the results of the binding affinity showed that the studied drugs and receptors might have anti-Covid-19 properties.

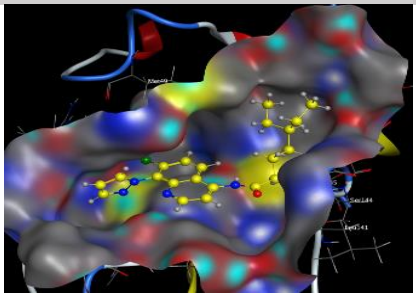
The inhibition constant is a key measure of how well a manufactured molecule works as a hit, lead, or therapeutic candidate (Ki value). A molecule must be in the micromolar (M) range to be a hit or lead compound, and a high potency is usually indicated by a low Ki value. Because the Ki values of the synthesized compounds ranged from 0.88 to 4.68 M, they were all considered hits and leaders. As listed in Table 1, the compounds with the lowest Ki values were AC8, AC10, AC3, and AC5. They could be used as a treatment (6).

Table 9: Molecular docking data

	Ligand	Receptor	Interaction	Distance	E (kcal/mol)	S (kcal/mol)	MicrMolar
ARC1	N 24	MET 165	H-donor	3.31	-0.50	-7.40	3.81
	6-ring	GLU 166	pi-H	3.64	-1.80		
	5-ring	GLN 189	pi-H	3.78	-1.20		
	5-ring	GLN 189	pi-H	4.21	-0.60		
ARC2	CL 14	GLN 192	H-donor	3.85	-0.70	-7.43	3.66
	6-ring	GLN 189	pi-H	4.20	-0.80		
ARC3	CL 14	ARG 188	H-donor	3.22	-0.40	-7.40	3.84
	O 28	ASN 142	H-acceptor	3.33	-0.60		
ARC4	O 27	MET 165	H-donor	3.77	-0.70	-7.46	3.48
	5-ring	HIS 41	pi-H	4.40	-0.80		
ARC5	C 23	GLU 166	H-donor	3.39	-0.70	-7.38	3.95
	5-ring	LEU 141	pi-H	4.13	-0.80		
ARC6	N 9	GLY 143	H-acceptor	3.46	-2.00	-7.28	4.68
	5-ring	GLY 143	pi-H	3.24	-0.70		
ARC7	C 23	MET 165	H-donor	3.98	-0.90	-7.67	2.44
	5-ring	LEU 167	pi-H	4.39	-1.00		
	6-ring	GLN 189	pi-H	3.55	-0.90		
ARC8	C 23	MET 165	H-donor	3.97	-0.90	-7.47	3.39
	5-ring	LEU 167	pi-H	4.43	-1.00		
	6-ring	GLN 189	pi-H	3.51	-0.60		
ARC9	C 23	MET 165	H-donor	3.79	-0.90	-7.38	3.98
	5-ring	LEU 167	pi-H	4.45	-0.60		
ARC10	C 23	165	H-donor	3.86	-0.80	-7.29	4.60

	6-ring	166	pi-H	3.60	-1.30		
	5-ring	189	pi-H	3.87	-0.70		
ARC11	O 28	HIS 163	H-acceptor	2.99	-2.40	-7.34	4.22
	C 13	HIS 41	H-pi	4.23	-0.60		
	5-ring	LEU 167	pi-H	4.32	-1.20		
ARC12	N 24	MET 165	H-donor	3.29	-0.40	-7.46	3.48
	5-ring	GLN 189	pi-H	4.07	-1.10		
	5-ring	GLN 189	pi-H	3.79	-0.80		
	Ligand	Receptor	Interaction	Distance	E (kcal/mol)	S (kcal/mol)	MicrMolar
AC1	N 9	CYS 145	H-acceptor	3.47	-1.20	-7.36	4.09
	6-ring	ASN 142	pi-H	3.93	-0.60		
AC2	N 11	GLY 143	H-acceptor	3.43	-1.30	-7.67	2.41
AC3	N 11	GLY 143	H-acceptor	3.43	-1.90	-7.75	2.12
	C 16	HIS 41	H-pi	3.93	-0.90		
	O 23	HIS 41	H-pi	3.40	-0.60		
	5-ring	THR 25	pi-H	4.13	-1.40		
AC4	N 9	CYS 145	H-donor	3.86	-0.60	-7.40	3.83
	CL 14	PHE 140	H-donor	3.11	-0.30		
	5-ring	ASN 142	pi-H	3.79	-1.70		
	5-ring	GLY 143	pi-H	3.32	-1.90		
	6-ring	MET 165	pi-H	3.85	-0.60		
AC5	C 25	ARG 188	H-donor	3.29	-0.70	-7.68	2.39
	6-ring	GLU 166	pi-H	4.07	-1.80		
AC6	6-ring	GLU 166	pi-H	3.95	-0.70	-7.45	3.51
	5-ring	LEU 167	pi-H	4.73	-0.60		
	5-ring	GLN 189	pi-H	4.66	-0.60		
AC7	O 23	ASN 142	H-acceptor	3.37	-0.40	-7.66	2.49
	O 23	GLY 143	H-acceptor	3.40	-0.60		
	6-ring	GLN 189	pi-H	3.55	-0.80		
AC8	O 22	CYS 145	H-donor	3.33	-0.40	-8.27	0.88
	6-ring	GLU 166	pi-H	4.16	-1.00		
	6-ring	GLU 166	pi-H	4.19	-0.70		
	5-ring	LEU 167	pi-H	4.63	-0.70		
AC9	O 22	CYS 145	H-donor	3.29	-0.30	-7.57	2.87
	O 22	MET 165	H-acceptor	3.40	-0.80		
	6-ring	GLU 166	pi-H	4.14	-0.80		
	6-ring	GLU 166	pi-H	4.13	-1.00		
AC10	C 23	MET 49	H-donor	3.82	-1.00	-7.83	1.84
	6-ring	GLU 166	pi-H	4.35	-1.40		
AC11	O 23	HIS 163	H-acceptor	3.16	-2.10	-7.59	2.76
	6-ring	GLN 189	pi-H	3.55	-0.60		
AC12	O 23	GLY 143	H-acceptor	3.00	-0.70	-7.47	3.38
	O 23	CYS 145	H-acceptor	3.25	-0.50		
	6-ring	GLU 166	pi-H	4.40	-0.60		
	6-ring	GLU 166	pi-H	4.08	-1.60		

ARC1



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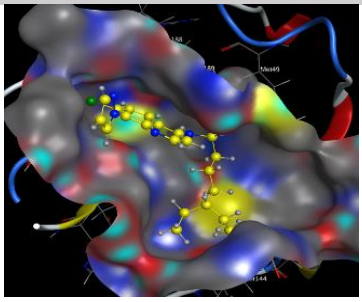

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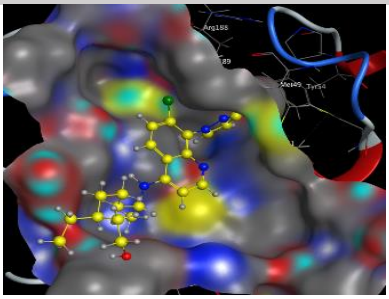

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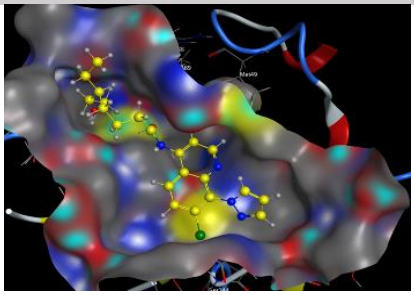

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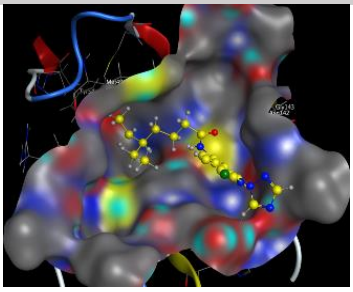

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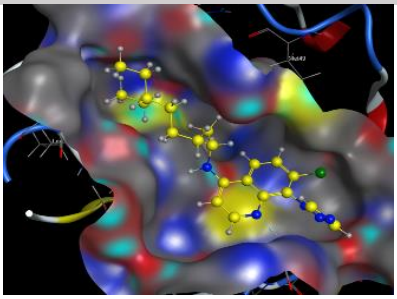

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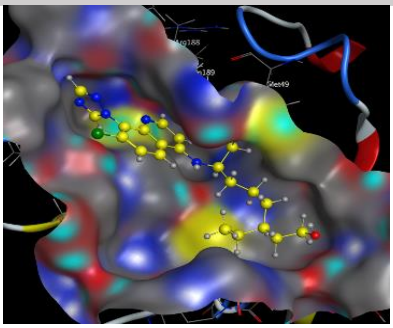

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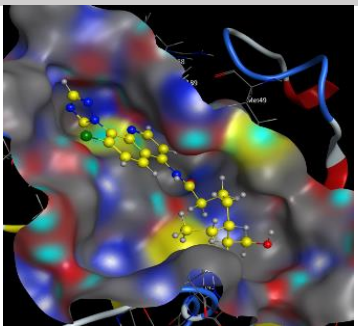
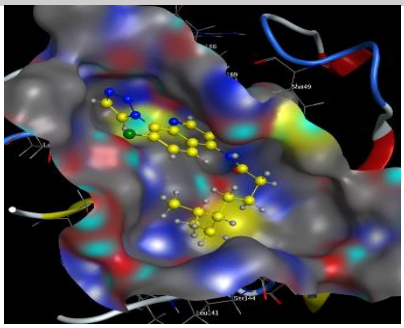


ARC9



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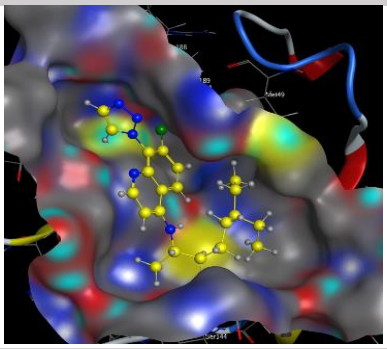

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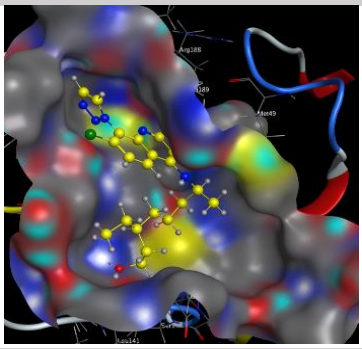

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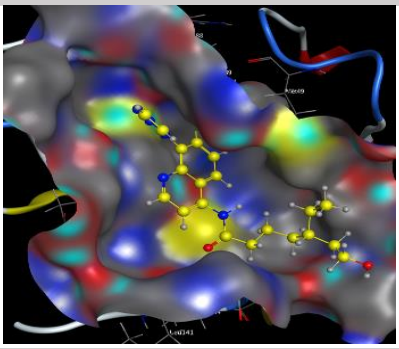

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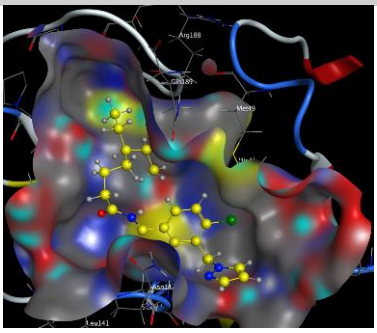

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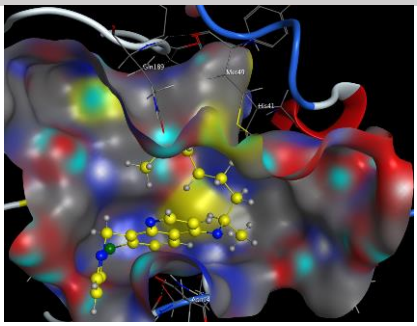

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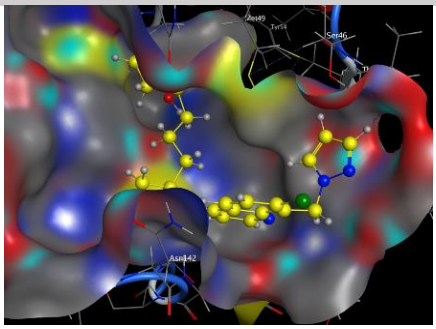

AC4

AC5

AC6

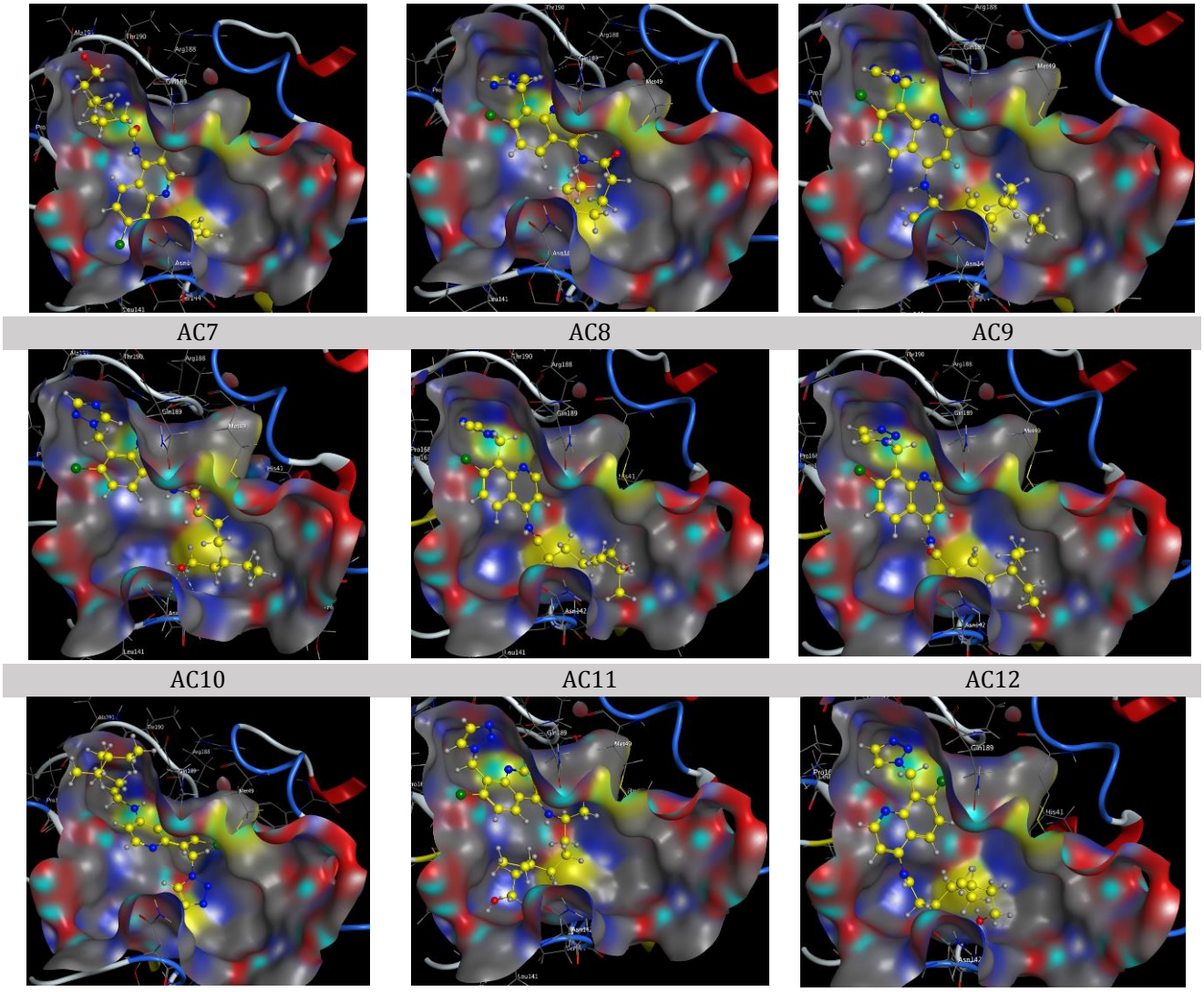

Figure 6: Molecular docking interactions

Conclusion

Our investigation led us to the conclusion that the rigid molecules ARC10 and ARC6 as well as the flexible compounds AC10 and AC5 passed the virtual physicochemical evaluation compared with the findings of the chloroquine parent compound. In addition, the compounds had the highest binding affinities, which suggested that they may have anti-Covid-19 properties.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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HOW TO CITE THIS ARTICLE

Adel M. Najar, Asma Eswayah, Moayed Ben Moftah, Ruwida Omar M.K., Eman Bobtaina, Mohamed Najwa, Tawfeg A. Elhisadi, Aeyad Tahani, Salha M.Tawati, Aliaa M. M.Khalifa, Aly Abdou, Ahmed Emhamed DowAltome. Rigidity and Flexibility of Pyrazole, s-Triazole, and v-Triazole Derivative of Chloroquine as Potential Therapeutic against COVID-19. *J. Med. Chem. Sci*., 2023, 6(9) 2056-2084

DOI: https://doi.org/10.26655/JMCHEMSCI.2023.9.14

URL: http://www.jmchemsci.com/article_169068.htmlV