Computational, Pharmacological Evaluation and Comparative Similarity against Chloroquine for Some New Designed Hybridized Molecules and their Potential Use as Antiviral against COVID-19 and Malaria

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ABSTRACT

Starting from the concept of "similar molecules exert similar biological activities" to modify structures of biologically active molecules or readily available drugs to improve their therapeutic activity or reduce side effects. Four designed 7-Chloroqunioline-N-Heterocyclic molecules that are derived from parent compound chloroquine (which recently has attracted wide international attention due to its potential activity against COVID-19) were investigated regarding QSAR and some electronic parameters compared to the original drug. Their chemical properties, biochemical properties, and physio-chemical properties were evaluated using computational chemistry. The method used for calculations was semi-empirical-geometry optimization-PM3. Single crystal X-ray crystallography data of Chloroquine and calculated data have been done using the same parameters. Surprisingly, the experimental and calculated data recorded the same values. Furthermore, in Silico evaluation of pharmacokinetics, drug-likeness and medicinal chemistry friendliness of four hybridized molecules compared to chloroquine by using SwissADME web tool confirm closeness of four hybrids to the chloroquine. The total energy, binding energy, dipole moment energy gap (HOMO-LUMO) and log p of one of compounds coded AB1-4Py were -7.6647.710 Kcalmol-1, -3981.323, 4.531, 8.161 eV, and 4.25 respectively. AB2-4py compound calculated total energy was -76007.6, Binding energy at - 4109.424, dipole moment at 4.464, energy gap (EHOMO-ELUMO) at 8.131 and log p at 4.70. The AB1-4py, AB2-4py and chloroquine reported same stability and bioactivities. From QSAR study, the value of Log P indicates hydrophobic nature. The recorded values of AB1-4Py and AB2-4py were completely agreed with those of chloroquine. Therefore, this study may valuable in the discovery of a new series of potential drugs for treatment of malaria or COVID-19.

Keywords: Chloroquine; COVID-19; Computational; Anti-viral; Hybridized Molecules; Medicinal chemistry.

INTRODUCTION

In December 2019, the outbreak of novel coronavirus that also known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or COVID-2019) was first reported in Wuhan, China. Since that, it widely spread in China as well as many other countries. Therefore, many research laboratories, clinical trials centers and cell culture studies are still ongoing trying to control the rapidly spreading and life threatening viral infection that can cause pneumonia induced death in approximately 2.5% of infected individual according to the latest report in March

14th 2020.At present, researches have proven that chloroquine may inhibit the growth of SARS-CoV-2 20. This finding has been supported by clinical studies conducted in approximately one hundred SARS-CoV-2 infected patients [1-5].

Chloroquine a 70 years old drug that has been used as prophylactic and therapeutic anti-malarial drug in endemic areas. Additionally, as daily treatment for autoimmune diseases, attracted wide attention due to the therapeutic efficacy it might have against COVID-19. The drug has been included officially in

federal guidelines for treatment of COVID-19 in Republic of China with many cautions due to its serious side effects [6,7].

Many studies suggest that chloroquine may exert its antiviral activity through inhibition of pH-dependent viral fusion/replication and prevention of viral envelope glycoprotein as well as host receptor protein glycosylation. The drug may also inhibit virion assembly in Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC)-like structure. In host the drug can exert its action by attenuation of the expression of pro-inflammatory factors that cause acute respiratory distress syndrome; the first cause of most of deaths in COVID-19 patients [8].

Actually; in new ages of medicinal chemistry and drug design the computational chemistry; molecular modeling and automated synthesis are utilized extensively by researches to help design diverse libraries of new drugs with more potency and less side effects. So, many antiviral drugs like Ritonavir, Indinavir, Zanamivir, Oseltamivir, Lopinavir and others have been discovered by computer-based methods. Therefore, these tools are considerable to be the working horse in many pharmaceutical companies help to resolve many global crises.

CLOGP is one of the most important program that was launched in 1980s and could predict the lipophilicity that could be related to predication of some molecular properties such as molecular volume, molecular surface area, transport through membranes, and binding to receptor surfaces, and hence to many different bioactivities. However, bioactivity of molecules can be estimated using computational Quantitative structure-activity relationship (QSAR) as well as some of their electronic structure such as HOMO/LUMO energy gap [9].

QSAR have been used to model most of the common biological activity of molecules such as bio concentration factor,biodegradation rate, carcinogenicity,drug absorption, drug metabolism, drug clearance,inhibition constant, mutagenicity, blood brain barrier (BBB) permeability, skin permeability,pharmacokinetics, receptor binding affinity,solubility and toxicity [10-23].

In addition, hybridized molecules especially with N-heterocyclic moieties are considered to be one of the most important classes of nitrogen containing heterocyclic compounds that exhibit various biological activities and have many applications in medicinal chemistry. Qunionline-triazoles molecules are good examples of these hybridized molecules that offer treatments for many types of diseases such as cancer and others [24-26].

In the present research, electronic properties and the QSAR studies were performed for four N-heterocyclic hybridized molecules in order to investigate the quantitative effect of the various Physico-Chemical parameters of four compounds closed to chloroquine. Two of the set hybridized molecules recorded values identical to that of chloroquine. In Silico evaluation of pharmacokinetics, drug-likeness and medicinal chemistry friendliness of four hybridized molecules compared to chloroquine by using SwissADME web tool confirm closeness of four hybrids to the chloroquine. Suggesting that a new series of drug could be synthesized to replace chloroquine [27].

SOFTWARE AND COMPUTATIONAL METHODS

Personal acer desktop PC with Windows XP, a 2.93 GHz Intel (R) core (TM) 2 Duo CPU, and 4.00 GB of RAM was used to run all the calculations. Semi-empirical PM3 quantum chemical calculation was carried out by the HyperChem (version 8) TM 8.0 Molecular Modeling program with root mean square (RMS) gradient 0.1 kcal/Åmol using PolakRibiere algorithm. The calculations for all compounds runs using semi-empirical-geometry optimization- PM3 methods. Physiochemical prediction of hybrid compound was performed by using SwissADME web tool [28-31].

BACKGROUND AND OBJECTIVES

Considerable attention should be given to the substituted quinoline ring specially in chloroquine as suggested treatment of COVID-19 pendamic. Quinoline ring is class of N-Heterocyclic compounds whose used widely as base for many of medications such as Moxifloxacin, Grepafloxacin, Ciprofloxacin and Cinchocaine. The presence of high electronegativity atom such as chloride in quinoline ring will affect bioactivity of the compound. Moreover, the N-heterocyclic rings such as qunioline environmental sensitive. So, the substitutions in quinoline ring may increase the bioactivityof molecules as well as increase their intermolecular interactions. The π-π-stacking between quinoline rings in anti-malarial treatments have been reported as one of the most important non-covalent interactions.Additionally, this kind of interactions reported as one of the most important interactions that increased molecular stability. As well as plays an important role in intermolecular recognition [32-40].

However, this interactions may include intercalation of DNA. Moreover, relevant noncovalent interaction patterns responsible for intermolecular recognition may enhance the biological functionality of our designed compounds.Recognition or self-assembly can be described as 'a process in which two or more components can spontaneously associate to form a larger, more-ordered structure through non-covalent interactions [41].

However, the hybridized molecules may increase their bio-functionality [26] through their components using weak interactions reversible assemble. Self-assembly here is generally driven by relatively weak interactions which are often electrostatic and can include π-π-stacking [26,41,42].

Tobacco mosaic virus (TMV) and protein sub-units spontaneously arrange around single strand of RNA to form a right handed helix with 16 ⅓ sub-units per helical turn were the natural examples of strict self-assembly [43].

RESULTS AND DISCUSSION

Semi-Empirical-Geometry Optimization-PM3

The hybridized molecules offer better treatment for different types of diseases.Molecules building their framework based on quinolone-N-Heterocyclic moieties (see Figure 1); can be classified as hybridized compounds. Despite the quinioline as base tend to be one of the most important unit in our life molecules due to its functionality in the life organism; its combination with bioactive moieties may produce a new

products with new functionality. Some QSAR parameters and some electronic properties of the hybridized molecules will be discussed below [25,26, 44].
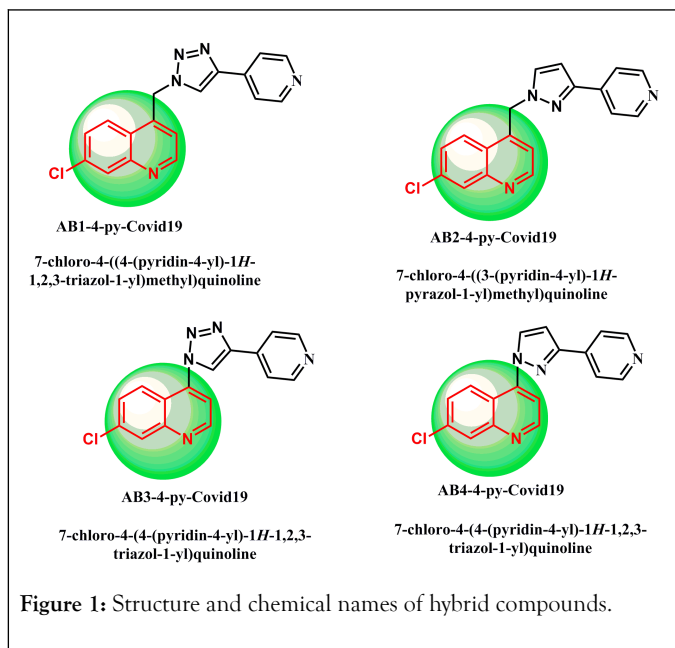

Figure 1: Structure and chemical names of hybrid compounds.

3D view of molecule AB1-4py and AB2-4py were presented in Figures 2 and 3 respectively. The HOMO, LUMO orbitals is very important to mention the chemical reactivity and region of chemical reactivity as well as indicate where the electrophilic and neucleophilic can be attached. The calculation values for all molecules were reordered in Table 1. The observed results that closed to the chloroquine recorded for compounds coded AB1-4py and AB2-4py. AB1-4py compound recorded total energy at -7.6647.710, binding energy at -3981.323, dipole moment at 4.531, energy gap (HOMO-LUMO) at 8.161 and log p at 4.25. Whereas, AB2-4py registered total energy, binding energy, dipole moment energy gap (HOMO-LUMO) and log p at -76007.626, -4109.424, 4.464,8.131 and log p 4.7 respectively. The AB1-4py, AB2-4py and chloroquine recorded same energy gap values. As the molecules stability can be measured based on the EHOMO/LUMO gap and all of AB1-4py, AB2-4py and chloroquine present same values; which main that the molecules have same stability. Moreover, the bioactivity of molecules can be estimated by log p;AB1-4py, AB2-4py and chloroquine recorded same values of lop p which is at 4; that reflect the three molecules may have same bioactivity [45-47].

Table1: Data of ABn-4Py (n=1,2,3,4) Semi-empirical-PM3-geometry optimization.

| Parameter	AB1-4Py	AB2-4Py	AB3-4Py	AB4-4Py	Chloroquine
Total energy Kcal/mol	-7.6647.710	76007.626-	73196.227-	72558.344-	-76971
Binding energy Kcal/mol	-3981.3	4109.424-	3697.868-	3828.1703-	-4788.2
Dipole moment (deby), D	4.531	4.464	3.063	3.25	4.097
EHOMO(eV)	-9.505	-9.301	-9.329	-9.069	-8.9217
ELOMO(eV)	-1.344	-1.178	-1.624	-1.438	-0.7871
Energy gap(eV)	8.161	8.131	7.705	7.631	8.1345
Surface area (Approx)	398.63	413.83	374.49	384.15	568.85
Surface Area (Grid)	532.54	543.54	497.18	500.53	596.39
Volume	882.72	895.65	826.33	834.03	1007.6
Polarizability	35.95	36.66	34.12	34.82	38.14
Reactivity	90.06	90.2	85.23	85.23	96.39
Log P	4.25	4.3	4.15	4.6	4.27
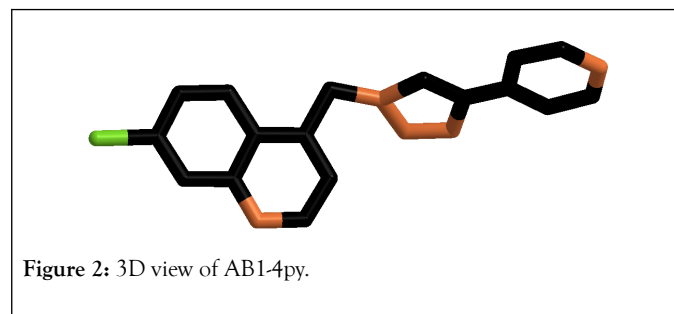
Figure 2: 3D view of AB1-4py.
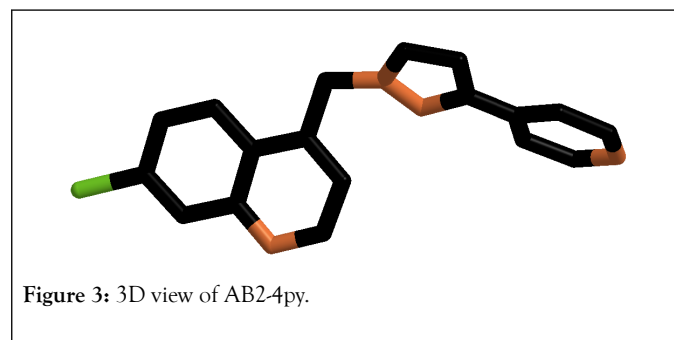
Figure 3: 3D view of AB2-4py.

Geometrical investigation of Chloroquine as reference compound

The crystal structure of chloroquine with atomic number presented in Figure 4. Bond length (Å) for experimental and calculated data. The recorded values of both crystal and calculated were closed as we can see that in Table 2. However, selected bond angle (˚) presented in Table 3. The experimental and calculated values seem in excellent agreement. The single crystal values of bond angles and bond lengths in good agreement with calculated values [38].

Table 2: Selected experimental and calculated bond lengths (Å).

	Experimental Bond length	Calculated Bond length		Experimental Bond angles	Calculated Bond angles
N(I)-C(2)	1.323 (6)	1.32303	C(15)-C(16)	1.499 (7)	1.51784
C(4)-N(9)	1.334 (6)	1.44267	C(l0)-C(19)	1.513 (7)	1.52561
N(9)-C(10)	1.481 (6)	1.49727	C(3)-C(4)	1.403 (6)	1.3787
C(13)-N(14)	1.485 (6)	1.49085	C(17)-C(18)	1.498 (8)	1.51639
N(14)-C(17)	1.495 (6)	1.4919	C(2)-C(3)	1.360 (6)	1.41881
N(14)-C(15)	1.511 (6)	1.49517	C(1 l)-C(12)	1.516 (6)	1.52171
C(12)-C(13)	1.513 (6)	1.52424	CI-C(7)	1.723 (5)	1.68559

Table 3: Selected experimental and calculated bond angle (˚).

	Calculated angles	Bond	Experimental Bond angles [38]		Calculated Bond angle	Experimental Bond angle [38]	Bond
C(4)-C(3)-C(2)	120.6 (5)		119.75	C(8)-C(7)-Cl	120.1 (4)	120.149	
N(9)-C(4)-C(3)	121.4 (5)		120.684	C(6)-C(7)-Cl	118.7 (4)	118.479	
C(10)-N(9)-C(4)	124.7 (4)		115.555	C(15)-N(14)-C(13)	108.3 (4)	113.747	
C(12)-C(11)-C(10)	113.9 (4)		110.634	C(18)-C(17)-N(14)	115.6 (5)	111.27	
N(14)-C(13)-C(12)	114.3 (4)		110.857	C(3)-C(2)-N(1)	122.4 (5)	122.373	
C(17)-N(14)-C(13)	114.7 (4)		112.099	C(19)-C(10)-C(11)	112.0 (4)	110.439	
C(16)-C(15)-N(14)	114.6 (4)		110.139	C(I I)-C(10)-N(9)	109.4 (4)	108.388	

Figure 4: Chemical structure of chloroquine shows atom numbering [38].
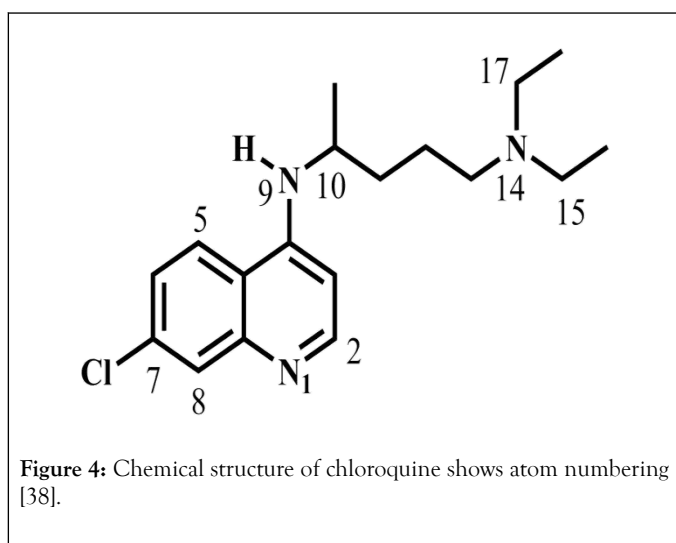
Physicochemical, pharmacokinetic, medicinal chemistry and drug likeness prediction

To qualify the proposed structures as candidates, the compounds molecular properties of Lipinski's rule of five were calculated using SwissADME web tool. The number of hydrogen bond acceptors and donors for all compounds were in accordance with Lipinski`s rule of five. The molecular weights of all compounds were within the range [48,49]. The lipophilicity property [50] (MLogP≤ 4.15, octanol-water partition coefficient) was in the range for all compounds and results are shown in Table 4.

Table 4: Lipinski`s rule of five for the four hybrids compounds.

Compounds	Mwt[a]	MLogP[b]	nHBA[c]	nHBD[d]	n violation s[e]
Rule	<500	< 4.15	<10	<5	0
AB1-Py	321.76	2.23	4	0	0
AB2-44-Py	320.78	2.48	3	0	0
AB3-4-Py	307.74	2.26	4	0	0
AB4-4-Pv	306.75	2.51	3	0	0
AB4-4-Py	306.75	2.51	3	0	0

Note: [a]Molecular Weight; [b]CalculatedLipophilicity (MLog Po/w); [c]Number of Hydrogen Bond Acceptors. [d]Number of Hydrogen Bond Donors; [e]Violations from Lipinski's Rule.

SwissADME also has computational filters that include Ghose, Egan,Veber, and Muegee developed by leading pharmaceutical companies and cheminfomaticians to evaluate the drug-likeness based on several parameters; Ghose evaluation by computing physicochemical property, presence of functional groups and important substructures, Egan predict the drug absorption based on physical processes involved in membrane permeability, Veber (GSK filter) model characterizes molecules as drug-like if they have 10 or fewer rotatable bonds and a PSA (polar surface area), Muegge (Bayer filter) model is a database-independent pharmacophore point filter that discriminates between drug-like and nondrug-like chemical matter. ketone, hydroxyl, sulfonyl and amine groups are considered to be the most important four functional motifs in drug-like molecules included in testing for all above mentioned filters;the four hybrids shows close likeness to the chloroquine with good scores the data are shown in supplementary I [49].

Finally, the medicinal chemistry was evaluated and result shown in Table 5 confirmed the likeness of the four hybridized molecules to chloroquine with acceptable synthetic accessibility.

Table 5 : Medicinal chemistry evaluation of hybrids.

Compounds	PAINS Alert	Brenk Alert	Lead Likeness	Synthetic Accessibility
AB1-4-Py	0	0	Yes	2.57
AB2-4-Py	0	0	Yes	2.36
AB3-4-Py	0	0	Yes	2.65
AB4-4-Py	0	0	Yes	2.32

Finally, Swiss ADME program evaluated the Pharmacokinetic properties of hybrids like, gastro-intestinal absorption, blood brain barrier permeability, inhibition the cytochrome P450 isoenzymes (CYP isoenzymes), and substrate P-glycoprotein gas demonstrated below in Table 6 all hybrids presented (yes) to CYP and all could substrate Pgp except compound coded AB3-4-Py [48].

Table 6: Pharmacokinetic evaluation of hybrids (GI: Gastro-Intestinal Absorption, BBB: Blood Brain Barrier, CYP: Cytochromes, P-gp: P-Glycoprotein.

Compounds	GI absorption	BBB perment	Pgp Substrate	CYPX Inhibition
AB1-4-Py	High	Yes	Yes	Yes
AB2-4-Py	High	Yes	Yes	Yes
AB3-4-Py	High	Yes	Yes	Yes
AB4-4-Py	High	Yes	Yes	Yes

CONCLUSION

Four molecules and chloroquine investigated using semi-empirical, geometry optimization and PM3 calculation methods and In-silico evaluation. Geometrically, the single crystal X-ray crystallography of chloroquine revealed that the data of bond lengths and bond angles completely agreed with calculated.

The two compounds AB1-4Py and AB2-4Py recorded bioactivity and electronic properties that are very close to the chloroquine. The N-heterocyclic units of molecules seem to be more flexible which may enhance the functionality of products. The two molecules and chloroquine; recorded same values of energy that is why the entire compound has same stability [49-51].

The bioactivity of molecules can be estimated by log p. AB1-4py, AB2-4py and chloroquine recorded same values of lop p which is 4; that reflect the three molecules have same bioactivity. Furthermore, we used the SwissADME virtual tools to further evaluate the medicinal chemistry, drug likeness, pharmacokinetics and physiochemical properties the results have proven closeness to chloroquine, hence these molecular hybrids are especially interesting for researchers to working with compounds as same as the chloroquine bioactivity; as antiviral therapies or antimalarial and may for COVID-19. Ultimately, biological evaluation and in vivo studies are required to validate the pharmacokinetics and pharmacodynamics of any potential patient drug.

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