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Research Article

Pryazolylpyridine and Triazolylpyridine derivative of hydroxychloroquine as Potential Therapeutic against COVID-19: Theoretical Evaluation

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ABSTRACT

In attempt to improve the biological activity of the well-known drug hydroxychloroquine (HCQ), eight derivatives (HQ1-4Py – HQ8-4Py) based on the core of HCQ were design and their electronic properties including frontier molecular orbitals, total energy and structural parameters were estimated at semi-empirical PM3 levels. Pharmacological parameters such as physicochemical, pharmacokinetics, drug-likeness and medicinal chemistry friendliness have been evaluated to estimate the drugs similarity. Introducing these moieties affect both electronic and drug likeness properties, HQ5-Py shows promised properties such large E_g and good clogP, The obtained results show that the suggested derivatives may represent a potential drug candidate for COVID-19.

Keywords: Molecular similarity, COVID-19, Hydroxychloroquine (HCQ).

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INTRODUCTION

In December 2019, a novel severe respiratory syndrome known as COVID-19 caused by the infection with SARS-CoV-2 virus first broke out in Wuhan, China and subsequently spread tragically worldwide.^{1,2} On March 11, 2020 it was declared by WHO as a pandemic.³ Approximately 13,27,440 infections and 593,369 deaths worldwide up to July 18, 2020 have been recorded and the number of COVID-19 cases is still on the rise. However, the possible explanation of the rapid and serious deterioration is cytokine release syndrome (CRS) called Cytokine storm and overproduction of immune cells that cause the rapid failure of vital systems in the human body and fetal damages to tissues.

There is an urgent need to identify effective and safe drug(s) that can target the virus and/or modulate the immune response.⁴ Chloroquine (CQ) is a synthesized anti-malarial drug with immunomodulatory effects, has been recommended by many researchers after exhibiting the promising inhibitory effect of SARS-CoV-2. This was supported by clinical studies conducted on infected patients.^{5, 6} Hydroxychloroquine (HCQ) an analogue of

chloroquine as demonstrated in Figure 1. is considered as one of the disease-modifying anti-rheumatic drugs used to treat rheumatic diseases with 40 % less toxicity than CQ in animals. HCQ had been tested in vitro against SARS-CoV-2 and demonstrated inhibitory effect for virus,⁷ which suggest that it might be a potential pharmacological agent in treatment of COVID-19.⁸ Although the mechanism of action of both drugs is not clearly elucidated in COVID-19, but researches suggested that both CQ and HCQ are basic compounds, therefore, they elevate the pH of intracellular organelles essential for viral membrane fusion.^{9,10} In addition, they could inhibit the SARS-CoV-2 permeation entry to the cell through changing the glycosylation of ACE2 receptor and spiking proteins. However, studies proposed that HCQ might be better than CQ in treatment of COVID-19 due to its ability to attenuate the acute progression of the infection.¹¹ It also confers the same antiviral activity in both pre- and post-infection stages, finally it has fewer side effects¹², safer profile in pregnancy, cheaper and more readily available.

Computer-Aided drug design (CADD) is an essential tool in drug discovery; these tools have a tremendous effect on both

time and cost of drug developments. This includes the estimation of the electronic, drug-likeness, pharmacokinetic, 3D-QSAR, and physicochemical properties of the target candidates.

Herein, we report the electronic properties including electronic reactivity descriptors, molecular electrostatic potential surfaces (MEPS), and electrostatic potential, also geometrical parameters such as bond lengths, angles, and dihedral angle conformation were reported and discussed. Pharmacologically, parameters such as physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness are also reported and analyzed for new designed molecules close to hydroxychloroquine.

Moreover, the rigidity and flexibility of molecules may affect the features of the target biological activity of designed molecules¹³. However, molecules with several rotatable bonds may adopt much different geometry, some of them

being favourable due to the low internal energies while the others are not. Thus, in our designed molecules we have been considered couple of features in order to get molecules close to hydroxychloroquine biologically and electronically. Actually, the hybridized molecules which have more than biologically active moieties were targeted as a continuation of our research interest in the design, synthesis, investigation of molecular similarity of novel hybridized molecules; N-heterocyclic based moieties¹⁴. Nowadays, drugs consist of quinolone such as QC and HCQ attracted more attention due to their activity against COVID-19¹⁵. Apparently, the main difference in chemical structure between chloroquine and hydroxychloroquine (Figure 1) as anti-malarial drugs is the presence of OH-group in hydroxychloroquine. However, from chemistry point view, the OH- increase the non-covalent interaction through its ability to form hydrogen bonding that may enhance the biological activity hence the anti-viral activity.

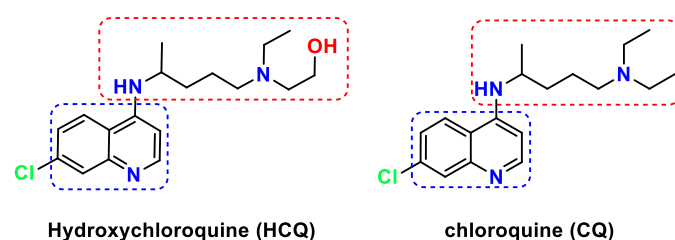


Figure 1: Chemical structure of Hydroxychloroquine (HCQ) and Chloroquine (CQ)

COMPUTATIONAL METHODS

Semi-empirical PM3 quantum chemical calculations were conducted using HyperChem 8.0 Molecular Modeling program with root mean square (RMS) gradient 0.1 kcal/Å mol using Polak Ribiere algorithm¹⁶, all compounds were optimized at the mention level followed by frequency calculation to ensure that all compounds are minima with no imaginary frequency. SwissADME web tool has been used to compute the pharmacological parameters¹⁷.

RESULTS AND DISCUSSION

Semi-empirical calculation

In biological system, the non-covalent interaction forces are the essential forces for molecular functionality. So the designed molecules have ability to form: (i) π - π -stacking; (ii) Hydrogen bonding; (iii) excellent coordinating site, and (iv) hydrophobic interaction¹⁸. All of the above non-covalent interaction are essential to hold supramolecular species together.¹⁸ However, 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'. Generally, non-covalent interactions are very important in biological systems^{18,19} and the crystal structure of HQC reported its ability to form some of the non-covalent interaction such as hydrogen bonding and π - π -stacking²⁰.

Figure 3 shows the chemical structure of designed molecules. However, the compounds designed using 7-chloroquinoline as core moiety and hydroxyl group. Moreover biological active units such as triazoles and others have been attached to the core unit to produce the candidate molecules. Molecules can be classified based on the connectivity to the 7-chloroquinoline into two classes (i) flexible molecules with methylene bridge between the core and the substituent and (ii) rigid molecules where the core is

attached directly to the substituent. The flexible molecules have high degree of movement through methylene group which may increase the solubility. The rigid molecule which connected directly to core, could increase the interactions with the active site of the protein. Notably, semi-empirical PM3 calculation method was used based on the excellent agreement of some geometric parameters such as bond lengths and bond angles (Table 1) between the single crystal crystallography and calculated data of HCQ.

Molecular modeling program permits to build and analyze different molecular structures and determine the molecular, electronic, and biological properties. After setting Semi-empirical MP3 method geometry optimization has been used to optimize the molecular structure to obtain a configuration characterized by a minimum free energy²¹. Within the geometry optimization the molecular symmetry calculated and performed both molecular symmetry and asymmetry properties²². However, all of calculation parameters such as total energy, dipole moment, binding energy, the HOMO, LUMO and others of candidate compounds reported based on optimal geometry. Moreover, the thermo-physical and electronic properties of designed molecules and hydroxychloroquine were listed in Table 2. Notably, the flexible molecules where unit 4-(1,2,3-triazol-4-yl)pyridin-2-ol or 4-(pyrazol-3-yl)pyridin-2-ol connected to the main unit (7-chloroquinoline) through -CH₂- reported thermo-physical values fingerprinting to parent molecule HCQ. Additionally, same observations have been reported of electronic properties. It should be noted that, the flexibility of pyrazole/pyridine and triazole/pyridine offer a suitable space for non-covalent interaction, which enhance new drugs functionality. The compound coded HQ1-4Py used as an example; the total energy, binding energy and HOMO/LUMO energy gap for molecule calculated to be -83428.19 Kcal/mol, -4089.28 Kcal/mol and 8.086 eV respectively; whereas for HQC were -83743.27 Kcal/mol, -4888.10 Kcal/mol and 8.0928 eV. The chemical reactivity of

molecules can be indicated from molecular orbitals. Although, HOMO/LUMO orbital indicate the electrophilic and nucleophilic attraction region in molecule as well as there is inverse relationship between E_{gap} and molecular chemical reactivity²¹.

The chemical structure of HCQ (Figure2) with atoms numbering. The Single Crystal X-Ray Crystallography data such as bond lengths and bond angles of HCQ were used to verified the selected method²⁰. However, some geometric parameters of calculated and experimental HCQ molecule have been presented in Table 1. The bond angle measured in ($^{\circ}$) and bond length in (\AA). Interestingly, excellent agreement between calculated and experimental data has been observed.

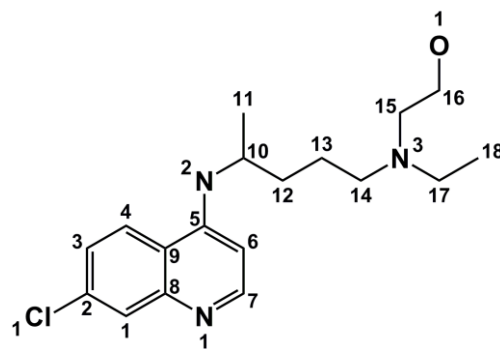


Figure 2: The structure of HCQ with atoms number

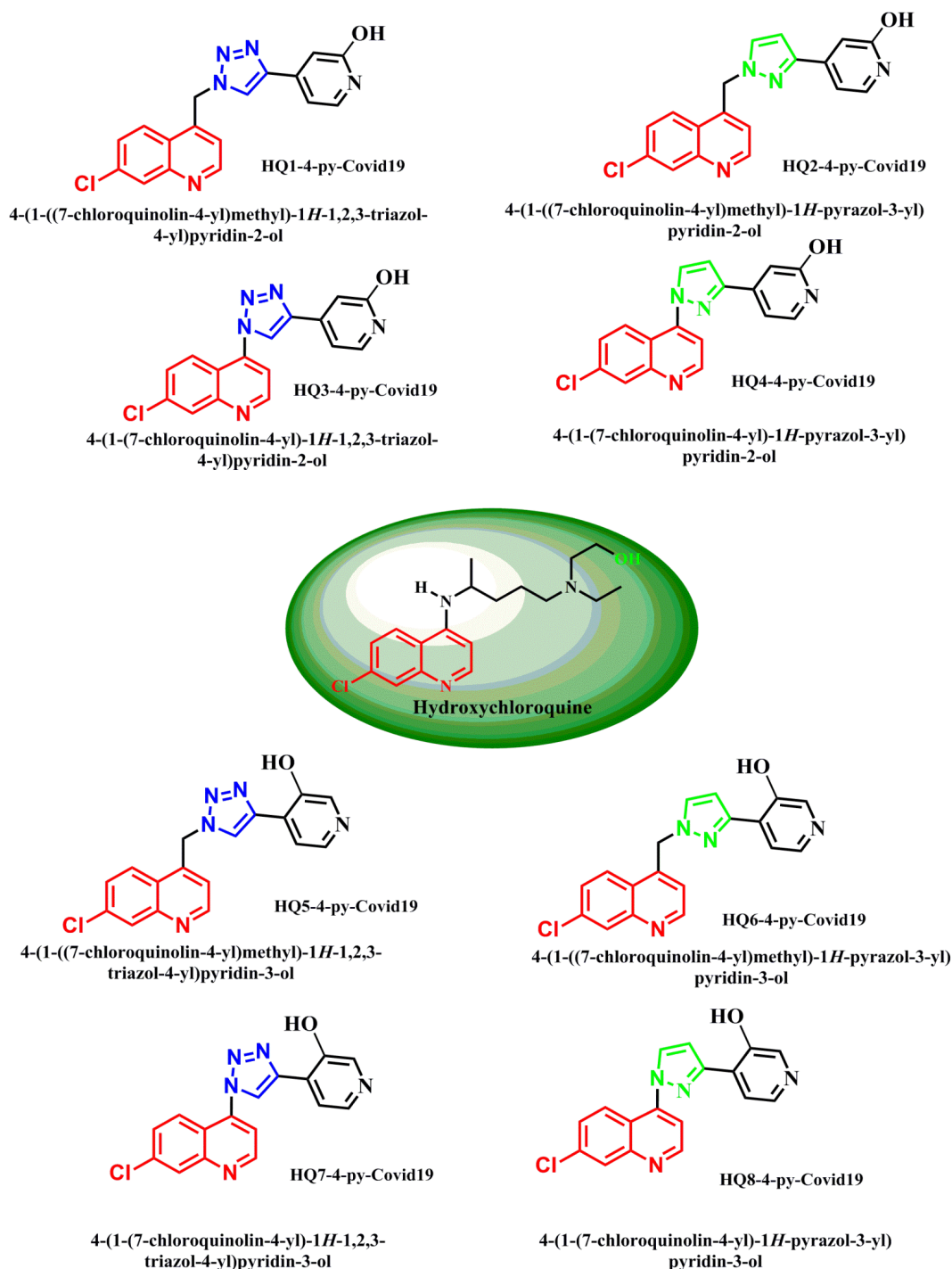


Figure 3: Chemical structure of hydroxychloroquine and new proposed derivatives

Table 1: Selected experimental and calculated bond lengths and angles

	Exp. Bond length	Calc. Bond length		Exp. Bond angles	Calc. Bond angles
N(1)-C(7)	1.30	1.32	N(1)-C(7)-C(6)	124.6	122.32
C(6)-C(5)	1.45	1.38	C(1)-N(1)-C(7)	120.7	119.35
C(16)-O(1)	1.41	1.41	C(5)-C(2)-C(10)	124.6	117.46
N(2)-C(10)	1.48	1.49	C(15)-C(16)-O	113.6	106.8
Cl-C(2)	1.74	1.70	N(3)-C(17)-C(18)	113.3	111.18

Bond angle (°) and Bond length (Å)

Table 2: Some calculated electronic and thermos-physical properties of HCQ and designed molecules

	Thermo-physical properties			Electronic properties			
	E	B. energy	Dipole mom. (Debye)	E _{LUMO} (eV)	E _{HOMO} (eV)	Energy gap (eV)	
HQ1-4Py	-83428.19	-4089.28	3.505	-1.324	-9.41	8.086	
HQ2-4Py	-82785.54	-4214.82	5.453	-1.201	-9.27	8.069	
HQ3-4Py	-79973.90	-3803.03	4.136	-1.668	-9.339	7.671	
HQ4-4Py	-79336.43	-3933.74	3.760	-1.489	-9.118	7.629	
HQ5-4Py	-83422.30	-4083.40	4.296	-1.266	-9.281	8.015	
HQ6-4Py	-82781.55	-4210.84	3.840	-1.117	-9.15	8.04	
HQ7-4Py	-79970.70	-3799.82	3.18	1.513	-9.142	7.629	
HQ8-4Py	-79330.96	-3928.27	2.16	-1.317	-8.891	7.574	
HCQ	-83743.27	-4888.10	3.653	-0.7872	-8.88	8.0928	

Total energy (T. energy), Binding energy (B. energy), dipole moment (dipole mom.)

Biological activity evaluation

In term of calculated QSAR parameters as indication of biological activity the cLog P value of hydroxychloroquine agreed with some of new designed molecules. Table 3 shows some QSAR calculation values of proposed compounds and hydroxychloroquine. All findings confirm that the molecules are hydrophobic to some extent. However, the closeness of calculated Log P value between HQC and HQ1-4Py has been observed at value 4.20 for both molecules suggesting that

HQ1-4Py and HCQ might have same biological activity; as the cLog P values plays as essential role for determination of molecular biological reactivity²¹ as well as the hydrophobicity often used to predict pharmacokinetics and pharmacodynamics²³. The closed molecules in reactivity to hydroxychloroquine were HQ1-4Py, HQ2-4Py, HQ5-4Py, HQ6-4Py. The reactivity values of HQC was 97.93 whereas for HQ1-4Py; 92.10, HQ2-4Py; 92.24, HQ5-4Py; 91.76 and HQ6-4Py; 91.89.

Table 3: Calculated QSAR parameters of designed molecules and hydroxychloroquine

	P. charge	S. area(Ap)	S. area(Gr)	Volume	Polarizability	Reactivity	cLog P
HQ1-4Py	0	411.20	547.37	903.63	36.59	92.10	4.20
HQ2-4Py	0	426.38	555.88	918.02	37.30	92.24	4.65
HQ3-4Py	0	387.01	509.68	847.79	34.75	87.27	4.10
HQ4-4Py	0	398.241	512.121	855.963	35.46	87.40	4.55
HQ5-4Py	0	397.84	543.45	901.28	36.59	91.76	3.96
HQ6-4Py	0	413.13	551.92	918.02	37.30	91.89	4.41
HQ7-4Py	0	371.41	507.31	843.40	34.75	86.92	3.87
HQ8-4Py	0	378.41	502.92	849.49	35.46	87.06	4.32
HQC	0	580.13	618.84	1030.66	38.78	97.93	3.49

Partial charge; (P.charge), Surface area (Approx); Sarea (Ap), Surface Area(Grid); Sarea (Gr)

Physicochemical and Pharmacokinetic Analysis

A comprehensive analysis of the drug-likeness properties of new hybridized molecules was performed and results were compared to HCQ by using SwissADME web tool. However, the proposed structures were qualified as candidates, the compounds molecular properties of Lipinski's rule of five.

were calculated. 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. The lipophilicity property ($MLogP \leq 4.15$, octanol-water partition coefficient) was in the range for all compounds and the results are shown in Table 4.

Table 4: Some Important Computed Physicochemical Properties of the newly eight designed molecules compared to HCQ

Compound	Mwt	n _{Rot}	HBA	TPSA	M LogP	Ali Log S	MR
HQ1-4-py	337.76	3	5	76.72	2.09	-4.02	91.34
HQ2-4-py	336.78	3	4	63.83	2.32	-4.31	93.54
HQ3-4-py	323.74	2	5	76.72	2.12	-4.08	86.92
HQ4-4-py	322.75	2	4	63.83	2.36	-4.38	89.13
HQ5-4-py	337.76	3	5	76.72	1.68	-3.67	91.34
HQ6-4-py	336.78	3	4	63.83	1.92	-3.96	93.54
HQ7-4-py	323.74	2	5	76.72	1.71	-3.74	86.92
HQ8-4-py	322.75	2	4	63.83	1.95	-4.03	89.13

Optimal range: molecular weight (MW) ≤ 600 , lipophilicity log or Moriguchi octane-water partition coefficient (M log P) ≤ 5 , aqueous solubility descriptor (Ali log S) ≤ 0 , hydrogen-bonded acceptor (HBA) ≤ 10 , topological polar surface area (TPSA) $\leq 150 \text{ \AA}^2$, number of rotatable bonds (n_{Rot}) ≤ 10 , and molar refractivity (MR) ≤ 155

The medicinal chemistry was evaluated, and the results are shown in Table 5 confirmed the likeness of the eight hybridized molecules to hydroxychloroquine with acceptable synthetic accessibility.

Table 5: Medicinal chemistry evaluation of the hybrid compounds

Compounds	PAINS Alert	Brenk alert	Lead likeness	Synthetic accessibility
HQ1-4-py	0	0	yes	2.65
HQ2-4-py	0	0	yes	2.5
HQ3-4-py	0	0	yes	2.72
HQ4-4-py	0	0	yes	2.49
HQ5-4-py	0	0	yes	2.68
HQ6-4-py	0	0	yes	2.43
HQ7-4-py	0	0	yes	2.73
HQ8-4-py	0	0	yes	2.43

Finally, Swiss ADME 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 g²⁴. As demonstrated below in Table 6 all hybrids presented high gastro-intestinal absorption and

being permeable to blood brain barrier. They also were (yes) to all CYP except HQ3-4-py and HQ7-4-py which did not inhibit CYP2C9. Eventually, they all could substrate Pgp except compounds coded HQ1-4-py, HQ3-4-py, HQ4-4-py and HQ7-4-py.

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	CYP ^x Inhibition
HQ1-4-py	High	Yes	No	Yes
HQ2-4-py	High	Yes	Yes	Yes
HQ3-4-py	high	Yes	No	Yes*
HQ4-4-py	High	Yes	No	Yes
HQ5-4-py	High	yes	yes	Yes
HQ6-4-py	High	Yes	Yes	Yes
HQ7-4-py	High	Yes	No	*Yes
HQ8-4-py	High	Yes	Yes	Yes

CYP^x are (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) *: means CYP2C9 is exception

CONCLUSION

In the present work in silico screening procedures including Semi-empirical MP3 calculation method and SwissADME web tool were used for comparison eight hybrid chemical structures with the parent compound hydroxychloroquine. Results have demonstrated excellent agreement between single crystal X-ray cystography data of HCQ and calculated data. However, we conclude that the flexible molecules recorded values closed to HCQ drug. Computationally, molecule coded HQ1-4Py reported identical electronic and thermo-physical values to HCQ. The electronic parameters such as HOMO/LUMO energy gap reflect that HQ1-4Py an HCQ may have same stability as well as may have same molecular reactivity. Moreover, some QSAR parameters of designed molecules reordered values in good agreement with HCQ, which may have same biological activity. The HQ5-4Py and HCQ recorded Log P values at 3 which reveal that the two molecules may have same molecular biological also may have same pharmacokinetics and pharmacodynamics properties. However, based on the geometric comparison of HQC; it has been noted that the calculated Log P values using HyperChem software may more accurate than what has been recorded using SwissADME tool.

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