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Research Article

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Theoretical study on the molecular structure of Quinoline and its derivatives as an anti- malaria drug

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ABSTRACT

Quantum mechanical calculation of the studied compounds for quinoline and its derivatives (4-amino quinoline, 4-carbonyl quinoline, 4-carboxyl quinoline, 4-hydroxyl quinoline and 4-methoxy quinoline) using semi-empirical and Density Functional Theory (DFT) has been carried out. The addition of substituents into the functional group of quinoline led to significant changes in the properties. 4- CHO- quinoline and 4- COOH- quinoline were found to be more stable using DFT, Moller Plesset and Hatree- Fock calculations. For the electronic properties of studied compounds, 4-CHO- quinoline and 4- COOH- quinoline have the lowest energy gap, indicating that these compounds are more reactive than other studied compounds. The properties studied suggest that 4-CHO quinoline and 4-COOH quinoline as a potential for anti- malaria drug.
Keywords: *DFT; energy gap; energy gap; quinoline and its derivatives*

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1. INTRODUCTION

Quinoline is used mainly as an intermediate in the manufacture of other products [1]. It is also used as a catalyst, a corrosion inhibitor, in metallurgical processes, in the manufacture of dyes, as a preservative for anatomical specimens, in polymers and agricultural chemicals, and as a solvent for resins and terpenes. It is also used as an antimalarial medicine. There is not much diversity in the application of quinoline but quinoline has various derivatives with a lot of applications, example is quinine. Quinine has antimalarial activities and is an alkaloid with plant origin. Some other derivatives of quinoline has antibiotic activities, example is 4-hydroxyl-2-alkylquinoline. Quinoline can therefore be said to have not only antimalarial properties but antibiotic activities as well.

Quinoline-containing antimalarial drugs, such as chloroquine, quinine and mefloquine, are mainstays of chemotherapy against malaria. The molecular basis of the action of these drugs is not completely understood, but they are thought to interfere with the hemoglobin, in an acidic food vacuole, producing free heme and reactive oxygen species as toxic by-products. Polymerization neutralizes the heme moieties and detoxification of free radical species by a vulnerable series of antioxidant mechanisms.

Chloroquine, a dibasic drug, is accumulated several thousand-fold in the food vacuole. The high intravacuolar chloroquine concentration is proposed to interfere with the polymerization of heme and/or the detoxification of the reactive oxygen species, effectively killing the parasite with its own metabolic waste. The more lipophilic quinoline methanol drugs, mefloquine and quinine do not appear to be concentrated so extensively in the food vacuole and may act on alternative targets in the parasite.

2-(Furan-2-yl)-4-phenoxy-quinoline derivatives are found to be inhibitors of lysozyme and β-glucuronidase release [2]. A quinoline derivative with potent anti-inflammatory effect in adjuvant arthritis rat model has also been developed [3]. Also, certain quinoline derivatives have been developed for anti-bacteria. [3]

This paper describes the molecular structural properties of quinoline and its derivatives using computational studies, and also the Quantitative Structural Activity Relationship (QSAR) of quinoline and its derivatives to show which compound is most suitable as anti- malaria drug.

2. Computational Details

Quantum chemical calculations were carried out on quinoline and its derivatives using semi empirical methods, Density Functional (DFT) Methods at B3LYP/ 6-31G*. This was done in different media (vacuum, ethanol and THF). MP2/ 6-31G* and Hatree- fock 6-31G* methods were also used to obtain the properties of the molecules such as thermodynamic properties, Quantitative Structure Activity Relationship, QSAR, and also electronic properties to obtain energy gap (E_g).

Heats of formation of all studied compounds were carried out using semi empirical methods. Thermodynamic properties, QSAR, electronic properties, geometric properties were fully optimized using Spartan 10 software on a 2.40 GHz and 64-bit operating system.

3. Results and Discussion

3.1 Geometric properties

The optimized structures of quinoline, 4-amino quinoline, 4-carbonyl quinoline, 4-carboxyl quinoline, 4-hydroxyl quinoline and 4-methoxy quinoline have Cs, C1, Cs, C1, Cs and Cs symmetries respectively at ground state. Bond length, bond angle, bond dihedral and bond length alternation were calculated using DFT calculation with B3LYP and 6.31G*. As shown in Table 1, the calculated values for selected bond lengths N_1-C_2, C_2-C_3, C_3-C_4 and C_6-C_7 in quinoline are 1.318Å, 1.418Å, 1.375Å and 1.377Å respectively, while the experimental values for the same bonds in quinoline are 1.393Å, 1.365Å, 1.427Å and 1.389Å respectively [4] Comparing the calculated and experimental values, it is observed that the experimental values are slightly higher than the calculated values except for the C_2-C_3 bond. Also, the calculated values for selected bond angles; C_2-C_3-C_4, C_3-C_4-C_1, N_1-C_5-C_9, C_2-N_1-C_5 in quinoline are 118.65°, 119.36°, 118.46° and 117.69° respectively (Table 2) while the experimental values are 117.8°, 121.4°, 121.6° and 117.50° respectively [4]. Addition of substituents in most cases increases the bond length. There is no pattern of change in the values of bond angles and dihedral; addition of substituent to quinoline causes slight changes.

Table 1: Showing geometry bond length in (Å)

Bonds	Quinoline	4-NH_2 – quinoline	4-OH-quinoline	4-COOH-quinoline	4-OCH_3-quinoline	4-CHO-quinoline	*Expt. values*
N_1-C_2	1.318	1.334	1.331	1.328	1.331	1.328	1.393
C_2-C_3	1.418	1.420	1.429	1.433	1.428	1.434	1.365
C_3-C_4	1.375	1.392	1.380	1.378	1.379	1.376	1.427
C_5-C_9	1.420	1.435	1.431	1.434	1.431	1.435	-
C_6-C_7	1.377	1.373	1.374	1.372	1.374	1.372	1.389

Expt[4]

Table 2: Showing Bond angle in degrees (°)

Selected bond angle	Quinoline	4-NH_2-quinoline	4-OH-quinoline	4-COOH-quinoline	4-OCH_3-quinoline	4-CHO-quinoline	*Expt. Values*
C_2-C_3-C_4	118.65	119.01	117.53	119.12	117.75	119.26	117.8
C_2-C_3-H_8	119.88	119.27	119.68	119.56	119.23	119.97	-
C_3-C_4-C_1	119.36	119.21	121.44	119.84	120.92	119.63	121.4
N_1-C_5-C_9	118.46	117.73	118.78	117.65	118.70	117.75	121.6
C_2-N_1-C_5	117.69	118.06	118.56	118.54	118.36	118.47	117.50
C_4-C_1-C_6	123.39	124.06	123.80	124.50	123.58	124.17	-
C_6-C_7-C_8	120.34	120.43	120.41	120.81	120.40	120.78	-

Expt[4]

3.2 Electronic properties

The energy gap between the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital calculated using DFT B3LYP/6-31G* (in vacuum, ethanol and THF), MP MP2/6-31G* and HF/6-31G* are shown in Table 4-5. The energy gap, also called band gaps, is a key factor which determines the reactivity [5-7] Only slight difference was observed in the energy gap values for quinoline and substituents, with the carbonyl and carboxyl substituents having the lowest energy gap (Table 6- 8). The lower the energy gap, the more reactive the compound, hence 4- carbonyl quinoline and 4- carboxyl quinoline are more reactive compared to other studied compounds.

Table 4: *Showing electronic Properties using DFT calculation with B3LYP and 6-31G* in vacuum, ethanol and THF*

	Vacuum			Ethanol			THF		
Compound	E_{LUMO} (eV)	E_{HOMO} (eV)	Eg (eV)	E_{LUMO} (eV)	E_{HOMO} (eV)	Eg (eV)	E_{LUMO} (eV)	E_{HOMO} (eV)	Eg (eV)
Quinoline	-1.38	-6.29	4.91	-1.49	-6.39	4.90	-1.43	-6.34	4.91
4-NH_2-quinoline	-1.01	-5.68	4.67	-1.12	-5.69	4.57	-1.05	-5.60	4.55
4-OH-quinoline	-1.11	-6.00	4.89	-1.26	-6.14	4.88	-1.22	-6.11	4.89
4-COOH-quinoline	-2.22	-6.47	4.25	-2.25	-6.55	4.30	-2.21	-6.50	4.29
4-OCH_3-quinoline	-1.04	-5.94	4.90	-1.27	-6.15	4.88	-1.18	-6.06	4.88
4-CHO-quinoline	-2.47	-6.53	4.06	-2.47	-6.53	4.06	-2.37	-6.49	4.12

Table 5: *Showing electronic Properties using MP2 and HF calculations with 6-31G**

Compound	E_{LUMO} (eV)	E_{HOMO} (eV)	Eg (eV)
Quinoline MP2	2.20	-8.25	10.45
Quinoline HF	2.44	-8.41	10.85
4-NH_2 quinoline MP2	2.48	-7.86	10.34
4-NH_2 quinoline HF	2.73	-7.96	10.69
4-OH quinoline MP2	2.46	-8.08	10.54
4-OH quinoline HF	2.71	-8.19	10.90
4-COOH quinoline MP2	1.27	-8.45	9.72
4-COOH quinoline HF	1.55	-8.56	10.11
4-OCH_3 quinoline MP2	2.54	-8.00	10.54
4-OCH_3 quinoline HF	2.79	-8.12	10.91
4-CHO quinoline MP2	1.04	-8.62	9.66
4-CHO quinoline HF	1.37	-8.75	10.12

3.3 Quantitative Structure Activity Relationship (QSAR)

The higher the polarizibility of a compound, the more reactive it is, also, the higher the logP of a compound, the higher its hydrophobicity. LogP is a driving force that determines the hydrophobicity effects of drugs and its biological activities [6-7]. Highly hydrophobic drugs tend to be toxic because they are retained within the body and finally metabolized; hence it is advisable to make the drug as hydrophilic as possible while it still retains its binding affinity to therapeutic protein target [8]. Considering the above conditions, 4- carboxyl quinoline and 4-methoxy quinoline can be used in anti-malaria and anti-bacteria drugs. This is because their logP values are intermediate; not too high (hydrophobic) and not too low (hydrophilic) as shown in Table 6-7.

Table 6: *Showing QSAR using DFT calculation with B3LYP and 6-31G* in vacuum, ethanol and THF*

	Vacuum				Ethanol				THF			
Compound	Dipole (debye)	Area (A^2)	LogP	Polarizability, (α), (A^3)	Dipole (debye)	Area (A^2)	LogP	Polarizability,α, (A^3)	Dipole (debye)	Area (A^2)	LogP	Polarizability,α, (A^3)
Quinoline	2.02	157.12	0.44	51.92	2.96	157.10	0.44	51.92	2.86	157.12	0.44	51.92
4-NH_2-quinoline	3.69	168.84	-1.28	52.80	5.76	168.77	-1.28	52.82	5.67	168.81	-1.28	52.82
4-OH-quinoline	2.62	165.33	-0.65	52.49	3.81	165.36	-0.65	52.50	3.41	165.35	-0.65	52.50
4-COOH-quinoline	1.12	184.66	-0.32	54.30	1.84	184.86	-0.32	54.29	1.48	184.81	-0.32	54.30
4-OCH_3-quinoline	3.18	186.15	-0.54	54.12	4.42	186.24	-0.54	54.13	4.33	186.21	-0.54	54.12
4-CHO-quinoline	3.25	177.92	-0.58	53.80	3.25	177.92	-0.58	53.81	2.98	177.92	-0.58	53.80

Table 7: Showing QSAR using MP2 and HF calculations with 6-31G*

Compound	Dipole (debye)	Area (A^2)	Log P	Polarizability,α, (A^3)
Quinoline MP2	2.06	157.17	0.44	50.63
Quinoline HF	2.17	155.74	0.44	50.43
4-NH_2- quinoline MP2	3.39	168.94	-1.28	51.47
4-NH_2- quinoline HF	3.48	167.34	-1.28	51.27
4-OH- quinoline MP2	2.51	165.37	-0.65	51.18
4-OH- quinoline HF	2.62	163.75	-0.65	50.97
4-COOH- quinoline MP2	1.33	185.07	-0.32	53.03
4-COOH- quinoline HF	1.46	182.97	-0.32	52.79
4-OCH_3- quinoline MP2	3.09	185.94	-0.54	52.79
4-OCH_3- quinoline HF	3.24	184.44	-0.54	52.58
4-CHO- quinoline MP2	2.34	178.00	-0.58	52.50
4-CHO- quinoline HF	2.40	176.35	-0.58	52.27

3.4 Solvent effect

DFT calculation which was done in vacuum, ethanol and THF showed very slight difference in solvent media. The values of thermodynamic properties, QSAR values and electronic properties in vacuum are almost similar to their corresponding values in ethanol and THF solvents. This implies that calculations can be done in any of the three media to give the best result.

4. Conclusion

From the calculation, considering all studied compounds, 4- carboxyl quinoline is the most stable with -590.34, -588.57, -586.79 values of ΔH with DFT, Moller Plesset and Hatree- Fock calculations respectively. For the electronic properties of studied compounds, only slight difference was observed in the energy gap values for quinoline and substituents, with the carbonyl and carboxyl substituents having the lowest energy gap, hence 4-carbonyl quinoline and 4- carboxyl quinoline are more reactive compared to other studied compounds. QSAR studies reveals that the higher the polarizability of a compound, the more reactive the compound. also the higher the logP of a compound, the higher its hydrophobicity. 4- carboxyl quinoline and 4-methoxy quinoline are suitable for use as anti-malaria and anti-bacteria drugs because their logP values are intermediate; not too high (hydrophobic) and not too low (hydrophilic). 4- Carbonyl quinoline and 4- carboxyl quinoline are the best compounds for use as anti- malaria drug. The properties studied suggest that these quinoline derivatives will be good as anti- malaria drug.

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