Antimalarial Activity of some Conjugated Arylhydrazones: *Ab Initio* Calculation of Nuclear Quadrupole Coupling Constants (NQCC)

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“Malaria” is a life-threatening blood disease in tropical regions that spreads by the bite of the Anopheles mosquito. Antimalarial medications are designed to cure or prevent this infection, and prosperous achievements in this area mostly depend on the knowing the drug-receptor interactions and active sites of medicine. This improvement can be achieved through understanding the electronic structure of compounds using calculated quadrupolar parameters of nuclei as an efficient theoretical method. In this research, conjugated hydrazones as new antimalarial drugs are investigated to find the correlation between their electronic structures and pharmaceutical behavior. To this aim, the effect of the various substituents and their position on quadrupolar parameters and charge distributions are examined by concepts of nuclear quadrupole resonance (NQR) spectroscopy. The results show that benzothiazole hydrazones are multi-central inhibitors. In addition to the charge density on N$_{13}$ atom, the presence of two vicinal oxygen atoms with high electron density in the benzene ring has the key role in the iron chelating and consequently antimalarial activity of these compounds. All calculations are performed at the HF/6-31G* level of theory using the Gaussian 03 program.

**Keywords:** Charge density, NQR, Gaussian, Benzothiazole hydrazones, Antimalarial drug

**INTRODUCTION**

Malaria is the deadly parasitic disease, affecting tropical and subtropical regions and causing more than one million deaths per year [1]. This infection is due to Plasmodium falciparum protozoa that infects humans through the bite of the Anopheles mosquito [2,3]. Plasmodium is able to penetrate hepatocytes and digests the host haemoglobin [4]. Among the *Plasmodium* species that causes malaria in humans, *P. falciparum* is the deadliest. Now recognized antimalarials have become more and more futile, with an alarming increase in the emergence of drug-resistant parasites. In this regard, prompting active exploration for a new generation of in vivo-active antimalarials is needed [2,5,6].

Some drugs consumed against malaria [7] are expected to prevent Plasmodium from eliminating heme [8]. Resistance to currently available antimalarial drugs [9], including artesinin derivatives [10], has become a major challenge in the control and potential eradication of malaria [11]. With an estimated 3.4 billion people being at risk of contracting this tropical parasitic disease [12], there is a critical need for the novel and chemically distinct therapeutic agents to develop effective and affordable drugs [13].

A new series of conjugated hydrazones were found to be active against malaria parasite in vitro, as well as in vivo in a murine model. These hydrazones may be able to interact with heme through its iron [14]. This sort of heme-interacting molecules can inhibit the hemolysis formation to induce parasite death.

In addition to the extensive clinical and biochemical investigations, the theoretical study of such compounds has risen lots of interest among the scientific community. Indeed, more recent works have been devoted to investigate
the reaction mechanism between the active part of medicine and molecular targets through quantum mechanical approach [15-17]. A detailed knowledge of the mechanism of drug action is very important in medicine development, and one can apply this information to improve the drug-receptor interactions needed for the required activity. Theoretical calculations, in peculiar calculating quadrupolar parameters of nuclei and evaluating electronic structure of these new antimalarials, seem to be a powerful technique for gaining a better understanding of these interactions.

In this work, our priority is to establish the relation between the electronic structures of some conjugated hydrazones and their antimalarial activity. So, we study the activity of hydrazones using Hartree-Fock (HF) calculations and nuclear quadrupole resonance [18] (NQR) parameters.

**COMPUTATIONAL DETAILS**

Geometry optimization was performed at the framework of the *ab initio* approach embedded in the Gaussian 03 program [19]. HF as computational method and 6-31G* as a valence double-zeta polarized basis set for all atoms were employed. Using the same level of theory (method/basis set) to calculate EFG for various atoms (in this work: \(^{2}\)H, \(^{17}\)O and \(^{14}\)N) let us predict the EFG qualitatively. Calibration of different levels of theory through comparing the obtained results with the experimental findings to find a reasonable method, results in the reliable quantitative values for EFGs. In the case of our target compounds, there are no reported experimental NQR parameters. Thus, for the sake of CPU time, a method and basis set such as HF/6-31G* may give us a faster qualitative prediction [20], although from ref [21], for the prediction of EFG properties of hydrogen nuclei and electron-rich atoms such as halides, DFT/B3LYP provides results even less reliable than Hartree-Fock theory."

Vibrational frequencies were calculated for all the optimized structures to verify a stationary point. The optimized structures were used as input for computation of the electric field gradient (EFG) tensor in the principal axes system as a necessary component for evaluating the quadrupolar parameters.

Due to practical limitations, determination of the charge distribution in molecules using a quantum mechanical approach has been shown to be an appropriate method [22]. Nuclear quadrupole resonance (NQR) spectroscopy has been employed to provide a better comprehension of the quadrupolar systems. This technique is related to the interaction of the electric field gradient with the quadrupole moment of the charge distribution around nuclei leading to the nuclear energy level splitting [23,24]. NQR parameters are reasonable indicators of the known charge distribution surrounding a nucleus because they are very sensitive to the electronic structure. The main objective of NQR spectroscopy is determining nuclear transition frequencies (i.e., energies) and making connection between those and a property of a material being studied. One of the requirements to use NQR spectroscopy is the availability of an isotope with a nuclear spin \(I > \frac{1}{2}\), which has a high isotopic abundance and is located at a site in a solid that has a symmetry lower than tetragonal.

Nuclear quadrupole coupling constant (NQCC) is the energy measurement parameter of the interaction between the electric quadrupole moments of the nuclei with EFG at the site of nuclei [18]. In this respect, the calculation of the EFG tensor at a nucleus is necessary [24]. The EFG at the nucleus resulting from its external charges is described using spatial derivatives of the corresponding electrostatic potential, \(V\), evaluated at the nucleus,

\[
eq \frac{e^2r}{\varepsilon_0} \quad i,j = X, Y, Z
\]

Thus, the EFG can be characterized by a real, symmetric, traceless \(3 \times 3\) tensor that in the principal axes system, the components satisfy the \(|q_{xx}| \geq |q_{yy}| \geq |q_{zz}|\) relationship.

A non-zero electric quadrupole moment arises from the nuclei with spin more than \(\frac{1}{2}\) that are classically non spherical. These quantities are usually expressed in units of \(10^{-24}\) cm\(^2\) = 1 barn.

Nuclear quadrupole coupling constant NQCC can be calculated by the following equation,

\[
\chi = \frac{e^2Q Q_{zz}}{h}
\]

where \(h\) is the Planck’s constant, \(Q\) is nuclear electric quadrupole moment, and \(Q_{zz}\) is the Z component of the EFG.
tensor in the principal axes system [25].

In this research, the nuclear electric quadrupole moments are considered as a simple constant or scaling parameter, and the recent values of $Q^{1H}=2558mb$, $Q^{14N}=2044mb$ and $Q^{2H}=286mb$ reported by Pyykko [26] are selected for calculations.

RESULTS AND DISCUSSION

The schematic geometry structure of substituted hydrazones is illustrated in Fig. 1. In this figure, quadrupolar atoms are numbered and substituents are specified as R, R1, R2, and R3 (introduced in Table 1).

Similar to our previous studies [27-29], in the present work, calculated NQCCs of a series of conjugated hydrazones are studied to find a possible correlation between their electronic structure and biological activity. As a further rationalization, the effect of the position of substituents on NQCC parameter and charge distribution are examined. In the case of NQCCs of the considered compounds for which no experimental data are available, the results of these calculations provide the qualitative predictions.

Charge Density of Nitrogen and Hydrogen Atoms

NQCCs of nuclei seem to be an appropriate criterion for better understanding of the atomic charge density and electronic structure of compounds, particularly drugs. In the first step, it is essential to calculate the EFG tensor at a nucleus to achieve theoretical calculation of NQCC. According to NQCC expression, Eq. (2), NQCC of nuclei is directly proportional to $q_{zz}$.

Charge density on the nucleus and symmetry of EFG around the quadrupolar nucleus are effective factors in the values of $q_{zz}$. It is evident that the importance of NQCC is to be found in different values of the field gradient for the same nucleus in different molecules. Nucleus with higher charge density has greater $q_{zz}$ and consequently larger $\chi$, while the non-symmetric EFG in atoms with nonbonding electron pairs, such as nitrogen and oxygen, the $q_{zz}$ and $\chi$ values are declined when their charge density increases [30]. Since the bond properties depend on electrons, it is possible to replace hydrogen atoms by its isotopic counterpart with higher nuclear spin, I = 1, deuterium, in our compounds, assuming that no structural changes will occur. Nuclear quadrupole coupling constant for the quadrupolar nuclei in the studied compounds are reported in Table 1.

Table 1 shows that regardless of different antimalarial activity of the considered materials, NQCC values of hydrogen (H1, H8, H11 and H14) and N12 atoms in all compounds are almost equal. Despite the similarities in the reported NQCC quantities for $^2$H and $^{14}$N12 atoms, they have different values for IC50. Thus, one of the interesting features extracted from the obtained results for these molecules is that the antimalarial activity is not related to the charge density around hydrogens and N12 atoms.

As reported in the literature [14], 5f compound is found to be the most active compound among the studied hydrazones. Sarkar et al. reported that 5f compound shows antimalarial activity in vivo against a lethal multidrug-resistant (MDR) strain of P. yoelii in a mouse model [14]. They showed that 5f has the lowest dissociation constant (KD) for heme interaction, as well as, the maximum inhibitory power against hemozoin formation. Concentration-dependent inhibition of both hemozoin formation and parasite growth was observed with 5f compound.

As reported in Table 1, it is obvious that the $^{14}$N13- NQCC values for the most effective antimalarial compounds (fifth series) are smaller than those of the other compounds (about 500 KHz less), implying the higher charge density around N13 atom in these compounds. The mentioned distinction between molecules in the fifth series
Table 1. Comparison of the Calculated NQCC for some Quadrupolar Atoms in Considered Conjugated Hydrazones (for $^2\text{H}$ in KHz and for $^{17}\text{O}$ and $^{14}\text{N}$ in MHz)

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<th>$x(^{14}\text{N},_1)$</th>
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Table 1. Continued

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*a Experimental value from Ref. [14].
and the others could be considered as a criterion for the activity of benzothiazole hydrazones. Accordingly, based on the calculated NQCC parameters, charge densities around $N_{13}$ of conjugated hydrazones have a dominant role in the biological activity of benzothiazole hydrazones and this nucleus may be considered as an active site.

**Charge Density of Oxygen Atoms in R1, R2 and R3 Substituents**

For many biochemical reactions involved in the growth and multiplication of the malaria parasite, iron is crucial, so that parasite growth can be inhibited by iron chelators. Deprivation of iron would affect the activity of cytochrome, ribonucleotide reductase, and other vital cellular functions and also inhibit the growth of the malaria parasite [30,31]. The parasite, by digesting the host hemoglobin, releases free heme which is very toxic to the parasite [2,32,33]. However, parasite converts toxic free heme into a less toxic hemozoin for its own survival [34]. Iron chelators interact with free heme ($Fe^{2+}$-protoporphyrin) through the iron at the center of heme, and consequently this action suggests their therapeutic effect by interference with the inert hemozoin formation.

Some reports [14] indicated that among the compounds tabulated in Table 1, hydroxylated hydrazones have antimalarial activity, while methoxylated hydrazones do not show this characteristic. The reaction between benzothiazole hydrazones and $Fe^{2+}$ of heme is necessary for the biological activity of these compounds; therefore atoms with high charge density, including oxygen in OH functional group, are good candidates for chelating a cation such as $Fe^{2+}$. This assumption is reinforced by the lower $IC_{50}$ value. As an example, we can refer to the 5f compound that has the most inhibitory (the lowest $IC_{50}$), and oxygen atom with the highest charge density (the lowest NQCC). The calculated NQCC of oxygen atoms in the substituted hydrazones are reported in Table 1. The mean value of $^{17}\text{O}$-NQCC in methoxylated hydrazones (a, b, c) is about 11.5 MHz, while this quantity in hydroxylated hydrazones (d, e, f) is about 10.5 MHz, about 1 MHz greater, so charge density on oxygen atom of OH in hydroxylated hydrazones is much more than that of OMe in the methoxylated ones.

Therefore, $N_{13}$ and O atoms of R1, R2 and R3 substituents have the key role in the antimalarial activity of considered conjugated hydrazones. Inspection of Table 1, in addition to the above mentioned points, shows that the vicinity of two oxygen atoms with high charge density is required for antimalarial activity. All of compounds in each series (1f, 2f, 3f, 4f and 5f) with two OH groups on neighboring carbons (R1 = OH, R2 = OH, R3 = H) have smaller $IC_{50}$, and subsequently higher antimalarial activity than the others in each series.

The experimental values for $IC_{50}$ are given in Table 1. Reported quantities show that 5f, substituted with benzothiazole, is the best inhibitor among the studied compounds in our research. In the following section, we will compare the effect of benzimidazole and benzoxazole as substituents (in 6 and 7 compounds) on the antimalarial activity, and predict their pharmaceutically effect based on their calculated NQCCs (Table 2).

The obtained results show that NQCCs for three mentioned effective atoms ($N_{13}$ in the molecular skeleton of hydrazones and the oxygen atoms in hydroxylated hydrazones) are almost equal for 5f, 6, and 7 compounds, and subsequently, various pharmaceutical effects for 5f, 6, and 7 compounds are not expected.

**CONCLUSIONS**

In this article, hydrazones and their substituted species were studied to explore the essential factors influencing on their antimalarial activity. To this aim, we employed quantum theory approach, HF/6-31G* level of theory, and computed the NQCC parameter for all our candidates in this research. NQCC, as a powerful tool, was used to predict the electronic charge density around the active sites that are susceptible to iron cation chelating.

According to the data obtained from charge distributions, it is concluded that quadrupolar parameters of nuclei can be used as a useful tool to understand the electronic structure of compounds. As inferred from the obtained NQCC quantities, charge densities of $N_{13}$ in conjugated hydrazones have a dominant role in the biological activity of benzothiazole hydrazones. In addition, vicinity of two oxygen atoms with high charge density is required for antimalarial activity. In this respect, the smaller $IC_{50}$ values are devoted to the f compounds in each series; 1f, 2f, 3f, 4f and 5f, due to the presence of OH functional
Table 2. Comparison of the Calculated NQCC for some Quadrupolar Atoms in Conjugated Hydrazones with Benzoxazole and Benzimidazole Substituents (for $^2$H in KHz and for $^{17}$O and $^{14}$N in MHz)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>$\chi(^2H_1)$</th>
<th>$\chi(^2H_2)$</th>
<th>$\chi(^2H_3)$</th>
<th>$\chi(^2H_4)$</th>
<th>$\chi(^{17}O_1)$</th>
<th>$\chi(^{17}O_2)$</th>
<th>$\chi(^{14}N)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>221.1</td>
<td>220.0</td>
<td>204.9</td>
<td>284.9</td>
<td>6.0</td>
<td>6.1</td>
<td>10.4</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>220.9</td>
<td>223.3</td>
<td>205.2</td>
<td>283.7</td>
<td>5.7</td>
<td>6.1</td>
<td>10.4</td>
</tr>
</tbody>
</table>

groups on neighboring carbons ($R_1 = OH$, $R_2 = OH$, $R_3 = H$). Therefore, they show higher antimalarial activity compared to the other molecules studied here. These results suggest that introducing appropriate substitution in benzothiazole hydrazones might facilitate their inhibitory effects. In other words, as well as $N_{13}$ in the molecular skeleton of hydrazones, the oxygen atoms in hydroxylated hydrozones affect benzothiazole hydrazones activities.

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