

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

M.A. Rafiee

Department of Chemistry, Payame Noor University, P.O. Box: 19395-3697 Tehran, Iran

(Received 17 January 2017, Accepted 5 July 2017)

“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 N₁₃ 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 artemisinin 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 hemozoin 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

*Corresponding author. E-mail: rafiee.marjan@gmail.com, PhD

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: ^2H , ^{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 $I > 1/2$, 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,

$$eq_{ij} = \frac{\partial^2 V}{\partial i \partial j} \quad i, j = X, Y, Z \quad (1)$$

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

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

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

$$\chi = \frac{e^2 Q q_{zz}}{h} \quad (2)$$

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 $Q(^{17}O)=25.58mb$, $Q(^{14}N)=20.44mb$ and $Q(^2H)=2.86mb$ 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 χ , while the non-symmetric EFG in atoms with nonbonding electron pairs, such as nitrogen and oxygen, the q_{zz} and χ values are declined when their charge density increases [30]. Since the bond properties depend on electrons, it is

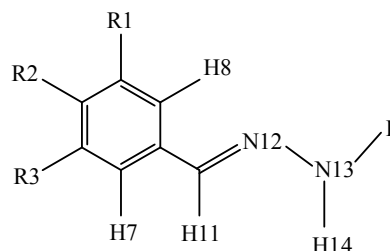


Fig. 1. Structure of conjugated hydrazones.

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 (H_7 , H_8 , H_{11} and H_{14}) and N_{12} atoms in all compounds are almost equal. Despite the similarities in the reported NQCC quantities for 2H and $^{14}N_{12}$ atoms, they have different values for IC_{50} . 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 N_{12} 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 $^{14}N_{13}$ -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 N_{13} 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 ^2H in KHz and for ^{17}O and ^{14}N in MHz)

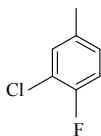
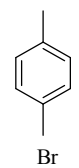
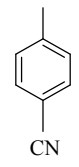
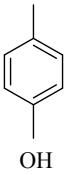
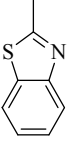
Compound	R	R1	R2	R3	$\chi(^2H_7)$	$\chi(^2H_8)$	$\chi(^2H_{11})$	$\chi(^2H_{14})$	$\chi(^{14}N_{12})$	$\chi(^{14}N_{13})$	$\chi(^{17}O_{inR1})$	$\chi(^{17}O_{inR2})$	$\chi(^{17}O_{inR3})$	IC50 ^a
1a		OMe	OMe	H	219.9	221.0	207.2	289.3	5.8	6.5	11.9	11.4	-	NA
1b		OMe	H	OMe	223.4	224.5	208.0	289.7	6.0	6.5	11.4	-	11.4	NA
1c		H	OMe	H	218.9	219.8	206.9	289.4	5.8	6.4	-	11.3	-	NA
1d		H	OH	H	218.8	219.8	206.9	289.4	5.8	6.5	-	10.5	-	59.48
1e		OH	H	OH	223.3	224.4	208.1	289.7	6.1	6.4	10.5	-	10.5	71.33
1f		OH	OH	H	221.1	221.5	207.4	289.4	5.9	6.5	10.4	10.5	-	42.96
2a		OMe	OMe	H	220.0	221.0	207.3	289.6	5.9	6.5	11.9	11.4	-	NA
2b		OMe	H	OMe	223.4	224.6	208.0	289.8	6.1	6.6	11.4	-	11.4	NA
2c		H	OMe	H	219.0	219.8	206.9	289.6	5.8	6.6	-	11.4	-	NA
2d		H	OH	H	218.9	219.8	207.0	289.6	5.8	6.6	-	10.5	-	62.16
2e		OH	H	OH	223.3	224.4	208.1	289.8	6.1	6.5	10.5	-	10.5	78.85
2f		OH	OH	H	221.1	221.5	207.5	289.5	5.9	6.4	10.3	10.5	-	65.56
3a		OMe	OMe	H	220.0	221.5	204.6	285.8	5.8	6.6	11.9	11.5	-	NA
3b		OMe	H	OMe	223.5	225.1	205.3	285.8	6.0	6.5	11.4	-	11.4	NA
3c		H	OMe	H	219.0	220.5	204.6	287.8	5.8	6.5	-	11.3	-	NA
3d		H	OH	H	219.1	220.3	204.5	287.8	5.8	6.6	-	10.5	-	>100
3e		OH	H	OH	221.3	224.8	205.7	286.9	6.1	6.4	10.5	-	10.5	>100
3f		OH	OH	H	221.2	222.1	204.8	285.8	5.9	6.4	10.4	10.5	-	89.44

Table 1. Continued

4a		OMe	OMe	H	220.2	221.5	205.0	284.3	5.9	6.4	11.9	11.4	-	NA	
4b		OMe	H	OMe	223.7	225.1	205.8	284.4	6.1	6.5	11.4	-	11.4	NA	
4c		H	OMe	H	219.4	219.4	205.6	290.5	6.0	6.6	-	11.3	-	NA	
4d		H	OH	H	219.4	220.4	205.6	290.5	6.0	6.6	-	10.5	-	92.98	
4e		OH	OH	H	OH	223.5	224.5	208.6	291.1	6.1	6.6	10.5	-	10.5	>100
4f		OH	OH	H	H	221.6	222.2	206.1	290.2	6.1	6.5	10.3	10.5	-	76.55
5a		OMe	OMe	H	H	221.0	220.7	205.6	284.4	5.8	6.0	11.9	11.6	-	>100
5b		OMe	H	OMe	223.4	223.6	205.8	283.7	5.9	6.0	11.4	-	11.4	NA	
5c		H	OMe	H	219.0	218.9	204.8	284.4	5.7	6.0	-	11.3	-	NA	
5d		H	OH	H	218.8	218.9	204.8	284.3	5.7	6.1	-	10.5	-	27.11	
5e		OH	H	OH	223.3	223.5	205.9	283.4	6.0	6.0	10.5	-	10.5	53.87	
5f		OH	OH	H	221.1	220.7	205.3	284.2	5.8	6.1	10.4	10.5	-	16.95	

^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^{II} -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 hydrozones have antimalarial activity, while methoxylated hydrozones 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}O -NQCC in methoxylated hydrozones (a, b, c) is about 11.5 MHz, while this quantity in hydroxylated hydrozones (d, e, f) is about 10.5 MHz, about 1 MHz greater, so charge density on oxygen atom of OH in hydroxylated hydrozones 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} s 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 pharmaceutical effect based on their calculated NQCCs (Table 2).

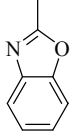
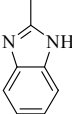
The obtained results show that NQCCs for three mentioned effective atoms (N_{13} in the molecular skeleton of hydrazones and the oxygen atoms in hydroxylated hydrozones) are almost equal for 5f, 6, and 7 compounds, and subsequently, various pharmaceutical effects for 5f, 6, and 7 compounds are not expected.

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 ^2H in KHz and for ^{17}O and ^{14}N in MHz)

Compound	R	R1	R2	R3	$\chi(^2\text{H}_7)$	$\chi(^2\text{H}_8)$	$\chi(^2\text{H}_{11})$	$\chi(^2\text{H}_{14})$	$\chi(^{14}\text{N}_{12})$	$\chi(^{14}\text{N}_{13})$	$\chi(^{17}\text{O}_{in R1})$	$\chi(^{17}\text{O}_{in R2})$
6		OH	OH	H	221.1	220.0	204.9	284.9	6.0	6.1	10.4	10.5
7		OH	OH	H	220.9	223.3	205.2	283.7	5.7	6.1	10.4	10.5

groups on neighboring carbons (R1 = OH, R2 = OH, R3 = 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 hydrazones affect benzothiazole hydrazones activities.

ACKNOWLEDGEMENTS

This research was financially supported by Payame Noor University, Tehran.

REFERENCES

- [1] Greenwood, B. M.; Fidock, D. A.; Kyle, D. E.; Kappe, S. H. I.; Alonso, P. L.; Collins, F. H.; Duffy, P. E., Malaria: progress, perils, and prospects for eradication. *J. Clin. Invest.*, **2008**, *118*, 1266-1276, DOI: 10.1172/JCI33996.
- [2] White, N. J., Antimalarial drug resistance. *J. Clin. Invest.* **2004**, *113*(8),1084-1092, DOI: 10.1172/JCI21682.
- [3] Kremsner, P. G.; x Peter Gottfried Kremsner Search for articles by this author Affiliations Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon Department of Parasitology, Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany Correspondence Correspondence to: Prof Peter G Kremsner, Department of Parasitology, Institute of Tropical Medicine, University of Tübingen, Wilhelmstrasse 27, 72074 Tübingen, Germany Krishna, S. Antimalarial combinations. LANCET, 2004,x Sanjeev Krishna Search for articles by this author Affiliations Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon Department of Cellular and Molecular Medicine, Saint George's Hospital Medical School, London, UK, 364(9430), 285-294, DOI: [http://dx.doi.org/10.1016/S0140-6736\(04\)16680-4](http://dx.doi.org/10.1016/S0140-6736(04)16680-4).
- [4] Egan, T. J. Haemozoin formation. *Mol. Biochem. Parasitol.* **2008**, *157*, 127-136, DOI: 10.1016/j.molbiopara.2007.11.005.
- [5] Alam, A.; Goyal, M.; Iqbal, M. S.; Pal, C.; Dey, S.; Bindu, S.; Maity, P.; Bandyopadhyay, U., Novel antimalarial drug targets: hope for new antimalarial drugs. *Expert. Rev. Clin. Pharmacol.* **2009**, *2*, 469-489, DOI: 10.1586/ecp.09.28.
- [6] Burrows, N. J.; Chibale, K.; Wells, T. N. C., The state of the art in anti-malarial drug discovery and development. *Curr. Top. Med. Chem.*, **2011**, *11*, 1226-1254, DOI: 10.2174/156802611795429194.
- [7] Timothy, J., Egan More Find articles by 'Timothy J Egan' Filter current search by 'Timothy J Egan' 7777-Bucher, C.; Sparr, C.; Schweizer, W. B.; Gilmour, R., fluorinated quinine alkaloids: Synthesis, X-ray structure analysis and antimalarial parasite

- chemotherapy. *Chem. Eur. J.*, **2009**, *15*, 7637-7647, DOI: 10.1002/chem.200900505.
- [8] Kannar, R.; Kumar, K.; Sahal, D.; Kukpeti, S.; Chauhan, V. S., Reaction of Artemisinin with haemoglobin: Implications for antimalarial activity. *Biochem. J.* **2005**, *385*, 409-418, DOI: 10.1042/BJ20041170.
- [9] WHO. World Malaria Report 2013. http://www.who.int/malaria/publications/world_malaria_report_2013/en/, accessed on February 30, 2015.
- [10] Arie, F.; Witkowski, B.; Amaratunga, C.; Beghain, J.; Langlois, A. C.; Khim, N.; Kim, S.; Duru, V.; Bouchier, C.; Ma, L.; Lim, P.; Leang, R.; Duong, S.; Sreng, S.; Suon, S.; Chuor, C. M.; Bout, D. M.; Menard, S.; Rogers, W. O.; Genton, B.; Fandeur, T.; Miotto, O.; Ringwald, P.; Le Bras, J.; Berry, A.; Barale, J. C.; Fairhurst, R. M.; Benoit-Vical, F.; Mercereau-Puijalon, O.; Menard, D. A., Molecular marker of artemisinin resistant plasmodium falciparum malaria. *Nature*, **2014**, *505*, 50-55, DOI: 10.1038/nature12876.
- [11] Miller, L. H.; Baruch, D. I.; Marsh, K.; Doumbo, O. K., The pathogenic basis of malaria. *Nature*, **2002**, *415*, 673-679, DOI: 10.1038/415673a.
- [12] Burrows, J. N.; Burlot, E.; Campo, B.; Cherbuin, S.; Jeanneret, S.; Leroy, D.; Spangenberg, T.; Waterson, D.; Wells, T. N.; Willis, P., Antimalarial drug discovery-the path towards eradication. *Parasitology*, **2014**, *141*, 128-139, DOI: 10.1017/S0031182013000826.
- [13] Wells, T. N.; Alonso, P. L.; Gutteridge, W. E., New medicines to improve control and contribute to the eradication of malaria. *Nat. Rev. Drug Discov.*, **2009**, *8*, 879-891, DOI: 10.1038/nrd2972.
- [14] Sarkar, S.; Siddiqui, A. A.; Saha, S. J.; De, R.; Mazumder, S.; Banerjee, C.; Iqbal, M. S.; Nag, S.; Adhikari, S.; Bandyopadhyaya, U., Antimalarial activity of small-molecule benzothiazole hydrazones. *Antimicrob. Agents. Ch.* **2016**, *60*, 4217-4228, DOI: 10.1128/AAC.01575-15.
- [15] Drew, M. G. B.; Metcalf, J.; Ismail, F. M. D., Antimalarial drugs based on artemisinin: DFT calculations on the principal reactions. *J. Mol. Struct-Theochem.* **2005**, *756*, 87-95, DOI: 10.1016/j.theochem.2005.08.010.
- [16] Fernández, I.; Robert, A., Peroxide bond strength of antimalarial drugs containing an endoperoxide cycle. Relation with biological activity. *Org. Biomol. Chem.*, **2011**, *9*, 4098-4107, DOI: 10.1039/C1OB05088E.
- [17] Moles, P.; Oliva, M.; Safont, V. S., Modeling the decomposition mechanism of artemisinin, *J. Phys. Chem. A*, **2006**, *110*, 7144-7158, DOI: 10.1021/jp0574089.
- [18] Slichter, C. P., Principles of magnetic resonance. springer-verlag, New York, 1992, Ch. 10.
- [19] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E. Jr.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., GAUSSIAN 03, Gaussian Inc. Pittsburgh, PA, 2003.
- [20] Sayed Alam, M.; Jebin, S.; Rahman, M. M.; Latiful Bari, Md.; Lee, D. U., Biological and quantitative-sar evaluations, and docking studies of (E)-N'-benzylidenebenzohydrazide analogues as potential antibacterial agent, *Excli J.*, **2016**, *15*, 350-361, DOI: <http://dx.doi.org/10.17179/excli2016-388>.
- [21] Rizzo, A.; Ruud, K.; Helgaker, T.; Salek, P.; Agren, H.; Vahtras, O. Sternheimer shieldings and EFG polarizabilities: a density-functional theory study, *Chem. Phys. Lett.*, **2003**, *372*, 377-385, DOI: 10.1016/S0009-2614(03)00410-X.
- [22] Andrew, R. L., Molecular modeling principles and applications. Longman, Singapore publishers,

- Singapore, 1997, Ch. 5.
- [23] Lucken, E. A. C., Nuclear quadrupole coupling constants. Academic Press, London, 1969, Ch. 1-4.
- [24] Graybeal, J. D., Molecular spectroscopy. McGraw Hill, Singapore, 1988, Ch. 10.
- [25] Cohen, M. H.; Reif, F., Quadrupole effects in nuclear magnetic resonance studies of solids. *Solid State Phys.*, **1975**, *5*, 321-438, DOI: [http://dx.doi.org/10.1016/S0081-1947\(08\)60105-8](http://dx.doi.org/10.1016/S0081-1947(08)60105-8).
- [26] Pyykko, P., Spectroscopic nuclear quadrupole moments. *Mol. Phys.*, **2001**, *99*, 1617-1629, DOI: [10.1080/00268970110069010](https://doi.org/10.1080/00268970110069010).
- [27] Rafiee, M. A.; Hadipour, N. L.; Naderi-manesh, H., The correlation study of quinoline derivatives and their pharmaceutical behavior by *ab initio* calculated NQR parameters. *J. Comput. Aided Mol. Des.*, **2004**, *18*, 215-220, DOI: [10.1023/B:JCAM.0000035201.67977.16](https://doi.org/10.1023/B:JCAM.0000035201.67977.16).
- [28] Rafiee, M. A.; Hadipour, N. L.; Naderimanesh, H., The role of charge distribution on the antimalarial activity of artemisinin analogues. *J. Chem. Inf. Model.* **2005**, *45*, 366-370, DOI: [10.1021/ci049812v](https://doi.org/10.1021/ci049812v).
- [29] Rafiee, M. A.; Partoee, T., Investigation of the binding affinity between styrylquinoline inhibitors and HIV integrase using calculated nuclear quadrupole coupling constant (NQCC) parameters (A theoretical *ab initio* study). *Bull. Korean Chem. Soc.* **2011**, *32*, 208-212, DOI: [10.5012/bkcs.2011.32.1.208](https://doi.org/10.5012/bkcs.2011.32.1.208).
- [30] Kumar, S.; Bandyopadhyay, U., Free heme toxicity and its detoxification systems in human. *Toxicol. Lett.*, **2005**, *157*, 175-188, DOI: [10.1016/j.toxlet.2005.03.004](https://doi.org/10.1016/j.toxlet.2005.03.004).
- [31] Kumar, S.; Das, S. K.; Dey S.; Maity, P.; Guha, M.; Choubey, V.; Panda, G.; Bandyopadhyay, U., Antiplasmodial activity of [(aryl)arylsulfanylmethyl] pyridine. *Antimicrob Agents Chemother.*, **2008**, *52*, 705-715, DOI: [10.1128/AAC.00898-07](https://doi.org/10.1128/AAC.00898-07).
- [32] Kumar, S.; Guha, M.; Choubey, V.; Maity, P.; Bandyopadhyay, U., Antimalarial drugs inhibiting hemozoin (beta-hematin) formation: a mechanistic update. *Life Sci.*, **2007**, *80*, 813-828, DOI: [10.1016/j.lfs.2006.11.008](https://doi.org/10.1016/j.lfs.2006.11.008).
- [33] Dey, S.; Bindu, S.; Goyal, M.; Pal, C.; Alam, A.; Iqbal, M. S.; Kumar, R.; Sarkar, S.; Bandyopadhyay, U., Impact of intravascular hemolysis in malaria on liver dysfunction: involvement of hepatic free heme overload, NF-B, activation, and neutrophil infiltration. *J Biol. Chem.*, **2012**, *287*, 26630-26646, DOI: [10.1074/jbc.M112.341255](https://doi.org/10.1074/jbc.M112.341255).
- [34] Francis, S. E.; Sullivan, D. J.; Jr, Goldberg, D. E., Hemoglobin metabolism in the malaria parasite *Plasmodium falciparum*. *Annu. Rev. Microbiol.*, **1997**, *51*, 97-123, DOI: [10.1146/annurev.micro.51.1.97](https://doi.org/10.1146/annurev.micro.51.1.97).