A Density Functional Study of $^{15}$N Chemical Shielding Tensors in Neocryptolepine Derivatives

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Abstract

Neocryptolepine, cryptolepine, and their analogous have shown in vitro activity against Plasmodium falciparum, the most dangerous among Plasmodium species and responsible for malaria infections in human. Malaria, the major parasitic infection in many tropical and subtropical regions is leading to more than one million deaths out of 400-500 million cases observy each year. A computational study was carried out to investigate the relationship between the $^{15}$N shielding tensors of indol and quinoline nitrogen’s and their antiplasmodial activity in neocryptolepine derivatives. The calculations were performed with the B3LYP method and 6–311++G** standard basis sets using the Gaussian 98 suite of programs. The results show the $\sigma_{11}$ is highly influenced due to the substitution for both indol and nitrogen and may be used as a probe the activity of neocryptolepine antiplasmodial derivatives.

Keywords: Malaria, Antiplasmodial activity, Drug, Neocryptolepine, NMR, DFT calculations.

Introduction

Neocryptolepine I and cryptolepine II, tetracyclic organic compounds consisting of quinoline and indol groups are receiving prime attention in recent years because of their antimalarial activities [1, 2]. These two indoloquinolines were first isolated from the roots of Cryptolepis triangularis, and then from Cryptolepis sanguinolenta [3-6]. In traditional medicine, Cryptolepis sanguinolenta is used in West and Central Africa as an antimalarial agent.

![Scheme 1](image-url)

Neocryptolepine (I)  Cryptolepine (II)
In this respect, neocryptolepine, cryptolepine (Scheme 1) and their analogous have shown in vitro activity against *Plasmodium falciparum*, the most dangerous of the Plasmodium species responsible for malaria infections in human.

Malaria, the major parasitic infection in many tropical and subtropical regions is leading to more than one million deaths out of 400-500 million cases each year [7]. As a result of the increasing resistance against antimalarial drugs, there is continuing need for new therapeutic agents. Neocryptolepine 1 and cryptolepine 2 are used as leading compounds for the synthesis of new antiplasmodial substances [8-11], among neocryptolepine shows lower cytotoxicity compared to cryptolepine.

Recently, Miert et al. [12] synthesized new 2- or 3- substituted neocryptolepine derivatives with more selective antiplasmodial activity than neocryptolepine. It was shown that 2-bromoneocryptolepine is four times more active than neocryptolepine.

The purpose of the present study was to investigate a relationship between $^{15}$N chemical shielding (CS) tensors of substituted neocryptolepine and their antiplasmodial activity. The CS tensors are unique parameters to use in QSAR studies, because of their incredible sensitivity to local electronic environment of particular nucleus. Therefore, the CS tensors calculations were performed for compounds deionized 1a-8a and ionized 1b-8b (Fig.1) forms of substituted neocryptolepine via density functional theory (DFT) approach.

**Computational Details**

Chemical shielding Hamiltonian, acting on a spin, I, is given by [13]:

$$H = -\gamma \hbar \sigma B_0 I$$

where $\gamma$, $B_0$ and $I$, are magnetogyric ratio, applied magnetic field and nuclear spin operator, respectively. The term, $\sigma$ is a second rank tensor called NMR chemical shielding tensor whose elements describe the size of chemical shielding as a function of molecular orientation in respect to the external magnetic field. This tensor is converted to a diagonal matrix with $\sigma_{11}$, $\sigma_{22}$ and $\sigma_{33}$ components where $\sigma_{33} > \sigma_{22} > \sigma_{11}$.

![Base form (1a-8a)](image1.png) ![salt form (1b-8b)](image2.png)
Figure 1. Structure of base and salt form of neocryptolepine and substituted neocryptolepine.

The isotropic chemical shielding $\sigma_{\text{iso}}$ parameters can be related to the principal components by following equations:

$$\sigma_{\text{iso}} = \frac{\sigma_{11} + \sigma_{22} + \sigma_{33}}{3}$$

DFT calculations were performed using Gaussian 98 suite of programs [14]. Among various modern functional for DFT calculation, Becke three parameter hybrid functional combined with Lee–Yang–Parr correlation functional designated B3LYP were used. The geometry optimizations were carried out at 6-31G* level and the chemical shielding tensors calculations were carried out with 6–311++G ** standard basis sets [15, 16].

Results and Discussion

In order to detect the possibility that variation in the electron density around the nitrogen nuclei explain changes in the neocryptolepine derivatives activity, we calculated the $^{15}$N shielding tensors of 2- or 3-substituted neocryptolepine derivatives 1-8 (Figure 1). These substituted neocryptolepine include halogen and CF$_3$ substitution at 2- or 3-position. The shielding tensors calculations were carried out at B3LYP/6-311++G** level of theory, and are summarized in Tables 1 and 2 for indol and quinoline nitrogen’s of compounds 1b-8b respectively.

Table 1. Calculated $^{15}$N chemical shielding tensors of indol in 1a-8b compounds in Figure1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\sigma_{11}$</th>
<th>$\sigma_{22}$</th>
<th>$\sigma_{33}$</th>
<th>$\sigma_{\text{iso}}$</th>
<th>$\Delta\sigma_{11}$</th>
<th>$\Delta\sigma_{22}$</th>
<th>$\Delta\sigma_{33}$</th>
<th>$\Delta\sigma_{\text{iso}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>-182.57</td>
<td>-9.11</td>
<td>201.94</td>
<td>3.42</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>2a</td>
<td>-184.69</td>
<td>-13.14</td>
<td>204.41</td>
<td>2.19</td>
<td>-2.12</td>
<td>-4.03</td>
<td>2.47</td>
<td>-1.23</td>
</tr>
<tr>
<td>3a</td>
<td>-184.74</td>
<td>-11.64</td>
<td>205.02</td>
<td>2.88</td>
<td>-2.17</td>
<td>-2.53</td>
<td>3.08</td>
<td>-0.54</td>
</tr>
</tbody>
</table>
Calculations were performed for positively charged quinoline nitrogen forms (ionized form) and deionized form of compounds (Figure 1). Actually, in basic conditions, nitrogen becomes positively charged (series b), but under acidic condition, compounds are in deionized form (series a). It seems that neocryptolepine exists essentially in salt form under physiological pH. However, two series results have shown the same, that $\sigma_{11}$ and $\sigma_{22}$ are shielded and $\sigma_{33}$ are deshielded from deionized to ionized forms. Thus, the following discussions are only based on salt forms and discussed under separate sections for indol and quinoline nitrogen’s of compounds 1b-8b.

Table 2. Calculated $^{15}$N chemical shielding tensors of quinoline in 1a-8b compounds in Figure 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\sigma_{11}$</th>
<th>$\sigma_{22}$</th>
<th>$\sigma_{33}$</th>
<th>$\sigma_{\text{iso}}$</th>
<th>$\Delta\sigma_{11}$</th>
<th>$\Delta\sigma_{22}$</th>
<th>$\Delta\sigma_{33}$</th>
<th>$\Delta\sigma_{\text{iso}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>33.28</td>
<td>103.70</td>
<td>183.58</td>
<td>106.86</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>2a</td>
<td>32.93</td>
<td>103.43</td>
<td>184.33</td>
<td>106.90</td>
<td>-0.35</td>
<td>-0.27</td>
<td>0.75</td>
<td>0.04</td>
</tr>
<tr>
<td>3a</td>
<td>33.05</td>
<td>103.83</td>
<td>185.50</td>
<td>107.46</td>
<td>-0.23</td>
<td>0.13</td>
<td>1.92</td>
<td>0.60</td>
</tr>
<tr>
<td>4a</td>
<td>32.78</td>
<td>104.73</td>
<td>185.36</td>
<td>107.62</td>
<td>-0.50</td>
<td>1.03</td>
<td>1.78</td>
<td>0.76</td>
</tr>
<tr>
<td>5a</td>
<td>33.03</td>
<td>102.11</td>
<td>183.80</td>
<td>106.31</td>
<td>-0.25</td>
<td>-1.59</td>
<td>0.22</td>
<td>-0.55</td>
</tr>
<tr>
<td>6a</td>
<td>36.25</td>
<td>103.19</td>
<td>183.63</td>
<td>107.69</td>
<td>2.97</td>
<td>-0.51</td>
<td>0.05</td>
<td>0.83</td>
</tr>
<tr>
<td>7a</td>
<td>35.15</td>
<td>103.33</td>
<td>183.65</td>
<td>107.38</td>
<td>1.87</td>
<td>-0.37</td>
<td>0.07</td>
<td>0.52</td>
</tr>
<tr>
<td>8a</td>
<td>31.06</td>
<td>100.85</td>
<td>183.82</td>
<td>105.25</td>
<td>-2.22</td>
<td>-2.85</td>
<td>0.24</td>
<td>-1.61</td>
</tr>
<tr>
<td>1b</td>
<td>12.28</td>
<td>86.06</td>
<td>195.32</td>
<td>97.89</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>2b</td>
<td>11.02</td>
<td>85.03</td>
<td>195.90</td>
<td>97.32</td>
<td>-1.26</td>
<td>-1.03</td>
<td>0.58</td>
<td>-0.57</td>
</tr>
<tr>
<td>3b</td>
<td>10.61</td>
<td>85.02</td>
<td>196.03</td>
<td>97.22</td>
<td>-1.67</td>
<td>-1.04</td>
<td>0.71</td>
<td>-0.67</td>
</tr>
<tr>
<td>4b</td>
<td>10.18</td>
<td>85.07</td>
<td>196.05</td>
<td>97.10</td>
<td>-2.10</td>
<td>-0.99</td>
<td>0.73</td>
<td>-0.79</td>
</tr>
</tbody>
</table>
The calculated $^{15}\text{N (indol) CS}$ tensors for neocryptolepine and its 2- or 3-substituted compounds are listed in Table 1. The shielding component differences of substituted and non-substituted (neocryptolepine), $\Delta\sigma$, are also listed in Table 1. Halogens (-F, -Cl, -Br and -I) as well as -CF$_3$ groups considered here are electron withdrawing substitutions.

In general, the results summarised in Table 1 illustrate that such substitutions in 2- or 3- position influence the CS tensors of indol nitrogen in different manner. As shown in Figure 1, the indol nitrogen in neocryptolepine derivatives is two rings far away from the substituted ring. Changes in shielding tensors components due to substitutions in indol ring are followed as $\Delta\sigma_{33} \equiv \Delta\sigma_{22} < \Delta\sigma_{11}$. In general, due to the substitution, $\sigma_{33}$ is deshielded, while components $\sigma_{22}$ is shielded. The changes in middle $\sigma_{22}$ and most of the $\sigma_{33}$ shielding components from neocryptolepine to substituted compounds are almost less than 1.8 ppm.

Based on the evaluations of the in vitro activity of 1-8 compounds by Miert et al., all derivatives, except compound 6, showed higher activity than neocryptolepine I.

The smallest activity of compound 6, maybe related to less changes in $\Delta\sigma_{11}$ between the derivatives. Among the halogen substituted neocryptolepine 2-Br (compound 2) and 2-I (compound 5) show the highest changes in $\sigma_{11}$ component, since these two compounds are more active than other halogen substitution. While the modified in position of Cl substituted has not shown significant changes in $\sigma_{11}$, however 2-Br shown approximately seven times more changes than 3-Br substitution, $\Delta\sigma_{11}$ (2-Br) = -4.77 ppm and $\Delta\sigma_{11}$ (3-Br) = 0.73 ppm. These differences are well reflected in their activity, IC$_{50}$ (2-Br) = 6 µM and IC$_{50}$ (3-Br) = 30 µM, where 2-Br is six times more active. Thus, the electronic changes that may be detected by CS tensors can indicate the differences in activity.

Such lower changes in $\sigma_{11}$ component may be related to their antiplasmodial activity. Based on the evaluations in vitro activity of 1-8 compounds by Miert et al. 3-bromoneocryptolepine (compound 6) with IC$_{50}$ = 30 µM and 3-Cl (compound 7) with IC$_{50}$ = 19.3 µM possesses lowest antiplasmodial activity among substituted compounds 1-8, while 2-Br substitution (compound 2) with IC$_{50}$ = 6 µM is the most active compounds.
Table 2 presents the individual $^{15}$N tensor components of quinoline nitrogen, as well as the differences in the tensors components upon substitution of neocryptolepine for compounds 1-8 in Figure 1. The results show that, the changes in $\sigma_{33}$ component of quinoline nitrogen due to the substitution are negligible. On the other hand, the $\sigma_{11}$ and $\sigma_{22}$ component of last three compounds 6-8 show more changes than 2-5 compounds. Furthermore, the $\sigma_{11}$ and $\sigma_{22}$ component of compounds 2-5 and CF3- substituted neocryptolepine are deshielded, while bromine 6 and chloride 7 substituted on 2-positions are shielded. The results of changes in shielding tensors components for halogen substitution at 2-position is on the contrary relative to substitution at 3-position.

The highest changes in tensors components belong to Br-substituted at 3-position by $\Delta \sigma_{11} = 6.15$, which is confirmed by their lowest antiplasmodial activity. On the other hand, compounds 2 and 5 with less deshiled $\sigma_{11}$ component show higher activity than the other derivatives. Thus, the $\sigma_{11}$ tensor component of quinoline nitrogen establishes a correlation with antiplasmodial activity of neocryptolepine derivatives. These special changes can be related to highest potency of 6 and lowest activity of 2.

**Conclusion**

The present study provide an explanation on the electronic effect due to the substitution in 2- or 3-position on neocryptolepine structure by calculation of $^{15}$N chemical shielding tensors of indol and quinoline nitrogen’s. Calculations show that $^{15}$N CS tensors components are useful tool to compare the behavior of antiplasmodial activity of neocryptolepine derivatives. Evaluation of CS tensors changes from bare to halogen substituted in 2- or 3-position indicate more deshielding in indol nitrogen and less deshielding in quinoline nitrogen for 2-Br and 2-I substituted neocryptolepine. This phenomenon may be related to their higher activity. On the other hand, 3-Br and 3-Cl derivatives with highest changes in quinoline nitrogen $\sigma_{11}$ CS tensors show the lowest activity among the other substitutions.

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**References**