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Relationship between ^{13}C NMR Parameters and Antimalarial activity of Cryptolepine Isosteres

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Abstract

Density functional theory calculations were applied to investigate ^{13}C Chemical Shielding (CS) tensors in cryptolepine (**1**) and its sulfur (**2**) and oxygen (**3**) isosteres. The results showed that the CS of carbon nuclei in these compounds may be divided into three types. First, carbons type **α**, are those directly bonded to X (X= NH, S, O) and σ_{33} shielding component of these carbons are deshielded in O isostere compared to N and S isosteres. The second group of carbons (**β**-carbons) is attached to α-carbons, in which σ11 components of S isostere differs from O and N isosteres. The third carbon group, γ-carbons are positioned at a distance of three interatomic bonds or greater away from X. The replacement of N by O or S in cryptolepine isosteres has negligible influence on all components of the later carbon type. The variations of CS components could be related to the inactivity of O isostere and broad spectrum activity of S isostere.

***Keywords*:** *Cryptolepine isosteres, Density functional theory, Chemical shielding, Drug, NMR.*

Introduction

Cryptolepine, **1** is an indoloquinoline alkaloid where isolated in 1929 from the roots of Cryptolepissanguinolenta, a plant used for the treatment of malaria in traditional medicine. In recent years, indoloquinoline, and its derivatives, due to its effect on various biological functions, have been used widely as a lead compound in drug design [1-5]. It was speculated that substitution of indoloquinolines could present a favorable route towards more potent and selective antimalarial activity by decreasing the DNA-interfering action, thus several series of substituted indoloquinoline have been synthesized [6-8]. In drug design, in addition to substitution of tetracyclic rings,

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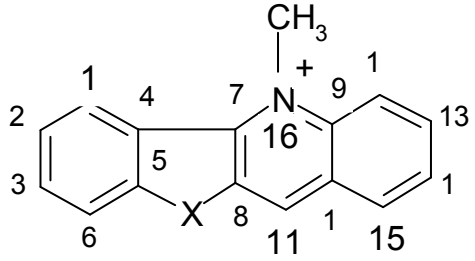
the N atom in indole ring may be substituted by other atoms, particularly S and O atoms, to enhance the desired biological properties [9,10]. For example, sulfur **2** and oxygen **3** isosteres of cryptolepine were synthesized and evaluated for their anti-infective activity by Seth Y. Ablordeppey and co-workers [10].



X=NH, S, O

Scheme 1. Cryptolepine (**1**) and its S (**2**) and O (**3**) isosteres.

They concluded that oxygen isostere is less potent than cryptolepine, while sulfur isostere appears as potent as cryptolepine with broad spectrum of activities. In this work, we used chemical shielding tensors, as sensitive parameters to the electronic structure, for evaluation of different activities of compounds **1–3.**

The calculation of nuclear magnetic resonance, NMR parameters using *ab initio* techniques has become a major and powerful tool to investigate the relation between molecular structure and biological activities of compounds [11-14]. The quantum chemical calculations yield shielding tensors components σ_{ii} (i=1,2,3), which can be related to chemical shift tensors δ_{ii} by subtracting the shielding value from the reference system. Chemical shift tensor components δ_{ii} can be obtained experimentally from solid state NMR, while the isotropic value δ_{iso} (the average of δ_{11}, δ_{22} and δ_{33}) is the only observable in solution NMR. These parameters are very sensitive to the electronic environment of nuclei and hence a useful tool to explore the electronic structure of molecules. Therefore, a more complete knowledge of the CS tensor components should yield a better understanding of molecular and electronic structure than just the isotropic value δ_{iso}.

The ^{13}C and ^{15}N tensors of quinolines and indoloquinolines have been the subject of a number of experimental and theoretical studies [13, 14]. In this paper, we interested to investigate the change in electronic structures by isosteric replacement in the cryptolepine scaffold and their activity profiles. To do this, first the molecular geometries of **1-3** compounds were optimized and then their ^{13}C NMR chemical shieldings were calculated based on the optimized geometries using density functional theory (DFT) approaches.

Computational details

The chemical shielding Hamiltonian acting on a spin,I, is given by [15]:

$$H=-\gamma\hbar\sigma B_0 I \qquad (1)$$

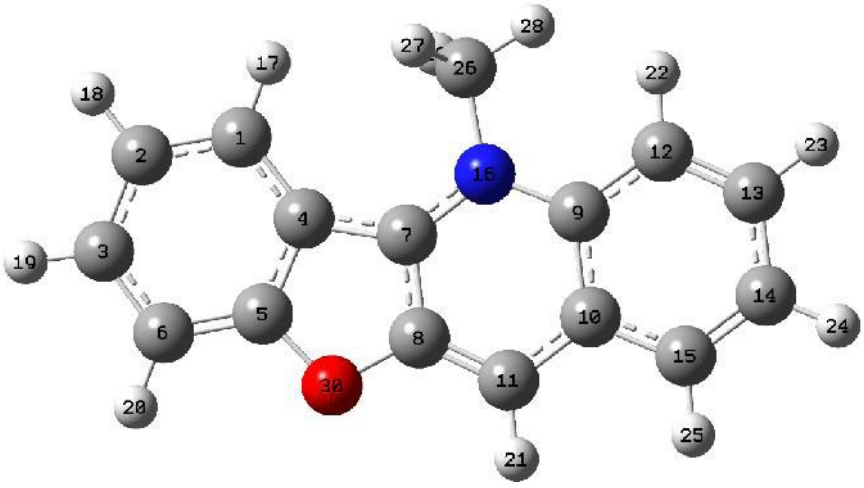
Where γ, B_0 and I are the magnetogyric ratio, applied magnetic field and nuclear spin operator, respectively. The term σ is a second rank tensor called NMR chemical shielding tensor whose elements describe the size of chemical shielding as a function of molecular orientation with respect to the external magnetic field. This tensor is converted to a diagonal matrix with σ11, σ22 and σ33 components where $\sigma_{33}>\sigma_{22}>\sigma_{11}$. The isotropic chemical shielding σiso parameters can be related to the principal components by following equations:

$$\sigma_{iso} = \frac{(\sigma_1 + \sigma_2 + \sigma_3)}{3} \qquad (2)$$

DFT calculations were performed using Gaussian 98 suite of programs [16]. The structure of compounds **1-3** were optimized using the Becke three parameter hybrid functional combined with the Lee–Yang–Parr correlation functional designated B3LYP and the 6-31G* basis set [17-20]. Then, the optimized structures were used to obtain shielding tensors in the gas phase and in solvent using the gauge included atomic orbital, GIAO, method [21]. Shielding calculations were performed using 6-311++G* and fully polarized 6-311++G** basis sets [22]. Solvent effects were included using the polarizable continuum model (PCM). The 1H and ^{13}C NMR chemical shifts were calculated by subtracting the shielding of the individual atoms from the calculated shieldings using the same method.

Results and discussion

In the present work, the calculations were carried out on ^{13}C shielding tensors of the already optimized molecular structure of **1-3** compounds (illustrated in Figure. 1) to investigate the relationship between electronic properties of these compounds and their different activities.



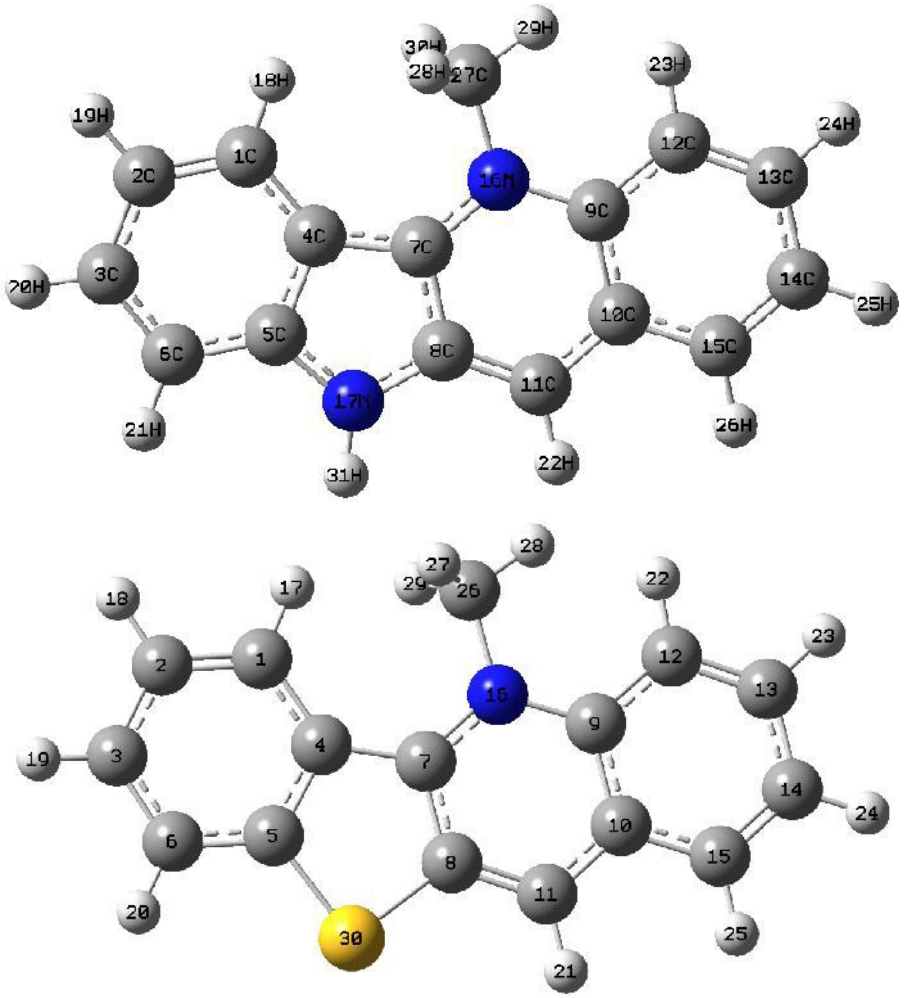


Figure 1. The optimized structures of cryptolepine (1) and its S (2) and O (3) isosteres.

First, a comparison was made between the calculated ^{1}H and ^{13}C NMR chemical shifts of the methyl group on the N-16 atoms of isosteres with the corresponding experimental values reported in Ref. [10]. The chemical shifts were calculated in gas phase, and also in $CHCl_3$ and DMSO solvents. As seen in Table 1, the results are in good agreement with the corresponding experimental values, particularly, where DMSO was taken as solvent [10].

Table 1. A comparison of calculated ^{13}C and ^{1}H NMR chemical shift values at $B_3LYP/6\text{-}311+ +G^*$and corresponding experimental values for **1-3** compounds.

	$^{13}C(\text{-}CH_3)$				$^{1}H(\text{-}CH3)$				$^{1}H(H\text{-}C11)$			
	Gas	$CHCl_3$	DMSO	Exp.	Gas	$CHCl_3$	DMSO	Exp.	Gas	$CHCl_3$	DMSO	Exp.
cryptolepine (**1**)	39.54	39.90	40.03	40.14	4.84	4.89	4.91	5.05	8.82	9.21	9.41	9.25
S(**2**) isostere	39.32	41.13	41.30	43.28	4.92	4.98	5.01	5.09	9.41	9.75	9.90	10.00
O(**3**) isostere	41.28	4.77	4.84	4.87	5.01	9.06	9.49	9.37	9.65	41.28	4.77	4.84

The ^{13}C shielding component tensors and chemical shielding isotropy of compounds **1-3** in DMSO solvent are presented in Table 2. Experimentally it has been shown that compound **3** has less activity than either **2** or **1**. Moreover, it was found that compound **2** is not only equipotent to 1, but also has even broader spectrum of activities than 1. With a closer look at the data in Table 2, one may find three carbon types in studied compounds **1-3**. We named these carbon types as **α, β** and γ in the following discussion. Carbons type α include C3 and C5, which are directly bonded to X atom. Carbons type **β** (C4, C6, C7 and C11) are bonded to α carbons. Carbons type γ are separated from X atom by three or more carbon bonds. As shown in Table 2, the chemical shielding tensor components inγcarbons group are almost unaffected by substitution of O or S atoms in the five-membered ring for N atom. The main reason could be due to the distances of γ-carbons, being far from X and so receive little influence from it. On the other hand, chemical shielding component σ33 of α type carbons in O isostere have significantly decreased compared to S and N isosteres (see Figure 2). It suggests that the inactivity of O isostere may be related to the low value of σ33 relative to N and S isosteres.

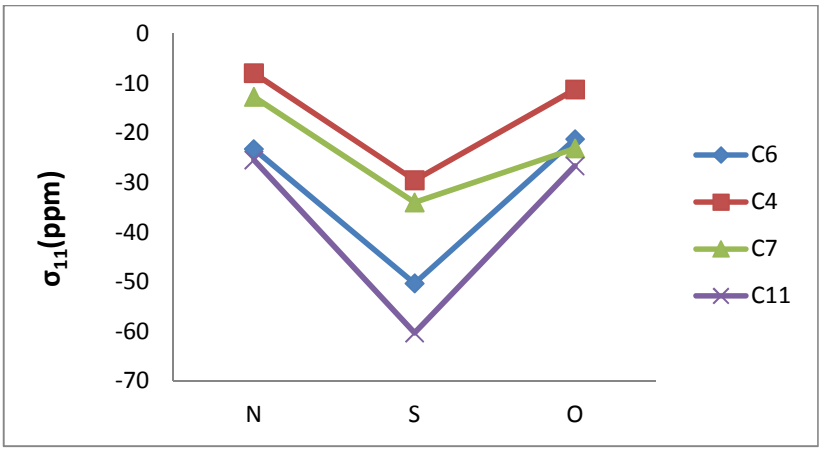


Figure 2. Illustration of σ_{33} components of **α**-carbons of cryptolepine (N) and its S and O isosteres.

As illustrated in Figure 3, chemical shielding component σ_{11} of **β** type carbons in S isostere are deshielded (decreased in electron density) compared to N and O isosteres. The broad spectrum activities of S isostere might be attributed to the low electron density of **β** type carbons.

Figure 3. Illustration of σ11 components of β-carbons of cryptolepine (N) and its S and O isosteres.

It is a general fact that the first elements in each group of periodic table show some properties which differ from the other elements in the group. The relatively large increase in atomic radius accounting from the first to the second member of a group in periodic table causes thus the first element to exert properties that are often quite different from the others, as for instance lower binding energy. In addition, there is no contribution of d orbital in electronic structure of the first elements in each group. In this respect, the S atom in the second row of periodic table has the capability of forming multivalent bonds and π-backbonding by using d orbitals. On the other words, π-backbonding formation between S and C=C withdraws electrons from **β** type carbons toward S and α type carbons, thus increasing the electron density at these atoms (Table 2). The specific behavior of S isostere as a high potent and multi-usage drug is probably due to the particular abovementioned electron densities of α and **β** type carbons.

Table 2. Calculated principal components of CS tensors for Cryptolepine and its S and O isosteres (**1**-**3**) in DMSO solvent at B3LYP/6-311+ +G* level of theory.

Atom type	cryptolepine (**1**)				Atom type	S-isostere(**2**)				Atom type	O-isostere(**3**)			
	σ_{11}	σ_{22}	σ_{33}	σ_{iso}		σ_{1}	σ_{22}	σ_{33}	σ_{iso}		σ_{1}	σ_{22}	σ_{33}	σ_{iso}
C1	-50.9	33.1	169.8	50.7	C1	-53.1	28.5	166.7	47.4	C1	-48.5	29.9	170.3	50.6
C2	-53.8	44.0	174.7	55.0	C2	-59.9	33.9	175.9	50.0	C2	-60.0	36.1	175.4	50.5
C3	-71.5	19.0	174.9	40.8	C3	-67.9	18.1	175.0	41.7	C3	-72.5	14.0	173.8	38.4
C4	-7.9	34.6	159.7	62.2	C4	-29.5	31.7	147.4	49.9	C4	-11.2	34.7	157.4	60.3
C5	-54.3	10.4	132.8	29.6	C5	-52.2	-6.8	131.7	24.2	C5	-68.8	14.0	95.3	13.5
C6	-23.2	47.7	170.6	65.1	C6	-50.3	36.5	168.8	51.7	C6	-21.2	41.1	170.3	63.4
C7	-12.7	-4.0	133.0	38.7	C7	-34.0	-0.9	122.1	29.1	C7	-23.1	-2.9	129.3	34.4
C8	-35.8	30.9	138.8	44.7	C8	-34.7	13.8	135.6	38.2	C8	-47.0	28.2	104.3	28.5
C9	-35.7	6.0	152.0	40.8	C9	-40.7	4.3	151.0	38.2	C9	-39.3	5.6	150.5	38.9
C10	-24.0	-11.0	184.2	49.7	C10	-21.3	-11.0	184.2	50.6	C10	-23.3	-12.0	181.8	48.8
C11	-25.4	17.6	160.3	50.8	C11	-60.3	5.4	158.5	34.5	C11	-26.6	14.2	159.2	48.9
C12	-32.5	43.8	174.6	62.0	C12	-32.3	41.9	174.2	61.3	C12	-32.8	41.9	175.3	61.5
C13	-70.1	22.1	173.8	41.9	C13	-74.4	17.3	173.3	38.7	C13	-72.8	17.7	174.3	39.8
C14	-61.0	32.2	176.2	49.1	C14	-62.9	28.6	176.0	47.2	C14	-63.0	28.6	176.8	47.5
C15	-57.9	34.4	158.1	44.8	C15	-56.9	31.0	158.6	44.2	C15	-59.4	31.9	159.1	43.9
N16	-31.7	49.9	192.7	70.3	N16	-44.5	41.0	189.3	61.9	N16	-32.3	45.8	190.8	68.1
N17	73.8	129.6	166.0	123.1	S30	145.4	372.4	459.1	325.6	O30	36.7	72.2	222.7	110.5

Conclusions

In the current work we have presented DFT calculations of the ^{13}C shielding tensors for cryptolepine isosteres **1-3**. The CS results show that carbon types **α** and **β** experience large changes in electron density, following substitution for N atom in cryptolepine with O or S atom. The calculated σ_{11} component of **β** type carbons in S isostere found to be significantly lower than the corresponding values in N and O isosteres. Also, based on these calculations, the σ_{33} component of α type carbons of O isostere diminish by about 30 ppm relative to S and N isosteres. It is thought that the broad activity of S isostere and less activity of O isostere is probably related to the electron densities of **α** and **β** type carbons as discussed.

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