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ORIGINAL PAPER

Probing ^{13}C chemical shielding tensors in cryptolepine and two bromo-substituted analogs for antiplasmodial activity

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Abstract Density functional theory calculations were applied to investigate ^{13}C chemical shielding tensors in cryptolepine and its bromo-substituted analogs, 2-bromocryptolepine and 2,7-dibromocryptolepine. The fact that bromo-substituted cryptolepine shows higher antiplasmodial activity than cryptolepine raises the question of whether this effect can be related to the electronic properties around carbon atoms. The results show that changes to the principal components of the shielding tensors upon substitution are significant. In particular, σ_{33} is the most affected tensor for carbons in the substituted ring, which could be related to the increased antiplasmodial activity of bromosubstituted cryptolepine. The analyses were also focused on atomic charges and dipole moment.

Keywords Cryptolepine · Malaria · Density functional theory · Chemical shielding · Antiplasmodial activity

Introduction

Cryptolepine (**1**), an indoloquinoline alkaloide, is the most potent antiplasmodial compound known; it is derived from the West African plant *Cryptolepis Sanguinolenta* [1–4]. In traditional medicine, a concoction of the root of this plant is used to treat a variety of health disorders including malaria. Four different *Plasmodium* species are responsible for malaria infection to humans: *P. vivax*, *P. ovale*, *P. malariae*, and, the most severe worldwide, *P.falciparum*. Malaria remains one of the most prevalent infectious diseases in the world. Approximately 247 million cases of malaria with nearly 1 million deaths, mostly of children under 5 years old, were reported in 2006 [5]. The World Health Organization have placed malaria besides tuberculosis and AIDS as a main infectious disease. One significant problem in the fight against malaria is the appearance of resistance to known treatment [6]. The continuing spread of drug-resistant malaria highlights the need for the development of new potential antimalarial drugs. Thus, much effort is focused around developing more potent drugs.

In recent years, cryptolepine has been used widely as a lead compound in drug design. It was speculated that substitution of cryptolepine could present a favorable route towards more potent and selective antimalarial activity by decreasing the DNA-interfering action, and several series of substituted cryptolepine have been synthesized [7–9]. For example, 2-bromocryptolepine (**2**) and 2,7-dibromocryptolepine (**3**) (Fig. 1) were found to be 2 and 10 times more potent than cryptolepine, respectively. Similarly, 2-bromosubstitution in neocryptolepine (an isomer of cryptolepine) shows higher and more selective antiplasmodial activity than its parent [10]. The presence of a halogen atom in the 7-position, indol ring "D", in addition to a halogen substituent in the quinoline ring, were found to be beneficial for activity. It is suggested that potential antimalarial compounds such as **3** involve other mechanism (s), such as DNA intercalation, in addition to the inhibition of hemozoin formation [9]. However, there is also a potential role for halogen bonding, e.g., Br…O interactions

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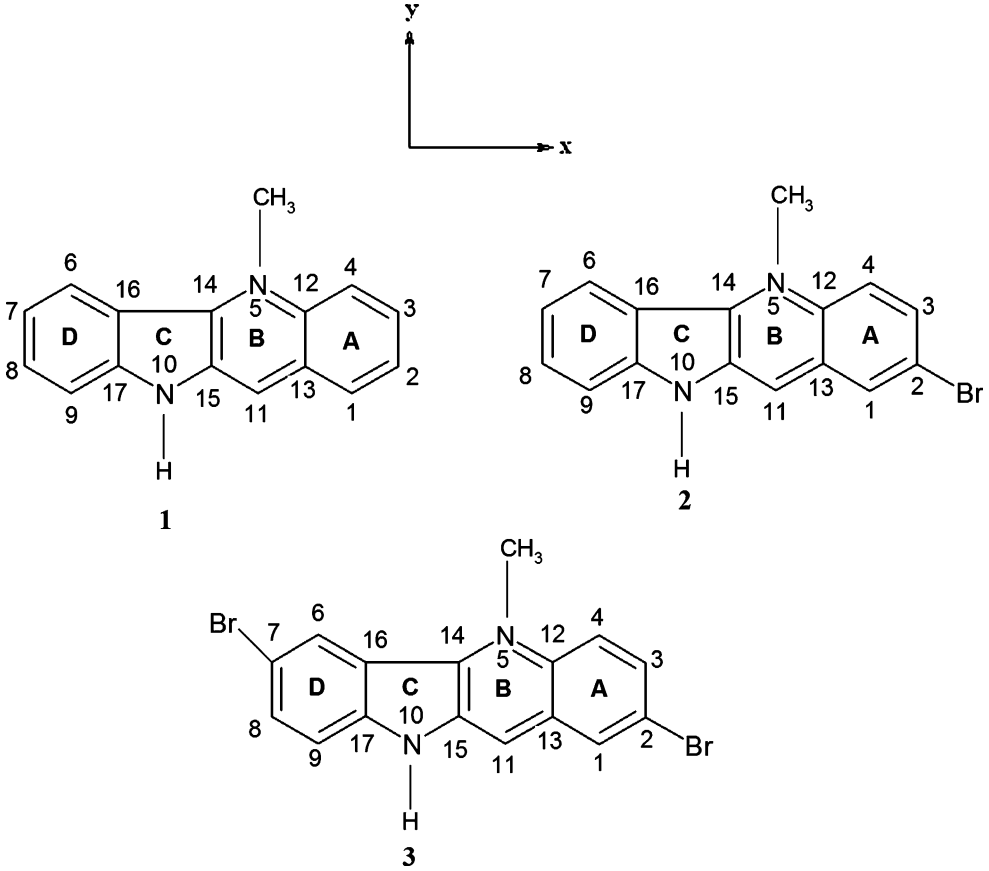

Fig. 1 Structure of cryptolepine (**1**), 2-bromocryptolepine **2**), and 2,7-dibrocryptolepine (**3**). The molecules are in *xy* plane, and the *z* frame axis is perpendicular to the rings

with heme or DNA, in the antiplasmodial activity of brominated cryptolepine. Halogen bonding refers to the non-covalent interactions of halogen atoms in one molecule and a negative site such as the lone pair electrons of a Lewis base in another [11]. There is growing recognition of the importance of halogen bonding in biology systems and in pharmacology. The significance of halogen bonding interactions in biomolecules is reviewed in reference [12].

The aim of this paper is to determine if electronic properties around carbon nuclei can be used as a marker to distinguish the different activity of compounds **1–3**. The calculation of nuclear magnetic resonance (NMR) parameters using ab initio techniques has become an important and powerful tool to investigate the relationship between molecular structure and the biological activity of compounds. The quantum chemical calculations yield shielding tensors components, σ_{ii} (i=1,2,3), which can be related to chemical shifts tensors, δ_{ii}, by subtracting the shielding value from the reference system. Chemical shifts 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 observable only in solution NMR. These parameters are very sensitive to the electronic environment of nuclei, and hence are a useful tool for exploring the electronic structure of molecules. Therefore, a more complete knowledge of the chemical shielding (CS) tensor components should yield a better understanding of molecular and electronic structure than just the isotropic value δ_{iso}. The ^{13}C tensors of quinolines and their N-oxide derivatives has been the subject of a number of experimental and theoretical studies [13–15]. Recently, we have studied ^{15}N shielding tensors in quinolines to shed light on the differences in activity between the two groups of quinolines [16]. The results show that the amino-substitution position significantly affects the CS tensors of ^{15}N shielding tensors of quinolines, and that this is related to their ability to interact with hematin [a by-product of hemoglobin degradation during the erythrocytic stage of malaria life cycle, aqua/hydroxoferriprotoporphyrin or H_2O/HO-Fe(III)PPIX]. Thus, we were encouraged to calculate CS tensors at each carbon for indoloquinolines (compounds **1–3**) to determine how bromosubstitutions affect tensor elements and cause substituted cryptolepine to be more active. The Merz–Kollman ESP charges and dipole moments of these compounds are also discussed.

Computational details

The chemical shielding Hamiltonian acting on a spin, *I*, is given by [17]:

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

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 CS 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 σ_{11}, σ_{22} and σ_{33} components where $\sigma_{33}>\sigma_{22}>\sigma_{11}$. The isotropic chemical shielding σ_{iso} parameters can be related to the principal components by the following equations:

$$\sigma_{iso} = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3 \quad (2)$$

Density functional theory (DFT) calculations were performed using the Gaussian 98 suite of programs [18]. The structure of indoloquinoline compounds **1–3** were optimized using the Becke three parameter hybrid functional combined with the Lee–Yang–Parr correlation functional designated B3LYP [19, 20] and the 6-31G* basis set [21, 22]. The optimized structures were then used to obtain shielding tensors using the gauge included atomic orbital (GIAO) method [23]. Shielding calculations were performed using 6-311+ G* and fully polarized 6-311++ G** basis sets [24]. This method and basis sets were previously tested on organic compounds and can produce reliable results for CS tensors and their orientations [16, 25–27]. The Merz–Kollman ESP charges [28, 29] were also calculated at B3LYP/6-311++G** level of theory.

Results and discussion

In the present study, we calculated the carbon shielding tensors of cryptolepine (**1**), 2-bromocryptolepine (**2**), and 2,7-dibromocryptolepine (**3**) to investigate the relationship between the electronic properties of these compounds and their differences in antimalarial activity. It was found that 2-bromocryptolepine **2** with an antiplasmodial IC50 (half maximal inhibitory concentration) of 0.26, and 2,7-dibromocryptolepine **3** with IC50 0.049, are nearly two- and ten-fold more active, respectively, than cryptolepine with an IC50 value of 0.44 [9]. The carbon numbering refers to the structures shown in Fig. 1. C1–C4 and C11–C13 belong to the A and B rings of quinoline, while C6–C9, C16, and C17 belong to the C and D of indole rings respectively. Cryptolepine is a fused ring system consisting of indole and quinoline rings; these rings are connected by C14 and C15. Calculations were carried out at the B3LYP method using 6-311++G** and 6-311+G* basis sets. Tables 1 and 2 list the calculated three principal shielding tensors, σ_{ii}, and the isotropic shielding σ_{iso} of **1–3** compounds for the two basis sets. The substituted and unsubstituted cryptolepine shielding differences $\Delta\sigma$ ($\Delta\sigma$ (2-bromocryptolepine) $=\sigma$ (**2**)$-\sigma$ (**1**) and $\Delta\sigma$ (2,7-dibromocryptolepine) $=\sigma$ (**3**)$-\sigma$ (**1**)) for each carbon are also depicted in Fig. 2. A quick look at the results reveals that the calculated parameters with the 6-311 ++ G** and 6-311+ G* basis sets are very consistent with each other, indicating that the basis sets were large enough for the purpose of computing CS tensors. In the remainder of the text, the values reported are based on the 6-311++ G** basis set results.

Although the substitutions do not significantly change σ_{iso} (except for the carbon containing the substitution), they do change the CS tensor components, σ_i, considerably. The bromo substitutions of cryptolepine affect not only CS tensors of carbons in the substituted A and D rings, but CS tensors of carbons 11, 14, and 15 in B and C as well. Changes in isotropic chemical shielding $\Delta\sigma_{iso}$ are 0.02–17.70 ppm, where CS components σ_{ii} show a larger range of 0.00–49.44 ppm from unsubstituted to bromosubstituted cryptolepine compounds **2** and **3**.

Both halogen-substituted compounds show significant changes in shielding tensors in the carbon containing the substitution and the ortho carbons, where σ_{33} is the most affected tensor element. These carbons are C1–C3 in the A ring of quinoline and C6–C8 in the D ring of indole. Both mono- and di-substituted cryptolepines show a similar trend in the changes of CS tensor for the A ring carbons due to the substitution. Furthermore, carbons belonging to the A and the D ring experience the same effect due to the substitution in compound **3**. Therefore, it seems that the CS tensor changes in the indol ring D due to the presence of Br in the 7-position, in addition to the Br substituent in the quinoline ring, are related to 10 times higher activity of cryptolepine **3** as compared cryptolepine **1**. Ortho carbons (C1 and C3 for compound **2** and C1, C3, C6, and C8 for Compound **3**) show an increase in σ_{11} component due to bromosubstitutions. The carbons at para positions C12 and C17 in the substituted rings experience changes in the σ_{11} component by 4–5 ppm. In compound **3**, while σ_{11} of meta carbons C4 and C16 are least influenced by the substitutions, and shielded by only approximately 0.6 ppm, the two other meta carbons C13 and C9 are shielded by more than 1.6 ppm. The opposite trend is observed on σ_{11}changes for C11 and C14 relative to C15 in the B ring, resulting from the substitution.

The *para* carbon C17 in dibromosubstituted cryptolepine is also shielded in $\sigma_{11}$by about 5 ppm compared to bare and mono-bromosubstituted cryptolepine. Ortho and meta carbons are shielded in σ_{22} component, where carbon containing the substitutions and para carbons are deshielded in both mono and disubstituted cryptolepine. Ortho carbons are shielded by approximately 5–10 ppm in σ_{11} and σ_{22}, and deshielded in σ_{33} by approximately 19–24 ppm. Among the carbons, ortho C1 in disubstituted cryptolepine is the most affected carbon in σ_{22} with $\Delta\sigma_{22}$=10.3 ppm. An

Table 1 Calculated principal components of carbon shielding (CS) tensors for cryptolepine and 2-bromocryptolepine, and 2,7-dibromocryptolepine at B3LYP/6-311++ G** level of theory. Values in parentheses are $\Delta\sigma$

Carbon	Cryptolepine				2-Bromocryptolepine				2,7-Dibromocryptolepine			
	σ_{11}	σ_{22}	σ_{33}	σ_{iso}	σ_{11}	σ_{22}	σ_{33}	σ_{iso}	σ_{11}	σ_{22}	σ_{33}	σ_{iso}
C1	−57.42	36.37	156.32	45.09	−51.96	46.14	136.79	43.66	−51.33	46.69	137.16	44.18
					(5.46)	(9.77)	(−19.53)	(−1.43)	(6.10)	(10.32)	(−19.16)	(−0.91)
C2	−62.68	28.23	175.89	47.15	−58.24	21.15	126.94	29.95	−58.82	19.73	127.43	29.45
					(4.44)	(−7.08)	(−48.95)	(−17.20)	(3.86)	(−8.50)	(−48.46)	(−17.70)
C3	−72.31	19.05	173.15	39.96	−65.07	26.80	148.22	36.65	−65.91	26.15	148.41	36.22
					(7.24)	(7.76)	(−24.93)	(−3.31)	(6.41)	(7.10)	(−24.73)	(−3.74)
C4	−31.10	46.72	173.49	63.04	−30.51	49.17	169.45	62.70	−30.81	49.46	168.70	62.45
					(0.59)	(2.44)	(−4.03)	(−0.33)	(0.29)	(2.74)	(−4.79)	(−0.59)
C6	−50.18	36.05	168.81	51.56	−49.67	35.04	168.23	51.20	−43.23	44.05	147.06	49.29
					(0.52)	(−1.01)	(−0.58)	(−0.36)	(6.95)	(8.00)	(−21.75)	(−2.26)
C7	−57.39	38.51	174.37	51.83	−57.58	38.44	174.31	51.72	−52.84	37.57	124.93	36.56
					(−0.19)	(−0.07)	(−0.06)	(−0.11)	(4.56)	(−0.94)	(−49.44)	(−15.27)
C8	−73.98	13.25	174.60	37.96	−74.32	14.17	174.31	38.05	−67.04	20.37	150.90	34.74
					(−0.34)	(0.91)	(−0.29)	(0.10)	(6.94)	(7.11)	(−23.70)	(−3.21)
C9	−22.42	48.99	169.28	65.28	−23.16	48.56	170.52	65.31	−20.78	49.15	167.16	65.17
					(−0.74)	(−0.43)	(1.24)	(0.02)	(1.64)	(0.16)	(−2.13)	(−0.11)
C11	−23.67	25.22	157.61	53.06	−20.21	27.66	157.61	55.02	−21.78	26.67	157.72	54.20
					(3.46)	(2.44)	(0.00)	(1.97)	(1.89)	(1.45)	(0.11)	(1.15)
C12	−34.81	7.64	151.48	41.44	−29.96	7.46	151.15	42.88	−30.51	6.74	151.30	42.51
					(4.85)	(−0.19)	(−0.33)	(1.45)	(4.31)	(−0.91)	(−0.18)	(1.07)
C13	−22.62	−9.58	183.93	50.58	−19.31	−8.70	178.56	50.18	−20.02	−8.51	178.01	49.82
					(3.30)	(0.88)	(−5.37)	(−0.39)	(2.59)	(1.07)	(−5.92)	(−0.75)
C14	−10.11	−4.09	132.59	39.46	−9.46	−4.12	131.93	39.45	−8.12	−0.23	132.48	41.38
					(0.65)	(−0.03)	(−0.66)	(−0.02)	(2.00)	(3.86)	(−0.11)	(1.92)
C15	−34.43	34.57	138.43	46.19	−35.73	34.49	136.30	45.02	−35.67	33.85	136.68	44.95
					(−1.30)	(−0.08)	(−2.13)	(−1.17)	(−1.24)	(−0.73)	(−1.75)	(−1.24)
C16	−6.65	35.78	159.23	62.79	−8.30	37.77	157.52	62.33	−6.39	38.26	154.04	61.97
					(−1.65)	(1.99)	(−1.71)	(−0.46)	(0.26)	(2.48)	(−5.19)	(−0.82)
C17	−55.32	15.94	131.74	30.79	−55.10	15.91	135.10	31.97	−50.31	15.22	133.21	32.71
					(0.22)	(−0.03)	(3.36)	(1.18)	(5.01)	(−0.72)	(1.47)	(1.92)

inspection of the CS tensors shows that the influence of the substituent on the shielding of the carbon atoms is not limited to the carbons on the A and D ring to which the substituent is attached. While C14 experiences small changes in σ_{11} and σ_{22} tensors in **2**, an increase in σ_{11} and σ_{22} tensors by 2.0 ppm and 3.9 ppm, respectively, is found in **3**. Furthermore, for both substituted cryptolepines, C11 and C15 show opposite changes in CS tensors, with C11 being shielded and C15 deshielded.

As shown in the results in Tables 1 and 2 and Fig. 2, the most significant changes in CS tensors are observed in the σ_{33} component. Most carbons in the substituted cryptolepine show a decrease in σ_{33} tensors. The tensor decreases average 7 ppm from **1** to **2** and 13.7 ppm from **1** to **3**. Upon bromosubstitution of cryptolepine, as observed for σ_{11} and σ_{22}, the substituted carbons and ortho carbons of the structure show significant changes in σ_{33} values. C2 and C7 are the most deshielded carbons by about 49 ppm, whereas ortho carbons change by 19–24 ppm. Here, the meta carbons also experience significant changes in the σ_{33} component. As a result, it seems that the significant decrease in the σ_{33} component for all carbons in the A ring of monosubstituted as well as for carbons in both A and D rings of dibromosubstituted cryptolepine could be related to higher activity of these compounds compared to bare cryptolepine. Decreasing isotropic values for carbons in A and D rings of substituted relative to unsubstituted cryptolepine is caused mainly by the σ_{33} component of carbons. Furthermore, C11–C17 in the B and D rings show changes in isotropic values that are comparable to changes

Table 2 Calculated principal components of CS tensors for cryptolepine and 2-bromocryptolepine, and 2,7-dibromocryptolepine at B3LYP/6-311+ G* level of theory. Values in parentheses are $\Delta\sigma$

Carbon	Cryptolepine				2-Bromocryptolepine				2,7-Dibromocryptolepine			
	σ_{11}	σ_{22}	σ_{33}	σ_{iso}	σ_{11}	σ_{22}	σ_{33}	σ_{iso}	σ_{11}	σ_{22}	σ_{33}	σ_{iso}
C1	−57.15	38.62	157.22	46.23	−52.00	47.88	137.20	44.36	−51.48	47.79	137.23	44.51
					(5.15)	(9.26)	(−20.03)	(−1.87)	(5.67)	(9.17)	(−19.99)	(−1.72)
C2	−62.05	29.99	176.34	48.09	−57.26	22.02	127.03	30.60	−58.05	20.60	127.74	30.10
					(4.79)	(−7.97)	(−49.30)	(−17.49)	(4.00)	(−9.39)	(−48.59)	(−17.99)
C3	−71.59	21.00	173.58	41.00	−64.69	28.59	149.07	37.65	−65.41	27.45	149.36	37.13
					(6.90)	(7.58)	(−24.51)	(−3.35)	(6.18)	(6.45)	(−24.23)	(−3.87)
C4	−31.35	49.00	173.75	63.80	−29.66	49.75	169.55	63.21	−30.10	50.27	169.30	63.16
					(1.69)	(0.74)	(−4.20)	(−0.59)	(1.25)	(1.27)	(−4.45)	(−0.65)
C6	−49.89	37.48	168.82	52.14	−49.50	36.78	168.44	51.90	−42.86	45.51	147.60	50.08
					(0.39)	(−0.70)	(−0.38)	(−0.23)	(7.03)	(8.03)	(−21.22)	(−2.05)
C7	−56.62	40.23	174.69	52.76	−57.10	40.12	174.76	52.59	−52.95	38.67	125.12	36.95
					(−0.48)	(−0.11)	(0.07)	(−0.17)	(3.67)	(−1.56)	(−49.57)	(−15.82)
C8	−73.44	15.05	174.53	38.72	−74.03	14.97	174.77	38.57	−66.76	21.91	151.45	35.54
					(−0.60)	(−0.08)	(0.23)	(−0.15)	(6.67)	(6.86)	(−23.08)	(−3.18)
C9	−21.88	50.63	169.81	66.19	−22.74	50.31	170.47	66.01	−20.19	50.66	167.66	66.04
					(−0.86)	(−0.32)	(0.66)	(−0.18)	(1.69)	(0.03)	(−2.15)	(−0.14)
C11	−23.62	27.03	158.32	53.91	−20.26	29.17	158.40	55.77	−21.63	28.18	157.91	54.82
					(3.36)	(2.14)	(0.08)	(1.86)	(1.99)	(1.15)	(−0.41)	(0.91)
C12	−34.40	7.96	151.09	41.55	−29.54	8.05	151.00	43.17	−30.49	7.02	150.62	42.38
					(4.86)	(0.09)	(−0.09)	(1.62)	(3.91)	(−0.94)	(−0.47)	(0.83)
C13	−21.72	−9.01	183.73	51.00	−19.72	−7.95	178.56	50.30	−19.69	−7.92	176.07	49.49
					(2.00)	(1.06)	(−5.17)	(−0.71)	(2.03)	(1.09)	(−7.66)	(−1.52)
C14	−9.93	−3.98	132.41	39.50	−9.11	−4.00	131.75	39.55	−8.42	0.17	131.76	41.17
					(0.82)	(−0.02)	(−0.66)	(0.04)	(1.51)	(4.15)	(−0.64)	(1.67)
C15	−33.57	34.94	138.06	46.48	−34.53	34.88	136.47	45.60	−34.89	34.96	136.39	45.49
					(−0.96)	(−0.06)	(−1.60)	(−0.87)	(−1.32)	(0.02)	(−1.68)	(−0.99)
C16	−6.22	36.93	158.99	63.23	−7.48	38.47	158.01	63.00	−5.96	39.04	154.18	62.42
					(−1.26)	(1.54)	(−0.98)	(−0.23)	(0.26)	(2.12)	(−4.82)	(−0.81)
C17	−53.94	16.43	131.90	31.46	−54.00	16.64	133.09	31.91	−48.94	15.97	133.27	33.43
					(−0.06)	(0.21)	(1.19)	(0.45)	(4.99)	(−0.46)	(1.37)	(1.97)

for carbons near to the substitutions (ortho and meta carbons) in the A and D rings.

The shielding tensor differences between bare and substituted cryptolepine can be explained by the relative orientations of carbons shielding tensors in the aromatic ring. Quantum chemical calculations can be used to obtain CS tensor orientations in the molecular frame axes. Previously, it has been indicated that quantum chemical calculation at the B3LYP/6-311++G** level can produce reliable results for CS tensor orientations [23, 24]. To fulfill this aim, the calculated CS tensors of the carbon atoms were analyzed systematically to obtain their relative orientations in molecular frame. Angles of the CS tensors with molecular frame axes for carbon atoms of compounds **1**–**3** are listed in Table 3. Dibromosubstituted cryptolepine exhibits significant changes in CS tensor orientations relative to bare and mono-substituted cryptolepine. The $\sigma_{11}$and σ_{22} components lie in the indoloquinoline plane (*xy*-plane of molecules), whereas the σ_{33} component is perpendicular to the plane. It is well known that in-plane components of the CS tensors, $\sigma_{11}$and σ_{22}, in aromatic rings are quite sensitive to changes in π-electron density, while the component perpendicular to the aromatic ring, σ_{33}, is largely unaffected by π-electron density. The σ_{33} component is affected by σ-electron density around the nuclei [13, 14, 30]. Halogen substitutions can change the electron density in aromatic systems by both inductive electron withdrawing effects due to their high electronegativity, and resonance-donating effects by its lone pair. Thus, carbons in the ortho position experience both resonance and inductive

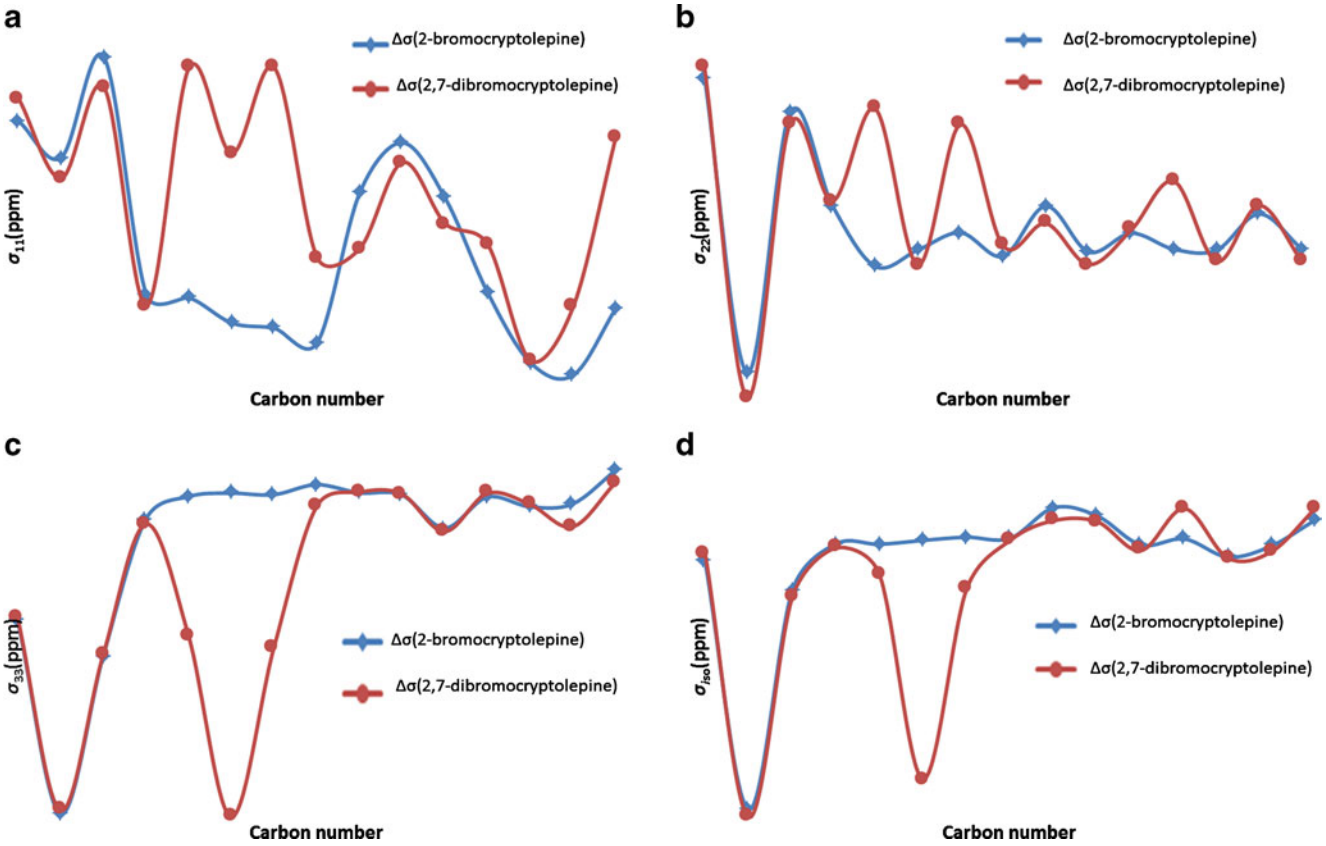

Fig. 2 Plots of differences shielding $\Delta\sigma$ (2-bromocryptolepine) and $\Delta\sigma$ (2,7-dibromocryptolepine for each carbon. **a** $\Delta\sigma_{11}$, **b** $\Delta\sigma_{22}$, **c** $\Delta\sigma_{33}$, **d** $\Delta\sigma_{iso}$

effects, whereas para carbons are affected mainly by resonance. Following the known relationship between CS tensors and π and σ electron density in aromatic rings, there is an increase in π electron density and a decrease in σ electrons in the ring containing the substitution (A ring in 2-bromo and A and D rings in 2,7-dibromo cryptolepine). The most striking changes caused by bromosubstitutions are observed for the σ_{33} component of carbon containing the substitutions, and ortho carbons, which comes from the perturbation in σ electron density around these carbons. The disturbed π electron density around C11 and C14, which are far from the substitutions, are detected by changes in σ_{11} and σ_{22}. Carbons that are two bonds away from the substitution feel the changes in electron density largely via the inductive effect, which is reflected mainly in the σ_{33} component of these meta carbons.

The calculated Merz–Kollman charges at B3LYP/6-311++G** for compounds **1-3** are shown in Fig. 3. We searched for possible correlations between shielding and charge changes, but found no striking correlations between them. There are only poor correlations, with R^2=0.61 for **2** and R^2=0.56 for **3**, between $\Delta\sigma_{22}$ tensor and point charge changes Δq. However, the ortho carbons show large changes from negative charge in **1** to positive charge in **2** and **3**. In contrast, the charge on carbon containing the substitution is more negative in **2** and **3** than in **1**. Although the partial charges and shielding of carbons do no coincide well, the correlation between charge and shielding components of C1–C3 and C6–C9 of compounds **1-3** with R^2>0.89 was found. The other carbons show a poor correlation between tensors and charges. For example, while σ_{22} component and charge of C12 are correlated by R^2=1.0, σ_{33} component and charge of this carbon are only related by R^2=0.06. Para carbon C12 in **A** ring changes from 0.159*e* (where *e* is the charge of an electron) in **1** to 0.361*e* in **3**. Overall, the total charges of carbons in A and D rings for dibromosubstituted cryptolepine are more positive by about 0.3*e* and 0.1*e*, respectively, than cryptolepine. Dipole moment orientations of the studied compounds are also depicted in Fig. 3. Calculations indicate that both the magnitude and orientation of the dipole moment for compounds **1**–**3** are different. The dipole moment of 2-bromocryptolepine with 7.16 Debye and 2,7-dibromosubstituted cryptolepine with 2.3 Debye are considerably greater than that of bare cryptolepine at 0.7 Debye. As mentioned earlier, potential antimalarial compounds such as **3** are involved in other mechanism(s) in addition to the inhibition of hemozoin formation. However, dipole moment orientation in cryptolepine **3** may be related to the significant electrostatic attraction of this compound with target molecules.

Table 3 Angles of the CS tensors component (degree) with molecular frame axes for carbon atoms in cryptolepine, 2-bromocryptolepine, and 2,7-dibromocryptolepine

		Cryptolepine			2-Bromocryptolepine			2,7-Dibromocryptolepine		
	σ_{ii}	x	y	z	x	y	z	x	y	z
C1	σ_{11}	70.79	160.79	90	69.58	159.58	90	110.86	20.86	90
	σ_{22}	160.79	109.21	90	159.58	110.42	90	20.86	69.14	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C2	σ_{11}	27.39	117.39	90	28.89	118.89	90	150.54	60.54	90
	σ_{22}	117.39	152.61	90	118.89	151.11	90	60.54	29.46	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C3	σ_{11}	44.86	45.14	90	45.03	44.97	90	135.03	134.97	90
	σ_{22}	45.14	135.14	90	44.97	134.97	90	134.97	44.79	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C4	σ_{11}	81.96	8.04	90	93.61	3.61	90	98.69	171.31	90
	σ_{22}	171.96	81.96	90	176.39	93.61	90	8.69	98.69	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C6	σ_{11}	87.49	2.51	90	100.55	10.55	90	88.37	178.37	90
	σ_{22}	177.49	87.49	90	169.45	100.55	90	1.63	88.37	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C7	σ_{11}	56.35	146.35	0	56.03	146.03	90	122.17	32.17	90
	σ_{22}	146.35	123.65	90	146.03	123.97	90	32.17	57.83	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C8	σ_{11}	9.91	80.09	0	9.66	80.34	90	169.94	100.06	90
	σ_{22}	80.09	170.49	90	80.34	170.34	90	100.06	10.06	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C9	σ_{11}	58.73	31.27	90	58.65	31.35	90	95.46	174.54	90
	σ_{22}	31.27	121.27	90	31.35	121.35	90	174.54	84.54	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C11	σ_{11}	96.94	6.94	90	103.1	13.1	90	95.46	174.54	90
	σ_{22}	173.06	96.94	90	166.9	103.1	90	5.46	95.46	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C12	σ_{11}	32.91	122.91	90	33	123	90	145.96	55.96	90
	σ_{22}	122.91	147.09	90	123	147	90	55.96	34.04	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C13	σ_{11}	169.9	79.9	90	142.28	52.28	90	41.51	131.51	90
	σ_{22}	100.1	169.9	90	127.72	142.28	90	48.49	41.51	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C14	σ_{11}	100.69	10.69	90	76.5	166.5	90	134.73	44.73	90
	σ_{22}	169.31	100.69	90	166.5	103.5	90	44.73	45.27	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C15	σ_{11}	54.94	35.06	90	55.73	34.27	90	125.65	144.35	90
	σ_{22}	35.06	125.51	90	34.27	124.27	90	35.65	125.65	90
	σ_{33}	90	90	0	90	90	0	90	0	0
C16	σ_{11}	25.07	64.93	90	23.59	66.41	90	157.36	112.64	90
	σ_{22}	64.93	154.93	90	66.41	156.41	90	112.64	22.64	90
	σ_{33}	90	90	0	90	90	0	90	90	0
C17	σ_{11}	57.44	147.44	90	58.64	148.64	90	121.21	31.21	90
	σ_{22}	147.44	122.56	90	148.64	121.36	90	31.21	58.79	90
	σ_{33}	90	90	0	90	90	0	0	90	0

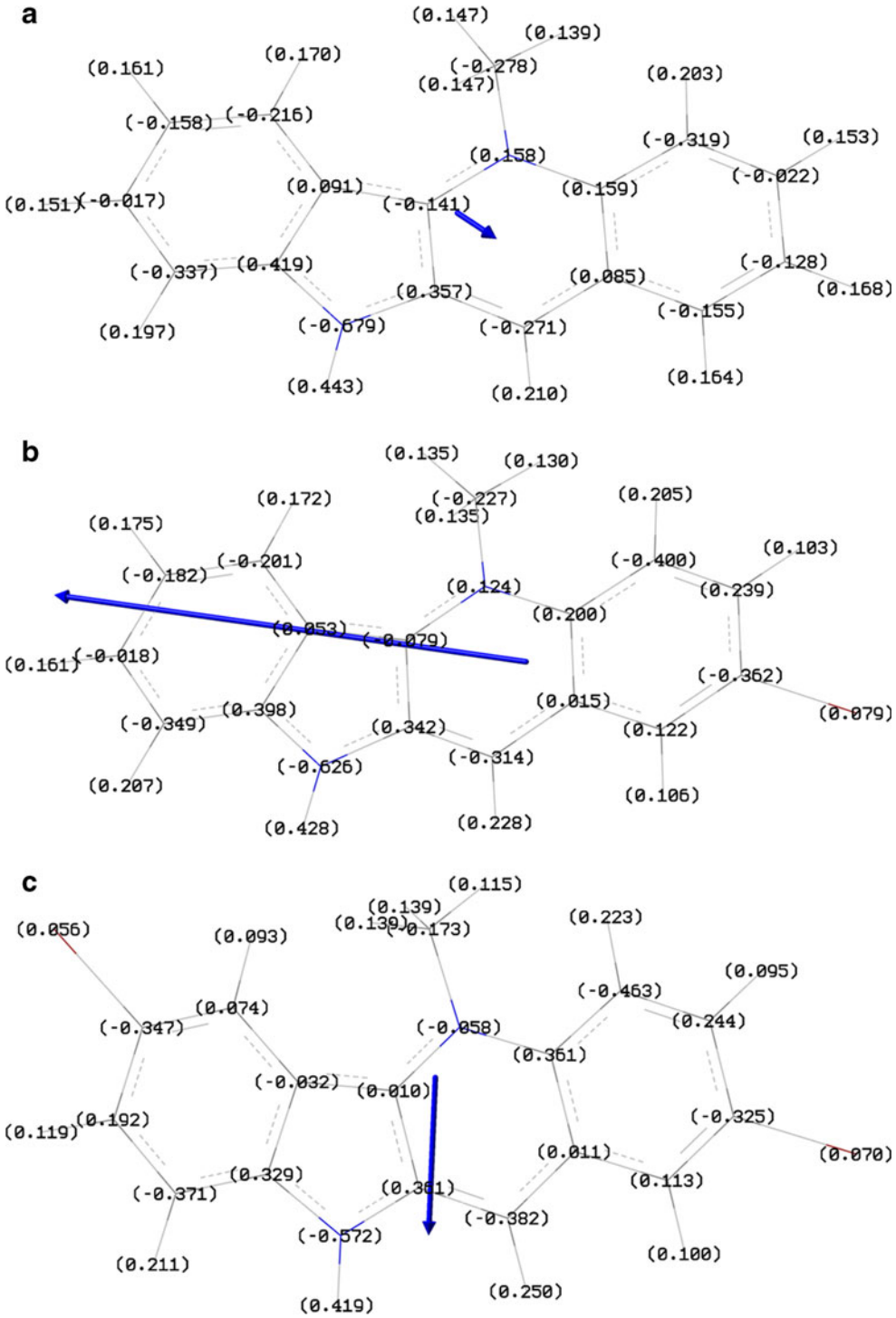

Fig. 3 The Merz–Kollman charges and Dipole moment orientation for **a** cryptolepine, **b** 2-bromocryptolepine, and **c** 2,7-dibromocryptolepine

Conclusions

Despite the fact that bromosubstitutions are recognized to enhance the antiplasmodial activity of cryptolepine, little direct information about this increased activity is available at the molecular level. In the present study, we addressed this question by attempting to explain the electronic effect of bromosubstitutions on the cryptolepine structure through calculations of ^{13}C chemical shielding tensors and atomic charges. Substituted and ortho carbons are most affected by the substitutions. Large decreases in the σ_{33} component and compensating increases in the σ_{11} tensors for A ring carbons of 2-bromocryptolepine and A and D rings of 2,7-dibromocryptolepine relative to bare cryptolepine were found. It is thought that the enhanced activity of bromo-substituted cryptolepine is related to decreasing σ electron

density and increasing π-electron density at ortho and para positions. The large changes in carbon atomic charges and the magnitude and orientation of dipole moments were also observed due to bromosubstitutions. These changes in electronic structure and properties may play a role in the binding of cryptolepine molecules to DNA, and hence aid the rational design of novel anti-malarial drugs.

References

1. Clinquart ED (1929) Bull Acad R Mèd 9:627–635
2. Delvaux E (1931) J Pharm Belg 13:955–959
3. Delvaux E (1931) J Pharm Belg 13:973–977
4. Gellert E, Hammet R, Schlittler EH (1951) Chim Acta 34:642–651
5. Oliveria AB, Dolabela MF, Braga FC, Jacome RLRP, Varotti FP, Povoa MM (2009) Acad Bras Cienc 81:715–740
6. Winstanley PA (2000) Parasitol Today 16:146–153
7. Wrigth CW (2005) Plant derived antimalarial agents: new leads and challenges. Phytochem Rev 4:55–61
8. Wrigth CW (2007) Recent developments in naturally derived antimalarials: cryptolepine analogues. J Pharm Pharmacol 59:899–904
9. Onyeibor O, Croft SL, Dodson HI, Feiz-Haddad M, Kendrick H, Millington NJ, Parapini S, Phillips RM, Seville S, Shnyder SD, Taramelli D, Wright CW (2005) J Med Chem 48:2701–2709
10. Van Miert S, Jonckers T, Cimanga K, Maes L, Maes B, Lemière G, Dommisse R, Vlietinck A, Pieters L (2004) Exp Parasitol 108:163–168
11. Politzer P, Lane P, Concha MC, Ma Y, Murray JS (2007) J Mol Model 13:305–311
12. Murray JS, Riley KE, Politzer P, Clark T (2010) Aust J Chem 63:1598–1607
13. Casabianca LB, De Dios AC (2006) J Phys Chem A 110:7787–7792
14. Casabianca LB, Faller CM, De Dios AC (2006) J Phys Chem A 110:234–240
15. De Dios AC, Tycko R, Ursos LMB, Roepe PD (2003) J Phys Chem A 107:5821–5825
16. Behzadi H, Esrafili ME, Beheshtian J, Hadipour NL, van der Spoel D (2009) Chem Phys Lett 476:169–200
17. Mehring M (1983) Principles of high resolution NMR in solids. Springer, Berlin
18. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Salvador P, Dannenberg JJ, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaroni I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (2001) Gaussian 98, Revision A.11). Gaussian Inc, Pittsburgh, PA
19. Becke AD (1988) Phys Rev A 38:3098–3100
20. Lee C, Yang W, Parr RG (1988) Phys Rev B 37:785–789
21. Rassolov VA, Pople JA, Ratner MA, Windus TL (1998) J Chem Phys 109:1223–1229
22. Gordon MS (1980) Chem Phys Lett 76:163–168
23. Wolinski K, Hilton JF, Pulay P (1990) J Am Chem Soc 112:8251–8260
24. Hehre WJ, Random L, PvR S, Pople JA (1989) Ab initio molecular orbital theory. Wiley, New York
25. Wu G, Dong S, Ida R, Reen N (2002) J Am Chem Soc 124:1768–1777
26. Esrafili MD, Behzadi H, Hadipour NL (2007) Biophys Chem 128:38–45
27. Tkaczyk M, Dawidowski M, Herold F, Wolska I, Wawer I (2010) J Mol Struct 975:78–84
28. Besler BH, Merz KM Jr, Kollman PA (1990) J Comput Chem 11:431–439
29. Singh UC, Kollman PA (1984) J Comput Chem 5:129–145
30. Strub H, Beeler AJ, Grant DM, Michl J, Cutts PW, Zilm KW (1983) J Am Chem Soc 105:3333–3334