

Quinoline alkaloids as intercalative topoisomerase inhibitors

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Abstract Quinoline alkaloids are abundant in the Rutaceae, and many have exhibited cytotoxic activity. Because structurally related antitumor alkaloids such as camptothecin and fagaronine are known to function as intercalative topoisomerase poisons, it is hypothesized that cytotoxic *Stauranthus* alkaloids may also serve as intercalative topoisomerase inhibitors. To test this hypothesis theoretically, ten *Stauranthus* quinoline alkaloids were examined for potential intercalation into DNA using a molecular docking approach. Four of the alkaloids (stauranthine, skimmianine, 3',6'-dihydroxy-3',6'-dihydrostauranthine, and *trans*-3',4'-dihydroxy-3',4'-dihydrostauranthine) were able to intercalatively dock consistently into DNA. In order to probe the intermolecular interactions that may be responsible for intercalation of these quinoline alkaloids, density functional calculations have been carried out using both the B3LYP and M06 functionals. M06 calculations indicated favorable π – π interactions between either skimmianine or stauranthine and the guanine–cytosine base pair. Furthermore, the lowest-energy face-to-face orientation of stauranthine with guanine is consistent with favorable dipole–dipole orientations, favorable electrostatic interactions, and favorable frontier molecular orbital interactions. Likewise, the lowest-energy face-to-face orientation of stauranthine with the guanine–cytosine base pair reveals favorable electrostatic interactions as well as frontier molecular orbital interactions. Thus, not only can quinoline alkaloids dock intercalatively into DNA, but the docked orientations are also electronically favorable.

Keywords Intercalation · DNA · Quinoline alkaloids · Docking · π – π interactions

Introduction

There are numerous antineoplastic agents that function by way intercalating into double-stranded B-DNA [1]. These intercalating antitumor drugs are typically planar aromatic heterocycles and function by forming a ternary cleavable complex with DNA and various DNA polymerases such as topoisomerases I and II [2–5]. Such compounds include the topoisomerase I poisons camptothecin and its derivatives [6], nitidine and fagaronine [7], as well as the topoisomerase II inhibitors mitoxantrone [8], ellipticine [9], and cryptolepine [10].

Quinoline alkaloids are abundant in the Rutaceae, and have been suggested to serve as signature compounds for this family [11–13]. A number of these compounds are planar aromatic heterocycles that have shown cytotoxic activity (for example, see [14–19]). The cytotoxic quinoline alkaloid lunacridine has been found to inhibit topoisomerase II [20], and a series of cytotoxic quinolines that inhibit topoisomerases have been synthesized [21–23]. Similarly, the makaluvamines [24] and pyridoacridines [25] are marine alkaloids that exhibit both topoisomerase I and topoisomerase II inhibition [26, 27]. In our group, using activity-directed preparative chromatographic methods, we have isolated a number of cytotoxic quinoline alkaloids from *Stauranthus perforatus*, and identified them using NMR techniques [28, 29]. Because of the structural similarities to known intercalating antitumor compounds, we hypothesize that the cytotoxic activities of quinoline alkaloids are due to DNA intercalation and/or inhibition of topoisomerase activity leading to apoptosis.

In order to test this hypothesis, we have carried out a molecular docking analysis of *Stauranthus* quinoline alkaloids with DNA to examine the steric requirements and constraints of intercalation of the quinoline alkaloids between DNA base pairs (BP). X-ray crystal structures have been solved for various intercalators with DNA,

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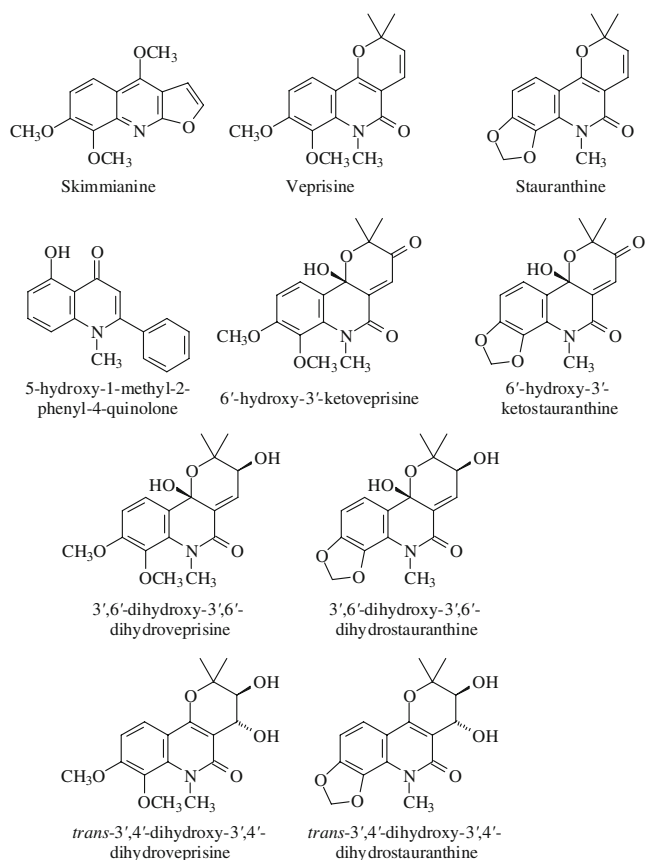


Fig. 1 The *Stauranthus* quinoline alkaloids examined in this work

including daunomycin [30], idarubicin [31], iododoxorubicin [32], morpholino-doxorubicins [33], 9-amino-*N*-(2-dimethylamino)ethyl]acridine-4-carboxamide [34], actinomycin D [35], nogalamycin [36], *bis*-daunomycin [37], cryptolepine [38], and ellipticine [39]. Similarly, NMR structures of intercalated complexes of DNA have been solved, including nogalamycin [40] and *bis*-daunorubicin

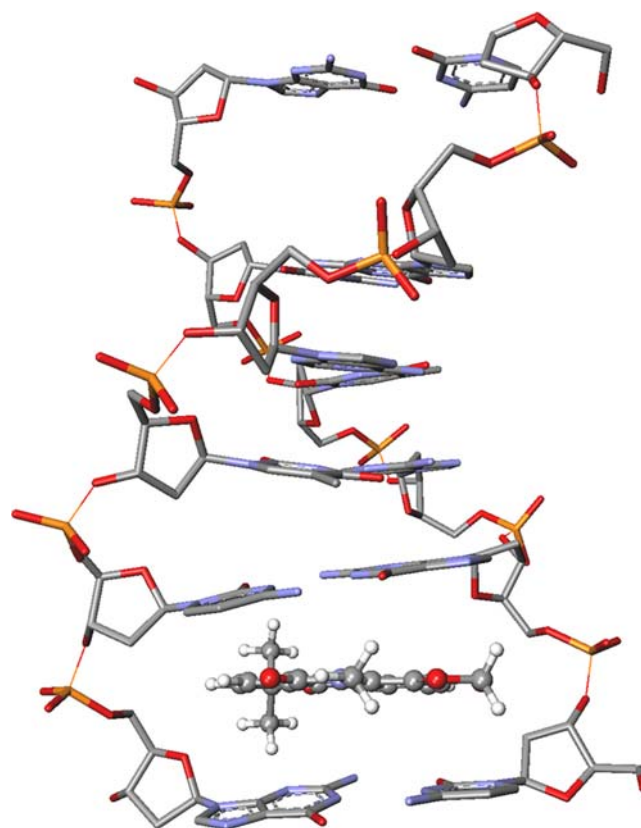


Fig. 2 ArgusDock lowest-energy docked orientation of stauranthine (ball and stick model) into the ellipticine binding site (G–C duplex) of DNA (wire figure) (from PDB: 1z3f)

[41]. In addition, the crystal structures of the ternary complex of human topoisomerase I, a 22 bp DNA duplex, with the intercalators topotecan [42] and camptothecin [43], have been reported. Analogous molecular docking investigations have been reported previously for camptothecin and camptothecin derivatives with the DNA-topoisomerase

Table 1 ArgusDock binding energies of best intercalated poses for quinoline alkaloids with DNA

Compound	Binding energy (kcal mol ⁻¹)				
	1z3f	1a9	1k4t	1t8i	1sc7
Skimmianine	-4.28	-4.34	-5.48	-5.91	-5.23
5-Hydroxy-1-methyl-2-phenyl-4-quinolone	-4.50 ^a	-4.25 ^a	-5.38 ^a	-5.52 ^a	-5.36 ^a
Stauranthine	-4.74	-4.76	-5.56	-5.52	-5.25
Veprisine	-4.80	None ^b	-5.34	-5.50	-5.20
6'-Hydroxy-3'-ketostauranthine	-4.69	None ^b	-5.30	None ^b	-5.24
6'-Hydroxy-3'-ketoveprisine	-4.30 ^a	None ^b	-5.16 ^a	None ^b	-5.22 ^a
3',6'-Dihydroxy-3',6'-dihydrostauranthine	-4.71	-4.79	-5.56	-7.30 ^c	-5.47
3',6'-Dihydroxy-3',6'-dihydroveprisine	-4.55 ^a	None ^b	-4.90 ^a	None ^b	-5.24 ^a
3',4'-Dihydroxy-3',4'-dihydrostauranthine	-4.80	-4.55	-6.52	-6.00	-5.31
3',4'-Dihydroxy-3',4'-dihydroveprisine	-4.82	None ^b	-5.58	None ^b	None ^b
Camptothecin ^c	-4.60	-4.86	-5.95	-5.92	-5.95
Ellipticine ^d	-4.79	-4.71	-5.66	-5.74	-5.40

^a Partial intercalation—the molecule does not insert completely between the base pairs (e.g., Fig. 4)

^b No intercalative binding pose found

^c Camptothecin is the co-crystallized ligand for crystal structure 1t8i

^d Ellipticine is the co-crystallized ligand for crystal structure 1z3f

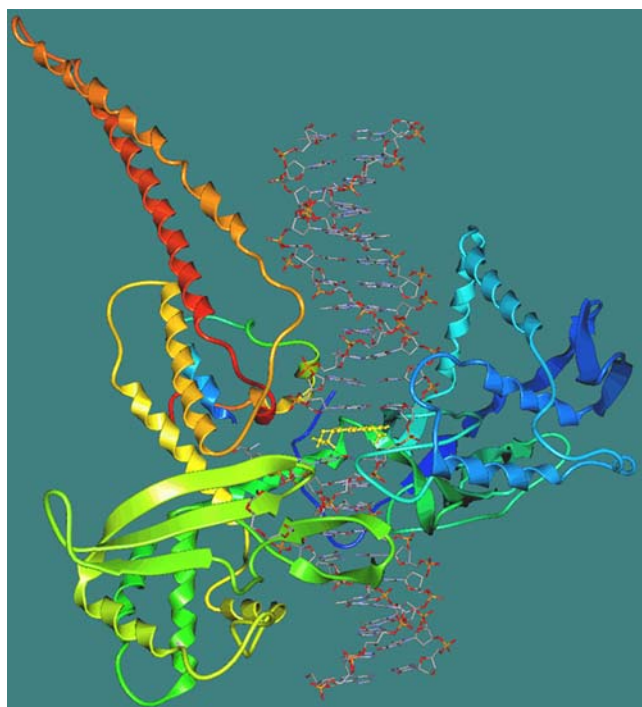


Fig. 3 X-ray crystal structure of human topoisomerase I (*ribbon structure*)–DNA complex (*wire figure*) (from PDB: 1k4t) with docked (intercalated) skimmianine (*yellow ball and stick model*) from ArgusDock molecular docking analysis

I complex [44], as well as substituted 9-arylacridines with the DNA-topoisomerase I complex [45].

We further hypothesize that, in addition to planar π intercalation, the π -stacked complexes are stabilized further by favorable, complementary frontier molecular orbital interactions [46, 47]. That is, the highest occupied molecular orbital (HOMO) of the C–G base pair has the

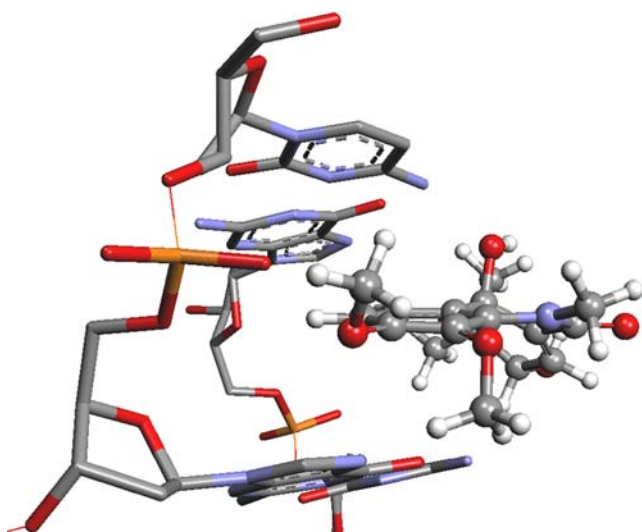


Fig. 4 ArgusDock docked structure of 3',6'-dihydroxy-3',6'-dihydroveprisine (*ball and stick model*) into the ellipticine binding site of DNA (*wire figure*, from PDB: 1z3f) showing only partial intercalation

correct nodal properties to overlap favorably with the lowest unoccupied molecular orbital (LUMO) of the intercalating quinoline alkaloids. Ab initio calculations at the MP2/6-31G*(0.25) level have been used to model the π stacking interactions between the known intercalators ethidium, daunomycin, ellipticine, and 4,6'-diaminide-2-phenylindole with adenine–thymine (AT) and cytosine–guanine (CG) [48]. These calculations revealed stable π – π interactions between the intercalators and the base pairs. DFT/B3LYP methods, on the other hand, were found to fail completely, and showed no energy minima. Ellipticine and derivatives have been similarly investigated [49]. Both hydrogen-bonding and π stacking interactions between psoralens and DNA base pairs have been examined using DFT/B3LYP as well as MP2 methods [50]. Ab initio MP2/6-31G** calculations predicted stable π – π interactions between either psoralen or 8-methoxypsoralen and the AT base pair; DFT/B3LYP, however, did not show an energy minimum. Kumar and co-workers [51] have examined the interaction of the intercalating carcinogen benzo(a)pyrene and its metabolites with the C–G base pair using the self-consistent-charge, density functional tight-binding (SCC-DFTB-D) method, augmented by an empirical London dispersion energy term. The optimized molecular geometries of the π – π complexes were in good agreement with experimental structures, and interaction energies were comparable with MP2 calculated energies. Similarly, π stacking interactions of mitoxantrone with adenine–thymine (AT) and cytosine–guanine (CG) have been modeled using the DFTB approximate DFT method, and mitoxantrone showed greater binding with CG [52]. Jena and Mishra [53] have calculated the molecular properties of camptothecin and analogs using DFT/B3LYP, and have predicted topoisomerase I activity based on the calculated properties. These workers have not, however, looked at π – π interactions between camptothecin and DNA base pairs.

In this present work, we have carried out ab initio investigations of the electronic π – π interactions between quinoline alkaloids and DNA base pairs using density functional theory (DFT) at the M06/6-31G* level. Aromatic π – π interactions have been the subject of numerous theoretical investigations into a number of interactions [54, 55], including benzene dimer (see [56–62] for recent high-level computational investigations), uracil dimer [63], naphthalene dimer [58], and nucleotide base pairs [64–66].

In order to account for electron correlations in these models, ab initio calculations have included very large basis sets with coupled cluster calculations with single and double substitutions with noniterative triple excitations [CCSD(T)] [56, 57, 60]. MP2 calculations have been shown to overestimate the effects of electron correlation in π – π interactions [67–70]. These high level ab initio

Table 2 Calculated molecular electronic descriptors for *Stauranthus* quinoline alkaloids and DNA base pairs

Compound	H^p_{B3LYP} ^a (kcal mol ⁻¹)	H^p_{M06} ^a (kcal mol ⁻¹)	$E_{(HOMO)}$ (eV)	$E_{(LUMO)}$ (eV)	MV ^b (Å ³)	SA ^c (Å ²)	μ^d (D)	O^e	χ^f	η^g	α^h	$\log P^i$	$E_{(hydration)^j}$ (kcal mol ⁻¹)
Skimminine	-562,654.14	-562,301.62	-5.60	-0.98	254.1	267.53	3.48	1.379	0.12	0.08	60.893	2.43	-5.80
5-Hydroxy-1-methyl-2-phenyl-4-quinolone	-516,115.30	-515,759.57	-5.88	-0.91	258.73	266.07	7.21	1.355	0.12	0.09	61.187	2.59	-8.07
Stauranthine	-611,239.12	-610,852.05	-5.52	-1.14	277.66	287.57	3.26	1.397	0.12	0.08	62.86	0.8	-4.20
Veprisine	-636,621.82	-636,210.94	-5.63	-1.17	306.54	317.16	3.13	1.443	0.12	0.08	65.185	0.77	-2.58
6'-Hydroxy-3'-keto-stauranthine	-705,623.41	-705,208.21	-6.36	-2.24	291.52	301	6.01	1.416	0.16	0.08	64.047	1.6	-6.91
6'-Hydroxy-3'-keto-veprisine	-731,007.85	-730,568.11	-6.52	-2.19	321.45	335.62	5.6	1.479	0.16	0.08	66.426	1.57	-5.06
3',6'-Dihydroxydihydro-stauranthine	-706,358.60	-705,943.07	-6.15	-1.16	295.93	305.33	3.53	1.422	0.13	0.09	64.199	0.77	-9.21
3',6'-Dihydroxydihydro-veprisine	-731,743.07	-731,303.01	-6.28	-1.12	325.81	339.68	3.08	1.483	0.14	0.09	66.583	0.74	-7.23
3',4'-Dihydroxydihydro-stauranthine	-706,380.59	-705,964.27	-6.13	-1.08	294.36	301.87	3.92	1.411	0.13	0.09	64.058	-0.79	-6.22
3',4'-Dihydroxydihydro-veprisine	-731,764.21	-731,323.36	-6.32	-1.10	324.12	335.38	3.82	1.47	0.14	0.1	66.433	-0.82	-4.43
Adenine-Thymine	-627,384.13	-626,988.06	-6.09	-0.54	278.15	312.3	2.38	1.516	0.12	0.1	62.624	0.18	-24.34
Cytosine-Guanine	-637,460.51	-637,068.03	-5.33	-0.93	268.88	298.68	6.43	1.483	0.11	0.08	62.144	-2.12	-23.65

^a Enthalpy (298.15 K)^b Molecular volume^c Surface area^d Dipole moment^e Ovality $\{O = SA/[4\pi(3MV/4\pi)^{2/3}]\}$ ^f Electronegativity $[\chi = -(E_{HOMO} + E_{LUMO})/2]$ ^g Hardness $[\eta = -(E_{HOMO} - E_{LUMO})/2]$ ^h Polarizability $[\alpha = 0.08(MV) - 0.97992\eta^2 + 41.3791]$ ⁱ Calculated log(octanol/water partition coefficient) using the Ghose-Crippen method [116]^j Hydration energy $(= E_{aqueous} - E_{vacuum})$ where $E_{aqueous}$ is calculated using the Cramer-Truhlar SM54 method [117, 118]

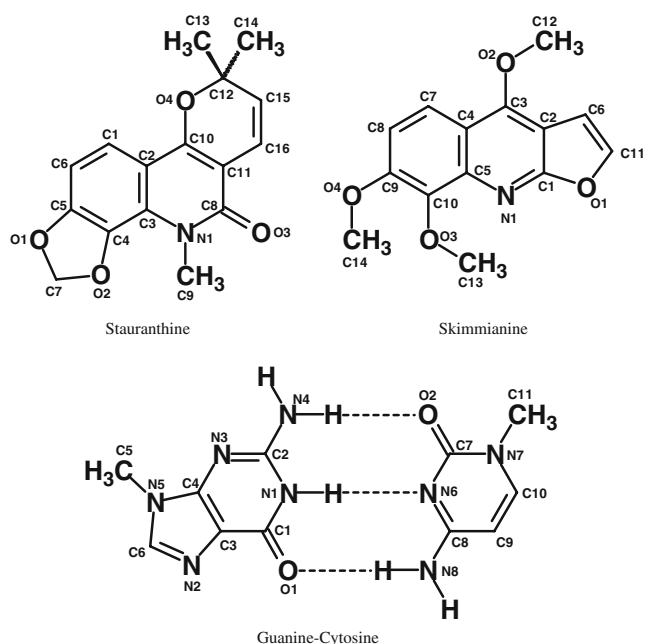


Fig. 5 SPARTAN atom numbering schemes for skimmianine, stauranthine, and guanine-cytosine

Table 3 Mulliken atomic charges for stauranthine, skimmianine, and guanine-cytosine from M06/6-31G* calculations

Stauranthine		Skimmianine		Guanine-cytosine	
Atom	Charge	Atom	Charge	Atom	Charge
C1	-0.22	C1	0.52	C1	0.63
C2	0.04	C2	0.04	C2	0.76
C3	0.34	C3	0.29	C3	0.10
C4	0.26	C4	0.06	C4	0.53
C5	0.35	C5	0.20	C5	-0.39
C6	-0.21	C6	-0.23	C6	0.20
C7	0.18	C7	-0.19	C7	0.77
C8	0.59	C8	-0.22	C8	0.59
C9	-0.39	C9	0.35	C9	-0.26
C10	0.32	C10	0.26	C10	0.10
C11	-0.02	C11	0.08	C11	-0.37
C12	0.27	C12	-0.27	N1	-0.77
C13	-0.49	C13	-0.25	N2	-0.51
C14	-0.49	C14	-0.24	N3	-0.61
C15	-0.20	N1	-0.60	N4	-0.87
C16	-0.14	O1	-0.49	N5	-0.50
N1	-0.64	O2	-0.52	N6	-0.63
O1	-0.56	O3	-0.54	N7	-0.47
O2	-0.57	O4	-0.54	N8	-0.84
O3	-0.56			O1	-0.59
O4	-0.59			O2	-0.58

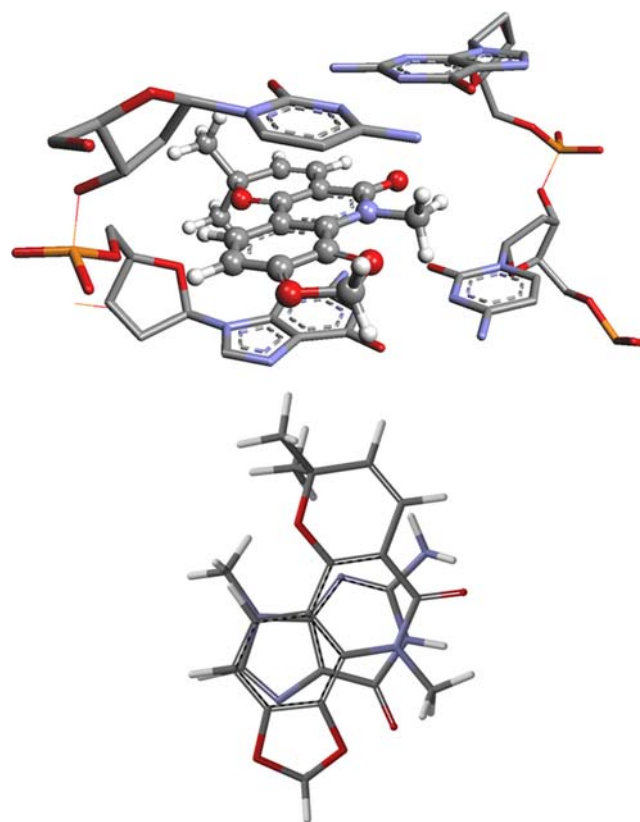


Fig. 6 ArgusDock lowest-energy docked intercalation orientation of skimmianine (*ball and stick model*) in the ellipticine binding site of DNA (*wire figure*, from PDB: 1z3f) (*top*) and the lowest-energy face-to-face orientation (M06/6-31G*) of stauranthine with guanine (*bottom*)

methods are very computationally demanding, however, and not suitable for molecular interactions of larger, biologically important molecules. In an effort to circumvent the computational costs, DFT methods have been employed. However, the widely used B3LYP and BLYP methods fail completely for π - π interactions [71–77]. Recently, DFT methods have been augmented with dispersion terms [58, 59, 61, 62, 76–79] to correct for these failures. Newly developed functionals such as MPWB1K [80], M05-2X [81], and M06-L [82] seem to sufficiently describe non-covalent interactions including π - π stacking [83–87].

Computational methods

Molecular docking

Molecular structures for the alkaloids were built using SPARTAN '08 for Windows [88], and geometries optimized using the MMFF 94 force field [89]. DNA-alkaloid docking studies were carried out based on the crystal structure of DNA crystallized with ellipticine (PDB: 1z3f) [39], the NMR structure of DNA complexed with *bis*-

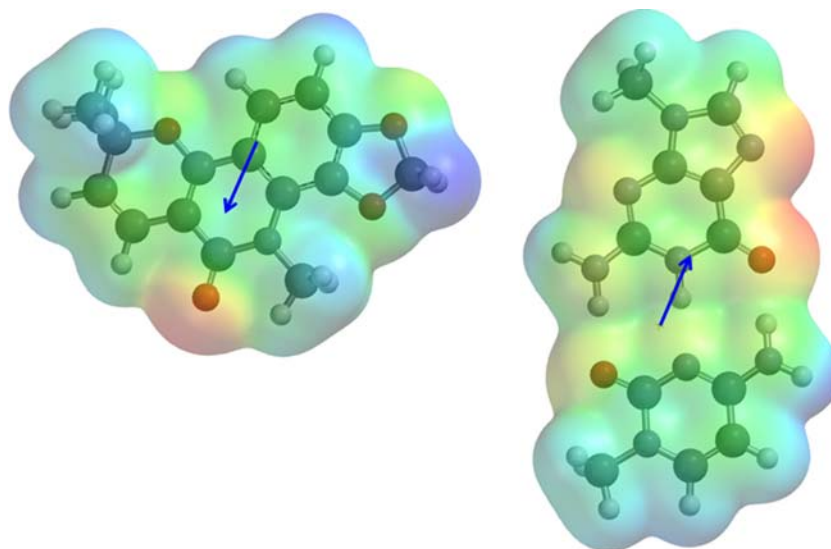


Fig. 7 Electrostatic potential maps (M06/6-31G*) of stauranthine (*left*) and guanine–cytosine (*right*) showing dipole moments (*dark blue arrows*)

daunorubicin (PDB: 1a19) [41], and crystal structures of DNA-topoisomerase I with topotecan (PDB: 1k4t) [42], camptothecin (PDB: 1t8i), and the synthetic indenoisoquinoline MJ-II-38 (PDB: 1sc7) [43]. The crystal structures were downloaded from the Protein Data Bank (PDB) using ArgusLab 4.0.1 [90]. These PDB structures provide a selection of DNA structures with known planar aromatic intercalators as well as crystal structures of DNA-topoisomerase I complexes. All solvent molecules and the co-crystallized inhibitor were removed from the structures to provide sterically unimpeded cavities for ligand docking. Molecular docking calculations for the quinoline alkaloids at the intercalation sites of DNA were undertaken using the

ArgusDock docking algorithm of ArgusLab 4.0.1 [90]. A box of $20 \times 20 \times 20$ Å (large enough to completely encompass the cavity/intercalation site) was centered around the intercalation site in order to allow each alkaloid ligand to explore potential binding poses. Larger box sizes were examined, but these only increased the number of non-intercalative binding poses. Different orientations of the alkaloids were examined and divided based on their energy values.

Ab initio molecular structures and energies

The calculations were carried out using SPARTAN '08 for Windows [88]. Both the popular B3LYP [91, 92] and the

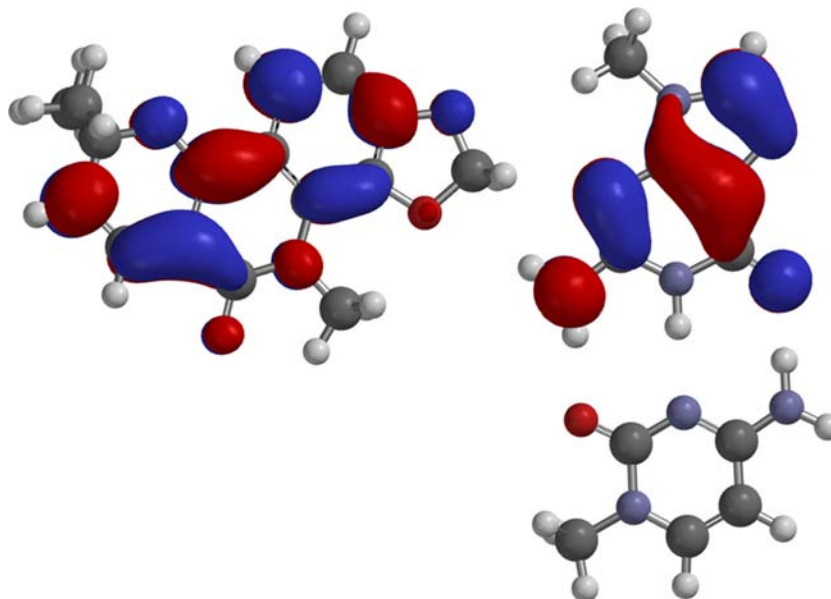


Fig. 8 The lowest unoccupied molecular orbital (LUMO) of stauranthine (*left*) and the highest occupied molecular orbital (HOMO) of guanine–cytosine (*right*) from M06/6-31G* calculations

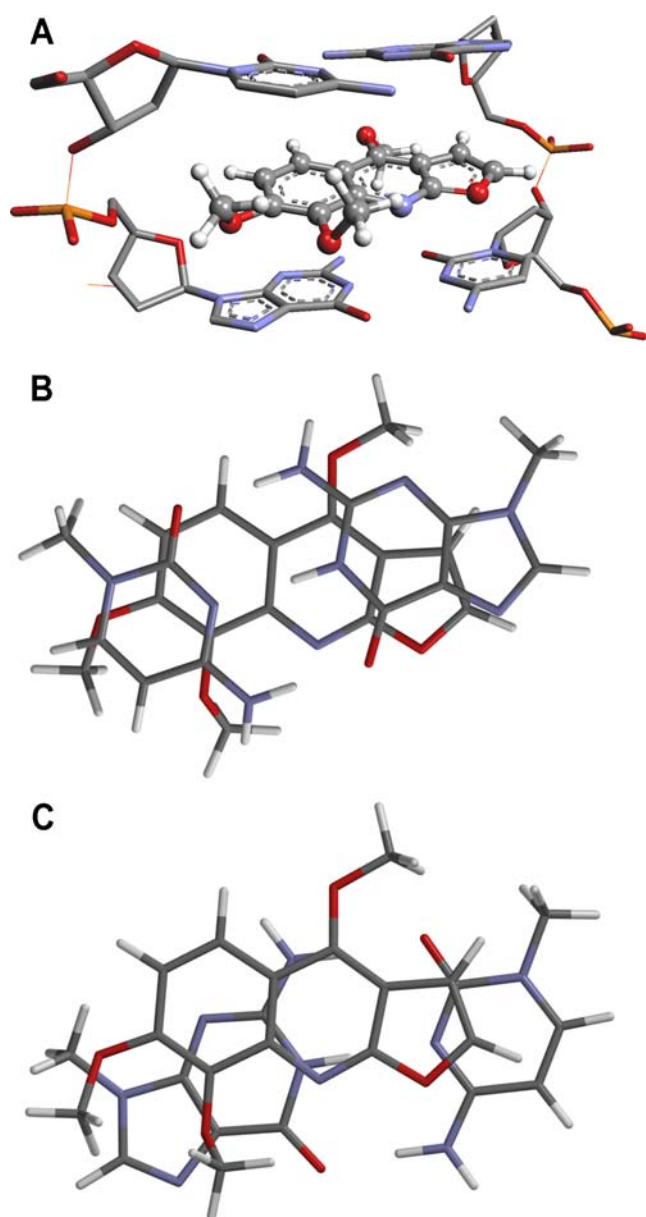


Fig. 9 Lowest-energy intercalation pose (ArgusDock) of skimmianine in DNA (**a**) and the geometry optimized (M06/6-31G*) structures for face-to-face interactions of skimmianine with C–G (**b**) and G–C (**c**)

recently developed M06 [82] functionals, were used together with the 6-31G* basis set [93] for the optimization of all stationary points in the gas phase. Frequency calculations were used to characterize stationary points as minima. All enthalpies are zero-point (ZPE) and thermally corrected. π – π interactions were carried out using Spartan '08 for Windows at the M06/6-31G* level. Several different orientations of the alkaloids (skimmianine and stauranthine and the C–G base pair (or G alone in the case of stauranthine), as indicated by the molecular docking preferred orientations, were carried out with complete geometry optimization.

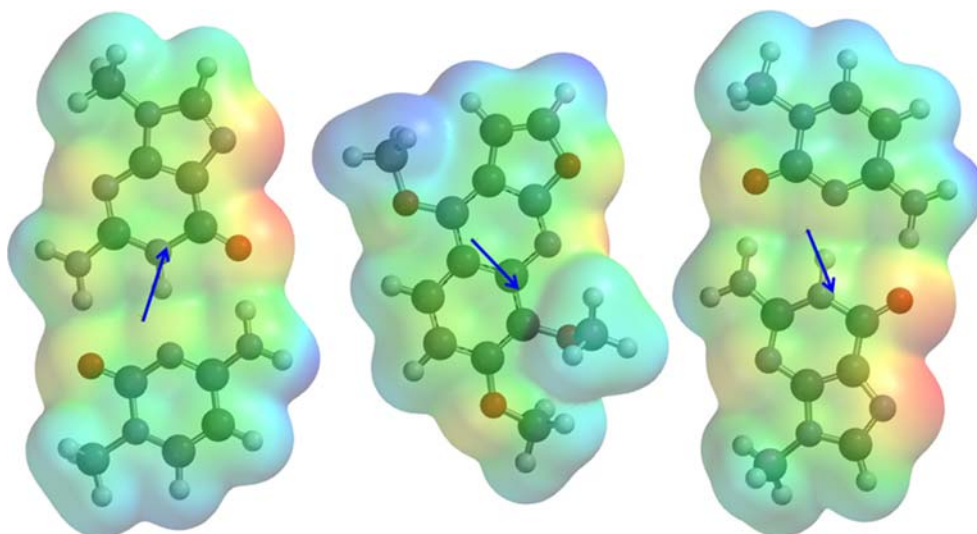
Results and discussion

Ten quinoline alkaloids were examined for potential intercalation into DNA (Fig. 1). Molecular docking analysis was carried out using structures of intercalated DNA (PDB access numbers 1z3f and 1a19) as well as topoisomerase I/DNA complexes (PDB access numbers 1k4t, 1t8i, and 1sc7). The intercalating interactions of the quinoline alkaloids are summarized in Table 1. Four quinoline alkaloids, stauranthine (Fig. 2), skimmianine (Fig. 3), 3',6'-dihydroxy-3',6'-dihydrostauranthine, and trans-3',4'-dihydroxy-3',4'-dihydrostauranthine were able to dock intercalatively into all five DNA structures, while two, veprisine and 6'-hydroxy-3'-ketostauranthine, docked successfully into four and three structures, respectively. The other quinoline alkaloids in this study presumably did not intercalate due to steric effects of non-coplanar appended substituents (see Fig. 4 for example). The intercalating docking energies of the quinoline alkaloids from this study are comparable to those for the known intercalating ligands camptothecin and ellipticine (Table 1). While skimmianine and stauranthine show average binding energies of around $5.1 \text{ kcal mol}^{-1}$, 3',6'-dihydroxydihydrostauranthine and 3',4'-dihydroxydihydrostauranthine have average binding energies nearly equal to that of camptothecin (5.6 , 5.4 , and $5.5 \text{ kcal mol}^{-1}$, respectively).

The electronic structures and properties of the quinoline alkaloids, as well as the AT and CG base pairs, have been calculated using DFT, B3LYP/6-31G* and M06/6-31G*. Molecular electronic descriptors are summarized in Table 2. The importance of these descriptors in the development of QSAR models has been reviewed [94–96], and utilized to examine anticancer activities of potential intercalators [97, 98]. In this present work, the molecular descriptors of the quinoline alkaloids that correlate best with molecular docking intercalation are the energies of the HOMO, the van der Waals surface areas, the ovalities, and the polarizabilities. That is, the best intercalating quinoline alkaloids tend to have higher E_{HOMO} , smaller surface areas, lower ovalities, and lower polarizabilities. Interestingly, hydrophobicity, as measured by $\log P$ or $E_{\text{hydration}}$ do not seem to correlate with intercalation.

Dipole–dipole interactions [99–101], electrostatic interactions [102, 103], and van der Waals interactions [104–106], as well as frontier molecular orbital interactions [107–110], may be responsible for energetically favorable intercalation of planar aromatic compounds into DNA. Using the lower-energy intercalated docked poses of skimmianine and stauranthine as a guide, different face-to-face orientations of skimmianine with guanine–cytosine and stauranthine with guanine were computationally examined at the M06/6-31G* level. Based on frontier molecular orbital theory [111], the important interactions of intercalated ligands with the base

Fig. 10 Electrostatic potential maps (M06/6-31G*) of skimmianine (*center*) and the two guanine-cytosine orientations corresponding to Fig. 9b (*left*) and Fig. 9c (*right*) showing dipole moments (*dark blue arrows*)



pairs are expected to be the LUMO of the quinoline alkaloid with the HOMO of the purine base [107, 108]. The HOMO of the C–G base pair is higher in energy than that of A–T, and should exhibit better interaction with the intercalated ligands. DNA intercalators generally show a preference for CG-rich regions [112–115]. Atom numbering schemes for stauranthine, skimmianine, and guanine–cytosine are presented in Fig. 5. Atomic charges, based on Mulliken population analysis, are listed in Table 3.

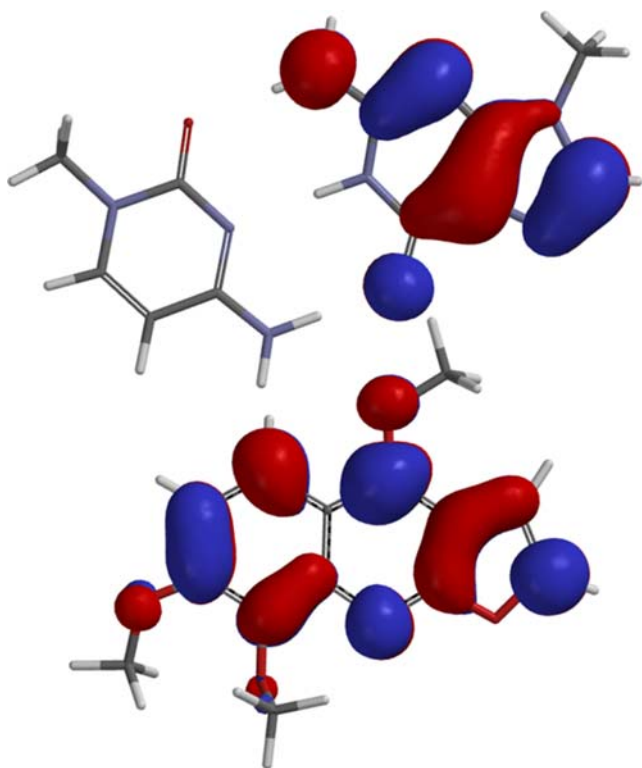


Fig. 11 Frontier molecular orbitals, HOMO of C–G (*above*) and LUMO of skimmianine (*below*) from M06/6-31G* calculations

The lowest-energy intercalation docking orientation (pose) from the molecular docking analysis for stauranthine corresponds to the M06/6-31G* lowest-energy orientation of stauranthine with guanine (Fig. 6). This particular orientation allows for favorable electrostatic interactions between stauranthine and guanine (see Fig. 7) as well as favorable dipole–dipole interactions (Fig. 7). In addition, there appears to be favorable complementary frontier molecular orbital overlap between the LUMO of stauranthine and the HOMO of guanine–cytosine in this orientation. Thus, for example, the LUMO lobe centered on C5 of stauranthine overlaps with the HOMO lobe centered on C6–N2 of guanine, the lobe on C3–C4 of stauranthine overlaps with the lobe centered on C3 of guanine, the lobe centered on C10 of stauranthine overlaps with the lobe located on N3 of guanine, and the lobe on C11 of stauranthine overlaps with the lobe on N4 of guanine (see Fig. 8).

The lowest-energy intercalation pose (ArgusDock) of skimmianine is consistent with two low-energy orientations of face-to-face M06/6-31G* structures (Fig. 9). The orientation shown in Fig. 9B is the lowest-energy (M06/6-31G*) face-to-face orientation of skimmianine with the cytosine–guanine base pair (4.4 kcal mol^{−1} lower in energy than the orientation in Fig. 9C). In this orientation (Fig. 9B), there are somewhat favorable dipole–dipole and electrostatic interactions between the skimmianine and the C–G base pair (see Fig. 10). For example, there are favorable electrostatic interactions between C1 of skimmianine and O1 of C–G, C3 of skimmianine and N1 of C–G, C6 of skimmianine and C3 of C–G, O2 of skimmianine and C2 of C–G, and O4 of skimmianine and C10 of C–G, in this orientation. Additionally, there seem to be some favorable frontier molecular orbital interactions available in this orientation. Thus, the lobe of the LUMO of skimmianine located on C11 would overlap with the HOMO lobe of

guanine centered on C3, the skimmianine LUMO lobe on C2–C6 overlaps with the guanine HOMO lobe on C2–N3, and the lobe on C3 of skimmianine overlaps with the lobe on N4 of guanine (see Fig. 11).

Summary and conclusions

Analysis of molecular docking of *Stauranthus* alkaloids into DNA suggests that some of these compounds may act as intercalating ligands with DNA. Skimmianine, stauranthine, 3',4'-dihydroxydihydrostauranthine, and 3',6'-dihydroxydihydrostauranthine, each docked intercalatively into all five DNA crystal structures examined. Veprisine and 6'-hydroxy-3'-ketostauranthine docked into four and three DNA structures, respectively, while 3',4'-dihydroxydihydroveprisine docked successfully into two DNA structures. Three of the quinoline alkaloids, 5-hydroxy-1-methyl-2-phenyl-4-quinolone, 6'-hydroxy-3'-ketoveprisine, and 3',6'-dihydroxydihydroveprisine, did not intercalate successfully into any of the DNA crystal structures. Two of the quinoline alkaloids, stauranthine and skimmianine, were examined further in terms of π - π interactions with guanine–cytosine using DFT(M06/6-31G*). The lowest energy docked poses (from the ArgusDock molecular docking analysis) of these two alkaloids are structurally consistent with the lowest-energy face-to-face π -stacking orientations as revealed by the DFT (M06) calculations. The orientations of the quinoline alkaloids with guanine–cytosine are such that there are favorable dipole–dipole, electrostatic, and frontier molecular orbital interactions (alkaloid LUMO with guanine HOMO) interactions, and these may serve to stabilize the π - π interactions between the intercalating ligand and the base pairs. We conclude, therefore, that intercalation of quinoline alkaloids is determined by steric interactions (as revealed in the ArgusDock molecular docking analysis), and that a combination of π - π electronic interactions serve to orient the intercalating ligands with respect to the base pairs of DNA.

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