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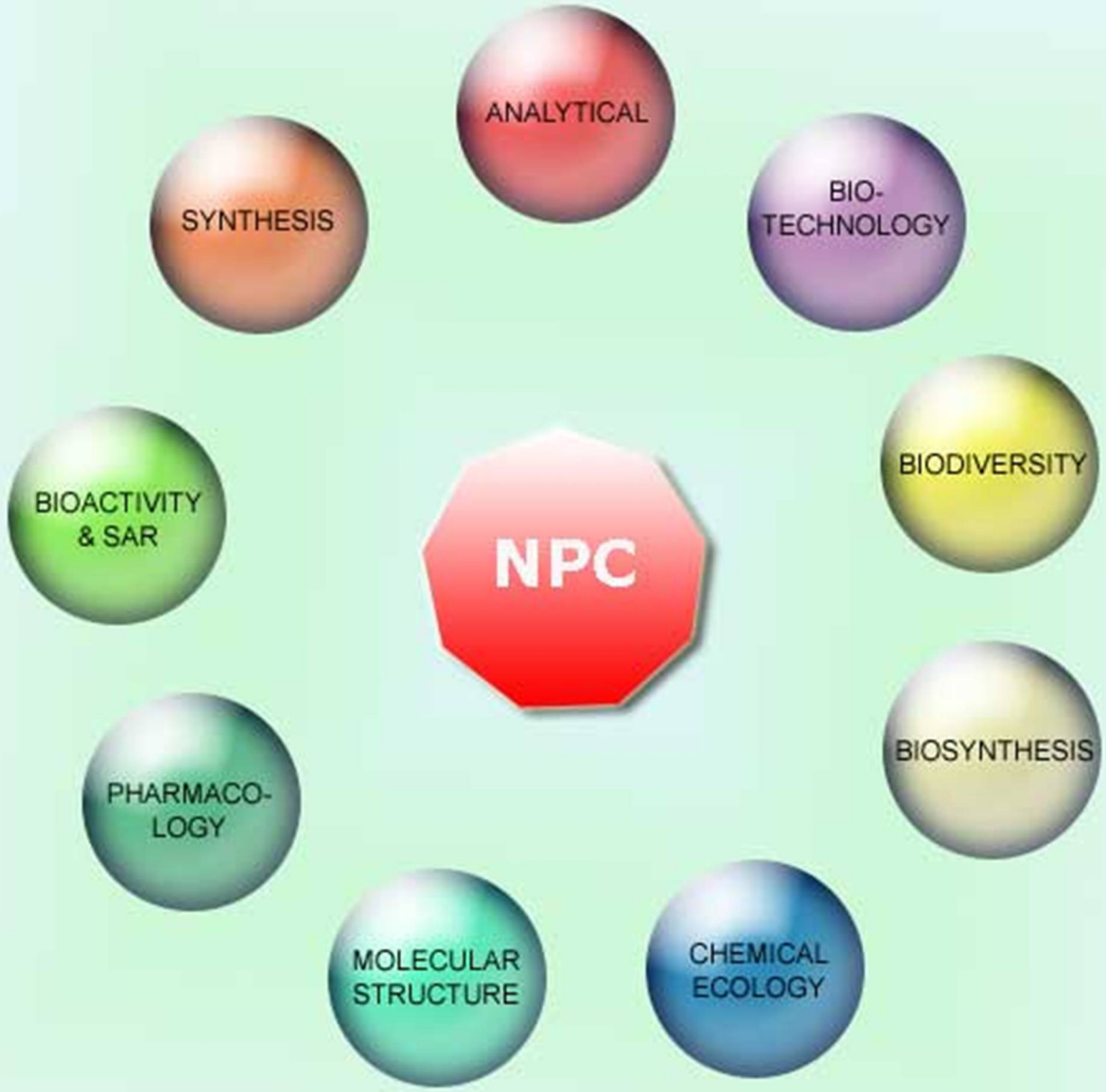

This Issue is Dedicated to
Prof. Dr. Hans-Jörg Schneider
On the Occasion of his 75th Birthday

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DNA Binding Studies of Vinca Alkaloids: Experimental and Computational Evidence

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Fluorescence studies on the indole alkaloids vinblastine sulfate, vincristine sulfate, vincamine and catharanthine have demonstrated the DNA binding ability of these molecules. The binding mode of these molecules in the minor groove of DNA is non-specific. A new parameter of the purine-pyrimidine base sequence specificty was observed in order to define the non-specific DNA binding of ligands. Catharanthine had shown 'same' pattern of 'Pu-Py' specificity while evaluating its DNA binding profile. The proton resonances of a DNA decamer duplex were assigned. The models of the drug:DNA complexes were analyzed for DNA binding features. The effect of temperature on the DNA binding was also evaluated.

Keywords: DNA binding constants, DNA interaction, Fluorescence, Drug-DNA binding, Methylene linker, Purine-pyrimidine (Pu-Py) specificity.

Natural alkaloids of different types are known to interact with nucleic acids [1]. Vinca alkaloids, obtained from *Catharanthus roseus*, are an important class of alkaloids that possess extensive therapeutic potential. They are indole based alkaloids having one or two indole rings in their structures. Vinblastine and vincristine (VLB, **1** and VCR, **2**) are used as anticancer agents for the treatment of various types of leukemia. The main activity profile of vinblastine and vincristine alkaloids is due to their reversible binding interactions with tubulin protein. It depolymerises the microtubular assembly, thereby arresting the cell division, resulting in cell death. Vinblastine is mainly useful for the treatment of Hodgkin's disease, lymphocytic lymphoma, histiocytic lymphoma, advanced testicular cancer, advanced breast cancer, Kaposi's sarcoma, and Letterer-Siwe disease [2].

The Vinca alkaloids (**1-4**) (Figure 1) possess features like several H-bond acceptor/donor atoms, planar ring systems, and a large aromatic skeleton that are essential for the DNA binding activity. Vinca alkaloids exhibit fluorescence, which is quenched as a result of drug binding to DNA oligomers. This prompted us to investigate the binding of these alkaloids (**1-3**) with double helical DNA oligomers.

Initially all the compounds (**1-4**) were tested using UV-absorbance spectroscopy and it was found that they gave an absorption maximum in or around 260 nm, a region where DNA oligomers (DNA-1 to DNA-4) also absorb. Due to this overlap of the absorbance maxima of these compounds, it was found that UV absorbance spectroscopy was not very suitable for evaluating drug-DNA binding in the current study. Consequently, UV fluorescence was chosen for evaluating the drug-DNA binding. Fluorescence quenching experiments were employed in order to decipher the DNA binding profile of the Vinca alkaloids. In addition, the structural halves of VLB, catharanthine (CTN) and vindoline (VDL), were also investigated for their individual binding contributions to the overall binding of VLB. Vinblastine (**1**) has 2 or 4 methylene groups attached to an indole nucleus in the nine-membered ring of catharanthine. This methylene linker provides extra flexibility to the VLB molecule in the event of substrate binding to furnish a stable drug:DNA complex. The difference between VLB and VCR is the presence of a -CHO group at the indoline ring nitrogen in the vindoline half. Vincamine (VCN), on the other hand, possesses only one indole nucleus in its structure.

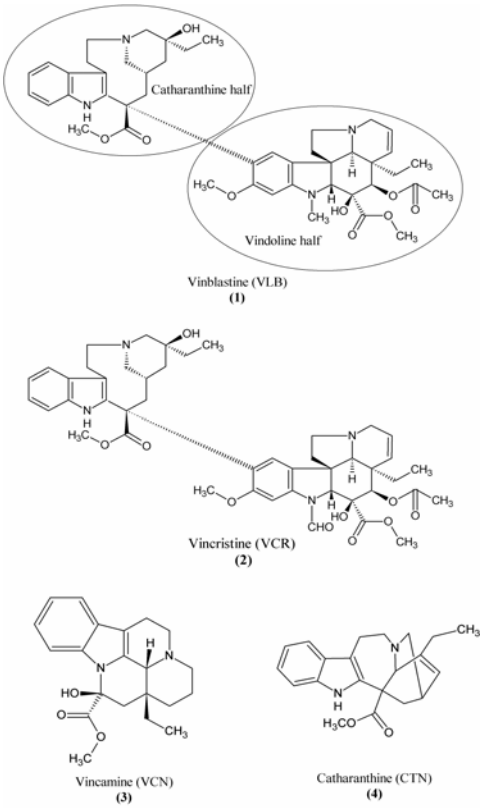

Figure 1: Structure of Vinca alkaloids **1-4**.

It was proposed to evaluate the DNA binding nature of VLB, VCR, VCN and the structural halves of VLB, viz. CTN and VDL. It was found that VLB (**1**), VCR (**2**), VCN (**3**) and CTN (**4**) gave consistent quenching of the fluorescence maxima after each addition of DNA (Figure 2). On the other hand, VDL did not offer any quenching of its fluorescence as a result of DNA binding. Vinblastine sulfate gave a fluorescence maximum at 362 nm when excited at 265 nm. The titration data obtained in fluorescence were fitted by the double reciprocal method (Figure 3) to collect the DNA binding constant K. As shown in Table 1, the values of the binding constant K were found to be of the order of 10^4 - 10^5 for vinblastine sulfate (**1**), and 10^3 - 10^5 for the other Vinca alkaloids (**2**, **3** and **4)**. This study showed that Vinblastine and other Vinca alkaloids bind with DNA oligomer duplexes suggesting a possible similarity in their DNA binding motifs.

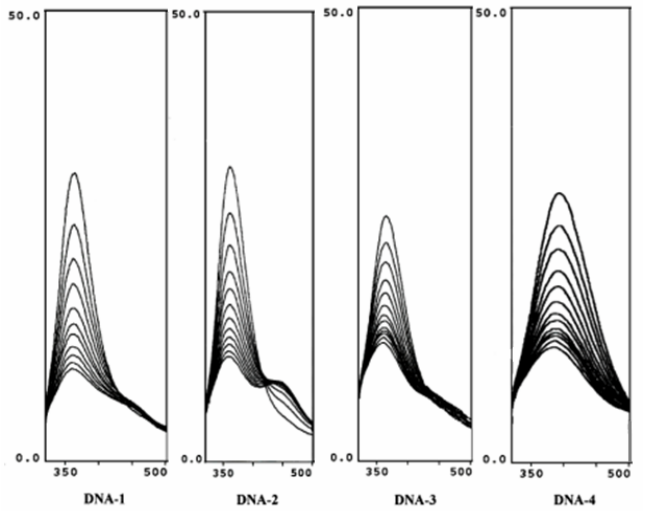

Figure 2: Fluorescence spectra of vinblastine sulfate titrations with DNA decamer sequences.

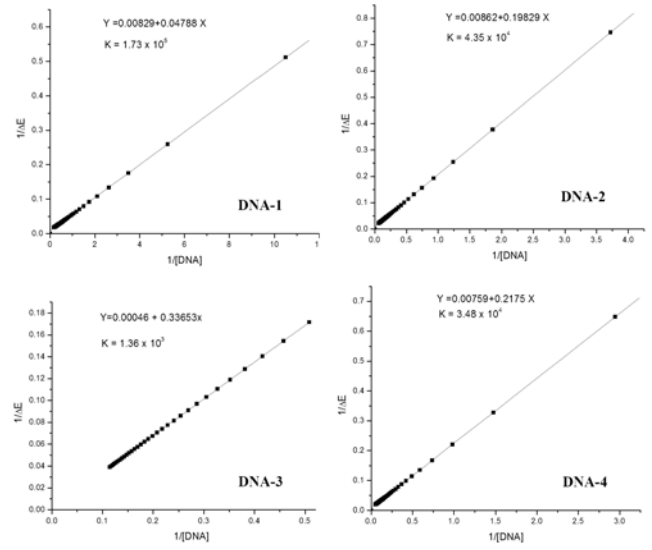

Figure 3: Double reciprocal plots of VLB: DNA titrations at 5°C.

The possibility of DNA base sequence specificity in the DNA binding of the vinblastine molecule was further evaluated using DNA decamer sequences designed to have a 4 base pair specific central core. In this study, four DNA decamers were used to assess the base sequence specificity of DNA binding interaction of vinblastine. To understand the interaction of vinblastine with specific DNA sequences**,** the drug was titrated with four different DNA decamers viz.

DNA-1: 5'-d(GATGGCCATC)$_2$
DNA-2: 5'-d(GATCCGGATC)$_2$
DNA-3: 5'-d(GCCAATTCCG)$_2$
DNA-4: 5'-d(GCCTTAACCG)$_2$

Temperature dependent DNA binding titrations were carried out in order to investigate if vinblastine sulfate had any DNA base sequence preference and to see the effect of temperature on the DNA binding strength of these drugs. The effects of temperature variation on the VLB: DNA complexes are summarized in Table 2.

Table 1: DNA binding patterns of vinblastine sulfate, vincristine sulfate, vincamine, and catharanthine at 25°C.

Alkaloids	Complex	K_{exp} (mole^{-1})
Vinblastine sulfate (1)	DNA-1	2.53 x 10^5
	DNA-2	1.29 x 10^5
	DNA-3	1.36 x 10^5
	DNA-4	6.17 x 10^4
Vincristine (2)	DNA-1	2.90 x 10^4
	DNA-2	2.41 x 10^4
	DNA-3	1.22 x 10^4
	DNA-4	4.10 x 10^4
Vincamine (3)	DNA-1	3.37 x 10^4
	DNA-2	2.95 x 10^4
	DNA-3	3.00 x 10^4
	DNA-4	5.27 x 10^3
Catharanthine (4)	DNA-1	1.95 x 10^4
	DNA-2	5.10 x 10^4
	DNA-3	1.35 x 10^5
	DNA-4	3.30 x 10^4

Table 2: Binding constant values (mole^{-1}) of vinblastine with four DNA sequences (DNA-1 to DNA-4) obtained from the double reciprocal method.

Complex	Binding constants at various temperatures		
	5°C	15°C	25°C
DNA-1	1.70 x 10^5	4.13 x 10^4	2.53 x 10^5
DNA-2	4.35 x 10^4	3.56 x 10^4	1.29 x 10^5
DNA-3	1.36 x 10^3	0.63 x 10^2	1.36 x 10^5
DNA-4	3.48 x 10^4	5.35 x 10^4	6.17 x 10^4

Features of DNA sequences (DNA-1 to DNA-4) in relation to their VLB binding: The characteristic feature of the selected DNA sequences (DNA-1 to DNA-4) is the presence of six G.C base pairs in each of them. However, DNA-1 possesses two 5'-GpC-3' base steps in each strand. DNA-2 possesses no such base steps from the 5' to 3' ends. On the other hand, DNA-3 and DNA-4 contain four 5'-GpC-3' base steps in their structures.

From the observations of binding constants, it appears that the binding of VLB with DNA sequences does not depend on the 5'-GpC-3' base steps since the binding constants of VLB: DNA-3 and VLB: DNA-4 are smaller as compared with DNA-1 and DNA-2 at lower temperatures, in spite of having a larger number of 5'-GpC-3' base sequences.

Since all four DNA sequences contain equal numbers of G.C base pairs (six) in their structures, it seems likely that their location on the DNA molecule affects the binding of VLB. Moreover, the central core in both DNA-3 and DNA-4 does not consist of G.C base pairs and consequently showed weaker binding with VLB, since the minor groove of the AT sequence is narrower to

accommodate the bulky molecule of VLB. The terminal G.C sequences, unlike the central core, are not contributing significantly to the binding due to their greater flexibility and accessibility to the solution environment. The possibility of a greater flexibility and exposure to water does not allow VLB to stay longer on the terminal G.C sequences leading to weaker drug-DNA interactions.

The DNA binding constant for the VLB:DNA-1 complex at 5°C revealed the stronger interaction of VLB with DNA-1 and DNA-2. On the other hand, the DNA binding of VLB with DNA-3 and DNA-4 was found to be weaker, indicating a slight preference for GC-specific sites. Multiple binding modes of VLB with DNA are also possible, as reported in the case of vincristine [3]. However, the exact nature of the multiple binding motifs is still unknown. The overall DNA binding nature of these alkaloids was found to be non-specific in terms of their sequence preference.

The plausible intercalation facilitated by the indole ring moiety in the case of small molecules could occur, as indicated by Schneider and coworkers [4]. Our previous study [5] forwarded the model that the molecule prefers to sit in the minor groove instead of preferentially intercalating between the DNA base pairs. The DNA binding results obtained in the fluorescence titration experiments (Table 1) clearly suggest that vinblastine has some interaction with DNA. However, this does not indicate the mode of interaction of the drug.

The structural features of the alkaloid-DNA complexes were further investigated using a molecular docking method. Minor groove docking was performed due to the fact that VLB and VCR are complex molecules with larger puckered regions, while possessing an indole ring as a planar structure. It is, therefore, suggested that the puckered regions of these molecules will provide hindrance to the entry of the molecules between the base pairs of the DNA double helix and precluding the possibility of complete insertion between the stack of DNA base pairs. In addition, with the absence of any strong positive charge in the ring system, it is quite likely that intercalation is not the favorable mode of binding. However, the possibility of partial intercalation cannot be ruled out, due to the presence of indole rings in the alkaloid structures.

Thermodynamic calculations are essential in order to complement the structural data. Contrary to a large family of DNA binding agents, all the compounds employed in this study were considered as having no formal charge. Consequently, the docking results using the DNADock program showed a large non-electrostatic contribution to the overall binding energy of these molecules.

Moderate DNA binding constants obtained by both experimental methods and PreDDICTA software indicate that the electrostatic interactions may not have significantly contributed to the DNA binding of these compounds. It was observed in the docking studies that van der Waal's forces and hydrophobic interaction have the most significant contribution in the DNA binding of these molecules. The possibility of the formation of H-bonds also exists due to the presence of H- bond donor (OH) and acceptor (=O) atoms in the indole alkaloids, as well as functional groups present in the minor groove of DNA structures (guanine-NH_2 group at position 2, and cytosine =O atom at position 2). These atoms may provide sufficient anchoring support for drug molecules to remain within the minor groove [7]. Moreover, this flexibility also affords the formation of a few new H-bonds between the drug and DNA atoms providing further stability to the drug-DNA complexes.

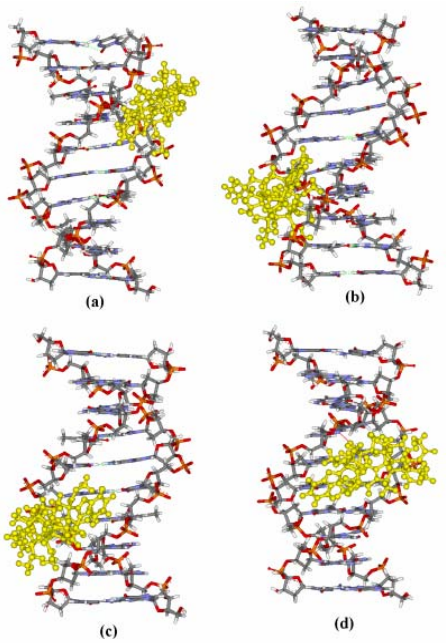

Figure 4: Docked poses of vinblastine sulfate with DNA decamer sequences. (a) VLB:DNA-1, (b) VLB:DNA-2, (c) VLB:DNA-3, (d) VLB:DNA-4.

Purine-Pyrimidine (Pu-Py) Specificity Pattern

This study was designed to find the DNA base sequence specific patterns of small molecules with designed DNA oligomers. However, the docked structures of Vinca alkaloids **1-4** showed purine-pyrimidine specific patterns, which could be important in designing lead compounds for specific sequences (Table 3). Purine-pyrimidine specificity has been observed in the case of the protein-DNA [8] and the drug-DNA complexes [9]. The analysis of docked structures was based on a base proximity model in which the DNA bases in the close immediacy of the bound molecule were taken into consideration. It should be considered in view of the fact that the two groups of nuclear bases, namely, purines (A or G) and pyrimidines (C or T), individually have a similar electron density cloud around them, and, as a result thereof, offering the same electron density and electrostatic potential for the purpose of drug binding.

The binding sites of VLB, VCN and CTN consisted of 3-base pairs while that of VCR consisted of 4-base pairs. Out of three DNA decamer sequences, the binding patterns of any two sequences were grouped based on their similarity. The exact match of purines and pyrimidines of the binding site was defined as 'Same' pattern. '1-Base altered' pattern was assigned to the groups that contain one altered base as purines or pyrimidine in both the docked structures of each group. It was observed that CTN gave binding to all 4 DNA oligomers 'same' pattern of purine-pyrimidine specific binding sites, while other alkaloids gave 'same' and '1-base altered' patterns.

Thus, we can herewith propose that purine-pyrimidine (Pu-Py) specificity patterns can be used as another broader measure of DNA binding specificity exhibited by a drug. In the case of non-specific DNA binding of drugs, the 'purine-pyrimidine' specificity can be employed as a tool to design efficient DNA binding drugs in the management of various disorders.

2D ^{1}H NOESY NMR data on DNA-2 assisted in the assignment of the individual proton chemical shifts. All the ^{1}H NMR chemical shift values were secured by deciphering the sequential inter- and

Table 3: Purine-pyrimidine specific patterns obtained from drug-DNA docked structures.

Alkaloids	Complex	Binding Site	Pu-Py Specificity	Binding Pattern
VLB (1)	DNA-1	5'-G_4-G_5-C_6	5'-Pu-Pu-Py	Same
	DNA-2	5'-G_7-A_8-T_9	5'-Pu-Pu-Py	
	DNA-3	5'-T_6-T_7-G_8	5'-Py-Py-Pu	1-Base altered
	DNA-4	5'-T_5-A_6-A_7	5'-Py-Pu-Pu	
VCR (2)	DNA-1	5'-$G_1A_2T_3G_4$	5'-Pu-Pu-Py-Pu	1-Base altered
	DNA-2	5'-$G_1A_2T_3C_4$	5'-Pu-Pu-Py-Py	
	DNA-3	5'-$G_1G_2C_3A_4$	5'-Pu-Pu-Py-Pu	1-Base altered
	DNA-4	5'-$G_1G_2C_3T_4$	5'- Pu-Pu-Py-Pu	
VCN (3)	DNA-1	5'-$A_2T_3G_4$	5'-Pu-Py-Pu	1-Base altered
	DNA-2	5'-$A_2T_3C_4$	5'-Pu-Py-Py	
	DNA-3	5'-$A_4A_5T_6$	5'-Pu-Pu-Py	Same
	DNA-4	5'-$G_1G_2C_3$	5'-Pu-Pu-Py	
CTN (4)	DNA-2	5'-A_2-T_3-C_4	5'-Pu-Py-Py	Same
	DNA-3	5'-A_5-T_6-T_7	5'-Pu-Py-Py	
	DNA-1	5'-T_3-G_4-G_5	5'-Py-Pu-Pu	Same
	DNA-4	5'-T_5-A_6-A_7	5'-Py-Pu-Pu	

intra-nucleotide cross-peaks between base protons and corresponding H1' protons in the finger print region (Fig. 5). Later, other regions of NOE cross-peaks (base proton-H3'; base proton-H4'; and base proton to H2'/H2" protons) were also analyzed. An unambiguous assignment of almost all DNA base protons and deoxyribose sugar protons was furnished and listed in Table 4. All the 10 intranucletide NOE crosspeaks for base-H3' protons were not resolved. In the base proton-H4' region of the 2D-NOESY experiment, however, only 5 intranucleotide NOE cross peaks were assigned for G1, A2, G6, G7, and A8 residues of the DNA-2 decamer duplex.

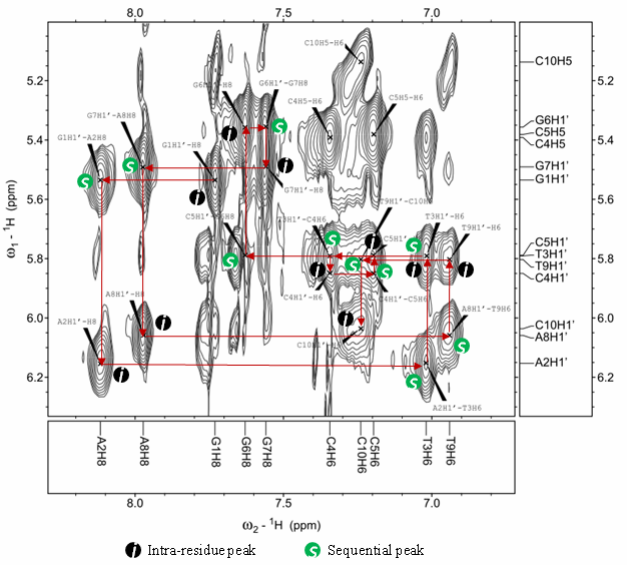

Figure 5: NOESY spectrum of 5'-d($G_1A_2T_3C_4C_5G_6G_7A_8T_9C_{10}$)$_2$ (DNA-2) sequence showing finger print region of the spectrum. Symbol ***i*** indicates the intra-nucleotide cross peaks between base proton and H1' proton, while symbol ***s*** signifies the inter-nucleotide cross peaks between H1' protons of one nucleotide and base protons (H6 or H8) of the next nucleotide of the DNA backbone.

1D ^{1}H NMR titration of vinblastine sulfate (**1**) with DNA decamer sequence DNA-2 was carried out in order to find any chemical shift change in the DNA spectrum after drug binding (Figure 6). The NMR titration was performed to obtain the 1:1 and 2:1 molar ratio of drug: DNA. However, no changes in the chemical shift values of either drug or DNA proton resonances were observed as a result of the drug-DNA complexation. We may conclude that drug binding to DNA was not observed at millimolar concentration by the NMR method in this case. This needs further experimentation using other NMR techniques.

Table 4: NOE cross peaks of various protons of DNA2.

Residue	H8/H6	H5	Me	H1'	H2'	H2"	H3'	H4'
G1	7.73	-	-	5.53	2.46	2.63	n.a.	4.35
A2	8.12	-	-	6.15	2.56	2.81	4.89	4.30
T3	7.02	-	1.18	5.79	1.93	2.31	4.89	n.a.
C4	7.35	5.39	-	5.81	1.94	2.29	n.a.	n.a.
C5	7.19	5.33	-	5.38	1.73	2.11	n.a.	n.a.
G6	7.63	-	-	5.36	2.48	2.53	4.83	4.14
G7	7.56	-	-	5.49	2.43	2.57	4.84	4.21
A8	7.97	-	-	6.05	2.41	2.74	4.83	4.26
T9	6.95	-	1.16	5.79	1.78	2.30	4.81	n.a.
C10	7.25	5.15	-	6.04	2.10	2.10	4.36	n.a.

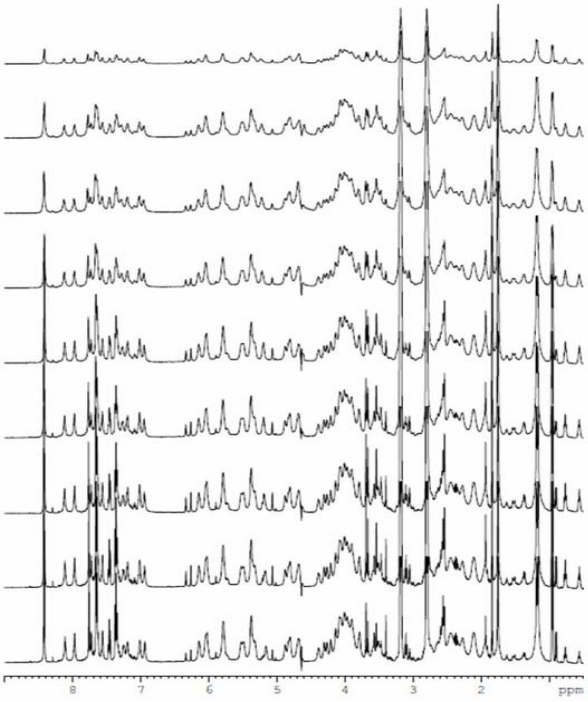

Figure 6: 1D proton NMR titration of VLB:DNA-2 complex.

Experimental

General: Vinblastine sulfate (VLB, 1), and other alkaloids were purchased from Sigma-Aldrich Chemicals Co., USA, and were used after checking for their purity by HPLC. Four DNA decamer sequences were purchased from Sigma-Aldrich as desalted base, viz, DNA-1 to DNA-4.

Stock solutions: Stock solutions of Vinca alkaloids (**1-4**) and DNA were made in 20 mM sodium phosphate buffer (5 mM Na_2HPO_4, 5 mM NaH_2PO_4, 1 mM $(Na)_2$EDTA and 3 mM NaCl) at pH 7.4. Concentrations of alkaloids (**1-4**) were determined volumetrically and those of DNA decamers (DNA-1 to DNA-4) spectrophotometrically using the molar extinction coefficients for DNA decamer sequences, ε_{260} = 95000 for DNA-1, ε_{260} = 92600 for DNA-2, ε_{260} = 93200 for DNA-3, ε_{260} = 96600 for DNA-4. All the compounds obeyed Beer's law in the concentration range employed. The DNA decamers were annealed slowly in the buffer solution. All solutions were freshly prepared and stored below freezing point, duly protected. No change in the optical properties of the compounds (**1-4**) or DNA was observed.

Fluorescence measurements: The fluorescence measurements were recorded on a Hitachi model F4010 spectrofluorimeter (Hitachi Ltd, Tokyo, Japan), where a fixed concentration of vinblastine and other indole derivatives were titrated with increasing concentration of DNA decamers in a fluorescence free quartz cuvette of 1 cm path length. The excitation band pass was fixed at 5 nm while different emission band pass wavelengths were used (5 nm, 10 nm & 20 nm). The scan speed of 240 nm/min was kept fixed during all the experiments. Fluorescence titration experiments of vinblastine and other alkaloids with calf thymus DNA were performed with an excitation band pass of 5 nm, and an emission band pass of 20 nm.

DNA docking: The DNA binding of Vinca alkaloids was studied by the molecular docking program (DNADock) and the energy calculation program (PreDDICTA) based on a specialized protocol for DNA minor groove binding. In the DNADock program, rigid body docking calculations allowed the drug to remain flexible to obtain a low energy conformation at a specific site in the DNA minor groove (Figure 4), taking into account the thermodynamic aspect of drug-DNA binding [6]. The final drug–DNA complex structures were subjected to binding free energy analysis using PreDDICTA software tool [6].

NMR methods: All the NMR experiments were recorded on a Bruker 500-AVANCE Spectrometer. 2D ^{1}H NOESY NMR data on DNA-2 was obtained with 300 ms mixing time. Chemical shifts are given in ppm. NMR experiments were conducted in a sodium phosphate buffer of pH 7.2 prepared in D_2O. The water resonance was used as the reference signal. NMR spectra were processed using Topspin software. 2D NOESY assignments were made using SPARKY software from UCSF.

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