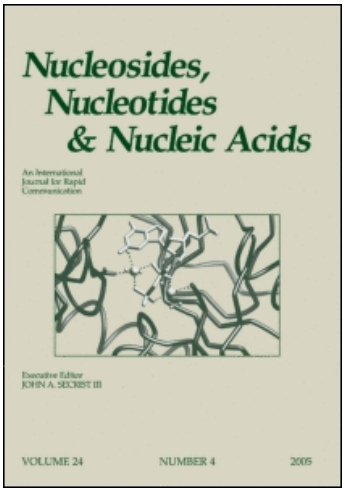

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Sequence Specific Chemical Recognition Of DNA

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SEQUENCE SPECIFIC CHEMICAL RECOGNITION OF DNA

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ABSTRACT: DNA intercalators which can covalently modify DNA, under specified conditions, have been synthesised. These compo- unds have been linked to heptathymildilic acid which has potential to recognise DNA sequence specifically, by triple helix formation.

Even though a great deal is known about DNA structure for quite some time, recognition of specific sequences of DNA by various natural enzymes with the faultless accuracy and precision is still far from satisfactory understanding. The chemistry of such molecular interactions has been investigated during the past decade. With genome sequencing venture on the anvil, recognition and cleavage of unique DNA sequence in total genome is in pressing demand. This would mean recognition of 12 to 15 base pairs for which there is no enzymatic precedence. A chemical design to achieve this level of selectivity would not only give tremendous impetus to human genome mapping but will also help in locating individual genes. There are around 3000 human genetic diseases identified and very little is known about the location or mode of action of the genes responsible for these diseases. The chemical principles being elucidated in DNA recognition may contribute to development of exquisitely precise agents that could control disease at the level of DNA itself. In addtion to what has been said above, such studies will be instrumental in learning more about recognition at molecular level in biological systems which is an area of unlimited importance.

Recognition of DNA in natural systems is achieved by base complementarity or DNA binding proteins. It was only logical to begin

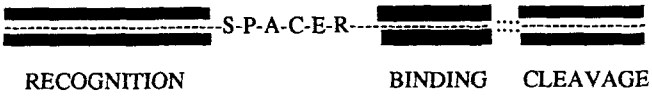

Fig. 1 Functional elements of a general 'chemical cleavage' design.

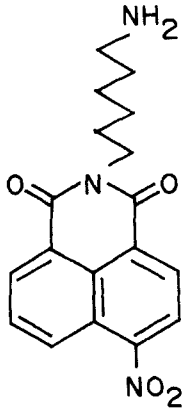

Fig. 2 Bifunctional intercalator, one of the 1,8 - naphthalimide derivatives, used in the present study.

with the same principle in the chemical approach also. Ability of some sequences to recognise DNA double helices by triple helix formation via Hoogsteen base pairing has been utilised in cleavage (1,2) or chemical modification (3) of DNA or inhibition of DNA binding proteins (4). This has also lead to fresh attempts to further investigate the triple helix formation (5) which is known for last three decades.

The other approach has been to attach such recognition elements to nonspecific nucleases (6) or to attach cleavage elements to sequence specific DNA binding proteins (7). Synthetic peptides have also been used for the same purpose with notable success (8,9). Basic design behind all these approaches has been towards the system shown in Fig. 1.

We have chosen DNA intercalators (Fig. 2) as the binding elements with two functional groups across the molecule to link recognition and

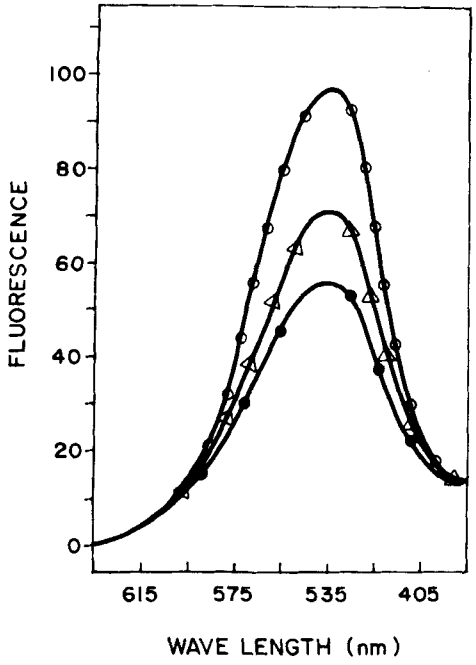

Fig. 3 Emission spectra of fluorescent labelled d(TTTTTTT) (-●-●-); in presence of calf thymus DNA at oligomer : ct DNA (phosphate) ratio of 1 : 20 (-△-△-) and the free intercalator (-○-○-). Excitation wavelength in all the measurements was 455 nm.

cleavage elements on the either sides. Various derivatives of 1,8-naphthalimide have been synthesised and their DNA binding properties are studied. These intercalators are highly water soluble and have strong fluorescence which helps great deal in following the molecular interactions. 4-nitro-(N-6'amino hexyl)-1,8-naphthalimide (Fig. 2) and its derivatives have been found to cleave double helical DNA when irradiated with high pressure mercury lamp for few a minutes at room temperature.

As the binding and cleavage properties of these compounds were, we undertook covalent linking of 4-nitro (N-6' amino hexyl) derivative (Fig. 2) with its amino function to 5' hydroxyl function of a hepta nucleotide, d(TTTTTTT) following a procedure that uses carbonyldiimidazole as activator, on solid support (10). After the deprotection and subsequent gel filtration column chromatography, the derivatised oligonucleotide was checked for its fluorescence properties (Fig. 3). The emission wavelength remains identical to the starting compound and upon addition of double helical DNA enhancement in fluorescence is seen. These observations indicate that intercalating and fluorescence properties of the compound are not affected by the modification and that the derivatised oligonucleotide can be used for sequence specific chemical cleavage. Work in direction is being pursued further with other derivatives of this parent compound.

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