Review Article

Supramolecular Interactions of Cyclobisintercaland Molecules with the Single Stranded DNA

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Abstract

The interactions of DNA with synthetic molecules is being widely studied to empower scientists with better tools for human survival and for the betterment of the quality of life. Cyclobisintercaland molecules or macrocycles are cyclic compound which are designed to non-covalently interact with the single stranded DNA. These kind of interactions open up a wide arena of therapeutics which could involve drugs and treatments based on non-covalent binding. This paper intends to outline the study conducted so far on cyclobisintercaland molecules engineered and their biological applications.

Keywords: Cyclobisintercalands; Macrocycles; Noncovalent Interactions; Single Stranded DNA; Supramolecular Chemistry.

Introduction

DNA is regarded as a 'blueprint of life'. Ever since its discovery as the biomolecule carrying all hereditary information, extensive research is being carried out to understand its beautiful complexity and attempts are regularly being made to powerfully manipulate it to benefit mankind. Information stored in the DNA is used after amplification by subsequent RNA and proteins to phenotypically express it into observable traits. This phenomenon of gene expression had been beautifully articulated as the 'central dogma' of molecular biology by Francis Crick in 1958 [1].

Study of the genetic basis of diseases has focused the attention of researchers towards creation of molecular drugs that can bind to the complex DNA structure and bring about a beneficial change in the subsequent gene expression. Although, small synthetic molecules as well as large molecular structures may be used as drugs for gene binding or manipulation, small molecules have an added advantage of easy transport into the cell.

Supramolecular interactions of synthetic molecules with DNA primarily include non-covalent forces involved in the spatial organization of the two molecules favouring their mutual interaction. Since interactions *in vivo* between the nucleic acid and small

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molecules are non-covalent, examining these interactions is necessary to mimic them and use them with synthetic molecules. These recently discovered interactions of synthetic molecules with nucleic acids is of importance to mimic and influence the biological processes. Among the plethora of molecules synthesized, those that react selectively with single stranded DNA are rare and hence the recognition of these sites by synthetic molecules is important as they could act as potential anti-viral agents. This review aims to provide a recapitulation of the research conducted to date on the supramolecular interactions of chemically synthesized cyclobisintercaland molecules with the single stranded DNA.

The DNA Single Strand

One of the greatest discoveries in the field of Molecular Biology was that of the structure of DNA double helix by James D. Watson and Francis H.C. Crick in 1953 [2]. Research since then has shown various other forms of DNA present in organisms.

Simplistically, a DNA is composed of 4 nucleotide bases- Adenine (A), Guanine (G), Thymine (T) and Cytosine (C).

Each nucleotide is attached to a deoxyribose sugar which is further attached to a phosphate molecule. The nucleotides are stacked on top of each other in the double helical structure with the sugar and phosphate molecules forming the backbone. The two polyanionic strands of DNA are intertwined around each other in the most energetically favorable manner and the bases pair via Hydrogen Bonds according to Watson-Crick base pairing rules (I.e. A=T and G $\equiv$ C). Another base pairing, known as Hoogsteen Base Pairing is present but rarely observed. {Note: Figure 1 is basic and included only for reader's reference}

The single stranded DNA in most cases is referred to as a reminiscent of the double strand. Melting experiments can usually generate single stranded DNA synthetically. Generally, in solutions, single stranded DNA is prepared by completely melting both the strands of the ds helical DNA. The ssDNA retain some preferred conformations but their shape can be easily geometrically distorted [3]. In nature, the single stranded DNA is found mostly in viruses. Viruses containing these ssDNA release their DNA into the host which is then transported to the nucleus for transcription. ssDNA virus are largely icosahedral shaped.

However, the exact 3-dimensional structure of the DNA depends on its environment and sequence.

Most supramolecular DNA research conducted includes broadly 4 main DNA structures:

1. DNA Single Strand – Photocleavage Studies, Abasic site recognition and Hairpin Structure

2. Double Stranded DNA - Helical and ds Circular DNA; A,B and Z DNA interactions.

   B DNA interactions are the most widely studied and include DNA binding majorly in these 5 sites:

   a.   Major Groove

   b.   Minor Groove

   c.   Sugar Phosphate Backbone

   d.   Intercalation between base pairs

   e.   Covalent binding/ Metal co-ordination to the bases [4]

3. DNA Triple Helix (Mainly DNA triple helix stabilization)

4. Tetraplex DNA or the G quadraplex

Binding of synthetic molecules to DNA/ polynucleotides includes 2 main approaches: synthesis of molecules that are sequence specific or of molecules that are structure specific. In accordance with the scope of this review, CBI interactions with single stranded DNA structures are discussed.

Cyclobisintercalands

The major synthetic molecules used to date to study single stranded DNA interactions include a broad range of macrocyclic compounds. For selective manipulation of the single stranded nucleotides by cleavage, the molecules capable of recognizing particular sequences/structures are attached with functional groups capable of cleavage.
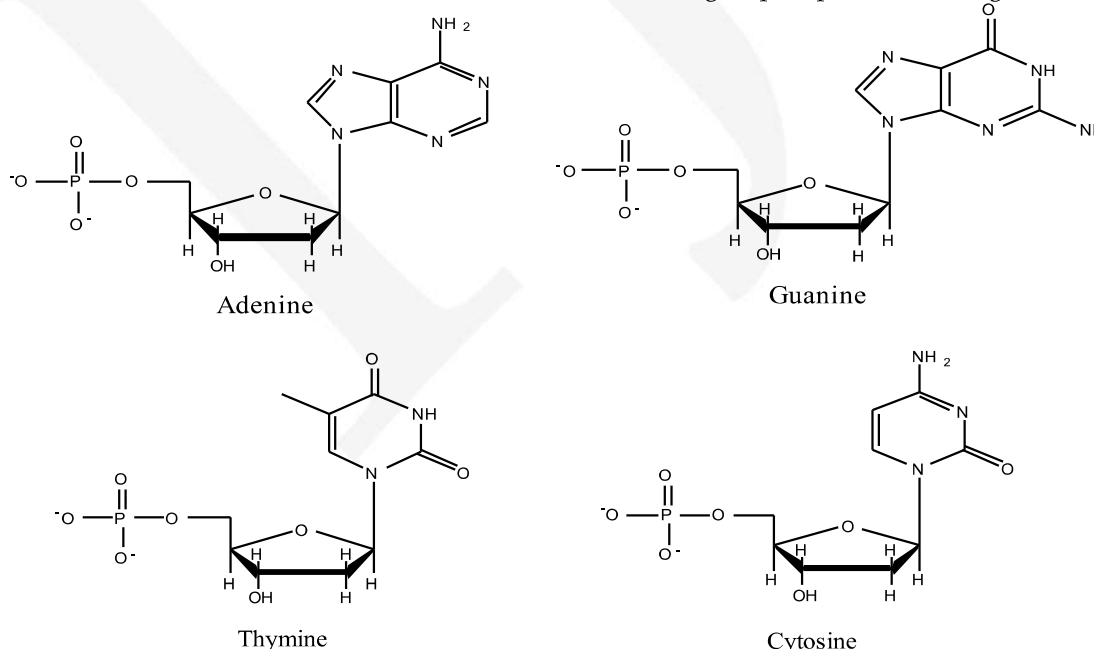

Adenine

Guanine

Thymine

Cytosine

Fig. 1: Deoxyribonucleotides

A class of molecules known as the cyclobisintercalands, have been closely studied in the past few years. These molecules contain 2 planar subunits attached to each other by flexible or rigid linkers/bridges (designed according to need). This arrangement gives them an appropriate structure which when separated by appropriate distances can bind to nucleic acids and serve its intended purposes.

A type of macrocyclic compound includes the cyclo-bisintercaland (CBI) molecules. CBIs incorporate intercalating molecules into a particular macrocyclic structure with defined geometrical properties. The general structure of these cyclo-bisintercalating molecules is shown in Figure 2a. These molecules preferentially bind to ssDNA rather than dsDNA as will be discussed below. The ss DNA binding with cyclo-bisintercaland molecules shows the presence of the ssDNA between the 2 intercalands as depicted in Figure 2 b.

Figure 3 further depicts the binding of CBI to single stranded DNA as compared to double stranded DNA. The preferential binding to single stranded DNA could be due to the fact that DNA binding to the ds DNA could be hindered by steric interactions of the ds framework and the chains acting as bridges between the two flat molecules [5].

The Macrocyclicbisintercalands containing porphyrin, diazapyrene, phenazine, naphthalene, acridine, anthracene and Phenanthridine have been synthesized for their applications in DNA intercalation. The synthesis has always been with the aim that it has a perfect geometry that can bind to polyanionic substrate (like nucleobases) strands and can be used in biological systems.

The positively charged CBI molecules, in aqueous solutions, strongly bind to anionic or neutral substrates.
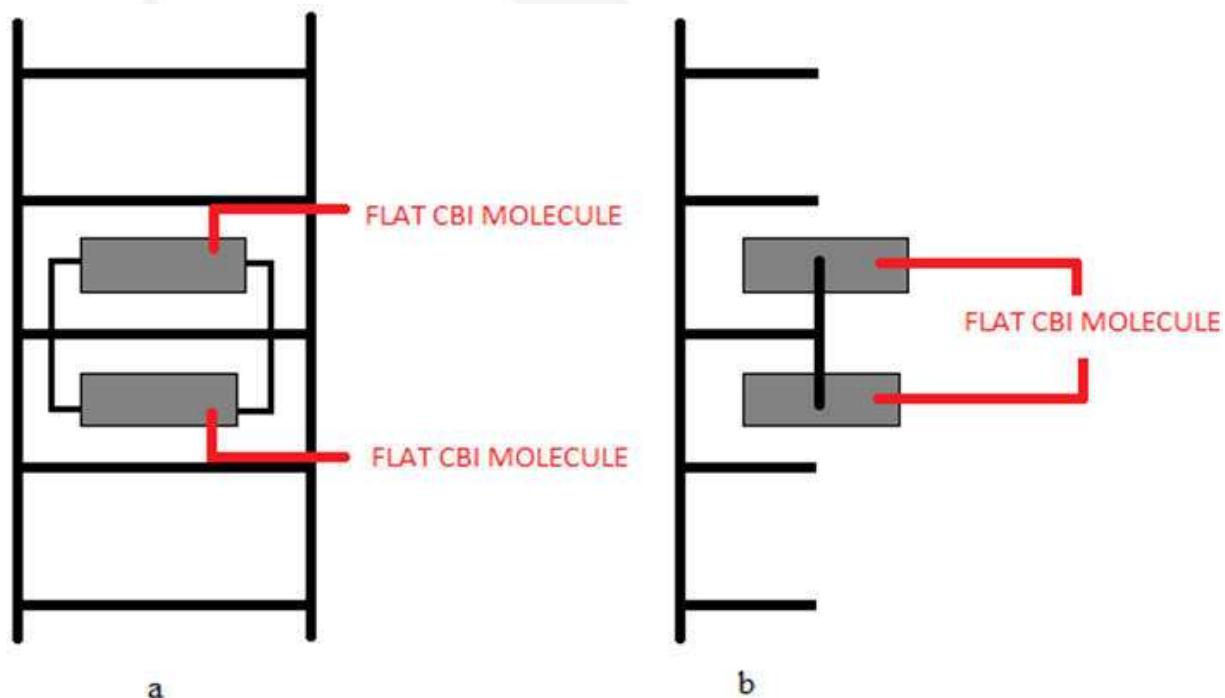

Fig. 2: Binding of the substrate (ssDNA) within the macrocyclic framework

Fig. 3: Binding of a cyclobisintercaland molecule to
a. double stranded DNA and
b. Single stranded DNA
Please note: all mentions in red are the marking for naming the molecules

Synthetic Supramolecular Interactions of the Single Stranded DNA

The most interesting development in the study of the CBI binding to the single stranded nucleic acids, is the ability of these CBI molecules to differentiate between single and double stranded DNA.

DNA Hairpins

Several times, in nature, including in the human body, various non-double stranded structures play a major role in gene expression. These include the recognition of structural probes by enzymes or molecular machines for transcription, translation, replication or splicing. Hairpin motifs particularly regulate several human gene transcriptions [6,7]. Moreover, these Hairpin structures have been associated with various human diseases including the human fragile X-chromosome syndrome [8],

human myotonic dystrophy [9] and promotion of 'kissing complex' of HIV dimerization [10,11]. All these factors make the study of Hairpin-binding compounds very useful to destabilize, form or manipulate this structure. In consideration of the scope of this paper, DNA Hairpin binding molecules have been discussed.

Majorly, the DNA Hairpin binding has been studied with respect to bisacridine molecules for their known preferential binding to single stranded structures. The experiments conducted have been recapitulated below:

1 (bisacridine) bound selectively to single stranded loops of the DNA hairpin structure while destabilizing double stranded polynucleotides. [5] The contribution of the above listed forces in the intercalation of the macrocyclic structure and the substrate was corroborated with experiments conducted on **2** [12].
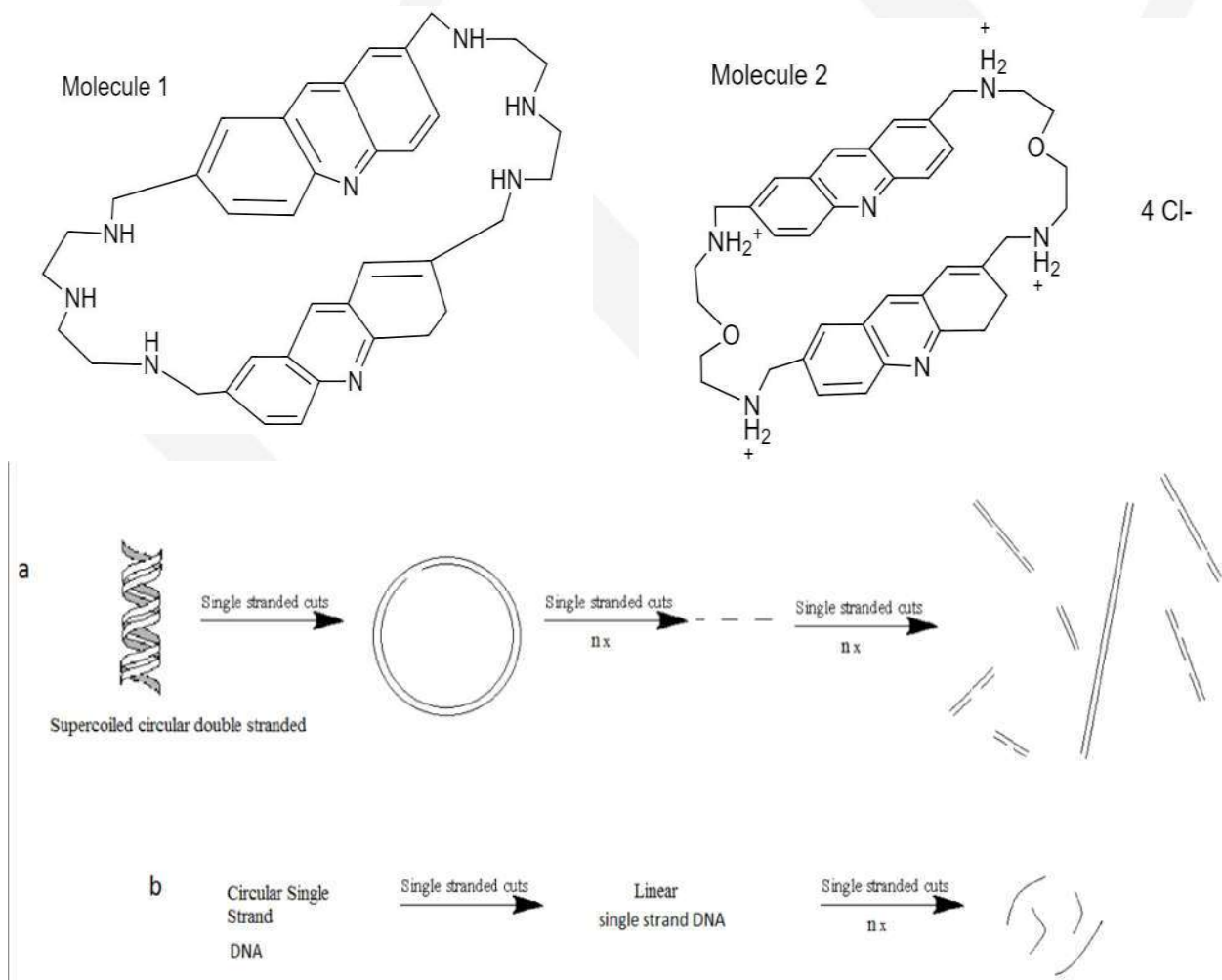

Fig. 4a: Single stranded cuts in the supercoiled double stranded DNA structure
b. Single stranded in circular single stranded DNA leading to formation of small DNA fragments

Another macrocyclic bisacridine molecule synthesized **(3)** containing positively charged flexible arms (that electrostatically bind with the phosphate groups of the oligonucleotide backbone) and uncharged flat acridine components (which stack themselves on the bases), was found to preferentially bind to and stabilize the DNA Hairpin structures. This macrocyclic molecule also was observed to stabilize the DNA Hairpin structure via a 25°C stabilization [13].

Successive competition experiments held verified the binding selectivity of the macrocyclic bisacridine **(3)** for DNA Hairpins compared to the double helical DNA. This selective affinity is the reason for a shift in the equilibrium observed from the duplex to the hairpin structures [14].

Molecular recognition of Nucleobases

In water, hydrophobic forces and electrostatic interactions play major roles.

Cyclo-bisintercaland receptor molecules based on acridine subunits synthesized were flat, positively charged and separated from each other by appropriate distances **(4)**. These molecules were soluble in water and were found to bind to nucleotides and nucleosides near biological pH. The results generated showed that the binding of these molecules could be used as a differentiator of purines and pyrimidine. On reaction with purine nucleotides, quenching of the emission was observed whereas on reaction with pyrimidine nucleotides, there was an enhancement of the fluorescence intensity. The results also established the contributions of electrostatic and hydrophobic interactions in the binding of the bisacridine molecules to the nucleobases [15]. The bisacridine macrocycles are however known to bind to flat substrates much more strongly than their parent bisnaphthalene compounds.

5 (a-c) containing crescent-shaped quinacridine structures joined by certain linkers were shown to bind to anionic aromatic nucleotides by electrostatic and ð stacking forces. These molecules were proven to bind to nucleoside monophosphates stoichiometrically in a 1:2 ratio and to nucleoside di and tri phosphates in a 1:1 stoichiometric ratio.

Molecule 3

Molecule 4

X=Y=LONE PAIR

Molecule 5
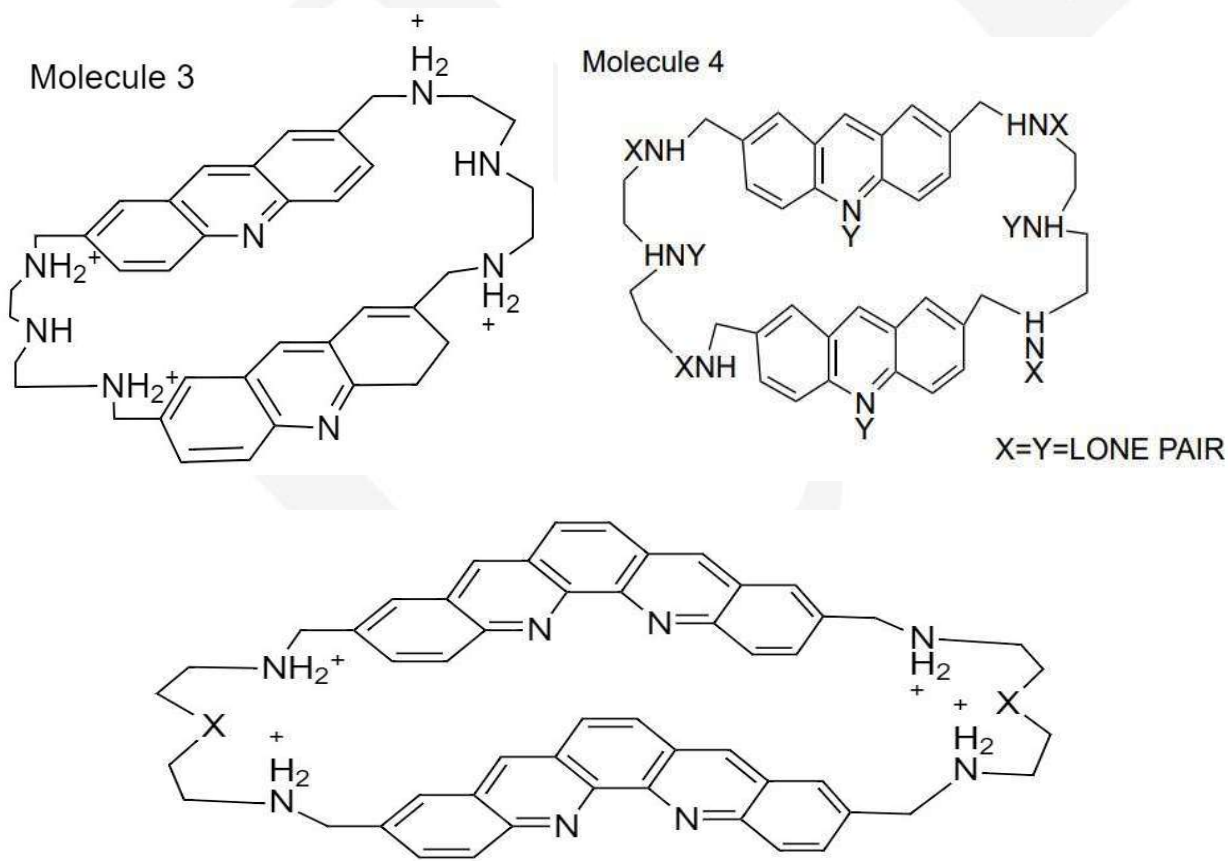
Higher affinities were recorded for guanosine derivatives and competition experiments even prove the binding selectivity for the guanosine derivatives in aqueous solution was preserved in the gas phase [16].

The bisporphyrin 6 was also shown to preferentially bind to single stranded DNA [5].

Naphthalene derivatives of these macrocyclic compounds, 7 (BisNP-O and BisNP-N) have been shown to bind to purines derivatives preferentially. 7 **BisBP-N** was also shown to destabilize the double helical structure of the DNA by binding presumably to the single stranded regions of the DNA [17].

CBI (Cyclo-bisintercaland) molecules such as bis-naphthalene **(8)** and bis-acridine **(3)** were studied to destabilize the double helical structure of the DNA. This property of theirs was predicted due to their preferential binding to single stranded oligonucleotides [18].

Photochemical Cleavage

DNA is capable of *in vitro* and *in vivo* photocleavage as has been shown by various experiments in the past [19]. For functional cyclointercaland receptors, which are capable of photocleavage, the inclusion of photoactive intercalating groups into macrocycles is necessary.

6 (bisporphyrin) has been shown to form more stable complexes with single stranded rather than double stranded polynucleotides. 6 was also tested for its Ss polynucleotide preferentiality by incubating and irradiating (for photocleavage) 6 with tRNAasp. The results obtained confirmed the binding sites of 6 with ssRNA and thus conclusively 6 prefers to bind to single stranded polynucleotides [5].

9 is a tetra-cation that essentially contains a rigid cavity for inclusion for aromatic substrates, photosensitizing intercalating phenazine subunits, electron acceptor viologen subunits. It was shown to cause significant nicks in the supercoiled DNA on irradiation. Kinetic studies conducted for this experiment also showed 9 to have a higher percent cleavage than its control counterpart 10 in the same defined time period [20].

2,7-Diazapyrenium di-cations (MDAP^{2+}) **(11)** had been shown to bind and photo-oxidize under irradiation with visible light molecular polyanions and thence, DNA. MDAP^{2+} was shown to entirely cleave supercoiled ds DNA under visible light

Molecule 6

Molecule 8

Molecule 7

X= O: BisNP-O
X= NH: BisNP-N

Molecule 9
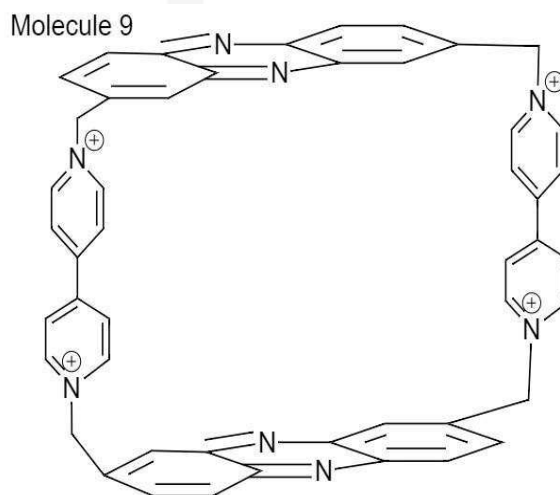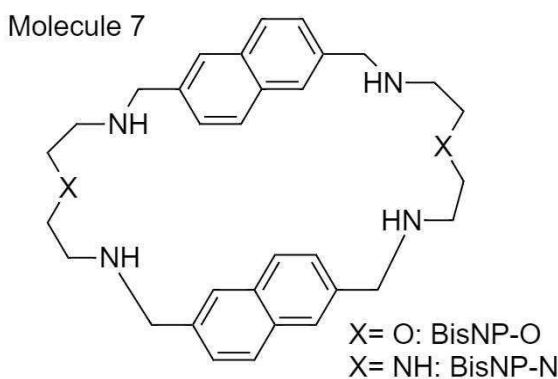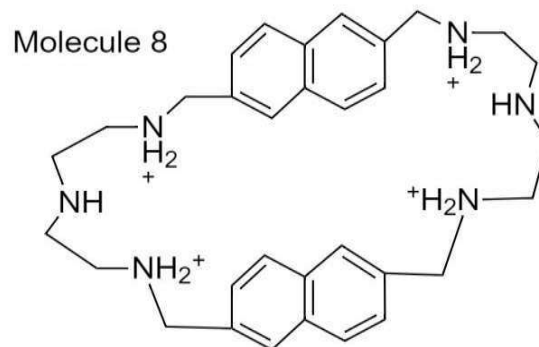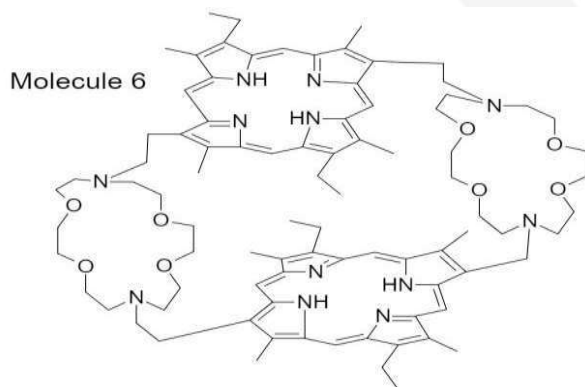
irradiation resulting in nicked circular DNA upon cleavage of one strand and in linear DNA on cleavage of both strands on further reaction.

In comparison, the bis-DAP[4+] **(12)** showed a greater degree of DNA cleavage generating multiple small fragments by cuts in both strands [21].

Photocleavage experiments have been mostly conducted on circular supercoiled dsDNA. The ds DNAs on being cut, changed to relaxed circular forms. This on further multiple cuts, gave linear ssDNA species.

Abasic Site

The formation of abasic sites results from the cleavage of a glycosidic bond from the DNA double helix structure. This act leaves behind a 2'-deoxyribose residue referred to as an AP site (apurinic/apyrimidinic). The formation of these sites has been shown to be accelerated greatly by the use of alkylating drugs. *In vivo* these AP sites are repaired by biological enzymes [22]. Being non-informative,

the abasic sites are regarded as mutagenic or lethal entities. 9-aminoellipticine, 3- aminocarbazole, Lys-Trp-Lys peptides, hybrid molecules, bisnaphtha-limide DMP 840, etc. have been engineered for their use as drugs related to abasic site [23].
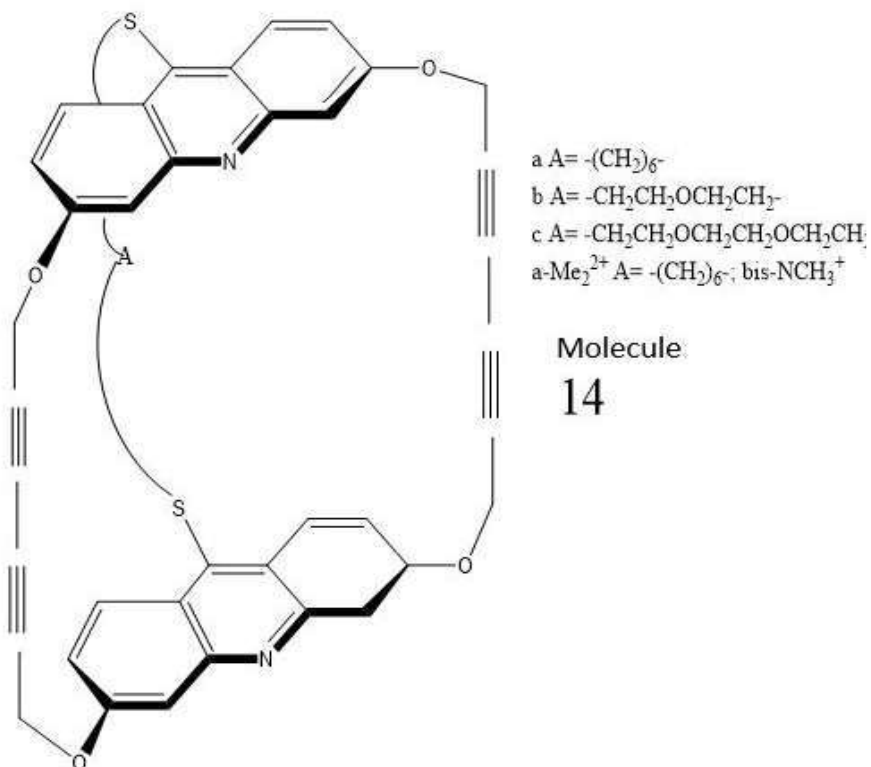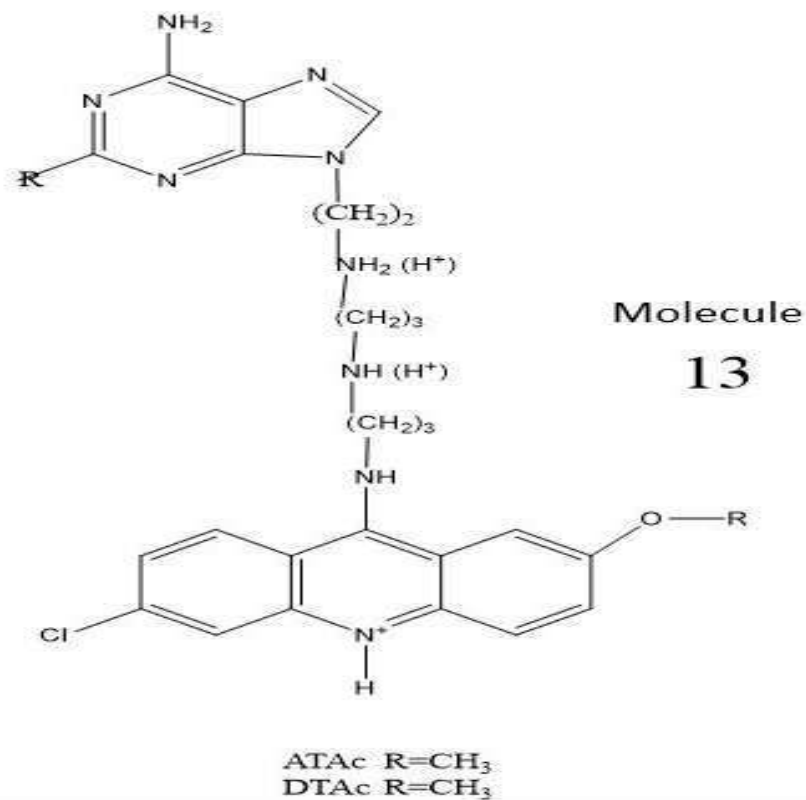
The abasic site is one of a strong thermodynamic destabilization of the ds DNA. Insertion of molecules such as the macrocyclic bisacridine leads to π-stacking interactions of acridine rings with base pairs and electrostatic interactions between the DNA groove floors and the linkers of the bisacridine macrocycle [23]. Mostly, the studies conducted on abasic site binding include bisacridine as they have already been shown to prefer single stranded structures such as the hairpin motifs. Hence, this can be extrapolated and they can be thought of as very useful binding probes for abasic DNA sites [22-25].

Adenine-triamino-acridine (ATAc), diaminopurine-triamino-acridine (DTAc) **(13)** synthesis has been reported. These structures recognize abasic sites in the DNA even at minute nanomolar concentrations and cleave the DNA at the AP-sites by β-elimination of the 3'-phosphate. They mimic the AP-endonuclease mechanism [22].

Molecule 10

Molecule 11

Molecule 12

MDAP[2+]

bis-DAP[4+]
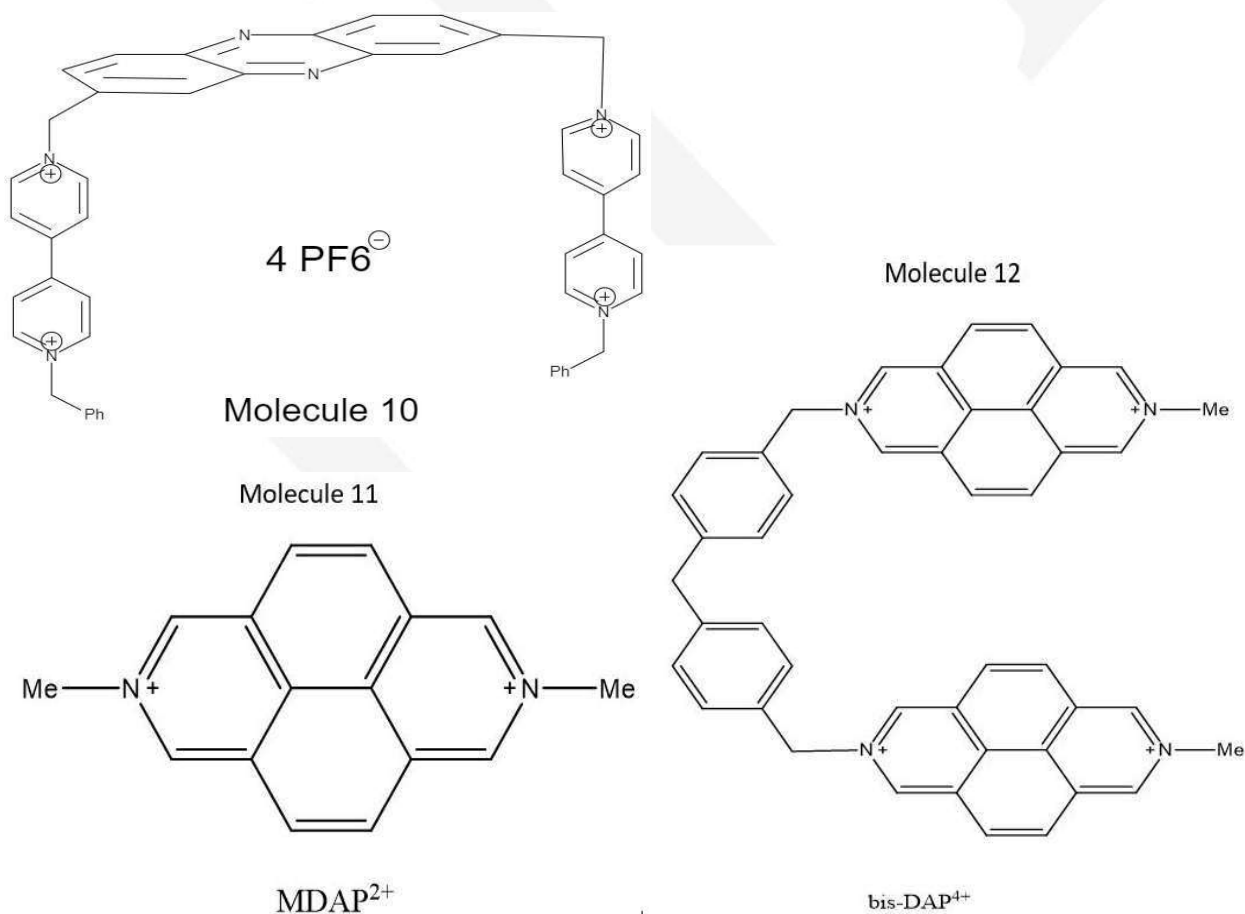
Finally, bisnaphthalene macrocycles synthesized **(7 BisNP-O)** were recorded to recognize T-T mismatch sites in ds DNA by one naphthalene ring occupying the region of the mismatched Thymine in the DNA while the other naphthalene ring binds at the A-T base pair. The polyammonium chains as usual, stabilize the complex [26].

Molecule **13**

ATAc R=CH$_3$
DTAc R=CH$_3$

a A= -(CH$_2$)$_6$-
b A= -CH$_2$CH$_2$OCH$_2$CH$_2$-
c A= -CH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-
a-Me$_2$$^{2+}$ A= -(CH$_2$)$_6$-; bis-NCH$_3$$^+$
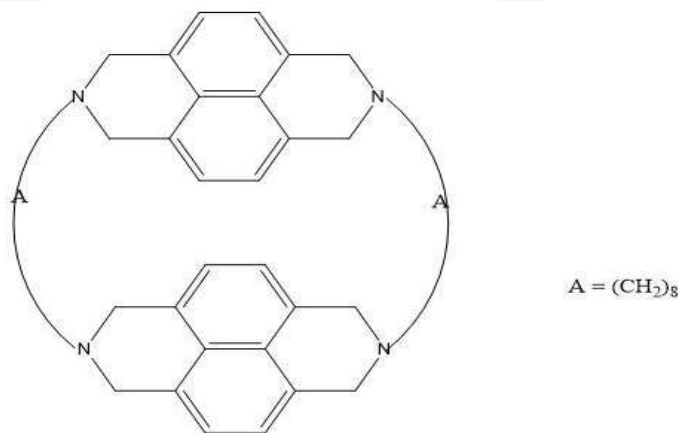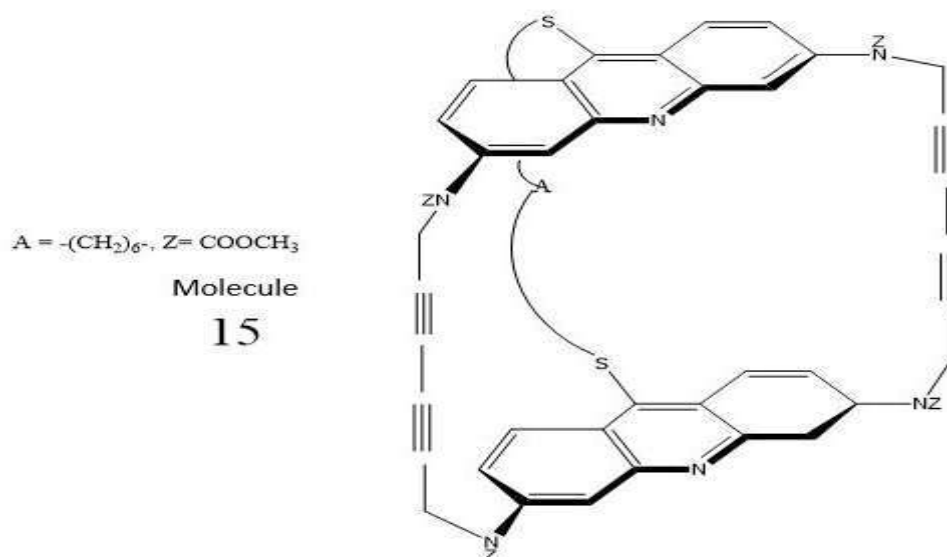
Molecule **14**

CBI Binding Properties

As mentioned earlier, synthesis of CBI molecules has been with the aim to create molecules either sequence specific or structure specific, which bind to the substrates in an environment similar to their *in vivo* characteristics. Amongst all species, the binding of flat **bisacridine** molecules **(14,15)** to the DNA has been widely studied. Some other acridine based bis-intercaland molecules synthesized have been shown to have a separation of about 4 Å similar to that of B-DNA. These molecules hence may also prove to be useful for binding and intercalation [27].

Another cyclo-bisintercaland **(16)** synthesized showed binding affinities to anionic substrates and hence may be able to bind to DNA [28].

Finally, cyclo-bisintercalands with *phenanthridine* subunits were synthesized containing two 8-amino-6-phenanthridinyl **(17-21)** and 8-amino-5-methylphenanthridinium-6-yl **(22)** respectively. These

molecules, on complexation with aromatic substances/cyclization showed a marked increase in their electronic absorption coefficient and their fluorescence intensity. Aforementioned bisacridine subunit based cyclointercalands showed opposite results i.e. their cyclic structures showed a decrease. Ethidium Bromide, a phenanthridine derivative, is one of the most widely used fluorescent tag and a typical ds intercalator. The hydrophobic environment found between the base pairs is mainly regarded as the primary cause for its fluorescence [29]. Ethidium Bromide has also been shown to specifically intercalate between the G/C base pairs of DNA Hairpin [30] A diasterioisomeric CBI structure of two positively charged phenanthridinium subunits joined by aminobisacetylenic bridges **(23 and 24)** with a distance of 4.5 Å was also shown to selectively bind to single stranded polynucleotides primarily due to its structural geometry which is favourable for the same [31].
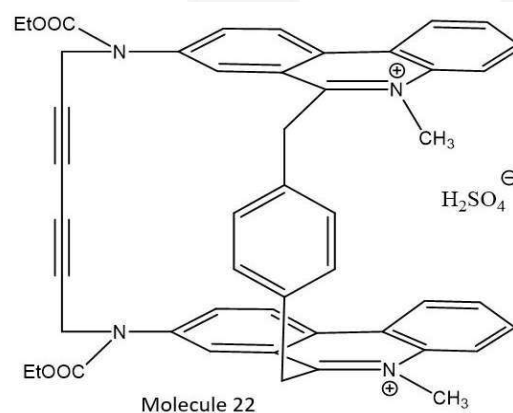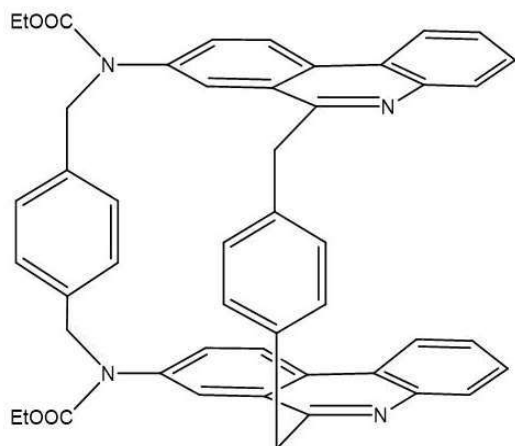

A = -(CH₂)₆-, Z= COOCH₃

Molecule 15

A = (CH₂)₈

Molecule 16

Molecules 17 to 20
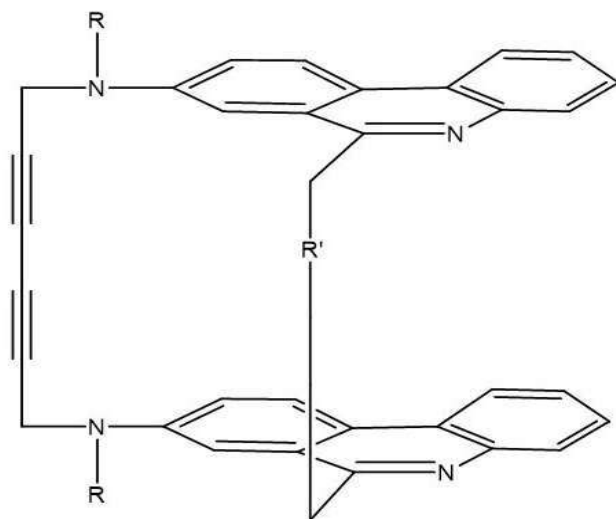
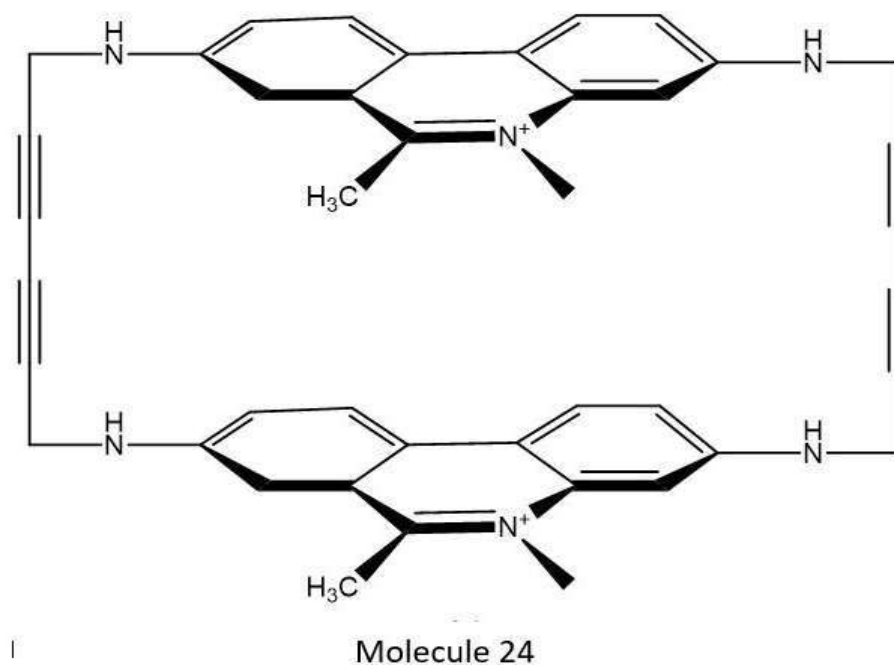|	R	R'
17	COOEt	$p\text{-}C_6H_4$
18	H	$p\text{-}C_6H_4$
19	COOEt	$(CH_2)_4$
20	H	$(CH_2)_4$

Molecule 21

Molecule 22
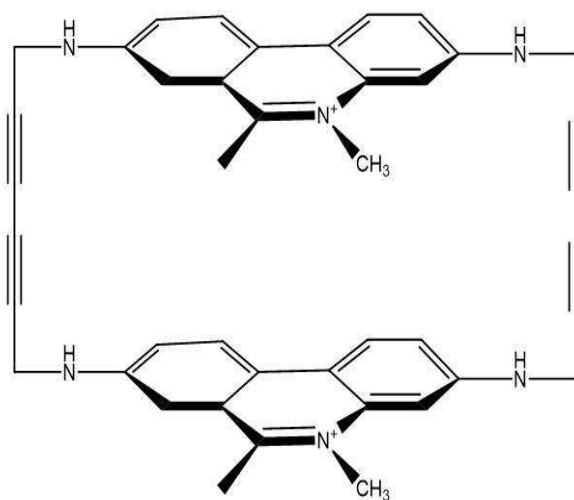
Molecule 23

Molecule 24

Conclusion

The DNA intercalation phenomenon is reminiscent of DNA base-stacking. Bis-intercalands have been shown to have lower residence time on intercalation with the DNA. This phenomenon has been postulated to be the reason behind lower anti-tumor activity of many intercalands *in vivo* [32].

As for the nucleotides, very high affinity constants were measured (between 10^4 and 10^8 M^{-1}) [15,33]. The stoichiometry of binding for all substrates measured was found to be in a 1:1 ratio. Concluding results, the stoichiometry, hypochromism of $\pi-\pi$ systems stacking and characteristics of aromatic surface areas indicate towards sandwich type structural geometry of the substrates in between the flat receptor molecules. Certain crystal structures have also confirmed this [34].

Although, research on single stranded DNA intercalation is in its infancy, the probable future application we can predict include its use as drugs for the treatment of human diseases. The experiments of CBIs *in vitro* are now being conducted in conditions similar to those *in vivo*. This has increased its scope of application for human use. Nonetheless, various drugs mentioned in this paper have reached the chemical trials phase. Extraordinary opportunities remain, as delving deeper into biological applications will require sophisticated techniques.

Acknowledgements

Conflict of Interest Statement

The author declares that there is no conflict of interest.

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