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MOLECULAR DOCKING STUDY OF THE INTERACTIONS BETWEEN CYANINE DYES AND DNA[†]

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Among the various fluorescent probes currently used for biomedical and biochemical studies, significant attention is paid to cyanine dyes possessing advantageous properties upon their complexation with biomolecules, particularly nucleic acids. Given the wide range of cyanine applications in DNA studies, a better understanding of their binding mode and intermolecular interactions governing the dye-DNA complexation would facilitate the synthesis of new molecular probes of the cyanine family with optimized properties and would lead to the development of new cyanine-based strategies for nucleic acid detection and characterization. In the present study, the molecular docking technique has been employed to evaluate the mode of interaction between one representative of monomethines (AK12-17), three trimethines (AK3-1, AK3-3, AK3-5), three pentamethines (AK5-1, AK5-3, AK5-9) and one heptamethine (AK7-6) cyanine dyes and B–DNA dodecamer d(CGCGAATTCGCG)2 (PDB ID: 1BNA). The molecular docking studies indicate that: i) all cyanines under study (except AK5-9 and AK7-6) form the most stable complexes with the minor groove of double-stranded DNA; ii) the cyanines AK5-9 and AK7-6 interact with the major groove of DNA due to their more extended structure and less hydrophilicity in comparison with the other examined dyes; iii) cyanine dye binding is governed by the hydrophobic and van der Waals interactions presumably with the nucleotide residues C9A, G10A (except AK3-1, AK3-5), A17B (except AK3-5, AK5-3) and A18B in the minor groove and the major groove residues C16B, A17B, A18B, C3A, G4A, A5A, A6A (AK5-9 and AK7-6); iv) all dyes under study (except AK3-1, AK3-5 and AK5-39) possess an affinity for adenine and cytosine residues, whereas AK3-1, AK3-5 and AK5-3 also interact with thymine residues of the double-stranded DNA.
Keywords: *Cyanine dyes; DNA; dye-DNA interactions; molecular docking*
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During the last decades cyanine dyes have become increasingly utilized across a wide range of research areas, such as laser technologies, optoelectronics, photoelectrochemistry, bioanalysis, pharmacology, medicine, etc. [1-5]. Likewise, these probes appeared to be particularly useful as molecular probes for biomedical studies [6-30]. More specifically, cyanine dyes were effectively used i) in cell labeling, including life-cell imaging [6,7], labeling neural circuits for the visualization of the structure and function of the brain [8,19], and stem cell tracking in neurodegenerative medicine [10, 11]; ii) detection of oxidative stress and reactive oxygen species [12-14], iii) for synthesis of the fluorescently labeled antibodies [15]; iv) in cancer research for tumor imaging in the fluorescence-guided surgery [16, 17] and in photodynamic therapy [18, 19]; v) for pathogen detection [20]; vi) in gene expression studies to measure the levels of specific mRNAs or miRNAs [20,21]; vii) in high-throughput screening assays to evaluate the effectiveness and toxicity of potential drug candidates [21], viii) for the detection of biomolecules and their interactions [22-25], to name only a few. However, one of the greatest potentials of cyanine dyes lies in their application in DNA research [26-32]. The advantageous photophysical properties of cyanines, such as long-lasting photostability, high brightness, low cytotoxicity, and the sharp increase in emission upon their association with nucleic acids, gave impetus for their use in DNA bioanalytical assays [27,28], sizing, and purification of DNA fragments [29], DNA damage detection [30]; DNA sequencing [31], etc. Given the wide range of cyanine applications in DNA studies, a better understanding of their binding mode and intermolecular interactions governing the dye-DNA complexation would facilitate the synthesis of new molecular probes of the cyanine family with optimized properties and would lead to the development of new cyanine-based strategies for nucleic acid detection and characterization.

In recent decades computational methods have been recommended as particularly useful for providing insights into interactions between potential ligands and their macromolecular targets, thereby significantly decreasing traditional resource requirements encountered in experimental testing [32]. Molecular docking and molecular dynamics simulation have been successfully applied to investigate the potential mode of binding of fluorescent dyes to DNA [33,34]. Despite significant progress in understanding the main structural requirements for the ideal fluorescent marker in DNA research, the mechanisms of the dye interactions with the targeted biomolecules need to be clarified. To fill this gap, the aim of the present study was to investigate the interactions between cyanine dyes and DNA using the molecular docking technique. More specifically, the potential binding sites of one representative of monomethines (AK12-17), three trimethines

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(AK3-1, AK3-3, AK3-5), three pentamethines (AK5-1, AK5-3, AK5-9) and one heptamethine dye (AK7-6) were characterized with the main purpose to determine the interactions governing the dye-DNA complexation and the structural requirements of cyanines responsible for their association. The structures of the dyes used in the study are presented in Figure 1.

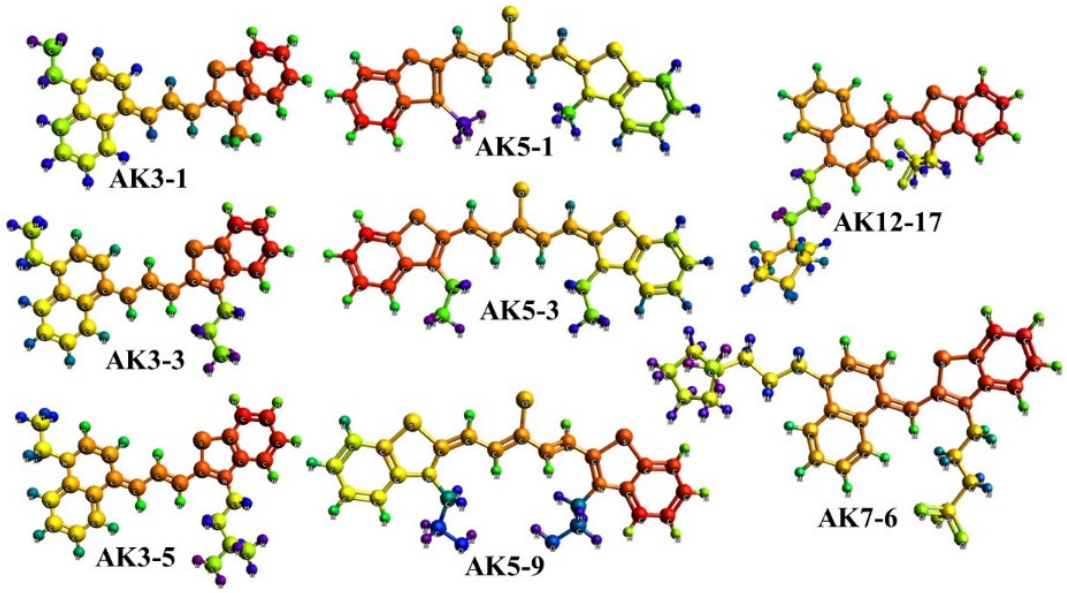

Figure 1. Structural formulas of the dyes under study (monomethines AK12-17, trimethines AK3-1, AK3-3, AK3-5, pentamethines AK5-1, AK5-3, AK5-9 and heptamethine AK7-6)

MATERIALS AND METHODS

Molecular docking studies

To define the most energetically favorable binding sites for the examined dyes on the DNA, the molecular docking studies were performed using the AutoDock (version 4.2) incorporated in the PyRx software (version 0.8) [35]. For the prediction of the docking poses the AutoDock tool utilizes an empirical scoring function based on the binding free energy of the complex [35]. This approach enables the automated docking of flexible ligands to a rigid macromolecular receptor. The crystal structure of the B–DNA dodecamer d(CGCGAATTCGCG)2 (PDB ID: 1BNA) was downloaded from the protein data bank (http://www.rcsb.org./pdb) and was used for the docking studies. The dye structures were built in MarvinSketch (version 18.10.0) and optimized in Avogadro (version 1.1.0) [36,37]. The docking studies were performed in two steps. Initially, the "blind docking" modeling was used to determine the most energetically favorable binding sites for the cyanine dyes on the DNA molecule. The grid size was set as 60 Å, 72 Å, and 119 Å along X, Y, and Z axes, respectively. The grid spacing was 0.375 Å. Next, the lowest binding energy conformer was selected from 10 different conformations for each docking simulation, and was applied for further analysis using the "targeted docking". The grid size was set as 37 Å, 48 Å, and 50 Å along X, Y, and Z axes, respectively.

RESULTS AND DISCUSSION

The investigation of molecular bases of various diseases requires a deep understanding of the underlying biochemical and biophysical processes. To this end, it is crucial to characterize and visualize biological processes and biomolecular functions at the tissular, cellular, and macromolecular levels. In this regard, a number of bioassays and diagnostic methods (including PCR analysis, flow cytometry, fluorescence spectroscopy, microscopy, etc.) utilize organic dyes as molecular probes. Understanding the interactions between small organic chromophores and macromolecules has become essential for designing the advanced molecular probes capable of operating within living cells and in vivo. Consequently, there is a constantly growing interest in the acquisition and successful application of novel selective biomolecular sensors. Among a variety of fluorescent probes currently used for biomedical and biochemical studies, significant attention is devoted to cyanine dyes possessing advantageous properties upon their complexation with biomolecules, particularly nucleic acids, since DNA serves as the main target for drugs in the treatment of many pathologies. The representatives of the monomethine [38], trimethine [39], pentamethine [40], and heptamethine [41] families were experimentally tested and recommended as effective molecular probes for DNA detection and characterization. However, the mechanism of their interaction with DNA needs to be clarified. Therefore, we selected the most effective DNA probes with different lengths of polymethine bridges in their structure to uncover the main determinants governing the strong complexation of these dyes with DNA. More specifically, the molecular docking technique was used to investigate the interactions and the structural factors responsible for the DNA complexation of one representative of monomethines (AK12-17), three trimethines (AK3-1, AK3-3, AK3-5), three pentamethines (AK5-1, AK5-3, AK5-9) and one heptamethine dye (AK7-6).

Initially, the "blind docking" calculation was performed using the maximally accessible dimensional grid in the Autodock software, allowing it to cover the full length of DNA and explore all possible binding sites. Schematic representations of the energetically most favorable dye complexes with double-stranded DNA are given in Figure 2.

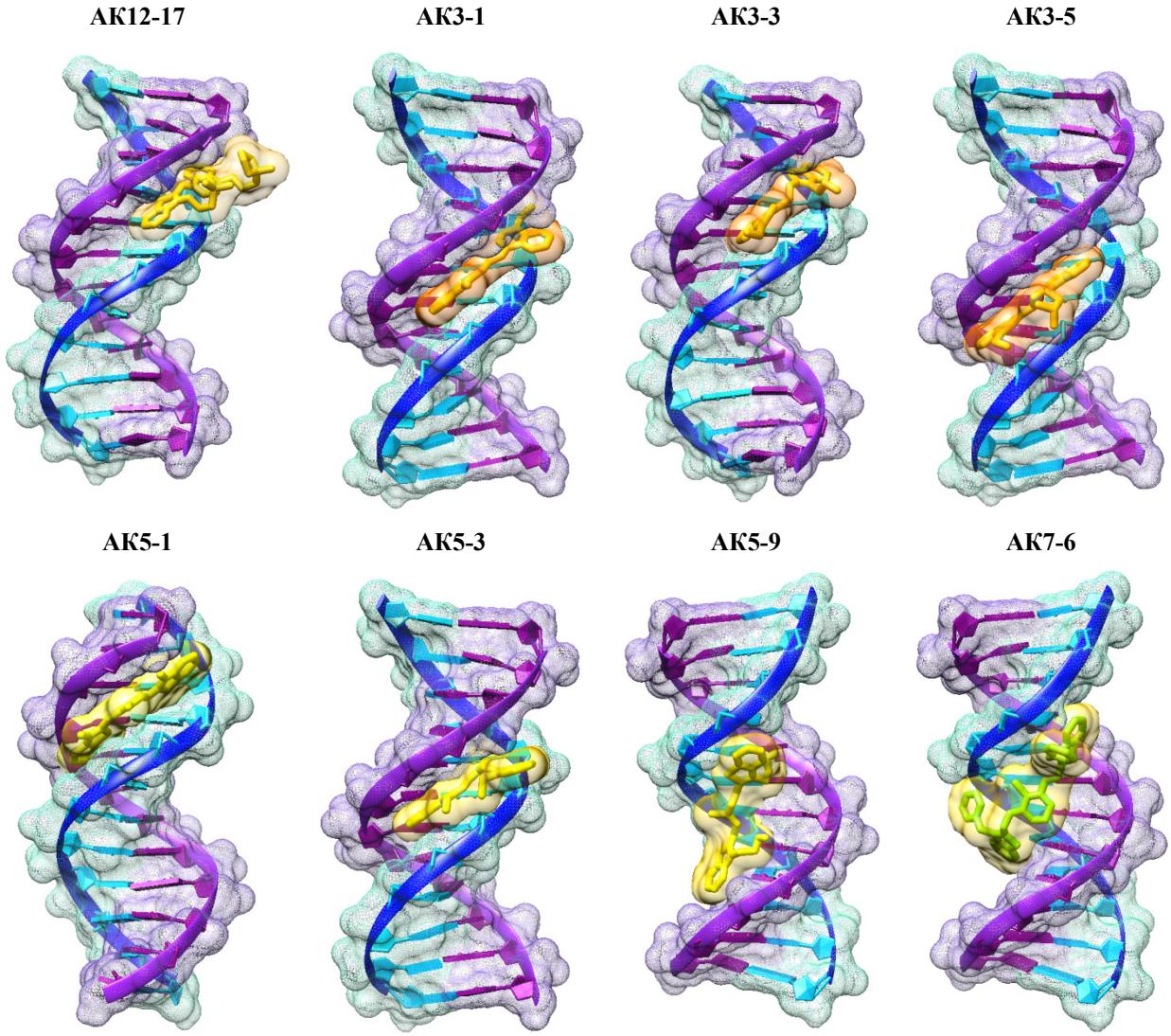

Figure 2. Schematic representation of the most energetically favorable dye-DNA complexes

Accumulating evidence suggests that cyanine dyes could interact with DNA through three primary binding modes: i) intercalation between adjacent base pairs, ii) groove binding, and electrostatic interaction of positively charged dye molecules with the phosphate backbone. The specific molecular mechanism by which cyanine dyes form complexes with nucleic acids relies heavily on the structural and physicochemical properties of the fluorophore (its planarity, conformational flexibility, etc.) as well as on the nucleic acid sequence and the dye-to-phosphate ratio. The molecular docking results indicate that both the minor and major DNA grooves may represent the sites for the dye binding. However, the minor groove is a more energetically favorable location for all cyanines under study except AK5-9 and AK7-6, for which the major grove binding was identified. It seems that significantly extended structure and less hydrophilicity of AK5-9 and AK7-6 make unfavorable their binding to the minor groove of the DNA [42]. The free energy binding score for the most energetically favorable docking poses of the selected compounds was found to rise in the order AK3-1 (-9,73 kcal/mol) → AK5-1 (-9,69 kcal/mol) → AK3-5 (-9,53 kcal/mol) → AK5-3 (-8,79 kcal/mol) → AK12-17 (-7,0 kcal/mol) → AK7-6 (-5,91 kcal/mol) → AK3-3 (-5,03 kcal/mol) → AK5-9 (-4,4 kcal/mol).

At the next step, the lowest binding energy conformers from the "blind docking" for each dye were selected and further used for the targeted docking with the grid spacing 0.375 A and the grid size 37 Å, 48 Å, and 50 Å along X, Y, and Z axes, respectively. Presented in Figure 3 and Table 1 are the results of the analysis of the most energetically favorable dye-DNA complexes obtained after the "targeted docking" in AutoDock after their characterization in the Discovery Studio. These data indicate that the dye association with DNA is predominantly driven by the hydrophobic interactions (Pi-Pi T-Shaped, Pi-alkyl) and van der Waals interactions for all dyes under study. More specifically, the dye binding to the minor groove was governed by the hydrophobic contacts and the van der Waals interactions preferably with the nucleotide residues C9A, G10A (except

AK3-1, AK3-5), A17B (except AK3-5, AK5-3) and A18B. The main nucleotide residues involved in the association of cyanine dyes AK5-9 and AK7-6 with DNA major groove were C16B, A17B, A18B, C3A, G4A, A5A and A6A. Likewise, the impact of the hydrophobic and van der Waals contacts was found to differ significantly between various dyes. Particularly, the docking results indicate that trimethine cyanine dyes form more van der Waals interactions in comparison with the monomethines and pentamethines. The lowest affinity of AK5-9 for the DNA major groove can be explained by the lower contribution (compared to those that observed for the cyanines associating with the minor groove) of van der Waals interactions. Indeed, the comparison of the intermolecular contacts formed between AK5-9 or AK3-1 and double-stranded DNA (the probe that has the highest affinity for DNA) indicates the higher value of van der Waals interactions with DNA for the latter one.

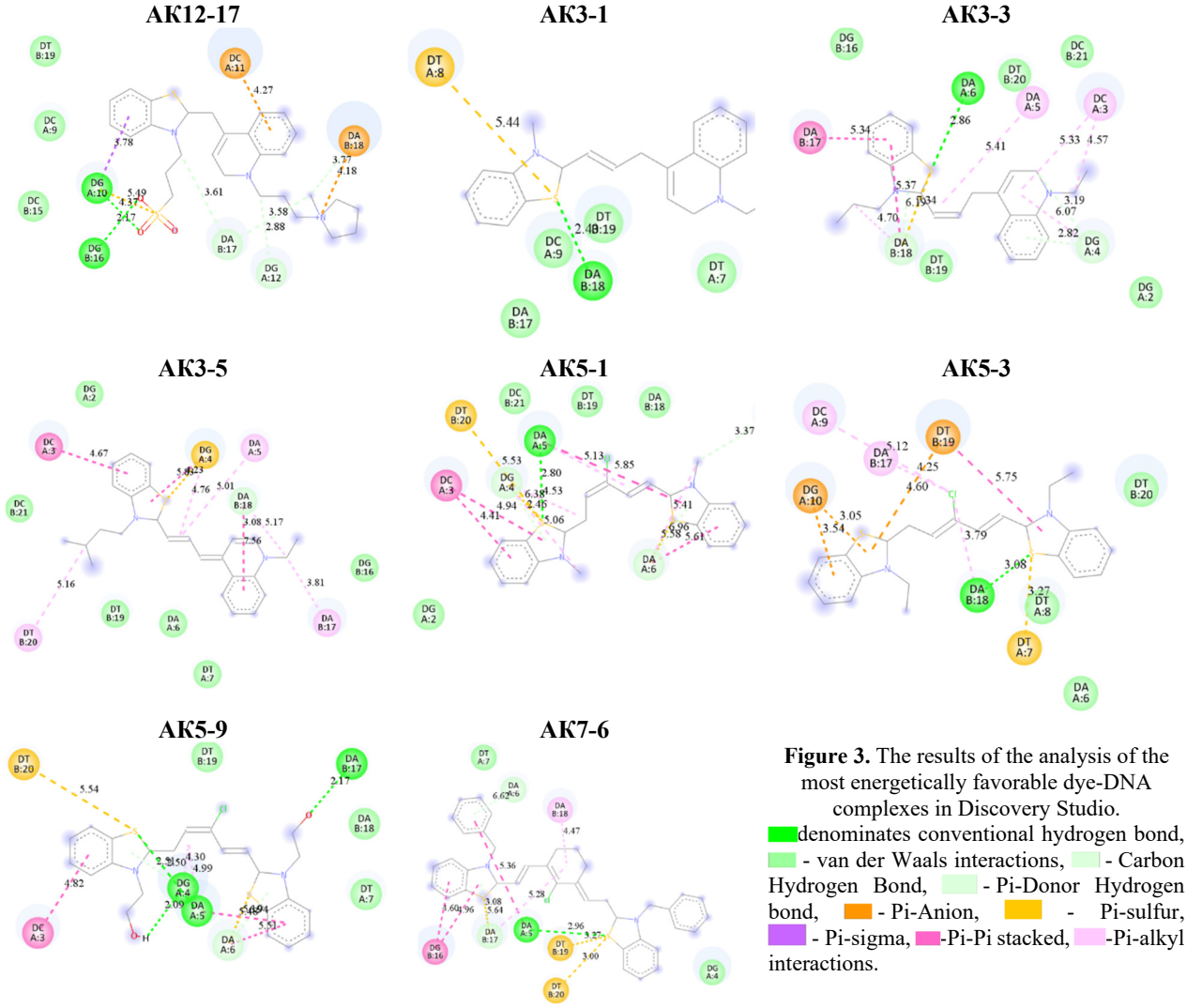

Figure 3. The results of the analysis of the most energetically favorable dye-DNA complexes in Discovery Studio. denominates conventional hydrogen bond, - van der Waals interactions, - Carbon Hydrogen Bond, - Pi-Donor Hydrogen bond, - Pi-Anion, - Pi-sulfur, - Pi-sigma, -Pi-Pi stacked, -Pi-alkyl interactions.

The obtained docking results indicate that the dye-DNA complexes are additionally stabilized by the hydrogen bonds (light green color in Figure 3). More specifically, the hydrogen bonds were formed predominantly with adenine (all dyes under study except AK3-5) and guanine (AK12-17) residues. Notably, all examined dyes (except AK3-1, AK3-5 and AK5-3) possess affinity to adenine and cytosine residues, whereas AK3-1, AK3-5 and AK5-3 also interact with thymine residues of the double-stranded DNA.

Table 1. The parameters of the dye-DNA complexation obtained by the "targeted docking" in AutoDock

Dye	Interactions and DNA residues.
AK12-17	Carbon hydrogen bond (DA, B:18, DA, B:17, DG, A:12), Pi-Alkyl (DC, A:11, DA, B:18), conventional hydrogen bond (DG, A:10, DG, B:16), van der Waals (DT, B:19; DC, A9; DC, B15)
AK3-1	Conventional hydrogen bond (DA, B:18), Pi-Sulfur (*DT, A:8),* van der Waals (DT, B19; DT, A7; DC, A9; DA, B17*)*
AK3-3	Pi-Alkyl (DA, B:18, DG, A:4, DC, A:3, DC, A:5, DC, A:6), Pi-Pi T-shaped (DA, B:18, DA, B:17), Pi-Donor Hydrogen Bond (DA, B:18, DG, A:4), conventional hydrogen bond (DA, A:6), van der Waals (DG, B16; DT, B20; DC, B21; DT, B19; DG, A2).

Dye	Interactions and DNA residues.
AK3-5	Pi-Alkyl (DA, B:18, DT, B:20, DA, B:17, DA, A:5, DG, A:4), Pi-Pi T-shaped (DG, A:4,), Pi-Sulfur (DG, A:4), van der Waals (DG, A2; DC, B21; DA, B18; DT, B19; DA, A6; DT, A7; DG, B16).
AK5-1	Pi-Donor Hydrogen Bond (DG, A:4, DA, A:6, DT, A:7), Pi-Alkyl (DG, A:4, DG, A:6), Pi-Pi T-shaped (DA, A:4, DA, A:6, DC, A:3), van der Waals (DC, B21; DT, B19; DA, B18; DG, A2)
AK5-3	Pi-Anion (DG, A:10, DT, B:19), Pi-Pi Stacked (DT, B:19), Pi- Alkyl (DC, A:9, DA, B:17, DA, B:18), Pi- Sulfur (DT, A:7), van der Waals (DT, B20; DT, A8; DA, A6), Conventional hydrogen bond (DA, B:18)
AK5-9	Conventional hydrogen bond (DA, B:17, DG, A:4), Pi- Donor Hydrogen bond (DG, A:4, DA, A:6), Pi- Alkyl (DG, A:4, DA, A:5), Pi-Pi T-shaped (DA, A:5, DA, A:6, DC, A:3), Pi-sulfur (DT, B:20), van der Waals (DT, B:19; DA, B18; DT, A7)
AK7-6	Pi- Alkyl (DA, B:17, DA, B:18), Pi-Pi T-shaped (DG, B:16), Pi-Sulfur (DA, B:17, DT, B:19, DT, B: 20), van der Waals (DT, A7; DG, A4)

CONCLUSIONS

To summarize, in the present study molecular docking technique was used to investigate the interactions between one representative of monomethines (AK12-17), three trimethines (AK3-1, AK3-3, AK3-5), three pentamethines (AK5-1, AK5-3, AK5-9) and one heptamethine (AK7-6) cyanine dyes and double-stranded DNA. It was found that all cyanines under study interact with DNA preferably via non-covalent groove binding mode with the lowest binding free energy ranging from −9.73 kcal/mol to -4,4 kcal/mol, depending on the dye structure. The obtained results indicate that the association of the dyes with double-stranded DNA is predominantly driven by the hydrophobic and van der Waals interactions. These findings are expected to be useful for further application of cyanine dyes in DNA studies and designing the advanced molecular probes.

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ДОСЛІДЖЕННЯ ВЗАЄМОДІЇ МІЖ ЦІАНІНОВИМИ БАРВНИКАМИ ТА ДНК МЕТОДОМ МОЛЕКУЛЯРНОГО ДОКІНГУ

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Серед різноманітних флуоресцентних зондів, які в даний час використовуються для біомедичних і біохімічних досліджень, значну увагу привертають ціанінові барвники, що характеризуються суттєвими перевагами при комплексоутворенні з біомолекулами, зокрема нуклеїновими кислотами. Враховуючи широкий спектр застосувань ціанінів при дослідженні ДНК, краще розуміння способів їх зв'язування та міжмолекулярних взаємодій, що регулюють утворення комплексу барвник-ДНК, сприяло б синтезу нових молекулярних зондів сімейства ціанінів з оптимізованими властивостями та призвело б до розробки нових стратегій на основі ціанінів для виявлення та характеризації нуклеїнових кислот. У даній роботі за допомогою молекулярного докінгу були досліджені механізми взаємодії одного представника монометинів (АК12-17), трьох триметинів (АК3-1, АК3-3, АК3-5), трьох пентаметинів (АК5-1, АК5-3, АК5-9) та одного гептаметинового (АК7-6) ціанінових барвників з додекамером B–DNA d(CGCGAATTCGCG)2 (PDB ID: 1BNA). Результати молекулярного докінгу вказують на те, що: i) усі досліджувані ціаніни (за винятком АК5-9 і АК7-6) утворюють найбільш стабільні комплекси із малою борозенкою дволанцюгової ДНК; ii) ціаніни АК5-9 і АК7-6 взаємодіють з великою борозенкою ДНК внаслідок їх більш розширеної структури і меншої гідрофільності у порівнянні з іншими барвниками; iii) зв'язування ціанінів регулюється гідрофобними та ван-дер-Ваальсовими взаємодіями із нуклеотидними залишками C9A, G10A (за винятком АК3-1, АК3-5), A17B (за винятком АК3-5, АК5-3) та A18B у малій борозенці ДНК та залишками великої борозенки C16B, A17B, A18B, C3A, G4A, A5A, A6A (АК5-9 та АК7-6); iv) усі досліджувані барвники (за винятком АК3-1, АК3-5 та АК5-39 мають спорідненість до залишків аденіну та цитозину, тоді як АК3-1, АК3-5 та АК5-3 також взаємодіють із залишками тиміну дволанцюгової ДНК.

Ключові слова: *ціанінові барвники; ДНК; взаємодії барвник-ДНК; молекулярний докінг*