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MOLECULAR DOCKING OF MONOMETHINE CYANINE DYES TO LYSOZYME AMYLOID FIBRILS[†]

Olga Zhytniakivska[a,*], Uliana Tarabara[a], Atanas Kurutos[b,c], Kateryna Vus[a], Valeriya Trusova[a], Galyna Gorbenko[a]

[a]*Department of Medical Physics and Biomedical Nanotechnologies, V.N. Karazin Kharkiv National University 4 Svobody Sq., Kharkiv, 61022, Ukraine*
[b]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences Acad. G. Bonchev str., bl. 9, 1113, Sofia, Bulgaria*
[c]*Department of Pharmaceutical and Applied Organic Chemistry, Faculty of Chemistry and Pharmacy Sofia University St. Kliment Ohridski, 1 blv. J. Bourchier, Sofia, 1164, Bulgaria*
**Corresponding Author: olga.zhytniakivska@karazin.ua*
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Protein aggregation into highly ordered supramolecular aggregates (amyloid fibrils) is the hallmark of many human diseases including the neurological disorders (Parkinson's, Alzheimer's and Huntington's diseases), type II diabetes, systemic amyloidosis, spongiform encephalopathies, etc. One of the simplest and effective methods for the identification and characterization of amyloid fibrils *in vitro* and the visualization of amyloid inclusions *in vivo* is based on the use of optical probes sensitive to the beta-pleated motifs. To design the new amyloid-sensing dyes or to optimize the use of the existing amyloid markers, it is crucial to have the sufficient knowledge of the fibril-dye binding interactions at the molecular and atomic levels. One of the most powerful tools capable of providing the atomic-level insights into the mechanisms of various types of biomolecular interactions is the molecular docking technique. In the present study, the molecular docking has been employed to investigate the interactions between the monomethine cyanine dyes and the lysozyme amyloid fibrils constructed from the K-peptide of lysozyme, GILQINSRW (the residues 54–62 of the wild-type protein). Using the AutoDOCK and the protein-ligand interaction profiler PLIP it was found that: i) the monomethines interact with the fibril surface (with the aromatic residues on the top of β-sheet or with the edges of the β-sheet); ii) the dye-fibril binding is governed by hydrophobic interactions, salt bridges and hydrogen bonds between the aliphatic substituents on the nitrogen atom of benzothiazole part of the dye molecules and amino acid side chains; iii) the variations in the cyanine structure and the lysozyme amyloid twisting do not exert significant effect on the binding mode of cyanines.
Keywords: Monomethine cyanine dyes, lysozyme amyloid fibrils, molecular docking.
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In the recent two decades the molecular docking technique have continuously attracted tremendous interest as a successful structure-based in silico method to gain atomic-level insights into the mechanisms of various types of biomolecular interactions [1-3], high-throughput drug screening [4-6] or understanding structure-activity relationships without knowing a priori the chemical structure of target modulators [7,8]. More specifically, the molecular docking has been used i) to develop antiviral drugs against the SARS-CoV-2 [9,10], inhibitors of hepatitis B [11] and HIV viruses [12]; ii) to determine a potential anticancer chemotherapeutic agents [13,14]; iii) for enzyme engineering [15]; iv) to assess the antithrombotic activity of the peptides [16]; v) to characterize the ligand-macromolecule of macromolecule-macromolecule interactions [17,18]; vi) to evaluate the ligand-receptor binding affinity [19, 20], to name only a few. In the above studies the molecular docking approach was used to pursue two basic goals: i) prediction of the ligand conformation along with its position and orientation within binding sites and ii) evaluation of the binding affinity [1]. One area where molecular docking appeared to be especially useful concerns the atomic-level characterization of the interactions between ligands and proteins in the amyloid state [21-24]. In this context, the detailed knowledge of the molecular interactions involved in the ligand-protein complexation made it possible to design the inhibitor compounds against amyloid aggregation [21,22] and to develop and improve the specific markers for spectroscopic detection of amyloid fibrils [23,24]. Notably, despite significant progress in the synthesis and characterization of the optical probes for detection of protein aggregates, the highly effective amyloid markers are still needed. Among the compounds possessing the excellent amyloid-sensing potential are cyanine dyes [25-33]. More specifically, cyanines have been applied: i) for detection of amyloid fibrils *in vitro* [25-27], ii) for *in vivo* fluorescent imaging of Aβ plaques in the Alzheimer's disease brain [28,29]; for monitoring the fibrillization kinetics of amyloid paired helical filaments [30]; for preventing and modulating protein fibrillization [31-33], to name only a few. Despite the numerous applications of the cyanine dyes in the amyloid research, the structural requirements for an ideal amyloid tracer remain unclear. Besides, the substituents in heterocyclic residues as well as the N-alkyl chain length have been found to modulate the amyloid-sensing ability of cyanine dyes [25,31].

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In the present work the molecular docking approach was used to investigate the atomistic details of the interactions between the novel monomethine cyanine dyes (Figure 1) and the model amyloid fibrils of lysozyme. The aim of the study was to determine both the potential binding sites of the cyanine dyes in the fibrillar lysozyme and to uncover the impact of the cyanine structure on the molecular interactions involved in the dye-protein complexation.

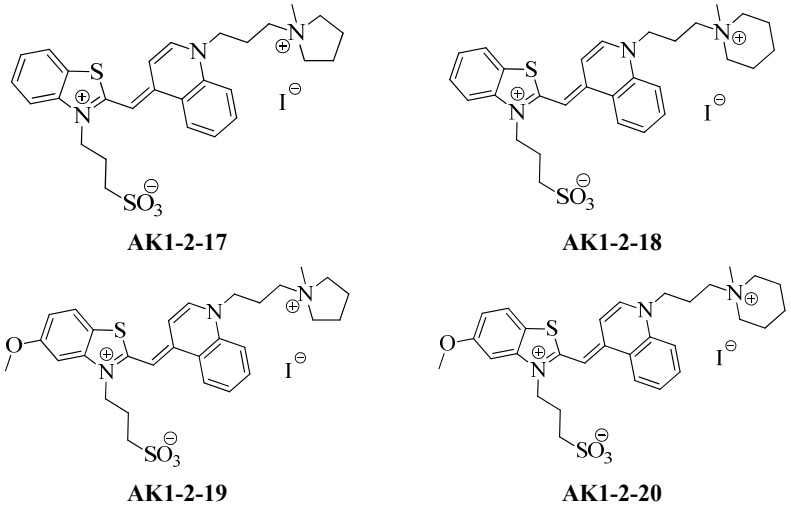

Figure 1. Structural formulas of monomethine cyanine dyes

METHODS

The model fibrils were built from the K-peptide of lysozyme, GILQINSRW (the residues 54–62 of the wild-type protein), using the CreateFibril tool as described previously [34]. More specifically, the lysozyme dimer was initially generated from the K-peptide monomer in the β-strand conformation using the PatchDock and Firedock tools [35,36]. Then, the CreateFibril software was used to generate the identical copies of the lysozyme dimer through stacking them side-by-side [37]. In such a manner, the lysozyme model fibrils with the length of 10 protein monomers were constructed. The distance between β-strands along the fibril axis and protofilament separation perpendicular to fibril axis were set as 5 Å. While creating the lysozyme fibrillar structures, we varied the rotation angle of monomers along the fibril axis from 0 to 20° degrees. In such a manner, five lysozyme fibrillar structures were created with the twisting angle 0°, 5°, 10°, 15° and 20°, referred to here as LzF-0, LzF-5, LzF-10, LzF-15, and LzF-20, respectively.

To define the most energetically favorable binding sites for the examined monomethine cyanine dyes on the firbrillar lysozyme, the molecular docking studies were performed using the AutoDock (version 4.2) incorporated in the PyRx software (version 0.8) [38]. AutoDock belongs to the non-commercial docking programs that implement a stochastic Lamarckian genetic algorithm for computing ligand conformations [38]. The thermodynamic stability of the ligand-receptor complexes was achieved by minimization of the scoring function which is based on the AMBER force field including van der Waals, hydrogen bonding, electrostatic interactions, conformational entropy and desolvation terms [38]. The AutoDock approach assumes the flexible ligand while the receptor is kept rigid during the docking procedure. The dye structures were built in MarvinSketch (version 18.10.0) and optimized in Avogadro (version 1.1.0) [39,40]. The docking poses were visualized with the UCSF Chimera software (version 1.14) [41]. To characterize the nature of the dye-protein interactions the protein-ligand interaction profiler PLIP (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) was used [42].

RESULTS AND DISCUSSION

Amyloid fibrils, the cross-β-sheet structures with β-strands orienting perpendicularly to the fibril long axis and β-sheets propagating in its direction, are known to provide several binding sites for small molecules (drugs, dyes, etc) [43,44]. These binding sites are located in the channels formed by the amino acid side chains of β-strands; exposed grooves on the β-sheet surface and the ends of the extended β-sheet [43,44]. At the first step of the study, to identify the monomethine-protein binding sites, as well as the nature of interactions involved in the dye complexation with the lysozyme fibrils, the AutoDock tool was used. The widely accepted model of amyloid structure assumes that the stacked pleated β-sheets are twisted in such a way that a repeating unit of 24 β-strands constitutes a full helical turn around the fibril axis [45] representing the twist of 15° between the neighboring β-strands [45]. Besides, assuming the heterogeneous nature of amyloid fibrils and the dye ability to display the different binding modes depending on the amyloid fibril structure [46,47], the molecular docking studies were performed using the lysozyme fibrils created with the twisting angles 0°, 5°, 10°, 15° and 20°. The energetically most favourable dye complexes with the fibrillar lysozyme structures are presented in Fig. 1, indicating that all cyanine dyes under study are capable of forming the stable complexes with the lysozyme fibrils.

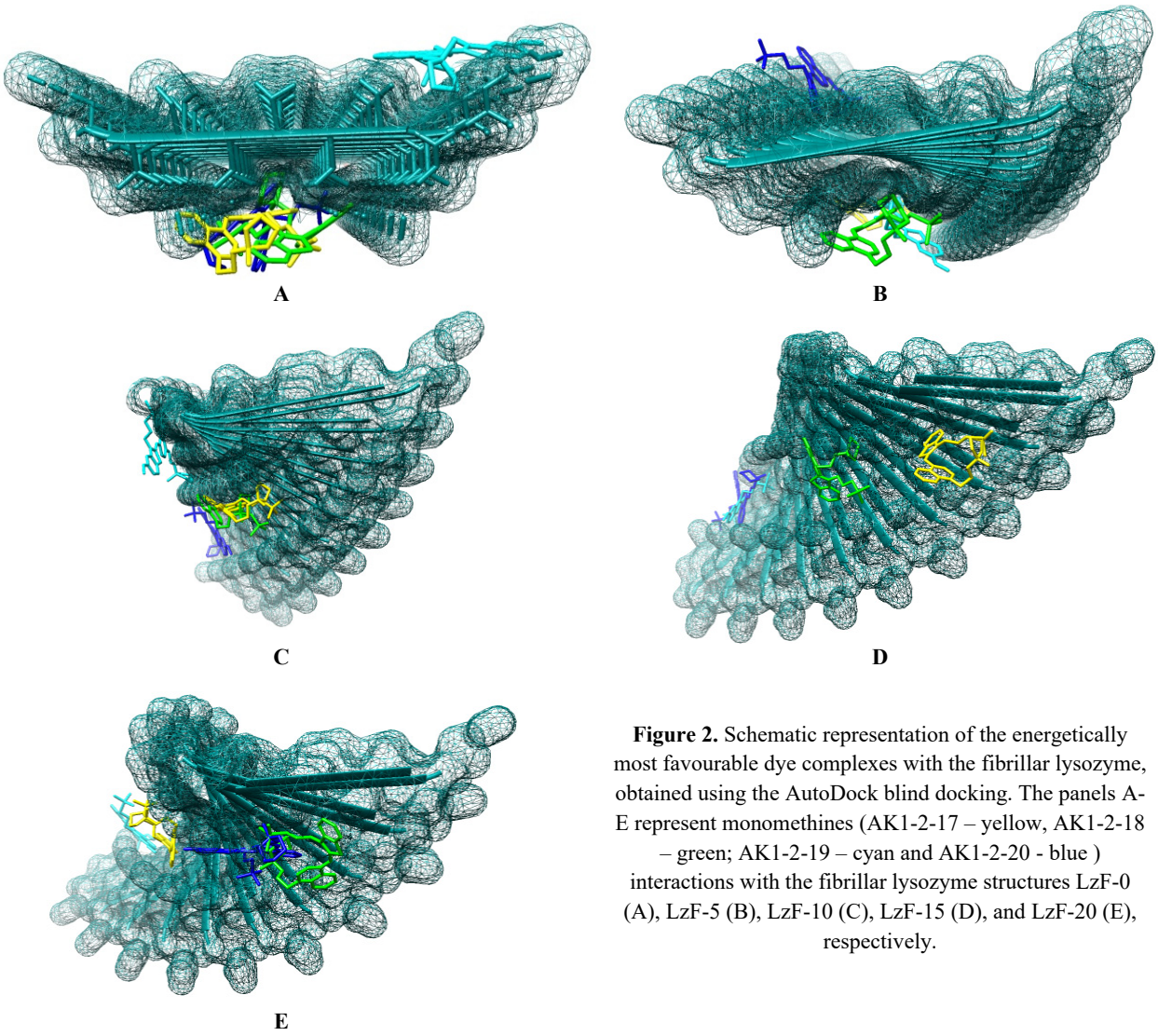

Figure 2. Schematic representation of the energetically most favourable dye complexes with the fibrillar lysozyme, obtained using the AutoDock blind docking. The panels A-E represent monomethines (AK1-2-17 – yellow, AK1-2-18 – green; AK1-2-19 – cyan and AK1-2-20 - blue) interactions with the fibrillar lysozyme structures LzF-0 (A), LzF-5 (B), LzF-10 (C), LzF-15 (D), and LzF-20 (E), respectively.

To characterize the nature of the interactions stabilizing the dye-fibril complex, the protein-ligand interaction profiler PLIP (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) was used [42]. It is well- known that the binding of specific probes to amyloid fibrils is governed by various types of intermolecular interactions among which hydrophobic and electrostatic interactions are the main contributors [31,43,46]. The examined monomethine dyes consist of large hydrophobic groups with a cationic charge. Therefore, it might be expected that these dyes interact with the lysozyme amyloid fibril predominantly via hydrophobic interactions. The above assumption was made based on the fact, that the lysozyme amyloid fibrils which were created from the K-peptide of lysozyme (GILQINSRW), contain only the positively charged amino acid residues. For this reason, electrostatic interactions cannot account for the anchoring of fluorophore molecule on the lysozyme fibril surface during the dye-protein complexation. Figure 3 represents the most favorable modes of interactions between the monomethine cyanine dyes and lysozyme amyloid fibrils obtained using the PLIP.

The results obtained with the PLIP server indicate that the dye association with amyloid fibrils LzF-15 is predominantly driven by the hydrophobic dye–protein interactions (dashed grey lines in the Figure 3). More specifically, the monomethine dye AK1-2-17 tends to form the hydrophobic contacts with Asn 16 B, Arg 18 B, Gln 23 C, Asn 25 C, Gln 32 D, Asn 34 D, whereas the AK1-2-18 probe interacts with Asn 52 F, Arg 54 F, Ile 57 G, Gln 59 G, Arg 72 H, Asn 79 I amino acid residues. The binding of the cyanine AK1-2-19 is governed predominantly by hydrophobic interactions between the dye molecule and the lysozyme residues Asn 142 P. Arg 114 P, Gln 149 Q, Asn 151 Q, Arg 153 Q, Gln 158 R, Asn 160 R, Asn 169 S, while the binding of the AK1-2-20 dye is characterized by the hydrophobic contacts with Arg 126 N, Gln 140 P, Asn 142 P, Arg 144 P, Asn 151 Q and Arg 153 Q. The binding affinity for the docked poses was equal to -14.37 kcal/mol (AK1-2-17), -22.16 kcal/mol (AK1-2-18), -20.58 kcal/mol (AK1-2-19) and 17,97 kcal/mol (AK1-2-20). The dye-LzF-15 complexes are additionally stabilized by the hydrogen bonds (blue solid lines in Figure 3) and salt bridges (orange dashed lines). More specifically, the hydrogen bonds were observed between the aliphatic substituents on the nitrogen atom of benzothiazole part of the dye molecules and Gln 14 B (AK1-2-17), Gln 68 N (AK1-2-18), Ser 125 N (AK1-2-19) and Gln 158 R (AK1-2-20) of the lysozyme amyloid fibrils. Moreover, it was found

that the cyanine dyes bearing the methylpyrrolidin group in the quinoline fragment (AK1-2-17, AK1-2-19) form the salt bridges between sulfonic acid in their structure and Arg 27 and Arg 126 amino acid residues, respectively.

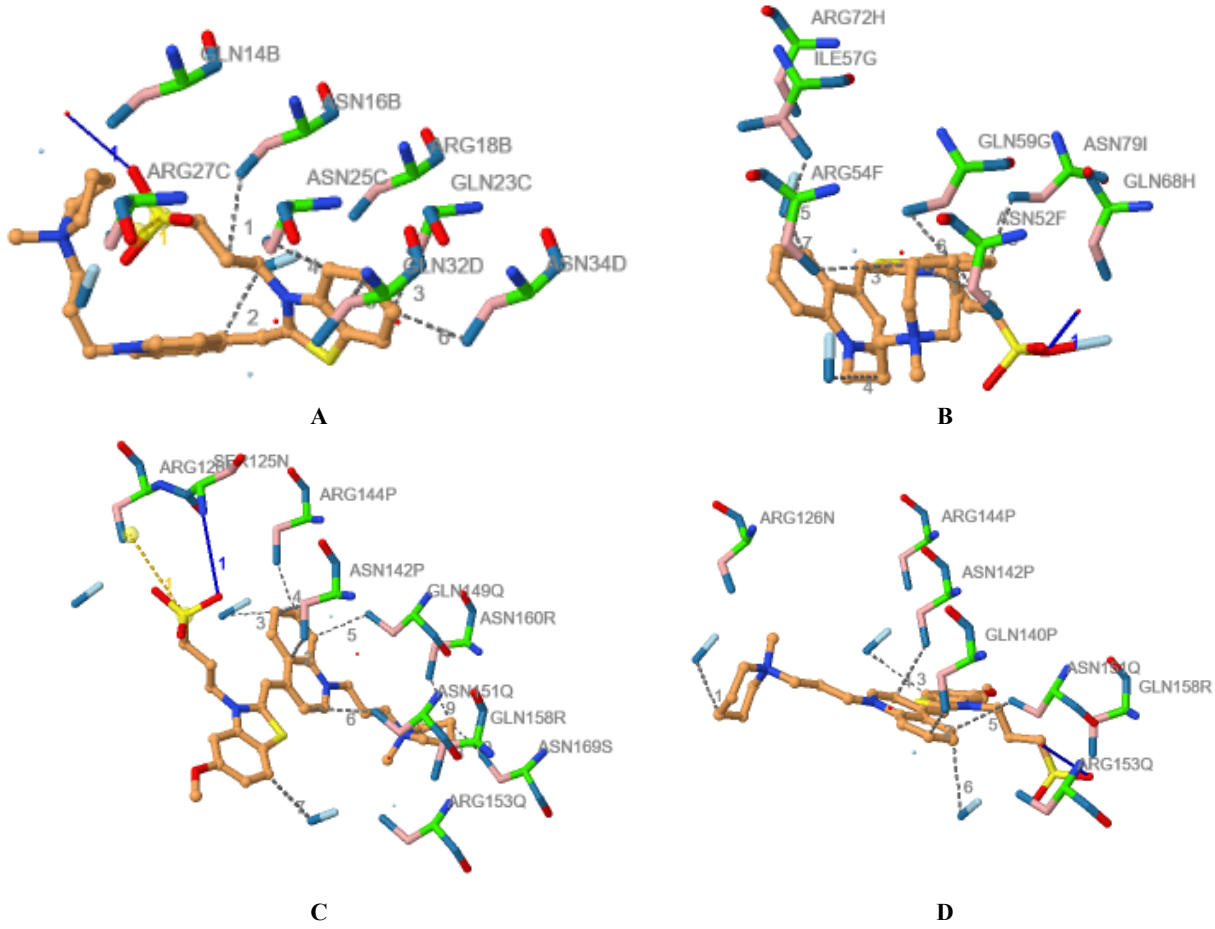

Figure 3. The binding of monomethines (AK1-2-17 – A, AK1-2-18 – B; AK1-2-19 – C and AK1-2-20 - D) to the fibrillar lysozyme analyzed by PLIP. The grey dashed lines represent the hydrophobic interactions between the dye molecules and amino acid residues, while the blue solid and orange dashed lines display the hydrogen bonds and salt bridges, respectively.

Notably, the differences in the cyanine structures as well as in the twisting of the lysozyme fibrils (Table 1) did not significantly affect the mode of cyanine binding. As can be seen in the Table 1, the investigated cyanine dyes interact with the fibril surface (with the aromatic residues on the top of β-sheet or with the edges of the β-sheet). The variation in the cyanine structure and the twisting of amyloid fibrils used for the docking led to the changes in the surrounding amino acid residues involved in the dye-protein complexation, whereas the binding energies remain almost unchanged. Besides, in all docking dye-protein systems we did not observe the insertion of the cyanine dyes into the fibril groove. The above binding mode is the most preferable for the ideal amyloid tracer [23, 25, 43, 46]. Specifically, the highest amyloid-sensing potential was observed for the probes, capable of associating with the superficial grooves of amyloid fibrils [23, 25, 43, 46].

Table 1. The parameters of the dye-fibril complexation predicted by PLIP.

Lysozyme fibril	Hydrophobic interactions	Hydrogen bonds	Salt bridges	Global energy, kcal/mol
AK1-2-17				
LzF-0	Gln 113 , Gln 122 , Asn 124, Arg 126 , Asn 133 , Asn 142	Gln 140	Gln140 - Sulfonicacid	-26.93
LzF-5	Gln 32, Gln 41, Asn 43, Arg 45, Gln 50, Asn 52, Arg 63	Gln 41		-18.42
LzF-10	Gln 95, Asn 97, Gln 104, Gln 113, Arg 117, Gln 122, Asn 124	Gln 95, Ser 107, Gln 113	Arg 108 - Sulfonicacid	-17.89
LzF-15	Asn 16, Arg 18, Gln 23, Asn 25, Gln 32, Asn 34	Gln 14	Arg 27 - Sulfonicacid	-14.37
LzF-20	Asn 88, Arg 90, Asn 97, Arg 99, Asn 106, Asn 115		-	-20.58

AK1-2-18				
LzF-0	Gln 113, Gln 140, Asn 142, Arg 144, Gln 149, Asn 151			-21.03
LzF-5	Gln 113, Asn 115, Gln 131, Arg 135, Gln 140, Asn 142	Gln 113, Gln 131		-22.19
LzF-10	Gln 77, Asn 79, Asn 88, Gln 95, Asn 97, Arg 99, Gln 104, Asn 106		Arg 90 - Sulfonicacid	-24.25
LzF-15	Asn 52 F, Arg 54 F, Ile 57 G, Gln 59 G, Arg 72 H, Asn 79 I	Gln 68		-22.16
LzF-20	Gln 5, Asn 7, Gln 14, Asn 16, Gln 23, Asn 25, Arg 27, Gln 32, Asn 34	Ser 17	Arg 18 - Sulfonicacid	-18.24
AK1-2-19				
LzF-0	Gln 5, Asn 7, Gln 14, Asn 25, Arg 27	Gln 32, Gln 50		-26.62
LzF-5	Asn 52, Asn 61, Gln 68, Asn 70, Arg 72, Asn 79, Agr 81		Arg 108- Sulfonicacid	-20.91
LzF-10	Arg 72, Gln 77, Gln 86, Asn 88, Asn 97, Arg 117 M	Trp 118, Gly 119	Gln 68 - Sulfonicacid	-16.55
LzF-15	Asn 142. Arg 114, Gln 149, Asn 151, Arg 153, Gln 158, Asn 160, Asn 169	Ser 125	Arg 126 - Sulfonicacid	-20.58
LzF-20	Asn 133, Asn 151, Arg 153			-16.94
AK1-2-20				
LzF-0	Asn 79, Arg 81, Gln 86, Asn 88, Asn 97	Gln 68		-18.16
LzF-5	Asn 61, Arg 63, Gln 68, Asn 70, Asn 79, Arg 81	Gln 50	Arg 54- Sulfonic acid	-20.29
LzF-10	Asn 34 D, Arg 36 D, Gln 41 E, Gln 50 F, Asn 52 F, Arg 63 G	GLn 59		-17.16
LzF-15	Arg 126, Gln 140, Asn 142, Arg 144, Asn 151, Arg 153	Gln 158		-17.97
LzF-20	Asn 16, Arg 18, Gln 23, Gln 32, Asn 34, Arg 36, Asn 43, Arg 45	Gln 41, Gln 50	Arg 63- Sulfonic acid	-19.16

In this context, it should be noted that insertion of many cyanine dyes into fibril grooves can also be driven by electrostatic (along with hydrophobic, H-bonds, π-stacking) dye-protein interactions [24, 31, 46]. However, the amyloid fibrils from the K-peptide of lysozyme (GILQINSRW) contain only the positively charged amino acid residues, while the dyes under study are also cationic in nature. Therefore, we expect that significant variations in the docking results may appear using amyloid fibrils created with other amino-acid sequences. Overall, the docking results presented here can be regarded as a starting point for elucidating the nature of cyanine-fibril binding that is important for the development and optimization of the fluorescent probes for amyloid fibril detection.

CONCLUSIONS

To summarize, in the present study the molecular docking technique was used to investigate the interactions between the novel monomethine cyanine dyes and the model amyloid fibrils of lysozyme. Using the AutoDOCK and the protein-ligand interaction profiler PLIP it was found that: i) the monomethines do not insert in the fibril groves and interact with the fibril surface; ii) the dye-fibril binding is governed by the hydrophobic interactions, salt bridges and hydrogen bonds between the aliphatic substituents on the nitrogen atom of benzothiazole part of the dye molecules and боковими залишками амінокислот; iii) the variations in the cyanine structure and in the lysozyme fibril twisting do not significantly influence the binding mode of cyanines under study. Overall, the obtained results can be useful for extending the application of cyanine dyes to amyloid fibril sensing.

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ORCID IDs

Olga Zhytniakivska, https://orcid.org/0000-0002-2068-5823; **Uliana Tarabara,** https://orcid.org/0000-0002-7677-0779
Atanas Kurutos, https://orcid.org/0000-0002-2068-5823; **Kateryna Vus,** https://orcid.org/0000-0003-4738-4016
Valeriya Trusova, https://orcid.org/0000-0002-7087-071X; **Galyna Gorbenko,** https://orcid.org/0000-0002-0954-5053

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МОЛЕКУЛЯРНИЙ ДОКІНГ МОНОМЕТИНОВИХ ЦІАНІНОВИХ БАРВНИКІВ З АМІЛОЇДНИМИ ФІБРИЛАМИ ЛІЗОЦИМУ

О. Житняківська[a], У. Тарабара[a], А. Курутос[b,c], К. Вус[a], В. Трусова[a], Г. Горбенко[a]

[a]Кафедра медичної фізики та біомедичних нанотехнологій, Харківський національний університет імені В.Н. Каразіна м. Свободи 4, Харків, 61022, Україна

[b]Інститут органічної хімії та фітохімії Академії Наук Болгарії, вул. Акад. Бончева, 9, 1113, Софія, Болгарія

[c]Кафедра фармацевтичної та прикладної органічної хімії, Факультет хімії та фармації Софійський університет імені Св. Климента Охридського, 1164, Софія, Болгарія

Агрегація білків у високовпорядковані супрамолекулярні агрегати є ознакою багатьох захворювань людини, включаючи неврологічні розлади (хвороби Паркінсона, Альцгеймера та Хантінгтона), діабет II типу, системний амілоїдоз, енцефалопатію, тощо. Самий простий і ефективний метод детектування та характеризації амілоїдних фібрил in vitro та візуалізації амілоїдних включень in vivo базується на використанні зондів, чутливих до бета-складчастих мотивів. Для створення нових амілоїд-специфічних барвників і оптимізації уже існуючих сполук, важливо розуміти на молекулярному та атомному рівнях механізми їх взаємодії у центрах зв'язування. Одним із особливо потужних методів, здатних забезпечити розуміння механізмів різних типів біомолекулярних взаємодій на атомному рівні, є метод молекулярного докінгу. У даній роботі метод молекулярного докінгу використовувався для дослідження взаємодії між монометиновими ціаніновими барвниками та модельними амілоїдними фібрилами, що були побудовані з K-пептиду лізоциму GILQINSRW (залишки 54–62 білка дикого типу). За допомогою програмного інтерфейсу AutoDOCK і профайлера білок-лігандної взаємодії PLIP встановлено: 1) монометини взаємодіють з поверхнею фібрили (з ароматичними залишками на вершині β-листа або з краями β-листа); ii) зв'язування барвників відбувається за рахунок гідрофобних взаємодій, сольових містків та водневих зв'язків між аліфатичними замісниками на атомі азоту бензотіазолової частини молекули барвника та амілоїдної фібрили лізоциму; iii) варіації в структурі ціанінів та в ступені скручування амілоїду лізоциму суттєво не впливають на характер взаємодії барвників з фібрилами.

Ключові слова: монометинові ціанінові зонди, амілоїдні фібрили лізоциму, молекулярний докінг