



(RESEARCH ARTICLE)



MOLECULAR DOCKING INVESTIGATION OF A DNA-RECOGNIZING MOLECULE AT THE KB DNA REGION

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International Journal of Science and Research Archive, 2026, 20(03), 968–979

Publication history: Received on 21 August 2026; revised on 27 September 2026; accepted on 29 September 2026

Article DOI: <https://doi.org/10.30574/ijrsra.2026.20.3.1835>

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ABSTRACT

Polyamide-based molecules have attracted considerable interest as sequence-recognizing agents that interact with biologically relevant DNA regions. In this study, we investigated the potential interaction of previously synthesized and characterized polyamide 6 (PA6) with the κB DNA region associated with the nuclear factor-κB (NF-κB) complex using molecular docking. The previously reported structural identity of PA6 was supported by spectroscopic and chromatographic characterization. We also evaluated the physicochemical and pharmacokinetic properties of PA6 using SwissADME.

We performed molecular docking against the crystallographic NF-κB–DNA complex (PDB ID: 1LE5), focusing the docking region on the central κB DNA sequence. The initial docking calculation generated 20 poses with predicted affinities ranging from -6.117 to -5.710 kcal mol⁻¹, with the highest-ranked pose at -6.117 kcal mol⁻¹. Several closely related poses showed RMSD values of approximately 2.29–2.67 Å, while alternative poses with similar docking scores displayed substantially different orientations. Detailed interaction analysis of the highest-ranked pose identified three conventional hydrogen bonds involving DA5, DA7, and DT8, together with additional contacts involving neighboring κB nucleotides. The interaction pattern was predominantly directed toward nucleobase atoms accessible from the major groove, supporting a major-groove-oriented recognition mode rather than a minor-groove binding mode.

To assess the robustness of the docking search, we performed an independent calculation using a different random seed. This calculation produced a best predicted affinity of -6.329 kcal mol⁻¹ and generated two hydrogen bonds involving DG3 and DC22. Although the corresponding top-ranked poses differed substantially in their overall orientation (cross-

run RMSD = 7.929 Å), both calculations localized PA6 within the κ B DNA region. They identified nucleobase-directed interactions in the same general sequence environment. Collectively, the results indicate that PA6 can adopt multiple favorable docking orientations within the κ B DNA region while retaining recurrent interactions with DNA bases. These findings provide structural insight into PA6's potential DNA-recognition properties and establish a computational basis for further experimental investigation of its interaction with κ B DNA.

Keywords: Polyamide 6; κ B DNA; NF- κ B; Molecular docking; DNA recognition; Hydrogen bonding; Major-groove interaction.

1 INTRODUCTION

Nuclear factor- κ B (NF- κ B) is a family of transcription factors that plays a central role in regulating immune responses, inflammation, cell survival, proliferation, and stress responses. The p50/p65 heterodimer is one of the best-characterized NF- κ B complexes and recognizes specific DNA sequences known as κ B elements. Dysregulated NF- κ B signaling has been associated with chronic inflammation and cancer, making the NF- κ B–DNA interface an important target for molecular and chemical investigation [1–6]. NF- κ B activity depends not only on the presence of the transcription factor but also on its ability to recognize specific κ B DNA sequences and form sequence-dependent interactions with the DNA duplex [7,8].

Structural studies have provided important insights into this recognition process. In particular, the crystal structure of the NF- κ B p50/p65 heterodimer bound to the interferon- β κ B site (PDB ID: 1LE5) provides a well-defined experimental model of NF- κ B–DNA recognition [9]. The structure demonstrates that NF- κ B establishes extensive interactions with the DNA duplex through a combination of base-specific and backbone contacts. Importantly, variations among κ B DNA sequences can influence the structure and interaction pattern of the resulting protein–DNA complex, suggesting that the DNA sequence itself contributes to the molecular recognition process [10,11].

DNA recognition by synthetic molecules has therefore attracted considerable interest as an alternative strategy for controlling transcriptional processes. The major and minor grooves of DNA provide chemically distinct surfaces with hydrogen-bond donors and acceptors that small molecules can exploit. Among the most successful DNA-recognition scaffolds are pyrrole–imidazole (Py–Im) polyamides, which were developed from the DNA-binding properties of natural products such as netropsin and distamycin A [12–15]. Appropriately arranged pyrrole and imidazole units can recognize specific DNA sequences through predictable interactions with Watson–Crick base pairs, providing a foundation for sequence-directed DNA recognition [16–18].

The potential biological applications of polyamides extend beyond simple DNA binding. Designed polyamides have been shown to interfere with transcription-factor recognition and to modulate gene expression by occupying specific regulatory DNA sequences [19–21]. Their ability to recognize DNA in more complex environments, including nucleosomal DNA, further supports their potential as chemical tools for studying and manipulating gene regulation [22]. Importantly, the interaction of a polyamide with DNA depends on its complete molecular architecture, including the identity and arrangement of heterocyclic units, linker structure, flexibility, and substituents [17,18,23].

Of particular relevance to the present study, pyrrole–imidazole polyamides have previously been investigated as inhibitors of NF- κ B DNA binding. Bremer and co-workers demonstrated that polyamides designed to recognize portions of an NF- κ B binding site could interfere with NF- κ B–DNA association. However, the effect depended on the precise DNA subsite the polyamide targeted [24]. This finding is particularly important because it shows that the biological consequences of polyamide recognition can depend strongly on the ligand's location and orientation on the DNA sequence. Thus, determining the interaction mode of an individual polyamide at a defined κ B site is an important step toward understanding its potential DNA-recognition behavior.

Polyamide 6 (PA6) investigated in the present work is a structurally distinct imidazole-containing polyamide previously synthesized and characterized by our group as NF-Im-Im- β -Dp. We prepared the compound by solid-phase synthesis and characterized it by ^1H NMR, ^{13}C NMR, and HPLC, with an analytical purity of approximately 96% [25]. The presence of multiple heteroatom-containing groups and a flexible molecular architecture makes PA6 a suitable candidate for investigating DNA recognition through molecular modeling. However, its actual interaction mode with a specific DNA sequence cannot be assumed solely from its classification as a polyamide.

In this study, we used molecular docking to investigate the potential interaction of PA6 with the κ B DNA region of the NF- κ B–DNA complex (PDB 1LE5). The docking analysis focused on the experimentally defined κ B sequence and evaluated the predicted binding orientations, docking affinities, structural clustering, hydrogen-bond interactions, and nucleotide-level contacts. We also performed an independent docking calculation with a different random seed to assess the robustness of ligand localization within the targeted DNA region. This approach aimed to determine whether PA6

could adopt favorable, recurrent orientations at the κ B site and to provide a structural hypothesis for its potential DNA-recognition mode. These computational observations are not intended to establish experimental binding affinity or NF- κ B inhibition, but to provide a molecular basis for subsequent experimental investigation of PA6–DNA interactions.

2 MATERIALS AND METHODS

2.1 Previously Synthesized DNA-Recognizing Molecule

We used polyamide 6 (PA6; NF-Im-Im- β -Dp), synthesized and characterized previously by our group, as the test molecule in the present computational investigation [25]. We characterized the synthesized compound by ^1H NMR and ^{13}C NMR spectroscopy, and evaluated its chromatographic purity by HPLC. The previously reported analytical data supported the structural identity of PA6 and indicated an HPLC purity of approximately 96%. The experimentally characterized structure was subsequently used as the basis for the computational investigation.

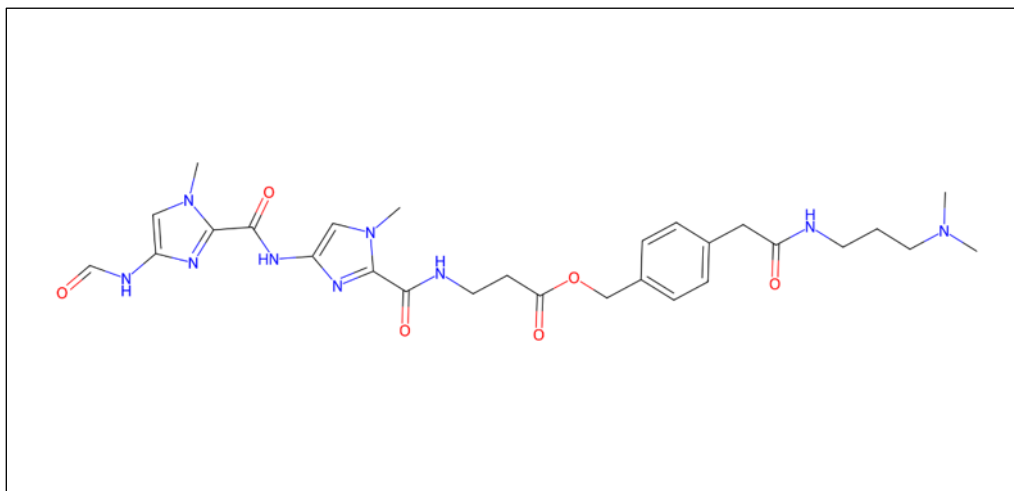


Figure 1: Chemical structure of the previously synthesized DNA-recognizing molecule (PA6; NF-Im-Im- β -Dp) investigated in the present study.

2.2 Ligand Preparation

The molecular structure of PA6 was converted into a three-dimensional structure and subjected to geometry minimization before docking. The minimized ligand was prepared using Open Babel and AutoDockTools (ADT). Hydrogen atoms and Gasteiger partial charges were assigned, and ADT defined rotatable bonds. The final minimized PA6 structure was saved in PDBQT format for molecular docking.

2.3 Preparation of the NF- κ B–DNA Structure

We obtained the crystallographic NF- κ B–DNA complex from the Protein Data Bank (PDB ID 1LE5). This structure contains the NF- κ B p50/p65 heterodimer bound to the interferon- β κ B DNA sequence. For this study, we isolated the DNA component (chains C and D) from the crystallographic complex. We removed solvent molecules and converted the resulting DNA structure to PDBQT format for docking.

We selected the central κ B region as the docking target. Based on the experimentally resolved DNA sequence, we used nucleotides C2–C11 (5'-GGGAAATTCC-3') and the corresponding complementary region D15–D24 to define the target region. The geometric center of these selected nucleotides was calculated as $x = 115.71$, $y = 26.60$, and $z = 9.25$ Å, which was subsequently used as the center of the docking search space.

2.4 Molecular Docking

Molecular docking was performed using AutoDock Vina version 1.2.7. We docked PA6 against the isolated κ B DNA region using the prepared DNA structure as the receptor. The docking box was centered at (115.71, 26.60, 9.25 Å) with dimensions of $30 \times 22 \times 22$ Å. We set the exhaustiveness parameter to 32 and generated up to 20 docking modes within an energy range of 4 kcal mol^{-1} .

We performed the initial docking calculation using random seed 12345. To assess the robustness of the docking search, a second independent calculation was performed using the same receptor, ligand, search space, and docking parameters but with random seed 67890.

Table 1: Molecular docking parameters used for PA6- κ B DNA docking.

Parameter	Setting
Docking software	AutoDock Vina 1.2.7
Receptor	1LE5 DNA chains C and D
Ligand	Minimized PA6
Center X	115.71 Å
Center Y	26.60 Å
Center Z	9.25 Å
Box size X	30 Å
Box size Y	22 Å
Box size Z	22 Å
Exhaustiveness	32
Number of modes	20
Energy range	4 kcal mol ⁻¹
First random seed	12345
Independent random seed	67890

2.5 Analysis of Docking Poses and Molecular Interactions

The generated docking poses were ranked by predicted Vina affinity. RMSD values were used to assess structural similarity between docking orientations and identify groups of closely related poses. We paid particular attention to the highest-ranked pose and to closely clustered poses with similar predicted affinities.

We analyzed intermolecular hydrogen bonds between PA6 and DNA nucleotides using ChimeraX version 1.12. We examined additional close contacts between the ligand and nucleotides within the κ B region to identify DNA bases and functional groups that may contribute to the predicted interaction. Protein–ligand contacts were also inspected in the intact NF- κ B–DNA complex to determine whether nearby protein residues were located around the docked PA6 orientation.

Two-dimensional interaction diagrams were generated using BIOVIA Discovery Studio Visualizer, while three-dimensional molecular representations and structural figures were prepared using ChimeraX and PyMOL.

2.6 Physicochemical and ADME Prediction

The physicochemical and pharmacokinetic properties of PA6 were evaluated using the SwissADME web platform. We recorded molecular weight, hydrogen-bond donor and acceptor counts, topological polar surface area, lipophilicity, aqueous-solubility estimates, gastrointestinal absorption, blood–brain barrier permeability, P-glycoprotein substrate prediction, and selected drug-likeness parameters.

The computational predictions were used for physicochemical characterization of PA6 and were not considered experimental measurements.

3 RESULTS AND DISCUSSION

3.1 Molecular Docking of Polyamide 6 with the κ B DNA Region

We performed molecular docking to investigate the potential recognition of Polyamide 6 (PA6) by the κ B DNA region of the NF- κ B complex. We used the DNA component of the crystallographic NF- κ B–DNA complex (PDB ID: 1LE5) as the docking receptor, with the search space centered on the experimentally defined κ B region. The docking calculation generated 20 possible PA6 orientations, with predicted affinities ranging from -6.117 to -5.710 kcal mol⁻¹ (Table 2).

The highest-ranked pose (Pose 1) exhibited a predicted affinity of -6.117 kcal mol⁻¹. Interestingly, Pose 2 displayed an almost identical predicted affinity of -6.111 kcal mol⁻¹, differing from Pose 1 by only 0.006 kcal mol⁻¹. Despite this small

difference in docking score, the RMSD between the two orientations was 12.75 Å, indicating substantially different conformations of PA6 on the DNA surface. Therefore, the docking score alone was not sufficient to select a unique binding mode.

Several other poses showed a combination of favorable predicted affinity and structural similarity to Pose 1. In particular, Poses 3–6 exhibited RMSD values of 2.29–2.67 Å, with predicted affinities between –5.989 and –5.877 kcal mol^{–1}. This cluster of structurally related poses suggests that the region occupied by Pose 1 represents a favorable interaction environment for PA6 rather than an isolated docking solution.

Table 2: Docking poses of PA6 at the κB DNA region generated using AutoDock Vina.

Pose	Predicted affinity (kcal mol ^{–1})	RMSD (Å)
1	–6.117	0.000
2	–6.111	12.750
3	–5.989	2.446
4	–5.927	2.422
5	–5.920	2.289
6	–5.877	2.674
7	–5.867	12.590
8	–5.864	2.552
9	–5.830	2.592
10	–5.794	2.428
11	–5.783	2.081
12	–5.779	2.651
13	–5.778	2.730
14	–5.773	2.493
15	–5.770	2.056
16	–5.739	3.190
17	–5.732	2.593
18	–5.728	3.481
19	–5.720	2.754
20	–5.710	2.281

The docking values should be regarded as predicted affinities rather than experimental binding constants. Nevertheless, the distribution of the top-ranked poses provides useful information about PA6's conformational adaptability on the DNA surface.

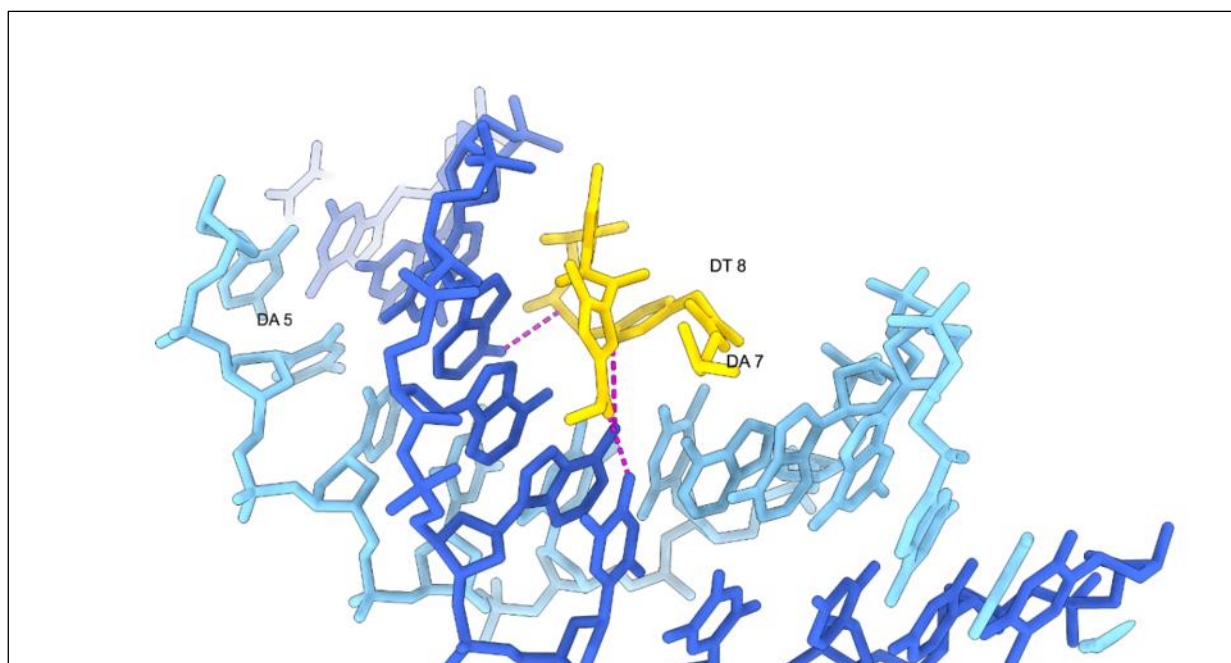


Figure 2: Overall three-dimensional localization of Polyamide 6 within the targeted κ B DNA region.

3.2 Detailed Interaction of PA6 with κ B DNA

Detailed analysis of the highest-ranked pose identified three conventional hydrogen bonds between PA6 and nucleotides within the targeted κ B region. These interactions involved DA5, DA7, and DT8 of the C DNA strand (Table 3).

The first hydrogen bond involved the N6 atom of DA5 and an oxygen atom of PA6, with a donor–acceptor distance of 3.175 Å. A second interaction involved the N6 atom of DA7 and a PA6 nitrogen atom at a distance of 3.626 Å. The third interaction involved a PA6 nitrogen atom and the O4 atom of DT8, with a donor–acceptor distance of 3.224 Å.

Table 3: Conventional hydrogen bonds identified in the highest-ranked PA6 docking pose.

DNA nucleotide	DNA atom	PA6 atom	D...A distance (Å)	Interaction
DA5 (C)	N6	O	3.175	Conventional H-bond
DA7 (C)	N6	N	3.626	Conventional H-bond
DT8 (C)	O4	N	3.224	Conventional H-bond

These interactions are particularly relevant because they involve nucleobase atoms rather than exclusively the phosphate backbone, suggesting that the predicted PA6 orientation is stabilized in part through direct recognition of the chemical features of the DNA bases.

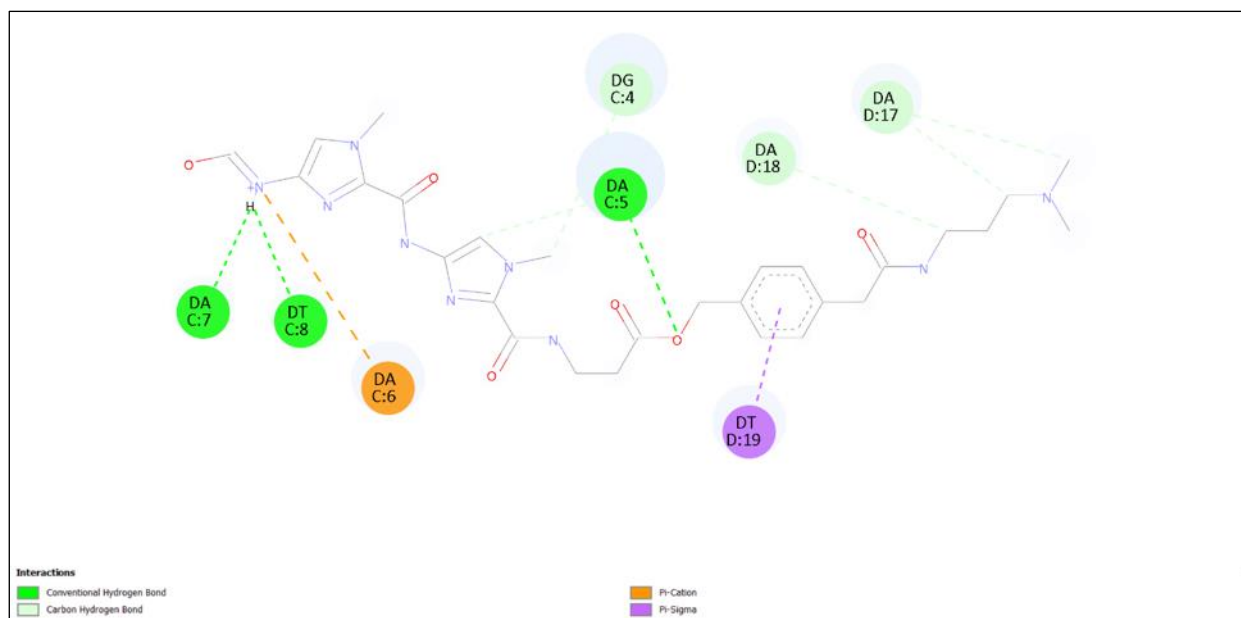


Figure 3: Two-dimensional interaction map of Polyamide 6 with the κ B DNA region, showing conventional hydrogen bonds and additional predicted interactions.

The two-dimensional interaction diagram in Figure 2 provides additional information beyond the conventional hydrogen bonds. Additional contacts involved DG4, DA6, DA17, DA18, and DT19, including carbon-hydrogen-bond-type interactions, a predicted π -cation interaction involving DA6, and a π -sigma interaction involving DT19. These interactions should be regarded as supporting contacts rather than being interpreted as equivalent to the three conventional hydrogen bonds. Nevertheless, their presence indicates that PA6 can interact simultaneously with several neighboring nucleotides.

3.3 Orientation of PA6 on the DNA Duplex

The three-dimensional representations in Figure 3 provide a clear structural view of the predicted PA6 orientation. The ligand is positioned close to the nucleobase-rich region containing DA5, DA7, and DT8, with its heteroatom-containing groups directed toward potential hydrogen-bonding sites on the DNA bases.

An interesting feature of the predicted complex is PA6's apparent major-groove-oriented arrangement. Classical pyrrole–imidazole polyamides are generally designed to recognize DNA through the minor groove, where specific arrangements of pyrrole and imidazole rings allow recognition of A·T and G·C base pairs.

The present docking result therefore does not simply reproduce the classical Py–Im recognition model. Instead, the structure of PA6 appears capable of adopting an alternative orientation in which its functional groups interact with nucleobase atoms accessible from the major-groove side. This finding is particularly interesting because PA6 contains two imidazole units together with additional flexible functional groups, allowing a broader range of conformational arrangements than a rigid classical polyamide.

However, the docking result should be described as a major-groove-oriented predicted pose, rather than experimental proof that PA6 is a major-groove binder. Experimental structural or biochemical studies would be required to establish the actual binding mode.

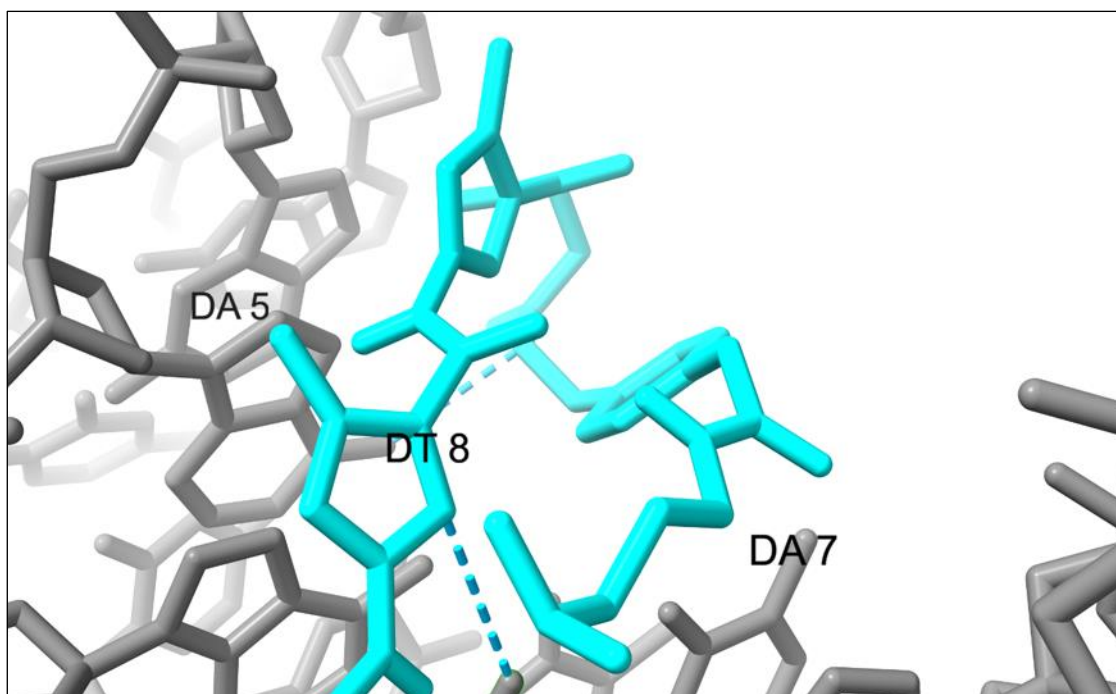


Figure 4: Close-up three-dimensional representation of the principal PA6–DNA interaction, highlighting DA5, DA7, and DT8.

3.4 Nucleotide-Level Contact Analysis

The contact analysis demonstrated that PA6 interacts with a relatively broad region of the DNA duplex. On the C strand, contacts were detected with DG4, DA5, DA6, DA7, and DT8, while contacts on the complementary D strand included DA17, DA18, and DT19.

Table 4: Representative nucleotide contacts observed for the highest-ranked PA6 pose.

Strand	Nucleotide	Representative atom(s)	Distance range (Å)
C	DG4	C8, N7	2.756, 3.467
C	DA5	C2' , OP2, C8, N6, N7	2.877 – 3.768
C	DA6	Base region	—
C	DA7	N6, N7	2.640–3.552
C	DT8	O4	3.224–3.270
D	DA17	N7	3.612–3.643
D	DA18	N6, N7	3.315–3.592
D	DT19	O4, C7	3.294–3.758

The contact pattern supports the view that the predicted interaction is not restricted to a single nucleotide. Instead, PA6 occupies an extended region of the DNA surface and establishes contacts with multiple neighboring bases.

Importantly, these observations demonstrate nucleotide-directed interaction within the selected κ B region, but they do not establish sequence selectivity on their own. Demonstrating true sequence selectivity would require comparison with one or more non- κ B DNA sequences under equivalent computational or experimental conditions.

3.5 PA6 within the NF- κ B–DNA Structural Environment

Although the primary docking receptor was the isolated DNA component, we subsequently examined the resulting PA6 pose within the intact NF- κ B–DNA complex. This analysis showed that PA6 is located in the structural environment formed by the NF- κ B p50/p65 heterodimer.

As shown in Figure 4, several protein residues are located around the PA6–DNA interaction region, including ARG246, GLN247, LYS218, LYS241, LYS272, GLN306, PRO189, and PRO243. These residues illustrate the structural proximity of the docked DNA region to the NF- κ B protein.

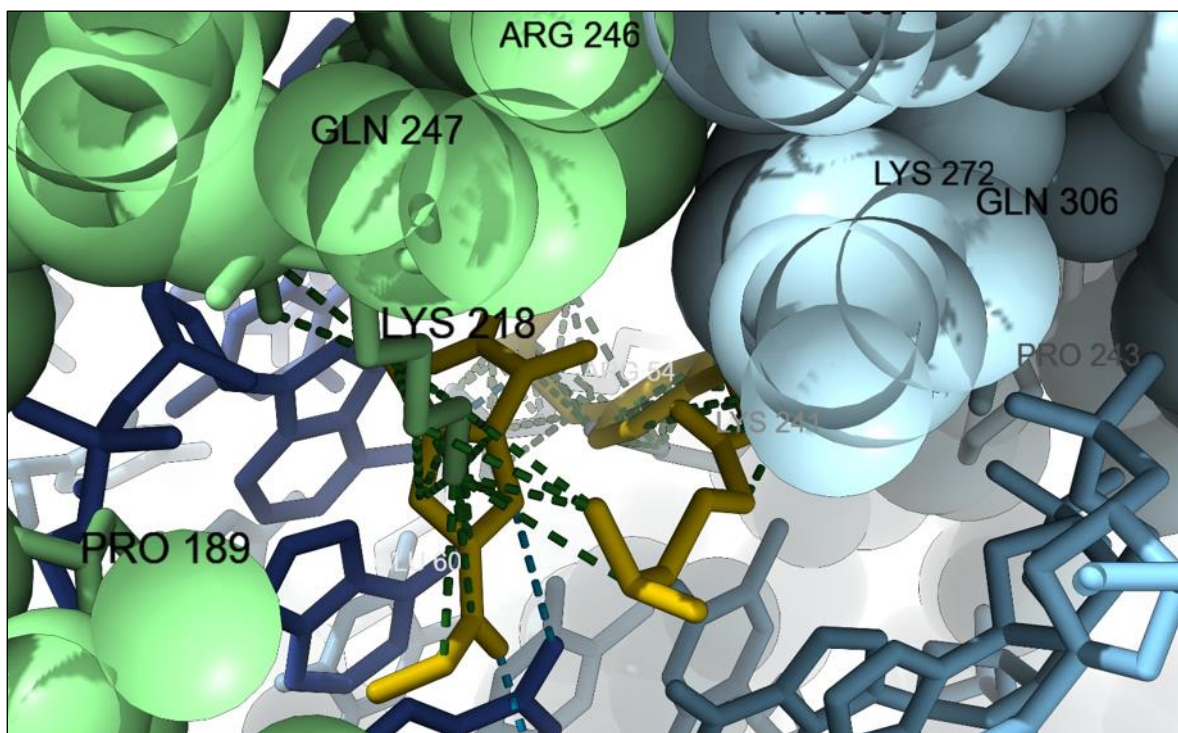


Figure 5: Localization of the docked Polyamide 6 molecule within the structural environment of the NF- κ B–DNA complex, showing nearby protein residues.

At present, these residues should be considered nearby rather than confirmed PA6-binding residues, because the primary docking calculation focused on DNA and we did not calculate a quantitative protein–PA6 interaction energy for each residue. Nevertheless, their proximity may be important because PA6 occupation of the DNA region could influence the accessibility or local environment of the NF- κ B recognition site.

This observation is consistent with the broader concept that DNA-binding polyamides can potentially interfere with transcription-factor recognition of DNA. In particular, previous experimental work demonstrated that pyrrole-imidazole polyamides could inhibit NF- κ B DNA binding depending on the subsite targeted within the NF- κ B recognition sequence.

3.6 Independent Docking Calculation and Reproducibility

Table 5: Comparison of the two independent docking calculations.

Parameter	Seed 12345	Seed 67890
Best affinity (kcal mol ⁻¹)	-6.117	-6.329
Lowest-ranked affinity (kcal mol ⁻¹)	-5.710	-5.929
Number of poses	20	20
Exhaustiveness	32	32
Docking box	30 × 22 × 22 Å	30 × 22 × 22 Å
Docking center (Å)	115.71, 26.60, 9.25	115.71, 26.60, 9.25
Random seed	12345	67890
Top-pose cross-run RMSD	\multicolumn{2}{c}{7.929 Å}	
H-bonds in top pose	3	2

To determine whether the observed docking behavior depended strongly on the stochastic search, a second docking calculation was performed using a different random seed (67890) while keeping all other parameters unchanged.

The second calculation produced a best predicted affinity of $-6.329 \text{ kcal mol}^{-1}$, compared with $-6.117 \text{ kcal mol}^{-1}$ in the first calculation. The difference between the two best scores was therefore only $0.212 \text{ kcal mol}^{-1}$.

Interestingly, the top-ranked poses from the two independent docking calculations were not structurally identical. The cross-run RMSD was $7.929 \text{ \AA}$, indicating a substantial difference in overall ligand orientation.

The second-seed top pose formed two hydrogen bonds. One involved DG3 N7 of the C strand and a PA6 nitrogen atom, with a donor–acceptor distance of $3.171 \text{ \AA}$. The second involved DC22 N4 and a PA6 oxygen atom, with a donor–acceptor distance of $3.416 \text{ \AA}$.

Table 6: Hydrogen bonds identified in the second-seed top-ranked pose.

DNA nucleotide	DNA atom	PA6 atom	D...A distance (Å)
DG3 (C)	N7	N	3.171
DC22 (D)	N4	O	3.416

The difference between the two docking runs is important. It indicates that the calculation does not support one uniquely determined PA6 conformation. Instead, PA6 appears capable of adopting several energetically favorable orientations in the DNA environment.

At the same time, the two calculations provide complementary evidence for favorable interaction with the targeted DNA environment. The first run produced the most detailed interaction network within the central κB region. In contrast, the second run independently identified a favorable pose with a nucleobase-directed interaction with DG3, which lies within the targeted region.

Therefore, the second docking calculation should not be interpreted simply as demonstrating that $-6.329 \text{ kcal mol}^{-1}$ represents a "better" binding state. Rather, it demonstrates search robustness at the level of favorable DNA localization while also revealing conformational variability of the predicted binding mode.

3.7 Overall Molecular Recognition Model

Taken together, the docking results support a model in which PA6 can adopt multiple favorable orientations within the κB DNA environment. The principal pose from the first calculation showed a predicted affinity of $-6.117 \text{ kcal mol}^{-1}$ and formed three conventional hydrogen bonds with DA5, DA7, and DT8, along with additional contacts involving neighboring nucleotides.

The occurrence of closely related poses with RMSD values of approximately $2.29\text{--}2.67 \text{ \AA}$ further supports a recurrent interaction orientation in the first docking calculation. Conversely, the very different second pose generated using seed 67890, with a cross-run RMSD of $7.929 \text{ \AA}$, shows that the docking procedure does not uniquely determine the exact orientation.

This combination of results suggests that conformational adaptability may be an important characteristic of PA6–DNA recognition. Rather than behaving as a rigid ligand that recognizes only one DNA geometry, PA6 may reorganize its flexible structure to establish favorable contacts with different regions of the DNA surface.

The principal interaction pattern is particularly interesting because it involves direct contacts with nucleobase atoms and is oriented toward the major-groove side of the DNA duplex. This differs from the classical minor-groove recognition model established for many Py–Im polyamides [12–18]. The result therefore raises the possibility that structural modifications incorporated into PA6 have altered the preferred interaction geometry relative to classical polyamide scaffolds.

3.8 Implications and Limitations

The present results provide a computational structural hypothesis rather than experimental evidence of PA6 binding or NF- κB inhibition. AutoDock Vina does not fully account for DNA flexibility, solvent organization, counterions, conformational entropy, or the dynamic behavior of the NF- κB –DNA complex. Furthermore, the primary receptor was the DNA component rather than the complete protein–DNA complex.

The absence of a non- κ B control sequence also prevents a definitive conclusion regarding sequence selectivity. Similarly, the difference between the two independent top-ranked poses indicates that the docking results should not be interpreted as establishing a single experimentally validated binding conformation.

Nevertheless, several observations are mutually supportive: PA6 repeatedly localized to the targeted DNA environment, the principal pose formed three conventional hydrogen bonds with κ B-region nucleotides, multiple additional nucleotide contacts were detected, and an independent docking search produced another favorable DNA-bound orientation. Together, these findings provide a rational structural basis for future experimental studies of PA6–DNA recognition.

Previous experimental work has already demonstrated that polyamides can interfere with NF- κ B–DNA recognition [24]. The present study extends this concept to PA6 by providing a molecular model of its potential interaction with a structurally characterized κ B DNA site. The most notable feature is the predicted major-groove-oriented recognition mode, which differs from the classical minor-groove paradigm of Py–Im polyamides.

Thus, this computational investigation suggests that PA6 can recognize and interact with the κ B DNA region through a combination of conventional hydrogen bonding and additional short-range interactions, while retaining sufficient conformational flexibility to accommodate alternative DNA-bound orientations. These findings provide a testable hypothesis for subsequent experimental DNA-binding and NF- κ B competition studies.

4 CONCLUSION

In this study, we investigated the potential interaction of Polyamide 6 (PA6) with the κ B DNA region of the NF- κ B–DNA complex (PDB ID: 1LE5) using molecular docking. The initial docking produced favorable predicted affinities ranging from -6.117 to -5.710 kcal mol $^{-1}$, with the highest-ranked pose showing three conventional hydrogen bonds involving DA5, DA7, and DT8, together with additional nucleotide contacts.

An independent docking calculation using a different random seed produced a similar favorable affinity (-6.329 kcal mol $^{-1}$) but a different ligand orientation (cross-run RMSD = 7.929 Å), indicating that PA6 can adopt multiple favorable conformations within the DNA environment. The principal pose displayed a major-groove-oriented interaction pattern, which is noteworthy because classical pyrrole–imidazole polyamides are generally associated with minor-groove recognition.

Overall, the results provide a structural hypothesis for PA6 recognition of the κ B DNA region and identify specific nucleotide interactions for experimental investigation. Further DNA-binding and NF- κ B competition studies are required to determine whether these predicted interactions translate into measurable biological activity.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

I would thank the pharmacy college at the University of Kufa for supporting me in completing this research.

Disclosure of conflict of interest

All authors confirm that no conflicts exist regarding this manuscript.

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