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AURORA B KINASE-TARGETED MOLECULAR DOCKING OF NOVEL COMPOUNDS: STRUCTURE-BASED IDENTIFICATION OF POTENTIAL ANTICANCER LEADS

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ABSTRACT
Aurora B kinase is a key regulatory component of the chromosomal passenger complex and plays an essential role in chromosome segregation and cytokinesis, making it an attractive molecular target for anticancer drug discovery. In the present study, molecular docking was employed to investigate the binding potential of newly synthesized compounds Ia–Ij and IIa–IIj toward human Aurora B kinase. The crystal structure of Aurora B kinase complexed with VX-680 (PDB ID: 4AF3; 2.75 Å resolution) was retrieved from the Protein Data Bank and prepared using Accelrys Discovery Studio 2.5. The binding site was defined around the co-crystallized VX-680 inhibitor using a 9.0 Å radius sphere. The synthesized compounds were prepared by three-dimensional structure generation and energy minimization using the CHARMm force field and subsequently docked into the Aurora B kinase active site using the LibDock protocol. The docking results revealed variable binding scores across the two-compound series. Among compounds Ia–Ij, Ic exhibited the highest LibDock score of 113.463, whereas IIh showed the highest score of 112.522 among compounds IIa–IIj. The predicted binding modes of Ic and IIh demonstrated favourable accommodation within the Aurora B kinase binding pocket, with hydrogen-bonding and hydrophobic interactions contributing to their predicted ligand–receptor recognition. These findings identified Ic and IIh as the most promising candidates within the investigated series and provide a structure-based rationale for their further biological evaluation as potential Aurora B kinase-targeting anticancer agents.

KEYWORDS: Aurora B kinase; molecular docking; LibDock; VX-680; structure-based drug design; Accelrys Discovery Studio; anticancer agents.

1. INTRODUCTION

Aurora kinases are a family of serine/threonine protein kinases that play essential roles in the regulation of chromosome segregation and accurate progression through mitosis [1]. Among the three members of the Aurora kinase family, Aurora A and Aurora B have attracted considerable attention as potential targets for anticancer drug discovery because of their critical involvement in mitotic progression and maintenance of genomic stability [2]. Aurora B is a core component of the chromosomal passenger complex (CPC), together with inner centromere protein (INCENP), survivin, and borealin, and is predominantly localized at centromeres and kinetochores during mitosis [3]. The kinase activity of Aurora B is required for phosphorylation of several substrates involved in chromosome condensation, kinetochore–microtubule attachment, and cytokinesis. Dysregulation of Aurora B activity has been associated with abnormal chromosome segregation, polyploidy, genomic instability, and malignant cellular proliferation, thereby supporting the development of selective Aurora B inhibitors as potential anticancer agents [4].

The catalytic activity of Aurora B is mediated through a structurally defined ATP-binding pocket that provides opportunities for the rational design of small-molecule inhibitors. Structural studies of Aurora B in complex with ATP-competitive inhibitors have provided valuable information regarding the molecular determinants governing ligand recognition within the kinase active site [5]. In particular, the crystal structure of human Aurora B kinase in complex with the potent inhibitor VX-680 (PDB ID: 4AF3) provides a suitable structural model for investigating ligand–protein interactions and identifying binding features that may contribute to inhibitory activity [6]. VX-680 occupies the ATP-binding region of Aurora B and establishes interactions with residues lining the catalytic pocket, making this crystallographic structure an appropriate template for structure-based evaluation of newly synthesized molecules [7].

Although several Aurora kinase inhibitors have been investigated, the development of new chemotypes with favourable binding characteristics remains an important objective in medicinal chemistry [8]. Molecular docking has become an integral component of contemporary structure-based drug design because it enables the prediction of ligand orientation within a protein binding site and provides qualitative information regarding hydrogen bonding, hydrophobic contacts, electrostatic interactions, and other non-covalent forces contributing to ligand recognition [9]. Docking-based analysis can therefore complement experimental biological studies by identifying

plausible binding modes and helping to rationalize structure–activity relationships among newly synthesized compounds. In particular, comparison of docking scores and interaction patterns across a congeneric series can provide useful insights into the structural features associated with enhanced target recognition [10].
In the present study, a series of newly synthesized compounds, designated Ia–Ij and IIa–IIj, were investigated for their potential interaction with human Aurora B kinase using a structure-based molecular docking approach. The crystallographic structure of Aurora B kinase in complex with VX-680 (PDB ID: 4AF3) was selected as the receptor model, and the ligand-binding region was defined on the basis of the co-crystallized inhibitor. The prepared compounds were subjected to molecular docking using the LibDock protocol implemented in Accelrys Discovery Studio 2.5, and the resulting poses were evaluated according to their LibDock scores and predicted protein–ligand interactions. Particular emphasis was placed on compounds exhibiting favourable docking scores and interactions with residues located within the Aurora B active site. This computational investigation was undertaken to identify promising Aurora B-binding candidates and to provide a molecular-level rationale for the observed or anticipated biological activity of the synthesized series, thereby supporting further optimization of these compounds as potential anticancer leads.

2. MATERIALS AND METHODS

2.1. Protein structure preparation

The three-dimensional crystal structure of human Aurora B kinase in complex with the co-crystallized inhibitor VX-680 was obtained from the Protein Data Bank (PDB) under accession code 4AF3 (Fig. 1). The crystal structure was determined at a resolution of 2.75 Å and contains Aurora B kinase in association with the inner centromere protein (INCENP). The crystallographic structure was selected as the receptor model because the co-crystallized VX-680 defines the experimentally characterized ligand-binding region of Aurora B kinase. Protein preparation was performed using Accelrys Discovery Studio 2.5. The Clean Protein protocol was employed to prepare the receptor for subsequent docking calculations. During protein preparation, missing hydrogen atoms were added, incomplete or missing structural components were addressed where applicable, atom orders of amino acid residues were standardized, and the protein structure was checked for structural completeness. The prepared Aurora B kinase structure was subsequently used as the receptor for molecular docking studies. The protein preparation procedure was performed according to previously reported protocols [11, 12].

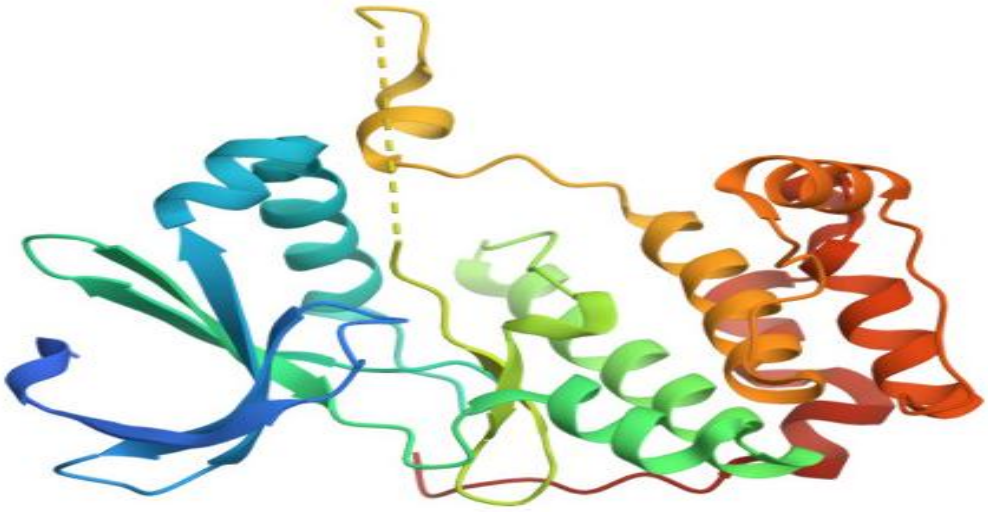

Fig. 1. Crystal structure of human Aurora B kinase in complex with VX-680 (PDB ID: 4AF3). The three-dimensional structure illustrates the Aurora B kinase catalytic domain and the position of the co-crystallized VX-680 inhibitor within the ATP-binding site.

2.2. Ligand preparation

The chemical structures of the synthesized compounds Ia–Ij and IIa–IIj were initially drawn using ChemSketch 12.0 (ACD/Labs) and exported in MOL2 format. The resulting structures were imported into Accelrys Discovery Studio 2.5 for ligand preparation. Appropriate ionization states, tautomers, and stereochemical configurations were generated where applicable, and duplicate conformations were removed to obtain a representative set of ligand structures. The three-dimensional conformations of the compounds were generated using the implemented conformational generation procedure. Geometry optimization and energy minimization were subsequently performed using the CHARMm force field. Initial minimization was carried out using the steepest descent algorithm, followed by the conjugate gradient algorithm until the specified convergence criteria were reached. The energy-minimized ligand structures were subsequently used for molecular docking calculations [13, 14].

2.3. Definition of the Aurora B kinase binding site

The active binding site of Aurora B kinase was defined using the Define and Edit Binding Site protocols implemented in Accelrys Discovery Studio 2.5. The position of the co-crystallized inhibitor VX-680 in the 4AF3

crystal structure was used to identify the experimentally relevant ligand-binding region. Initially, the co-crystallized VX-680 molecule was selected and the Define Sphere from Selection option was used to generate a binding-site sphere centered on the inhibitor. A spherical binding region with a radius of 9.0 Å around the co-crystallized ligand was subsequently defined as the docking site. This region encompassed the principal residues surrounding the VX-680 binding pocket and was maintained consistently for docking of all synthesized compounds [15].

2.4. Molecular docking using LibDock

Molecular docking studies were performed using the LibDock module of Accelrys Discovery Studio 2.5. LibDock is a high-throughput, site-feature-based docking algorithm that identifies favourable ligand orientations within a predefined receptor binding site. The algorithm uses interaction hotspots representing favourable polar and apolar regions of the binding pocket to generate and evaluate ligand poses. The prepared compounds Ia–Ij and IIa–IIj were individually docked into the predefined 9.0 Å Aurora B kinase binding site. During docking, ligand conformations were oriented with respect to the interaction hotspots within the receptor pocket, and the resulting poses were evaluated according to their predicted interaction characteristics and LibDock scores. The generated poses were ranked according to their LibDock scores, with higher scores considered indicative of more favourable predicted ligand–receptor recognition within the defined docking protocol [16].

For each compound, the docking pose showing the most favourable LibDock score together with a plausible interaction pattern within the Aurora B kinase active site was selected for subsequent analysis. The docking results were evaluated by comparing the LibDock scores, electrostatic energy, van der Waals energy, and predicted interactions of the synthesized compounds with residues constituting the Aurora B kinase binding pocket [17].

2.5. Analysis and visualization of protein–ligand interactions

The binding orientations of the docked compounds were examined using the two-dimensional and three-dimensional interaction analysis tools available in Accelrys Discovery Studio 2.5. The selected docking poses were inspected to identify hydrogen-bond interactions, hydrophobic contacts, electrostatic interactions, and other non-covalent interactions between the synthesized compounds and amino acid residues lining the Aurora B kinase binding site. Particular attention was given to the interaction patterns of compounds exhibiting comparatively high LibDock scores. The binding modes of the representative compounds Ic and IIh were visualized in both three-dimensional and two-dimensional representations to illustrate their orientation within the Aurora B kinase active site and their key ligand–residue interactions. The docking results were subsequently compared across the Ia–Ij and IIa–IIj series to identify compounds with favourable predicted binding characteristics and to provide a structural rationale for their potential Aurora B kinase inhibitory activity [18, 19].

2.6. Docking score analysis

The docking performance of the synthesized compounds was assessed using the LibDock score generated by Accelrys Discovery Studio 2.5. The corresponding electrostatic and van der Waals energy values were also recorded for each docked compound. These parameters were used comparatively to examine the predicted contribution of non-covalent interactions to ligand recognition within the Aurora B kinase binding pocket. Among the evaluated compounds, compound Ic exhibited the highest LibDock score within the Ia–Ij series (113.463), whereas compound IIh exhibited a LibDock score of 112.522 within the IIa–IIj series. The corresponding interaction profiles of these compounds were therefore examined in greater detail to determine their predicted binding modes and their interactions with the Aurora B kinase active site [20, 21].

3. RESULTS AND DISCUSSION

3.1. Molecular docking analysis

Molecular docking studies were performed to investigate the binding characteristics of the synthesized compounds Ia–Ij and IIa–IIj within the ATP-binding region of human Aurora B kinase. The crystal structure of Aurora B kinase complexed with VX-680 (PDB ID: 4AF3) was used as the receptor model. The co-crystallized ligand-defined binding pocket provided a structurally relevant site for evaluating the binding orientations and interaction profiles of the synthesized compounds. The docking analysis was performed using the LibDock protocol implemented in Accelrys Discovery Studio 2.5. The calculated LibDock scores, electrostatic energies, and van der Waals energies for compounds Ia–Ij are presented in Table 1. All compounds in this series exhibited favourable LibDock scores, ranging from 99.675 to 113.463. Among the evaluated compounds, Ic exhibited the highest LibDock score (113.463), followed by Ih (106.491), If (106.386), Ii (106.145), Id (106.135), Ij (105.530), Ig (101.465), Ia (100.155), Ib (99.868), and Ie (99.675). The comparatively higher LibDock score of Ic indicates a favourable predicted fit of this molecule within the defined Aurora B kinase binding pocket under the applied docking protocol.

Table 1. LibDock docking parameters of compounds Ia–Ij against human Aurora B kinase (PDB ID: 4AF3).

Compound	Molecular formula	Electrostatic energy	Van der Waals energy	LibDock score
Ia	$C_{13}H_{14}N_4O$	−23.742	5.140	100.155
Ib	$C_{15}H_{18}N_4O$	−29.335	5.682	99.868
Ic	$C_{15}H_{16}N_4O_2$	−25.994	2.740	113.463

Id	$C_{16}H_{18}N_4O$	−34.825	5.081	106.135
Ie	$C_{23}H_{18}N_4O$	−25.818	5.370	99.675
If	$C_{23}H_{30}N_4O$	−24.110	3.385	106.386
Ig	$C_{18}H_{16}N_4O$	−15.956	5.110	101.465
Ih	$C_{15}H_{18}N_4O$	−22.518	5.393	106.491
Ii	$C_{19}H_{24}N_4O$	−25.562	5.171	106.145
Ij	$C_{14}H_{16}N_4O$	−28.865	4.795	105.530

Compound Ic showed an electrostatic energy of −25.994 and a Van der Waals energy of 2.740, indicating that its predicted binding profile was influenced by favourable electrostatic contributions together with Van der Waals interactions. In comparison, compound Id displayed the most negative electrostatic energy in the Ia–Ij series (−34.825) but showed a lower LibDock score of 106.135. This observation indicates that the LibDock ranking is not determined solely by electrostatic interactions and reflects the combined contribution of ligand–receptor recognition features considered by the docking algorithm. Similarly, compound If showed a LibDock score of 106.386, with electrostatic and van der Waals energies of −24.110 and 3.385, respectively. The docking results for compounds IIa–IIj are summarized in Table 2. The LibDock scores for this series ranged from 85.344 to 112.522. Among these compounds, IIh exhibited the highest LibDock score (112.522), followed by IIg (108.155), IIf (98.926), IIi (99.936), IIj (99.645), IIa (89.396), IIc (88.951), IId (96.682), IIe (96.376), and IIb (85.344). The high LibDock scores observed for IIh and IIg suggest favourable predicted accommodation of these molecules within the Aurora B kinase binding site.

Interestingly, IIh exhibited a relatively high LibDock score of 112.522, despite its electrostatic energy (13.426) being less favourable than that observed for several compounds in the series. This further demonstrates that the LibDock score represents an integrated assessment of ligand–receptor interactions rather than a direct measure of a single energetic component. Compound IIg also showed a comparatively high LibDock score (108.155) with electrostatic and van der Waals energies of 14.913 and 5.468, respectively. In contrast, IIb displayed the lowest LibDock score (85.344) among the investigated compounds, suggesting comparatively less favourable predicted recognition within the defined binding site.

Table 2. LibDock docking parameters of compounds IIa–IIj against human Aurora B kinase (PDB ID: 4AF3).

Compound	Molecular formula	Electrostatic energy	Van der Waals energy	LibDock score
IIa	$C_{21}H_{19}N_5O_3$	−12.702	3.561	89.396
IIb	$C_{23}H_{23}N_5O_3$	−7.384	3.833	85.344
IIc	$C_{22}H_{21}N_5O_3$	−15.200	4.574	88.951
IId	$C_{23}H_{23}N_5O_3$	−16.462	5.380	96.682
IIe	$C_{26}H_{21}N_5O_3$	−19.220	4.840	96.376
IIf	$C_{27}H_{29}N_5O_3$	12.940	4.421	98.926
IIg	$C_{31}H_{35}N_5O_3$	14.913	5.468	108.155
IIh	$C_{31}H_{23}N_5O_3$	13.426	4.973	112.522
IIi	$C_{23}H_{21}N_5O_4$	−25.146	1.764	99.936
IIj	$C_{24}H_{23}N_5O_3$	−11.206	3.141	99.645

3.2. Comparative docking profile of the synthesized compounds

Comparison of the two-compound series revealed that Ic and IIh were the highest-ranked compounds in their respective series, with LibDock scores of 113.463 and 112.522, respectively. The difference between these scores was relatively small, indicating that both compounds exhibited favourable predicted interactions with the Aurora B kinase binding pocket under identical docking conditions. The LibDock score of Ic was also higher than that of all other compounds evaluated in the present study, whereas IIh represented the most favourable compound within the IIa–IIj series. The overall docking profile suggests that structural modifications within the synthesized series substantially influenced their predicted recognition by Aurora B kinase. Compounds possessing higher LibDock scores may adopt orientations that provide a more favourable combination of polar, hydrophobic, electrostatic, and steric interactions within the binding cavity. However, the docking scores should be interpreted as relative computational indicators of binding-site compatibility rather than direct experimental measurements of binding affinity. The representative binding modes of the two highest-ranked compounds, Ic and IIh, were therefore examined in greater detail. The three-dimensional and two-dimensional interaction diagrams are presented in Figs. 2 and 3, respectively.

3.3. Binding mode of compound Ic

Compound Ic displayed the highest LibDock score (113.463) among all compounds investigated, indicating the most favourable predicted docking performance in the present study. The three-dimensional and two-dimensional representations of its binding mode within the Aurora B kinase active site are shown in Fig. 2. The docked orientation of Ic demonstrated that the molecule was accommodated within the defined Aurora B kinase binding cavity and established two hydrogen-bond interactions with residues located in the active-site region. In addition to these hydrogen bonds, the ligand exhibited hydrophobic contacts with surrounding residues, providing additional non-covalent stabilization of the docked complex. The combination of hydrogen-bonding and hydrophobic interactions is consistent with the high LibDock score obtained for Ic. The electrostatic energy of Ic was −25.994, while its van der Waals energy was 2.740. The favourable electrostatic contribution, together with the observed hydrogen-bonding pattern and hydrophobic contacts, provides a plausible structural explanation for the high docking score of this compound. These interactions suggest that Ic can be favourably accommodated within the Aurora B kinase binding pocket and identify it as a suitable candidate for further experimental evaluation.

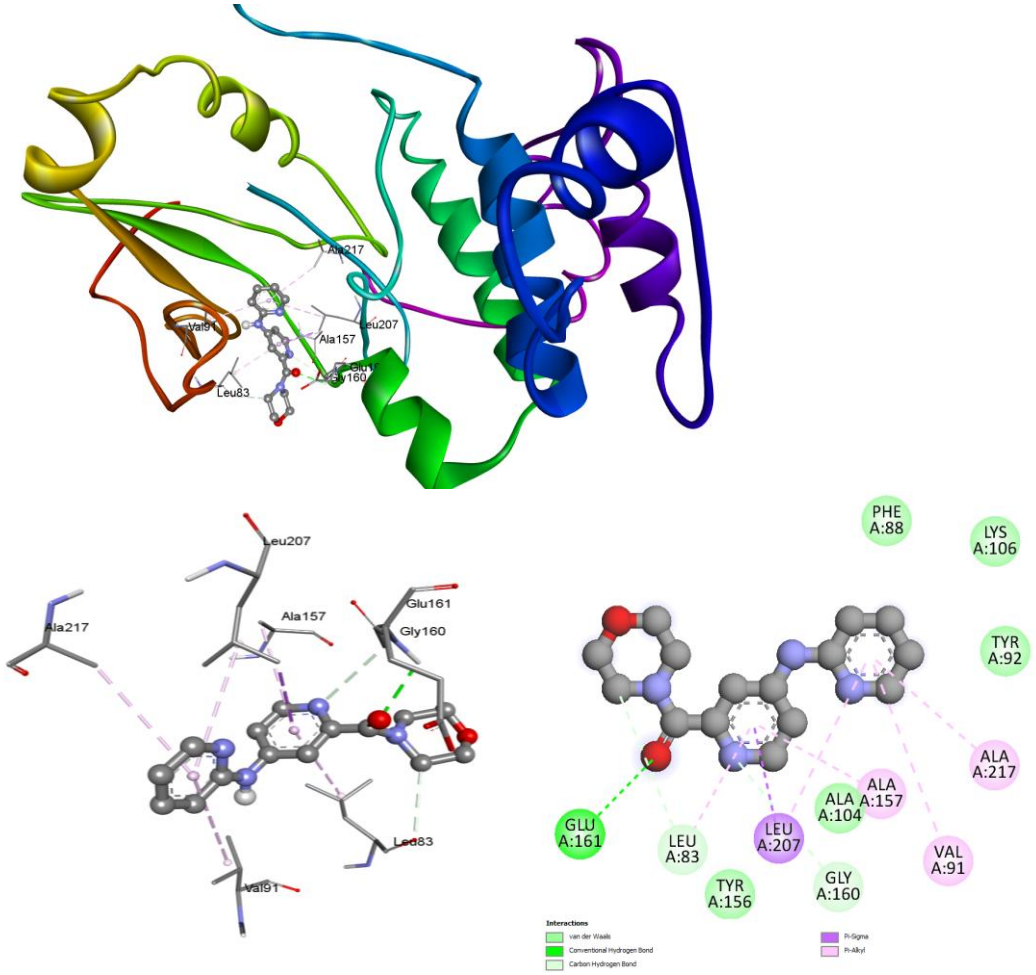

Fig. 2. Predicted binding mode of compound Ic within the active site of human Aurora B kinase (PDB ID: 4AF3). (A) Three-dimensional representation of the docked complex showing the orientation of Ic within the Aurora B kinase binding pocket and its surrounding residues. (B) Two-dimensional interaction diagram illustrating the predicted hydrogen-bonding and hydrophobic interactions between compound Ic and the amino acid residues of the active site.

3.4. Binding mode of compound IIh

Compound IIh exhibited the highest LibDock score among the second series, with a score of 112.522, and was therefore selected for detailed binding-mode analysis. Its predicted three-dimensional and two-dimensional interactions with Aurora B kinase are illustrated in Fig. 3. The docking pose showed that IIh was favourably positioned within the Aurora B kinase binding cavity and formed stabilizing non-covalent interactions with residues surrounding the active site. The predicted interaction pattern included hydrogen-bonding and hydrophobic contacts, which may contribute to the favourable accommodation of the ligand within the receptor pocket. The relatively high LibDock score suggests that the spatial and chemical features of IIh are compatible with the interaction environment of the Aurora B kinase binding site. The electrostatic and van der Waals energies calculated for IIh were 13.426 and 4.973, respectively. Although its electrostatic energy was less favourable than

that of several compounds in the series, IIh nevertheless achieved a high LibDock score, highlighting the contribution of the overall geometric and interaction complementarity between the ligand and receptor. The predicted binding orientation of IIh consequently supports its prioritization for further biological investigation.

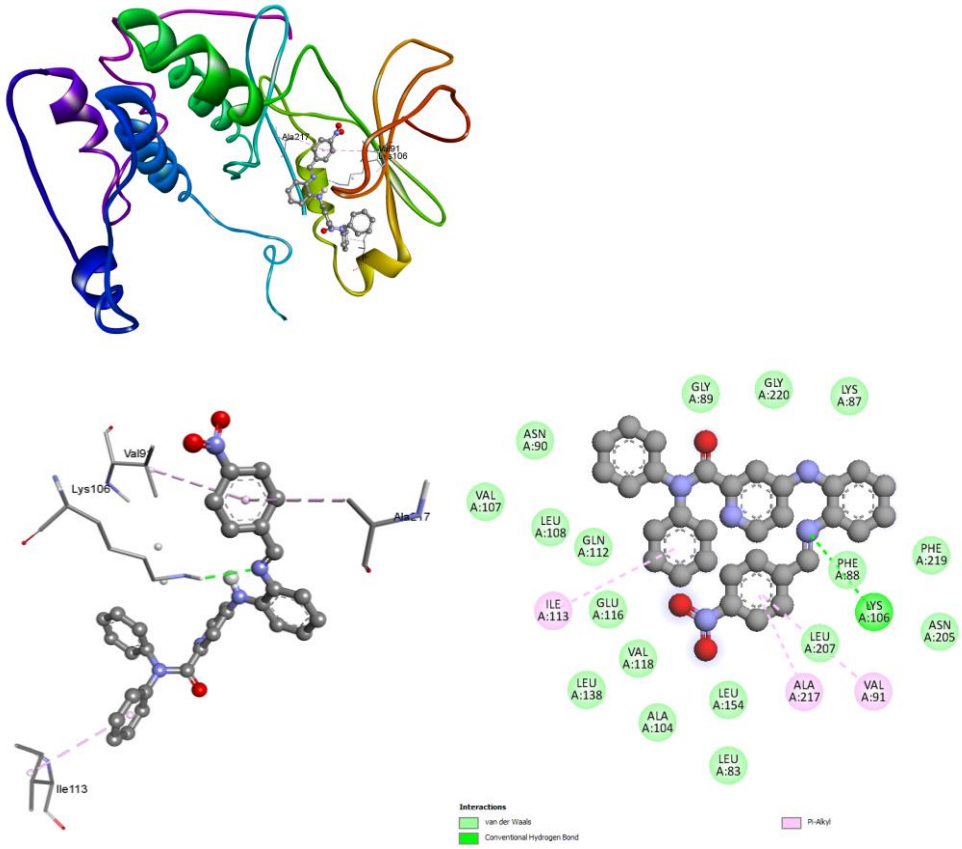

Fig. 3. Predicted binding mode of compound IIh within the active site of human Aurora B kinase (PDB ID: 4AF3). (A) Three-dimensional representation of the docked complex showing the orientation of IIh within the Aurora B kinase binding pocket and its surrounding residues. (B) Two-dimensional interaction diagram illustrating the predicted hydrogen-bonding and hydrophobic interactions between compound IIh and the amino acid residues of the active site.

3.5. Structure-based interpretation of the docking results

Taken together, the docking results identified Ic and IIh as the most prominent compounds in the two investigated series, based on their LibDock scores of 113.463 and 112.522, respectively. The superior docking scores of these compounds relative to their respective series indicate favourable predicted recognition of the Aurora B kinase active site. The detailed interaction analysis further showed that the selected compounds could establish multiple non-covalent contacts, including hydrogen bonds and hydrophobic interactions, within the receptor cavity. The docking results provide a molecular-level rationale for prioritizing Ic and IIh for further biological studies. Nevertheless, because docking scores are computational predictions and do not directly establish biochemical potency or experimental binding affinity, the predicted interactions should be considered supportive evidence and correlated with in vitro Aurora B kinase inhibition and cellular anticancer activity. Overall, the docking analysis provides useful structure-based information for understanding the potential Aurora B kinase recognition of the synthesized compounds and for guiding subsequent structure–activity relationship investigations.

CONCLUSION

Molecular docking studies provided useful structural insights into the potential interaction of the newly synthesized compounds Ia–Ij and IIa–IIj with human Aurora B kinase. Using the crystal structure of Aurora B kinase complexed with VX-680 (PDB ID: 4AF3) and the LibDock docking protocol, considerable differences in the predicted binding profiles of the synthesized compounds were observed. Compound Ic, with a LibDock score of 113.463, exhibited the highest docking score among the entire investigated series, while compound IIh showed the highest score within the second series (112.522). Detailed binding-mode analysis indicated that both compounds could be favourably accommodated within the Aurora B kinase binding pocket and were capable of forming hydrogen-bonding and hydrophobic interactions with residues lining the active site. These computational findings support the prioritization of Ic and IIh for further investigation. However, the docking results represent predictive evidence and should be correlated with experimental Aurora B kinase inhibition, cellular

antiproliferative activity, selectivity, and other pharmacological studies to establish their therapeutic potential. Overall, the present study provides a rational structure-based basis for further optimization of these compounds as potential Aurora B kinase-directed anticancer leads.

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