Л.Н. Гумилев атындағы Еуразия ұлттық университетінің ХАБАРШЫСЫ.
BULLETIN of L.N. Gumilyov Eurasian National University.
ВЕСТНИК Евразийского национального университета имени Л.Н. Гумилева.
ISSN: 2616-7034. eISSN: 2663-130X

IRSTI 34.15.15, 31.21.15, 31.25.15 https://doi.org/10.32523/2616-7034-2025-150-1-134-154
Research article

Endogenous purines as natural ligands of the A_{2B} adenosine receptor

M. Satkanov*[1], E. Chupakhin[1]

[1] *Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

**Corresponding author:satkanov.mereke@gmail.com*

Abstract. Endogenous purines are essential regulators of various physiological functions, including immune response, inflammation, and neurotransmission. While adenosine has long been considered the primary ligand for adenosine receptors, recent evidence suggests that other purines may also interact with these receptors, particularly the A_{2B} adenosine receptor (A_{2B}AR). This study investigates the potential role of endogenous purines as natural ligands of A_{2B}AR using molecular docking. The results demonstrate a high binding affinity of purines for A_{2B}AR, suggesting their functional relevance in receptor-mediated signaling. Additionally, A_{2B}AR plays a crucial role in immune regulation by influencing T-cell differentiation and cytokine production. Modulating its activity through endogenous purines may have significant implications for inflammation-related diseases, including cancer and neurodegenerative disorders. The findings provide new insights into the purinergic control of the adenosinergic system and highlight the potential of targeting A2BAR in therapeutic strategies. However, further studies, including *in vitro* and *in vivo* experiments, are necessary to confirm the physiological relevance of these interactions. This research expands our understanding of purinergic signaling and opens new avenues for the development of pharmacological interventions aimed at modulating immune and inflammatory responses.

Keywords: A_{2B} adenosine receptor, purinergic signaling, immune modu-lation, inflammation and neurodegeneration, molecular docking analysis

Received: 29.02.2025. Accepted: 31.03.2025. Available online: 04.04.2025

Introduction

Adenosine receptors (ARs) are G protein-coupled receptors that play crucial roles in various physiological processes, including inflammation, cardiovascular function, and neurotransmission [1, 2]. The four AR subtypes (A_1, A_{2A}, A_{2B}, and A_3) have unique pharmacological profiles and tissue distributions, making them promising therapeutic targets for numerous diseases [2, 3]. ARs modulate neurotransmission in the central nervous system, interfering with dopaminergic, glutamatergic, and other neurotransmitter systems, which suggests potential applications in treating neuropsychiatric disorders [4]. Recent advancements in AR pharmacology have led to the development of new ligands and strategies for receptor activation, showing promise in treating conditions such as cancer, inflammatory diseases, and metabolic disorders [3]. However, the ubiquitous distribution of ARs presents challenges in achieving selective and site-specific modulation [1, 3]. Significantly, the A_{2B} adenosine receptor (A_{2B}AR) is a low-affinity receptor with wide distribution, making it a target of interest in various pathological conditions [5].

The A_{2B}AR has become a significant target in various pathological conditions, including inflammatory diseases, cardiovascular disorders, and metabolic dysfunctions [6,7]. A_{2B}AR activation plays a crucial role in alcoholic hepatitis by regulating cAMP levels and the NF-κB pathway, potentially reducing inflammation and steatosis [8]. While A2BAR antagonists have shown promise in treating airway inflammation, gastrointestinal disorders, and cancer, only a few have entered clinical trials [6]. Recent research has focused on developing allosteric modulators for A_{2B}AR, which offer advantages over orthosteric ligands by fine-tuning tissue responses to endogenous agonists [5]. These modulators may prove beneficial in managing chronic obstructive pulmonary disease, protecting the heart from ischemic injury, and promoting bone formation [5]. Overall, A_{2B}AR-targeted therapies represent a promising avenue for treating various human diseases.

Interestingly, initially A_{2B}AR was considered less physiologically relevant due to its low affinity for adenosine, has gained attention for its upregulation during hypoxia and inflammation [9,10]. Studies using genetic and pharmacological approaches have demonstrated A_{2B}AR's tissue-protective role in various acute disease models [10, 11]. Additionally, the adenosine metabolite inosine has been identified as a functional agonist of the related A_{2A} receptor, exhibiting a unique signaling bias compared to adenosine [12]. This finding suggests that inosine may play a role in prolonging adenosine receptor activation in vivo, given its longer half-life. These advances provide new insights into purinergic signaling and potential other purines, such as inosine, guanosine, and their metabolites, which may contribute to A_{2B}AR modulation. These alternative ligands could influence receptor signaling, offering new insights into the physiological and pathological roles of the A_{2B}AR receptor.

An understanding of the interaction between endogenous purines and A_{2B}AR could provide valuable information for the development of pharmaceuticals. While synthetic compounds targeting A_{2B}AR have shown promise in preclinical and early clinical studies, the presence of natural ligands raises important questions about receptor selectivity, competitive binding, and functional outcomes [13-15]. Some endogenous purines have been suggested to exert

protective effects in ischemic injury, neuroinflammation, and metabolic regulation, indicating their potential as modulators of A_{2B}AR activity [16, 17].

This study investigates endogenous purines as natural ligands of A_{2B}AR and their influence on receptor signaling pathways using an AlphaFold-modeled receptor and molecular docking. This approach enables a detailed analysis of ligand-binding characteristics and their potential impact on receptor signaling mechanisms. A deeper understanding of these interactions may reveal new aspects of A_{2B}AR pharmacology and regulation and provide insights into the potential use of purines as biomarkers or therapeutic targets in diseases associated with A_{2B}AR dysfunction.

Materials and research methods

3D Model of the Adenosine Receptor

3D structures of the active and inactive conformations of the adenosine receptor type A_{2B} (A_{2B}AR) were obtained by the program AlphaFold2-MultiState AI (https://gpcrdb.org/structure/homology_models) [18,19].

Ligand Molecules

Based on structural similarities, it was hypothesized that all-natural purine nucleosides and purines could interact with the target proteins during the ligand library compilation for molecular docking [20]. Analysis of databases and literature led to the identification of two antagonists and one selective agonist that were used in this study.

Adenosine ($C_{10}H_{13}N_5O_4$) is a nucleoside composed of an adenine base linked to D-ribose, playing a key role in nucleic acid structure, energy metabolism, and cell signaling (PubChem CID: 60961) [21]. Inosine ($C_{10}H_{12}N_4O_5$) is structurally similar, participating in metabolic pathways and nitrogen compound exchange (PubChem CID: 135398641) [22]. Xanthosine ($C_{10}H_{12}N_4O_6$) serves as a metabolic intermediate (PubChem CID: 164959), while guanosine ($C_{10}H_{13}N_5O_5$) is crucial for genetic information transfer and cellular regulation (PubChem CID: 135398634) [23, 24].

Adenine ($C_5H_5N_5$) is a fundamental purine base in DNA, RNA, and ATP, essential for energy transfer (PubChem CID: 190) [25]. Hypoxanthine ($C_5H_4N_4O$) is an intermediate in purine metabolism (PubChem CID: 135398638), while xanthine ($C_5H_4N_4O_2$) is a precursor to biologically active compounds (PubChem CID: 1188) [26–29]. Guanine ($C_5H_5N_5O$) is a key nucleobase involved in genetic coding and cellular processes (PubChem CID: 135398635) [30].

Caffeine ($C_8H_{10}N_4O_2$) is a xanthine-derived alkaloid that acts as a non-selective A2BAR antagonist, enhancing wakefulness and cognitive function (PubChem CID: 2519) [31–33]. MCP-NECA ($C_{21}H_{20}N_8O_3$) is a potent A_{2B}AR antagonist with potential applications in pain relief and neurodegenerative disease treatment (PubChem CID: 5310960) [34]. BAY 60-6583 ($C_{19}H_{17}N_5O_2S$) is a selective A_{2B}AR agonist with strong affinity, used to investigate A_{2B}-mediated pathways in inflammation, cardiovascular diseases, and cancer (PubChem CID: 135398635) [35]. These compounds provide valuable tools for exploring purinergic signaling and potential therapeutic applications.

Hardware and software

Molecular docking was carried out on a homemade computer, the system includes the motherboard ASRock Super Alloy B250 Pro4, video cards MSI NVIDIA GeForce GTX 1050 Ti 4Gb, Gigabyte NVIDIA GeForce GTX 1050 Ti 4Gb, processor Intel Pentium G4600, RAM Kingston Fury Beast KF432C16BBK2/16 16, permanent memory SSD Kingston SA400S37 480 Gb. To perform rigid molecular docking, we used the AutoDock Vina GPU program [36-38]. AutoDock is a program developed for molecular docking. It is mainly used for protein-ligand docking, including taking into account mobile protein residues. However, during the study, difficulties were identified in working on AutoDock Vina running on the CPU, and AutoDock Vina GPU, which runs on Linux, was adapted to work on Windows. The program itself was downloaded from open access on the GitHub website (https://github.com/DeltaGroupNJUPT/Vina-GPU-2.0).

Rigid Docking Using AutoDock

To perform molecular interaction, we used Rigid docking, which assumes the stability of the molecule and a specific binding site. The binding site was determined by the reference structure of the A_{2B}AR in AutoDock, and a Grid Box was also built on this basis with coordinates [39]. Also, a script with a configuration using the Grid Box coordinates was written to perform docking. The protein was also prepared in AutoDock, with the water removed from the structure, polar hydrogens added, and the charge calculated using Gasteiger [39,40]. The ligand molecule was also prepared in the same way after the structure was converted from SDF to PDB. Docking was performed with ligand and protein files in PBDQT format after preparation in AutoDock [36–38].

Visualization and Statistical Analysis

Molecular docking results were visualized and analyzed using PyMOL [41]. Structural alignments, ligand-receptor interactions, and binding poses were examined to identify key interactions contributing to ligand affinity. Statistical validation of docking results was performed by conducting docking simulations on five independent models of A_{2B}AR to ensure reproducibility [42]. Meaning energies and standard deviations were calculated to assess the stability of predicted binding interactions. This approach enabled a comprehensive comparison between rigid and flexible docking methods, providing a detailed understanding of ligand binding behavior in both active and inactive states of A_{2B}AR.

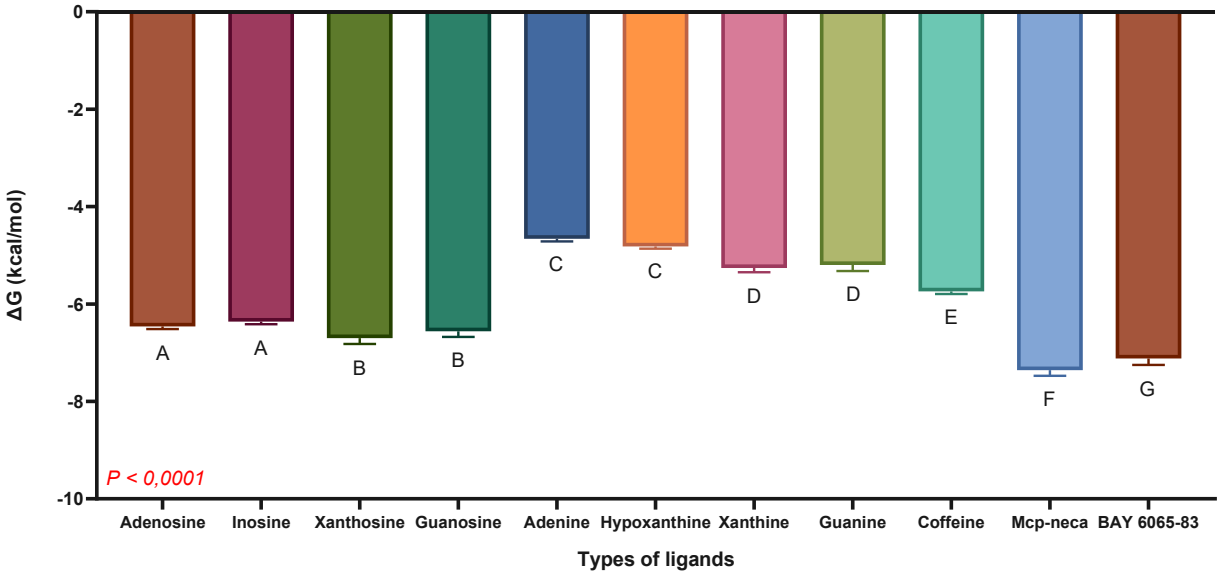
Results

In silico analysis of nucleotide binding to the inactive A_{2B}AR

In this study, molecular docking of 11 ligands with the inactive form of the A_{2B} adenosine receptor (A_{2B}AR) was performed to identify key interactions (Figure 1). The affinity of the compounds and their ability to bind to the receptor's active site were evaluated. The obtained data allowed for the determination of structural features influencing ligand interactions with A_{2B}AR. Statistical analysis was conducted using one-way analysis of variance (ANOVA) with a significance level of $P < 0.0001$, followed by Tukey's multiple comparisons test to assess differences between the ligands and the control group. The data confirms statistically significant differences in the affinity of the compounds studied for A_{2B}AR.

Adenosine was considered both a control and an experimental molecule, as its interaction with A_{2B}AR in the cryo-EM structure has already been described [21, 43]. Initially, an analysis

of adenosine binding revealed 16 possible binding variations, driven by different ligand conformations. The binding free energy (ΔG) analysis showed a minimum value of −5.8 kcal/mol and a maximum of −6.5 kcal/mol. The results indicate that adenosine binds to A2BAR in its inactive state through interactions with residues ASN254, GLU174, PHE173, HIS280, and ALA82. ASN254 is localized in the α6-helix, GLU174 and PHE173 in the α5-helix, ALA82 in the α3-helix, and HIS280 in the α7-helix (Figure 2A). The mobility of these helices, as demonstrated by TM analysis, is necessary for conformational changes and the release of the Gs protein subunit [19].



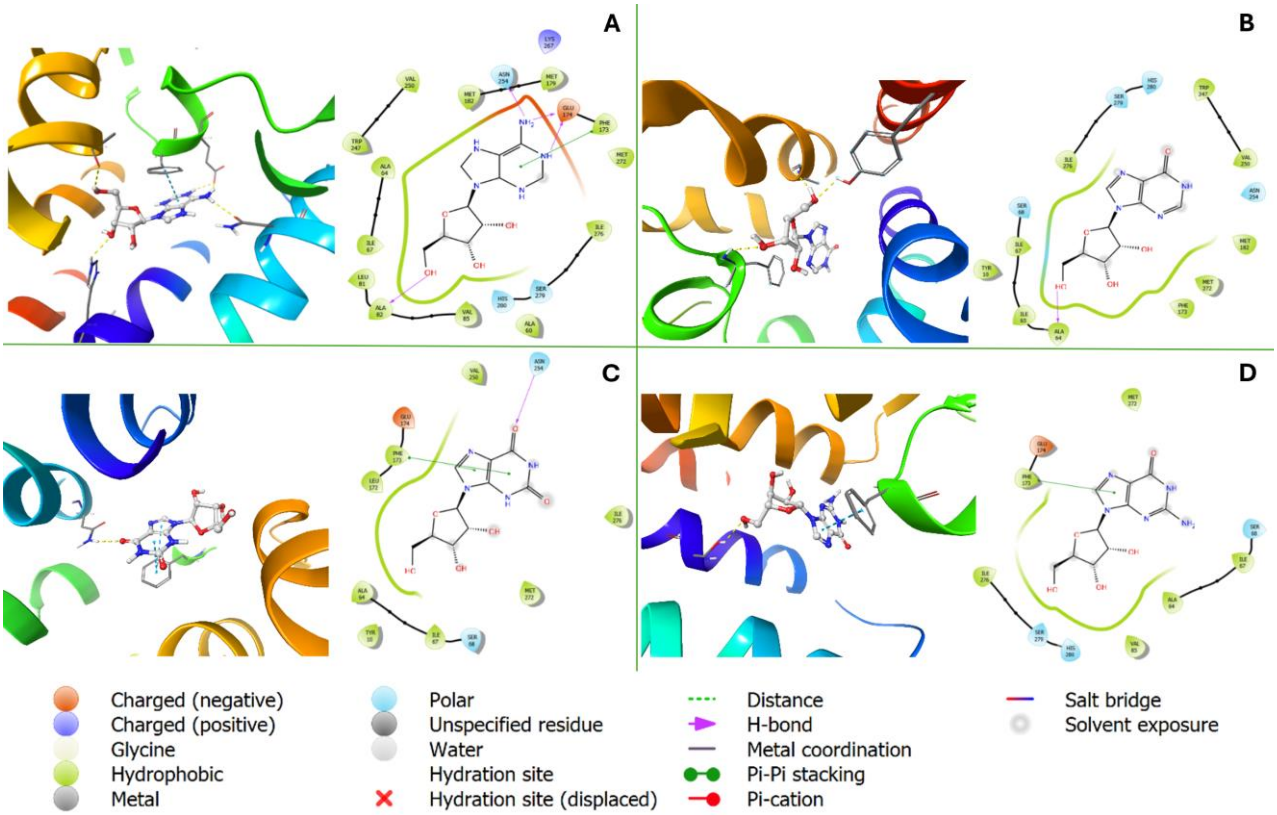
Note: Columns labeled with the same letters do not show statistically significant differences, whereas different letters indicate statistically significant differences.

Figure 1. Changes in ΔG upon ligand binding to the inactive A_{2B}AR

A hydrogen bond is formed between the amino group of adenosines at the 6-position of the purine ring and the carboxamide group of ASN254. The secondary amino group of adenosines at the 1-position of the purine ring may interact with the carboxyl group of GLU174. PHE173 participates in a π-π interaction between its benzene ring and the pyrimidine ring of the ligand. The hydroxyl group at the 5'-position of ribose forms a hydrogen bond with ALA82, while HIS280 interacts with the hydroxyl group of ribose at the 4'-position. These interactions have also been described in a study on the active structure of A_{2B}AR obtained by cryo-EM, further demonstrating that docking with AlphaFold-predicted structures is relevant for conducting molecular simulations [19,43].

Inosine was selected for docking due to its structural similarity to adenosine, with the only difference being the substitution of the amino group at the 6-position of the purine ring with an oxygen atom [22]. The maximum binding affinity of inosine (ΔG = -6.5 kcal/mol) was found to be comparable to that of adenosine. However, unlike adenosine, inosine interacts with A_{2B}AR exclusively through its ribose moiety, without involving the purine ring. The primary

interactions occur with residues ALA64, PHE173, and TYR10, located in the α2-, α5-, and α1-helices, respectively (Figure 2B). Inosine forms hydrogen bonds between the hydroxyl groups of its ribose moiety and the amide bond of the polypeptide chain at PHE173, as well as with the hydroxyl group of TYR10. These findings suggest a potential role for inosine as a physiological antagonist of A_{2B}AR.



Note: α1 - red; α2 - orange; α3 - ochre-yellow; α4 - lemon; α5 - green; α6 - turquoise; α7 - blue.

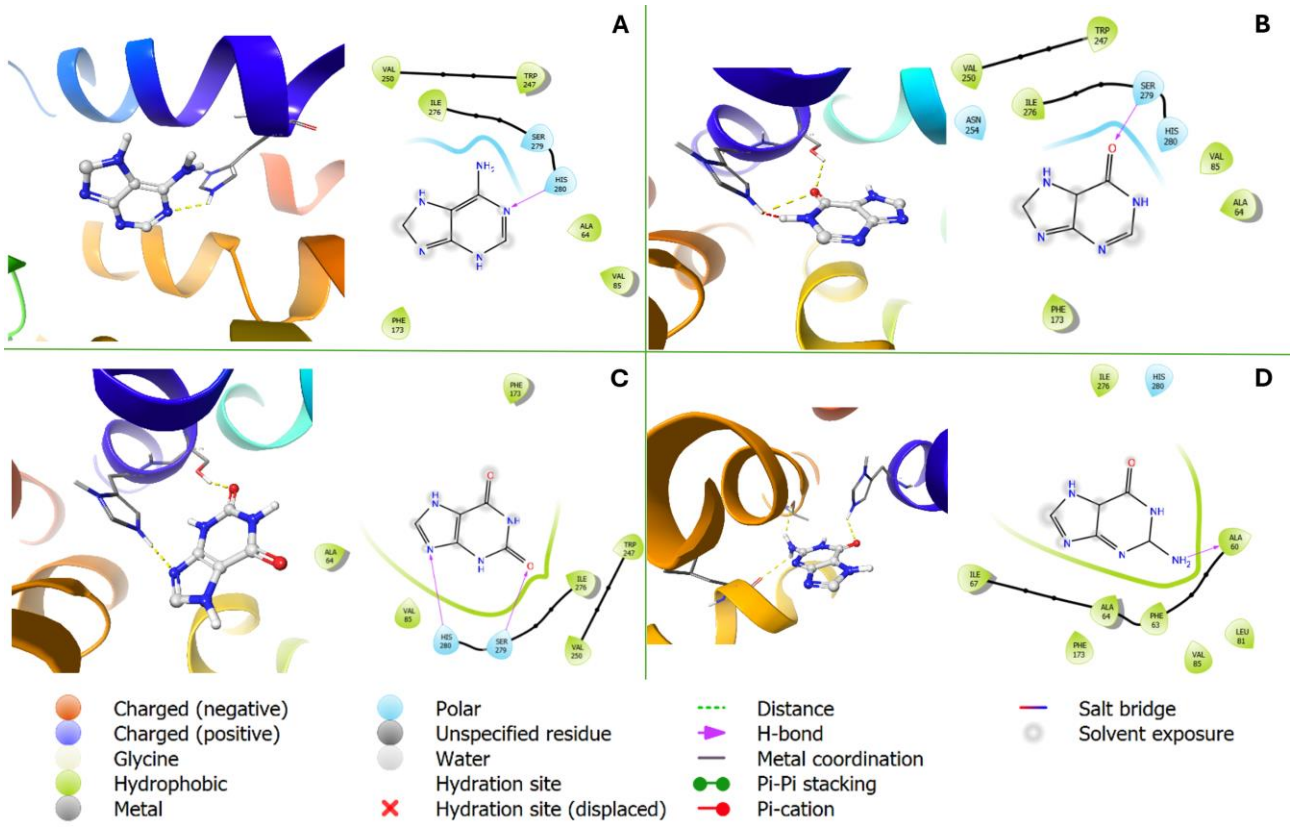
Figure 2. 3D and 2D visualization of molecular interactions between **(A)** Adenosine, **(B)** Inosine, **(C)** Xanthosine, and **(D)** Guanosine and the binding site of the inactive A_{2B}AR

Xanthosine, a less common purine nucleoside, was tested to assess its binding capacity to the inactive form of A_{2B}AR. Docking analysis revealed that xanthosine exhibits a higher binding affinity (ΔG = -6.9 kcal/mol) compared to adenosine and inosine. The structural distinction of xanthosine lies in the presence of an additional oxygen atom at the 2-position of the purine ring, which may contribute to stronger receptor binding.

The most stable conformation of xanthosine interacts with PHE173 and ASN254, located in the α5- and α6-helices, respectively (Figure 2C). PHE173 forms a double π-π interaction with the purine ring of the ligand, whereas adenosine exhibited only a single interaction. ASN254 forms a hydrogen bond between its carboxamide amino group and the oxygen at the 6-position of the purine ring. The absence of interaction with GLU174 and the altered position of the secondary amino group may indicate a potential agonistic activity of xanthosine toward A_{2B}AR.

Guanosine, the fourth tested nucleoside, is structurally similar to inosine but differs by the presence of an amino group at the 2-position of the purine ring. Docking analysis revealed that guanosine exhibits a higher binding affinity (ΔG = -6.7 kcal/mol) compared to adenosine. The primary interactions of guanosine with the receptor occur through residues PHE173 (α5-helix) and SER279 (α7-helix). PHE173 forms a π-π interaction with the benzene ring of the ligand, while SER279 participates in hydrogen bond formation with the hydroxyl group of the ribose at the 5'-position (Figure 2D). These findings suggest a potential role for guanosine as a physiological antagonist of A_{2B}AR.

Adenine is a derivative of adenosine lacking the ribose moiety. Molecular docking results indicated that its affinity for A_{2B}AR is lower than that of adenosine. The maximum and minimum binding free energies were ΔG = -4.7 and ΔG = -4.3 kcal/mol, respectively. Visualization of interactions demonstrated that adenine forms a single hydrogen bond between the tertiary amino group at the 1-position of the purine ring and the secondary amino group of HIS280 (Figure 3A). This amino acid is located on the α7-helix, which could potentially influence the conformation of the α8- and α1-helices. However, the lack of additional interactions suggests that adenine does not exert a significant effect on A_{2B}AR as either an agonist or an antagonist.



Note: α1 - red; α2 - orange; α3 - ochre-yellow; α4 - lemon; α5 - green; α6 - turquoise; α7 - blue.

Figure 3. 3D and 2D visualization of molecular interactions between **(A)** Adenine; **(B)** Hypoxanthine; **(C)** Xanthine; and **(D)** Guanine and the binding site of the inactive A_{2B}AR

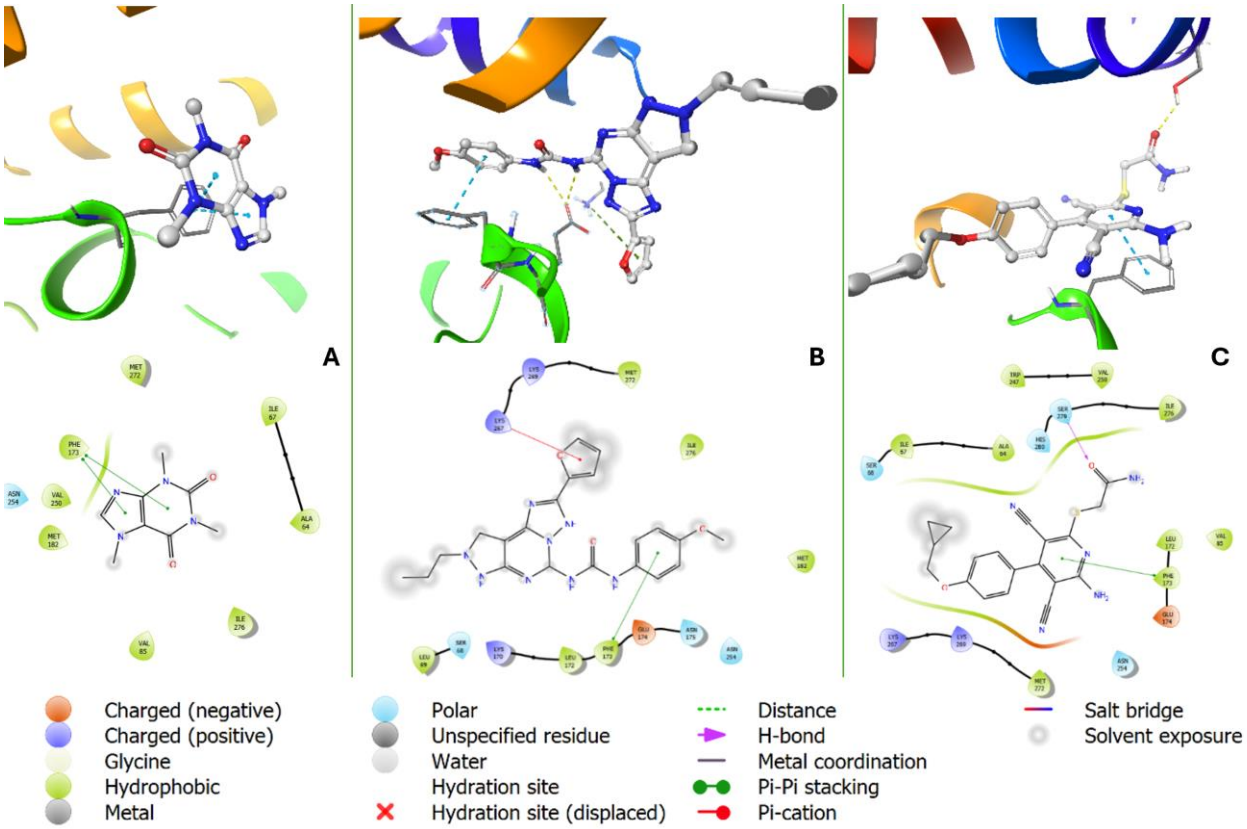
Hypoxanthine has been theoretically considered as a potential A2BAR antagonist, providing the rationale for its molecular docking analysis [44]. However, literature data indicate low receptor affinity for alloxazine under physiological conditions in vitro and in vivo. The obtained results demonstrated that hypoxanthine exhibits a lower affinity for A_{2B}AR compared to adenosine, with the best binding free energy recorded at ΔG = -4.9 kcal/mol. 2D and 3D visualizations revealed that the molecule forms two hydrogen bonds with the α7-helix of the receptor via HIS280 and SER279 (Figure 3B). Hypoxanthine interacts with HIS280 through the secondary amino group at the 1-position of the purine ring, while SER279 forms a hydrogen bond with its carbonyl group at the 6-position. These interactions suggest that binding to the α7-helix may influence the α1-helix, altering the binding pocket and potentially inhibiting the receptor.

Xanthine, a derivative of hypoxanthine, has been considered a potential antagonist of adenosine receptors. However, existing data suggests its possible role as an A_{2B}AR agonist. The primary structural difference between xanthine and hypoxanthine lies in the presence of an additional oxygen atom at the 2-position of the purine ring. Docking results revealed that xanthine exhibits a higher affinity for the receptor compared to hypoxanthine, with the best binding free energy recorded at ΔG = -5.4 kcal/mol. Visualization showed that xanthine forms similar interactions with HIS280 and SER279 but with additional functional contributions from the oxygen at the 2-position and the tertiary amino group at the 9-position (Figure 3C).

Guanine is the last of the naturally occurring purine bases circulating in the human body [30]. It differs from xanthine by the substitution of an oxygen atom at the 2-position of the purine ring with a primary amino group. Molecular docking revealed a similar binding free energy (ΔG = -5.4 kcal/mol), indicating its high affinity for A_{2B}AR. Visualization demonstrated that guanine interacts with three amino acid residues located in different receptor domains: LEU81 (α3-helix), ALA60 (α2-helix), and HIS280 (α7-helix). Hydrogen bonds are formed between LEU81 and the primary amino group at the 2-position of the purine ring, between ALA60 and the same group, as well as between HIS280 and the oxygen at the 6-position of the purine ring (Figure 3D). Potential conformational changes in these structural elements may lead to a reduction in the binding pocket size, making guanine a promising low-affinity antagonist of A_{2B}AR.

Caffeine is a well-known non-selective antagonist of adenosine receptors [31-33]. Numerous antagonists with specificity for different adenosine receptor subtypes have been synthesized based on their molecular structure. In this study, caffeine was used as a reference molecule to assess the inhibitory potential of the purine ring concerning the inactive form of the A_{2B}AR adenosine receptor.

Molecular docking analysis revealed two possible conformations of caffeine that could interact with A_{2B}AR in its inactive state (Figure 4A). Further molecular interaction analysis identified a key π-π interaction between caffeine and the PHE173 residue, which is known to play a significant role in receptor activation. Given the importance of this residue in receptor function, this interaction suggests that caffeine may act as a competitive inhibitor by interfering with ligand binding at the active site. These findings support the established role of caffeine as an effective modulator of adenosine receptor activity, further validating its function as a benchmark compound in receptor inhibition studies.



Note: α1 - red; α2 - orange; α3 - ochre-yellow; α4 - lemon; α5 - green; α6 - turquoise; α7 - blue.

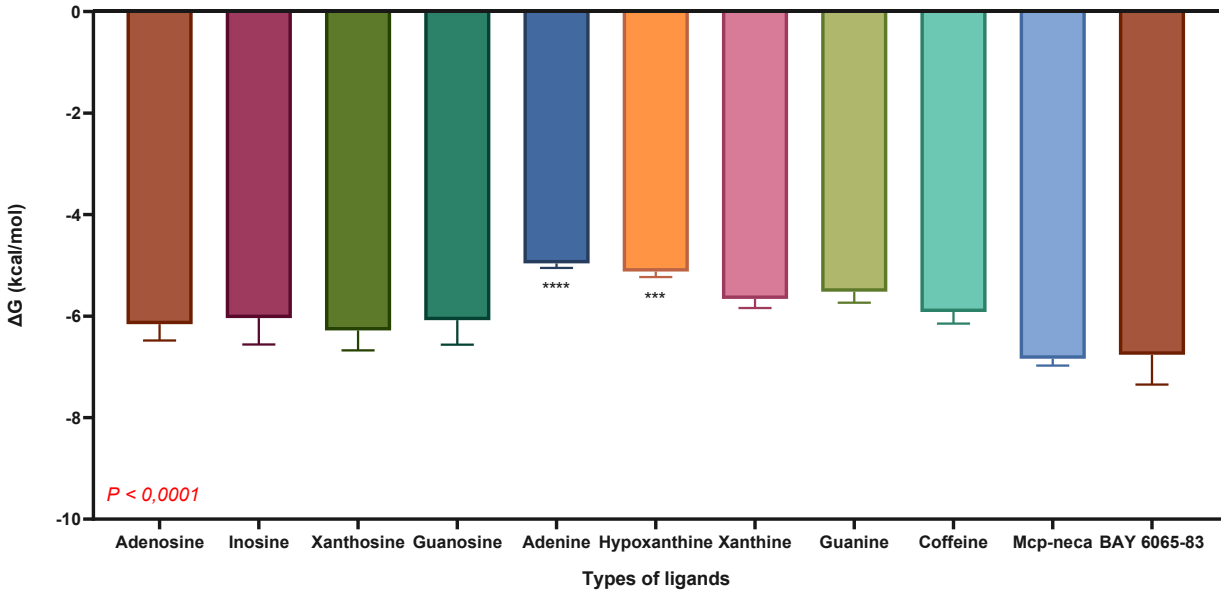
Figure 4. 3D and 2D visualization of molecular interactions of **(A)** Caffeine, **(B)** Mcp-neca, **(C)** BAY 6065–83 with the A_{2B}AR binding site

Mcp-neca, as previously described, is an antagonist of both A_{2B} and A3 AR [34]. In this study, molecular docking of Mcp-neca was performed with both inactive and active forms of A_{2B}AR to elucidate its inhibition mechanisms. The results indicate a significantly higher affinity of Mcp-neca compared to adenosine (ΔG = -7.5 kcal/mol, with a minimum value of ΔG = -6.8 kcal/mol). Interaction visualization (Figure 4B) revealed that Mcp-neca interacts with at least three amino acid residues: PHE 173, GLU 174, and LYS 267. The PHE 173 residue, located in the α5-helix, participates in a π-π interaction with the ligand's benzene ring, potentially stabilizing the complex. GLU 174 forms hydrogen bonds, which may restrict α5-helix mobility and prevent G-protein activation. The most significant contribution to affinity is likely to come from the π-cation interaction between the positively charged LYS 267 and the ligand's aromatic system. Thus, Mcp-neca acts as a competitive antagonist by blocking the active site and preventing adenosine

The final tested ligand was BAY 6065–83, known as a selective A_{2B}AR agonist. Analysis of cryo-EM structures identified active conformations of the receptor interacting with BAY 6065–83. Molecular docking results showed that the ligand's highest affinity was ΔG = -7.3 kcal/mol. Interaction visualization (Figure 4C) revealed two key interactions: a π-π interaction with PHE 173 (α5-helix) and a hydrogen bond with SER 279 (α7-helix). These interactions are characteristic of both adenosine receptor agonists and antagonists. Thus, BAY 6065–83 exhibits specific interactions with A_{2B}AR that may play a crucial role in its activation.

In silico analysis of nucleotide binding to the active $A_{2B}AR$

After molecular docking with the inactive form of the A2BAR receptor, similar calculations were performed for its active form. The study covered 11 different ligands, including natural purines as well as selective and non-selective antagonists and agonists (Figure 5). The analysis identified potential agonists (xanthosine), antagonists (inosine, guanosine, guanine), and molecules with no significant effect (adenine). The roles of xanthine and hypoxanthine remain uncertain.

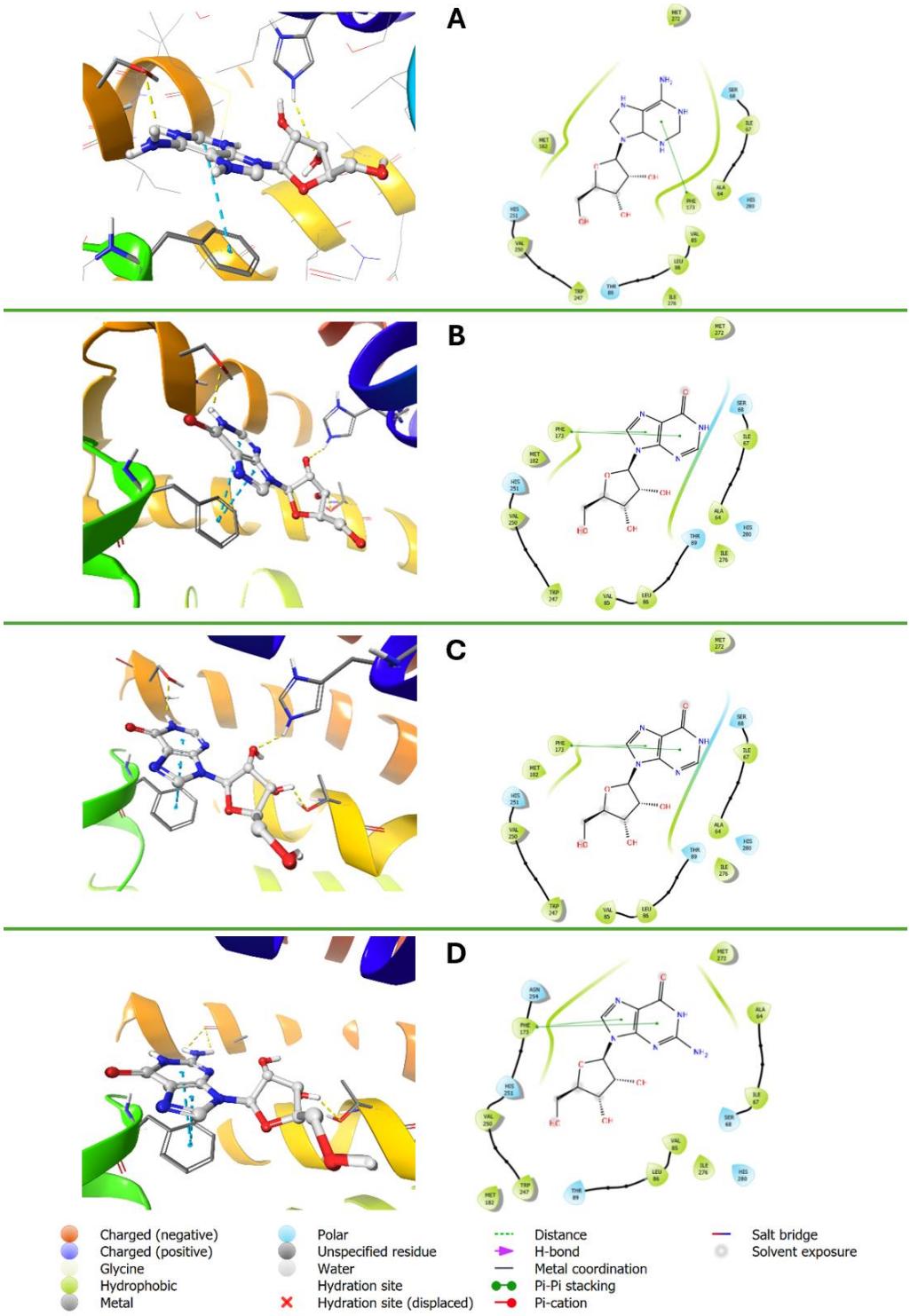


Note: Tukey's multiple comparison test was used to assess statistical significance relative to adenosine. Columns without labels are not significant, whereas asterisks indicate significance.

Figure 5. Change ΔG for ligand binding to the active $A_{2B}AR$

This section focuses on the analysis of natural nucleosides to confirm their functional role, as well as the selective antagonist MCP-NECA and the selective agonist BAY 6065–83. Affinity evaluation is based on binding free energy, analyzed only for the most stable complexes. Additionally, the interaction patterns of these ligands with key receptor residues were examined to provide further insights into their binding mechanisms.

The ΔG values for interactions between the active form of $A_{2B}AR$ and adenosine, inosine, xanthosine, and guanosine did not show significant differences in affinity (Figure 5). Among them, adenosine exhibited the lowest affinity (ΔG = -6.6 kcal/mol), while guanosine demonstrated the highest binding affinity (ΔG = -6.9 kcal/mol). The presumed agonist xanthosine displayed an intermediate ΔG value of -6.8 kcal/mol. Molecular interaction analysis revealed that all potential agonists form a π-π interaction with the hydrophobic residue PHE 173 (α5-helix). Adenosine, inosine, and xanthosine establish a hydrogen bond with HIS 280 (α7-helix) via the ribose moiety. Additionally, inosine, xanthosine, and guanosine interact with THR 89 (α2-helix), whereas guanosine, unlike the other molecules, forms a hydrogen bond with ALA 64 instead of SER 68 (Figure 6).



Note: α1 - red; α2 - orange; α3 - ochre-yellow; α4 - lemon; α5 - green; α6 - turquoise; α7 - blue.

Figure 6. 3D and 2D visualization of molecular interactions of **(A)** Adenosine, **(B)** Inosine, **(C)** Xanthosine, and **(D)** Guanosine with the binding site of the active $A_{2B}AR$

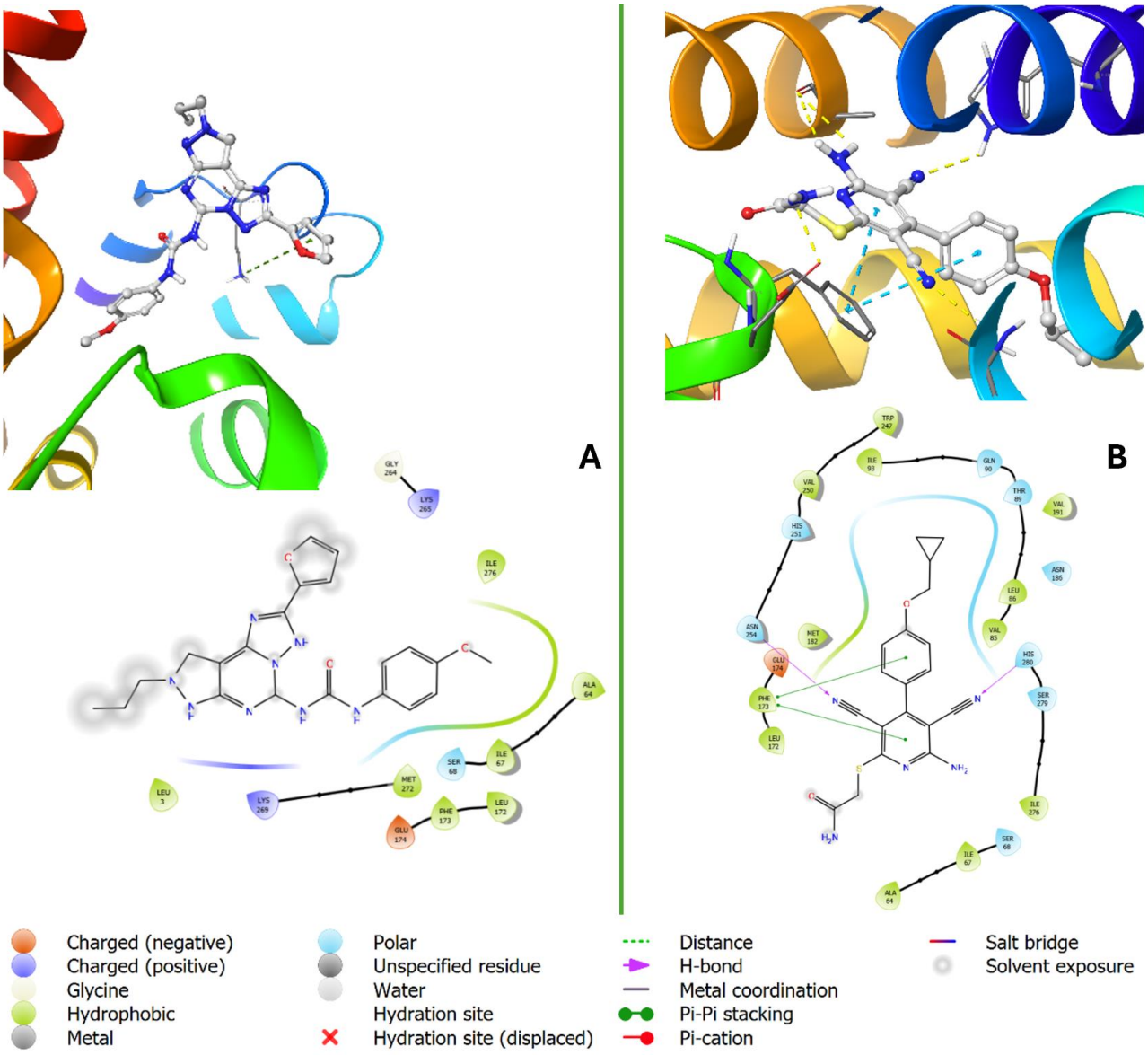
The data obtained suggest that xanthosine is likely to be an agonist of A_{2B}AR, as its interactions align with known parameters of agonistic activity. However, the influence of an additional hydrogen bond with THR 89 remains unclear and may merely enhance affinity without inducing conformational changes in the receptor. Inosine and guanosine also exhibit agonistic potential, but their interactions with key amino acids differ, which could indicate possible antagonistic activity of guanosine.

A literature review on the potential role of inosine in A_{2B}AR signaling revealed conflicting evidence. While several studies demonstrate that inosine interacts with A_{2A}AR adenosine receptors, these findings cannot be directly extrapolated to A_{2B}AR due to significant differences in their signaling mechanisms. A_{2A}AR primarily couples to Gs proteins, leading to increased intracellular cAMP levels, whereas A2BAR can couple to both Gs and Gq proteins, resulting in more complex and context-dependent signaling pathways. Studies on A_{2A}AR typically employ adenosine concentrations of 30 nM and 100 nM, whereas research on A2BAR indicates that this receptor has a relatively low affinity for its natural agonist, with a Ki value of 15,000 nM (equivalent to 15 μM) [12, 45, 46]. Interestingly, one study also utilized a significantly higher inosine concentration of 100 mM, which showed an increase in dynamic mass redistribution. However, this experiment was conducted on cells overexpressing A_{2A}AR, raising concerns about the validity of the observed effects [12]. Given the distinct functional roles and signaling pathways of A_{2A}AR and A_{2B}AR, it remains unclear whether inosine acts as an agonist, antagonist, or neutral ligand for A_{2B}AR. Direct functional assays are necessary to determine their precise activity.

These findings highlight the complexity of nucleoside-receptor interactions and suggest that further investigation is needed to determine the precise functional roles of inosine and guanosine in A_{2B}AR signaling. Future studies should aim to clarify whether their effects are context-dependent and whether variations in receptor expression levels influence their agonistic or antagonistic properties. It is important to note that in two separate experiments, the A_{2A} receptor antagonist [3H]ZM 241385 was used as a control agent to assess the binding of inosine to this receptor. However, this compound is also known to act as an A_{2B} antagonist, raising concerns regarding the validity of these findings. As a result, we cannot fully accept these data as definitive evidence [44]. Consequently, we propose the hypothesis that inosine may act as an A2BAR antagonist, but further experimental validation is required.

In this study, the selective antagonist Mcp-neca and the selective agonist BAY 6065–83 were analyzed in complex with the active form of A2BAR. The calculated binding free energy was ΔG = -7.4 kcal/mol for BAY 6065–83 and ΔG = -7.0 kcal/mol for Mcp-neca. Molecular docking results indicate that MCP-NECA loses a significant portion of its interactions in the active state of the receptor, although it retains π-π interactions with amino acid residues of the α7-helix.

In contrast, BAY 6065–83 exhibits interaction patterns similar to those of adenosine. Specifically, PHE 173 (α5-helix) forms a π-π interaction, while hydrogen bonds are established with HIS 280 (α7-helix), ALA 64 (α2-helix), GLU 174 (α5-helix), and ASN 254 (α5-helix). These findings suggest that BAY 6065–83 engages key structural elements involved in receptor activation, reinforcing its role as a potent A_{2B}AR agonist.



Note: α1 - red; α2 - orange; α3 - ochre-yellow; α4 - lemon; α5 - green; α6 - turquoise; α7 - blue.

Figure 7. 3D and 2D visualization of molecular interactions of **(A)** Mcp-neca, **(B)** BAY 6065–83 with the binding site of the active $A_{2B}AR$

Discussion

$A_{2B}AR$ plays a crucial role in various physiological processes, including inflammation, immune modulation, and vascular regulation [6-13]. Previously, adenosine and its analogs were considered to be the primary ligands for this receptor. However, our findings indicate that

all endogenous purines may also interact with A_{2B}AR. In this study, we have demonstrated that endogenous purines exhibit a high affinity for A_{2B}AR, as confirmed by molecular docking analysis. These results expand the current understanding of the role of purines in the regulation of the adenosinergic system and may have significant physiological and pharmacological implications.

Studies have shown that A_{2B}AR is involved in the differentiation of CD4+ T cells into regulatory T cells *(Tregs)* [47]. The work of Hiroko Nakatsukasa *et al.* demonstrated that A_{2B}AR antagonists inhibit Foxp3 expression and IL-10 production without affecting CD4+ T cell activation. These findings highlight the pivotal role of A_{2B}AR in immune regulation. Regulatory T cells play a crucial role in maintaining peripheral immune tolerance and suppressing excessive immune responses. Notably, a reduction in *Treg* numbers has been associated with enhanced antitumor immunity [47,48]. Consequently, A_{2B}AR antagonists, by inhibiting *Treg* differentiation, may enhance the effectiveness of immune responses against tumor cells.

In the study by Matthias Seifert et al., the influence of A_{2A} and A_{2B} adenosine receptors on murine CAR-T cells was investigated [49]. It was established that the non-specific adenosine receptor agonist NECA reduces the release of IFN-γ, IL-2, and TNF-α in a dose-dependent manner [49]. CAR-T cells predominantly express A2A and A2B AR; however, the potential expression of A1 and A3 AR cannot be ruled out. Given that the EC50 values for NECA are 14 nM (A1), 20 nM (A_{2A}), 2.4 μM (A_{2B}), and 6.2 nM (A_3), it can be inferred that the observed reduction in cytokine secretion may also be influenced by the activation of A_1 and A_3 receptors, rather than being exclusively attributed to A_{2A} and A_{2B} [49,50].

Literature data confirm that the primary immunosuppressive effect of adenosine in CAR-T cells is mediated through the A_{2A} receptor [51]. Consequently, its activation suppresses the production of pro-inflammatory cytokines, which may be linked not only to the Gαs protein but also to the involvement of Gβ/γ subunits. Experimental data indicate that at low concentrations of the A_{2A} antagonist AB928 (<10 nM, EC50 = 2 nM), the secretion of pro-inflammatory cytokines is also reduced [52]. This suggests that A2B signaling in CAR-T cells may activate the Gq pathway, promoting differentiation without directly affecting cytokine synthesis. In contrast, A_{2B} antagonists inhibit differentiation while having no significant impact on cytokine production.

Inflammation plays a crucial role in the development of neurodegenerative disorders such as Alzheimer's and Parkinson's disease. Neuroinflammation, characterized by elevated levels of pro-inflammatory cytokines and activated microglia, contributes to disease progression [53]. Chronic microglial activation leads to increased production of inflammatory mediators, forming a vicious cycle of neuronal damage and further inflammation [54]. Protein aggregates, common in neurodegenerative diseases, can both induce and exacerbate neuroinflammation [53]. In Parkinson's disease, immune alterations in response to extracellular α-synuclein may modulate disease progression [55]. While it remains unclear whether neuroinflammation is a primary cause or secondary consequence of neurodegeneration, targeting inflammatory processes has emerged as a promising therapeutic strategy [53,54]. The activation of adenosine receptors, particularly A_{2B}, may influence neuroinflammatory processes by modulating immune cell activity in the central nervous system. Our findings suggest a potential role for endogenous purines in regulating inflammation through A2B receptors, opening new avenues for exploring their involvement in the pathogenesis of neurodegenerative diseases.

Despite the significance of our results, this study has certain limitations. Our conclusions are currently based solely on molecular docking, which indicates potential interactions between endogenous purines and the A_{2B} adenosine receptor. However, additional biochemical studies, including experiments on cell lines and in vivo models, are necessary to confirm their physiological role.

If A_{2B} AR indeed influences T-cell differentiation, this could present new opportunities for immunotherapy. On one hand, activation of this receptor may promote the development of regulatory T cells (Treg), which are essential for controlling autoimmune diseases and inflammatory processes. On the other hand, the inhibition of A_{2B} AR could enhance anti-tumor immunity by suppressing Treg differentiation and increasing the activity of effector T cells. Future research should focus on elucidating the effects of endogenous purines on A_{2B} AR in the context of immune regulation, which could provide valuable insights into their potential therapeutic applications in cancer and inflammatory diseases.

Author Contributions

M.S. – conceptualization; **M.S.–** methodology; **M.S**.– investigation; **M.S.–** validation; **M.S.–** data curation; **M.S. –** visualization; **M.S. –** writing – original draft; **M.S.** and **E.Ch.** – writing – review & editing.

Funding

The authors declare that this work was not supported by any grants or external funding.

Acknowledgments

We express our sincere gratitude to Nurzhan Abdukarimov for his assistance with the software setup and the Vina AutoDock GPU installation.

Conflicts of Interest

The authors declare no conflict of interest.

Compliance with ethical standards

This article does not contain a description of studies performed by the authors involving people or using animals as objects.

References

1. Wang J, Bhattarai A, Do HN, et al. Molecular Simulations and Drug Discovery of Adenosine Receptors. Molecules 2022; 27. https://doi.org/10.3390/molecules27072054.

2. Pasquini S, Contri C, Borea PA, et al. Adenosine and Inflammation: Here, There and Everywhere. International Journal of Molecular Sciences 2021; 22. https://doi.org/10.3390/ijms22147685.

3. Vincenzi F, Pasquini S, Contri C, et al. Pharmacology of Adenosine Receptors: Recent Advancements. Biomolecules 2023; 13. https://doi.org/10.3390/biom13091387.

4. Pasquini S, Contri C, Merighi S, et al. Adenosine Receptors in Neuropsychiatric Disorders: Fine Regulators of Neurotransmission and Potential Therapeutic Targets. International Journal of Molecular Sciences 2022; 23. https://doi.org/10.3390/ijms23031219.

5. Barresi E, Martini C, Da Settimo F, et al. Allosterism vs. Orthosterism: Recent Findings and Future Perspectives on A2B AR Physio-Pathological Implications. Frontiers in Pharmacology 2021; 12. https://doi.org/10.3389/fphar.2021.652121

6. Francucci B, Dal Ben, Diego, Lambertucci, Catia, et al. A patent review of adenosine A2B receptor antagonists (2016-present). Expert Opinion on Therapeutic Patents 2022; 32:689-712. https://doi.org/10.1080/13543776.2022.2057222.

7. Effendi WI, Nagano T, Kobayashi K, et al. Focusing on Adenosine Receptors as a Potential Targeted Therapy in Human Diseases. Cells 2020; 9. https://doi.org/10.3390/cells9030785.

8. Zhao N, Xia G, Cai J, et al. Adenosine receptor A2B mediates alcoholic hepatitis by regulating cAMP levels and the NF-KB pathway. Toxicology Letters 2022; 359:84-95. https://doi.org/10.1016/j.toxlet.2022.01.012.

9. Vecchio EA, White PJ, May LT. The adenosine A2B G protein-coupled receptor: Recent advances and therapeutic implications. Pharmacology & Therapeutics 2019; 198:20-33. https://doi.org/10.1016/j.pharmthera.2019.01.003.

10. Aherne CM, Kewley EM, Eltzschig HK. The resurgence of A2B adenosine receptor signaling. Biochimica et Biophysica Acta (BBA) - Biomembranes 2011; 1808:1329-39. https://doi.org/10.1016/j.bbamem.2010.05.016.

11. Sun Y, Huang P. Adenosine A2B Receptor: From Cell Biology to Human Diseases. Frontiers in Chemistry 2016; 4. https://doi.org/10.3389/fchem.2016.00037

12. Welihinda AA, Kaur M, Greene K, et al. The adenosine metabolite inosine is a functional agonist of the adenosine A2A receptor with a unique signaling bias. Cellular Signalling 2016; 28:552-60. https://doi.org/10.1016/j.cellsig.2016.02.010.

13. Ingersoll SA, Laroui H, Kolachala VL, et al. A2BAR expression in non-immune cells plays an important role in the development of murine colitis. Digestive and Liver Disease 2012; 44:819-26. https://doi.org/10.1016/j.dld.2012.05.013.

14. Kalla RV, Zablocki J, Tabrizi MA, et al. Recent Developments in A2B Adenosine Receptor Ligands. In: Wilson CN, Mustafa SJ, editors. Adenosine Receptors in Health and Disease, Berlin, Heidelberg: Springer Berlin Heidelberg; 2009, p. 99-122. https://doi.org/10.1007/978-3-540-89615-9_4.

15. Pran Kishore Deb. Progress in the Development of Agonists, Antagonists, and Allosteric Modulators of Adenosine Receptors. Current Pharmaceutical Design 2019; 25:2695-6. https://doi.org/10.2174/1381612825251909161001 49.

16. Dai S-S, Zhou Y-G. Adenosine 2A receptor: a crucial neuromodulator with bidirectional effect in neuroinflammation and brain injury 2011; 22:231-9. https://doi.org/10.1515/rns.2011.020.

17. Maria P. A, Geoffrey B. Purinergic Signalling: Pathophysiological Roles. Japanese Journal of Pharmacology 1998; 78:113-45. https://doi.org/10.1254/jjp.78.113.

18. Pándy-Szekeres G, Caroli J, Mamyrbekov A, et al. GPCRdb in 2023: state-specific structure models using AlphaFold2 and new ligand resources. Nucleic Acids Research 2023; 51:D395-402. https://doi.org/10.1093/nar/gkac1013.

19. Satkanov M, Chupakhin E. The Potential of AlphaFold2-Predicted Adenosine Receptor Structures in Drug Discovery and Molecular Modeling. BULLETIN of the LN Gumilyov Eurasian National University BIOSCIENCE Series 2024;146:188–204. https://doi.org/10.32523/2616-7034-2024-146-1-188-204.

20. Miura S, Kiya Y, Hanzawa H, et al. Small Molecules with Similar Structures Exhibit Agonist, Neutral Antagonist or Inverse Agonist Activity toward Angiotensin II Type 1 Receptor. PLOS ONE 2012; 7:e37974. https://doi.org/10.1371/journal.pone.0037974.

21. Nuñez-Rios JD, Ulrich H, Díaz-Muñoz M, et al. Purinergic system in cancer stem cells. Purinergic Signalling 2025; 21:23-38. https://doi.org/10.1007/s11302-023-09976-5.

22. Lopez-Ibañez J, Pazos F, Chagoyen M. Predicting biological pathways of chemical compounds with a profile-inspired aproach. bioRxiv 2021:2021.03.02.433511. https://doi.org/10.1101/2021.03.02.433511.

23. Seeger C, Poulsen C, Dandanell G. Identification and characterization of genes (xapA, xapB, and xapR) involved in xanthosine catabolism in Escherichia coli. Journal of Bacteriology 1995; 177:550-16. https://doi.org/10.1128/jb.177.19.5506-5516.1995.

24. Barsotti C, Pesi R, Giannecchini M, et al. Evidence for the Involvement of Cytosolic 5′-Nucleotidase (cN-II) in the Synthesis of Guanine Nucleotides from Xanthosine *. Journal of Biological Chemistry 2005; 280:13465-9. https://doi.org/10.1074/jbc.M413347200.

25. Di Iorio P, Ciccarelli R. Adenine-Based Purines and Related Metabolizing Enzymes: Evidence for Their Impact on Tumor Extracellular Vesicle Activities. Cells 2021;10. https://doi.org/10.3390/cells10010188.

26. Furuhashi M. New insights into purine metabolism in metabolic diseases: role of xanthine oxidoreductase activity. American Journal of Physiology-Endocrinology and Metabolism 2020;319:E827–34. https://doi.org/10.1152/ajpendo.00378.2020.

27. Yamamoto T, Moriwaki Y, Takahashi S. Effect of ethanol on metabolism of purine bases (hypoxanthine, xanthine, and uric acid). Clinica Chimica Acta 2005; 356:35-57. https://doi.org/10.1016/j.cccn.2005.01.024.

28. Harkness RA. Hypoxanthine, xanthine and uridine in body fluids, indicators of ATP depletion. Journal of Chromatography B: Biomedical Sciences and Applications 1988; 429:255-78. https://doi.org/10.1016/S0378-4347(00)83873-6.

29. Kapri A, Pant S, Gupta N, et al. Recent Advances in the Biological Significance of Xanthine and its Derivatives: A Review. Pharmaceutical Chemistry Journal 2022; 56:461-74. https://doi.org/10.1007/s11094-022-02661-8.

30. Cadet J, Douki T, Gasparutto D, et al. Oxidative damage to DNA: formation, measurement and biochemical features. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 2003; 531:5-23. https://doi.org/10.1016/j.mrfmmm.2003.09.001.

31. Lin Z, Wei J, Hu Y, et al. Caffeine Synthesis and Its Mechanism and Application by Microbial Degradation, A Review. Foods 2023; 12. https://doi.org/10.3390/foods12142721.

32. Basu S, Barawkar DA, Ramdas V, et al. A2B adenosine receptor antagonists: Design, synthesis and biological evaluation of novel xanthine derivatives. European Journal of Medicinal Chemistry 2017; 127:986-96. https://doi.org/10.1016/j.ejmech.2016.11.007.

33. Buscariollo DL, Breuer GA, Wendler CC, et al. Caffeine Acts via A1 Adenosine Receptors to Disrupt Embryonic Cardiac Function. PLOS ONE 2011;6:e28296. https://doi.org/10.1371/journal.pone.0028296.

34. Varani K, Gessi S, Merighi S, et al. Pharmacological characterization of novel adenosine ligands in recombinant and native human A2B receptors. Biochemical Pharmacology 2005;70:1601–12. https://doi.org/10.1016/j.bcp.2005.08.018.

35. Hinz S, Lacher SK, Seibt BF, et al. BAY60-6583 Acts as a Partial Agonist at Adenosine A2B Receptors. The Journal of Pharmacology and Experimental Therapeutics 2014; 349:427-36. https://doi.org/10.1124/jpet.113.210849.

36. Tang S, Chen R, Lin M, et al. Accelerating AutoDock Vina with GPUs. Molecules 2022;27. https://doi.org/10.3390/molecules27093041.

37. Ding J, Tang S, Mei Z, et al. Vina-GPU 2.0: Further Accelerating AutoDock Vina and Its Derivatives with Graphics Processing Units. J Chem Inf Model 2023; 63:1982-98. https://doi.org/10.1021/acs.jcim.2c01504.

38. Yu Y, Cai C, Wang J, et al. Uni-Dock: GPU-Accelerated Docking Enables Ultralarge Virtual Screening. J Chem Theory Comput 2023; 19:3336-45. https://doi.org/10.1021/acs.jctc.2c01145.

39. Morris GM, Huey R, Olson AJ. Using AutoDock for Ligand-Receptor Docking. Current Protocols in Bioinformatics 2008;24:8.14.1-8.14.40. https://doi.org/10.1002/0471250953.bi0814s24.

40. Zhang D, Li ,Haisheng, Wang ,Huixian, et al. Docking accuracy enhanced by QM-derived protein charges. Molecular Physics 2016; 114:3015-25. https://doi.org/10.1080/00268976.2016.1213908.

41. Yuan S, Chan HCS, Hu Z. Using PyMOL as a platform for computational drug design. WIREs Computational Molecular Science 2017; 7:e1298. https://doi.org/10.1002/wcms.1298.

42. Mathai N, Chen Y, Kirchmair J. Validation strategies for target prediction methods. Briefings in Bioinformatics 2020; 21:791-802. https://doi.org/10.1093/bib/bbz026.

43. Cai H, Xu Y, Guo S, et al. Structures of adenosine receptor A2BR bound to endogenous and synthetic agonists. Cell Discovery 2022; 8:140. https://doi.org/10.1038/s41421-022-00503-1.

44. Hayallah AM, Sandoval-Ramírez J, Reith U, et al. 1,8-Disubstituted Xanthine Derivatives: Synthesis of Potent A2B-Selective Adenosine Receptor Antagonists. J Med Chem 2002; 45:1500-10. https://doi.org/10.1021/jm011049y.

45. Erices JI, Niechi I, Uribe-Ojeda A, et al. The low affinity A2B adenosine receptor enhances migratory and invasive capacity in vitro and angiogenesis in vivo of glioblastoma stem-like cells. Frontiers in Oncology 2022;12.

46. Welihinda AA, Kaur M, Raveendran KS, et al. Enhancement of inosine-mediated A2AR signaling through positive allosteric modulation. Cellular Signalling 2018; 42:227-35. https://doi.org/10.1016/j.cellsig.2017.11.002.

47. Nakatsukasa H, Tsukimoto M, Harada H, et al. Adenosine A2B receptor antagonist suppresses differentiation to regulatory T cells without suppressing activation of T cells. Biochemical and Biophysical Research Communications 2011; 409:114-9. https://doi.org/10.1016/j.bbrc.2011.04.125.

48. Nishikawa H, Sakaguchi S. Regulatory T cells in tumor immunity. International Journal of Cancer 2010; 127:759-67. https://doi.org/10.1002/ijc.25429.

49. Seifert M, Benmebarek M-R, Briukhovetska D, et al. Impact of the selective A2AR and A2BR dual antagonist AB928/etrumadenant on CAR T cell function. British Journal of Cancer 2022; 127:2175-85. https://doi.org/10.1038/s41416-022-02013-z.

50. NECA | Non-selective Adenosine Agonists. Tocris Bioscience n.d. [cited 2024 March]. Available from: https://www.tocris.com/products/neca_1691

51. Li N, Tang ,Na, Cheng ,Chen, et al. Improving the anti-solid tumor efficacy of CAR-T cells by inhibiting adenosine signaling pathway. OncoImmunology 2020; 9:1824643. https://doi.org/10.1080/2162402X.2020.1824643.

52. Etrumadenant (AB928) | 99.8%(HPLC) | Adenosine Receptor antagonist. SelleckchemCom n.d. [cited 2024 March]. Available from: https://www.selleckchem.com/products/ab928.html.

53. Zhang W, Xiao D, Mao Q, et al. Role of neuroinflammation in neurodegeneration development. Signal Transduction and Targeted Therapy 2023; 8:267. https://doi.org/10.1038/s41392-023-01486-5.

54. Deepak Kumar Kaushik, Anirban Basu. A Friend in Need May Not be a Friend Indeed: Role of Microglia in Neurodegenerative Diseases. CNS & Neurological Disorders - Drug Targets 2013; 12:726-40. https://doi.org/10.2174/18715273113126660170.

55. Gelders G, Baekelandt V, Van der Perren A. Linking Neuroinflammation and Neurodegeneration in Parkinson's Disease. Journal of Immunology Research 2018; 2018:4784268. https://doi.org/10.1155/2018/4784268.

Эндогендік пуриндер A_{2B} аденозин рецепторының табиғи лигандтары ретінде

М. Сатканов*[1], Е. Чупахин[1]

[1]Иммануэль Кант атындағы Балтық федералды университеті, Калининград, Ресей Федерациясы

Аңдатпа. Эндогендік пуриндер әртүрлі физиологиялық функциялардың, соның ішінде иммундық жауаптың, қабынудың және нейротрансмиссияның маңызды реттеушілері болып табылады. Аденозин ұзақ уақыт бойы аденозиндік рецепторлар үшін негізгі лиганд болып саналғанымен, соңғы деректер басқа пуриндердің де осы рецепторлармен, атап айтқанда A_{2B} аденозиндік рецепторларымен (A_{2B}AR) әрекеттесе алатынын көрсетеді. Бұл зерттеу молекулалық докинг арқылы A_{2B}AR табиғи лигандтары ретінде эндогендік пуриндердің әлеуетті рөлін зерттейді. Нәтижелер пуриндердің A_{2B}AR-ға жоғары жақындығын көрсетеді, бұл олардың осы рецептор арқылы болатын сигнал беру жолдарындағы функционалдық маңыздылығын көрсетеді. Сонымен қатар, A_{2B}AR Т жасушаларының дифференциациясына және цитокиндердің өндірісіне әсер ету арқылы иммундық реттеуде шешуші рөл атқарады. Оның белсенділігін эндогендік пуриндермен модуляциялау ісік және нейродегенеративті бұзылыстарды қоса, қабыну ауруларын емдеуге айтарлықтай әсер етуі мүмкін. Алынған деректер аденозинергиялық жүйенің пуринергиялық бақылауы туралы жаңа түсініктер береді және терапевтік мақсат ретінде A_{2B}AR әлеуетін көрсетеді. Дегенмен, осы өзара әрекеттесулердің физиологиялық маңыздылығын түпкілікті растау үшін *in vitro* және *in vivo* эксперименттерін қоса, қосымша зерттеулер қажет. Бұл зерттеу пуринергиялық сигнализация туралы түсінігімізді кеңейтеді және иммундық және қабыну реакциясын модуляциялауға бағытталған фармакологиялық араласуды дамыту үшін жаңа жолдарды ашады.

Түйін сөздер: A_{2B} аденозин рецепторы, пуринергиялық сигнализация, иммундық модуляция, қабыну және нейродегенерация, молекулалық докинг талдауы

Эндогенные пурины как естественные лиганды A_{2B} рецептора аденозина

М. Сатканов*[1], Е. Чупахин[1]

[1]Балтийский федеральный университет им. Иммануила Канта, Калининград, Российская Федерация

Аннотация. Эндогенные пурины являются важными регуляторами различных физиологических функций, включая иммунный ответ, воспаление и нейротрансмиссию. Хотя аденозин долгое время считался основным лигандом аденозиновых рецепторов, последние данные свидетельствуют о том, что другие пурины также могут взаимодействовать с этими рецепторами, в частности, с A_{2B}-аденозиновым рецептором (A_{2B}AR). В данном исследовании изучается потенциальная роль эндогенных пуринов как природных лигандов A_{2B}AR с использованием молекулярного докинга. Результаты демонстрируют высокую аффинность пуринов к A_{2B}AR, что указывает на их функциональную значимость в сигнальных путях, опосредованных этим рецептором. Кроме того, A_{2B}AR играет ключевую роль в иммунной регуляции, влияя на дифференцировку Т-клеток и продукцию цитокинов. Модуляция его активности эндогенными пуринами может иметь значительное значение для лечения воспалительных заболеваний, включая рак и нейродегенеративные расстройства. Полученные данные дают новые представления о пуринергическом контроле аденозинергической системы и подчеркивают перспективность A_{2B}AR как терапевтической мишени. Однако для окончательного подтверждения физиологической значимости этих взаимодействий необходимы дополнительные исследования, включая эксперименты *in vitro* и *in vivo.* Это исследование расширяет понимание пуринергической сигнализации и открывает новые возможности для разработки фармакологических вмешательств, направленных на модуляцию иммунного и воспалительного ответа.

Ключевые слова: A_{2B} рецептор аденозина, пуринергическая сигнализация, иммунная модуляция, воспаление и нейродегенерация, молекулярный стыковочный анализ

Сведения об авторах:

Сатканов Мереке **–** магистр в области химии, аспирант, Балтийский федеральный университет имени Иммануила Канта, Институт медицины и наук о жизни, Высшая школа живых систем, Калининград, 236041, Российская Федерация.

Чупахин Евгений **–** к.х.н., доцент, Балтийский федеральный университет имени Иммануила Канта, Институт медицины и наук о жизни, Высшая школа живых систем, Калининград, 236041, Российская Федерация.

Авторлар туралы мәліметтер:

Сатканов Мереке – химия саласындағы магистр, PhD докторанты, Иммануэль Кант атындағы Балтық федералды университеті, Медицина және өмір туралы ғылымдар институты, Тірі жүйелердің жоғары мектебі, Калининград, 236041, Ресей Федерациясы.

Чупахин Евгений – химия ғылымдарының кандидаты, доцент, Иммануэль Кант атындағы Балтық федералды университеті, Медицина және өмір туралы ғылымдар институты, Тірі жүйелердің жоғары мектебі, Калининград, 236041, Ресей Федерациясы.

Authors' information:

Satkanov Mereke – Master in the field of chemistry, PhD student, Immanuel Kant Baltic Federal University, Institute of Medicine and Life Sciences, Higher School of Living Systems, Kaliningrad, 236041, Russian Federation.

Chupakhin Evgeny – Candidate of chemical sciences, Associate Professor, Immanuel Kant Baltic Federal University, Institute of Medicine and Life Sciences, Higher School of Living Systems, Kaliningrad, 236041, Russian Federation.