Design, Molecular Docking, and Pharmacokinetic Evaluation of Thioimidazole-4-one Derivatives for Asthma Treatment

Noor Mohammed Mousa، **Abdull Jabar Attia, Karima Fadhil Ali, **** Vesen Atiroğlu**

**Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Mustansiriyah University, Baghdad, Iraq.*

**** Department of Pharmaceutical Chemistry, college of Pharmacy, Mustansiriyah University, Baghdad, Iraq.*

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Corresponding Author email:
noor-moh@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0009-0006-9495-6987

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Abstract:

This study investigates the design, molecular docking, and swissadme properties of thioimidazole-4-one derivatives as potential therapeutic agents targeting the A2A adenosine receptor for asthma treatment. Computational molecular docking (GOLD) was performed using the A2A receptor complexed with theophylline (PDB ID: 5MZJ), and the Suggested compounds were compared to theophylline to evaluate binding affinity. Docking results revealed that the proposed compounds showed stronger binding affinities than theophylline, with several compounds (e.g., 5y and 3y) exhibiting superior PLP fitness scores. These compounds formed hydrogen bonds and hydrophobic interactions with key residues of the A2A receptor, such as ASN253, TYR271, and GLU169, suggesting their potential to modulate asthma-related mechanisms like airway constriction and inflammation. ADME analysis, conducted using the Swiss ADME server, indicated that compounds Y1–Y6 possessed favorable pharmacokinetic properties, including good gastrointestinal absorption, moderate bioavailability, and no P-glycoprotein interactions, making them suitable for oral administration. However, compounds Y7 and Y8 exhibited lower gastrointestinal absorption and increased polarity, suggesting the need for further structural optimization. The findings suggest that these thioimidazole-4-one derivatives are promising candidates for asthma therapy, with potential for further development based on their molecular docking results and ADME profiles.

key words: Thioimidazole-4-one derivatives, A2A adenosine receptor, ADME analysis, Molecular docking, and Asthma therapy.

تصميم الالتحام الجزيئي وتقييم الدوائية لمشتقات ال ثيوإيميدازول-4-ون كعلاج للربو

نور محمد موسى*,عبد الجبار خلف عطية, كريمة فاضل علي*, وسن عادل مهدي*****

**فرع الكيمياء الصيدلانية / كلية الصيدلة / جامعة المستنصرية / بغداد، العراق*

***علوم كيمياء/كلية العلوم/ جامعة المستنصرية / بغداد، العراق*

**** مركز أبحاث وتطبيقات المواد الطبية الحيوية والمغناطيسية وشبه الموصلة / جامعة ساكاريا / ساكاريا، تركيا.*

الخلاصة

تبحث هذه الدراسة في تصميم مشتقات الثيوإيميدازول-4-ون الالتحام الجزيئي (الدوكنك)، وخصائص الامتصاص والتوزيع والتمثيل الغذائي والإخراج (ADME) كمركبات علاجية محتملة تستهدف مستقبل A2A الأدينوسيني لعلاج الربو. تم إجراء المحاكاة الجزيئية باستخدام بنية مستقبل A2A المرتبط مع الثيوفيلين(PDB ID: 5MZJ) ، حيث تمت مقارنة المركبات قيد الدراسة بالثيوفيلين لتقييم قوة ارتباطها بالمستقبل. أظهرت نتائج المحاكاة أن المركبات تمتلك تقارب ارتباط أعلى مقارنة بالثيوفيلين، مع تفوق بعض المركبات مثل 5 y و3 yمن حيث درجات.PLP أظهرت المركبات قدرتها على تكوين روابط هيدروجينية وتفاعلات كارهة للماء مع بقايا رئيسية في مستقبلA2A ، بما في ذلك ASN253 و TYR271وGLU169، مما يشير إلى إمكانية تأثيرها على آليات مرضية مرتبطة بالربو مثل تضيق الشعب الهوائية والالتهاب.أما تحليلADME ، الذي تم باستخدام خادم Swiss ADME ، فقد كشف أن المركبات Y1–Y6 تتمتع بخصائص علاجية مناسبة، تتضمن امتصاصًا جيدًا في الجهاز الهضمي، وتوافرًا حيويًا معتدلًا، وعدم تفاعل مع بروتينP-glycoprotein ، مما يجعلها مرشحة للإعطاء الفموي. في المقابل، أظهرت المركبات Y7 و Y8امتصاصًا منخفضًا في الجهاز الهضمي وزيادة في القطبية، مما يستدعي الحاجة إلى تحسين هيكلي إضافي. تشير هذه النتائج إلى أن مشتقات الثيوإيميدازول-4-ون تُعد واعدة كعلاجات محتملة للربو، مع إمكانية تطويرها مستقبلًا استنادًا إلى نتائج المحاكاة الجزيئية وملفات ADME الخاصة بها.

الكلمات المفتاحية :مشتقات الثيوإيميدازول-4-ون، مستقبل A2A الأدينوسيني، تحليل،ADME الالتحام الجزيئي، علاج الربو.

1.Introduction

Asthma is a chronic condition that causes the airways in the lungs to become inflamed and constricted[1], resulting in respiratory challenges such as coughing, chest tightness, wheezing, and difficulty breathing[2]. This inflammation triggers muscle contractions around the airways, while the airway lining swells, leading to a reduced airflow capacity[3]. Common triggers include dust mites, animals (such as pet dander or hair), certain medications like NSAIDs and aspirin, changes in weather (often cold conditions), airborne substances (pollution), and physical activity. Other allergens like mold and pollen can also provoke asthma symptoms[4].

The manifestations of asthma vary among individuals[5], with some experiencing symptoms continuously or mainly during physical exertion[6]. Many individuals with asthma experience periods of flare-ups interspersed with symptom-free intervals. Others may endure chronic shortness of breath, with occasional worsening episodes. Coughing or wheezing might be the primary symptom for some[7]. Asthma attacks can occur suddenly or develop gradually over hours or days, ranging from mild to life-threatening if airflow becomes severely restricted. Severe attacks often require medical attention, including hospitalization, where treatments such as oxygen, medications, and breathing support may be administered[8].

Imidazolidine is a five-membered heterocyclic compound composed of two nitrogen atoms and three non-adjacent carbon atoms[9, 10], with the molecular formula $C_3H_8N_2$. It is considered a saturated derivative of imidazole[11]. Imidazolidine primarily exists in two tautomeric forms: 2-imidazolidine (1,3-diaza-2,4-cyclopentane) and 4-imidazolidine. Imidazolidine rings is highly versatile frameworks in organic chemistry, often utilized as intermediates in synthesizing bioactive compounds[12], such as imidazolidine-2-thiones and imidazolidin-2-ones (hydantoins). These derivatives exhibit significant anti-inflammatory, antibacterial, and antiviral activities. The presence of electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) in a molecule influences its reactivity and ability to undergo chemical modifications.

EDGs increase electron density, making the molecule more nucleophilic and reactive toward electrophiles, facilitating reactions like electrophilic aromatic substitution. In contrast, EWGs decrease electron density, making the molecule more electrophilic and reactive toward nucleophiles, enabling nucleophilic substitutions or additions. By strategically placing EDGs and EWGs, chemists can control the reactivity and selectivity of a molecule, guiding it toward specific functionalizations or modifications.[13].Imidazolidine is also known as 1,3-diazacyclopentane (1). Its oxo derivative is referred to as imidazolidinone (2), while its thioxo derivative is termed imidazolidinthione (3). The compound 1,3-imidazolidine-2,4-dione, also called hydantoin, contains a reactive cyclic urea core. Sulfur-based analogs of hydantoins are known as thiohydantoins (4), where one or both carbonyl groups are replaced by thiocarbonyl groups[14], as illustrated in Figure (1).

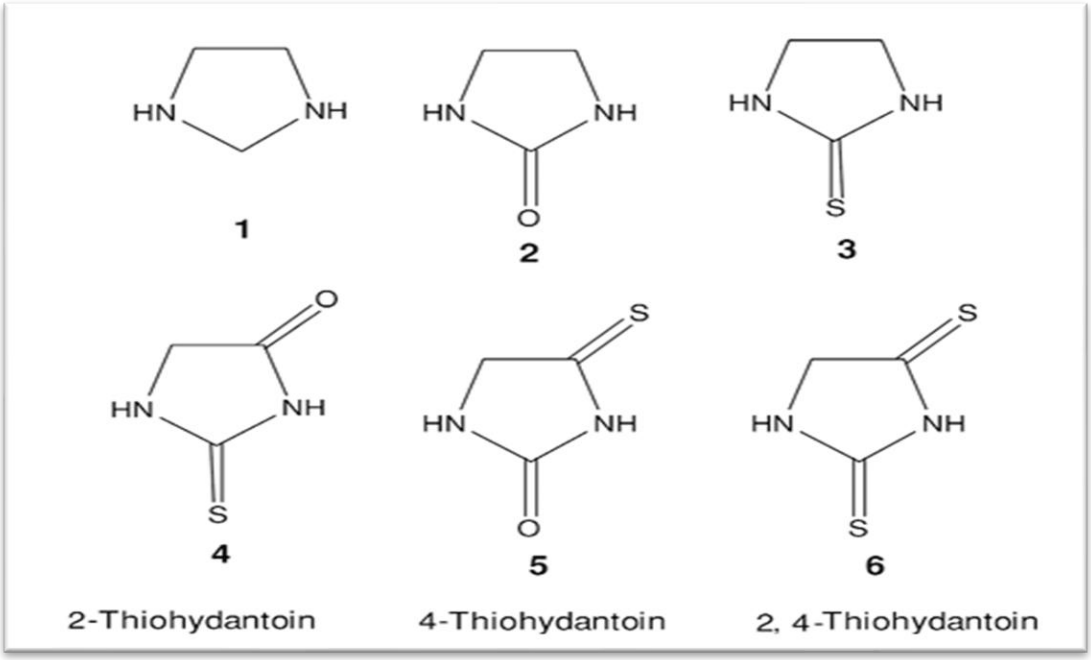


Figure (1): imidazole and itis oxo and thioxo derivatives.

The increasing evidence linking adenosine to the pathophysiology of asthma has sparked interest in investigating all adenosine receptor subtypes as potential therapeutic targets for asthma treatment[15]. Experimental studies have demonstrated that adenosine contributes to various asthma-related processes, including airway constriction, mucus production, and inflammation. As a result. The A2A receptor, predominantly expressed on inflammatory cells associated with asthma, has also gained attention. Activation of the A2A receptor increases cAMP levels by stimulating adenylate cyclase, and selective A2A receptor agonists are currently undergoing evaluation in human trials, although initial findings on their efficacy are mixed[16].

Molecular docking simulations were employed to investigate the molecular

core[17], providing critical insights into the development of pharmaceuticals. This technique is a key tool for predicting the affinity, receptor interactions, and biological activity of compounds[18]. Evaluating a molecule in silico physicochemical properties, such as size, solubility, polarity, flexibility, saturation, and lipophilicity, is crucial during the early stages of drug development to determine its therapeutic potential[19].

SwissADME is a powerful tool offering free access to predictive models for physicochemical properties[20], drug-likeness, pharmacokinetics, and medicinal chemistry. It includes unique features like the Bioavailability Radar, iLOGP, and BOILED Egg models. The frequent failures in drug discovery are often attributed to poor pharmacokinetics (PK) and toxicity profiles[21].The Quantitative structure-activity/property relationships (QSARs/QSPRs)group has developed methods for predicting essential physicochemical parameters, including toxicity, P-gp efflux, blood-brain barrier (BBB) penetration, partition coefficients, solubility, absorption, and permeability[22].

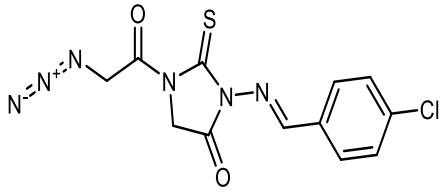
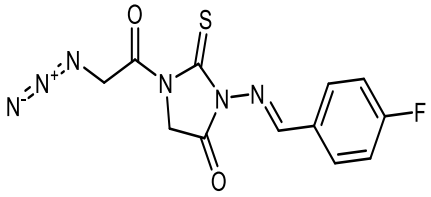
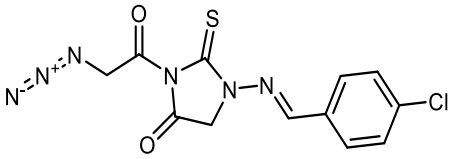
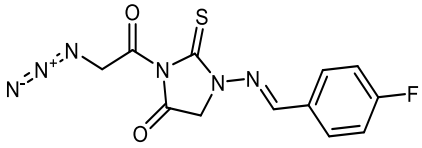
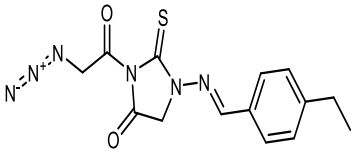
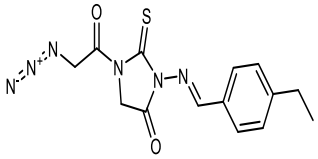
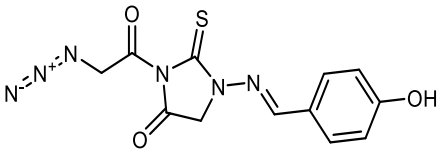
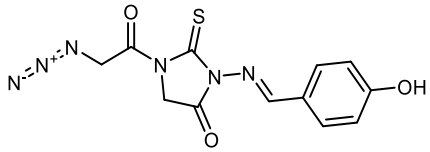
This study demonstrates the significance of synthesizing and evaluating thioimidazole-4-one derivatives as potential therapeutic agents targeting the A2A adenosine receptor. These compounds may offer promising prospects for regulating airway inflammation and smooth muscle tone, ultimately contributing to the development of more effective treatments for asthma management."

3.COMPUTATIONAL METHOD

The structural design of the proposed compounds, specifically thioimidazole-4-one derivatives, was guided by an extensive literature review conducted by our research team. An in-silico modeling study was performed to evaluate the potential effects of these compounds on the A2A adenosine receptor in complex with theophylline (PDB ID: 5MZJ)[23].

Estimation of the compounds' compatibility within the protein cavity, including the formation of hydrogen bonds and other short-range interactions[24]. ADME properties of the compounds were assessed using the Swiss ADME server[25].

Table (1), Structures of proposed Derivatives.

 (*E*)-1-(2-azidoacetyl)-3-((4-chlorobenzylidene)amino)-2-thioxoimidazolidin-4-one **1y**	 (*E*)-1-(2-azidoacetyl)-3-((4-fluorobenzylidene)amino)-2-thioxoimidazolidin-4-one **2y**
 (*E*)-3-(2-azidoacetyl)-1-((4-chlorobenzylidene)amino)-2-thioxoimidazolidin-4-one **3y**	 (*E*)-3-(2-azidoacetyl)-1-((4-fluorobenzylidene)amino)-2-thioxoimidazolidin-4-one **4y**
 (*E*)-3-(2-azidoacetyl)-1-((4-ethylbenzylidene)amino)-2-thioxoimidazolidin-4-one **5y**	 (*E*)-1-(2-azidoacetyl)-3-((4-ethylbenzylidene)amino)-2-thioxoimidazolidin-4-one **6y**
 (*E*)-3-(2-azidoacetyl)-1-((4-hydroxybenzylidene)amino)-2-thioxoimidazolidin-4-one **7y**	 (*E*)-1-(2-azidoacetyl)-3-((4-hydroxybenzylidene)amino)-2-thioxoimidazolidin-4-one **8y**

3.1 Ligand Preparation of Our Compound

The chemical structures of the ligands (M1 to M8) were drawn using ChemOffice software (ChemDraw 22.2.0) and their energies were minimized using Chem3D software to prepare them for the docking process[26].

3.2 Molecular Docking: Preparation of the Protein Receptor

The study was conducted on an HP computer system equipped with an Intel® Core i3 processor (8th Gen) and 12 GB of RAM. Necessary software installations included the Hermes visualizer application, ChemDraw Professional (v.22.2), and the fully licensed version of Genetic Optimization for Ligand

Docking (GOLD) (v.22.2, Cambridge, England) developed by the Cambridge Crystallographic Data Centre (CCDC). The chemical compositions of the ligands were drawn using the ChemOffice suite (v.2022, 22.0.0, x64 bit)[27]. The SwissADME web-based software (accessible at www.swissadme.ch) was utilized for ADME studies of the designed substances. The compounds' chemical structures, created using ChemOffice, were converted into SMILE names for further evaluation. Polarity and lipophilicity were assessed using the BOILED Egg model[28] .

The 3D structure of the active target, the A2A adenosine receptor complexed with theophylline (PDB ID: 5MZJ), was prepared for docking. The GOLD Hermes module was used for receptor preparation, and re-docking of co-crystallized ligands was performed to validate the docking procedure, utilizing data from the Protein Data Bank (PDB)[29].

Accurate tautomeric states and ionization of amino acid residues were ensured by adding polar hydrogen atoms. Crystallographic water molecules were removed, except for HOH 2509, HOH 2530, HOH 2546, HOH 2549, and HOH 2565, which play a role in the active site and facilitate ligand-protein interactions. The receptor structure, A2A adenosine receptor A2AR-StaR2-bRIL, complexed with theophylline at a resolution of 2.0 Å, was finalized. The active site was determined by extracting the original ligand's interaction region, and all protein residues within 10 Å of the reference ligand were included in the docking process[30].

The Hermes visualization tool in the CCDC GOLD suite was utilized to prepare the receptor for docking[31]. Default docking parameters were applied, generating 10 new ligand poses. Early termination was disabled, and the highest-ranked conformation was selected based on the PLP fitness scoring function, which uses a piecewise linear potential (PLP fitness). The docking results, saved as. mol2 files, included detailed information on docked poses, binding free energy, and optimal binding modes. A thorough analysis of these results identified the amino acid residues within the A2A adenosine receptor involved in ligand interactions[32].

3.3 ADME Prediction

The pharmacokinetic profile of the compounds, including ADME parameters[33], was evaluated using the SwissADME platform. Additional attributes such as bioavailability, P-gp affinity, and blood-brain barrier (BBB) penetration were also analyzed[34]. This process aimed to ensure the safety and efficacy of the compounds while eliminating those with poor ADME properties, which are more likely to fail during the drug development process[35]. Each compound was designed using ChemDraw, and its chemical name was converted into a SMILES format using the SwissADME server[36].

4. Result and Discussion

The results show that thioimidazole-4-one derivatives exhibit stronger binding affinities than theophylline to the A2A adenosine receptor, with favorable interactions at key receptor sites. ADME analysis indicates good oral bioavailability for most compounds, suggesting their potential as effective candidates for asthma therapy.

4.1 Molecular Docking

Virtual screening (VS) is a process used to identify compounds by fitting them to the target receptor using computational tools[37]. The docking results reveal whether protein atoms and ligands are hydrogen-bonded and have short contact distances. High levels of hydrogen bond interactions and hydrophobic interactions enhance the biological activity required for the substrate to bind to the active site[38].

For this study, the stabilized A2A adenosine receptor A2AR-StaR2-bRIL complexed with theophylline (PDB code: 5MZJ, resolution 2.0 Å) was used. The compounds were compared with theophylline as a reference in docking studies[39], and the 5MZJ structure was chosen for the analysis. The compounds were ranked based on their PLP fitness in the active site complex formation[40].

The protein-ligand interaction fitness of the docked compounds and theophylline on the A2A adenosine receptors is shown in Tables (2) and (3). The docking results indicate that all the designed compounds demonstrate better binding energy with the receptor's active site, consistent with expectations for the A2A adenosine receptor. The ligands bind to the receptor's amino acid residues through hydrogen bonds, hydrophobic interactions, and other short-range interactions[41].

Docking analysis revealed that the amino acid residues of the A2A adenosine receptor's active site, such as ASN253, HIS278, ALA81, LYS153, GLU169, MET279, MET270, PHE168, LEU249, LEU167, and ILE274, interact via hydrogen bonds and short-range contacts with the final ligand library, showing promising anti-asthma activity.

All compounds show strong binding affinity to the A2A adenosine receptor compared to theophylline.

Table (2), Molecular docking analysis of the designed compounds with the A2A adenosine receptor

No.	Ligand Name	PLPfitness (Average Values)	H-bond interactions	Hydrophobic interactions
1	theophylline	78.01	HIS278, 167 ALA81	ASN253, HIS278, and ALA81
2	1y	90.4	TYR (274) ASN (253) PHE (168) GLU (167)	ASN (253), GLU (169), LEU (167), TYR (271), PHE (168), LEU (249), MET (270) and TYR (271).
3	2y	86.9	ASN (253) TYR (274)	ASN (253), LEU (167), MET (270), LEU (267), LEU (249), GLU (169), TYR (271), ILE (274), and PHE (168).
4	3y	90.9	ASN (253) HIS (250) GLU (167)	TYR (271), LEU (169), PHE (168), ASN (253), LEU (249), GLU (169), and MET (270).
5	4y	86.4	ASN (253) TYR (271)	ASN (253), LEU (274), LEU (249), ILE (274), MET (270), PHE (167), TYR (271), GLU (169), LEU (167), ILE (274), and PHE (168).
6	5y	92.6	TYR (271) ASN (253) HIS (250)	TYR (271), LEU (249), ASN (253), PHE (169), MET (270), LEU (167),

				LEU (249), GLU (169), and LEU (267).
7	6y	90.4	ASN (253) MET (177) TYR (271)	ASN (253), GLU (169), LEU (249), LEU (167), MET (270), and PHE (168), TYR (271), ALA (63).
8	7y	81	LEU (267) GLU (167) ASN (253)	MET (270), LEU (167), GLU (169), LEU (249), PHE (168), and ASN (253).
9	8y	87.2	ASN (253) TYR (271)	LEU (167), MET (270), GLU (167), LEU (274), PHE (168), and ASN (253) and PHE (168).

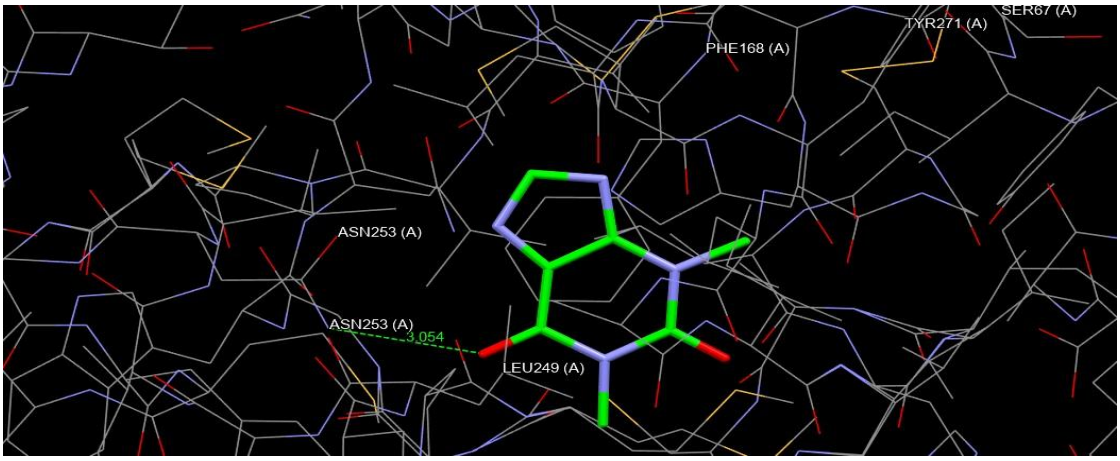


Figure (1), The three-dimensional structural representation illustrates the chemical interactions of theophylline

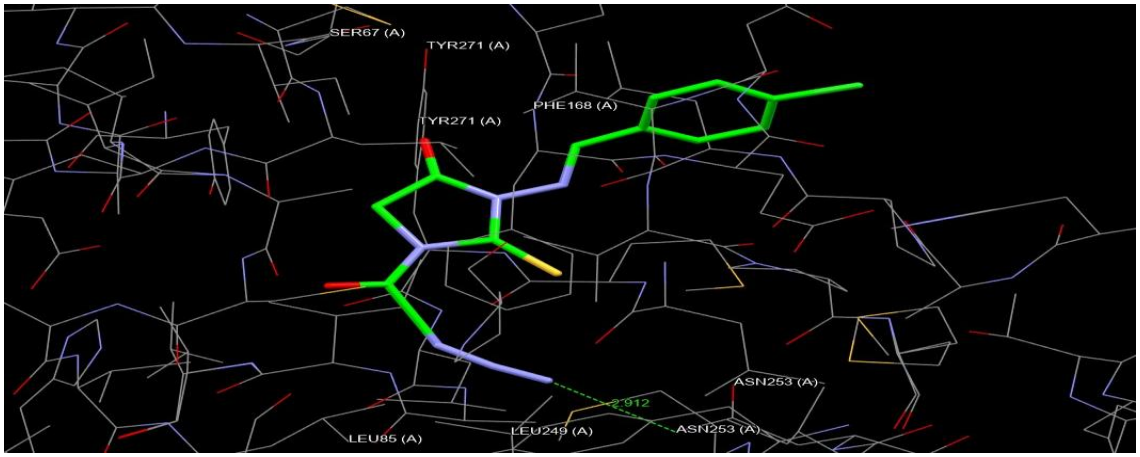


Figure (2), The three-dimensional structural representation illustrates the chemical interactions of the compound (1y)

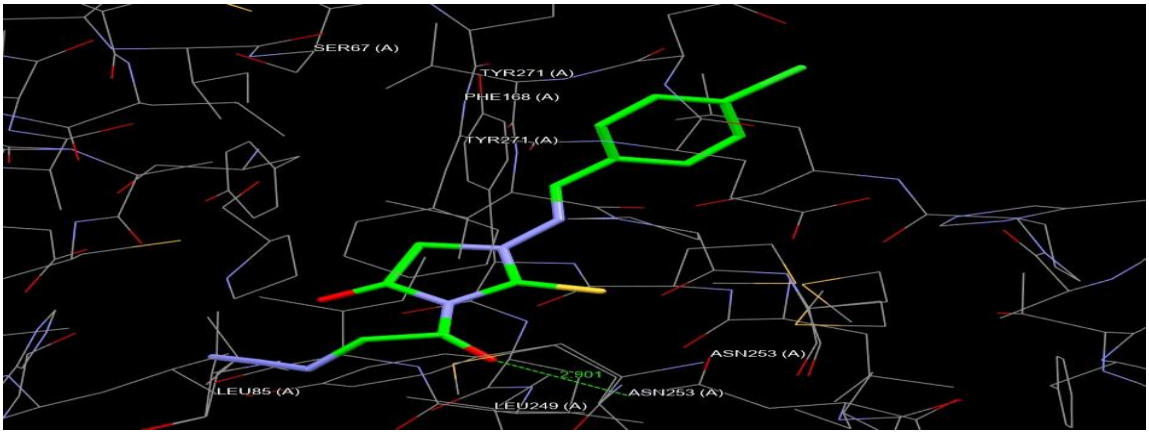


Figure (3), The three-dimensional structural representation illustrates the chemical interactions of the compound (2y)

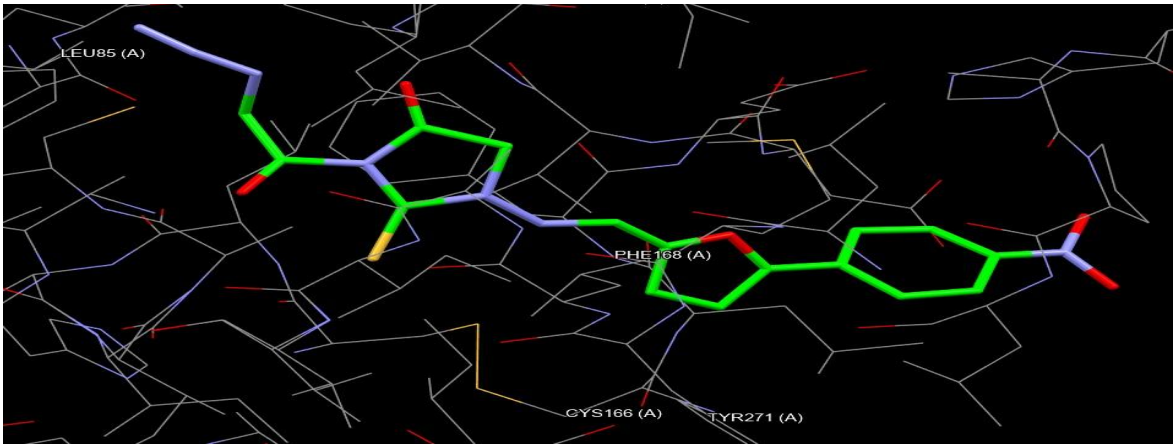


Figure (4), The three-dimensional structural representation illustrates the chemical interactions of the compound (3y)

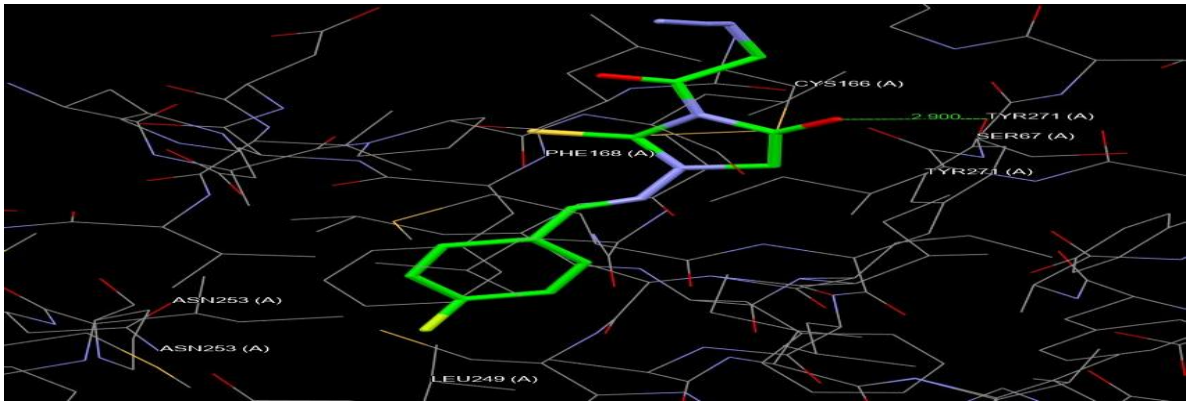


Figure (5), The three-dimensional structural representation illustrates the chemical interactions of the compound (4y)

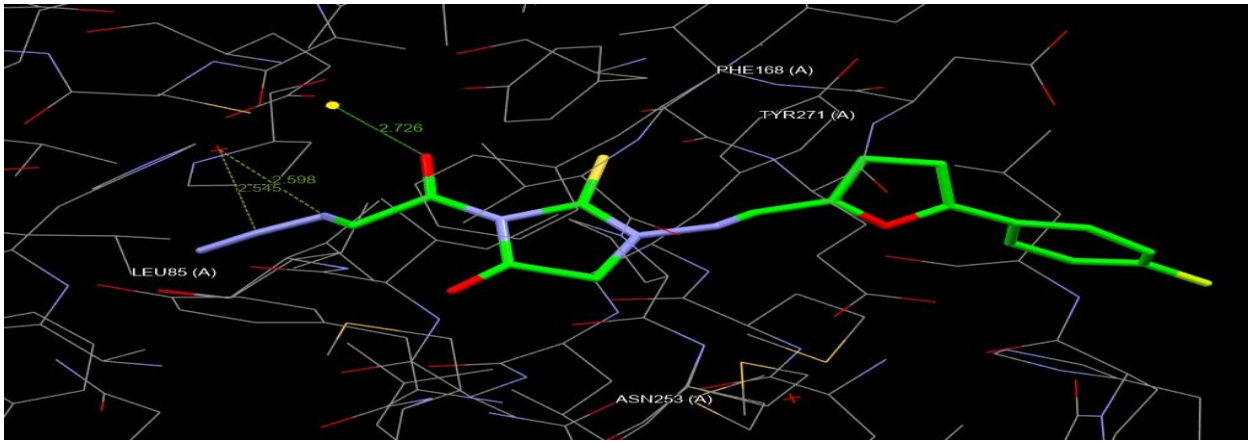


Figure (7), The three-dimensional structural representation illustrates the chemical interactions of the compound (6y)

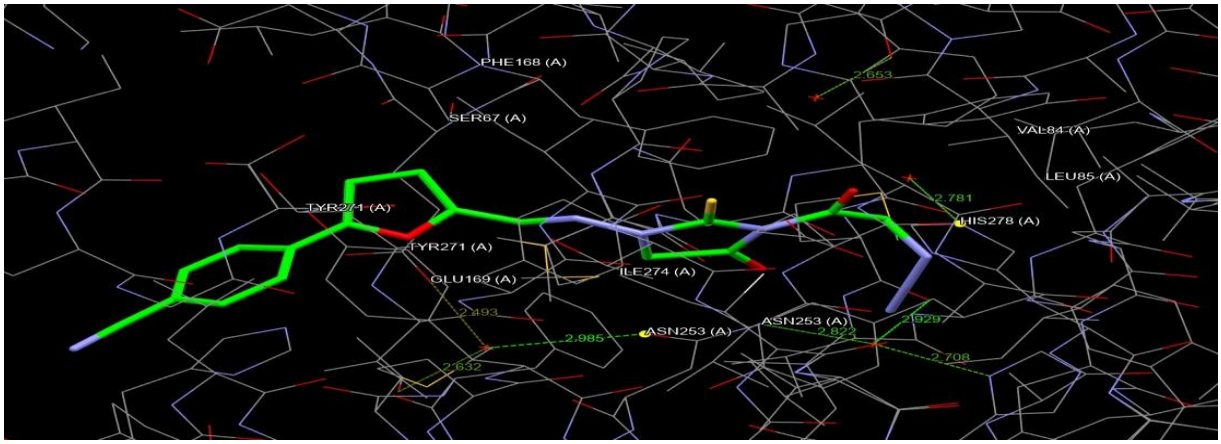


Figure (8), The three-dimensional structural representation illustrates the chemical interactions of the compound (7y)

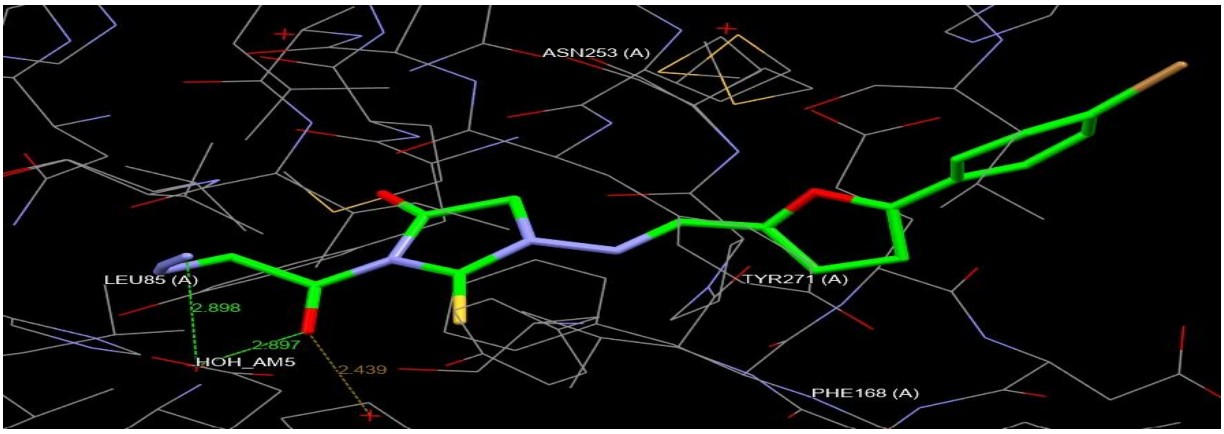


Figure (9), The three-dimensional structural representation illustrates the chemical interactions of the compound (8y)

4.2 ADME

Lipinski's rule of five, used to predict the properties of developed chemical compounds via the SwissADME server, are gaining popularity in pharmaceutical research due to their effectiveness and cost-efficiency[42], is a set of guidelines used to predict the drug-likeness of a compound. According to the rule, for a compound to have a higher likelihood of being an effective oral drug, it should meet the following criteria: its molecular weight should be less than or equal to 500 Da (Daltons), the octanol-water partition coefficient (logP) should be 5 or lower, it should have no more than 5 hydrogen bond donors (HBD), no more than 10 hydrogen bond acceptors (HBA), and no more than 10 rotatable bonds. These parameters help assess a compound's potential for adequate absorption, permeability, and bioavailability when taken orally. The permeability glycoprotein (P-gp) is expected to transport certain compounds out of the central nervous system (CNS); compounds not expected to be exported by P-gp are represented by red dots (P-gp-) and blue dots (P-gp+)[43]. Table (3), explain that.

Table (3): Pharmacokinetic Properties of All Proposed Compounds

Compound name	M.wt (g/mole)	n-HBA	n HBD	TPSA (^{0}A2)	MR (m3/mol)	GI absorption	BBB permeability	Bioavailability score	Lipinski violation	Pgp
Y1	336.76	6	0	134.82	88.66	High	No	0.55	0	No
Y2	336.34	7	0	134.82	90.53	High	No	0.55	0	No
Y3	336.76	6	0	134.82	95.58	High	No	0.55	0	No
Y4	336.34	7	0	134.82	88.61	High	No	0.55	0	No
Y5	330.36	6	0	134.82	93.42	High	No	0.55	0	No
Y6	330.36	6	0	134.82	93.42	High	No	0.55	0	No
Y7	318.31	7	1	155.05	85.67	Low	No	0.55	0	No
Y8	318.31	7	1	155.05	85.67	Low	No	0.55	0	No

The presented data outlines the pharmacokinetic properties of compounds Y1 through Y8, highlighting their potential as drug candidates. All compounds have molecular weights below 500 g/mol, satisfying Lipinski's criteria for drug-likeness. Y1-Y6 exhibit favorable properties, including high gastrointestinal (GI) absorption and moderate bioavailability (score 0.55), attributed to their optimal topological polar surface area (TPSA) of 134.82 Å^2. They are not substrates for P-glycoprotein (P-gp) and show no Lipinski violations, making them strong candidates for oral administration. In contrast, Y7 and Y8, with higher TPSA (155.05 Å^2) and one hydrogen bond donor (HBD), demonstrate low GI absorption, likely due to their increased polarity. None of the compounds are blood-brain barrier (BBB) permeable, suggesting reduced central nervous system (CNS) effects, which may be advantageous for targeting peripheral systems. While Y1-Y6 show promising profiles for systemic use, Y7 and Y8 may require structural optimization to improve their absorption and overall pharmacokinetics. The absence of P-gp substrate activity across all compounds is noteworthy, minimizing the risk of efflux-mediated drug resistance.

5. Conclusions

Molecular docking results revealed that the compounds exhibit strong binding affinities to the receptor's active site, with several compounds (such as [5y] and [3y])

demonstrating superior PLP fitness scores compared to theophylline. ADME analysis, highlighted that most of the compounds (Y1 to Y6) possess favorable pharmacokinetic properties, including good gastrointestinal absorption, moderate bioavailability, and a lack of P-glycoprotein (P-gp) interactions, making them suitable for oral administration. None of the compounds are predicted to cross the blood-brain barrier (BBB), which could limit CNS-related side effects, enhancing their peripheral therapeutic potential. Overall, the study identifies promising candidates for further development as asthma therapies targeting the A2A adenosine receptor.

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