GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 12 (357) Декабрь 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

GEORGIAN MEDICAL NEWS
No 12 (357) 2024

DESIGN, MOLECULAR DOCKING, MOLECULAR DYNAMICS, AND EVALUATION OF NOVEL LIGANDS TARGETING BETA-2 ADRENERGIC RECEPTOR FOR ASTHMA THERAPEUTICS

Noor Mohammed Mousa[1]*, Abdull Jabar Attia[2], Karima Fadhil Ali[1].

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

[2]*College of sciences, Mustansiriyah University, Baghdad, Iraq.*

Abstract.

This study investigates the design and molecular docking of novel ligands targeting the beta-2 adrenergic receptor [β2AR], a critical protein involved in bronchoconstriction and asthma regulation. Utilizing molecular docking simulations, we evaluated the binding affinities of synthesized compounds, including compound 1, compound 5, and the reference drug salbutamol, against β2AR. The docking studies were conducted using GOLD software, and binding interactions were analyzed to identify key residues responsible for ligand binding and receptor activation. The results revealed that all tested compounds, particularly compound 1 and compound 5, demonstrated strong binding to the β2AR, with binding energies comparable to salbutamol. Key residues such as SER 207, PHE 289, LYS 305, and ASP 192 played significant roles in stabilizing the receptor-ligand interactions. The presence of functional groups like NO2 and NC in the synthesized compounds enhanced their affinity, suggesting that structural modifications could optimize β2AR binding. These findings provide valuable insights into the molecular mechanisms underlying β2AR-ligand interactions and highlight the potential of compounds 1 and 5 as promising candidates for further development into β2 agonists for asthma treatment. Salbutamol, as a well-established β2 agonist, served as a benchmark for evaluating the efficacy of the novel ligands, confirming the feasibility of designing β2AR-targeting therapeutics with improved potency and selectivity.

Key words. Beta-2 adrenergic receptor [β2AR], salbutamol, molecular docking, molecular dynamics, and ligand design.

Introduction.

Beta-2 adrenergic receptor agonists are a class of medications that selectively stimulate beta-2 adrenergic receptors [1], primarily located in the smooth muscle of the airways, uterus, and blood vessels. These drugs are widely used in respiratory medicine for their ability to relax bronchial smooth muscle [2], providing effective bronchodilation. This makes them essential in the treatment of conditions such as asthma and chronic obstructive pulmonary disease [asthma][3], where airway constriction is a primary concern. Beta-2 agonists work by activating adenylate cyclase through receptor stimulation, increasing cyclic AMP levels and promoting smooth muscle relaxation [4]. They are categorized into short-acting agents, such as salbutamol, for quick relief of acute bronchospasm, and long-acting agents, like salmeterol, for maintenance therapy. Their high specificity for beta-2 receptors reduces systemic side effects, making them a cornerstone in managing airway diseases [5].

Imidazolidinone derivatives are a class of heterocyclic compounds known for their diverse pharmacological properties [6], including anti-inflammatory [7], analgesic [8], anticancer [9], antiviral [10], and antibacterial effects [11]. Their unique structure, characterized by nitrogen and carbonyl groups, plays a critical role in facilitating interactions with various biological targets, a key enzyme in the inflammatory pathway. This ability to modulate inflammation positions imidazolidinone derivatives as promising candidates for addressing conditions associated with airway inflammation, including bronchoconstriction [12].

In bronchoconstriction, the narrowing of airways is often driven by inflammatory processes and hyperresponsiveness [13], which are mediated by the release of pro-inflammatory mediators such as prostaglandins and leukotrienes. Imidazolidinone derivatives can potentially inhibit the synthesis of prostaglandins [14], thereby reducing airway inflammation and smooth muscle contraction. Additionally, their anti-inflammatory properties may help alleviate airway hyperresponsiveness and prevent further narrowing of the bronchi [15], offering therapeutic potential for conditions like asthma and chronic obstructive pulmonary disease [COPD][15]. Further research into their specific mechanisms in the respiratory system could pave the way for developing targeted therapies to manage bronchoconstriction and its associated symptoms [16].

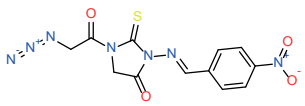
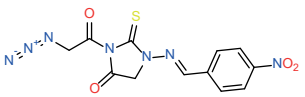
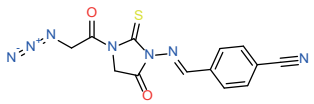
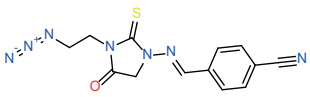
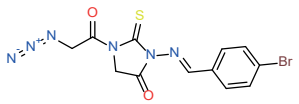
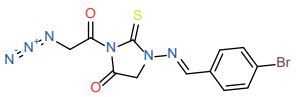
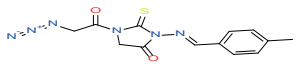
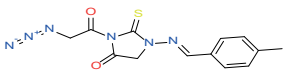
Salbutamol [16], a selective beta-2 adrenergic receptor agonist, is commonly used as a bronchodilator to relieve bronchoconstriction in conditions such as asthma and chronic obstructive pulmonary disease [COPD][17]. Its action involves stimulating beta-2 adrenergic receptors on bronchial smooth muscle, leading to the activation of adenylate cyclase, an increase in cyclic AMP levels, and subsequent relaxation of airway smooth muscle [17]. This mechanism directly counteracts bronchoconstriction, providing rapid relief from airway narrowing [18]. When used alongside partial agonist beta blockers, the interaction can be complex [19]. Partial agonist beta blockers, while designed to provide a baseline level of beta receptor activity [18], also exhibit antagonistic effects that may inhibit the full activation of beta-2 receptors by salbutamol. This can reduce the bronchodilatory efficacy of salbutamol [20], particularly if the partial agonist beta blocker has significant activity at beta-2 receptors. However, because partial agonists maintain some intrinsic activity at beta receptors, they are generally less likely to completely negate the effects of salbutamol compared to non-selective or full beta blockers [21].

This work is significant because there is a strong need for safer and more effective therapies to manage bronchoconstriction in conditions like asthma and COPD [22]. While current bronchodilators, such as beta-2 adrenergic receptor agonists,

provide rapid relief by relaxing airway smooth muscle, their prolonged or inappropriate use can lead to tolerance, side effects, and reduced efficacy [23]. The synthesis of the eight compounds involved a multi-step process, starting with the condensation of aromatic aldehydes and thiosemicarbazide in ethanol under reflux. The resulting Schiff bases were further reacted with ethyl chloroacetate in the presence of sodium acetate to form the corresponding thioimidazolidinone derivatives. Subsequent modifications included acylation with chloroacetyl chloride in dioxane using triethylamine as a base, followed by azidation using potassium iodide and sodium azide under reflux. Each step was carefully monitored, and the final products were purified by recrystallization from ethanol to ensure high purity and yield. The goal is to develop novel beta-2 adrenergic receptor agonists that maintain potent bronchodilatory effects with improved selectivity and reduced systemic side effects. Advances in drug design, focusing on optimizing receptor interactions and minimizing off-target effects [24], could result in more effective therapies with enhanced safety profiles for managing bronchoconstriction [25].

Table 1 presents the eight designed compounds featuring a beta-2 adrenergic receptor agonist structure. This study utilizes computational molecular docking [26], to examine how these newly developed derivatives interact with the beta-2 adrenergic receptor. The binding affinities of compounds [1, 2, 3, 4, 5, 6, 7 and 8] were evaluated in relation to their interaction with the beta-2 receptor to determine the strength and nature

Table 1. *Structures of eight designed compounds.*

1] [E]-1-[2-azidoacetyl]-3-[[4-nitrobenzylidene] amino]-2-thioxoimidazolidin-4-one 	**5] [E]-3-[2-azidoacetyl]-1-[[4-nitrobenzylidene] amino]-2-thioxoimidazolidin-4-one** 
2] [E]-4-[[[3-[2-azidoacetyl]-5-oxo-2-thioxoimidazolidin-1-yl] imino] methyl] benzonitrile 	**6] [E]-4-[[[3-[2-azidoacetyl]-4-oxo-2-thioxoimidazolidin-1-yl]imino]methyl]benzonitrile** 
3] [E]-1-[2-azidoacetyl]-3-[[4-bromobenzylidene] amino]-2-thioxoimidazolidin-4-one 	**7] [E]-3-[2-azidoacetyl]-1-[[4-bromobenzylidene] amino]-2-thioxoimidazolidin-4-one** 
4] [E]-1-[2-azidoacetyl]-3-[[4-methylbenzylidene] amino]-2-thioxoimidazolidin-4-one 	**8] [E]-3-[2-azidoacetyl]-1-[[4-methylbenzylidene] amino]-2-thioxoimidazolidin-4-one** 

of their binding. In silico ADME [Absorption, Distribution, Metabolism, and Excretion] [27], analysis was performed to assess the pharmacokinetic properties and drug-likeness of the compounds. Molecular dynamics simulations [MDS][28,29], over 100 nanoseconds were carried out on the compound with the most favorable docking, further confirming the stability and binding interaction with the beta-2 receptor.

Computational Methods.

Ligand Preparation:

The LigPrep tool transforms 2D structures into 3D models. These 3D structures 29], along with their activity values, are utilized to refine and generate conformers for each minimized ligand [30], using the OPLS [Optimized Potentials for Liquid Simulations] force field to prepare the ligands for molecular docking analysis [31].

ADMET Prediction:

To assess the safety of candidate compounds during drug development, preclinical research on safety and pharmacokinetics is essential [32]. The pharmacokinetic properties of eight imidazolidinone derivatives [32,33], including absorption, distribution, metabolism, and excretion [ADME], were analyzed using the freely accessible Swiss-ADME tool [http://www.swissadme.ch]. This analysis helps determine the characteristics related to bioavailability and cellular permeability [34].

Molecular Docking:

Molecular docking evaluation study and molecular modeling drug design [35] were carried out by Glide software [Maestro 13.5] under Schrodinger software [Schrodinger, 2023] running on Windows 10 operating system on workstation [Intel[R] Core [TM] i7-10750 @ 2.60 GHz, 16.00 GB RAM][36]. The crystal structure of Cryo-EM structure of the partial agonist salbutamol-bound beta2 adrenergic receptor-Gs protein complex. Were got from protein data bank beneath PDB code: 7DHI with 3.26 Å crystallographic resolution [37]. The Protein preparation steps occurred by using suitable program for preparation and optimization. Ligand structure preparation occurred by utilizing Ligprep program prior to docking to determine and add of hydrogens in order to obtain the optimal orientation and ionization position with low energy conformations of all ligands by OPLS4 force field [38]. The grid box was set by set an atom of the ligand with kept the default settings and best docking orientation was kept. Then processing docking using glide and analysis the result depends on docking score and interaction between our ligand and references drugs with amino acid residues [39].

Molecular Dynamics Simulation:

A 100-nanosecond simulation was done to check how stable the complex molecular dynamic simulation is and how the ligand-receptor binding mode works [40]. The Desmond program in Schrodinger software was used on a Linux system for this experiment [41]. First, the receptor and ligand were mixed in a simple point charge [SPC] water model. They were put inside an orthorhombic box. To neutralize the system, sodium and chloride ions were added to a 50 mM solution. The simulation

ran using the NPT ensemble, keeping the temperature steady at 300 K and pressure at 1.01325 bar. During this, an energy value of 1.2 was maintained, with results recorded every 100 picoseconds. The OPLS3e force field was applied all through the molecular dynamic simulation. Following the dynamic simulation analysis, the Simulation Interaction Diagram generated trajectories. These trajectories, along with root-mean-square deviation [RMSD], root-mean- square fluctuation [RMSF], and protein-ligand contacts, were analyzed to interpret the stability and interactions of the protein- ligand complex [42].

Results and Discussion.

Molecular Docking Analysis:

We performed molecular docking simulations to analyze how potential ligands interact with the beta-2 adrenergic receptor [PDB code: 7DHI] as agonists at a molecular level. The analysis of the docking results helped us understand the expected binding and activation of the receptor by these ligands [43]. The molecular docking results highlight the binding interactions and affinities of eight compounds and a reference molecule [salbutamol] with a target protein. The docking score is not as crucial as the interactions formed with amino acid residues. While salbutamol has a better docking score (-7.89), my compounds exhibit more and stronger interactions with key residues, making them potentially superior. The docking score primarily reflects the ligand's positioning within the receptor, but the actual binding interactions are far more important in determining stability and activity. Compounds 1 and 5, for example, not only form hydrogen bonds with SER 207—a residue not involved in salbutamol binding—but also establish multiple non-hydrogen interactions with PHE 289, LYS 305, and ASP 192. In contrast, salbutamol, despite its higher score, relies on fewer interactions. This indicates that my compounds may have a more stable and effective binding mode than salbutamol, emphasizing their potential as novel β2AR agonists. As show in Table 2 and Figures (1-6).

Table 2. *Binding Energies for final compounds [2] and salbutamol docked with [7DHI].*

Comp	Docking score	Glide RMSD	No. of bonds	Hydrogen bindding Residues	Functional group	No. of other bonds	Other bind Residues
1	-6.12	0.99	1	SER 207	NO2	3	PHE 289 LYS 305 ASP 192
2	-5.71	0.86	1	SER 207	NC	3	PHE 289 LYS 305 ASP 192
3	-5.63	0.33	-	-	-	4	ASP 192 LYS 305 PHE 289 SER 207
4	-5.32	1.75	1	PHE 193	N=N=N	1	LYS 305
5	-6.31	0.67	1	SER 207	NO2	3	PHE 289 LYS 305 ASP 192
6	-6.05	2.02	1	SER 207	NC	4	PHE 289 PHE 193 ASP 192 LYS 305
7	-4.66	1.75	-	-	-	2	PHE 289 SER 207
8	-4.83	0.69	1	PHE 193	N=N=N	2	ASP 192 LYS 305
SALBUTAMOL	- 7.89	0.43	6	ASN 312 [2] ASP 113 [2] SER 203 SER 207	OH & NH2+ NH2+ & OH OH OH	2	ASP 113 PHE 193

Table 3. *Computational predictions of the pharmacokinetic properties of the designed 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
1	347.31	8	0	180.64	92.47	low	No	0.55	1	No
2	327.32	7	0	158.61	88.36	low	No	0.55	0	No
3	381.21	6	0	134.82	91.35	High	No	0.55	0	No
4	316.34	6	0	134.82	88.61	High	No	0.55	0	No
5	361.34	8	0	180.64	96.72	low	No	0.55	1	No
6	327.32	7	0	158.61	88.36	low	No	0.55	0	No
7	381.21	6	0	134.82	91.35	High	No	0.55	0	No
8	316.34	6	0	134.82	88.61	High	No	0.55	0	No

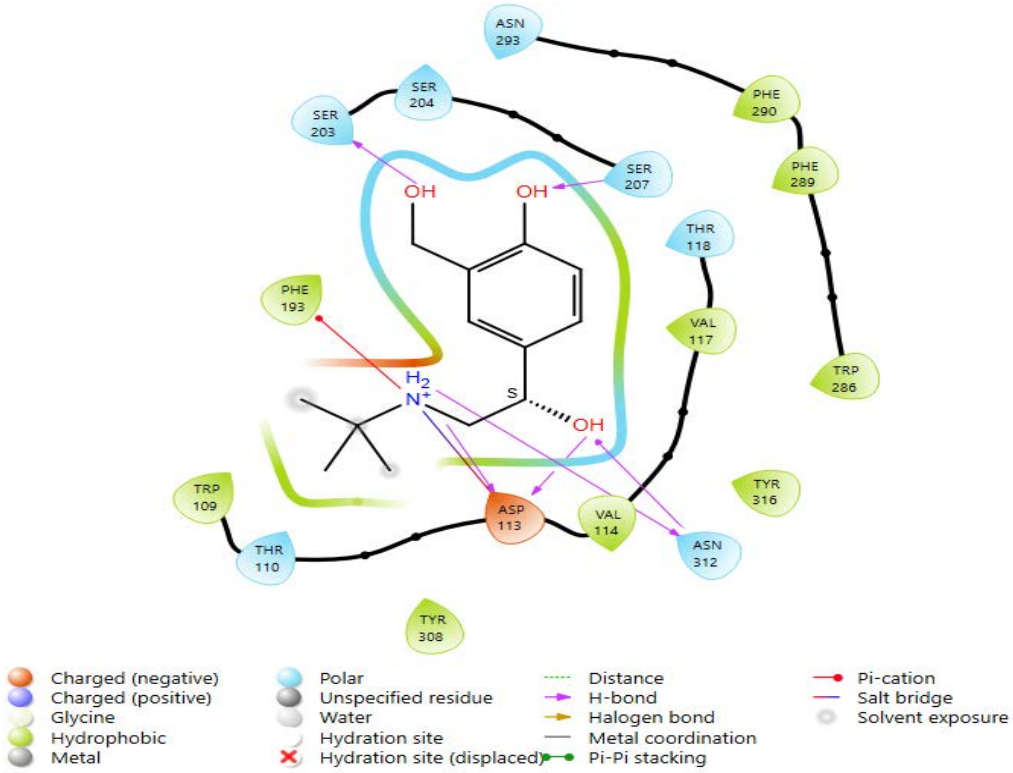


Figure 1. *2D shape of interaction mode of Salbutamol.*

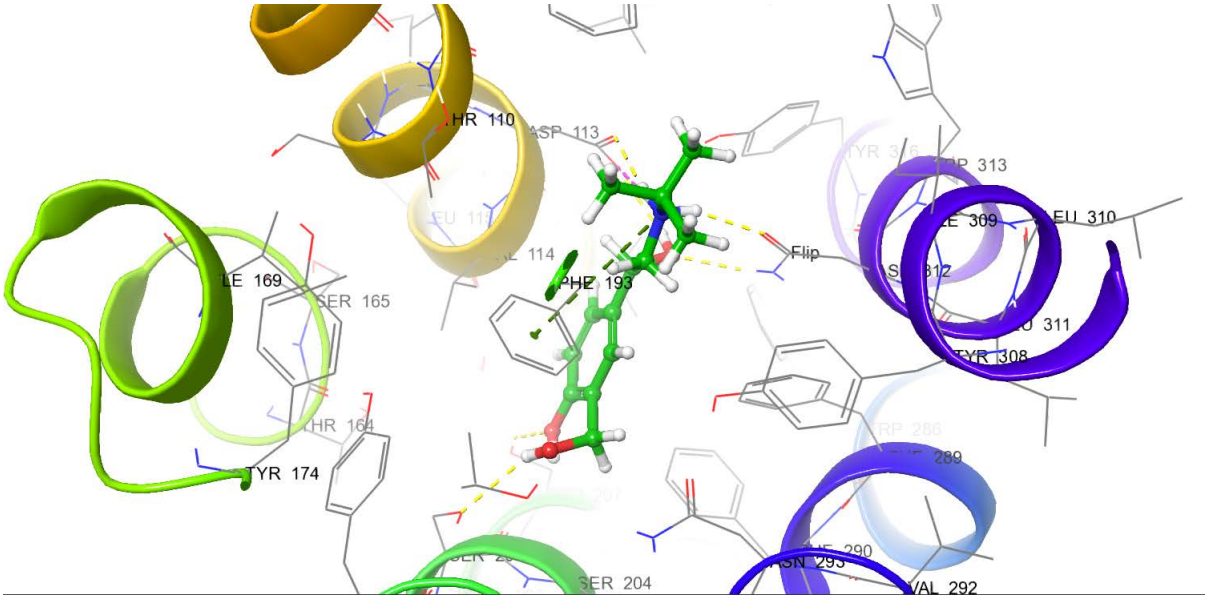


Figure 2. *3D shape of interaction mode of Salbutamol.]H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking].*

Compounds 1 and 5 demonstrated strong binding scores of -6.12 and -6.31, respectively, suggesting high affinity. Both compounds formed a single hydrogen bond with the residue SER 207, with the functional group NO2 playing a critical role in the interaction. Additionally, these compounds engaged in three non-hydrogen interactions with the residues PHE 289, LYS 305, and ASP 192, indicating stable multi-residue interactions. This binding pattern aligns with the general trend of SER 207 being a key hydrogen bonding residue for strong binders.

Compound 2 showed moderate binding with a docking score of -5.71. Like compounds 1 and 5, it formed one hydrogen bond with SER 207, and the NC functional group contributed to this interaction. It also shared the same three non-hydrogen bonding residues [PHE 289, LYS 305, and ASP 192] as compounds 1 and 5, which might explain its relatively strong but slightly lower binding affinity.

Compound 3, with a docking score of -5.63, also exhibited moderate binding but did not form any hydrogen bonds. However, it engaged in four non-hydrogen interactions with residues ASP 192, LYS 305, PHE 289, and SER 207, suggesting

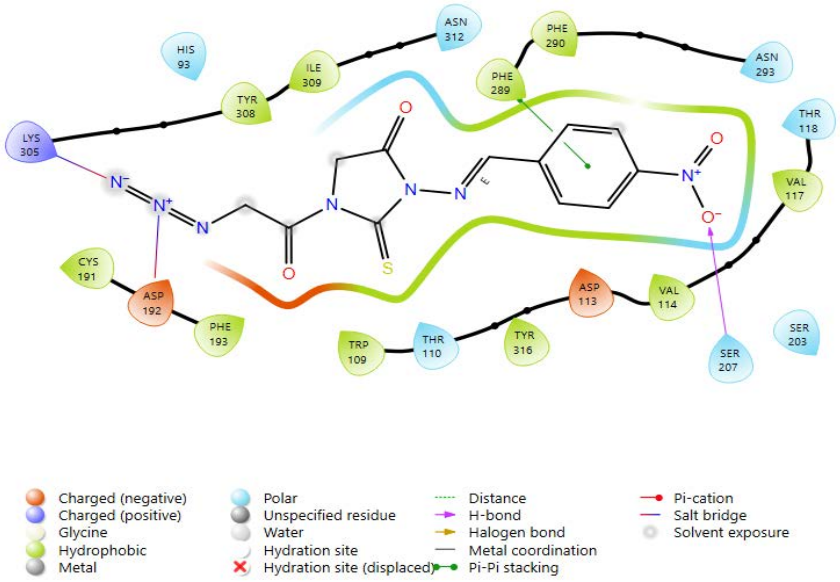


Figure 3. *2D shape of interaction mode of COMPOUND [1].*

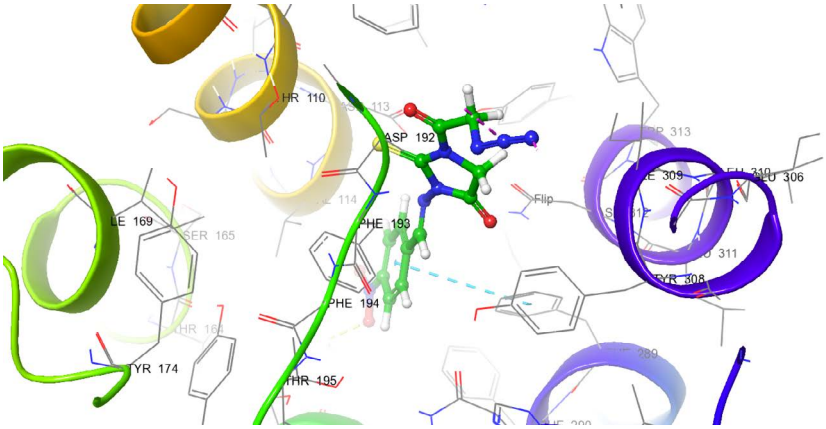


Figure 4. *3D shape of interaction mode of Compound [1].]H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking].*

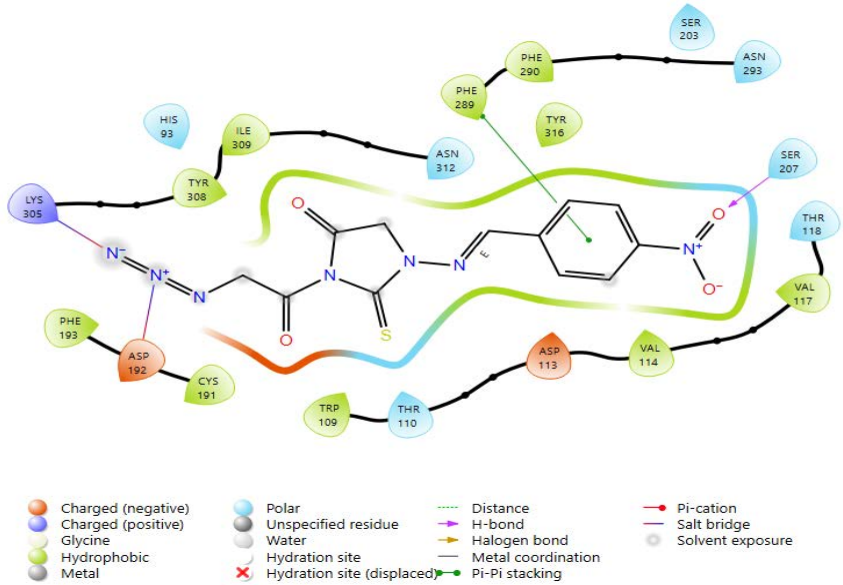


Figure 5. *2D shape of interaction mode of COMPOUND 5.*

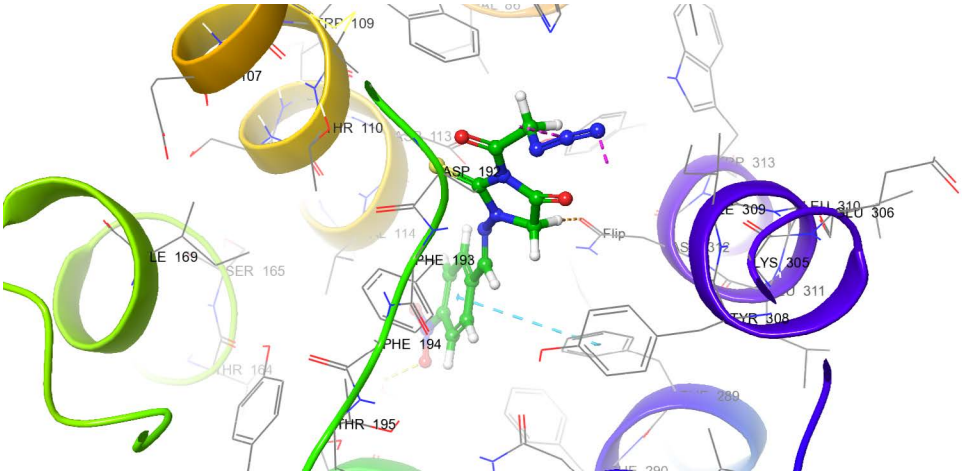


Figure 6. *3D shape of interaction mode of COMPOUND 5 H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking].*

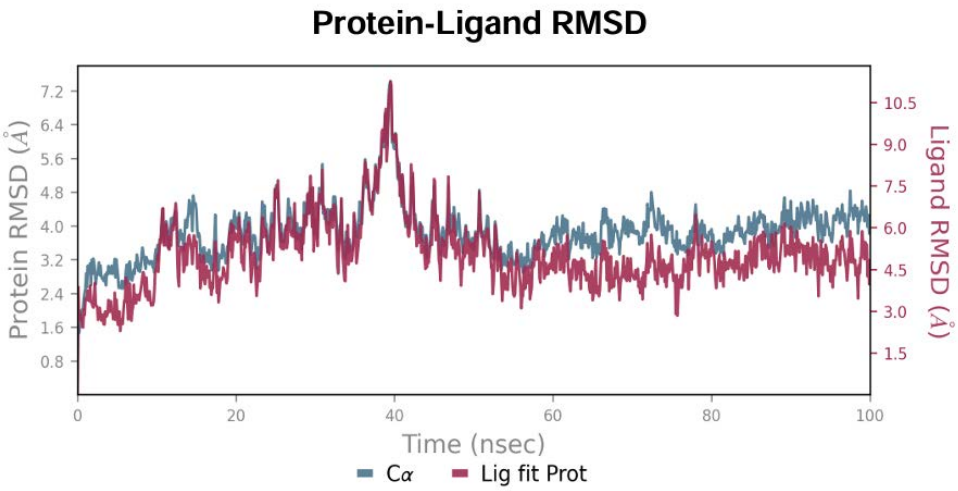


Figure 7. *RMSD of the atoms of protein and the ligand over time [compound 5-7DHI].*

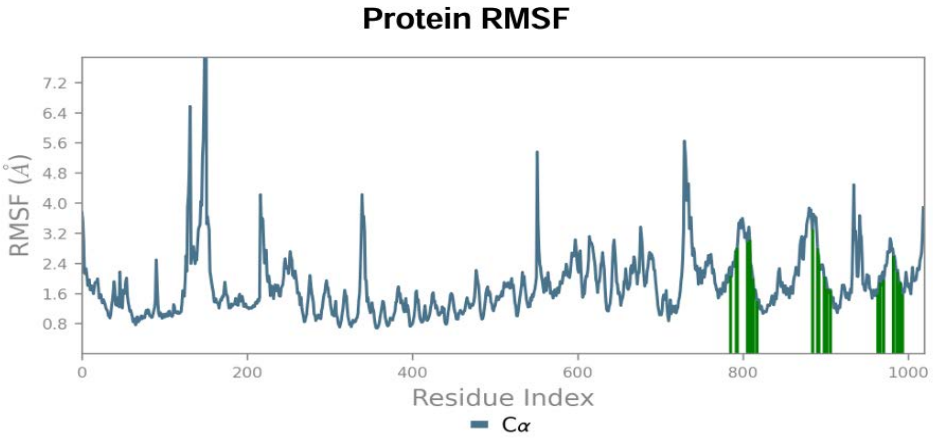


Figure 8. *RMSF plot of the protein [compound 5-7DHI].*

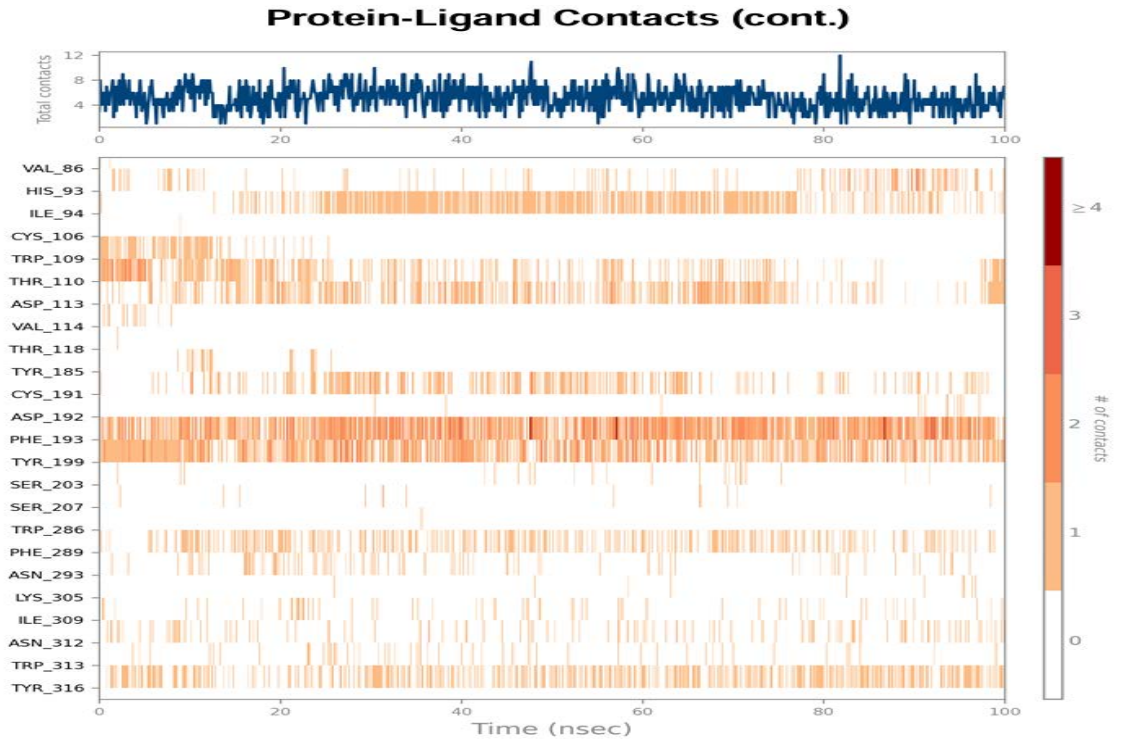


Figure 9. *Protein-ligand interactions during Time [compound 5-7DHI].*

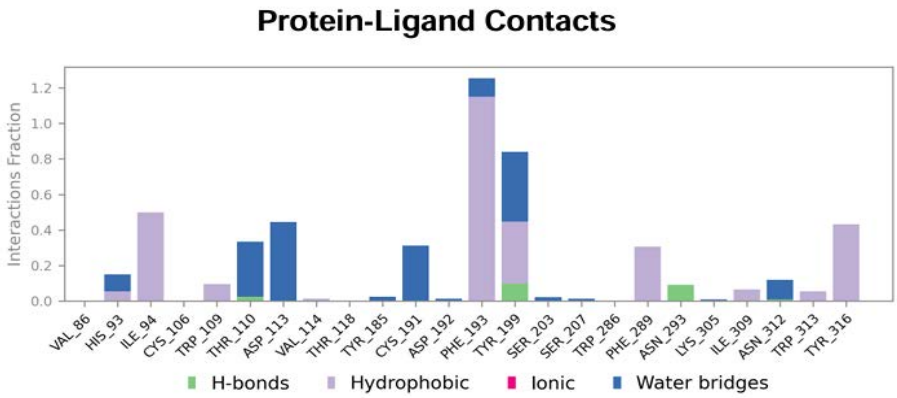


Figure 10. *Protein-ligand contact histogram [compound 5-7DHI].*

that while hydrogen bonding was absent, other interactions compensated to stabilize its binding.

Compound 4 displayed the weakest binding among the higher-ranked compounds, with a docking score of -5.32. It formed one hydrogen bond with PHE 193 and had the functional group N=N=N facilitating the interaction. Additionally, it only engaged in one non-hydrogen interaction with LYS 305, which might account for its lower binding affinity compared to other compounds.

Compound 6 exhibited strong binding, with a docking score of -6.05. It formed a hydrogen bond with SER 207, with the NC functional group playing a role. Furthermore, it showed robust non-hydrogen bonding interactions with four residues: PHE 289, PHE 193, ASP 192, and LYS 305, highlighting its ability to interact with multiple critical residues.

Compound 7 had the weakest binding affinity overall, with a docking score of -4.66. It did not form any hydrogen bonds and only engaged in two non-hydrogen interactions with PHE 289 and SER 207, which likely explains its poor binding performance. Compound 8, with a score of -4.83, performed slightly better than compound 7. It formed a single hydrogen bond with PHE 193, with the N=N=N functional group facilitating the interaction and engaged in two non-hydrogen bonds with ASP 192 and LYS 305.

Salbutamol, the reference molecule, exhibited the best binding score of -7.89, underscoring its high affinity for the target protein. It formed six hydrogen bonds with key residues, including two bonds each with ASN 312 and ASP 113, and one bond each with SER 203 and SER 207. Its functional groups, OH and NH2+, were crucial in establishing these interactions. Additionally,

salbutamol engaged in two non-hydrogen interactions with ASP 113 and PHE 193, making it the most stable and versatile binder in this study.

The docking results reveal several key insights. Compounds 1, 5, and salbutamol showed the strongest binding affinities, with salbutamol outperforming all other compounds. The hydrogen bonding residue SER 207 was a common feature among the strongest binders, indicating its critical role in stabilizing ligand-receptor interactions. Non-hydrogen bonding residues like PHE 289, LYS 305, and ASP 192 were also frequently involved, emphasizing their importance in overall binding stability.

The functional groups NO2 [in compounds 1 and 5] and NC [in compounds 2 and 6] were effective in facilitating hydrogen bonding, suggesting that such groups could be key structural elements in designing potent ligands. Conversely, compounds like 3 and 7, which lacked sufficient hydrogen bonding interactions, exhibited weaker binding. The role of diverse non-hydrogen interactions was also highlighted, as compounds like 6 and 3, despite moderate binding scores, engaged multiple residues through non-hydrogen bonds.

Salbutamol's superior performance can be attributed to its high number of hydrogen bonds and its ability to interact with multiple residues, showcasing its optimal structure for binding. This makes it an excellent reference for designing new compounds with similar functional groups and interaction profiles. Overall, the results suggest that designing ligands with functional groups capable of forming strong hydrogen bonds with SER 207 and engaging residues like PHE 289, LYS 305, and ASP 192 could lead to potent inhibitors or activators for the target protein.

Our work aimed to examine the binding of beta-2 adrenergic receptor agonists with salbutamol instead of other agonists. Salbutamol is an ideal reference for assessing the effectiveness and selectivity of other beta-2 receptor agonists due to its high selectivity for the beta-2 receptor over other adrenergic receptors. Research shows that salbutamol binds to the beta-2 receptor in a distinct way, making it crucial for developing specific agonists. The structure and binding features of salbutamol have been extensively studied, providing a solid reference point for comparison. Salbutamol forms precise hydrogen bonds and hydrophobic contacts with key residues in the beta-2 receptor's binding pocket, which are critical in determining the efficacy of new agonists. Additionally, salbutamol has been used in numerous molecular docking and simulation studies as a reference compound due to its well-documented pharmacological properties. Its crystal structure data is available in the Protein Data Bank, enhancing the reliability and stability of comparisons and allowing us to better understand the potential of novel beta-2 receptor agonists.

Molecular Dynamics Simulations:

Studying how ligands affect specific proteins through molecular dynamics [MD] simulations is crucial due to the role of conformational stability in theoretical analyses. This research explores the conformational stability of Beta-2 adrenergic receptor agonists, including compound 5 and salbutamol, over a 100-nanosecond period. By evaluating the RMSD of the Beta-2 adrenergic receptor agonist backbone [44], we examined the influence of compound 5 on the receptor's structure over time, focusing on changes in conformation and interactions with the ligands. The simulation results provide valuable structural insights into the physical alterations occurring within the protein [45].

The Root Mean Square Deviation [RMSD] over time is calculated by averaging the changes in the position of a selected atom [in Ångströms] over 50 nanoseconds in relation to a reference frame for a given frame. RMSD values between 1 and 3 Å suggest a well-balanced protein structure, as shown in (Figure 7).

Protein RMSD:

Measuring the Root Mean Square Deviation [RMSD] of the protein during the simulation provides important insights into its structural dynamics. Globular proteins that are compact typically exhibit fluctuations within the range of 1-7 Å. Deviations exceeding this range suggest significant conformational changes throughout the simulation. The graph highlights the areas of the protein that undergo the most noticeable oscillations. An average protein RMSD of 2.4 Å, falling within the typical range, indicates that the protein remained stable over the 100 ns simulation period, as shown in (Figure 7).

Protein RMSF:

The Root Mean Square Fluctuation [RMSF] of the protein during the simulation provides insights into localized fluctuations along its chain. The peaks on the graph highlight regions where the protein experiences significant variations. In the Ligand Contacts analysis, protein residues interacting with the ligand are indicated by green vertical bars. This analysis reveals that the protein amino acids interacting with the ligand remain closely associated, with fluctuations of less than one Å, illustrating how the compound [5] stable binding groups interact with the protein's amino acids. as shown in (Figure 8).

Ligand RMSF:

The Ligand Root Mean Square Fluctuation [L-RMSF] is a valuable metric for describing changes in the position of ligand atoms during the simulation. It provides insights into the entropic effects on the binding process as well as the interactions between ligand fragments and the protein. To calculate the L-RMSF, the protein backbone is first used to align the protein-ligand complex, followed by the determination of RMSF based on the ligand's heavy atoms. The L-RMSF measurements for Compound 5, shown in (Figure 8), were less than 4 Å.

Protein-Ligand Contacts [cont.]:

The normalized counts of protein-ligand interactions during the simulation are presented as stacked bar charts in the figure. The upper panel provides a summary of all distinct interactions between the ligand and the protein, while the lower panel shows the residue-ligand interactions for each trajectory frame. Residues that form numerous specific interactions with the ligand are represented in darker shades of orange, as indicated by the scale on the right side of (Figure 9).

Protein-Ligand Contacts:

Interactions between the protein and the ligand can be tracked and analyzed throughout the simulation. The plot illustrates the

different types of interactions occurring, including hydrogen bonds, hydrophobic interactions, ionic interactions, and water bridges. It shows that during the simulation, hydrophobic interactions and water bridging predominantly account for the majority of the interactions with amino acid residues, as depicted in (Figure 10).

Drug-Likeness Evaluation:

Lipinski's Rule of 5 suggests that for a drug to be effective when administered orally [46], it should have specific characteristics: fewer than ten hydrogen bond acceptors, fewer than five hydrogen bond donors, a molecular weight under 500, and a LogP value of less than 5. Adhering to these guidelines can increase the likelihood of a drug's success in oral administration. Additionally, the topological polar surface area [TPSA], a key factor influencing bioavailability, should be under 140 Å [47,48]. Some of these compounds exhibit excellent properties and fall within Lipinski's rules, making them highly promising drug candidates. Although the TPSA value exceeds 140 Å, this can be optimized through other approaches. Importantly, the overall physicochemical properties remain within acceptable ranges according to Lipinski's Rule of Five. Key parameters such as molecular weight, logP, hydrogen bond donors, and acceptors align well with drug-likeness criteria, ensuring good bioavailability potential. Additionally, in certain cases, compounds with higher TPSA can still demonstrate favorable absorption characteristics under specific conditions, further supporting their potential as viable drug candidates. All the designed compounds in the study show, improving their potential for oral bioavailability [49]

Conclusion.

Molecular docking results demonstrate that compounds 1, 5, and salbutamol exhibit strong binding affinities with the beta-2 adrenergic receptor, primarily through interactions with key residues like SER 207, PHE 289, LYS 305, and ASP 192. Functional groups such as NO2 and NC enhance binding stability, suggesting their potential in designing effective beta-2 agonists for treating bronchoconstriction-related diseases. Salbutamol remains a valuable reference for optimizing ligand design.

Acknowledgements.

I am grateful for the assistance with this work provided by the pharmaceutical chemistry department at the College of Pharmacy/Mustansiriyah University [www.uomustansiriyah.edu.iq] in Baghdad, Iraq.

Conflict of interest statement.

There have been none disclosed by the authors.

REFERENCES

1. Matera M. G, Rogliani P, Calzetta L, et al. An overview of the efficacy and safety of β2-adrenoceptor antagonists for the treatment of chronic obstructive pulmonary disease. Expert Opinion on Drug Safety. 2024;23:833-844.
2. Challa P, Epstein D. L. Adrenergic agents: Blockers and agonists. In Chandler and Grant's Glaucoma. CRC Press. 2024:133-148.
3. Aboulata A.A, Shatla I. M. Physiology and immunology of the adrenergic anti-inflammatory pathway. The Egyptian Journal of Immunology. 2024;31:46-57.
4. Fairhurst R. Adventures with the β2-adrenoceptor: A career-long interest in agonizing one of the most widely studied GPCRs. Chimia. 2024;78:483-498.
5. Liu S, Anderson P. J, Rajagopal S, et al. G protein-coupled receptors: A century of research and discovery. Circulation Research. 2024;135:174-197.
6. Dewangan S, Rawat V, Singh Thakur A. Imidazolidinone derivatives as pioneering anticancer agents: Unraveling insights through synthesis and structure-activity exploration. Chemistry Select. 2024;9:e202401379.
7. Rao G.D, Bendi A. Imidazole and benzimidazole derivatives as anti-inflammatory agents. In Heterocyclic Anti-Inflammatory Agents: A Guide for Medicinal Chemists. Bentham Science Publishers. 2024:47-69.
8. Sahib M.A, Mahdi M.F. Molecular docking, synthesis, characterization, and preliminary evaluation of some new 3-ethyl-1H-indole derivatives as potential COX-2 inhibitors. Adv J of Chem, Sec A. 2025;8:948-960.
9. Kumawat M.K, Yadav N, Kumar K. Anticancer properties of spirooxindole derivatives. In Spirooxindole. Elsevier. 2024:333-367.
10. Ahmad S, Alam M. Z, Salma U, et al. A review on recent progress in synthesis and biological activities of thiadiazole and its derivatives. Journal of Molecular Structure. 2024:138438.
11. Chilamakuru N. B, Singirisetty T, Bodapati A, et al. Schiff base-mediated synthesis of novel imidazolidine-4-one derivatives for potential antimicrobial and anthelmintic activities. Luminescence. 2024;39:e70026.
12. Kosmalski T, Kupczyk D, Baumgart S, et al. A review of biologically active oxime ethers. Molecules. 2023;28:5041.
13. Bradding P, Porsbjerg C, Côté A, et al. Airway hyperresponsiveness in asthma: The role of the epithelium. Journal of Allergy and Clinical Immunology. 2024.
14. Jude J.A, Panettieri Jr R.A. Bronchomotor tone imbalance evokes airway hyperresponsiveness. Expert Review of Respiratory Medicine. 2024;18:835-841.
15. Navratilova Z, Kominkova E, Petrek M. The immune response in the pathophysiology of pulmonary. Human Physiology Annual Volume. 2024:25.
16. Ora J, De Marco P, Gabriele M, et al. Exercise-induced asthma: Managing respiratory issues in athletes. Journal of Functional Morphology and Kinesiology. 2024;9:15.
17. Panahi S, Shahrokhian S, Ghalkhani M. Single-walled carbon nanotube coated with Ponceau4R-doped over-oxidized polypyrrole as a sensitive sensor for voltammetric monitoring of salbutamol. Diamond and Related Materials. 2024;141:110705.
18. Kabanov D, Vrana Klimovic S, Beckerová D, et al. Salbutamol attenuates arrhythmogenic effect of aminophylline in a hPSC-derived cardiac model. Scientific Reports. 2024;14:27399.
19. Armaya'u U, Ariffin M. M, Loh S. H, et al. Enhanced removal of salbutamol in water solution using Cu-based magnetic designed metal–organic frameworks: Kinetics and isothermal models and statistical analysis. Arabian Journal for Science and Engineering. 2024;49:439-458.

20. Armaya'u U, Ariffin M. M, Loh S. H, et al. Enhanced removal of salbutamol in water solution using Cu-based magnetic designed metal–organic frameworks: Kinetics and isothermal models and statistical analysis. Arabian Journal for Science and Engineering. 2024;49:439-458.
21. Mozo Vives B, Mainguy-Seers S, Lavoie J. P. Comparative study of the bronchodilator efficacy and adverse effects of salbutamol and hyoscine butylbromide in horses with severe asthma. Journal of Veterinary Internal Medicine. 2024;38:1835-1841.
22. Ma L.H, Jia L, Bai L. Safety outcomes of salbutamol: A systematic review and meta-analysis. The Clinical Respiratory Journal. 2023;17:1254-1264.
23. Karakioulaki M, Papakonstantinou E, Goulas A, et al. The role of atopy in COPD and asthma. Frontiers in Medicine. 2021;8:674742.
24. Ashmawy R, Zaki A, Baess A, et al. Efficacy and safety of inhaled heparin in asthmatic and chronic obstructive pulmonary disease patients: A systematic review and a meta-analysis. Scientific Reports. 2023;13:13326.
25. Abbas M, Verville J, Mroue K. Resolution of bronchoconstriction with positive airway pressure after intravenous adenosine. The American Journal of Emergency Medicine. 2021;44:481.e1-481.e2.
26. Van Meerbeke S. W, McCarty M, Petrov A.A, et al. The impact of climate, aeroallergens, pollution, and altitude on exercise-induced bronchoconstriction. Immunology and Allergy Clinics. 2025;45:77-88.
27. Paggi J.M, Pandit A, Dror R.O. The art and science of molecular docking. Annual Review of Biochemistry. 2024:93.
28. Ecker G.F. In silico ADME modeling. In Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays. 2024:1-27.
29. Tang Y, Fu Z, Raos G, et al. Molecular dynamics simulation of adhesion at the asphalt-aggregate interface: A review. Surfaces and Interfaces. 2024;44:103706.
30. Banerjee S, Baidya S.K, Ghosh B, et al. Exploring the key structural attributes and chemico-biological interactions of pyridinone-based SARS-CoV-2 3CLpro inhibitors through validated structure-based drug design strategies. Heliyon. 2024;10.
31. Mandal S.K, Puri S, Kumar B.K, et al. Targeting lipid-sensing nuclear receptors PPAR [α, γ, β/δ]: HTVS and molecular docking/dynamics analysis of pharmacological ligands as potential pan-PPAR agonists. Molecular Diversity. 2024;28:1423-1438.
32. Riaz R, Parveen S, Shafiq N, et al. Virtual screening, ADME prediction, drug-likeness, and molecular docking analysis of Fagonia indica chemical constituents against antidiabetic targets. Molecular Diversity. 2024:1-22.
33. Wan H. What ADME tests should be conducted for preclinical studies? ADMET and DMPK. 2013;1:19-28.
34. Fan M, Yang W, Peng Z, et al. Design, synthesis, molecular docking, and ADME prediction evaluation of phenyloxazole derivatives as α-glucosidase inhibitors. Journal of Molecular Structure. 2023;1292:136142.
35. Broni E, Striegel A, Ashley C, et al. Molecular docking and dynamics simulation studies predict potential anti-ADAR2 inhibitors: Implications for the treatment of cancer, neurological, immunological, and infectious diseases. International Journal of Molecular Sciences. 2023;24:6795.
36. Soni V. In silico molecular docking studies of cell-penetrating peptide and doxorubicin toward multiple tumor receptors. Asian Journal of Pharmaceutics AJP. 2024:18.
37. Alvarez J, Shoichet B. Virtual screening in drug discovery. CRC Press. 2005.
38. Singh H.R, Tiwari P, Deb P. K, et al. Larvicidal activity, molecular docking, and molecular dynamics studies of 7-[trifluoromethyl] indolizine derivatives against Anopheles arabiensis. Molecular Diversity. 2024:1-18.
39. Liu T, Yin H, Hu Q, et al. Small molecule compound DHPA screened by computer-aided drug design and molecular dynamics simulation inhibits neuroblastoma cell proliferation by targeting TrkB. ACS Omega. 2024;9:42227-4244.
40. Vander Meersche Y, Cretin G, Gheeraert A, et al. ATLAS: Protein flexibility description from atomistic molecular dynamics simulations. Nucleic Acids Research. 2024;52:D384-D392.
41. Tiemann J.K, Szczuka M, Bouarroudj L, et al. MDverse, shedding light on the dark matter of molecular dynamics simulations. Elife. 2024;12:RP90061.
42. Rizo J, Sari L, Jaczynska K, et al. Molecular mechanism underlying SNARE-mediated membrane fusion enlightened by all-atom molecular dynamics simulations. Proceedings of the National Academy of Sciences. 2024;121:e2321447121.
43. Lou J. S, Su M, Wang J, et al. Distinct binding conformations of epinephrine with α-and β-adrenergic receptors. Experimental & Molecular Medicine. 2024;56:1952-1966.
44. da Fonseca A.M, Caluaco B.J, Madureira J. M. C, et al. Screening of potential inhibitors targeting the main protease structure of SARS-CoV-2 via molecular docking, and approach with molecular dynamics, RMSD, RMSF, H-bond, SASA, and MMGBSA. Molecular Biotechnology. 2024;66:1919-1933.
45. Kutlu A, Çapkın E, Adacan K, et al. Fc–FcγRI complexes: Molecular dynamics simulations shed light on ectodomain D3's potential role in IgG binding. ACS Omega. 2024.
46. Haritha M, Sreerag M, Suresh C.H. Quantifying the hydrogen-bond propensity of drugs and its relationship with Lipinski's rule of five. New Journal of Chemistry. 2024;48:4896-4908.
47. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017;7:42717.
48. Reese T. C, Devineni A, Smith T, et al. Evaluating physiochemical properties of FDA-approved orally administered drugs. Expert Opinion on Drug Discovery. 2024;19:225-238.
49. Price E, Weinheimer M, Rivkin A, et al. Beyond Rule of Five and PROTACs in modern drug discovery: Polarity reducers, chameleonicity, and the evolving physicochemical landscape. Journal of Medicinal Chemistry. 2024;67:5683-5698.