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QUALIFICATION WORK

on the topic: « **APPLICATION OF MEDICINAL CHEMISTRY APPROACHES IN THE SEARCH FOR NEW ACTIVE PHARMACEUTICAL INGREDIENTS IN A SERIES OF OXADIAZOLE DERIVATIVES »**

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ANNOTATION

This qualification work aims to contribute to the development of new and effective drugs by applying modern approaches in medicinal chemistry to the search for new APIs in a series of oxadiazole derivatives. Docking studies and calculations of physicochemical and ADMET properties will be conducted to predict the compounds' potential biological activity, drug-likeness, and safety profile. The most promising compound ***2.2*** was selected, which has the best affinity for the nootropic target and a favorable pharmacokinetic profile. The work consists of an introduction, 3 chapters, general conclusions, a list of references, addition part. It is set out on 48 pages, includes, 4 tables, 21 pictures, 36 references.

Key words: medicinal chemistry**,** docking, oxadiazole, Lipinski's Rule of Five, ADMET properties.

АНОТАЦІЯ

Ця кваліфікаційна робота має на меті сприяти розробці нових ефективних лікарських засобів в ряду похідних оксадіазолу шляхом застосування сучасних підходів у медичній хімії до пошуку нових АФІ. Док-дослідження та розрахунки фізико-хімічних властивостей і властивостей ADMET проведені для прогнозування потенційної біологічної активності модельованих сполук, подібності з лікарськими засобами та профілю безпеки. Найбільш перспективною сполуку обрано 2.2, яка має найкращу спорідненість до ноотропної мішені та сприятливий фармакокінетичний профіль. Робота складається зі вступу, 3 розділів, загальних висновків, списку використаної літератури, додатків. Викладено на 48 сторінках, містить 4 таблиці, 21 малюнок, 36 посилань на літературні джерела.

Ключові слова: медична хімія, докінг, оксадіазол, правило п'яти Ліпінського, властивості ADMET.

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LIST OF ABBREVIATIONS

CMC	Computational Medicinal Chemistry
AI	Artificial Intelligence
ML	Machine Learning
FBDD	Fragment-based Drug Design
VS	Virtual Screening
LBVS	Ligand-Based Virtual Screening
SBVS	Structure-Based Virtual Screening
MD	Molecular Dynamics
HTVS	high-throughput virtual screening
QSAR	Quantitative Structure-Activity Relationship
HTS	high-throughput screening

INTRODUCTION

Actuality of subject. Computational medicinal chemistry has become an increasingly popular approach to aid in the search for new active pharmaceutical ingredients (APIs). This approach uses in silico methods to predict the biological activity, physicochemical properties, and potential toxicity of compounds before experimental testing, reducing the time and cost associated with drug discovery. In this thesis, computational medicinal chemistry approaches will be applied to a series of oxadiazole derivatives to identify promising drug candidates for further testing. Docking studies and calculations of physicochemical and ADMET properties will be conducted to predict the compounds' potential biological activity, drug-likeness, and safety profile.

Purpose of work. In this thesis, we aim to analyze the literature data on modern approaches used in medicinal chemistry to find new APIs, focusing on oxadiazole derivatives. Our study will involve a virtual database of 10 compounds of oxadiazole derivatives, and we will use in silico activity prediction methods, docking studies, and calculation of physicochemical and ADMET properties to select promising compounds for biological testing.

Objectives of the study:

- ✓ Analyze literature data on modern approaches used in medicinal chemistry to find new active pharmaceutical ingredients;
- ✓ Select objects, *in silico* activity prediction method, and activity type;
- ✓ Select biotargets and conduct docking studies;
- ✓ Test compounds for compliance with the Lipinski Rules;
- ✓ Analyze the results and select promising compounds for biological testing for activity in in vivo experiments.

The object of the research. Virtual database of 10 compounds of oxadiazole derivatives

The subject of the research. Online prediction of activity and bioavailability of 10 compounds of oxadiazole derivatives.

Methods of the research. Logical and structural approach, docking studies, calculation physic-chemical and ADMET properties.

The practical value of the results. It has been proved that all 10 studied compounds of oxadiazole derivatives are promising for the search for APIs. The compound was found to be the most promising for the synthesis and experimental studies of activity.

Approbation of the research results. The materials of the qualification work were presented at the XXIX International Scientifical and Practical Conference of Young Scientists and Students TOPICAL ISSUES OF NEW MEDICINES DEVELOPMENT in the form of thesis: Testing of new oxadiazole derivatives for compliance with lipinski rules / I. Makane, L. O. Perekhoda // Актуальні питання створення нових лікарських засобів: матеріали XXIX міжнародної науково-практичної конференції молодих вчених та студентів (19-21 квітня 2023 р., м. Харків). – Kharkiv: NUPh, 2023. – P. 20-21. As a result of the conference, a participant certificate and diploma were received.

The structure of the work. The qualification work includes an introduction, a review of scientific and patent literature, two experimental chapters, general conclusions, and a list of references. The work is presented on 48 pages, includes 4 tables, 21 figures, 36 sources of literature.

CHAPTER I

COMPUTATIONAL MEDICINAL CHEMISTRY APPROACHES TO BIOLOGICAL ACTIVITY PREDICTION

Review of literature

Drug discovery relies heavily on computational medicinal chemistry (CMC), which makes it possible to anticipate small molecule behavior and its interactions with biological systems. Although there have been tremendous advancements in this area recently, it originally began in the early 1960s when chemistry's use of computers was first introduced.

In the beginning, computers were exploited to decipher mathematical equations that expounded molecular characteristics, such as electronic compositions and spectroscopic data. Nevertheless, with the development of faster computers, more sophisticated algorithms were established, enabling researchers to emulate chemical reactions and scrutinize chemical architectures [1].

In the late 1970s, Molecular Mechanics surfaced as one of the earliest molecular modeling techniques. This approach portrays molecules as a collection of interconnected balls and springs, while also computing the energies associated with their interactions. Molecular Mechanics calculations are utilized to predict the relative stabilities of different molecular conformations, as well as to evaluate the fluctuations in free energy that arise from molecular interactions. During this same time period, Molecular Dynamics also emerged as a technique, simulating the movements of molecules over time by solving Newton's laws of motion.

The 1980s is considered a pivotal era in the field of drug discovery due to the development of Quantitative Structure-Activity Relationship (QSAR) models. These models have revolutionized the process of linking a molecule's chemical structure with its biological activity. By utilizing statistical methods, QSAR models establish a correlation between chemical properties such as molecular weight, lipophilicity, and hydrogen bond donors and acceptors, and biological activity. This approach has proven to be highly effective in predicting the activity

of new compounds and improving the activity of existing ones, simplifying the identification of potential drug candidates for researchers [2].

QSAR models operate on the premise that a compound's physicochemical properties can be utilized to predict its biological activity. This is done by utilizing a set of molecular descriptors that provide quantitative evaluations of various aspects of a molecule's structure and properties. By linking these descriptors with biological activity data, QSAR models can forecast the activity of new compounds against a particular target.

During the 1990s, cheminformatics emerged as a new field aiming to use computational methods to analyze and manage large amounts of chemical data. Cheminformatics applies a range of techniques, including data mining, machine learning, and network analysis, to identify trends, cluster similar molecules, and predict the properties of novel compounds.

One of the main goals of cheminformatics is to make sense of vast amounts of chemical data generated through various experimental methods. Cheminformatics techniques can process large datasets and extract valuable insights with the aid of computer programs and algorithms. In order to improve medication design and development, data mining can be utilized to find patterns and trends in chemical data [3].

A crucial step in the drug development process is the use of cheminformatics, which involves grouping compounds together depending on how structurally related they are. By grouping molecules with similar structures, cheminformatics techniques can identify potential drug candidates and optimize the properties of existing ones. Another useful application of cluster analysis is in drug development, where it can help anticipate the biological activity of novel drugs.

Since its origins in the 1960s, computational medicinal chemistry (CMC) has advanced significantly. Many improvements have been made in this area recently, and numerous new trends have also arisen. The following are some current developments in computational medicinal chemistry:

In recent years, computational medicinal chemistry has increasingly included artificial intelligence (AI) and machine learning (ML). They evaluate enormous amounts of chemical and biological data, forecast novel therapeutic targets, and find prospective medication candidates.AI and ML techniques can also be utilized to optimize drug design by predicting a drug's molecular properties and its interactions with biological systems [4].

High-throughput virtual screening

Virtual screening is an essential tool in drug discovery, and the recent advancements in computational power have enabled the screening of large chemical libraries. HTVS techniques use advanced algorithms to identify potential drug candidates quickly. Traditional drug discovery processes are being sped up and made less expensive by using these techniques [5].

Fragment-based drug design (FBDD) is a new approach to creating drugs that uses smaller molecules as building blocks to find prospective medication candidates. FBDD can be used to design drugs with higher potency and specificity by targeting specific areas of a protein or enzyme Quantum computing is a developing topic in computational chemistry that has the power to completely transform the subject. The simulation and prediction of chemical interactions can both be dramatically accelerated by quantum computing. More advancement is required before using quantum computing as a useful tool for the discovery of novel treatments, as it is still in its early phases of practical use [6]. A computer technique for simultaneously optimizing multiple parameters is called multi-objective optimization. Throughout the drug development process, this technique is used to enhance the molecular properties of a therapeutic candidate, such as potency, selectivity, and pharmacokinetic parameters. This approach might make it possible to identify pharmacological candidates with a higher likelihood of performing well in clinical trials.

Big data analytics: This technique is used to examine big quantities of chemical and biological information. Using this strategy, the data are mined for helpful data

using cutting-edge machine learning and statistical approaches. The use of big data analytics can be utilized to find new therapeutic targets, foresee drug toxicity, and improve drug design. [7]

1.1. Classification of virtual screening methods

Due to their capacity to quickly and efficiently find new drug candidates, virtual screening (VS) approaches have become effective tools in the process of drug development. The two types of VS techniques are ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS). LBVS methods rely on the similarity of molecules to known active compounds, while SBVS methods use the 3D structure of the target protein to predict the binding affinity of a ligand. In this article, we will review the different methods of virtual screening and their application in the search for new active pharmaceutical ingredients (APIs) in oxadiazole derivatives.

Ligand-based virtual screening (LBVS) encompasses several methods, including pharmacophore-based, shape-based, and quantitative structure-activity relationship (QSAR)-based methods. Pharmacophore-based methods aim to identify ligands with a similar 3D arrangement of chemical features to known active compounds. In contrast, shape-based methods utilize the shape and electrostatic properties of molecules to identify ligands that complement the shape and charge distribution of the binding site. QSAR-based methods use mathematical models to correlate the structure of a molecule with its biological activity. LBVS techniques have been used to screen large compound libraries to identify new drug candidates for various targets.[8]

Structure-based virtual screening (SBVS) methods include molecular docking and molecular dynamics (MD) simulations. Molecular docking predicts the binding pose and binding affinity of a ligand by fitting it into the binding site of a protein using scoring functions. MD simulations use molecular mechanics to simulate the movement of molecules over time and can be used to predict binding affinities and binding pathways

Comparison of Ligand-based and Structure-based Virtual Screening Methods

LBVS methods are faster and less computationally demanding than SBVS methods but require a known active compound or a set of active compounds. SBVS methods, on the other hand, can identify novel active compounds without the need for known active compounds but are computationally more demanding and require knowledge of the target protein's structure.

Examples of Successful Applications of Virtual Screening Methods

Virtual screening methods have been successfully applied in the search for new APIs in oxadiazole derivatives. For example, pharmacophore-based LBVS methods have been used to identify compounds with similar pharmacophore features to known active compounds. Shape-based LBVS methods have been used to identify oxadiazole derivatives with similar 3D shapes to known active compounds. QSAR-based methods have been used to predict the activity of oxadiazole derivatives based on their molecular descriptors. Molecular docking has been used to predict the binding affinities of oxadiazole derivatives to the target protein. In each case, the virtual screening methods have identified promising candidates for further experimental testing.

Virtual screening methods benefits and limitations

Virtual screening techniques are best known for their speedy and economical identification of new drug candidates. In addition to speeding up the drug discovery process, virtual screening can lower the number of compounds that need to undergo experimental testing. However there are drawbacks to virtual screening techniques, such as the requirement for precise target protein models and the possibility of false positives and false negatives. The expected activity of the discovered compounds should therefore be confirmed by using virtual screening techniques in addition to experimental techniques.[8,9,10]

1.2. ADME Properties and Lipinski's Rule of Five

The pharmacokinetic characteristics of a medicine or substance are described by the abbreviation ADME. It stands for Absorption, Distribution, Metabolism, and Excretion, four crucial procedures that affect how long and at what concentration a drug remains in the body. Knowing a drug's ADME features is essential for drug development since they impact a drug candidate's efficacy and safety during the discovery stage. A drug's efficacy and toxicity can be affected by its absorption, distribution, metabolism, and removal in the body.

Poor ADME properties can lead to low bioavailability, poor tissue distribution, and accumulation in certain organs, resulting in toxicity or inadequate therapeutic effects.[11]

Considering ADME properties early in the drug discovery process can help identify potential issues and enable medicinal chemists to optimize drug candidates for improved pharmacokinetic properties. In the end, this can increase the likelihood that clinical trials will be successful and improve patient outcomes by resulting in the creation of medications with superior efficacy and safety profiles.

Early on in the drug development process, ADME research and computer modeling can be used to find compounds with favorable ADME profiles and gain understanding of how alterations to the chemical structure can change a compound's attributes. Additionally, a thorough understanding of a drug candidate's ADME properties can help inform dosing regimens, identify potential drug interactions, and aid in regulatory approval. The optimization of ADME properties in oxadiazole derivatives can be achieved through various chemical modifications and rational drug design strategies. One approach is to modify the functional groups present in the oxadiazole core structure, which can affect its physicochemical properties and ultimately its ADME profile.

For instance, adding polar functional groups like hydroxyl or carboxyl groups could alter a substance's pharmacokinetic properties by making it more water soluble and less lipophilic. Yet, the addition of lipophilic groups can also make the molecule more permeable to membranes and boost absorption.

Another approach is to modify the substituents present in the aromatic rings of the oxadiazole structure. Substituents can affect the electronic and steric properties of the molecule, which can influence its ADME properties. For instance, electron-withdrawing substituents like nitro groups can make a molecule less polar and more lipophilic, improving membrane permeability. In contrast, substituents that donate electrons, such amino or hydroxyl groups, can make a molecule more polar and less lipophilic, increasing its water solubility.

Rational drug design strategies can also be used to optimize ADME properties. Before a molecule is manufactured and evaluated, the properties of probable compounds are predicted using computational methods. Novel oxadiazole derivatives' ADME features can be predicted using QSAR modeling, molecular docking, and molecular dynamics simulations, and substances with favorable pharmacokinetic profiles can be found.. By combining computational methods with chemical modifications, it is possible to design oxadiazole derivatives with optimal ADME properties for therapeutic use.

Computational Methods for Predicting ADME Properties of Oxadiazole Derivatives.

In the case of oxadiazole derivatives, QSAR modeling can be used to establish relationships between the physicochemical properties of the compounds and their ADME properties, such as absorption, distribution, metabolism, and excretion. By training these models on experimental data from similar compounds, they can accurately predict the ADME properties of novel oxadiazole derivatives.

This method is very helpful for locating drugs with desired pharmacokinetic characteristics, such as high oral bioavailability, slow clearance, and long half-life. By maximizing the physicochemical characteristics of the compounds by chemical alterations and logical drug design, guided by the forecasts from the QSAR models, these advantageous qualities can be attained

Overall, the use of computational methods, including QSAR modeling, has revolutionized the drug discovery process, allowing for more efficient

identification of potential drug candidates with favorable ADME properties and reducing the time and cost associated with traditional experimental methods.

The limitations of using computational approaches to predict ADME properties, and how can they be addressed

While computational methods such as QSAR modeling are useful in predicting ADME properties, they are not without limitations. One limitation is the availability and quality of experimental data on similar compounds, which is necessary for training the models. In addition, the accuracy of the predictions may be affected by the complexity of the biological system and the potential for unforeseen interactions.

Another drawback is that potential toxicity and metabolic problems, which are crucial elements in medication development, are not taken into account. For instance, a substance's ADME qualities might be good, yet the body might still find it harmful because of how particular enzymes break it down.

Combining computational techniques with experimental tests and in vivo research is crucial to overcoming these constraints. This makes it possible to verify computational predictions and gives us a better grasp of the compound's pharmacokinetic characteristics. Aside from that, utilizing integrated strategies that include data from numerous sources.

such as high-throughput screening and computational modeling, can improve the accuracy of ADME property predictions and help prioritize compounds for further development.

Overall ADME profiling is an essential component of drug discovery and development, as it allows for the identification and optimization of drug candidates with favorable pharmacokinetic properties. By integrating ADME profiling early in the drug discovery process and utilizing computational approaches to streamline the process and reduce costs, One important aspect of understanding the ADME properties of drug candidates is their ability to pass Lipinski’s Rule of Five. [12,13]

Lipinski’s Rule of Five

Lipinski's Rule of Five is one of the most frequently used methods to predict a drug's oral bioavailability. In 1997, Christopher Lipinski introduced this rule as part of a set of guidelines based on the physicochemical characteristics of substances that are expected to have strong oral bioavailability and permeability. Therefore, these substances are more likely to become successful medications. The rule is based on the fact that most orally delivered medications used in clinical settings share comparable physicochemical characteristics. It consists of four criteria, namely, molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors. According to the rule, a compound is more likely to have good oral bioavailability and permeability if it meets these criteria.

1. Molecular weight: The compound's molecular weight should be under 500 Da. This is due to the fact that bigger substances have lower permeabilities and are more likely to be broken down or eliminated by the body.
2. Lipophilicity: The compound's logP value should be less than 5. This statistic measures the compound's propensity to dissolve in lipid-like environments, with a high logP value indicating a high level of lipophilicity. Substances that are either too hydrophilic or overly lipophilic can face poor bioavailability, which is a common problem.
3. Hydrogen bond donors: The quantity of hydrogen bond donors (such as the -OH and -NH groups) must be no more than 5. Too many hydrogen bond donors in a compound can lead to strong interactions with water, which reduces the likelihood that the compound can traverse cell membranes and reach its intended destination.
4. Hydrogen bond acceptors: The number of hydrogen bond acceptors (e.g. -C=O and -C=N groups) should be less than or equal to 10. Compounds with too many hydrogen bond acceptors tend to be highly polar and form strong interactions with water, which can hinder their absorption and distribution in the body.[14]

Examples of oxadiazole derivatives that meet Lipinski's Rule of Five

The oxadiazole derivative 2-phenyl-5-(pyridine-4-yl)-1,3,4-oxadiazole (PPPO), which has been explored for its potential as an antibacterial medication, is an example of an oxadiazole derivative that abides by Lipinski's Rule of Five and demonstrates promising biological activity. PPPO was found to have significant antibacterial activity against both Gram-positive and Gram-negative bacteria, including drug-resistant strains like methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa, according to a study printed in the journal European Journal of Medicinal Chemistry. A strong prospect for further research and development as an antibacterial medication, PPPO was shown to have favorable pharmacokinetic characteristics and low toxicity [15]

Exploring Exceptions to Lipinski's Rule of Five: Drugs with Favorable Pharmacokinetic Properties.

Lipinski's Rule of Five has been a foundation in drug discovery for predicting the oral bioavailability and permeability of substances based on their physicochemical features. The constraints of this rule and the requirement to take other factors into account while developing new medications are emphasized by the countless examples of drugs that defy this rule while yet displaying positive pharmacokinetic features.

One of the prominent examples is the medication imatinib (Gleevec), which is used to treat gastrointestinal stromal tumors and chronic myeloid leukemia. Imatinib has a molecular weight of 589 g/mol, which is higher than the Lipinski's Rule of Five criterion of 500 g/mol. Nonetheless, it is an effective drug in treating these diseases because of its excellent oral bioavailability and minimal risk of drug-drug interactions.

Another case is the drug vancomycin, which is used to treat serious bacterial infections. Vancomycin defies Lipinski's Rule of Five due to its high molecular weight of 1449 g/mol and high LogP value of 1.9. Yet, due to its action mechanism

and capacity to target particular bacterial strains, it continues to be a very powerful medication.

These deviations to Lipinski's Rule of Five highlight how important it is to consider additional important factors during the drug development process, such as the target disease, pharmacological activity, and mechanism of action. Although Lipinski's Rule of Five is a helpful guideline, it shouldn't be the only standard used for developing new medications.

Limitations and Criticisms of Lipinski's Rule of Five in Drug Discovery

Although Lipinski's Rule of Five is frequently used in drug discovery, it has recently come under fire for several of its shortcomings. Lipinski's Rule of Five has drawn criticism for oversimplifying the intricate relationships between medicines and the human body. The rule assumes that a drug's molecular weight, LogP, hydrogen bond donors, and hydrogen bond acceptors are the only variables affecting its pharmacokinetic properties, however this may not always be the case. For instance, the guideline doesn't consider how specific functional groups may affect a medicine's effectiveness or toxicity.

Furthermore, Lipinski's Rule of Five was created expressly for pharmaceuticals taken by mouth; it could not be applicable to medications taken by other means, such as injection or inhalation. Moreover, the rule does not consider how drug formulation factors like particle size or solubility may affect pharmacokinetics.

Lipinski's Rule of Five may be biased against particular pharmacological classes, which is another drawback. For instance, the rule might perform less well in forecasting the pharmacokinetic characteristics of more recent drug classes, like biologics, because they have distinct chemical structures and modes of action from conventional small molecule medications.

Despite these limitations and criticisms, Lipinski's Rule of Five remains a useful tool in drug discovery. The rule provides a straightforward guideline for identifying potential lead compounds with favorable pharmacokinetic properties,

particularly for oral drugs. By evaluating a candidate's molecular weight, LogP, hydrogen bond donors, and hydrogen bond acceptors, researchers can quickly assess a compound's potential for oral bioavailability and permeability.

It's crucial to remember, though, that choosing drug candidates shouldn't only be based on Lipinski's Rule of Five. In the process of finding new drugs, other elements like the target disease, pharmacological activity, and mechanism of action should also be taken into account. Also, the use of computational techniques and experimental assays can offer more information about the potential efficacy and safety of a medication candidate [16].

Future Developments and Modifications of Lipinski's Rule of Five in Drug Development

In recent years, researchers have also worked to refine and improve Lipinski's Rule of Five using computational methods and machine learning techniques. One proposed modification is the inclusion of additional physicochemical properties that can impact a drug candidate's pharmacokinetic properties. For example, the topological polar surface area (TPSA) has been suggested as a useful parameter to consider in addition to Lipinski's Rule of Five. TPSA reflects the surface area of a molecule that is polar and can form hydrogen bonds, which can impact a drug's solubility and permeability.

Using artificial intelligence (AI) and machine learning to create more precise predictive models for drug pharmacokinetics is another adjustment that might be made. It might be feasible to discover more intricate links between a drug's chemical qualities and its pharmacokinetics by training AI models on big datasets of well-known medications and their pharmacokinetic characteristics

Additionally, there has been interest in expanding Lipinski's Rule of Five to other routes of administration besides oral administration. This could entail creating distinct regulations for various routes of administration or changing the current regulation to take into consideration certain physicochemical features that are crucial for various routes of administration.

In addition to these modifications, there is also interest in developing more specific guidelines for certain drug classes, which may have different physicochemical properties and require different criteria for evaluation. This could involve developing new rules or modifying existing guidelines to better fit the unique properties of these drug classes.

Overall, while Lipinski's Rule of Five remains a valuable tool in drug development, there is always room for improvement and refinement. By incorporating additional physicochemical properties, utilizing machine learning and AI, and developing more specific guidelines for different drug classes and routes of administration, it may be possible to improve the accuracy and usefulness of Lipinski's Rule of Five in predicting the pharmacokinetic properties of drug candidates.[17]

1.3. Molecular docking

Computational medicinal chemistry involves the use of various computational methods and tools to aid in the design, discovery, and optimization of new drug candidates. One of the key concepts in this field is molecular docking, which may be used to predict the kind of binding and affinities a small molecule therapeutic candidate will have for a specific target protein.

In the field of computational medicinal chemistry, molecular docking is a computer technique utilized to predict the binding affinity of a ligand to a target protein. This process involves generating various conformations of both the ligand and protein, then computationally "docking" them together to determine the best possible binding pose and estimate the binding free energy between the two molecules.

There are two main types of molecular docking methods used in computational medicinal chemistry: rigid docking and flexible docking.

Rigid docking involves keeping the target protein fixed and allowing the ligand to move freely within its binding site. This approach assumes that the protein remains

in a static conformation upon ligand binding. Rigid docking is a faster method and is commonly used in the initial stages of drug discovery to identify potential lead compounds with good binding affinity.

Contrarily, flexible docking permits both the protein and the ligand to move and be flexible throughout the docking procedure. This method for predicting binding affinity is more accurate since it takes into consideration the conformational modifications that the protein may undergo following ligand binding. Flexible docking is a more computationally intensive process, but it can provide a more realistic representation of the actual binding process.

Flexible docking methods are commonly used in the later stages of drug discovery, where the goal is to optimize the binding affinity of lead compounds and design more potent drug candidates. In flexible docking, the protein is allowed to undergo conformational changes upon ligand binding, which can help to identify potential binding sites and optimize ligand-protein interactions. Additionally, flexible docking can also help to identify potential off-target effects of a drug candidate, which is crucial for drug safety and efficacy.[18,19]

Using Molecular Docking to Identify Potential Oxadiazole Derivatives for Targeted Disease Treatment

When it comes to oxadiazole derivatives, molecular docking can be utilized to find substances that have the potential to attach to a particular protein target engaged in a specific disease process.

In order to uncover potential oxadiazole derivatives utilizing molecular docking, the first step is to select a protein target that is understood to be involved in the desired disease process. Searches in the literature, genetic research, and bioinformatics analysis are just a few methods for locating this protein target. The following stage involves determining the three-dimensional structure of a protein target. This can be done using both experimental methods like X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy and computer methods like homology modeling.

The next step is to prepare the oxadiazole derivatives for docking. This involves optimizing the structures of the compounds and adding any missing atoms or bonds. The ligand structures are then saved in a suitable file format that can be read by the docking software.

The protein and ligand structures are then loaded into the docking software, and the docking simulation is run. The software will generate multiple conformations of the ligand and protein and then computationally "dock" them together to identify the best possible binding pose and estimate the binding free energy between the two molecules.

After the docking simulation is complete, the results are analyzed to identify potential oxadiazole derivatives that have the highest predicted binding affinity to the target protein. These compounds can then be further tested in vitro and in vivo to determine their efficacy and safety as potential drug candidates for targeted disease treatment.[20]

Successful Examples of Oxadiazole Derivatives Identified through Molecular Docking

Several studies have successfully identified oxadiazole derivatives with potential therapeutic activity through molecular docking. For instance, in a study aimed at identifying potential inhibitors of the protein kinase CK2, a series of oxadiazole derivatives were docked to the active site of the protein using AutoDock Vina. The study identified several oxadiazole derivatives with high binding affinity to the protein, which were further evaluated in vitro and exhibited potent inhibitory activity against CK2.

Another study aimed at identifying potential inhibitors of the bacterial enzyme MurB, involved in cell wall biosynthesis, used molecular docking to screen a library of oxadiazole derivatives. The study identified several oxadiazole derivatives that docked successfully to the active site of the enzyme and exhibited potent inhibitory activity against MurB, highlighting the potential of oxadiazole derivatives as antimicrobial agents.

These effective examples show how molecular docking can be an effective technique for drug discovery, particularly when it comes to the identification and enhancement of oxadiazole derivatives with potential therapeutic efficacy. To achieve accurate and effective outcomes, it is crucial to take into account a number of variables when choosing an appropriate docking program, including as precision, speed, and user-friendliness [21].

Limitations of Molecular Docking in Predicting the Binding Affinity of Oxadiazole Derivatives and Their Solutions

Despite its many advantages, there are some limitations to this technique that must be addressed.

One of the main limitations of molecular docking is the inability to account for solvent effects and protein flexibility. Solvent molecules and protein dynamics can significantly affect the binding affinity of a ligand, and neglecting these factors can lead to inaccurate predictions. One approach to address this limitation is by incorporating explicit water molecules into the docking simulation or using more advanced docking algorithms that account for protein flexibility.

Another limitation is the accuracy of force fields used to describe the interactions between the ligand and the protein. Force fields are mathematical functions that describe the potential energy between atoms in a molecule, and choosing an appropriate force field is crucial for accurate molecular docking. However, no single force field is universally applicable to all systems, and choosing the wrong force field can result in inaccurate predictions. One solution to this problem is to use multiple force fields and compare the results to improve accuracy.

The size and complexity of the target protein and the ligand also pose limitations to molecular docking. Larger proteins and ligands can make the docking process computationally expensive and time-consuming. One approach to address this limitation is by using more efficient algorithms or simplifying the protein or ligand structure without significantly affecting its biological activity [22].

In conclusion, molecular docking is a powerful tool in drug discovery, but it has its limitations that must be addressed to obtain accurate predictions. Incorporating solvent effects and protein flexibility, choosing appropriate force fields, and optimizing computational efficiency are some of the solutions to overcome the limitations of molecular docking.

Conclusion to chapter 1

In conclusion, computational medicinal chemistry has become an integral part of the drug discovery process, offering numerous advantages over traditional experimental methods. In this review, we have discussed the historical perspective and current trends in computational medicinal chemistry, as well as key concepts such as ligand-based vs. structure-based drug design, virtual screening, ADME properties, Lipinski's Rule of Five, and molecular docking. We have also provided a classification of virtual screening methods and a comparison of ligand-based and structure-based virtual screening methods. Additionally, we have provided examples of successful applications of virtual screening methods in predicting the biological activity of oxadiazole derivatives.

Furthermore, we discussed the importance of ADME properties in drug discovery and introduced Lipinski's Rule of Five as a guideline for drug design. Finally, we explored the concept of molecular docking and its limitations, as well as provided case studies of successful docking predictions for oxadiazole derivatives. Overall, computational medicinal chemistry continues to evolve and play a critical role in the discovery and development of new drugs.

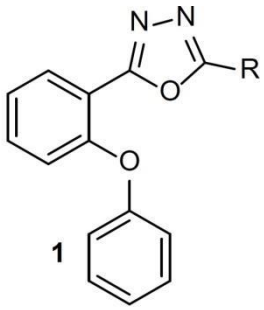
Chapter 2.

1,3,4-OXADIAZOL CYCLE AS PERSPECTIVE BASE OF SEARCH FOR NEW ACTIVE PHARMACEUTICAL INGREDIENTS

Oxadiazoles are five-membered heteroaromatic rings containing two carbons, two nitrogens, and one oxygen atom, and they exist in different regioisomeric forms. Oxadiazoles are frequently occurring motifs in druglike molecules, and they are often used with the intention of being bioisosteric replacements for ester and amide functionalities.

2.1 Oxadiazole derivatives with CNS effects (anticonvulsant)

A number of studies on the targeted synthesis of anticonvulsants are devoted to oxadiazole derivatives. Scientists synthesize few phenoxyphenyl-1,3,4-oxadiazole derivatives, structure 1. Anticonvulsant activity of the synthesized compounds 1 was determined as an *in-vivo* model for evaluating benzodiazepine effect [23].



1

R = H, OH, NH_2, SH, SCH_3

Examples of Oxadiazole Derivatives Used as Anticonvulsants

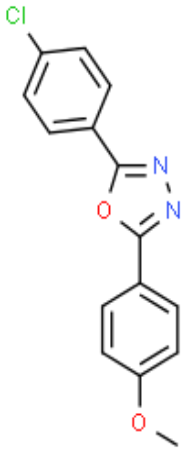
Sulfonamide-based oxadiazoles are a class of organic compounds that have been studied for their potential anticonvulsant properties. These compounds contain a sulfonamide group and an oxadiazole ring in their structure, which give them unique chemical and physical properties. Oxadiazoles have been shown to possess a wide range of biological activities, including anticonvulsant activity,

making them an important class of compounds for the development of new medications for the treatment of seizures.

Studies have shown that sulfonamide-based oxadiazoles exhibit potent anticonvulsant activity in animal models of seizures. The two examples mentioned,

2.2 Oxadiazole derivatives with CNS effects (nootropic activity)

(2,4-dichlorophenyl)-5-(methylsulfanyl)-1,3,4-oxadiazole and 2-(4-chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole, have been extensively investigated for their anticonvulsant properties.



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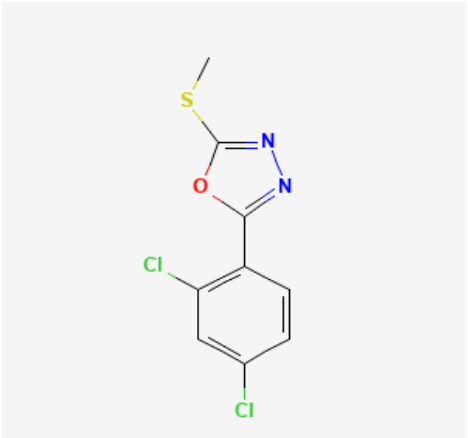


3

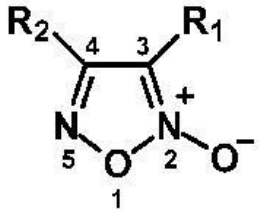
In one study, the anticonvulsant activity of these compounds was evaluated using the maximal electroshock seizure models in mice [24]. The study found that these compounds significantly reduced the duration of seizures and increased the seizure threshold in the animals. Additionally, the compounds showed low toxicity and good tolerability, suggesting that they may be promising candidates for the development of new anticonvulsant medications.

The mechanism of action by which sulfonamide-based oxadiazoles exert their anticonvulsant activity is not fully understood. However, it is believed that these compounds modulate the activity of certain ion channels in the brain, such as voltage-gated sodium and calcium channels, which play a crucial role in the

generation and propagation of seizures. By modulating the activity of these ion channels, sulfonamide-based oxadiazoles may help to restore the normal electrical activity of neurons in the brain, thereby reducing the likelihood of seizures[25].

Furoxans structure 4, Extensive research has been conducted on furoxans, a type of oxadiazole derivative, due to their potential as anticonvulsant agents. These compounds possess a unique molecular structure consisting of a five-membered ring with a nitro group and an oxygen atom. Animal studies have demonstrated the potent anticonvulsant activity of furoxans, indicating their potential in the development of new anticonvulsant medications.

Despite the promising results, the precise mechanism by which furoxans exert their anticonvulsant effects remains unclear. However, there is a belief that they modulate the activity of specific ion channels in the brain, which are responsible for regulating neuronal electrical activity. These ion channels play a critical role in the generation and propagation of seizures. Furoxans may aid in the restoration of normal ion channel activity, thereby reducing the likelihood of seizures occurring [26].



4

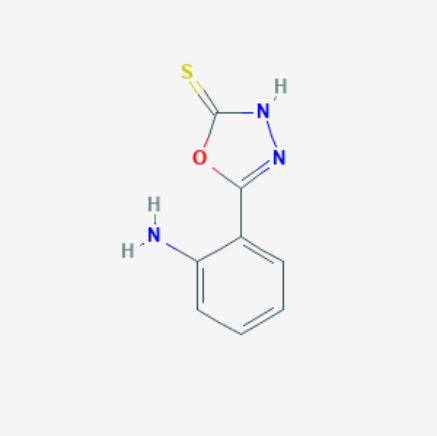
1,3,4-Oxadiazole-2(3H)-Thione: A Potential Nootropic Compound

Nootropic compounds are known for their cognitive-enhancing effects, and 1,3,4-oxadiazole-2(3H)-thione is one such compound that has gained attention for its nootropic activity. This oxadiazole derivative has been studied in animal models and has shown promising results in improving learning and memory retention.

A study found that 1,3,4-oxadiazole-2(3H)-thione improved cognitive performance in rats by enhancing their learning and memory retention abilities . The exact

mechanism by which this compound exerts its nootropic effects is not fully understood, but it is believed to modulate the activity of certain neurotransmitters and receptors in the brain. In addition to improving cognitive function, 1,3,4-oxadiazole-2(3H)-thione has also been found to increase acetylcholine levels in the brain. Acetylcholine is a neurotransmitter that plays a critical role in learning and memory processes. It is believed that the increase in acetylcholine levels may contribute to the nootropic effects of this compound [27].

Overall, the studies conducted on 1,3,4-oxadiazole-2(3H)-thione suggest that it may be a promising compound for the development of new nootropic medications. However, further research is needed to fully understand its mechanism of action and its potential as a therapeutic agent.



5

5-(4-Chlorophenyl)-1,3,4-oxadiazole-2-amine is an oxadiazole derivative that has shown potential as a nootropic compound, this oxadiazole derivative has gained attention for its ability to improve cognitive function in animal models.

A study conducted on this compound found that it enhanced spatial memory and learning in rats. The rats were given the compound orally, and their cognitive abilities were assessed using a Morris water maze test. The study found that the rats treated with the compound had improved spatial learning and memory retention compared to the control group [28].

The exact mechanism by which 5-(4-Chlorophenyl)-1,3,4-oxadiazole-2-amine exerts its nootropic effects is not fully understood. However, it is believed

that the compound modulates the activity of certain neurotransmitters and receptors in the brain. The study also found that the compound increased levels of acetylcholine and brain-derived neurotrophic factor (BDNF) in the brain. Acetylcholine is a neurotransmitter that plays a critical role in learning and memory processes, while BDNF is a protein that is important for the growth and survival of neurons [29].

The increase in acetylcholine levels is thought to contribute to the nootropic effects of the compound, as acetylcholine is known to enhance cognitive function. The increase in BDNF levels is also significant, as it suggests that the compound may have neuroprotective effects and promote neuronal growth and survival, which could potentially benefit individuals with cognitive impairments [30].

Overall, the study conducted on 5-(4-Chlorophenyl)-1,3,4-oxadiazole-2-amine suggests that it may be a promising nootropic compound. However, further research is needed to fully understand its mechanism of action and its potential as a therapeutic agent.

2.3 Generating a virtual database based of oxadiazole derivatives on a logical and structural approach

We plan to construct virtual hypothetical structures that will have nootropic activity based on the analysis of literature data on the structure of known nootropics and using a logical structural approach. We plan to modify the oxadiazole cycle by introducing substituents of different nature, which will allow us to evaluate *in silico* the effect of substituents on the activity and optimize the search for new effective compounds in this series of derivatives. In case the planned compounds are found to be promising, their synthesis involves the introduction of substituents into the structure at different positions of the phenyl ring at the stage of cycle formation.

The planned structures are shown in Table 2.1 .

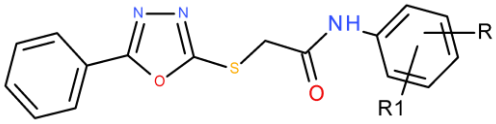


Table 2.1

The planned structures Oxadiazole derivatives

Number structures	R	R^1
2.1	4-C_2H_5	H
2.2	4-$OCHF_2$	H
2.3	4-$COOC_2H_5$	H
2.4	2-CH_3	3-CH_3
2.5	2-Cl	5-Cl
2.6	3-Cl	4-Cl
2.7	2-Cl	5-CF_3
2.8	4-CH_3	H
2.9	3-CH_3	H
2.10	2-CH_3	H

Conclusion to Chapter 2

In summary, 1,3,4-oxadiazol derivative have been extensively studied for their potential as active pharmaceuticals ingredient, particularly in the development of anticonvulsant and nootropic medication.

Sulfonamide-based oxadiazoles and Furoxans have shown potent anticonvulsant activity, likely by modulating the activity of specific ion channels in the brain, Further research is needed to understand the mechanisms of action of these compounds.

Chapter 3.

COMPUTER PREDICTION FOR THE PHARMACOLOGICAL, PHARMACOKINETIC PROFILE OF THE TESTED COMPOUNDS

3.1. Calculation ADME properties and to the Lipinski's Rule of Five for the tested compounds

Chris Lipinski was one of the first to point out that medicines generally have physicochemical and structural properties within certain limits. In 1997, Lipinski formulated empirical rules (Lipinski's rules) to assess the drug-eligibility of compounds, based on the observation that most drugs are relatively small and lipophilic molecules. These rules describe the molecular properties and pharmacokinetics of drugs in the human body, including their absorption, distribution, metabolism, and excretion. According to the Lipinski rules, a drug candidate compound must meet the following criteria:

The with Lipinski's rule of five - formulation

Poor absorption or permeation are more likely when:

1. *There are more than 5 H-bond donors.*
2. *The distribution coefficient in the octanol/water system (log P) is no more than 5;*
3. *The molecular weight is over 500.*
4. *There are more than 10 H-bond acceptors.*
5. *The number of rotating non-terminal bonds (Rot B) is no more than 10*

All the structures of substances ***2.1-2.10*** were generated by us using the Molinspiration program in 2D format and converted to mSMILES. The resulting mSMILE looks like a sequence of atoms:

https://www.molinspiration.com/cgi-bin/properties

miSMILES***2.1:*** CCc3ccc(NC(=O)CSc2nnc(c1ccccc1)o2)cc3

N-(4-ethylphenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miSMILES***2.2 :***O=C(CSc2nnc(c1ccccc1)o2)Nc3ccc(OC(F)F)cc3

N-[4-(difluoromethoxy)phenyl]-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miSMILES***2.3:*** CCOC(=O)c3ccc(NC(=O)CSc2nnc(c1ccccc1)o2)cc3

Ethyl4-({[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetyl}amino)benzoate

miSMILES***2.4:*** Cc3cccc(NC(=O)CSc2nnc(c1ccccc1)o2)c3C

N-(2,3-dimethylphenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miSMILES***2.5:***O=C(CSc2nnc(c1ccccc1)o2)Nc3cc(Cl)ccc3Cl

N-(2,5-dichlorophenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miSMILES***2.6:***O=C(CSc2nnc(c1ccccc1)o2)Nc3ccc(Cl)c(Cl)c3

N-(3,4-dichlorophenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miSMILES***2.7:***O=C(CSc2nnc(c1ccccc1)o2)Nc3cc(C(F)(F)F)ccc3Cl

N-[2-chloro-5-(trifluoromethyl)phenyl]-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miSMILES***2.8:***Cc3ccc(NC(=O)CSc2nnc(c1ccccc1)o2)cc3

2-((5-Phenyl-1,3,4-oxadiazol-2-yl)thio)-N-(p-tolyl)acetamide

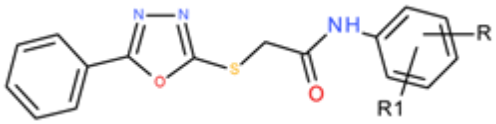
miSMILES***2.9:***Cc3cccc(NC(=O)CSc2nnc(c1ccccc1)o2)c3

N-(3-methylphenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miSMILES***2.10:***Cc1ccccc1NC(=O)CSc3nnc(c2ccccc2)o3

2-((5-Phenyl-1,3,4-oxadiazol-2-yl)thio)-N-(o-tolyl)acetamide

At the next stage of our research, we calculated the parameters that determine the compliance of anilides of 5-phenyl-1,3,4-oxadiazol-2-yl-thioacetic acid with Lipinski's Five Rules. The calculations were performed using the 2D structure of compounds



2.1-2.10

It is important to note that the rule of five does not allow for quantification of oral absorption, and compounds that do not violate any of the five criteria are not necessarily orally bioavailable, but if two or more of the requirements of the rule are not met, there is a high risk of low bioavailability of the compound.

We have tested the planned compounds according to Lipinski's rules, and the results are presented in Table 3.1

Table 3.1

Results of calculating the compliance of compounds with Lipinski's five rules

Chemical compound number	Molecular weight	The distribution coefficient in the octanol/water system (log P)	H-bond acceptors	H-bond donors	Number of rotating non-terminal bonds (Rot B)
2.1	339	4.25	5	1	6
2.2	377	3.95	6	1	7
2.3	383	3.88	7	1	8
2.4	339	4.13	5	1	5
2.5	380	4.62	5	1	5
2.6	380	4.63	5	1	5
2.7	413	4.83	5	1	6
2.8	325	3.78	5	1	5
2.9	325	3.76	5	1	5
2.10	325	3.73	5	1	5

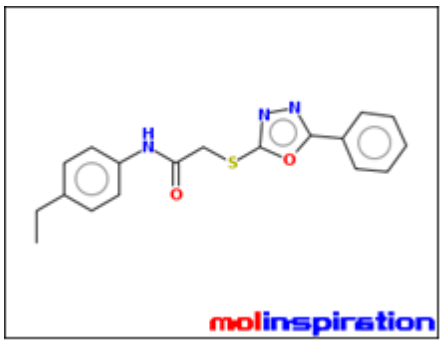
The molecular weight for 10 anilides of 5-phenyl-1,3,4-oxadiazol-2-yl-thioacetic acid is in the range from 325 to 413.

The distribution coefficient in the octanol/water system for 10 anilides of 5-phenyl-1,3,4-oxadiazol-2-yl-thioacetic acid is in the range from 3.73 to 4.83.
The number of H-bond acceptors from 5 to 7. The number of H-bond donors are 1. Number of rotating non-terminal bonds from 5 to 8.

Analyzing the results of the calculation of the drug-like criteria (Table 3.1), it can be stated that all compounds anilides of 5-phenyl-1,3,4-oxadiazol-2-yl-thioacetic acid comply with the Lipinski rule.

Therefore, it is advisable to conduct further experimental biological studies of the compounds.

Experimental part



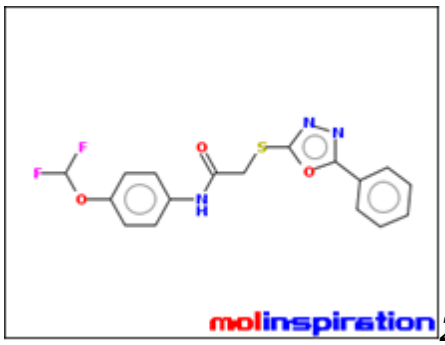
CCc3ccc(NC(=O)CSc2nnc(c1ccccc1)o2)cc3

N-(4-ethylphenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miLogP	4.25
TPSA	68.02
natoms	24
MW	339.42
nON	5
nOHNH	1
nviolations	0
nrotb	6
volume	299.80

Based on the Lipinski rule of five, the molecular properties of the compound meet the rule, as all values fall within the acceptable range. The compound has a miLogP value of 4.25, TPSA of 68.02, molecular weight of 339.42, and 6 rotatable bonds. The number of hydrogen bond donors is 1, and there are no Lipinski rule violations.

Overall, these properties suggest that this molecule has good drug-like properties and may be a promising candidate for drug development.



2.2

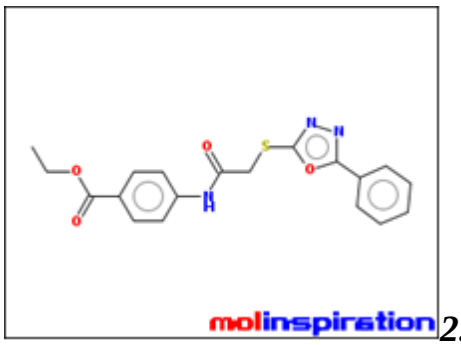
O=C(CSc2nnc(c1ccccc1)o2)Nc3ccc(OC(F)F)cc3

N-[4-(difluoromethoxy)phenyl]-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miLogP	3.95
TPSA	77.26
natoms	26
MW	377.37
nON	6
nOHNH	1
nviolations	0
nrotb	7
volume	302.11

This molecule meets the Lipinski rule. MW < 500: The molecular weight of this molecule is 377.37, which is less than 500. H-bond acceptors <= 10: This

molecule has 6 H-bond acceptors, which is less than or equal to 10. H-bond donors <= 5: This molecule has 1 H-bond donor, which is less than or equal to 5. LogP <= 5: The LogP value of this molecule is 3.95, which is less than or equal to 5.



2.3

Ethyl4-({[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetyl}amino)benzoate

miLogP	3.88
TPSA	94.33
natoms	27
MW	383.43
nON	7
nOHNH	1
nviolations	0
nrotb	8
volume	327.76

This molecule meets Lipinski's rule of five, as all the criteria are within the acceptable range:

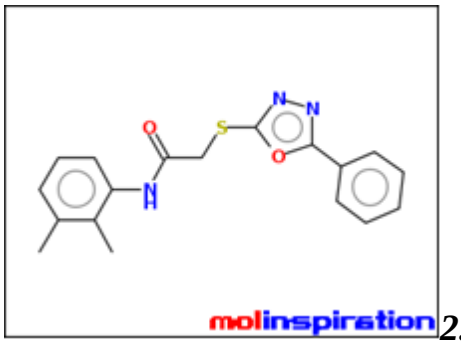
MW (molecular weight) is less than 500, which is 383.43 in this case.

LogP (octanol-water partition coefficient) is less than 5, which is 3.88 in this case.

H-bond donors (number of hydrogen bond donors) is less than or equal to 5, which is 1 in this case.

H-bond acceptors (number of hydrogen bond acceptors) is less than or equal to 10, which is 7 in this case.

Therefore, this molecule is predicted to have good oral bioavailability.

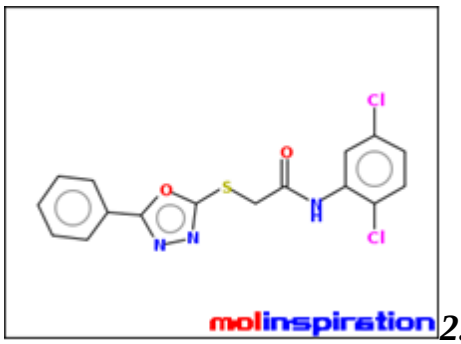


2.4

N-(2,3-dimethylphenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miLogP	4.13
TPSA	68.02
natoms	24
MW	339.42
nON	5
nOHNH	1
nviolations	0
nrotb	5
volume	299.55

This molecule has a moderate lipophilicity with a miLogP of 4.13, a moderate TPSA of 68.02, and a moderate molecular weight of 339.42. It has 5 oxygen and nitrogen atoms, which is within the limit set by the Lipinski rule of 5. It also has no violations in the rule of 5, and has a moderate number of rotatable bonds and a moderate molecular volume. Overall, based on these properties, this molecule has a reasonable chance of being orally bioavailable.

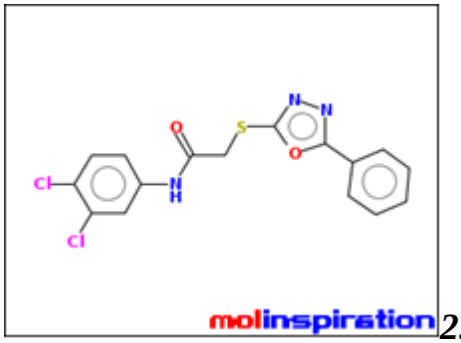


2.5

N-(2,5-dichlorophenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miLogP	4.62
TPSA	68.02
natoms	24
MW	380.26
nON	5
nOHNH	1
nviolations	0
nrotb	5
volume	293.50

Based on the given molecular descriptors, this molecule has a moderate to high lipophilicity (miLogP of 4.62), a small polar surface area (TPSA of 68.02), a moderate molecular weight (MW of 380.26), and a low number of oxygen atoms (nON of 5) and rotatable bonds (nrotb of 5). The molecule has no violations of Lipinski's rule of five, which suggests good oral bioavailability.

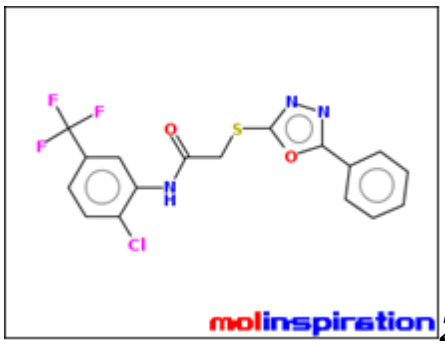


2.6

N-(3,4-dichlorophenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miLogP	4.62
TPSA	68.02
natoms	24
MW	380.26
nON	5
nOHNH	1
nviolations	0
nrotb	5
volume	293.50

This molecule has a high miLogP value, which suggests that it is relatively hydrophobic. Its TPSA value is low, indicating that it has limited polar surface area. The number of atoms, molecular weight, and volume of the molecule are relatively large. It has a moderate number of oxygen and nitrogen atoms, and only one of these atoms has hydrogen bonding capacity. The number of rotatable bonds is moderate. The molecule does not violate Lipinski's rule of five. Overall, the molecule may have potential as a drug candidate due to its lack of violations of Lipinski's rule and moderate physicochemical properties



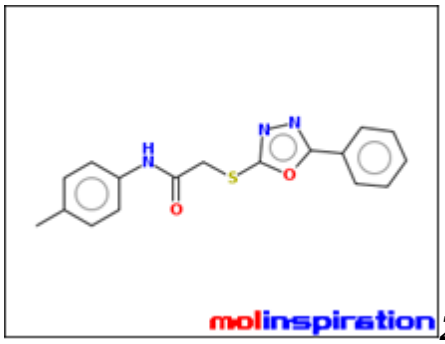
2.7

N-[2-chloro-5-(trifluoromethyl)phenyl]-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miLogP	4.83
TPSA	68.02
natoms	27

MW	413.81
nON	5
nOHNH	1
nviolations	0
nrotb	6
volume	311.26

This compound appears to be within Lipinski's Rule of Five. It has a miLogP value of 4.83, which is below the threshold of 5, a TPSA value of 68.02, which is below the threshold of 140, a molecular weight of 413.81, which is below the threshold of 500, and a number of rotatable bonds of 6, which is below the threshold of 10.



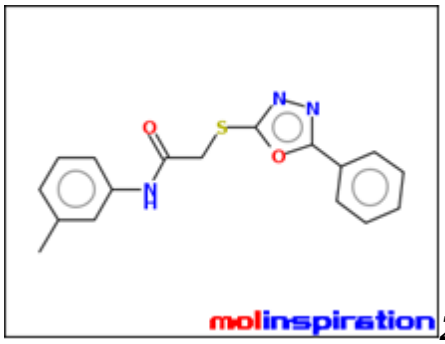
2.8

2-((5-Phenyl-1,3,4-oxadiazol-2-yl)thio)-N-(p-tolyl)acetamide

miLogP	3.78
TPSA	68.02
natoms	23
MW	325.39
nON	5
nOHNH	1
nviolations	0
nrotb	5
volume	282.99

The compound has a molecular weight (MW) of 325.39 g/mol, which is below the threshold of 500 g/mol. The compound has 5 H-bond donors (nON) and 1 H-bond acceptor (nOHNH), which is below the threshold of 5 and 10,

respectively. The compound also has a LogP value of 3.78, which is below the threshold of 5. Finally, the compound has no more than 10 rotatable bonds (nrotb), which is below the threshold of 10. Therefore, this compound meets all the criteria of Lipinski's rule of five.



2.9

N-(3-methylphenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

miLogP	3.76
TPSA	68.02
natoms	23
MW	325.39
nON	5
nOHNH	1
nviolations	0
nrotb	5
volume	282.99

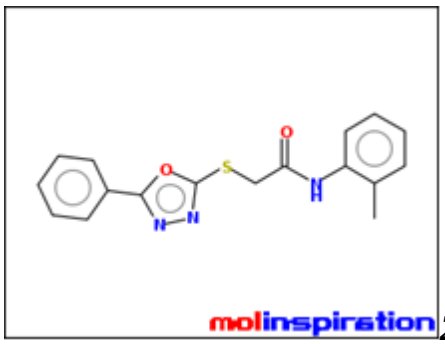
Based on the information provided, this compound appears to meet Lipinski's rule of five as it satisfies all four criteria:

Molecular weight less than or equal to 500 (MW = 325.39)

LogP less than or equal to 5 (miLogP = 3.76)

Number of hydrogen bond acceptors less than or equal to 10 (TPSA = 68.02)

Number of hydrogen bond donors less than or equal to 5 (nOHNH = 1)



2.10

2-((5-Phenyl-1,3,4-oxadiazol-2-yl)thio)-N-(o-tolyl)acetamide

miLogP	3.73
TPSA	68.02
natoms	23
MW	325.39
nON	5
nOHNH	1
nviolations	0
nrotb	5
volume	282.99

this molecule meets Lipinski's rule of five with a miLogP of 3.73, a TPSA of 68.02 Å², a molecular weight of 325.39 g/mol, and a number of rotatable bonds of 5. The number of hydrogen bond acceptors (nON) and the number of hydrogen bond donors (nOHNH) are also within the recommended ranges.

3.2. Computer prediction for the nootropic activity of the tested compounds

Docking is a method which predicts the preferred orientation of one molecule to a second when a ligand and a target are bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions. One can think of molecular docking as a problem of*"lock-and-key"*, in which one wants to find the correct relative orientation of the *"key"*which will open up the *"lock"* (where on the surface of the lock is the key hole, which direction to turn the key after it is inserted, etc.). Here, the protein

can be thought of as the “lock” and the ligand can be thought of as a “key”. Molecular docking may be defined as an optimization problem, which would describe the “best-fit” orientation of a ligand that binds to a particular protein of interest. However, since both the ligand and the protein are flexible, a *“hand-in-glove”* analogy is more appropriate than *“lock-and-key”*. During the course of the docking process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustment resulting in the overall binding is referred to as "induced-fit". Molecular docking research focuses on computationally simulating the molecular recognition process. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized [31-32-33].

In our studies, a library of compounds containing 1,3,4-oxadiazole scaffolds, aromatic, alkyl inclusions, and acceptor substituents was designed using logical-structural analysis and a "hybrid-pharmacophore approach." An important strategy of modern research is to use a methodology for binding new ligands to relevant biological targets. For receptor-oriented flexible docking, the Autodock 4.2 software package was used. Ligands were prepared using the MGL Tools 1.5.6 program. The Ligand optimization was performed using the Avogadro program. To perform calculations in the Autodock 4.2 program the output formats of the receptor and ligand data were converted to a special PDBQT format [31]. The active macromolecule center of the nootropic targets (PDB ID: 5UOW) from the Protein Data Bank (PDB) was used as a biological targets for docking [32-33]. The receptor maps were made in MGL Tools and AutoGrid programs. Water molecules, ions, and the ligand were removed from the PDB file. At this point all the residues in the active site are selected. The 16 residues are: Ser36, His90, Tyr92, Ala120, Ala121, Gly122, Tyr188, Glu189, Val205, Gly206, Met207, Ser208, Thr230, Asn231, His243, Val246. Two water molecules are also selected. The visual analysis of complexes of substances in the active center of the nootropic targets PDB ID: 5UOW was performed using the Discovery Studio Visualizer

program. Magenta marks a surface where the protein needs H-acceptors (e.g. -C=O), blue marks a surface where the protein needs H-donors, and cream marks the hydrophobic surface. The pocket surface is colored so that it is easy to design ligands. Ligands that bind well should have H-bond acceptors (e.g. -C=O) groups touching the red surface and N-H groups with the N-H bond poking through the surface (Fig. 2.1.).

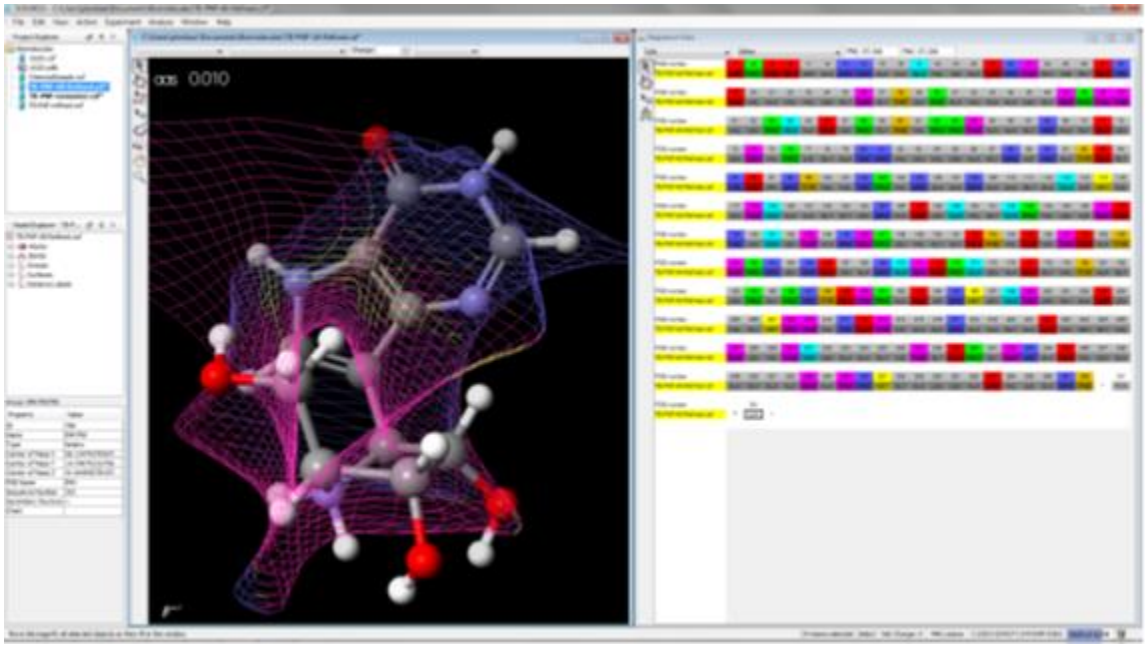


Fig. 2.1. Active receptor site glutamate (NMDA) receptors (PDB ID: 5UOW)

Ligand ***2.2*** in active site glutamate (NMDA) receptors (PDB ID: 5UOW) was shown in Fig 2.2

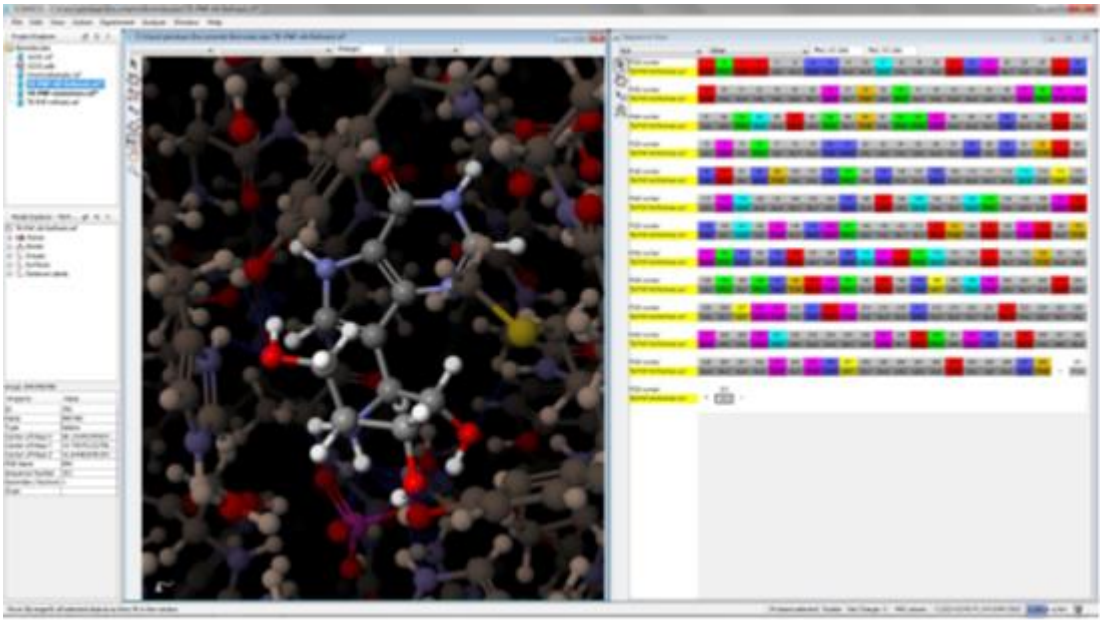


Fig. 2.2. Ligand 2.2 in Active receptor site glutamate (NMDA) receptors (PDB ID: 5UOW)

The created structures were subjected to "fast docking" to establish affinity for known nootropic target [34]. In the fields of computational chemistry and molecular modelling, scoring functions are mathematical functions used to approximately predict the binding affinity between two molecules after they have been docked. one of the molecules is a small organic compound (derivatives oxadiazol) and the second is the drug's biological target such as a protein nootropic receptor.[35] The values of Affinity DG, free binding energy, and binding coefficients for the best conformational positions of the test compounds in combination with glutamate (NMDA) receptors (PDB ID: 5UOW) were shown in Table 2.1

Table 1.

The values of Affinity DG, free binding energy, and binding coefficients for the best conformational positions of the test compound in combination with glutamate (NMDA) receptors (PDB ID: 5UOW)

Molecule	**5UOW**		
	Affinity DG*,	EDoc*	Ki μM *

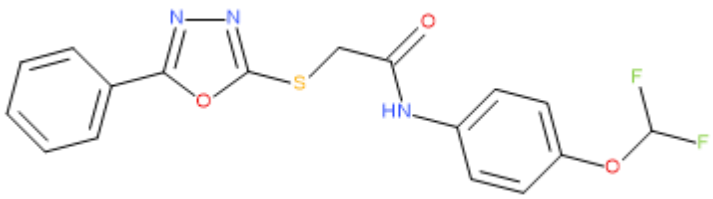
2.1	-5.2	-2.25	0.898
2.2	-5.8	-3.10	34.02
2.3	-4.2	-3.91	253.81
2.4	-4.4	-3.13	31.95
2.5	-5.5	-4.91	252.56
2.6	-4.6	-2.89	48.29
2.7	-5.5	-3.46	399.22
2.8	-5.7	-3.96	325.64
2.9	-5.5	-3.46	399.22
2.10	-5.7	-2.96	325.64
Piracetam	-4.7	-3.98	1220
Nebracetam	-5.9	-5.18	158.48
Pramiracetam	-5.4	-3.85	1490

Note * Affinity DG, kcal/mol

*EDoc kcal/ mol

*Ki μM micromolar

Based on the results of molecular docking, it can be concluded that all synthesized molecules have an affinity for nootropic target. According to the results of the fast docking study, the most promising substance 2.2 was selected, which has the best affinity to the nootropic target (-5,8), which even exceeds the affinity of Piracetam (-4,7) and Pramiracetam (-5,4).



Leader compound molecule **2.2**

Absolute leader compound molecule **2.2 a** forms a complex with the N-methyl-d-aspartate receptor (PDB ID: 5UOW) due to the π-σ bond between the phenyl moiety and Val 745 residues. Binding π-σ also occurs between the

oxadiazol moiety and the Val540 residue. Stabilize the complex of π-Alk interactions between the oxadiazol fragment and amino acid residues Ile538, Ala 726, Val540, Arg 661.The next stage of docking is the analysis of the geometric location leader compound in the active site of the respective biotarget. A detailed description of the interaction as a ligand to receptors (PDB ID: 5UOW) was performed to the Fig. 2.3.

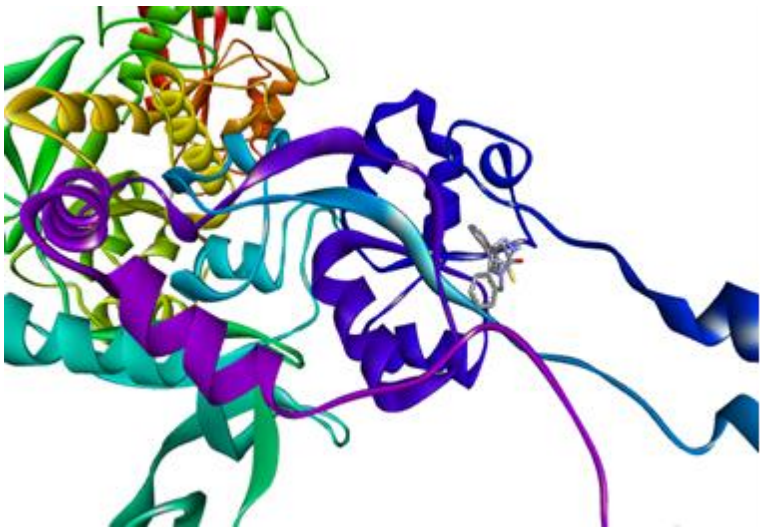


Fig. 2.3. Superposition of molecule **2.2** in complex with the N-methyl-d-aspartate receptor (NMDAR) (PDB ID: 5UOW)

The values of interatomic distances in the active site of the biotargets (PDB ID: 5UOW) between fragments of the compound 2.2 and amino acid residues, categories and types of intermolecular interactions were shown in Tabl. 2.2.

Tabl. 2.2.

The values of interatomic distances in the active site of the biotargets (PDB ID: 5UOW) between fragments of the compound 2.2 and amino acid residues, categories and types of intermolecular interactions

5UOW		
Distance, Å	Category	Types
3,65787	Hydrophobic	Pi-Sigma
3,71501	Hydrophobic	Pi-Sigma
3,93087	Hydrophobic	Pi-Sigma
4,72009	Hydrophobic	Pi-Alkyl
4,93486	Hydrophobic	Pi-Alkyl
4,55643	Hydrophobic	Pi-Alkyl
4,9538	Hydrophobic	Pi-Alkyl
4,80372	Hydrophobic	Pi-Alkyl
4,62651	Hydrophobic	Pi-Alkyl

Among the tested molecules, those selected that have the best values of evaluation functions can be subjected to experimental screening.

Experimental part

We have carried out docking studies of 10 compounds of the generated base to nootropic targets. All chemical structures were generated using BIOWIA 2019 software.

The target was selected from the protein database. Docking studies were performed using the Autodock 4.2 program.

Preliminary was carried out 3D-optimization of structures by molecular mechanics MM + semi-empirical quantum mechanical method PM3 (Fig. 4.2). The optimization of the cleaned molecules was done through MO-G computational application that computes and minimizes the energy of heat of formation. The MO-G computational application solves the Schrodinger equation for the best geometry of the ligand molecules. The augmented Molecular Mechanics (MM2/MM3) parameter was used for optimizing the molecules up to its lowest stable energy state. This energy minimization was done until the energy change is less than 0.001 kcal/mol or the molecules are updated almost 300 times [36]. For automated docking of ligands into the active sites we used genetic algorithm with a fast and simplified Potential of Mean Force (PMF) scoring scheme. PMF uses atom types, which are similar to the empirical force fields used in Mechanics and Dynamics.

For receptor-oriented flexible docking, the Autodock 4.2 software package was used. Ligands were prepared using the MGL Tools 1.5.6 program. The Ligand optimization was performed using the Avogadro program. To perform calculations in the Autodock 4.2 program the output formats of the receptor and ligand data were converted to a special PDBQT format. The following docking parameters were set: the translational step was 2 Å, the torsional freedom coefficient was 0.2983. The cluster tolerance is 2 Å. External lattice energy - 1000, maximum initial energy - 0, maximum number of attempts - 10 000. Number of structures in

the population - 150, maximum number of stages of energy estimation - 2500000, maximum number of generations - 27 000, number of structures that pass to the next generation - 1, the level of gene mutation - 0.02, the level of the crossover - 0.8, the method of the crossover - arithmetic. The α-Gaussian distribution parameter is equal to 0, the β-parameter of Gaussian distribution is 1.

Conclusions to Chapter 3.

1. Selected a nootropic biotarget RCSB Protein Data Bank
2. Conducted docking studies of a virtual database of 10 oxadiazole derivatives;
3. Calculations of physicochemical and ADMET properties have conducted
4. Conducted test compounds for compliance with the Lipinski Rules;

General conclusions

1. Docking studies and calculations of physicochemical and ADMET properties will be conducted to predict the compounds' potential biological activity, drug-likeness, and safety profile. According to the research results, all compounds are promising nootropic agents
2. The most promising compound ***2.2*** was selected, which has the best affinity for the nootropic target and a favorable pharmacokinetic profile.

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APPENDICES

APPENDIX A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ГРАМОТА

нагороджується

Макане Ілхам

у секційному засіданні студентського наукового товариства кафедри медичної хімії

XXIX Міжнародна науково-практична конференція молодих вчених та студентів **«Актуальні питання створення нових лікарських засобів»**

В.о. ректора Національного фармацевтичного університету Алла КОТВІЦЬКА

19-21 квітня 2023 р.
м. Харків

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

СЕРТИФІКАТ УЧАСНИКА

Цим засвідчується, що

Ilham Makane
Scientific supervisor: Perekhoda L.O.

брав(ла) участь у роботі
XXIX Міжнародної науково-практичної конференції молодих вчених та студентів
«АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»

В.о. ректора Національного фармацевтичного університету Алла КОТВІЦЬКА

19-21 квітня 2023 р, м. Харків

National University of Pharmacy

Faculty for foreign citizens' education
Department medicinal chemistry
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
Lina PEREKHODA
"_22nd_" of August 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Ilham MAKANE

1. Topic of qualification work: « Application of medicinal chemistry approaches in the search for new active pharmaceutical ingredients in a series of oxadiazole derivatives », supervisor of qualification work: Lina PEREKHODA, Head of Medicinal Chemistry Department, professor.

approved by order of NUPh from "6th" of February 2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: April 2023.

3. Outgoing data for qualification work: Docking studies and calculations of physicochemical and ADMET properties will be conducted to predict the compounds' potential biological activity, drug-likeness, and safety profile.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): _ Analyze literature data on modern approaches used in medicinal chemistry to find new active pharmaceutical ingredients; select objects, *in silico* activity prediction method, and activity type; select biotargets and conduct docking studies; test compounds for compliance with the Lipinski Rules; analyze the results and select promising compounds for biological testing for activity in in vivo experiments.

5. List of graphic material (with exact indication of the required drawings):

Tables – 4, pictures – 2

6. Consultants of chapters of qualification work

Chapters	**Name, SURNAME, position of consultant**	**Signature, date**	
		assignment was issued	**assignment was received**
Chapters 1	Lina PEREKHODA, Head of Medicinal Chemistry Department, professor	September 2022	October 2022
Chapters 2	Lina PEREKHODA, Head of Medicinal Chemistry Department, professor	November 2022	November 2022
Chapters 3	Lina PEREKHODA, Head of Medicinal Chemistry Department, professor	January 2023	January 2023

7. Date of issue of the assignment. 22/02/2023

CALENDAR PLAN

№ з/п	**Name of stages of qualification work**	**Deadline for the stages of qualification work**	**Notes**
1	Writing a literature review	Oct.-Nov. 2022	**done**
2	Planning a virtual database of oxadiazole derivative compounds. Conducting molecular docking studies for the compounds of the virtual base	Nov. 2022 – Jan. 2023	**done**
3	Testing of virtual base connections for compliance with Lipinski's rules	Jan. – March 2023	**done**
4	Formalization of the qualification work	April 2023	**done**

An applicant of higher education Ilham MAKANE

Supervisor of qualification work Lina PEREKHOD

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі медичної хімії**				
Макане Ілхам	Використання підходів медичної хімії в пошуку нових активних фармацевтичних інгредієнтів в ряду похідних оксадіазолу	Application of medicinal chemistry approaches in the search for new active pharmaceutical ingredients in a series of oxadiazole derivatives	проф. Перехода Л.О.	проф. Кошовий О.М.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу щодо академічного плагіату у кваліфікаційній роботі здобувача вищої освіти

№ 112684 від « 28 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Макане Ілхам, 5 курсу,_групи, спеціальності 226 Фармація, промислова фармація, на тему:

«Використання підходів медичної хімії в пошуку нових активних фармацевтичних інгредієнтів в ряду похідних оксадіазолу / Application of medicinal chemistry approaches in the search for new active pharmaceutical ingredients in a series of oxadiazole derivatives», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,

Професор **Інна ВЛАДИМИРОВА**

1%

32%

Ф А2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Ilham MAĸANE

on the topic: «Application of medicinal chemistry approaches in the search for new active pharmaceutical ingredients in a series of oxadiazole derivatives».

Relevance of the topic. The qualification work of Ilham MAKANE is devoted to optimizing the development of new drugs by using computer technologies that save money and reduce the number of laboratory animals in the experiment, which is always a pressing task in pharmaceutical science.

Practical value of conclusions, recommendations and their validity. The reliability of the obtained research results is beyond doubt, given that the most modern, well-known computer programs developed in European countries were used to conduct in silico studies.

Assessment of work. The work is performed at a high scientific level, the conclusions are logical and reasonable. The overall evaluation of the work is positive.

General conclusion and recommendations for admission to defense. Ilham MAKANE's qualification work meets the existing requirements in terms of relevance and scope of research and can be recommended for defense by the Examination Commission.

Scientific supervisor _____ Lina Perekhoda

« 7th» of April 2023

Ф А 2.2.1-32-356

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Ilham MAKANE

on the topic: «Application of medicinal chemistry approaches in the search for new active pharmaceutical ingredients in a series of oxadiazole derivatives».

Relevance of the topic. The qualification work of Ilham MAKANE is devoted to the targeted search for new biologically active substances with nootropic action in a series of oxadiazole derivatives.

Theoretical level of work. All scientific positions and conclusions formulated by Ilham Makane are based on the results of theoretical and experimental studies, are presented correctly and are scientifically sound.

Author's proposals on the research topic. Based on the results of computer prediction, the prospects for the synthesis of 10 investigated oxadiazole derivatives were determined and experimental testing of one compound for nootropic activity in laboratory animals was recommended.

Practical value of conclusions, recommendations and their validity. Computer prediction of nootropic activity is a theoretical and practical basis for the targeted synthesis and further experimental studies of the nootropic activity of a new substance from the oxadiazole group.

Limitations of the work. No significant shortcomings were found.

General conclusion and evaluation of the work. The qualification work of Ilham MAKANE is performed at a high scientific level, neatly executed, meets all the requirements in terms of the volume of research conducted and can be recommended for defense at the EC

Reviewer _____ **Prof. Oleg KOSHOVYI**

«14th» of April 2023

Ф А2.2.1-91-287

ВИТЯГ

з протоколу засідання кафедри медичної хімії

№ 10 від 21 квітня 2023 р.

ПРИСУТНІ: проф. Ліна ПЕРЕХОДА, доц. Вадим ЗУБКОВ, доц. Ірина СИЧ, доц. Віталій ЯРЕМЕНКО, доц. Ілля ПОДОЛЬСЬКИЙ, доц. Наталія КОБЗАР, доц. Марина РАХІМОВА, доц. Маргарита СУЛЕЙМАН, ас. Олена БЕВЗ, ас. Ольга ВІСЛОУС.

ПОРЯДОК ДЕННИЙ:

Звіт про стан виконання кваліфікаційної роботи здобувачки вищої освіти факультету підготовки іноземних громадян Фм18(5.0)-04, спеціальності «226 Фармація, промислова фармація», освітньої програми Фармація Ілхам МАКАНЕ на тему: «Застосування підходів медичної хімії для пошуку нових активних фармацевтичних інгредієнтів у ряді похідних оксадіазолу».

СЛУХАЛИ: доповідь здобувачки вищої освіти факультету підготовки іноземних громадян Фм18(5.0)-04, спеціальності «226 Фармація, промислова фармація», освітньої програми Фармація Ілхам МАКАНЕ на тему: «Застосування підходів медичної хімії для пошуку нових активних фармацевтичних інгредієнтів у ряді похідних оксадіазолу», керівник завідувачка каф. медичної хімії, д.фарм.н., проф. Ліна ПЕРЕХОДА

УХВАЛИЛИ: рекомендувати кваліфікаційну роботу Ілхам МАКАНЕ до офіційного захисту в Екзаменаційній комісії.

Зав. кафедри медичної хімії,
професор **Ліна ПЕРЕХОДА**

Секретар кафедри медичної хімії,
доцент **Марина РАХІМОВА**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувачка вищої освіти Ілхам МАКАНЕ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Застосування підходів медичної хімії для пошуку нових активних фармацевтичних інгредієнтів у ряді похідних оксадіазолу».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувачка вищої освіти Ілхам МАКАНЕ виконала кваліфікаційну роботу у повному обсязі у відповідності до виданого завдання та у встановлені терміни.

Керівник кваліфікаційної роботи

_____ Ліна ПЕРЕХОДА

«07» квітня 2023 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувачка вищої освіти Ілхам МАКАНЕ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
медичної хімії

_____ Ліна ПЕРЕХОДА

« 21квітня» 2023 року

Qualification work was defended

of Examination commission on

«___» of June 2023

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /