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Computer-aided evaluation of targets and biological activity spectra for new piperidine derivatives

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Abstract

Background: The unique ability of piperidine to combine with various molecular fragments makes it possible to use its chemical structure to create new drugs with potential pharmacological effects. However, preliminary studies are required to predict the activity of new compounds in order to determine the direction of further preclinical studies.

Aim: This study aims at determining the potential targets and spectrum of biological activity of new piperidine derivatives by the in silico method.

Material and methods: Prediction of the effects on targets and the spectrum of biological activity of three new piperidine derivatives synthesized at the Bekturov Institute of Chemical Sciences JSC was analyzed in this study. The chemical structures of these compounds were studied in silico using the web tool SwissTargetPrediction to identify the most likely protein targets. PASS (Prediction of Activity Spectra for Substances) online tool was used to predict the possible pharmacological activity of the studied compounds.

Results: New modified piperidine derivatives are able to affect different enzymes, receptors, transport systems, voltage-gated ion channels, thereby providing a wide range of biological activities applicable in various fields of medicine. These substances represent interest in the treatment of cancer, central nervous system diseases, as local anesthetic, antiarrhythmic and antimicrobial agents, and are promising for pharmacological activity demonstration in preclinical studies.

Conclusion: A comprehensive analysis of the above results leads to the conclusion that the compounds under study should be considered as potential substances for the design of new highly effective medicinal agents with a wide range of practical applications.

Key words: piperidine derivatives, computer prediction, biological activity spectra, SwissTargetPrediction, PASS, in silico

Introduction

The search and study of low-toxic compounds that can serve as a basis for the development of new drugs is a very relevant area of modern research. New compounds of piperidine derivatives represent a particular interest in this field. Piperidine derivatives have been intensively studied for a long time as promising substances for the development of new drugs. The chemical structure of piperidine has a unique ability to combine with other molecular fragments. This fact allows its extensive use as an effective base and heterocyclic system for the development of new compounds and derivatives thereof [1]. Due to this reason, piperidine fragments are now widely used for the development of new drugs. Over the last decade, several thousand different piperidine derivatives have been reported in preclinical and clinical studies [2]. Numerous studies confirm that many substituted piperidine derivatives can exhibit a broad spectrum of pharmacological activity, including antineoplastic, antimicrobial, antiviral and antifungal, anti-inflammatory and central nervous system activities [3-5]. The chemical structure of piperidine is found

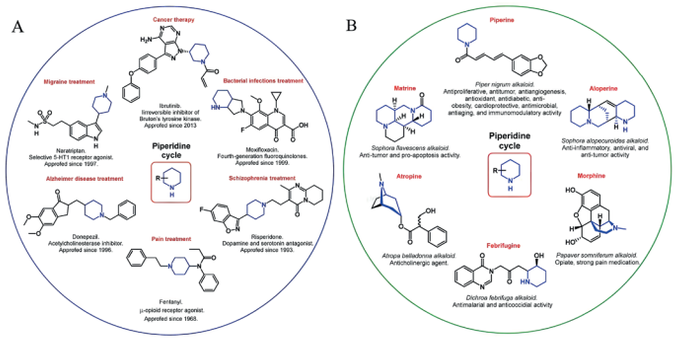

Figure 1 - Piperidine derivatives used in medical practice: A, Synthetic piperidine derivatives. B, natural piperidine derivatives. Reprinted from "Piperidine Derivatives: Recent Advances in Synthesis and Pharmacological Applications" by Frolov N.A. and Vereshchagin A.N., 2023, International journal of molecular sciences, 24(3), 2937

in various groups of drugs (Figures 1a) and many biologically active alkaloids used in medicine (Figures 1b) [6]. The piperidine ring is one of the constituent parts of the chemical structure of the local anesthetics bupivacaine and ropivacaine widely used in clinical practice [7]. Piperidine derivatives with analgesic activity, such as promedol, fentanyl, are widely used in various fields of medicine nowadays. Haloperidol and risperidone are the most commonly used antipsychotics from the group of piperidine derivatives. Tiagabine containing this structural component is actively used as an antiepileptic agent [8].

Research on active substances has long been carried out independently of the purpose and mechanism of action and in most cases has been based on available knowledge and intuitive or empirical approaches. Advances in technology have transformed drug discovery into a targeted, multidisciplinary, hypothesis-driven approach in which exposure to specific targets is of primary importance [9]. Determining the spectrum of biological activity plays an important role in drug development. The spectrum of biological activity depends directly on the chemical structure and reflects not only different pharmacological effects but physiological, biochemical mechanisms of action, including specific toxicity [10].

The development and research of new medicines is a time-consuming and costly multi-stage process [11, 12]. The use of automated and computerized laboratories facilitates research, but excludes completely high drop-out rates for various reasons [13]. Thus, researchers may be faced with a loss of invested resources and time in the preclinical and clinical trial phases. The search for strategies to reduce costs and shorten development times for potential medicines is therefore currently required direction [14].

One of the solutions is the application of computer modelling (in silico) based on artificial intelligence (AI). Using AI computational models to process, manage and integrate large amounts of data from various fields will enable target recognition analysis and identification of new compounds. Thus, the use of chemical structure of compounds for drug design and subsequent pre-screening becomes an important tool for experimental research. Performing virtual screening before starting experiments has great potential. Computer-aided prediction will speed up the process, increase efficiency, optimize costs and reduce drop-out in the early stages of research. The strategy of computer prediction of atomic and molecular properties of compounds is now widely used, making it possible to predict physical and chemical characteristics, pharmacokinetic properties and search for correlations between them and toxicological activity [14-17]. Computer modelling can be used as an initial step in selecting the safest substances from the vast array of chemical compounds. The online resource PASS (Prediction of Activity Spectra for Substances) is one of the platforms used to identify BAS (Biological Activity Spectrum) [10]. The SwissDrugDesign project includes a number of web-based tools for drug design and analysis [18].

The prediction results validity of this software is reflected in the results of a number of preclinical studies. Thus, the high efficiency of pharmacological screening through the use of computer predictive spectrum prediction was established in the study of A. Dairov et al. on the anti-inflammatory and analgesic effects of the new acanthosterone steroid compound. Earlier *in vivo* experimental studies of the arglabin derivative on its anticancer effect also prove the validity of the computer prediction data [19, 20]. The spectrum of biological activity of chicory herb extract determined by the *in silico* method according to G. Adamov correlates with the literature data on experimental studies of anti-inflammatory properties, antioxidant and immunomodulatory effects [21]. According to a study by M. Basanagouda et al. of coumarin-4-acetic acid derivatives showed a high likelihood of anti-inflammatory and analgesic effects in prediction, confirmed by experimental work on appropriate models [22]. In a study by Jiawen Han et al. the results of SwissADME (absorption, distribution, metabolism and excretion) and SwissTarget showed the potential activity of Curculigoside A with target identification, which provided an explanation for the mechanism of therapeutic effects in osteoporosis and rheumatoid arthritis [23].

In present investigation, we were interested in deeper *in silico* analysis of the chemical structure of three new piperidine derivatives, not previously studied. Therefore, the chemical formulas of these compounds were tested using special web tools of Swiss and PASS computer programs. Since piperidine derivatives have been reported to exhibit various pharmacological effects, we needed to identify a number of potential target classes and assess the probability of the presence of certain types of activity in this series of compounds. In addition, the obtained prediction results will play a key role in the further stage of selecting experimental models of the detected effects at the level of preclinical studies. That's why; the aim of the study was to determine potential targets and the spectrum of biological activity of new piperidine derivatives by *in silico* method.

Material and methods

Three new derivatives of azaheterocycles LAS-250, LAS-251 and LAS-252 (LAS is a laboratory code for local anesthetic substance) were identified as objects of study. This group of compounds was synthesized at the A.B. Bekturov Institute of Chemical Sciences JSC. The studied substances belong to the derivatives of hexamerous saturated heterocycles. One compound is a substituted piperidine (one nitrogen atom in heterocycle), two others have two nitrogen atoms (derivatives of 1,4-piperazine). In addition, the molecules have aromatic substituents (two phenyl substituents or α-naphthalene ring). The identification of potential targets and types of activity was determined by analyzing the chemical structure using the *in silico* method.

The identification of potential targets was performed on the SwissDrugDesign software platform (developed by SIB - Swiss Institute of Bioinformatics), using the online web tool SwissTargetPrediction in version 2023 (http://www.swisstargetprediction.ch/). After entering the chemical structure of the substance under study, this resource predicts the most likely targets of the protein structure with a selection of the expected

species (*Homo sapiens, Mus musculus, Rattus norvegicus*). The prediction principle is based on searching for ligand and descriptor similarities with similar molecules entered into the program. The database consists of experimentally active 376342 compounds and 3068 macromolecular targets. The predictive ability of this computer model has been validated on an external test suite of experimentally active compounds [24, 25].

Prediction of the biological activity spectrum of the studied compounds was carried out using the online PASS software on the Way2Drug platform in version 2023 (http://way2drug.com/). This web- resource was designed by a multidisciplinary team of researchers in drug search and development at the Research and Development Institute of Biomedical Chemistry named after V.N. Orekhovich (Russia, Moscow). The chemical structures of the compounds under study were entered into the online program, followed by processing of the entered information using a prediction algorithm based on a Bayesian approach. The software uses the data from the training sample and ensures high prediction accuracy. Evaluation of the biological activity spectrum is based on the analysis of the chemical structure of the substance with the training sample and then the results of the analysis are displayed as an ordered list of expected activities. The probabilities of presence (P_a) and absence (P_i) for each type of intended effect are used to judge its potential presence. The results of the prediction are arranged by default in descending order of the P_a-P_i difference. The spectrum generated by the software includes those types of activity for which the condition $P_a>P_i$ is met. It should be noted that a prediction of $0.3<P_a<0.7$ will indicate the highest probability, and $P_a>0.7$ will indicate a sufficiently high chance of detecting the activity in the following stages of the survey [26, 27].

Results

Potential targets prediction

A SwissTargetPrediction web tool analysis of the prediction of virtual structures of the compounds under study highlighted the main classes of putative targets in preclinical studies in laboratory rats (*Rattus norvegicus*). As can be seen in the results presented (Figures 2, 3, 4), all the compounds studied can affect a wide range of targets, including enzymes (proteases and kinases), families A and C G-protein-coupled receptors, voltage-gated ion channel and electrochemical transporter.

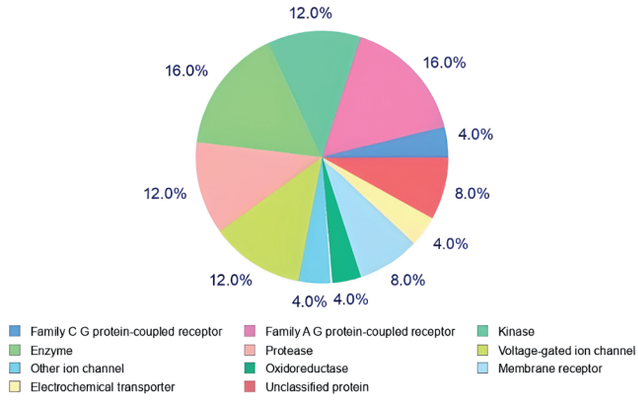

Figure 2 - The target classes of LAS-250 in preclinical research on laboratory rats identified by SwissTargetPrediction web tool

It should be noted that a significant part of the probable target classes of all compounds are enzymes. The highest activity on kinases was detected in LAS-250 and is 12%. LAS-251 has a smaller effect on kinases (6%). LAS-252 has the lowest efficiency (4%). However, LAS-252 may have a more pronounced effect on proteases (16%) in comparison with other compounds. The new piperidine derivatives LAS-250 and LAS-251 have an equal probability of acting on the oxidoreductase. Based on the evidence found, a number of targets should be identified for each compound individually. For example, the enzymes phosphatase and hydrolase were identified among the predicted targets for LAS-252. The predicted target enzyme typical only for LAS-251 was lyase.

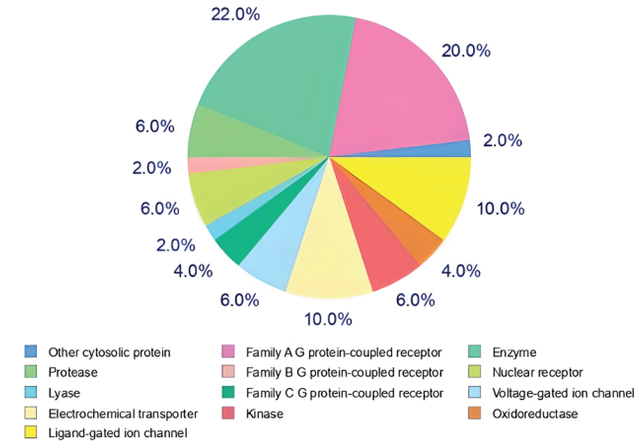

Figure 3 - The target classes of LAS-251 in preclinical research on laboratory rats identified by SwissTargetPrediction web tool

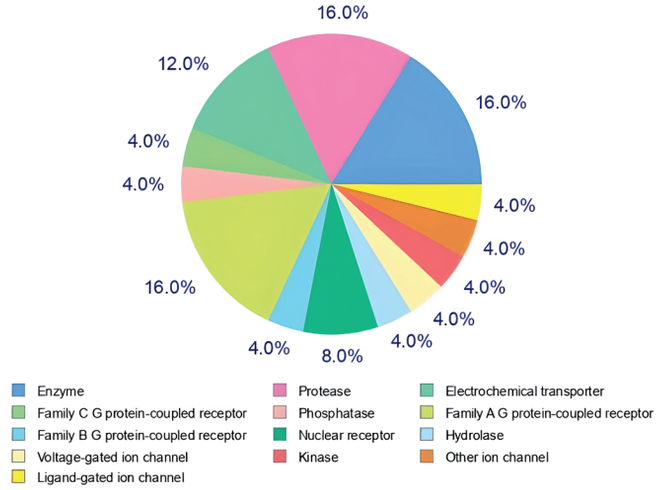

Figure 4 - The target classes of LAS-252 in preclinical research on laboratory rats identified by SwissTargetPrediction web tool

During the analysis of the possible effect on the receptors we found similar classes. The predicted effect on the receptors is not significantly different. The compounds studied have little difference in effect on family A G-protein-coupled receptor with a slight 4% advantage in LAS-251. The effect on the family C G-protein-coupled receptor is absolutely equal for all piperidine derivatives is 4%. LAS-251 and LAS-252 are also slightly possible to influence the family B G-protein-coupled receptor. In addition, LAS-250 differs from other compounds by the presence of some membrane receptors as a target. While LAS-251 and LAS-252 classes of nuclear receptors have been identified.

Evaluation of target prediction revealed 2 classes of ion channels for a series of compounds. LAS-250 has a higher affinity to the voltage-gated ion channel, which is 2 and 3 times higher than LAS-251 and LAS-252, respectively. According to the results received on the effect on ligand-gated ion channel, piperidine derivatives differ slightly from each other, and the difference is 6%.

Compounds LAS-251 and LAS-252 have almost equal effect on electrochemical transporter in contrast to the MAV-250 showing the lowest level of prediction.

Pharmacological activities prediction

Since a biological action spectrum is predicted for the compounds studied, those effects and mechanisms were selected from the data set whose probability of occurrence met the condition $P_a \geq 0.5$ (Figures 5, 6, 7). Probabilities "to be active" (P_a) did not exceed 0.8 (80%). The highest probability of having effects was found for LAS-251 ($0.799 < P_a < 0.554$). The predicted activity probability for LAS-250 was $0.804 < P_a < 0.480$. The lowest activity values were observed for LAS-252, where the maximum value of $P_a = 0.642$ and the minimum was 0.498.

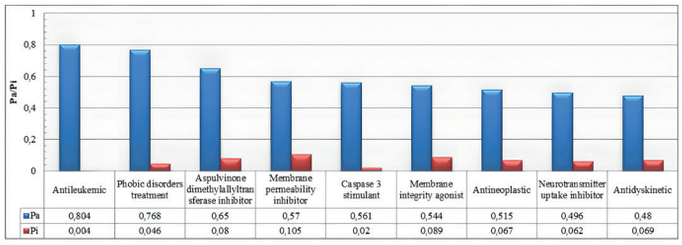

Figure 5 - Biological activity spectra of LAS-250 with the probabilities "to be active" (Pa) and "to be inactive" (Pi) evaluated by PASS

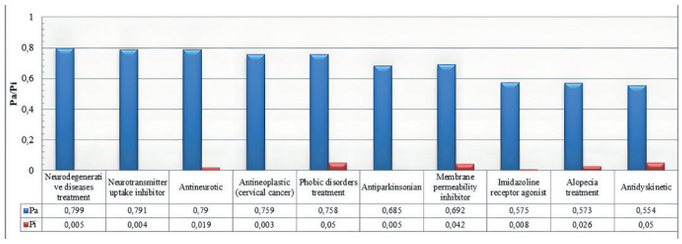

Figure 6 - Biological activity spectra of LAS-251 with the probabilities "to be active" (Pa) and "to be inactive" (Pi) evaluated by PASS

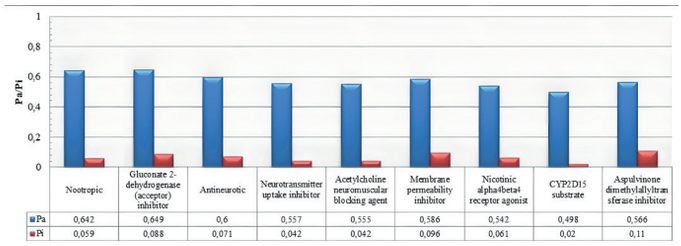

Figure 7 - Biological activity spectra of LAS-252 with the probabilities "to be active" (Pa) and "to be inactive" (Pi) evaluated by PASS

All the chemical structures of the studied compounds showed activity in the inhibition of membrane permeability and neurotransmitter uptake to varying degrees. By the identified mechanisms of action, LAS-251 outperformed the remaining compounds in terms of predicted activity ($P_a \sim 0.7$). Compounds LAS-250 and LAS-252 showed little difference in these values ($0.496 < P_a < 0.586$). The inhibition of membrane permeability by piperidine derivative LAS-250 is probably responsible for the membrane stabilizing effect ($P_a = 0.544$) revealed by the results prediction.

Pharmacological effects affecting the central nervous system, where the highest probability of prognosis was observed, made up a large proportion. LAS-251 has sufficiently high probability of antineurotic ($P_a = 0.79$) and antiparkinsonian ($P_a = 0.685$) activities, can be used for the treatment of neurodegenerative diseases ($P_a = 0.799$). Also, this piperidine derivative probably stimulates imidazoline receptors ($P_a = 0.575$) located in the brain and in the periphery. The predictive data showed that LAS-250 and LAS-251 had the highest and almost equal Pa values for use in the treatment of phobic disorders ($P_a \sim 0.76$) and a lower probability of antidyskinetic effect ($0.48 < P_a < 0.554$). The piperidine derivative LAS-252 also has a potential antineurotic effect ($P_a = 0.6$) and differs from other compounds in the presence of nootropic action ($P_a = 0.642$).

Probability analysis revealed the presence of antitumor activity for LAS-250 and LAS-251. It should be noted that the chemical structure of LAS-250 suggests a high chance of detecting an antileukemic effect ($P_a = 80\%$) in subsequent studies, in contrast to LAS-251, where significant efficacy is possible in the treatment of cervical cancer. The antineoplastic activity of LAS-250 may be related to the process of apoptosis activation due to the detected stimulatory effect on caspase-3 ($P_a = 0.561$).

The detected mechanism of aspulvinone dimethylallyltransferase inhibition is common to LAS-250 and LAS-252, with 65% and 57% probability of their presence, respectively.

A number of significant pharmacological effects should be noted, the prediction of which is unique to each compound. LAS-252 can be used as a gluconate 2-dehydrogenase inhibitor ($P_a = 0.649$), acetylcholine neuromuscular blocking agent ($P_a = 0.555$), nicotinic alpha4beta4 receptor agonist ($P_a = 0.542$), CYP2D15 substrate ($P_a = 0.498$). Potential application of LAS-251 is of interest in the treatment of allopecia ($P_a = 0.573$).

Discussion

The development and release of new medicines in today's world is time-consuming and capital-intensive because of the various risks involved from the discovery to the later stages. The experience of the global pharmaceutical industry shows a low success rate of drug design in all therapeutic areas [28]. A recent study of 21143 compounds found an overall success rate of only 6.2% [29]. The key to solving these problems is to develop mechanisms to maximize the use of information derived from basic science. Advances in basic biological and chemical research, as well as in bioinformatics and artificial intelligence, represent great potential for the production of new drugs. Artificial intelligence has transformed drug design and development over the past decade [28-30]. Nowadays, it is a fair assumption to say that heterocyclic compounds play a significant role in the pharmaceutical industry. Among them, one of the most important and widely used for drug design is the piperidine cycle. The piperidine cycle is present in more than twenty pharmacological groups as well as alkaloids. A review of scientific studies in the last five years found more than 7000 publications related to piperidine [6].

This article describes the results of a study, based solely on the structural formula of the substance, on the computer prediction of targets and variations in biological activities of previously unexplored new piperidine derivatives, using computer software. The use of computer prediction at the initial stage will enable researchers to identify the most promising areas of preclinical research and select experimental *in vivo/in vitro* models in accordance with the detected targets and types of activity. The results obtained predicting potential targets and the spectrum of biological activity have in most cases been confirmed in the results of many scientific *in vivo* or *in vitro* studies of compounds from the piperidine derivatives group.

The results of our study revealed many classes of targets, including various enzymes, receptors, channels and transport

systems. The prognostic data of the compounds presented in this article demonstrate the presence of significant effects on enzyme which correlates with the world research data. As well as in our study piperidine derivatives are capable of affecting various enzymes including kinases [31-34], viral proteases [35-37], hydrolases [38-40] and others [41-45], thereby realizing a wide range of activities. Based on the facts presented, the data obtained in the study may indicate the possible influence of compounds on the processes of inflammation, carcinogenesis, enzymatic activity of viruses, neuroprotection and other functional changes in the cardiovascular system and metabolism [31-45].

A number of publications have reported the discovery of piperidine transporters [46-49], voltage-gated potassium, calcium, sodium ion channels [50-52] and membrane [53-55] and G-protein-coupled receptors [56, 57] as targets, which is also consistent with the SwissTargetPrediction data in this investigation. Accordingly, the probable effect on target classes in our case may cause the presence of both peripheral antiarrhythmic and local anaesthetic effects, and central effects such as anticonvulsant and antidepressant [58].

SwissTargetPrediction results are consistent with many of the pharmacological effects and mechanisms identified by the PASS web resource. Numerous studies confirm the antitumor activity of piperidine derivatives through their action on various enzymes, receptors of paramount importance [59]. The above-mentioned target enzymes (kinases, protein kinase, proteases, polymerase, reductase, aromatase) are the key points of application of drugs incorporating this chemical fragment as an antitumor agent [59]. Also supporting the probable presence of antineoplastic action according to PASS results of LAS-250 compound is undoubtedly the identified effect on caspase-3, which is known to be the most abundant and important member of the family of cysteine proteases involved in apoptosis [60]. The targets of voltage-gated ion channels identified in the analysis as a predictor of pharmacological activity confirms the probability of an inhibitory effect on membrane permeability and consequently the provision of membrane stabilizing action. Effects on ion channels have been shown to provide local anaesthetic, antiarrhythmic, anticonvulsant, antidepressant, neuroprotector and other effects [61-63]. The compounds studied have a high probability of developing pharmacological effects of central nervous system. The probable ability to inhibit neurotransmitter uptake by piperidine derivatives is promising for the treatment of some central nervous system diseases [64-66]. PASS analysis of the compounds predicts anti-parkinsonian and anti-dyskinetic activities associated with neurodegenerative processes, which is also found in the publications of experimental and in silico studies of other piperidine derivatives [67-69]. The likelihood of antimicrobial, antiviral and anti-inflammatory effects of the studied substances has been associated with inhibition of aspulvinone dimethylallyltransferase [70, 71]. The results also revealed the ability of LAS-252 to affect the biotransformation process by using CYP2D15, which is a human orthologue (CYP2D6), leading to amino acid changes in canine liver microsomes [72]. According to the results obtained, this compound can influence neuromuscular conduction regulated by cholinergic activity through a direct stimulatory effect on nicotinic alpha4beta4 receptors responsible for neurotransmission in parts of the central and peripheral nervous system. This process promotes skeletal muscle tone and various cognitive effects in the brain [73]. LAS-251 has potential antihypertensive activity due to its stimulatory effect on imidazoline receptors [74]. Possible mechanisms of piperidine derivatives to be effective in the treatment of allopecia remain unclear and require further investigation and research.

Thus, all of the compounds in question can most likely be classified as having different types of biological activity.

Conclusion

A new line of piperidine derivatives showed promising results. Comprehensive analysis of the results presented in the article leads to the conclusion that the investigated new piperidine derivatives LAS-250, LAS-251, LAS-252 should be considered as potential substances for the development of novel highly effective drugs with a wide spectrum of practical application. The obtained prediction data are confirmed in previous studies on different series of substances from the piperidine group. The obtained by Swiss prognostic data demonstrate the most significant varying degrees effect of compounds among other targets on enzymes such as kinases, proteases, oxidoreductases, as well as a more specific effect on phosphotase, hydrolase and lyase. Both voltage-gated and ligand gated ion channels, as well as electrochemical transporters, were found as targets for the studied substances. The results of the PASS analysis showed a high probability of various effects realized by the identified targets. All the studied chemical structures of compounds showed activity in inhibiting the permeability of membranes, causing a membrane-stabilizing effect. The detected effect of neurotransmitter uptake is important in a CNS diseases development. The possible prospect of using the studied piperidine derivatives in the treatment of neurotic and phobic disorders, neurodegenerative diseases and Parkinson's disease is of particular interest. Probability analysis revealed the presence of antitumor activity for LAS-250 (antileukemic) and LAS-251 (cervical cancer). LAS-252 can be used as gluconate 2-dehydrogenase inhibitor, acetylcholine neuromuscular blocking agent, nicotinic alpha4beta4 receptor agonist, CYP2D15 substrate. Virtual screening to determine the main targets and pharmacological activity confirmed the activity of these compounds to continue further research at the level of preclinical studies. The data of this investigation allow selecting the appropriate areas of experimental work to confirm the potential effects by next *in vivo* or *in vitro* methods.

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