

# Experimental study of the pharmacological activity of new azaheterocycles derivatives: A literature review

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## Abstract

Diseases associated with the pathology of the cardiovascular system are one of the key causes of death all over the world. In particular, arrhythmia may entail the most severe complications, including unexpected death. With high-tech advances, antiarrhythmic drugs remain an integral part of both therapy and prevention. However, the existing arsenal of drugs often does not provide the necessary clinical effect, and therapy is associated with a high risk of severe adverse events. Another significant problem today is the administration of low-toxic drugs that provide effective anesthesia with a sufficient depth and duration of action. Currently, there is also the problem of the limited effectiveness of many drugs with antitumor, antimicrobial, antiviral, antifungal, anti-inflammatory activity and action on the central nervous system. One of the solutions to address the existing problems in these areas is the search and study of compounds that may serve as a basis for the development of new drugs. Given the membrane-stabilizing action by influencing ion channels, new derivatives of azaheterocycles - compounds of piperidine and piperazine are of particular interest in these areas of medicine. According to domestic studies, new piperidine derivatives during screening and in-depth studies showed pronounced local anesthetic activity during infiltration and conduction anesthesia. The results of a number of studies confirm the presence of antiarrhythmic activity in piperidine derivatives. Experimental data on the synthesis and study of the pharmacological activity of new derivatives of piperidine and piperazine in world practice prove their promise for the creation of drugs in various fields of medicine in the future.

**Key words:** piperidines, piperazines, preclinical studies, pharmacological activity

## Introduction

Cardiac arrhythmia accounts for a significant proportion of cardiovascular diseases and result from numerous complications leading to disability and death all over the world. In modern conditions, with important technological advances in drug-free treatment, the administration of antiarrhythmic drugs remains an integral part of pharmacotherapy and prevention of arrhythmia. Many antiarrhythmics used in clinical practice have not been derived as a result of a systematic development process, taking into account the effect on specific targets and electrophysiological mechanisms of arrhythmia. The appointment of drugs available in the clinic is accompanied

by toxic effects from the organs and arrhythmogenic action. Combination therapy with other drugs further increases the risk of adverse events. A comprehensive study of the electrophysiological features of the rhythm disturbances and the discovery of new potential targets did not result in the development of drugs that were superior to the existing ones [1-4].

Local anesthetics are widely used to relieve pain during medical procedures in various areas of medical practice. However, their use in everyday practice is associated with the risk of various adverse reactions, including life-threatening ones. Also, the increase in the number of medical procedures with local anesthesia increases

the hypersensitivity reactions. Despite local administration, increase in serum concentration of drugs may have a toxic effect on the central nervous system and cardiovascular system. In particular, the widespread bupivacaine, in addition to the risk of neurotoxicity inherent for all anesthetics, can also have cardiotoxic effect. One of the solutions to reduce toxicity is to develop micro- or nano-encapsulated forms to provide controlled drug release [5-8]. The results of modern research also show various areas of medicine, where derivatives of piperidine and piperazine are promising compounds for the creation of effective drugs. Thus, in world medical practice, there is an obvious need for safer and more effective antiarrhythmic drugs. In this regard, the search and discovery of new compounds for the development of antiarrhythmics and local anesthetics with high activity and at the same time low toxicity should also become one of the solutions to address the above problems.

## Materials and methods

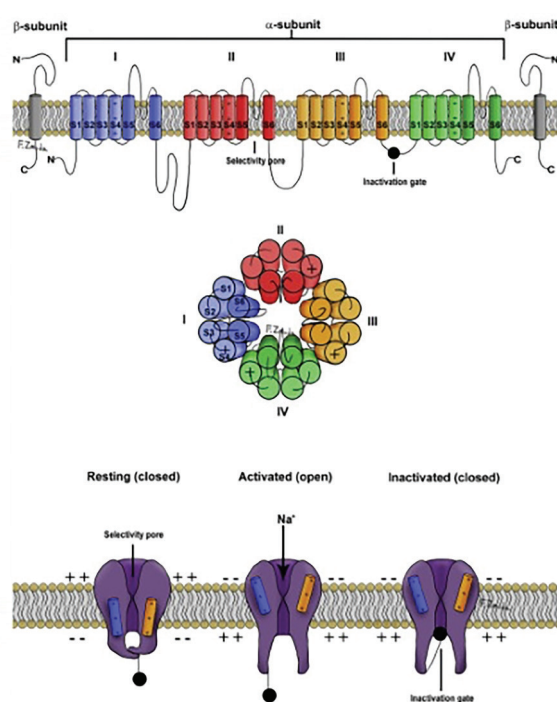
The aim: to study the experience of experimental studies of the pharmacological effects of new derivatives of piperidine and piperazine in domestic and foreign scientific centers. The literature review includes an analysis of foreign scientific publications of scientific electronic databases Elsevier, PubMed, Web of Science, Google Scholar, as well as the results of research presented in domestic publications. The criteria for inclusion in this review were: studies containing experimental data on the study of the pharmacological properties of piperidine and piperazine derivatives in English and Russian over the past 10 years (2010-2021).

## Results

### Effect on ion channels

Research in recent decades has proven that the local anesthetic effect is achieved by influencing a specifically important target – protein of sodium ( $\text{Na}^+$ ) channels (Figure 1).

**Figure 2** - Structure and configurations of the voltage gated  $\text{Na}^+$  channel. Reprinted from "Basic pharmacology of local anaesthetics" by A. Taylor and G. McLeod, 2020, BJA Education, 20(2), p. 35.



Also at therapeutic concentrations, local anesthetics may affect potassium ( $\text{K}^+$ ) and calcium ( $\text{Ca}^{2+}$ ) channels. It is the effect on these channels causes the certain adverse events. It should be noted that local anesthetic drugs have a lower affinity for potassium channels. Due to the inhibition of  $\text{K}^+$  channels, taking into account their contribution to the repolarization process, the action potential is expanded when using this group of drugs. Another type, being ATP-sensitive potassium channels in the heart muscle was found to be sensitive to the action of lidocaine and bupivacaine. This explains the occurrence of toxic and other adverse events from other organs. The effect on voltage-dependent calcium channels is achieved due to the similarity of their structure with sodium channels. In its turn, more than 20 different ion channels are involved in the action potential, which reflects the activity of the heart muscle. In addition, the key factor of the development of arrhythmia is a disorder of the trans-membrane flow of  $\text{Na}^+$ ,  $\text{Ca}^{2+}$  и  $\text{K}^+$  ions. Most antiarrhythmics are ion-channel blockers by mechanism of action, like local anesthetics. For example, the local anesthetic lidocaine is an effective antiarrhythmic drug for the treatment of ventricular arrhythmia. A study using Rosetta structural computer modeling has shown that both antiarrhythmic and local anesthetics have a common receptor site on the sodium channel of the heart [9-11]. Drugs of other pharmacological groups also influence the sodium channels as targets, but they bind to different sites and differ in the mechanism of action. Many drugs used in clinical practice are blockers of the ion-conducting system. The example is anticonvulsants, antidepressants, neuroprotectors, and other groups of drugs [12]. Ion channels play a central role as drug targets and serve as a key basis for the development of new drugs. From this perspective, the membrane-stabilizing action of piperidine and piperazine derivatives, by influencing the ion channels, determines the presence of not only antiarrhythmic and local anesthetic effects, but also other pharmacological effects, which is of the utmost interest and significance of their study.

### Results of domestic studies

Derivatives of piperidine and piperazine have been intensively studied for a long time. The Institute of Chemical Sciences of the Republic of Kazakhstan named after A. B. Bekturov has been actively studying the synthesis of new substituted derivatives. Department of Pharmacology, Kazakh National University named after S.D. Asfendiyarov is conducting research to study the safety and identify the least toxic and most active compounds among new aza-heterocycles. Certain progress has been achieved in the study of local anesthetic and antiarrhythmic effects.

The compound [1- (2-ethoxyethyl)-4-ethynyl-benzoyloxy-piperidine hydrochloride] (laboratory code - Local Anesthetic Substance / LAS-23), named Kazkain is of particular interest for clinical medicine. In the course of screening and in-depth studies of local anesthetic activity during infiltration anesthesia, Kazkain effectively acted in 0.1% solution. The anesthetic effect in terms of the duration of total anesthesia and total duration was also higher than the comparative drugs. But with increase in the studied concentration, a decrease in this difference with reference drugs was observed. The results of in-depth study also showed a pronounced local anesthetic activity during infiltration and conduction anesthesia. The index of Kazkain anesthesia in 0.1% solution definitely exceeded the corresponding indices of trimecaine - 1.5 times, lidocaine - 5.1 and novocaine - 5.3 times. It should be noted that there are advantages in the duration of total anesthesia over all reference drugs: trimecaine (11 times), lidocaine (7.5 times). Both ether groups of the chemical structure

determine the lipoidotropy of the compound, and hence the effect on the local anesthetic activity. In preclinical trials, this compound did not have a significant effect on the central nervous and cardiovascular systems, respiration. No general toxic, allergenic and local irritating effects were observed. Replacement of the radical with the nitrogen atom of the synthesized homologue of Kazkain hydrochloride 1-(3-ethoxypropyl)-4-ethynyl-4-benzoyloxypiperidine under the laboratory code LAS-134 allowed to enhance the local anesthetic effect [13].

Research activities to investigate new piperidine derivatives obtained through targeted synthesis as potential local anesthetics continued.

Local anesthetic activity of piperidine derivative (1-(3-n-butoxypropyl)-4-benzoyloxypiperidine hydrochloride) under the code LAS -54, synthesized in the laboratory of chemistry of synthetic and natural drugs of the Institute of Chemical Sciences named after A.B. Bekturov in combination with a vasoconstrictor was studied by G. Pichkhadze et al. (2012). In previous experimental studies, LAS - 54 demonstrated high activity in infiltration, conduction and spinal anesthesia. In terms of toxicity, this compound is comparable to lidocaine. The combination of 0.25% solution of the compound with adrenaline increased the duration of total anesthesia and the duration of general action by almost 2 times with infiltration anesthesia using the tail flick method. However, 0.5% concentration with adrenaline exceeded the anesthesia indices by approximately 1.3 times and 1.4 times, respectively. Analysis of the results of LAS -54 with a vasoconstrictor during infiltration anesthesia using the method of abdominal wall infiltration in rabbits and conduction anesthesia using the "tail flick" method and electrical stimulation of the lower dental nerve in a rabbit also showed an increase in the indices of total anesthesia and total duration of action. In a series of experiments to study the spinal anesthesia, it was determined that in terms of total anesthesia parameter, LAS - 54 with adrenaline exceeded the effect of LAS - 54 by 1.5 times. Thus, the combination with a vasoconstrictor for various types of anesthesia increases the duration of action, which is of particular importance for clinical administration [14].

Other compounds among new synthesized piperidine derivatives showed to a different extent, a pronounced local anesthetic activity during infiltration and conduction anesthesia in the study of G. Pichkhadze et al. (2014, 2015). One of the most promising LAS - 174 caused the deepest anesthesia in 0.25% solution during infiltration anesthesia, and its action was longer than all comparative drugs. The duration of total anesthesia was statistically higher than that of trimecaine by 1.6 times, lidocaine by 2.25 and novocaine by 3.2 times. The compound LAS -166 had a rather pronounced infiltration anesthesia. In 0.25% solutions, LAS - 166 did not differ in the index of anesthesia from trimecaine, it was stronger than lidocaine and novocaine. Compound LAS - 175 during conduction anesthesia in 1% solutions caused a complete block of conduction for 82.5 minutes (duration of total anesthesia), which exceeded the statistically relevant values of other compounds. The total duration of action of LAS - 175 also statistically exceeded that of all tested compounds and comparative drugs. Compounds LAS - 173 had a rather pronounced activity in this type of anesthesia [15, 16].

D. Kadyrova et al. (2017) in a screening study of local anesthetic activity during infiltration anesthesia (in guinea pigs using the Bulbring and Wade method) of a number of new piperidine derivatives identified the most effective compound LAS - 205. According to the results of a preclinical trial of acute toxicity, the substance under study was found to be low toxic

when administered subcutaneously to white mice. The lethal dose (LD50) was  $625.3 \pm 27.2$ , which is 2.7 times higher than lidocaine and 1.3 times than novocaine. The anesthesia index of 0.25% solution was statistically higher than the relevant value of the comparative drugs. The duration of total anesthesia as an indicator of activity of the LAS -205 compound, lasted 28.3 minutes. Compound LAS - 205 also exceeds all comparative drugs and other studied compounds in this series in terms of the total duration of action. The duration of action of LAS - 205 is 52.1 minutes. For comparison, trimecaine, lidocaine and novocaine act shorter by 1.36; 1.7 and 1.8 times, respectively [17].

According to the results of a study conducted by M. Amirkulova (2017), the most effective of all the studied compounds were LAS - 212, LAS - 213 and LAS - 215. These compounds caused deep anesthesia in 0.25% solutions and showed the maximum effect determined by Bulbring and Wade methods. At the indicated concentration, their anesthesia indices were equal to 36 and exceeded the appropriate indices of trimecaine by 1.2 times, lidocaine by 1.5 times and novocaine by 1.44 times. The study revealed the advantages of LAS -212, LAS - 213 and LAS - 215 over comparative drugs in terms of the duration of total anesthesia and the total duration of action [18].

In a study of the antiarrhythmic activity conducted by K. Esetova et al. (2012) on experimental model of calcium chloride arrhythmia, active compounds were identified under the laboratory code LAS - 100, LAS - 97. The antiarrhythmic effect of LAS - 100 was observed in 100% and was 1.5 times higher than lidocaine in this indicator and 3 times higher than etmozine. LAS - 97 showed the same efficacy as lidocaine, but higher than etmozine. The effective dose (ED50) of the piperidine derivative LAS -100 was 3 and 4 times lower than lidocaine and etmozine, respectively. In experiments on the aconitine model of arrhythmia, high activity was established for the compounds LAS -83 and LAS -100. With this arrhythmia, ED50 of the mentioned compounds also exceeded those of the reference drugs. During the study of acute toxicity after subcutaneous administration, all compounds showed less toxic effect, thus, the relative toxicity of the LAS -100 compound was 0.25 and 0.29 of the toxicity of lidocaine and etmozine. A number of advantages of these compounds indicate their prospects as potential antiarrhythmics and require further in-depth study [19].

The search for low-toxic and highly active antiarrhythmic compounds among the newly synthesized piperidine derivative was continued by K. Esetova et al. (2017). Compounds under laboratory codes LAS - 189, LAS - 190, LAS -191 were studied. Results of the screening study allow us to establish that all compounds are less toxic than lidocaine and etmozine. In the study of antiarrhythmic activity, the compound LAS - 189 had practically no effect. The best results in terms of antiarrhythmic effect were demonstrated by the compound LAS - 190 with calcium chloride arrhythmia 1.25 times higher than the activity of lidocaine and 2.5 times higher than etmozine, with the survival rate of laboratory animals - 83.3% [20].

Thus, the presented results of studies prove the local anesthetic and antiarrhythmic activity in piperidine derivatives. A number of compounds have advantages over the drugs used in clinical practice. In this connection, they are promising compounds for the development of new drugs based on them and require further in-depth study. The study of new synthesized derivatives of piperidine and piperazine will be continued in future studies.



## Study of piperidine and piperazine derivatives in world practice

Piperidine has the potential to combine with other molecular fragments, which allows it to be actively used as an effective scaffold. The piperazine matrix also exhibits versatile binding properties that provide selective ligands for a variety of biological targets. Therefore, fragments of piperidine and piperazine are widely used to create new derivatives. It is known that many substituted piperidine and piperazine derivatives exhibit antitumor, antimicrobial, antiviral and antifungal, anti-inflammatory activity and effect on the central nervous system [21-24].

The results of recent studies show various areas of medicine, where derivatives of piperidine and piperazine are promising compounds for the development of effective drugs.

In the treatment of cancers, various groups of chemotherapeutic agents are used, but mortality rates due to oncology prevail all over the world. The current problem is the limited efficacy of many compounds and moderate selectivity against cancer cells. Therefore, the search and development of new drugs continues intensively. According to the results of a number of recent studies, antitumor activity was observed in some derivatives of piperidine and piperazine. Thus, Yanqun Zeng et al. (2015) based on virtual screening of fragments, piperidine derivatives were developed as inhibitors of Heat Shock Protein (HSP70), which is essential in the regulation of apoptosis. Compounds HSP70-36/37/40/43/46 showed antitumor activity by blocking the proliferation of tumor cells in six cell lines of breast cancer. Also, inhibition of the growth of cells resistant to lapatinib was observed, not only in the case of breast tumor, but also in other tumor cell lines. In the study, pyrimidine was found to be more active than thiazole, therefore, R1 of ring A was substituted from thiazole to pyrimidine. The methylthio group at the R1 position was suitable for better functioning of the compound. These substituents showed better antitumor activity than substitutions with chlorine and fluorine. It should be noted that the position of substituent is crucial in the activity of compounds. In the event of replacing 2-substituents with 4-substituents, the degree of inhibition noticeably reduced. Improvement of antitumor activity was observed when placing R3 of C ring in the ortho and/or para position. These findings may facilitate the development of new therapeutic approaches and new drugs successfully used in the treatment of drug-resistant cancer [25].

In another study by Manouchehrizadeh E. et al. (2020), a number of new piperidine and piperazine derivatives of dichloroacetate was developed (antitumor agent - inhibitor of pyruvate dehydrogenase kinases). The synthesized compounds showed better interaction with pyruvate dehydrogenase isoenzymes. The results showed moderate efficacy and much higher antitumor activity of these compounds than dichloroacetate [26].

The synthesized derivatives of 1-(4-substitutedbenzoyl)-4-(4-chlorobenzhydryl) piperazine demonstrated in one of the studies by Yarim M. et al. (2012), high cytotoxic activity on growing cells of different tumor lines of the liver, large intestine, stomach, breast and endometrium in vitro. After penetration into the cell, 5a compound of this derivative showed a long-term effect, which is evidence of stable in situ activity. The piperazine structure has the universal ability to bind and provide ligands with high efficiency for various potential targets. Therefore, the piperazine scaffold forms the basis of molecule [24].

According to research by the University of Eastern Finland, the compounds Piperazine and Piperidine Triazole Ureas have

been developed as monoacylglycerol lipase (MAGL) inhibitors. MAGL releases arachidonic acid as the main substrate of neuroinflammatory prostaglandins. According to the results, the new compounds JKK-046 and JKK-048 have shown high in vitro efficacy, exceeding the efficacy of currently existing leading MAGL inhibitors under the same conditions. MAGL inhibition may have great therapeutic potential in the treatment of neurodegenerative diseases and cancer. Promising results can be achieved in the treatment of metabolic disorders, in particular insulin resistance [27].

Also advances were made by Kaya B. et al. (2017) in the synthesis of new derivatives 2-[4-(pyrimidin-2-yl)piperazin-1-yl]-2-oxoethyl 4-substituted piperazine-1-carbodithioate, active in inhibiting monoamine oxidase enzymes (MAO-A and MAO-B). MAO inhibitors are one of the most widely used groups of antidepressants that regulate the metabolism of serotonin and norepinephrine. The basis for their synthesis was (pyrimidin-2-yl)piperazin. 1-(2-Pyrimidinyl)piperazinyl, being an important ligand class of the 5-HT<sub>1A</sub> receptor and active metabolite of azapirones. Azapirones are widely used in clinical practice (buspirone), have anxiolytic and antidepressant activity. It was also previously known about antidepressant activity of piperazine derivatives. The inhibitory activity of synthesized compounds (2a-n) to monoamine oxidases was determined by in vitro fluorimetric method. The new compounds have shown efficacy and selectivity against MAO-A enzyme. High efficiency was provided by compounds 2j and 2m, carrying 4-nitrophenyl and diphenylmethyl fragments, respectively [28].

There are prospects for the use of piperazine derivatives in the development of anti-tuberculosis drugs. Thus, in a study by Chandran M. et al. (2015) new derivatives of benzothiazinone-piperazine, synthesized by molecular hybridization, exhibited inhibitory activity against DNA gyrase of *Mycobacterium tuberculosis* with a lower cytotoxic effect. Compounds with a nitro group at the R1 position and chlorine group at the R2 positions manifested effective inhibition [29].

Identified compound 1 (cyclohexyl(4-(isoquinolin-5-ylsulfonyl)piperazin-1-yl)methanone) in a study sponsored by the More Medicines for Tuberculosis consortium is one of several low molecular weight inhibitors of inosine-5'-monophosphate dehydrogenase (IMPDH) of *Mycobacterium tuberculosis*. Research results in this area show that piperazine and isoquinoline rings are essential in the implementation of anti-tuberculosis activity [30].

As a result of research by Dou D. et al. (2012), two first-generation piperazine derivatives were identified that are active against norovirus infection. In this case, the anti-noroviral activity depended on the nature of substituent in the ring. These results may serve as a starting point for further study of the mechanism of action and molecular targets and will open the way for the development of new drugs against norovirus infection [31].

Antiviral activity among aromatic heterocyclic substituted piperidine and piperazine derivatives was also studied by Zhang X. et al. (2013). These compounds were identified by virtual screening based on the VP1 protein structure of the enterovirus. Their further evaluation showed high efficiency as inhibitors of enterovirus 71 and Coxsackievirus A16. Analysis of the structure-activity relationship revealed the effect of space volume of the 4-electron donating group of substituent in the phenoxy ring and the length of alkyl linker on the activity against enterovirus in vitro. However, these factors did not affect the antiviral activity against Coxsackievirus A16. The study mentioned a weak cytotoxic effect of the most active compounds (9e, 8e) against

Vero cell lines. Thus, these compounds are promising options for optimizing treatment against these viruses [32].

Therapy of *Candida albicans* infections is difficult due to the rapid development of drug resistance and limited number of antifungal drugs. In a study by Zhao S. et al. (2018), certain compounds among new synthesized derivatives of (1-aryloxy-2-hydroxypropyl)-phenylpiperazine inhibited the morphological transition and virulence of *Candida albicans* without affecting the growth rate. It was found that some compounds were able to reduce the formation of hyphae in fungal cells by more than 50% and showed inhibitory activity against adhesion and biofilm formation by more than 85%. In addition, the introduction of a group of halogens improves the preventive effect of biofilms. 2,4-dichlorophenol derivatives showed a strong inhibitory activity, while the phenol derivatives showed a weak effect and 4-hydroxybiphenyl derivatives showed moderate activity. It should be noted that the new compound (1-(4-ethoxyphenyl)-4-(1-biphenylol-2-hydroxypropyl)-piperazine) not only showed significant weakening of virulence, but also did not have a cytotoxic effect on human cells even in high concentrations. This group of compounds can be used as a basis for the development of drugs for the treatment of infectious diseases associated with *Candida albicans* [33].

According to studies by Filipova A. et al. (2020), a range of new substituted derivatives of 1-(2-hydroxyethyl) piperazine were developed and synthesized, exhibiting protection from radioactive emission. Some of the compounds presented for the study exhibited a protective effect on human cells in vitro against radiation-induced apoptosis. The researchers also noted low cytotoxicity in vivo. In general, some compounds are subject to further study as potential drugs with radioprotective activity [34].

Marcinkowska M. et al. (2018) synthesized a series of N-arylpiperazine derivatives of 4,4-dimethylisoquinoline-1,3(2H,4H)-dione with antiplatelet activity evaluated on in vitro models. These substances are strong antagonists of alpha 2B receptor. The most active compound 3 demonstrated effective inhibition of platelet aggregation induced by collagen, adenosine diphosphate and adrenaline. In the course of the study, the critical importance of arylpiperazine fragment was determined for the adequate interaction with the required receptors. Also, this fragment provides a charge-enhanced hydrogen bond between the nitrogen atom of piperazine ring and Asp3.32 residue of the alpha 2B receptors. The impact on alpha 2B receptors as a new target opens up the potential for the development of a new therapeutic strategy of antiplatelet therapy, and can be effectively used in the future in patients with resistance or intolerance to aspirin [35].

As a potential antipsychotic, Kaczor AA et al. (2020) investigated N-(2-Hydroxyphenyl)-1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidine-4 Carboxamide (D2AAK4). This compound is a multipurpose ligand for the aminergic G-protein-coupled receptor. In the study, D2AAK4 at a dosage of 100 mg/kg reduced amphetamine-induced hyperreactivity, thereby implying antipsychotic activity [36]. Another study by Rathore A. et al. (2021) also showed promising effect against dopamine and serotonin receptors of various piperidine and piperazine derivatives. When different heterocyclic groups joint the main rings, antipsychotic activity is significantly enhanced. In this area, new antipsychotics were synthesized in the laboratory, and some drugs (Lu AE58054, PF-04802540, ORG25935, DMXB-A, Bitopertin and ABT-126) are already at the stage of clinical trials [37].

## Conclusion

The chemical structure of piperidine and piperazine are versatile in the ability to bind to other molecular fragments and incorporate various substituents and radicals. All this allows to actively use these structures as a scaffold to create new derivatives in various fields of medicine. The focus of domestic research on the study of the pharmacological activity of new compounds is based on the mechanism of action and the presence of membrane stabilizing properties. This gives rise to an active search for new local anesthetic and antiarrhythmic drugs. The sphere of foreign research is aimed at finding solutions to urgent problems in clinical practice associated with the development of new groups of drugs based on piperidine and piperazine derivatives. These are the most pressing problems of modern medicine, such as the search for new antiviral, antibacterial, antifungal agents. Derivatives of piperidine and piperazine have shown promising results in experiments to study other properties that are no less relevant for clinical practice - antiplatelet, antipsychotic and other properties. These data are the rationale for experimental research by domestic scientists and the creation of new directions in the search for promising compounds. The review has shown the effectiveness of many compounds already synthesized, which are of particular interest for the development of new drugs and new therapeutic approaches in the treatment of many diseases.

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## References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135(10):146-603. <https://doi.org/10.1161/CIR.0000000000000485>
2. Jianshi L, Hong W, Lingfang W, Lin Z, Xin L, Yi K, Ke W, Yongqiang Y, Taurine-magnesium coordination compound, a potential antiarrhythmic complex, improves aconitine-induced arrhythmias through regulation of multiple ion channels. *Toxicology and Applied Pharmacology*. 2018;356:182-190. <https://doi.org/10.1016/j.taap.2018.08.008>
3. Heijman J, Ghezelbash S, Dobrev D. Investigational antiarrhythmic agents: promising drugs in early clinical development. *Expert Opin Investig Drugs*. 2017;26(8):897-907. <https://doi.org/10.1080/13543784.2017.1353601>
4. Grigor'eva S. A., Karimova R. G. Antiarrhythmic effect of bromonitric acid derivatives on calcium chloride model of arrhythmia. [in Russian] *Vestnik medicinskogo instituta «Reaviz»: reabilitaciya, vrach i zdorov'e*. 2016;1(21):82-86.
5. Murillo L., Juergen E, Henrik J, Éverton C, Rosanna I, Daniele R, et al. Probing the dynamics of complexed local anesthetics via neutron scattering spectroscopy and DFT calculations, *International Journal of Pharmaceutics*. 2017;524(1-2):397-406. <https://doi.org/10.1016/j.ijpharm.2017.03.051>

6. Grzanka A, Wasilewska I, Śliwczyńska M, Misiólek H. Hypersensitivity to local anesthetics. *Anaesthesiol Intensive Ther.* 2016;48(2):128-34. <https://doi.org/10.5603/AIT.a2016.0017>
7. Becker DE, Reed KL. Local anesthetics: review of pharmacological considerations. *Anesth Prog.* 2012;59(2):90-101. <https://doi.org/10.2344/0003-3006-59.2.90>
8. Cherobin ACFP, Tavares GT. Safety of local anesthetics. *An Bras Dermatol.* 2020;95(1):82-90. <https://doi.org/10.1016/j.abd.2019.09.025>
9. A Scholz. Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels. *British Journal of Anaesthesia.* 2002;89(1):52-61. <https://doi.org/10.1093/bja/aef163>
10. Stanley N, Göran D, Leif C. Model systems for the discovery and development of antiarrhythmic drugs. *Progress in Biophysics and Molecular Biology.* 2008;98(2-3):328-339. <https://doi.org/10.1016/j.pbiomolbio.2008.10.009>
11. Nguyen PT, DeMarco KR, Vorobyov I, Clancy CE, Yarov-Yarovoy V. Structural basis for antiarrhythmic drug interactions with the human cardiac sodium channel. *Proc Natl Acad Sci U S A.* 2019;116(8):2945-2954. <https://doi.org/10.1073/pnas.1817446116>
12. Tikhonov DB, Zhorov BS. Mechanism of sodium channel block by local anesthetics, antiarrhythmics, and anticonvulsants. *J Gen Physiol.* 2017;149(4):465-481. <https://doi.org/10.1085/jgp.201611668>
13. Kadyrova D, Pichkhadze G, Praliev K, YU V. Kazkain – perspektivnyj otechestvennyj mestnyj anestetik (Kazkain is a promising domestic local anesthetic) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2010;5(3):221-224.
14. Muhamedzhanova G, Pichkhadze G, Praliev K, Kadyrova D, Esetova K, Nasyrova S et al. Mestnoanesteziruyushchaya aktivnost' proizvodnogo piperidina (MAV-54) v kombinacii s vazokonstriktorom (Local anesthetic activity of a piperidine derivative (LAS-54) in combination with a vasoconstrictor) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2012;2:352-354.
15. Pichkhadze G, Muhamedzhanova G, Kadyrova D, Kim I, Esetova K. Izuchenie mestnoanesteziruyushchej aktivnosti pri infil'tracionnoj anestezii v ryadu vnov' sintezirovannyh proizvodnyh piperidina (Study of local anesthetic activity during infiltration anesthesia in a series of newly synthesized piperidine derivatives) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2014;4:275-277.
16. Pichkhadze G, Kadyrova D, Smagulova G, Praliev K, Raimkulova K. Poisk soedinenij s mestnoanesteziruyushchej aktivnost'yu pri provodnikovoj anestezii (Search for compounds with local anesthetic activity during conduction anesthesia) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2015;2:532-534.
17. Kadyrova D, Amirkulova M, Smagulova G, Satbaeva E, Kim I, Anan'eva L. Mestnoanesteziruyushchaya aktivnost' i ostraya toksichnost' ryada proizvodnyh piperidina (Local anesthetic activity and acute toxicity of a number of piperidine derivatives) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2017;2:267-269.
18. Amirkulova M, Kadyrova D, Satbaeva E, Smagulova G., Praliev K, YU V. Eksperimental'noe izuchenie mestnoanesteziruyushchej aktivnosti novyh proizvodnyh piperidinana modeli infil'tracionnoj anestezii (Experimental study of the local anesthetic activity of new piperidine derivatives in the model of infiltration anesthesia) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2017;3:330-331.
19. Esetova K, Nasyrova S, Imashova SH., Muhamedzhanova G, Ajtzhanova G, Amirkulova M. Izuchenie protivoaritmicheskoy aktivnosti i toksichnosti vnov' sintezirovannyh proizvodnyh piperidina (Study of antiarrhythmic activity and toxicity of newly synthesized piperidine derivatives) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2012;2:45-47.
20. Esetova K, Kadyrova D, Smagulova G, Kim I. Skriningovye issledovaniya protivoaritmicheskoy aktivnosti i ostroj toksichnosti novyh sintezirovannyh proizvodnyh piperidina (Screening studies of antiarrhythmic activity and acute toxicity of new synthesized piperidine derivatives) [in Russian]. *Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta.* 2017;2:265-266.
21. Bibek Pati I, Subhasis Banerjee. Importance of Piperidine Moiety in Medicinal Chemistry Research: A Review. *Journal of Pharmacy Research.* 2012;5(12):5493-5509.
22. Goel P, Alam O, Naim MJ, Nawaz F, Iqbal M, Alam MI. Recent advancement of piperidine moiety in treatment of cancer- A review. *Eur J Med Chem.* 2018;5(157):480-502. <https://doi.org/10.1016/j.ejmech.2018.08.017>
23. Gong-Qing Liu, Till Opatz. Recent Advances in the Synthesis of Piperidines: Functionalization of Preexisting Ring Systems. In: Chapter 2, Eric F.V. Scriven, Christopher A. Ramsden editors. *Advances in Heterocyclic Chemistry. Academic Press.* 2018; 107-234. <https://doi.org/10.1016/bs.aihch.2017.10.001>
24. Yarim M, Koksall M, Durmaz I, Atalay R. Cancer cell cytotoxicities of 1-(4-substitutedbenzoyl)-4-(4-chlorobenzhydryl)piperazine derivatives. *Int J Mol Sci.* 2012;13(7):8071-8085. <https://doi.org/10.3390/ijms13078071>
25. Yanqun Z, Ruiyuan C, Tianhong Z, Song Li, Wu Z. Design and synthesis of piperidine derivatives as novel human heat shock protein 70 inhibitors for the treatment of drug-resistant tumors. *European Journal of Medicinal Chemistry.* 2015;97:19-31. <https://doi.org/10.1016/j.ejmech.2015.04.043>
26. Manouchehrizadeh E, Mostoufi A, Tahanpesar E. et al. Design, Synthesis, Molecular Docking and Biological Activity of New Piperidine and Piperazine Derivatives of Dichloroacetate as Potential Anticancer Agents. *Pharm Chem J.* 2020;54:148–153. <https://doi.org/10.1007/s11094-020-02172-4>
27. Niina A, Juha R, Casandra R, et al. Piperazine and Piperidine Triazole Ureas as Ultrapotent and Highly Selective Inhibitors of Monoacylglycerol Lipase. *Chemistry & Biology.* 2013;20(3):379-390. <https://doi.org/10.1016/j.chembiol.2013.01.012>
28. Kaya B, Yurttaş L, Sağlık BN, Levent S, Özkay Y, Kaplancikli ZA. Novel 1-(2-pyrimidin-2-yl) piperazine derivatives as selective monoamine oxidase (MAO)-A inhibitors. *J Enzyme Inhib Med Chem.* 2017;32(1):193-202. <https://doi.org/10.1080/14756366.2016.1247054>
29. Chandran M, Renuka J, Sridevi JP, Pedgaonkar GS, Asmitha V, Yogeewari P, Sriram D. Benzothiazinone-piperazine derivatives as efficient Mycobacterium tuberculosis DNA gyrase inhibitors. *Int J Mycobacteriol.* 2015;4(2):104-115. <https://doi.org/10.1016/j.ijmyco.2015.02.002>
30. Singh V, Pacitto A, Donini S, et al. Synthesis and Structure-Activity relationship of 1-(5-isoquinolinesulfonyl)piperazine analogues as inhibitors of Mycobacterium tuberculosis IMPDH. *Eur J Med Chem.* 2019;174:309-329. <https://doi.org/10.1016/j.ejmech.2019.04.027>



31. Dou D, He G, Mandadapu SR, et al. Inhibition of noroviruses by piperazine derivatives. *Bioorg Med Chem Lett*. 2012;22(1):377-379. <https://doi.org/10.1016/j.bmcl.2011.10.122>
32. Zhang X, Wang H, Li Y, et al. Novel substituted heteroaromatic piperazine and piperidine derivatives as inhibitors of human enterovirus 71 and coxsackievirus a16. *Molecules*. 2013;18(5):5059-5071. <https://doi.org/10.3390/molecules18055059>
33. Zhao S, Huang JJ, Sun X, Huang X, Fu S, Yang L, Liu XW, He F, Deng Y. (1-aryloxy-2-hydroxypropyl)-phenylpiperazine derivatives suppress *Candida albicans* virulence by interfering with morphological transition. *Microb Biotechnol*. 2018;11(6):1080-1089. <https://doi.org/10.1111/1751-7915.13307>
34. Filipova A, Marek J, Havelek R, Pejchal J, Jelicova M, Cizkova J, et al. Substituted Piperazines as Novel Potential Radioprotective Agents. *Molecules*. 2020;25(3):532. <https://doi.org/10.3390/molecules25030532>
35. Marcinkowska M, Kotańska M, Zagórska A, et al. Synthesis and biological evaluation of N-aryl piperazine derivatives of 4,4-dimethylisoquinoline-1,3(2H,4H)-dione as potential antiplatelet agents. *J Enzyme Inhib Med Chem*. 2018;33(1):536-545. <https://doi.org/10.1080/14756366.2018.1437155>
36. Kaczor AA, Targowska-Duda KM, Silva AG, Kondej M, Biała G, Castro M. N-(2-Hydroxyphenyl)-1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidine-4-Carboxamide (D2AAK4), a Multi-Target Ligand of Aminergic GPCRs, as a Potential Antipsychotic. *Biomolecules*. 2020;10(2):349. <https://doi.org/10.3390/biom10020349>
37. Rathore A, Asati V, Kashaw SK, Agarwal S, Parwani D, Bhattacharya S, Mallick C. The Recent Development of Piperazine and Piperidine Derivatives as Antipsychotic Agents. *Mini Rev Med Chem*. 2021;21(3):362-379. <https://doi.org/10.2174/1389557520666200910092327>