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Prospects for Creating New Medicines Based on Nitrogen-Containing Organic Compounds

Akzhonas Ermekovna Khamitova[1*], Dmitriy Aleksandrovich Berillo[2]

*[1, 2]Department of pharmaceutical and Toxicological chemistry, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
***Corresponding Author:** Akzhonas Ermekovna Khamitova, Department of pharmaceutical and Toxicological chemistry, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, Tel: 87024363952; E-Mail: akzhonas_94@mail.ru

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Abstract

The search for new, effective and safe (low toxicity) medicines remains an urgent problem. Many compounds containing piperidine, morpholine and piperazine series are widely used in medicine and belong to the important group of biologically active compounds. The informational and literary search was conducted for the development of new nitrogen-containing heterocyclic biologically active compounds. This review summarizes the results of piperidine, morpholine and piperazine as potential sources of biologically active substances. To analyze the ways of chemical synthesis, to study the biological activity of new biologically active compounds based on nitrogen-containing organic compounds and to consider currently known drugs based on piperidine, morpholine and piperazine. Scientific papers, review articles and patents in the field of synthesis of piperidine, morpholine and piperazine derivatives. Synthesis and determination of the biological activity of new derivatives of piperidine, morpholine and piperazine. The main search criteria were studies over the past 10 years, the inclusion criteria were the chemical synthesis and the study of the biological activity of the obtained new derivatives of piperidine, morpholine and piperazine. The chemical modification of known molecules makes it possible to create medicinal substances that have a more pronounced pharmacological effect and less side effects. The targeted synthesis and study of the pharmacological properties of new derivatives of the piperidine, morpholine, and piperazine series, which additionally contain pharmacophore groups as substituents, is of considerable theoretical and practical interest.

Keywords: Piperidine derivatives; Morpholine derivatives; P iperazine derivatives; Drug research; Heterocycles; Structure-activity relationship

Introduction

In the modern scientific field, a wide variety of methods for the development of new drugs are utilized, starting from the various options for in silico screening (SAR, QSAR, docking) predicting the probability of bioactivity to the detection and study of biologically active substances of plant and animal origin, or their reproduction by synthesis and obtaining various modifications of molecules. One of the most common, well-known ways of finding new drugs is the chemical modification of compounds with known biological activity [1]. The main task of drug discovery is to create more active, less toxic new drugs that differ from those already known. Whichever way of creating novel drugs is chosen, the final result should be aimed at ensuring the quality, safety and effectiveness of drugs [2].

One of the challenges of the pharmaceutical industry is to expand the arsenal of compounds used as active pharmaceutical ingredients to create innovative, more effective and safe drugs. Among the directions developed all over the world for the search for new drugs, derivatives of saturated nitrogen heterocycles, and primarily piperidine, receive the greatest attention, since they constitute the structural basis of a number of compounds such as Promedol, Drotaverin, Richlocaine (Figure 1) [3]. To date, tens of thousands of compounds of these series have been synthesized and studied, more than three hundred of them are widely used in medical practice as medicines [4].

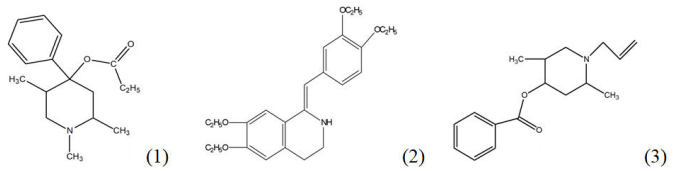


Figure 1: Structural formulas of Promedol (1), Drotaverin (2), Richlocaine (3).

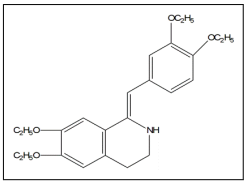
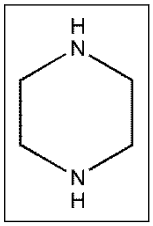
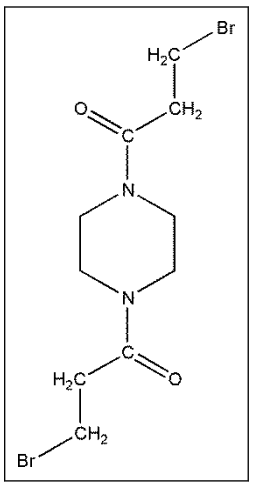
The history of drug use and calculation methods for modeling the biological activity of SAR, QSAR and docking predict that piperidine is the structural basis of a number of drugs with different pharmacological actions [5].

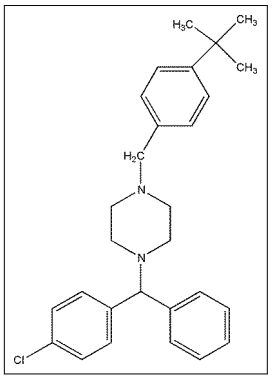
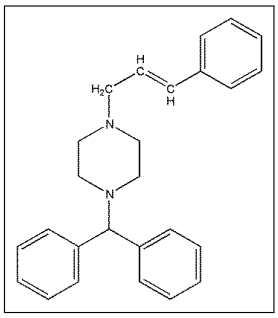
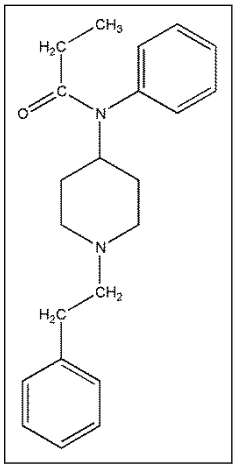
Piperidine derivatives are widely used as synthetic drugs with analgesic (Trimepiridine, Fentanyl), its salts have bactericidal and bacteriostatic activity, also cholinolytic (trihexyphenidyl hydrochloride), antidiarrheal (Loperamide) and antihistamine (Ketotifen-4,9-(1-methyl-4-piperidylidene)-10H-benzo [4,5] cyclohepta [1,2-b] thiophen-10-one in the form of fumarate), Loratadine (ethyl ester 4-(8-chloro-5, 6-dihydro-11H-benzo [5,6] cyclohepta [1,2-b] pyridin-11-ylidene)-1-piperidine-carboxylicacid))pharmacological activity [6].

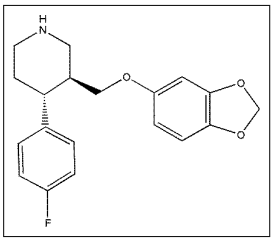
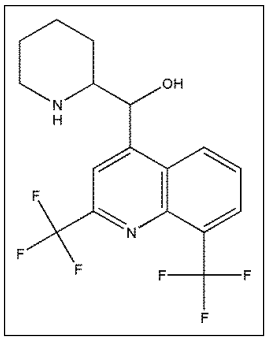
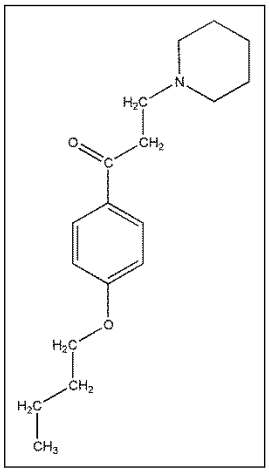
Piperidine derivatives also exhibit anti-tumor, anti-tuberculosis, anti-inflammatory effects. The properties of

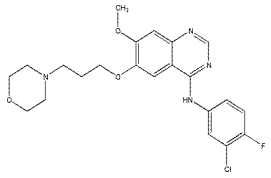
piperidine derivatives depend on the nature of the side chains and their orientation. It is known that the pharmacological activity of drugs of the piperidine series depends on the substituents in the cycle and on the structure of the radicals at the nitrogen atom [7]. The inhibitory activity of a substance depends on pH due to the dissociation of functional groups or protonation, therefore, the pKa of the active pharmaceutical substance should be taken into account (Table 1). Since some compounds exist in solution as a mixture of tautomers and one of them has a pharmacological activity that is different from the other. The most active species are ketone or its hydrated form in comparison with enol or enolate [8].

Table 1: Pharmacological activity and toxicity of drugs derived from piperidine and piperazine.

No	Formula	LD50	pKa	Pharmacological activity
1	 Drotaverin	2.5733 mol/kg	7,4	Relieves spasm of smooth muscles of the gastrointestinal tract and genitourinary system [9]
2	 Piperazine	1.6247 mol/kg	9,56	Anthelmintic action, treatment of partial intestinal obstruction caused by ascaris worms [10]
3	 Pipobroman or 1,1'-(Piperazine-1,4-diyl)bis(3-bromopropan-1-one)	3.1778 mol/kg	-0,72	Antineoplastic agent, treatment of polycythemia and refractory chronic myeloid leukemia [11]

4	 Buklizin or 1-[(4Chlorophenyl)(phenyl)methyl]-4-[4-(2-methyl-2-propanyl)benzyl]piperazine	2.5190 mol/kg	8,04	Prevention and treatment of nausea, vomiting and dizziness associated with motion sickness and dizziness [12]
5	 Cinnarizine or 1-benzhydryl-4-[(E)-3phenylprop-2-enyl]piperazine	2.0618 mol/kg	8,1	Improves cerebral circulation, treats syndromes of vestibular origin [13]
6		3.9836 mol/kg	8,77	Chronic pain anesthetic [14]

	Fentany or N-phenyl-N-[1-(2phenylethyl) piperidin-4-yl] propanamide			
7	 Paroxetine or (3S,4R)-3-(1,3-benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine	2.8239 mol/kg	9,77	Antidepressant, anxiolytic [15]
8	 Mefloquine or [2,8 bis(trifluoromethyl)quinolin-4-yl]-piperidin-2-ylmethanol	2.9133 mol/kg	9,46	Antimalarial [16]
9	 Diklonin or 1-(4-Butoxyphenyl)-3-(1piperidinyl)-1-propanon	2.3661 mol/kg	8,36	Local anesthetic [17]

10	 Gefitinib or N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4ylpropoxy)quinazolin-4-amine	2.5141 mol/kg	6,85	Treatment of metastatic non-small cell lung cancer [18]

As a result of the literary search, many publications and scientific works aimed at the synthesis of new compounds based on the piperidine cycle were identified, for example, as a result of condensation of hydroxylamine with 1- (2-ethoxyethyl) -3-methyl-4-oxopiperidine, oxime and its esters were synthesized (acetate, propionate, benzoate). Propionic ester hydrochloride 1-(2-ethoxyethyl)-3-methyl-4-ketoxympiperidine was studied for analgesic, antispasmodic and antihistaminic activity. The bioactivity were compared with the parameters of model drugs such as Tramal, Drotaverin and Diphenhydramine showing that this compound has a pronounced analgesic activity and, in terms of the duration of the overall effect, exceeds Tramal by 1.5 times [3].

Zharmenova's research group searching for drugs with more effective analgesic activity based on piperidine fragment, synthesized derivatives of 1-(3-isopropoxypropyl)-4-(2-thiopicolinamino) piperidine have shown to varying degrees expressed local anesthetic activity in infiltration and conduction anesthesia and turned out to be less toxic than the model substance Dicaine (2-(dimethylamino) ethyl-4- (butylamino) benzoate) [19].

The local anesthetic activity and acute toxicity of a number of new piperidine derivatives indicated that the new compounds are more effective than model drugs such as Trimecaine, Lidocaine, and Procaine in terms of the depth of anesthesia (anesthesia index), the duration of complete anesthesia and the total duration of the anesthetic effect when administered subcutaneously, and turned out to be of low toxicity compared with reference drugs. The comparative indicator LD50 of one of the obtained compounds is 2.7 times higher than that of Lidocaine, 1.6 times higher than that of Trimecaine and 1.3 times higher than that of Procaine [20].

A number of new 2,4-diaminopyrimidines containing piperidine and piperazine moieties have been tested for antiproliferative activity. The piperidine derivatives showed much stronger antitumor activity against four human cancer cell lines (HepG2, A549, MDA-MB-231 and MCF-7) than commercial drug Fluorouracil [21].

It was found that novel piperidine derivatives - 1- (2-ethoxyethyl) -4-octinyl-4 acyloxypiperidines have anesthetic, antispasmodic and immunosuppressive effects [22].

There is a study devoted to the synthesis of a new series of piperidine-substituted triazine derivatives (Figure 2) and the investigation of its antiviral activity, namely, the assessment of their activity against HIV. Most of the compounds illustrated high activity against HIV-1 with EC50 values at a lower nanomolar concentration of 7.0-9.2 nM in comparison with model drug Nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido [3,2-b:2',3'-e] [1,4] diazepin-6-one), Delavirdine (N- [2-[4-[3-(propan-2-ylamino)pyridin-2-yl]piperazine-1-carbonyl]-1H-indol-5-yl] methanesulfonamide), Zidovudine (3'-azido-3'-deoxythymidine) and Dideoxycytidine, and higher activity against the resistant mutant K103N / Y181C strain than for nevirapine and delavirdine [23].

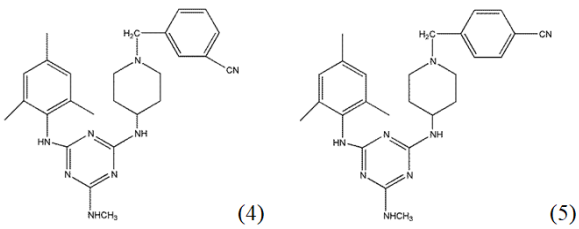


Figure 2: Triazine derivatives with 4-amino substituted piperidine [23].

Active pharmaceutical ingredients containing Piperidine-moiety have low toxicity, well-established synthesis on the industrial scale and the revealing of high local anesthetic activity [24].

The antibacterial activity of 2,6-disubstituted piperidin-4-one derivatives exhibiting an inhibitory activity on the growth of pathogenic bacteria strains such as Staphylococcus aureus, Bacillus subtillis, Escherichia coli, Pseudomonas aerugenosa [25].

The variety of scientific directions for working with the piperidinyl moiety, we can conclude that there are a wide range of chemical reactions that allow one to obtain the piperidine ring in the structure with quantitative yields, for example, the synthesis is the reduction of pyridine derivatives, in particular picolinic acid, at certain conditions existing in zwitterionic state [26].

Piperidine is an important pharmacophore, heterocyclic system in the drug development due to its wide range of therapeutic uses and the chemical reactions ability of the piperidine cycle (Figure 3) [27].

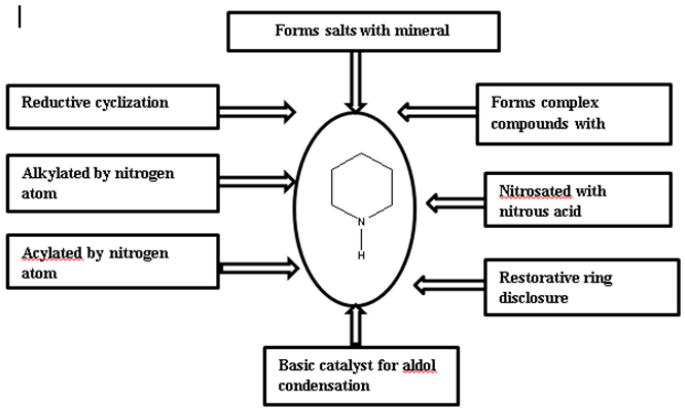


Figure 3: Chemical properties of piperidine.

According to the data in the field of the synthesis of new piperidine derivatives, the progress has been made in 1,3 dipolar cycloaddition with the formation of a 2-spiropiperidine derivative. Condensation of the open-chain hydroxylamine of ketone (6) followed by the displacement of covalently bound chlorine resulted in 1,3-dipole (7), which undergoes cycloaddition to generate tricycle (8). Then the N-O bond was reductively split with Zn/ AcOH to bring about 2-spiropiperidine (9) with good yield (Figure 4).

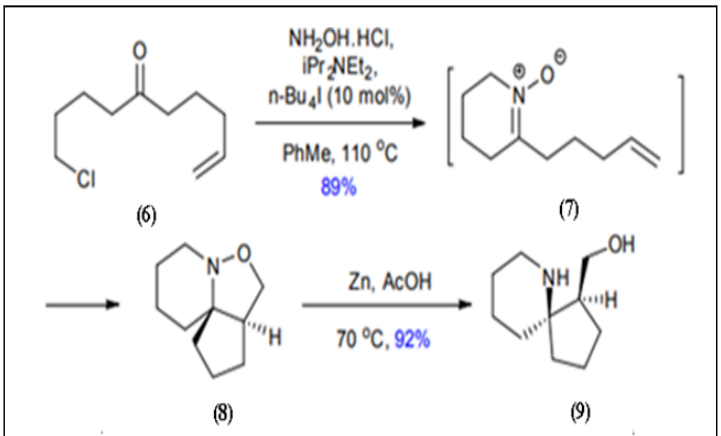


Figure 4: 2-spiropiperidine production reaction [28]

There is a quite extraordinary method of synthesis, including intramolecular cyclization, rearrangement and recyclization reactions, for example, an enantiomer pure cyclization of the substrate (10) was exposed to the indirect cyclization in the presence of trifluoromethanesulfonic acid to obtain 2-spiropyrrolidine (11).

At the following step the ester was reduced to alcohol group (12) by the use of LiAlH4, that followed by treatment under Appel conditions to result a thiocyanate 2-spiropiperidine derivative (13) (Figure 5) [28].

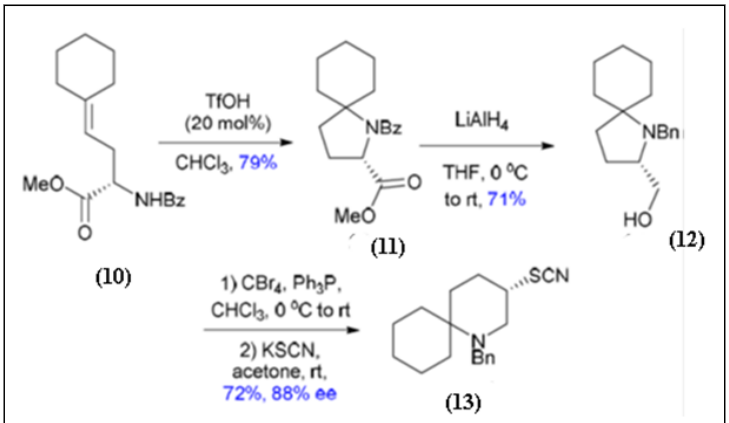


Figure 5: Preparation of 2-spiropiperidine derivative [28]

One of the popular strategies to obtain piperidine derivatives is Dieckmann condensation carried out under the mild conditions (Figure 6) [8].

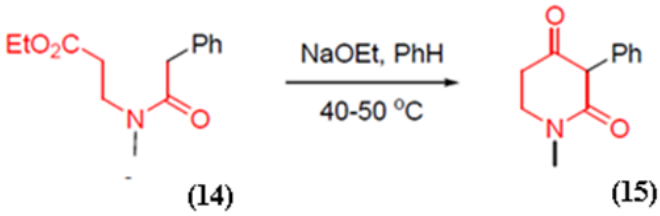


Figure 6: Condensation of an ester to dione [8].

The currently known compound paroxetine (3S-trans) -3-(1,3-Benzodioxol-5-yloxy) methyl) -4- (4-fluorophenyl) -piperidine) is used in medical practice as an antidepressant, according to the chemical structure is a trans-3,4-disubstituted piperidine derivative with a secondary amino group. The review devoted to several synthetic approaches of synthesis of this compound in recent years [29].

In recent decades, the number of available heterocyclic compounds used as substrates for the creation of the new, more effective drugs has increased. These derivatives include piperazine and morpholine moieties, which are part of a number of important substances. For instance, piperazine adipenate used as an antihelminthic agent, antihistamines widely used in clinical practice, such as Zodak, Zyrtec, Levocetirizine, Cetrin, Parlazin, as an active substance cetirizine and levocetirizine (Figure 7) [30].

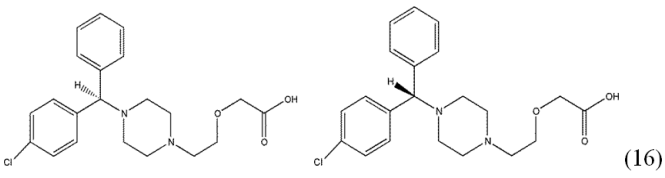


Figure 7: Structural formulas of levocetirizine and cetirizine (±) - (2- (4 - ((4-chlorophenyl) phenylmethyl] -1-piperazinyl) ethoxy) acetic acid).

Morpholine is a universal fragment, a privileged pharmacophore with a wide range of pharmacological activity due to different mechanisms of action. The ability of morpholine

to increase the efficiency of a molecule through molecular interactions with a target protein or alter pharmacokinetic properties has allowed researchers to synthesize the morpholine ring efficiently and turn it on to develop various compounds with a variety of medicinal properties [31].

Studies by Fazylov's research group in the field of synthesis of novel compounds from morpholine provides data on the synthesis and evaluation of the phagocytosis-stimulating and cytotoxic activity of pyrazole derivatives of morpholine, namely the compound N- (3,5-dimethyl-1H-pyrazol-1yl) amide of N-morpholylacetic acid [32].Reduction of 2-(4-chlorophenyl)-3-morpholin-4-yl-1-(4-alkoxyphenyl)propan-1-ones with lithium aluminum hydride resulted in 2-(4-chlorophenyl)-3-morpholin-4-yl-1-(4-alkoxyphenyl) propan-1-ols this derivative has pronounced anticonvulsant and peripheral n-cholinolytic activity, however did not possess antibacterial activity [33].

A morpholine derivative (Amorolfine) is used in medicine as an antifungal agent for local application [34]. There is an information about 15 analogues of known morpholine-containing derivatives based on antifungal drugs fenpropimorph (cis-2,6-dimethyl-4-{2-methyl-3-[4-(2-methyl-2-propanyl)phenyl]propyl} morpholine, fenpropidine (1-[(RS)-3-(4-tert-butylphenyl)-2 methylpropyl] piperidine) and amorolfine, synthetically modified by the inclusion of silicon.Twelve analogues have shown potent antifungal activity against various human fungal pathogens such as Candida albicans, Candida glabrata, Candida tropicalis, Cryptococcus neoformans and Aspergillus niger. The analogue of fenpropimorph showed a higher fungicidal potential compare to the reference drugs fenpropidin, fenpropimorph and amorolfine [35].

Mamatha et al. synthesized compound 4-(2-[5-(4-fluorophenyl)-[1, 3, 4] oxadiazol 2 ylsulfanyl] ethyl) morpholine and studied antibacterial, antioxidant, anti-tuberculosis, antidiabetic activity. Moreover, it was illustrated molecular docking of the interaction of this compound with the InhA protein (which is the protein encoded by the Inh gene, the gene encoding the protein of mycobacteria). Thus, the compound showed high anti-tuberculosis activity at a minimum inhibitory concentration of 3.12μg/ml [36].

The synthesis of morpholine containing hydrazones and its anticancer activity were studied. The antitumor potential of all new compounds has been tested against human cancer cell lines such as HepG2 (hepatocellular liver cancer) and MCF-7 (human breast adenocarcinoma). The resulting compounds had a significant cytotoxic effect against HepG2 with an IC50 value of 6.31±1.03μmol/l compared to standard well known drug doxorubicin (IC50 value 6.00±0.80μmol/l); some of the synthesized compounds possessed strong cytotoxicity towards MCF-7 with an IC50 of 7.08±0.42μmol/l compared to standard tamoxifen (IC50=11.00±0.40 μmol/l) [37].

Information on the synthesis and studies of a number of complexes of metals Cu (II), Co (II), Zn (II) with Schiff's bases containing derivatives of 4-(4-aminophenyl) morpholine indicate anticancer activity on human hepatocarcinoma cell lines (HepG2). Schiff's base derivative and its zinc (II) complex showed inhibitory activity against human gastric cancer cell lines [38].

The wide range of pharmacological activities of piperazine derivatives made them indispensable bases for the development of new drugs.

Al-Ghorbani's research group provides additional evidence that the piperazine structure is contained in many commercially available screening compounds and bioactive molecules [39]. Piperazine derivatives are used in medical practice as an neuroleptic (Clozapine (8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo [b, e][1, 4]-diazepine)), an antidepressant (Vortioxetine (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine)) and anxiolytic (Buspirone)[40].

The piperazine scaffold has been used to synthesize a variety of structurally dissimilar derivatives that have been tested for anti-noroviral activity in a cell-based replicon system. The results of the study reveal that piperazine derivatives have antinoviral activity [41].

In a study by Gurdal Enise Ece et al. devoted to the synthesis of ten benzothiazole-piperazine derivatives, the cytotoxic activity of the compounds on the cell lines of hepatocellular (HUH-7), breast (MCF-7) and colon cancer (HCT-116) in vitro is reported, of all compounds the greatest cytotoxic effect for all tested cancer cell lines showed N-(6-methylbenzothiazol-2-yl)-2-[4-(pyridin-4-yl) piperazinyl] [42].

The Zhou Cheng-He's research group synthesized a number of azole-containing piperazine derivatives and tested it for antibacterial, antifungal and cytotoxic activity in vitro. Compounds 1- (4 -((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl)-2-(1H-imidazol-1-yl) ethanone and 1-(4 -(((4-chlorophenyl) (phenyl)methyl)piperazin-1-yl)-2-(2-phenyl-1H-imidazol-1-yl) ethanone showed high broad spectrum antimicrobial efficacy against all tested strains with MIC values ranging from 3, 1 to 25.0μg/ml, and demonstrated activity comparable to standard widely us ed drugs chloramphenicol and fluconazole [43].

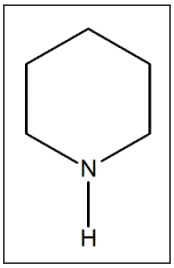
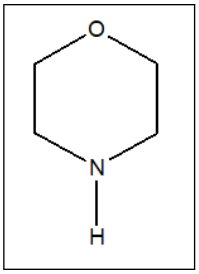
β-elemene (1-methyl-1-vinyl-2,4-diisopropenylcyclohexane) is an active component of the Curcuma Wenyujin medicinal plant with antitumor activity [44]. In order to enhance the antitumor activity, five new piperazine derivatives of β-elemene, 13- (3-methyl-1-piperazinyl)-β-elemene (I), 13- (cis-3,5-dimethyl-1-piperazinyl)-β-elemene (II), 13-(4-ethyl-1-piperazinyl)-β-elemene (III), 13-(4-isopropyl-1-piperazinyl)-β-elemene (IV) and 13-piperazinyl-β-elemene (V). The antiproliferative and apoptotic effects of these derivatives were tested on human leukemia cell lines. Compounds I, II and V containing a secondary amino group showed higher activity in inhibiting cell growth and inducing apoptosis than III and IV. The ability of compound I to induce apoptosis was related to the formation of hydrogen peroxide (H2O2), a decrease in the mitochondrial membrane potential and activation of caspase-8 [45].

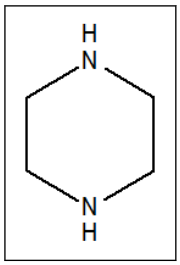
Rahul V. Patel et al. synthesized a number of new analogues of s-triazine were obtained, that were studied for antibacterial, antifungal and anti-cancer activities. Of the 21 synthesized s-triazine derivatives, it is more effective against pathogenic

bacterial strains (Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris, Shigella flexneria), fungies (Aspergillus niger, Aspergillus fumigatus, Aspergillus clavatus, Candida albicans) and cytotoxicity against human prostate cancer cell lines: 4-(4-(4 methylpiperazin-1-yl)-6-(quinolin-4-yloxy)-1,3,5-triazin-2- ylamino)-2 trifluoromethyl-benzonitrile, 4-(4-(3,5 dimethylpiperidin-1-yl)-6-(quinolin-4-yloxy)-1,3,5-triazin-2- ylamino)-2-trifluoromethyl benzo nitrile and 4-(4-(Quinolin-4- yloxy)-6-(4-(3-(trifluoro-methyl) phenyl) piperazin-1-yl)-1,3,5- triazin-2-ylamino)-2-trifluoro-rmethyl-benzo-nitrile indicated the best activity [46].

In connection with the above, the targeted synthesis and study of the biological activity of novel derivatives of the piperidine, morpholine and piperazine series, possessing a wide range of pharmacological activity (Table 2) is of considerable interest in the development of medicine [40, 47].

Table 2: Pharmacological activity of piperidine, morpholine and piperazine derivatives.

No	Compounds	Pharmacological activity
1	Piperidine derivatives 	Antagonist of the nicotinic α2β2 receptor
		5-Hydroxytryptamine Release Stimulant
		Treatment of phobic disorders
		Reduces membrane permeability
		Antidepressant
		Cardiovascular analeptic
		Anti-ischemic, cerebral
		Imidazoline receptor agonist
		Antidyskinetic
		Fibrinolytic
		G-protein coupled receptor kinase inhibitor
		Protein kinase inhibitor
2	Morpholine derivatives 	Attention Deficit / Hyperactivity Disorder treatment
		NADPH peroxidase inhibitor
		Chloride peroxidase inhibitor
		Glyoxylate reductase inhibitor
		Reduces membrane permeability
		Antidepressant
		Cardiovascular analeptic
		Anti-ischemic, cerebral
3	Piperazine derivatives	Polyamine transport ATPase inhibitor
		Kinase inhibitor
		Protein disulfide reductase (glutathione) inhibitor

		Inhibitor of creatininase
		Treatment of phobic disorders
		Anti-ischemic, cerebral
		Fibrinolytic
		Acetylesterase inhibitor
		5-Hydroxytryptamine release stimulant

Although there are scientific publications, inventions in the field of drug discovery, not all pharmaceutically active substances and results of bio screening are being put into medicinal practice, since the creation of a new drug requires the large financial costs and time investments [48]. Therefore, in order to reduce resources in recent years, computer programs have been used to create new drugs, which help to build a model of the structure of future compounds, this gives a clear idea of the geometry of not only the entire molecule, but also to predict their biological effect, to perform screening, to look at the interaction with proteins [49].

Nitrogen-containing organic compounds, namely piperidine, morpholine and piperazine, are part of widely applied pharmaceutical active substances in medicine, have high chemical activity, which makes it possible to synthesize novel compounds possessing higher efficiency and safety.

Trends in the synthesis of active pharmaceutical ingredients based on derivatives of piperidine, morpholine and piperazine, which can in the future be produced on the industrial level, new original drugs for the treatment of tuberculosis, cancer and other serious diseases have been revealed. The promising methods for modification of organic structures for the synthesis of heterocycles have been identified. Moreover, the data were obtained on the novelty of the planned structures of derivatives of piperidine, morpholine and piperazine.

As objects of our research, we selected derivatives of β-aminopropanoic acid hydrazides piperidine, morpholine and piperazine, which, according to the preliminary data and QSAR predictions, are more likely to have anti-tuberculosis, antimalarial, radioprotective and antieczematic activity [50].

Our current research devoted to the synthesis of precursors and leads, their chemical study, and experimental confirmation of the predicted biological activity in vitro and in vivo.

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11. Drugbank (2021) Pipobroman is an antineoplastic agent used to treat cancer. Pipobroman 3:39-40
12. Drugbank (2021) Buclizine is an antihistamine and antiemetic drug for the treatment of allergy symptoms and prevention of nausea and vomiting. Buclizine 3:39-41
13. Drugbank (2021) Cinnarizine is a drug used for the management of labyrinthine disorder symptoms, including vertigo, tinnitus, nystagmus, nausea, and vomiting. Cinnarizine 1:39-40
14. Drugbank (2021) Fentanyl is an opioid analgesic used in anesthesia, for breakthrough cancer pain, or round the clock pain management. Fentanyl 23:48-49
15. Drugbank (2021) Paroxetine is a selective serotonin reuptake inhibitor used to treat major depressive disorder, panic disorder, OCD, social phobia, generalized anxiety disorder, the vasomotor symptoms of menopause, and premenstrual dysphoric disorder. Paroxetine 23:48-49
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