

Pharmacological Applications of Piperidine Derivatives

Subjects: [Chemistry](#), [Medicinal](#)

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Piperidine is a six-membered heterocycle including one nitrogen atom and five carbon atoms in the sp³-hybridized state. Piperidine-containing compounds represent one of the most important synthetic medicinal blocks for drugs construction, and their synthesis has long been widespread. It can be unequivocally stated that heterocyclic compounds play a significant part in the pharmaceutical industry, and one of the most common in their structure is the piperidine cycle.

piperidines

derivatives

biological

1. Introduction

The piperidine cycle is utterly common in pharmaceuticals. Its derivatives are used in over twenty drug classes [\[1\]](#), including anticancer agents [\[2\]\[3\]\[4\]\[5\]\[6\]\[7\]](#), drugs for Alzheimer's disease therapy [\[8\]](#), antibiotics [\[9\]](#), analgesics [\[10\]\[11\]](#), antipsychotics [\[12\]\[13\]\[14\]](#), antioxidants [\[15\]\[16\]](#), etc. (**Figure 1**).

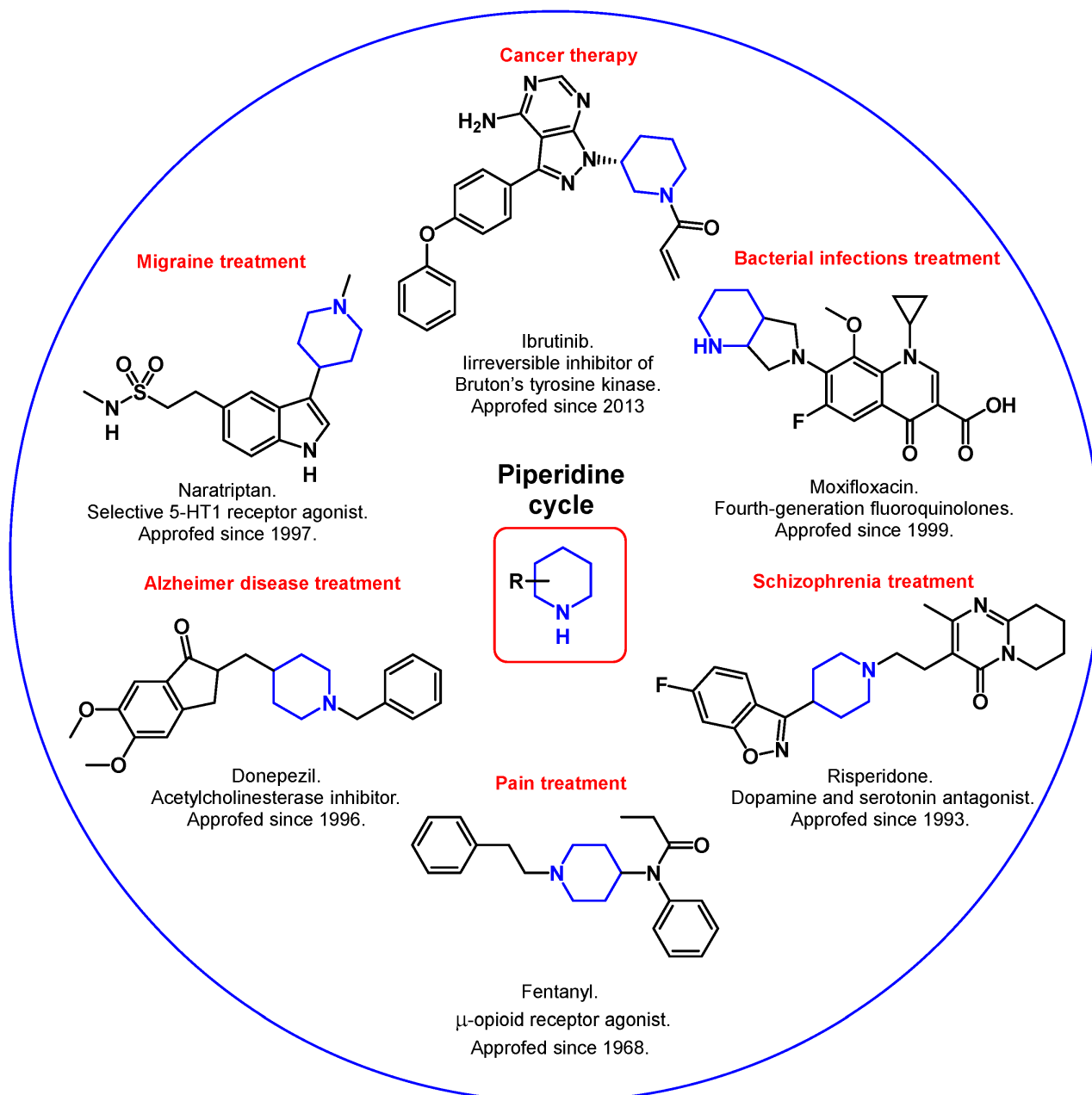


Figure 1. Synthetic piperidine derivatives in medicine.

Moreover, piperidines are also a part of many alkaloids showing biological activity (**Figure 2**). For example, the well-known atropine (used clinically for the treatment of vomiting, nausea, and bradycardia [\[17\]](#)); an effective agent for slowing the development of myopia [\[18\]](#)) and morphine (analgesic for severe pain relief [\[19\]](#)); used as a third-line therapy in the treatment of neuropathic pain [\[20\]](#)) contain a fused piperidine ring.

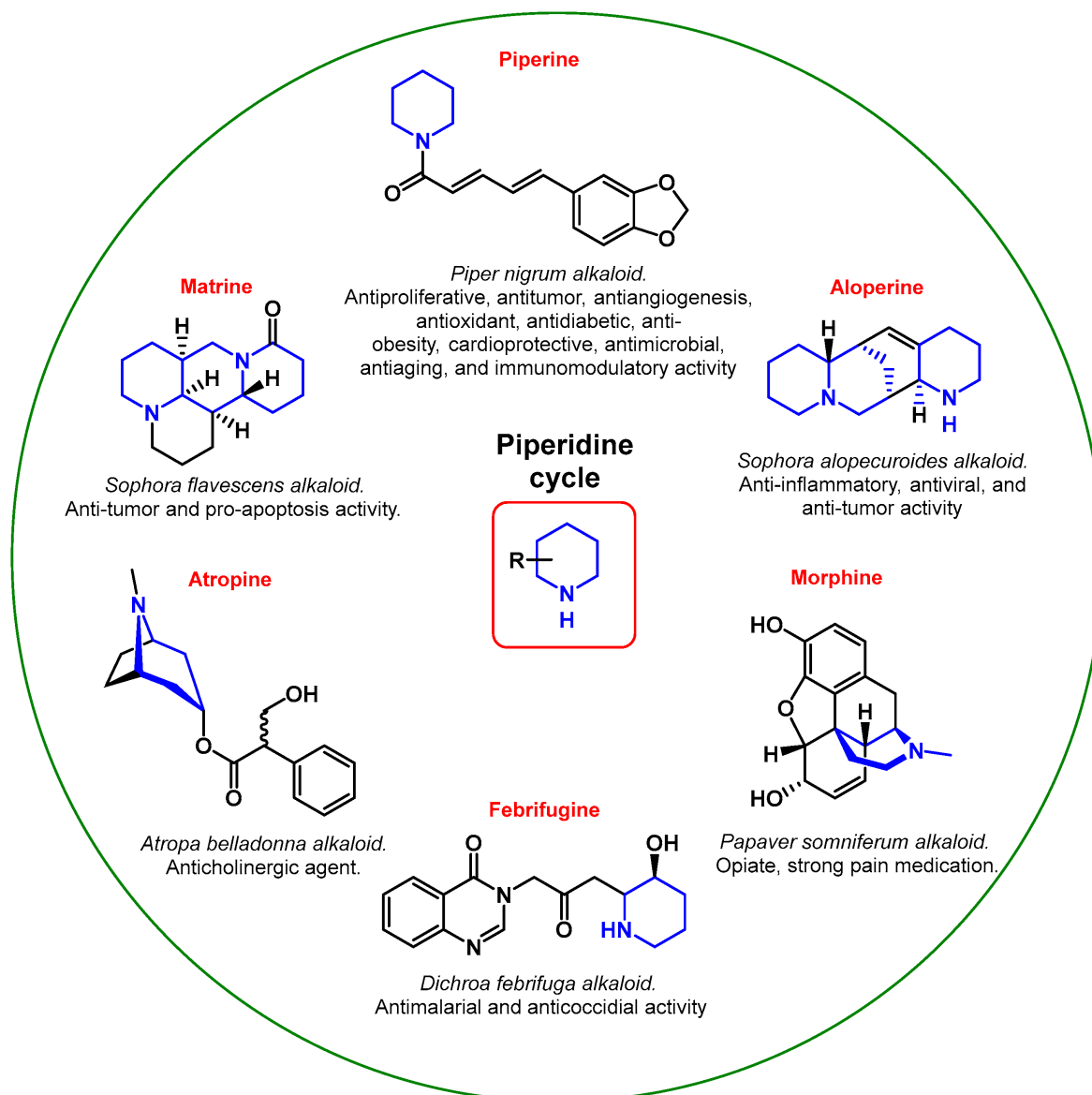


Figure 2. Pharmacological properties of natural piperidine derivatives.

Piperine, a derivative of piperidine and the main active chemical component of black pepper, is attracting more and more attention from researchers, despite the fact that it was discovered more than 200 years ago. It is believed that piperine has a broad scope of beneficial biological properties, from antibacterial to anticancer [21][22][23][24][25]. Aloperine and Matrine—an alkaloid of the *Sophora* containing two fused piperidine rings at once—and their derivatives showed antiviral, anti-inflammatory, and antitumor properties [26][27]. Febrifugine and its synthetic analog halofuginone are efficiently used as antiparasitic drugs [28].

Along with already known drugs, the scientific community constantly proposes new biologically active piperidine scaffolds. Further, researchers will discuss recent discoveries in the biological evaluation of synthetic potential drugs containing the piperidine moiety. Particular attention was paid to four pharmaceutical groups: cancer (pro-tumorigenic receptor inhibitors, apoptosis initiators), infectious and parasitic diseases (biocides), Alzheimer's

disease (anticholinergics), and neuropathic pain (analgesics). The choice of drug groups was based on current trends and relevance in the medical community.

2. Cancer Therapy

Cancer is one of the biggest health problems worldwide, with nearly 10 million deaths reported in 2020 according to WHO. A lot of resources are spent on the development of new drugs for fighting cancer, but despite all efforts, innate and acquired resistance mechanisms are often observed [29]. Therefore, screening for new developments and breakthroughs in this area is very important and relevant.

Piperidine moieties are often used in anticancer drug construction [3][7]. Herein, the recent proposals and developments of scientists on this subject will be briefly discussed.

Arumugam et al. synthesized spirooxindolopyrrolidine-embedded piperidinone **1** with potential anticancer activity through three-component 1,3-dipolar cycloaddition and subsequent enamine reaction [30]. The resulting product showed slightly better cytotoxicity and apoptosis induction in the FaDu hypopharyngeal tumor cells model than the reference drug bleomycin. The authors followed the “escape from flatland” approach, which was popularized throughout recent years [31][32][33] and was successfully used in the development of anti-cancer agents [34][35][36]. This approach suggests that more saturated and three-dimensional structures will interact better with binding sites of proteins. Therefore, the authors reasoned that the spirocyclic structure played a key role in the biological activity of compound **1**.

Li et al. developed IκB kinase (IKKb) inhibitor **2** as an EF24 analog [37]. EF24 is a piperidinone derivative with potential activity against lung, breast, ovarian, and cervical cancer [38][39]. The activation of IKKb is one of the major factors of NF-κB transcription, which induces chronic inflammation in carcinomas, leading to desmoplasia and neoplastic progression [40]. The new analog **2** possessed better IKKb inhibitory properties than the reference drug. The active component with the piperidine moiety developed a stable hydrophobic interaction with the IKKb catalytic pocket. The structure–activity relationship shows that the presence of a nitrogen atom in the cycle is optimal, and any substitution in the ketone bridge is not favorable for IKKb inhibition.

A series of 2-amino-4-(1-piperidine) pyridine derivatives **3**, as the clinically Crizotinib-resistant anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 kinase (ROS1) dual inhibitor, was designed by Zhang et al. [41]. ALK was originally discovered in anaplastic large cell lymphoma as a transmembrane receptor tyrosine kinase [42]. It was found that ALK is involved in the development of non-small cell lung cancer, neuroblastoma, diffuse large B-cell lymphoma, anaplastic thyroid cancer, rhabdomyosarcoma, ovarian cancer, esophageal squamous cell, colorectal, and breast carcinomas, etc. [43][44]. ROS1 was discovered more recently as a similar enzyme to ALK. ROS1 rearrangements were identified in glioblastoma, cholangiocarcinoma, gastric cancer, ovarian cancer, soft-tissue sarcomas, breast cancer etc. [45]. Crizotinib—the first approved ALK/ROS1 dual inhibitor—also includes the piperidine moiety [46]. Despite the fact that the piperidine fragment did not form any bonds with the active site of the receptor, its introduction was the most optimal for the desired pharmacological properties compared to other

substituents. In the case of substance **3**, piperidine derivatives (namely, (S or R)-ethyl piperidine-3-carboxylate) were used as the starting components for chiral optimization [41]. The piperidine ring was essential for chiral optimization. Piwnica-Worms et al. obtained radiolabeled fluoro-analogs of the commercial ALK inhibitors crizotinib **4**, alectinib **5**, and ceritinib **6** [47]. The products have a potential for brain metastases treatment due to their enhanced CNS pharmacokinetic properties. It is worth noting that the introduction of fluoroethyl groups did not affect the inhibitory properties of parent drugs, while it enhanced their ability to pass through blood–brain barrier.

Onnis et al. conducted a synthesis of benzenesulfonamide with a piperidinyl-hydrazidoureido linker as potent carbonic anhydrase (CA) II (**7**), IX (**8**), and XII (**9**) inhibitors [48]. CAs are metalloenzymes localized in the cytosol, mitochondria, membranes, and secreted substances of living organisms. CAs are involved in the catalysis of chemical processes (the hydration of carbon dioxide to bicarbonate, the conversion of cyanate to carbamic acid, etc.) and esterase activity [49]. Two out of the sixteen known types of CA (CA IX and CA XII) are found in vertebrate tumor cells. Their inhibition is an effective way to control the growth, progression, and metastasis of cancerous tumors [50]. Currently, the leading compound among CA IX and XII inhibitors is SLC-0111, which is in phase I/II of clinical trials for the management of hypoxic tumors [51][52]. The authors used SLC-0111 as the parent drug, incorporating a piperidinyl-hydrazidoureido linker in its structure to improve binding selectivity with CA. The piperidine residue was also introduced to assess rigidity [48].

Benzoylpiperidine scaffold **10** with antitumor activity via monoacylglycerol lipase (MAGL) inhibition was constructed by Granchi et al. [53][54]. Fluorine atoms and the meta-substitution of the benzene ring enhanced the inhibition properties. MAGL is responsible for the inactivation of the brain's endocannabinoid 2-arachidonoylglycerol. Moreover, MAGL indirectly controls the levels of free fatty acids, as well as other lipids with pro-inflammatory or pro-oncogenic effects, therefore causing pain and cancer progression [55]. Sekhar et al. developed spirochromanone analog **11** with significant activity against the breast cancer cell line and Murine melanoma, as well as the ability to induce apoptosis [56]. The authors combined known pharmacophore structures to achieve the best anti-proliferative and anti-cancer effects.

Jeong et al. synthesized piperidine-embedded anticancer agents with particularly good activity on androgen-refractory cancer cell lines (ARPC) [57]. The authors showed that compound **12** was a ligand to the M3 muscarinic acetylcholine receptor (M3R), which is presented in ARPC (**Figure 3**). M3R activation stimulates cell proliferation, resistance to apoptosis, and metastasis and is responsible for the early progression and invasion of colorectal cancer tumors [58][59][60].

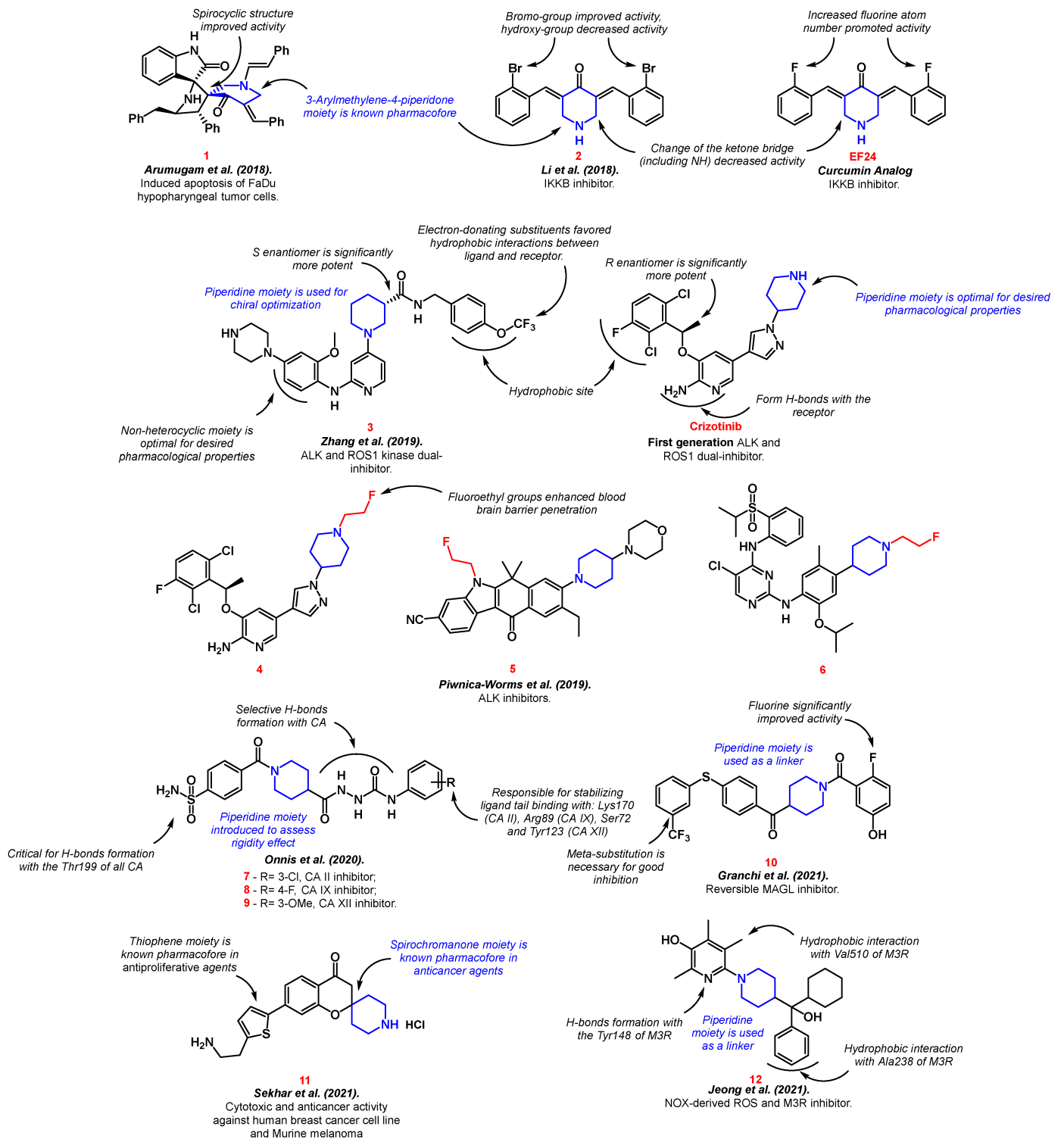


Figure 3. Structure–activity relationship of piperidine derivatives with anticancer activity [30][37][41][46][47][48][53][54][56]

[57].

3. Alzheimer Disease Therapy

Alzheimer disease is one of the most lethal and burdening illnesses of the last century. It has no definite treatment other than symptomatic treatment and results in death 6 years after diagnosis, on average [61]. The oldest theory of

Alzheimer's disease is the cholinergic hypothesis, which suggests that the illness is caused by the loss of cholinergic innervation [62].

The neurotransmitter acetylcholine is one of many vital components for normal brain function. Deficiency of the cholinergic system has been observed in the brains of Alzheimer's disease patients, leading to the pathophysiology of learning and memory impairment [63]. The main goal of modern therapy is to maintain the level of acetylcholine through the inhibition of cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [64]. Currently, the leading drug among acetylcholinesterase inhibitors is Donepezil, a piperidine derivative.

Martinez et al. proposed indolylpiperidine analog **13** of Donepezil [65]. The active agent was capable of inhibiting both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzymes. Moreover, the authors discovered unusual conformational changes in the molecule depending on the binding site. Thus, compound **13** was extended in AChE interaction and flopped in BuChE interaction. Liu et al. expanded this field with 4-N-phenylaminoquinoline derivative **14** [66] via piperidine moiety introduction to a previously reported lead compound [67]. Piperidine incorporation improved the brain exposure of the resulting dual inhibitor. In addition, the compound showed antioxidant and metal chelating properties.

In 2018, Gobec et al. designed selective BuChE inhibitor **15** [68]. Two cationic nitrogen atoms were essential for selectivity and good inhibition properties. Further, the authors conducted a detailed structure–activity relationship study of *N*-alkylpiperidine carbamates [69]. Structures with an *N*-benzyl moiety were superior in cholinesterase inhibition, and a terminal alkyne group was essential for efficient monoamine oxidase B inhibition. Thus, compounds **16–18** were selected as the best in the series. Moreover, a study by Malawska and Gobec outlined a multi-targeted approach to Alzheimer's disease treatment. Novel 1-Benzylpyrrolidine-3-amine derivatives with piperidine groups **19** and **20** expressed both antiaggregatory and antioxidant effects [70]. Along with dual cholinesterase inhibition, compounds **19–20** also targeted the beta secretase enzyme.

Beta secretase is also known as beta-site amyloid precursor protein cleaving enzyme-1 (BACE-1). It has been established that the inhibition of BACE-1 prevents the accumulation of amyloid beta [71][72]. According to the current concept of Alzheimer's disease based on the amyloid hypothesis, deposits of amyloid beta and tau proteins cause neurodegeneration and cognitive impairment [73].

The benzyl-piperidine group (Donepezil-like) is often a necessary part for the successful inhibition of cholinesterase receptors. The AChE enzyme includes two active anionic binding sites: catalytic and peripheral. The benzyl-piperidine group provides good binding to the catalytic site, interacting with Trp84, Trp279, Phe330, and Phe331 [74]. Therefore, the selection of various substituents on top of the benzyl-piperidine residue is a well-established approach in the synthesis of new active agents for combatting Alzheimer's disease. Thus, pyrrolizine **21** [75], fluorine **22** [76], thiazole **23** [77], indoline **24** [78], benzofuran **25** [79], thiophene **26** [80], and chromene **27** [81] groups have been effectively incorporated and biologically evaluated by various authors. The structure–activity relationship is shown in **Figure 4**.

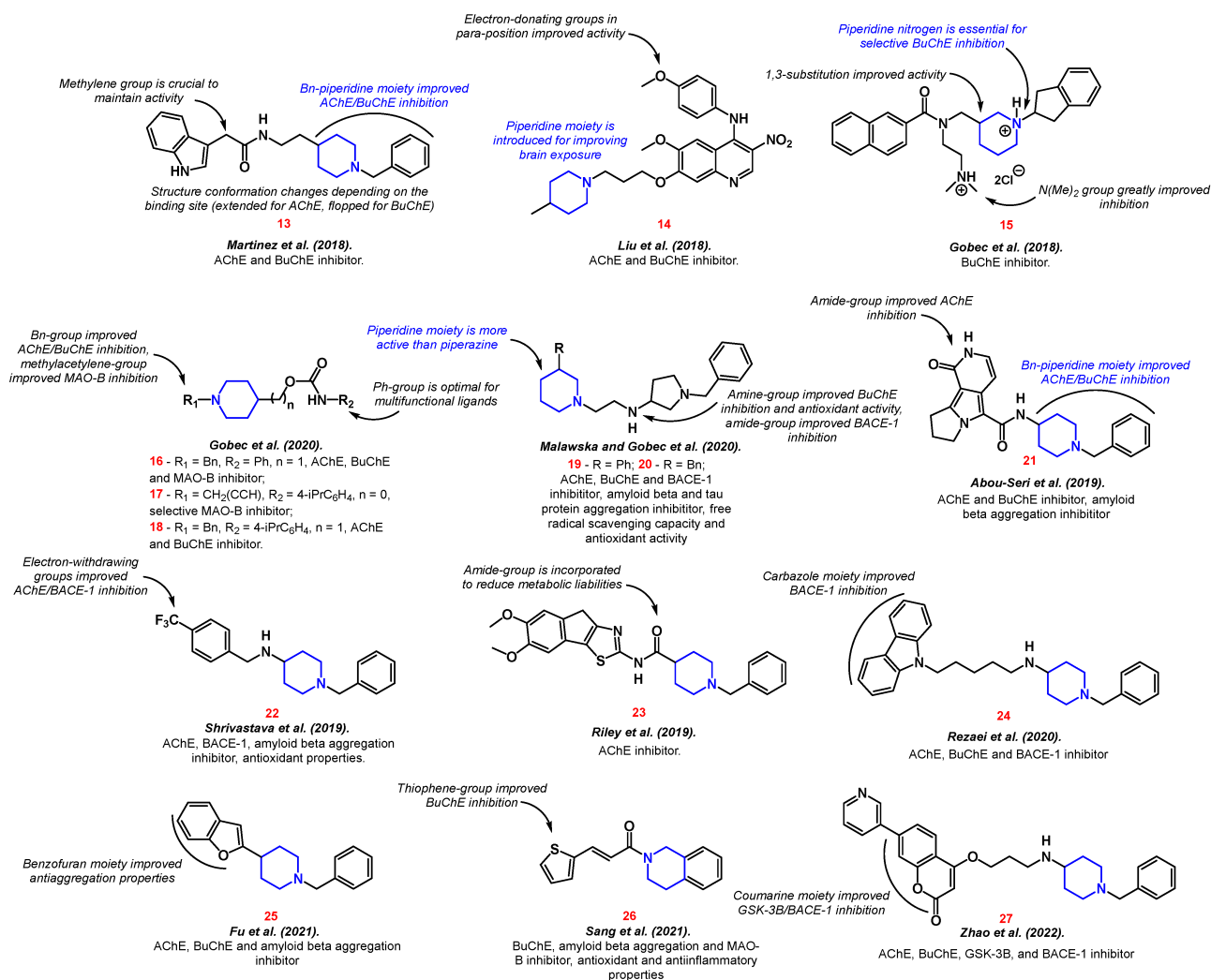


Figure 4. Piperidine derivatives as potential drugs for Alzheimer disease therapy [65][66][67][68][69][70][75][76][77][78][79][80][81].

It is worth noting that research on multifunctional active agents is prevalent compared to compounds that affect only one target. Therefore, along with inhibitors of cholinesterase receptors, attention is also paid to inhibitors of monoamine oxidase 16–17, 26 [69][80], amyloid beta and tau protein aggregation 19–20, 22, 25–26 [70][76][79][80], BACE-1 19–20, 22, 24, 27 [70][76][78][81], as well as the presence of anti-inflammatory 26 [80], anti-radical 19–20 [70], and antioxidant properties 19–20, 22, 26 [70][76][80].

Drawing conclusions from the analyzed data, it can be said that the piperidine group affects the inhibition of cholinesterase receptors and serves as a constructing (linker) part.

4. Biocides

Biocides are chemical compounds designed to neutralize, suppress, or prevent the action of harmful organisms, namely, pathogenic bacteria, fungi, viruses, parasites, etc. [82]. As noted earlier, piperidine derivatives find use in this class of pharmaceuticals.

In recent years, a number of works on the topic can be noted. However, due to the wide variety of human pathogens, it is not possible to point out one template structure for all types of activities.

Thus, piperidine moieties were represented in structures with antifungal properties **28–30**. Compounds containing tartaric acid fragment **28–29** inhibited chitin synthase, therefore suppressing a growth of five fungi strains (*C. albicans* ATCC 76615, *A. fumigatus* GIMCC 3.19, *C. albicans* ATCC 90023, *C. neoformans* ATCC 32719, *A. flavus* ATCC 16870) [83]. The resulting compounds combined two pharmacophores: 2,8-Diazaspiro [4.5]decane-1-one and a tartaric acid residue with a substituted aminobenzene. When designing the structure, the authors were guided by the “escape from flatness” theory (which was mentioned earlier) and the enzyme inhibition potential of the chosen moieties. Long-tailed 4-aminopiperidines **30** have proven to be effective against fungi of the genus *Aspergillus* and *Candida* via fungal ergosterol biosynthesis inhibition [84]. Ergosterol is one of the most abundant fungal cell membrane sterols. It is responsible for membrane permeability and fluidity [85].

Piperidine-containing fluoroquinolones analogs, namely, bafloxacin **31**, were proposed by Liu et al. [86]. Along with the good inhibition values on MRSA, *P. aeruginosa*, and *E. coli*, the new compounds showed good biocompatibility and potential two-targeted action via cell walls destruction and interaction with IV-DNA and DNA gyrase. Piperidinyl “tails” structures **32** possessed inhibition properties against streptomycin-starved *Mycobacterium tuberculosis* 18b (SS18b) and H37Rv strains [87]. Compound **32** consists of various known tubercular pharmacophores with piperidine as a linker.

The benzyl-piperidines activity against different viruses was shown. Thus, 4,4-disubstituted *N*-benzyl piperidines **33** inhibited the H1N1 influenza virus through specific hemagglutinin fusion peptide interaction [88]. Nayagam et al. discovered the potential inhibitor of SARS-CoV2 with piperidine core **34** [89]. Compound **34** possessed a better binding affinity with the SARS-CoV2 main protease than Remdesivir, with five binding pockets interaction compared to two.

Compounds with a piperidine backbone structure have shown antiparasitic properties on *T. brucei* (the main cause of African trypanosomiasis) **35** [90] and *P. falciparum* (the cause of the deadliest type of malaria) **36–37** [91][92] (Figure 5).

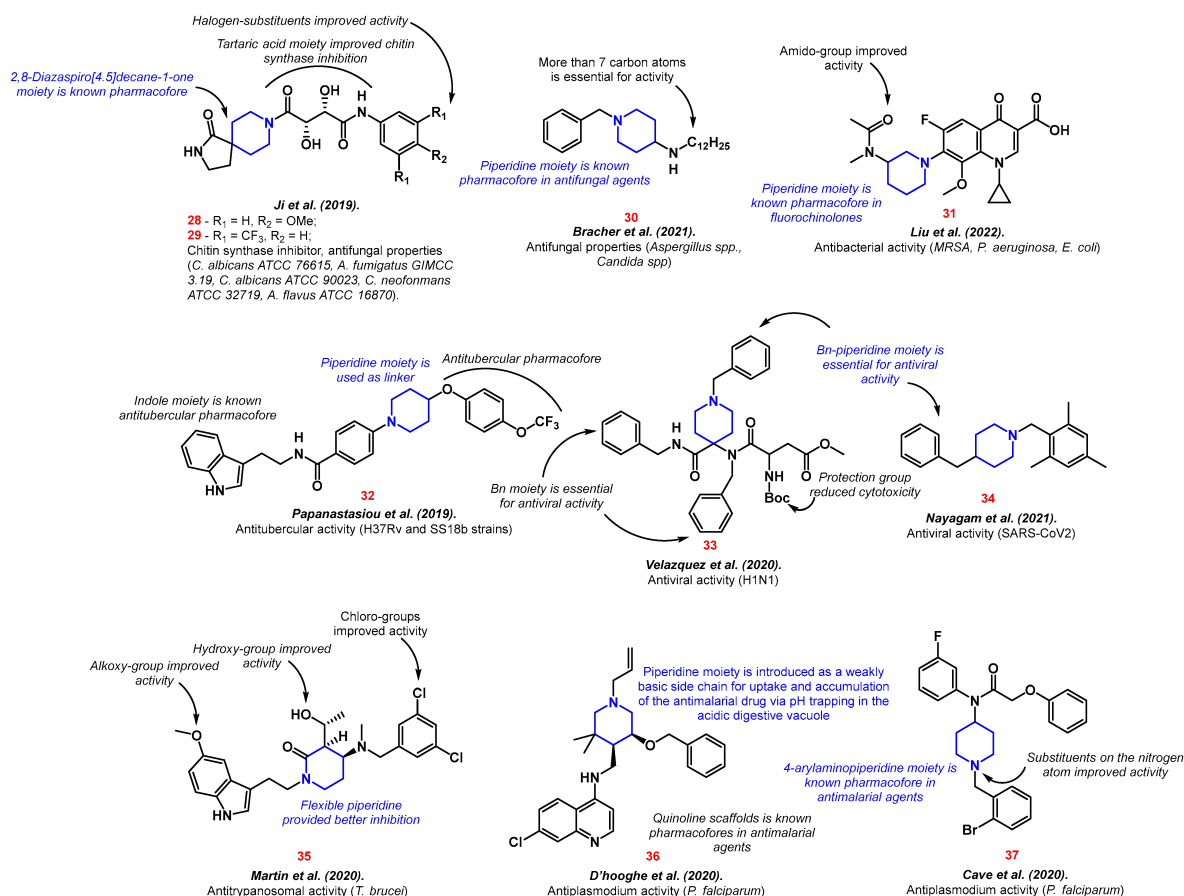


Figure 5. Piperidine derivatives with antimicrobial activity [83][84][86][87][88][89][90][91][92].

5. Neuropathic Pain Therapy

Neuropathic pain occurs as a result of the pathological excitation of neurons in the peripheral or central nervous system, which is caused by neurological diseases with damage to peripheral fibers and central neurons [93]. The modern approach to the treatment of neuropathic pain includes three lines of pharmacotherapy. Most of the piperidine derivatives are part of opioids, which are the second and, in some cases, the third line of treatment [20].

Opioid receptors are divided into four similar types: μ -opioid (MOR), δ -opioid (DOR), κ -opioid (KOR), and nociceptin/orphanin FQ peptide receptor (NOP) [94][95]. MOR and DOR are the main targets of opioid agonists. MOR agonists cause euphoria and help with coping with stress; however, their use causes serious side effects and physical dependence, leading to overdose [96]. One of the main synthetic piperidine-containing opioids is fentanyl.

Most often, opioid derivatives serve as the starting point for the discovery of new types of analgesics. Thus, derivatives of nordsufentanil with amino acids **38** were developed [97], the synthesis of the main metabolites of carfentanil **39** was reproduced [98], and new analogs of tramadol **40** were proposed [99]. All compounds showed a strong affinity for MOR.

In order to achieve a dual effect ligand, Lee et al. created a hybrid based on Pethidine, also known as meperidine, and a transient receptor potential cation channel subfamily V member 1 (TrpV1) antagonist **41** [100]. TrpV1 functions are widely linked to the generation of pain [101]. This combination potentially increases the anti-inflammatory effect and treatment efficiency.

Navarrete-Vázquez et al. developed a haloperidol analog **42** as a σ_1 receptor antagonist [102]. The σ_1 receptor plays a role in various regulatory processes, including pain reduction [103]. Therefore, Chen et al. proposed novel piperidine propionamide derivatives **43–44** as dual agonists of μ -opioid and σ_1 receptors [104][105].

Lastly, CA inhibition is another prominent therapeutic target in neuropathic pain treatment. Thus, Supuran et al. synthesized piperidine-embedded 4-oxo-spirochromanes **45** with high activity against CA II and CA VII (Figure 6) [106].

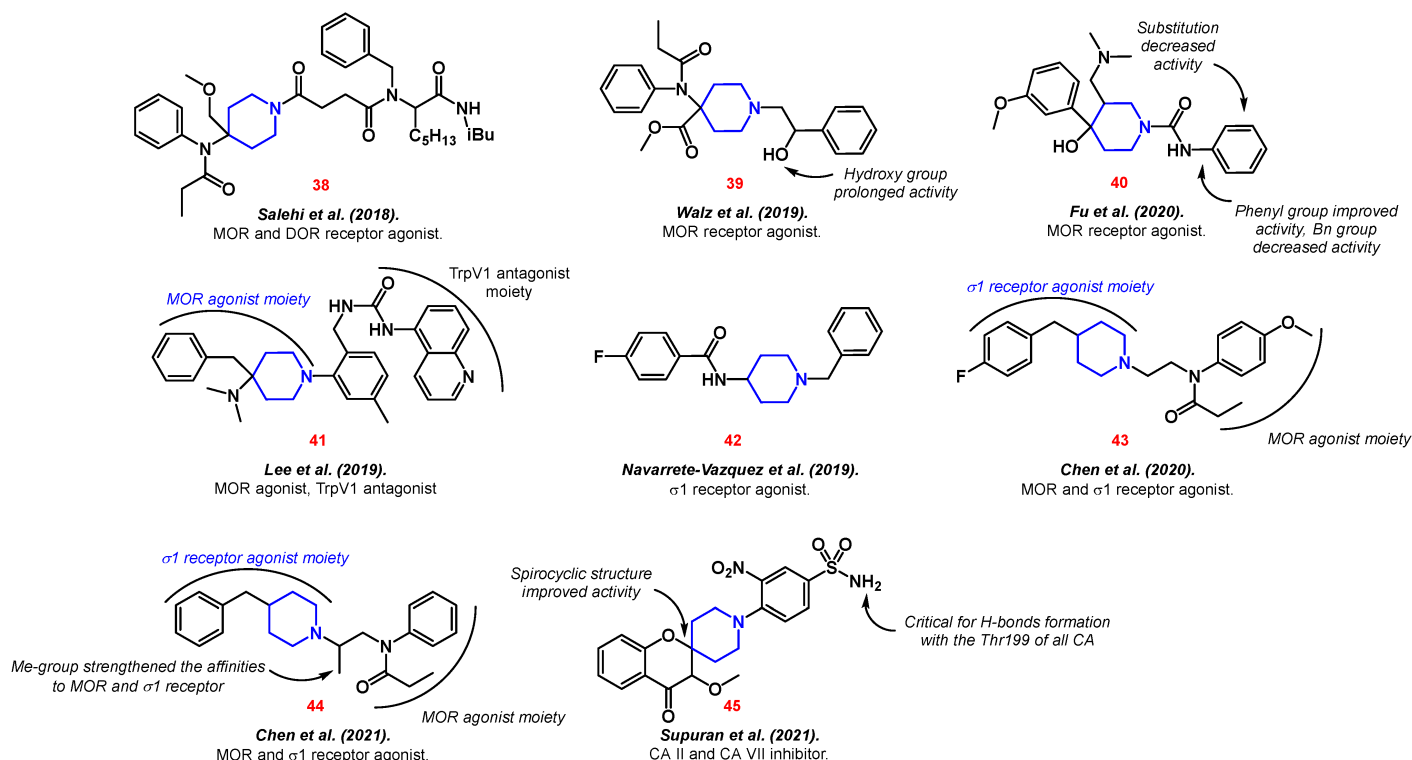


Figure 6. Piperidine derivatives as potential drugs for neuropathic pain disorders [97][98][99][100][102][104][105][106].

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