

Review

Cognitive impairment in endocrine and metabolic disorders: the role of sigma-1 receptors and the potential of pyrrole derivatives

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Abstract

In today's global population aging environment cognitive impairment appears to be increasingly prevalent and become one of the leading causes of disability and mortality in the world. Increasing life expectancy is accompanied by more frequent occurrence of neurodegenerative and metabolically provoked lesions of the central nervous system. In addition to age-related changes, endocrine pathology plays a significant role in the development of cognitive deficiency. This pathology includes diabetes mellitus, thyroid diseases, metabolic syndrome and adrenal pathology. Key pathogenic mechanisms are oxidative stress, neurological inflammation, calcium homeostasis disturbances, endothelial dysfunction and mitochondrial disorders. Sigma-1 receptors (S1R) are of special attention in current studies. They perform the function of intracellular chaperones and regulate a wide range of neural processes including neuroplasticity, synaptic transmission and cellular homeostasis. S1R activation is associated with neuroprotective effects, decrease of neurological inflammation and improvement of cognitive functions. Pyrrole derivatives as potential S1R ligands are considered among the promising areas of pharmacotherapy. They combine antioxidant, anti-inflammatory and neuroprotective properties. Modern S1R agonists including Pridopidine, Blarcamesine and Dimethyltryptamine in particular, are of special interest. They demonstrate positive results in preclinical and clinical studies. Therefore, targeting of Sigma-1 receptors is a promising approach to the development of new effective means for the correction of cognitive impairment, especially in patients with metabolic and endocrine disorders.

Keywords: endocrine disorders, metabolic disorders, cognitive impairment, Sigma-1 receptors, pyrroles

Introduction

Dynamics of a global life expectancy demonstrates a continuous increase due to innovations in health care and better well-being of the population. While life expectancy was under 60 years in the last century, it reached nearly 70 years in 2019, and it is projected to rise to 82 years by 2075 [1]. At the same time, demographic aging is associated with an increasing prevalence of age-related disorders including cognitive impairment. According to the World Health Organization, there

were over 55 million people worldwide living with dementia in 2020. Forecasts suggest that this number will double every 20 years, reaching 82 million by 2030 and 155 million by 2050 [2].

The role of endocrine and metabolic disorders in the development of cognitive deficiency

In addition to age, endocrine pathology occurring due to hormonal imbalance and metabolic changes is



one of the causes of cognitive impairment, since it affects the cerebral function [3]. Hormones regulate neuroplasticity, metabolism in the nerve cells and circulation, therefore any deviation from the norm can result in deterioration of memory, attention and thinking. Diabetic encephalopathy, for example, is known to be characterized by decreased intelligence, low speed of information processing and memory deterioration. Both hyperglycemia and hypoglycemia produce a negative effect on neurons. Type 2 diabetes mellitus significantly increases the risk of dementia, particularly Alzheimer's disease (often referred to as type 3 diabetes) by several times [4]. Oxidative stress of confirmed to be a key factor provoking cognitive deficiency in diabetes [5], obesity [6], which is a significant problem of public health and becomes especially relevant in the context of growing global diabetes prevalence and population aging.

It is important to note that diabetes-associated cognitive dysfunction (DACD) occurs in 13.5% of patients with diabetes mellitus. Dementia is the second leading cause of death among DM patients. Du M. *et al.* (2023) in their study in a mouse model of T1D (Streptozotocin, 50 mg/kg, intra-abdominal 5 days) established that an elevated glucose level decreases S1R expression in the hippocampus astrocytes leading to an excessive formation of contacts between the endoplasmic reticulum (ER) and mitochondria, activation of ER stress response (axis PERK-eIF2 α -ATF4-CHOP), intensified synthesis of C3 complement component and release of C3a anaphylatoxin. Interaction of C3a with C3aR receptors on neurons caused synaptic degradation – decreased levels of PSD-95 and synaptophysin, reduced dendritic spine density in the hippocampal CA1 area and spatial memory impairment (Y-maze test and Morris water labyrinth). Administration of S1R PRE-084 agonist (0.25 mg/kg intra-abdominally 3 times a week during 8 weeks) made all the above parameters normal. It should be noted that a direct blockade of C3aR receptor with the antagonist SB290157 reproduced a neuroprotective effect of PRE-084, confirming a causal role of the astrocytic complement cascade in pathogenesis of DACD [7].

Literary sources admit [8] that thyroid diseases (hypo- and hyperthyroidism) result in general inhibition, short-term memory impairment, depressive states, and reduced concentration or difficulty focusing due to nervous system overstimulation. Metabolic syndrome considerably increases the risk of development of mild cognitive impairment (MCI) [9]. Adrenal pathology, for example Cushing's syndrome, causes

hippocampal atrophy, which directly correlates with memory and cognitive impairment [10].

Considering the above, it can be stated that cognitive impairment is a leading cause of disability and the second leading cause of mortality in the world, and they are the main factors promoting social burden [11].

Since current approaches to the treatment of amnesic disorders in the majority of cases are not sufficiently effective, there is a need to find new compounds able to better decrease the signs of depression and improve cognitive functions. One of the promising targets to develop such drugs is Sigma-1 receptors [12]. An interesting target demonstrating promising results concerning treatment of many neurological and neurodegenerative disorders is pyrrole derivatives for the development of Sigma-1 (σ 1) receptor ligands acting as agonists or modulators.

Therefore, the objective of our study was to carry our literary search for new compounds with pronounced antioxidant and anti-inflammatory properties able to effectively decrease lesions of the nervous tissue and restore impaired function of neurons, which will promote correction of cognitive impairment.

Pyrrole derivatives as promising compounds

Our attention was focused on pyrrole derivatives. Literary sources indicate that pyrrole is a nitrogen-containing heterocyclic 5-membered ring, characterized by a wide range of application in the pharmaceutical area. Various pharmacological studies indicate anti-inflammatory and anti-nociceptive activity of different pyrrole derivatives [13, 14]. Certain of these compounds demonstrated selective inhibition of cyclooxygenase-2 (COG-2) and significant suppressive effect on prostaglandin production [15]. Thus, considerable efforts were directed to synthesis of pyrrole compounds as COG-2 inhibitors for the treatment of inflammatory diseases. The studies on their application in neurodegenerative states such as Parkinson's disease are still ongoing [16].

Pyrrole derivatives are a promising class of compounds for the development of the ligands of Sigma-1 (σ 1) receptors acting as agonists or modulators.

Sigma-receptors as a therapeutic target

Σ – receptors are classified into two subtypes known as Sigma-1 receptor (S1R) and Sigma-2 receptor (S2R). Sigma-1 receptors are multifunctional proteins

located in the membranes of the endoplasmic reticulum. They play an important role in the intracellular signalization, interacting with various receptors, ion channels, lipids and kinases. Disorders of their function or the level of their expression may promote the development of various pathologies including depression and memory impairment in particular. Therefore, the effect on Sigma-1 receptors is considered as a potentially effective approach to the treatment of diseases of the central nervous system [12].

S1R is a multifunctional protein with a mass of 25kDa that is ligand-regulated and acts as a chaperone on endoplasmic reticulum membranes and regulates inter-organelle signalization. S1Rs play an important biological role in cognitive processes providing regulation of Ca^{2+} -signaling, neuroplasticity control, modulation of the neuromediator systems (glutamatergic and dopaminergic in particular), and possess anti-apoptotic action as well. Their activation promotes better learning and memory, decreases neurological inflammation and increases neuron survival, which is stipulated by their ability to act as multi-target regulators through their interaction with NMDA-receptors, ion channels and GPCR-receptors [17]. S2R is a transmembrane protein of the endoplasmic reticulum with binding site. Its molecular identity is defined as TMEM97. It is a biological marker of rapidly dividing cells. Therefore, our attention was attracted to the first type, since S1R agonists possess various S1R-mediated signaling functions that in general can be characterized as neuroprotective ones [18].

S1R is a ligand-regulated protein widely expressed in many organs including the nervous system. It plays an important role in the modulation of neuronal physiology and synaptic plasticity [19]. Many S1R agonists possess neuroprotective action, and S1R loss accelerates neurodegenerative phenotypes [20]. Neuroprotection due to S1R activation is achieved through the variety of signaling functions that promote cellular homeostasis and synaptic stability [21].

In recent years, many studies have described numerous S1R functions, which help maintain an adequate cellular homeostasis. S1R was first described as an opioid receptor [11]. Later it was termed as a calcium-sensitive ligand-regulated endoplasmic reticulum chaperone [19]. In scientific literature, the endoplasmic reticulum (ER) is known as the most functional cell organelle [22]. Therefore, it is not surprising that S1R is associated with a number of mechanisms (for example, response to stress, Ca^{2+} homeostasis, lipid metabolism, autophagy etc.). To understand S1R biological func-

tions better, it is necessary to clarify ER structure, its organization and functions. As a continuous interconnected membrane network, the ER exhibits two major domains including nuclear envelope and peripheral ER. The nuclear envelope consists of two flat membrane biological layers of the ER, which after laying create internal and external nuclear membranes [23]. According to the morphological findings of the peripheral ER were visualized by means of electronic microscopy and classified into rough ER (RER) and smooth ER (SER). On the one hand, RER is characterized by the presence of ribosomes bound with ER membrane, and now called ER plates. On the other hand, SER does not contain ribosomes on its membrane and now is called ER tubules [22, 24]. Both plates and tubules originate from the external membrane [25]. Despite the relationship, the external membrane, plates and tubules are associated with different functions and are spatially separated, which explains various biological functions of S1R.

Nowadays, S1R is known as a unique protein not related to any traditional class of opioid receptors, considering its ability to bind a multitude of ligands, and is thus officially classified as a non-opioid intracellular receptor [26]. Although it is important to know that S1R does not completely respond to generally accepted definition as a “receptor”, considering the lack of a direct activation of signaling pathways after ligand binding. This receptor is expressed in many organs and systems, but it demonstrates the highest protein expression in the liver, placenta and brain (especially in the cerebellum, hippocampus, basal ganglia and cerebral cortex). It is important to note that brain transcriptomic data are indicative of higher S1R expression in glial cells than in neurons [11].

Pharmacological modulation of Sigma-1 receptors

S1R agonists act as “enhancers” of neuronal survival through several mechanisms. One of them is reducing brain edema, which is confirmed by preclinical studies with PRE-084 drug. In the case, when the drug was administered immediately after injury, significant decrease of edema and neurological deficiency were indicated [27, 28]. Another mechanism is control over neurological inflammation. Thus, S1R modulators are able to decrease chronic hyperactivity of the microglia, which after an injury instead of help begins to destroy healthy tissues [29]. At the same time, modulators of these receptors are indicated to possess mitochondrial

protection by means of maintenance of cell energy balance and blockade of excessive calcium release, which is the main cause of neuronal death after traumatic brain injury [30].

Preclinical findings concerning neuroprotective potential of PRE-084 in diabetes mellitus are of special attention. Du M. *et al.* (2023) in their study in a mouse model of T1D, C57BL/6 (Streptozotocin, STZ) demonstrated that PRE-084 administration (0.25 mg/kg into the abdomen, three times a week during 8 weeks) made disturbed astrocytic ER mitochondria contact normal, inhibited PERK-branch activation of ER-stress (decrease of BIP, p-eIF2 α , ATF4, CHOP) and reduced release of C3a complement component by astrocytes. This prevented synaptic degradation in the hippocampal CA1, increased the levels of PSD-95 and synaptophysin, and restored spatial memory according to the results of Y-maze test and Morris water labyrinth. These results are indicative of an astrocytic axis ER-stress $\rightarrow$ C3/C3a complement $\rightarrow$ synaptic loss as a crucial pathogenic mechanism of cognitive dysfunction in type 1 diabetes mellitus [7].

Simultaneously, Shi L. *et al.* (2025) in their model of T2D on rats Sprague-Dawley (combination STZ with high fat diet, HFD+STZ) demonstrated that PRE-084 activates the signal cascade ERK/CREB $\rightarrow$ BDNF increase $\rightarrow$ PSD-95 increase in the hippocampal CA1 neurons. The specificity of this mechanism is confirmed by dual pharmacological blockade. S1R agonist BD1047 eliminated PRE-084 effect on a receptor level, and a TrkB receptor agonist – ANA-12 on the level of BDNF-dependent transduction. Therapy with PRE-084 significantly improved performance of Morris water labyrinth test and decreased brain atrophy (according to CT visualization) and death of the hippocampal neurons (according to histological analysis). The results obtained are indicative of the fact that the neurotrophic axis S1R/ERK/CREB/BDNF is the second, independent of the astrocytic one, therapeutic mechanism in DACD. It can be of a certain therapeutic value in type 2 diabetes mellitus [31].

Thus, two independent studies consistently demonstrate the neuroprotective potential of the S1R agonist PRE-084 in both major types of diabetes mellitus – through complementary molecular mechanisms. This strengthens the evidence base for the concept of S1R targeting as a promising approach to correct cognitive impairment in metabolic endocrine pathologies.

Another highly selective Sigma-1 receptor agonist currently undergoing clinical trials as a potential means of treatment for Huntington's disease and amyotrophic

lateral sclerosis (ALS) is Pridopidine. Certain scientific studies presented the evidence that it helps to restore the structure of the mitochondria-associated membrane of the endoplasmic reticulum, make calcium balance and autophagy normal, decreases endoplasmic reticulum stress, improves mitochondrial function and reduces the level of oxidative lesion. Moreover, it intensifies axonal transport, stimulates the secretion of brain-derived neurotrophic factor (BDNF), and improves synaptic plasticity and dendritic spine density. In preclinical models, Pridopidine exhibits a pronounced neuroprotective effect. It is characterized by a biphasic dose-response effect, typical for S1R agonists. Due to its effect on basic mechanisms of cellular survival, Pridopidine is considered as a promising means able to modify the course of a disease in various lesions of the nervous system [32].

The scientific literature sources reviewed indicate that most specific compounds are in the stage of their active development or testing for related conditions, which provides a basis for their administration in the treatment of brain lesions accompanied by cognitive impairment. For example, Blarcamesine has completed Phase IIb/III trials for Alzheimer's and Rett's diseases with positive results obtained in restoring cellular homeostasis. According to Anavex Life Sciences, Blarcamesine is known to demonstrate the ability to stop microglial inflammation, which is critical for recovery, especially after head injury [33].

Dimethyltryptamine (DMT/AP-188) is a sigma receptor agonist stimulating neuroplasticity through the increase of BDNF level [34].

Summarizing the above, it can be stated that further development of pharmacological approaches directed to S1R modulation, may contribute to the creation of effective strategies for the treatment of cognitive impairment caused by endocrine and metabolic disorders.

Conclusions

Cognitive impairment is a global medical and social issue, with its prevalence increasing due to population aging and the growing incidence of metabolic and endocrine diseases. Sigma-1 receptors (S1Rs) are key regulators of cellular homeostasis and neuronal function, and their activation exerts pronounced neuroprotective effects, making them promising therapeutic targets. Pyrrole derivatives represent a promising class of compounds for the development of new

pharmacological agents due to their antioxidant, anti-inflammatory, and potentially Sigma-1 receptor-mediated effects. Modern Sigma-1 receptor agonists, including pridopidine, blarcamesine, and others, have demonstrated promising results in preclinical and clinical studies, supporting the rationale for further research in this area. In particular, preclinical studies of PRE-084 in models of type 1 and type 2 diabetes mellitus have demonstrated two complementary mechanisms of S1R-mediated neuroprotection: inhibition of astrocytic ER stress and the C3/C3a complement cascade, as well as activation of the neuronal ERK/CREB/BDNF signaling axis. Both mechanisms converge on the restoration of synaptic PSD-95 protein and improvement of spatial memory in the hippocampus, further supporting the potential of S1R-targeted approaches for the correction of cognitive impairment associated with diabetes.

Conflict of interest

The authors declare no conflict of interest.

References

- Chang AY, Bolongaita S, Cao B, Castro MC, Karlsson O, Mao W et al. Epidemiological and demographic trends and projections in global health from 1970 to 2050: a descriptive analysis from the third Lancet Commission on Investing in Health, Global Health 2050. *Lancet*. 2025;406(10506):940-9. doi: 10.1016/S0140-6736(25)00902-X.
- Washington L. Dementia and the aging population: cognitive screening within correctional health. *Int J Prison Health*. 2023;19(1):63-76. doi: 10.1108/IJPH-08-2021-0070.
- Kim HK, Song J. Hypothyroidism and Diabetes-Related Dementia: Focused on Neuronal Dysfunction, Insulin Resistance, and Dyslipidemia. *International Journal of Molecular Sciences*. 2022;23(6):2982. <https://doi.org/10.3390/ijms23062982>.
- Huai JX, Chang EE, Zhu YR, Ma WL, Lv TS, Sun J et al. Diabetic encephalopathy: metabolic reprogramming as a potential driver of accelerated brain aging and cognitive decline. *Front Cell Dev Biol*. 2025;13:1701406. doi: 10.3389/fcell.2025.1701406.
- Kan W, Qu M, Wang Y, Zhang X, Xu L. A review of type 2 diabetes mellitus and cognitive impairment. *Front. Endocrinol*. 2025;16:1-11. doi: 10.3389/fendo.2025.1624472.
- Li H, Ren J, Li Y, Wu Q, Wei J. Oxidative stress: The nexus of obesity and cognitive dysfunction in diabetes. *Front. Endocrinol*. 2023;14:1-13. doi: 10.3389/fendo.2023.1134025.
- Du M, Jiang T, He S, Cheng B, Zhang X, Li L et al. Sigma-1 Receptor as a Protective Factor for Diabetes-Associated Cognitive Dysfunction via Regulating Astrocytic Endoplasmic Reticulum-Mitochondrion Contact and Endoplasmic Reticulum Stress. *Cells*. 2023;12(1):197. doi: 10.3390/cells12010197.
- Lekurwale V, Acharya S, Shukla S, Kumar S. Neuropsychiatric Manifestations of Thyroid Diseases. *Cureus*. 2023;15(1):e33987. doi: 10.7759/cureus.33987.
- Qiu S-D, Zhang D-D, Ma L-Y, et al. Associations of metabolic syndrome with risks of dementia and cognitive impairment: A systematic review and meta-analysis. *Journal of Alzheimer's Disease*. 2025;105(1):15-27. doi:10.1177/13872877251326553.
- Ben-Shlomo A, Koh M, Kremen S, Wertheimer J. Cognitive Assessment in Adults With Adrenal Cortisol Insufficiency: Challenges and Opportunities. *Endocr Rev*. 2026;47(1):24-51. doi: 10.1210/endrev/bnaf029.
- Lachance V, Bélanger SM, Hay C, Le Corvec V, Banouvang V, Lapalme M et al. Overview of Sigma-1R Subcellular Specific Biological Functions and Role in Neuroprotection. *Int J Mol Sci*. 2023;24(3):1971. doi: 10.3390/ijms24031971.
- Kinga Sałaciak, Karolina Pytka. Revisiting the sigma-1 receptor as a biological target to treat affective and cognitive disorders. *Neuroscience & Biobehavioral Reviews*. 2022;132:1114-1136. <https://doi.org/10.1016/j.neubiorev.2021.10.037>.
- Zlatanova-Tenisheva H, Vladimirova S. Experimental screening for analgesic and anti-inflammatory effect of novel compounds with a pyrrole heterocycle. *Pharmacia*. 2024;71:1-10. <https://doi.org/10.3897/pharmacia.71.e121943>.
- Mogilski S, Kubacka M, Redzicka A, Kazek G, Dudek M, Malinka W et al. Antinociceptive, anti-inflammatory and smooth muscle relaxant activities of the pyrrolo[3,4-d]pyridazinone derivatives: Possible mechanisms of action. *Pharmacol Biochem Behav*. 2015;133:99-110. doi: 10.1016/j.pbb.2015.03.019.
- Ju Z, Li M, Xu J, Howell DC, Li Z, Chen FE. Recent development on COX-2 inhibitors as promising anti-inflammatory agents: The past 10 years. *Acta Pharm Sin B*. 2022;12(6):2790-2807. doi: 10.1016/j.apsb.2022.01.002.
- Javid H, Saeedian Moghadam E, Farahmandfar M, Manouchehrabadi M, Amini M, et al. Biological Activity of Novel Pyrrole Derivatives as Antioxidant Agents Against 6-OHDA Induced Neurotoxicity in PC12 Cells. *Iran J Pharm Res*. 2023;22(1):e140450. doi: <https://doi.org/10.5812/ijpr-140450>.
- Drewes N, Fang X, Gupta N, Nie D. Pharmacological and Pathological Implications of Sigma-1 Receptor in Neurodegenerative Diseases. *Biomedicines*. 2025;13(6):1409. doi: 10.3390/biomedicines13061409.
- Kargbo RB. Sigma-1 and Sigma-2 Receptor Modulators as Potential Therapeutics for Alzheimer's Disease. *ACS Med Chem Lett*. 2021;12(2):178-179. doi: 10.1021/acsmchemlett.1c00002.
- Shokr MM, Badawi GA, Elshazly SM, Zaki HF, Mohamed AF. Sigma 1 Receptor and Its Pivotal Role in Neurological Disorders. *ACS Pharmacol Transl Sci*. 2024;8(1):47-65. doi: 10.1021/acspstci.4c00564.
- Ryskamp DA, Korban S, Zhemkov V, Kraskovskaya N, Bezprozvanny I. Neuronal Sigma-1 Receptors: Signaling Functions and Protective Roles in Neurodegenerative Diseases. *Front Neurosci*. 2019;13:862. doi: 10.3389/fnins.2019.00862.
- Malar DS, Thitilertdech P, Ruckvongacheep KS, Brimson S, Tencomnao T, Brimson JM. Targeting Sigma Receptors for the Treatment of Neurodegenerative and Neurodevelopmental Disorders. *CNS Drugs*. 2023;37(5):399-440. doi: 10.1007/s40263-023-01007-6.
- Perkins HT, Allan V. Intertwined and Finely Balanced: Endoplasmic Reticulum Morphology, Dynamics, Function, and Diseases. *Cells*. 2021;10(9):2341. <https://doi.org/10.3390/cells10092341>

23. Deolal P, Scholz J, Ren K, Bragulat-Teixidor H, Otsuka S. Sculpting nuclear envelope identity from the endoplasmic reticulum during the cell cycle. *Nucleus*. 2024;15(1):2299632. doi: 10.1080/19491034.2023.2299632.
24. Wijayawardene NN, Hyde KD, Mikhailov KV, Goto BT, Santiago Alcma, Tokarev YS et al. Families of nonDikarya fungi. *Mycosphere*. 2025;16(1):4063–4445, <https://doi.org/10.5943/mycosphere/16/1/32>.
25. Schwarz DS, Blower MD. The endoplasmic reticulum: structure, function and response to cellular signaling. *Cell Mol Life Sci*. 2016;73(1):79–94. doi: 10.1007/s00018-015-2052-6.
26. Morató X, Fernández-Dueñas V, Pérez-Villamor P, Valle-León M, Vela JM, Merlos M et al. Development of a Novel $\sigma 1$ Receptor Biosensor Based on Its Heterodimerization with Binding Immunoglobulin Protein in Living Cells. *ACS Chem Neurosci*. 2023;14(11):2201–7. doi: 10.1021/acchemneuro.3c00206.
27. Motawe ZY, Abdelmaboud SS, Cuevas J, Breslin JW. PRE-084 as a tool to uncover potential therapeutic applications for selective sigma-1 receptor activation. *Int J Biochem Cell Biol*. 2020;126:105803. doi: 10.1016/j.biocel.2020.105803.
28. Griesmaier E, Posod A, Gross M, Neubauer V, Wegleiter K, Hermann M et al. Neuroprotective effects of the sigma-1 receptor ligand PRE-084 against excitotoxic perinatal brain injury in newborn mice. *Exp Neurol*. 2012 Oct;237(2):388–95. doi: 10.1016/j.expneurol.2012.06.030.
29. Shi M, Chen F, Chen Z, Yang W, Yue S, Zhang J et al. Sigma-1 Receptor: A Potential Therapeutic Target for Traumatic Brain Injury. *Front Cell Neurosci*. 2021;15:685201. doi: 10.3389/fn-cel.2021.685201.
30. Koshenov Z, Ofiaz FE, Hirtl M, Pilic J, Bachkoenig OA, Gottschalk B et al. Sigma-1 Receptor Promotes Mitochondrial Bioenergetics by Orchestrating ER Ca²⁺ Leak during Early ER Stress. *Metabolites*. 2021; 11(7):422. <https://doi.org/10.3390/metabol11070422>
31. Shi L, Wang M, Yu R, An Y, Wang X, Zhang Y et al. Sigma-1 receptor agonist PRE-084 increases BDNF by activating the ERK/CREB pathway to rescue learning and memory impairment caused by type II diabetes. *Behav Brain Res*. 2025;484:115493. doi: 10.1016/j.bbr.2025.115493.
32. Gershoni Emek N, Tan AM, Geva M, Fekete A, Abate C, Hayden MR. Pridopidine, a Potent and Selective Therapeutic Sigma-1 Receptor (S1R) Agonist for Treating Neurodegenerative Diseases. *Pharmaceuticals (Basel)*. 2025;18(12):1900. doi: 10.3390/ph18121900.
33. Macfarlane S, Grimmer T, Teo K, O'Brien TJ, Woodward M, Grunfeld J et al. Blarcamesine for the treatment of Early Alzheimer's Disease: Results from the ANAVEX2-73-AD-004 Phase IIB/III trial. *J Prev Alzheimers Dis*. 2025;12(1):100016. doi: 10.1016/j.tjpad.2024.100016.
34. Colosimo FA, Borsellino P, Krider RI, Marquez RE, Vida TA. The Clinical Potential of Dimethyltryptamine: Breakthroughs into the Other Side of Mental Illness, Neurodegeneration, and Consciousness. *Psychoactives*. 2024;3(1):93–122. <https://doi.org/10.3390/psychoactives3010007>.