МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
КАФЕДРА ФІЗИЧНОЇ РЕАБІЛІТАЦІЇ І ЗДОРОВ'Я

VIII науково-практична internet-конференція
з міжнародною участю

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VIIIth scientific and practical
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«MECHANISMS OF PATHOLOGICAL PROCESSES DEVELOPMENT AND DISEASES, THEIR PHARMACOLOGICAL CORRECTION»

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Механізми розвитку патологічних процесів і хвороб та їх фармакологічна корекція : матеріали VII науково-практичної internet-конференції з міжнародною участю, м. Харків, 20 жовтня 2025 р. Х. : НФаУ, 2025, 258 с.

Збірник містить матеріали VIII науково-практичної internet-конференції з міжнародною участю «Механізми розвитку патологічних процесів і хвороб та їх фармакологічна корекція». В матеріалах конференції розглянуто сучасні проблеми медицини і фармації: молекулярні основи патології, клітинні та гуморальні механізми розвитку захворювань; роль генетичних факторів у патогенезі захворювань; механізми розвитку патологічних процесів і хвороб; вікова патофізіологія; проблемні аспекти хвороб цивілізації; клінічна патофізіологія; питання викладання патофізіології; експериментальна терапія найбільш поширених захворювань; фармакологічна корекція патологічних процесів; проблеми та перспективи створення лікарських препаратів різної спрямованості дії; інформаційні технології і автоматизація наукових досліджень з розробки лікарських засобів; створення нутрицевтичних засобів та виробів медичного призначення; маркетингові дослідження сучасного фармацевтичного ринку; нанотехнології у фармації; таргетна терапія захворювань людини; трансляційна медицина; новітні технології діагностики та лікування; біомедичні технології; вплив сучасних технологій на здоров'я людини; актуальні питання фізичної реабілітації та сучасні технології збереження здоров'я людини; ментальне здоров'я та інновації у медико-психологічній реабілітації військовослужбовців в умовах воєнного стану; глобальні проблеми громадського здоров'я.

Для широкого кола наукових і практичних працівників медицини та фармації.

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Mechanisms of pathological processes development and diseases, their pharmacological correction: collected papers of to the VIIIth scientific and practical internet-conference for the international participation, Kharkiv, October 20, 2025. Kh.: NUPh, 2025, 258 p.

Collected papers includes the materials of VIIth scientific and practical internet-conference for the international participation «Mechanisms of pathological processes development and diseases, their pharmacological correction». The modern problems of pathophysiology were considered the materials of the Conference: molecular basis of pathology, cellular and humoral mechanisms of disease development; role of genetic factors in the pathogenesis of diseases; mechanisms of pathological processes and diseases development; age-related pathophysiology; problematic aspects of the diseases of civilization; clinical pathophysiology; issues of pathophysiology teaching; experimental therapy of the most common diseases; pharmacological correction of pathological processes; problems and prospects for the development of medicines with different orientation of action; information technology and automation of scientific research on drug create; development of nutraceutical drugs and products for medical purpose; marketing research of the modern pharmaceutical market; nanotechnology in pharmacy; targeted therapy of human diseases; translational medicine; the latest diagnostic and treatment technologies; biomedical technologies; impact of modern technologies on human health; current issues of physical rehabilitation and modern technologies for preserving human health; mental health and innovations in medical and psychological rehabilitation of military personnel under martial law; global public health issues.

For a wide audience of scientific and practitioners of medicine and pharmacy.

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STRUCTURAL AND FUNCTIONAL APPROACHES TO THE DESIGN OF MULTITARGET CHOLINESTERASE INHIBITORS

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Introduction. Disruption of cholinergic neurotransmission is one of the earliest and most significant pathological events in neurodegenerative disorders, particularly in Alzheimer's disease (AD). Progressive loss of cholinergic neurons in the basal forebrain and decreased levels of acetylcholine in cortical and hippocampal regions correlate strongly with cognitive decline and memory deficits. Acetylcholinesterase (AChE), the key enzyme responsible for terminating synaptic transmission through hydrolysis of acetylcholine, is therefore a central molecular target in the treatment of AD. Currently, AChE inhibitors (AChEIs) such as donepezil, rivastigmine, and galantamine represent the principal therapeutic agents for symptomatic management of mild to moderate AD. By increasing acetylcholine concentrations in synaptic clefts, these drugs temporarily restore cholinergic neurotransmission and improve cognitive performance. However, their effectiveness is limited to symptomatic relief and declines as neurodegeneration progresses, underscoring the urgent need for novel agents with broader and more sustained activity. Recent studies have revealed that AChE is involved not only in neurotransmitter hydrolysis but also in several pathogenic processes, including β-amyloid aggregation, oxidative stress, and apoptosis. This multifaceted role positions AChE as a multifunctional therapeutic target, suitable for the development of multitarget inhibitors capable of modulating several disease mechanisms simultaneously.

Aim. To analyze the crystallographic structures of AChE available in the Protein Data Bank (PDB) and to evaluate current strategies for the design of AChE inhibitors for the treatment of neurodegenerative disorders.

Materials and Methods. Data sources included the Protein Data Bank (PDB), the PubMed database maintained by the U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH), and the Discovery Studio software package.

Results. The search for novel AChE inhibitors is based on an in-depth understanding of molecular interactions between selective ligands and the enzyme, particularly donepezil, which binds simultaneously to the catalytic active site (CAS) and the peripheral anionic site (PAS) (PDB ID: 5NAU). This dual binding mechanism ensures enhanced efficacy and additional neuroprotective properties, forming the basis for the design of new multitarget compounds.

A promising direction involves the synthesis of coumarin derivatives, which combine AChE inhibition with antioxidant and anti-amyloid activities. For example, the coumarin-based inhibitor (±)-cis-1 (PDB ID: 6TT0) exhibits high nanomolar potency toward AChE, serving as a model multitarget agent of the new generation.

Chirality of AChE inhibitors plays a crucial role in determining binding affinity and safety profiles. Separation of racemates such as (±)-cis-1 into individual enantiomers can enhance selectivity, reduce toxicity, and optimize pharmacodynamic

properties. Thus, a stereoselective design strategy is essential for developing effective and safe multitarget AChEIs.

Beyond its classical role in acetylcholine hydrolysis, AChE is involved in pathological processes such as β-amyloid aggregation, oxidative stress, and apoptosis, supporting its consideration as a multifunctional therapeutic target in neurodegeneration. Combination therapy with AChE inhibitors and NMDA receptor antagonists (e.g., memantine) may produce synergistic effects and slow the progression of neurodegenerative disorders.

An additional promising direction in multitarget AD therapy is the structural modification of known AChE inhibitors incorporating a polyphenolic pharmacophore. According to the amyloid hypothesis, β-amyloid (Aβ) fibrillation is a major pathogenic event in AD; thus, combining anti-amyloid and anticholinesterase activities within one molecule represents a rational strategy for developing disease-modifying agents. Natural polyphenols such as (−)-epigallocatechin gallate (EGCG) and tannic acid effectively inhibit Aβ fibrillation but have limited clinical application due to poor blood–brain barrier (BBB) penetration, instability, and susceptibility to auto-oxidation. To overcome these limitations, a structural hybridization approach based on rivastigmine – a second-generation inhibitor that crosses the BBB and pseudo-irreversibly inhibits AChE – has been proposed. Modification of the aromatic ring of rivastigmine and its active metabolite NAP by introducing one or two hydroxyl groups yields compounds capable of simultaneously inhibiting AChE and preventing Aβ aggregation (PDB ID: 6EUE). This forms a multitarget "rivastigmine – NAP analogue" system, in which the carbamylated form provides anticholinesterase activity, while the released polyphenolic fragment exerts anti-amyloid effects. The carbamyl group also enhances metabolic stability and prevents auto-oxidation.

Incorporating stereoselectivity into the design of such derivatives further increases selectivity and safety, as different enantiomers display distinct affinities for CAS and PAS. Therefore, the combination of a polyphenolic pharmacophore with a chiral AChE inhibitor scaffold can lead to the development of novel dual-action neuroprotective drugs.

Conclusions. AChE remains the principal pharmacological target for the treatment of cognitive impairments in neurodegenerative diseases. A multitarget approach to AChE inhibitor design enables simultaneous modulation of several pathogenic mechanisms, including cholinergic dysfunction, β-amyloid aggregation, oxidative stress, and neuroinflammation. Dual binding of inhibitors at the CAS and PAS ensures enhanced efficacy, stability, and duration of action, as demonstrated for donepezil and its structural analogues. Chirality significantly affects the affinity, selectivity, and pharmacokinetic properties of inhibitors; therefore, stereoselective design enhances therapeutic potential and safety. The obtained results confirm the relevance of a structural–functional approach to the creation of next-generation multitarget AChE inhibitors capable of improving cognitive functions and modulating key mechanisms of neurodegeneration.

Keywords: acetylcholinesterase, acetylcholinesterase inhibitors, multitarget activity, Alzheimer's disease; neurodegeneration, chirality; stereoselectivity.