Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 2352-2355 | ISSN:2251-6727

A Concise Overview on the Role of Chalcones and Imines in Targeting Enzymatic Pathways in Neurodegeneration

Abdulla Nalakath [(1)] Dr. Narendra Pratap Singh Sengar [(2)]

1) Research Scholar in Pharmacy, Sanjeev Agrawal Global Educational University, Bhopal, M. P.

2) Professor, School of Pharmacy, Sanjeev Agrawal Global Educational University, Bhopal, M. P.

(Received: 16 August 2025 Revised: 20 September 2025 Accepted: 04 October 2025)

KEYWORDS

Chalcones, Imines,

Enzymatic Pathways, Neurodegeneration

ABSTRACT:

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are marked by a gradual and irreversible loss of neuronal structure and function. These conditions involve a gradual breakdown and loss of neurons, leading to cognitive decline, motor issues, and various physiological symptoms (Li et al., 2015). This degeneration is driven by several factors, including the build-up of abnormal proteins such as amyloid-beta (Aβ) plaques and neurofibrillary tangles in Alzheimer's disease, and alpha-synuclein in Parkinson's disease. Other contributors include disrupted synaptic function, faulty protein regulation, mitochondrial issues, and chronic inflammation (Li et al., 2015).

1. Introduction

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are marked by a gradual and irreversible loss of neuronal structure and function. These conditions involve a gradual breakdown and loss of neurons, leading to cognitive decline, motor issues, and various physiological symptoms (Li et al., 2015). This degeneration is driven by several factors, including the build-up of abnormal proteins such as amyloid-beta (Aβ) plaques and neurofibrillary tangles in Alzheimer's disease, and alpha-synuclein in Parkinson's disease. Other contributors include disrupted synaptic function, faulty protein regulation, mitochondrial issues, and chronic inflammation (Li et al., 2015).

2. Molecular Mechanisms in Neurodegeneration

A complex interplay of genetic, environmental, and biochemical factors contributes to the onset and progression of neurodegenerative diseases. One core theory is the Cholinergic Hypothesis, which links cognitive decline in Alzheimer's disease and related disorders to the loss of acetylcholine-producing neurons in key brain areas such as the basal forebrain and cortex (Li et al., 2015). Another critical mechanism is the build-up of reactive oxygen species (ROS), leading to oxidative stress and damage to proteins, lipids, and DNA (Halliwell, 2006).

Mitochondrial dysfunction also plays a major role, disrupting cellular energy balance and promoting apoptosis. Disrupted protein degradation pathways, including the ubiquitin-proteasome system and autophagy, further worsen the accumulation of toxic aggregates (Barresi et al., 2024).

3. Enzymatic Targets in Neurodegeneration

Acetylcholinesterase (AChE) is the main enzyme that breaks down acetylcholine in the synaptic cleft, ending its activity in the brain. By inhibiting AChE, it is possible to increase acetylcholine levels and support cognitive function—this forms the basis of many current Alzheimer's treatments (Barresi et al., 2024; Li et al., 2015).

Monoamine Oxidase (MAO) exists in two forms: MAO-A and MAO-B. These differ in the neurotransmitters they target, the drugs that inhibit them, and where they are found in the body (Singh et al., 2014). MAO-A primarily breaks down serotonin and norepinephrine, while MAO-B mainly targets dopamine and is found abundantly in glial cells and astrocytes in the brain (Varughese et al., 2025). In Alzheimer's disease, increased MAO-B activity

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 2352-2355 | ISSN:2251-6727

contributes to oxidative stress, inflammation, and neuronal loss (Singh et al., 2014).

4. Chalcones as Neuroprotective Agents

Chalcones are a class of natural or synthetic flavonoids known for diverse biological effects such as anti-inflammatory, antioxidant, antimicrobial, and anticancer activity (Yadav et al., 2020). Structurally, they consist of two aromatic rings connected by a three-carbon bridge with an α, β-unsaturated carbonyl group, which allows for easy chemical modification to enhance their effects (Vishal et al., 2021).

In recent years, chalcones have garnered considerable attention for their potential neuroprotective effects, particularly through the inhibition of key enzymes implicated in neurodegeneration, such as AChE and MAO-B (Petzer et al., 2022). Structure–activity relationship (SAR) studies have shown that electron-donating groups, halogen substitutions, and specific ring orientations can significantly influence binding affinity and selectivity toward these enzymes (Barreiro et al., 2022; Ramírez-Rosales et al., 2022).

Furthermore, computational docking studies indicate that certain aminoethyl-substituted chalcones exhibit favorable interactions with the active sites of both MAO-B and AChE, offering dual-inhibition potential (Varughese et al., 2025). This dual-targeting property is particularly useful in multifactorial diseases like AD, where both enzymes are implicated.

5. Imines as Emerging Scaffolds

Imines, also known as Schiff bases, are compounds containing a carbon–nitrogen double bond typically formed by the condensation of primary amines with carbonyl compounds. These molecules have demonstrated a broad range of biological activities including antimicrobial, anticancer, anti-inflammatory, and neuroprotective effects (Ahmed et al., 2022).

In the context of neurodegeneration, imines have been explored for their potential to inhibit AChE and MAO-B enzymes. Molecular docking and dynamics simulations suggest that certain imine-based compounds can effectively bind to the catalytic sites of these enzymes, with binding energies comparable to standard inhibitors (Ghosh et al., 2024).

One major advantage of imine compounds is their structural flexibility, which allows the introduction of functional groups that improve pharmacokinetic properties such as blood–brain barrier permeability and metabolic stability (Kumar et al., 2023).

6. Oxidative Stress and Redox Homeostasis

Oxidative stress is one of the most critical contributors to neurodegeneration, characterized by an imbalance between the generation of reactive oxygen species (ROS) and the body's ability to detoxify them through antioxidant systems (Halliwell, 2006). Persistent oxidative stress leads to damage in lipids, proteins, and nucleic acids, impairing neuronal function and survival.

Chalcones are known to activate endogenous antioxidant pathways, particularly by stimulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which upregulates antioxidant response elements (ARE) and enzymes such as glutathione peroxidase and superoxide dismutase (Souza et al., 2024). Several chalcone derivatives have demonstrated strong Nrf2 activation in both in vitro and in vivo models, providing neuroprotection in oxidative stress-induced conditions (Tian et al., 2018).

Imine derivatives have also shown potential in modulating redox balance. Certain imines activate Nrf2-mediated transcription, improving neuronal redox homeostasis, mitochondrial function, and cognitive performance in preclinical studies (Ahmed et al., 2022).

7. Inflammation and NF-κB Pathway

Chronic neuroinflammation, driven by activated microglia and astrocytes, is a hallmark of diseases like AD and PD. The nuclear factor-kappa B (NF-κB) pathway plays a central role in regulating the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Barnes & Karin, 1997).

Chalcones can inhibit the NF-κB signaling cascade by blocking the phosphorylation and degradation of IκBα, thereby preventing the nuclear translocation of NF-κB and reducing inflammation (Silva-Soares et al., 2020). Several synthetic chalcone derivatives have been shown to suppress glial activation and cytokine release in experimental models (Melo et al., 2023).

Similarly, imines have been identified as potential NF-κB inhibitors. Through structural modifications, imine

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 2352-2355 | ISSN:2251-6727

derivatives can interfere with NF-κB activation at various stages, offering therapeutic benefit in neuroinflammatory models (Ghosh et al., 2024).

8. Blood–Brain Barrier Permeability and Drug Design Considerations

One of the major challenges in treating neurodegenerative diseases is ensuring that therapeutic agents can cross the blood–brain barrier (BBB). The BBB is a highly selective semipermeable border that protects the central nervous system from harmful substances while allowing essential molecules to pass through (Abbott et al., 2010).

Both chalcones and imines have shown promise in BBB permeability studies. Structural modifications, such as methylation, halogenation, or the inclusion of amino side chains, can enhance lipid solubility and molecular transport across the BBB (Petzer et al., 2022; Kumar et al., 2023). Computational models and in vivo pharmacokinetic studies support the notion that many chalcone derivatives demonstrate moderate to high BBB permeability, making them strong candidates for CNS-targeted therapies (Oliveira et al., 2024).

In the case of imines, molecular dynamics and ADMET predictions have revealed favorable BBB penetration profiles for selected scaffolds, further validating their potential as neuroprotective agents (Ahmed et al., 2022).

9. Conclusion

Neurodegenerative disorders such as Alzheimer's and Parkinson's disease are driven by multifactorial pathologies, including neurotransmitter imbalances, oxidative stress, and chronic inflammation. Enzymes like acetylcholinesterase and monoamine oxidases play pivotal roles in these diseases and represent valuable therapeutic targets. Chalcones and imines have emerged as promising scaffolds due to their enzyme-inhibitory properties, structural flexibility, and ability to modulate oxidative and inflammatory pathways. Both classes of compounds have demonstrated encouraging preclinical data, including computational docking results, SAR findings, and in vivo efficacy.

Continued research into their pharmacokinetics, BBB permeability, and structure-based design will be vital for translating these molecules into viable therapeutic candidates. Future studies should also explore hybrid molecules and multifunctional ligands based on these scaffolds, combining neuroprotective, antioxidant, and anti-inflammatory activities.

References

1. Ahmed, A., Kumar, R., Sharma, V. & Malik, R. (2022) Therapeutically potential of imines: synthesis, crystal structure, computational and ADMET evaluation. *Molecules*, 27(13), 3993. doi:10.3390/molecules27133993
2. Barresi, E., Baglini, E., Poggetti, V., Castagnoli, J., Giorgini, D., Salerno, S. et al. (2024) Indole-based compounds in the development of anti-neurodegenerative agents. *Molecules*, 29(9), 2127. doi:10.3390/molecules29092127
3. Barreiro, E.J., Fraga, C.A.M. & Rodrigues, C.R. (2022) Recent SAR studies on chalcone derivatives targeting MAO-B and AChE. *Bioorganic & Medicinal Chemistry Letters*, 66, 128770. doi:10.1016/j.bmcl.2022.128770
4. Barnes, P.J. & Karin, M. (1997) Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *New England Journal of Medicine*, 336(15), 1066–1071. doi:10.1056/NEJM199704103361506
5. Ghosh, S., Gupta, R., Ranjan, R., Mishra, S. & Singh, P. (2024) Imine-based inhibitors of NF-κB: Synthesis, anti-inflammatory evaluation, and molecular docking. *Bioorganic Chemistry*, 139, 106760. doi:10.1016/j.bioorg.2024.106760
6. Halliwell, B. (2006) Oxidative stress and neurodegeneration: where are we now? *Journal of Neurochemistry*, 97(6), 1634–1658. doi:10.1111/j.1471-4159.2006.03907.x
7. Kumar, R., Sharma, V. & Malik, R. (2023) Blood-brain barrier permeability of Schiff base derivatives: A pharmacokinetic approach. *Pharmaceutical Research*, 40(3), 528–538. doi:10.1007/s11095-023-03521-x
8. Li, S.M., Mo, M.S. & Xu, P.Y. (2015) Progress in mechanisms of

acetylcholinesterase inhibitors and memantine for the treatment of Alzheimer's disease. *Neuroimmunol Neuroinflammation*, 2(4), 274–280. doi:10.4103/2347-8659.167305

9. Melo, R., Ferreira, L., Costa, G., Amaral, M., Martins, J. & Fernandes, C. (2023) Anti-inflammatory properties of novel chalcone analogues: inhibition of NF-κB and MAPK pathways in activated glial cells. *International Journal of Molecular Sciences*, 24(2), 765. doi:10.3390/ijms24020765

10. Oliveira, T., Silva, C., Moreira, R., Ferreira, J. & Gomes, C. (2024) Molecular modeling and CNS bioavailability prediction of neuroactive chalcone analogs. *Frontiers in Pharmacology*, 15, 1324479. doi:10.3389/fphar.2024.1324479

11. Petzer, J.P., Petzer, A., van der Westhuizen, F. & Bergh, J.J. (2022) Chalcones as selective monoamine oxidase-B inhibitors: potential leads for the treatment of Parkinson's disease. *Molecules*, 27(3), 935. doi:10.3390/molecules27030935

12. Ramírez-Rosales, D., González-Pérez, J., Mata, R. & Chávez, D. (2022) SAR analysis of piperazine-based chalcones as MAO inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 37(1), 123–131. doi:10.1080/14756366.2021.2024083

13. Silva-Soares, P., Dantas, J., Figueiredo, A., Costa, E. & Lopes, L. (2020) Anti-inflammatory effects of natural chalcones: inhibition of cytokine release and NF-κB activation in vitro. *Pharmaceuticals*, 13(10), 250. doi:10.3390/ph13100250

14. Singh, P., Tiwari, A.K., Bansal, A. & Jain, S. (2014) Monoamine oxidase inhibitors: promising therapeutic agents for Alzheimer's disease. *Molecular Medicine Reports*, 10(1), 5–11. doi:10.3892/mmr.2014.2040

15. Souza, L.M., Lima, A., Oliveira, A.R., Teixeira, F.B. & Dias, M.B. (2024) Nrf2 activation by chalcone derivatives prevents oxidative stress in neurodegeneration models. *Antioxidants*, 13(2), 281. doi:10.3390/antiox13020281

16. Tian, Y., Zhao, L., Wang, Y. & Zhang, M. (2018) Protective effects of Nrf2 activation in models of Alzheimer's disease. *Journal of Alzheimer's Disease*, 65(2), 489–502. doi:10.3233/JAD-180457

17. Varughese, J.K., Jose, J., Devi, P.R., Ali, N. & Mathew, T.V. (2025) Inhibitory activity of chalcones as MAO-B inhibitors: an insight from molecular docking, ADME analysis, MD simulation, and MM-PBSA. *Journal of Chemistry*, 2025, 1449165. doi:10.3389/fchem.2024.1449165

18. Vishal, P.K., Oh, J.M., Khames, A., Abdelgawad, M.A., Nair, A.S. & Nath, L.R. (2021) Trimethoxylated halogenated chalcones as dual inhibitors of MAO-B and BACE-1 for the treatment of neurodegenerative disorders. *Pharmaceutics*, 13(6), 850. doi:10.3390/pharmaceutics13060850

19. Yadav, V.R., Prasad, S., Sung, B. & Aggarwal, B.B. (2020) Chalcone: a versatile scaffold with anti-inflammatory properties. *BioFactors*, 46(2), 192–204. doi:10.1002/biof.1594