RESEARCH PAPER

Donepezil–Coumarin Hybrid Heterocyclic Scaffolds as Multi-Target Directed Ligands for Neurodegenerative Disorders: Design Strategies, Synthesis, Structure–Activity Relationships and Therapeutic Perspectives—A Review

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ABSTRACT

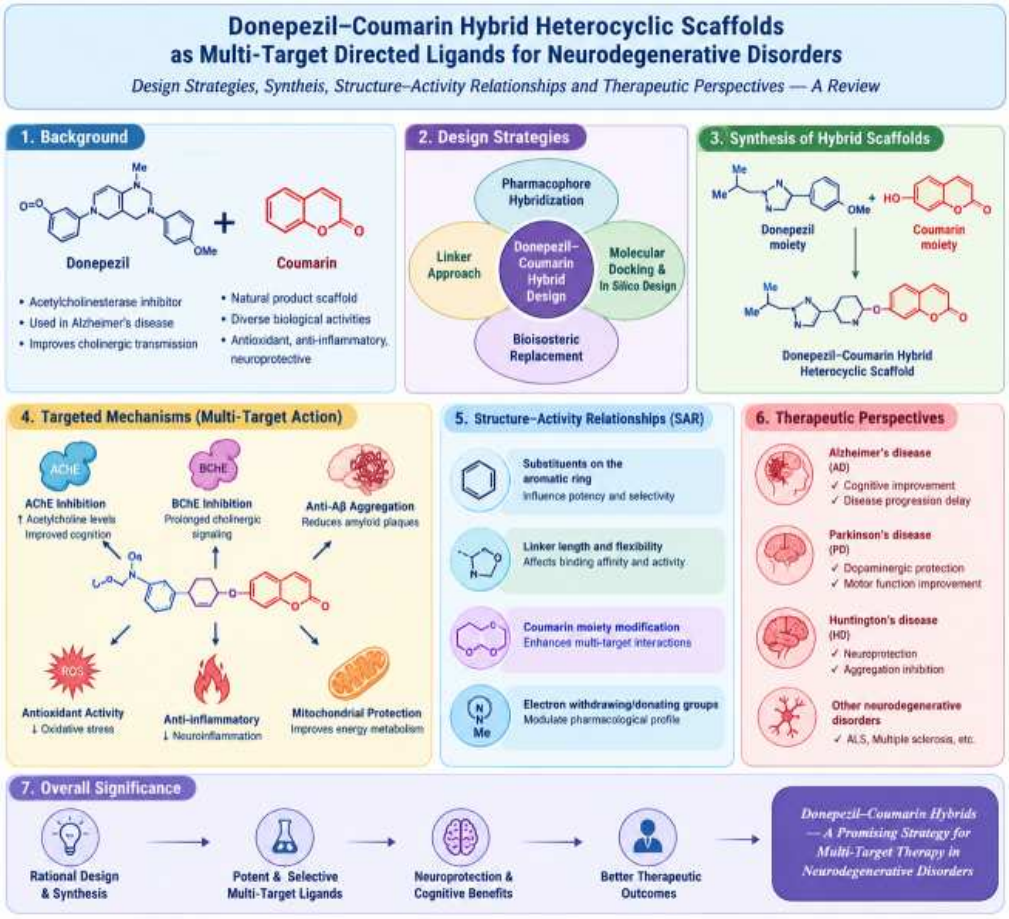
Neurodegenerative disorders, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), represent major therapeutic challenges because of their complex and interconnected pathological mechanisms. Cholinergic dysfunction, amyloid-β (Aβ) aggregation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, metal dyshomeostasis and monoamine oxidase-B (MAO-B) activity collectively contribute to neuronal degeneration. Conventional single-target drugs such as donepezil provide symptomatic improvement primarily through acetylcholinesterase (AChE) inhibition but do not adequately address the multiple pathological pathways involved in disease progression. The multi-target-directed ligand (MTDL) strategy has consequently emerged as an attractive medicinal-chemistry approach in which a single molecule is rationally designed to modulate two or more disease-relevant targets. Donepezil is an especially valuable pharmacophore because its N-benzylpiperidine moiety provides strong cholinesterase recognition, whereas coumarin represents a privileged heterocyclic scaffold with reported cholinesterase, MAO-B, antioxidant, anti-amyloid and metal-chelating properties. The combination of these pharmacophores therefore offers a rational basis for multifunctional neuroprotective agents. The first dedicated series of donepezil–coumarin hybrids demonstrated simultaneous inhibition of AChE, butyrylcholinesterase (BuChE) and MAO-B, with selected compounds exhibiting blood–brain barrier permeability and low neurotoxicity. Subsequent studies involving coumarin–benzotriazole, coumarin–dithiocarbamate, coumarin–triazole, coumarin–quinoline and other heterocyclic hybrids have further established the potential of coumarin-based MTDLs. Recent advances have expanded the therapeutic profile toward BACE-1, glycogen synthase kinase-3β (GSK-3β), Aβ aggregation, tau pathology, oxidative stress and neuroinflammation. This review critically discusses the pharmacological rationale, hybridization strategies, synthetic approaches, structure–activity relationships, molecular mechanisms, computational approaches, biological evaluation and translational limitations of donepezil–coumarin and related heterocyclic MTDLs. Particular emphasis is placed on linker engineering, substitution at the 3-, 4-, 5- and 7-positions of coumarin, dual-site AChE binding, CNS drug-likeness and optimization of multifunctionality without compromising pharmacokinetic properties. The review identifies important design opportunities for next-generation donepezil–coumarin hybrids with improved target coverage, selectivity, brain exposure, metabolic stability and in vivo efficacy.

Keywords: Alzheimer's disease; acetylcholinesterase; coumarin; donepezil; heterocyclic hybrids; multi-target-directed ligands; monoamine oxidase-B; neurodegeneration; structure–activity relationship.

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GRAPHICAL ABSTRACT



1. INTRODUCTION

Neurodegenerative disorders are characterized by progressive neuronal dysfunction and neuronal loss and include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease and related dementias. Among these conditions, AD is the most common cause of dementia and is associated with progressive deterioration of memory, cognition and functional capacity. Its pathogenesis is multifactorial and involves abnormalities in cholinergic neurotransmission, amyloid-β (Aβ) metabolism, tau phosphorylation, oxidative stress, mitochondrial function, neuroinflammation, synaptic dysfunction and metal homeostasis.[1–4]

The complexity of AD has challenged the traditional "one drug–one target" approach. Acetylcholinesterase inhibitors such as donepezil, rivastigmine and galantamine mainly improve cholinergic neurotransmission, while memantine modulates pathological glutamatergic signalling. These agents can provide symptomatic benefit but do not comprehensively modulate the interconnected molecular events responsible for neuronal degeneration.[1,5] Consequently, multi-target-directed ligands (MTDLs), capable of simultaneously interacting with multiple disease-relevant targets, have emerged as an important strategy for anti-neurodegenerative drug discovery.[6–8]

Donepezil is a clinically established AChE inhibitor and possesses a characteristic N-benzylpiperidine pharmacophore responsible for interaction with the active-site region of AChE. Its established clinical use, CNS penetration and well-characterized pharmacological profile make it an attractive molecular

template for hybrid-drug design.[9],[10] However, donepezil alone has limited activity against several pathological mechanisms, including Aβ aggregation, MAO-B-mediated oxidative stress and metal-associated neurotoxicity.

Coumarin, consisting of a benzopyrone core, is a privileged medicinal-chemistry scaffold with broad biological activities. Coumarin derivatives have demonstrated AChE and BuChE inhibition, MAO-B inhibition, antioxidant activity, inhibition of Aβ aggregation, metal chelation and neuroprotective effects.[11]–[14] These properties make coumarin particularly suitable for incorporation into MTDLs.

The rational fusion of the N-benzylpiperidine pharmacophore of donepezil with coumarin was first systematically investigated by Xie et al., who reported a series of donepezil–coumarin hybrids with dual cholinesterase/MAO-B inhibition.[15] This study provided a foundation for subsequent development of coumarin-based MTDLs incorporating triazole, benzotriazole, dithiocarbamate, quinoline, chalcone, benzofuran and other heterocyclic pharmacophores.[16]–[23]

The present review therefore focuses on the evolution of donepezil–coumarin and structurally related heterocyclic MTDLs, emphasizing molecular design, synthetic strategies, SAR, biological activities, computational approaches and future opportunities for neurodegenerative drug development.

2. MULTIFACTORIAL PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

2.1 Cholinergic dysfunction

A major biochemical abnormality in AD is degeneration of cholinergic neurons and reduction of acetylcholine-mediated neurotransmission. AChE rapidly hydrolyses acetylcholine within the synaptic cleft, and inhibition of AChE increases synaptic acetylcholine concentration. AChE therefore remains an important validated symptomatic target.[5],[6]

The AChE structure contains a deep catalytic gorge with a catalytic active site (CAS) and peripheral anionic site (PAS). Molecules capable of simultaneously interacting with both regions may inhibit catalytic activity and potentially interfere with AChE-associated facilitation of Aβ aggregation. This dual-site concept is particularly relevant to hybrid molecules containing spatially separated pharmacophores.

2.2 Amyloid-β aggregation

Aberrant production, oligomerization and deposition of Aβ peptides represent important components of AD pathology. Soluble Aβ oligomers are particularly associated with synaptic dysfunction and neuronal toxicity. Therefore, inhibition of Aβ self-aggregation or AChE-induced Aβ aggregation is an important objective in MTDL design.[6],[24]

2.3 Tau hyperphosphorylation

Hyperphosphorylated tau contributes to formation of neurofibrillary tangles and destabilization of neuronal microtubules. GSK-3β is one of the kinases implicated in tau phosphorylation and has therefore attracted attention as an additional MTDL target. Recent coumarin derivatives have been designed to simultaneously modulate AChE, BACE-1 and GSK-3β.[25]

2.4 Oxidative stress and mitochondrial dysfunction

The brain is particularly susceptible to oxidative damage because of its high oxygen requirement and abundance of polyunsaturated fatty acids. Excess reactive oxygen species (ROS) contribute to lipid peroxidation, protein oxidation, mitochondrial dysfunction and neuronal apoptosis. MAO-B is relevant because oxidative deamination generates hydrogen peroxide and can contribute to oxidative stress. Coumarin derivatives possessing MAO-B inhibitory and antioxidant properties can therefore complement the cholinesterase activity of donepezil.[12],[13]

2.5 Neuroinflammation

Activated microglia and astrocytes contribute to chronic neuroinflammation through production of cytokines and inflammatory mediators. Persistent neuroinflammation can exacerbate oxidative stress, synaptic damage and neuronal death. Thus, future MTDLs should ideally combine cholinesterase inhibition with antioxidant and anti-inflammatory neuroprotection.

2.6 Metal dyshomeostasis

Abnormal regulation of copper, iron and zinc may promote oxidative stress and influence Aβ aggregation.

Coumarin derivatives have attracted interest as potential metal-chelating pharmacophores.[26] Incorporating appropriately positioned oxygen- or nitrogen-containing donor groups may therefore expand the target profile of donepezil–coumarin hybrids.

3. MULTI-TARGET-DIRECTED LIGAND STRATEGY

The MTDL concept involves incorporating multiple pharmacophores into a single molecular entity capable of interacting with several pathological targets. Compared with combination therapy, a single MTDL can potentially provide coordinated target engagement while reducing pharmacokinetic variability associated with administering multiple drugs.[6–8]

MTDLs can be broadly designed using three approaches:

1. **Pharmacophore fusion:** two pharmacophores are directly integrated into one molecular framework.
2. **Pharmacophore linking:** two pharmacophores are connected through an optimized linker.
3. **Pharmacophore merging:** essential structural features of two ligands are condensed into a new scaffold.

Donepezil–coumarin hybrids predominantly follow pharmacophore fusion/linking principles. The N-benzylpiperidine region contributes cholinesterase recognition, whereas the coumarin domain contributes additional enzyme inhibition and antioxidant/anti-aggregation properties.

4. MEDICINAL-CHEMISTRY RATIONALE FOR DONEPEZIL–COUMARIN HYBRIDS

4.1 Donepezil as the cholinesterase pharmacophore

Donepezil contains an indanone and N-benzylpiperidine arrangement. Its pharmacophoric architecture permits strong interaction within the AChE gorge. Modification of the donepezil framework has consequently been explored extensively to obtain multifunctional ligands.[9,27]

The N-benzylpiperidine component is particularly useful for hybridization because it can retain cholinesterase-binding characteristics while allowing attachment to a second pharmacophore.

4.2 Coumarin as a multifunctional pharmacophore

Coumarin provides a rigid aromatic lactone system capable of π–π stacking and hydrogen-bonding interactions. Substitution at positions 3, 4, 5, 6, 7 and 8 allows extensive structural optimization. Several studies indicate that 7-hydroxy, 7-alkoxy and 4-substituted coumarins can exhibit significant enzyme inhibition and neuroprotective effects.[11,14,28]

4.3 Complementarity of donepezil and coumarin

The combination provides a logical pharmacophore complement:

Donepezil component → AChE/BuChE recognition

Coumarin component → MAO-B/anti-Aβ/antioxidant/metal-binding potential

Linker → controls distance, flexibility, molecular weight, lipophilicity and BBB permeability

This design can generate molecules capable of simultaneous interaction with multiple pathological targets.

5. DEVELOPMENT OF DONEPEZIL–COUMARIN HYBRIDS

The seminal study by Xie et al. reported novel donepezil–coumarin hybrids designed by combining the N-benzylpiperidine moiety of donepezil with coumarin.[15] Most compounds demonstrated AChE and BuChE inhibition together with selective MAO-B inhibition.

Compound **5m** was particularly important, showing IC_{50} values of 0.87 μM and 0.93 μM against eeAChE and eqBuChE, respectively. Against human enzymes, it demonstrated IC_{50} values of 1.37 μM for hAChE, 1.98 μM for hBuChE and 2.62 μM for hMAO-B. Kinetic studies indicated mixed-type AChE inhibition, while molecular modelling suggested simultaneous interaction with the CAS, PAS and mid-gorge regions. The compound also showed BBB permeability and no significant toxicity in SH-SY5Y cells.[15]

These findings established an important design principle: **maintaining the cholinesterase-binding contribution of the donepezil pharmacophore while introducing a second aromatic heterocycle capable of MAO-B and other target interactions.**

6. NATURAL-COUMARIN-DONEPEZIL HYBRID DEVELOPMENT

A later investigation involving natural coumarins isolated from *Nardostachys jatamansi* generated an additional coumarin–donepezil hybrid. The hybrid showed dual inhibition of AChE and BuChE with IC_{50} values of 1.22 and 3.09 μM, respectively. Molecular modelling and enzyme kinetics suggested non-competitive inhibition of AChE. Importantly, the compound crossed the BBB and inhibited Aβ self-aggregation.[29]

This study is significant because it expanded the original donepezil–coumarin concept from dual ChE/MAO-B inhibition toward **dual cholinesterase inhibition plus anti-amyloid activity**.

7. RELATED COUMARIN–HETEROCYCLE HYBRIDS

7.1 Coumarin–dithiocarbamate hybrids

Dithiocarbamate-containing coumarin hybrids have been investigated as AChE/MAO-B MTDLs. He et al. reported compounds with strong dual activity; compound 8g showed balanced hAChE and hMAO-B inhibition, BBB penetration and neuroprotective activity. It also improved cognitive dysfunction in a scopolamine-induced mouse model.[30]

The dithiocarbamate group may provide additional hydrogen-bonding and metal-interaction capacity, illustrating how heterocyclic/functional-group incorporation can expand the pharmacological profile of coumarin.

7.2 Coumarin–benzotriazole hybrids

Coumarin–benzotriazole hybrids designed around the donepezil skeleton represent another important development. Compound 13b showed potent AChE inhibition with an IC_{50} of 0.059 μM and exhibited mixed-type inhibition. SAR analysis suggested that a three-carbon linker between coumarin and triazole was favorable.[31]

This observation demonstrates the importance of **linker length and conformational geometry** in dual-site AChE binding.

7.3 Coumarin–benzofuran hybrids

Coumarin–benzofuran hybrids were developed as donepezil-mimetic multifunctional compounds. These molecules were investigated for AChE inhibition, antioxidant activity and Aβ aggregation inhibition, supporting the use of fused/linked aromatic heterocycles for multifunctional anti-AD drug design.[32]

7.4 Coumarin–triazole hybrids

The 1,2,3-triazole ring is attractive because it can be introduced through copper-catalysed azide–alkyne cycloaddition (“click chemistry”). Triazoles provide hydrogen-bonding capacity and structural rigidity and can function as pharmacophore connectors. Recent coumarin-based hybrids have demonstrated strong AChE inhibition and Aβ aggregation inhibition.[33],[34]

7.5 Coumarin–quinoline hybrids

Quinoline is another privileged heterocycle with established relevance to Aβ, cholinesterases and BACE-1. Recent coumarin–quinoline hybrids demonstrated multifunctional anti-AD activity, including inhibition of Aβ-related processes, ChE and BACE-1. A lead compound showed BBB permeability and improved cognitive performance in APP/PS1 transgenic mice, accompanied by attenuation of oxidative stress, inflammation and Aβ deposition.[35]

8. STRUCTURE–ACTIVITY RELATIONSHIP OF DONEPEZIL–COUMARIN MTDLs

8.1 Importance of the coumarin substitution pattern

The 7-position is particularly useful for introducing aromatic, alkoxy or amino-containing substituents. 7-hydroxy/7-alkoxy groups can improve hydrogen bonding and modulate lipophilicity. Recent reviews indicate that substitution at positions 3, 4 and 7 can substantially influence AChE, MAO-B and neuroprotective activity.[28]

8.2 Linker optimization

The linker is one of the most important determinants of MTDL performance. Excessively short linkers may prevent simultaneous interaction with spatially separated binding regions, whereas excessively long flexible chains can increase entropy, molecular weight and metabolic susceptibility.

Available SAR data indicate that intermediate alkyl linkers can favor dual-site AChE binding. In particular,

a three-carbon linker has been reported as favorable in coumarin–benzotriazole hybrids.[31]

8.3 Aromatic substitution

Electron-donating groups such as methoxy and hydroxy can enhance hydrogen-bonding interactions but may also alter metabolic stability. Halogen substitution can increase lipophilicity and potentially improve hydrophobic interactions, although excessive lipophilicity can negatively affect pharmacokinetics.

8.4 Heterocyclic incorporation

Triazole, benzotriazole, quinoline, thiazole, dithiocarbamate and benzofuran groups provide additional vectors for hydrogen bonding, π-stacking and hydrophobic interactions. Their incorporation may increase target coverage but should be balanced against molecular size and CNS drug-likeness.

8.5 Dual-site AChE interaction

The most attractive MTDL architecture is one that allows one pharmacophore to occupy the CAS while the second extends toward the PAS. Such dual-site interaction may produce potent inhibition and potentially interfere with AChE-associated Aβ aggregation.

9. SYNTHETIC STRATEGIES

The synthesis of donepezil–coumarin hybrids can generally be organized into three stages:

Stage I: Preparation of substituted coumarin intermediates

Substituted coumarins can be prepared using established condensation reactions such as Pechmann condensation or related approaches, followed by selective O-alkylation, C-alkylation or functionalization.

Stage II: Installation of a linker

Hydroxy- or amino-functionalized coumarins can be reacted with α,ω-dibromoalkanes or related bifunctional linkers. This provides a terminal bromide/amine/azide/alkyne suitable for attachment to the donepezil pharmacophore.

Stage III: Pharmacophore coupling

The functionalized coumarin can subsequently be coupled with N-benzylpiperidine derivatives through nucleophilic substitution, amide formation, reductive amination or click chemistry.

The synthesis of the original donepezil–coumarin series employed functionalized coumarin intermediates followed by reaction with dibromoalkanes and coupling with the donepezil-derived N-benzylpiperidine fragment.[15]

For triazole-containing systems, azide–alkyne cycloaddition offers a particularly versatile strategy because it enables rapid generation of analogue libraries.

10. BIOLOGICAL EVALUATION STRATEGY

A systematic biological evaluation of novel donepezil–coumarin MTDLs should include the following stages.

10.1 Cholinesterase inhibition

- hAChE
- hBuChE
- IC_{50} determination
- Selectivity index
- Reversibility studies
- Kinetic characterization

10.2 MAO inhibition

- hMAO-A
- hMAO-B
- Selectivity ratio
- Reversible/irreversible inhibition
- Competitive/non-competitive kinetics

10.3 Aβ-related assays

- $A\beta_{1–42}$ self-aggregation
- AChE-induced Aβ aggregation
- Thioflavin-T fluorescence assay
- Transmission electron microscopy where appropriate

10.4 BACE-1 and GSK-3β

For next-generation MTDLs, BACE-1 and GSK-3β assays should be incorporated because simultaneous targeting of amyloidogenic processing and tau

phosphorylation can increase disease-relevant target coverage.

10.5 Antioxidant activity

DPPH, ABTS, ROS measurement and cellular oxidative-stress assays can provide initial evidence of antioxidant activity. However, chemical radical-scavenging assays should not be interpreted as direct evidence of CNS neuroprotection.

10.6 Neuroprotection

SH-SY5Y cells and other neuronal models may be used for evaluating protection against H_2O_2-, Aβ-, rotenone- or other stress-induced cytotoxicity.

10.7 BBB permeability

BBB penetration should be assessed using physicochemical prediction followed by appropriate experimental models. CNS drug-likeness should be considered early rather than after extensive synthesis.

10.8 In vivo efficacy

Promising compounds should progress to:

- scopolamine-induced cognitive impairment;
- Morris water maze;
- Y-maze;
- novel object recognition;
- biochemical oxidative-stress markers;
- AChE activity in brain tissue;
- Aβ/tau analysis where relevant;
- neuroinflammatory markers.

11. ROLE OF MOLECULAR DOCKING AND COMPUTATIONAL DESIGN

Computational methods have become integral to modern MTDL development. Molecular docking can identify interactions within the AChE CAS, PAS and gorge, whereas docking to MAO-B, BACE-1 or GSK-3β can rationalize multifunctional activity.

Molecular dynamics simulations can provide information regarding stability of ligand–protein complexes beyond static docking poses. QSAR models and machine-learning methods can further identify structural descriptors associated with activity.[17],[36]

For future donepezil–coumarin research, a **multi-target computational workflow** should ideally involve:

1. ligand-library generation;
2. physicochemical and CNS drug-likeness filtering;
3. AChE docking;
4. BuChE docking;
5. MAO-B docking;
6. BACE-1/GSK-3β docking;
7. Aβ interaction modelling;
8. molecular dynamics simulations;
9. ADMET prediction;
10. experimental validation.

Importantly, docking scores alone should not be interpreted as proof of biological activity.

12. RECENT DEVELOPMENTS AND EMERGING DESIGN DIRECTIONS

The field has moved beyond simple ChE inhibition. Recent coumarin studies have explored multifunctionality involving AChE, BuChE, BACE-1, GSK-3β, Aβ aggregation, MAO-B, oxidative stress and metal dyshomeostasis.[25],[26],[35],[37]

A 2026 review of coumarin-based MTDLs emphasized AChE/BuChE inhibition, Aβ aggregation, BACE-1 inhibition, MAO-B modulation, antioxidant activity and metal chelation, while highlighting linker length, substitution pattern and BBB permeability as important determinants of activity.[37]

Similarly, a recent 2026 review of donepezil-based hybrids concluded that modification of the indanone or benzylpiperidine regions can produce multifunctional ligands with cholinesterase inhibition, anti-amyloid activity, antioxidant effects, metal chelation and MAO inhibition. Importantly, despite encouraging preclinical results, donepezil-based hybrid molecules have not yet established clinical efficacy as disease-modifying agents.[38]

These findings indicate that the next generation of donepezil–coumarin hybrids should not merely maximize AChE potency. Instead, **balanced polypharmacology** should be the primary objective.

13. PROPOSED DESIGN BLUEPRINT FOR NEXT-GENERATION DONEPEZIL–COUMARIN HYBRIDS

Based on the available literature, a rational design strategy can be proposed:

Donepezil N-benzylpiperidine pharmacophore
↓
Optimized C3/C4/C7-substituted coumarin pharmacophore
↓
3–5 atom flexible/semirigid linker
↓
Optional triazole/benzotriazole/quinoline heterocycle
↓
AChE + BuChE + MAO-B + Aβ + antioxidant/metal-chelating activity

The ideal molecule should possess:

- hAChE IC_{50} preferably in submicromolar range;
- balanced hBuChE activity;
- selective MAO-B inhibition;
- Aβ aggregation inhibition;
- antioxidant/neuroprotective activity;
- adequate aqueous solubility;
- acceptable cLogP;
- moderate molecular weight;
- limited polar surface area;
- BBB permeability;
- metabolic stability;
- low hepatotoxicity;
- low neuronal cytotoxicity.

Rather than combining every possible target into one molecule, target selection should be driven by **mechanistic complementarity and quantitative target engagement**.

14. LIMITATIONS AND TRANSLATIONAL CHALLENGES

Despite promising results, several challenges remain.

First, many MTDLs demonstrate strong enzyme inhibition but lack sufficient validation in disease-relevant animal models. Second, excellent docking scores do not necessarily translate into pharmacological activity. Third, increasing the number of pharmacophores can increase molecular weight, lipophilicity and metabolic liability, potentially compromising BBB penetration.

Another major challenge is achieving balanced activity. Excessively potent AChE inhibition can produce cholinergic adverse effects, whereas broad MAO inhibition may produce undesirable pharmacology. Therefore, **selectivity and target balance are as important as potency**.

Furthermore, many studies use scopolamine-induced cognitive impairment, which is useful for preliminary pharmacological screening but does not reproduce the complete pathology of AD. Greater emphasis should therefore be placed on transgenic models, chronic treatment, pharmacokinetic/pharmacodynamic relationships and direct target engagement.

Finally, current evidence supports donepezil–coumarin hybrids as **preclinical lead compounds rather than established disease-modifying therapeutics**.

15. FUTURE PERSPECTIVES

Future research should focus on five major directions.

15.1 Rational multi-target optimization

Target combinations should be selected based on disease biology rather than simply combining pharmacophores with known activity.

15.2 CNS-oriented medicinal chemistry

BBB penetration, free-brain concentration and CNS exposure should be incorporated into early lead optimization.

15.3 Advanced computational methods

Machine learning, molecular dynamics, free-energy calculations and multi-target QSAR may accelerate identification of balanced MTDLs.

15.4 Disease-relevant biological models

APP/PS1 and tauopathy models should complement conventional scopolamine models. Biomarkers of Aβ, tau, oxidative stress and neuroinflammation should be measured simultaneously.

15.5 Combination with targeted delivery

If systemic pharmacokinetic limitations remain, selected donepezil–coumarin hybrids could potentially be explored using CNS-directed nanocarriers or other

drug-delivery approaches. However, delivery systems should be investigated only after establishment of a sufficiently strong pharmacological lead.

16. CONCLUSION

Donepezil–coumarin hybridization represents a rational and promising medicinal-chemistry strategy for developing multifunctional agents against neurodegenerative disorders. Donepezil contributes a clinically validated cholinesterase-binding pharmacophore, whereas coumarin provides a versatile scaffold capable of supporting cholinesterase, MAO-B, antioxidant, anti-amyloid and metal-related activities. The seminal donepezil–coumarin series established the feasibility of simultaneous ChE and MAO-B inhibition, while subsequent coumarin–heterocycle hybrids have expanded the concept toward Aβ aggregation, BACE-1, GSK-3β, oxidative stress and neuroinflammation.

Current SAR evidence indicates that coumarin substitution pattern, linker length, heterocyclic incorporation and physicochemical properties strongly influence multifunctionality and CNS accessibility. The major challenge is therefore not simply to develop highly potent inhibitors but to obtain **balanced, brain-penetrant, metabolically stable and safe MTDLs with experimentally validated target engagement**.

The future of donepezil–coumarin research lies in integrating medicinal chemistry, computational modelling, pharmacokinetics, disease-relevant animal models and biomarker-driven pharmacology. Such an integrated approach may enable development of next-generation MTDLs that move beyond symptomatic cholinesterase inhibition toward genuine disease-modifying neuroprotection.

TABLE 1. Major therapeutic targets relevant to donepezil–coumarin MTDLs

Target/pathway	Role in neurodegeneration	Desired action of hybrid
AChE	Acetylcholine hydrolysis; cholinergic deficit	Inhibition
BuChE	Cholinergic dysfunction, particularly during disease progression	Inhibition
MAO-B	Oxidative deamination and ROS generation	Selective inhibition
Aβ aggregation	Oligomerization and plaque formation	Inhibition
BACE-1	Amyloidogenic Aβ production	Inhibition
GSK-3β	Tau hyperphosphorylation	Inhibition/modulation
ROS	Oxidative neuronal injury	Scavenging/reduction
Metal ions	Aβ aggregation and oxidative stress	Controlled chelation
Neuroinflammatory pathways	Microglial/astrocytic activation	Modulation

TABLE 2. Representative coumarin-based multifunctional scaffolds

Hybrid class	Principal targets	Important finding
Donepezil–coumarin	AChE, BuChE, MAO-B	Compound 5m showed balanced ChE/MAO-B activity
Coumarin–donepezil natural-product derivative	AChE, BuChE, Aβ	BBB penetration and Aβ aggregation inhibition
Coumarin–dithiocarbamate	AChE, MAO-B	Potent dual inhibition and cognitive benefit in mice
Coumarin–benzotriazole	AChE, Aβ	Potent AChE inhibition; linker-dependent SAR
Coumarin–benzofuran	AChE, Aβ, oxidative stress	Multifunctional anti-AD activity
Coumarin–triazole	AChE, Aβ, antioxidant pathways	Click chemistry enables analogue generation

Hybrid class	Principal targets	Important finding
Coumarin–quinoline	AChE, BACE-1, Aβ, neuroprotection	Recent studies demonstrate in vivo efficacy
Coumarin–eugenol/triazole	AChE, Aβ, oxidative stress	Potent AChE and Aβ inhibition

TABLE 3. Proposed evaluation cascade for new donepezil–coumarin hybrids

Stage	Evaluation
1	Molecular design and pharmacophore modelling
2	Docking against AChE/BuChE/MAO-B/BACE-1/GSK-3β
3	ADMET and BBB prediction
4	Chemical synthesis and structural characterization
5	hAChE/hBuChE enzyme assays
6	MAO-A/MAO-B selectivity
7	Aβ aggregation assay
8	BACE-1/GSK-3β assays
9	Antioxidant and neuroprotection assays
10	BBB permeability
11	Pharmacokinetic evaluation
12	Cognitive and disease-relevant animal models

ABBREVIATIONS

AD – Alzheimer's disease
Aβ – Amyloid-β
ACh – Acetylcholine
AChE – Acetylcholinesterase
BuChE – Butyrylcholinesterase
BACE-1 – β-site amyloid precursor protein cleaving enzyme-1
BBB – Blood–brain barrier
CAS – Catalytic anionic site
GSK-3β – Glycogen synthase kinase-3β
MAO – Monoamine oxidase
MAO-B – Monoamine oxidase-B
MTDL – Multi-target-directed ligand
PAS – Peripheral anionic site
PD – Parkinson's disease
ROS – Reactive oxygen species
SAR – Structure–activity relationship

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest associated with this manuscript.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the conception, literature analysis, drafting, critical revision and final approval of the manuscript.

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