Design and synthetic approach of novel hybrid molecules for treatment of Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is an irreversible, progressive, neurodegenerative disorder and the foremost cause of senile dementia worldwide. Several hypotheses elucidating the initial neurodegeneration in the disease have been proposed, among which the two most widely accepted are cholinergic and amyloid hypotheses (Tiwary et al., 2019).

Most of the currently used therapeutic agents are primarily centering towards the improvement of acetylcholine (ACh) brain levels by inhibiting the function of AChE (acetylcholinesterase) enzyme. Among these AChE inhibitors (AChEIs), donepezil, bearing N-benzylpiperidine and indanone moiety, represents one of the most successful drug molecules in current AD treatment. Unlike other AChEIs, donepezil shows selective and potent inhibitory activity against the enzyme, targeting both main binding sites of the enzyme (catalytic anionic site-CAS and peripheral active site - PAS), thus acting like AChE and Aβ aggregation inhibitor.

Since AD has a multifactorial pathoetiology, designing such multi-target-directed ligands (MTDLs) able to concurrently modulate multiple targets is the most convenient and rational approach for developing novel agents for its treatment. This multi-targeted action, combined with favorable pharmacokinetics and safety-profile, makes donepezil a supreme candidate for further modification and optimization, eventually leading to enhancement of its selectivity, efficacy and potency (Kareem et al., 2021).

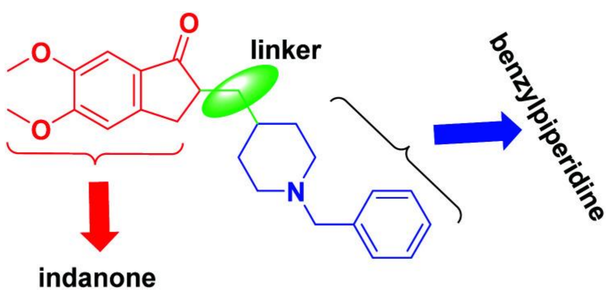


Figure 1: Structural features of donepezil (Davis and Eckroat, 2021)

Design of coumarin-isatin-triazole hybrids for treatment of Alzheimer's disease

Development of therapeutic agents for AD which act at multiple targets can be achieved by merging two or more pharmacophores within a single molecule, usually generating compounds with higher affinity and efficacy compared to the parent molecules. This approach is known as *molecular hybridization* (Abdolmaleki and Ghasemi, 2017).

Regarding previously published data, some **coumarine** (2H-chromen-2ones) and **isatin** (1H-indole-2,3-dione) derivatives have been reported to exhibit potent inhibitory activity towards AChE. Additionally, distinctive structure and electronic features of N-heterocycles such as **triazoles** might be beneficial for the development of novel drug compounds, including AD drugs, concerning their activity as AChE inhibitors (Davis and Eckroat, 2021).

According to aforementioned particulars, we have designed a series of novel coumarin-triazole-isatin hybrids. These three moieties can be incorporated in a single molecule, possibly improving the binding interactions with the AChE.

As mentioned before, AChE has two distinctive binding sites, referred as PAS, located at the rim of the gorge and CAS at the terminal part of the active site gorge. Indanone moiety of the donepezil interacts with PAS, while N-benzylpiperidine with CAS (Kareem et al., 2021). In designed series, coumarin represents a surrogate of indanone moiety of donepezil, potentially binding with PAS. Triazole ring, on the other hand, as a structural surrogate of piperidine ring of N-benzylpiperidine moiety, similary as isatin, can interact with CAS (Davis and Eckroat, 2021). Therefore, hybrid molecules with theoretical biological features as donepezil are obtained.

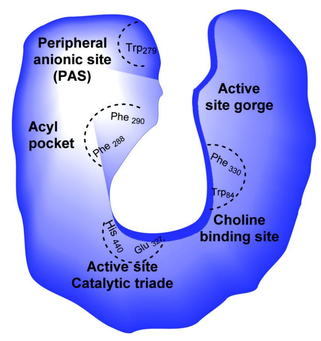
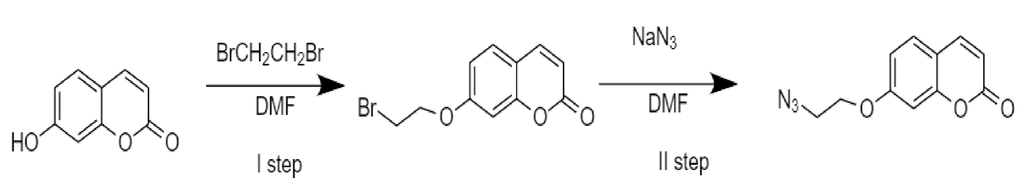


Figure 2: Schematic representation of AChE binding sites; His: histidine, Glu: glutamate, Phe: phenylalanine, Trp: tryptophan (Kareem et al., 2021)

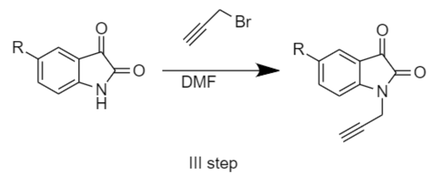
Proposed synthetic pathway of coumarin-isatin-triazole hybrids

The proposed synthetic pathway of coumarin-isatin-triazole hybrids, as an example, is presented on the subsequent schemes:

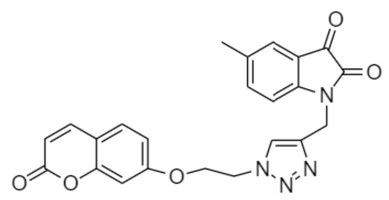
I step: Bromoalkylated coumarines are yielded when selected hydroxy coumarines react with dibromoalkanes.
II step: Bromoalkylated coumarines obtained in step I react with sodium azide (NaN3), a strong nucleophile, leading to synthesis of analogous N-azidoalkyl coumarins.



III step: Consequently, isatin derivatives can be propargilated using propargyl bromide, creating particular 1-(prop–2-ynl)indoline-2,3–dione products.



IV step: The final molecules, corresponding coumarin-triazole-isatin hybrids can be prepared from N-azidoalkyl coumarins and 1-(prop–2-ynl)indoline-2,3–diones in the presence of the catalytic amount of copper sulfate and reducing agent such as sodium ascorbate, employing Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) – typical "click" reaction.



coumarin-isatin-triazole hybride

Conclusion

On this poster, design tactic for rational incorporation of coumarin, isatin and triazole moieties into a single molecule was described and consecutive synthetic pathway was defined. Nevertheless, actual synthesis and successive *in vitro* biological evaluation should be performed in order to confirm or reject theoretical strategy described in this poster.

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