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Short communication

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. Even though the particular molecular mechanisms for the pathogenesis of AD have not been fully understood, several hypotheses have been proposed, elucidating the initial neurodegeneration in the disease. Among these, 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. Some of these AChE inhibitors (AChEI) have been successfully employed in clinical practice for AD management, but some of them are related to serious side effects and are only acting for the palliative treatment in the early stages of AD (Marucci et al., 2021). Among AChEIs, donepezil, bearing *N*-benzylpiperidine and indanone moiety, represents one of the most successful drug molecules in current AD treatment. Unlike other drugs in AChEI class, 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).

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

Recently, a hybridized approach based on MTDLs has received considerable attention in developing therapeutic agents for AD which act at multiple targets. This 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, known as molecular hybridization has already provided drug candidates for several clinical trials (Abdolmaleki and Ghasemi, 2017).

Regarding previously published data, some coumarine (2*H*-chromen-2ones) and isatin (1*H*-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 (Bhagat et al., 2021; 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

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PAS (Bhagat et al., 2021). Triazole ring, on the other hand, as a structural surrogate of piperidine ring of *N*-benzylpiperidine moiety, similary as isatin, can interact with CAS (Bhagat et al., 2021; Davis and Eckroat, 2021). Therefore, hybrid molecules with theoretical biological features as donepezil are obtained. Considering the dual AChE (due to binding CAS affinity) as well as Aβ aggregation inhibitory activity of donepezil (attributed to interactions with PAS), the designed series of hybrid compounds are anticipated as multifunctional anti-Alzheimer agents.

Proposed synthetic pathways of coumarin-isatin-triazole hybrids

Designed hybrids can be synthetized via a series of chemical reactions utilizing click chemistry approach. Since being introduced in late 90s, click chemistry has become a prevalent topic in organic synthesis, considering its modularity, simplicity, ease of purification, stereospecificity and high yields of resulting products (Meghani et al., 2017).

Via initial step of the proposed synthesis, bromoalkylated coumarines are yield when selected hydroxy coumarines react with dibromoalkanes. This first reaction in the synthetic pathway of proposed hybrids is a typical Williamson reaction, which is a general method where ether is produced by combining alkoxide and organohalide via an S_N2 reaction. Since alkoxide ions are highly reactive, carbonate base or potassium hydroxide are most often used for their *in situ* generation. A wide range of solvents can be used, but protic and apolar solvents show a tendency of slowing down the reaction, so acetonitrile and *N*,*N*-dimethylformamide (DMF) are commonly used.

In the following step, previously obtained bromoalkylated coumarines react with sodium azide (NaN_3), a strong nucleophile, leading to nucleophilic displacement reaction and creating analogous *N*-azidoalkyl coumarins.

Consequently, isatin derivatives can be propargilated using propargyl bromide in the presence of K_2CO_3 in DMF through an S_N2 reaction, creating particular 1-(prop–2-ynl)indoline-2,3–dione products.

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). This reaction between azides and terminal alkynes to form 1,2,3-triazoles is a classic example of a click reaction. It is greatly regiospecific and leads to formations of 1,4-substituted products. It usually does not require high temperatures and can be completed in a range of solvents and over wide pH ranges. Furthermore, it proceeds much more faster compared to uncatalyzed version of the reaction (Hein et al., 2008).

Conclusion

In this short communication, 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 paper.

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