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Research paper

Discovery of imidazopyridines containing isoindoline-1,3-dione framework as a new class of BACE1 inhibitors: Design, synthesis and SAR analysis

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Dedicated to Professor Abbas Shafiee (1937–2016) for his lifetime achievement in pharmaceutical sciences research and education

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ABSTRACT

Alzheimer's disease is characterized by chronic neurodegeneration leading to dementia. The main cause of neurodegeneration is considered to be the accumulation of amyloid-β. Inhibiting BACE1 is a well-studied approach to lower the burden of amyloid-β aggregates. We designed a series of imidazopyridines-based compounds bearing phthalimide moieties as inhibitors of BACE1. The compounds **8a-o** were synthesized by the Groebke–Blackburn–Bienaymé three-component reaction of heteroaromatic amidines, aldehydes and isocyanides. Evaluating the BACE1 inhibitory effects of the synthesized compounds revealed that introducing an aminocyclohexyl moiety in the imidazopyridine core resulted in a significant improvement in its BACE1 inhibitory potential. In this regard, compound **8e** was the most potent against BACE1 with an IC_{50} value of 2.84 (±0.95) μM. Molecular docking revealed that the nitrogen atom of imidazopyridines and the oxygen atom of the phenoxypropyl linker were involved in hydrogen bound interactions with Asp228 and Asp32 of BACE1 active site, respectively. The phthalimide moiety oriented toward the flap pocket and interacted with phe108, Ile110, Trp115, Ile118 through van der Waal's and hydrophobic interactions. These findings demonstrate that imidazopyridines-based compounds bearing phthalimide moiety have the potential to decrease amyloid-β levels and ameliorate the symptoms of Alzheimer's disease.

1. Introduction

Alzheimer's disease is a neurodegenerative disorder and the most common cause of dementia in the elderly [1]. The pathogenesis of the disease is often described by the "Amyloid Cascade Hypothesis" (ACH) [2], which suggests that the deposition of amyloid beta (Aβ) is the first pathological event that causes neuronal death and eventually leads to dementia. Two proteases known as β- and γ-secretase endoproteolyze the amyloid precursor protein (APP) to produce the Aβ peptide. β-Secretase is active in most tissues of the body [3,4]; however, β-site amyloid precursor protein cleaving enzyme-1 (BACE1) is the major β-secretase in the CNS compared to BACE2 (close homolog of BACE1), which has a more widespread expression pattern? [5]. BACE1 activity is increased in the brains of patients with sporadic Alzheimer's disease [6]. Consequently, BACE1 inhibitors have emerged as ideal candidates for the treatment of Alzheimer's disease by preventing Aβ accumulation and aggregation [7–9]. The first generation of BACE1 inhibitors were designed based on peptide analogs of APP [10]. Although they have shown high *in vitro* inhibitory activity, unfavorable *in vivo* pharmacological properties were observed due to low blood-brain barrier (BBB) permeability or oral bioavailability.

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Hence, developing non-peptidic BACE1 inhibitors is of particular interest.

Among various non-peptidic scaffolds, amidine- or guanidine-containing heterocycles were found to be suitable inhibitors due to the formation of a hydrogen-bond network with the catalytic aspartyl dyad of BACE1 [11–13]. Recently, Merck has introduced a guanidine-based drug for Alzheimer's disease known as Verubecestat (MK-8931) currently in phase II/III trials [14]. Verubecestat is a potent inhibitor of BACE1 with an IC_{50} value of 0.4 nM [15]. The X-ray cocrystal structure confirmed hydrogen-binding interactions between the amidine moiety and the BACE1 catalytic dyad. High-affinity binding toward the relatively hydrophobic S1 and S3 subsites results from a diaryl amide substituent that occupies the above-mentioned subsites in BACE1. MK-8931 has favorable physicochemical properties including stability at physiological pH, oral absorption, high cellular permeability and high BBB penetration [15]. The results suggest that the presence of pyridine and guanidine moieties results in satisfactory curative effects. More recently, Al-Tel et al. introduced imidazopyridines with structure **A** (Fig. 1) as novel β-secretase inhibitors [16]. Three derivatives of compound **A** showed IC_{50} values of 5.51, 2.48, and 2.24 μM where X was replaced with hydrogen, fluorine, and methoxy, respectively.

In addition, other studies reported isoindoline-1,3-dione (phthalimide) derivatives (compound C, Fig. 1) as cholinesterase and Aβ aggregation inhibitors with neuroprotective effects. These compounds did not show cytotoxicity and had therapeutic potential for treating Alzheimer's disease [17]. Our previous study on phenyliminochromene carboxamide derivatives bearing bromophenyl piperazine moieties (compound B, Fig. 1) suggested that the introduction of an isoindoline-1,3-dione moiety into the piperazine pendant results in a significant improvement in BACE1 inhibitory activity ($IC_{50} = 0.098$ μM) and suppression of Aβ production in N2a-APPswe cells (% Inhibition of $A\beta_{1-40}$ production = 39.4 at 10 μM). Phthalimide moiety could be considered as a non-peptidyl framework with low-molecular weight involved in hydrophobic interaction with hydrophobic residue of the S2 sub-pocket of active site and the network of hydrogen bonding interactions with Arg235, Thr23 and Gly230. This observation might partially explain the significant inhibitory potential resulted from the incorporation of phthalimide moiety into the BACE1 inhibitor scaffold [18].

As part of our ongoing research to design and synthesize novel anti-Alzheimer's agents [19–21], we focused on an imidazopyridine core as a promising scaffold for inhibiting BACE1. To this end, we employed molecular hybridization and bioisosterism replacement approaches to identify novel non-peptidic inhibitors with aspartyl binding motifs as new entities for the inhibition of this enzyme (Fig. 1). Our design is based on bioisosteric replacement of the phenyl linker with a phenoxypropyl one (compound A, Fig. 1) to increase the flexibility of the linker and to allow the inhibitor to properly access and orient itself within the active site of BACE1. Different secondary amines were incorporated into the structure to investigate the importance of substituted groups at the 3-position of the imidazopyridines. Our pervious results [18] prompted us to replace the benzimidazole group of compound **A** with a phthalimide pendant to improve the anti-BACE1 effects and enhancing the accessibility to the S2-sub pocket of the active site [18].

2. Results and discussion

2.1. Chemistry

The synthetic procedure for the preparation of imidazopyridines bearing phthalimide moiety **8** is depicted in Scheme 1. Reaction of phthalimide **1** and 1,3-dibromopropane **2** in the presence of K_2CO_3 in refluxing acetone gave 2-(3-bromopropyl)isoindoline-1,3-dione **3**. Next, the reaction of compound **3** and 4-hydroxyaldehyde derivative **4** in the presence of K_2CO_3 in DMF at 80 °C gave the desired aldehyde **5**.

The target compounds were prepared through the reaction of

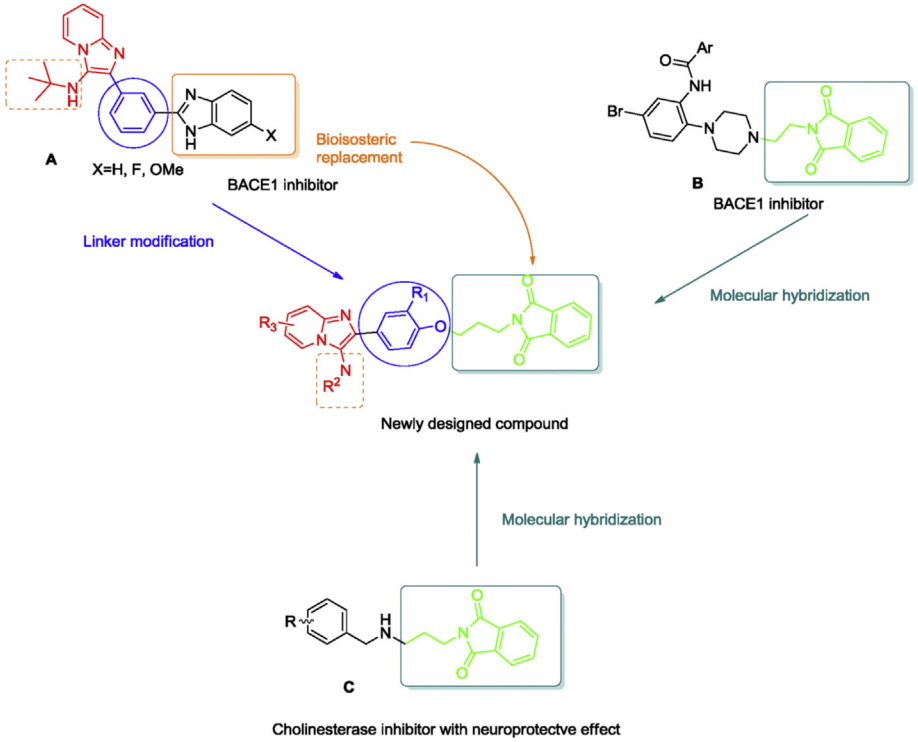

Fig. 1. Chemical structure of previously reported BACE1 inhibitors; imidazopyridines A, isoindoline-1,3-dione (phthalimide) containing derivative B, cholinesterase inhibitor with neuroprotective effect C and our newly hybridized imidazopyridine-based derivatives as potential novel anti-Alzheimer agents.