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Research paper

Discovery of benzimidazole derivatives as modulators of mitochondrial function: A potential treatment for Alzheimer's disease

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ABSTRACT

In this study, we designed a library of compounds based on the structures of well-known ligands of the 18 kDa translocator protein (TSPO), one of the putative components of the mPTP. We performed diverse mitochondrial functional assays to assess their ability to restore cells from Aβ-induced toxicity in vitro and in vivo. Among tested compounds, compound **25** effectively improved cognitive function in animal models of AD. Given the excellent in vitro and in vivo activity and a favorable pharmacokinetic profile of compound **25**, we believe that it can serve as a promising lead compound for a potential treatment option for AD.

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder, known as the most common cause of dementia associated with impairments of cognitive functions and memory [1]. The mechanism of AD pathogenesis still remains largely unknown, however, amyloid-β (Aβ) is recognized as the major hallmark of AD [2,3]. Not only Aβ is the main component of the amyloid plaques found in AD patients, but many recent studies have found that high levels of cellular Aβ cause mitochondrial dysfunction [4,5]. Since mitochondria are responsible for a diverse array of cellular processes such as energy production, metabolism, and cell death, the aftermath of mitochondrial dysfunction in neuronal cells would be particularly devastating. Moreover, given the protective functions of mitochondria against oxidative stress and protein misfolding, mitochondrial dysfunction further aggravates and even accelerates the progression of AD [6]. It has been suggested that the accumulation of Aβ disrupts intracellular Ca^{2+} homeostasis [7] and results in apoptosis of neurons [8]. Furthermore, mitochondrial Aβ appears to interact with cyclophilin D (CypD) and promotes opening of the mitochondrial permeability transition pore (mPTP), a multimeric protein complex in the inner membrane of mitochondria [8,9]. Opening of the mPTP induces the depolarization of the

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mitochondrial membrane potentials ($\Delta\Psi_m$), which in turn allows for uncontrolled passage of cytosolic solutes, damaging mitochondrial structure. This structural damage leads to mitochondrial dysfunction, the consequences of which include the impairment of energy production, the initiation of cell death pathways, and the accumulation of neurotoxic proteins [9].

Prolonged opening of the mPTP has been observed in many diseases such as myocardial reperfusion injury [10], amyotrophic lateral sclerosis (ALS) [11,12], traumatic brain injury [13], and AD [14], therefore, many research efforts have focused on finding regulators of the mPTP [13,15,16]. However, considering that the complete structure of the mPTP has not been fully characterized, identifying specific regulators of the mPTP is a challenging task. According to several hypothetical models, the mPTP appears to contain at least four proteins [16,17]; CypD, a voltage-dependent anion channel (VDAC), the adenine nucleotide translocator (ANT), and the 18 kDa translocator protein (TSPO) [18,19]. It has been suggested that natural compounds such as cyclosporine A [20], sangliferin A [21], and bongkrekic acid [22] appear to bind these putative components of the mPTP, and regulate its opening. Several recent studies have identified small molecule modulators of the mPTP that can restore cellular viability from Aβ-induced mitochondrial dysfunctions [23,24].

The 18 kDa TSPO has been studied extensively due to its involvement in chronic inflammation and neurological disorders [25,26]. Although it was first introduced as peripheral benzodiazepine receptor (PBR), later it was found to be expressed throughout the whole body including the brain, therefore renamed as TSPO. Recent reports suggesting its regulatory roles in the mPTP opening have drawn renewed attention to TSPO as a novel therapeutic target for neurodegenerative diseases [25,27,28]. In spite of much interest, small molecule ligands of TSPO remain relatively scarce in literature, and only a few compounds with a benzodiazepine core have been developed to date for diagnostic imaging and therapeutic applications [29]. We believe that structurally diverse sets of compounds would facilitate the identification of novel ligands with desirable physicochemical properties, therefore, set out to design new compounds by employing ligand-based virtual screening. Based on the virtual screening results, we designed and synthesized a library of compounds containing a benzimidazole scaffold. Biological activity of the synthesized library was evaluated by determining the mitochondrial membrane potential, ATP production, and ROS generation in cells suffering Aβ induced mitochondrial dysfunction. In addition, we tested a few selected compounds in both acute and transgenic (Tg) mice models of AD to assess their effects on the cognitive impairment. We performed in vitro binding assays of the most active compound for TSPO to confirm its target-specific activity, and analyzed its binding interactions *via* molecular docking studies.

2. Results and discussion

2.1. Pharmacophore modeling and virtual screening

To design TSPO ligands with a novel scaffold, we first generated a common feature pharmacophore model based on the structures of the previously reported neuroprotective TSPO ligands. A ligand-based pharmacophore model was generated by commercially available pharmacophore generation program, Catalyst/HipHop. To generate common feature pharmacophore models, five representative TSPO ligands were collected from the Integrity® database of Prous, and were used as training set compounds: 2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)-*N*,*N*-dihexylacetamide (FGIN-1-27, K_i for TSPO = 3.25 nM), *N*,*N*-dibutyl-2-(6,8-dichloro-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)acetamide (K_i for TSPO = 2.68 nM), *N*-(4-chloro-2-phenoxyphenyl)-*N*-(2-isopropoxybenzyl)acetamide (DAA1097, IC_{50} for TSPO = 0.92 nM), *N*-(2,5-dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106, IC_{50} for TSPO = 1.6 nM), and *N*-(*sec*-butyl)-1-(2-chlorophenyl)-*N*-methylisoquinoline-3-carboxamide (PK-11195, IC_{50} for TSPO = 1.1 nM) [25]. From this set of compounds, two pharmacophore models (model 1 and 2) were generated by differing in ring aromatic and hydrophobic feature options. Model 1 consists of one hydrogen bond acceptor, one hydrophobic aromatic and four hydrophobic features, whereas model 2 includes six different common features: one hydrogen bond acceptor, two ring aromatic, and three hydrophobic features. Instead of the hydrophobic aromatic feature in model 1, the ring aromatic feature was varied in model 2 to cover the hydrophobic property and to introduce a planar or flexible ring aromatic substituent in the hit compounds. Based on these two pharmacophore models, our in-house library as well as commercial libraries from Asinex (AsinexGold, 229,398 compounds; AsinexPlatinum, 125,231 compounds, Asinex, Moscow, Russia, www.asinex.com) and ChemDiv (693,042 compounds, ChemDiv, Inc. California, USA, www.chemdiv.com) have been utilized for virtual screening. Through the BEST flexible search of the databases, 278 compounds (model 1: 172; model 2: 106) were selected by fit values (3.50 out of 6.00) from the two models. Among them, 22 compounds (**VS001**–**VS022**, Table S1) were manually selected based on fit values, structural diversity, and the presence of essential functionality. All the selected compounds (**VS001**–**VS022**) share a common bicyclic core ring: 3*H*-imidazo[4,5-*c*]pyridine (**VS001**–**VS007**), 1*H*-benzo[*d*]imidazole (**VS008**–**VS010**), and 1*H*-imidazo[4,5-*b*]pyridine (**VS011**–**VS022**).

All 22 compounds were initially screened by mitochondrial functional assays including JC-1 assay and ATP production assay. Interestingly, three 1*H*-benzo[*d*]imidazole compounds (**VS008**–**VS010**) demonstrated excellent recovery of mitochondrial membrane potential (over 50% at 5 μM) in the JC-1 assay (see supplementary material, Table S1). Moreover, compound **VS008** showed suitable mapping with the built pharmacophore model (model 2) which is illustrated in Fig. 1A. Compounds **VS008**–**VS010** were further screened by the ATP production assay. **VS008** again showed moderate recovery of ATP production (20% at 5 μM) in Aβ treated cells, while **VS009** and **VS010** did not appear to affect ATP production. Therefore, we decided to focus on **VS008** as our lead compound **1** (Fig. 1B).

2.2. Chemistry

Based on the structure of compound **1**, we designed a library of benzimidazole derivatives, compounds **10**–**32**, which contained various functional groups corresponding to the common feature pharmacophore model (Fig. 1B). After performing preliminary mitochondrial functional assays with compounds **1** and **10**–**32**, we modified the existing scaffold to have diverse hydrophobic groups (**36**–**44**) as well as an additional hydrogen bond donor (**51**–**53**).

The benzimidazole derivatives **10**–**32** were synthesized by following the pathway described in Scheme 1. Substituted *N*-(2-iodophenyl)amide compounds **4a**–**f** were prepared *via* nucleophilic addition-elimination of the 2-iodoaniline **2** to aryl-substituted acyl chlorides **3a**–**f**. Compounds **4a**–**f** were then converted to the corresponding benzimidazole analogues **7a**–**f** *via* Ullmann-type condensation reaction in moderate yields ranging 40 to 60%. On the other hand, compounds **7g** and **7h** were obtained *via* an intramolecular cyclization of compounds **5a**–**b** with 2-(2,6-dichlorophenyl)acetic acid **6** in the presence of polyphosphoric acid (PPA) [30]. The *N*-alkylation of compounds **7a**–**h** with methyl 2-bromoacetate generated compounds **8a**–**h**, and the subsequent

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