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Synthesis and evaluation of biaryl derivatives for structural characterization of selective monoamine oxidase B inhibitors toward Parkinson's disease therapy

Seul Ki Yeon [a,b,1], Ji Won Choi [a,b,1], Jong-Hyun Park [a,1], Ye Rim Lee [a,c,1], Hyeon Jeong Kim [a,b], Su Jeong Shin [a,b], Bo Ko Jang [a], Siwon Kim [a,d], Yong-Sun Bahn [b], Gyoonhee Han [b], Yong Sup Lee [c], Ae Nim Pae [a,c,d], Ki Duk Park [a,c,d,*]

[a] Convergence Research Center for Diagnosis, Treatment and Care System of Dementia, Korea Institute of Science and Technology, Seoul, Republic of Korea
[b] Department of Biotechnology, Yonsei University, Seoul, Republic of Korea
[c] KHU-KIST Department of Converging Science and Technology, Kyung Hee University, Seoul, Republic of Korea
[d] Division of Bio-Medical Science &Technology, KIST School, Korea University of Science and Technology, Seoul, Republic of Korea

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ABSTRACT

Benzyloxyphenyl moiety is a common structure of highly potent, selective and reversible inhibitors of monoamine oxidase B (MAO-B), safinamide and sembragiline. We synthesized 4-(benzyloxy)phenyl and biphenyl-4-yl derivatives including halogen substituents on the terminal aryl unit. In addition, we modified the carbon linker between amine group and the biaryl linked unit. Among synthesized compounds, **12c** exhibited the most potent and selective MAO-B inhibitory effect (hMAO-B IC_{50}: 8.9 nM; >10,000-fold selectivity over MAO-A) as a competitive inhibitor. In addition, **12c** showed greater MAO-B inhibitory activity and selectivity compared to well-known MAO-B inhibitors such as selegiline, safinamide and sembragiline. In the MPTP-induced mouse model of Parkinson's disease (PD), **12c** significantly protected the tyrosine hydroxylase (TH)-immunopositive DAergic neurons and attenuated the PD-associated behavioral deficits. This study suggests characteristic structures as a MAO-B inhibitor that may provide a good insight for the development of therapeutic agents for PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder characterized by marked motor deficits such as resting tremor, bradykinesia, rigidity and postural instability.[1] These motor symptoms are mostly associated with dopamine (DA) depletion caused by a profound loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc). However, the exact mechanisms causing neurodegeneration are not yet known.[2–4]

Recently, several studies have reported that the expression level of monoamine oxidase B (MAO-B) in human brain increases with age, and activity is highly increased in the substantia nigra of PD patients.[5,6] MAOs are localized on the outer membrane of mitochondria, particularly in the liver and brain, and catalyze the oxidative deamination of monoamine neurotransmitters such as dopamine.[7] In addition, the reaction catalyzed by MAOs result in the production of hydrogen peroxide (H_2O_2) which causes oxidative stress and neuronal cell death.[8,9] There are two isoforms, MAO-A and MAO-B. MAO-A is localized in catecholaminergic neurons and selectively inhibited by low concentrations of clorgyline (**1**), whereas MAO-B is abundant in serotonergic neurons and astrocytes, and selectively inhibited by potent inhibitors selegiline (**2**) and rasagiline (**3**) (Fig. 1).[10–12]

Selegiline and rasagiline, selective and potent MAO-B inhibitors, are the most widely used drugs for the therapy of PD by either

Abbreviations: AD, Alzheimer's disease; DA, dopamine; DAergic, dopaminergic; hMAO-A, human monoamine oxidase A; hMAO-B, human monoamine oxidase B; HRP, horseradish peroxidase; IC_{50}, the half maximal inhibitory concentration; i.p., intraperitoneal; K_i, inhibition constant; K_m, Michaelis constant; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PBS, phosphate buffer saline; PD, Parkinson's disease; PFA, paraformaldehyde; *p.o.*, peroral; ROS, reactive oxygen species; S.E.M, standard error of mean; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; V_{max}, maximal velocity.

* Corresponding author at: Convergence Research Center for Diagnosis, Treatment and Care System of Dementia, Korea Institute of Science and Technology, 5 Hwarang-ro, 14-gil, Seongbuk-gu, Seoul 136-791, South Korea.
E-mail address: kdpark@kist.re.kr (K.D. Park).

[1] These authors contributed equally to the work.

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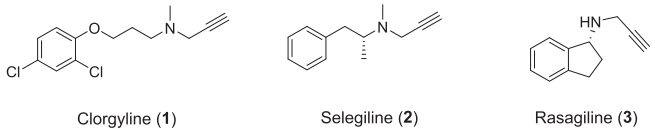

Fig. 1. Chemical structures of irreversible MAO-B inhibitors.

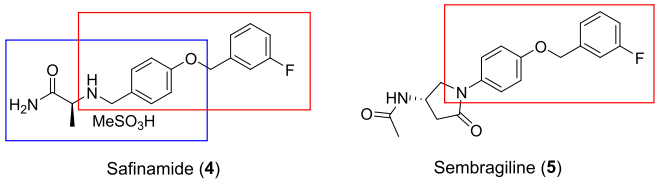

Fig. 2. Chemical structures of reversible MAO-B inhibitors.

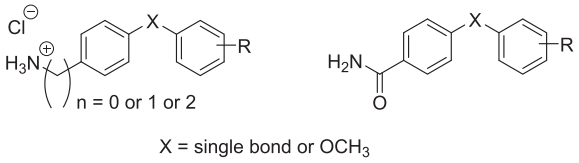

Fig. 3. Representative chemical structures of biaryl derivatives.

mono-therapy or in combination with the levodopa, the dopamine prodrug, resulting in the increase of dopamine.[13,14] However, selegiline and rasagiline are irreversible MAO-B inhibitors and showed undesirable adverse effects in long term treatment of PD such as hallucinations and headaches. Recent studies have been shown that the irreversibility of MAO-B inhibition may contribute short-lived action.[15] Accordingly, the development of selective and reversible MAO-B inhibitors could reduce undesirable adverse effects and maintain the effectiveness in long-term use for the treatment of neurodegenerative diseases. Recently, safinamide (**4**, Xadago™, Fig. 2), a highly selective and reversible MAO-B inhibitor, was approved for the treatment of mild-to-late PD patients as an add-on therapy to stable dose of levodopa alone or in combination with other PD medications.[16] However, safinamide may cause disadvantageous effects due to other biological properties such as selective sodium channel blockade, calcium channel modulation, and inhibition of stimulated release of glutamate.[17–20] Sembragiline (**5**, RG-1577, Fig. 2) is another potent reversible MAO-B inhibitor for the treatment of Alzheimer's disease (AD). MAO-B activity is linked to the production of reactive oxygen species (ROS) that can cause neuronal damage. Sembragiline was expected to slow progression of neurodegeneration by reducing oxidative stress. However, it failed to demonstrate benefit of the primary endpoint in clinical trial phase 2.[21,22] Interestingly, two recent potent and selective MAO-B inhibitors have common moieties, ((3-fluorobenzyl)oxy)phenyl group (Fig. 2, red box).

In this study, we asked if compounds conforming to the biaryl linked unit exhibited MAO-B inhibitory activity. First, we synthesized substituted (4-(benzyloxy)phenyl)-methylammonium chlorides. Next, we modified the carbon linker between amine group and the biaryl linked unit (Fig. 3). In addition, we prepared biphenyl-4-yl derivatives wherein the aryl linker (X) is a single bond (Fig. 3). We reported that the substituted (4-(benzyloxy)phenyl)-ethylammonium chlorides exhibited potent and selective MAO-B inhibitory activities. One of the compounds with the highest potency was further evaluated for *in vivo* efficacy in the MPTP-induced mouse model of PD.

Recently, some biaryl derivatives in our study have been reported their biological activities such as anticonvulsant activity[23] and trace amine-associated receptor agonist effects.[24] However, this is the first report to propose structural features for the excellent activity of MAO-B inhibitors by variously modifying the biaryl linker and the carbon linker. Thus, this study can provide insight into the development of new potential MAO-B inhibitors for PD therapy.

2. Results and discussion

2.1. Selection of compounds

According to recent literature, safinamide (**4**) has emerged as a new therapeutic agent for the treatment of PD through MAO-B inhibition. We divided safinamide into two parts (the blue and the red boxes in Fig. 2) to determine the part that affected the MAO-B inhibitory effects. We found that (4-((3-fluorobenzyl)oxy) phenyl)methanaminium chloride (**7f**) corresponding to the red box showed much potent than compound **15** corresponding to blue box (IC_{50} hMAO-B = 0.926 μM vs >10 μM). Sembragiline (**5**, RG-1577), a reversible MAO-B inhibitor, has a ((3-fluorobenzyl) oxy)phenyl group in common with safinamide. We observed that 4-((3-fluorobenzyl)oxy)benzenaminium chloride (**10e**) corresponding to the red box in **5** inhibited MAO-B activity. Accordingly, we prepared 4-(benzyloxy)phenyl and biphenyl-4-yl derivatives which included various substituents on the terminal aryl unit. We also modified the carbon linker between amine group and the biaryl linked unit.

2.2. Synthesis

Compounds **7** and **8** were prepared in two steps (Scheme 1). Using a slightly modified method from the previous method, we prepared the Williamson ether coupled products **6** by treating 4-cyanophenol with the appropriate substituted benzyl bromide and potassium carbonate (K_2CO_3). Lithium aluminum hydride ($LiAlH_4$) reduction of the nitrile group in **6a**–**6k** afforded the amines, which were immediately converted to the corresponding aminium chlorides **7a**–**7k**. The conversion of nitriles (**6a**–**6k**) to amides by partial hydrolysis with KOH afforded benzamide derivatives **8a**–**8f**. To prepare 4-nitrophenoxy benzene derivatives **9a**–**9f**, we synthesized 4-nitrophenol and the appropriate substituted benzyl bromide using the similar method above except reaction solvent (DMF) (Scheme 2). 4-nitrophenoxy benzene derivatives **9a**–**9f** were reduced to benzenaminium chlorides **10a**–**10f** by platinum (II) oxide under hydrogen gas (Scheme 2). Compounds **11** were prepared by Williamson ether coupling using *tert*-butyl (4-hydroxyphenethyl)carbamate and the substituted benzyl bromide. Deprotection of boc-group by 4.0 M hydrogen chloride in dioxane gave ethanaminium chlorides **12a**–**12j** (Scheme 3). The (biphenyl-4-yl) ethanaminium chlorides were prepared using Suzuki coupling of *N*-boc-2-(4-bromophenyl)ethylamine (**13**) with the appropriate, commercially available substituted aryl boronic acids to give the boc-protected amines, which then were immediately deprotected and converted to their hydrochloride salts **14a**–**14j** using HCl (Scheme 4).

2.3. Inhibitory activities of the synthesized compounds against monoamine oxidase B

The synthesized compounds were evaluated for inhibitory activities of human MAO-A and MAO-B using recombinant enzymes. The enzyme inhibition assay on test compounds was performed using Amplex Red reagents and the inhibitory activity was determined by spectrophotometrically measuring the resorufin formation at 570 nm. The inhibitory potencies (IC_{50} values) for all