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Letter

(Hetero-)(arylidene)arylhydrazides as Multitarget-Directed Monoamine Oxidase Inhibitors

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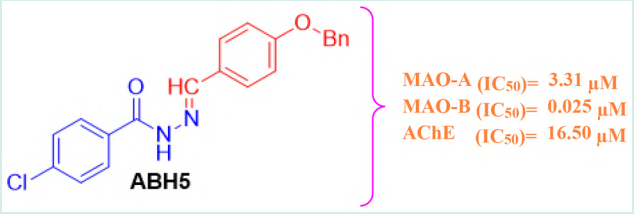
ABSTRACT: Fourteen (hetero-)(arylidene)arylhydrazide derivatives (**ABH1**−**ABH14**) were synthesized, and their inhibitory activities against monoamine oxidases (MAOs) and acetylcholinesterase (AChE) were evaluated. Compound **ABH5** most potently inhibited MAO-B with an IC_{50} value of 0.025 ± 0.0019 μM; **ABH2** and **ABH3** exhibited high IC_{50} values as well. Most of the compounds weakly inhibited MAO-A, except **ABH5** (IC_{50} = 3.31 ± 0.41 μM). Among the active compounds, **ABH2** showed the highest selectivity index (SI) of 174 for MAO-B, followed by **ABH5** (SI = 132). **ABH3** and **ABH5** effectively inhibited AChE with IC_{50} values of 15.7 ± 6.52 and 16.5 ± 7.29 μM, respectively, whereas the other compounds were weak inhibitors of AChE. **ABH5** was shown to be a reversible competitive inhibitor for MAO-A and MAO-B with K_i values of 0.96 ± 0.19 and 0.024 ± 0.0077 μM, respectively, suggesting that this molecule can be considered as an interesting candidate for further development as a multitarget inhibitor relating to neurodegenerative disorders.



KEYWORDS: *(Hetero-)(arylidene)arylhydrazide, MAOs, AChE, Kinetics, Docking analysis, Multitarget inhibitor*

Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative disorder characterized by the impairment of cognitive functions that leads to memory deficit.[1] Molecular signatures of AD include the deposition of β-amyloid plaques, increase in free radical-based oxidative stress, and diminished levels of acetylcholine.[2] Several lines of evidence concerned with the multifactorial pathogenesis of AD suggest that the conventional "one drug-one target" concept does not always guarantee for the success in AD treatment.[3] For example, disregulated levels of the enzyme monoamine oxidase-B (MAO-B) in brain cells leads to excessive production of hydrogen peroxide responsible for cellular degeneration in AD patients and aging of the brain.[4] Recent *in vivo* two-photon imaging studies showed a clear evidence for elevated MAO-B enzyme activity around amyloid β-plaques in aged AD mice.[5] This finding suggests that the progress of age-related AD may also be associated with increased levels of MAO-B activity.

A new class of MAO-B inhibitors comprised of two aryl or heteroaryl rings connected through a short spacer have recently been described.[6] Such spacers as α,β-unsaturated ketones,[7−13] pyrazoline,[14] hydrazones,[15,16] and anilide/enamides[17,18] have received attention (Figure 1). Here we describe an expansion of this theme to 14 (hetero-)(arylidene)arylhydrazides, with an investigation of their inhibitory activity toward two forms of MAO and acetylcholinesterase (AChE). The most potent compound identified in these *in vitro* tests was further analyzed by molecular docking to identify potential interactions at the binding sites of MAO-B and AChE.

Compounds **ABH1**−**ABH14** were prepared by the straightforward condensation of corresponding hydrazides and aldehydes in moderate yields (51−74%, Table 1).[19] Six compounds (**ABH1**−**ABH6**) were derived from 4-chlorobenzohydrazide and eight compounds (**ABH7**−**ABH14**) were derived from isonicotinohydrazide.

The 14 compounds were tested for their MAOs and AChE inhibitory potencies by literature methods,[20,21] using toloxatone and clorgyline as positive controls for MAO-A, lazabemide and pargyline for MAO-B, and tacrine for AChE (Table 2). Recombinant human MAO-A and MAO-B were employed, with kynuramine (0.06 mM = 1.7 × K_m) and benzylamine (0.3 mM = 2 × K_m) as substrates, respectively. Compounds **ABH1**−**ABH6** showed potent inhibitory activity against MAO-B with residual activities of <35% at 10 μM concentration, except **ABH4** (71.3%). **ABH5** was found to have the highest inhibitory activity against MAO-B with an IC_{50} of 0.025 μM, followed by **ABH2** and **ABH3** (IC_{50} = 0.23 and 0.58 μM, respectively) (Table 2). In contrast, eight compounds (**ABH7**−**ABH14**) derived from isonicotinohydrazide had weak inhibitory activities against MAO-B with residual activities of > ∼ 40% at 10 μM, and

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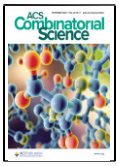

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