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Synthesis and biological evaluation of novel marine-derived indole-based 1,2,4-oxadiazoles derivatives as multifunctional neuroprotective agents

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ABSTRACT

Phidianidines (**1**), isolated from the marine opisthobranch mollusk *Phidiana militaris*, present the first example of natural products possessing an 1,2,4-oxadiazole ring system and show various bioactivities. However, the structure–activity relationship study related to **1** has not been reported yet. As our ongoing effect toward marine-derived potential neuroprotective agents, a series of phidianidine-based derivatives have been synthesized and evaluated for neuroprotective effects against amyloid-β_{25-35} ($A\beta_{25-35}$)-, hydrogenperoxide (H_2O_2)-, and oxygen–glucose deprivation (OGD)-induced neurotoxicity in SH-SY5Y cells. The bioassay results indicated that some of analogs, especially **2q** and **2r**, exhibited good in vitro neuroprotective effects in the above three screening models. The preliminary SAR study indicated that substituent groups introduced to the benzene ring play a crucial role in their bioactivity. In particular, the linear alkoxy group at 4-position favors the neuroprotective activity, while a bulky group could lead the activity decrease or loss. These findings could provide an alternative strategy for the development of novel indole-based 1,2,4-oxadiazole derivatives for the treatment of Alzheimer's disease.

Alzheimer's disease (AD), the most common form of dementia, is multifaceted neurodegenerative brain disorder featured by loss of memory, progressive deficits in cognitive functions, and severe behavioral abnormalities.[1] Currently, approximate 35 million people worldwide are believed to suffer from AD, and with the aging of the population this number is expected to triple by 2050 if no efficient treatment is developed.[2] To date, although some acetylcholinesterase inhibitors (e.g., donepezil, galantamine) could exert beneficial role in improving AD symptom, no effective treatment has been proved to stop the progress of AD. Therefore, there is an urgent need for developing new anti-AD drugs that are safe and effective with minimal side effects.

Although the histopathogenesis of AD is still unknown, it is hypothesized that the accumulated amyloid-β-peptide (Aβ), triggering critical intracellular signaling pathways that lead to cell stress and apoptosis, is considered as one of the original cause of AD.[3] Moreover, oxidative stress which results from excessive reactive oxygen species (ROS) production and insufficient antioxidant defense systems is commonly observed and may contribute to the progress of AD.[4] Hydrogen peroxide (H_2O_2) produced during the redox process is the main form of ROS, which causes protein and lipid peroxidation and DNA damage and cell death.[5] In addition, cerebral ischemia characterized by insufficient oxygen and glucose supply will result in imbalanced energy metabolism and at last cell death, which is also believed to be a cause of AD.[6,7] As an in vitro model of cerebral ischemia, oxygen–glucose deprivation (OGD) has now been widely used.[8,9] Based on these observations, discovering novel compounds with multi-effects on protecting neurons from toxicity induced by Aβ, H_2O_2, and OGD may be an effective strategy to develop anti-AD drugs.

Marine natural products (MNPs) proved to be a tremendous source for research and development of candidate/clinical drugs.[10] In particular, there is a growing interest from the community of medicinal chemistry in the development of novel marine neuroprotective agents over the last few decades.[11,12] Our group has focused on isolation, synthesis and biological evaluation of MNPs for many years,[13–15] and recently two novel 1,2,4-oxadiazole alkaloids,

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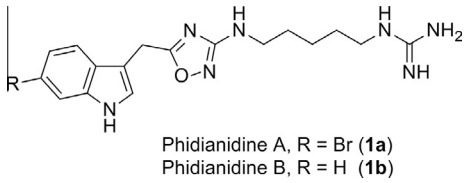

Figure 1. The structures of phidianidines A (**1a**) and B (**1b**).

phidianidines A (**1a**) and B (**1b**) (Fig. 1), had been isolated from the shell-less marine opisthobranch mollusk *Phidiana militaris* by our group in collaboration with Gavagnin's group.[16] These phidianidines are particularly of interest because they present the first example of natural products possessing an 1,2,4-oxadiazole ring system, and meanwhile showed strong antitumor activity against C6 and HeLa cells with the IC_{50} values within nanomolar range. In addition, phidianidine A was found to be a new antagonist of CXCR4, an important pharmacological target for treating HIV infection, rheumatoid arthritis, and cancer development/progression and metastasization.[17] However, both phidianidines showed only 5–30% inhibition on NCI 60 cell lines and no toxicity against HEK293 cell lines at 10 μM.[18,19] Interestingly, they were found to be selective inhibitors of the dopamine transporter and selective agonists of the μ-opioid receptor, indicating that they are useful for developing novel ligands for CNS targets or analgesics due to their unique pharmacological profiles.[19,20]

The bioactivities of phidianidines toward diverse pharmacological targets are not surprising given their interesting structural features: (i) indole fragment is a common but important pharmacophore widely presented in numerous bioactive natural products or drugs for the CNS disorders;[21,22] (ii) the 1,2,4-oxadiazole ring system, known as an ester isostere, is present in various compounds with β-amyloid imaging function in AD and anti-oxidant activity;[23,24] (iii) meanwhile the compounds incorporating guanidine fragment also have potential application in the treatment of neurodegenerative disorders (e.g., AD) and inflammation.[25–27] All the above observations strongly suggested that these phidianidines might have potential value in the treatment of neurodegenerative disorders, such as AD, that stimulated our great interest in the research of their neuroprotective activity.

Since there is no information associated to the SAR study of **1**, at the beginning the aminophenyl- and aminopyrimidine-substituted furan ring moiety were arbitrarily used to replace the alkylguanidinium side chain resulting into the production of phidianidine mimic **2a** and **2b** (Fig. 2). The cytotoxicity of **2a** and **2b** against HL-60 and A549 cell lines were first evaluated. At the concentration of 10 μM, both compounds showed very weak toxicity (26–35% inhibition on HL-60; 2.0–4.2% inhibition on A549). Then, their neuroprotective effects against $Aβ_{25–35}$-, H_2O_2-, and OGD-induced neurotoxicity in human SH-SY5Y neuroblastoma cells were evaluated. The results from the neuroprotective bioassay indicated that compound **2a** was inactive in the abovementioned cell models even at the concentration of 10 μM, but the compound

Table 1
The neuroprotective of compounds against $Aβ_{25–35}$-induced neurotoxicity in SH-SY5Y cells

Compd	Cell viability[a] (%)		Compd	Cell viability (%)	
	1 μM	10 μM		1 μM	10 μM
2a	N.A.[b]	N.A.	**2m**	N.A.	92.1
2b	N.A.	92.4	**2n**	N.A.	92.1
2c	N.A.	N.A.	**2o**	N.A.	N.A.
2d	N.A.	N.A.	**2p**	N.A.	91.5
2e	N.A.	N.A.	**2q**	N.A.	89.1
2f	N.A.	N.A.	**2r**	90	115.5
2g	N.A.	N.A.	**2s**	N.A.	93.3
2h	N.A.	N.A.	**2t**	N.A.	84.8
2i	N.A.	80.3	**2u**	N.A.	83.9
2j	N.A.	100.0	**2v**	N.A.	83.5
2k	89.7	114.2	**11a**	N.A.	N.A.
2l	N.A.	93.3	**11b**	N.A.	106.0
			EGCG	N.T.[c]	96.2

[a] The neuroprotective effect of these compounds on $Aβ_{25–35}$-induced neurotoxicity in SH-SY5Y cells. The cell viability in control was taken as 100%, and the average value of cell viability under $Aβ_{25–35}$ exposure was 69.77% ± 3.14. The positive control is epigallocatechin gallate (EGCG).
[b] N.A. means not active.
[c] N.T. means not tested.

2b displayed significant neuroprotective effect against $Aβ_{25–35}$-induced injuries in SH-SY5Y cells (94.2% of cell viability at 10 μM), similar level with the positive control EGCG at 10 μM (cell viability: 96.2%). These data are shown in Table 1. In addition, compound **2b** also showed neuroprotective activity against OGD-induced injuries in SH-SY5Y cells with 18.96% of increase in cell viability at 1 μM. These positive pharmacological data allowed **2b** to be a potential anti-AD hit compound.

Based on our preliminary result, a series of **2b** derivatives possessing indole-based 1,2,4-oxadiazoles skeleton with different side chain were prepared and evaluated for neuroprotective activities against $Aβ_{25–35}$-, H_2O_2-, and OGD-induced neurotoxicity in SH-SY5Y cells.

The preparation of **2a** and **2b** was accomplished by using the general method outlined in Scheme 1. The commercially available 5-bromo-2-furaldehye **3** was reacted with hydroxylamine hydrochloride in EtOH overnight to afford aldoxime **4** in 90% yield,[24] and the following mild dehydration of **4** catalyzed by $[RuCl_2(p\text{-cymene})]_2$ under refluxing CH_3CN produced nitrile **5** in 70% yield.[28] The intermediate **6** was obtained in 85% yield by the treatment of **5** with hydroxylamine hydrochloride,[29] and then compound **6** was reacted with indole-3-acetic acid **8** to give the key intermediate **7** in two steps with 60% yield.[18,30] Finally, the intermediate **7** was converted into **2a** and **2b** in good yield by reacting with different boronic acid pinacol ester under Suzuki cross-coupling conditions.[31]

Another serieses of target compounds, **11a**, **11b** (possessing thiofuran or benzene instead of furan) and **2c–2v**, were prepared via a similar synthetic route with that of compound **2a** and **2b** (Schemes 2 and 3). Thus, a total of twenty-four new compounds had been prepared.

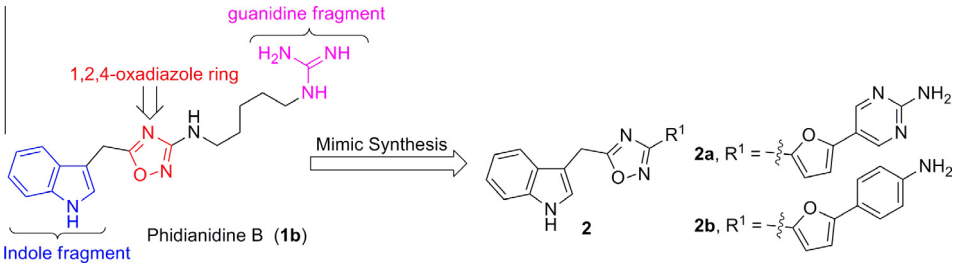

Figure 2. The synthesis of phidianidine B mimic.