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# Neuroprotective metabolites from the endophytic fungus *Penicillium citrinum* of the mangrove *Bruguiera gymnorrhiza*

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ABSTRACT

Two new compounds, named as (*Z*)-7,4′-dimethoxy-6-hydroxy-aurone-4-*O*-*β*-glucopyranoside (**1**), and (1*S*,3*R*,4*S*)-1-(4′-hydroxyl-phenyl)-3,4-dihydro-3,4,5-trimethyl-1H-2-benzopyran-6,8-diol (**2**), were isolated from the endophytic fungus *Penicillium citrinum* of *Bruguiera gymnorrhiza*. Their structures were elucidated on the basis of spectroscopic analysis. Additionally, compound **1** exhibited potent neuroprotective activity in 1-methyl-4-phenylpyridinium-induced oxidative damage in PC12 cells.
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## 1. Introduction

Over the last decade, many new metabolites with diverse pharmacological activities have been isolated and identified from marine-derived fungi (Blunt et al., 2010). Mangroves, woody plants growing at the interface between land and sea in tropical or subtropical latitudes, create unique ecological environments that host rich assemblages of species (Kathiresan and Bingham, 2001). Metabolites from the fungi, especially the endophytic fungi in mangroves are a rich source of new natural products (Bai et al., 2015; Liu et al., 2014; Wang et al., 2014). Among these endophytic fungi, *Penicillium* is one of the major contributors, whose secondary metabolites have been reported to possess many kinds of bioactivities, such as antitumor and antimicrobial effects (Du et al., 2010; Wang et al., 2013; Xin et al., 2009). This paper describes the isolation and characterization of a new aurone glycoside, (*Z*)-7,4′-dimethoxy-6-hydroxy-aurone-4-*O*-*β*-glucopyranoside (**1**), as well as a new citrinin derivative, (1*S*,3*R*,4*S*)-1-(4′-hydroxyl-phenyl)-3,4-dihydro-3,4,5-trimethyl-1H-2-benzopyran-6,8-diol (**2**), from endophytic fungus *Penicillium citrinum* of *Bruguiera gymnorrhiza*, one kind of mangrove plants. Oxidative stress played an important role in the pathogenesis of neural diseases, which can be induced by *in vitro* administration of cytotoxic agents (Lee et al., 2005; Luo et al., 2012). Exposure of neurons to such cytotoxic agents will result in the activation of a cascade of intracellular toxic events to cause alteration of the mitochondrial membrane permeability, induce the release of cytochrome-c from the mitochondrial to nucleus, activate caspase-related apoptosis protein and facilitate the formation of apoptosome complex, resulting in DNA cleavage and neuronal cell death (Leuner et al., 2007). Supplementation of exogenous antioxidants has their effects in curtailing the oxidative damage to cellular macromolecules. This study was conducted to find new neuroprotective agents in oxidative stress-induced neurodegenerative models.

## 2. Results and discussion

*Compound* **1**: An orange-red amorphous powder. The molecular formula $C_{23}H_{24}O_{11}$ was deduced from HR-ESI-MS *m*/*z*: 477.1385 $[M+H]^+$ (calcd. for $C_{23}H_{25}O_{11}$, 477.1392). The $^1H$ NMR spectrum (Table 1) exhibited two methoxy signals at *δ* 3.82 (3H, s, $CH_3$-4′) and 3.61 (3H, s, $CH_3$-7), six signals of olefinic protons at *δ* 5.65 (1H, s, H-5), 7.83 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.14 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), and 6.38 (1H, s, H-10), and signals of one glucose moiety at *δ* 3.21–4.92. Analyzing the $^1H$, $^{13}C$ NMR, and 2D NMR (HMBC, HSQC, and NOESY) data, **1** was deduced to be an aurone glucoside (Huang et al., 2008). The $^{13}C$ NMR spectrum displayed 23 carbon signals, including 14 olefinic carbons, one carbonyl, two methoxy groups, and six O-substituted carbons. The HMBC correlations

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**Table 1**
$^{1}$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) date of compound **1** in DMSO-$d_6$ ($\delta$ in ppm, $J$ in Hz).

| No. | $\delta_H$ | $\delta$c |
|---|---|---|
| 2 | | 146.5 |
| 3 | | 178.2 |
| 4 | | 156.6 |
| 5 | 5.65(1H, s) | 81.2 |
| 6 | | 161.4 |
| 7 | | 135.5 |
| 8 | | 169.4 |
| 9 | | 109.4 |
| 10 | 6.38(1H, s) | 105.1 |
| 1′ | | 126.1 |
| 2′/6′ | 7.83(1H, d, $J$ = 8.5) | 131.4 |
| 3′/5′ | 7.14(1H, d, $J$ = 8.5) | 116.1 |
| 4′ | | 158.9 |
| 1″ | 3.82(3H, s) | 53.7 |
| 2″ | 3.61(3H, s) | 59.2 |
| Glc-1 | 4.92(1H, d, $J$ = 7.5) | 98.8 |
| Glc-2 | 3.23(1H, m) | 73.2 |
| Glc-3 | 3.29(1H, m) | 75.9 |
| Glc-4 | 3.21(1H, t, $J$ = 8.5) | 68.4 |
| Glc-5 | 3.33(1H, m) | 74.8 |
| Glc-6 | 3.72(1H, d, $J$ = 11.0) | 60.2 |
| | 3.49(1H, dd, $J$ = 11.0, 5.5) | |

**Table 2**
$^{1}$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) date of compound **2** in DMSO-$d_6$ ($\delta$ in ppm, $J$ in Hz).

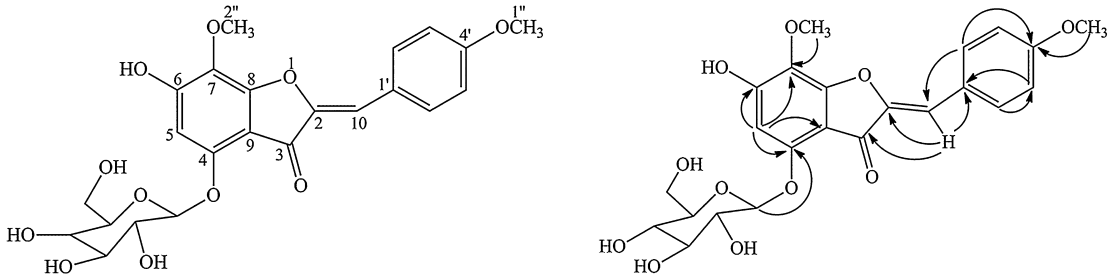
| No. | $\delta_H$ | $\delta_C$ |
|---|---|---|
| 1 | 5.65(1H, s) | 72.5 |
| 3 | 3.39(1H, m) | 71.7 |
| 4 | 2.63(1H, m) | 36.4 |
| 5 | | 112.5 |
| 6 | | 156.1 |
| 7 | 6.26(1H, s) | 98.7 |
| 8 | | 152.7 |
| 9 | | 114.2 |
| 10 | | 138.9 |
| 11 | 1.22(3H, d, $J$ = 6.5) | 19.1 |
| 12 | 1.07(3H, d, $J$ = 7.0) | 18.3 |
| 13 | 1.89(3H, s) | 10.5 |
| 1′ | | 134.2 |
| 2′/6′ | 6.97(1H, d, $J$ = 8.5) | 128.5 |
| 3′/5′ | 6.58(1H, d, $J$ = 8.5) | 115.6 |
| 4′ | | 158.4 |
| 4′-OH | 9.29(1H, s) | |
| 6-OH | 8.87(1H, s) | |
| 8-OH | 8.79(1H, s) | |

were observed from H-2″ to C-7; from H-1″ to C-4′; from H-5 to C-4, C-6, C-7, C-9; from H-10 to C-2, C-3, C-1′; from H-2′ to C-3′; from H-3′ to C-1′; from H-6′ to C-4′, C-10 and from H-Glc-1 to C-4 (Fig. 1), suggesting the structure as 7,4′-dimethoxy-4,6-dihydroxy-aurone. The $\beta$ configuration of glucose was suggested by the coupling constant of the anomeric proton $\delta$ 4.92 (1H, d, $J$ = 7.5 Hz, H-Glc-1). HMBC data showed a correlation between H-Glc-1 ($\delta$ 4.92, 1H, d, $J$ = 7.5 Hz,) and C-4 ($\delta$ 156.6), indicating the glucose moiety was attached to C-4 of the aglycon. These assignments were further confirmed by the NOESY spectrum which showed correlations between protons H-10 ($\delta$ 6.38, 1H, s) and H-2′, H-6′ ($\delta$ 7.83, 2H, d, $J$ = 8.5 Hz,), H-5 ($\delta$ 5.65, 1H, s) and H-Glc-1 ($\delta$ 4.92, 1H, d, $J$ = 7.5 Hz). The *Z*-stereochemistry at C-10 was determined by the lower chemical shift of C-10 ($\delta$ 105.1) according to a reference (Pelter et al., 1979). Furthermore, *E*-stereochemistry has higher chemical shifts at C-10 ($\delta$ 118–122) (Agrawal, 1989). So the structure of compound **1** was elucidated as (*Z*)-7, 4′-dimethoxy-6-hydroxyl-auraone-4-*O*-$\beta$-glucopyranoside.

*Compound* **2**: $[\alpha]_D^{25}$ +45.5 (*c* 0.1, MeOH), was obtained as a yellow gum. The molecular formula $C_{18}H_{20}O_4$ was deduced from HR-ESI-MS *m*/*z*: 299.1277 $[M-H]^-$ (calcd. for $C_{18}H_{19}O_4$, 299.1285). The NMR data (Table 2) revealed eighteen carbon signals, including three methyls, seven quaternary carbons, and eight methines. The plane structure of **2** was revealed through COSY and HMBC spectrum analyses (Fig. 2). The COSY correlations of H-2′/6′ with H-3′/5′, the HMBC correlations from H-2′/6′ to C-4′, H-3′/5′ to C-1′ and C-4′, 4′-OH to C-3′, C-4′ and C-5′ demonstrated the existence of a 1,4-substituted benzene ring. The COSY correlations of H-11 with H-3, H-12 with H-4, as well as the HMBC correlations from H-1 to C-3, C-9 and C-10, H-3 to C-1 and C-10, H-4 to C-9 and C-10 demonstrated the existence of a multi-substituted dihydropyrane. The HMBC correlations of H-1 with C-1′, C-2′ and C-6′, as well as H-2′/6′ with C-1 linked first benzene ring to the dihydropyrane *via* C-1 and C-1′. Furthermore, the HMBC correlations of H-13 with C-5, C-6 and C-10, H-7 with C-5, C-6, C-8 and C-9, 6-OH with C-5, C-6 and C-7, as well as 8-OH with C-7, C-8 and C-9 linked the second benzene ring to the dihydropyrane *via* C-9 and C-10.

The relative configuration of **2** was assigned on the basis of the NOESY correlations of H-1 and H-4 with H-11 as well as H-3 with H-12. The absolute configuration of **2** was determined by comparison of its specific optical rotation value ($[\alpha]_D^{25}$ +45.5) with those of penicitrinol C ($[\alpha]_D^{25}$ +33.2) (Chen et al., 2011) and penicitrinol F ($[\alpha]_D^{25}$ +24.8) (Nong et al., 2013), which suggested that the absolute configuration of **2** was also 1*S*,3*R*,4*S*. So, the structure of **2** was elucidated as (1*S*,3*R*,4*S*)-1-(4′-hydroxyl-phenyl)-3,4-dihydro-3,4,5-trimethyl-1H-2-benzopyran-6,8-diol.

Compound **2** showed weak neuroprotective effect in 1-methyl-4-phenylpyridinium ($MPP^+$)-induced toxicity in PC12 cells. However, pre-incubation of compound **1** with PC12 cells for 24 h significantly decreased the $MPP^+$-induced neurotoxicity, shown by elevating the cell viability (Fig. 3). In addition, pre-incubation of compound **1** would elevate the mitochondrial membrane potential, decrease the formation of DNA fragmentation, and inhibit the activities of caspase-3 and caspase-9 in $MPP^+$-treated PC12 cells (Figs. 4–6).




**1**

**Fig. 1.** Structure and key HMBC correlations of compound **1**.

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