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**A trace alkaloid, oleraisoindole A from *Portulaca oleracea* L. and its anticholinesterase effect**

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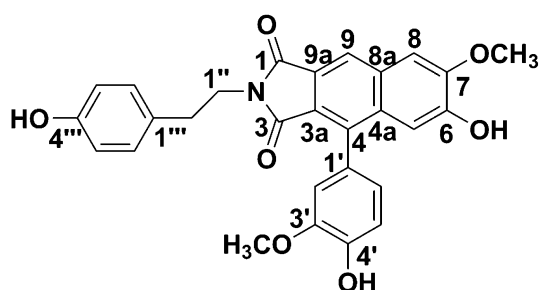
**Abstract**

A new trace alkaloid possessing the lignan structure, named oleraisoindole A, was obtained from the extract of the *Portulaca oleracea* L.. The structure of oleraisoindole A was elucidated by 1D and 2D NMR and high resolution electrospray ionization time-of-flight mass spectroscopic methods. The compound presented an anticholinesterase effect with the IC<sub>50</sub> value of 60.4 μM.

**Keywords:** *Portulaca oleracea* L.; alkaloids; anticholinesterase effect

## 1. Introduction

*Portulaca oleracea* L., a member of the Portulacaceae family has been used as a vegetable, spice and medicine since the times of the ancient Egyptian and was popular in England during the Middle Ages 33 (Okafor et al. 2014). In China, *P. oleracea* is a traditional Chinese medicine well-known for its pharmacological function of removing heat, counteracting toxicity, cooling blood, hemostasia and antidysentery (The Pharmacopoeia Commission of PRC, 2015) owing to its many bioactive compounds, including alkaloids (Li et al. 2017; Xu et al. 2017; Zhao et al. 2018; Xiu et al. 2018), flavonoids (Yang et al. 2018; Yang et al. 2018), coumarins (Awad 1994), lignans (Ma et al. 2018), phenolic acids (Erkan 2012), terpenoids (Elkhayat et al. 2008). As alkaloids are the main components of the plant and presents many bioactivities, such as antiinflammatory (Meng et al. 2016; Jiang et al. 2018), antimalarial (Frederich et al. 2008) and antioxidant activities (Racková et al. 2004), etc.. Therefore, the aim of the study is to isolate alkaloids, a trace new alkaloid, named oleraisoindole A (Figure 1) was finally obtained from the extract of *P. oleracea*. In addition, its anticholinesterase effect was studied as Alzheimer's disease has (AD) related to acetylcholinesterase (AChE) (Howes et al. 2003).



**Figure 1. Structure of Oleraisoindole A.**

## 2. Results and discussion

Oleraisoindole A (1 mg, purity of > 99% with UHPLC) was obtained as a pale yellow powder, which turned orange and cyan after spraying Dragendorff reagent and ferric chloride on a TLC plate. UV-Vis (MeOH)  $\lambda_{\text{max}}$ : 284 nm. IR (KBr)  $\nu_{\text{max}}$ : 3425, 1756, 1706, 1600, 1515, 1400, 1265, 1212  $\text{cm}^{-1}$ . Its molecular formula was identified as  $\text{C}_{28}\text{H}_{23}\text{NO}_7$  with 18 degrees of unsaturation based on a molecular ion peak at  $m/z$  484.1404  $[\text{M}+\text{H}]^+$  in the HR-ESI-TOF-MS (calcd. for  $\text{C}_{28}\text{H}_{23}\text{NO}_7$ , 484.1401) and the NMR data (Table S1, in supplementary material). A 3-spin system was found, which linked to carbon C-4 at  $\delta_{137.0}$  and defined a 1,3,4-trisubstituted phenyl moiety based on  $^1\text{H}$ - $^1\text{H}$  coupling pattern, COSY and HMBC experiment. There is also a typical of *para*-disubstituted phenyl ring, in which C-2'' was linked to C-1''' as the HMBC spectrum shows the correlation H-2'''/C-2''. The  $^1\text{H}$ - $^1\text{H}$  COSY and DEPT spectrum shows the correlation position 1'' ( $\delta_{\text{H}}3.66$ ,  $\delta_{\text{C}}39.0$ )/2'' ( $\delta_{\text{H}}2.74$ ,  $\delta_{\text{C}}32.9$ ). The highfield chemical shift of position 2'' was obviously different with that of the oleraisoindole (Table S2 and Figure S1 in supplementary material) previously isolated in our lab (Jiang et al. 2018) meaning that  $\text{CH}_2$  in oleraisoindole A only connected to position 1'' that was typical of  $\text{CH}_2$  connected to N, and N linked to C-1 and C-3. In HMBC, H-1'' correlated to carbonyl groups C-1 and C-3 at  $\delta_{166.9}$  and 167.4, respectively. In  $^1\text{H}$ -NMR, only three singlet CH signals and nine quaternary carbons were remained and attached to the established peripheral groups. Protons H-8 and H-9 were not coupled to each other. Nevertheless, they correlated in ROE indicating that they were close to each other but not attached to a single phenyl ring. Altogether, these indications led to position two periprotons on a naphthalene moiety. Based on the strong ROE correlation between methyl group and H-8, the methoxy substituent at the C-7

position was determined. H-9 correlated to C-4a and H-8 which based on HMBC and ROE, respectively. This further confirms the relative positions of H-8 and H-9. H-9 also correlated to C-1 and C-3a. It was therefore to link C-1 to C-9a, and the C-3 linked C-3a is reasonable based on chemical shift of the quaternary carbon C-3a ( $\delta$ 121.6). Since the singlet proton H-5 at  $\delta$ 7.12 correlated to both C-6 and C-7, it should to be placed in paraposition with respect to H-8. H-5 also correlated to C-4 and C-8a from their weak correlation, and the ROE correlation between H-5 and H-6' confirmed the position of the tetrasubstituted phenyl ring. The last carbon C-9a remained was  $\delta$ 124.9 compared with that of oleraisoindole (Table S2). As a result, the compound was identified as the 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-2-(4-hydroxyphenethyl)-7-methoxy-1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione and was given the trivial name oleraisoindole A (Experimental section, in supplementary material).

Among these natural products, alkaloids are considered to be the most promising candidates for use in the treatment of AD, such as physostigmine (eserine) have been long recognized as acetyl- and butyrylcholinesterase (BChE) inhibitors, due to their complex nitrogen-containing structures (Pereira et al. 2010). The inhibition of AChE, the key enzyme in the breakdown of acetylcholine, is currently the main pharmacological strategy available for AD (Konrath et al. 2013). Consequently, the anticholinesterase effect of oleraisoindole A was determined using a microplate assay with the sample of concentrations from 2.5 to 40  $\mu$ M, and inhibited 50% of AChE activity (IC<sub>50</sub>) were presented in Table S3. Figure S14 showed that the anticholinesterase effect of oleraisoindole A was dose-dependent. Anticholinesterase effect was determined according to the modified Ellman method (Ellman et al. 1961). The sample solutions in methanol was diluted into five different concentrations and the AChE solution in buffer of PBS (pH 8.0, containing 0.1 mol/L Na<sub>2</sub>HPO<sub>4</sub> and

NaH<sub>2</sub>PO<sub>4</sub>) were mixed in wells a 96-well microplate. Then incubated for 10 minutes at 37°C and added 5,5-dithiobis-2-nitrobenzoic acid (DTNB) to the buffer. Finally, acetylthiocholine iodide (ATCI) was added and the absorbance was monitored spectrophotometrically at 405 nm. The same concentration of eserine was used as a positive control. Instead of samples, methanol was included in the blank control.

Each sample was measured in parallel five times and the percentage of inhibition of AChE was calculated using the following formula (Šinko et al. 2007):

Anticholinesterase effect (%) = [(Ablank – Asample)/Ablank] × 100% where, Asample is the absorbance of the test compound, and Ablank is the absorbance of the blank control. The anticholinesterase effect was evaluated by the value of IC<sub>50</sub>, and values are expressed as the means ± SD for n = 5.

#### **4. Conclusion**

A trace (1 mg) new alkaloid, oleraisoindole A possessing the lignan structure was isolated from the extract of *P. oleracea* of 250 kg, and its structure was complicated that only can be determined by 600 MHz NMR with cryogenic probe. In addition, oleraisoindole A presented anticholinesterase effect with an IC<sub>50</sub> value of 60.4 μM.

#### **Supplementary material**

Supporting information can be found in the online version of this article.

#### **Disclosure statement**

The authors have no conflicts of interest to disclose.

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