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Amberboin and lipidiol: X-ray crystalographic data, absolute configuration and inhibition of cholinesterase

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ABSTRACT

The phytochemical investigation of the extract of *Volutaria abyssinica* (A. Rich.) C. Jeffrey (Asteraceae) resulted in the identification of the two sesquiterpene lactones, *i.e.* amberboin and lipidiol. Amberboin and lipidiol are interesting tricyclic sesquiterpene lactone derivatives with a guaianolide skeleton. In the current study, the absolute structure and absolute configuration of amberboin were determined for the first time. The structure of amberboin was unambiguously determined with the single crystal X-ray measurements and the absolute configuration of the seven chiral centers was determined to be C2(*R*), C3(*R*), C4(*S*), C7(*R*), C10(*S*), C11(*R*) and C12(*R*). The biological investigation of both compounds **1** and **2** against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) showed that both compounds are promising inhibitors of AChE with IC_{50} values of 0.79 ± 0.03 μM and 0.52 ± 0.01 μM for amberboin and lipidiol, respectively, while amberboin (IC_{50} = 0.58 ± 0.13 μM) also effectively inhibited BChE. Additionally, in order to get a better understanding of the inhibition mechanism and also the crucial amino acids contributing to the interactions between the ligands and protein atoms, the catalytic domains of the complexes were studied using molecular modeling approaches. The results suggested that the ligands were quite accommodated inside the binding domains and able to form strong polar and nonpolar contacts with the active site amino acids.

1. Introduction

The chemical investigation of *Volutaria abyssinica* (A. Rich.) C. Jeffrey (Asteraceae) resulted in the identification of amberboin (**1**) and lipidiol (**2**) as the major sesquiterpene lactones with a guaianolide skeleton among other compounds (Marzouk, 2015). The sesquiterpene lactones represent chemically and biologically important class of natural products (Chadwick et al., 2013; Chaturvedi, 2011; Elsebai et al., 2016c). One of them is the artemisinin, the known antimalarial drug, which was discovered by You you Tu (Tu, 2011), the 2015 Nobel laureate in medicine, and recently, the sesquiterpene lactones, *e.g.* cynaropicrin and grosheimol isolated from the wild Egyptian artichoke, exhibited outstanding activities against hepatitis C virus (HCV) (Elsebai et al., 2016a, 2016b, 2016c).

Compound **1** was previously isolated from other plant species in Asteraceae, *e.g. Amberboa lippii* D. C. (syn. *Centaurea lippii* L.) (Bermejo Barrera et al., 1969; Gonzalez et al., 1970, 1967), *Centaurea sinaica* (Al-easa et al., 1990; Al-Easa and RIZK, 1992), and *C. pannonica* (Heuff.) Simonk (Milošević Ifantis et al., 2013). The structure of amberboin was first suggested by Bermejo et al. (Bermejo Barrera et al., 1969), and proved through chemical derivatization and limited ^{1}H-NMR data by Gonzalez et al. (1970). The complete structure elucidation through spectroscopic means including 1D- and 2D-NMR as well as the verification of the relative stereochemistry of amberboin and the related sesquiterpene lactone lipidiol were first carried out by Marzouk (2015). The absolute stereochemistry of the compounds is still to be explored, which is one of the main objectives of this work. The determination of absolute configuration is a challenging issue for the natural and organic products and is extremely important for many reasons. In the current work, we attempted to describe the determination of the absolute structure of amberboin through x-ray crystallography and bioactivity evaluation of compounds **1** and **2** against cholinesterase (ChE) enzyme family, which consists of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). These are

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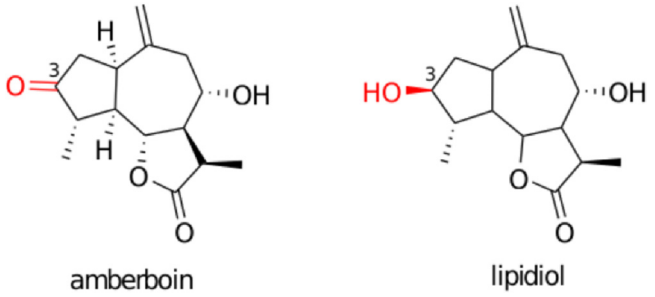

Fig. 1. Structures of amberboin and lipidiol isolated from *Volutaria abyssinica* (A. Rich.) C. Jeffrey.

the key enzymes, playing a main target in the pathogenesis of Alzheimer's disease (García-Ayllón et al., 2011).

2. Results and discussion

2.1. Crystal data of compound 1

Needle crystals (m. p. 148–149 °C) of amerboin were formed from a solvent mixture of chloroform and methanol. The complete crystallographic data were presented in supporting information (S1-S4).

$C_{15}H20O4$, molecular weight = 264.31, T = 100 (2). It crystallized in the orthorhombic system, space group $P2_12121$, Z = 12 with three molecules in a unit cell (Fig. 1) of dimensions a = 8.1309 (2) Å, b = 16.0234 (3) Å, c = 30.9255 (6) Å, α = 90.00, β = 90.00, γ = 90.00, V = 4029.12 (15) Å^3; crystal size 0.41 × 0.18 × 0.16 mm. The refinement was made in F^2, $R[F^2 > 2\sigma(F^2)] = 0.030$, w$R(F^2) = 0.076$, $R_{int} = 0.036$. The absolute configuration was determined on the basis of the Flack parameter 0.03 (4).

The unit cell contains three independent molecules as in Fig. 2. An ORTEP view for only one molecule showing the relative stereochemistry including ring conformation and the configurations of the hydroxyl group and methyl could be confirmed is given in Fig. 3. In the molecule, there are three rings A, B and C: rings A and B are trans-connected *via* a bridge between C3 and C12, rings B and C are cis-connected *via* a bridge between C7 and C11. Ring B cycloheptane has a nearly ideal chair conformation, while rings A and C have puckered conformations. The hydroxyl oxygen atom O3 is connected in an equatorial *e*-orientation to C4 in ring B. The methyl group C15 is connected in an axial *a*-orientation to C10 in ring C. The two methyl groups C13 and C15 are connected in an axial *a*- and equatorial *e*- orientations to C2 and C10, respectively.

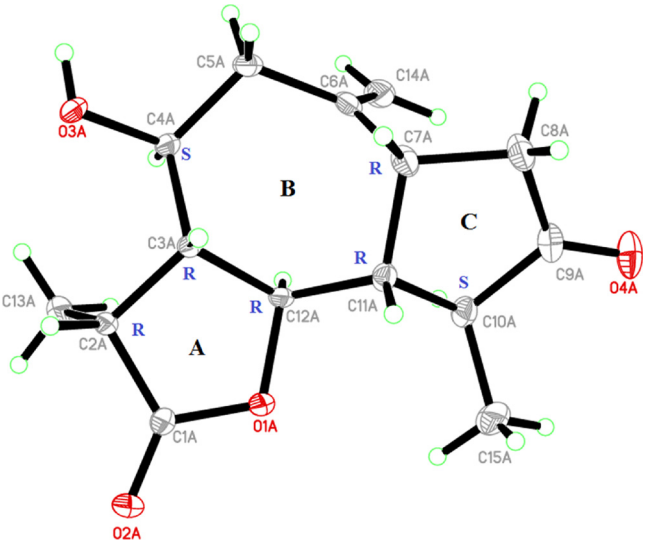

Fig. 3. ORTEP diagram of compound **1** drawn at 50% ellipsoids for non-hydrogen atoms showing the absolute configuration. Two molecules have been omitted for clarity.

The molecules packing in the crystal structure is stabilized *via* two

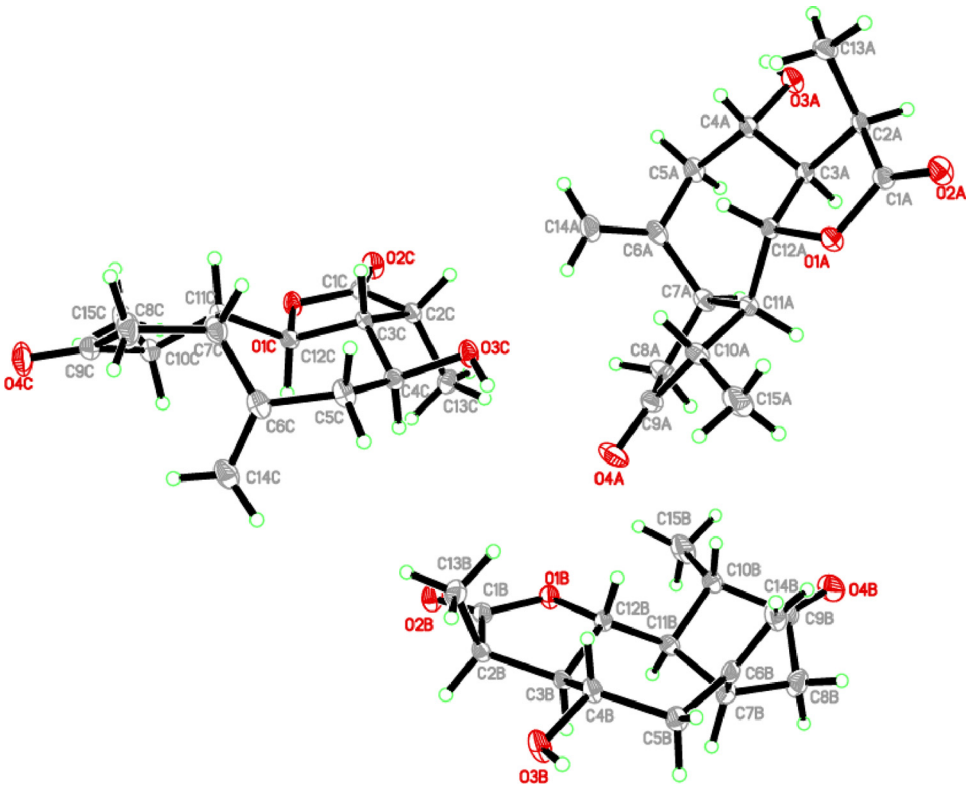

Fig. 2. ORTEP diagram of compound **1** drawn at 40% ellipsoids for non-hydrogen atoms.

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