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New α-Glucosidase inhibitors from the resins of *Boswellia species* with structure–glucosidase activity and molecular docking studies

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ABSTRACT

Phytochemical investigation of the oleo-gum resins from *Boswellia papyrifera* afforded one new triterpene, named 3α-hydroxyurs-5:19-diene (**1**) together with twelve known compounds including eight triterpenoids (**2–9**), two diterpenoids (**10** and **11**) and two straight chain alkanes (**12** and **13**). Similarly ten more known compounds were isolated from the resin of *Boswellia sacra* including one triterpene (**20**) and nine boswellic acids (**14–19** and **21–23**). Herein the compound **2** was first time reporting from natural source along with complete NMR assignment, while compounds **3–11** are known, but reported for the first time from the resin of *B. papyrifera*. The structure elucidation was done by advance spectroscopic ^{1}D and ^{2}D NMR techniques viz., ^{1}H, ^{13}C, DEPT, HSQC, HMBC, and COSY, and NEOSY, ESI-MS and compared with the reported literature. All compounds were evaluated for their α-glucosidase inhibitory activity and as result eight of them **1**, **3**, **10**, **11**, **15**, and **17–19** were found significantly active against α-glucosidase with an IC_{50} value ranging from 15.0 ± 0.84 to 80.3 ± 2.33 µM, while **21** exhibited moderate activity with IC_{50} of 799.9 ± 4.98 µM. Furthermore, two compounds **24** and **25** were synthesised from **16** and **17** to see the effect of carboxyl group in structural-activity relationship (SAR) study. Compounds **24** and **25** retained good α-glucosidase inhibition as compared to **16** and **17**, indicating that carboxylic group play a key role in SAR. In addition, the aforementioned activity of all the active compounds was first time reported for their α-glucosidase inhibition potential. The molecular docking studies showed that all the active compounds well accommodate in the active site of the enzyme. Moreover pharmacokinetic properties of the compounds were predicted *in silico,* suggesting that the compounds possess drug like properties and excellent ADMET profile.

1. Introduction

Diabetes mellitus mostly characterized by hyperglycemia and their complications (neuropathy, nephropathy and retinopathy) increase the morbidity and mortality risks for the patients [1,2]. It is estimated that about 90% of the world's diabetic people have Type 2 diabetes mellitus [3–5]. Poor control of the post-prandial glucose levels, related with type-2 diabetes mellitus, leads to on-set of atherosclerosis and other cardiovascular disorders [6,7]. *α*-Glucosidase enzyme (EC 3.2.1.20) catalyzes the cleavage of oligosaccharides to glucose in the small intestine. Its inhibition can contribute to the control over the post-prandial hyperglycemia and thereby prevents diabetic complications [8]. *α*-Glucosidase inhibitors (AGIs), such as acarbose, voglibose and miglitol, compete with the oligosaccharides for the binding of the enzyme and successfully decrease the post-prandial glucose levels in type-2 diabetes patients [8]. However, these classic AGIs are known to cause flatulence, diarrhea and abdominal discomfort and having low efficacy with high IC_{50} values against the enzyme [9].

Clinically approved anti-diabetic drugs have restricted safety alarms, and temporally improve blood glucose levels, improves diabetes complications, as well as in the treatment of obesity [10] but accompanied with gastrointestinal side-effects [11]. The consumption of natural products is known to have anti-diabetic effects, offering numerous exciting potentials for the future progress and development of successful therapies [5,10]. Due to the essential role of this enzyme in hyperglycemia and specially the side effects of the existing drugs, the basic requirement is to discover safe and effective enzyme inhibitors as an approach to effectively control the diabetic disorders.

The oleo gum resin (frankincense) of *Boswellia* species and its individual components has shown numerous biological applications

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including anti-inflammatory, leukotriene biosynthesis-inhibitory and anti-tumor activities [12–15]. A group of pentacyclic triterpenoids (Boswellic acids; BAs) are usually isolated from the resins of *Boswellia* spp. and considered the key bioactive components of frankincense [16]. Their biological activities against ulcerative colitis, asthma, chronic colitis, hepatitis, inflammation, and arthritis are well documented [14,17–23]. BAs are also reported to inhibit growth and effect apoptosis in brain tumors, colon cancer cells, malignant glioma cells, and leukemia cells [24–27].

Boswellia papyrifera (Del.) Hochst., mostly grows in Sudanian and Sahelian regions and their oleo-gum resin is used medically in treatment of rheumatism, menorrhagia, amenorrhoea, vaginal infections, ulcers, sores, polyuria, syphilis, bronchitis, scrofulous affections, inflammations, asthma, diarrhea, and nervous diseases [28–30]. Previous phytochemical studies on the stem bark and resins of *B. papyrifera* resulted in the isolation of stilbene glycosides, BAs, β-sitosterol and incensole derivatives [29,31–36]. The gum resins of *Boswellia sacra* Fluckiger (The Omani frankincense) are used against dental infections, digestive system, stomach aches, arthritis, muscle pain, as well as for the treatment of colds, fever, cough, and asthma [37]. However, limited reports are available on the phytochemical investigations and glucosidase activity of the title resin, BAs and frankincense obtained from these plants [37–42].

We herein report the first α-glucosidase effect of the boswellic acids isolated from *B. papyrifera* and *B. sacra* and their synthetic derivatives along with structural-activity relationship. In addition, the molecular docking studies were also performed, in order to evaluate their mode of binding interaction with the active site of enzyme as well as *in silico* pharmacokinetic prediction.

2. Experimental section

2.1. General

ESI-MS spectra were recorded on a Waters Quattro Premier XE Mass Spectrometer (Waters, Milford, MA). NMR (Multinuclear and multidimensional) spectra were recorded on an NMR (BRUKER) spectrometer operating at 600 MHz for ^{1}H (150 MHz for ^{13}C) with cryoprobe prodigy. The chemical shift data are presented in ppm (δ) units and the coupling constants (J) w given in Hz. IR spectra were recorded on a Bruker, ATR-Tensor 37 spectrophotometer. Optical rotations ($[\alpha]_D^{25}$) were measured on a KRUSS P3000 polarimeter (A. Kruss Optronic, Germany). For TLC (Thin Layer Chromatography), pre-coated aluminum sheets (silica gel 60F-254, E. Merck) were used. Visualizations of the TLC plates were attained under the UV light at 254 and 366 nm and also by spraying with the ceric sulfate reagent.

2.2. Plant material and identification

The *B. papyrifera* resin was collected (Sudan) and provided by Dr. Saifeldin Elnegrabi and authenticated by Dr. Mustafa Mansi (Botanist), Department of Biological Sciences and Chemistry (DBSC), University of Nizwa, Oman. The *B. sacra* resin samples were collected from the various locations in Oman and were also supplied by a trustful partner (Mr. Saleh Al-Amri). The specimens (BPSR-01/2014; BSHR-01/2012) were deposited in the Herbarium of the Chair of Oman's Medicinal Plants and Marine Natural Products (COMPMNP).

2.3. Extraction and isolation

The air-dried powder material of *B. papyrifera* resin (1.5 kg) was finely extracted with MeOH (2.0 L) at r.t. (3 × 2 days) and evaporated under reduced pressure to yield a yellow semi-solid MeOH residue (1.3 kg). The MeOH residue was subjected to Vacuum Liquid Chromatography (VLC) using 10, 20, 30 and 50% EtOAc/*n*-hexane to afford five major fractions (BPF_{1-5}). Fraction (BPF_1, 10% *n*-hexane/EtOAc) was subjected to silica gel column chromatography (CC) using 5 and 10% EtOAc/*n*-hexane as an isocratic mobile phase to get four sub-fractions ($BPSF_{1-4}$). After taking TLC, sub fraction ($BPSF_2$) was further chromatographed on CC to afford compounds **10** and **11** using *n*-hexane as a mobile phase along with some semi-pure compounds, which were later on loaded directly on recycling preparative HPLC. These two compounds **12** and **13**, using $CHCl_3$ solvent HPLC system stabilized with 0.6% EtOH, were eluted as a UV-inactive compound at a retention time of 44.7 min and 46.0 with 3.5 ml/min flow rate, respectively. Fraction (BPF_2), 20% *n*-hexane/EtOAc, was loaded on a silica gel column chromatography using gradient mobile phase of 10, 20 and 30% EtOAc/*n*-hexane to get one new (**1**) (5.5 mg) and eight known compounds **2–9**.

Similarly, the air-dried ground material (500 g) of *B. sacra* resin was exhaustively extracted with 100% MeOH at room temperature. The extract was evaporated to yield the residue (370 g). The MeOH extract (370 g) was subjected to CC (SiO_2 (1000 g; 70–230 mesh; Merck; *n*-hexane/EtOAc up to 50%EtOAc, and then washed by pure EtOAc) yielded ten fractions (BSF_{1-10}). After taking TLC, three fractions BSF_{4-7} (40–70% EtOAc/*n*-hexane) were combine together and subjected to column chromatography, using gradient solvent system of EtOAc/*n*-hexane to get a mixture of two compounds **17** (Rf = 0.6) and **18** (Rf = 0.4) (4:6 EtOAc/*n*-hexane), which were further purified by recycling chloroform HPLC and eluted as a UV-active compounds at a retention time of 42 min with 4 ml/min flow rate. Fraction three (BSF_3) of the first column was subjected to silica gel column using gradient solvent system of EtOAc/*n*-hexane and obtained four compounds **14–16** and **19** which were farther purified by recycling chloroform HPLC. Similarly, chromatographic separation of fraction two (BSF_3) was done using gradient solvent system and afforded three compounds **20–23**. Furthermore, two compounds **24** and **25** were synthesized from **16** and **17** using the previous protocols [43,44].

2.4. 3α-hydroxyurs-5:19-diene (*1*)

Colorless amorphous powder; **UV (MeOH)λ_{max}** = 220 (3.87); **mp**: 154–156 °C; **$[\alpha]_D^{25}$** = +27° (MeOH, c = 0.13); **IR (solid) υ_{max}** = 3405, 2940, 2870, 1634, 1461, 1115, 1020, 920; **Q-TOF LC/MS** = *m/z* 447.3455 ($C_{30}H_{48}NaO$; calc. 447.3514); **^{1}HNMR ($CDCl_3$, 600 MHz):** δ 5.08 (1H, t = 5.4 Hz, H-6), 3.41 (1H, t = 3.0 Hz, H-3), 2.05, 1.90 (2H, m, H-21), 2.09, 1.95 (2H, m, H-7), 1.66 (3H, s, H- 29), 1.58 (3H, s, H-30), 1.56 (1H, br. s, H-9), 1.44 (1H, m, H-18), 1.39 (1H, m, H-13), 0.94 (6H, s, H-24, 27), 0.89 (3H, s, H-28), 0.84 (6H, s, H-23, 26), 0.74 (3H, s, H-25); **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 134.2 (C-5), 133.3 (C-19), 130.8 (C-20), 125.2 (C-6), 75.9 (C-3), 50.1 (C-18), 50.0 (C-8), 44.8 (C-9), 44.0 (C-4, 14), 37.6 (C-10), 37.1 (C-17), 36.4 (C-12), 36.3 (C-13), 30.7 (C-1), 29.7 (C-22), 28.1 (C-2), 28.0 (C-28), 27.2 (C-16), 25.8 (C-7), 25.7 (H-29), 24.9 (C-15), 24.4 (H-30), 22.2 (C-23), 21.4 (C-21), 19.9 (C-26), 18.8 (C-11), 18.6 (C-27), 17.6 (C-24), 15.5 (C-25).

2.5. Methyl 3β-acetoxyurs-12-en-24-oate (*2*)

White amorphous powder; **UV (MeOH)λ_{max}** = 224; **mp**: 186–188 °C (reported: 189–190 °C; **$[\alpha]_D^{25}$** = +73.2° (MeOH, c = 0.25; reported: +71.9° [45]; **IR (solid) υ_{max}** = 3424 (OH), 1738 (CH_3CO), 1710 ($COOCH_3$), 1610 (C=C), 1456, 1376, and 1275 cm^{-1}; **Q-TOF LC/MS** = 513.4114 $[M+H]^+$, (calculated = 513.4124, $C_{33}H_{52}O_4$); **^{1}HNMR ($CDCl_3$, 600 MHz):** δ 5.14 (1H, t = 3.5 Hz, H-11), 4.48 (dd, J = 9.0, 6.0 Hz, H-3), 3.64 (3H, s, OCH_3-33), 2.29 (2H, t = 7.2 Hz, H-11), 2.02 (3H, s, CH_3-32), 1.51 (1H, br. s, H-9), 1.50 (1H, dd, J = 12.0, 3.1 Hz, H-5), 1.28 (1H, d = 12.6 Hz, H-18), 1.23 (3H, s, H-23), 1.14 (1H, m, H-19), 1.07 (3H, s, H-28), 1.04 (3H, s, H-26), 0.94 (3H, s, H-25), 0.89 (3H, s, H-27), 0.86 (d = 6.6 Hz, H-30), 0.83 (d = 6.5 Hz, H-29); **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 174.0 (C-24), 171.5 (C-31), 139.5 (C-13), 124.3 (C-12), 80.8 (C-3), 59.0 (C-18), 55.2 (C-5), 47.6 (C-9), 42.2 (C-8), 42.1 (C-14), 41.5 (C-22), 40.0 (C-4), 39.6 (C-19), 39.5 (C-

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