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New water soluble glycosides of 11-keto-β-boswellic acid: A paradigm

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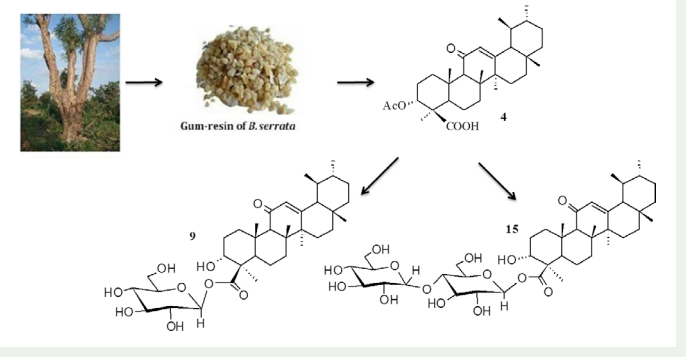
ABSTRACT

Though several glycosides of various triterpenes are known, but surprisingly no boswellic acid glycosides are reported so far. With a view to make water soluble boswellic acids, prepared glycosides of 11-keto boswellic acid for the first time. Naturally occurring boswellic acids which are anti-inflammatory agents are lipophylic in nature and thus, become a limiting factor in terms of their bioavailability. Among boswellic acids, 11-keto-β-boswellic acid is found to exhibit superior biological activity and hence successfully prepared its glucosyl and maltosyl derivatives viz., 11-keto-β-boswellic acid-24-O-β-D-glucopyranoside (**9**) and 11-keto-β-boswellic acid-24-O-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranoside (**15**) which are water soluble. Both these compounds are soluble in water to the extent of 10% (w/w) which is very significant.



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Boswellia seratta; boswellic acids; glycosylation; bioavailability

1. Introduction

The gum resin of *Boswellia serrata* is well known in Ayurveda, the ancient Indian system of medicine, as dhup or salai guggal. Triterpenoids present in *Boswellia serrata* Roxb. (Burseraceae) oleo gum resin have been shown to be effective against rheumatoid arthritis, chronic colitis, ulcerative colitis, skin allergies and ulcers, peritumoural brain edema, osteo-arthritis and inflammation (Shenvi et al. 2014). Boswellic acids are pentacyclic triterpenic

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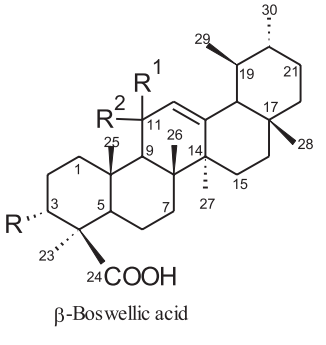
acids (Figure 1) obtained from the gum resin exudate of *Boswellia serrata* (Pardhy & Bhattacharya 1978).

Studies proved that among the various boswellic acids 11-keto-β-boswellic acid (β-KBA) and 3-acetyl-11-keto-β-boswellic acid (β-AKBA) have been observed to be more active (Ammon 2010). Although boswellic acids have been well studied and associated with immense therapeutic values such as anti-inflammatory, anticancer, antibacterial, (Safayhi et al.1992; Sailer et al. 1996) but their applications have been limited due to their poor bioavailability. The lipophilic molecules are reluctantly absorbed in the biological systems. Administration of high dose of boswellic acids is undesirable as it will burden liver and can become hepatotoxic. Hence, it is necessary to achieve by some way, an increase in absorption of boswellic acids into biological systems so that their potentials can be exploited safely at required dosage. One approach to increase the bioavailability of the lipophilic boswellic acids has been to administer them along with fibre rich or high fat containing food (Singh et al. 1996). But this approach is not desirable as it would alter the taste and not easily palatable. A second approach would be to make their glycosides - prodrug model. Prodrugs are often designed to improve bioavailabilty when a drug is poorly absorbed from gastrointestinal tract (Hacker et al. 2009). Many herbal extracts used in medicine contain glycosides of active agent, which are hydrolysed in the intestines to release the active aglycone. In case of salicin which is a β-D-glucopyranoside is cleaved by esterases to release salicylic acid (Sneader 2000). Though several triterpenoid glycosides are known (Uvarova et al. 1973; Gauthier et al. 2009; James & Dubery 2009; Sheng & Sun 2011; Schwarz et al. 2014), but so far boswellic acid glycosylation is not reported. Since 11-keto-β-boswellic acid exhibits superior bioactivity over other naturally occurring boswellic acids, we have prepared successfully for the first time its water soluble glucosyl and maltosyl derivatives.

2. Results and discussion

Peracetyl bromo-α-D-glucose (**6**) was prepared by peracetylation of glucose by the procedure adopted earlier in our laboratory (Shenvi et al. 2016). Glycosyl bromide thus, prepared was treated with 3-acetyl-11-keto-β-boswellic acid (**4**) in presence of silver carbonate using acetonitrile as a solvent to obtain boswellic acid glycoside (Figure 2) with about 50% yield. Further, yields of glycosides of boswellic acids were improved up to 80–85% by altering the solvent media to anhydrous dichloromethane and anhydrous toluene. The results are tabulated (Table S1).



β-Boswellic acid

1: R^1, R^2=H, R=H (β-BA; β-Boswellic acid)
2: R^1, R^2=O, R=H (β-KBA; 11-keto- β-Boswellic acid)
3: R^1, R^2=H, R=OAc (β-ABA; 3-acetyl-β-Boswellic acid)
4: R^1, R^2=O, R=OAc (β-AKBA; 3-acetyl-11-keto- β-Boswellic acid)

Figure 1. Prominent boswellic acids obtained from gum resin of *Boswellia serrata*.

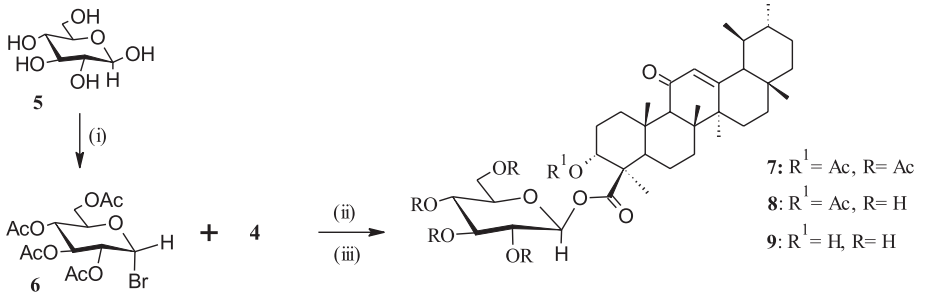


Figure 2. Glucoconjugate of 3- acetyl-11-keto-β-boswellic acid.
Note: **Conditions and reagents:** (i) HBr/AcOH; (ii) Ag_2CO_3/Sovents (Table S1) or K_2CO_3/toluene at 100 °C; (iii) For compound **8**, Na_2CO_3/MeOH/$CHCl_3$; For compound **9**, Na_2CO_3/MeOH.

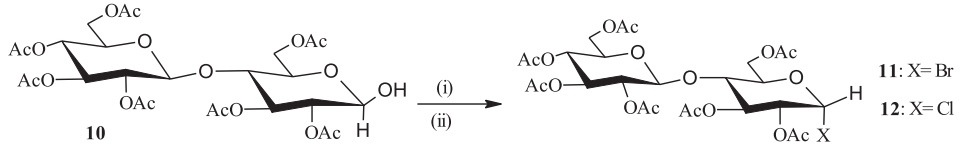


Figure 3. Peracetylated maltosyl bromide and maltosyl chloride.
Note: **Reagents and conditions:** (i) HBr/AcOH, 6 h; (ii) CH_3COCl, $Zn(OAc)_2.2H_2O$.

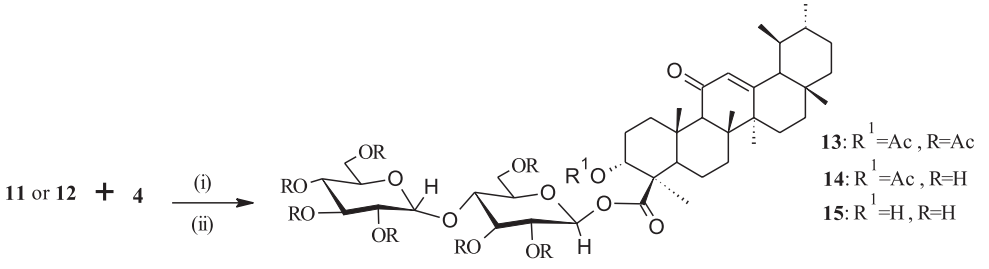


Figure 4 Maltoconjugate of 3-acetyl-11-keto-β-boswellic acid.
Note: **Reagents and conditions:** (i) K_2CO_3/toluene at 100°C (ii) For compound **14**, Na_2CO_3/MeOH/$CHCl_3$; For compound **15**, Na_2CO_3/MeOH.

Glycosylation of boswellic acid with disaccharide would definitely lead to higher hydrophilic conjugates of boswellic acids. Hence, we tried glycosylation of boswellic acid using maltose. Maltose was peracetylated [Ac_2O, Et_3 N/DMAP (catalytic amount), DMF, rt, 12 h] followed by anomeric bromination using HBr/AcOH at ice cold temperature to get maltosyl bromide (**11**) or chlorination using acetyl chloride and catylatic amount of zinc acetate to get maltosyl chloride (**12**) (Figure 3). The maltosyl bromide/chloride thus, obtained was used for glycosylation of 3-acetyl-11-keto-β-boswellic acid to obtain the corresponding maltoside **13** in 70% yield (Figure 4). Maltoside (**13**) was then deacetylated using sodium carbonate in methanol/chloroform and in methanol alone at room temperature to obtain partially deacetylated (**14**) and completely deacetylated (**15**) products, respectively. The decetylated glycoside and maltoside of 11-keto-β-boswellic acid i.e. compounds **9** and **15** are easily soluble in water to the extent of 10% (w/w) which is a very significant observation. We plan to study their bio-efficacy and report the results elsewhere.

3. Experimental

3.1. General

Melting points were recorded on an Acro melting point apparatus using a calibrated thermometer. Thin layer chromatography (TLC) and column chromatography (CC) were performed with TLC silica gel 60 F_{254}, Merck and silica gel (200–400 mesh), respectively. Thin layer chromatograms were developed using hexane: EtOAc (8:2, v/v) and compounds were detected by H_2SO_4 spray (10%) with subsequent heating at 100–120 °C for 4–5 min. IR spectra were recorded on Thermo-Nicolet instrument in KBr discs. NMR spectra were recorded with TMS as internal standard on a Bruker and Jeol 400 MHz NMR spectrometers. The chemical shifts are expressed in δ (ppm) units and the coupling constants (*J*) are given in Hz.

4. Plant material

Boswellia Serratta gum resin was obtained from Natural Remedies; Plot No. 5B, Veerasandra Industrial Area, 19th K.M.Stone, Hosur Road; Electronic city (Post); Bangalore-560100; India

4.1. Isolation of boswellic acids (1–4)

The *Boswellia serrata* gum resin lumps (1 kg) were crushed and treated with methanol (2 L × 2) in a percolator. Combined methanolic extracts were evaporated under reduced pressure at 45 °C to obtain thick brown residue (450 g). Details of isolation of all four boswellic acids are provided in the supplement (Experiment S1).

4.2. General procedure for preparation of glucose and maltose peracetate

To a solution of glucose (**5**, 5 g, 27.7 mmol), TEA (16.85 g, 166.6 mmol), DMF (150 mL) and catalytic amount of DMAP was added AC_2O (16.99 g, 166.6 mmol) drop wise maintaining the temperature at 0 °C for 5–6 h. Completion of reaction was monitored by TLC, then added aqueous solution of sodium hydrogen sulphate drop wise to the reaction mixture under stirring till it attained pH~8.Then reaction mixture was extracted with EtOAc (2 × 50 mL) and combined organic layer was washed with water (2 × 50 mL), dried over Na_2SO_4 and evaporated to dryness under vacuum. Likewise maltosyl peracetate was prepared using twice the quantity of reagents.

4.3. General procedure for preparation of glucosyl bromide (6) and maltosyl bromide (11)

To glucose/maltose peracetate (3 g) was added 15 mL of 33% HBr in AcOH at 0 °C, slowly allowed the reaction to come to room temperature under stirring and maintained for 45 min. DCM (80 mL) was added to the reaction mixture and the solution was dropped into ice-cold water. Separated the organic layer and then washed with solution of $NaHCO_3$, water and dried over Na_2SO_4. Organic layer was evaporated under vacuum to obtain required compounds, which were stored in refrigerator.

4.4. General preparation of maltosyl chloride (12)

To a solution of maltose (**10**, 3 g, 8.765 mmol) in DMF (10 mL) was added TEA (8.42 g, 83.36 mmol) and acetyl chloride (6.49 g, 82.47 mmol) by maintaining the temperature at 0 °C. Stirred the reaction mixture at that temperature for 6–7 h and then added Zn $(OAc)_2.2H_2O$ (0.1 mmol) for completion of the reaction. To the reaction mass added EtOAc (2 × 50 mL) and collected ethyl acetate layer, then washed the organic layer with 5% $NaHCO_3$ (2 × 25 mL) solution, then with water and dried over Na_2SO_4 .The organic layer on evaporation under vacuum gave the required product.

4.5. Synthesis of 11-keto- β-boswellic acid-24-O-β-D-tetraacetylglucopyranoside (7)

To a solution of 3-acetyl-11-keto-β-boswellic acid (**4**, 900 mg, 1.75 mmol) in toluene (30 mL), added tetraacetyl-α-D-glucopyranosyl bromide (**6**, 1.45 g, 3.54 mmol) in presence of K_2CO_3 (122 mg, 0.885 mmol) along with 4 Å molecular sieves and heated to 100 °C for 4 h. Completion of the reaction was monitored by TLC. Concentrated the toluene layer, then added the EtOAc (30 ml), washed the EtOAc layer with water twice and concentrated ethyl acetate layer to dryness to get crude product (2.03 g). The crude product was subjected to silica column chromatography and eluted with hexane; EtOAc mixture (increasing polarity) and isolated the pure product **7** (86% yield).

White crystalline solid, $C_{46}H_{66}O_{14}$, mp: 170–172 °C, +13.39° (*c* = 1, MeOH).

IR (KBr, ν_{max}): 3484, 2979, 2928, 1755, 1660, 1618, 1457, 1436, 1373, 1224, 1076, 1039 cm^{-1}.

^1H NMR ($CDCl_3$, 400 Hz); δ 0.80 (3H, d, J = 6.4 Hz, –HC– $C\underline{H}_3$), 0.83 (3H, s, CH_3), 0.95 (3H, bs, CH_3), 1.06 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.20–1.60 (17H), 2.00 (3H, s, OAc), 2.01 (3H, s, OAc), 2.02 (3H, s, OAc), 2.03 (3H, s, OAc), 2.08 (3H, s. OAc), 2.12–2.18 (2H, m), 2.39 (1H, s), 2.53 (1H, m), 3.80–3.84 (1H, m), 4.04–4.08 (1H, m), 4.20–4.25 (1H, m), 5.09–5.13 (1H, m), 5.23 (1H, d, J = 3.2 Hz), 5.26 (1H, s), 5.28 (1H, bs), 5.54 (1H, s, C = C$\underline{H}$–CO), 5.76 (1H, d, J = 8.0 Hz, α-H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.10, 17.41, 18.11, 18.76, 20.54 (4 × C), 21.12, 21.28, 22.88, 23.43, 27.18, 27.52, 28.84, 29.12, 29.68, 30.91, 32.81, 33.97, 34.53, 37.39, 39.33, 40.91, 43.75, 45.05, 46.82, 50.65, 59.05, 60.31, 61.57, 68.12, 70.08, 72.52, 72.72 (2 × C), 91.33, 130.49 (vinylic), 164.90 (vinylic), 169.22 (COOR), 169.42 (COOR), 170.01 (COOR), 170.06 (COOR), 170.45 (COOR), 174.05 (COOR), 199.12 (C=O).

HRMS-ESI: m/z $[M + Na]^+$ for $C_{46}H_{66}O_{14}Na$; calculated 865.4350; observed 865.4352.

4.6. Synthesis of 3-acetyl-11-keto-β-boswellic acid-24-O-β-D-glucopyranoside (8)

Details are provided in supplement (Experiment S2).

4.7. Synthesis of 11-keto-β-boswellic acid-24-O-β-D-glucopyranoside (9)

Added acetyl glycoside of 3-acetyl-11-keto-β-boswellic acid (**7**, 200 mg, 0.31 mmol) and Na_2CO_3 (73.8 mg, 0.70 mmol) to methanol (5 mL), maintained at ambient temperature for 2 days and completion of the reaction was monitored by TLC ($CHCl_3$: MeOH, 10%), evaporated methanol and added water (2 mL) to the reaction mass and extracted with EtOAc (2 × 20 mL).

Combined ethyl acetate layer was dried over Na_2SO_4 and concentrated under vacuum to get the product **9** (95% yield).

White solid, $C_{36}H_{56}O_9$, mp: 160–162 °C, +13.28° (*c* = 1, MeOH).

IR (KBr, $\nu_{max,}$): 3420, 2974, 2924, 2268, 2861, 1740, 1729, 1654, 1618, 1457, 1436, 1384, 1261, 1205, 1075, 1031 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 Hz); δ 0.75 (3H, d, J = 5.2 Hz, –HC–C<u>H</u>$_3$), 0.79 (3H, s, CH_3), 0.93 (3H, bs, CH_3), 0.98 (3H, bs, CH_3), 1.09 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.29 (3H,s, CH_3), 1.36–2.26 (16H, m), 3.14–3.22 (5H, m), 3.45 (1H, m), 3.61 (1H, m), 3.83 (1H, m), 4.38 (1H, m), 4.55 (1H, bs), 4.96 (1H, bs), 5.03 (1H, s), 5.17 (1H, d, J = 6.0 Hz), 5.31 (1H, d, J = 8.0 Hz, α-H), 5.42 (1H, s, C=C<u>H</u>–CO).

^{13}C-NMR (DMSO-$d_{6,}$ 100 MHz): δ 13.43, 17.09, 17.95, 18.39, 20.08, 20.92, 24.38, 25.94, 26.61, 26.91, 28.42, 30.38, 32.41, 33.53, 37.05, 38.44, 38.67, 43.39, 43.30, 44,57, 47.25, 48.09, 48.58, 58.15, 59.80, 60.71, 68.32, 69.59, 72.63, 76.74, 77.71, 93.94,129.71 (vinylic), 164.20 (vinylic), 175.12 (COOR), 198.38 (C=O).

HRMS-ESI: m/z $[M + Na]^+$ for $C_{36}H_{56}O_9Na$; calculated 655.3822; observed 655.3823.

4.8. Synthesis of 3-acetyl-11-keto-β-boswellic acid-24-O-α-D-tetraacetyl glucopyranosyl-(1 → 4)-β-D-triacetylglucopyranoside (13)

To a solution of 3-acetyl-11-keto-β-boswellic acid (**4**, 0.5 g, 0.976 mmol) in toluene (30 mL), added maltosyl bromide (1.26 g, 1.76 mmol) in presence of K_2CO_3 (0.20 mg, 1.44 mmol) along with 4 Å molecular sieves heated at 100 °C for 4 h. Completion of the reaction was monitored by TLC. The toluene layer was concentrated, then EtOAc (30 mL) was added and the EtOAc layer was washed with water twice, dried over anhydrous Na_2SO_4 and concentrated to dryness to get crude product (2.03 g). Purified the crude product through silica column using hexane; EtOAc mixture with increasing polarity and isolated the pure product (**13**) in 70% yield. When reaction was carried out with maltosyl chloride **13** was obtained in 89% yield.

White crystalline solid, $C_{58}H_{82}O_{22}$, mp: 218–220 °C, +20.12° (*c* = 1, MeOH).

IR (KBr, ν_{max}): 3484, 2980, 2928, 1756, 1660, 1618, 1457, 1436, 1373, 1224, 1076, 1039 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 Hz); δ 0.80 (3H, d, J = 6.4 Hz, –HC–C<u>H</u>$_3$), 0.82 (3H, s, CH_3), 0.95 (3H, bs, CH_3), 1.05 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.20–1.31 (12H, m), 1.33 (3H, s, CH_3), 1.99 (3H, s, OAc), 2.00 (3H, s, OAc), 2.02 (3H, s, OAc), 2.04 (3H, s, OAc), 2.05 (3H, s, OAc), 2.08 (6H, s, 2xOAc), 2.09 (3H, s, OAc), 2.11- 2.54 (7H, m), 3.81–3.83 (2H, m), 3.92–9.94 (2H, m), 4.03 (1H, t, J = 8.8 Hz), 4.06 (1H, m), 4.19–4.25 (2H, m), 4.42 (1H, dd, J = 2.4 Hz and 12.0 Hz), 4.85 (1H, dd, J = 4.0 Hz and 10.4 Hz), 5.02–5.07 (2H, m), 5.28–5.37 (3H, m), 5.41 (1H, d, J = 4.0 Hz, β-H), 5.53 (1H, s, C = C<u>H</u>–CO), 5.78 (1H, d, J = 8.4 Hz, α-H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.20, 14.11, 17.42, 18.18, 18.76, 20.49, 20.58, 20.67, 20.86, 21.13, 21.29, 22.69, 23.09, 23.46, 27.21, 27.55, 28.85, 29.36, 29.70, 30.93, 31.93, 32.82, 33.99, 34.52, 37.40, 39.30, 40.93, 43.76, 45.05, 46.83, 50.58, 59.06, 60.29, 61.52, 62.36, 68.03, 68.61, 69.36, 70.06, 70.90, 72.60, 72.92 (2 × C), 75.29, 90.99, 95.73, 130.53 (Vinylic), 164.83 (vinylic), 169.45 (COOR), 169.84 (COOR), 170.05 (COOR), 170.20 (2 × COOR), 170.50 (COOR), 170.58 (COOR), 173.81 (2 × COOR), 199.02 (C=O).

4.9. Synthesis of 3-acetyl-11-keto-β-boswellic acid-24-O-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranoside (14)

The details are provided in supplement (Experiment S3).

4.10. Synthesis of 11-keto-β-boswellic acid-24-O-α-D-glucopyranosy-(1 → 4)-β-D-glucopyranoside (15)

Added acetyl maltoside of 3-acetyl-11-keto-β-boswellic acid (**13**, 200 mg, 0.174 mmol) and Na_2CO_3 (73.8 mg, 0.70 mmol) to methanol (5 mL) and maintained at ambient temperature for 3 days. Completion of the reaction was monitored by TLC ($CHCl_3$: MeOH, 10%), evaporated methanol and added water (2 mL) to the reaction mass and extracted with EtOAc (2 × 20 mL). Combined ethyl acetate layer was dried over Na_2SO_4 and concentrated under vacuum to get the product **15** (yield 95%).

White solid, $C_{42}H_{66}O_{14}$, mp: 206–208 °C, +23.18° (*c* = 1, MeOH).

IR (KBr, $\nu_{max,}$): 3401, 2924, 2855, 1735, 1657, 1618 1457, 1436, 1384, 1262, 1221, 1050, 1031 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 Hz); δ 0.77 (3H, d, J = 6.4 Hz, –HC–C$\underline{H}_3$), 0.85 (3H, s,CH_3), 0.92 (3H, brs, CH_3), 0.98 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.24 (3H, s,CH_3), 1.40–2.25 (21H), 3.40–3.43 (3H,m), 3.48–3.50 (2H,m), 3.83 (1H, brs), 4.37 (1H, t, J = 5.6 Hz), 4.56 (2H, m), 4.91(2H, m), 5.04 (1H, brs), 5.31(1H, d, J = 3.6 Hz, β-H), 5.36 (1H, d, J = 7.6 Hz, α-H), 5.43 (1H, brs), 5.51 (1H, brs), 5.57 (1H, brs).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.44, 17.09, 17.95, 18.38, 20.07, 20.92, 24.36, 25.93, 26.61, 26.90, 28.42, 28.98, 30.37, 32.39, 33.53, 37.04, 38.43, 38.66, 40.38, 43.31, 44.56, 47.26, 48.07, 48.38, 58.15, 59.79, 60.28, 60.77, 68.31, 69.88, 72.18, 72.39, 73.44, 75.94, 76.33, 79.10, 93.69, 100.80, 129.69 (vinylic), 164.26 (vinylic), 175.09 (COOR), 198.40 (C=O).

HRMS-ESI: m/z $[M + Na]^+$ for $C_{42}H_{66}O_{14}Na$; calculated 817.4350; observed 817.4351.

5. Conclusion

Though 11-keto-β-boswellic acid is found to exhibit superior biological activity among boswellic acids its usage is constrained because of its liphophilicity. In order to overcome this, successfully prepared for the first time its glucosyl and maltosyl derivatives viz., 11-keto-β-boswellic acid-24-O-β-D-glucopyranoside (**9**) and 11-keto-β-boswellic acid-24-O-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranoside (**15**) which are water soluble. Both these compounds are soluble in water to the extent of 10% (w/w) which is very significant.

Supplementary material

Copies of the ^{1}H NMR, ^{13}C NMR, HRMS of compounds 7, 8, 9, 13, 14 and 15 are separately attached.

Acknowledgements

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Disclosure statement

No potential conflict of interest was reported by the authors.

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