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Synthetic studies in butenonyl C-glycosides: Preparation of polyfunctional alkanonyl glycosides and their enzyme inhibitory activity

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ABSTRACT

A simple synthesis of phenyl butenoyl C-glycosides has been achieved by Aldol condensation of peracetylated glycosyl acetones with aromatic aldehydes followed by deacetylation with methanolic NaOMe. The selected butenoyl C-glycosides on conjugate addition of diethyl malonate resulted in polyfunctional alkanonyl glycosides in good yields. The butenoyl C- and alkanoyl C-glycosides were evaluated for their α-glucosidase, glucose-6-phosphatse and glycogen phosphorylase enzyme inhibitory activities in vitro. Three of the synthesized (**3**, **5** and **9**) showed potent enzyme inhibitory activities as compared to standard drugs. Compounds **3, 5** and **9** were evaluated in vivo too displaying significant activity as compared to standard drugs acarbose and metformin.

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Carbohydrates constitute one of the most abundant biomolecule in nature and are widely expressed as glycolipids and glycoproteins.[1] The carbohydrate moiety as epitope in several glycoconjugates are known to play central role in displaying various biological responses such as immune response, inflammation, metastasis, bacterial and viral infections among others.[2] The glycosidic cleavage and liberation of monosachharides from oligosachharides in the body are controlled by different enzymes. Glycosidases, glucose-6-phosphatase and glycogen phosphorylases are extremely important in homeostatic regulation of blood glucose levels and therefore of prime importance in diabetes and many other diseases.[3]

Therefore, inhibitors or elevators of these enzymes have many potential medical applications.[2–7] While inhibitors of glycosidases in general have therapeutic values as anticancer, antiviral and antibacterial, the inhibitors of intestinal α-glycosidases in particular have been used to treat diabetes through the lowering of blood glucose levels. Several α-glycosidase inhibitors are in the clinics for the treatment of Type 2 diabetes[8] and many other drugs in the market.[9]

Inhibitors of glucose-6-phosphatase and glycogen phosphorylase have also great potential as drug candidate via lowering of blood glucose levels by inhibition of glycogen phosphorylase provides an alternative method to treat diabetes.[10]

Several C-glycosides of synthetic and natural product origins are known as glycosidase inhibitors (Fig. 1).[11] Many *O*-alkyl glycosides have recently been reported to be associated with different biological activities.[12]

C-Glycosides are being used as building blocks for the synthesis several natural products and also as potential enzyme inhibitors.[13] The biological activity in C-glycosides is due to the fact that the conformational differences between the O- (or N-) glycosides and the C-linked analogue are minimal.[14] Moreover, C-glycosides are more stable than *O*- or N-glycosides since the natural anomeric center has been transformed from a hydrolytically labile *O* or *N* acetal link to an ether. As a result, stereoselective synthesis of C-glycosides has been a challenging task for organic chemists.[15] We have been involved in design and development of antitubercular agents from simple sugar derivatives.[16–19] Current reports that diabetic patients are prone to tuberculosis have led us to explore molecules having both antidiabetic and antitubercular activity.[20,21] In this context we have synthesized C- phenylbutenoyl glycosides and carried out their Michael addition reaction with diethylmalonate to get polyfunctional C-alkanoyl glycosides. The synthetic

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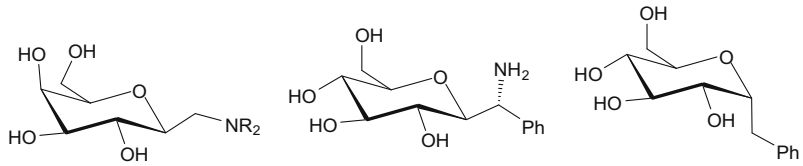
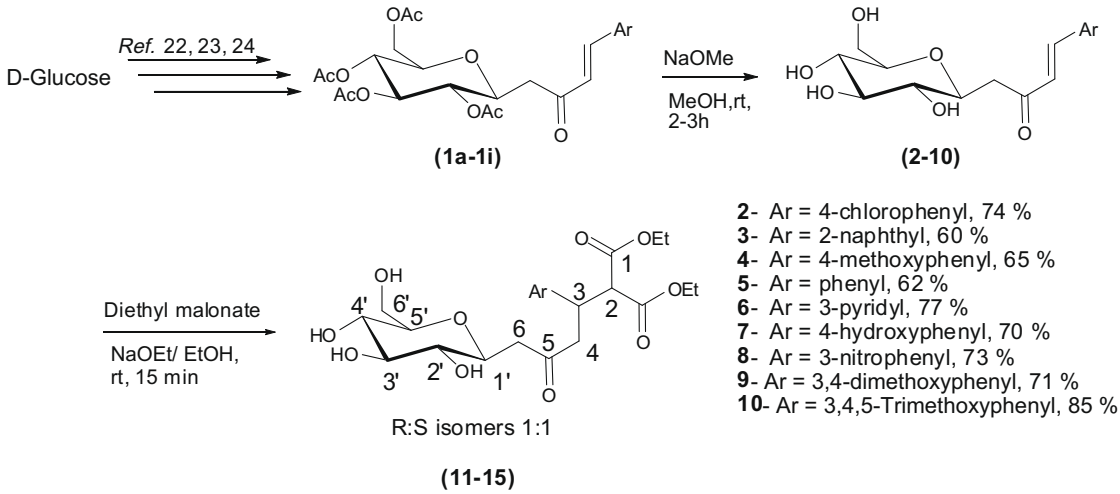


Figure 1. Glycosidase inhibitors.

method is ecofriendly and economical as readily available reagents and chemicals are used and all the reactions are performed at ambient temperature. The compounds were evaluated for α-glucosidase, glucose-6-phosphatase and glycogen phosphorylase inhibitory activity in vitro and antidiabetic activity of active compounds was confirmed using in vivo animal models. The presence of other potential functional groups in the molecule has potential for further explorations in different disease areas.

(*E*)-1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(aryl)-but-3-en-2-ones (**1a–i**) were prepared by the aldol condensation of respective aromatic aldehydes (substituted/unsubstituted) with 1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)propan-2-one following the earlier protocol.[22–24] Deacetylation of all the acetyl group in the molecules resulted in respective (*E*)-1-(β-D-glucopyranosyl)-4-(aryl)but-3-en-2-ones (**2–10**) in good yields.[25] The structures of all these compounds were accordance with their spectroscopic data. The IR spectra of compounds **2**–**10** exhibited absorption bands at around 3400 cm^{-1} and 1650 cm^{-1} indicating the presence of hydroxyl groups of the sugar and α, β-unsaturated ketone group, respectively. ESMS of all the compounds displayed $M+H^+$ peaks corresponding to their molecular weight. In the ^1H NMR spectrum of compound **2**, olefinic protons appeared as two distinct doublets at δ 7.58 and δ 6.96 (*J* = 16.2 Hz), indicating a *trans* geometry of double bond. The aromatic protons of the phenyl ring were observed as doublets each integrating two protons at δ 7.75 and δ 7.48 with *J* value 8.3 Hz. The exchangeable protons pertaining to the hydroxyl groups appeared as two doublets, one singlet and one triplet at δ 5.07 (*J* = 5.5 Hz), δ 4.90 (*J* = 4.2 Hz), δ 4.88, and δ 4.36 (*J* = 5.3 Hz), respectively. The splitting of hydroxyl protons is due to adjacent *CH* or CH_2 protons. H-5′ and H-6a′ of sugar moiety appeared as multiplet at around δ *3.65–3.57* and one proton H-6b′ at δ 3.37 while the anomeric proton (H-1′) appeared as a multiplet at around δ *3.18–3.15*. The other four protons H-2′, H-3′, H-4′ of the sugar ring and one of the aglycon methylene protons (H-1a) appeared as multiplet at around δ *3.11–2.93*. The other aglycon methylene proton (H-1b) appeared as dd at δ 2.70 with $J_{1b,1'}$ = 8.6 Hz and $J_{1a,1b}$ = 16.2 Hz. ^{13}C NMR spectrum of compound **2,** a signal at δ 198.9 accounted the carbonyl carbon while the signals for aromatic carbons were observed at δ 135.7, δ 134.3. The two olefinic carbons appeared at δ 141.4 and δ 128.3. All the sugar ring carbons appeared at δ 81.6, δ 79.9, δ 76.6, δ 74.4 and 71.1 while the aglycon methylene carbon appeared at δ 44.3. Almost similar patterns were observed ^1H NMR and ^{13}C NMR spectra of other compounds as well.

Michael reaction of the above (*E*)-1-(β-D-glucopyranosyl)-4-(4′-chlorophenyl)but-3-en-2-one (**2**) with diethyl malonate in presence of catalytic amount of sodium ethoxide/ethanol resulted in 6-(β-D-glucopyranosyl)-2-carbethoxy-3-((*R*,*S*)-4″-chlorophenyl)-5-oxo-ethylhexanoate (**11**) as diastereoisomeric mixtures in good yields (Scheme 1).[26] The diastereoisomeric mixtures were inseparable by column chromatography. The structure of the above glycoside **11** was established on the basis of its spectroscopic data. The ESMS of compound **11** displayed 519.5 $(M+18)^+$ peak corresponding to its molecular weight. In the ^1H NMR spectrum of compound **11,** the signals corresponding to olefinic protons at δ 7.58 and δ 6.96 (in compound **2)** were not observed while one methine proton (H-2) of the aglycone moiety was observed as multiplet merged with carbethoxy (OCH_2) protons as at around δ *4.00–3.93*. The other methine proton H-3 appeared as multiplet at around δ *3.68–3.52* and two methylene protons (H-4) were observed along with two glycone methine protons as multiplet at around δ *3.18–2.94*. In the ^{13}C NMR spectrum of **11,** two carbonyl carbons of carbethoxy appeared at δ 168.8, and δ 168.2, while the ketonic carbon was observed at δ 208.5 and C-2,



Scheme 1. Synthesis of (*E*)-1-(β-D-glucopyranosyl)-4-(aryl)but-3-en-2-ones and 6-(β-D-glucopyranosyl)-2-carbethoxy-3-((*R*,*S*)aryl)-5-oxo-ethylhexanoate (**2–15**).

C-3 appeared at δ 57.4, δ 39.7, respectively. The signals corresponding to the three methylene carbons (C-4, C-6 and C-6′) were observed at δ 62.3, δ 61.8 and δ 61.4.

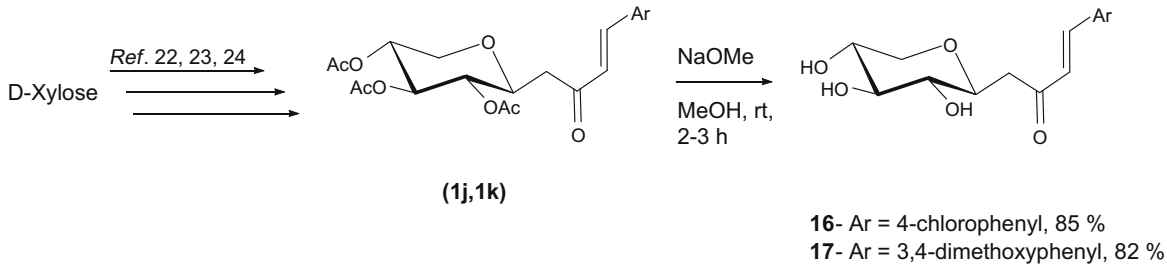
Similar Michael addition of diethyl malonate with the deacetylated alkenoyl glycosides (**3, 5, 6, 9**) led to the formation of respective 6-(β-D-glucopyranosyl)-2-carbethoxy-3-((*R*,*S*)aryl)-5-oxo-ethylhexanoate (**12**, **13, 14, 15**), respectively as diastereoisomeric mixtures in moderate to good yields. The compounds were isolated by column chromatography and characterized on the basis of their spectroscopic data. The ^{1}H NMR and ^{13}C NMR spectral data, the chemical shifts and splitting pattern of different protons and carbons of these compounds were similar to those described for the above compound **11**.

In order to see the effect of other sugars on the α-glucosidase inhibitory activity, (*E*)-1-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)-4-(4″-chlorophenyl)but-3-en-2-one and (*E*)-1-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)-4-(3,4-dimethoxyphenyl)but-3-en-2-one were deacetylated with NaOMe/MeOH to give the respective glycosides (*E*)-1–(β-D-xylopyranosyl)-4-(4-chlorophenyl)but-3-en-2-one (**16**) and (*E*)-1-(β-D-xylopyranosyl)-4-(3,4-dimethoxyphenyl)but-3-en-2-one (**17**) (Scheme 2) in moderate yields. The compounds were isolated by column chromatography and characterized on the basis of their spectroscopic data.

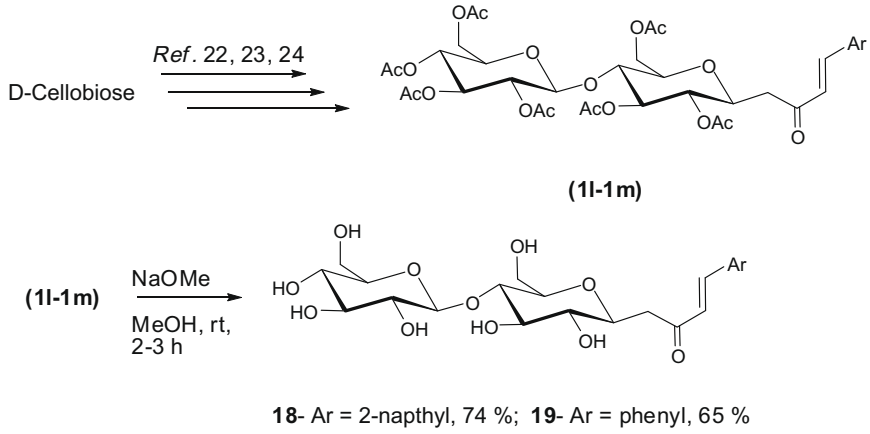
During biological evaluation the Michael adducts were not active as compared to their olefinic counterparts, therefore we did not carry out Michael reaction of diethyl malonate with the above alkenoyl glycosides.

Finally, deacetylation of a disaccharide derived (*E*)-1-(2′,3′,6′,2″,3″,4″,6″-hepta-*O*-acetyl-β-cellobiosyl)-4-(2-napthyl)but-3-en-2-one and (*E*)-1-(2′,3′,6′,2″,3″,4″,6″-hepta-*O*-acetyl-β-cellobiosyl)-4-phenylbut-3-en-2-one (under the above experimental condition led to the formation respective (*E*)-1-(β-cellobiosyl)-4-(2-napthyl)but-3-en-2-one (**18**) and (*E*)-1-(β-cellobiosyl)-4-phenylbut-3-en-2-one (**19**) in good yields (Scheme 3). The compounds synthesized were evaluated against the α-glucosidase purified from rat intestine and Glucose-6-phosphatase and glycogen phosphorylase purified rat liver following earlier protocols.[27–30] Table 1 shows the percent inhibitory activity of screened compounds against different enzymes. As evident from the table 1 the above compounds inhibited or elevated α-glucosidase, glucose-6-phosphatase and glycogen phosphorylase enzymes to a different extent at 100 μM concentration. The α-glucosidase inhibitory activity ranges from 2.3% to 70.7% at the experimental concentration of the compounds. A closure look into inhibitory activity reveals that among all the compounds only compound **9** with 3,4-dimethoxyphenyl substituent exhibits good α-glucosidase inhibitory activity at 100 μM (IC_{50}, 51.5 μM) as compared to standard drug acarbose. Among all the compounds only two compounds **2** and **5** inhibited glucose 6-phosphatase enzyme significantly to the extent of 25.3% and 49.7% (IC_{50} = 87.0 μM), respectively, while the standard drug sodium *orh-to*-vandate inhibited to the extent of 39% only. Out of the above glycosides synthesized compounds **2**, **3**, **4**, **6**, **13**, **15**, **17** and **18** showed significant inhibition of glycogen Compound **3** with naphthyl moiety in alkenonyl glycoside proved to be potent inhibitor of glycogen phosphorylase with an IC_{50} value 98.0 μM. The above three most potent compounds **3**, **5** and **9**, showing activity against three different enzymes were further evaluated in vivo in validated animal models, that is, Sucrose loaded rat model (SLM) and streptozotocin induced diabetic rat model.[31] Results are summarized in Table 2; Table 3.

Figure 2 shows the blood glucose profile of sucrose loaded rats treated with test compounds. It is evident from the results that compound **3** and **9** show significant improvement in glucose tolerance. The average activity profile of compounds **3**, **5**, **9** and the standard drug metformin is shown in Table 2. The effect exerted by compound **3** and **9** (25.0%, $p < 0.05$ and 26.7%, $p < 0.05$, respectively) is comparable with the standard drug metformin (31.2%,



Scheme 2. Synthesis of (*E*)-1-(β-D-xylopyranosyl)-4-(aryl)but-3-en-2-one (**16, 17**).



Scheme 3. Synthesis of (*E*)-1-(β-D-cellobiosyl)-4-(aryl)but-3-en-2-one (**18**, **19**).

Table 1
α-Glucosidase, glucose-6-phosphatase, and glycogen phosphorylase inhibitory activity of compounds (**2–19**)

Compounds	% Activity (100 μM)		
	α-Glucosidase inhibition	Glucose-6-phosphatase inhibition	Glycogen phosphorylas inhibition
2	−5.97	−25.3	−36.2
3	−16.9	−7.7	−52.4
4	−32.3	−9.7	−37.2
5	−10.4	−49.7	+7.3
6	−35.4	−8.1	−28.9
7	−30.7	+4.2	−3.4
8	−10.0	+8.0	+15.6
9	−70.7	+15.0	−5.9
10	−25.0	+4.7	−19.6
11	−10.0	−6.0	−5.4
12	−20.0	+4.6	−14.7
13	−45.0	−3.3	−25.9
14	−20.0	+37.6	−11.7
15	−2.3	−36.2	−24.0
16	−8.3	+4.7	−19.6
17	−16.6	−19.9	−21.5
18	NIL	−3.9	−8.3
19	−24.6	−16.3	−30.8
Acarbose	−39.0	–	–
Sodium-*ortho*-vandate	–	−39.0	–

Table 2
Antihyperglycaemic effect of in vitro of selected compounds and the standard drug-metformin in sucrose loaded hyperglycaemic rats

Compounds	Dose (mg/kg)	% Activity
9	100	26.7*
3	100	25.0*
5	100	19.5
Metformin	100	31.2*

* $p < 0.05$.

Table 3
Antihyperglycaemic activity of in vitro compounds and standard drug Metformin in sucrose-challenged STZ-induced diabetic rats

Compound	Dose (mg/kg)	% Antihyperglycaemic activity	
		5 h	24 h
3	100	14.2*	10.3
5	100	2.91	12.1
9	100	14.1*	13.4
Metformin	100	26.9**	21.4*

* $p < 0.05$.
** $p < 0.01$.

$p < 0.05$) whereas the compound **5** shows mild effect (19.5%) at the same dose level of 100 mg/kg.

Table 3 and Figure 3 represent the average antihyperglycaemic activity profile of compound **3**, **5**, **9** and standard drug metformin in the streptozotocin-induced diabetic rats post sucrose-load. It is evident from the results that compounds **3** and **9** caused a significant decline of 14.2% ($p < 0.05$) and 14.1% ($p < 0.05$) in the hyperglycaemia of the diabetic rats post sucrose-load after 5 hour interval, respectively. The standard drug metformin at the same dose level of 100 mg/kg showed a blood glucose lowering effect of 26.9% ($p < 0.01$) after 5 h interval. Compound **5** has no effect on blood glucose level of treated animals.

In conclusion, we have developed a method for the syntheses of polyfunctionalised alkenyl and alkanonyl glycosides and evaluated their enzyme inhibitory activities against three enzymes α-glucosidase, glucose-6-phosphatase and glycogen phosphorylase. Three compounds **3**, **5** and **9** showed potent inhibition against glycogen phosphorylase, glucose-6-phosphatase and α-glucosidase, respectively. The compounds **3** and **9** caused a significant decline in the hyperglycaemia of the diabetic rats post sucrose-load. The other compounds of the series hold potential to be transformed into other molecules of great chemotherapeutic importance.

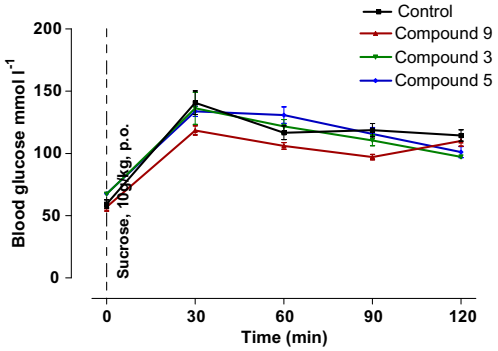


Figure 2. Effect of in vitro active compounds and metformin on blood glucose level of sucrose loaded rats at various time intervals. Values are mean ± S.E. of five rats in each group.

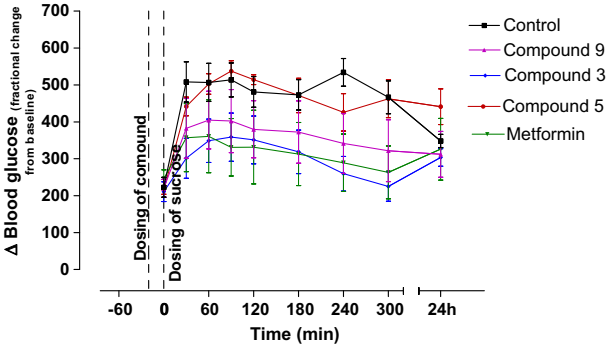


Figure 3. Effect of in vitro active compounds and metformin on blood glucose level of streptozotocin induced diabetic rats at various time intervals. Values are mean ± S.E. of five rats in each group.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.136.

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25. *Typical procedure for the synthesis of (E)-1- (β-D-Glucopyranosyl)-4-(4′-chlorophenyl) but-3-en-2-one* (**2**): To a stirring solution of (*E*)-1- (2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl) -4-(4-chlorophenyl)but-3-en-2-one (2.0 g, 3.89 mmol) (**1a**) in methanol at 25 °C, a solution of sodium methoxide (10 mL, 1.94 mmol) was added. The reaction mixture was stirred till the disappearance of the starting material (TLC). Amberlite IR 120 (H^+) resin was added to the reaction mixture and stirred for further 10 min. The reaction mixture was filtered and the filtrate was concentrated in vacuum to afford the deacetylated product **2** as a colorless solid (1.0 g, yield 74%); mp 178–179 °C; R_f 0.5 (1:10, MeOH:$CHCl_3$); $[\alpha]_D^{25}$ −9.59 (c 0.05, MeOH); ESMS m/z = 343 $(M+H)^+$, IR (KBr) ν_{max} cm^{-1}: 3399 (OH stretching), 1630 (C=O); ^1H NMR (300 MHz, DMSO) δ 7.75 (d, J = 8.3 Hz, 2H, ArH), 7.58 (d, J = 16.2 Hz, 1H, H-4), 7.48 (d, J = 8.3 Hz, 2H, ArH), 6.96 (d, J = 16.2 Hz, 1H, H-3), 5.07 (d, J = 5.5 Hz, 1H, OH), 4.90 (d, J = 4.2 Hz, 1H, OH), 4.88 (s, 1H, OH), 4.36 (t, J = 5.3 Hz, 1H, OH), 3.65–3.57 (m, 2H, H-5, H-6b′), 3.37 (m, 1H, H-6′a), 3.18–3.15 (m, 1H, H-1′), 3.06 (m, 4H, H-2′, H-3′, H-4′, H-1a), 2.70 (dd, $J'_{1b,1}$ = 8.6 Hz, $J_{1a,1b}$ = 16.2 Hz, H-1b, 1H). ^{13}C NMR (50 MHz, DMSO) δ 198.9 (C=O), 135.7, 134.3 (Ar-C), 141.48 (C-4), 128.3 (C-3), 131.0, 129.8 (ArCH), 81.6, 79.9, 76.6, 74.4, 71.1 (CH), 62.0 (C-6′), 44.3 (C-1).
26. *Typical procedure for syntheses of 6-(β-D-glucopyranosyl)-2-carbethoxy-3-((R,S)4″-phenyl)-5-oxo-ethylhexanoate* (**11**): To a stirred solution of ((*E*)-1-(β-D-glucopyranosyl)-4-(4′-chlorophenyl)but-3-en-2-one (**2**), (0.5 g, 1.46 mmol) and diethyl malonate (0.22 mL, 1.46 mmol) in ethanol, a solution of sodium ethoxide (3 mL, 0.48 mmol) was added at ambient temperature and stirring was continued till the disappearance of the starting material on the TLC plates. The reaction was neutralized by the addition of Amberlite IR 120 (H^+) resin. Stirred the reaction mixture further for 10 min., filtered the resin and the filtrate was concentrated under vacuum. The product **11** was purified by column chromatography using methanol/chloroform (2:10), elute as a colorless liquid (0.48 g, yield 65%); R_f 0.4 (1:10, MeOH:$CHCl_3$); $[\alpha]_D^{25}$ −6.96 (c 0.05, MeOH); ES–MS m/z = 519.5 $(M+18)^+$, IR (neat) ν_{max} cm^{-1}: 3389 (OH stretching), 1726 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.19 (m, 4H, ArH), 5.30–4.50 (m, OH × 4), 4.21–4.12 (m, 2H, OCH_2), 4.00–3.93 (m, 3H, H-6′ and H-2), 3.68–3.52 (m, 4H, CH, H-3 and OCH_2), 3.41 (s, 2H, CH × 2), 3.18–2.94 (m, 4H, CH_2, CH × 2), 2.78–2.70 (m, 1H, 6Ha), 2.56–2.49 (m, 1H, 6Hb), 1.26–1.21 (m, 3H, OCH_2CH_3), 1.05 (t, J = 7.11 Hz, 3H, OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.5, 168.8, 168.2, 139.7, 133.1, 130.3, 128.9, 69.8, 75.5, 76.1, 77.4, 79.8, 57.4, 39.7, 14.3, 14.1.
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31. *Antihyperglycaemic activity evaluation (a). Effect in sucrose loaded rat model:* Male albino rats of Wistar strain were selected for this study. Fasting blood glucose level of each animal was checked by glucometer using glucostrips after an overnight starvation. Animals showing blood glucose level between 60 and 80 mg/dl at 0 min were finally selected and divided into groups of five animals in each. Rats of experimental group were administered the suspension of the test sample orally prepared in 1.0% gum acacia (vehicle) at desired dose levels, that is, 250 mg/kg body weight in case of plant extracts and 100 mg/kg in case of standard antidiabetic drug, that is, metformin. Animals of control group were given an equal amount of 1.0% gum acacia and termed as sham control. An oral sucrose load of 10 g/kg body weight was always given to each animal exactly after 30 min post administration of the test sample/ vehicle. Blood glucose profile of each rat was again determined at 30, 60, 90 and 120 min post administration of sucrose by glucostrips. Food but not water was withheld from the cages during the course of experimentation.(b) *Effects in Streptozotocin induced diabetic rat model:* Male albino rats of Sprague Dawley strain were selected and made diabetic by intraperitoneal administration of streptozotocin at a dose level of 45 mg/kg body weight (prepared in 100 mM citrate buffer, pH 4.5) to overnight fasted rats. Blood glucose profile was again checked after 48 h and animals showing blood glucose values between 180 and 270 mg/kg at −20 and 0 min (baseline) were included in the experiments and termed diabetic. The diabetic animals were divided into groups were administered suspension of the desired test sample prepared in 1% gum acacia at desired dose levels (250 mg/kg) in case of plant extracts and 100 mg/kg in case of metformin). Animals of control group were given an equal amount of 1% gum acacia and termed as sham control. A sucrose load of 2.5 g/kg was given to each animal orally exactly after 30 min post administration of the test sample/vehicle. Blood glucose profile of animals of all groups was again checked at 30, 60, 90, 120, 180, 240 and 300 min post administration of sucrose. Food but not water withheld from the cages during the course of experimentation.