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FULL PAPER

Synthesis of 4-*C*-β-D-Glucosylated Isoliquiritigenin and Analogues for Aldose Reductase Inhibition Studies

Mannem Rajeswara Reddy,[a] Indrapal Singh Aidhen,[a]* Utkarsh A. Reddy,[b] Geereddy Bhanuprakash Reddy,[b] Kundan Ingle,[c] Sami Mukhopadhyay[c]

Dedicated to Professor Richard R. Schmidt on the occasion of his 84th Birthday

Abstract: Inspired from natural product isoliquiritine, an *O*-glucoside and the corresponding aglycone chalcone, isoliquiritigenin (ISL), several *C*-glucosylated chalcones and dihydrochalcones have been synthesized and evaluated for aldose reductase (AR) inhibition activity, for the first time. The initial inputs from molecular docking studies were also encouraging. Claisen-Schmidt condensation reaction between 4-*C*-glucosylated benzaldehyde, a key building block developed during the synthetic efforts and acetophenones enabled convenient access to the targeted compounds in good yields. Excellent AR inhibition has been observed with *C*-glucosylated ISL with IC_{50} value of 21 μM. This is similar to the chalcone ISL, displaying IC_{50} of 19 μM. In the light of limited aqueous solubility of ISL, the observed AR inhibition with *C*-glucosylated ISL, gains importance. Additionally, the studies have revealed significance of the oxygenation pattern on the aromatic residue and paved way for the identification of few more new compounds with equally promising AR inhibition.

Introduction

Chalcones are emerging as privileged scaffold[1] and have shown promise in the management of diabetes through variety of mechanisms.[2] The chalcone, isoliquiritigenin (ISL) (**1**)[3] and its dihydrochalcone analogue, davidigenin (**2**)[4] isolated from Glycyrrhizae radix and Artemisia plant respectively have shown ALR2 inhibition activity similar to flavonoid, quercetin **3**, a well-known ALR2 inhibitor.[5] Subsequent biostudies with synthetic chalcones[6] and molecular docking studies[7] indicate the presence of hydroxy groups in the A-ring as an essential feature for the optimal activity from chalcones. However, the hydroxyl-substituted chalcones have inadequate water solubility and bioavailability. Given the fact that glucosylation of low molecular weights compounds is a promising approach for enhancing water solubility, improved stability and bioavailability, we proposed to synthesize and evaluate, 4-*C*-glucosylated isoliquiritigenin (**4**), it's dihydro derivative **5** in particular and several analogues, thereof, represented by structure **6**, for ALR2 inhibition activity. The 4-*O*-glucosylated ISL, known as isoliquiritine **7** is present in natural sources,[8] however the well-known greater hydrolytic stability of *C*- verses *O*-glycosides, emboldened us in favor of *C*-glucosylated **4** and **5** as our targets for synthesis and biostudies (Figure 1).

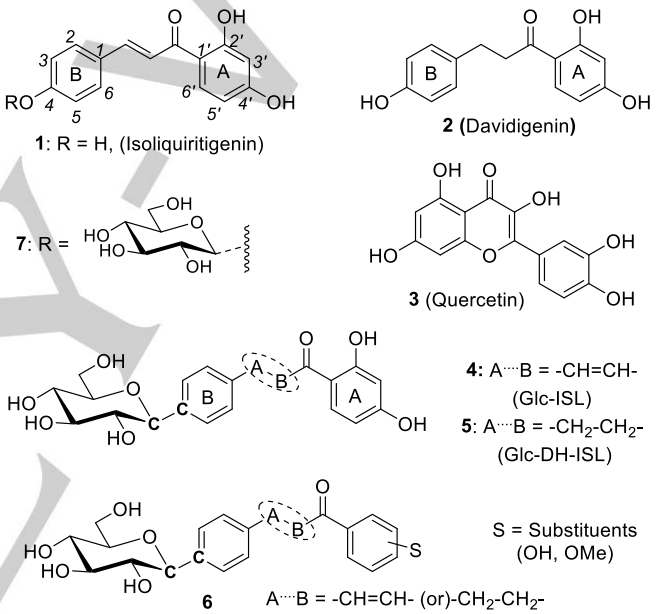

Figure 1. Proposed D-glucosylated chalcones **4** and dihydrochalcones **5**.

Before undertaking synthesis and biostudies, docking studies (see infra) were performed for understanding the promising features, if any, with the proposed *C*-glucosylated targets **4** and **5**. Although ISL **1**, and the proposed *C*-glucosylated targets **4** and **5** had favourable docking scores in arbitrary units of -70.37, -53.47 and -72.38 respectively, the key stabilizing and favourable binding interactions at the active site were significantly more with the proposed new targets **4** and **5**, compared to ISL. These observations further inspired us to undertake synthesis of proposed new targets and evaluate their ALR inhibition. Presented herein are the results of these findings.

Results and Discussion

1. Molecular Docking Studies.

1.1 Selection and Preparation of Protein Structure

The X-ray structure of human Aldose Reductase (PDB ID 1PWM X-Ray resolution of 0.92 Å) in complex with NADP and the inhibitor fidarestat was obtained from the RCSB Protein Bank

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(RCSB pdb). Crystallographic protein structure downloaded from protein data bank contains various potential problems which must be resolved. These issues involved removal of water and other co-crystal ligands, addition of hydrogen atoms and assigning correct charges to protein structures.

Preparation of protein structures for docking purpose were performed using VLife Molecular Design Suite (VLifeMDS®).[9]

1.2 Preparation of the Ligands

The structures of compounds isoliquiritigenin **1**, glucosylated isoliquiritigenin **4** and the reduced (C=C double bond reduced) glucosylated isoliquiritigenin **5** were generated using the 2D Draw tool of the VLifeMDS®.The 2D structures were prepared for docking by adding hydrogen atoms and energy minimized using force field MMFF with RMSD gradient of 0.01 kcal/mol Å. Conformations of the molecules were generated using a Monte Carlo method with an RMSD cutoff of 0.7. All these steps were carried out using VLifeMDS®.[9]

1.3 Docking Study

The following molecular docking study was carried out with an aim to rationalise the background for synthesizing the different G glucosylated isoliquiritigenin molecules with respect to their inhibitory activity towards aldose reductase in the light of designing novel promising anti-diabetic agents.

The active site used for docking was determined by the key active site residues as cited in published literature.[10,11] The software VLife Molecular Design Suite (VLifeMDS®)[9] has been utilized for carrying out the molecular docking. Piecewise Linear Pairwise Potential (PLP)[12] was used as the dock scoring function. The PLP empirical score is in arbitrary units.

All the three ligands **1, 4,** and **5** were docked in to the binding site of the PDB (Aldose Reductase (1pwm)). Analysis of the docking results was based on both the docking score (PLP) as well as the binding interactions with active site residues.[10,11]

1.4 Docking Results and Analysis

The favourable stabilizing key binding interactions are significantly more in both *C*-glucosylated targets **4** (Glc-ISL) and **5 (**Glc-DH-ISL**)** as compared to natural product isoliquiritigenin **1** (ISL). While ISL has favourable binding interactions: H-bond interaction with LEU300A and Pi Stacking with TRP20A, and TRP219A, the molecule **4** captures favourable binding interactions: H-bond interactions with HIS110A, CYS298A and Pi stacking interaction with TRP20A and TRP219A as well as hydrophobic interactions with VAL47A, TRP111A, CYS298A whereas molecule **5** (Glc-DH-ISL) captures favourable binding interactions: H-bond interactions with GLN183A, CYS298A and Pi stacking interactions with TRP20A, TYR209A, TRP219A, HIS110A as well as hydrophobic interactions with CYS298A. This clearly shows that both the proposed targets **4** and **5** are able to capture more favourable binding interactions in the active site of aldose reductase, compared to natural product ISL **1**. This understanding motivated us to synthesize compounds **4** and **5** for evaluating their aldose reductase inhibition activity. The best docked poses presenting key binding interactions as discussed above are depicted in Figures 2-4. In case of the 3D images, the active site surface of aldose reductase (1pwm) is shown in picture (c), whereas the other picture (b) is without the surface, for clarity of visualising the binding interactions. Different binding interactions of the ligands in the active site are shown in different colours together with the colour code for ease of understanding.

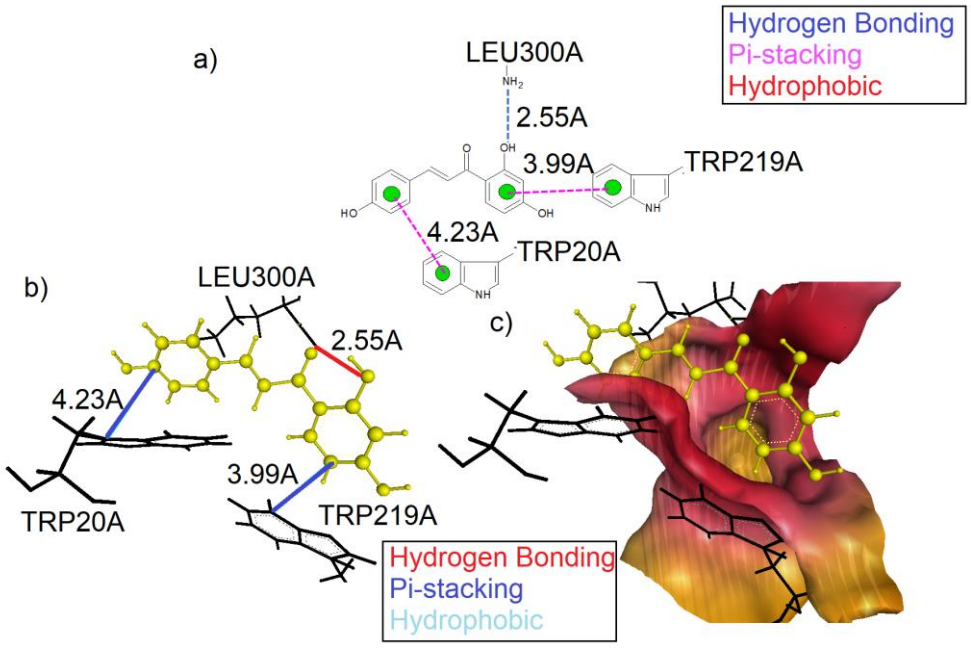


Figure 2. Molecular docking images of ISL **1**, (a) 2D, (b) 3D and (c) 3D Pocket & Interactions.

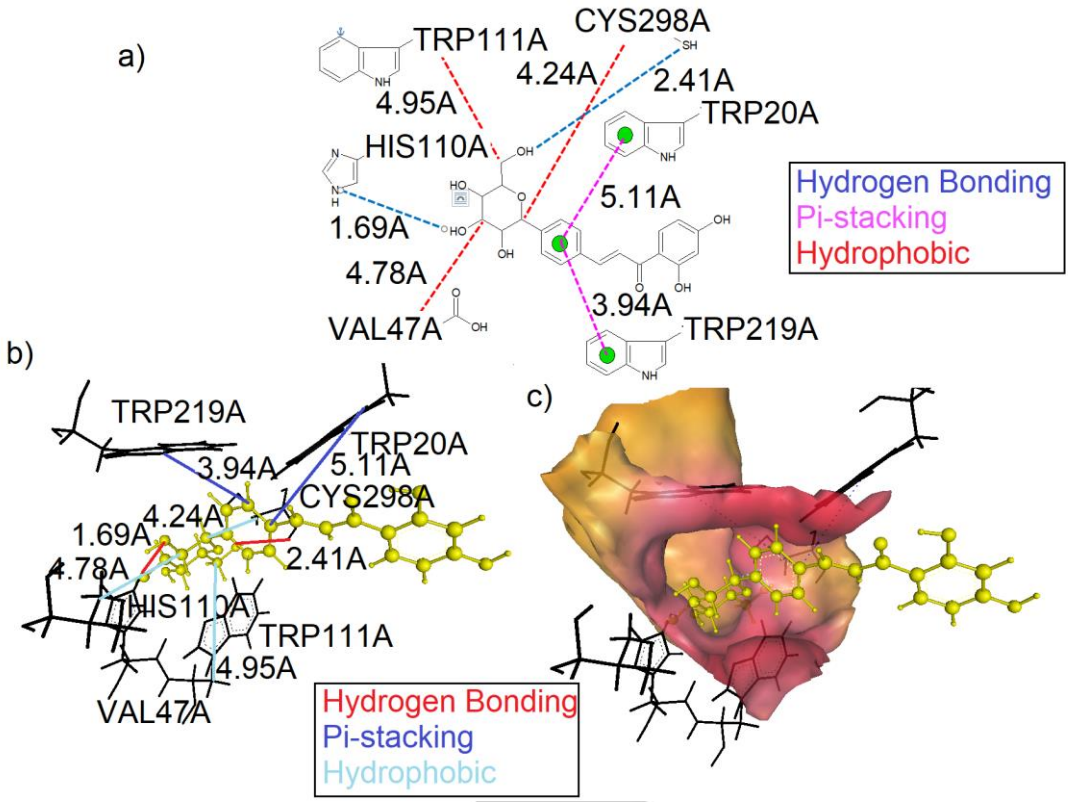


Figure 3. Molecular docking images for **4**, (a) 2D, (b) 3D and (c) 3D Pocket & Interactions.

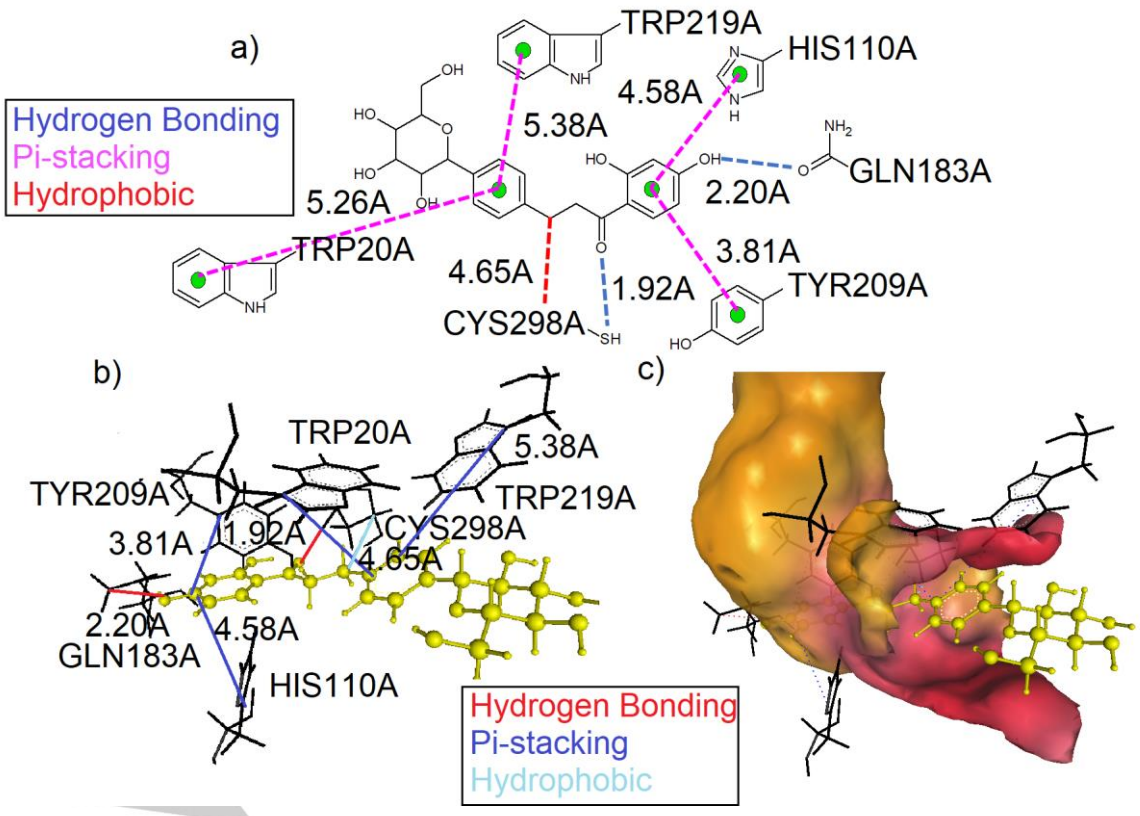


Figure 4. Molecular docking images for **5**, (a) 2D, (b) 3D and (c) 3D Pocket & Interactions.

In all the 2D images the aromatic interactions mean Pi-stacking interactions. It is interesting to note that while the resorcinol unit, aromatic ring A, in natural product, ISL **1** captures favourable key binding interactions with the active site of aldose reductase (Figure 2), surprisingly with the Glc-ISL, **4**, the best docked pose has glucosyl residue capturing the favourable binding interactions with the active site (Figure 3) and the resorcinol aromatic ring A of Glc-ISL, **4** is out of the active site pocket. In case of Glc-DH-ISL, compound **5**, the best docked pose (Figure 4) once again has favourable binding with the resorcinol unit, aromatic ring A, similar to that observed for the natural product **1.** Compound **5** being a dihydrochalcone, the apparent contrast between **4** and **5** may be because of the additional conformational freedom available in **5** from free C-C rotation along the α, β carbon atoms. The observed interactions compensate towards overall favourable binding and these are reflected in the fact that both the structures **4** and **5** have favourable docking scores (in arbitrary units) of -53.47 and -72.38 respectively.

To rationalize the surprise element between compound **1** and **4** and with the understanding that the interactions between a molecule and its receptor need not necessarily correspond to minimum energy, guided docking of compound **4** was carried out forcing the resorcinolic aromatic ring A inside the aldose reductase active site. The results of this guided docking studies afforded poor docking scores indicating that these docked poses of Glc-ISL, **4** are unfavorable for binding in the active site pocket of aldose reductase. The docked poses, in fact showed severe steric clashes of the glucosyl group with the surrounding aldose reductase residues. In this context, the analogues of substrate **4** with varying substituents in ring A, apparently, should have identical bioactivity, until and unless the electronic effects of the substituents get transmitted via the π-conjugated framework and alter the primary interactions of the portion of the moleccule inside the pocket. The synthesis of compound **4**, **5** and their analogues, along with the results of biostudies are presented below.

2. Chemistry

The synthesis of targeted compounds **4**, **5** and analogues essentially banked on the classical Claisen Schmidt condensation reaction between suitably protected 4-*C*-glucosylated benzaldehyde and acetophenones and subsequent deprotections. To begin with and to provide some degree of orthogonality among protections on the glucosyl and aromatic residue part from acetophenones, we envisaged **8a** and **8b** as the key building block for the synthetic scheme (Figure 5).

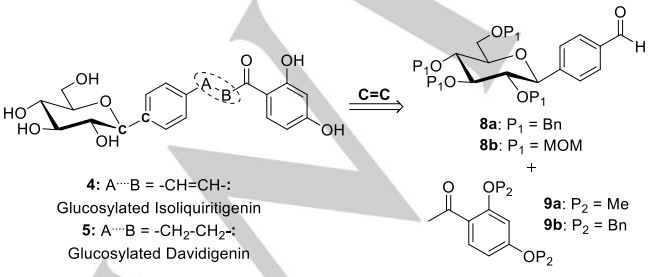
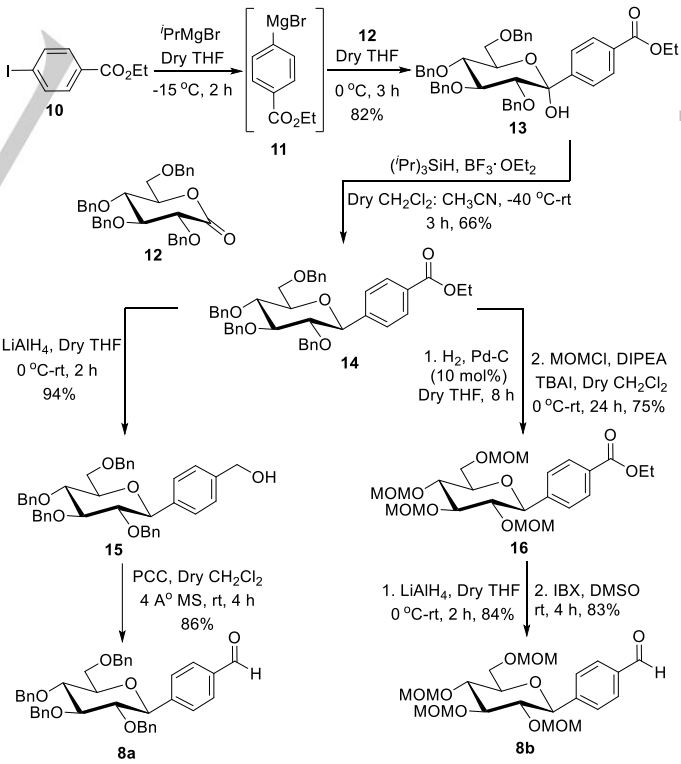


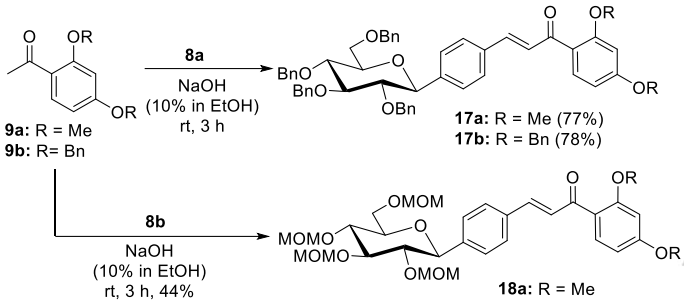
Figure 5: Retrosynthetic scheme for glucosylated target **4** and **5**.

Synthesis of hitherto unknown building blocks **8a** and **8b** was readily achieved as described in synthetic scheme 1. It involved formation of functionalized aryl magnesium bromide from ethyl-4-iodobenzoate **10** using well known and elegant procedure developed by Knochel's group[13] and addition onto protected D-gluconolactone **12**[14] for the desired C-C bond formation. A metal-halogen exchange reaction was performed between the isopropylmagnesium bromide (prepared *in situ*) and ethyl-4-iodobenzoate **10** for the formation of arylmagnesium bromide **11**. To the formed Grignard reagent, was added D-gluconolactone **12.** The reaction afforded after work-up and purification the β-anomer product **13** in 82%. Reductive anomeric deoxygenation in lactol **13** was carried out using triisopropylsilane and $BF_3{\cdot}OEt_2$. The reduction was clean and afforded the desired compound **14** in 66% yield with exclusive selectivity. It merits to mention that the use of more commonly used, triethylsilane, showed low selectivity and this has been also observed in the literature.[15] Reduction with $LiAlH_4$, followed by oxidation of the benzylic alcohol **15** with PCC afforded the desired aldehyde **8a** in 86% yield, over two steps. A single step reduction of ester **14** with DIBAL-H afforded a mixture of desired aldehyde **8a** and over reduced product **15**. Reductive hydrogenolysis of compound **14** with Pd-C **(**10 mol%**),** and subsequent treatment of the resultant tetrol with chloromethyl methyl ether in presence of Hunig's base in anhydrous CH_2Cl_2 generated the O-MOM protected compound **16** in 75% yield, over two steps**.** Subsequent reduction with lithium aluminum hydride and oxidation of benzylic alcohol with IBX in presence of DMSO furnished the O-MOM protected 4-*C*-glucosylated benzaldehyde **8b** as a pale-yellow color gum in good yields (Scheme 1).



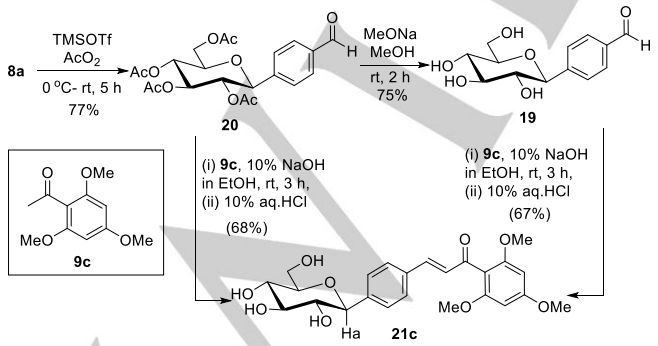
Scheme 1. Synthesis of key building blocks **8a** and **8b**.

Both the building blocks **8a** and **8b** underwent the expected condensation with requisite 2, 4-disubstituted acetophenone **9a**[16] in presence of alcoholic (ethanol) 10% NaOH, at room temperature affording the corresponding chalcone **17a** and **18a** respectively in good yields (Scheme 2). However, the simple and final removal of ether protections in **17a** and **18a** was not trouble free. The use of BBr_3 for deprotection resulted in formation of a complex mixture of products as observed from NMR spectrum (^1H, ^{13}C). Even with the use of TMSOTf at low temperature (-40 ^oC), the deprotection attempt was not successful. The reaction lead to decomposition of the starting material. The chalcone **17b** prepared from benzyl ether protected acetophenone **9b**[17] also presented similar difficulties in final deprotection.



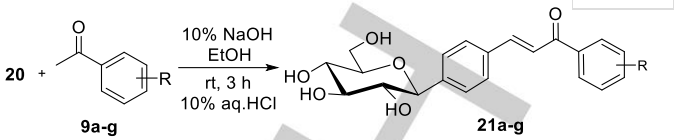
Scheme 2. Synthesis of protected chalcones **17a-b** and **18a**.

The frustration of deprotection on the D-glucosyl residue at the final stages, emboldened us to investigate the formation of chalcone with protection free aldehyde **19**, which will obviate the aforesaid need of deprotection at the final stages. The protection-free aldehyde **19** was easily prepared from the corresponding benzyl ether protected aldehyde **8a** in two steps. The benzyl ether protections in aldehyde **8a** were removed using TMSOTf (1.5 eq.) in presence of acetic anhydride as solvent. The reaction afforded the corresponding peracetylated product **20** in 77% yield. Subsequent deacetylation with NaOMe in presence of MeOH gave the desired protection free aldehyde **19** as a colorless solid in good yield (Scheme 3).



Scheme 3. Synthesis of protection free building block **19** from **8a**.

Table 1. Synthesis of methoxy substituted chalcones **21a-g.**

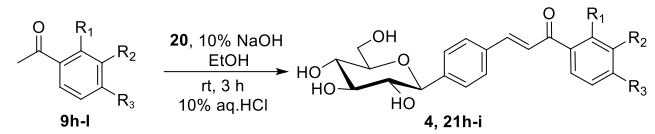


Entry	9	21	Yield [a]
1	**9a:** R = 2, 4-$(OMe)_2$	**21a:** R = 2, 4-$(OMe)_2$	73%
2	**9b:** R = 2, 4-$(OBn)_2$	**21b:** R = 2, 4-$(OBn)_2$	65%
3	**9d:** R = 2-OH-4,6-$(OMe)_2$	**21d:** R = 2-OH-4,6-$(OMe)_2$	57%
4	**9e:** R = 3,4-$(OMe)_2$	**21e:** R = 3,4-$(OMe)_2$	69%
5	**9f:** R = 4-(OMe)	**21f:** R = 4-(OMe)	62%
6	**9g:** R = 2, 4, 6-$(OBn)_3$	**21g:** R = 2, 4, 6-$(OBn)_3$	63%

[a] Isolated Yield

The aldehyde **19** in fact underwent trouble free Claisen-Schmidt reaction with **9c**, as a representative acetophenone furnishing the corresponding chalcone **21c** in 67% yield. The obtainment of the chalcone **21c** was confirmed by ^1H NMR spectrum. The doublet present at 4.19 ppm represents the anomeric proton (Ha), the coupling constant 9.5 Hz confirmed the β-orientation, whereas two doublets present at 6.98 and 7.34 ppm represent the two olefinic protons of chalcone and the coupling constant 16.0 Hz confirms the *trans*-geometry of the enone functionality. Even the peracetylated aldehyde **20** condensed with acetophenone **9c**, with equal ease (Scheme 3)**.** Basic conditions during condensation assured the facile and convenient removal of the acetyl group protections in the same pot. The generality of the scheme was demonstrated with several other acetophenones (Table 1).

Our earlier experience of facing difficulties in removal of the ether protections on the glucosyl and aromatic part, we first chose the acetyl or benzoyl protected, 2,4-dihydroxy acetophenone **9h** or **9i** respectively for condensation with the peracetylated aldehyde **20** towards the synthesis of targeted compound **4.** This was with the premise that the basic conditions will not only enable condensation but would also ensure, de-acylation on glucosyl and aromatic ring together. To our surprise, no condensation occurred and only mere recovery of de-acetylated building block **19** was seen. This could be presumably due to faster rates for the deacylation reaction compared to condensation reaction. In order to circumvent this failure, the MOM ether protected 2, 4-dihydroxy acetophenone **9j** was explored for condensation with aldehyde **20**. To our satisfaction, condensation occurred affording the corresponding targeted 4-*C*-glucosylated isoliquiritigenin **4** in 67% isolated yield, after acidic work-up, which affected the removal of MOM protection (Scheme 4). The developed protocol was generalized with two other MOM protected acetophenones **9k** and **9l.** The corresponding products **21h** and **21i**, containing hydroxyl functionality like isoliquiritigenin on the aromatic ring were obtained in similar yields.



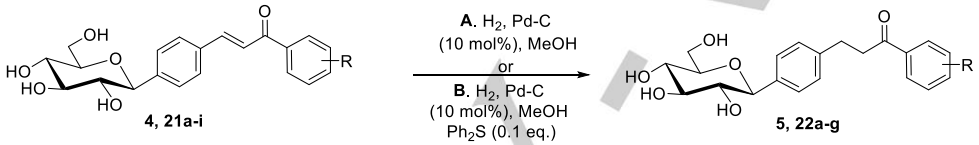
9h: $R_1 = R_3$ = OAc, R_2 = H
9i: $R_1 = R_3$ = OBz, R_2 =H
9j: $R_1 = R_3$ = OMOM, R_2 = H
9k: $R_2 = R_3$ = OMOM, R_1 = H
9l: $R_1 = R_2$ = H, R_3 = OMOM

4: $R_1 = R_3$ = OH, R_2 = H (67%)
21h: $R_2 = R_3$ = OH, R_1 = H (69%)
21i: $R_1 = R_2$ = H, R_3 = OH (68%)

Scheme 4. Synthesis of target compound **4** and it's analogues **21h-i**.

The synthesis of dihydrochalcones involved simple hydrogenation, using, Pd-C (10 mol%) under H_2 balloon pressure (1 atm). The chalcones **4/21b, 21c,** and **21g** afforded the corresponding dihydrochalcones **5, 22b** and **22e** respectively in good yields. In case of other chalcones, **21a**, **21e-f** and **21h-i** unwanted partial or complete reduction of the carbonyl group was also observed. Such an observation of aromatic carbonyl group reduction to methylene compounds via the intermediacy of benzylic alcohol under Pd/C-catalyzed hydrogenation condition is well reported.[18] The addition of a sulfur containing additive such as diphenylsulfide (Ph_2S) prevents the reduction of carbonyl group in chalcones during hydrogenation[19] and this was used for the chemoselective hydrogenation of the olefin functionality alone. Addition of 0.1 equivalent of Ph_2S into the reaction mixture, during the hydrogenation of **21a** and **21e-i** afforded the corresponding desired dihydro chalcones **22a-g** in good yields as shown in the table 2. The synthesized D-glucosylated chalcones and dihydrochalcones were subjected to biological studies.

Table 2. Synthesis of dihydrochalcones **5** and **22a-g** from appropriate chalcones



Entry	21	Condition/t	22	Yield [a]	Entry	21	Condition/t	22	Yield [a]
1	**21a**	B/18 h	**22a:** R = 2, 4-$(OMe)_2$	73%	5	**21f**	B / 24 h	**22d:** R = 4-(OMe)	76%
2	**21b**	A/10 h	**5:** R = 2,4-$(OH)_2$	77%	6	**21g**	A / 12 h	**22e:** R = 2, 4, 6-$(OH)_3$	78%
3	**21c**	A/10 h	**22b:** R = 2, 4, 6-$(OMe)_3$	68%	7	**21h**	B / 24 h	**22f:** R = 3,4-$(OH)_2$	67%
4	**21e**	B/24 h	**22c:** R = 3, 4-$(OMe)_2$	64%	8	**21i**	B / 18 h	**22g:** R = 4-(OH)	61%

[a] Isolated yield

Biological Studies

As expected, to our delight, both *C*-glucosylated ISL **4** and *C*-glucosylated davidigenin **5** have exhibited the promising AR inhibitory activity. The natural product, ISL (**1**), showed 91% inhibition at 100 μM concentration, whereas *C*-glucosylated ISL, **4**, exhibited 100% inhibition at 120 μM concentration. The loss in activity with compound **21a** (8% inhibition at 200 μM), the methyl ether derivative of **4** corroborates the importance of phenolic hydroxyls and their positioning. The oxygenation pattern and the number of phenolic hydroxyls in aromatic ring A seems to be crucial for activity. Chalcones containing tri-oxygenated aromatic ring A with oxygenation pattern being 2,4,6 essentially showed no activity (compound **21c**, **21d**). The chalcone **21h**, di-oxygenated and positional isomer of *C*-glucosylated ISL, had 61% inhibition at 120 μM and the corresponding methyl ether derivative compound **21e**, exhibited 100% inhibition at 200μM. The chalcone **21i** with mono-oxygenated ring A, had no activity, even at 250μM while it's methyl ether derivative **21f** showed extremely good activity with 100% inhibition at 200μM.

Compare to chalcones, all the corresponding dihydrochalcones were relatively less active. The *C*-glucosylated davidigenin **5**, exhibited AR inhibitory activity of 57% and 73% at 120 μM and

Table 3. IC_{50} values for the important chalcones and dihydrochalcones comparing with ISL.

Entry	Compound	IC_{50} (μM)	Entry	Compound	IC_{50} (μM)
1	**ISL[a]**	19.00	5	**21e**	145.0
2	**4**	21.00	6	**22f**	245.0
3	**21h**	55.00	7	**22e**	336.0
4	**5**	72.00			

[a] Natural product

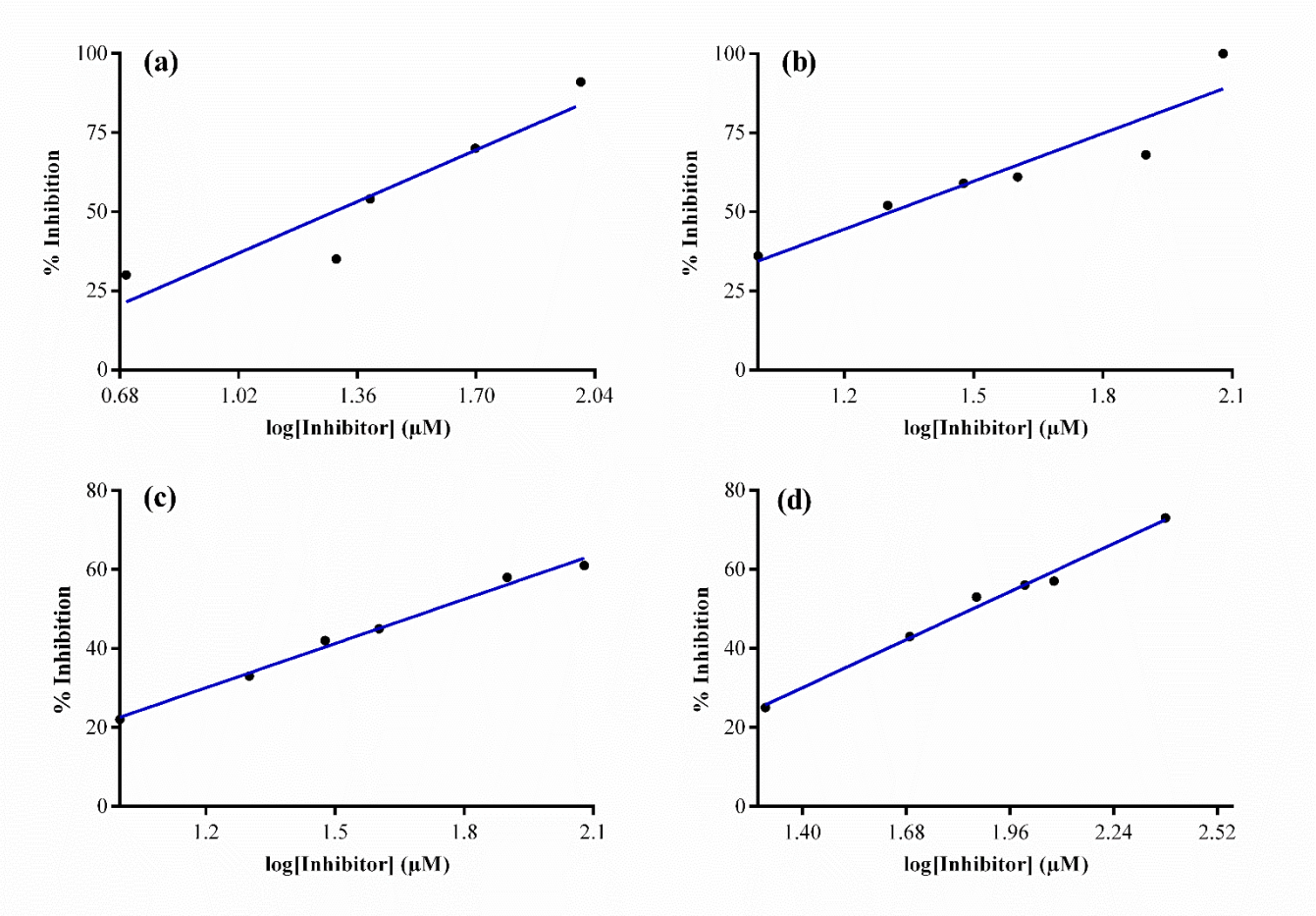


Figure 6. IC_{50} Graphs (a) **ISL,** (b) Compound **4,** (c) Compound **21h,** and (d) Compound **5.**

240 μM respectively. The compounds **22e** and **22f** showed moderate activity with 38% and 48% at 240 μM respectively, while other dihydro chalcones **22a**, **22b**, **22c**, **22d**, and **22g** were not active (≤15%) even at higher concentration (250 μM). The IC_{50} values of the six promising compounds are presented in Table 3 and the data of three most promising compounds among them are graphically represented in Figure 6.

Conclusions

The synthesized 4-*C*-glucosylated chalcones in general and *C*-β-D-glucosylated isoliquiritigenin **4** in particular are indeed showing good AR inhibition. These synthetic compounds are easily accessible through the Claisen-Schmidt condensation reaction between 4-*C*-glucosylated benazaldehyde **20**, a key building block developed in the scheme and appropriate acetophenones **9a-l.** Chemoselective reduction of the double bond in the chalcones under hydrogenation conditions, using diphenyl sulfide (Ph_2S) as additive, afforded convenient access to the corresponding dihydrochalcones **5** and **22a-g**, without any reduction or over reduction of the carbonyl group. The synthetic work and biostudies have enabled identification of a three new chalcones **21h, 21e** and **21f** with equally promising activity. While **21h** displays 61% inhibition at 120 μM, the other two chalcones **21e** and **21f** showed 100% inhibition at 200μM. The variation in the experimentally observed bio-activity of chalcones (compounds **21a**, **21c-f, 21h, 21i**), analogues of Glc-ISL, compound **4**, with varying substituents on the resorcinolic aromatic ring A, reflects, probable transmission of electronic effects of the substituents via the π conjugated framework comprising of carbonyl group and double bond. The relayed electronic effects of the substituents, being different, due to the nature and position of the substituents, alters the binding efficacy of the portion inside the pocket, differently, and this is reflected in the observed bioactivity.

Our research findings will be of relevance and importance, given the fact that search of aldose reductase inhibitors (ARIs) for the prevention and/or arrest of long-term diabetic complications resulting from hyperglycemia remains unabated and focus clearly

shifting towards small sized organic molecules from natural sources in the recent times.[20]

Experimental Section

All reactions were carried out in an oven dried glassware. Solvents used for column chromatography were laboratory reagent grade. Solvents were distilled from CaH_2 (CH_2Cl_2, DMF), Na/Benzophenone for THF and Mg/I_2 (MeOH). Reactions were performed under nitrogen atmosphere. NMR spectra were recorded at 293 K, unless stated otherwise. Thin layer chromatography was performed on aluminum plates coated with silica gel 60. Visualization was observed by U.V. light or by dipping into a solution of cerium (IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10 % sulfuric acid (250 mL) followed by charring on a hot plate. Melting points were determined in capillaries. All compounds were purified by silica gel column chromatography (100-200 mesh), using respective solvent system. ^{1}H (400 MHz and 500 MHz) and ^{13}C (100 MHz and 125 MHz) high resolution NMR experiments were recorded on BRUKER AV 400 and 500 FT NMR spectrometer using tetramethylsilane (TMS) as an internal standard. ^{1}H NMR spectra were referenced to $CDCl_3$ (δ =7.26 ppm), MeOH [D_4] (δ = 3.34 ppm) and central line of DMSO [D_6] (δ =2.5 ppm), whereas ^{13}C NMR spectra were referenced to the central line of $CDCl_3$ (δ =77.16 ppm), MeOH [D_4] (δ = 49.15 ppm) and DMSO [D_6] (δ =39.5 ppm). Multiplicities are given as, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiple, and br. s = broad singlet. IR spectra was recorded with a JASCO-FT/IR-4100 Spectrometer with a NaCl cell. HRMS were recorded with a Agilent technologies 6545-QTOF mass spectrometer by using the ESI technique at 10 eV.

ethyl 4-(2,3,4,6-tetra-*O*-benzyl-1-hydroxy-β-D-glucopyranos)benzoate 13:

An oven dried two necked round bottom flask was charged with magnesium turnings (0.71 g, 29.6 mmol) and catalytic amount of I_2 was added. The flask was pre-heated under vacuum to activate the magnesium and anhydrous THF (25 mL) was added. At stirring isopropylbromide (1.26 mL, 16.7 mmol) was added slowly, after 5 min the mixture was strongly self heated. As the magnesium turnings were finished, ethyl-4-iodobenzoate **10** (4.05 g, 14.8 mmol) in anhydrous THF was added to the reaction mixture at -15 °C slowly and stirring was continued for 2 h at the same temperature. To the resulting yellow color solution was added lactone **12** (4.0 g, 7.4 mmol) in anhydrous THF for 15 min at -15 °C, and the solution was warmed to 0 °C, allowed to stir for 3 h at same temperature. The solution was diluted with cold aq. NH_4Cl solution, aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic layer was washed with brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes, 1:3) affording the lactol **13** (4.2 g, 82%) as a light yellow color gum; R_f = 0.4 (EtOAc/hexanes, 1:4); $[\alpha]^{23}_D$ = -9.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3 H), 3.3 (s, 1 H), 3.54 (d, *J* = 9.2 Hz, 2 H), 3.72 (dd, *J* = 10.8, 2.0 Hz, 1 H), 3.80-3.85 (m, 3 H), 4.05-4.09 (m, 1 H), 4.10-4.12 (m, 1H), 4.16-4.19 (m, 1 H), 4.39 (q, *J* = 7.2., 2 H), 4.43 (d, *J* = 8.0 Hz, 1 H), 4.54 (d, *J* = 12.4 Hz, 1 H), 4.61-4.66 (m, 2H), 4.87 (d, *J* = 10.8 Hz, 1 H), 4.90 (s, 1 H), 6.93-6.96 (m, 2 H), 7.14-7.23 (m, 4 H). 7.25-7.33 (m, 14 H). 7.69 (d, *J* = 8.8 Hz, 2 H), 8.03 (d, *J* = 8.8 Hz, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (CH_3), 62.7 (CH_2), 68.9 (CH_2), 72.2 (CH), 73.3 (CH_2), 75.1 (CH_2), 75.5 (CH_2), 75.7 (CH_2), 78.2 (CH), 83.5 (CH), 84.6 (CH), 97.8 (C), 126.3 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 129.4 (CH), 130.6 (C), 137.9 (C), 138.1 (C), 138.3 (C), 138.5 (C), 146.9 (C), 166.4 (C). IR ($CHCl_3$): $\tilde{\nu}$ = 1103, 1370, 1532, 1701, 2873, 3226 cm^{-1}. HRMS: Calcd for $C_{43}H_{44}O_8Na$ $[M+Na]^+$ 711.2933, found 711.2941.

Ethyl-4-(2,3,4,6-tetra-*O*-benzylglucopyranosyl)benzoate 14:

To a solution of lactol **13** (2.8 g, 4.06 mmol) in a mixture of acetonitrile:dichloromethane (1:1, 30 mL) was added triisopropylsilane (2.25 g, 5.90 mmol) at room temperature under nitrogen atmosphere. Subsequently, $BF_3{\cdot}OEt_2$ was added to the reaction mixture at -30 °C for 5 min then the reaction was stirred at room temperature for 3 h. After completion, the reaction mixture was diluted with sat. $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3x100 mL), resultant organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexanes, 85:15) affording compound **14** (1.8 g, 66%) as a colorless solid. R_f = 0.6 (EtOAc/hexanes, 1:4); m.p. = 82-84 °C; $[\alpha]^{23}_D$ = 43.3 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3 H), 3.4 (t, *J* = 9.2 Hz, 1 H), 3.61 (d, *J* = 8.0 Hz, 1 H), 3.77-3.81 (m, 5 H), 4.30 (d, *J* = 11.6 Hz, 1 H), 4.36-4.42 (m, 3 H), 4.56 (d, *J* = 12.4, 1 H), 4.62-4.65 (m, 2 H), 4.86 (d, *J* = 11.2 Hz, 1 H), 4.91-4.95 (m, 2 H), 6.91-6.93 (m, 2 H), 7.19-7.25 (m, 5 H). 7.28-7.34 (m, 13 H). 7.53 (d, *J* = 8.4 Hz, 2 H), 8.04 (d, *J* = 8.8 Hz, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (CH_3), 61.0 (CH_2), 69.0 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.1 (CH_2), 75.7 (CH_2), 78.2 (CH), 79.3 (CH), 81.1 (CH), 84.0 (CH), 86.0 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.5 (CH), 130.2 (C), 137.9 (C), 138.1 (C), 138.2 (C), 138.5 (C), 144.2 (C), 166.5 (C). IR ($CHCl_3$): $\tilde{\nu}$ = 1185, 1417, 1543, 1691, 2891, 2967 cm^{-1}. HRMS: Calcd for $C_{43}H_{44}O_7Na$ $[M+Na]^+$ 695.2984, found 695.2992.

4-(2,3,4,6-tetra-*O*-benzylglucopyranosyl)benzylic alcohol 15:

To a solution of **14** (5.8 g, 8.6 mmol) in anhydrous THF (60 mL) was added $LiAlH_4$ (0.7 g, 17.24 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 2 h. After completion, the reaction mixture was diluted with slow addition of H_2O and filtered. The filtrate was extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexanes, 2:3) to give the title compound **15** as a colorless gum (5.1 g, 94%). R_f = 0.3 (EtOAc/hexanes, 2:3); $[\alpha]^{23}_D$ = -119.1 (c = 7.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.49-3.53 (m, 1 H), 3.59-3.60 (m, 1 H), 3.74-3.81 (m, 5 H), 4.25 (d, *J* = 9.6 Hz, 1 H), 4.36 (d, J = 10.0 Hz, 1 H), 4.54 (d, *J* = 12.4, 1 H), 4.63-4.65 (m, 2 H), 4.69 (s, 2 H), 4.85-4.95 (m, 3 H), 6.92-6.93 (m, 2 H), 7.18-7.23 (m, 5 H). 7.28-7.37 (m, 15 H). 7.46 (d, *J* = 8.0 Hz, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.1 (CH_2), 69.1 (CH_2), 73.5 (CH_2), 74.9 (CH_2), 75.1 (CH_2), 75.7 (CH_2), 78.3 (CH), 79.3 (CH), 81.4 (CH), 84.3 (CH), 86.7 (CH), 126.8 (CH), 127.6 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 137.7 (C), 138.2 (C), 138.3 (C), 138.7 (C), 138.7 (C), 140.9 (C). IR ($CHCl_3$): $\tilde{\nu}$ = 1178, 1396, 1519, 2901, 2987, 3412 cm^{-1}. HRMS: Calcd for $C_{41}H_{42}O_6Na$ $[M+Na]^+$ 653.2879, found 653.2865.

4-(2,3,4,6-tetra-*O*-benzylglucopyranosyl)benzaldehyde 8a:

To a solution of **15** (5.5 g, 8.7 mmol) in anhydrous dichloromethane (60 mL) was added PCC (3.7 g, 17.46 mmol) and molecular sieves powder (4 A°, 3 g) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 4 h. After completion, the reaction mixture was filtered, the filtrate was washed with sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexanes, 1:4) to give the title compound **8a** as a colorless solid (4.7 g, 86%). R_f = 0.3 (EtOAc/hexanes, 1:4); m.p. = 127-129 °C; $[\alpha]^{23}_D$ = 67.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.47 (t, *J* = 7.2 Hz, 1 H), 3.60-3.63 (m, 1 H), 3.77-3.84 (m, 5 H), 4.32 (d, *J* = 9.5 Hz, 1 H), 4.44 (d, *J* = 10.5, 1 H), 4.55-4.63 (m, 2 H), 4.64-4.65 (m, 1 H), 4.87 (d, *J* = 10.5 Hz, 1 H), 4.90-4.95 (m, 2 H), 6.91-6.93 (m, 2 H), 7.17-7.21 (m, 4 H). 7.27-7.32 (m, 14 H). 7.61 (d, *J* = 8.0 Hz, 2 H), 7.86 (d, *J* = 8.5 Hz, 2 H), 10.02 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 69.0 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.7 (CH_2),

78.2 (CH), 79.4 (CH), 81.0 (CH), 84.0 (CH), 86.8 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.6 (CH), 136.2 (C), 137.3 (C), 138.1 (C), 138.2 (C), 138.5 (C), 146.2 (C), 192.0 (C). IR ($CHCl_3$): $\tilde{\nu}$ = 1156, 1419, 1558, 1777, 2871, 2992, cm^{-1}. HRMS: Calcd for $C_{41}H_{40}O_6Na$ $[M+Na]^+$ 651.2722, found 651.2704.

Ethyl-4-(2,3,4,6-tetra-*O*-methoxymethyl-*β*-D-glucopyranosyl)benzoate 16:

Step 1: To a stirred solution of compound **14** (1.7 g, 2.52 mmol) in anhydrous THF (20 mL) was added Pd-C (10 mol %) (0.268 g, 0.252 mmol) at room temperature. The reaction mixture was stirred under an atmosphere of H_2 with balloon pressure until starting material was disappeared on TLC. The mixture was filtered through celite and the solvent was removed in vacuo. The resultant residue was further purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:9) to give the tetrol (0.720 g, 91%) as a colorless foam. R_f = 0.5 ($MeOH/CH_2Cl_2$, 1:9); $[\alpha]^{23}_D$ = 93.5 (c = 0.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 3.19-3.2 (m, 1 H), 3.21-3.24 (m, 1 H), 3.32-3.33 (m, 1 H), 3.36-3.41 (m, 1 H), 3.62 (dd, *J* = 12.0, 5.2 Hz, 1 H), 3.77-3.81 (m, 1 H), 4.11 (d, *J* = 9.6 Hz, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.88 (d, *J* = 8.4 Hz, 2 H), ^{13}C NMR (100 MHz, CD_3OD): δ = 13.2 (CH_3), 60.7 (CH_2), 61.7 (CH_2), 70.4 (CH), 75.1 (CH), 78.3 (CH), 80.8 (CH), 81.5 (CH), 127.5 (CH), 128.7 (CH), 129.6 (C), 145.0 (C), 166.6 (C). IR (KBr): $\tilde{\nu}$ = 1136, 1558, 1693, 2871, 2992, 3430 cm^{-1}. HRMS: Calcd for $C_{15}H_{20}O_7Na$ $[M+Na]^+$ 335.1106, found 335.1100

Step2: In a flame-dried two-necked round-bottomed flask was charged with above resulted tetrol (0.8 g, 2.56 mmol) in anhydrous dichloromethane (10 mL), upon cooling the suspension in an ice bath (0 °C), diisopropylethylamine (3.53 mL, 20.51 mmol) was added dropwise. The suspension was stirred at the same temperature for an additional 10 min and then chloromethylmethylether (1.55 mL, 20.51 mmol) was added slowly. After stirring for another 15 min at the same temperature tetrabutylammoniumiodide (3.8 g, 10.24 mmol) was added and then solution was allowed to attain room temperature. The reaction was stirred in darkness for 24 h, the solution gradually turned into red in color and was cooled to 0 °C, saturated NH_4Cl (10 mL) solution was added and the organic layer was extracted with dichloromethane (3 × 70 mL), dried over Na_2SO_4, and concentrated to give the title compound **16** as a colorless gum (1.03 g, 82%), after column chromatography on silica gel (EtOAc/hexanes, 2:3). R_f = 0.3 (EtOAc/hexanes, 1:4); $[\alpha]^{23}_D$ = -181.4 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.2 Hz,3 H), 2.76 (s, 3 H), 3.34 (s, 3 H, OMe), 3.38 (s, 6 H), 3.55 (t, *J* = 9.2 Hz, 1 H), 3.61-3.65 (m, 2 H), 3.72 (dd, *J* = 11.6, 4.8 Hz, 1 H), 3.78 (t, *J* = 8.8 Hz, 1 H), 3.92 (d, *J* = 10.8 Hz, 1 H), 4.05 (d, *J* = 6.4 Hz, 1 H), 4.25 (d, *J* = 6.4 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 4.45 (d, *J* = 6.4 Hz, 1 H), 4.66 (s, 2 H), 4.78 (d, *J* = 6.4 Hz, 1 H), 4.86−4.93 (m, 3 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 8.0 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3), 55.3 (OMe), 55.9 (OMe), 56.4 (2xOMe), 61.0 (CH_2), 66.7 (CH_2), 75.3 (CH) 77.1 (CH), 78.8 (CH), 80.0 (CH), 81.2 (CH), 83.7 (CH), 96.6 (CH_2), 97.5 (CH_2), 98.6 (CH_2), 98.7 (CH_2) 127.5 (CH), 128.7 (CH), 130.3 (C), 143.7 (C), 166.4 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1136, 1558, 1693, 2871, 2992, 3430 cm^{-1}. HRMS: Calcd for $C_{23}H_{36}O_{11}Na$ $[M+Na]^+$ 511.2155, found 511.2155.

4-(2,3,4,6-tetra-*O*-methoxymethyl-*β*-D-glucopyranosyl)benzaldehyde 8b:

Step 1: The ester **16** (3.9 g, 7.99 mmol), $LiAlH_4$ (0.455 g, 11.98 mmol) and anhydrous THF (40 mL) were treated according to the procedure used for the synthesis of compound **15**, to give the resultant alcohol, after column chromatography on silica gel as a colorless gum (2.97 g, 84%). R_f = 0.3 (EtOAc/hexanes, 2:3); $[\alpha]^{23}_D$ = -96.4 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.8 (s, 3 H), 3.33 (s, 3 H), 3.45 (s, 6 H), 3.55 (t, *J* = 9.2 Hz, 1 H), 3.57-3.59 (m, 1 H), 3.62 (t, *J* = 9.6 Hz, 1 H), 3.69-3.78 (dd, *J* = 11.6, 4.8 Hz, 2 H), 3.92 (dd, *J* = 11.2, 2.0 Hz, 1 H), 4.03 (d, *J* = 6.4 Hz, 1 H), 4.17 (d, *J* = 9.6 Hz, 1 H), 4.40 (d, *J* = 6.4 Hz, 1 H), 4.65 (s, 4 H), 4.78 (d, *J* = 6.4 Hz, 1 H), 4.86−4.93 (m, 3 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (OMe), 55.8 (OMe), 56.5 (2xOMe), 64.8 (CH_2), 66.8 (CH_2), 77.1 (CH) 78.7 (CH), 80.2 (CH), 81.5 (CH), 83.7 (CH), 96.7 (CH_2), 97.4 (CH_2), 98.6 (CH_2), 98.7 (CH_2) 126.7 (CH), 128.1 (CH), 138.1 (C), 141.1 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1217, 1558, 2871, 2992, 3510 cm^{-1}. HRMS: Calcd for $C_{21}H_{34}O_{10}K$ $[M+K]^+$ 485.1789, found 485.1790.

Step 2: To a solution of above resultant compound (3.6 g, 8.1 mmol) in DMSO (40 mL) was added IBX (3.4 g, 12.16 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 4 h. After completion, the reaction mixture was diluted with H_2O, then filtered, the filtrate was extracted with EtOAc, the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexanes, 1:4) to give the title compound **8b** as a colorless gum. (2.97 g, 83%). R_f = 0.6 (EtOAc/hexanes, 2:3); $[\alpha]^{23}_D$ = 23.4 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.6 (s, 3 H), 3.32 (s, 3 H), 3.38 (s, 6 H), 3.55 (t, *J* = 9.2 Hz, 1 H), 3.54-3.63 (m, 2 H), 3.66-3.67 (m, 1 H), 3.71 (t, *J* = 8.4 Hz, 1 H), 3.87 (d, *J* = 11.2 Hz, 1 H), 4.02 (d, *J* = 6.8 Hz, 1 H), 4.21 (d, *J* = 9.6 Hz, 1 H), 4.42 (d, *J* = 6.8 Hz, 1 H), 4.60 (s, 2 H), 4.70 (d, *J* = 6.8 Hz, 1 H), 4.80 (s, 2 H), 4.84−4.85 (m, 1 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 9.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.32 (OMe), 55.9 (OMe), 56.6 (2xOMe), 66.8 (CH_2), 77.1 (CH) 78.9 (CH), 80.0 (CH), 81.1 (CH), 83.8 (CH), 96.7 (CH_2), 97.6 (CH_2), 98.7 (CH_2), 98.8 (CH_2) 128.7 (CH), 129.7 (CH), 136.3 (C), 145.6 (C), 192.0 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1189, 1283, 1514, 1784, 2886, 2992 cm^{-1}. HRMS: Calcd for $C_{21}H_{32}O_{10}Na$ $[M+Na]^+$ 467.1893, found 467.1887.

General procedure for the preparation of chalcones:

To a solution of substituted acetophenone (2 equiv.) in 10% ethanolic NaOH (1 g NaOH in 10 mL EtOH) was added 4-*C*-glucosylated benzaldehyde building block **20 or 8a or 8b** (1 equiv.) in EtOH at room temperature. The reaction mixture was stirred at same temperature for 3 h, then diluted by adding aq. HCl (10%). The solution was concentrated under reduced pressure, the resultant residue was purified by column chromatography on silica gel using appropriate solvent system as eluent.

(*E*)-1-(2',4'-dimethoxyphenyl)-3-(4-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl)phenyl)chalcone 17a:

Building block **8a** (0.28 g, 0.445 mmol), acetophenone **9a** (0.16 g, 0.89 mmol), 10% alcoholic NaOH (3 mL) and EtOH (2 mL) were treated according to the general procedure, to give the title compound **17a** as a colorless gum (0.27 g, 77%). R_f = 0.3 (EtOAc/hexanes, 1:4); $[\alpha]^{23}_D$ = 79.4 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.50 (t, *J* = 8.8 Hz, 1 H), 3.60-3.61 (m, 1 H), 3.77-3.78 (m, 1 H), 3.79-3.80 (m, 1 H), 3.81-3.82 (m,2 H), 3.85-3.86 (m,1 H), 3.87 (s, 3 H), 3.91 (s, 3 H), 4.26 (d, *J* = 9.6 Hz, 1 H), 4.42 (d, *J* = 10.4 Hz, 1 H), 4.54-4.63 (m, 1 H), 4.63-4.66 (m, 2 H), 4.86-4.89 (m, 1 H), 4.92-4.97 (m, 2 H), 6.50 (d, *J* = 2.0 Hz, 1 H), 6.57 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 6.90-6.93 (m, 2 H), 7.17-721 (m, 5 H), 7.28-7.30 (m, 4 H), 7.32-7.34 (m, 9 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.54 (d, *J* = 15.6 Hz, 1 H) 7.59 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 15.6 Hz, 1 H), 7.77 (d, *J* = 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$); δ = 55.6 (OMe), 55.8 (OMe), 69.1 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.7 (CH_2), 78.3 (CH), 79.3 (CH), 81.3 (CH), 84.1 (CH), 86.7 (CH), 98.7 (CH), 105.2 (CH), 122.2 (C), 127.3 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 132.9 (CH), 135.4 (C), 137.5 (C), 138.1 (C), 138.3 (C), 138.6 (C), 141.2 (CH), 141.7 (CH), 160.4 (C), 164.2 (C), 190.5 (CO). IR ($CHCl_3$): $\tilde{\nu}$ = 1216, 1439, 1561, 1689, 2881, 3018, cm^{-1}. HRMS: Calcd for $C_{51}H_{51}O_8$ $[M+H]^+$ 791.3583, found 791.3577.

(*E*)-1-(2',4'-dibenzyloxyphenyl)-3-(4-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)phenyl)chalcone 17b:

Building block **8a** (0.3 g, 0.48 mmol), acetophenone **9b** (0.23 g, 0.71 mmol), 10% alcoholic NaOH (4 mL) and EtOH (3 mL) were treated according to the general procedure, to give the title compound **17b** as a colorless solid (0.348 g, 78%). R_f = 0.4 (EtOAc/hexanes, 1:4); m.p. = 78-80 °C; $[\alpha]^{23}_D$ = 117.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 3.46-3.50 (m, 1 H), 3.59-3.61 (m, 1 H), 3.78-3.82 (m, 5 H), 4.24 (d, *J* = 9.5 Hz, 1 H), 4.40 (d, *J* = 10.5 Hz, 1 H), 4.57 (d, *J* = 12.0 Hz, 1 H), 4.65-4.67 (m, 2 H), 4.87-4.96 (m, 3 H), 5.11-5.12 (m, 4 H), 6.66-6.68 (m, 2 H), 6.89-6.91 (m, 2 H), 7.15-7.22 (m, 5 H), 7.24-7.39 (m, 21 H), 7.40-7.44 (m, 6 H), 7.64 (d, *J* = 15.5 Hz, 1 H), 7.69 (d, *J* = 15.5 Hz, 1 H), 7.88 (d, *J* = 9.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$); δ = 69.1 (CH_2), 70.3 (CH_2), 70.9 (CH_2), 73.5 (CH_2), 74.9 (CH_2), 75.1 (CH_2), 75.7 (CH_2), 78.3 (CH), 79.4 (CH), 81.3 (CH), 84.2 (CH), 86.7 (CH), 100.5 (CH), 106.6 (CH), 122.3 (C), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.7 (CH), 133.4 (CH), 135.3 (C), 135.8 (C), 136.2 (C), 137.5 (C), 138.1 (C), 138.3 (C), 138.6 (C), 141.0 (CH), 141.6 (CH), 159.7 (C), 163.4 (C), 189.7 (CO). IR ($CHCl_3$): $\tilde{\nu}$ = 1189, 1491, 1568, 1691, 2917, 3087, cm−1. HRMS: Calcd for $C_{63}H_{59}O_8$ $[M+H]^+$ 943.4209, found 943.4208.

(*E*)-1-(2',4'-dimethoxyphenyl)-3-(4-(2,3,4,6-tetra-*O*-methoxymethyl-*β*–D-glucopyranosyl)phenyl)chalcone 18a:

Building block **8b** (0.18 g, 0.40 mmol), acetophenone **9a** (0.088 g, 0.48 mmol), 10% alcoholic NaOH (2 mL) and EtOH (2 mL) were treated according the general procedure, to give the title compound **18a** as a colorless gum (0.108 g, 44%). R_f = 0.5 (EtOAc/hexanes, 1:1); $[\alpha]^{23}_D$ = -114.4 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (s, 3 H), 3.34 (s, 3 H), 3.45 (s, 3 H), 3.46 (s, 3 H), 3.52-3.65 (m, 3 H), 3.70-3.74 (m, 1 H), 3.77 (t, *J* = 8.8 Hz, 1 H), 3.89 (s, 3 H), 3.91-3.94 (m, 4 H), 4.10 (d, *J* = 6.4 Hz, 1 H), 4.21 (d, *J* = 9.2 Hz, 1 H), 4.48 (d, *J* = 6.4 Hz, 1 H), 4.66 (s, 2 H), 4.78 (d, *J* = 6.8 Hz, 1 H), 4.86−4.91 (m, 2 H), 4.92 (d, *J* = 6.4 Hz, 1 H), 6.50 (d, *J* = 2.4 Hz, 1 H), 6.56 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 16.0 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.65 (d, *J* = 15.6 Hz, 1 H), 7.76 (d, *J* = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3 (OMe), 55.5 (OMe), 55.7 (OMe), 56.8 (OMe), 56.5 (2xOMe), 66.8 (CH_2), 77.1 (CH) 78.8 (CH), 79.9 (CH), 81.3 (CH), 83.8 (CH), 96.7 (CH_2), 97.5 (CH_2), 98.6 (CH_2), 98.7 (CH_2), 105.2 (CH), 122.1 (CH), 127.3 (CH), 128.2 (CH), 128.4 (CH), 132.9 (CH), 135.5 (C), 140.0 (C), 141.5 (C), 160.4 (C), 164.2 (C), 190.4 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1168, 1296, 1498, 1658, 2896, 2982 cm−1. HRMS: Calcd for $C_{31}H_{43}O_{12}$ $[M+H]^+$ 607.2754, found 607.2766.

4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzaldehyde 20:

An oven dried round bottom flask was charged with compound **8a** (4.4 g, 6.99 mmol) in acetic anhydride (50 mL) at room temperature. To that solution, trimethylsilyl trifluoromethanesulfonate (1.8 mL, 10.49 mmol) was added at 0 °C, slowly. Then the reaction mixture was allowed to stirr at room temperature for 5 h. The reaction mixture was diluted with H_2O, dropwise, and extracted with EtOAc (3x100 mL). The combined organic layer was washed with sat. $NaHCO_3$ solution (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resultant crude product was purified by column chromatography on silica gel (EtOAc/hexanes, 2:3) to afford the peracetylated compound **20** (2.38 g, 77%) as a colorless solid. R_f = 0.3 (EtOAc/hexanes 1:2); m.p = 90-92 °C; $[\alpha]^{27}_D$ = -78.3 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.83 (s, 3H), 2.00 (s, 3H), 2.07 (s, 3H), 2.10 (s, 3 H), 3.87 (ddd, *J* = 7.0 Hz, 4.5 Hz, 2.0, 1 H), 4.18 (dd, *J* = 12.5 Hz, 2.0 Hz, 1 H), 4.31 (dd, *J* = 12.5 Hz, 5.0 Hz, 1 H), 4.49 (d, *J* = 9.5 Hz, 1 H), 5.10 (t, *J* = 10.5 Hz, 1 H), 5.24 (t, *J* = 10.0 Hz, 1 H), 5.36 (t, *J* = 9.5 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.87 (d, *J* = 8.0 Hz, 2 H), 10.01 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.3 (CH_3), 20.6 (2 X CH_3), 20.7 (CH_3), 62.2 (CH_2), 68.4 (CH), 72.5 (CH), 74.0 (CH), 76.2 (CH), 79.5 (CH), 127.7 (CH), 129.7 (CH), 136.6 (C), 142.8 (C), 168.7 (CO), 169.4 (CO), 170.3 (CO), 170.6 (CO), 191.7 (CHO). IR ($CHCl_3$): $\tilde{\nu}$ = 1576, 1697, 1783, 2896, 2982 cm−1. HRMS: Calcd for $C_{21}H_{25}O_{10}$ $[M+H]^+$ 437.1447, found 437.1459.

4-(β-D-glucopyranosyl)benzaldehyde 19:

A round bottom flask was charged with Compound **20** (1.1 g, 2.52 mmol) in MeOH (15 mL) at room temperature. To that solution, NaOMe (0.068 mg, 1.26 mmol) was added and stirred the reaction mixture for 2 h at same temperature. Then the reaction mixture was neutralized with 10% HCl (1 mL) and concentrated under reduced pressure. The resultant crude product was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 1:9) to afford the title compound **19** (0.51 g, 75%) as a colorless solid. R_f = 0.3 (MeOH/CH_2Cl_2, 1:2); m.p = 126-128 °C; $[\alpha]^{27}_D$ = -164.3 (c 0.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD); δ = 3.35 (m, 1 H), 3.46 (m, 2 H), 3.53 (m, 1 H), 3.75 (d, *J* = 10.8 Hz, 1 H), 3.92 (d, *J* = 11.6 Hz, 1 H), 4.27 (d, *J* = 9.2 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.90 (d, *J* = 8.0 Hz, 2 H). 10.00 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD); δ = 61.6 (CH_2), 70.3 (CH), 75.1(CH), 78.3 (CH), 80.8 (CH), 81.5 (CH), 128.1 (CH), 128.9 (CH), 136.1 (C), 146.6 (C), 192.6 (CHO). IR ($CHCl_3$): $\tilde{\nu}$ = 1567, 1769, 2896, 3101, 3402 cm−1. HRMS: Calcd for $C_{13}H_{16}O_6Na$ $[M+Na]^+$ 291.0844, found 291.0835.

(*E*)-1-(2',4'-dimethoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21a:

Aldehyde **20** (0.25 g, 0.57 mmol), 2', 4'-dimethoxyacetophenone **9a** (0.15 g, 0.916 mmol), 10% ethanolic NaOH (2.5 mL), EtOH (4 mL) were treated as described in the general procedure for 2 h to give the title compound **21a**, after column chromatography on silica gel (MeOH/CH_2Cl_2, 1:9) as a light yellow color solid (0.18 g, 73%); R_f = 0.4, (MeOH/CH_2Cl_2, 1:9); m.p = 92-94 °C. $[\alpha]^{23}_D$ = -141.6 (c 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.39 (d, *J* = 9.0 Hz, 1 H), 3.17-3.21 (m, 1 H), 3.47 (d, *J* = 9.5 Hz, 1 H), 3.53 (d, *J* = 8.5 Hz, 1 H), 3.75 (dd, *J* = 12.0, 5.0 Hz, 1 H), 3.86 (s, 3 H), 3.89-3.93 (m, 4 H), 4.20 (d, *J* = 9.0 Hz, 1 H), 6.59-6.61 (m, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.56-7.58 (m, 2 H), 7.61 (d, *J* = 8.5 Hz, 2 H), 7.67-7.68 (m, 1 H), ^{13}C NMR (125 MHz, CD_3OD): δ = 54.8 (CH_3), 54.9 (CH_3), 61.7 (CH_2), 70.5 (CH), 75.1 (CH), 78.4 (CH), 80.7 (CH), 81.7 (CH), 98.1 (CH), 105.5 (CH), 121.3 (C), 126.7 (CH), 127.7 (CH), 128.1 (CH), 132.3 (C), 134.7 (CH), 141.8 (C), 141.9 (C),160.8 (C), 164.9 (C), 191.2 (C). IR (KBr): $\tilde{\nu}$ = 1137, 1596, 1656, 2912, 2982 cm−1. HRMS: Calcd for $C_{23}H_{26}O_8Na$ $[M + Na]^+$ 453.1525, found 453.1526.

(*E*)-1-(2',4'-dibenzyloxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21b:

Aldehyde **20** (0.1 g, 0.37 mmol), 2', 4'-dibenzyloxyacetophenone **9b** (0.327 g, 0.746 mmol), 10% ethanolic NaOH (3 mL), EtOH (3 mL) were treated as described in the general procedure for 2 h to give the title compound **21b**, after column chromatography on silica gel (MeOH/CH_2Cl_2, 1:9) as a light yellow color solid (0.188 g, 65%); R_f = 0.5, (MeOH/CH_2Cl_2, 1:9); m.p = 118-120 °C. $[\alpha]^{23}_D$ = -141.6 (c 0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.12-3.16 (m, 1 H), 3.20-3.22 (m, 1 H), 3.24-3.26 (m, 1 H), 3.27-3.31 (m, 1 H), 3.46-3.51 (m, 1 H), 3.71-3.74 (m, 1 H), 4.06 (d, *J* = 9.5 Mz, 1 H), 4.88 (d, *J* = 6.0 Hz, 1 H), 4.98-5.00 (m, 2 H), 5.24-5.25 (m, 4 H), 6.67 (dd, *J* = 8.5 Hz, 2.0 Hz, 2 H), 6.95 (d, *J* = 2.5 Hz, 1 H), 7.38-7.44 (m, 10 H), 7.49-7.54 (m, 5 H), 7.62 (d, *J* = 16.0 Hz, 1 H), 7.69 (d, *J* = 16.0 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 61.8 (CH_2), 70.1 (CH_2), 70.7 (CH_2), 70.8 (CH), 75.2 (CH), 78.8 (CH), 81.4 (CH), 81.7 (CH), 100.9 (CH), 107.5 (CH), 121.9 (C), 127.2 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129. 0 (CH), 132.8 (C), 134.3 (CH), 136.7 (C), 136.9 (C), 141.6 (CH), 143.9 (C), 159.8 (C), 163.5 (C), 189.1 (C). IR (KBr): $\tilde{\nu}$ = 1198, 1596, 1663, 2912, 2982 cm − 1. HRMS: Calcd for $C_{35}H_{35}O_8$ $[M+H]^+$ 583.2331, found 583.2331.

(*E*)-1-(2',4',6'-trimethoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21c:

Aldehyde **20** (0.20 g, 0.74 mmol), 2', 4', 6'-trimethoxyacetophenone **9c** (0.313 g, 1.49 mmol), 10% ethanolic NaOH (2.0 mL), EtOH (3 mL) were treated as described in the general procedure for 2 h to give the title compound **21c**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as a light green color solid (0.24 g, 68%); R_f = 0.3, ($MeOH/CH_2Cl_2$, 1:9); m.p = 98-100 ºC; $[\alpha]^{23}_D$ = -229.96 (c 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.33-3.35 (m, 1 H), 3.41-3.45 (m, 2 H), 3.47-3.53 (m, 1 H), 3.74 (dd, *J* = 12.0, 5.0 Hz, 1 H), 3.79 (s, 6 H), 3.90 (s, 3 H), 3.91 (d, *J* = 12.5 Hz, 1 H), 4.20 (d, *J* = 9.5 Hz, 1 H), 6.32 (s, 2 H), 6.97 (d, *J* = 16.0 Hz, 1 H), 7.34 (d, *J* = 16.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), ^{13}C NMR (125 MHz, CD_3OD): δ = 54.6 (CH_3), 54.9 (2xCH_3), 61.7 (CH_2), 70.4 (CH), 75.1 (CH), 78.4 (CH), 80.7 (CH), 81.7 (CH), 90.5 (CH), 110.7 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH), 134.2 (C), 142.3 (C), 144.8 (CH), 158.8 (C), 163.1 (C), 195.7 (C). IR (KBr): $\tilde{\nu}$ = 1212, 1496, 1642, 2844, 2992 cm^{-1}. HRMS: Calcd for $C_{24}H_{29}O_9$ $[M+H]^+$ 461.1811, found 461.11814.

(*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21d:

Aldehyde **20** (0.18 g, 0.74 mmol), 2'-hydroxy, 4', 6'-dimethoxyacetophenone **9d** (0.121 g, 1.49 mmol), 10% ethanolic NaOH (2.0 mL), EtOH (3 mL) were treated as described in the general procedure for 2 h to give the title compound **21d**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as yellow color solid (0.105 g, 57%); R_f = 0.3, ($MeOH/CH_2Cl_2$, 1:9); m.p = 100-102 ºC; $[\alpha]^{23}_D$ = -171 (c 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 3.37 (t, *J* = 9.2 Hz, 1 H), 3.44-3.48 (m, 2 H), 3.52 (t, *J* = 9.2 Hz, 1 H), 3.74 (dd, *J* = 12.0, 5.2 Hz, 1 H), 3.86 (s, 3 H), 3.91 (d, *J* = 12.4 Hz, 1 H), 3.96 (s, 3 H) 4.20 (d, *J* = 9.6 Hz, 1 H), 6.12 (s, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 16.4 Hz, 1 H), 7.57 (d, *J* = 16.0 Hz, 1 H), ^{13}C NMR (100 MHz, CD_3OD): δ = 54.7 (CH_3), 55.1 (CH_3), 61.7 (CH_2), 70.4 (CH), 75.1 (CH), 78.4 (CH), 80.8 (CH), 81.7 (CH), 90.7 (CH), 93.4 (CH) 105.9 (CH), 127.2 (CH), 127.6 (CH), 128.1 (CH), 134.9 (C), 141.6 (CH), 141.9 (C), 162.7 (C), 166.6 (C), 167.4 (C), 192.7 (C). IR (KBr): $\tilde{\nu}$ = 1186, 1498, 1648, 2896, 2996 cm^{-1}. HRMS: Calcd for $C_{23}H_{27}O_9$ $[M+H]^+$ 447.1655, found 447.1648.

(*E*)-1-(3',4'-dimethoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21e:

Aldehyde **20** (0.2 g, 0.45 mmol), 3', 4'-dimethoxyacetophenone **9e** (0.123 g, 0.687 mmol), 10% ethanolic NaOH (2.0 mL), EtOH (3 mL) were treated as described in the general procedure for 2 h to give the title compound **21e**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as dark yellow color solid (0.135 g, 69%); R_f = 0.3, ($MeOH/CH_2Cl_2$, 1:9); m.p = 104-106 ºC. $[\alpha]^{23}_D$ = -223.9 (c 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.38 (d, *J* = 9.5 Hz, 1 H), 3.42-3.48 (m, 2 H), 3.52 (t, *J* = 8.5 Hz, 1 H), 3.74 (dd, *J* = 12.0, 5.5 Hz, 1 H), 3.91-3.92 (m, 4 H), 3.94 (s, 3 H), 4.21 (d, *J* = 9.5, Hz, 1 H), 7.10 (d, *J* = 8.5 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 2.0 Hz, 1 H), 7.75 (dd, *J* = 8.0 Hz, 2 H), 7.79-7.80 (m, 2 H), 7.73-7.75 (dd, *J* = 8.5, 2.0 Hz, 1 H), ^{13}C NMR (125 MHz, CD_3OD): δ = 55.1 (CH_3), 55.1 (CH_3), 61.7 (CH_2), 70.5 (CH), 75.1 (CH), 78.4 (CH), 80.8 (CH), 81.7 (CH), 110.3 (CH), 110.7 (CH), 121.1 (CH), 123.5 (CH), 127.9 (CH), 128.1 (CH), 130.1 (C), 134.5 (C), 142.1 (C), 143.5 (CH), 149.3 (C), 153.8 (C), 189.2 (C). IR (KBr): $\tilde{\nu}$ = 1196, 1507, 1644, 2891, 2987 cm^{-1}. HRMS: Calcd for $C_{23}H_{27}O_8$ $[M+H]^+$ 431.1705, found 431.1703.

(*E*)-1-(4'-methoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21f:

Aldehyde **20** (0.35 g, 0.45 mmol), 4'-methoxyacetophenone **9f** (0.24 g, 0.916 mmol), 10% ethanolic NaOH (3 mL), EtOH (4 mL) were treated as described in the general procedure for 3 h to give the title compound **21f,** after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as light brown color solid (0.198 g, 62%); R_f = 0.5, ($MeOH/CH_2Cl_2$, 1:9); m.p = 172-174 ºC. $[\alpha]^{23}_D$ = -141.9 (c 0.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.13-3.16 (m, 1 H), 3.17-3.21 (m, 1 H), 3.22-3.25 (m, 1 H), 3.27-3.30 (m, 1 H), 3.45-3.51 (m, 1 H), 3.72 (dd, *J* = 11.2, 5.2 Hz, 1 H), 3.88 (s, 3 H), 4.08 (d, *J* = 9.6 Hz, 1 H), 4.50 (t, *J* = 5.6 Hz, 1 H), 4.89 (d, *J* = 6.0 Hz, 1 H), 4.98-5.01 (m, 2 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 15.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.94 (d, *J* = 15.2 Hz, 1 H), 8.23 (d, *J* = 8.8 Hz, 2 H), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.0 (CH_3), 61.8 (CH_2), 70.7 (CH), 75.2 (CH), 78.8 (CH), 81.4 (CH), 81.7 (CH), 114.5 (CH), 122.0 (CH), 128.6 (CH), 128.7 (CH), 130.9 (C), 131.4 (CH), 134.3 (C), 143.4 (C),143.6 (C), 163.6 (C), 187.8 (C). IR (KBr): $\tilde{\nu}$ = 1146, 1286, 1596, 1656, 2912, 2982 cm^{-1}. HRMS: Calcd for $C_{22}H_{25}O_7$ $[M+H]^+$ 401.1600, found 401.1592.

(*E*)-1-(2',4',6'-tribenzyloxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21g:

Aldehyde **20** (0.27 g, 0.1 mmol), 2', 4', 6'-tribenzyloxyacetophenone **9g** (0.67 g, 2.0 mmol), 10% ethanolic NaOH (4 mL), EtOH (4 mL) were treated as described in the general procedure for 2 h to give the title compound **21g**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as a light yellow color solid (0.23 g, 64%); R_f = 0.5, ($MeOH/CH_2Cl_2$, 1:9); m.p = 126-128 ºC. $[\alpha]^{23}_D$ = -141.6 (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD 1:1): δ = 3.36-3.42 (m, 2 H), 3.44-3.47 (m, 2 H), 3.78-3.81 (m, 2 H), 3.92 (d, *J* = 12.0 Hz, 1 H), 5.04-5.05 (m, 4 H), 5.09-5.13 (m, 2 H), 6.67 (s, 2 H), 7.00 (d, *J* = 16.0 Hz, 1 H), 7.09 (d, *J* = 7.6 Hz, 2 H), 7.25-7.28 (m, 8 H), 7.37-7.42 (m, 3 H), 7.43-7.46 (m, 3 H), 7.49-7.51 (m, 2 H), 7.67 (d, *J* = 15.2 Hz, 1 H), 7.89 (d, *J* = 16.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$:CD_3OD): δ = 62.0 (CH_2), 70.1 (2xCH_2), 70.7 (CH_2), 71.3 (CH), 74.6 (CH), 78.1 (CH), 79.9 (CH), 81.4 (CH), 93.3 (CH), 126.7 (CH), 127.3 (C), 127.4 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 134.4 (C), 134.9 (C), 135.1 (C), 136.2 (CH), 141.3 (C), 142.2 (CH), 157.5 (2xC), 161.6 (C), 195.2 (C). IR (KBr): $\tilde{\nu}$ = 1862, 1568, 1674, 2896, 2986 cm^{-1}. HRMS: Calcd for $C_{42}H_{41}O_9$ $[M+H]^+$ 689.2750, found 689.2744.

(*E*)-1-(2',4'-dihydroxyphenyl)-3-(4-β–D-glucopyranosyl)phenyl)chalcone 4:

Aldehyde **20** (0.290 g, 0.664 mmol), 2', 4'-(bismethoxymethoxy) acetophenone **9j** (0.245 g, 1.33 mmol), 10% ethanolic NaOH (4.0 mL), EtOH (5 mL) were treated as described in the general procedure for 3 h to give the title compound **4**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:4) as yellow color solid (0.18 g, 67%); R_f = 0.5, ($MeOH/CH_2Cl_2$, 1:4); m.p = 192-194 ºC. $[\alpha]^{23}_D$ = -148.9 (c = 0.2, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.26-3.28 (m, 1 H), 3.34-3.37 (m, 2 H), 3.40-3.41 (m, 1 H), 3.63 (d, *J* = 11.0, 1 H), 3.81 (m, 1 H), 4.10 (d, *J* = 9.5 Hz, 1 H), 6.20 (s, 1 H), 6.34 (d, *J* = 7.0 Hz, 1 H), 7.41-7.43 (m, 2 H), 7.64 (m, 2 H), 7.72 (s, 2 H), 7.90 (d, *J* = 7.5 Hz, 1 H), ^{13}C NMR (125 MHz, CD_3OD): δ = 61.7 (CH_2), 70.4 (CH), 75.1 (CH), 78.3 (CH), 80.8 (CH), 81.7 (CH), 102.4 (CH), 107.9 (CH), 113.2 (C), 120.4 (CH), 128.1 (CH), 128.2 (CH), 132.2 (CH), 134.5 (C), 142.3 (C), 143.5 (CH), 165.2 (C), 166.2 (C), 195.7 (C). IR (KBr): $\tilde{\nu}$ = 1176, 1506, 1648, 2888, 2996 cm^{-1}. HRMS: Calcd for $C_{21}H_{23}O_8$ $[M+H]^+$ 403.1392, found 403.1385.

(*E*)-1-(3',4'-dihydroxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21h:

Aldehyde **20** (0.33 g, 0.756 mmol), 3', 4'-(bismethoxymethoxy) acetophenone **9k** (0.363 g, 1.512 mmol), 10% ethanolic NaOH (4.0 mL), EtOH (6 mL) were treated as described in the general procedure for 3 h to give the title compound **21h**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:4) as yellow color solid (0.21 g, 69%); R_f = 0.5, ($MeOH/CH_2Cl_2$, 1:4); m.p = 140-142 ºC: $[\alpha]^{23}_D$ = -156.7 (c 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.39 (d, *J* = 9.5 Hz, 1 H), 3.44-3.48 (m, 2 H),

3.52 (t, *J* = 9.0 Hz, 1 H), 3.74 (dd, *J* = 12.0, 5.5 Hz, 1 H), 3.92 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.21 (d, *J* = 9.5 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.61 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.71 (s, 1 H), 7.73-7.75 (m, 3 H), ^{13}C NMR (125 MHz, CD_3OD): δ= 61.7 (CH_2), 70.5 (CH), 75.1 (CH), 78.4 (CH), 80.8 (CH), 81.7 (CH), 114.5 (CH), 115.0 (CH), 121.4 (CH), 122.3 (CH), 127.8 (CH), 128.1 (CH), 130.1 (C), 134.6 (C), 142.1 (C), 143.5 (CH), 145.3 (C), 151.0 (C), 189.4 (C). IR (KBr): $\tilde{\nu}$ = 1186, 1496, 1652, 2912, 2996 cm^{-1}. HRMS: Calcd for $C_{21}H_{23}O_8$ $[M+H]^+$ 403.1392, found 403.1385.

(*E*)-1-(4'-hydroxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)chalcone 21i:

Aldehyde **20** (0.20 g, 0.458 mmol), 4'-(methoxymethoxy)-acetophenone **9l** (0.165 g, 0.916 mmol), 10% ethanolic NaOH (3.0 mL), EtOH (3 mL) were treated as described in the general procedure for 2 h to give the title compound **21i**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as light brown color solid (0.12 g, 68%); R_f = 0.4, ($MeOH/CH_2Cl_2$, 1:9); m.p = 192-194 °C; $[\alpha]^{23}_D$ = -219.08 (c 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 3.35-3.40 (m, 1 H), 3.44-3.46 (m, 2 H), 3.50-3.54 (m, 1 H), 3.75 (dd, *J* = 12.0, 4.8 Hz, 1 H), 3.92 (d, *J* = 11.2 Hz, 1 H), 4.21 (d, *J* = 9.2 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 7.78-7.79 (m, 2 H), 8.05 (d, *J* = 8.8 Hz, 2 H), ^{13}C NMR (100 MHz, CD_3OD): δ = 61.7 (CH_2), 70.4 (CH), 75.1 (CH), 78.4 (CH), 80.8 (CH), 81.7 (CH), 115.1 (CH), 121.3 (CH), 127.9 (CH), 128.1 (CH), 129.5 (C), 131.0 (CH), 134.6 (C), 142.2 (C), 143.5 (CH), 163.1 (C), 195.7 (C). IR (KBr): $\tilde{\nu}$ = 1182, 1517, 1656, 2896, 2968 cm−1. HRMS: Calcd for $C_{21}H_{23}O_7$ $[M+H]^+$ 387.1443, found 387.1434.

General procedure for the hydrogenations of chalcones:

To the solution of chalcone (1 equiv.) in methanol was added Pd/C (0.1 equiv., condition A) or Pd/C and Ph_2S as additive (0.1 equiv. of each, condition B) at room temperature. To remove the air inside the reaction flask, two vacuum cycles with hydrogen gas was purged. The reaction mixture was vigorously stirred at room temperature under hydrogen atmosphere (H_2, balloon pressure) until the complete consumption of chalcone. The reaction mixture was filtered using a pad of celite, the filtrate was concentrated, and resultant residue was purified by column chromatography on silica gel to provide the dihydrochalcones.

1-(2',4'-dimethoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)dihydrochalcone 22a:

Chalcone **21a** (0.120, 0.278 mmol), Pd/C (0.030 g, 0.028), Ph_2S (0.01 mL, 0.028 mmol) and MeOH (3 mL) were treated as described in the general procedure, condition B, for 18 h to give the title compound **22a**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as colorless solid (0.088 g, 73%); R_f = 0.4, ($MeOH/CH_2Cl_2$, 1:9); m.p = 75-77 °C; $[\alpha]^{23}_D$ = -229.3 (c 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 2.95 (t, *J* = 7.6 Hz, 2 H), 3.25 (t, *J* = 7.6 Hz, 2 H), 3.37-3.46 (m, 3 H), 3.47-3.51 (m, 1 H), 3.71 (dd, *J* = 12.0, 4.8 Hz, 1 H), 3.88-3.91 (m, 7 H), 4.12 (d, *J* = 9.2 Hz, 1 H), 6.58-6.61 (m, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 30.1 (CH_2), 45.0 (CH_2), 54.7 (CH_3), 61.8 (CH_2), 70.6 (CH), 74.9 (CH), 78.4 (CH), 80.7 (CH), 82.1 (CH), 97.8 (CH), 105.5 (CH), 120.3 (C), 127.7 (CH), 127.7 (CH), 132.1 (C), 137.0 (CH), 141.4 (C),161.1 (C), 165.1 (C), 200.3 (C). IR (KBr): $\tilde{\nu}$ = 1146, 1512, 1678, 2978, 3010 cm−1. HRMS: Calcd for $C_{23}H_{29}O_8$ $[M+H]^+$ 433.1862, found 433.1862.

1-(2',4'-dihydroxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)dihydrochalcone 5:

Chalcone **21b** (0.240, 0.348 mmol), Pd/C (0.037 g, 0.034) and MeOH (3 mL) were treated as described in the general procedure, condition A, for 10 h to give the title compound **5**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as a colorless solid (0.108 g, 77%); m.p = 123-125 °C; $[\alpha]^{23}_D$ = -146.3 (c 0.3, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ= 2.95 (m, 2 H), 3.29 (m, 2 H), 3.40-3.44 (m, 3 H), 3.51 (d, *J* = 9.5 Hz, 1 H), 3.72-3.75 (m, 1 H), 3.90-3.94 (m, 1 H), 4.14-4.16 (m, 1 H), 6.58 (s, 1 H), 6.29 (s, 1 H), 6.401 (d, *J* = 8.4 Hz, 1 H), 7.28-7.30 (m, 2 H), 7.38-7.40 (m, 2 H), 7.76 (d, *J* = 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 33.7 (CH_2), 42.8 (CH_2), 65.7 (CH_2), 74.5 (CH), 78.9 (CH), 82.3 (CH), 84.7 (CH), 86.0 (CH), 106.2 (CH), 111.6 (CH), 116.6 (C), 131.6 (CH), 131.7 (CH), 136.1 (C), 141.1 (C), 144.8 (C), 168.8 (C), 168.9 (C), 207.6 (C). HRMS: Calcd for $C_{21}H_{25}O_8$ $[M+H]^+$ 405.1549, found 405.1544.

1-(2',4',6'-trimethoxyphenyl)-3-(4-β–D-glucopyranosyl)phenyl)dihydrochalcone 22b:

Chalcone **21c** (0.160, 0.347 mmol), Pd/C (0.037 g, 0.034) and MeOH (3 mL) were treated as described in the general procedure, condition A, for 10 h to give the title compound **22b**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as colorless solid (0.109 g, 68%); R_f = 0.4, ($MeOH/CH_2Cl_2$, 1:9); m.p =72-74 °C; $[\alpha]^{23}_D$ = -112.3 (c = 0.3, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.29 (t, *J* = 7.5 Hz, 2 H), 3.03 (t, *J* = 7.5 Hz, 2 H), 3.36-3.45 (m, 3 H), 3.49 (t, *J* = 8.5 Hz, 1 H), 3.71 (dd, *J* = 12.0, 5.5 Hz, 1 H), 3.76 (s, 6 H), 3.83 (s, 3 H), 3.88 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.11 (d, *J* = 9.5 Hz, 1 H), 6.22 (s, 2 H), 7.18 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), ^{13}C NMR (125 MHz, CD_3OD): δ = 29.4 (CH_2), 45.8 (CH_2), 54.6 (CH_3), 54.9 (2xCH_3), 61.7 (CH_2), 70.6 (CH), 74.9 (CH), 78.4 (CH), 80.7 (CH), 82.0 (CH), 90.3 (CH), 112.7 (CH), 127.6 (CH), 127.7 (CH), 137.0 (CH), 141.0 (C), 158.3 (2xC), 163.0 (C), 204.7 (C). IR (KBr): $\tilde{\nu}$ = 1212, 1522, 1648, 2882, 2998 cm−1. HRMS: Calcd for $C_{24}H_{31}O_9$ $[M+H]^+$ 463.1968, found 463.1966.

1-(3',4'-dimethoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)dihydrochalcone 22c:

Chalcone **21e** (0.110, 0.258 mmol), Pd/C (0.027 g, 0.025), Ph_2S (0.01 mL, 0.025 mmol) and MeOH (3 mL) were treated as described in the general procedure, condition B, for 24 h to give the title compound **22c**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as colorless solid (0.07 g, 64%); R_f = 0.4, ($MeOH/CH_2Cl_2$, 1:9); m.p =114-116 °C; $[\alpha]^{23}_D$ = -149.8 (c 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 3.02 (t, *J* = 7.6 Hz, 2 H), 3.29 (t, *J* = 7.2 Hz, 2 H), 3.44-3.48 (m, 2 H), 3.43 (t, *J* = 9.2 Hz, 1 H), 3.49 (t, *J* = 8.0 Hz, 1 H), 3.70 (dd, *J* = 12.0, 4.8 Hz, 1 H), 3.87-3.90 (m, 7 H), 4.11 (d, *J* = 9.6 Hz, 1 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 7.25 (d, *J* = 7.6 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.61 (s, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ= 29.8 (CH_2), 39.3 (CH_2), 54.9 (CH_3), 55.1 (CH_3), 61.7 (CH_2), 70.5 (CH), 74.9 (CH), 78.4 (CH), 80.7 (CH), 82.1 (CH), 110.1 (CH), 110.3 (CH), 122.8 (CH), 127.7 (CH), 127.8 (CH), 129.8 (C), 137.2 (C), 141.1 (C), 149.0 (CH), 153.6 (C), 198.9 (C). IR (KBr): $\tilde{\nu}$ = 1198, 1510, 1686, 2896, 2960 cm−1. HRMS: Calcd for $C_{23}H_{29}O_8$ $[M+H]^+$ 433.1862, found 433.1862.

1-(4'-methoxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)dihydrochalcone 22d:

Chalcone **21f** (0.155, 0.387 mmol), Pd/C (0.041 g, 0.039), Ph_2S (0.01 mL, 0.039 mmol) and MeOH (3 mL) were treated as described in the general procedure, condition B, for 24 h to give the title compound **22d,** after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as colorless solid (0.119 g, 76%); R_f = 0.5, ($MeOH/CH_2Cl_2$, 1:9); m.p = 134-136 °C; $[\alpha]^{23}_D$ = -232.1 (c 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ= 3.00 (t, *J* = 7.2 Hz, 2 H), 3.27 (t, *J* = 7.2 Hz, 2 H), 3.36-3.41 (m, 2 H), 3.42-3.43 (m, 1 H), 3.46-3.52 (m, 1 H), 3.71 (dd, *J* = 12.0, 5.2 Hz, 1 H), 3.87-3.90 (m, 4 H), 4.11 (d, *J* = 9.2 Hz, 1 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.96 (d, *J* = 8.8 Hz, 2 H), ^{13}C NMR (100 MHz, CD_3OD): δ = 29.7 (CH_2), 39.4 (CH_2), 54.6 (CH_3), 61.8 (CH_2), 70.5 (CH), 74.9 (CH), 78.3 (CH), 80.7 (CH), 82.1 (CH), 113.5 (CH), 127.7 (CH), 127.8 (CH), 129.7 (C), 130.9 (CH), 137.2 (C), 141.4 (C),163.8 (C), 198.8

(C). IR (KBr): ν˜ = 1186, 1526, 1696, 2996, 3080 cm−1. HRMS: Calcd for $C_{22}H_{26}O_{7}Na$ [M+Na]$^+$ 425.1576, found 425.1568.

1-(2',4',6'-trihydroxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)dihydrochalcone 22e:

Chalcone **21g** (0.10, 0.171 mmol), Pd/C (0.02 g, 0.017) and MeOH (2 mL) were treated as described in the general procedure, condition A, for 12 h to give the title compound **22e**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as colorless solid (0.056 g, 78%); m.p = 138-140 °C. $[\alpha]^{23}_D$ = -194.1 (c 0.6, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 2.92 (t, *J* = 7.5 Hz, 2 H), 3.02-3.05 (m, 2 H), 3.36-3.42 (m, 3 H), 3.43-3.45 (m, 1 H), 3.49 (t, *J* = 8 5, 1 H), 3.70 (dd, *J* = 12.0, 5.5 Hz, 1 H), 3.88 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.12 (d, *J* = 9.5 Hz, 1 H), 6.22 (s, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), ^{13}C NMR (125 MHz, CD_3OD): δ = 29.4 (CH_2), 45.8 (CH_2), 54.6 (OMe), 54.9 (2xOMe), 61.8 (CH_2), 70.6 (CH), 74.9 (CH), 78.4 (CH), 80.7 (CH), 82.1 (CH), 90.3 (CH), 112.4 (CH), 127.6 (CH), 127.7 (CH), 137.0 (CH), 141.0 (C), 158.3 (C), 163.0 (C), 204.7 (C). HRMS: Calcd for $C_{21}H_{25}O_9$ [M+H]$^+$ 421.1498, found 421.1492.

1-(3',4'-dihydroxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)dihydrochalcone 22f:

Chalcone **21h** (0.120, 0.298 mmol), Pd/C (0.031 g, 0.029), Ph_2S (0.005 mL, 0.029) and MeOH (2 mL) were treated as described in the general procedure, condition B, for 24 h to give the title compound **22f**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as colorless solid (0.08 g, 67%); m.p = 134-136 °C: $[\alpha]^{23}_D$ = -146.1 (c 0.6, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 2.99 (t, *J* = 7.6 Hz, 2 H), 3.22 (t, *J* = 7.6 Hz, 2 H), 3.39-3.46 (m, 3 H), 3.47-3.51 (m, 1 H), 3.70 (dd, *J* = 12.0, 5.2 Hz, 1 H), 3.87-3.90 (m, 1 H), 4.11 (d, *J* = 9.2 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.42-7.44 (m, 2 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 29.9 (CH_2), 39.3 (CH_2), 61.7 (CH_2), 70.5 (CH), 74.9 (CH), 78.4 (CH), 80.7 (CH), 82.0 (CH), 114.4 (CH), 114.5 (CH), 121.6 (CH), 127.7 (CH), 127.8 (CH), 129.8 (C), 137.1 (C), 141.1 (C), 145.0 (CH), 150.7 (C), 199.1 (C). HRMS: Calcd for $C_{21}H_{24}O_8Na$ [M+Na]$^+$ 427.1368, found 427.1366.

1-(4'-hydroxyphenyl)-3-(4-(β–D-glucopyranosyl)phenyl)dihydrochalcone 22g:

Chalcone **21i** (0.07, 0.181 mmol), Pd/C (0.02 g, 0.018), Ph_2S (0.002 mL, 0.018 mmol) and MeOH (3 mL) were treated as described in the general procedure, condition B, for 18 h to give the title compound **22g**, after column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) as colorless solid (0.042 g, 61%); R_f = 0.5, ($MeOH/CH_2Cl_2$, 1:9); m.p = 88-90 °C; $[\alpha]^{23}_D$ = -182.1 (c 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 3.00 (t, *J* = 7.2 Hz, 2 H), 3.26 (t, *J* = 7.2 Hz, 2 H), 3.38-3.41 (m, 2 H), 3.43-3.45 (m, 1 H), 3.47-3.49 (m, 1 H), 3.68-3.73 (m, 1 H), 3.89 (d, *J* = 12.4 Hz, 1 H), 4.12 (d, *J* = 9.2 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.88 (d, *J* = 8.0 Hz, 2 H), ^{13}C NMR (100 MHz, CD_3OD): δ = 29.8 (CH_2), 39.3 (CH_2), 61.8 (CH_2), 70.5 (CH), 74.9 (CH), 78.4 (CH), 80.7 (CH), 82.1 (CH), 114.8 (CH), 127.7 (CH), 127.8 (CH), 128.1 (C), 130.4 (CH), 137.1 (C), 141.1 (C),162.3 (C), 198.9 (C). IR (KBr): ν˜ = 1573, 1693, 2996, 3417 cm−1. HRMS: Calcd for $C_{21}H_{25}O_7$ [M+H]$^+$ 389.1600, found 389.1592.

Biological assay:

Crude aldose reductase (AR) was prepared from rat lens. Eyeballs were removed from 12-week-old WNIN male rats obtained from National Center for Laboratory Animal Services, National Institute of Nutrition, Hyderabad. Animal care and protocols were in accordance with and approved by Institutional Animal Ethics Committee. Lenses were dissected by posterior approach and homogenized in 9 volumes of 100 mM potassium phosphate buffer pH 6.2. The homogenate was centrifuged at 12,000x g for 30 min at 4 °C and the resulting supernatant was used as the source of AR. For inhibition studies concentrated stocks of compounds were prepared in water/DMSO mixture. Various concentrations of inhibitors were added to the assay mixture and incubated for 5 min before initiating the reaction by NADPH. The percent of inhibition with test compounds was calculated considering the AR activity in the absence of inhibitor as 100%.[21]

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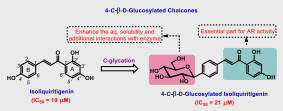

Inspired from natural product isoliquiritigenin (ISL), to enhance the bioavailability of ISL, 4-*C*-glucosylated isoliquiritigenin and several *C*-glucosylated chalcones have been synthesized and evaluated for aldose reductase (AR) inhibition activity. Excellent AR inhibition has been observed with *C*-glucosylated ISL with IC_{50} value of 21 μM which is similar to the chalcone ISL (IC_{50} of 19 μM). The studies have revealed few new analogues with promising activity.

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Synthesis of 4-*C*-β-D-Glucosylated Isoliquiritigenin and Analogues for Aldose Reductase Inhibition Studies