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Benzyl *C*-Analogues of Dapagliflozin

Synthesis of Benzyl *C*-Analogues of Dapagliflozin as Potential SGLT2 Inhibitors

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Abstract: Sodium-glucose co-transporter (SGLT) inhibitors are a novel class of therapeutic agents for the treatment of type 2 diabetes based on blocking of renal reabsorption of glucose. Dapagliflozin, a *C*-aryl glucoside, has emerged as a successful drug in the market based on this concept. We have synthesized hitherto unreported *C*-benzyl glucoside analogues of Dapagliflozin carrying the same aglycon present in the drug. The synthetic strategy involves *in situ* generation of functionalized arylmagnesium bromide with Weinreb-amide (WA) functionality for the first time, and addition on to the 1-β-formyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside for the synthesis of a *C*-benzyl glucoside building block **16.** The WA functionality therein enabled variation in the nature of the distal ring of biarylmethane aglycon for convenient access to other analogues. All the new compounds were screened for their sodium-glucose co-transporters (SGLT1 and SGLT2) inhibition activity using cell-based nonradioactive fluorescence glucose uptake assay. Among them, **14** with IC_{50}: 0.64 nM emerged as the most potent SGLT2 inhibitor with the best selectivity for inhibition of SGLT2 (IC_{50}:0.64 nM) over SGLT1 (IC_{50}: 500 nM) as compare to Dapagliflozin. On the other hand, compound **15a** exhibited moderate selectivity for inhibition of SGLT2 (IC_{50}: 4.94 nM) over SGLT1 (IC_{50}: 68.46 nM). These results presented herein amply demonstrate the promise of *C*-benzyl analogues of Dapagliflozin as novel SGLT2 inhibitors for future investigations.

Introduction

The inhibition of sodium-glucose linked transporter 2 (SGLT2) protein present in the kidney and responsible for reabsorption of glucose, has emerged as successful and novel strategy for the treatment of type 2 diabetes,[1] which is insulin-independent. The SGLT2 inhibition enables urinary excretion of glucose and thereby reduction of elevated blood glucose levels during hyperglycemic situation. The inspiration derived from the natural product phlorizin **1**,[2] as the first SGLT2 inhibitor, has come long-way and has paid rich dividends to the medicinal chemists community engaged in the journey of drug discovery. Following the initial disclosure of orally active phenol-*O*-glucoside SGLT2 inhibitor **2b** (T-1095),[3] a large number of *O*-glucosides including T1095 **2b**,[3] Sergliflozin (**3b**)[4] and Remogliflozin (**4**)[5] for SGLT2 inhibition have been developed (Figure 1).

The significance of *C*-glucosides as metabolically more stable and with improved pharmacokinetic profiles, paved their way for successfully emerging as drugs for type 2 diabetes, based on SGLT2 inhibition. To date, under the *C*-glucosides class, Dapagliflozin (**5**),[6] Canagliflozin[7] (**6**), Empagliflozin[8] (**7**) and Ipragliflozin[9] (**8**), Ertugliflozin[10] (**9**) have been approved by the FDA for the treatment of type 2 diabetes, and many other SGLT2 inhibitors are under different phases of clinical trials.[11] Pre- and post-discovery period of Dapagliflozin, has witnessed several structural modifications in the glycone or aglycon part and the efforts continue to remain unabated in the synthetic community. Compounds resulting from the variation in the glycone part are represented by Ertugliflozin[10] (**9**), Tofogliflozin[12] (**10**), and Luseogliflozin[13] (**11**) (Figure 2).

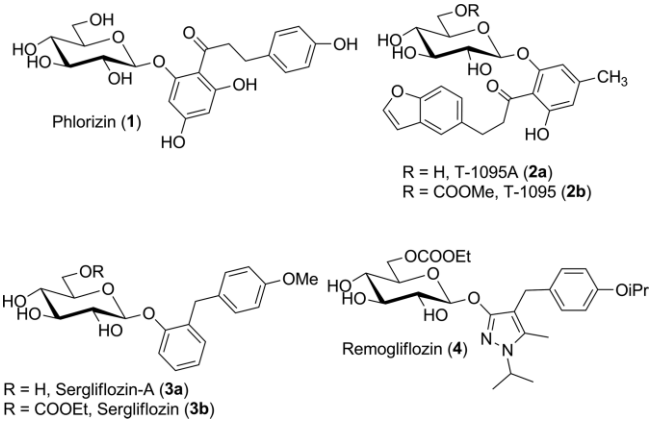

Figure 1. Examples of some *O*-glucoside as SGLT inhibitors.

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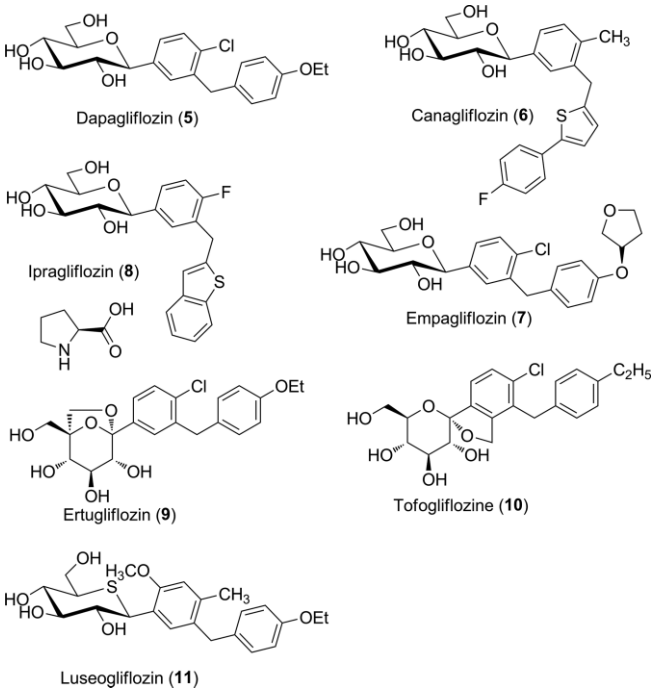


Figure 2. Important *C*-glucosides as SGLT2 inhibitors.

Nomura, in 2013, probably inspired by the partial success of *O*-glucosides and the aglycon part present in Dapaglifozin, synthesized and evaluated the *N*-glucoside **12**[14] for SGLT2 inhibition. Although **12** exhibited strong hSGLT2 inhibitory activity (IC_{50}= 3.9 nM) comparable to **13** (IC_{50}= 5.1 nM) its hydrolytic stability remained a challenge. In the recent past,[15] inspired from the success of Dapagliflozin (**5**), a *C*-aryl-glucoside, we had aimed at the synthesis of hitherto unreported and challenging *C*-benzyl-glucoside **14** in particular and analogues **15** resulting from the variation in the distal aryl ring of biarylmethane-aglycon part present in Dapagliflozin.

In the context, that the original lead molecule from nature, phlorizin **1**, had one atom spacer (oxygen) between glucosyl residue and the aglycon part, the proposed targets **14**/**15** parallels the concept by replacing the oxygen atom with an isosteric, methylene-unit between the glucosyl residue and the biarylmethane-aglycon for ensuring the hydrolytic stability (Figure 3).

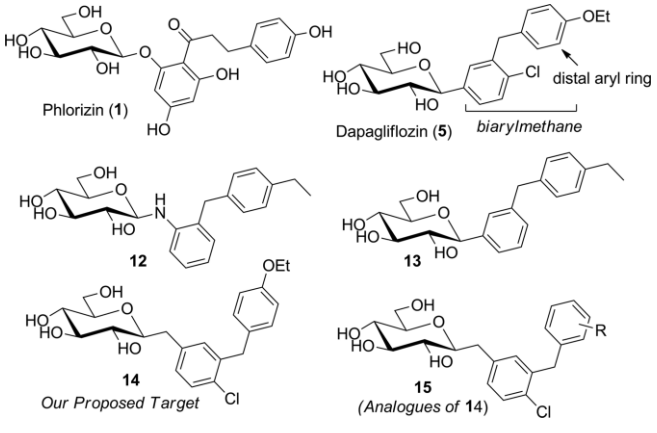


Figure 3. Proposed target molecules.

Results and Discussion

To achieve this objective of synthesizing target **14** and **15**, we envisaged functionalised *C*-benzyl glucosides **16** with electrophilic Weinreb-amide functionality (WA) as the key building block. The WA-functionality would provide the necessary handle for further derivatization and chemistry leading to diverse set of new molecules for biostudies (Figure 4). Paul Knochel's elegant contribution towards synthesis of functionalized arylmagnesium reagents[16] in presence of electrophilic functional groups such as cyano, nitro, amide and ester, provided the necessary confidence in proposing **16** as the key building block. Although, Paul Knochel's work has enabled access to functionalized arylmagnesium halides containing cyano, nitro, amide and ester as electrophilic functional groups, synthesis of functionalized arylmagnesium halides with WA functionality in particular remains unexplored. This provided additional impetus, for undertaking synthesis of building block **16**, because of our continued interest in the use of WA functionality for synthetic endeavours.[17] The synthetic scheme envisages addition of functionalized Grignard reagent **18** onto aldehyde **17** for synthesis of benzyl-*C*-glucoside building block **16**. Literature reports available for the synthesis of *C*-benzyl glycosides are relatively few[18] compared to C-aryl-glycosides.

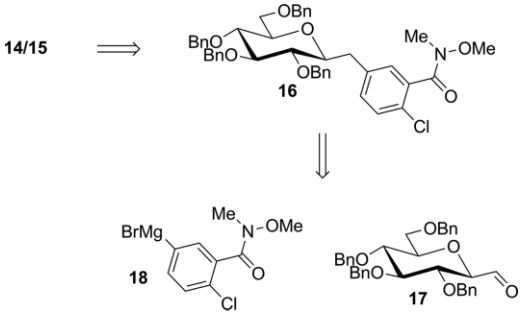
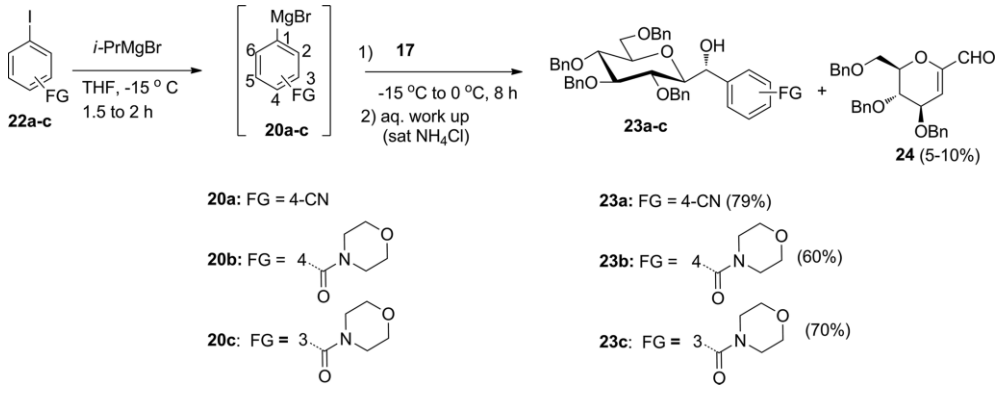


Figure 4. Key building block **16** for synthesis of targets **14/15**.

Before embarking upon synthesis of the building block **16** in particular, through the proposed strategy, a model reaction between functionalized aryl-Grignard agents **20** and aldehyde **17** was undertaken (Figure 5). Multi-gram quantities of aldehyde **17**, 1-β-formyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside were easily accessible in three steps using 2,3,4,6-Tetra-*O*-benzyl-D-glucono-1,5-lactone **21** as a starting material, by a literature known method.[19] In a model reaction, 4-iodobenzonitrile **22a** in anhydrous THF was treated with isopropylmagnesium bromide (*i*PrMgBr) at –15 °C for 1.5 to 2 h to affect the magnesium iodide exchange as reported in Paul Knochel's method.[16] The nascent magnesiated reactive intermediate **20a**, so formed in the reaction vessel was trapped by addition of the requisite aldehyde **17** as electrophile. The reaction temperature was gradually increased from –15 to 0 °C. The stirring was continued at 0 °C temperature for 8 h. To our delight clean reaction ensued resulting in the formation of expected addition product **23a** as a single diastereoisomer[20] in 79 % yield along with glycal **24** as a minor side product (5–10 %) (Scheme 1). Spurred from this successful model reaction, we undertook generalization of this scheme with the preparation of the



Scheme 1. Synthesis of functionalized hydroxyl *C*-benzyl glucosides **23a-c**.

organomagnesium bromides **20b-c** with varying position of morpholine amide functionality from corresponding functionalized aryl iodides **22b-c.** Successful in situ formation of organomagnesium bromides **20b** and **20c** occurred at –0 °C and enabled addition onto aldehyde **17** resulting in the formation of the addition products **23b** and **23c** respectively in good yields (Scheme 1). All the addition products **23a-c** were obtained as single isomers, accompanied with formation of the glycal **24**, as separable minor side product.

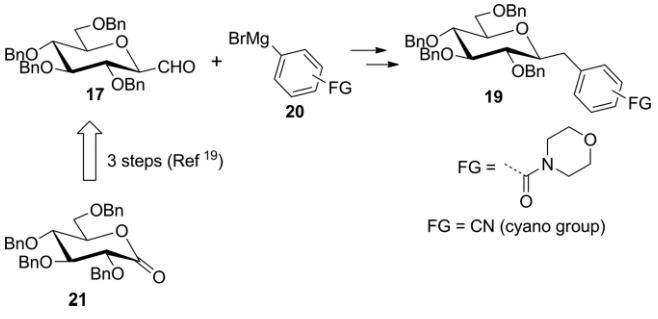
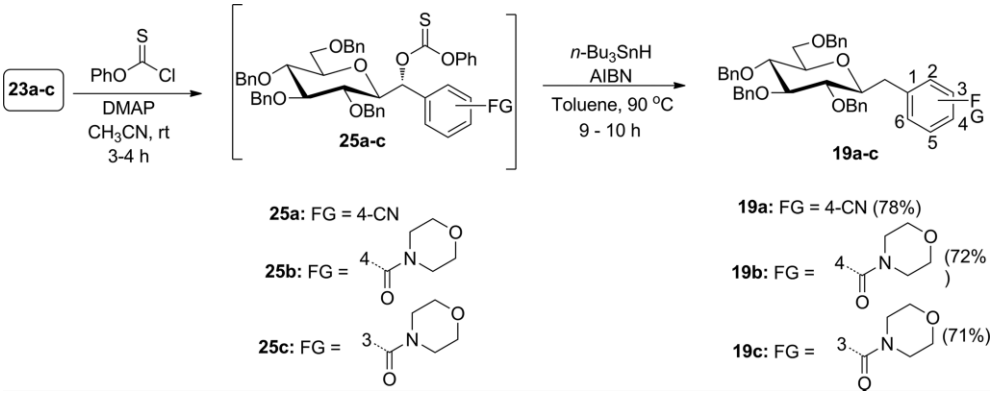


Figure 5. Addition of functionalized Grignard agent **20** onto aldehyde **17**.

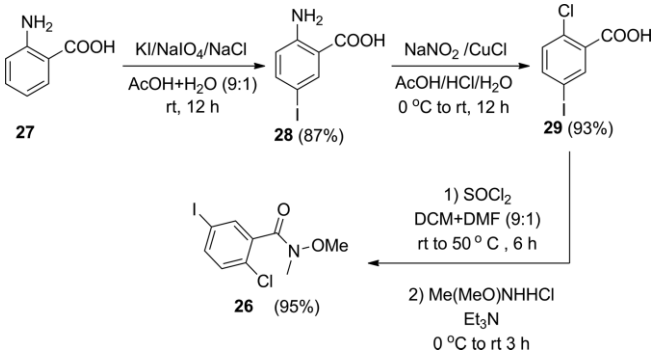
Although the stereochemistry of the addition product was inconsequential, as the product **23a-c** awaited immediate deoxygenation for the synthesis of the targeted *C*-benzyl glucosides represented by general structure **19**, we delved into assignment of the stereochemistry at the new chiral centre, for completeness of the study. As an illustrative example, the stereochemistry of the newly formed chiral centre in compound **23a** was confirmed as *R*-configuration, with the use of extensive 2D NMR experiments including 2-D Double Quantum Filtered Correlation Spectroscopy (DQF-COSY), Total Correlation Spectroscopy (TOCSY), Nuclear Overhauser Effect Spectroscopy (NOESY) and Heteronuclear-Single Quantum correlation (HSQC) experiments.[20] Although our initial efforts to deoxygenate compounds **23a-c**, at the benzylic site using BF_3·OEt_2/Et_3SiH or TFA/Et_3SiH were unsuccessful, the same could be achieved using two step protocol employing Barton–McCombie deoxygenation method. The thionocarbonate derivatives **25a-c** were readily obtained at room temperature in quantitative yields, through reaction of substrates **23a-c** with phenyl chlorothionocarbonate (PTC–Cl)[21] in the presence of 4-dimethylaminopyridine (DMAP) as base and in dry acetonitrile as solvent. These compounds **25a-c** were subjected to radical de-oxygenation using tri-*n*-butyl tin hydride (*n*Bu_3SnH) and azobisisobutyronitrile (AIBN) as initiator in dry toluene at 90 °C. Clean reaction ensued in 9–10 hours affording the functionalized benzyl *C*-glucosides **19a-c** in good to moderate yields (Scheme 2).

Having successfully synthesized functionalized *C*-benzyl glycosides **19a-c**, we now focused our efforts towards the synthesis of specific *C*-benzyl glucoside building block **16**, envisaged for targeted compounds **14/15** stated in our objectives.



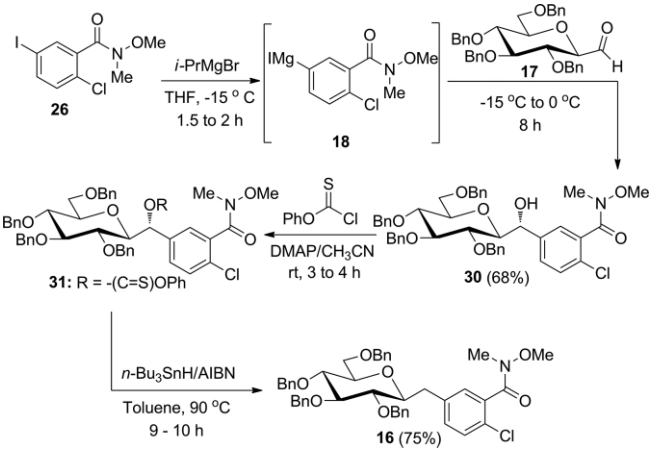
Scheme 2. Synthesis of functionalized *C*-benzyl glucosides **19a-c**.

The requisite starting aryl iodide **26** containing WA, needed for the formation of corresponding Grignard reagent banked on the carboxylic acid **29**. Although this is commercially available, its prohibitive cost prompted us to synthesize this from cheap and commercially available anthranilic acid **27** (Scheme 3). We have developed a two-step procedure, not reported for the preparation of carboxylic acid **29**, which involved iodination followed by Sandmeyer's reaction for chlorination. Iodination of anthranilic acid **27** was achieved using literature procedure[22] and this furnished the iodinated anthranilic acid **28** in good yields. The diazotization reaction followed by replacement of diazonium group with chloro-group using CuCl[23] gave the desired carboxylic acid **29** in good yield. The acid **29** was now converted into the corresponding Weinreb-amide **26** using standard protocol (Scheme 3).



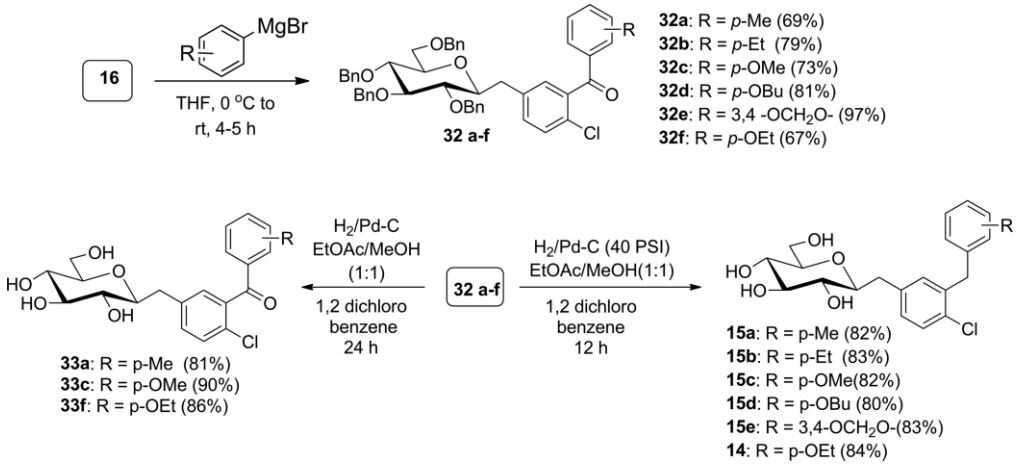
Scheme 3. Synthesis of functionalized WA-based aryl iodide **26**.

The functionalized arylmagnesium bromide **18** could be easily formed under Paul Knochel's condition from iodide **26** and was added onto the aldehyde **17**. Clean reaction ensued, furnishing the corresponding addition product **30** as a single isomer in 68 % yield (Scheme 4). Subsequent deoxygenation using Barton–McCombie deoxygenation method as described in earlier Scheme 2 afforded the key building block **16**. The formation of compound **16** was unambiguously confirmed through NMR spectroscopy and molecular constitution by mass spectral analysis. In the ^{1}H-NMR of compound **16**, the presence of signals centred at 2.73 (dd, *J* = 14.5 Hz and 9.0 Hz) and 3.10 (dd, *J* = 14.5 Hz and 2.0 Hz) were most characteristics for the newly formed methylene *(-CH$_2$-)* unit at anomeric centre. The clear singlet at 3.18 ppm and broad singlet at 3.50 indicates the presence of *-NCH$_3$, -NOCH$_3$* units in the molecule and their corresponding ^{13}C-NMR peaks were appeared at 32.5 and 61.22 respectively. Further molecular constitution was confirmed by the presence of the molecular ion peak [M + H] at 736.3041 in HRMS spectrum, corresponding to molecular formula $C_{44}H_{47}O_7NCl$. As envisaged, the WA functionality in the building block **16**, afforded the much-needed diversity point for further chemistry. The addition of various arylmagnesium bromides and obtainment of benzyl *C*-glucosyl diaryl ketones **32a-f** in good yields, amply demonstrated the usefulness of this building block (Scheme 5).



Scheme 4. Syntheses of key building block **16**.

Among all the synthesized compounds (**32a-f**) the simple hydrogenation conditions [H_2 (ballon)/Pd-C] for debenzylation was successful only on compounds **32a**, **32c** and **32f** and the reaction afforded the corresponding de-protected *C*-benzyl-glucosyl ketones **33a, 33c** and **33f** in good yields. With the remaining substrates (**32b**, **32d**, **32e**) the same hydrogenation procedure for debenzylation was unsuccessful and TLC showed formation of multiple products. Presumably it suggested either partial debenzylation or possible reduction of keto functionality



Scheme 5. Synthesis of C-benzyl analogues of Dapagliflozin **14** and **15a-e**.

and further over reduction to methylene group. With this assumption and anticipating that keto functionality can also be reduced under high pressure hydrogenation conditions, compounds **32a-f** were subjected to hydrogenation under pressure of 40 psi units. To our satisfaction, we could affect complete reduction, besides the desired, debenzylation and the synthesis of targeted *C*-benzyl analogues of Dapagliflozin **14** and **15a-e** was achieved in good yields (Scheme 5).

Evaluation of SGLT1 and SGLT2 Activity

The in vitro inhibitory potential of all nine newly synthesized *C*-benzyl analogues of Dapagliflozin (**14**, **15a-e** and **33a, 33c** and **33f**) were screened using cell based nonradioactive fluorescent glucose uptake assay[24] for functional screening of sodium-glucose co-transporters SGLT1 and SGLT2 determined at excitation/emission maxima of ~465/540 nm. SGLT1and SGLT2 transfected Human Embryonic Kidney (HEK293) cells were propagated at 37 °C in 5 % CO_2 in Dulbecco's minimal essential medium (DMEM) supplemented with 1.0 % of penicillin-streptomycin and 10 % heat inactivated fetal bovine serum (FBS). The cells were cultured in a 90mm dish in DMEM with 10 % FBS until 70–80 % confluences obtained for further use for screening SGLT1and SGLT2 inhibition activity. To measure SGLT1 and SGLT2-mediated glucose uptake,[24b–24c] transfected stable HEK cells were plated separately at 2×10^5/well in 12-well plate; all culture medium was removed from each well and replaced with 100 μL of culture medium with newly synthesized Dapagliflozin analogues (**14**, **15a-e** and **33a, 33c** and **33f**) at five different concentrations ranging from 0.1 to 500 nM.

After half an hour, a fluorescently labelled 2-deoxyglucose analog, 2-NBDG (2-deoxy-2- [(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]-D-glucose) was added to the plates and incubated for 30 min. After washing three times, cells were then lysed and fluorescence of aliquots from the lysate was measured at excitation/emission maxima of 465/540nm. Dapagliflozin, a FDA approved SGLT2 inhibitor was used as a reference compound in this fluorescent based in vitro activity evaluation system. The IC_{50} values (concentration to inhibit 50 % D-glucose uptake in cells) of new *C*-benzyl analogues of Dapagliflozin (**14**, **15a-e** and **33a, 33c** and **33f**) were determined from the glucose uptake inhibition curves with reference to Dapagliflozin. IC_{50} values obtained for synthetic compounds (**14**, **15a-e** and **33a, 33c** and **33f**) are presented in Table 1. All nine new analogues (**14**, **15a-e** and **33a**, **33c** and **33f**) showed SGLT1 and SGLT2 inhibition activity with IC_{50} ranging from 0.64 to >500 nM (Table 1). Among nine new analogues, the compound **15e** with 3,4-methylenedioxy unit at distal ring and compound **33f** with keto functionality between proximal and distal ring exhibited SGLT2 inhibition at higher concentrations (IC_{50} for **15e**: 149.57 nM and for **33f**: >500 nM). The other analogues such as, **15c** with 4-methoxy, **15d** with 4-butyloxy, and **15b** with 4-ethyl substituent at distal ring exhibited moderate SGLT2 inhibition as compare to Dapagliflozin with IC_{50} values 24.03, 118.15 and 64.28 nM respectively (Table 1). However, the compound **15a** (IC_{50} 4.94 nM) with 4-methyl unit at distal ring showed better SGLT2 inhibition as compare to Dapagliflozin. Strikingly, among all the nine derivatives, compound **14** with same aglycon unit which is present in Dapagliflozin exhibited the SGLT2 inhibition at very lower concentration (IC_{50}: 0.64 nM) as compare to Dapagliflozin (IC_{50}: 8.16 nM).

Table 1. Evaluation of SGLT1 and SGLT2 activity.

Entry	Compound	SGLT1 (IC_{50}, nM)[a]	SGLT2 (IC_{50}, nM[a]	SGLT1/SGLT2
1	Dapagliflozin[b]	>500	8.16	61.27
2	**14**	500.00	0.64	781.25
3	**15a**	68.46	4.94	13.85
4	**15b**	7.86	64.28	0.12
5	**15c**	380.73	24.03	15.84
6	**15d**	>500	118.15	>4.23
7	**15e**	>500	149.57	>3.34
8	**33a**	>500	49.30	>10.14
9	**33c**	404.68	87.75	4.61
10	**33f**	40.58	>500	<0.08

[a] All compounds were evaluated at a concentration of 10 mM. [b] Dapagliflozin was the reference compound.

We next correlated selectivity index of all the compounds **14**, **15a-e**, **33a, 33c** and **33f** for SGLT2 over SGLT1 inhibitory activities and corresponding results are presented in Table 1. Among all the derivatives (**14** and **15a-e**) having a methylene (*-CH_2-*) linker between proximal and distal ring, the compound **14** (IC_{50}: 0.64 nM for SGLT2 and 500 nM for SGLT1) showed higher selectivity towards SGLT2 over SGLT1 as compare to Dapagliflozin, (SGLT1/SGLT2 ratio for **14** is 781 and for Dapagliflozin is >61). Similarly, compound **15a** (IC_{50}: 4.94 nM for SGLT2 and 68.46 nM for SGLT1) with 4-methyl unit at distal ring showed moderate selectivity (13.85) towards SGLT2 to over SGLT1 (Table 1).

Surprisingly selectivity comparison among **33a**, **33c** and **33f** with keto functionality between proximal and distal ring exhibited different selectivity towards SGLT2 over SGLT1, the compounds **33a** (IC_{50}: 49.30 for SGLT2 and >500 for SGLT1) with 4-methyl and **33c** (IC_{50}: 87.75 for SGLT2 and 404.68 for SGLT1) with 4-methoxy unit at distal ring showed better selectivity towards SGLT2 over SGLT1. Whereas, compound **33f** (IC_{50}:40.58 for SGLT1 and >500 for SGLT2) with 4-ethoxy substituent at distal ring exhibited more selectivity towards SGLT1 over SGLT2.

Cytotoxicity Assay Cell Line

A549-cells (Human Lung Adenocarcinoma Epithelial Cell Line) and HEK293 cells (Human Embryonic Kidney Cell Line) were used for the cytotoxicity assay. HEK293 and A549 cell lines were maintained in Dulbecco's modified Eagle's medium (DMEM, Genetix) containing 10 % heat-inactivated fetal bovine serum, 100 U/mL penicillin, 100 U/mL streptomycin, at 37 ^{0}C in a humidified atmosphere of 5 % CO2.

In vitro Cytotoxicity Assay and Results

The cytotoxicity of all synthesized compounds was measured by means of a colorimetric cell culture assay using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide). 1×10^4 cells/well were plated in 100 μL DMEM, supplemented with 10 % FBS in each well of 96-well cell culture plates and incu-

bated for 24 h at 37 °C in a CO_2 incubator. The appropriate concentrations of the compounds were made and added to the wells with respective vehicle, DMSO. After 24 h of incubation, 20 μL MTT (2 mg/mL) was added to each well and the plates were further incubated for 4 h. Supernatant was removed from each well, formazan crystals that were formed during 4h incubation were dissolved in 100 μL of DMSO, and the absorbance was recorded at 540-nm wavelength using UV Visible spectrophotometer (MULTISCAN GO, Thermo Scientific). Percentage of cell viability was calculated as 100 % × (absorbance of the drug treated cells – absorbance of the blank)/(absorbance of the DMSO treated control cells – absorbance of the blank). Percentage inhibition was calculated as (100 - % cell viability). Here, blank means wells containing medium but lacking cell.

Our cytotoxicity assay (Table 2) showed that Doxorubicin, a well-known anti-cancer drug, kills both HEK293 cells as well as A549 cells. The IC_{50} value of Doxorubicin for both HEK293 and A549 cells are 86.9 μM and 0.763 μM, respectively. However, none of the compounds used for SGLT2 assays shown any cytotoxicity as compared to Doxorubicin.

Table 2. Cytotoxicity (IC_{50}) assay.

Entry	Compounds	IC_{50} Values [μM] HEK 293 cells	IC_{50} Values [μM] A549 cells
1	**14**	>100 μM	>100 μM
2	**15a**	>100 μM	>100 μM
3	**15b**	>100 μM	>100 μM
4	**15c**	>100 μM	>100 μM
5	**15d**	>100 μM	>100 μM
6	**15e**	>100 μM	>100 μM
7	**33a**	>100 μM	>100 μM
8	**33c**	>100 μM	>100 μM
9	**33f**	>100 μM	>100 μM
10	Doxorubicin[a]	86.9 μM	0.763 μM

[a] Doxorubicin was the reference compound.

Conclusions

Preparation of functionalized arylmagnesium halides containing electrophilic WA-amide functionality has been achieved for the first-time using Paul Knochel's procedure. This has enabled synthesis of a new building block **16** containing WA-functionality as handle for further chemistry leading to *C*-benzyl-glucosides. The building block **16** has enabled convenient synthesis of new *C*-benzyl analogues of Dapaglifozin, proposed by us, carrying the same aglycon part, that present in the successful drug, Dapagliflozin. The synthesized *C*-benzyl analogues showed equally good SGLT2 inhibition for possibly opening new directions.

Experimental Section

General Materials and Methods: All reactions were carried out in oven-dried glassware under the inert atmosphere of nitrogen, using commercially supplied distilled solvents used as such. Tetrahydrofuran was dried and distilled from Na–Ph_2CO, whereas, dichloromethane and *N,N*-dimethylformamide were distilled from Calcium hydride. Hexanes refer to the petroleum fraction with bp 40–60 °C. Column chromatography was carried out by using 100–200 mesh silica gel as stationary phase and ethyl acetate, dichloromethane, methanol, hexanes as mobile phase. Thin-layer chromatography was performed on pre-coated silica gel F_{254} aluminium plates with visualization under short UV light or by staining with Hanessian, iodine, Bayer's reagent and anisaldehyde as spray reagents. Melting points were obtained using a melting point apparatus and are uncorrected. Infrared spectra were recorded using KBr pellet and the absorptions are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded at 400; 500 MHz Spectrometer with chemical shifts (δ) quoted in parts per million (ppm) and coupling constants (J) recorded in Hertz (Hz). ^{13}C NMR spectra were recorded at 100 or 125 MHz. HRMS were recorded on a MICRO – Q TOF mass spectrometer by using ESI technique at 10 eV.

General Procedure for Synthesis of Compounds 23a-c: Isopropylmagnesium bromide (*i*PrMgBr) was generated prior to its use from corresponding pre-cleaned magnesium matel (3.39 mmol), iodine (one crystal) and roasted this mixture at 55 °C water bathe temperature under vacuum for 5 minutes and was allowed to room temperature under nitrogen atmosphere, to this anhydrous THF (4.0 mL), followed by 2-bromo propane (3.39 mmol) was added and keep water bath temperature once again 55 °C until initiation of the reaction, after initiation water bath under reaction flask was removed and continued the reaction at room temperature until complete consumption of magnesium metal. After successful generation of isopropylmagnesium bromide, the reaction flask was shifted to −15 °C prior addition of functionalized aryl iodides **22a,** whereas 0 °C in case of functionalized aryl iodides **22b-c** and to this isopropylmagnesium bromide at appropriate temperature was added functionalized aryl iodides (1.358 mmol) dissolved in dry THF (4.0 mL) then stirred the reaction mixture at same temperature for 1.5 to 2 h to effect complete metal-iodine exchange. To this functionalized arylmagnesium bromides **20a-c** was added aldehyde **17** (0.5 g, 0.905mmol) pre-dissolved in dry THF (5 mL). Then reaction temperature was gradually increased from −15 °C to 0 °C in case of functionalized arylmagnesium bromides **20a** whereas retained at 0 °C in case of functionalized arylmagnesium bromides **20b-c** and stirring was continued at the same temperature for 8 to 10 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (20 mL), and then extracted into ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried with anhydrous sodium sulfate then filtered. The filtrate was concentrated under vacuum and the resulting crude products were purified by silica-gel column chromatography.

4-((*R*)-Hydroxy((*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)benzonitrile (23a): Yield: 0.28 g (79 %); R_f = 0.3 (EtOAc/hexanes, 3:7); white solid; $[\alpha]_D^{25}$ = +12.18 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ:7.54 (d, *J* = 8.4 Hz, 2H, ortho to CN, ArH); 7.43 (d, *J* = 8.0 Hz, 2H,meta to CN, ArH); 7.35–7.18 (m, 20H, 4 × ArH); 4.97 (d, *J* = 10.8 Hz, PhC*Ha*Hb-1H); 4.92–4.89 (m, $PhCH_2$, H-7, 3H); 4.82 (d, *J* = 10.8 Hz,PhC*Ha*Hb 1H); 4.73 (d, *J* = 11.2 Hz,PhCH*aHb*- 1H); 4.58 (d, *J* = 10.8 Hz, PhC*Ha*Hb 1H); 4.43 (s, $PhCH_2$, 2H); 3.80–3.71 (m, H-2, H-3, 2H); 3.66–3.57 (m, H-6, H-4, 3H); 3.39 (d, *J* = 8.4 Hz, H-1, 1H); 3.36–3.33 (m, H-5 1H); 3.09 (bs, 1H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ:147.7 (C); 138.5 (C); 138.1 (C); 138.0 (C); 132.0 (CH); 128.7 (CH); 128.6 (CH); 128.5 (CH); 128.2 (CH); 128.0 (CH); 127.9 (CH); 127.86 (CH); 127.8 (CH); 127.7 (CH); 127.2 (CH); 119.0 (C); 111.2 (C); 87.1 (CH); 81.2 (CH); 78.9 (CH); 78.3 (CH); 78.2 (CH); 75.7 (CH_2); 75.4 (CH_2); 75.2 (CH_2); 73.4 (CH_2); 71.08 (CH); 68.9 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2925, 2861, 2365, 2223, 1495, 1448, 1216, 767 cm^{-1}. HRMS-ESI: Calcd. For $C_{42}H_{42}NO_6$ [M + H]: 656.3012, found 656.3026.

(4-((*R*)-Hydroxy((*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)-

(Morpholino)methanone (23b): Yield: 0.4 g (60 %); R_f: 0.1 (EtOAc + Hexanes 4:6); white gummy solid; $[\alpha]_D^{29}$ = +4.41 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 8.0 Hz, 2H, ortho to amide, ArH); 7.35–7.20 (m, 22H, ArH); 5.01–4.95 (m, H-7, $PhCH_2$, PhC*Ha*Hb-, 4H); 4.88 (d, *J* = 10.8 Hz, PhC*Ha*Hb-, 1H); 4.80 (d, *J* = 10.8 Hz, PhCHa*Hb*- 1H); 4.60 (d, *J* = 11.2 Hz, PhC*Ha*Hb-, 1H); 4.54–4.44 (m, $PhCH_2$, 2H); 3.85–3.60 (m, 14H); 3.48 (d, *J* = 9.6 Hz, H-1, 1H); 3.36 (d, *J* = 9.6 Hz, H-5, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5 (amid); 144.4 (C); 138.5 (C); 138.3 (C); 138.2 (C); 138.1 (C); 138.0 (C); 134.1 (C); 128.6 (C); 128.57 (CH); 128.53 (CH); 128.5 (CH); 128.0 (CH); 127.9 (CH); 127.8 (CH); 127.84 (CH); 127.80 (CH); 127.7 (CH); 127.6 (CH); 127.4 (CH); 127.0 (CH); 126.7 (CH); 87.1 (CH); 81.4 (CH); 78.7 (CH); 78.4 (CH); 78.1 (CH); 75.6 (CH_2); 75.3 (CH_2); 75.1 (CH_2); 73.4 (CH_2); 70.9 (CH); 68.8 (CH_2); 66.9 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3058, 3022, 2919, 2856, 2362, 2339, 1629, 1454, 1429, 1111, 1022, 698 cm^{-1}. HRMS-ESI: Calcd. For $C_{46}H_{50}O_8N$ [M + H]: 744.3536 found 744.3530.

(3-((*R*)-Hydroxy((*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)-(Morpholino)methanone (23c): Yield: 0.47g (70 %); R_f: 0.1 (EtOAc + Hexanes 5:5); white gummy solid; $[\alpha]_D^{25}$ = +8.61 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.45 (d, *J* = 8.0 Hz,1H, ArH); 7.39–7.24 (m, 20H, ArH); 7.18–7.16 (m, 3H, ArH); 4.97–4.92 (m, H-7, $PhCH_2$, PhC*Ha*Hb, 4H); 4.83 (d, *J* = 11.0 Hz,PhCHa*Hb*- 1H); 4.77 (d, *J* = 11.0 Hz, PhC*Ha*Hb-, 1H); 4.57 (d, *J* = 11.0 Hz, PhCHa*Hb*-, 1H); 4.43 (AB quartet, *J* = 15.0 Hz, $PhCH_2$, 2H); 3.83–3.60 (m, 11H); 3.48 (d, *J* = 9.5 Hz, 2H); 3.35–3.33 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6 (amide); 142.9 (C); 138.6 (C); 138.2 (C); 138.1 (C); 138.0 (C); 135.1 (C); 128.66 (C); 128.6 (CH); 128.5 (CH); 128.0 (CH); 127.9 (CH); 127.88 (CH); 127.8 (CH); 126.1 (CH); 125.1 (CH); 118.3 (CH); 117.4 (CH); 114.5 (CH); 87.1 (CH); 81.4 (CH); 78.7 (CH); 78.4 (CH); 78.1 (CH); 75.7 (CH_2); 75.3 (CH_2); 75.1 (CH_2); 73.4 (CH_2); 70.9 (CH); 69.0 (CH_2); 66.9 (CH_2); 48.2 (CH_2); 42.6 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2922, 2861, 2400, 1625, 1455, 1431, 1215, 1111, 1063, 929, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{46}H_{50}O_8N$ [M + H]: 744.3536 found 744.3531.

(*2R,3S,4R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-6-carbaldehyde (24): Yield: 5–10 % in each individual case; R_f: 0.2 (EtOAc + Hexanes 4:6); gummy liquid; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.14 (s, 1H, CHO), 7.27–7.15 (m,15 H, ArH), 5.75 (d, *J* = 3.2 Hz, olefinic H, 1H), 4.75–4.45 (m, 3 × $PhCH_2$-, 6H), 4.30–4.28 (dd, *J* = 10.5 Hz, 1H, CH), 4.10–4.07 (m,1H), 3.94–3.90 (m, 1H), 3.79–3.77 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ: 186.3 (C=O), 151.7 (C) 138.0, 137.9, 137.7, 128.7, 128.5, 128.1, 128.0, 127.8, 117.1(CH), 77.8, 75.8, 74.2, 73.7, 71.7, 67.8 ppm. HRMS-ESI: Calcd for $C_{28}H_{28}O_5Na$ [M + Na]: 467.1834, found 467.1816.

General Procedure for De-oxygenation of Compounds 23a-c:

Step-I: To a stirred solution of substrates **23a-c** in anhydrous acetonitrile (33 mL for 1.0 mmol) under nitrogen atmosphere was added 4-(Dimethylamino) pyridine (DMAP) (5.0 equiv.) and phenyl chlorothionocarbonate(PTC-Cl) (2.0 equiv.). The reaction mixture was stirred at room temperature for 3 to 4h. On completion of reaction, the reaction mixture was evaporated under reduced pressure, and the obtained crude residues were purified by silica-gel column chromatography. The thiono-carbonates intermediates **25a-c** were obtained in good to excellent yields, **25a** (88 %); **25b** (90 %); **25c** (93 %).

Step-II: The above-mentioned compounds **25a-c** obtained from step –I were dissolved in dry toluene (27 mL for 1 mmol) and to the solution was added tributyltin hydride (nBu_3SnH) (2 mmol, 2 equiv.) and AIBN (0.23 equiv.). The reaction mixture was stirred and heated at 90 °C for 9–10 hours in each individual case. The toluene in the reaction mixture was removed under vacuum and the de-oxygenated product obtained were purified by using silica-gel column chromatography. The spectral and analytical data of the product **19a-c** are given below.

4-(((*2S,3S,4R,5R,6R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)-methyl)tetrahydro-2H-pyran-2-yl)methyl)benzonitrile (19a): Yield: 0.114 g (78.0 %); R_f: 0.4 (EtOAc/hexanes, 2:8); white solid (mp = 92–94 °C); $[\alpha]_D^{31}$ = –0.60 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 8.5 Hz, 2H, ortho to -CN, ArH); 7.37–7.26 (m, 20H, 4 × ArH); 7.21 (d, *J* = 6.5 Hz, 2H,meta to -CN, ArH); 4.96–4.82 (m, 4H, 2 × $PhCH_2$); 4.65 (d, *J* = 11.0 Hz, 1H, $PhCH_aH_b$); 4.61 (d, *J* = 11.0 Hz, 1H, $PhCH_aH_b$); 4.53 (q, *J* = 12.0 Hz, 2H, $PhCH_2$); 3.71 (t, *J* = 9.0 Hz, 1H, H-5); 3.66–3.63 (m, 3H, H-4, H-6); 3.48 (t, *J* = 9.0 Hz, 1H, H-1); 3.36–3.32 (m, 2H, H-2, H-3); 3.15 (d, *J* = 14.0 Hz, 1H, -CHC*H*aHbPh); 2.75 (dd, J_1 = 14.5 Hz, J_2 = 9.0 Hz, 1H, -CHCHa*H*bPh) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.6 (C); 138.5 (C); 138.2 (C); 138.16 (C); 138.13 (C); 131.9 (CH); 130.5 (CH); 128.7 (CH); 128.6 (CH); 128.5 (CH); 128.50 (CH); 128.1 (CH); 128.0 (CH); 127.9 (CH); 127.8 (CH); 127.7 (CH); 119.2 (C); 110.1 (C); 87.4 (CH); 81.6 (CH); 79.4 (CH); 78.9 (CH); 78.6 (CH); 75.7 (CH_2); 75.2 (CH_2); 75.1 (CH_2); 73.5 (CH_2); 69.0 (CH_2); 38.0 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3065, 3020, 2923, 2858, 2228, 1606, 1454, 1360, 1215, 842, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{42}H_{41}NO_5Na$ [M + Na]: 662.2882, found 662.2872.

Morpholino(4-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2 yl)methyl)phenyl)methanone (19b): Yield: 0.12g (72 %); R_f: 0.3 (EtOAc + Hexanes 4:6); white solid (mp = 72–74 °C); $[\alpha]_D^{31}$ = –3.58 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.18 (m, 24H); 4.96–4.80 (m, 4H, 2 × $PhCH_2$); 4.67–4.48 (m, 4H, 2 × $PhCH_2$); 3.74–3.62 (m, 11H); 3.50–3.45 (m, 2H); 3.33–3.31 (m, 2H); 3.14 (d, *J* = 14.4 Hz, 1H, -CHC*H*aHbPh); 2.74 (dd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, 1H, -CHCHa*Hb*Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6 (amid); 141.1 (C); 138.6 (C); 138.4 (C); 138.27 (C); 138.2 (C); 133.1 (C); 129.8 (CH); 128.6 (CH); 128.5 (CH); 128.4 (CH); 127.9 (CH); 127.8 (CH); 127.79 (CH); 127.7 (CH); 127.6 (CH); 127.1 (CH); 87.4 (CH); 81.6 (CH); 79.8 (CH); 79.0 (CH); 78.7 (CH); 75.6 (CH_2); 75.2 (CH_2);75.0 (CH_2); 73.5 (CH_2); 69.0 (CH_2); 67.0 (CH_2); 37.7 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 3007, 2903, 2857, 1633, 1511, 1454, 1428, 1361, 1277, 1215, 699 cm^{-1}. HRMS-ESI: Calcd. For $C_{46}H_{50}O_7N$ [M + H]: 728.3587 found 728.3600.

Morpholino(3-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)methanone (19c): Yield: 0.15g (71 %); R_f: 0.3 (EtOAc + Hexanes 4:6); white gummy solid; $[\alpha]_D^{32}$ = +1.94 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.18 (m, 24H, ArH); 4.96–4.80 (m, 4H, 2 × $PhCH_2$); 4.67–4.48 (m, 4H, 2 × $PhCH_2$); 3.- 3.62 (m, 11H); 3.50–3.45 (m, 2H); 3.33–3.31 (m, 2H); 3.14 (d, *J* = 14.4 Hz, 1H, -CHC*H*aHbPh); 2.74 (dd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, 1H, -CHCHa*Hb*Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7 (amid); 139.5 (C); 138.6 (C); 138.3 (C); 138.2 (C); 135.2 (C); 131.3 (C); 128.6 (CH); 128.59 (CH); 128.5 (CH); 128.49 (CH); 128.46 (CH); 128.2 (CH); 128.0 (CH); 127.9 (CH); 127.8 (CH); 127.79 (CH); 127.7 (CH); 87.5 (CH); 81.9 (CH); 79.9 (CH); 79.0 (CH); 78.7 (CH); 75.7 (CH_2); 75.3 (CH_2); 75.1 (CH_2); 73.5 (CH_2); 69.2 (CH_2); 67.0 (CH_2); 37.9 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3022, 3000, 2905, 2856, 1635, 1514, 1454, 1426, 1361, 1277, 1215, 700 cm^{-1}. HRMS-ESI: Calcd. For $C_{46}H_{49}O_7N$ Na [M + Na]: 750.3407 found 750.3415.

General Procedure for Synthesis of Molecule (29):

(i) 2-Amino-5-iodobenzoic Acid (28): To a mixture of anthranilic acid **27** (5 g, 36.461 mmol) $NaIO_4$ (7.89 g, 36.461 mmol) and NaCl (4.26 g, 72.922 mmol) in Acetic acid (110 mL) + H_2O (12.0 mL) was added KI (6.05 g, 36.46 mmol) slowly portion wise over a period of 15 min at room temperature, then stirring was continued at same temperature for additional 8 to 10 h. Reaction mixture was diluted

with water (200 mL) followed by extracted into DCM (3 × 100 mL) then the combined organic extracts were dried with anhydrous sodium sulfate and filtered, filtrate was evaporated under reduced pressure furnished the compound **28** in 87 % (8.4 g) as black colour solid, ^{1}H NMR (500 MHz, [D$_6$]DMSO) δ: 7.90 (d, *J* = 2.1 Hz, 1H), 7.43(dd, J_1 = 8.4 Hz, J_2= 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO) δ: 168.7 (CO), 151.9(CH), 142.5 (CH), 138.4 (C), 119.5 (CH), 112.4 (C), 74.6 (C) ppm.

(ii) 2-Chloro-5-iodobenzoic acid (29): To a solution of compound **28** (1g, 3.78 mmol) in acetic acid (AcOH) (13 mL) + concentrate HCl (10 mL) at 0 °C was added $NaNO_2$ (0.26 g, 3.786 mmol) in 5 mL of H_2O. then stirring was continued at 0 °C for 30 min, finally to this reaction mixture CuCl (0.75 g, 7.573 mmol) dissolved in HCl (10 mL) was added slowly, then reaction flask was shifted from 0 °C to room temperature and stirring was continued there for 10 h, reaction mixture was poured into ice cold water (30 mL) and extracted into ethyl acetate (2 × 20 mL), then the combined organic extracts were dried with anhydrous sodium sulfate and filtered, filtrate was concentrated under reduced pressure, the obtained crude compound was purified by column chromatography provided the title compound **29**.

Yield:1.0g (93 %); R_f: 0.2 (EtOAc + Hexanes 3:7); light white solid; ^{1}H NMR (500 MHz, [D$_6$]DMSO) δ: 8.04 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, J_1 = 8.4 Hz, J_2= 2.4 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO) δ: 169.1 (CO), 140.2(CH), 139.2 (CH), 133.9 (C), 132.9 (CH), 132.0 (C), 92.9 (C) ppm and this data was well consisted with data obtained from commercially available material.

(iii) 2-Chloro-5-iodo-*N*-methoxy-*N*-methylbenzamide (26): To a solution of compound **29** (2 g, 7.078 mmol) in dry DCM (20 mL) + dry DMF (2 mL) at 0 °C under nitrogen atmosphere was added thionyl chloride $SOCl_2$ (0.72 mL, 9.909 mmol) then reflux the reaction mixture in-between 45 to 50 °C for 6h. Reaction mixture was shifted to 0 °C followed by Me(MeO)NHHCl (0.82 g, 8.493 mmol) and Et_3N (4.64 mL, 35.39 mmol) were added slowly. Stirring was continued for additional 3 to 4 h from 0 °C to r.t., reaction mixture was diluted with water (50 mL) and extracted into DCM (2 × 20 mL), then the combined organic extracts were dried with anhydrous sodium sulfate, filtered and filtrate was evaporated under reduced pressure, then obtained crude compound was purified by column chromatography furnished the titled compound **26**.

Yield: 2.2g (95 % in 82:18 rotamers); R_f: 0.3 (EtOAc + Hexanes 2:8); light white solid (mp = 76–78 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 –7.61 (m, 2H); 7.12 (d, *J* = 8.8 Hz, 1H); 3.86 (s, 0.7 H, -$NOCH_3$); 3.47 (s, 3H, -$NOCH_3$); 3.35 (s, 3H, -NCH_3); 3.11 (s, 0.7 H, -NCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6 (CO), 139.2 (CH); 137.2 (C); 136.8 (CH); 136.2 (CH); 131.2 (C); 130.7 (C); 90.8 (C); 61.6 (-$NOCH_3$); 32.3 (-NCH_3) ppm. HRMS-ESI: Calcd. For $C_9H_{10}NO_2ClI$ [M + H]: 325.9445 found 325.9427.

General Procedure for Synthesis of Compound 30:

To a stirred solution of isopropylmagnesium bromide (*i*PrMgBr) in dry THF (4 mL) at –15 °C was added aryl iodide **26** (0.425g, 1.358 mmol) dissolved in dry THF (5 mL), then stirring was continued at the same temperature for 1.5 to 2 h, during this period reaction mixture colour was changed from colourless to slight yellow colour and at this point the nicely azeotroped electrophile **17** (0.5 g, 0.905 mmol) in dry THF (5 mL) was added, then slowly the reaction temperature was increased from –15° to 0 °C and stirring was continued there for 8 h. The reaction mixture was quenched with saturated ammonium chloride solution (25 mL) followed by extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried with anhydrous sodium sulfate then filtered. The filtrate was concentrated under vacuum and the resulting crude products were purified by silica-gel column chromatography furnished titled compound **30** in good yield as presented below.

2-Chloro-5-((*R*)-hydroxy((*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl) methyl)-*N*-methoxy-*N*-methylbenzamide (30): Yield: 0.5 g (68 %); R_f: 0.1 (EtOAc + Hexanes 3:7); colourless gummy solid; $[\alpha]_D^{31}$ = +1.51 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32–7.16 (m, 23H, ArH); 4.96–4.88 (m, 4H, H-7, $PhCH_2$-, PhC*Ha*Hb-); 4.80 (d, *J* = 10.5 Hz, PhCHa*Hb*-, 1H); 4.75 (d, *J* = 11.0 Hz,PhC*Ha*Hb- 1H); 4.57 (d, *J* = 10.5 Hz, PhCHa*Hb*-, 1H); 4.43 (AB quartet, *J* = 12.0 Hz,$PhCH_2$, 2H); 3.78 (t, *J* = 8.5 Hz, 1H); 3.72 (t, *J* = 9.0 Hz, 1H); 3.64–3.56 (m, NOMe, H –4, 4H); 3.44–3.32 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.67 (C); 138.4 (C); 138.3 (C); 137.9 (C); 134.9 (C); 129.5 (C); 129.2 (CH); 128.6 (CH); 128.5 (CH); 128.48 (CH); 128.3 (C); 127.9 (CH); 127.8 (CH); 127.77 (CH); 127.72 (CH); 127.7 (CH); 127.6 (C); 127.5 (C); 126.0 (CH); 87.1 (CH); 81.4 (CH); 78.9 (CH); 78.4 (CH); 78.3 (CH); 75.6 (CH_2); 75(CH_2); 75.0 (CH_2); 70.6 (CH); 69.0 (CH_2); 61.2 (OCH_3); 32.4 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2925, 2869, 1715, 1448, 1366, 1277, 1215, 1096, 1027, 768 cm^{-1}. HRMS-ESI: Calcd. For $C_{44}H_{47}O_8NCl$ [M + H]: 752.2990 found 752.3003.

General Procedure for Synthesis of Building Block 16:

Step-I: To a stirred solution of compound **30** (0.9 g, 1.111 mmol) in anhydrous acetonitrile (33 mL) under nitrogen atmosphere was added 4-(Dimethylamino) pyridine (DMAP) (0.745 g, 6.105 mmol) and phenyl chlorothionocarbonate(PTC-Cl) (0.3 mL, 2.442 mmol) and reaction mixture was stirred at room temperature for 3 to 4 h, reaction mixture was evaporated under reduced pressure and obtained crude residue was purified by column chromatography provided the corresponding intermediates **31** in 90 % yield (0.9 g) as white fluffy solid.

Step-II: Tributyltin hydride (nBu$_3$SnH) (0.5 mL, 1.91 mmol) and AIBN (0.03 g) were added to a stirred solution of compound **31** (0.85 g, 0.958 mmol) in dry toluene (26 mL). Heat the reaction mixture at 90 °C for 9 to 10h, reaction mixture was evaporated under reduced pressure and obtained crude compound was purified by using column chromatography furnished the building block **16**.

2-chloro-*N*-methoxy-*N*-methyl-5-(((*2S,3S,4R,5R,6R*)-3,4,5-tris-(benzyloxy)-6-((benzyloxy) methyl)tetrahydro-2H-pyran-2-yl)-methyl)benzamide (16): Yield: 0.31 g (75 %); R_f: 0.3 (EtOAc + Hexanes 2:8); White solid (mp = 60–62 °C); $[\alpha]_D^{31}$ = –6.16 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 100 °C) δ**:** 7.34–7.20 (m, 23H, ArH); 4.85–4.82 (m, 3H, $PhCH_2$, PhC*Ha*Hb); 4.73 (d, *J* = 11.0 Hz, 1H, PhCHa*Hb*); 4.67 (d, *J* = 11.0 Hz, 1H, PhC*Ha*Hb); 4.57 (d, *J* = 11.0 Hz, 1H, PhCHa*Hb*); 4.44 (AB quartet, *J* = 12.5 Hz, 2H, $PhCH_2$); 3.73 (t, *J* = 9.0 Hz, 1H, H-5); 3.61–3.54 (m, 3H, H-4, H-6); 3.50–3.41 (m, 4H, H-1, -OCH_3); 3.29 (t, *J* = 9.5 Hz, 1H, H-2); 3.18 (bs, 4H, H-3, CH_3); 3.09 (dd, J_1 = 14.5 Hz, J_2 = 2.5 Hz, 1H, -CHC*Ha*HbPh); 2.71 (dd, J_1 = 14.5 Hz, J_2 = 8.5 Hz, 1H, -CHCHa*Hb*Ph); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 100 °C) δ: 138.4 (C); 138.1 (C); 138.0 (C); 131.1 (C); 129.4 (C); 128.5 (C); 128.1 (C); 128.0 (CH); 127.9 (CH); 127.44 (CH); 127.4 (CH); 127.3 (CH); 127.29 (CH); 127.26 (CH); 127.2 (CH); 127.17 (CH); 127.15 (CH); 127.10 (CH); 127.08 (CH); 127.04 (CH); 126.9 (CH); 85.7 (CH); 81.3 (CH); 78.3 (CH); 78.0 (CH); 77.9 (CH); 74.0 (CH_2); 73.6 (CH_2); 72.1 (CH_2); 68.9 (CH_2); 60.5 (OCH_3); 36.4 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3025, 2929, 2870, 1715, 1447, 1368, 1287, 1215, 1096, 1037, 777 cm^{-1}. HRMS-ESI: Calcd. For $C_{44}H_{47}O_7NCl$ [M + H]: 736.3041 found 736.3060.

General Procedure for Grignard Addition Reaction on Building Block (16): Various substituted phenylmagnesium bromides were prepared prior to their use by reaction of commercially available

substituted bromobenzenes (1.360 mmol) with pre-cleaned magnesium metal (0.032g, 1.360 mmol) in dry THF (2 mL) under nitrogen atmosphere, after generation of arylmagnesium bromides, the reaction flask was shifted to 0 °C and to this building block **16** (0.2 g, 0.272 mmol) in dry THF (2 mL) was added, then stirring was continued at 0 °C to room temperature for 4 to 5 h. reaction mixture was quenched by caution addition of saturated ammonium chloride solution (15 mL) followed by extracted in to ethyl acetate (2 × 15 mL), ethyl acetate layer was washed with water (15 mL), brine (15 mL) and dried with anhydrous sodium sulfate followed by concentrated under reduced pressure, then obtained crude residues were purified by silica gel column chromatography provided the corresponding keto compounds **32a-f** in good to excellent yields as presented below.

(2-Chloro-5-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)(p-tolyl) methanone (32a): Yield: 0.125 g (86 %); R_f: 0.5 (EtOAc + Hexanes 2:8); white solid (mp = 90 –92 °C); $[\alpha]_D^{32}$ = –2.497 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 8.0 Hz, 2H, ArH); 7.32–7.16 (m, 25H, ArH); 4.94–4.86 (m, 3H, $PhCH_2$, PhC*H*aHb); 4.81 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.62 (d, *J* = 11.2 Hz, 1H, PhC*H*aHb); 4.57 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.46 (AB quartet, *J* = 12.0 Hz, 2H, $PhCH_2$); 3.70 (t, *J* = 8.8 Hz, 1H, H-5); 3.65–3.57 (m, 3H, H-4, H-6); 3.43 (t, *J* = 8.8 Hz, 1H, H-1); 3.41–3.29 (m, 2H, H-2, H-3); 3.09 (d, *J* = 14.4 Hz, 1H. -CHC*H*aHbPh); 2.68 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H, -CHCHa*H*bPh); 2.40 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.2 (CO); 144.7 (C); 138.6 (C); 138.5 (C); 138.27 (C); 138.2 (C); 138.15 (C); 137.8 (C); 134.2 (C); 132.4 (CH); 130.4 (CH); 130.2 (CH); 129.7 (CH); 129.4 (CH); 129.0 (CH); 128.64 (CH); 128.64 (CH); 128.6 (CH); 128.55 (CH); 128.51 (CH); 128.48 (CH); 128.0 (CH); 127.9 (CH); 127.83 (CH); 127.80 (CH); 127.7 (CH); 87.4 (CH); 81.6 (CH); 79.6 (CH); 79.0 (CH); 78.6 (CH); 75.7 (CH_2); 75.3 (CH_2); 75.1 (CH_2); 73.5 (CH_2); 69.0 (CH_2); 37.1 (CH_2); 21.9 (CH_3) ppm. IR ($CHCl_3$): ṽ = 3020, 2933, 2847, 1659, 1604, 1473, 1416, 1215, 928, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{49}H_{47}O_6ClNa$ [M + Na]: 789.3061 found 789.2248.

(2-Chloro-5-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)(4-ethylphenyl)methanone (32b): Yield: 0.110 g (80 %); R_f: 0.5 (EtOAc + Hexanes 2:8); white solid (mp = 66–68 °C); $[\alpha]_D^{32}$ = +0.22 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.0 Hz, 2H, ArH); 7.31–7.16 (m, 25H, ArH); 4.94–4.85 (m, 3H, $PhCH_2$, PhC*H*aHb); 4.80 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.62 (d, *J* = 11.2 Hz, 1H, PhC*H*aHb); 4.58 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.46 (AB quartet, *J* = 12.0 Hz, 2H, $PhCH_2$); 3.70 (t, *J* = 9.2 Hz, 1H, H-5); 3.65–3.58 (m, 3H, H-4, H-6); 3.43 (t, *J* = 8.8 Hz, 1H, H-1); 3.34–3.30 (m, 2H, H-2, H-3); 3.10 (d, *J* = 14.0 Hz, 1H, -CHC*H*aHbPh); 2.72–2.66 (m, 3H, -CHCHa*H*b, -CH_2CH_3); 1.24 (t, *J* = 7.6 Hz, 3H, -CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.16 (CO); 150.8 (C); 138.6 (C); 138.55 (C); 138.3 (C); 138.27 (C); 138.2 (C); 137.8 (C); 134.4 (C); 132.4 (C); 130.5 (CH); 130.2 (CH); 129.7 (CH); 129.1 (C); 128.63 (CH); 128.6 (CH); 128.5 (CH); 128.4 (CH); 128.2 (CH); 128.00 (CH); 127.9 (CH); 127.8 (CH); 127.77 (CH); 127.7 (CH); 87.4 (CH); 81.7 (CH); 79.7 (CH); 79.0 (CH); 78.7 (CH); 75.7 (CH_2); 75.2 (CH_2); 75.1 (CH_2); 73.6 (CH_2); 69.0 (CH_2); 37.2 (CH_2); 29.1 (CH_2); 15.2 (CH_3) ppm. IR ($CHCl_3$): ṽ = 3020, 2967, 2925, 2867, 1667, 1604, 1454, 1356, 1215, 766, 700, and 671 cm^{-1}. HRMS-ESI: Calcd. For $C_{50}H_{49}O_6ClNa$ [M + Na]: 803.3217 found 803.3116.

(2-Chloro-5-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)(4-methoxyphenyl)methanone (32c): Yield: 0.15 g (73 %); R_f: 0.5 (EtOAc + Hexanes 2:8); white solid (mp = 98–100 °C); $[\alpha]_D^{32}$ = –1.93 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 9.0 Hz, 2H, ArH); 7.31–7.22 (m, 20H, ArH); 7.18–7.17 (m, 3H, ArH); 6.88 (d, *J* = 8.5 Hz, 2H, ArH); 4.94–4.88 (m, 3H, $PhCH_2$, PhC*H*aHb); 4.81 (d, *J* = 11.0 Hz, 1H, PhCHa*H*b); 4.63 (d, *J* = 11.0 Hz, 1H, PhC*H*aHb); 4.58 (d, *J* = 10.5 Hz, 1H, PhCHa*H*b); 4.46 (AB quartet, *J* = 12.0 Hz, 2H, $PhCH_2$); 3.83 (s, 3H, -OCH_3); 3.70 (t, *J* = 9.0 Hz, 1H, H-5); 3.65–3.59 (m, 3H, H-4, H-6); 3.45 (t, *J* = 9.0 Hz, 1H, H-1); 3.42–3.30 (m, 2H, H-2, H-3); 3.10 (d, *J* = 14.5 Hz, 1H, -CHC*H*aHbPh); 2.69 (dd, J_1 = 14.5 Hz, J_2 = 9.0 Hz, 1H, -CHCHa*H*bPh) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 194.1 (CO); 164.1 (C); 138.65 (C); 138.60 (C); 138.3 (C); 138.2 (C); 138.1 (C); 137.8 (C); 132.6 (CH); 132.2 (CH); 130.1 (CH); 129.6 (CH); 129.0 (CH); 128.6 (CH); 128.58 (CH); 128.53 (CH); 128.5 (CH); 128.4 (CH); 128.0 (CH); 127.9 (CH); 127.88 (CH); 127.8 (CH); 127.78 (CH); 127.76 (CH); 127.7 (CH); 113.9 (CH); 87.4 (CH); 81.7 (CH); 79.6 (CH); 79.0 (CH); 78.6 (CH); 75.7 (CH_2); 75.2 (CH_2); 75.1 (CH_2); 73.5 (CH_2); 69.0 (CH_2); 55.6 (OCH_3); 37.2 (CH_2) ppm. IR ($CHCl_3$): ṽ = 3019, 2933, 2854, 1658, 1598, 1511, 1455, 1359, 1252, 1216, 700, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{49}H_{47}O_7ClNa$ [M + Na]: 805.3010 found 805.2907.

(4-Butoxyphenyl)(2-chloro-5-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)-phenyl)methanone (32d): Yield: 0.125 g (81 %); R_f: 0.5 (EtOAc + Hexanes 2:8); white solid (mp = 70–72 °C); $[\alpha]_D^{32}$ = –2.845 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 9.2 Hz, 2H, ArH); 7.31–7.21 (m, 21H, ArH); 7.18–7.16 (m, 2H, ArH); 6.87 (d, *J* = 8.8 Hz, 2H, ArH); 4.94–4.85 (m, 3H, $PhCH_2$, PhC*H*aHb); 4.80 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.63 (d, *J* = 11.2 Hz, 1H, PhC*H*aHb); 4.58 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.46 (AB quartet, *J* = 12.0 Hz, 2H, $PhCH_2$); 3.99 (t, *J* = 6.4 Hz, 2H, -OCH_2CH_2-); 3.70 (t, *J* = 8.8 Hz, 1H, H-5); 3.68–3.58 (m, 3H, H-4, H-6); 3.44 (td, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H, H-1); 3.34–3.29 (m, 2H, H-2, H-3); 3.10 (dd, J_1 = 14.0 Hz, J_2 = 1.6 Hz, 1H, -CHC*H*aHbPh); 2.68 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H, -CHCHa*H*bPh); 1.77 (quintet, *J* = 7.2 Hz, 2H, -$OCH_2CH_2CH_2CH_3$); 1.48 (sextet, *J* = 7.6 Hz, 2H, -$OCH_2CH_2CH_2CH_3$); 0.97 (t, *J* = 7.6 Hz, 3H, -$OCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.1 (CO); 163.8 (C); 138.7 (C); 138.6 (C); 138.3 (C); 138.27 (C); 138.2 (C); 137.8 (C); 132.7 (CH); 132.2 (CH); 130.1 (CH); 129.7 (CH); 129.5 (CH); 129.0 (CH); 128.65 (CH); 128.6 (CH); 128.55 (CH); 128.5 (CH); 128.48 (CH); 128.0 (CH); 127.9 (CH); 127.83 (CH); 127.8 (CH); 127.7 (CH); 114.4 (CH); 87.4 (CH); 81.7 (CH); 79.7 (CH); 79.0 (CH); 78.7 (CH); 75.7 (CH_2); 75.3 (CH_2); 75.1 (CH_2); 73.6 (CH_2); 69.0 (CH_2); 68.1 (CH_2); 37.2 (CH_2); 31.2 (CH_2); 19.3 (CH_2); 13.9 (CH_3) ppm. IR ($CHCl_3$): ṽ = 3022, 2943, 2869, 1658, 1598, 1477, 1455, 1254, 1217, 1169, 699, 624 cm^{-1}. HRMS-ESI: Calcd. For $C_{52}H_{53}ClO_7Na$ Cl [M + Na]: 847.3479 found 847.3642.

Benzo[d][1,3]dioxol-5-yl(2-chloro-5-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)methanone (32e): Yield: 0.2 g (93 %); R_f: 0.5 (EtOAc + Hexanes 2:8); light white solid (mp = 78–80 °C) $[\alpha]_D^{32}$ = –1.91 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.17 (m, 25H, ArH); 6.76 (d, *J* = 8.0 Hz, 1H, ArH); 6.01 (s, 2H, -OCH_2O-); 4.94–4.85 (m, 3H, $PhCH_2$, PhCHa*Hb*); 4.81 (d, *J* = 10.4 Hz, 1H, PhC*Ha*Hb); 4.63 (d, *J* = 11.2 Hz, 1H, PhCHa*Hb*); 4.58 (d, *J* = 10.8 Hz, 1H, PhC*Ha*Hb); 4.47 (AB quartet, *J* = 12.0 Hz, 2H, $PhCH_2$); 3.72–3.59 (m, 4H, H-6, H-5, H-4); 3.43 (t, *J* = 8.8 Hz, 1H, H-1); 3.33–3.29 (m, 2H, H-3, H-2); 3.09 (d, *J* = 14.0 Hz, 1H, -CHCHa*Hb*Ar); 2.68 (dd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, 1H, -CHC*Ha*HbAr) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.7 (CO); 152.5 (C); 148.4 (C); 138.6 (C); 138.5 (C); 138.2 (C); 137.8 (C); 132.3 (CH); 131.5 (C); 130.0 (C); 129.7 (CH); 128.9 (CH); 128.64 (CH); 128.6 (CH); 128.5 (CH); 128.0 (CH); 127.9 (CH); 127.8 (CH); 127.78 (CH); 127.75 (CH); 127.7 (CH); 109.2 (CH): 108.0 (CH); 102.1 (CH_2); 87.4 (CH): 81.7 (CH); 79.66 (CH); 79.0 (CH); 78.7 (CH); 75.7 (CH_2); 75.2 (CH_2); 75.1 (CH_2); 73.5 (CH_2); 69.0 (CH_2); 37.2 (CH_2) ppm. IR ($CHCl_3$): ṽ = 3020, 2917, 2861, 1652, 1605, 1442, 1359, 1293, 1258, 1215, 1096, 623 cm^{-1}. HRMS-ESI: Calcd. For $C_{49}H_{45}O_8ClNa$ [M + Na]: 819.2803 found 819.2702.

(2-Chloro-5-(((*2S,3S,4R,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)(4-ethoxyphenyl)methanone (32f): Yield: 0.13 g (80 %); R_f: 0.4 (EtOAc + Hexanes 2:8); white solid (mp = 94–96 °C); $[\alpha]_D^{32}$ = –2.46 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ: 7.71 (d, *J* = 8.8 Hz, 2H, ArH); 7.34–7.18 (m, 23H, ArH); 6.89 (d, *J* = 8.4 Hz, 2H, ArH); 4.96–4.90 (m, 3H, $PhCH_2$, PhC*H*aHb); 4.82 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.65 (d, *J* = 11.2 Hz, 1H, PhC*H*aHb); 4.60 (d, *J* = 10.8 Hz, 1H, PhCHa*H*b); 4.48 (AB quartet, *J* = 12.0 Hz, 2H, $PhCH_2$); 4.08 (q, *J* = 7.2 Hz, 2H, -OCH_2CH_3); 3.72 (t, *J* = 8.4 Hz, 1H, H-5); 3.67–3.60 (m, 3H, H-4, H-6); 3.46 (t, *J* = 9.2 Hz, 1H, H-1); 3.36–3.32 (m, 2H, H-2, H-3); 3.12 (d, *J* = 14.4 Hz, 1H, -CHC*H*aHbPh); 2.70 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H, -CHCHa*H*bPh); 1.44 (t, *J* = 6.8 Hz, 3H, -OCH_2CH_3) ppm**.** ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.1 (CO); 163.6 (C); 138.6 (C); 138.3 (C); 138.2 (C); 138.15 (C); 137.7 (C); 132.7 (CH); 132.2 (CH); 130.1 (CH); 129.7 (CH); 129.5 (C); 129.0 (C); 128.64 (CH); 128.6 (CH); 128.55 (CH); 128.5 (CH); 128.4 (CH); 128.0 (CH); 127.9 (CH); 127.8 (CH); 127.4 (CH); 127.7 (CH); 87.4 (CH); 81.6 (CH); 79.6 (CH); 79.0 (CH); 78.6 (CH); 75.7 (CH_2); 75.2 (CH_2); 75.1 (CH_2); 73.5 (CH_2); 68.9 (CH_2); 63.9 (CH_2); 37.1 (CH_2); 14.7 (CH_3) ppm. IR ($CHCl_3$): ṽ = 3020, 2925, 2858, 1659, 1591, 1513, 1313, 1254, 1170, 1048, 846, 699 cm^{-1}. HRMS-ESI: Calcd. For $C_{50}H_{49}O_7Na$ N Cl [M + Na]: 819.3166 found 819.3057.

General Procedure for De-benzylation of Compounds 32a-f: To a solution of above all keto compounds **(32a-f)** in MeOH/EtOAc (1:1) (3 mL for 0.208 mmol) was added 10 % Pd-C (0.15 equiv.) followed by 1,2 dichloro benzene (20 equiv.) then de-gassed the reaction mixture with hydrogen gas for two times then stirring was continued at room temperature under hydrogen balloon condition for 24 h. This condition yielded de-benzylated keto compounds **(33a, 33c, 33f)**. With the use of Parr hydrogenation apparatus and hydrogen pressure of 40-PSI, complete reduction occurred and the products **15a-e** and **14** were obtained. The reaction work-up included filtration through celite bed and concentration of the filtrate under reduced pressure. The obtained crude product residues were purified by silica-gel column chromatography using 5–10 % methanol in dichloromethane as mobile phase.

(2-Chloro-5-(((*2S,3R,4R,5S,6R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)(*p*-tolyl)methanone (33a): Yield: 0.04 g (81 %); R_f: 0.3 (MeOH + DCM 1:9); white solid (mp = 152–154 °C); $[\alpha]_D^{32}$ = –8.07 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ: 7.69 (d, *J* = 8.0 Hz, 2H, ArH); 7.49 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H, ArH); 7.41 (d, *J* = 8.0 Hz, 1H, ArH); 7.37 (d, *J* = 2.0 Hz, 1H, ArH); 7.34 (d, *J* = 8.0 Hz, 2H, ArH); 3.76 (dd, J_1= 11.5 Hz, 1H, H-6, Hb); 3.60 (dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H, H-6, Ha); 3.40–3.33 (m, 4H, H-3, H-4, 2 × OH); 3.26 (t, *J* = 9.5 Hz, 1H, H-1); 3.22 (dd, J_1 = 14.5 Hz, J_2 = 2.0 Hz, 1H, -CHCHa*H*bAr); 3.18–3.14 (m,1H, H-5); 3.10 (t, *J* = 9.0 Hz, 1H, H-2); 2.80 (dd, J_1 = 14.5 Hz, J_2 = 8.0 Hz, 1H, -CHC*H*aHbAr); 2.44 (s, 3H, -CH_3) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ: 195.6 (CO); 145.0 (C); 138.2 (C); 138.0 (C); 133.9 (C); 132.4 (CH); 130.0 (CH); 129.9 (CH); 129.1 (CH); 128.2 (CH); 80.1 (CH); 79.7 (CH); 78.4 (CH); 73.2 (CH); 70.4 (CH); 61.5 (CH_2); 36.5 (CH_2); 20.3 (CH_3) ppm. IR ($CHCl_3$): ṽ = 3022, 2925, 1658, 1650, 1563, 1452, 1218, 1086, 770, 671 cm^{-1}. HRMS-ESI: Calcd. For $C_{21}H_{23}O_6ClNa$ [M + Na]: 429.1183 found 429.1083.

(2-Chloro-5-(((*2S,3R,4R,5S,6R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)(4-methoxyphenyl)methanone (33c): Yield: 0.072 g (90 %); R_f: 0.3 (MeOH + DCM 2:8); white solid (mp = 158–160 °C); $[\alpha]_D^{32}$ = –16.66 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.75 (d, *J* = 8.4 Hz, 2H, ArH); 7.45 (d, *J* = 8.4 Hz, 1H, ArH); 7.38 (d, *J* = 8.4 Hz, 1H, ArH); 7.34 (s, 1H, ArH); 7.01 (d, *J* = 8.4 Hz, 2H, ArH); 3.88 (s, 3H, -OCH_3); 3.74 (d, *J* = 10.8 Hz, 1H, H-6, Hb); 3.59 (dd, J_1 = 12.0 J_2 = 5.2 Hz, 1H, H-6, Ha); 3.39–3.10 (m, 3H); 3.25 (d, *J* = 9.6 Hz, 1H, H-1); 3.21 (d, *J* = 6.0 Hz, 1H, -CHCHa*H*bAr); 3.16–3.10 (m, 2H); 3.05 (t, *J* = 9.2 Hz, H-2); 2.78 (dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz, 1H, -CHC*H*aHbAr) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ: 198.1 (CO); 168.0 (C); 141.5 (C); 135.7 (CH); 133.3 (CH); 132.6 (CH); 132.5 (CH); 131.5 (C); 117.1 (CH); 83.5 (CH); 83.1 (CH); 81.8 (CH); 76.6 (CH); 73.8 (CH); 64.9 (CH_2); 58.2 (OCH_3); 39.9 (CH_2) ppm. IR ($CHCl_3$): ṽ = 3020, 2925, 2844, 1652, 1598, 1427, 1216, 1118, 1090, 1023, 929, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{21}H_{23}O_7$ Cl [M + H]: 423.1172 found 423.1205.

(2-Chloro-5-(((*2S,3R,4R,5S,6R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)methyl)phenyl)(4-ethoxyphenyl)methanone (33f): Yield: 0.07 g (86 %); R_f: 0.3 (MeOH + DCM 2:8); white solid (mp = 166–168 °C); $[\alpha]_D^{32}$ = +1.96 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, [D_6]DMSO) δ: 7.67 (d, *J* = 7.0 Hz, 2H, ArH); 7.44 (bs, 2H, ArH); 7.28 (s, 1H, ArH); 7.03 (d, *J* = 7.5 Hz, 2H); 4.11 (bs, 2H, OCH_2CH_3); 3.55 (d, *J* = 10.5 Hz, 1H, H-6, Hb); 3.34 (d, *J* = 8.5 Hz, 1H, H-6, Ha); 3.25 (bs, 1H); 3.16 (bs, 1H, H-1); 3.07 (d, *J* = 14.1 Hz, 1H, -CHCHa*H*bAr); 3.01 (bs, 2H); 2.90 (bs 1H, -CHCHa*H*bAr); 2.65 (dd. J_1 = 11.9 Hz, J_2 = 7.4 Hz, 1H, -CHC*H*aHbAr); 1.32 (bs, 3H, -OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO) δ: 193.4 (CO); 163.6 (C); 138.9 (C); 138.2 (C); 132.8 (CH); 132.6 (CH); 130.2 (CH); 129.6 (CH); 129.1 (C); 127.5 (C); 115.1 (CH); 81.0 (CH); 79.6 (CH); 78.6 (CH); 73.5 (CH); 70.9 (CH); 64.2 (CH_2); 61.8 (CH_2); 36.9 (CH_2); 14.9 (CH_3) ppm. IR ($CHCl_3$): ṽ = 3345, 2928, 2855, 1655, 1600, 1435, 1217, 1119, 1050, 1023, 987, 675 cm^{-1}. HRMS-ESI: Calcd. For $C_{22}H_{25}O_7Na$ Cl [M + Na]: 459.1187 found 459.1172.

(*2S,3R,4R,5S,6R*)-2-(4-Chloro-3-(4-methylbenzyl)benzyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (15a): Yield: 0.023 g (82 %); R_f: 0.4 (MeOH + DCM 1:9); white gummy solid; $[\alpha]_D^{32}$ = –10.76 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.22 (d, *J* = 8.0 Hz, 1H, ArH); 7.19 (bs, 1H, ArH); 7.14–7.11 (m, 1H, ArH); 7.05 (bs, 4H, ArH); 3.99 (bs, 2H, $ArCH_2Ar$); 3.72 (dd, J_1 = 12.0 Hz, J_2 = 2.0, 1H, H-6, Hb); 3.58 (dd, J_1 = 11.6 Hz, J_2 = 5.2 Hz, 1H, H-6, Ha); 3.29–3.20 (m, 4H); 3.10–3.01 (m, 3H); 2.64(dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz, 1H, -CHC*H*aHbAr); 2.27 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ: 140.4 (C); 140.2 (C); 138.9 (C); 137.5 (C); 134.5 (C); 133.6 (CH); 131.0 (CH); 130.8 (CH); 130.7 (CH); 130.6 (CH); 82.2 (CH); 80.7 (CH); 75.6 (CH); 72.7 (CH); 63.8 (CH_2); 40.4 (CH_2); 38.8 (CH_2); 21.9 (CH_3) ppm. IR ($CHCl_3$): ṽ = 3380, 3020, 2922, 2851, 1512, 1476, 1421, 1215, 1088, 1039, 767, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{21}H_{25}ClO_5Na$ [M + Na]: 415.1390 found 415.1288.

(*2S,3R,4R,5S,6R*)-2-(4-Chloro-3-(4-ethylbenzyl)benzyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (15b): Yield: 0.06 g (83 %); R_f: 0.4 (MeOH + DCM 1:9); white solid (mp = 56–58 °C); $[\alpha]_D^{32}$ = –11.54 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.27–7.24 (m, 2H, ArH); 7.16 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H, ArH); 7.10 (bs, 4H, ArH); 4.03 (bs, 2H, $ArCH_2Ar$); 3.74 (dd, J_1 = 11.6 Hz, J_2 = 2.0 Hz, 1H, H-6, Hb); 3.60 (dd, J_1 = 12.0 Hz, J_2 = 5.6 Hz, 1H, H-6, Ha); 3.35–3.30 (m, 4H); 3.26 (t, *J* = 8.8 Hz, 1H, H-1); 3.14–3.05 (m, 3H); 2.68 (dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz, 1H, -CHC*H*aHbAr); 2.60 (q, *J* = 7.6 Hz, 2H, -CH_2CH_3); 1.21 (t, *J* = 7.6 Hz, 3H, -CH_2CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ: 144.0 (C); 140.4 (C); 140.2 (C); 139.2 (C); 134.6 (C); 133.6 (CH); 131.0 (CH); 130.8 (CH); 130.7 (CH); 129.7 (CH); 82.2 (CH); 80.7 (CH); 75.6 (CH); 72.7 (CH); 63.8 (CH_2); 40.4 (CH_2); 38.8 (CH_2); 30.3 (CH_3); 17.0 ppm. IR ($CHCl_3$): ṽ = 3465, 3020, 1512, 1477, 1421, 1215, 1090, 1035, 924, 767, 669, 623 cm^{-1}. HRMS-ESI: Calcd. For $C_{22}H_{27}O_5Na$ Cl [M + Na]: 429.1445 found 429.1415.

(*2S,3R,4R,5S,6R*)-2-(4-Chloro-3-(4-methoxybenzyl)benzyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (15c): Yield: 0.055 g (82 %); R_f: 0.4 (MeOH+ DCM 1.5:8.5); light white solid (mp = 102–104 °C), $[\alpha]_D^{32}$ = –30.93 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.26–7.23 (m, 2H, ArH); 7.17–7.11 (m, 3H, ArH); 6.83 (d, *J* = 7.6 Hz,

2H, ArH); 4.00 (bs, 2H, $ArCH_2Ar$); 3.77–3.74 (m, 4H, -OCH_3, H-6); 3.63 (dd, J_1 = 10.8 Hz, J_2 = 4.0 Hz, 1H, H-6); 3.34–3.25 (m, 4H, H-1, H-4, H-5, OH); 3.14–3.06 (m, 3H, -CHCHa*Hb*Ar, H-2, H-3); 2.70 (dd, J_1 = 14.0 Hz, J_2 = 8.4 Hz, 1H, -CHC*Ha*HbAr); ^{13}C NMR (100 MHz, CD_3OD) δ: 159.5 (C); 139.7 (C); 139.3 (C); 133.6 (CH); 133.1 (C); 132.6 (C); 130.8 (CH); 130.1 (CH); 129.9 (CH); 114.8 (CH); 81.31 (CH); 79.8 (CH); 74.7 (CH); 71.8 (CH); 62.9 (CH_2); 55.6 (OCH_3); 39.1 (CH_2); 37.9 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3426, 3020, 2918, 2861, 1612, 1512, 1476, 1424, 1215, 1088, 1036, 928, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{21}H_{25}O_6ClNa$ [M + Na]: 431.1339 found 431.1235.

(*2S,3R,4R,5S,6R*)-2-(3-(4-Butoxybenzyl)-4-chlorobenzyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (15d): Yield: 0.05 g (80 %); R_f: 0.4 (MeOH + DCM 2:8); white gummy solid; $[\alpha]_D^{32}$ = –1.48 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ: 7.25 (d, *J* = 8.0 Hz, 1H, ArH); 7.22 (d, *J* = 1.5 Hz, 1H, ArH); 7.16 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H, ArH); 7.10 (d, *J* = 8.5 Hz, 2H, ArH); 6.82 (d, *J* = 8.5 Hz, 2H, ArH); 3.99 (bs, 2H, $ArCH_2Ar$); 3.94 (t, *J* = 6.5 Hz, 2H, -O*C*H_2(CH_2)$_3$$CH_3$); 3.74 (dd, J_1 = 12.0 Hz, J_2 = 2.5 Hz, 1H, Hb, H-6); 3.61 (dd, J_1 = 12.0 Hz, J_2 = 5.5 Hz, 1H, H-6,Ha); 3.34–3.30 (m, 4H); 3.26 (t, *J* = 9.5 Hz, 1H, H-1); 3.14–3.10 (m, 2H); 3.07 (t, *J* = 9.0 Hz, 1H, -CHCHa*Hb*Ar); 2.68 (dd, J_1 = 14.5 Hz, J_2 = 8.5 Hz, 1H, -CHC*Ha*HbAr); 1.74 (quintet, *J* = 7.0 Hz, 2H, -OCH_2C*H*$_2CH_2CH_3$); 1.51 (sextet, *J* = 7.5 Hz, 2H, -OCH_2CH_2C*H*$_2CH_3$); 0.99 (t, *J* = 7.5 Hz, 3H, -$OCH_2CH_2CH_2$*C*H_3) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ: 157.6 (C); 138.4 (C); 137.9 (C); 132.2 (CH); 131.7 (C); 131.3 (C); 129.4 (CH); 128.7 (CH); 128.5 (CH); 114.0 (CH); 79.9 (CH); 78.4 (CH); 73.3 (CH); 70.4 (CH); 67.3 (CH_2); 61.5 (CH_2); 37.7 (CH_2); 36.6 (CH_2); 31.2 (CH_2); 18.9 (CH_2); 12.8 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3443, 3020, 1651, 1216, 1090, 1024, 770, 669 cm^{-1}. HRMS-ESI: Calcd. For $C_{24}H_{31}O_6$ Cl Na [M + Na]: 473.1809 found 473.1706.

(*2S,3R,4R,5S,6R*)-2-(3-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-chlorobenzyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (15e): Yield: 0.05 g (83 %); R_f: 0.5 (MeOH + DCM 1.5:8.5); brown colour gummy solid; $[\alpha]_D^{32}$ = –18.24 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.25 (d, *J* = 8.0 Hz, 1H, ArH); 7.23 (d, *J* = 2.0 Hz, 1H, ArH); 7.16 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H, ArH); 6.73–6.70 (m, 1H, ArH); 6.68–6.66 (m, 2H, ArH); 5.88 (s, 2H, -OCH_2O-); 3.97 (s, 2H, $ArCH_2Ar$); 3.76 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H, H-6, Hb); 3.62 (dd, J_1 = 11.6 Hz, J_2 = 5.2 Hz, 1H, H-6, Ha); 3.33–3.25 (m, 4H); 3.17–3.06 (m, 3H); 2.68 (dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz, 1H, -CHC*Ha*HbAr) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ: 149.0 (C); 147.3 (C); 139.5 (C); 139.4 (C); 135.0 (C); 133.6 (CH); 132.6 (CH); 130.3 (CH); 129.9 (CH); 122.8 (CH); 110.2 (CH); 108.9 (CH); 102.0 (CH_2); 81.3 (CH); 79.8 (CH); 74.7 (CH); 71.8 (CH); 62.9 (CH_2); 39.6 (CH_2); 37.9 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3402, 3020, 2924, 2886, 1605, 1504, 1486, 1441, 1215, 1091, 1040, 929 cm^{-1}. HRMS-ESI: Calcd. For $C_{21}H_{23}O_7$ Cl Na [M + Na]: 445.1132 found 445.1031.

(*2S,3R,4R,5S,6R*)-2-(4-Chloro-3-(4-ethoxybenzyl)benzyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (14): Yield: 0.07 g (84 %); R_f: 0.4 (MeOH + DCM 2:8); white solid (mp = 90–92 °C); $[\alpha]_D^{32}$ = –14.36 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ: 7.25 (d, *J* = 8.0 Hz, 2H, ArH); 7.22 (s, 1H, ArH); 7.15 (d, *J* = 8.0 Hz, 1H, ArH); 7.10 (d, *J* = 7.5 Hz, 1H, ArH); 6.81 (d, *J* = 7.0 Hz, 2H); 4.00–3.99 (m, 4H, -OCH_2, $ArCH_2Ar$); 3.75 (d, *J* = 11.5 Hz, 1H, -CHa*H*b, H-6); 3.62 (dd, J_1 = 12.0 Hz, J_2 = 5.0 Hz, 1H, -*CHa*Hb, H-6); 3.35–3.25 (m, 4H); 3.13–3.06 (m, 3H); 2.69 (dd, J_1 = 14.0 Hz, J_2 = 8.5 Hz, 1H, -CHCHaHbAr); 1.37 (t, *J* = 7.0 Hz, 3H, -OCH_2CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ: 158.8 (C); 139.8 (C); 139.3 (C); 133.6 (C); 133.1 (C); 132.6 (CH); 130.8 (CH); 130.1 (CH); 129.9 (CH); 115.4 (CH); 81.3 (CH); 79.8 (CH); 74.7 (CH); 71.8 (CH); 64.4 (CH_2); 62.9 (CH_2); 39.1 (CH_2); 37.9 (CH_2); 15.2 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3364, 3019, 1613, 1473, 1424, 1213, 1081, 1042, 924, 770, 671 cm^{-1}. HRMS-ESI: Calcd. For $C_{22}H_{27}O_6ClNa$ [M + Na]: 445.1496 found 445.1395.

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Benzyl *C*-Analogues of Dapagliflozin

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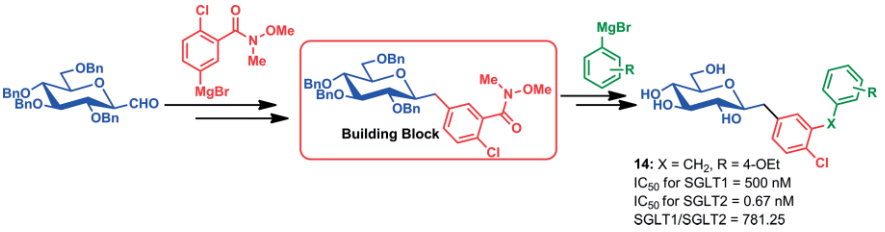
Synthesis of Benzyl *C*-Analogues of Dapagliflozin as Potential SGLT2 Inhibitors



A convenient synthetic strategy has been developed for the synthesis of C-benzyl analogues of dapagliflozin. The In vitro sodium-glucose co-transporters (SGLT1 and SGLT2) inhibition activity of all new compounds exhibits - promising results, particularly, compound **14** emerged as the most potent SGLT2 inhibitor with the best selectivity for inhibition of SGLT2 (IC_{50}:0.64 nM) over SGLT1 (IC_{50}: 500 nM) as compare to Dapagliflozin.

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