Asian Journal of Chemistry; Vol. 38, No. 7 (2026), 1960-1966
ASIAN JOURNAL OF CHEMISTRY
https://doi.org/10.14233/ajchem.2026.36011

Simple and Selective Synthesis of Critical α-Anomer Impurity of SGLT2 Inhibitors: Empagliflozin, Dapagliflozin and Canagliflozin

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Received: 14 March 2026 *Accepted*: 25 June 2026 *Published online*: 3 July 2026 AJC-224121

The present study focuses on the selective synthesis of α-anomer impurities in SGLT2 inhibitors, namely empagliflozin, dapagliflozin and canagliflozin. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are very important medication used for the treatment of type 2 diabetes. However, their safety profiles and therapeutic efficacy may be impacted by the existence of isomeric impurities. Herein, a simple and effective synthetic method is given to obtain these crucial α-anomers using aryl halides with C1-glycosyl halides using zinc powder, nickel(II) chloride hexahydrate and 4,4′-dimethoxy-2,2′-bipyridine in good yields. The obtained results serve as a foundation for standardizing quality control procedures and highlight the significance of thorough impurity profiling in pharmaceutical development. In addition to improving knowledge of SGLT2 inhibitors, this work advances the larger endeavor of guaranteeing patient safety through strict pharmaceutical procedures.

Keywords: SGLT2 inhibitors, Empagliflozin, Dapagliflozin, Canagliflozin, α-Anomer, Pharmaceutical impurities, Quality control.

INTRODUCTION

Empagliflozin, dapagliflozin and canagliflozin (Fig. 1) are important class of sodium-glucose cotransporter-2 (SGLT2) and widely used for the treatment of Type 2 diabetes. Several reports are present in the literature for the synthesis of β-anomer which is the API candidate [1,2]. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder disease, characterised by persistent metabolic dysregulation. It is caused by insufficient insulin secretion and insulin resistance, leading to impaired glucose intake and utilisation. Recent epidemiological data show that the incidence of T2DM has risen sharply. It is estimated that by 2030, the increase in T2DM individuals will increases up to 439 million [3-5]. Sodium-dependent glucose cotransporter (SGLT) has emerged as a novel target for the treatment of type 2 diabetes in recent decades [6-8].

Up to 90% of renal glucose reabsorption is attributed to SGLT2 [9-11]. Inhibition of SGLT2 can reduce blood sugar levels by promoting excessive excretion of glucose in urine. Due to its new mechanism of action and fewer side effects, SGLT2 is considered as a promising target for treating T2DM.

Empagliflozin, dapagliflozin and canagliflozin are β-C-aryl glucosides, showing a carbon-carbon bond between the anomeric position of a glucose moiety and an aromatic ring system [12]. Owing to the potent and selective biological activity of the β-anomer, achieving selective β-C-glycosidic bond formation is a key challenge in synthetic carbohydrate chemistry [13]. But during the synthesis of β-C-glycosidic bond formation of α-C-glycosidic bond formation was also observed due to the rapid reaction conditions. Despite the structural similarity between α- and β-C-aryl glucosides, their biological and pharmacological activities differ considerably. Therefore, minimizing the formation of the α-C-aryl glucoside as a process-related impurity is crucial to maintain the desired drug potency [14,15].

Several synthetic methods were reported in the literature, which suffer with poor selectivity, lengthy reaction sequences and low yields [16,17]. On the other hand, few of the methods selectively reported β-C-aryl glucosides while the

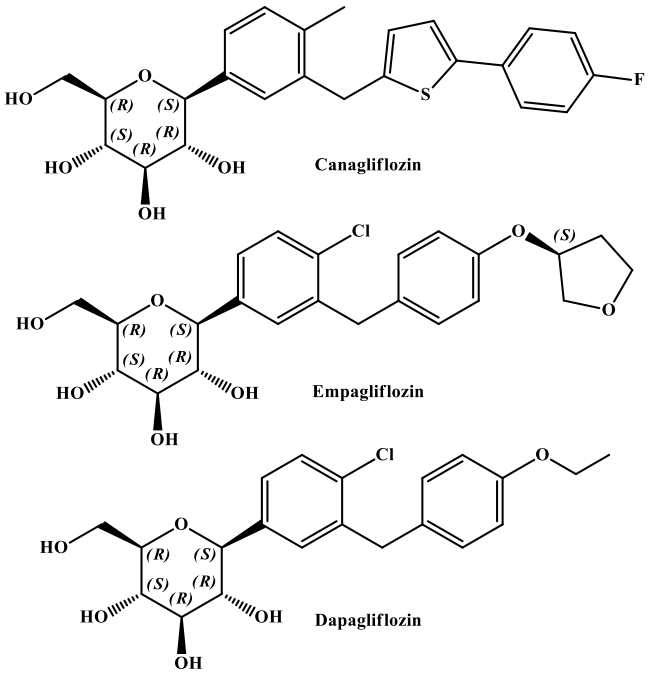


Fig. 1. Structures of empagliflozin, dapagliflozin and canagliflozin

selective synthesis of the α-anomers remains challenging. Based on our group's interest in the synthesis of process-related impurities, which are indispensable for pharmaceutical development and regulatory compliance [18-23], herein, a practical zinc- and nickel-catalyzed strategy for the selective synthesis of the α-anomeric impurities of empagliflozin, dapagliflozin and canagliflozin is reported (Fig. 2). This protocol features mild reaction conditions, inexpensive and readily available catalysts and reagents, and affords the corresponding α-C-aryl glucosides in good yields with excellent α-selectivity.

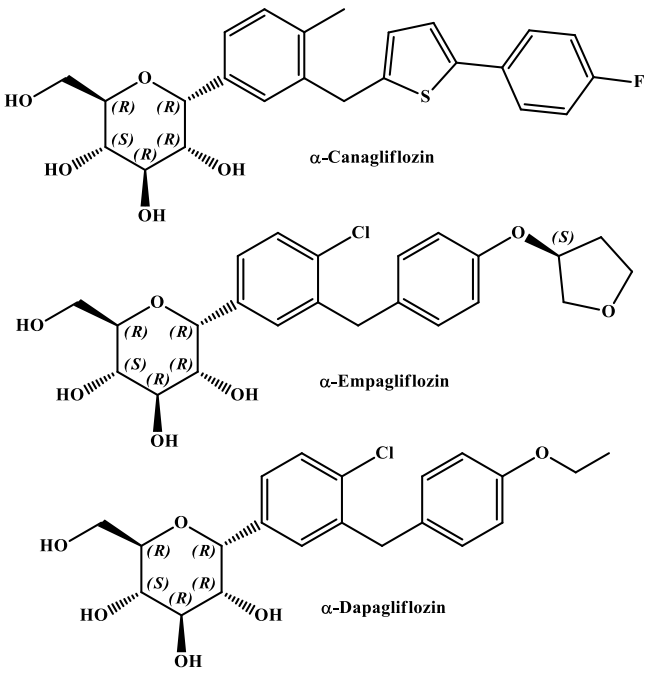


Fig. 2. Structures of α-anomers of empagliflozin, dapagliflozin and canagliflozin

This study demonstrates the broad applicability of a single synthetic method across diverse SGLT2 inhibitors, fulfilling a critical need in pharmaceutical research and quality control. By delivering increased yields, successful gram-scale synthesis and the first effective generation of α-anomer impurity reference standards, this work offers immediate practical advancements for the field. All the synthesised compounds were analysed by ^{1}H NMR, ^{13}C NMR, mass analysis. These compounds serve as essential reference standards for pharmaceutical quality control and regulatory compliance.

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without further purification. ^{1}H NMR spectra were recorded in DMSO-d_6 at room temperature on a Varian Mercury spectrometer plus 400 MHz using TMS as an internal standard. ^{13}C NMR spectra were obtained from a Varian Mercury plus 100 MHz spectrometer in DMSO-d_6 at room temperature. The optimized chromatographic conditions described in the HPLC section provided excellent chromatographic separation of empagliflozin, dapagliflozin, canagliflozin, and their related impurities.. TLC analyses were performed on Merck silica gel 60F_{254} plates.

The α:β ratios reported in the manuscript were determined primarily by ^{1}H NMR spectroscopy through integration of the characteristic anomeric proton signals corresponding to the α- and β-anomers. The stereochemical assignments were further supported by the observed coupling constants (*J* values) of the anomeric protons and comparison with reference standards. In addition, the identity and purity of the isolated compounds were confirmed by HPLC, ^{1}H & ^{13}C NMR, IR and mass spectrometry analyses. To avoid ambiguity, the experimental section has been revised to explicitly state the method used for determination of the α:β ratios and the analytical techniques employed for compound characterisation.

Experimental procedure for the synthesis of α-anomer of canagliflozin

General procedure for nickel-catalysed coupling reaction between aryl halide and tetraacetyl glycosyl bromide: A stirred mixture of aryl halide (13.0 g, 0.0359 mol) and tetraacetyl glycosyl bromide (14.79 g, 0.0359 mol) was treated with zinc powder (8.70 g, 0.1331 mol), nickel(II) chloride hexahydrate (1.71 g, 0.0071 mol), 4,4′-dimethoxy-2,2′-bipyridine (2.33 g, 0.0108 mol) and magnesium chloride (6.51 g, 0.0683 mol) under a nitrogen atmosphere. The reaction vessel was evacuated and backfilled with nitrogen three times to ensure an inert environment. The reaction mixture was cooled to 10-15 ºC. N,N-Dimethylacetamide (DMAc, 260 mL, 20 vol) was added slowly under stirring while maintaining the internal temperature below 15 ºC. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 14-16 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was quenched into ice-cold water (1000 mL) and diluted with ethyl acetate. The resulting suspension was filtered through Celite pad to remove insoluble inorganic salts and then the pad was washed thoroughly with ethyl acetate. The aqueous phase was extrac-

ted with ethyl acetate (3 × 500 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 21 g of crude product. The crude residue was purified by column chromatography over silica gel (100-200 mesh) using 11-12% ethyl acetate in hexane as eluent to afford 12.6 g of desired compound **10** as a pale green gummy solid.

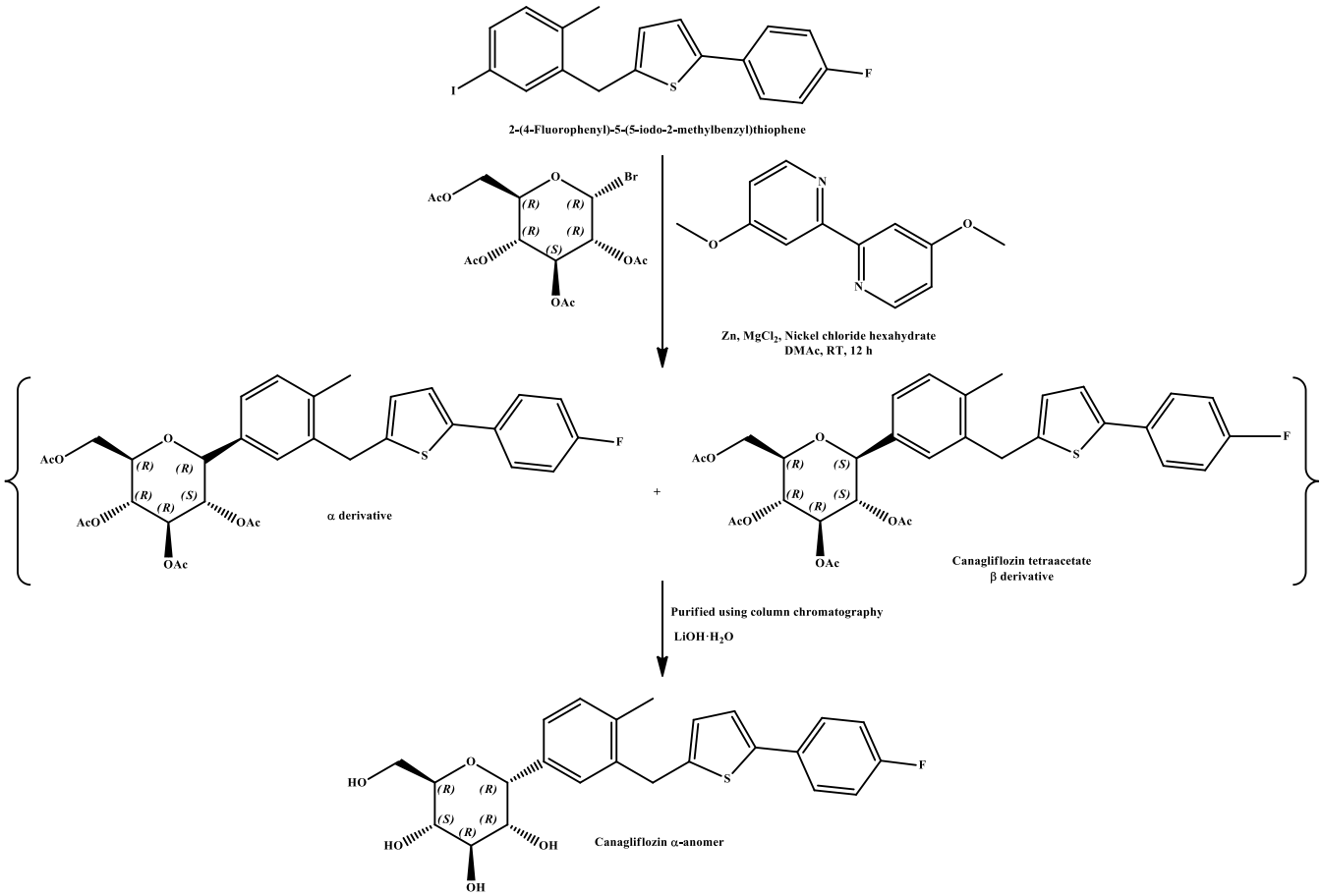
Tetraacetyl α-anomer of empagliflozin: Pale brown gummy solid, yield: 71.8%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.36-7.37 (m, 3H), 7.10-7.12 (d, *J* = 8.4 Hz, 2H), 6.77-6.79 (d, *J* = 8.0 Hz, 2H), 5.44-5.46 (t, 1H), 5.25-5.29 (m, 2H), 5.05-5.09 (t, 1H), 4.88 (br, 1H), 4.25-4.28 (m, 2H), 3.88-4.10 (m, 7H), 3.72 (m, 1H), 2.13-2.17 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.89 (s, 3H); MS [ES+]: *m/z* 641.26 [M + Na]$^+$; Exact mass: Calculated ($C_{31}H_{35}ClO_{11}$) 618.19; HPLC purity: 96.30%.

Tetraacetyl α-anomer of canagliflozin: Pale green gummy solid, yield: 64.6%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.40-7.48 (m, 4H), 7.19-7.21 (d, *J* = 8.0 Hz, 1H), 7.00-7.04 (m, 3H), 6.68-6.69 (d, *J* = 4.0 Hz, 1H), 5.59 (m, 1H), 5.30-5.34 (m, 2H), 5.08-5.13 (t, 1H), 4.23-4.27 (dd, *J* = 5.2 Hz, 1H), 4.13-4.14 (d, 2H), 4.03-4.07 (dd, *J* = 3.2 Hz, 1H), 3.73 (m, 1H), 2.29 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H) and 1.94 (s, 3H); MS [ES+]: *m/z* 613.28 [M + H]$^+$ & 635.28 [M + Na]$^+$; Exact mass: Calculated ($C_{32}H_{33}FO_9S$) 612.18; HPLC purity: 97.09%.

Tetraacetyl α-anomer of dapagliflozin: Pale yellow gummy solid, yield: 71.7%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.36-7.37 (m, 3H), 7.09-7.11 (dd, *J* = 2.0 Hz, 2H), 6.80-6.82 (dd, *J* = 2.0 Hz, 2H), 5.43-5.47 (m, 1H), 5.23-5.28 (m, 2H), 5.05-5.09 (m, 1H), 4.24-4.29 (dd, *J* = 5.2 Hz, 1H), 3.96-4.11 (m, 5H), 3.70-3.74 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.88 (s, 3H) and 1.37-1.40 (t, 3H); MS [ES$^+$]: *m/z* 577.66 [M + H]$^+$ and 599.70 [M + Na]$^+$; Exact mass: Calculated ($C_{29}H_{33}ClO_{10}$) 576.18; HPLC purity: 92.30%.

General procedure for deprotection to get α-anomer: To a stirred solution of compound **10** (12.0 g, 0.0192 mol) in THF (120 mL, 10 vol) and methanol (60 mL, 5 vol) at room temperature was added dropwise an aqueous solution of LiOH (6.54 g, 0.156 mol) in water (28 mL, 5 vol.) at 10-15 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 12-14 h. The progress of the reaction was monitored by TLC and MS analysis. After completion of the reaction, the solvents were removed under reduced pressure. The resulting residue was diluted with water (200 mL) and the pH was adjusted to 6 using aqueous citric acid solution at 10-15 ºC. The suspension was stirred for 10 min and the precipitated solid was collected by filtration. The solid was washed with water (50 mL) followed by hexane (60 mL) and dried under vacuum to afford the product compound **5** as an off-white solid (7.2 g).

To optimize the reaction conditions, 2-(4-fluorophenyl)-5-(5-iodo-2-methylbenzyl)thiophene, a key intermediate of canagliflozin, was selected as the model substrate (**Scheme-I**). Tetraacetyl glycosyl bromide served as the glycosyl donor



Scheme-I: Synthesis of α-anomer of canagliflozin

and various reaction parameters were systematically investigated to maximize the yield and α-selectivity of the desired canagliflozin impurity. The optimization results are shown in Table-1.

α-Anomer of empagliflozin: Off-white solid, yield: 75.8%; IR (KBr, ν_{max}, cm^{-1}): 3317, 1236, 848; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.58-7.58 (d, 1H), 7.52-7.54 (dd, *J* = 1.6 Hz, 1H), 7.34-7.36 (d, *J* = 8.0 Hz, 1H), 7.09-7.11 (d, 2H), 6.81-6.83 (dd, 2H), 5.20 (br, 1H), 5.11 (br, 1H), 4.94-4.97 (br, 2H), 4.87-4.88 (d, *J* = 4.0 Hz, 1H), 4.51 (t, 1H), 3.96 (s, 2H), 3.64-3.87 (m, 5H), 3.53 (br, 3H), 3.25-3.26 (m, 2H), 2.15-2.20 (m, 1H) and 1.91-1.94 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 155.47, 138.92, 137.86, 131.55, 131.28, 130.92, 129.64, 128.56, 127.68, 115.17, 76.92, 76.52, 72.78, 72.65, 72.51, 72.27, 70.20, 66.37, 60.71, 37.76, 32.42; MS [ES$^+$]: *m/z* 473.35 $[M + Na]^+$; Exact mass: Calculated ($C_{23}H_{27}ClO_7$) 450.14; HPLC purity: 97.64%. $[\alpha]_D^{20}$ = +18º to +25º (C = 1% in MeOH).

α-Anomer of canagliflozin: Off-white solid, yield: 72.8%; ; IR (KBr, ν_{max}, cm^{-1}): 3394, 1507, 1229, 1022; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.57-7.60 (m, 2H), 7.51 (s, 1H), 7.45-7.47 (d, *J* = 8.0 Hz, 1H),7.27-7.28 (d, *J* = 4.0 Hz, 1H), 7.17-7.22 (m, 2H), 7.10-7.12 (d, *J* = 8.0 Hz, 1H), 6.79-6.80 (d, *J* = 4.0 Hz, 1H), 5.17-5.18 (d, 1H), 5.06-5.07 (d, 1H), 4.91-4.92 (d, *J* = 4.0 Hz,1H), 4.88-4.89 (d, 1H), 4.47-4.49 (t, 1H), 4.10 (s, 2H), 3.59-3.69 (m, 2H), 3.50-3.54 (m, 2H), 3.21-3.29 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 162.60, 160.18, 143.73, 137.60, 137.26, 134.19, 130.57, 129.66, 129.24, 126.99, 126.91, 126.65, 126.31, 123.42, 116.01, 115.80, 75.94, 73.51, 72.89, 72.75, 70.44, 60.85, 33.61, 18.69; MS [ES$^+$]: *m/z* 467.37 $[M + Na]^+$; Exact mass: Calculated ($C_{24}H_{25}FO_5S$) 444.14; HPLC purity: 98.98%. $[\alpha]_D^{20}$ = +45º to +48º (C = 1% in MeOH).

α-Anomer of dapagliflozin: Off-white solid, yield: 78%; IR (KBr, ν_{max}, cm^{-1}): 3396, 1244, 840; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.57 (brs, 1H), 7.52-7.54 (dd, 1H), 7.34-7.36 (d, *J* = 8.0 Hz, 1H), 7.08-7.10 (d, 2H), 6.81-6.83 (d, 2H), 5.22-5.23 (d, 1H), 5.11-5.12 (d, 1H), 4.95-4.96 (d, *J* = 4.0 Hz, 1H), 4.87-4.88 (d, 1H), 4.52-4.55 (t, 1H), 3.93-3.99 (m, 4H), 3.53-3.67 (m, 4H), 3.16-3.29 (m, 2H), 1.23-1.31 (t, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 156.89, 138.90, 137.98, 131.30, 131.21, 130.92, 129.56, 128.58, 127.69, 114.28, 76.51, 72.82, 72.53, 70.22, 62.87, 60.72, 37.82, 14.69; MS [ES$^+$]: *m/z* 431.33 $[M + Na]^+$; Exact mass: Calculated ($C_{21}H_{25}ClO_6$) 408.13; HPLC purity: 99.58%. $[\alpha]_D^{20}$ = +22º to +28º (C= 1% in MeOH).

RESULTS AND DISCUSSION

A nickel-catalyzed reductive coupling strategy was employed for the stereoselective synthesis of α-C-aryl glucosides through coupling of aryl halides with tetraacetyl glycosyl bromides at the C1 position. The observed α-selectivity is attributed to the use of O-acetyl-protected glucosyl bromides, where the participating C2-acetyl group facilitates an SN^2-like displacement, preferentially leading to the formation of the α-anomer [24,25].

As shown in Table-1, both the product yield and α/β selectivity were strongly influenced by the catalyst loading. Increasing the loading of $NiCl_2{\cdot}6H_2O$ from 10 to 20 mol% (entries 1-3) significantly improved the α-selectivity. A slight enhancement in both yield and selectivity was further achieved by increasing the amount of zinc (entry 4). Solvent screening demonstrated that DMAc was superior to the other solvents examined, affording the highest yield and selectivity (entries 4-6). Increasing the reaction temperature from 60 to 80 ºC (entries 6-7) enhanced the yield (45-78%) and α/β-selectivity (3:1 to 8:1). However, temperatures above 80 ºC decreased the yield due to decomposition of the glycosylated product (entry 8).

Under the optimized conditions (entry 7), the α-anomer was readily isolated from the β-isomer by simple column chromatography. The α/β ratio was determined by both ^{1}H NMR spectroscopy and HPLC analysis. A plausible reaction mechanism involves the *in situ* reduction of $NiCl_2$ to Ni(0) by zinc, followed by oxidative addition of the aryl halide to the nickel center. Subsequent transmetalation with the glycosyl bromide and reductive elimination furnish the desired C-aryl glucoside through C–C bond formation. Moreover, the optimized protocol was successfully extended to the synthesis of α-anomeric impurities of other SGLT2 inhibitors. The α-anomer of empagliflozin was obtained in 78% yield, while the corresponding dapagliflozin analogue was isolated in 70% yield, demonstrating the general applicability of the methodology.

The α-configuration of the synthesized compounds was confirmed by NMR spectroscopy. In canagliflozin, the anomeric proton (H-1) of the α-anomer appeared as a doublet at δ 4.91-4.92 ppm with a coupling constant of *J* = 4.0 Hz, characteristic of the axial-equatorial relationship between H-1 and H-2 in α-D-glucopyranosides. In contrast, the β-anomer exhibited a doublet at δ 3.95-3.98 ppm with a larger coupling constant of *J* = 8.0 Hz, consistent with a diaxial arrangement.

TABLE-1
OPTIMISATION OF REACTION CONDITIONS

Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Reductant (equiv.)	Temp. (ºC)	Yield (%)	α:β ratio
1	$NiCl_2{\cdot}6H_2O$ (10)	dmbipy (20)	DMF	Zn (3.0)	60	45	3:1
2	$NiCl_2{\cdot}6H_2O$ (15)	dmbipy (30)	DMF	Zn (3.0)	60	58	4:1
3	$NiCl_2{\cdot}6H_2O$ (20)	dmbipy (40)	DMF	Zn (3.0)	60	72	6:1
4	$NiCl_2{\cdot}6H_2O$ (20)	dmbipy (40)	DMAc	Zn (4.0)	60	74	7:1
5	$NiCl_2{\cdot}6H_2O$ (20)	dmbipy (40)	DMF	Zn (4.0)	60	68	6:1
6	$NiCl_2{\cdot}6H_2O$ (20)	dmbipy (40)	NMP	Zn (4.0)	60	62	5:1
7	$NiCl_2{\cdot}6H_2O$ (20)	dmbipy (40)	DMAc	Zn (4.0)	80	78	8:1
8	$NiCl_2{\cdot}6H_2O$ (20)	dmbipy (40)	DMF	Zn (4.0)	100	65	7:1

The ^{13}C NMR spectrum provided additional confirmation, with the anomeric carbon (C-1) resonating at δ 73-75 ppm for the α-anomers compared with δ 78-80 ppm for the corresponding β-anomers. Similar spectral characteristics were observed for the α-anomers of empagliflozin and dapagliflozin, confirming their stereochemical assignments. For ease of comparison, the ^{1}H and ^{13}C NMR data of all synthesized compounds are compiled in Tables 2-4.

Conclusion

In this study, a simple, efficient and stereoselective method is successfully accomplished for the synthesis of the α-ano-

TABLE-2
^{1}H NMR AND ^{13}C NMR CHEMICAL SHIFT VALUES OF CANAGLIFLOZIN AND CANAGLIFLOZIN α-ANOMER

Position number	^{1}H NMR chemical shifts		^{13}C NMR chemical shifts	
	Canagliflozin	Canagliflozin α-anomer	Canagliflozin	Canagliflozin α-anomer
1	2.26 (s, 3H)	2.33 (s, 3H)	18.81 (CH3)	18.69 (CH_3)
2	–	–	137.37 (C)	137.26 (C)
3	–	–	129.66 (C)	129.66 (C)
4	4.07-4.17 (m, 2H)	4.10 (s, 2H)	33.45 (CH_2)	33.61 (CH_2)
5	-		143.63 (C)	143.73 (C)
6	6.79-6.80 (d, *J* = 4.0 Hz, 1H)	6.79-6.80 (d, *J* = 4.0 Hz, 1H)	126.25 (CH)	126.31 (CH)
7	7.27-7.28 (d, *J* = 4.0 Hz, 1H)	7.27-7.28 (d, *J* = 4.0 Hz, 1H)	126.36 (CH)	126.65 (CH)
8	–	–	138.23 (C)	137.60 (C)
9	–	–	126.99 (C)	126.99 (C)
10	7.57-7.61 (m, 1H)	7.57-7.60 (m, 1H)	126.91 (CH)	126.91 (CH)
11	7.11-7.22 (m, 1H)	7.45-7.47 (d, 1H)	115.77 (CH)	115.80 (CH)
12	–	–	160.16 & 162.59 (CF)	160.18 & 162.60 (CF)
13	–	–	–	–
14	7.11-7.22 (m, 1H)	7.51 (brs, 1H)	115.99 (CH)	116.01 (CH)
15	7.57-7.61 (m, 1H)	7.57-7.60 (m, 1H)	129.07 (CH)	129.24 (CH)
16	–	–	–	–
17	7.11-7.22 (m, 1H)	7.10-7.12 (d, *J* = 8.0 Hz, 1H)	134.94 (CH)	134.19 (CH)
18	–	–	140.23 (C)	140.24 (C)
19	3.96-3.98 (d, *J* = 8.0 Hz, 1H)	4.91-4.92 (d, *J* = 4.0 Hz, 1H)	78.49 (OCH)	72.89 (OCH)
20	3.69-3.71 (m, 1H)	3.50-3.69 (m, 1H)	70.43 (OCH)	70.44 (OCH)
21	4.89 (br, 1H)	5.17-5.18 (d, 1H)	–	–
22	3.14-3.34 (m, 1H)	3.21-3.34 (m, 1H)	81.21 (OCH)	73.51 (OCH)
23	4.89 (br, 1H)	5.06-5.07 (d, 1H)	–	–
24	3.14-3.34 (m, 1H)	3.21-3.34 (m, 1H)	74.69 (OCH)	72.75 (OCH)
25	4.89 (br, 1H)	4.88-4.89 (d, 1H)	–	–
26	3.42-3.46 (dd, 1H)	3.50-3.69 (m, 1H)	81.33 (OCH)	75.94 (OCH)
27	3.14-3.34 (m, 2H)	3.50-3.69 (m, 2H)	61.44 (OCH_2)	60.85 (OCH_2)
28	4.43 (br, 1H)	4.47-4.49 (t, 1H)	–	–
29	–	–	–	–
30	7.11-7.22 (m, 1H)	7.17-7.22 (m, 1H)	123.39 (CH)	123.42 (CH)
31	7.11-7.22 (m, 1H)	7.10-7.12 (d, *J* = 8.0 Hz, 1H)	130.51 (CH)	130.57 (CH)

TABLE-3
^{1}H NMR AND ^{13}C NMR CHEMICAL SHIFT VALUES OF EMPAGLIFLOZIN AND EMPAGLIFLOZIN α-ANOMER

Position number	^{1}H NMR chemical shifts		^{13}C NMR chemical shifts	
	Empagliflozin	Empagliflozin α-anomer	Empagliflozin	Empagliflozin α-anomer
1	3.94-4.03 (m, 1H)	4.87-4.88 (d, *J* = 4.0 Hz, 1H)	74.72 (OCH)	72.51 (OCH)
2	3.68-3.88 (m, 1H)	3.53-3.87 (m, 1H)	72.31 (OCH)	72.27 (OCH)
3	3.68-3.88 (m, 1H)	3.25-3.31 (m, 1H)	76.94 (OCH)	72.65 (OCH)
4	3.41-3.47 (m, 1H)	3.25-3.31 (m, 1H)	70.29 (OCH)	70.20 (OCH)
5	3.68-3.88 (m, 1H)	3.53-3.87 (m, 1H)	81.24 (OCH)	76.92 (OCH)
6	–	–	–	–
7	4.80-4.82 (d, 1H)	4.94-4.97 (br, 1H)	–	–
8	4.92-4.97 (m, 1H)	5.11 (brs, 1H)	–	–
9	3.08-3.31 (m, 2H)	3.53-3.87 (m, 2H)	61.36 (OCH_2)	60.71 (OCH_2)
10	4.41-4.44 (t, 1H)	4.51 (t, 1H)	–	–
11	–	–	137.76 (C)	137.86 (C)
12	7.33-7.34 (d, *J* = 4.0 Hz, 1H)	7.52-7.54 (dd, *J* = 1.6 Hz, 1H)	130.85 (CH)	130.92 (CH)
13	–	–	139.72 (C)	138.92 (C)

14	–	–	131.94 (C)	131.55 (C)
15	7.36-7.38 (d, *J* = 8.0 Hz, 1H)	7.58-7.58 (d, *J* = 1.6 Hz, 1H)	129.69 (CH)	129.64 (CH)
16	7.22-7.24 (d, *J* = 8.0 Hz, 1H)	7.34-7.36 (d, *J* = 8.0 Hz, 1H)	127.42 (CH)	127.68 (CH)
17	3.94-4.03 (m, 1H)	3.96 (s, 2H)	37.64 (CH_2)	37.76 (CH_2)
18	–	–	131.58 (C)	131.28 (C)
19	7.10-7.12 (d, 1H)	7.09-7.11 (d, 1H)	128.70 (CH)	128.56 (CH)
20	6.82-6.84 (d, 1H)	6.81-6.83 (dd, 1H)	115.17 (CH)	115.17 (CH)
21	–	–	155.49 (CO)	155.47 (CO)
22	6.82-6.84 (d, 1H)	6.81-6.83 (dd, 1H)	115.17 (CH)	115.17 (CH)
23	7.10-7.12 (d, 1H)	7.09-7.11 (d, 1H)	128.70 (CH)	128.56 (CH)
24	–	–	–	–
25	–	–	–	–
26	3.68-3.88 (m, 1H)	3.53-3.87 (m, 2H)	78.31 (OCH_2)	72.78 (OCH_2)
27	4.92-4.97 (m, 1H)	4.94-4.97 (br, 1H)	80.70 (OCH)	76.52 (OCH)
28	1.91-2.21 (m, 2H)	1.91-2.20 (m, 2H)	32.46 (CH_2)	32.42 (CH_2)
29	3.08-3.31 (m, 2H)	3.53-3.87 (m, 2H)	66.42 (OCH_2)	66.37 (OCH_2)
30	–	–	–	–
31	4.92-4.97 (m, 1H)	5.20 (brs, 1H)	–	–

TABLE-4
^{1}H NMR AND ^{13}C NMR CHEMICAL SHIFT VALUES OF DAPAGLIFLOZIN AND DAPAGLIFLOZIN α-ANOMER

Position number	^{1}H NMR chemical shifts		^{13}C NMR chemical shifts	
	Dapagliflozin	Dapagliflozin α-anomer	Dapagliflozin	Dapagliflozin α-anomer
1	3.92-4.02 (m, 1H)	4.95-4.96 (d, *J* = 4.0 Hz, 1H)	78.29 (OCH)	72.68 (OCH)
2	3.07-3.26 (m, 1H)	3.17-3.29 (m, 1H)	70.28 (OCH)	70.22 (OCH)
3	3.07-3.26 (m, 1H)	3.17-3.29 (m, 1H)	80.69 (OCH)	72.82 (OCH)
4	3.07-3.26 (m, 1H)	3.53-3.67 (m, 1H)	74.69 (OCH)	72.53 (OCH)
5	3.07-3.26 (m, 1H)	3.53-3.67 (m, 1H)	81.20 (OCH)	76.51 (OCH)
6	–	–	–	–
7	4.92-4.94 (d, 1H)	5.22-5.23 (d, 1H)	–	–
8	4.81-4.82 (d, 1H)	4.87-4.88 (d, 1H)	–	–
9	3.40-3.71 (m, 2H)	3.53-3.67 (m, 2H)	61.34 (OCH_2)	60.72 (OCH_2)
10	4.41-4.44 (t, 1H)	4.52-4.55 (t, 1H)	–	–
11	–	–	137.79 (C)	137.98 (C)
12	7.315-7.319 (d, *J* = 1.6 Hz, 1H)	7.52-7.54 (dd, 1H)	130.79 (CH)	130.92 (CH)
13	–	–	139.67 (C)	138.90 (C)
14	–	–	131.20 (C-Cl)	131.21 (C-Cl)
15	7.35-7.37 (d, *J* = 8.4 Hz, 1H)	7.57 (br, 1H)	129.55 (CH)	129.56 (CH)
16	7.21-7.23 (dd, *J* = 2.0 Hz, 1H)	7.34-7.36 (d, *J* = 8.0 Hz, 1H)	127.34 (CH)	127.69 (CH)
17	3.92-4.02 (m, 2H)	3.93-3.99 (m, 2H)	37.64 (CH_2)	37.82 (CH_2)
18	–	–	131.90 (C)	131.30 (C)
19	–	–	–	–
20	6.81-6.83 (d, 1H)	6.81-6.83 (d, 1H)	114.27 (CH)	114.28 (CH)
21	–	–	156.88 (OC)	156.89 (OC)
22	6.81-6.83 (d, 1H)	6.81-6.83 (d, 1H)	114.27 (CH)	114.28 (CH)
23	7.08-7.10 (d, 1H)	7.08-7.10 (d, 1H)	128.65 (CH)	128.58 (CH)
24	–	–	–	–
25	7.08-7.10 (d, 1H)	7.08-7.10 (d, 1H)	128.65 (CH)	128.58 (CH)
26	4.92-4.94 (d, 1H)	5.11-5.12 (d, 1H)	–	–
27	3.92-4.02 (m, 2H)	3.93-3.99 (m, 2H)	62.87 (OCH_2)	62.87 (OCH_2)
28	1.27-1.31 (t, 3H)	1.27-1.31 (t, 3H)	14.68 (CH_3)	14.69 (CH_3)

meric impurities of the clinically important SGLT2 inhibitors empagliflozin, canagliflozin and dapagliflozin. The methodology is based on a $NiCl_2$-catalyzed reductive coupling of aryl halides with tetraacetyl glycosyl bromide, affording the desired α-C-aryl glucosides in good to excellent yields with high anomeric selectivity. The protocol employs safe, mild reaction conditions and readily available, cost-effective reagents, making it suitable for laboratory and process-scale applications. The synthesized α-anomers were fully characterised by ^{1}H NMR, ^{13}C NMR, HRMS and HPLC analyses, confirming their structures and stereochemistry. These well-characterised compounds can serve as valuable reference standards for impurity profiling, analytical method development and quality control in the pharmaceutical industry.

ACKNOWLEDGEMENTS

The authors are thankful to SVAK Life Sciences and KL University for supporting this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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