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AN EFFICIENT SYNTHESIS FOR EMPAGLIFLOZIN (AN INHIBITOR OF SGLT-2)

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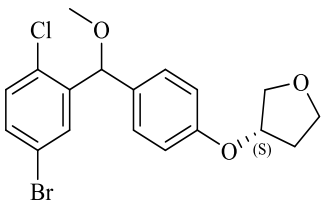
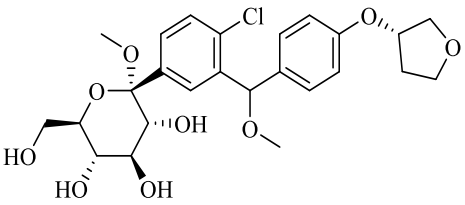
ABSTRACT

Empagliflozin (5) is a promising candidate in SGLT2 inhibitors. An efficient synthetic process consisting usage of two novel intermediates namely [(5-Bromo-2-chlorophenyl) {4-[(3S)-tetrahydrofuran-3-yloxy] phenyl} methyl [Compound **9**] and 1-*C*-[4-chloro-3-(methoxy{4-[(3*S*)-tetrahydrofuran-3-yloxy]phenyl} methyl) phenyl]- α -D-glucopyranose [Compound **12**] has been developed to produce compound 5**.** This manuscript describes the comprehensive experimentation of this innovative and scale-up with ease synthetic route.



Compound 9



Compound 12

INTRODUCTION

Empagliflozin belongs to a class of Pyranosyl-oxy-substituted benzene derivatives and has an enhanced inhibitory effect on SGLT2 in vitro and in vivo, while having improved pharmacological or pharmacokinetic properties when compared with other type-2 diabetic medications. Sodium glucose cotransporters (SGLTs) have recently attracted considerable attention as new drug targets for the treatment of diabetes[1] SGLT2 could provide a well-tolerated and highly effective method of glycemic control.[2] A lot of different compounds

have been reported as SGLT2 inhibitors.[3–6] They are generally divided into two classes, O-glucosides and C-glucosides. Sergliflozin[7] (1) and Remogliflozin[8] (2) are representatives of the O-glucosides, Dapagliflozin[9] (3) Canagliflozin[10] (4) and Empagliflozin (5) are the representatives of O-glucosides.

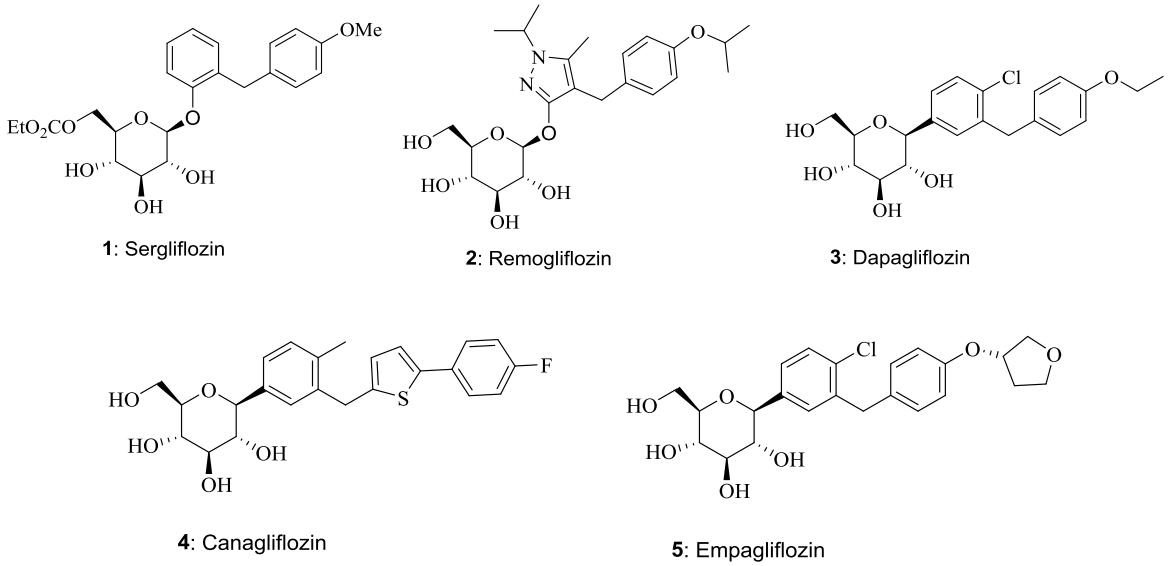
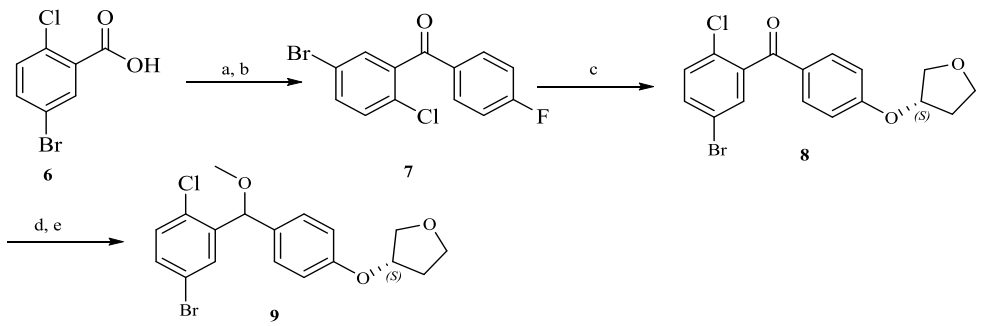


Figure 1: Selected examples of SCGLT2 inhibitors.

Chemistry

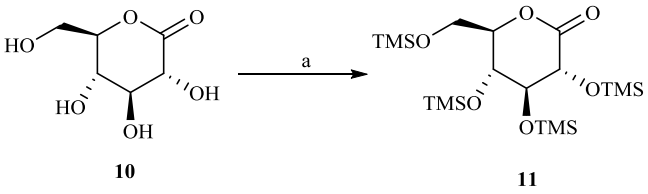
Synthesis of novel intermediate i.e. (5-Bromo-2-chlorophenyl)-{4-[3S)-tetrahydrofuran-3-yloxy] phenyl}methyl (**9**) methyl was carried out as depicted in Scheme-1. This synthetic scheme consists, reaction of 5-Bromo-2-chlorobenzoic acid (**6**) with oxalyl chloride using dichloromethane as solvent to afford 5-Bromo-2-chlorobenzoic acid chloride, which on reaction with fluorobenzene by means of Friedel-Crafts reaction produces compound (**7**). Thereafter, aromatic substitution of compound (**7**) with (S)-(+)-3-Hydroxytetrahydrofuran in presence of potassium tert. butoxide yields compound (**8**). Finally, reduction of keto group present in **8**, using sodium borohydride in methanol provides corresponding hydroxy compound which on methoxylation with methane sulfonic acid yields compound (**9**).



[a]Reagents: (a) $(COCl)_2$, DMF, CH_2Cl_2; (b) Fluorobenzene, $AlCl_3$, CH_2Cl_2; (c) t-BuOK, THF, (S)-tetrahydrofuran-3-ol; (d) $NaBH_4$, MeOH; (e) CH_3SO_3H, MeOH ,

Scheme 1: Synthesis of Compound 9[a].

Scheme-2 comprises of synthetic scheme for the preparation of Persilylated gluconolactone (**11**). D-Glucono-1,5-lactone (**10**), on reaction with Trimethylsilyl chloride in presence of N-Methylmorpholine produces Persilylated gluconolactone (**11**).

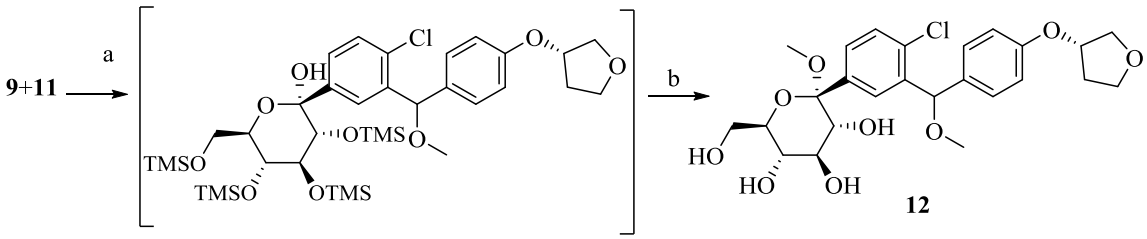


10 **11**

[a] Regents: (a) NMM, TMSCl, THF

Scheme 2: Synthesis of Persilylated gluconolactone 11[a].

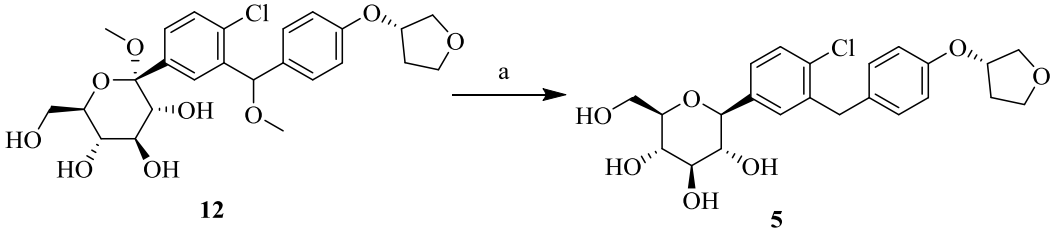
Scheme-3 comprises a synthetic scheme to produce compound 12. In presence of n-Butyllithium, compound (**9**) on reaction with Persilylated gluconolactone (**11**) yields protected coupled product, which further reacts with methane sulfonic acid in methanol to produce compound (**12**).



[a] Reagents: (a) n-BuLi, THF; (b) CH_3SO_3H, MeOH

Scheme 3: Synthesis of Compound 12[a].

Empagliflozin (**5**) were prepared, by following the synthetic route as depicted in Scheme- 4. Reduction of **12**, using aluminum chloride/ triethylsilane in acetonitrile/ dichloromethane produces Empagliflozin (**5**).



12

[a] Reagents: (a) $AlCl_3$, Et_3SiH, ACN, CH_2Cl_2, EtOAc, EtOH

Scheme 4: Synthesis of Empagliflozin 5[a].

Experimental section

All reactions were carried out under an argon or nitrogen atmosphere. All solvents and reagents were purchased from commercial sources without further drying. 1H NMR spectra were recorded on ***Bruker 300MHz Avance NMR spectrometer***. Chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane (δH 0.00) as an internal standard. Data are presented as follows: chemical shift (δ, ppm), integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). Mass spectra (MS) were measured ***Agilent 1100 Series LC-MSD-TRAP-SL system*** mass spectrometer.

Example 1: Preparation of compound 7

Under nitrogen atmosphere, oxalyl chloride (65.2 g, 0.51 moles) was added to a slurry of 5-bromo-2-chlorobenzoic acid (**6**, 100 g, 0.42 moles) and a catalytic amount of N, N-dimethylformamide (5 ml) in methylene dichloride (250 ml) slowly at 15-25ºC and stirring was continued at 21-25ºC. After completion of reaction, the reaction mass was concentrated to remove excess oxalyl chloride. Obtained residue was diluted with fluorobenzene (200 g) and cooled to 15-25ºC. Thereafter, aluminum chloride was added portion-wise (65.2 g, 0.48 moles), and keeping the reaction mass temperature below 25ºC. After reaction completion, reaction was quenched into precooled dilute hydrochloric acid at 5-25ºC. After 60 minutes of stirring at 20-25ºC, reaction mass was extracted with methylene chloride (once with 500 ml, then with 250 ml). The combined organic layer was washed with 10% aqueous sodium hydroxide solution (250 ml), water (350 ml), and 10% aqueous sodium chloride solution (350 ml) sequentially. Thereafter, organic layer was concentrated and obtained residue was treated with isopropyl alcohol to precipitate compound **7** as a white solid (110 g). 1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.81(dd, 2H), 7.59-7.55(dd, 2H), 7.50(d, 1H), 7.34(t, 1H), 7.16(d, 1H); m/z 313 (M+1).

Example 2: Preparation of compound 8

A solution of potassium tert-butoxide (53.6 g, 0.477 mole) in tetrahydrofuran (550 ml) was slowly added to a mixture of compound **7** (100 g, 0.32 mole) and (S)-tetrahydrofuran-3-ol (31.5m g, 0.351 mole) in tetrahydrofuran (260 ml) over a period of 90 minutes at 2-6°C. The reaction mass was maintained at 7-10ºC. After completion of the reaction, precooled water (5-18ºC, 285 ml) was added to quench the reaction. The reaction mass was extracted with toluene (once with 285 ml, then with 145 ml) to the reaction mixture at 20-25ºC. Thereafter,

the combined organic layer was washed with aqueous sodium chloride solution (10%, 290 ml) and concentrated under reduced pressure. Obtained residue was crystallized in isopropyl acetate (200 ml) to afford compound **8** as a solid (90 g). 1H NMR (300 MHz, $CDCl_3$) δ 7.77(d, 2H), 7.48(d, 1H), 7.56-7.52(dd, 1H), 7.33(d, 1H), 6.91(d, 2H), 5.03-5.00 (m, 1H), 4.06-3.98 (m, 4H), 2.33-2.12 (m, 2H); m/z 381 (M+1)

Example 3: Preparation of compound 9

Compound **8** (100 g) was added to methanol (800 ml). Sodium borohydride (14.9 g, 0.39 moles) was then added lot-wise at 20-25ºC. After completion of the reaction, methanol (600 ml) at 20-25ºC. Thereafter, methane sulfonic acid (100 g) diluted in methanol (40 ml) was added slowly and stirring was continued at 20-30ºC. After completion of reaction, the pH of reaction mass was adjusted to 7.3 with aqueous sodium bicarbonate solution. Afterward, the reaction mass was concentrated under reduced pressure while maintaining the temperature below 50ºC. Obtained residue was diluted with water (800 ml) and the product was extracted with toluene (2 x 500 ml). Obtained combined organic layer was washed with 10% aqueous sodium chloride, concentrated and crystallized in isopropyl alcohol and water to yield compound **9** (90 g). 1H NMR (300 MHz, DMSO-d6) δ 7.72(d, 1H), 7.53-7.51(dd, 1H), 7.39, 7.24(d, 1H), 6.89(d, 2H), 5.50(s, 1H), 4.89(t, 1H), 3.87-3.71(m, 4H), 3.26(s, 3H), 2.23-2.16(m, 1H), 1.95-1.90(m, 1H); m/z 367 (M-17+1)

Example 4: Preparation of compound 11

After cooling Compound **10** (100 g) and N-methylmorpholine (450 g) in 1000 ml of tetrahydrofuran to -5°C, 350 g of trimethylsilyl chloride was added dropwise and stirred the contents for 1 hr. at ambient temperature, 5h at 35°C and again 14 hrs. at ambient temperature. Thereafter, 1500 ml of toluene was added and cooled before charging 2500 ml of water. Organic phase was separated off and washed with aq. sodium dihydrogen phosphate solution (1500 ml) and water (1500 ml) sequentially. Thereafter, organic layer was concentrated to afford compound **11** as a liquid (250 g). 4.19-4.21(m, 1H), 4.02-4.05(m, 1H), 3.67-3.85(m, 4H), 0.09-0.15(m, 36H); m/z 467 (M+H)

Example 5: Preparation of compound 12

Under nitrogen atmosphere, to a mixture of Compound **9** (50g, 0.109 moles) in tetrahydrofuran (750 ml), 2, 3, 4, 6-tetrakis-O-(trimethylsilyl)-D-glucopyranone (**11**, 88 g, 0.188 moles) was added at 25-35ºC and cooled to -75 to -70ºC over a period of 30-60 minutes. n-butyllithium (1.6 M in hexane, 155 ml) was added over a period of 60-90 minutes

at same temperature and stirring was maintained until the reaction completed. After completion of the reaction, 10% aqueous ammonium chloride solution was added to the reaction mass over a period of 30 minutes at -70 to -30ºC. Thereafter, the reaction mixture was diluted with ethyl acetate (500 ml) and the temperature was raised to 25-35ºC. After separating organic layer, aqueous layer extracted with ethyl acetate (200 ml). Combined organic layer was washed with water (500 ml) and aqueous 10%w/v sodium chloride solution (500 ml) sequentially. Organic layer was concentrated under reduced pressure, maintaining the temperature below 40ºC to produce crude oil (120 g). Obtained residue was dissolved in methanol (1000 ml) and cooled to 0-5ºC. After adding, a solution of methane sulfonic acid (12 g, 0.125 moles) in methanol (240 ml) at 0-5ºC, reaction temperature was raised to 25-35ºC and stirred over night at the same temperature. Thereafter, a saturated sodium bicarbonate solution (150 ml) was added and reaction mass was concentrated under reduced pressure at below 45ºC. Obtained, residue was dissolved in methylene dichloride (625 ml) and washed with water (625 ml) and 10% aqueous sodium chloride solution (625 ml) sequentially. Organic layer was concentrated under reduced pressure at 40-45ºC and traces of methylene dichloride were distilled off using n-heptane (100 ml). To the obtained foamy mass, n-heptane (300 ml) was added, stirred and filtered to yield compound **12** as a solid (45 g).

1H NMR (300 MHz, DMSO-d6) δ 7.75-7.83(dd, 1H), 7.35-7.48(m, 2H), 7.18-7.27 (dd, 2H), 6.85(t, 2H), 5.50(m, 1H), 4.98-5.01(m, 2H), 4.78-4.91(m, 2H), 4.57-4.59(m, 1H), 3.69-3.89(m, 5H), 3.51-3.62(m, 1H), 3.42-3.38(m, 2H), 3.25(d, 3H), 3.17-3.20(m, 1H), 2.96(d, 3H), 2.85-2.91(m, 1H), 2.13-2.25(m, 1H), 1.90-1.93(m, 1H); m/z 528 ($M+NH_4$)

Example 6: Preparation of Empagliflozin of compound 5

Under dry nitrogen atmosphere, aluminum chloride (27.5 g) was added to dichloromethane (75 ml) at 25-35ºC and resulting suspension was cooled to 0-5ºC. Acetonitrile (100 ml) was added slowly to this mixture at 0-20ºC. Thereafter, triethylsilane (20.5 g) was added while maintaining the temperature at 0 to 5ºC. A solution of compound **12** (25 g) in a mixture of dichloromethane (175 ml) and acetonitrile (125 ml) was added slowly over a period of 30 minutes at 0-5ºC. Thereafter, the reaction temperature was raised to 20-25ºC and stirred at the same temperature until the reaction accomplished. After completion, the reaction mixture was again cooled to 0 to 5ºC and precooled water (150 ml) was added slowly to quench the reaction. Thereafter, the contents were concentrated under reduced pressure at temperature

below 45ºC. Obtained residue was slurried in water (150 ml) and recrystallized in ethanol to afford Empagliflozin (**5**) as a white solid. 1H NMR (300 MHz, DMSO-d6) δ 7.33-7.39(m, 1H), 7.33-7.39(m, 1H), 7.21-7.25(m, 1H), 7.11(d, 2H), 6.83(d, 2H), 4.94-4.98(m, 3H), 4.85(d, 1H), 4.47(d, 1H), 3.93-4.04(m, 3H), 3.67-3.88(m, 5H), 3.40-3.47(m, 1H), 3.07-3.28(m, 4H), 2.12-2.24(m, 1H), 1.88-1.96(m, 1H); m/z 451 (M+1)

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