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(54) Title: A PROCESS FOR THE PREPARATION OF GLIFLOZIN AGLYCONES

(57) Abstract: The present invention relates to a novel process for the preparation of gliflozin aglycone through a telescopic approach using ortho-lithiation of 1,4-dihalobenzene followed by reacting with corresponding aromatic or heteroaromatic aldehydes and reduction of the resulted in diarylmethanol or (aryl)(heteroaryl)methanol intermediate as key steps.

A PROCESS FOR THE PREPARATION OF GLIFLOZIN AGLYCONES

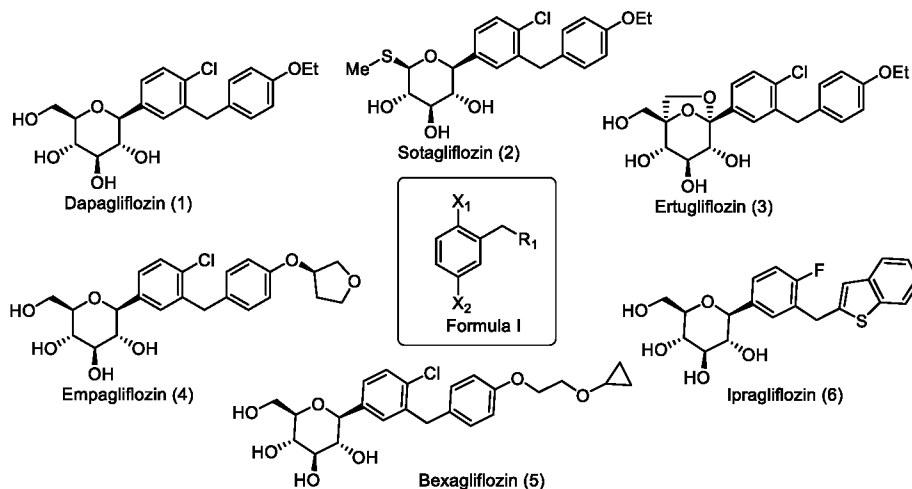
FIELD OF THE INVENTION

The present invention relates to a process for the preparation of gliflozin aglycones.

- 5 The present invention particularly relates to a process for the preparation of gliflozin aglycone through a telescopic approach using ortho-lithiation of 1,4-dihalobenzene followed by reacting with corresponding aromatic or heteroaromatic aldehydes to produce intermediates as the key step and reduction of the intermediate to obtain gliflozin aglycone.

BACKGROUND OF INVENTION

- 10 Structurally, gliflozins consist of two fragments, sugar and aglycone, and some representative gliflozins are depicted in Scheme 1, such as Dapagliflozin (1), Sotagliflozin (2), Ertugliflozin (3), Empagliflozin (4), Bexagliflozin (5), and Ipragliflozin (6) (WO2010022313A2, WO2009026537A1).

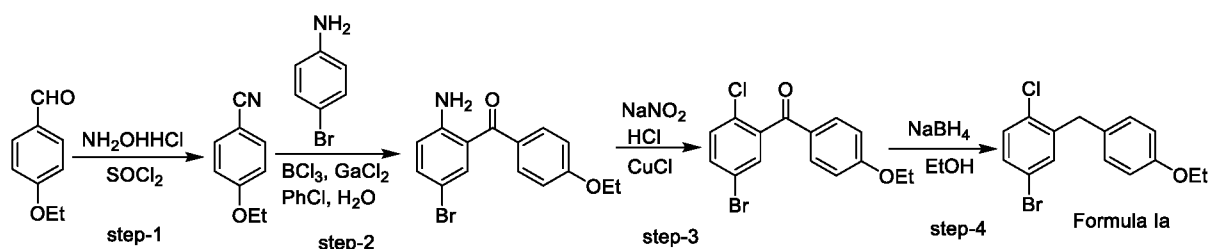


15 **Scheme 1.** Representative gliflozins 1-6

- Generally, sugar fragment synthesis is straightforward, but aglycone's (Formula I) synthesis is challenging and contributes substantially to the final gliflozin's manufacturing cost. Noticeably, the synthesis of aglycone (Formula I) in a cost-effective manner directly impacts the overall production expenses. Existing synthetic routes for aglycones are lengthy and time-consuming. For example, 5-bromo-2-chloro-4'-ethoxydiphenylmethane of a
- 20

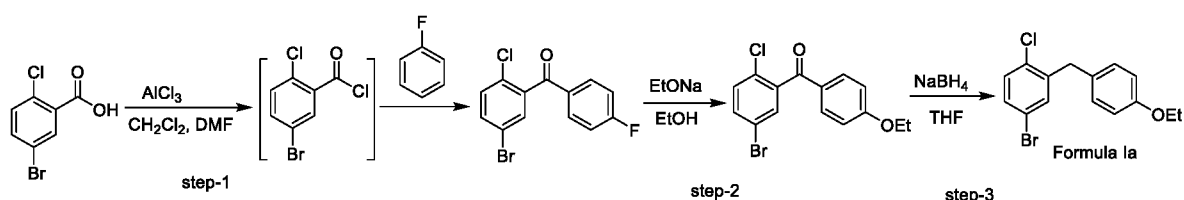
compound of Formula Ia (wherein X_1 and X_2 are selected from the group consisting of Cl, Br, F and I and R_1 is selected from substituted aryl and heteroaryl groups) is a key intermediate for the preparation of several gliflozins (Scheme 1).

The prior arts, such as CN10852184A and CN107311847B, disclose the preparation of aglycone of Formula Ia starting from 4-ethoxybenzaldehyde using Friedel-Crafts reaction as the key step (Scheme 2), overall in four steps.



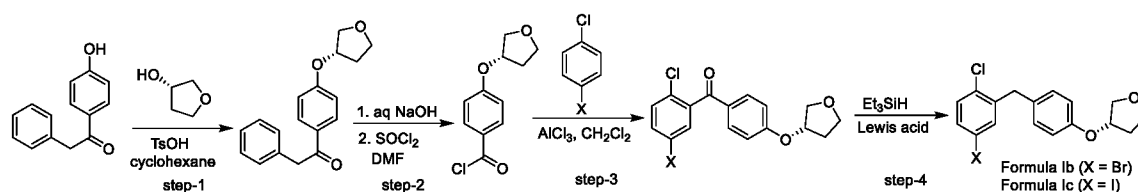
Scheme 2.

CN108752184 A discloses the preparation of aglycone of Formula Ia starting from 5-bromo-2-chlorobenzoic acid, converting it to corresponding acyl chloride and reacting with fluorobenzene using Friedel-Crafts reaction as the key step (Scheme 3).



Scheme 3.

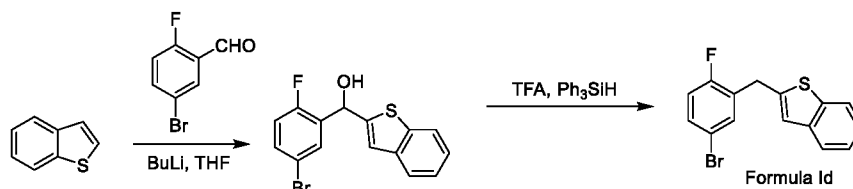
CN113121476 A discloses the preparation of aglycone of Formula Ib and Formula Ic using Friedel-Crafts reaction as a key step (Scheme 4).



Scheme 4.

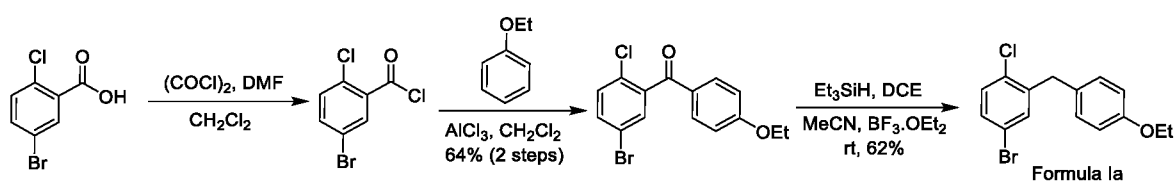
CN108623558 A discloses the preparation of aglycone of Formula Id, involving deprotonation of heterocyclic compound (benzothiophene) using $n-BuLi$ followed by

reacting with an aromatic aldehyde, and reduction of the resulted secondary alcohol (Scheme 5).



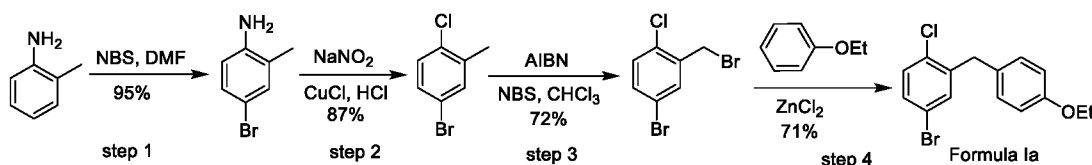
Scheme 5.

In addition to the above prior arts, there are prior arts such as US6414126; US6515117; US7375213; US2009/0118,201; PCT/IB2014/065726 disclose the commercially available 5-bromo-2-chlorobenzoic acid, which is first converted to 5-bromo-2-chlorobenzoyl chloride in the presence of oxalyl chloride. The subsequent, Friedel-Crafts acylation of phenetole with 5-bromo-2-chlorobenzoyl chloride furnished a mixture of regioisomers (7:1), and the required *p*-benzophenone is the major (J. Med. Chem. 2008, 51, 1145). Then, this *p*-benzophenone derivative was subjected to reduction to provide an aglycone of Formula Ia (Scheme 6). This synthesis involves three steps with only a 40% overall yield. Further, the Friedel-Crafts reaction generates unwanted by-products, and temperature fluctuations during the keto functionality reduction step; an acetonitrile addition is also observed, resulting in an impurity, *N*-acetyl-5-bromo-2-chloro-4'-ethoxydiphenylmethanamine (US 6,515,117; PCT/IB2014/065726).



Scheme 6. Synthesis of Ia from 5-bromo-2-chlorobenzoic acid

Another approach is to use *O*-methyl aniline as the starting material through bromination, diazonium chlorination, benzyl chlorination, and alkylation (Scheme 7). The process route benzylation uses AIBN, which will produce highly toxic cyanide during the reaction process, causing severe pollution and a lengthy approach, such as patent CN104478670.



Scheme 7.

In general, prior arts suggest that Friedel-Crafts acylation is a key step for synthesizing gliflozin aglycone (Formula I). It may lead to a mixture of regioisomers, low yield, lengthy steps, unwanted by-products, and toxicity. Further, the method disclosed in the prior art
5 CN108623558 is confined to only the deprotonation of benzothiophene using n-BuLi. Therefore, synthesizing the gliflozin aglycone of Formula I in a shorter, general, safer, and economically viable synthetic route is preferred, which would intensely reduce the gliflozin's production cost.

Other references may be made to patent applications, US 7,772,191; WO2006/120,208;
10 US7,662,790; US 8,283,454; WO2013/152,654; US8,802,842; US9,193,751, US2005/233,988; WO2004/080,990; WO2005/012,326; WO2009/022,010; CN107163092 A; WO2022116507 A1; IN2013CH06139 A; CN114380775 A; CN109456315 A; CN108276396 A; CN105481915 A; CN113121476A; CN108623558A; and research publications, J. Med. Chem. 2014, 57, 1236; and Org. Lett., 2014, 16,4090, which disclose
15 the synthesis of other aglycones of Formula I following a similar synthetic sequence, mainly using Friedel-Crafts reaction as an inevitable step, as shown for the compound of Formula Ia (Scheme 6).

Therefore, synthesizing the gliflozin aglycone of Formula I in a shorter, safer, and economically viable synthetic route would intensely reduce gliflozin's production cost.

OBJECTIVES OF THE INVENTION

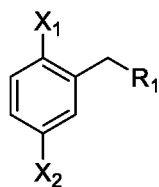
In order to overcome these limitations described in the prior art, the main aim of the present invention is to provide a cost-effective, scalable process in a reduced number of steps for the preparation of the gliflozin aglycone of Formula I, which serves as a key intermediate for the synthesis of several gliflozins.

25 The main objective of the present invention is to provide gliflozin aglycone through ortho-lithiation of 1,4-dihalobenzene, followed by reacting with corresponding aromatic or heteroaromatic aldehydes and reduction of the resulted intermediate (Formula II).

Yet another objective is to provide gliflozin aglycone through a telescopic approach using ortho-lithiation of 1,4-dihalobenzene followed by reacting with aromatic or heteroaromatic aldehydes and reduction of the intermediate to yield gliflozin aglycone.

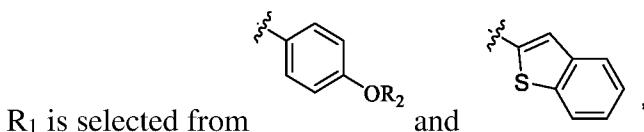
SUMMARY OF THE INVENTION

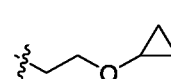
- 5 Accordingly, the present invention provides a process for preparation of gliflozin aglycones compound of formula I,



Formula I

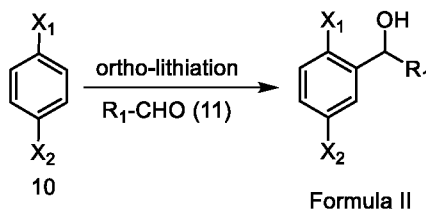
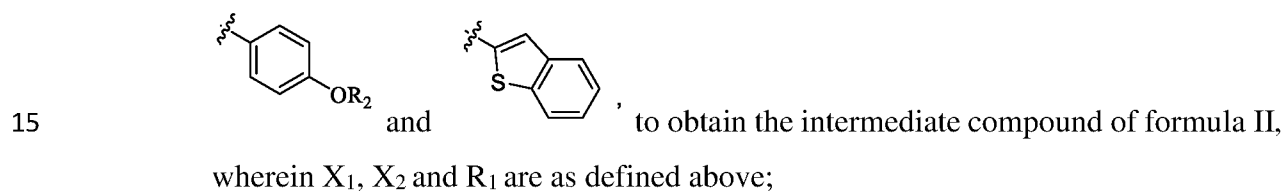
wherein X_1 and X_2 are selected from the group consisting of Cl, Br, F and I; and



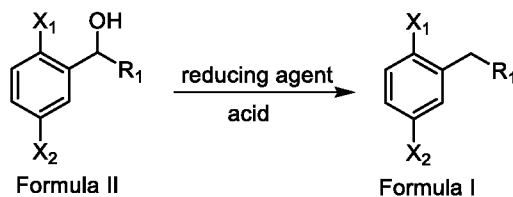
- 10 where R_2 is selected from the group consisting of Me, Et, iPr, Bu,  and  ;

comprising the steps of:

- (i) ortho-lithiation of 1,4-dihalobenzene (10) using a base and a solvent followed by reacting with an aldehyde of formula R_1 -CHO (11), wherein R_1 is selected from



- (ii) reduction of the intermediate of Formula II using a reducing agent in the presence of an acid and a solvent to obtain gliflozin aglycone formula I,



wherein X_1 , X_2 and R_1 are as defined above.

- 5 In an embodiment of the present invention, the gliflozin aglycone compound of formula I is prepared without isolating the intermediate compound of formula (II).

In an embodiment of the present invention, the base used in step (i) is selected from the group consisting of LITMP (lithium tetramethylpiperidide), LiHMDS (lithium hexamethyldisilazide), KHMDS (potassium hexamethyldisilazide), NaHMDS (sodium hexamethyldisilazide), and LDA (lithium diisopropylamide).

10

In a preferred embodiment of the present invention, the base is LDA.

In an embodiment of the present invention, the solvent is selected from the group consisting of toluene, ether, THF, DCE, and DCM.

In an embodiment of the present invention, the acid is selected from Bronsted or Lewis acid; selected from the group consisting of BF_3OEt_2 , TFA, acetic acid, H_2SO_4 , HCl, TiCl_4 , FeCl_3 , citric acid, benzoic acid.

15

In a preferred embodiment of the present invention, the acid is BF_3OEt_2 .

In an embodiment of the present invention, the reducing agent is selected from Et_3SiH and Me_3SiH .

- 20 In a preferred embodiment of the present invention, the reducing agent is Et_3SiH .

In a preferred embodiment the solvent used in step (ii) is selected from DCE and DCM.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The term “halo” refers to the present invention of F, Cl, Br, and I.

The term “ortho-lithiation” refers to the present invention removal of the proton using base by differentiating acidifying effects of protons adjacent to halogen/ortho to halogen, preferably adjacent to F and Cl. In general, ortho-lithiation is carried out at lower
 5 temperatures, such as -78°C to -10°C and using lithium bases.

The term “aryl” refers to the present invention as an optionally substituted aromatic ring system, preferably substituted benzene.

The term “heteroaryl” refers to the present invention as an aryl having at least one heteroatom selected from nitrogen, oxygen or sulfur in the ring structure. The ring structure
 10 may be monocyclic, bicyclic or tricyclic, optionally having fused rings, such as furan, thiophene, benzothiophene, pyrrole, pyridine, bipyridine, picolyimine, γ -pyran, γ -thiopyran, phenanthroline, pyrimidine, bipyrimidine, pyrazine, indole, coumarone, thionaphthene, carbazole, dibenzofuran, dibenzothiophene, pyrazole, imidazole, benzimidazole, oxazole, thiazole, dithiazole, isoxazole, isothiazole, quinoline, bisquinoline,
 15 isoquinoline, bisisoquinoline, acridine, chromene, phenazine, phenoxazine, phenothiazine, triazine, thianthrene, purine, bisimidazole and bisoxazole.

The term “substituted” as used herein refers to substitution with any one or any combination of the following substituents: fluorine, chlorine, bromine and iodine; hydroxy; nitro; cyano; oxo ($=\text{O}$); thioxo ($=\text{S}$); azido; nitroso; amino; hydrazino; formyl; alkyl; alkoxy; aryl;
 20 haloalkyl groups such as trifluoromethyl, tribromomethyl and trichloromethyl; haloalkoxy groups such as $-\text{OCH}_2\text{Cl}$, $-\text{OCHF}_2$ and $-\text{OCF}_3$; arylalkoxy groups such as benzyloxy and phenylethoxy; cycloalkyl; $-\text{O-cycloalkyl}$; aryl; alkoxy; heterocyclyl; heteroaryl; alkylamino; $-\text{O-CH}_2\text{-cycloalkyl}$; $-\text{COOR}^a$; $-\text{C(O)R}^b$; $-\text{C(S)R}^a$; $-\text{C(O)NR}^a\text{R}^b$; $-\text{NR}^a\text{C(O)NR}^b\text{R}^c$; $-\text{N(R}^a\text{)SOR}^b$; $-\text{N(R}^a\text{)SO}_2\text{R}^b$; $-\text{NR}^a\text{C(O)OR}^b$; $-\text{NR}^a\text{R}^b$; $-\text{NR}^a\text{C(O)R}^b$;
 25 $\text{NR}^a\text{C(S)R}^b$; $-\text{SONR}^a\text{R}^b$; $-\text{SO}_2\text{NR}^a\text{R}^b$; $-\text{OR}^a$; $-\text{OR}^a\text{C(O)OR}^b$; $-\text{OC(O)NR}^a\text{R}^b$; OC(O)R^a ; $-\text{OC(O)NR}^a\text{R}^b$; $-\text{R}^a\text{NR}^b\text{R}^c$; $-\text{R}^a\text{OR}^b$; $-\text{SR}^a$; $-\text{SOR}^a$ and $-\text{SO}_2\text{R}^a$; R^a , R^b and R^c each independently represents hydrogen atom; substituted or unsubstituted groups selected from alkyl; aryl; arylalkyl; cycloalkyl; heterocyclyl; heteroaryl and heteroarylalkyl; R^a , R^b and R^c are also combined to form a 3-7 membered ring having 0-2 hetero atoms.

The term "alkoxy" refers to the present invention -O-alkyl group, alkyl group refers to optionally substituted C1-10 straight or branched alkyl group and aliphatic heterocyclic compounds

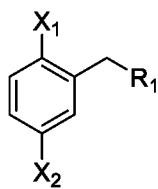
The term "base" refers to the present invention as an organic or inorganic base such as lithium, potassium, and sodium, selected from LITMP, LiHMDS, KHMDS, NaHMDS and LDA.

The term "acid" refers to the present invention as Bronsted or Lewis acid selected from BF_3OEt_2 , TFA, acetic acid, H_2SO_4 , HCl, TiCl_4 , FeCl_3 , citric acid, benzoic acid.

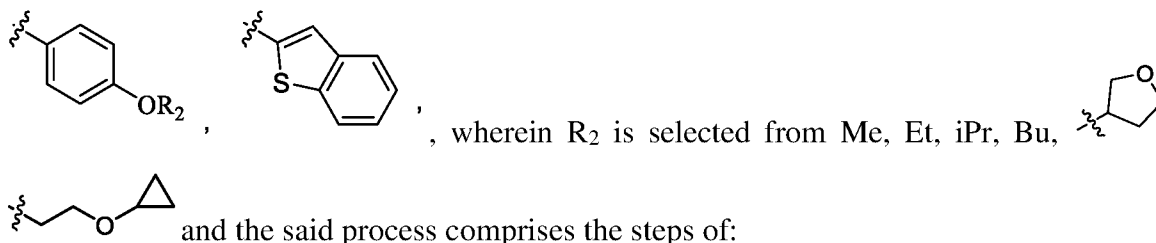
The term "reducing agent" refers to the present invention as selected from Et_3SiH , Me_3SiH , NaBH_3 , $\text{NaBH}(\text{OAc})_3$, NaBH_3CN , H_2 in the presence of Pd/C.

The term "solvent" refers to the present invention as selected from, but not limited to "ester solvents" such as ethyl acetate, methyl acetate, isopropyl acetate, n-butyl acetate and the like; "ether solvents" such as tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether (MTBE), 1,4-dioxane and the like; "hydrocarbon solvents" such as toluene, hexane, heptane, pet ether, xylene, cyclohexane and the like; "polar aprotic solvents" such as dimethyl acetamide, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone and the like; "ketone solvents" such as acetone, methylethyl ketone, methylisobutyl ketone and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, *tert*-butanol and the like; "chloro solvents" such as dichloromethane, chloroform, dichloroethane, carbon tetrachloride and the like; "nitrile solvents" such as acetonitrile, butyronitrile, isobutyronitrile and the like; "polar solvent" such as water or mixtures thereof.

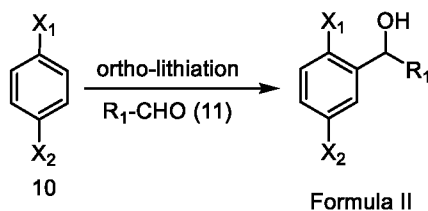
The present invention provides a process for synthesizing the gliflozin aglycone of Formula I,



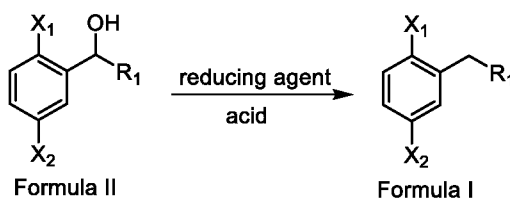
Formula I, wherein X_1 and X_2 are selected from halo such as Cl, Br, F & I; R_1 is selected from optionally substituted aryl or heteroaryl, preferably



- 5 (i) ortho-lithiation of 1,4-dihalobenzene (10) using the base and suitable solvents followed by reacting with corresponding aromatic or heteroaromatic aldehyde (11) to obtain the corresponding diarylmethanol or (aryl)(heteroaryl)methanol intermediates of compound of formula II.

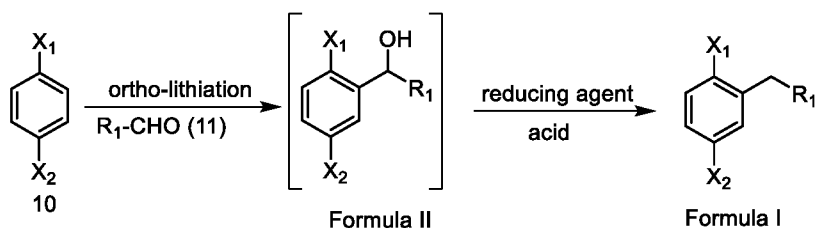


- 10 (ii) reduction of the resulted in diarylmethanol or (aryl)(heteroaryl)methanol intermediate of Formula II (obtained from step-i) using reducing agents in the presence of acid in suitable solvents to obtain gliflozin aglycone of formula I.

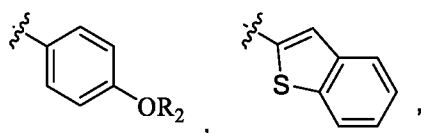


In an embodiment of the present invention, the resulted in diarylmethanol or (aryl)(heteroaryl)methanol intermediate compound of formula II (obtained from step -i) was reduced using reducing agents in the presence of acid in suitable solvents to obtain gliflozin

aglycone of formula I in a telescopic approach, without isolating the compound of Formula II.

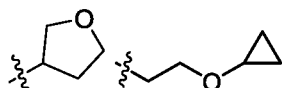


In a preferred embodiment of the present invention, R_1 is selected from

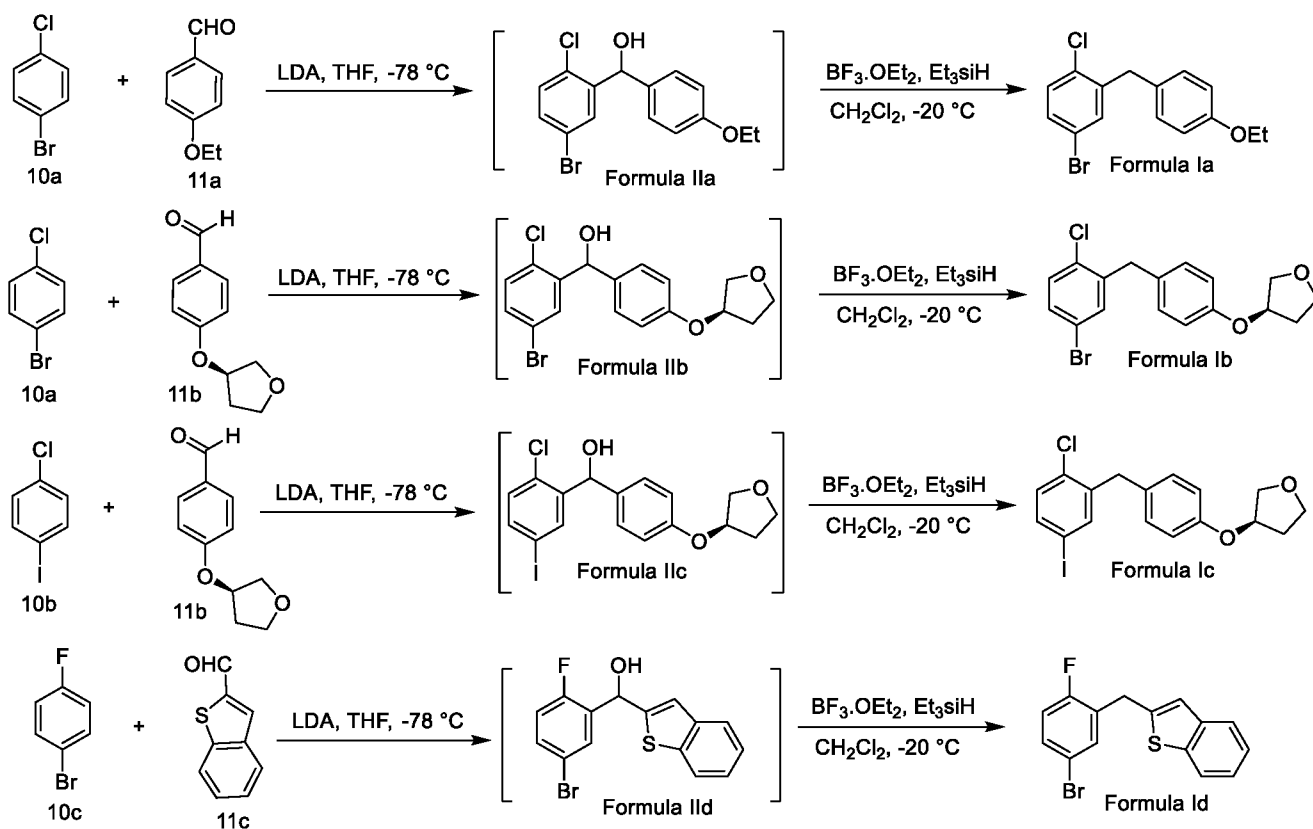


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In a preferred embodiment of the present invention R_2 is selected from Me, Et, iPr, Bu,



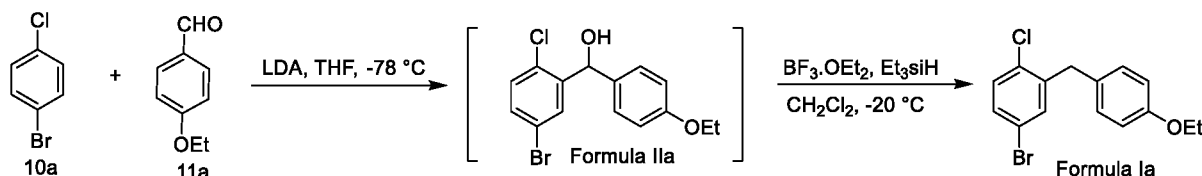
The specific embodiment of the process is represented as follows in Scheme 8.



Scheme 8

EXAMPLES:

1. 4-Bromo-1-chloro-2-(4-ethoxybenzyl) benzene (Ia):

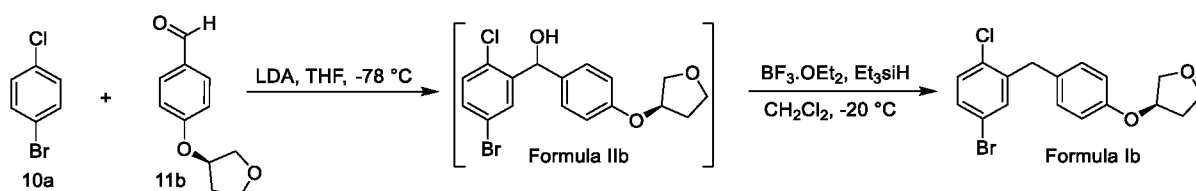


- 5 N-BuLi (1.6 M in hexane, 35.91 mL, 57.45 mmol, 1.1 equiv) was added to a stirred solution of *N,N*-diisopropylamine (8.29 mL, 57.45 mmol, 1.1equiv) in THF (57.45ml) at -78°C under argon atmosphere, the resulting solution was stirred for 45 minutes. 1-Bromo-4-chlorobenzene (**10a**) (10 g, 52.23 mmol, 1equiv) in THF (100 mL) was slowly cannulated and stirred for 45 minutes. Then, 4-ethoxybenzaldehyde (**11a**) (8.77 mL, 62 mmol, 1.2
- 10 equiv) in dry THF (65 mL) was slowly cannulated to the reaction mixture, and stirred for 5 h at -78°C . After completion of the reaction, it was quenched with aqueous NH_4Cl solution, extracted with EtOAc, washed with brine solution, and dried over anhydrous sodium sulphate. Organic solvents were evaporated under reduced pressure. The resulting crude oil was purified by silica gel to get a compound **IIa** (14 grams 78%) as a white solid. **^1H NMR (400 MHz, CDCl_3):** δ 7.89 (d, $J = 2.5$, 0.5H), 7.72 (d, $J = 2.5$, 0.5H), 7.46 (d, $J = 8.45$, 0.5H), 7.36 (dd, $J = 10.92$, 8.45, 0.5H), 7.32 – 7.25 (m, 2H), 7.20 (d, $J = 8.45$, 0.5H), 7.15 (dd, $J = 10.92$, 8.45, 0.5H), 6.95 – 6.85 (m, 2H), 6.07 (d, $J = 13.61$, 1H), 4.04 (q, $J = 7.0$, 2H), 2.32 (brs, 1H) 1.43 (t, $J = 7.0$, 3H). **^{13}C NMR (125 MHz, CDCl_3):** δ 158.8, 144.4, 143.1, 133.9, 133.5, 133.4, 131.5, 131.2, 130.9, 130.6, 128.9, 128.6, 128.4, 128.2, 120.9,
- 15 (400 MHz, CDCl_3): δ 7.89 (d, $J = 2.5$, 0.5H), 7.72 (d, $J = 2.5$, 0.5H), 7.46 (d, $J = 8.45$, 0.5H), 7.36 (dd, $J = 10.92$, 8.45, 0.5H), 7.32 – 7.25 (m, 2H), 7.20 (d, $J = 8.45$, 0.5H), 7.15 (dd, $J = 10.92$, 8.45, 0.5H), 6.95 – 6.85 (m, 2H), 6.07 (d, $J = 13.61$, 1H), 4.04 (q, $J = 7.0$, 2H), 2.32 (brs, 1H) 1.43 (t, $J = 7.0$, 3H). **^{13}C NMR (125 MHz, CDCl_3):** δ 158.8, 144.4, 143.1, 133.9, 133.5, 133.4, 131.5, 131.2, 130.9, 130.6, 128.9, 128.6, 128.4, 128.2, 120.9,
- 20 120.2, 114.5, 74.3, 72.2, 63.4, 14.8. **IR (neat):** ν_{max} 3357, 2977, 2929, 1609, 1508, 1455, 1390, 1240, 1172, 1092, 1044, 1018, 922, 897, 807, 755, 739, 645, 628, 597, 581. **HRMS (ESI) m/z** calculated for $\text{C}_{15}\text{H}_{13}\text{BrClO}_2$ [$\text{M}-\text{H}$] $^+$: Calcd 338.9787, found 338.9776.

- Triethyl silane (4.68 mL, 29.32 mmol, 2 equiv) was slowly added to a stirred solution of the compound of Formula (**IIa**) (5 g, 14.66 mmol, 1 equiv) in dry DCM at -20°C .
- 25 Followed by 50% wt. solution of $\text{BF}_3\cdot\text{OEt}_2$ (3.65 mL, 14.66 mmol, 1 equiv) was slowly added and stirred for another 20 minutes. After completion of the reaction, it was quenched with saturated aqueous NaHCO_3 solution and extracted 2-3 times with DCM. Combined organic layers were washed with brine solution and dried over anhydrous sodium sulphate.

Solvents were evaporated under reduced pressure, and the resulting crude was purified by silica gel to get a compound **Ia** (4 g 84%) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.32 - 7.22 (m, 3H), 7.11 (d, *J* = 8.7, 2H), 6.87 (d, *J* = 8.7, 2H), 4.04 (q, *J* = 7.05, 2H), 4.01 (s, 2H), 1.43 (t, *J* = 7.05, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 157.6, 141.3, 133.5, 133.1, 130.9, 130.5, 130.4, 130.0, 120.4, 114.6, 63.4, 38.2, 14.9; IR (neat): ν_{max} 2979, 2927, 1885, 1611, 1508, 1462, 1389, 1299, 1238, 1175, 1042, 918, 806, 772, 691, 613; HRMS (ESI) *m/z* calculated for C₁₅H₁₃BrClO [M-H]⁺: 322.9838 found 322.9827.

2. (S)-3-(4-(5-Bromo-2-chlorobenzyl)phenoxy)tetrahydrofuran (**Ib**):

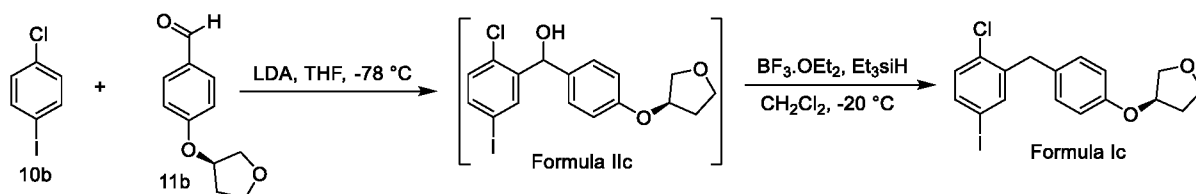


N- BuLi (1.6 M in hexane, 3.59 mL, 5.74 mmol, 1.1 equiv) was slowly added to a stirred solution of N, N-diisopropylamine (0.79 mL, 5.74 mmol, 1.1 equiv) in THF (5.2 mL) at -78 °C under argon condition, the resulting solution was stirred for 45 minutes. 1-Bromo-4-chlorobenzene **10a** (1g, 5.22 mmol, 1 equiv) in THF (10 mL) was slowly cannulated and stirred for 45 minutes, (S)-4-((tetrahydrofuran-3-yl) oxy) benzaldehyde (**11b**) (1.20 g, 6.26 mmol, 1.2 equiv) in THF (6 mL) was slowly cannulated to the reaction mixture, and stirred for 5 h at -78 °C. After completion of the reaction, it was quenched with aqueous NH₄Cl solution, extracted with EtOAc, washed with brine solution, dried over anhydrous sodium sulphate, solvents were evaporated under reduced pressure. The resulting crude oil was purified by silica gel to get a compound **Ib** in (1.34 g, 67%) as a colorless oil.

Triethylsilane (0.66 mL, 4.17 mmol, 2 equiv) was slowly added to a stirred solution of the compound of Formula (**IIb**) (0.8 g, 2 mmol, 1 equiv) in DCM at -20 °C. Followed by BF₃.OEt₂ (0.26 mL, 2 mmol, 1equiv) was slowly added, and stirred for 20 minutes. After completion of the reaction was quenched with saturated aq. NaHCO₃ solution and extracted 2-3 times with DCM. Combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate. Solvents were evaporated under reduced pressure. The resulting crude was purified by silica gel to get a compound **Ib** in (0.5 g, 65%) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.23-7.20 (m, 1H), 7.19-7.14 (m, 2H) 7.02 (d, *J* = 8.52 Hz, 2H), 6.74 (d, *J* = 8.52 Hz, 2H), 4.86-4.80 (m, 1H), 3.95-3.87 (m, 5H), 3.86-3.79 (m, 1H), 2.15-2.03 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 156.1, 141.2, 133.5, 133.1, 130.9, 130.6, 130.0, 120.49, 115.5, 73.17, 67.2, 38.2, 33.05; IR (neat): ν_{max} 2927, 2859, 1611, 1508, 1383, 1240, 1179, 1089, 813, 689, 646.

3. (S)-3-(4-(2-Chloro-5-iodobenzyl)phenoxy)tetrahydrofuran (Iba):

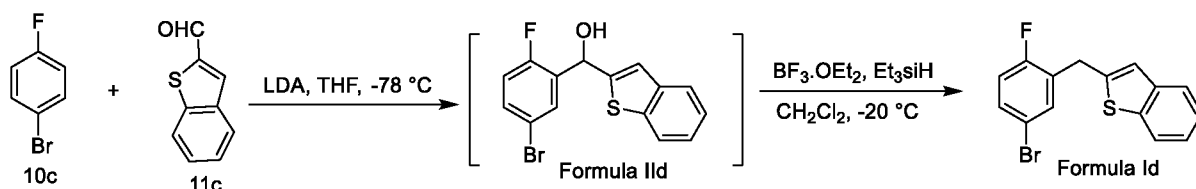


N- BuLi (1.6 M in hexane, 2.8 mL, 4.62 mmol, 1.1equiv) was added to a stirred solution of N, N-diisopropylamine (0.66 mL, 4.62 mmol, 1.1 equiv) in THF (4.2 mL) at -78 °C under argon condition, the resulting solution was stirred for 45 minutes. 1- Chloro-4-iodobenzene **10b** (1 g, 4.20 mmol, 1 equiv) in THF (8 mL) was slowly cannulated and stirred for 45 minutes, (S)-4-((tetrahydrofuran-3-yl)oxy) benzaldehyde **11b** (0.96 g, 5.04 mmol, 1.2 equiv) in THF (6 mL) was slowly cannulated to the reaction mixture, and stirred for 5 h at -78 °C. After completion of the reaction, it was quenched with aqueous NH₄Cl solution, extracted with EtOAc, washed with brine solution, dried over anhydrous sodium sulphate, solvents were evaporated under reduced pressure. The resulting crude oil was purified by silica gel to get the compound **IIc** in (1.34 g, 74%) as a yellow oil.

Triethylsilane (0.59 mL, 3.7 mmol, 2 equiv) was slowly added to a stirred solution of the compound of Formula (**IIc**) (0.8 g, 1.8 mmol. 1 equiv) in DCM at -20 °C. Followed by BF₃·OEt₂ (0.45 mL, 1.8 mmol, 1 equiv) was slowly added, and stirred for 20 minutes. After completion of the reaction, it was quenched with saturated aq. NaHCO₃ solution and extracted 2-3 times with DCM. Combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate, solvents were evaporated under reduced pressure. The resulting crude was purified by silica gel to get a compound of Formula **Ic** in (0.5 g 65%) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.23 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 7.07 (m, 1H), 6.79 (d, J = 8.8 Hz, 2H), 4.88 (m, 1H), 4.00-3.94 (m, 5H), 3.91-3.85 (m, 1H), 2.22-2.10 (m, 2H); **¹³C NMR (400 MHz, CDCl₃):** δ 156.1, 141.4, 139.6, 136.6, 134.2, 131.2, 131.0, 130.0, 115.5, 91.6, 77.3, 73.1, 67.2, 38.0, 33.0; **IR (neat):** ν_{max} 2922, 2853, 1610, 1508, 1507, 1460, 1379, 1300, 1238, 1176, 1076, 1043, 995, 815, 807, 611, 564.

4. 2-(5-Bromo-2-fluorobenzyl)benzo[b]thiophene (1d) :



nBuLi (1.6 M in hexane, 3.92 mL, 6.28 mmol, 1.1 equiv) was slowly added to a stirred solution of N,N-diisopropylamine (0.90 mL, 6.28 mmol, 1.1 equiv) in THF (5.7 mL) at -78 °C under argon condition, the resulting solution was stirred for 45 minutes. 4-Bromofluorobenzene **10c** (1 g, 5.71 mmol, 1 equiv) in THF (10 mL) was slowly cannulated and stirred for 45 minutes, benzo thiophene-2-carbaldehyde **11c** (1 g, 6.82 mmol, 1.1 equiv) in THF (6 mL) was slowly cannulated to the reaction mixture, and stirred for 5 h at -78 °C. After completion of the reaction, it was quenched with aqueous NH₄Cl solution, extracted with EtOAc, washed with brine solution, dried over anhydrous sodium sulphate, solvents were evaporated under reduced pressure. The resulting crude oil was purified by silica gel to get a compound **IIId** in (1.3 g, 67.75%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 7.84 - 7.78 (m, 2H), 7.75 - 7.71 (m, 1H), 7.48 - 7.42 (m, 1H), 7.39 - 7.30 (m, 2H), 7.20 (s, 1H), 7.02, - 6.94 (m, 1H), 6.41 (s, 1H), 2.57 (brs, 1H); **¹³C NMR (125 MHz, CDCl₃):** δ 160.0, 157.5, 146.4, 139.7, 139.2, 132.6, 132.5, 132.0, 131.8, 130.5, 130.5, 124.5, 124.4, 123.8, 122.4, 121.5, 117.4, 117.2, 117.19, 66.5, 66.4; **IR (neat):** ν_{max} 3358, 2921, 2851, 1711, 1478, 1338, 1247, 1166, 1108, 1013, 938, 814, 744, 725, 615, 556; **HRMS (ESI) m/z** calculated for C₁₅H₁₃BrClO [M-H]⁺: 344.9541 found 344.9536.

Triethylsilane (0.473 mL, 2.96 mmol, 2 equiv) was slowly added to a stirred solution of the compound of Formula (**IIId**) (0.5 g, 1.48 mmol, 1 equiv) in DCM at -20 °C. Followed by BF₃.OEt₂ (0.370 mL, 1.48 mmol, 1 equiv) was slowly added; and stirred for 20 minutes. After completion of the reaction, it was quenched with saturated aq. NaHCO₃ solution and

extracted 2-3 times with DCM. Combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate, and solvents were evaporated under reduced pressure. The resulting crude oil was purified by silica gel to get a compound **Id** in (0.31 g, 65%) as a yellow liquid.

5 **¹H NMR (400 MHz, CDCl₃):** δ 7.64 (d, J = 8.00 Hz, 1H), 7.54 (d, J = 8.00 Hz, 1H), 7.28 - 7.07 (m, 4H), 6.89 (s, 1H), 6.81 (t, J = 9.0 Hz, 1H), 4.05 (s, 2H); **¹³C NMR (125 MHz, CDCl₃):** δ 160.8, 158.9, 147.4, 139.8, 139.4, 129.87, 129.8, 129.7, 127.7, 127.7, 124.5, 124.5, 124.3, 123.7, 122.4, 121.2, 115.6, 115.5, 67.06, 67.03; **IR (neat):** ν_{max} 3057, 2919, 2849, 1576, 1480, 1433, 1308, 1234, 1171, 1110, 1014, 857, 810, 723, 653, 618, 591,
10 557. **MS (FAB) m/z:** 322 (M+H)⁺, calcd for C₁₀H₁₅BrFS: 321.

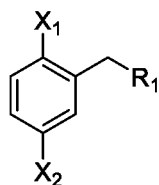
ADVANTAGES OF THE INVENTION

The advantages of the present invention are given below.

1. An efficient and shorter route for synthesizing gliflozin aglycone.
- 15 2. Telescopic approach of gliflozin aglycones through addition and reduction.
3. Operationally simple and amenable to scaling up.
4. The purification and/or isolation are straightforward.

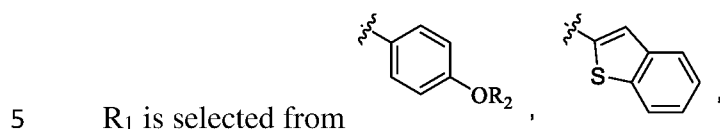
WE CLAIM:

1. A process for preparation of gliflozin aglycones compound of formula I,



Formula I

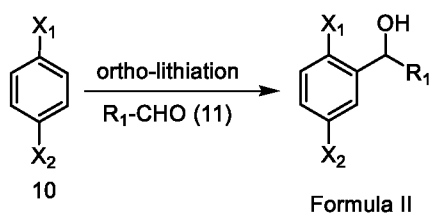
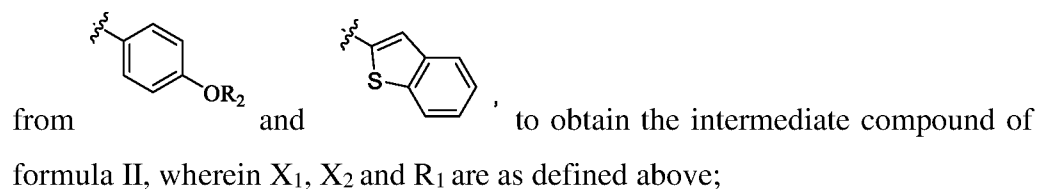
wherein X₁ and X₂ are selected from the group consisting of Cl, Br, F and I;



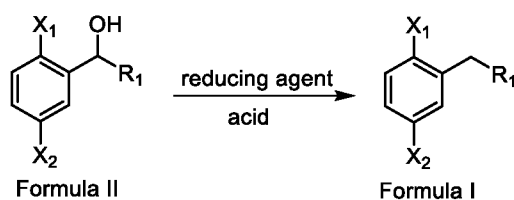
where R₂ is selected from the group consisting of Me, Et, iPr, Bu, and ;

comprising the steps of:

- 10 (iii) ortho-lithiation of 1,4-dihalobenzene (10) using a base and a solvent followed by reacting with an aldehyde of formula R₁-CHO (11), wherein R₁ is selected



- 15 (iv) reduction of the intermediate of Formula II using a reducing agent in the presence of an acid and a solvent to obtain gliflozin aglycone formula I.



2. The process as claimed in claim 1, wherein the gliflozin aglycone compound of formula I is prepared without isolating the intermediate compound of formula (II).
3. The process claimed in claim 1, wherein the base is selected from the group consisting of LITMP (lithium tetramethylpiperidide), LiHMDS (lithium hexamethyldisilazide), KHMDs (potassium hexamethyldisilazide), NaHMDS (sodium hexamethyldisilazide), and LDA (lithium diisopropylamide).
5
4. The process claimed in claim 1, wherein the base is LDA.
5. The process claimed in claim 1, wherein the solvent used in step (i) is selected from the group consisting of toluene, ether and THF.
- 10 6. The process as claimed in claim 1, wherein the acid is selected from Bronsted or Lewis acid; selected from the group consisting of BF_3OEt_2 , TFA, acetic acid, H_2SO_4 , HCl, TiCl_4 , FeCl_3 , citric acid, benzoic acid.
7. The process as claimed in claim 1, wherein the acid is BF_3OEt_2 .
8. The process as claimed in claim 1, wherein the reducing agent is selected from Et_3SiH and Me_3SiH .
15
9. The process as claimed in claim 1, wherein the reducing agent is Et_3SiH .
10. The process claimed in claim 1, wherein the solvent used in step (ii) is selected from DCE and DCM.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2024/052131

A. CLASSIFICATION OF SUBJECT MATTER

C07C15/16, C07C25/18, C07D307/04, C07D333/54 Version=2025.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016280619 A1 (SUN PHARMA IND LTD)& 29 SEP 2016 (29-09-2016) see claims-1-4, example 1a, 1b,	1-10
Y	WO 2018142422A1 (INDOCO REMEDIES LTD) & 09 AUG 2018 (09-08-2018) see claims 1-13, abstract, examples-1-5	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21-02-2025

Date of mailing of the international search report

21-02-2025

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2024/052131

Citation	Pub.Date	Family	Pub.Date
US 2016280619 A1	29-09-2016	EP 3063116 A1	07-09-2016
		IN 201617018451 A	31-08-2016
		WO 2015063726 A1	07-05-2015
WO 2018142422 A1	09-08-2018	IN 201721003897 A	03-08-2018