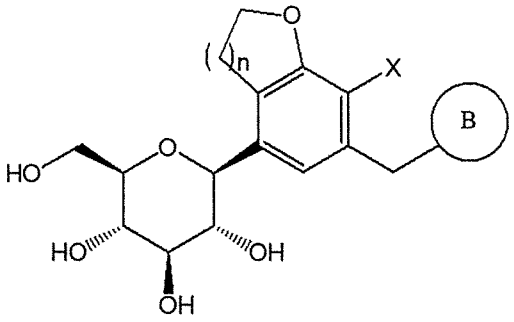
binding site between the diphenylmethane derivative and the heterocycloalkyl ring is in an α-form, a β-form, or a racemic form thereof.

For example, the compound of Chemical Formula I may be a compound of the following Chemical Formula Ia:

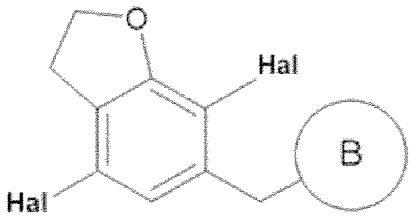
[Chemical Formula Ia]




wherein B, n, and X are as defined above.

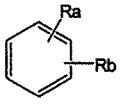
According to one aspect of the present invention, there is provided a method for producing a compound of the following Chemical Formula 9, which is an intermediate used to produce the diphenylmethane derivative of Chemical Formula I:

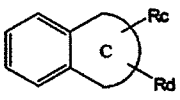
[Chemical Formula 9]




wherein:

Hal are each independently a halogen, and

B is 

(B-1) or 

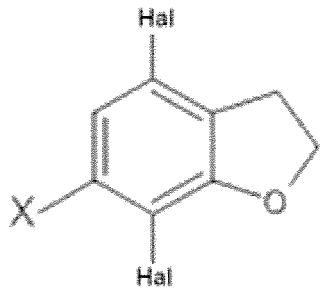
(B-2),

wherein Ra, Rb, Rc, and Rd are each independently hydrogen, a halogen, hydroxy,

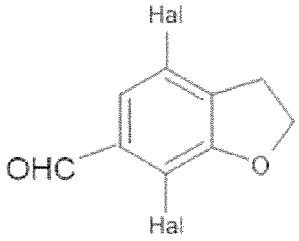
Formula 5; and

reacting a compound of Chemical Formula 7 with the compound of Chemical Formula 6 to obtain a compound of Chemical Formula 8:

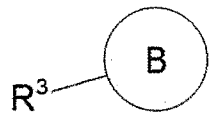
[Chemical Formula 5]



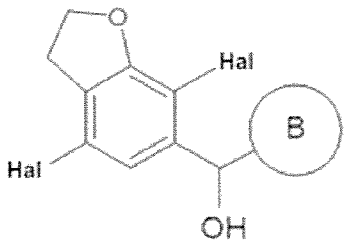

[Chemical Formula 6]



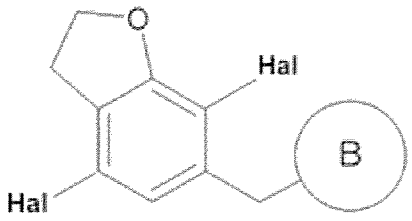

[Chemical Formula 7]




[Chemical Formula 8]

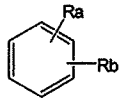


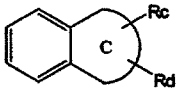

[Chemical Formula 9]




wherein:

$R^3$, X, and Hal are each independently a halogen, and

B is 

(B-1) or 

(B-2),

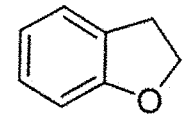
wherein Ra, Rb, Rc, and Rd are each independently hydrogen, a halogen, hydroxy, mercapto, cyano, nitro, amino, carboxy, oxo, a C1-7 alkyl, a C1-7 alkylthio, a C2-7 alkenyl, a C2-7 alkynyl, a C1-7 alkoxy, a C1-7 alkoxy-C1-7 alkyl, a C2-7 alkenyl-C1-7 alkyloxy, a C2-7 alkynyl-C1-7 alkyloxy, a C3-10 cycloalkyl, a C3-7 cycloalkylthio, a C5-10 cycloalkenyl, a C3-10 cycloalkyloxy, a C3-10 cycloalkyloxy-C1-7 alkoxy, a phenyl-C1-7 alkyl, a C1-7 alkylthio-phenyl, a phenyl-C1-7 alkoxy, a mono- or di-C1-7 alkylamino, a mono- or di-C1-7 alkylamino-C1-7 alkyl, a C1-7 alkanoyl, a C1-7 alkanoylamino, a C1-7 alkylcarbonyl, a C1-7 alkoxycarbonyl, carbamoyl, a mono- or di-C1-7 alkylcarbamoyl, a C1-7 alkylsulfonylamino, phenylsulfonylamino, a C1-7 alkylsulfinyl, a C6-14 arylsulfanyl, a C6-14 arylsulfonyl, a C6-14 aryl, a 5-13-membered heteroaryl, a 5-10-membered heterocycloalkyl, a 5-10-membered heterocycloalkyl-C1-7 alkyl, or a 5-10-membered heterocycloalkyl-C1-7 alkoxy;

ring C is a C3-10 cycloalkyl, a C5-10 cycloalkenyl, a C6-14 aryl, a 5-13-membered heteroaryl, or a 5-10-membered heterocycloalkyl;

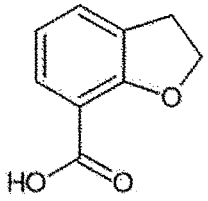
the alkyl, the alkenyl, the alkynyl, and the alkoxy are each independently unsubstituted or have one or more substituents selected from the group consisting of a halogen, hydroxy, cyano, nitro, amino, mercapto, a C1-7 alkyl, and a C2-7 alkynyl;

Formula 8 (step 7):

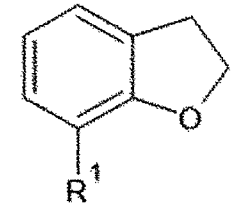
[Chemical Formula 1]



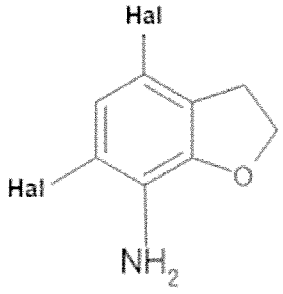
[Chemical Formula 2]



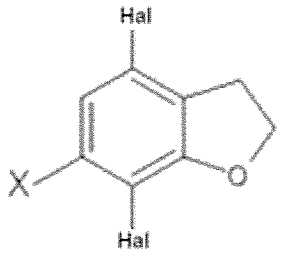
[Chemical Formula 3]



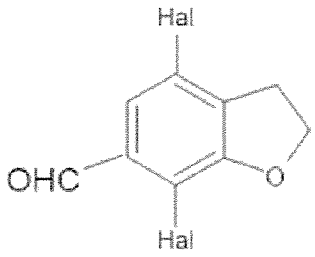
[Chemical Formula 4]



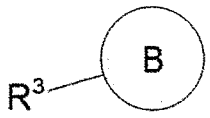
[Chemical Formula 5]



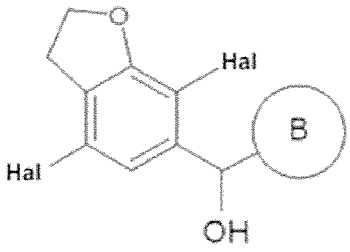

[Chemical Formula 6]



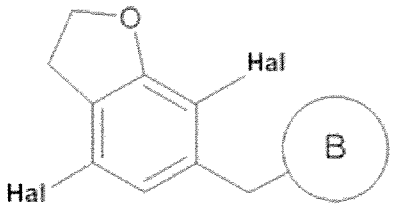

[Chemical Formula 7]




[Chemical Formula 8]



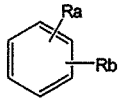

[Chemical Formula 9]

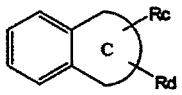



wherein:

$R^1$ is $NH_2$,

Hal, $R^3$ and X are each independently a halogen, and

B is 

(B-1) or 

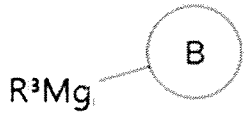
(B-2),

wherein Ra, Rb, Rc, and Rd are each independently hydrogen, a halogen, hydroxy, mercapto, cyano, nitro, amino, carboxy, oxo, a C1-7 alkyl, a C1-7 alkylthio, a C2-7 alkenyl, a C2-7 alkynyl, a C1-7 alkoxy, a C1-7 alkoxy-C1-7 alkyl, a C2-7 alkenyl-C1-7 alkyloxy, a C2-7 alkynyl-C1-7 alkyloxy, a C3-10 cycloalkyl, a C3-7 cycloalkylthio, a C5-10 cycloalkenyl, a C3-10 cycloalkyloxy, a C3-10 cycloalkyloxy-C1-7 alkoxy, a phenyl-C1-7 alkyl, a C1-7 alkylthio-phenyl, a phenyl-C1-7 alkoxy, a mono- or di-C1-7 alkylamino, a mono- or di-C1-7 alkylamino-C1-7 alkyl, a C1-7 alkanoyl, a C1-7 alkanoylamino, a C1-7 alkylcarbonyl, a C1-7 alkoxycarbonyl, carbamoyl, a mono- or di-C1-7 alkylcarbamoyl, a C1-7 alkylsulfonylamino, phenylsulfonylamino, a C1-7 alkylsulfinyl, a C6-14 arylsulfanyl, a C6-14 arylsulfonyl, a C6-14 aryl, a 5-13-membered heteroaryl, a 5-10-membered heterocycloalkyl, a 5-10-membered heterocycloalkyl-C1-7 alkyl, or a 5-10-membered heterocycloalkyl-C1-7 alkoxy;

ring C is a C3-10 cycloalkyl, a C5-10 cycloalkenyl, a C6-14 aryl, a 5-13-membered heteroaryl, or a 5-10-membered heterocycloalkyl;

the alkyl, the alkenyl, the alkynyl, and the alkoxy are each independently unsubstituted or have one or more substituents selected from the group consisting of a halogen, hydroxy, cyano, nitro, amino, mercapto, a C1-7 alkyl, and a C2-7 alkynyl;

the cycloalkyl, the cycloalkenyl, the aryl, the heteroaryl, and the heterocycloalkyl are each independently unsubstituted or have one or more substituents selected from the group consisting of a halogen, hydroxy, cyano, nitro, amino, mercapto, a C1-4 alkyl, and a C1-4 alkoxy; and




The process of obtaining the compound of Chemical Formula 9 from the compound of Chemical Formula 8 (step 7) may be performed using known methods. The compound of Chemical Formula 9 may be obtained by reducing the compound of Chemical Formula 8 according to the information disclosed in Korean Patent Publication No. 2017-0142904 (Patent Document 2), but the present invention is not limited thereto.

According to the above method, the compound of Chemical Formula 9, which corresponds to an important intermediate for the compound of Chemical Formula I as an SGLT inhibitor, and the compound of Chemical Formula I, which is a final target compound, may be obtained with high yield and high quality through a total of 7 short reaction steps using the compound of Chemical Formula 1, which is more easily commercially available, as a starting material. Also, the method for producing an SGLT inhibitor has excellent economic efficiency because the SGLT inhibitor may be produced without special equipment such as an ozone generator.

According to another exemplary embodiment of the present invention, the compound of Chemical Formula 9 may be produced using a method which includes: obtaining a compound of Chemical Formula 11 from a compound of Chemical Formula 10; reacting a compound of Chemical Formula 12 with the compound of Chemical Formula 11 to obtain a compound of Chemical Formula 13; and obtaining the compound of Chemical Formula 9 from the compound of Chemical Formula 13.

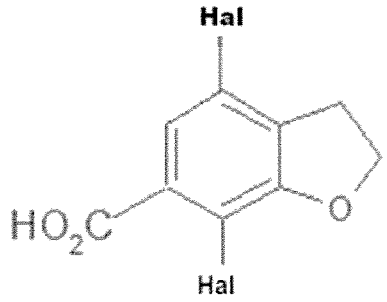
The present invention provides a method for producing a compound of Chemical Formula 9, which includes the following steps:

obtaining a compound of Chemical Formula 11 from a compound of Chemical Formula 10;

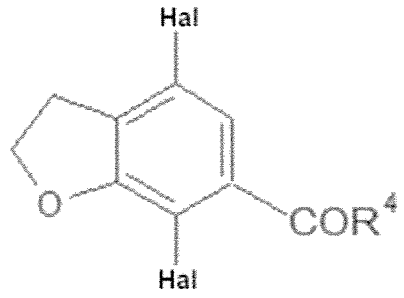
reacting a compound of Chemical Formula 12 with the compound of Chemical Formula 11 to obtain a compound of Chemical Formula 13; and

obtaining the compound of Chemical Formula 9 from the compound of Chemical Formula 13:

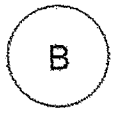
[Chemical Formula 10]



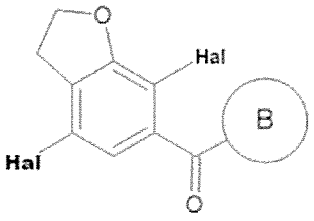

[Chemical Formula 11]



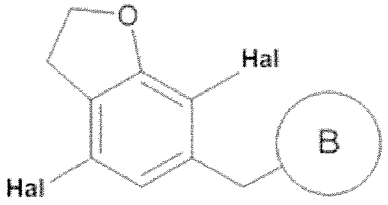

[Chemical Formula 12]




[Chemical Formula 13]

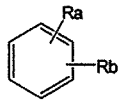


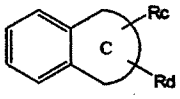

[Chemical Formula 9]




wherein:

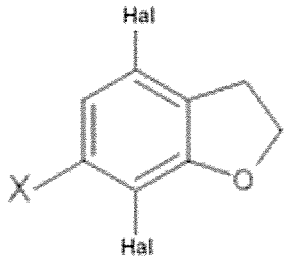
Hal and $R^4$ are each independently a halogen, and

B is 

(B-1) or 

(B-2),

wherein Ra, Rb, Rc, and Rd are each independently hydrogen, a halogen, hydroxy, mercapto, cyano, nitro, amino, carboxy, oxo, a C1-7 alkyl, a C1-7 alkylthio, a C2-7 alkenyl, a C2-7 alkynyl, a C1-7 alkoxy, a C1-7 alkoxy-C1-7 alkyl, a C2-7 alkenyl-C1-7 alkyloxy, a C2-7 alkynyl-C1-7 alkyloxy, a C3-10 cycloalkyl, a C3-7 cycloalkylthio, a C5-10 cycloalkenyl, a C3-10 cycloalkyloxy, a C3-10 cycloalkyloxy-C1-7 alkoxy, a phenyl-C1-7 alkyl, a C1-7 alkylthio-phenyl, a phenyl-C1-7 alkoxy, a mono- or di-C1-7 alkylamino, a mono- or di-C1-7 alkylamino-C1-7 alkyl, a C1-7 alkanoyl, a C1-7 alkanoylamino, a C1-7 alkylcarbonyl, a C1-7 alkoxycarbonyl, carbamoyl, a mono- or di-C1-7 alkylcarbamoyl, a C1-7 alkylsulfonylamino, phenylsulfonylamino, a C1-7 alkylsulfinyl, a C6-14 arylsulfanyl, a C6-14 arylsulfonyl, a C6-14 aryl, a 5-13-membered heteroaryl, a 5-10-membered heterocycloalkyl, a 5-10-membered heterocycloalkyl-C1-7 alkyl, or a 5-10-membered heterocycloalkyl-C1-7 alkoxy;

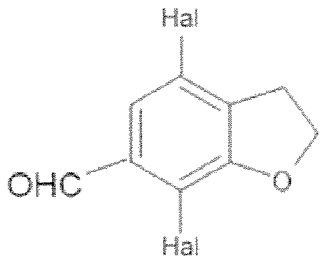



wherein:

Hal and X are each independently a halogen.

According to another exemplary embodiment, the compound of Chemical Formula 10 may be obtained by converting an aldehyde group in the compound of Chemical Formula 6 to a carboxyl group:

[Chemical Formula 6]

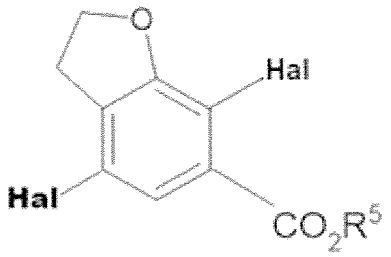



wherein:

Hal are each independently a halogen.

According to still another exemplary embodiment, the compound of Chemical Formula 10 may be obtained by carboxylating the compound of Chemical Formula 14:

[Chemical Formula 14]



wherein:

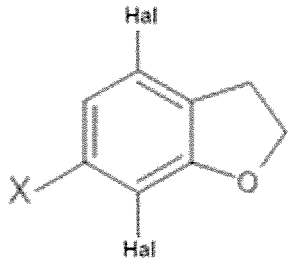
Hal are each independently a halogen, and

$R^5$ is a C1-4 alkyl.

Meanwhile, the compound of Chemical Formula 6 may be synthesized from the compound of Chemical Formula 5 or the compound of Chemical Formula 14.

According to one exemplary embodiment of the present invention, the compound of Chemical Formula 6 may be obtained by selectively converting the substituent X in the compound of Chemical Formula 5 to an aldehyde group. This process is as described above:

[Chemical Formula 5]




wherein:

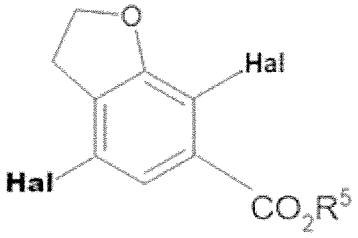
Hal and X are each independently a halogen.

According to yet another exemplary embodiment, the compound of Chemical Formula 6 may be obtained by:

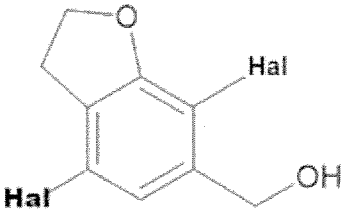
obtaining a compound of Chemical Formula 15 from the compound of Chemical Formula 14, and

obtaining the compound of Chemical Formula 6 from the compound of Chemical Formula 15:

[Chemical Formula 14]




[Chemical Formula 15]




wherein:

Hal are each independently a halogen, and

$R^5$ is a C1-4 alkyl.

In the methods of producing a compound of Chemical Formula 10 from 1) a compound of Chemical Formula 5, 2) a compound of Chemical Formula 6, or 3) a compound of Chemical Formula 14 and producing a compound of Chemical Formula 9 from the compound of Chemical Formula 10, the compound of Chemical Formula 12 is used. The compound of Chemical Formula 12 is cheaper than the compound of Chemical Formula 7 used in the conventional schemes, and the use of the compound of Chemical Formula 12 may address problems caused by the impurities generated during the production of Chemical Formula 7, thereby obtaining the high-quality compound of Chemical Formula 9 and the final target material.

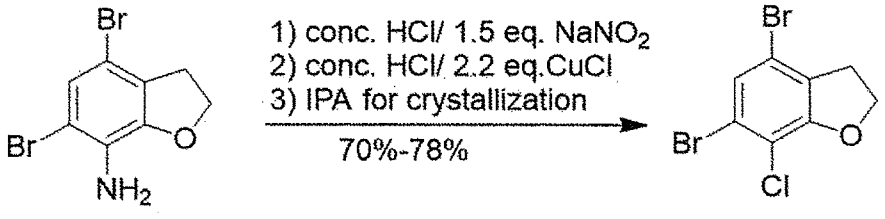
[Advantageous Effects]

According to the present invention, the compound of Chemical Formula 9, which

solution was washed with ethanol (1 L) and put into the aqueous solution. After the reaction solution was stirred for 30 minutes, ethanol was removed by vacuum concentration. After the temperature was lowered to 15°C to 25°C, the crystals were then filtered. The crystals were washed with water (6 L), and then dried under vacuum at 50°C to 60°C for 16 hours to obtain the title compound (1.5 kg, 92%).

$^1$H NMR (61 MHz, $CDCl_3$) δ7.07(s, 1H), 4.65(t, $J$ = 8.5 Hz, 2H), 3.91(s, 2H), 3.17(t, $J$ = 8.5 Hz, 2H); $[M+H]^+$ 294

**Step 4: 4,6-Dibromo-7-chloro-2,3-dihydrobenzofuran (c50)**




**c49** **c50**

HCl (15 L) was added to a reactor, and the temperature was lowered to 0°C to 5°C. Thereafter, 4,6-dibromo-2,3-dihydrobenzofuran-7-amine (c49: 3.0 kg, 1 eq) was added thereto and stirred for 10 minutes. Then, a solution obtained by dissolving sodium nitrite (1.1 kg, 1.5 eq) in water (2 L) was added dropwise to the reactor and stirred at 0°C to 5°C for 30 minutes. As the crystals dissolved, the red solution turned black. c-HCl (12.6 L) was added to another reactor, and copper (I) chloride (2.2 kg, 2.2 eq.) was added thereto. Then, the mixture was heated to 50°C to 60°C, and the reaction solution was added thereto and stirred at 50°C to 60°C for 30 minutes to terminate the reaction. After it was confirmed that the reaction was completed, the reaction mixture was cooled to 0°C to 10°C, and water (20 L) was added to terminate the reaction. The mixture was stirred for 30 minutes, filtered, and washed with water (5 kg). Then, the filtered crystals were dissolved in DCM (20 L). To