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ORIGINAL ARTICLE

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Radiolabeling of ^{11}C-sertraline by fast and easy loop method with [^{11}C]CH_3OTf

Hak Jeong Lee,[a,b] Jae Min Jeong,[a,*] Sang-Yoon Lee, [b] Tatsuo Ido,[b]

[a]Department of Nuclear Medicine, Seoul National University College of Medicine and Institute of Radiation Medicine, Medical Research Center, Seoul, Korea; [b]Neuroscience Research Institute, Gachon University, 24, Namdong-daero 774 beon-gil, Namdong-gu, Incheon, Korea; [b]Department of Neuroscience, College of Medicine, Gachon University, 191, Hambangmoe-ro, Yeonsu-gu, Incheon, Korea

ABSTRACT

Cis-(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tertrahydro-N-methyl-1-naphthalenamine (sertraline) hydrochloride from among selective serotonin reuptake inhibitors (SSRIs) is a treatment of major depression. For the differential diagnosis by metabolizing serotonin in a patient with neurological disorders, the radiolabeled ^{11}C-sertraline was developed for non-invasive positron emission tomography in living brain and use the evaluation of new drug for SSRIs. We release the results of a fast and easy radiolabeling method applied a one-step loop method with [^{11}C]CH_3OTf for routine clinical applications of ^{11}C-sertraline. 1 mg of a precursor for ^{11}C-sertraline in 0.1 mL DMF and 5 μL of 1N NaOH, were injected into the loop of semi-prep high-performance liquid chromatography (HPLC). [^{11}C]CH_3OTf was passed through the loop at room temperature (RT). The ^{11}C-sertraline was separated by the semi-preparative HPLC. ^{11}C-sertraline was eluted at 28.0 min was collected and evaluated by analytical HPLC and mass spectrometer. The total radiolabeling efficiency of ^{11}C-sertraline was 30.7±8.7%. The specific activity was 64.8±51.4 GBq/μmol. The radiochemical and chemical purities were higher than 99%. The mass spectrum of the product showed m/z peaks at 307.1 (M+1), indicating the mass of sertraline. By the one-step loop method with [^{11}C]CH_3OTf, ^{11}C-sertraline could be quickly and easily prepared for clinical application.

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Key Word: ^{11}C-sertraline, PET, [^{11}C]CH_3OTf, Loop method, SSRI

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) plays an important role in several neurological disorders such as anxiety, depression, obsessive compulsive disorder, feeding disorder, schizophrenia, Alzheimer's disease, and sexual disorder (1-4). Selective serotonin reuptake inhibitors (SSRIs) have been developed for the treatment of depression by increasing the level of 5-HT in synaptic cleft (5). A SSRI, cis-(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tertrahydro-N-methyl-1-naphthalenamine (sertraline, 1) hydrochloride, was developed for treatment of major depression (6-8). ^{11}C-sertraline ($T_{1/2}$ = 20.4 min) was developed for the study of the serotonergic system in vivo with positron emission tomography by labeling with [^{11}C]CH_3I (9). However, the method with [^{11}C]CH_3I was necessary to improve because of the time-consuming labeling method. In the present study, we used the more reactive [^{11}C]CH_3OTf (14) instead of

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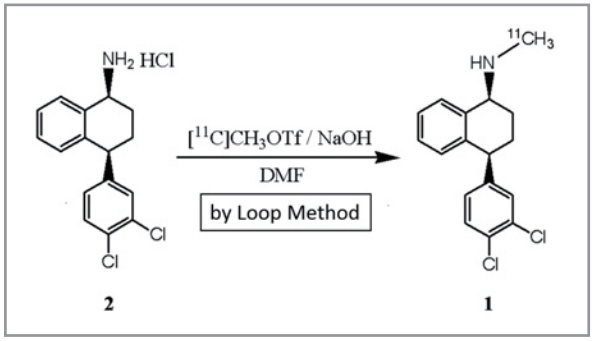
Correspnding Author : Jae Min Jeong, Department of Nuclear Medicine, Seoul National University Hospital, 28 Yongon-dong Jongno-gu, Seoul 110-744 Korea, Tel: +82-2-2072-3805, Fax: +82-2-745-7690, e-mail: jmjng@snu.ac.kr
AUTHOR EMAIL ADDRESS : Hak Jeong Lee: yes2hack@gachon.ac.kr / Jae Min Jeong: jmjng@snu.ac.kr /
Sang-Yoon Lee: rchemist@gachon.ac.kr Tel: 032-460-9032, fax: 032-460-8230 / Tatsuo Ido: ido@gachon.ac.kr

[^{11}C]CH_3I to achieve the milder reaction condition with the loop method (10-13). Also for preparing a precursor of 11C-sertraline, cis-(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tertrahydro-1-naphthalenamine (norsertraline, 2) hydrochloride, it was synthesized by one of the reported methods (15). We describe here the fast and easy preparation of ^{11}C-sertraline by the loop method with [^{11}C]CH_3OTf for routine clinical applications. (Scheme 1)



Scheme 1. Synthesis of ^{11}C-sertraline by the loop method with [^{11}C]CH_3OTf.

Materials and Methods

1. Materials

(S)-tetralone(5) was purchased from AmplaChem, Inc. Sertraline·hydrochloride was donated by department of pharmacology in Seoul National University College of Medicine. All other chemicals were obtained from Aldrich, Fluka, or Sigma (Milwaukee, WI, USA) and were used as received without a further purification.1H NMR spectra were recorded in an AL300FT (Jeol ltd., Tokyo, Japan) using TMS as an internal standard. Mass spectrometry was performed by an Alliance 3100 mass detector (Waters Corp., Milford, MA, U.S.A.). The radioactivity of ^{11}C-isotope was measured by a dose calibrator (Atomlab 100; Biodex, New York, NY, U.S.A.). The purification of norsertraline hydrochloride and ^{11}C-sertraline and the analysis of ^{11}C-sertraline were carried out by the semi-preparative High Performance Liquid Chromatography (HPLC) (Binary Gilson 321 pump, Gilson UV/Vis-155 detector, 506C interface module (Gilson Inc., Middleton-Wisconsin, U.S.A.). [^{11}C]CO_2 gas was produced using the ^{14}N(p,α)^{11}C reaction by proton beam irradiation for 10 min at N_2 gas (99.9999%, containing a little O_2 gas < 1 ppm) on cyclotron (Ebco Technologies, Vancouver, Canada, 13 MeV).

2. Synthesis of norsertraline HCl

The synthesis of norsertraline hydrochloride was followed by the method reported in the paper (15). 5 (2 g, 6.87 mmol) and (R)-tert-butylsulfinamide ((R)-TBSA, 0.92 g, 7.56 mmol) dissolved in anhydrous THF(15 mL) in a 50 ml flask and stirred. Titanium ethoxide (3.135 g, 13.7 mmol, 20 wt % solution in ethanol) dissolved in 15 ml EtOH added to the mixture and reacted at 70°C for 20 hr. The mixture cooled off at RT and added 24 wt % aqueous NaCl (10 mL). THF (20 mL) was added for the dilution. The mixture was filtered through a celite and washed with THF (5 mL) for three times. The eluate was concentrated by a rotary evaporator. The aqueous layer was extracted with toluene (15 mL) and toluene/ethyl acetate (2:1 v/v, 30 mL) and the organic layer was washed with aqueous NaCl (5 mL) and water (4 mL). The organic layer was concentrated by a rotary evaporator and purified by a column chromatography on silica gel (20% EA/hex, Rf = 0.24). The separated compound was concentrated by a rotary evaporator and dried under vacuum. The refined product of (R)-tert-butylsufinimide group, (4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-N-tert-butylsulfinimide(4), was confirmed by chemical analysis compared with the paper (15) : yield 66%.

4 (1.8g, 4.6 mmol) dissolved in methanol was stirred at -5 °C. 0.5M sodium borohydride (NaBH4, 0.94g, 24.8 mmol) dissolved in EtOH 40 mL was added dropwisely for 2 hr. The reaction mixture was stirred at 0-5 °C until acquiring compound 3 (= 3 hr). The reaction progress was monitored by thin layer chromatography (TLC) on silica gel (EA :

Hex = 2 : 8, Rf = 0.19). cis-(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-N-tert-butylsulfinamide (3) and trans-(1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-N-tert-butylsulfinamide (trans-isomer) was separated by HPLC (Column: Waters XTerra RP-18, 10 X 250 mm, 10 μm; Waters, Milford, Ma, U.S.A.; Eluent: Gradient 50-100% MeCN in 10 mM HCl, 4 ml/min; UV: 215 nm). The retention times of 3 and trans-isomer were 19.6 and 20.3 min respectively. 3 collected at 19.3 min by the prep-HPLC was concentrated by rotary evaporator and dried under vacuum. The refined cis-form 3 was confirmed by chemical analysis: yield 57%; the HPLC purity of 3 was ≥ 99%.

3 was added with HCl (4 N) in methanol (4 mL) and stirred for till the reaction was complete. 6 N aqueous NaOH (7 g) added the mixture for neutralization between pH 7 to 8. Methanol in the mixture was removed by a rotary evaporator. The aqueous layer was extracted from the mixture using 8 mL diethyl ether 2 times and concentrated by a rotary evaporator. After cooling 2N HCl in diethyl ether (5 mL) added slowly. Norsertraline of HCl salt was precipitated. The precipitate was washed with 4 mL of diethyl ether and dried under vacuum. The refined norsertraline HCl was confirmed by chemical analysis: yield 69%; the HPLC purity of the norsertraline HCl was ≥ 98%.

3. Preparing $[^{11}C]CH_3OTf$ from $[^{11}C]CO_2$

AgOTf-Graphpac GC was made for synthesis $[^{11}C]CH_3OTf$ in the previous paper (16). The synthesis of $[^{11}C]CH_3I$ from $[^{11}C]CO_2$ was used by the method of using LAH and HI (17). Captured $[^{11}C]CH_3I$ in a reaction vial heated for evaporation at 120ºC. The $[^{11}C]CH_3I$ gas was blown by N_2 gas (99.999%) and passed through each cartridges filled with $Mg(ClO_4)_2$ and Na_2HPO_4. for drying moisture. $[^{11}C]CH_3OTf$ was synthesized by $[^{11}C]CH_3I$ gas through AgOTf-Graphpac GC column heated at 230ºC.

4. Radiosynthesis of ^{11}C-sertraline with the loop method

The automatic ^{11}C-methylation module, reported in the previous paper (18), was used for the radiosynthesis of 11C-sertraline applied with the loop method (12). 1 mg of norsertraline separated in 4 mL vial was dissolved in DMF 0.1 mL. Then, 5 μL of 1N NaOH was added in the loop of HPLC. Those solutions were injected into the stainless-steel loop (2 mL) on the prep HPLC with a hamilton syringe. $[^{11}C]CH_3OTf$ was blown to the loop by N_2 gas (99.999%) at 20 ml/min for 3 min. 11C-sertraline was separated by the prep-HPLC (Column: Waters XTerra RP-8, 10 X 250 mm, 10 μm; Waters, Milford,s Ma, U.S.A.; Eluent: EtOH 55% in 10mM phosphate buffer at pH 7; flow rate: 3 mL/min; RT; 215 nm wavelength). The retention times of ^{11}C-sertraline was 28 min. ^{11}C-sertraline collected from HPLC and diluted with a saline and finally sterilized by filtration (0.22 μm, Millex GS filter). The collected ^{11}C-sertraline was analyzed by analytical HPLC (Column: Waters XBridge™ RP-18, 4.6 X 100 mm, 3.5 μm; Waters, Milford, Ma, U.S.A.; Eluent: 35% MeCN in D.W.(Both contained 0.05% TFA) ; flow rate: 1 mL/min; UV: 215 nm). The captured product after the decay of ^{11}C-sertraline was measured by LC-MS.

Result and Discussion

1. Synthesis of norsertraline HCl

Norsertraline as a precursor was synthesized by the method introduced in the paper (15). 5 in THF was reacted with (R)-tert-butylsulfinamide under Ti(OEt)4

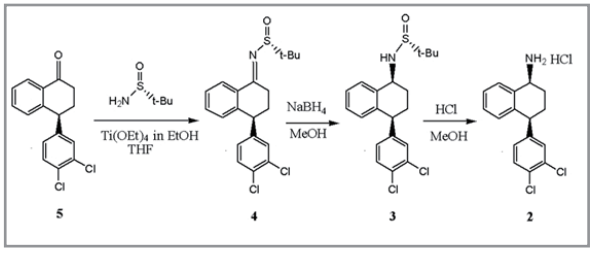


Figure 1. Synthesis of ^{11}C-sertraline by the loop method with $[^{11}C]CH_3OTf$.

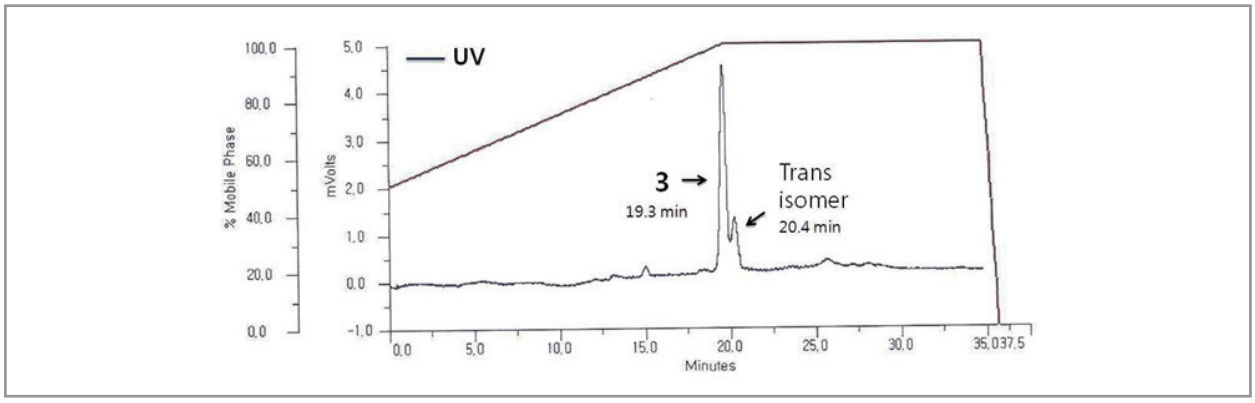


Figure 2. HPLC chromatogram for purification of cis and trans isomers of 1-N-tert-butylsulfinamide group. (Column: Waters, XTerra RP18, 10 X 250 mm, 10 μm; Eluent: Gradient 50-100% MeCN in 10 mM HCl (Oblique line), 4 ml/min; UV: 215 nm)

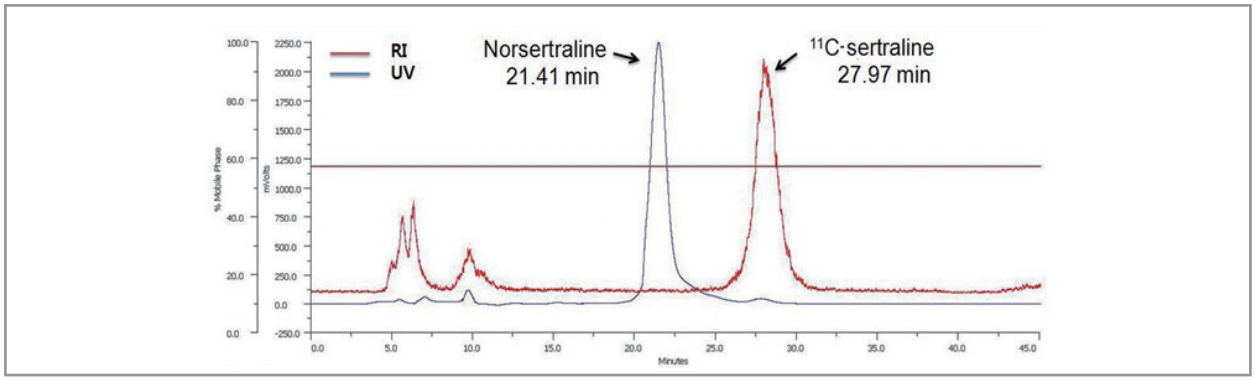


Figure 3. HPLC chromatogram of ^{11}C-sertraline for purification. (Column: Waters XTerra RP-8, 10 X 250 mm, 10 μm; Eluent: EtOH 55% in 10mM phosphate buffer at pH 7; flow rate: 3 mL/min; at RT; UV: 215 nm)

as a catalyst for synthesizing 4. 4 in MeOH was reacted with $NaBH_4$ for a reduction of (R)-tert-butyl sulfinyl imine (15). 3 and trans-isomer were produced. The predominant 3 at 80% was purified by the prep-HPLC. The retention times of 3 and trans-isomer by the prep-HPLC were 19.3 and 20.4 min, respectively. (Figure 2) 3 was hydrolyzed for the elimination of (R)-tert-butylsulfyl group by HCl in methanol (15). The resulting norsertraline HCl was synthesized by 2N HCl in diethyl ether.

2. Radiosynthesis of ^{11}C-sertraline by the loop method with [^{11}C]CH_3OTf.

The radioactivity of [^{11}C]CO_2 generated for 10 min by the cyclotron was 21.43±0.96 GBq at end of bombardment (EOB). The [^{11}C]CO_2 was transferred to the automatic ^{11}C-methylation module (18) for converting [^{11}C]CH_3OTf. By the loop method, ^{11}C-sertraline was separated by the prep-HPLC at 28 min. (figure 3) The radiochemical yield of ^{11}C-sertraline in the prep-HPLC was 72.6±8.4%. The radiochemical yield of ^{11}C-sertraline from [^{11}C]CO_2 was 30.7±8.7%. The total required time for radiolabeling and purification of ^{11}C-sertraline took 40±1 min from EOB. The radioactivity of ^{11}C-sertraline was 6.57±0.90 GBq at EOB. The absolute yield of final radiopharmaceutical products after 40 min for radiolabeling ^{11}C-sertraline was 1.69±0.23 GBq. (figure 4)

3. Analysis of ^{11}C-sertraline

The identity of ^{11}C-sertraline compared with sertraline as a

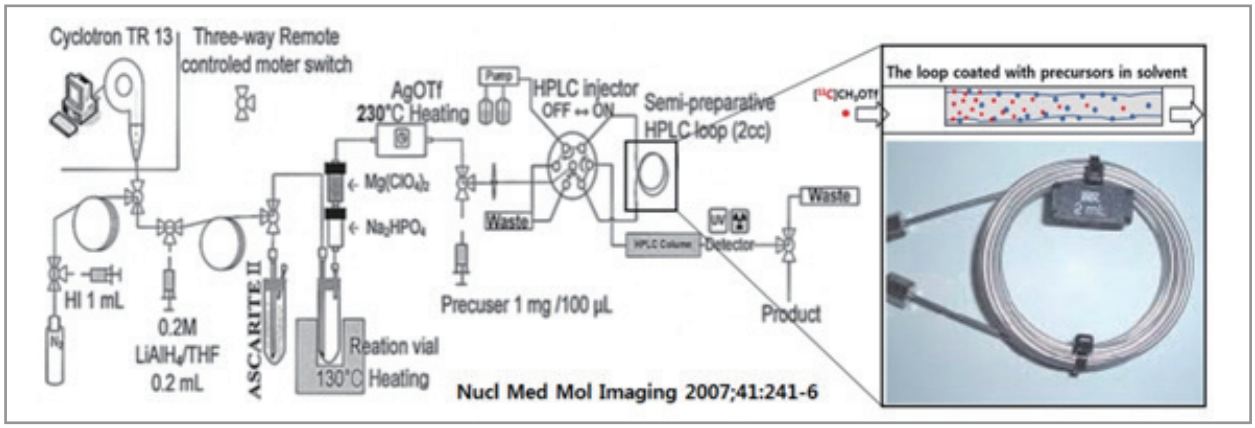


Figure 4. The radiolabeling system by fast and easy loop method with [^{11}C]CH_3OTf

standard was confirmed by the analytical HPLC and LC-MS. The retention times of ^{11}C-sertraline and sertraline were the same 14.1 min in the analytical HPLC. The LC/MS spectra for the resulting product of decayed ^{11}C-sertraline after collected from HPLC and diluted with a saline and sterilized by filtration was predominantly showed m/z peaks at 307 (M+H), 329 (M+Na), indicating a molecular weight of 306 amu like a sertraline. The chemical and radiochemical purity of 11C-sertraline measured by analytical HPLC was ≥98.2% and ≥99.5%, respectively. The specific activity of 11C-sertraline was 64.8±51.4 GBq/μmol.

Conclusion

^{11}C-sertraline was radiolabeled by the loop method with [^{11}C]CH_3OTf. The precursor of ^{11}C-sertraline was prepared with synthesizing the cis form of norsertraline. This study could improve the performance by applying the radiolabeling method of ^{11}C-sertraline with [^{11}C]CH_3OTf by the fast and easy loop method compared with the conventional method using [^{11}C]CH3I. The previous radiolabeling reaction by the method with [^{11}C]CH3I was heated to 120 ° C for 8 min. However, this study was optimized by directly injecting just for 3 min on the HPLC loop with mild condition and without reaction vessel. This loop method has fast and easy advantages by eliminating the radiolabeling reaction vessel for convenience. In addition, the by-products of ^{11}C-sertraline by dimethylation of its amine weren't produced when using the loop methods with [^{11}C]CH_3OTf but produced when using the method with [^{11}C]CH_3I. It is expected because the radiolabeling reaction on the loop was done for an abbreviated time at RT. Also, if the best temperature of the

Table 1. Synthesis data and production yields for ^{11}C-sertraline

Reaction time with [^{11}C]CH3OTf	≤ 3 min, at RT
Radiochemical yield in prep HPLC by [^{11}C]CH_3OTf	72.6±8.4%
Radiochemical yield	30.7±8.7% (EOB)
Absolute yield of final radiopharmaceutical product solution	1.69±0.23 GBq
Synthesis time	40±1 min (EOB)
Chemical purity	≥ 99.2%
Radiochemical purity	≥ 99.5%
Specific activity (EOB)	64.8±51.4 GBq/μmol

radiolabeling reaction on the loop could be regularly set, its efficiency should increase more. The final reaction yield was improved from 20% to 31% and the reaction time was also reduced from 50 min to 40 min from EOB, compared with the method using [^{11}C]CH_3I (9). Furthermore, if the HPLC condition are adjusted, the separation time will be reduced by over 10 min.

Acknowledgments

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