Synthesis of F-18 Labeled Capecitabine Using [^{18}F]F_2 Gas as a Tumor Imaging Agent†

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5-Fluorouracil (5-FU) is commonly applied to the treatment of various types of cancers including renal cell carcinoma (RCC), and rapidly metabolized by enzyme dihydropyrimidine dehydrogenase (DPD).[1] However, 5-FU is poorly selective to tumor and highly toxic in bone marrow, central nervous system, gastrointestinal tract (GI-tract), and skin. Thus, many compounds have been developed for advanced selectivity and to reduce toxicity such as UFT, 5-ethynyluracil, S-1, cyclic ftorafur, doxofluridine, and capecitabine.[2] In particular, other modified fluorinated pyrimidines improve the effects of continuous infusion of 5-FU and employ some tumor specific enzymes to convert prodrug to 5-FU.

Capecitabine (N^4-*n*-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine, **1**), a prodrug of 5-FU, is the first and only orally-administered fluoropyrimidine approved for the use as a second-line therapy of metastatic breast cancer, gastric, colorectal, bladder cancer and other solid malignancies.[3] Capecitabine is changed to 5-FU by three enzymes such as carboxyesterase, cytidine deaminase (cyd deaminase) and thymidine phosphorylase (dThdPase) mainly located in liver and tumors. The biotransformation of capecitabine to 5'-deoxy-5-fluorocytidine (5'-DFCR) intends to occur preferentially in the liver compared with the GI-tract, rusulting in minimizing the accumulation of 5-FU in the GI-tract. Conversion of 5'-deoxy-5-fluorouridine (5'-DFUR) to 5-FU is enzymatically catalyzed by dThdPase, which is much higher expressed in many types of human tumors than in healthy tissues (Figure 1).[4] For this reason, it is thought that capecitabine has an improved bioavailability and selective distribution to be more effective than 5-FU. Based on the superiority of capecitabine in physiological environment, capecitabine, labeled with positron emitter such as fluorine-18 or carbon-11, may serve as a solid tumor imaging agent and enable noninvasive monitoring of the levels of tumor specific enzymes using Positron Emission Tomography (PET).

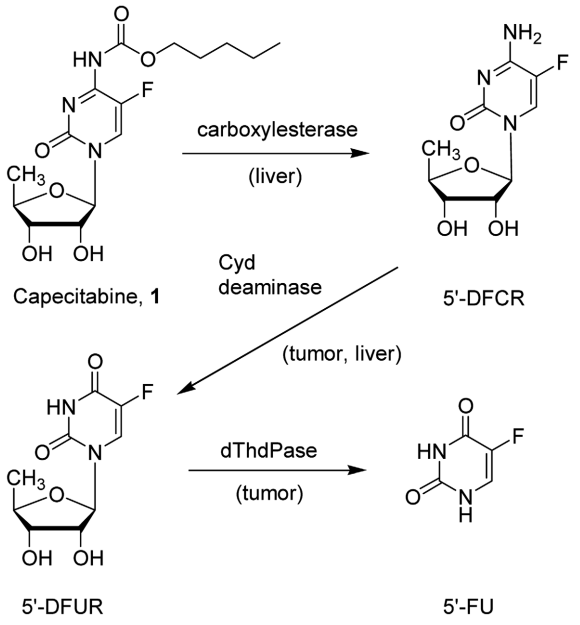

Figure 1. Metabolic pathway of capecitabine.

Generally, fluorination of aromatic compounds can be labeled by electrophilic substitution, but these processes provide fluorinated compounds with low specific activities. To get fluorine-18 labeled aromatic compounds with high specific activity, nucleophilic substitution aromatic fluorination is better. But this type reactions are still undergone only limited precursors containing good leaving groups such as nitro- and trimethylammonium triflate in electron deficient aromatic compound. Recently, there was a report that fluorine-18 labeled capecitabine was prepared by nucleophilic substitution of the 2',3'-di-*O*-acetyl-5'-deoxy-5-nitro-N^4-(*n*-pentyloxycarbonyl)cytidine with [^{18}F]fluoride ion in the presence of Kryptofix[2.2.2] in about 20-30% radiochemical yield.[5] Herein, we describe the different synthetic method of F-18 labeled capecitabine analogue using electrophilic fluorination with [^{18}F]F_2 gas generated by bombardment of a labeling source with 13.2 MeV proton beam and HPLC purification profile. The [^{18}F]F_2 was produced using the ^{18}O(p,n)^{18}F reaction, because the production yield using the ^{18}O(p,n)^{18}F was 2.5-fold higher than the ^{20}Ne(d,α)^{18}F and the proton beam irradiation was easier than the deuterium beam.

The precursor for electrophilic [^{18}F]fluorination, 5'-deoxy-N^4-(*n*-pentyloxycarbonyl)cytidine (**12**), was synthesized from the commercially available stating material D-ribose (**2**) through nine steps as shown in Scheme 1 and 2. An

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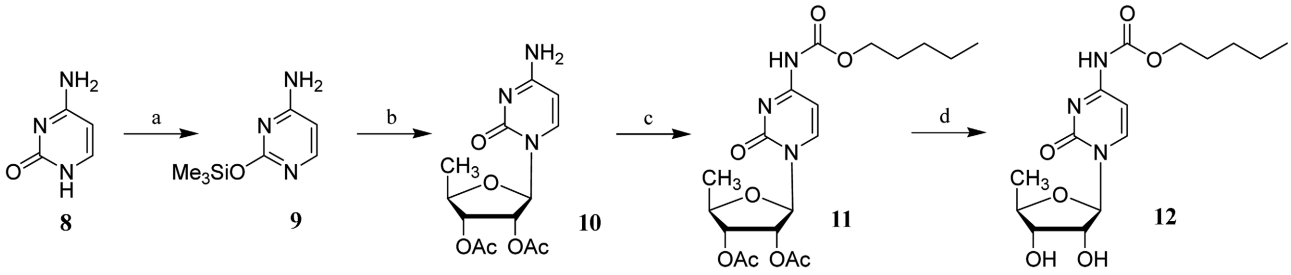
Scheme 1. a) MeOH, conc. H_2SO_4, rt, 24 h; b) $CuSO_4$, conc. H_2SO_4, acetone, rt, 20 h; c) TsCl, pyridine, $CHCl_3$, 0 °C to rt, 24 h; d) $LiAlH_4$, ether:toluene (8 : 2), reflux, 22 h; e) i) acetic acid, 0 °C, 1 min; ii) acetic anhydride, 0 °C to rt, 20 h.



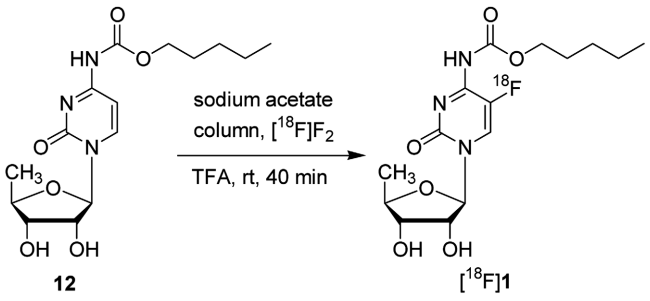
Scheme 2. a) HMDS, TMSCl, CH_3CN, reflux, 3 h; b) **7**, NaI, TMSCl, molecular sieves 4 Å, CH_3CN, rt, 3 h; c) *n*-amyl chloroformate, pyridine, $CHCl_3$, 0 °C to rt, 1 h; d) 1% NaOH/MeOH, 0 °C, 1 h.

intermediate, 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside (**7**), was obtained by some modifications according to known procedures as shown in Scheme 1.[5,6]

Starting material **2** was converted into methylated D-ribose **3** by the reaction with methanol in the presence of sulfuric acid. 2,3-*O*-Isopropyliden-1-*O*-methyl-D-ribofuranoside (**4**) was obtained by treating **3** with cupric sulfate and sulfuric acid in acetone in 65% yield. Tosylation of alcohol **4** was performed by the reaction with tosyl chloride in pyridine to give the tosylate, 2,3-*O*-isopropyliden-1-*O*-methyl-5-*O*-tosyl-D-ribofuranoside (**5**) in 85% yield. The tosylate **5** was converted into 5-deoxy-2,3-*O*-isopropyliden-1-*O*-methyl-D-ribofuranoside **6** by the treatment with $LiAlH_4$ (1 M $LiAlH_4$ in diethyl ether) in ether:toluene (8 : 2) solution. The hydrolysis of compound **6** with aqueous acetic acid solution followed by a protection reaction with acetic anhydride gave the intermediate 5-deoxy-1,2,3-*O*-triacetyl-D-ribofuranoside (**7**, 53%).

Precursor of capecitabine, 5'-deoxy-N^4-(*n*-pentyloxycarbonyl)cytidine was performed as shown in Scheme 2. Cytosine **8** was reacted with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and chlorotrimethylsilane (TMSCl) to provide cytosine trimethylsilyl moeity, which was directly reacted with the intermediate **7** in the presence of sodium iodide, TMSCl and molecular sieves 4 Å in dry acetonitrile to give glycosidation product 2',3'-di-*O*-acetyl-5'-deoxycytidine in 45% yield. The acylation of N^4-amino group of compound **10** with *n*-pentyl chloroformate under pyridine afforded **11** in 78% yield. 5'-Deoxy-N^4-(*n*-pentyloxycarbonyl)cytidine **12** was obtained by 1% NaOH in MeOH in 48% yield. For reference standard, 5'-deoxy-5-fluoro-N^4-(*n*-pentyloxycarbonyl)cytidine (Xeloda; Capecitabine; **1**), was extracted with methanol from Xeloda tablet (Roche).

Radioisotope $[^{18}F]F_2$ gas was produced through the $^{18}O(p,n)^{18}F$ reaction using 13.2 MeV proton beam. To introduce F-18 at C5-position of capecitabine, precursor of capecitabine (10 mg) was dissolved in 10 mL of trifluoroacetic acid. The eluant from the cartridge was bubbled into a reaction vessel for 40 min at ambient temperature. After trifluoroacetic acid was evaporated under reduced pressure, fluorine-18 adducts were dissolved in 2 mL of HPLC eluent. F-18 labeled capecitabine was purified by high-performance liquid chromatography (HPLC). The fraction at 16-18 min was collected (Figure 2) and it was confirmed to be desired



Scheme 3. Labeling of capecitabine using $[^{18}F]F_2$ gas.

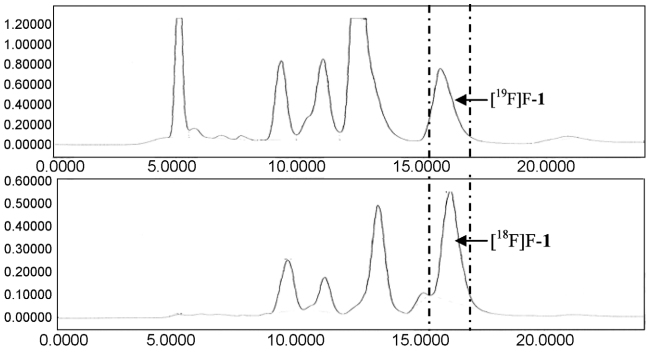


Figure 2. The radiochromatograms of $[^{18}F]$capecitabine reaction mixture. [Econosil silica (Alltech), 10 μ, 250 × 10 mm, mobile phase: isopropanol/CH_2Cl_2/hexane = 1/2/7 [v/v/v], flow rate: 3 mL/min, upper: UV (267 nm), bottom: RA].

compound by co-injection with authentic capecitabine analogue. After HPLC separation, eluant was evaporated and dissolved in physiological solvent. Total elapsed labeling time was 90-110 min.

In conclusion, we have established the $[^{18}F]F_2$ gas target for electrophilic F-18 substitution and fluorine-18 was introduced at C5-position of capecitabine using $[^{18}F]F_2$ gas by electrophilic fluorination. Precursor of capecitabine, 5'-deoxy-N^4-(*n*-pentyloxycarbonyl)cytidine was obtained from D-ribose through nine steps. We produced F-18 labeled capecitabine from the mixture of saturated $[^{18}F]F_2$ gas passing through with $NaOAc{\cdot}3H_2O$ column. After finishing synthesis, the desired compound was purified by HPLC system. Radiochemical yield and radiochemical purity were 5-15% and >95%, respectively.

Experimental Section

All commercial reagents and solvents were used without further purification unless otherwise specified. Thin layer chromatography (TLC) was performed on Merck 60 F_{254} silica plates and visualized by UV. Column chromatography was performed on silica gel 70-230 mesh. NMR spectra were recorded on a Bruker–300 and chemical shifts were reported in δ units (ppm) from internal standard tetramethylsilane. High Performance Liquid Chromatography (HPLC) was carried out on a Young-Lin System (Young-Lin Instrument, Korea) with a semi preparative column (Econosil Silica, 10 μ, 10 × 250 mm from Alltech) and simultaneously monitored by a Young-Lin UV instrument (267 nm) and NaI(Tl) radioactivity detector. $[^{18}F]F_2$ gas was produced with MC-50 cyclotron by irradiation of $[^{18}O]O_2$ at Korea Institute of Radiological and Medical Sciences (KIRAMS). Radio-TLC was measured on a Bioscan AC-3000 scanner (Washington D.C., U.S.A.). All radiochemical yields are decay-corrected unless noted. The synthesis of the precursor, 5'-deoxy-N^4-(*n*-pentyloxycarbonyl)cytidine (**12**), was performed with the modifications according to procedures reported in the literature.[5,6]

2,3-*O*-Isopropylidene-1-*O*-methyl-D-ribofuranoside (4). A mixture of D-ribose (**2**, 12.0 g, 80 mmol) in methanol (200 mL) and sulfuric acid (1 mL) was stirred for 24 h at room temperature. After pyridine (50 mL) was added in the reaction solution, mixture was evaporated in reduced pressure with toluene and acetone (R_f = 0.38, 20% MeOH/$CHCl_3$) to give **3**. Without further purification, crude mixture was dissolved in acetone (250 mL). After cupric sulfate (12.1 g, 76 mmol) and sulfuric acid (1.2 mL) was added, reaction mixture was stirred for 20 h at room temperature and then filtered. The residue solution was added aq. ammonia (8 mL) and filtered again. The filtered solution was evaporated with EtOH and toluene. The mixture was purified column chromatography (0-2% MeOH/CH_2Cl_2) to give a yellow oil **4** (65%), which was used for the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.49 (s, 3H), 3.25 (dd, *J* = 10.2, 2.7 Hz, 1H), 3.44 (s, 3H), 3.62-3.73 (m, 2H), 4.43-4.45 (m, 1H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 4.98 (s, 1H).

2,3-*O*-Isopropylidene-1-*O*-methyl-5-*O*-tosyl-D-ribofuranoside (5). Compound **4** (12.2 g, 60 mmol) was dissolved in pyridine (180 mL). Tosyl chloride (12.0 g, 63 mmol) in chloroform (30 mL) was added to the solution and stirred at room temperature for 24 h. The mixture was poured in ice water (200 mL) and extracted with dichloromethane. Organic layer was evaporated under vacuum, dried and the crude product was purified with column chromatography (0-2% MeOH/CH_2Cl_2) to give **5** (18.3 g, 85%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22 (s, 3H), 1.42 (s, 3H), 2.43 (s, 3H), 3.01 (s, 3H), 3.87-3.93 (m, 1H), 4.04-4.07 (m, 1H), 4.19-4.24 (m, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.63 (d, *J* = 6.0 Hz, 1H), 4.92 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H).

5-Deoxy-2,3-*O*-isopropyliden-1-*O*-methyl-D-ribofuranoside (6). 2,3-*O*-Isopropylidene-1-*O*-methyl-5-*O*-tosyl-D-ribofuranoside (**5**, 5.0 g, 14 mmol) was dissolved in ether (80 mL) and toluene (20 mL). After 1 M $LiAlH_4$ in diethyl ether (46 mL) was slowly added and refluxed for 22 h then cooled. Ethyl acetate (10 mL) and water (2 mL) were added then removed by evaporation and dried under vacuum to give a light yellow oil **6**. Collected compound was used for the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.0 Hz, 3H), 1.31 (s, 3H), 3.33 (s, 3H), 4.34 (q, 1H), 4.51 (d, *J* = 6.0 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 4.94 (s, 1H).

5-Deoxy-1,2,3-*O*-triacetyl-D-ribofuranoside (7). Compound **6** (480 mg, 2.55 mmol) was dissolved in acetic acid (12 mL) and stirred for about 1 min at room temperature. After acetic anhydride (1.2 mL) was added at 0 °C, reaction mixture was stirred for several minutes. Sulfuric acid (0.66 mL) was added in reaction solution and stirred for 20 h at room temperature then slowly poured in ice water (200 mL). After the solution was extracted with ethyl acetate and dichloromethane, organic phase was dried over sodium sulfate and the solvent was removed by evaporation to give colorless oil. It was purified by column chromatography (100% CH_2Cl_2) to give a product as a colorless oil **7** (351 mg, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.0 Hz, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 4.23-4.31 (m, 1H), 4.84-4.86 (m, 0.6H), 5.08-5.12 (m, 0.2H), 5.21 (d, *J* = 3.0 Hz, 1H), 5.30-5.35 (m, 0.2H), 6.13 (s, 1H).

2',3'-*O*-Diacetyl-5'-deoxycytidine (10). The mixture of cytosine **8** (2.0 g, 18 mmol) in HMDS (10 mL) and TMSCl (2 mL) was refluxed for 3 h under N_2 atmosphere. The solvent was removed by evaporation to give **9**. To combination, sodium iodide (1.9 g, 12.5 mmol), chlorotrimethylsilane (1.36 g, 12.5 mmol), and molecular sieves 4 Å (200 mg) were added in dry acetonitrile (40 mL) then stirred for several minutes. After 5-deoxy-1,2,3-*O*-triacetyl-D-ribofuranoside (**7**, 1.0 g, 4.0 mmol) was added, reaction mixture was stirred for 30 min at room temperature. Then trimethylsilylated base **9** in acetonitrile (5 mL) was added to the mixture. After the mixture was stirred at room temperature for 3 h, filteration gave a solution, which was

washed by 1 N $NaHCO_3$, 10% sodium thiosulfate solution, and water then dried over sodium sulfate. The solvent was removed by evaporation to give a crude product, which was purified by column chromatograghy (10% MeOH/$CHCl_3$) to give a vacuum dried product as a white solid **10** (560 mg, 45%): ^{1}H NMR (300 MHz, DMSO-d_6) δ1.31 (d, J = 6.3 Hz, 3H), 1.99 (d, J = 6.0 Hz, 3H), 2.06 (d, J = 5.4 Hz, 3H), 4.01-4.06 (m, 1H), 4.57-4.62 (m, 0.2H), 4.87-4.90 (m, 0.2H), 5.06-5.10 (m, 0.6H), 5.39-5.43 (m, 1H), 5.71-5.80 (m, 2H), 7.25-7.34 (brd, 2H), 7.59-7.66 (q, 1H).

5'-Deoxy-2',3'-*O*-diacetyl-N^4-(*n*-pentyloxycarbonyl)cytidine (11). A mixture of 5'-deoxy-2',3'-*O*-diacetylcytidine (**10**, 800 mg, 2.57 mmol) in dichloromethane (80 mL) and pyridine (5 mL) was cooled to 0 °C and *n*-pentyl chloromate (550 mg, 3.67 mmol) was added by dropwising. The mixture was stirred for 1 h at 0 °C. After extracted with ether, reaction mixture was washed by sat. $NaHCO_3$. The organic layer was dried over sodium sulfate and purified by column chromatography (70% EtOAC/hexane) to give a light yellow solid **11** (852 mg, 78%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85-0.90 (m, 3H), 1.28-1.33 (m, 7H), 1.37-1.63 (m, 2H), 1.97 (s, 3H), 2.11 (s, 3H), 4.11 (t, J = 3.3 Hz, 2H), 4.69-4.73 (m, 1H), 4.90 (t, J = 2.9 Hz, 1H), 5.40 (t, J = 2.1 Hz, 1H), 5.89 (d, J = 2.1 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H).

5'-Deoxy-N^4-(*n*-pentyloxycarbonyl)cytidine (12). 5'-Deoxy-2',3'-*O*-diacetyl-N^4-(*n*-pentyloxycarbonyl)cytidine (**11**, 350 mg, 0.82 mmol) was dissolved in methanol (10 mL). Aqueous solution of 1% NaOH was added dropwisely until the reaction is completed which is monitored by TLC at 0 °C. Aqueous solution of HCl (0.5 N) was added to adjust pH to 7. The reaction mixture was extracted by excess ethyl acetate. The organic layer was dried and purified by column chromatography (1 : 50 MeOH/CH_2Cl_2) to give a pale yellow solid **12** (134 mg, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ0.89-0.93 (m, 3H), 1.31-1.41 (m, 4H), 1.45 (d, J = 6.3 Hz, 3H), 1.65-1.67 (m, 2H), 4.05-4.08 (m, 1H), 4.17 (t, J = 6.9 Hz, 2H), 4.33-4.39 (m, 1H), 4.41-4.44 (m, 1H), 4.67 (brs, 1H), 5.39 (brs, 1H), 5.71 (d, J = 1.8 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 8.26 (brs, 1H).

Reference Standard, 5'-Deoxy-5-fluoro-N^4-(*n*-pentyloxycarbonyl)cytidine (Xeloda; Capecitabine; 1). Two Xeloda tablet (Roche) was ground to powder. After the powder was dissolved in methanol (100 mL), mixture solution was stirred for 30 min at room temperature. Methanol solution was filtered and evaporated. The obtained solid was recrystallized with MeOH to give standard **1** as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, J = 7.5 Hz, 3H), 1.29-1.34 (m, 7H), 1.58-1.62 (m, 2H), 3.67 (q, J = 6.0 Hz, 1H), 3.88 (qt, J = 6.0 Hz, 1H), 4.03-4.10 (m, 3H), 5.05 (d, J = 6.0 Hz, 1H), 5.41 (d, J = 6.0 Hz, 1H), 5.65-5.67 (m, 1H), 7.99 (brs, 1H), 10.54 (brs, 1H).

Production of $[^{18}F]F_2$ Gas.[7] Radioisotope $[^{18}F]F_2$ gas was produced through the $^{18}O(p,n)^{18}F$ reaction using a MC-50 cyclotron. Proton beam was degraded from 30 MeV to 13.2 MeV using the cooling water (3.7 mm) and aluminum plate (0.7 mm × 2). About 15.0-20.0 GBq $[^{18}F]F_2$ was generated by bombardment of labeling source: 1st irradiated to 99% $[^{18}O]O_2$ gas with 30 μA beam for 60-120 min and 2nd irradiated 30 μA for 20-30 min to 1% F_2/Ar in an aluminum target body. $[^{18}F]$Acetyl hypofluorite (AcO$[^{18}F]$F) was generated by passing $[^{18}F]F_2$ through a 4.8 × 52 mm (inside diameter[ID]) cartridge containing tightly packed NaOAc·$3H_2O$.

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