

# Syntheses of $^{18}\text{F}$ -5-Fluorouracil, $^{18}\text{F}$ -Fluorouridine and $^{18}\text{F}$ -5-Fluoro-2'-deoxyuridine

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III. 5 Syntheses of  $^{18}\text{F}$ -5-Fluorouracil,  $^{18}\text{F}$ -5-Fluorouridine and  $^{18}\text{F}$ -5-Fluoro-2'-deoxyuridine

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In our cyclotron,  $^{18}\text{F}\text{-F}_2$  has been produced by the  $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$  nuclear reaction.<sup>1)</sup> We have studied the syntheses of various  $^{18}\text{F}$ -radiopharmaceuticals by the use of  $^{18}\text{F}\text{-F}_2$ . 5-Fluorouracil (FU) is a useful pharmaceutical, which has been utilized as an anti-neoplastic agent for the treatment of a variety of disseminated solid tumor.<sup>2)-4)</sup> We tried the  $^{18}\text{F}$ -labeling of FU and its relative compounds for the application of tumor scanning agents. The metabolic pathway of FU is shown in fig. 1. FU has been considered to be metabolated to 5-fluorouridine (FUR) or 5-fluoro-2'-deoxyuridine (FdUR), followed by their phosphate derivatives. It has been also considered that 5-fluorouridine-5'-diphosphate (FUDP) is corporated in RNA, while 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP) acts as a blocking agent of thymidylate synthetase and thereby prevents the incorporation of deoxyuridine in DNA.<sup>5)</sup> In this way, not only FU but FUR and FdUR are expected to be useful for the antitumor pharmaceuticals. In these aspects, we selected the following three compounds (5-fluorouracil (FU), 5-fluorouridine (FUR) and 5-fluoro-2'-deoxyuridine (FdUR)) for the aimed  $^{18}\text{F}$ -labeling compounds and performed the comparative studies of their usefulness as radiopharmaceuticals for the tumor scanning by administrating them to mice bearing AH109A tumor. In this paper, we report the syntheses of  $^{18}\text{F}\text{-FU}$ ,  $^{18}\text{F}\text{-FUR}$  and  $^{18}\text{F}\text{-FdUR}$  and the differences of their behaviours in mice.

MATERIALS AND METHODS

The synthesis of  $^{18}\text{F}\text{-FU}$  has been reported by R. M. Lambrecht, C. Mantescu, J. S. Fowler et al.<sup>6)</sup> and the  $^{18}\text{F}$ -labeling of FUR has been performed by Chyng-Yann Shiue, J. S. Fowler, R. R. MacGregor et al.<sup>7)</sup> We synthesized  $^{18}\text{F}\text{-FU}$ ,  $^{18}\text{F}\text{-FUR}$  and  $^{18}\text{F}\text{-FdUR}$  with a few modifications.

Production of  $^{18}\text{F}\text{-F}_2$  ;  $^{18}\text{F}\text{-F}_2$  was produced from the deuteron bombardment of a neon-fluorine gas mixture (0.05 % fluorine in neon) by the  $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$  nuclear reaction in a nickel target chamber at a pressure of 25 atm for 1 hr at a current of 10 uA.

Synthesis of  $^{18}\text{F}$ -5-Fluorouracil ( $^{18}\text{F}\text{-FU}$ ) ; The  $^{18}\text{F}\text{-F}_2$  produced was purged through the target chamber (flow rate : 100 ml/min ; total time : 25-30 min) into the solution of 5 mg (45 umol) of uracil in 4 ml of trifluoroacetic acid at 0°C (ice water bath). The solvent was removed with a stream of nitrogen. The oily residue was sublimed under reduced pressure to give  $^{18}\text{F}\text{-FU}$ . 10-15 mCi of  $^{18}\text{F}\text{-FU}$  was obtained. The synthetic route and the synthetic method of  $^{18}\text{F}\text{-FU}$  are respectively shown in chart 1 and fig. 2.

Synthesis of  $^{18}\text{F}$ -5-Fluorouridine ( $^{18}\text{F}$ -FUR) ; The  $^{18}\text{F}$ - $\text{F}_2$  produced was purged through the target chamber (flow rate : 100 ml/min ; total time : 25-30 min) into the solution of 6 mg (16  $\mu\text{mol}$ ) of 2',3',5'-tri-O-acetyluridine in 3 ml of glacial acetic acid in a reaction vessel at room temperature. The reaction mixture was then transferred to a round-bottom flask and evaporated in vacuo to give  $^{18}\text{F}$ -2',3',5'-tri-O-acetyl-5,6-dihydro-5-fluoro-6-acetoxyuridine. Its compound was dissolved in 1 ml of 28 % sodium methoxide - methanol solution and 2 ml of methanol and evaporated to dryness. The residue was dissolved in water for chromatographic separation of  $^{18}\text{F}$ -FUR. Chromatographic separation were obtained on cation exchange column (AG 50W,  $\text{H}^+$  form), eluted with water. The eluate was evaporated in vacuo and the residue was extracted with ethyl acetate : acetone : water (V/V 70/40/5) and then passed through a silica gel column, followed by being passed through an alumina column, eluted with same solvent system. The eluate was evaporated in vacuo to give 5-10 mCi of  $^{18}\text{F}$ -FUR. The synthetic route and the synthetic method of  $^{18}\text{F}$ -FUR are respectively shown in chart 2 and fig. 3.

Synthesis of  $^{18}\text{F}$ -5-Fluoro-2'-deoxyuridine ( $^{18}\text{F}$ -FdUR) ;  $^{18}\text{F}$ -FdUR was synthesized in the same method as  $^{18}\text{F}$ -FUR. In the synthesis of  $^{18}\text{F}$ -FdUR, 6 mg (21  $\mu\text{mol}$ ) of 3',5'-di-O-acetyl-2'-deoxyuridine was used as the starting material. 5-10 mCi of  $^{18}\text{F}$ -FdUR was obtained. The synthetic route and the synthetic method of  $^{18}\text{F}$ -FdUR are respectively shown in chart 2 and fig. 3.

Radiochemical analysis of  $^{18}\text{F}$ -FU,  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR ; The radiochemical purity of  $^{18}\text{F}$ -FU,  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR was determined by HPLC (column : u-Bondapak C-18 ; eluent : 10 mM  $(\text{NH}_4)_2\text{HPO}_4$  aqueous solution ; flow rate : 2 ml/min). The radiochemical purity of  $^{18}\text{F}$ -FU,  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR was found to be respectively >94 %, 90-95 % and 98 % (fig. 4).

## RESULTS AND DISCUSSION

We improved the syntheses as follows ; (1) in the synthesis of  $^{18}\text{F}$ -FU, the temperature of the sublimation was maintained at 150°C during the first 10 min and finally was slowly raised to 180°C. (2) in the syntheses of  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR, the step of passing through an alumina column was freshly added. By these modifications, the co-sublimation of impurity was prevented and  $^{18}\text{F}^-$  was completely removed.  $^{18}\text{F}$ -FU,  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR were obtained in high radiochemical purity.

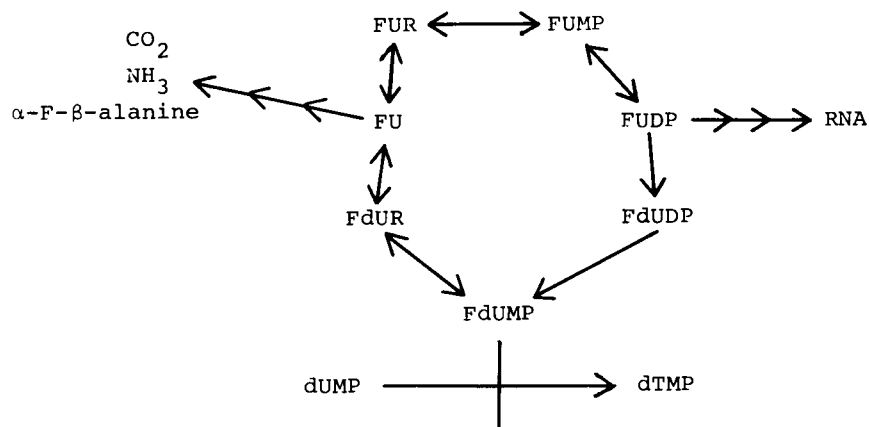
In the additional reaction of uracil with  $^{18}\text{F}$ - $\text{F}_2$ , only one  $^{18}\text{F}$  was seemed to add to uracil because the radioactivity was not reduced to one-half in the step of sublimation. In this case, the intermediate has been considered to be mono  $^{18}\text{F}$  and mono trifluoroacetoxy adduct of uracil (chart 1). In the cases of syntheses of  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR, as well as that of  $^{18}\text{F}$ -FU, their intermediates have been also considered to be mono  $^{18}\text{F}$  adducts (chart 2,  $^{18}\text{F}$ -FUR :  $^{18}\text{F}$ -2',3',5'-tri-O-acetyl-5,6-dihydro-5-fluoro-6-acetoxyuridine ;  $^{18}\text{F}$ -FdUR :  $^{18}\text{F}$ -3',5'-di-O-acetyl-5,6-dihydro-5-fluoro-6-acetoxy-2'-deoxyuridine).

The time required for the synthesis of  $^{18}\text{F}$ -FU was 60 min and that of  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR was 1.5-2 hr from the bubbling of  $^{18}\text{F}$ - $\text{F}_2$ . We have developed the rapid syntheses of  $^{18}\text{F}$ -FU,  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR in answer to the need for frequent production of them.

The distributions of  $^{18}\text{F}$ -FUR and  $^{18}\text{F}$ -FdUR were studied by  $\beta$ -ray scintigraphy (fig. 5). Consequently, it has become apparent that all three compounds were faintly uptaken in tumor (AH109A) and very highly in small intestine and the contents.  $^{18}\text{F}$ -FUR was also distributed in salivary glands and in whole body, while  $^{18}\text{F}$ -FdUR was only distributed in small intestine. These results show that  $^{18}\text{F}$ -FdUR is hopeful as a radiopharmaceutical for the tumor scanning except in small intestine.

#### References

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- FU : 5-Fluorouracil
- FUR : 5-Fluorouridine
- FUMP : 5-Fluorouridine-5'-monophosphate
- FUDP : 5-Fluorouridine-5'-diphosphate
- FdUDP : 5-Fluoro-2'-deoxyuridine-5'-diphosphate
- FdUMP : 5-Fluoro-2'-deoxyuridine-5'-monophosphate
- FdUR : 5-Fluoro-2'-deoxyuridine
- dUMP : 2'-Deoxyuridine-5'-monophosphate
- dTMP : Thymidine-5'-monophosphate

Fig. 1. Overall Pathway of Fluorouridine Nucleoside Metabolism.

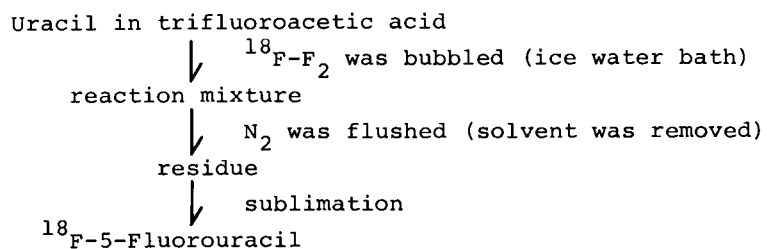


Fig. 2. Synthetic Method of <sup>18</sup>F-5-Fluorouracil.

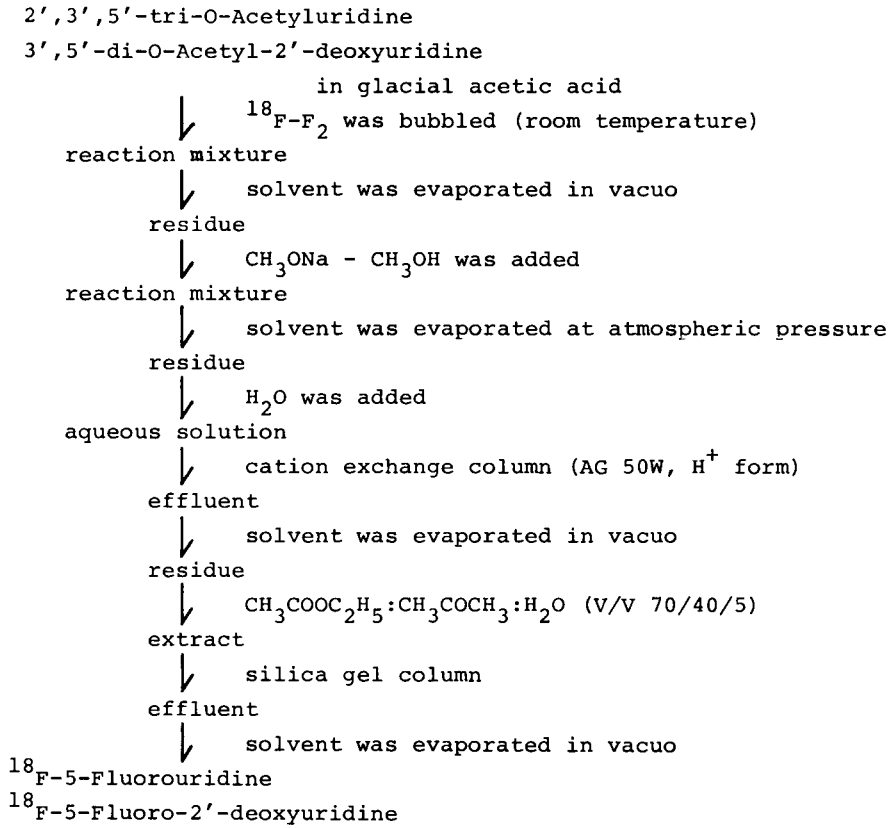
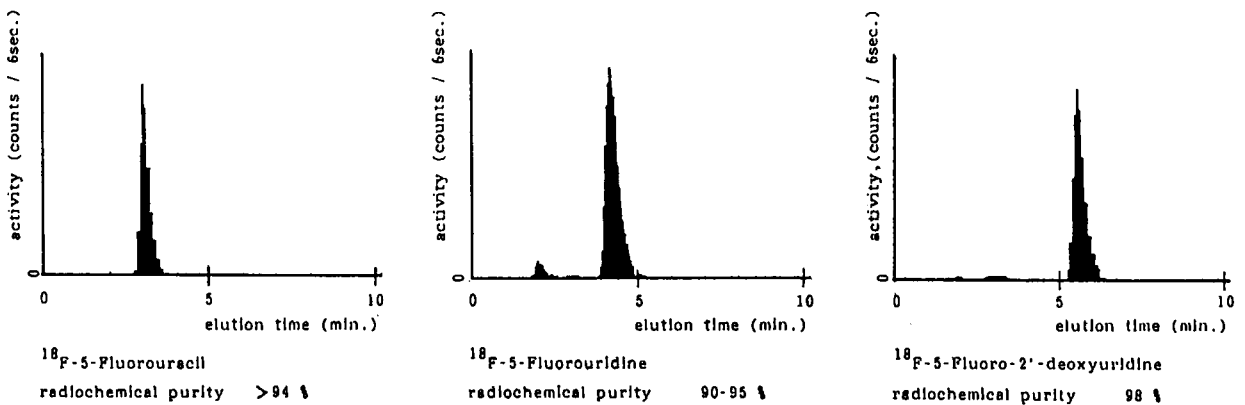


Fig. 3. Synthetic Method of  $^{18}\text{F-5-Fluorouridine}$  and  $^{18}\text{F-5-Fluoro-2'-deoxyuridine}$ .

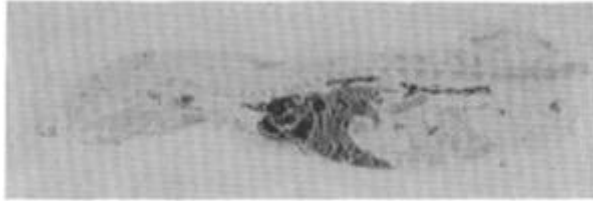


Analytical conditions

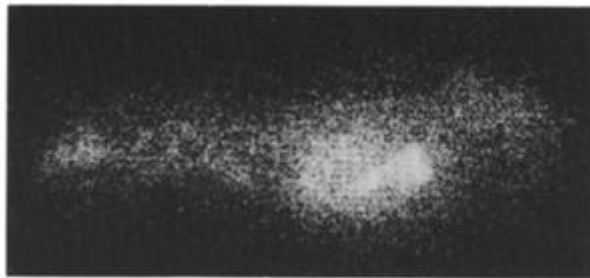
Column : u-Bondapak C-18  
 Eluent : 10 mM  $(\text{NH}_4)_2\text{HPO}_4$   
 Flow rate : 2 ml / min.

Fig. 4. Analysis of  $^{18}\text{F-5-Fluorouracil}$ ,  $^{18}\text{F-5-Fluorouridine}$  and  $^{18}\text{F-5-Fluoro-2'-deoxyuridine}$ .

$^{18}\text{F}$ -5-Fluorouridine

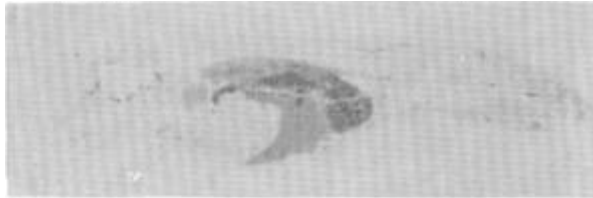


(A) Picture of Section

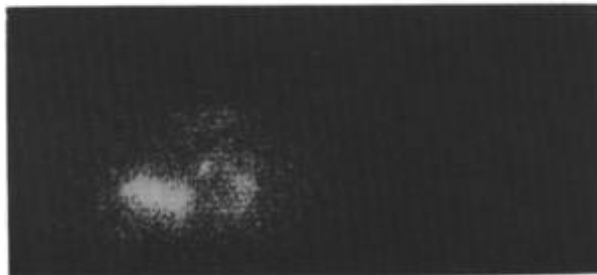


(B)  $\beta$ -Ray Scintigram

$^{18}\text{F}$ -5-Fluoro-2'-deoxyuridine



(A) Picture of Section



(B)  $\beta$ -Ray Scintigram

Fig. 5. (A) Picture of section and (B)  $\beta$ -Ray scintigram of  $^{18}\text{F}$ -5-Fluorouridine and  $^{18}\text{F}$ -5-Fluoro-2'-deoxyuridine in mice bearing AH109A tumor at 60 min.

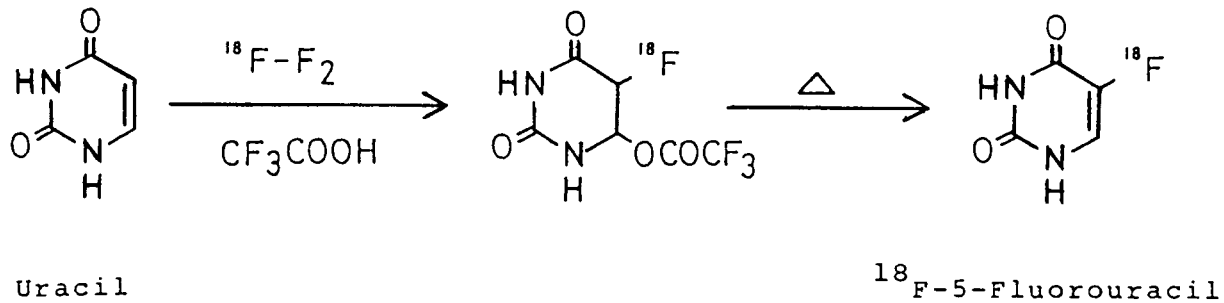


Chart 1. Synthesis of <sup>18</sup>F-5-Fluorouracil.

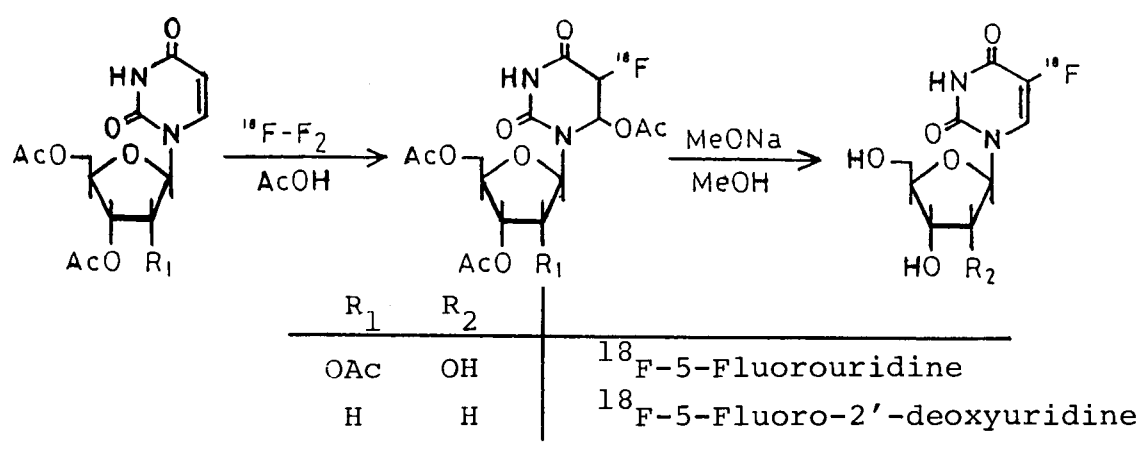


Chart 2. Syntheses of <sup>18</sup>F-5-Fluorouridine and <sup>18</sup>F-5-Fluoro-2'-deoxyuridine.