SYNTHESIS OF 2-[^{18}F]-FLUOROISONICOTINIC ACID HYDRAZIDE, A POTENTIAL RADIOTRACER FOR TUBERCULOSIS DIAGNOSIS.

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Isonicotinic acid hydrazide (isoniazid) is one of the most effective agents in tuberculosis therapy (1). This agent rapidly permeates the bacterial cell membrane via passive diffusion (2). The central nervous system tuberculosis is being observed in patients who are intravenous drug abusers, with AIDS and AIDS-related complex (3). MRI and contrast-enhanced CT has been the methods of choice for non-invasive diagnosis of this elusive form of tuberculosis. Nonetheless, these imaging methods have been limited in cases where the lesions are > 5mm (4,5). Therefore, radiopharmaceuticals for diagnosis of tuberculosis may become important. Very few attempts have been made to develop isonicotinic acid and derivatives for the same application (6,7). As part of an on-going research effort to develop precusors for radiofluorination of proteins and peptides via prosthetic groups approach, we have synthesized ethyl 2-[^{18}F]-fluoroisonicotinate (7) and 2-[^{18}F]-fluoroisonicotinic acid hydrazide (8).

The synthetic approach for preparation of 2-[^{18}F]-fluoroisonicotinic acid hydrazide (12) entailed a seven sequence of reactions delineated in figure 1. The starting material 2-amino-4-picoline (1) was treated with hydrobromic acid, bromine and sodium nitrite followed by oxidation with potassium permanganate to give 2-bromo-4-picolinic acid (3). This was heated at 160°C with dimethylamine and potassium carbonate in a closed system followed by refluxing in ethanol in the presence of sulfuric acid to afford ethyl-2-(dimethylamine) isonicotinate (5). The key precursor ethyl-2-(N,N,N-trimethylammonium)isonicotinate triflate (6) was prepared by treatment of (5) with methytrifluoromethanesulfonate according to the procedure described by Haka et al. (8). Treatment of the precursor (6) using catalyzed nucleophlic no-carrier-added radiofluoride produced by the ^{18}O(p,n)^{18}F nuclear reaction on ^{18}O-enriched (95 %) water and Kryptofix 222 as nucleophilic catalyst in anhydrous acetonitrile at 100°C gave ethyl 2-[^{18}F]-fluoroisonicotinate (7) in greater than 90% radiochemical yield (decay corrected) within five minutes reaction time. This method in comparison with the replacement of halogen by

fluoride procedure appear to be advantageous in the synthesis of high radiochemical yield fluorine-18 labelled compound in shorter time. The ether extract of compound (7) evaporated and residue was re-dissolved in ethanol and treated with hydrazine then heated for 15 minutes in a boiling water to obtain 2-[^{18}F]-fluoroisonicotinic acid hydrazide (8) in quantitative radiochemical yield. Work up of this product by HPLC on C18 column (Econosil,10μ, 250 x 10 mm) eluted at 2 mL/min with methanol/water/formic acid (80/20/0.1 v/v) gave radiochemically and chemically pure compound (8) (figure 2). The total radiosynthesis time was approximately 35 minutes.

This synthetic approach hold considrable promise as a rapid and simple method for fluorination of radiopharmaceuticals of high radiochemical yield. To our knowledge this is the first report of fluorinated radiopharmaceuticals which may be useful for tuberculosis diagnosis.

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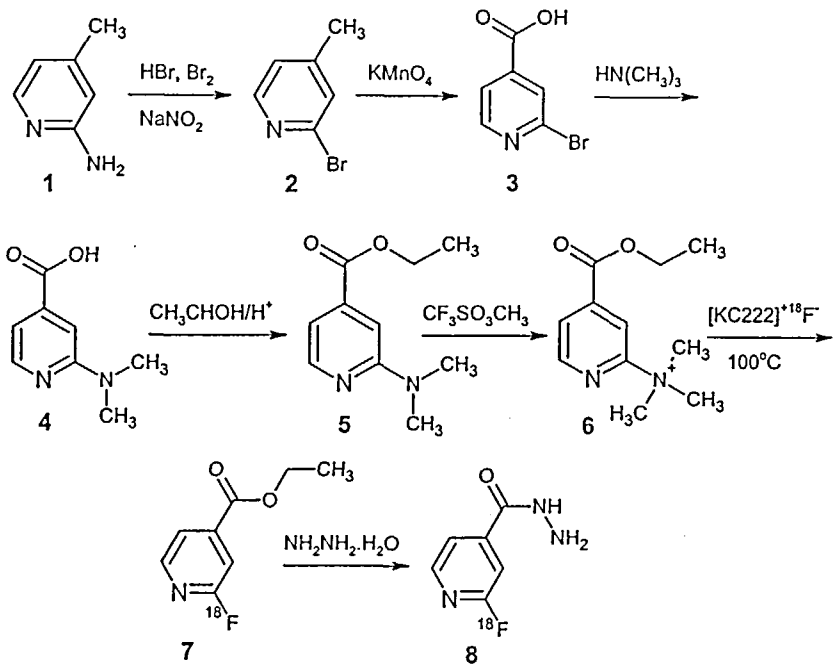

Figure 1. Radiosynthesis of 2-[^{18}F]-fluoroisonicotinic acid hydrazide and the precusor molecules. All the key intermediates were characterized by MS and NMR.

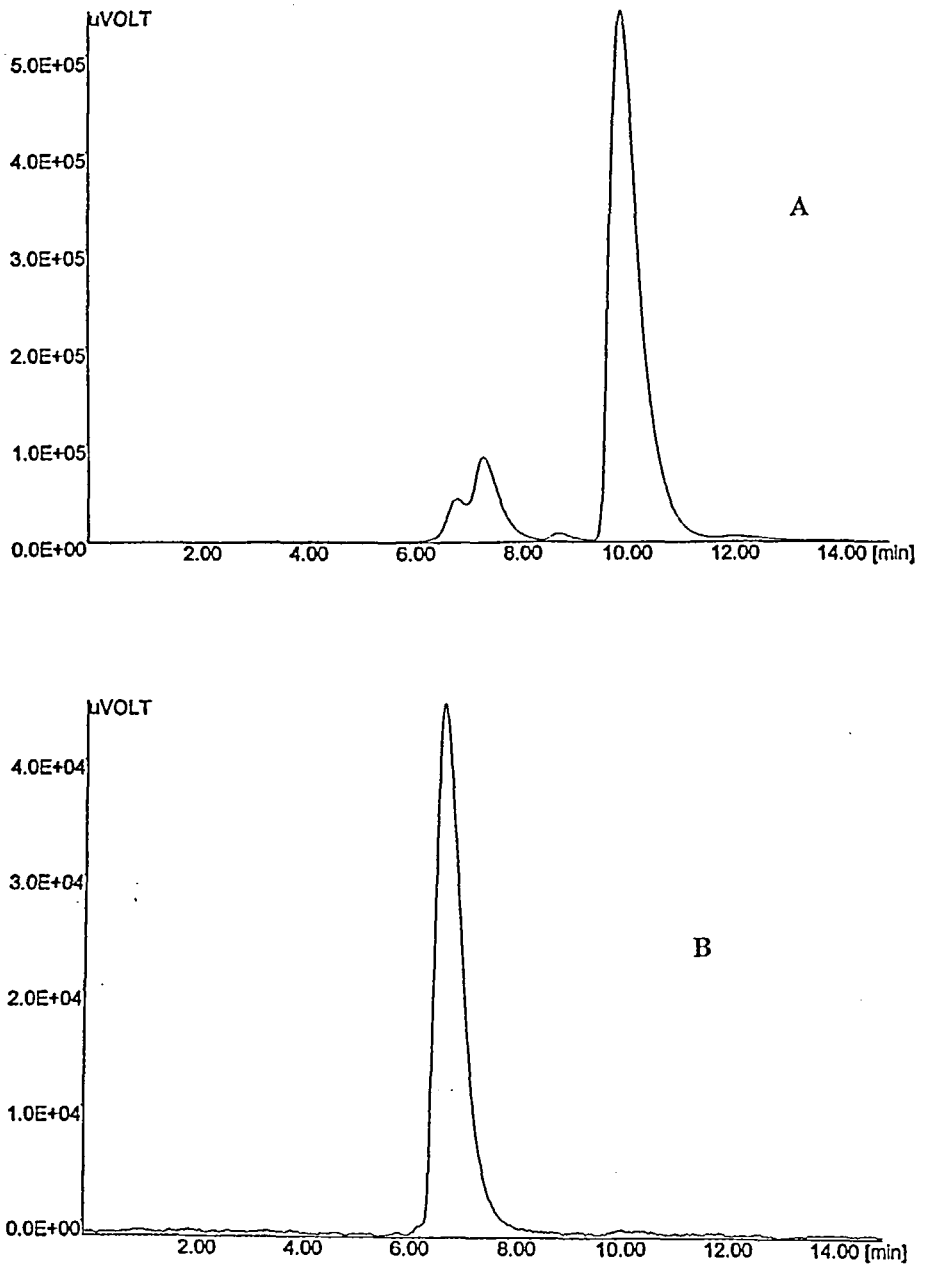

Figure 2. Typical HPLC analysis of (A) ethyl 2-[^{18}F]-fluoroisonicotinate and (B) 2-[^{18}F]-fluoroisonicotinic acid hydrazide reaction mixtures.