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A remote controlled system for the preparation of 7 α -fluoro-17 α -methyl 5 α -dihydrotestosterone ([¹⁸F]FMDHT) using microwave

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Abstract

For non-invasive imaging of the prostate cancer, we synthesized 7 α -fluoro-17 α -methyl 5 α -dihydrotestosterone ([¹⁸F]FMDHT) for androgen receptor mediated PET imaging. Preliminary *in vitro* and *in vivo* evaluations of this compound show promise. We designed and implemented a remote controlled system for reliable, efficient, and safe handling of radioactivity during the radiochemical synthesis of [¹⁸F]FMDHT. The key features of this report are the microwave assisted radiochemical synthesis, increased radiochemical yields, improved radiochemical purity, reduced overall synthesis time, and remote controlled automation of the entire synthesis. The overall synthesis using microwave reaction took 60 – 70 min and provided the desired product in 20 – 30% radiochemical yields with >99% radiochemical purity.

Introduction

Androgen receptors (AR) play an important role in the normal growth, cell differentiation, and maintenance of prostate epithelium. Both the primary and metastatic prostate cancers express AR to similar extent (Mohler, et al., 2004). The prostate cancer growth depends on AR-signaling that activates over-expression of AR-regulated genes such as prostate specific antigen (PSA) and others (Gelman, 2002). Because of its direct relevance to prostate cancer growth, the current diagnosis relies on rising PSA levels as an indicator for prostate cancer and disease progression. Despite the routine use of PSA measurement to assess disease progression in the clinic, this method is not reliable and underscores the need to develop a more accurate and reliable diagnostic tool. Therefore, developing an AR-based ligand for the diagnosis of prostate cancer has been the goal of many laboratories including ours.

Testosterone and 5 α -dihydrotestosterone (5 α -DHT) are two major endogenous androgens that bind specifically to the AR with 5 α -DHT exhibiting more potency. Earlier, Labaree et al (Labaree, et al., 1999) reported the synthesis of 7 α -fluoro-17 α -methyl 5 α -dihydrotestosterone (FMDHT). This compound showed higher binding affinity to AR when compared to 5 α -DHT and other related structural analogues. In addition, binding to other receptors was negligible for this compound, thus exhibiting high specificity towards AR (Labaree *et al.*, 1999). To explore its utility as a PET imaging agent for AR, we radio-labeled FMDHT with fluorine-18 to generate 7 α -[¹⁸F]fluoro-17 α -methyl 5 α -dihydrotestosterone ([¹⁸F]FMDHT) and assessed its binding and distribution *in vivo*. *In vivo* evaluations of [¹⁸F]FMDHT showed preferential uptake in androgen receptor positive tissue and a low uptake in the normal tissues (Garg, et

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al., 2001). In biodistribution studies performed using castrated rats, the specific to non-specific uptake ratios were >7 at one hour post injection. When the receptor sites were blocked by using a saturating dose of 5 α -DHT, uptake of this ligand in receptor sites was reduced to levels similar to that for the control tissues. These results demonstrated a specific, competitive, and saturable binding of this ligand to AR expressing tissues. More recently, we reported improved tissue distribution pattern of [^{18}F]FMDHT in rats castrated using Cetrorelix, a GnRH antagonist (Garg, et al., 2007). Although, we observed encouraging and positive biological findings for this ligand, the radiochemical synthesis of this ligand remained sub-optimum and needed improvements.

Earlier, we synthesized [^{18}F]FMDHT by reacting [^{18}F]fluoride with 7 β -tosyl-17 α -methyl 5 α -dihydrotestosterone (tosylate) dissolved in acetonitrile and heating the reaction solution at 70 $^{\circ}$ - 80 $^{\circ}\text{C}$ for 45 min by using conventional thermal heating. Subsequent purification using HPLC yielded the desired product in 3-5% radiochemical yields. These modest yields produced sufficient quantities of product allowing us to perform preliminary binding and biodistribution studies in rodents. To further characterize the biological potential of this ligand, it was imperative for us to optimize its radiochemical synthesis. Towards that goal, we explored alternate strategies to improve radiochemical yields. Microwave assisted synthesis of chemicals and radiopharmaceuticals has recently emerged as a powerful tool (Dolle, 2005; Wang, et al., 2005). This technique reduces the reaction transformation time to a fraction of time needed for the conventional heating. Encouraged from these reports, we assessed the utility of utility of microwave method in synthesizing [^{18}F]FMDHT. In addition, we planned to construct an automated system for remote handling of [^{18}F]FMDHT synthesis. Herein, we report an efficient and improved synthesis of [^{18}F]FMDHT using microwave technique and the adaptation of this procedure to a remote controlled method to reduce radiation exposure to the production staff.

Materials and methods

Radioactivity levels in tissues were assessed with a Packard Cobra γ -counter. High pressure liquid chromatography (HPLC) was performed in isocratic mode with a Varian 9010 LC pump, a variable wavelength 9050UV VIS detector (Varian Corp, Palo Alto, CA, USA), and a radioisotope detector (Bioscan Inc, WA, USA) attached to Varian's chromatography software package (Varian Corp, Palo Alto, CA, USA). The HPLC system used for purification of [^{18}F]FMDHT was a C-18 reverse-phase ODS, 10 $\times$ 250 mm 5 μ column (Phenomenex) eluted with $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (50:50) at 3 mL/min. Quality control of purified product was performed using a Varian HPLC system using a microsorb reverse phase Varian C-18 250 $\times$ 4.6 mm, 5 μ column eluted with $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (50:50) at 1 mL/min. The kryptofix solution was prepared by dissolving 120 mg of K222 and 720 mg K_2CO_3 in 720 μL of water followed by adding 12 mL of acetonitrile. QMA cartridge was activated by washing the cartridge with 5mL of sodium bicarbonate solution (1N), followed by 10mL of sterile water, and then drying it by passing air through the cartridge for ~ 30 seconds. The microwave reactions were performed using a CEM Discover microwave system (CEM, NC, USA).

Radiochemical synthesis of 7- α -[^{18}F]fluoro 17 α -methyl-5- α -dihydrotestosterone (7 α - ^{18}F -MDHT)

7- β -tosyl-17 α -methyl-5- α -dihydrotestosterone (tosylate) was used as our starting material for radio-fluorination reaction and was synthesized as previously described with minor modifications (Labaree *et al.*, 1999). Instead of using TBA- ^{18}F , for the current reactions we used F-18 fluoride solubilized in kryptofix K222/ K_2CO_3 solution in acetonitrile. Briefly, aqueous [^{18}F]fluoride was produced using $^{18}\text{O}(\text{p}, \text{n})^{18}\text{F}$ reaction on 95+% enriched [^{18}O] water with 45 μA beam current in a large volume [^{18}F]fluoride target. After irradiation, the bolus of

3.0 mL ^{18}O - H_2O containing 500 - 800 mCi of ^{18}F -fluoride was transferred from the cyclotron on to a QMA cartridge in the hot cell to recover O-18 water, followed by elution of ^{18}F fluoride from the cartridge using kryptofix/ K_2CO_3 solution (1.5 mL). The water from the eluant was evaporated azeotropically ($2 \times 500 \mu\text{L}$ acetonitrile) using an oil bath maintained at 100-110°C and a gentle stream of argon as described (Garg, et al., 1994). The ^{18}F fluoride was re-dissolved in 1.0 mL of acetonitrile. Several radiochemical reactions could be performed from one batch of ^{18}F fluoride by transferring small aliquots of radioactivity (50 – 100 mCi) from the reaction vessel 1 into reaction vessel 2 by using sample aliquot loop as shown in figure 1.

Conventional heating method— ^{18}F fluoride was reacted with 400 - 600 μg of tosylate dissolved in 300 - 500 μL of acetonitrile. The reaction mixture was heated for 45 min in an oil bath maintained at 70-80°C. The reaction mixture was cooled, diluted with H_2O and purified by HPLC as described. The fractions containing the desired product were combined, solvent evaporated under a stream of argon, and the resulting residue reconstituted in phosphate buffered saline.

Microwave assisted reaction— ^{18}F fluoride was transferred to microwave reaction vessel containing 400 - 600 μg tosylate dissolved in 300 - 500 μL acetonitrile. The reaction was performed using the following settings: Microwave power 300W max, ramp time 1 min, maximum pressure 150 psi, maximum temperature 90°C and a reaction time of 1.5 min or 5.0 min. After the reaction time expired, the reaction mixture was cooled to $< 50^\circ\text{C}$ and was injected onto the HPLC column as described earlier.

Remote handling apparatus

The synthesis was adapted for remote handling of reaction vessels and for transfers of radioactivity at various stages. The schematic presentation of the remote handling system is shown in Figure 1.

The system consisted of two parts. The first part aided in receiving of ^{18}F fluoride, drying the radioactivity via azeotropic removal of O-18 water, and performing the reaction with precursor. The second part of this module consisted of the HPLC purification step where the reaction mixture was loaded on to a semi-preparative column to separate the desired product from the reaction mixture.

Initially, the ^{18}F fluoride was delivered from the cyclotron room onto a QMA cartridge to trap ^{18}F fluoride and to recover O-18 water. Once the delivery is finished and the O-18 water was collected, contents from the QMA cartridge were eluted with Kryptofix solution and delivered into reaction vessel 1 (RV1) through a delivery line connected via a three way valve (V3). After azeotropic removal of water, ^{18}F fluoride was resolubilized in acetonitrile and either a small aliquot or the entire bolus was transferred in to RV2 via the sample loop for fluoro for tosyl exchange reaction. After the reaction was completed, the reaction mixture was loaded onto the HPLC column for purification. The desired peak was collected and the solvent was evaporated using a rotary evaporator.

Construction and functioning of the remote module

The valves and connections for various functions are shown in figure 1. The valves and switches activate remotely via flip switches on the control box located on the outside of the hot cell. The syringes were also routed to the outside of the hot cell by using teflon lines. The ^{18}F Fluoride was delivered to reaction vessel RV1 via a three way valve V1. The common port of V1 was connected to a QMA cartridge and the other two ports were connected to a 3 mL syringe (K_2CO_3) and ^{18}F Fluoride delivery line from the cyclotron, respectively. The distal end of the QMA cartridge was attached to the common port of a three-way valve V2. The other two ports

of V2 were connected to an O-18 water recovery vial and to another three-way valve V4. Once the [^{18}F]Fluoride bolus was ready for delivery, the V1 and V2 were activated and the radioactivity was delivered onto the QMA cartridge and the O-18 water was collected in water recovery vial. After the [^{18}F]Fluoride was deposited, the V1 and V2 were switched back to off position, plunger of the 3 mL syringe S1 containing K222/ K_2CO_3 solution was pushed and the [^{18}F]Fluoride was collected in reaction vessel RV1. The V7 was activated to apply vacuum for the radioactivity bolus to pass through V2 and V4 and into RV1. The other side of V4 was attached to V5 to help supply acetonitrile in to RV1 via syringe S2 or to supply the argon gas via V6 when needed.

The three prongs on RV1 cap allowed attaching three different delivery lines to accomplish the following functions: to receive [^{18}F]fluoride/deliver argon gas via V1, V2, V4 path, and to add acetonitrile via V5, V4 path; to provide vent/vacuum via V7; and to draw and distribute aliquots of resolubilized radioactivity to RV2 via V8 and a sample loop for multiple reactions from a single [^{18}F]fluoride production run.

Once the [^{18}F]Fluoride was collected in RV1, it was dried azeotropically aided by acetonitrile delivered through syringe S2. After complete drying, the radioactivity was resolubilized in acetonitrile for further use. To transfer activity from RV1 to reaction vessel 2 (RV2), the V8 was activated and the desired amount of radioactivity was drawn in the fluid loop by applying a pull on syringe S3. Once the desired amount of radioactivity was drawn (as measured by radioactivity detector placed near the loop), V8 was deactivated and the [^{18}F]Fluoride was delivered to RV2 which was preloaded with tosyl precursor. Once the radioactivity is delivered to RV2, the radiochemical synthesis was initiated.

After the radiochemical synthesis (using either conventional heating or a microwave assisted method), V9 and V10 were activated and the reaction mixture was diluted with an HPLC buffer by adding the contents of the HPLC loop into RV2 by pushing S4 plunger. The contents of RV2 were then withdrawn in the HPLC loop by pulling on S4 plunger. The V9 and V10 were deactivated and the Rheodyne valve was switched to the load position to load contents onto the HPLC column. The HPLC effluents were collected in the waste collection bottle and the desired peak was collected in a fraction collection vessel by activating V11. The acetonitrile was subsequently evaporated on a rotary evaporator and the residue was reconstituted in a buffered saline solution.

Quality control

The radiochemical purity of [^{18}F]FMDHT was determined using the HPLC method. After evaporating the solvent and reconstituting in the desired buffer, a small aliquot (~100 – 200 μL) of the product was withdrawn for quality control (QC) assays. A small fraction of this sample was injected on the QC HPLC column and was eluted using 50% acetonitrile in water at a flow rate of 1 mL/min.

Results

Similar to that reported earlier, the radiochemical yields remained low using the conventional heating methods. On an average, we collect about 2 - 3 mCi of [^{18}F]FMDHT from ~100 mCi of starting [^{18}F]Fluoride. Figure 2A is a representative HPLC chromatograph from the conventional heating method. The product was eluted from the HPLC at a retention volume of ~45 mL (R_t = 15.2 min) and the precursor (tosylate) was eluted at ~69 mL (R_t = 23 min) using this system (UV trace not shown). The radiochemical yields for the desired product ranged from 2 - 5 % (EOS). Typical radiochemical purity of the product ranged between 91 – 98% with an overall synthesis time of ~ 110 - 120 min. Because of poor radiochemical separation leading to low radiochemical purity, a second HPLC purification was necessary. The total

synthesis time for the conventional heating method with two HPLC purifications was 175 ± 20 min.

In contrast, we obtained better radiochemical yields and radiochemical purity using the microwave assisted reaction. Average radiochemical yields, as determined from the HPLC elution was $14 \pm 5\%$ ($n = 5$). Increasing the reaction time from 1.5 min to 5 min further improved radiochemical yields. Average radiochemical yields from eight microwave reactions performed at 5 min was $24 \pm 7\%$ (Garg, et al., 2005) with a radiochemical purity of $>99\%$. Typical HPLC chromatograms from microwave reactions are shown below (Figure 2b– 1.5 min; Figure 2c– 5.0 min). The overall synthesis time was $\sim 60 - 70$ min.

Discussions

Previously, we reported the synthesis of 7α - $[^{18}\text{F}]$ fluoro- 17α -methyl 5α -dihydrotestosterone using nucleophilic displacement ($\text{S}_{\text{N}}2$ type) of tosylate group with F-18 from 7β -tosyl- 17α -methyl 5α -dihydrotestosterone. After HPLC purification, this method yielded the desired product in low radiochemical yields. Changing reaction temperature between 65°C and 95°C range did not alter reaction yields. Nonetheless, raising the reaction temperature to $> 100^\circ\text{C}$ resulted in decomposition of the precursor with little change in overall radiochemical yields. Increasing the reaction time did not improve radiochemical yields either. In contrast, short half-life of F-18 (110 min) resulted in lower overall yields because of the decay of radioactivity with time. Our attempts to further modify reaction conditions including altering reaction temperature, precursor quantities, and reaction solvent did not help improve the radiochemical yields. Although, we produced sufficient quantity of $[^{18}\text{F}]$ FMDHT to conduct initial experiments, a more reliable, high yielding and possibly a remote handling procedure was necessary to further characterize this promising radioligand. Towards that goal, we explored various strategies to enhance radiochemical yields and to adapt our synthesis for remote operation.

In our earlier report, nucleophilic displacement of tosyl group with F-18 fluoro group and using conventional thermal heating conditions led to low radiochemical yields of the desired product. An additional problem with low yielding synthesis was the inadequate HPLC separation of the product. As seen from the chromatogram in Figure 2a, the radioactivity trace remained above the base-line well beyond the first peak elution and remained high at desired peak elution time, perhaps due to slow elution of large amounts of unreacted $[^{18}\text{F}]$ fluoride and other radioactive byproducts from HPLC column. This poor separation led to low radiochemical purity of $[^{18}\text{F}]$ FMDHT. To further improve radiochemical purity, use of a second HPLC purification was assessed. This additional step although improved the radiochemical purity to $>98\%$, it added more than an hour of additional time. Additional time needed for the second purification decreased the overall quantity of the product due to radiochemical decay and losses from vessel to vessel transfers. Low radiochemical yields and purity underscored the need to examine alternate reaction conditions. Besides improving the radiochemical yields, a robust and perhaps automated synthesis of this ligand was deemed necessary.

Recently, several investigators reported improved radiochemical yields and reduced overall synthesis time by using microwave (Dolle, et al., 1999; Kahn, et al., 2006; Kumar, et al., 2002). Some of these reports stress the importance of selecting appropriate solvent for microwave assisted reactions. Recently, Kishore Kumar *et al* (Kishore Kumar, et al., 2006) explored the use of dielectric loss (ϵ'') values as a guide of solvent's efficiency in converting microwave energies to thermal energies and reported acetonitrile as a preferred solvent amongst three solvents studied (Kishore Kumar *et al.*, 2006). Encouraged from these reports, we evaluated the utility of microwave assisted reaction to synthesize $[^{18}\text{F}]$ FMDHT and opted for acetonitrile ($\epsilon'' = 2.325$) as the solvent of choice. Besides its preferred ϵ'' value for

microwave reactions, it also matched our reaction solvent used in the conventional heating experiments. Initially, we reacted 400 μ g tosylate precursor with 50 - 100 mCi of [18 F]fluoride in 500 μ L acetonitrile. The reaction vessel was placed in the microwave cavity and the power was set to 300W max with a ramp time of 2 min followed by a reaction time of 1.5 min or for 5 min. After the reaction was complete, the entire reaction bolus was loaded onto a preparatory HPLC column to isolate the desired product. The chromatograms from the two HPLC separations are shown in figure 2b (1.5 min reaction) and 2c (5 min reaction), respectively.

Automation of this procedure using remote controlled electrically actuated switches helped reduce radiation exposure during the synthesis while improving the reliability of the synthesis. The entire system is compact and can be handled from outside the hot-cell or a lead-cave and is easy to set up and clean for subsequent syntheses.

The radioactivity from the cyclotron is delivered to reaction vessel #1 via a QMA cartridge that trapped [18 F]fluoride and helped recover O-18 water. The [18 F]fluoride was eluted from the QMA cartridge using a kryptofix/potassium carbonate mixture and further dried for the water contents azeotropically by heating in an oil bath using acetonitrile as the solvent. Reaction vessel RV2 has been preloaded with the precursor and by using syringe SV3 (attached to the fluid loop); either the entire bolus or a small portion of the resolubilized activity was transferred to RV2. Since microwave reaction does not allow for the reaction vessel with delivery and add lines attached, these lines were pulled out from the vessel before inserting the vial into the microwave. After the reaction was completed, these lines were inserted through the vessel septa using spinal needles. For the conventional heating method, the lines remained intact for the duration of the reaction. After the reaction was completed, the reaction contents were transferred to the HPLC loop (a Rheodyne valve) using a remote draw from a 20 cc syringe S4. Once the loop was loaded, the Rheodyne valve was switched to the inject position and contents of the loop were transferred on to the HPLC column. The contents were ultimately pushed through the semi-preparatory HPLC column, a UV detector, a radioactivity detector, and a three way valve (V11) and in a waste collect vial until the desired peak was detected on the chromatogram. At that time, the valve V11 was activated and the desired product was diverted to the product collection vial. Subsequently, the solvent was evaporated using a rotary evaporator and the residue was reconstituted in buffered saline.

One of the complicating factors to adopt our semi remote system to microwave reaction was the need for a closed reaction system configuration for the procedure. Since the microwave electronics reads reaction vessel pressures to adjust for the heating and cooling, capping the vessel with pressure transducer was necessary. To accomplish this, it was imperative that we remove all delivery lines from the reaction vessel to start the microwave and insert these lines back in RV2 after the reaction was completed for further HPLC purification. Although, using long forceps was adequate to accomplish this step, it remains cumbersome. An alternative would be to adapt an open vessel reaction configuration. Nonetheless, we have not yet evaluated the utility of an open-vessel configuration for the [18 F]FMDHT synthesis.

The major advantages of using microwave assisted reaction were an improved radiochemical yields and reduced synthesis time. These factors further enhanced radiochemical purity of the collected product due to improved separation of desired product from un-reacted [18 F]fluoride and other byproducts. Recent advancements in micro-fluidics and micro-channel synthesis device may provides additional tools to possibly improve radiochemical synthesis for promising ligand such as [18 F]FMDHT.

In conclusion, an automated (remote controlled) synthetic procedure has been established for the production of [18 F]FMDHT. Microwave assisted reaction conditions improved radiochemical yields to 20 -30 % and decreased the reaction time to 60 – 70 min. Microwave

assisted reactions typically gave better radiochemical yields, radiochemical purity, and was expedient when compared to conventional heating procedure.

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Figure 1.

Semi-automated synthesis for drying $[^{18}\text{F}]$ fluoride, aliquoting $[^{18}\text{F}]$ fluoride for multiple reactions from single production run, and HPLC purification. The solid arrows and arrows with a dot in 3-way valve indicates normally open (NO) position; the other path is normally closed (NC) and requires activation to open. All solenoid valves are controlled from a switch box that is located outside the hot cell. All the four syringes are also located outside the hot cell.

Figure 2A **Figure 2B**

Figure 2C **Figure 2.**

Figure 2a. HPLC chromatogram from a typical HPLC purification after conventional heating method. The first peak eluted at 5-6 min followed by a long tail. The radioactive trace remained well above the base line even as the product peak eluted at ~14 -16 min, leading to poor radiochemical purity.

Figure 2b. HPLC chromatogram from a 1.5 min reaction conducted in microwave. The first peak eluted at ~5-6 min followed by a tail similar to that seen from conventional heating method as shown in fig 2a. The radioactivity trace reached closer to the base line before the product peak began to elute at ~14-16 min, providing better separation.

Figure 2c. HPLC chromatogram from a 5 min reaction conducted in microwave. The first peak is eluting at ~5-6 min with minimal tailing and eventually follows the base line by 12 min. The product peak eluted at ~14-16 min with a good separation and leading to better radiochemical purity for the final product.

Scheme 1.
Radiochemical Synthesis of $[^{18}\text{F}]$ FMDHT