

Improved synthesis and purification of *meta*-[¹⁸F]fluorobenzylguanidine (mFBG) for clinical use

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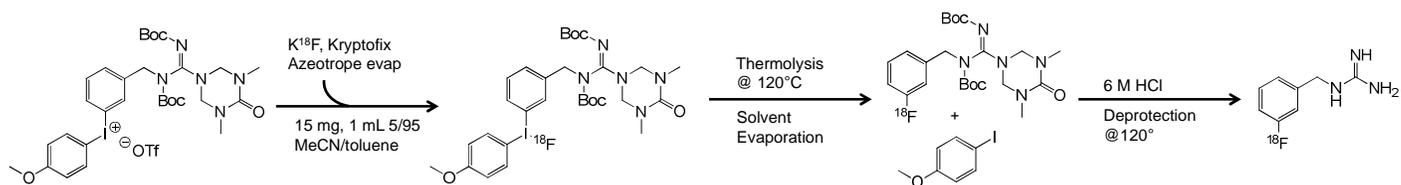
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Objectives: Recent work has indicated that *meta*-[¹⁸F]fluorobenzylguanidine (mFBG) possesses advantages, including shorter uptake time and better resolution, over mIBG for the diagnosis and staging of neuroblastoma tumors.¹ Current literature methods describe manual production of low-yielding fluorobenzyl nitrile followed by reduction, multiple extractions, and gradient HPLC purification. Final overall yields after reformulation were 10-11% with a synthesis time of 3 hours.^{2,3} Our goal for this work was to develop a facile, automated synthesis for clinical production with improved yields while avoiding the need for reformulation of the final product.

Methods: Using an IBA Synthera[®] automated synthesizer, [¹⁸F]fluoride ion was separated from target [¹⁸O]water using QMA resin and elution with a Kryptofix 2.2.2/potassium carbonate solution in acetonitrile and water. The solvent was removed under argon flow with reduced pressure and heating to 110°C. The diaryliodonium salt [¹⁸F]mFBG precursor, dissolved in dry acetonitrile and toluene, was added to the reactor for fluorination at room temperature followed by thermolysis 120°C to generate the protected intermediate. Solvent removal with argon flow under reduced pressure was followed by deprotection (hydrochloric acid, 120°C) to afford mFBG product. The solution was diluted with HPLC eluent (10% ethanol/10 mM HCl), and the compound was purified on a semi-prep Hamilton PRP-1 HPLC column.



Results: Fully automated production of *meta*-[¹⁸F]fluorobenzylguanidine was achieved using an IBA Synthera[®] in 53 minutes with purification. Average, final yield was 21% (n = 4, 29% decay-corrected) with radiochemical purity of > 97%. Isocratic HPLC purification in ethanol and HCl allowed easy preparation for injection by dilution and pH adjustment with buffer with no reformulation necessary.

Conclusions: Significant improvements in the preparation of mFBG were demonstrated by conversion from manual to automated synthesis and a reduction in synthetic steps. This method shows promise with a 2-fold improvement in yield, 2-fold reduction of the synthesis time, and simplification of the purification over previously reported methods. Optimization and quality control testing for patient use are currently underway.

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References: [1] Zhang H, et al. (2014) Clin Cancer Res, 20(8): 2182-2191. [2] Garg, PK, et al. (1994) Nucl Med Biol, 21(1): 97-103. [3] Zhang et al., Eur J Nucl Med Mol Imaging (2014) 41:322-332.