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Rapid and efficient synthesis of [^{18}F]fluoronicotinamides, [^{18}F]fluoroisonicotinamides and [^{18}F]fluorobenzamides as potential pet radiopharmaceuticals for melanoma imaging

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In an attempt to simplify nucleophilic radiofluorination reactions to be amenable for automation, a series of [^{18}F]fluoronicotinamides, [^{18}F]fluoroisonicotinamides and [^{18}F]fluorobenzamides were synthesized using one-step synthetic approach involving displacement reactions on trimethylammonium-nicotinamide, trimethylammonium-isonicotinamide and trimethylammonium-benzamide precursors. Based on starting [^{18}F]-fluoride, radiochemical yields and purities were found to be greater than 90 and 97%, respectively, within 20 min synthesis time and, without high-performance liquid chromatography purification. This synthetic approach holds great promise as a rapid and simple method for the automated radiofluorination of [^{18}F]fluoronicotinamides, [^{18}F]fluoroisonicotinamides and [^{18}F]fluorobenzamides with high radiochemical yield and very short preparation time.

Keywords: ^{18}F-fluorination; ^{18}F-fluoronicotinamide; ^{18}F-fluoroisonicotinamide; ^{18}F-fluorobenzamide; melanoma targeting; PET radiopharmaceuticals

Introduction

Advancement of scintigraphic tumor imaging is highly determined by the development of more tumor-specific radiotracers. Selective high-affinity binding radiotracers have shown promises in improvement of the specificity and sensitivity of nuclear medicine imaging procedures. The widespread of melanin pigmentation in most of melanoma tumor cells has been targeted with radioiodinated aminoalkyl-iodobenzamides, -nicotinamides and -isonicotinamides based radiopharmaceuticals for diagnostic purposes. These efforts were initiated by the synthesis and biological evaluation of *N*-(2-diethylaminoethyl)-4-[^{125}I]iodobenzamide two decades ago.[1] The high melanotic tumor uptake of iodobenzamide in melanoma-bearing mice has led to the development of series of radioiodinated benzamide compounds as potential melanoma imaging probes.[2–8] Owing to the high affinity of [$^{123/131}$I]iodobenzamide radiotracers toward melanocytes and favorable tissue distribution characteristics, some of these radiotracers were further pursued in melanoma patients and exhibited selective and sensitive detection of melanoma and its metastases.[9–13] Lately, a series of [^{123}I]iodonicotinamides were developed and biologically evaluated as potential imaging and staging of metastatic melanoma.[14] These findings demonstrated that *N*-(2-diethylaminoethyl)-5-[^{123}I]iodonicotinamide exhibits highest melanotic tumor uptake and the nature of nicotinamide greatly contributed to the rapid clearance from the body. With the increased use of positron emission tomography in diagnostic imaging, there has been great interest in the development of positron-emitting radiopharmaceuticals for early detection and characterization of cancer, molecular assessment of treatment effects and more fundamental understanding of the disease process.[15] Recently, *N*-(2-diethylaminoethyl)-4-[^{18}F]fluorobenzamide was synthesized using a sequence of reactions with more than 2.5 h overall synthesis time.[16] Biodistribution studies of this compound showed a rapid and high melanotic tumor uptake and low residual activity in normal tissues signifying the enhanced imaging potential of this radiotracer. More recently, series of [^{18}F]fluoronicotinamides were prepared and displayed high tumor uptake and rapid body clearance predominantly via renal pathway.[17] These radiofluorinated nicotinamides were prepared in one radiosynthetic step, using [^{18}F]fluoro to chloronicotinamide exchange reaction under elevated temperature (150°C), followed by high performance liquid chromatography (HPLC) purification and the radiochemical yields of these compounds were ranged between 35 and 55% in 40 min synthesis time. As part of our on-going research effort to develop precursors for radiofluorination of bioactive molecules, we here report the synthesis of series of [^{18}F]fluoronicotinamides, [^{18}F]fluoroisonicotinamides and [^{18}F]fluorobenzamides using a rapid, simple and efficient synthetic approach.

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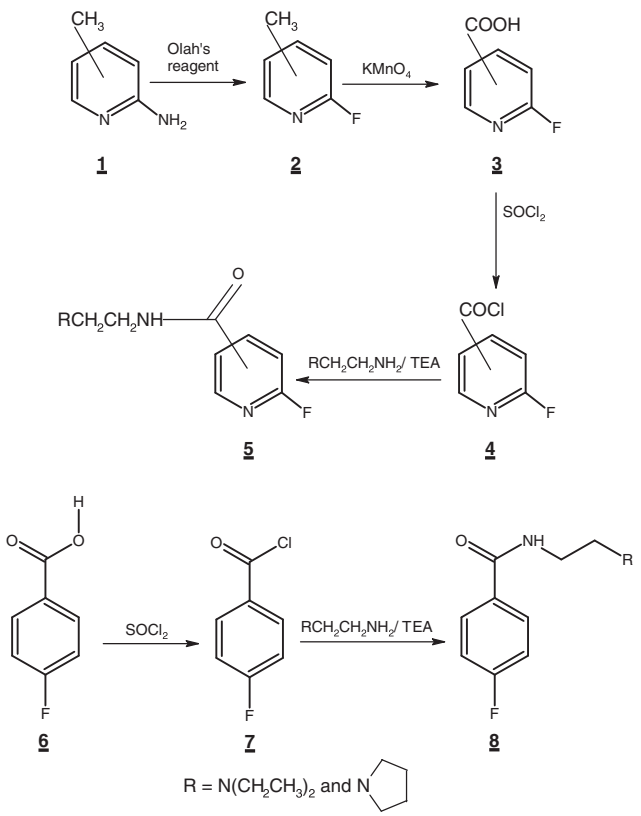
Experimental

The chemicals used in the study were all analytical reagent grade purchased from Aldrich and were used without further purification unless stated. Acetonitrile (ACN) was kept over molecular sieves. Sep-Pak cartridges were purchased from Waters-Millipore. TLC-SG sheets were purchased from Gelman Sciences Inc. HPLC analysis was carried out on Econosil C-18 reversed phase column (analytical, 250 mm × 4.6 mm). The solvent system used was non-linear gradient (eluant A, water with 0.1% TFA; eluant B, ACN with 0.1% TFA; gradient, 0–60% B, 60–60% B and 60–0% B over 10 min each at flow rate of 1.0 mL/min). A Jasco chromatographic system equipped with a variable wavelength ultraviolet monitor and in tandem with a Canberra flow through radioactivity detector was used. Ultraviolet absorption was monitored at 254 nm. Chromatograms were acquired and analyzed using BORWIN software. Mass spectroscopy was run on Quattra electrospray mass spectrometer (ES-MS). NMR was run on JEOL (400 MHz) Spectrometer with TMS as the reference.

N-[2-(diethylamino)ethyl]-2-fluoroisonicotinamide 5a, *N*-[2-(diethylamino)ethyl]-6-fluoronicotinamide 5b

Compounds **2**, **3**, **4**, **7**, **9**, **10** and **14** in Schemes 1 and 2 were synthesized utilizing the methods reported by AlJammaz *et al*.,[18] Amartey *et al*.,[19] Kilbourn *and* colleagues[20] and Stöcklin and colleagues[21]. As a general procedure A, 2-fluoropyridine-4-carboxylic acid **3a**, (50 mg, 0.35 mmol) was placed in a 25 mL flask containing dichloromethane (5 mL) followed by the addition of thionylchloride (500 μL, 10.25 mmol). Mixture was stirred for 5 h then excess of excess thionylchloride and volatile components were removed under reduced pressure. The yellowish residue was re-solublilized in dichloromethane (5 mL) followed by drop-wise addition of a mixture of *N*,*N*-diethylethane-1,2-diamine (46 μL, 0.32 mmol) and triethylamine (50 μL, 0.36 mmol). Mixture was then refluxed for 3 h followed by evaporation till dryness and column chromatography separation using methanol:ethyl acetate (8:2) solvent system to yield **5a** as an oily yellowish material in 66% yield. The attained ES-MS $[M+1]^+ = 240$. ^{1}H NMR ($CDCl_3$): δ 8.56 (d, 1H, H2), 8.42 (s, 1H, H5), δ 7.81 (d, 1H, H3), δ δ 3.48 (q, 2H, H9), δ 2.93 (t, 2H, H10), δ 2.64 (q, 4H, H12,14), δ 1.34 (t, 6H, H13,15).



Scheme 1. Synthesis of the reference fluoroisonicotinamide, fluoronicotinamide (**5a-d**) and fluorobenzamide (**8a,b**) compounds.

The same general procedure A was applied to 6-fluoropyridine-3-carboxylic acid **3b** to produce (after column chromatography separation using methanol:ethylacetate (8:2) solvent system) **5b** as an oily yellowish material in 92% yield. The attained ES-MS $[M+1]^+ = 240$. ^{1}H NMR ($CDCl_3$): δ 8.73 (s, 1H, H2), δ 8.43 (q, 1H, H5), δ 7.18 (d, 1H, H4), δ 3.47 (q, 2H, H9), δ 3.47 (q, 4H, H12,14), δ 3.05 (t, 2H, H10), δ 1.34 (t, 6H, H13,15).

2-fluoro-[*N*-(2-pyrrolidin-1-yl)ethyl)]isonicotinamide 5c, 6-fluoro-[*N*-(2-pyrrolidin-1-yl)ethyl]nicotinamide 5d

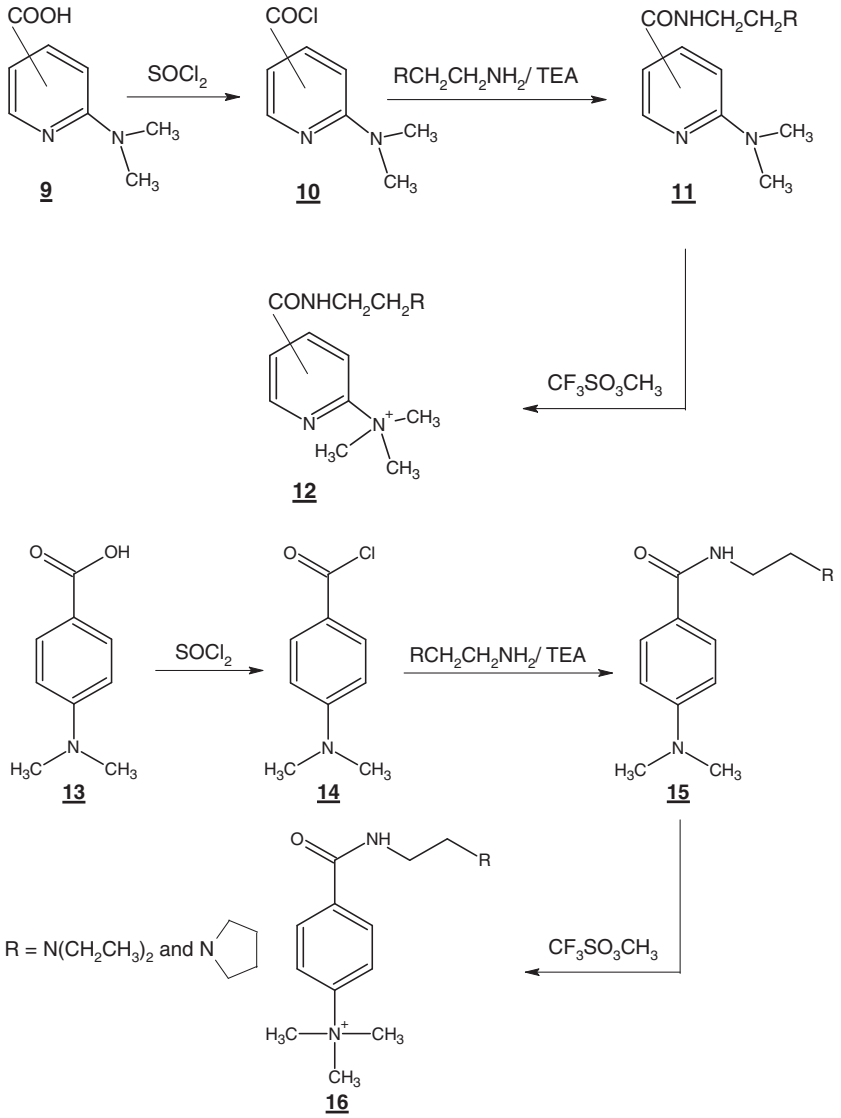
The above general procedure A was applied to the reaction of 2-(pyrrolidin-1-yl)ethanamine (40.6 μL, 0.32 mmol) with compounds **3a** (50 mg, 0.35 mmol) and **3b** (50 mg, 0.35 mmol), respectively, followed by column chromatography separation using methanol:ethyl acetate (8:2) solvent system, to give **5c** and **5d** as oily yellowish residues in 70 and 88%, respectively. The attained ES-MS $[M+1]^+ = 238$ for both **5c** and **5d**. ^{1}H NMR ($CDCl_3$): δ 8.64 (d, 1H, H2), δ 8.42 (s, 1H, H5), δ 7.71 (d, 1H, H3), δ 3.47 (q, 2H, H9), δ 3.01 (t, 2H, H10), δ 2.77 (t, 4H, H12,15), δ 1.34 (q, 4H, H13,14) for **5c** and δ 8.72 (s, 1H, H2), δ 8.40 (d, 1H, H5), δ 7.16 (d, 1H, H4), δ 3.46 (q, 2H, H9), δ 3.02 (t, 2H, H10), δ 1.85 (t, 4H, H12,15), δ 1.36 (q, 4H, H13,14) for **5d**.

N-[2-(diethylamino)ethyl]-4-fluorobenzamide 8a, 4-fluoro-[*N*-(2-pyrrolidin-1-yl)ethyl]benzamide 8b

General procedure A was applied to the reaction of 4-fluorobenzoic acid **6** (150 mg, 1.07 mmol) with *N*,*N*-diethylethane-1,2-diamine (138 μL, 0.96 mmol) and 2-(pyrrolidin-1-yl)ethanamine (122 μL, 0.96 mmol), respectively, followed by column chromatography separation using methanol:ethyl acetate (8:2) solvent system, to furnish **8a** and **8b** as oily colorless residues in 74 and 79% yields, respectively. The attained ES-MS $[M+1]^+ = 239$ for **8a** and 237 for **8b**. ^{1}H NMR ($CDCl_3$): δ 7.84 (dd, 2H, H3,5), δ 7.18 (dd, 2H, H2,6), δ 3.48 (q, 2H, H9), δ 2.65 (m, 6H, H10,12,14), δ 1.10 (t, 6H, H13,15) for **8a** and δ 7.87 (dd, 2H, H3,5), δ 7.19 (d, 2H, H2,6), δ 3.54 (q, 2H, H9), δ 2.72 (t, 2H, H10), δ 2.63 (q, 4H, H12,15), δ 1.82 (t, 4H, H13,14) for **8b**.

N-[2-(diethylamino)ethyl]-2-(dimethylamino)isonicotinamide 11a, *N*-[2-(diethylamino)ethyl]-6-(dimethylamino)nicotinamide 11b

General procedure A was applied to the reaction of 2-(dimethylamino)pyridine-4-carboxylic acid **9a** (150 mg, 0.9 mmol) and 6-(dimethylamino)pyridine-3-carboxylic acid **9b** (150 mg, 0.9 mmol) with *N*,*N*-diethylethane-1,2-diamine (146 μL, 0.81 mmol), followed by column chromatography separation using methanol:ethyl acetate (8:2) solvent system, to furnish **11a** and **11b** as oily yellowish residues in 56 and 64% yields, respectively. The attained



Scheme 2. Synthesis of trimethylammonium isonicotinamide, nicotinamide (**12a-d**) and benzamide (**16a,b**) triflate precursors.

ES-MS $[M+1]^+ = 265$ for both **11a** and **11b**. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H, H2), δ 8.49 (s, 1H, H5), δ 8.05 (d, 1H, H3), δ 3.77 (q, 2H, H9), δ 3.36 (m, 6H, H10,12,14), δ 1.36 (q, 6H, H13,14), δ 1.24 (s, 6H, H6) for **11a** and δ 8.95 (s, 1H, H2), δ 8.35 (d, 1H, H5), δ 7.65 (d, 1H, H4), δ 3.57 (q, 2H, H9), δ 3.18 (t, 2H, H10), δ 1.77 (q, 4H, H12,14), δ 1.34 (t, 6H, H13,15), δ 1.24 (s, 6H, H6) for **11b**.

2-(dimethylamino)-*N*-[2-(pyrrolidin-1-yl)ethyl]isonicotinamide 11c, 6-(dimethylamino)-*N*-[2-(pyrrolidin-1-yl)ethyl]nicotinamide 11d

General procedure A was applied to the reaction of compounds **9a** (150 mg, 0.9 mmol) and **9b** (150 mg, 0.9 mmol) with 2-(pyrrolidin-1-yl)ethanamine (103 μL, 0.96 mmol) followed by column chromatography separation using methanol:ethyl acetate (8:2) solvent system to furnish **11c** and **11d** as oily yellowish residues in 56 and 66%, respectively. The attained ES-MS $[M+1]^+ = 263$ for both **11c** and **11d**. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H, H2), δ 8.24 (s, 1H, H5), δ 7.55 (d, 1H, H3), δ 3.73 (q, 2H, H9), δ 2.17 (t, 2H, H10), δ 2.09 (t, 4H, H12,15), δ 1.37 (q, 4H, H13,14), δ 1.24 (s, 6H, H6) for **11c** and δ 8.94 (s, 1H, H2), δ 8.66 (d, 1H, H5), δ 7.26 (d, 1H, H4), δ 3.47 (q, 2H, H9), δ 2.17 (t, 2H, H10), δ 1.95 (t, 4H, H12,15), δ 1.35 (t, 4H, H13,14), δ 1.24 (s, 6H, H6), for **11d**.

4-[2-(diethylamino)ethylaminocarbonyl]pyrid-2-yltrimethylammonium triflate 12a, 3-[2-(diethylamino)ethylaminocarbonyl]pyrid-6-yltrimethylammonium triflate 12b

As a general procedure B, compounds **11a** (120 mg, 0.45 mmol) and **11b** (120 mg, 0.45 mmol) were dissolved in dry dichloromethane (3 mL) in separate flasks and were purged with nitrogen for 5 min. Methyl trifluoromethanesulfonate (52 μL, 0.45 mmol) was added to both solutions through rubber septum. The mixtures were stirred at ambient temperature for overnight. Reaction mixtures were then concentrated under reduced pressure to obtain a yellowish paste. Upon treatment with cold ether, yellowish oily residues were formed, separated out and dried in a desiccator to give **12a** and **12b** in 85 and 94% yields, respectively. The attained ES-MS $[M+1]^+ = 280$ for both **12a** and **12b**. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H, H2), δ 8.50 (s, 1H,

H5), δ 8.06 (d, 1H, H3), δ 3.77 (q, 2H, H9), δ 3.37 (m, 6H, H10,12,14), δ 1.38 (q, 6H, H13,14), δ 1.24 (s, 9H, H6) for **12a** and δ 8.97 (s, 1H, H2), δ 8.36 (d, 1H, H5), δ 7.56 (d, 1H, H4), δ 3.54 (q, 2H, H9), δ 3.19 (t, 2H, H10), δ 1.77 (q, 4H, H12,14), δ 1.36 (t, 6H, H13,15), δ 1.24 (s, 9H, H6), for **12b**.

4-[2-(pyrrolidin-1-yl)ethylaminocarbonyl] pyrid-2-yltrimethylammonium triflate 12c, 3-[2-(pyrrolidin-1-yl)ethylaminocarbonyl] pyrid-6-yltrimethylammonium triflate 12d

General procedure B was applied to the reaction of compounds **11a** (120 mg, 0.45 mmol) and **11b** (120 mg, 0.45 mmol) with methyl trifluoromethanesulfonate (52 μL, 0.45 mmol) to furnish **12c** and **12d** as oily yellowish residues in 75 and 70% yields, respectively. The attained ES-MS $[M+1]^+ = 278$ for both **11c** and **11d**. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H, H2), δ 8.25 (s, 1H, H5), δ 7.54 (d, 1H, H3), δ 3.72 (q, 2H, H9), δ 2.15 (t, 2H, H10), δ 2.09 (t, 4H, H12,15), δ 1.37 (q, 4H, H13,14), δ 1.24 (s, 9H, H6) for **11c** and δ 8.95 (s, 1H, H2), δ 8.65 (d, 1H, H5), δ 7.25 (d, 1H, H4), δ 3.48 (q, 2H, H9), δ 2.15 (t, 2H, H10), δ 1.96 (t, 4H, H12,15), δ 1.35 (t, 4H, H13,14), δ 1.24 (s, 9H, H6) for **11d**.

***N*-[2-(diethylamino)ethyl]-4-(dimethylamino) benzamide 15a, 4-(dimethylamino)-*N*-[(2-pyrrolidin-1-yl)ethyl] benzamide 15b**

General procedure A was applied to the reaction of 4-(dimethylamino)benzoic acid **13a** (150 mg, 0.91 mmol) with *N*,*N*-diethylethane-1,2-diamine (118 μL, 0.82 mmol) and 2-(pyrrolidin-1-yl)ethanamine (104 μL, 0.82 mmol), respectively, followed by column chromatography separation using methanol:ethyl acetate (8:2) solvent system, to furnish **15a** and **15b** as oily colorless residues in 52 and 55% yields, respectively. The attained ES-MS $[M+1]^+ = 263$ for **15a** and 261 for **15b**. ^{1}H NMR ($CDCl_3$): δ 7.79 (dd, 2H, H3,5), δ 6.90 (dd, 2H, H2,6), δ 3.25 (q, 2H, H9), δ 2.60 (m, 6H, H10,12,14), δ 1.22 (s, 6H, H4), δ 1.12 (t, 6H, H13,15) for **15a** and δ 7.95 (dd, 2H, H3,5), δ 7.29 (d, 2H, H2,6), δ 3.56 (q, 2H, H9), δ 2.52 (t, 2H, H10), δ 2.31 (q, 4H, H12,15), δ 1.89 (t, 4H, H13,14), δ 1.21 (s, 6H, H4) for **15b**.

4-[2-(diethylamino)ethylaminocarbonyl]phenyltrimethylammonium triflate 16a, 4-[2-(pyrrolidin-1-yl)ethylaminocarbonyl]phenyltrimethylammonium triflate 16b

General procedure B was applied to the reaction of compounds **15a** (125 mg, 0.47 mmol) and **15b** (125 mg, 0.47 mmol) with methyl trifluoromethanesulfonate (54 μL, 0.47 mmol) to provide **16a** and **16b** as oily yellowish residues in 54 and 65% yields, respectively. The attained ES-MS $[M+1]^+ = 278$ for **16a** and 276 for **16b**. ^{1}H NMR ($CDCl_3$): δ 7.79 (dd, 2H, H3,5), δ 6.94 (dd, 2H, H2,6), δ 3.21 (q, 2H, H9), δ 2.65 (m, 6H, H10,12,14), δ 1.22 (s, 9H, H4), δ 1.19 (t, 6H, H13,15) for **16a** and δ 7.77 (dd, 2H, H3,5), δ 6.92 (d, 2H, H2,6), δ 3.31 (q, 2H, H9), δ 2.52 (t, 2H, H10), δ 2.06 (q, 4H, H12,15), δ 1.86 (t, 4H, H13,14), δ 1.22 (s, 9H, H4) for **16b**.

Radiosynthesis

*N-[2-(diethylamino)ethyl][^{18}F]-2-fluoroisonicotinamide [^{18}F]-**5**[a], N-[2-(diethylamino)ethyl][^{18}F]-6-fluoronicotinamide [^{18}F]-**5b**, [^{18}F]-2-fluoro-[N-(2-pyrrolidin-1-yl)ethyl)]isonicotinamide [^{18}F]-**5c**, [^{18}F]-6-fluoro-[N-(2-pyrrolidin-1-yl)ethyl]nicotinamide [^{18}F]-**5d***

Aqueous [^{18}F]-fluoride was produced by the ^{18}O (p,n) ^{18}F reaction. The fluoride activity (2–10 mCi, 74–370 MBq) was trapped on ion exchange cartridge, eluted with Kryptofix 2.2.2 (5 mg) and potassium carbonate (1 mg) in ACN:H_2O solution (950 μL:50 μL), followed by azeotropic evaporation to dryness with aliquots of ACN. The solid residue was resolubilized in ACN (0.2 mL) containing one of the aryltrimethylammonium triflate precursors **12a–d** (2 mg). The reaction mixture was heated in capped 2 mL reaction-vial at 90°C for 5 min. The [^{18}F]-**5a–d** products were taken up in ether (2 × 1 mL) and passed through Sep-Pak silica cartridge. The ether solution was evaporated to dryness under gentle stream of nitrogen, then residues were resolubilized in saline and passed through 0.22 μm pore membrane filter for further studies. Radiochemical yields for [^{18}F]-**5a-d** were 92 ± 1.2, 93 ± 2.2, 92 ± 2.1 and 93 ± 1.8%, respectively.

*N-[2-(diethylamino)ethyl][^{18}F]-4-fluorobenzamide [^{18}F]-**8a**, [^{18}F]-4-fluoro-[N-(2-pyrrolidin-1-yl)ethyl]benzamide [^{18}F]-**8b***

The desired compounds [^{18}F]-**8a,b** were radiofluorinated using the arylmethylammonium triflate precursors **16a,b** (5 mg) and following the radiofluorination procedure mentioned above. Final products [^{18}F]-**8a**,**b** were resolubilized in saline and passed through 0.22 μm pore membrane filter for further studies. Radiochemical yields for [^{18}F]-**8a,b** were 91 ± 2.2 and 92. ± 1.9%, respectively.

Partition coefficient

100 μL of the final solution of any of the radiofluorinated compounds ([^{18}F]-**5a-d** or [^{18}F]-**8a,b**), were added into a test tube each containing 1 mL of n-octanol and 0.9 mL of buffered water (pH = 7.3). The tubes were shaken for 1 min. After partial separation of the phases by gravity, 0.7 mL of each phase was transferred to separate tubes and centrifuged at 5000 rpm for 5 min. Duplicate 0.2 mL aliquots of each phase were taken for γ-radioactivity measurement and the partition coefficient was determined by the function: Partition coefficient = Log_{10} (counts in n-octanol layer/counts in aqueous layer).

Results and discussion

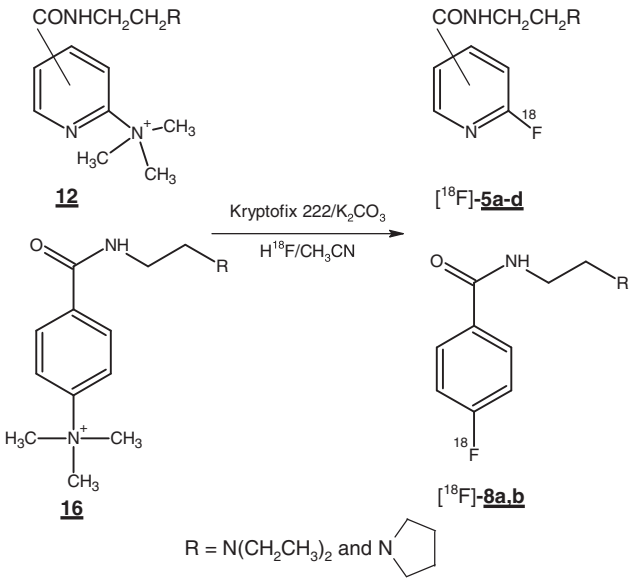
Chemistry

Scheme 1 outlines the synthesis of reference compounds *N*-[2-(diethylamino)ethyl]-2-fluoroisonicotinamide **5a**, *N*-[2-(diethylamino)ethyl]-6-fluoronicotinamide **5b**, 2-fluoro-[*N*-(2-pyrrolidin-1-yl)-ethyl)]isonicotinamide **5c**, 6-fluoro-[*N*-(2-pyrrolidin-1-yl)ethyl]nicotinamide **5d**, *N*-[2-(diethylamino)ethyl]-4-fluorobenzamide **8a** and 4-fluoro-[*N*-(2-pyrrolidin-1-yl)ethyl]benzamide **8b** using the general procedure A. These compounds were characterized by physical, chromatographic and spectral data and were in agreement with the anticipated structures (see the *experimental* part). The desired reference compounds **5a–d** and **8a,b** were obtained in reasonably good to excellent chemical yield (66–92%) and in greater than 95% chemical purity after column chromatography as colorless oil for the latter and yellowish oily material for the former. All **5a–d** and **8a,b** compounds were eluted at ~9.4 and ~10.5 min, respectively, using analytical HPLC column. Scheme 2 entails several reaction sequences for the preparation of intermediates, *N*-[2-(diethylamino) ethyl]-2-(dimethylamino)isonicotinamide **11a**, *N*-[2-(diethylamino) ethyl]-6-(dimethylamino)nicotinamide **11b**, 2-(dimethylamino)-*N*-[2-(pyrrolidin-1-yl)ethyl]isonicotinamide **11c**, 6-(dimethylamino)-*N*-[2-(pyrrolidin-1-yl)ethyl]nicotinamide **11d**, *N*-[2-(diethylamino)ethyl]-4-(dimethylamino)benzamide **15a**, 4-(dimethylamino)-*N*-[(2-pyrrolidin-1-yl)ethyl]benzamide **15b** and their corresponding aryltrimethylammonium triflate precursors **12a–d** and **16a,b**. The intermediates

11a–d and **15a,b** were obtained using general procedure A, as colorless oil for the latter and yellowish oily material for the former in good chemical yield (52–66%) and high purity (97%) after column chromatography. Methyl trifluoromethanesulfonate was used to convert intermediates **11a–d** and **15a,b** to their **12a–d**, and **16a,b** triflate precursors using the general procedure B (see the *experimental* part). The ammonium triflate precursors were obtained in good to excellent chemical yield (54–94%) and in greater than 97% chemical purity as yellowish oil material for **12a–d** and colorless oily substance for **16a,b**. These precursors were characterized by physical, chromatographic and spectral data and were in agreement with the anticipated structures (see the *experimental* part).

Radiochemistry

The rapid and efficient synthetic approach for the preparation of [^{18}F]-**5a**, [^{18}F]-**5b**, [^{18}F]-**5c**, [^{18}F]-**5d**, [^{18}F]-**8a** and [^{18}F]-**8b** (Scheme 3) was performed with only one simple radiosynthetic step. The key precursors aryltrimethylammonium triflates **12a–d** and **16a,b** were treated using classical catalyzed nucleophlic substitution on an ammonium-leaving group with no-carrier-added radiofluoride as described by Al Jammaz *et al*.[18] and Kilbourn and colleagues[20]. The final radiofluorinated compounds [^{18}F]-**5a-d** and [^{18}F]-**8a,b** were taken up by ether, which was followed by passing through Sep-Pak silica cartridge to remove polar impurities before evaporation to dryness and then dilution with saline for further studies. The overall radiochemical yields for all these radiotracers were constantly greater than 90% (based on starting [^{18}F]-fluoride) and radiochemical purities were always greater than 97% as determined by HPLC (Figures. 1 and 2) and confirmed by TLC-SG. By avoiding multi-step radiosynthesis and HPLC purification step for the preparation of [^{18}F]fluoronicotinamides and [^{18}F]fluorobenzamides reported recently[16,17], the total synthesis time for these radiotracers was reduced to less than 20 min. In addition, the measured specific activity for radiofluorinated compounds [^{18}F]-**5a–d** and [^{18}F]-**8a,b** were always >1000 mCi/μmol. Hence, these radiofluorinated compounds would be suitable for biochemical studies such as radioligand binding assays. This synthetic approach in comparison with the other methods[16,17] appears to be advantageous and holds considerable promise in the synthesis of [^{18}F]-fluoroisonicotinamides, [^{18}F]-fluoronicotinamides and [^{18}F]-fluorobenzamides in high radiochemical yield (>90%, based on starting [^{18}F]-fluoride), in a shorter synthesis time (<20 min), using a less laborious procedure and being amenable for automation.



Scheme 3. Radiosynthesis of [^{18}F]fluoroisonicotinamides, [^{18}F]fluoronicotinamides ([^{18}F]-**5a-d**) and [^{18}F]fluorobenzamides ([^{18}F]-**8a,b**) compounds.

Moreover, the calculated partition coefficient for radiofluorinated compounds [^{18}F]-**5a–d** and [^{18}F]-**8a,b** were found around -0.7 and $+0.8$, respectively, representing a low degree of lipophilicity for the former and moderate degree of lipophilicity for the latter compounds.

Conclusion

We have developed synthetic schemes leading to the procurement of key precursors needed for rapid and one-step radiofluorination method for the production of series of [^{18}F]fluoroisonicotinamides and -nicotinamides **5a–d** and [^{18}F]fluorobenzamides **8a,b**. The overall radiochemical yields for both [^{18}F]-**5a–d** and [^{18}F]-**8a,b** radiotracers were greater than

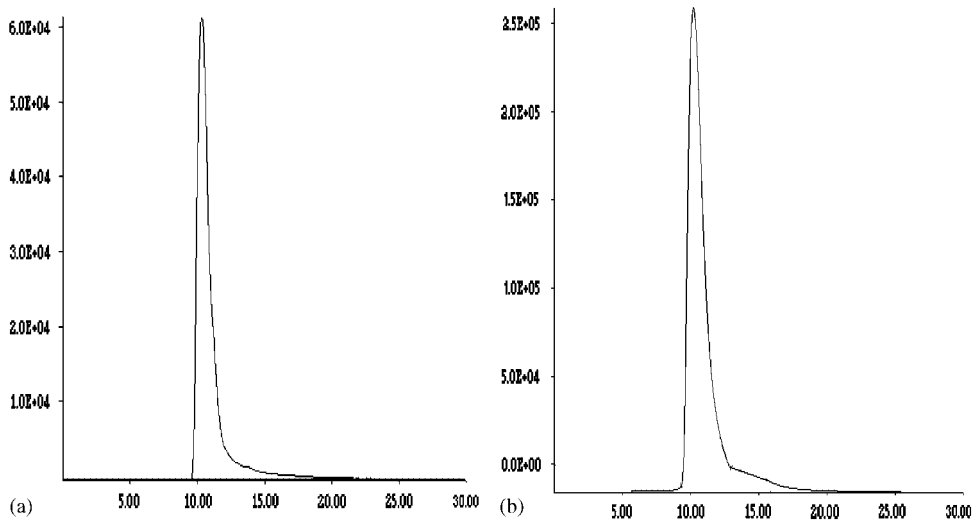


Figure 1. HPLC radiochromatograms of [^{18}F]fluoroisonicotinamides **5a** (A) and [^{18}F]fluoronicotinamides **5b** (B).

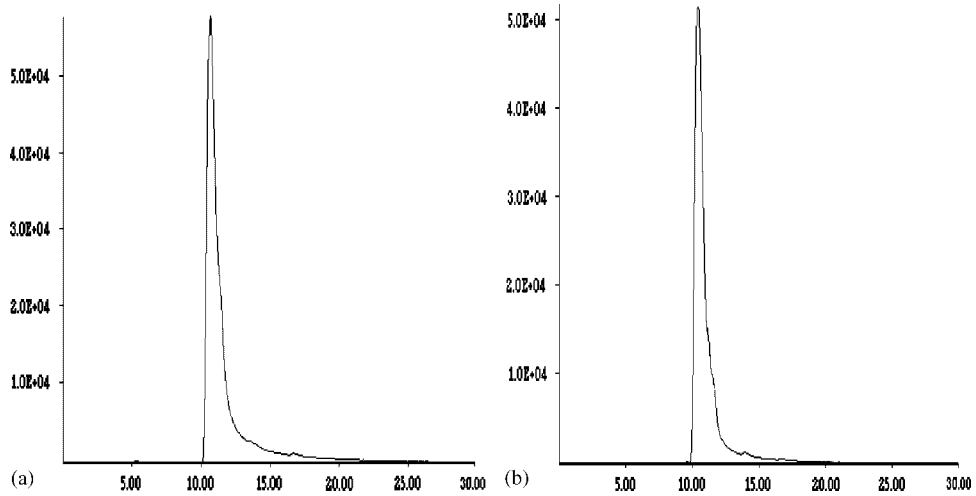


Figure 2. HPLC radiochromatograms of [^{18}F]fluorobenzamides **8a,b** (A and B).

90% (based on starting [^{18}F]-fluoride) with total synthesis time of less then 20 min. Radiochemical purities of these radiotracers were always greater than 97% without the need of HPLC purification, which makes this method a simple and amenable for automation.

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