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Novel Indole Derivatives as Potential Imaging Agents for Alzheimer's Disease

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Alzheimer's disease (AD), the most common form of sporadic or late-onset dementia, is characterized by progressive cognitive and functional impairment. Although the clinical tests currently performed are rather accurate, a definitive diagnosis can still only be made by examining the brain tissue after death. Post-mortem diagnosis of AD relies in part on the accurate detection of senile plaques (SPs) and neurofibrillary tangles (NFTs), the two major defining neuropathological features of AD.[1-3] While NFTs consist of bundles of filaments of hyperphosphorylated microtubule-associated protein, tau,[4] SPs contain mainly insoluble $A\beta_{40}$ and $A\beta_{42}$ peptides which are produced by a sequence of proteolytic cleavages from the amyloid precursor protein (APP). By targeting the cortical Aβ load, *in vivo* imaging by SPECT or PET has the potential to support both the earlier diagnosis by assessing a histologically confirmed AD-specific target and the monitoring of the effects of amyloid lowering therapeutic approaches.

Currently, several promising amyloid PET tracers were designed and successfully synthesized to image SPs or NFTs or both *in vivo* and have been used in clinical trial. Based on the benzothiazole and stilbene core structures, the two PET tracer compounds [^{11}C]PIB[5,6] and [^{11}C]SB-13[7,8] (Fig. 1) were designed and reported to image SPs in AD brain. [^{11}C] BF-227 is another potential probe containing a benzoxazole core, and neuropathologic staining has demonstrated preferential binding of this agent to dense amyloid deposits in AD brain.[9] [^{18}F]FDDNP[10-12] (Fig. 1) was shown to accumulate in SP- and NFT-dense brain areas. Kung *et al*. reported on the [^{123}I]IMPY[13-15] (Fig. 1) as candidate radiotracer for imaging SPs by SPECT. The positively charged quaternary heterocyclic nitrogen of the benzothiazolium group of the β-sheet specific staining dye thioflavine T limits the brain entry of this potential pharmacophore while its uncharged and lipophilic derivatives [^{11}C]6-Me-BTA-1[16] and BTA-1[17] (Fig. 2) enter the brain in amounts sufficient for imaging by PET and show some preference for SPs staining. On the contrary, the quinoline based [^{11}C]BF-158 (Fig. 2) demonstrated preferred labeling of NFTs in AD brain sections by *in vitro* autoradiography.[18]

By combining the chemical structures of SP-preferring benzothiazole and NFT-preferring quinoline, we have designed and synthesized a series of fluorinated indole derivatives by removing one C atom from the large conjugated 6-membered

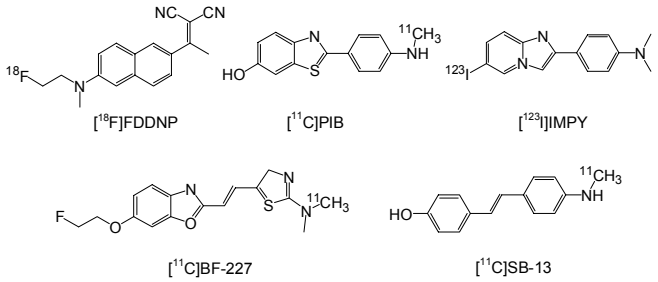


Figure 1. Structure of previously reported radiotracers for imaging amyloid plaques.

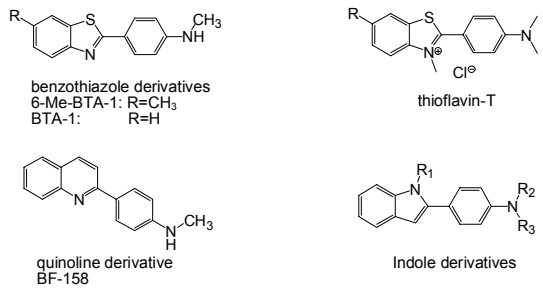


Figure 2. Structural difference/comparison between benzothiazole, quinoline and indole derivatives intended for application in plaque imaging.

quinoline ring system for radiolabelling with ^{18}F (Fig. 2). The resulting 5-membered indole structure offers the possibility to introduce a methyl group into the N-indole ring without parallel introduction of a positive charge into the molecule. The new compounds were investigated for their potential to displace the well described thioflavin-based β-sheet ligand [^{125}I]IMPY from its binding sites in postmortem AD brain. By this way, we expect that these compounds can be used to image SPs or NFTs or both.

Experimental Section

General. All the reagents used for chemical synthesis were commercial products without any further purification. ^{1}H-NMR,

^{13}C-NMR, and ^{19}F-NMR spectra were obtained on the Mercury-400BB "felix" spectrometer, mercury-300BB "jutta", or Gemini-200BB "Paul" with TMS as internal standard. Coupling constants are reported in Hertz. The multiplicity is defined by s (singlet), d (doublet), t (triplet), b (broad), and m (multiplet). Elementary analysis was determined by the elementar Vario EL III. Mass Spectrum was achieved by Mariwer Biospectrometry (applied biosystem, MS-TOF).

4-(1*H*-Indol-2-yl)benzenamine (3a): A mixture of **1a** (1.08 g, 10 mmol) and **2a** (1.35 g, 10 mmol) was added to 10 g of PPA and stirred at 80 °C for 5 h. After being cooled down to room temperature, the reaction mixture was poured into 200 mL of aqueous Na_2CO_3 solution and extracted with ethyl acetate (3 × 50 mL). The organic layer was separated, washed with brine, dried with anhydrous Na_2CO_3. The mixture was purified by column chromatography (EtOAc : petroleum ether = 1 : 2) to get yellowish solid (0.9 g; yield: 47%). The compounds **3b** and **3c** were prepared by the same method as **3a**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.26 (2H, b), 6.55 (1H, s), 6.62 (2H, d, J = 8.8 Hz), 6.91 (1H, t, J = 7.6 Hz), 6.98 (1H, t, J = 7.6 Hz), 7.30 (1H, d, J = 7.6 Hz), 7.41 (1H, d, J = 7.2 Hz), 7.51 (2H, d, J = 7.2 Hz), 11.15 (1H, b). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 95.4, 110.8, 114.0, 119.0, 119.1, 120.0, 120.3, 126.1, 129.1, 136.6, 139.2, 148.4. EI-MS *m*/*z* 209.12 [M^+], (Calcd for 209.11). *anal.* Calcd for $C_{14}H_{12}N_2$: C, 80.740; H, 5.810; N, 13.450. Found: C, 80.345; H, 5.860; N, 13.450.

4-(1*H*-Indol-2-yl)-*N*-methylbenzenamine (3b): (70% yield, yellowish solid) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.89 (3H, s), 3.87 (1H, b), 6.66 (1H, s), 6.62 (2H, d, J = 8.8 Hz), 7.09 (1H, t, J = 7.2 Hz), 7.14 (1H, t, J = 7.6 Hz), 7.37 (1H, d, J = 7.6 Hz), 7.51 (2H, d, J = 8.4 Hz), 7.59 (1H, d, J = 7.6 Hz), 8.21 (1H, b). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.8, 97.8, 110.7, 112.8, 120.1, 120.2, 121.5, 121.6, 126.5, 129.8, 136.6, 139.0, 149.2. EI-MS *m*/*z* 223.10 [M^+], (Calcd for 223.12). *anal.* Calcd for $C_{15}H_{14}N_2$: C, 81.050; H, 6.350; N, 13.450. Found: C, 81.11; H, 6.344; N, 12.57.

4-(1-Methyl-1*H*-indol-2-yl)benzenamine (3c): (0.73 g, yield 47%, yellowish solid) ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.70 (3H, s), 3.78 (2H, b), 6.45 (1H, s), 6.75 (2H, d, J = 8.6 Hz), 7.09 (1H, t, J = 7.2 Hz), 7.20 (1H, t, J = 7.6 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.58 (1H, d, J = 7.8 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 31.2, 100.7, 109.6, 115.0, 119.8, 120.3, 121.3, 123.1, 128.2, 130.7, 138.2, 142.2, 146.4, EI-MS *m*/*z* 223.14 [M^+], (calcd for 223.12). *anal.* Calcd for $C_{15}H_{14}N_2$: C, 81.050; H, 6.350; N, 13.450. Found: C, 81.14; H, 6.280; N, 12.50.

1-(4-(Methylamino)phenyl)ethanone (2b): 2a (1 g, 7.4 mmol) was dissolved in pyridine (3 mL). Ac_2O (3 mL) was added and stirred for 30 minutes at 0 °C. The precipitate was filtrated, to get the product 4-acetylaminoacetophenone 1 g; yield 77%. To a solution of this acetyl derivative (0.2 g, 1.13 mmol) in anhydrous DMF (5 mL), was added NaH (48 mg, 2.0 mmol) at 0 °C within 30 min, CH_3I (0.213 g, 1.5 mmol) was dropped slowly into the reaction mixture at 0 °C, keeping stirring for additional 1 h at room temperature. The mixture was quenched in 20 mL cool water, extracted with ethyl acetate and the solvent was evaporated. The residue was suspended in HCl (3 M) (20 mL) and refluxed for 5 h, neutralized with Na_2CO_3, and purified with column chromatography to get the product (**2b**, 0.17 g, yield 65%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.50 (3H, s), 2.90 (3H, s), 4.25 (1H, b), 6.56 (2H, d, J = 8.7 Hz), 7.84 (2H, d, J = 8.7 Hz).

***N*-Methyl-4-(1-methyl-1*H*-indol-2-yl)benzenamine (3d):** Compound **3c** (70 mg, 0.32 mmol) was dissolved in MeOH (10 mL) containing $NaOCH_3$ (86 mg, 1.6 mmol). Paraformaldehyde (48 mg, 1.6 mmol) was added and the reaction mixture was refluxed for 6 hours. After cooling down to 0 °C, $NaBH_4$ (64 mg, 1.6 mmol) was added in portion and the mixture was refluxed for additional 2 h and then diluted with the 50 mL of cool water, extracted with ethyl acetate (3 × 20 mL). The organic layer was separated, washed with water and brine, dried (Na_2CO_3) and purified by column chromatography (ethyl acetate : petroleum ether = 1 : 4) to get yellowish solid (57 mg, yield 76%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.90 (1H, s), 3.73 (3H, s), 3.87 (1H, b), 6.47 (1H, s), 6.70 (2H, d, J = 7.8 Hz), 7.12 (1H, t, J = 7.5 Hz), 7.21 (1H, t, J = 7.5 Hz), 7.34 (3H, d, J = 8.7 Hz), 7.61 (1H, d, J = 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 30.8, 31.2, 100.5, 109.5, 112.3, 119.8, 120.2, 121.2, 121.6, 128.3, 130.6, 138.2, 142.5, 149.2. EI-MS *m*/*z* 237.17 [M^+], (Calcd for 237.14). *anal.* Calcd for $C_{16}H_{16}N_2$: C, 81.670; H, 6.430; N, 11.910. Found: C, 81.495; H, 6.785; N, 11.935.

***N*-(2-Fluoroethyl)-4-(1*H*-indol-2-yl)benzenamine (4a):** A mixture of compound **3a** (0.1 g, 0.48 mmol), 1-bromo-2-fluoroethane (0.34 mg, 2.7 mmol) and Na_2CO_3 (0.1 g, 0.94 mmol) in dioxane (5 mL) was sealed in the bottle and stirred at 110 °C for 5 days. After being cooled to room temperature, the reaction mixture was poured into 40 mL of cold water, extracted with ethyl acetate, and purified by column chromatography to get the yellowish solid. 37 mg, yield 30%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.34 (1H, q, J = 5.4 Hz), 3.43 (1H, q, J = 5.4 Hz), 4.48 (1H, t, J = 5.4 Hz), 4.64 (1H, t, J = 5.4 Hz), 6.03 (H, t, J = 6 Hz), 6.58 (1H, s), 6.68 (2H, d, J = 8.1 Hz), 6.91 (1H, t), 6.98 (1H, t, 7.5 Hz), 7.30 (1H, d, J = 8.1 Hz), 7.42 (1H, d, J = 7.5 Hz), 7.58 (2H, d, J = 8.7 Hz), 11.18 (1H, b). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 42.9, 43.2, 81.4, 83.6, 95.6, 110.7, 112.2, 119.0, 119.1, 120.2, 120.3, 126.1, 129.0, 136.7, 138.9, 148.1. ^{19}F-NMR (282 MHz, DMSO-d_6) δ -220.7. EI-MS *m*/*z* 255.09 [M^+], (Calcd for 255.13). *anal.* Calcd for $C_{16}H_{15}N_2F$: C, 75.570; H, 5.950; N, 11.02. Found: C, 75.390; H, 5.911; N, 11.055.

***N*-(2-Fluoroethyl)-4-(1*H*-indol-2-yl)-*N*-methylbenzenamine (4b):** A mixture of compound **3b** (50 mg, 0.2 mmol), 1-bromo-2-fluoroethane (0.25 g, 2 mmol) and Na_2CO_3 (0.11 g, 1 mmol) in MeCN (2 mL) was sealed in a bottle and heated to 80 °C. The reaction mixture was purified according to the **4a** synthetic method to get yellowish solid (**4b**) 22 mg, yield 47%. The compounds **4c** and **4d** were synthesized using **3c** and **3d** respectively by the same method as **4b**. The compound **4e** was synthesized using **3d** and 1-iodo-3-fluoropropane by the similiar reaction described in the preparation of **4b**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.07 (3H, s), 3.66 (1H, t, J = 5.1 Hz), 3.74 (1H, t, J = 5.1 Hz), 4.56 (1H, t, J = 5.1 Hz), 4.71 (1H, t, J = 5.1 Hz), 6.67 (1H, s), 6.78 (2H, d, J = 9.0 Hz), 7.09 (1H, t, J = 6.9 Hz), 7.15 (1H, t, J = 7.2Hz), 7.36 (1H, d, J = 8.1 Hz) 7.54 (2H, d, J = 9.0 Hz), 7.59 (1H, d, J = 7.5 Hz), 8.21 (1H, b). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 39.2, 52.6, 52.9, 80.8, 83.0, 97.9, 110.7, 112.6, 120.18, 120.22, 121.1, 121.6, 126.5, 129.8, 136.7, 138.8, 148.7. EI-MS *m*/*z* 269.14 [M^+], (Calcd for 269.15). *anal.* Calcd for $C_{17}H_{17}N_2F$: C,

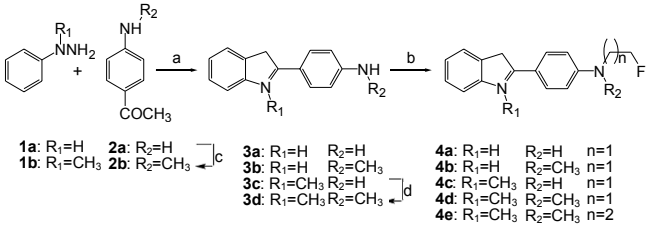
76.090; H, 6.390; N, 10.440. Found: C, 75.855; H, 6.420; N, 10.455.

***N*-(2-Fluoroethyl)-4-(1-methyl-1*H*-indol-2-yl)benzenamine (4c):** (yellowish solid, yield 54%) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.49 (1H, q, J = 5.2 Hz), 3.55 (1H, q, J = 5.2 Hz), 3.74 (3H, s), 4.16 (1H, b), 4.62 (1H, t, J = 4.8 Hz), 4.74 (1H, t, J = 4.8 Hz), 6.48 (1H, s), 6.74 (2H, d, J = 8.8 Hz), 7.13 (1H, t, J = 7.2 Hz), 7.22 (1H, t, J = 8.0 Hz), 7.35 (1H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.61 (1H, d, J = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.2, 44.1, 44.3, 81.7, 83.3, 100.6, 109.6, 113.0, 119.8, 120.2, 121.3, 122.5, 128.2, 130.7, 138.2, 142.1, 147.4. EI-MS *m*/*z* 269.24 [M^+], (Calcd for 269.15). *anal.* Calcd for $C_{17}H_{17}N_2F$: C, 76.090; H, 6.390; N, 10.440. Found: C, 75.725; H, 6.565; N, 10.120.

***N*-(2-Fluoroethyl)-*N*-methyl-4-(1-methyl-1*H*-indol-2-yl) benzenamine (4d):** (yellowish solid, yield 69%) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.09 (3H, s), 3.69 (1H, t, J = 5.2 Hz), 3.74 (3H, s), 3.75 (1H, t, J = 5.2 Hz), 4.60 (1H, t, J = 5.2 Hz), 4.72 (1H, t, J = 5.2 Hz), 6.48 (1H, s), 6.81 (2H, d, J = 8.8 Hz), 7.13 (1H, t, J = 7.2 Hz), 7.22 (1H, t, J = 7.6 Hz), 7.34 (1H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.8 Hz), 7.61 (1H, d, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.2, 39.2, 52.6, 52.9, 81.1, 82.8, 100.5, 109.6, 112.1, 119.8, 120.2, 121.1, 121.2, 130.6, 128.3, 138.2, 142.2, 148.6. EI-MS *m*/*z* 283.18 [M^+], (Calcd for 283.16). *anal.* Calcd for $C_{18}H_{19}N_2F$: C, 76.570; H, 6.780; N, 9.920. Found: C, 76.235; H, 7.051; N, 9.516.

***N*-(3-Fluoropropyl)-*N*-methyl-4-(1-methyl-1*H*-indol-2-yl) benzenamine (4e):** (yellowish solid, yield 38%) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.98 (1H, m), 2.07 (1H, m), 3.03 (3H, s), 3.57 (2H, t, J = 6.6 Hz), 3.749 (3H, s), 4.48 (1H, t, J = 5.4 Hz), 4.64 (1H, t, J = 5.4 Hz), 6.48 (1H, s), 6.81 (2H, d, J = 8.7 Hz), 7.13 (1H, t, J = 7.5 Hz), 7.28(1H, t, J = 7.5 Hz), 7.34 (1H, d, J = 7.8 Hz), 7.40 (2H, d, J = 8.7 Hz), 7.61(1H, d, J = 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.1, 28.4, 31.2, 38.7, 48.7, 48.8, 80.8, 83.0, 100.4, 109.5, 111.9, 119.8, 120.2, 120.6, 121.1, 128.3, 130.6, 138.3, 142.3, 148.8. ^{19}F-NMR (282 MHz, $CDCl_3$) δ -221.4. EI-MS *m*/*z* 297.24 [M^+], (Calcd for 297.39). *anal.* Calcd for $C_{19}H_{21}N_2F$: C, 77.000; H, 7.140; N, 9.450. Found: C, 76.605; H, 7.199; N, 9.421.

Biological evaluation. 30 μm thick brain sections were obtained from frozen cortical tissue by cryostat sectioning mounted on glass microscope slides, dried at room temperature and stored at −25 °C until experiment. The frozen sections were thawed, incubated in 4% PBS-buffered paraformaldehyde on ice for 60 min, washed twice with PBS on ice for 3 min each, incubated in xylene at room temperature for 5 min, and eventually in 100%, 100%, 95%, 85% and 75% EtOH at room temperature for 1 min each. The PFA-fixed and xylene-incubated sections were dried at room temperature for 15 min and incubated with [^{125}I]IMPY alone or in the presence of 100 μM IMPY to determine the nonspecific binding or 100 μM of the test compounds in PBS containing 10% EtOH at room temperature for 1 h. The sections were then incubated two times in saturated Li_2CO_3 in 40% EtOH and once in 40% EtOH for 2 min each. The sections were dried at room temperature and exposed with ^{125}I-sensitive imaging plates (Fuji Film, Tokyo, Japan) for 12 h. The screen plates were analysed using image analysis system BAS-1800 II Bioimaging Analyzer (Fuji Film, Japan). Quantitative analysis of the digitized autoradiopgraphs was performed by computer assisted microdensitometry (Aida 2.31, raytest, Germany) by measuring the photostimulated luminescence (PSL) per brain section and the area of the respective brain section (mm^2). For each brain section, the ratio PSL/mm^2 was calculated and expressed in % of the specific binding of [^{125}I]IMPY. Three independent experiments were performed.



Reagents and conditions: (a) PPA, 80 °C; (b) FCH_2CH_2Br or $FCH_2CH_2CH_2I$, Na_2CO_3, MeCN, 80 °C or dioxane, 100 °C; (c) Ac_2O; NaH, CH_3I, DMF, 0 °C; HCl (3 M) reflux; (d) $(CH_2O)n$, $NaOCH_3$, CH_3OH, $NaBH_4$, 0 °C

Scheme 1

Results and Discussion

The Fischer-Indole synthesis has been widely studied and applied for the preparation of indole derivatives.[19] Polyphosphoric acid (PPA), as catalyst and solvent, plays an important role in the one-pot reaction.[20] As shown in Scheme 1, **3a** was synthesized from **1a** and **2a** in PPA at 80 °C. **2a** was acetylated first by acetic anhydride in pyridine followed by methylation with CH_3I and NaH in DMF. After removal of the acetyl group (3 M HCl), *N*-methylaminoacetophenone (**2b**) was obtained, which was used to synthesize indole **3b** with high yield. **3c** was achieved by reaction of **1b** with **2a** according to the same procedure as described for **3a**. The anilino group in **3c** was monomethylated with paraformaldehyde, $NaOCH_3$ and $NaBH_4$ in methanol to get **3d**. The 2-fluoroethyl derivatives **4a-d** were achieved by the alkylation of **3a-d** with 1-bromo-2-fluoroethane in dioxane or acetonitrile in the presence of Na_2CO_3. The homologous compound **4e** was prepared from **3d** and 1-fluoro-3-iodopropane with the same method of **4b**. The ^{1}H-, ^{13}C-, ^{19}F-NMR spectra, MS spectra and elemental analysis for all final compounds and intermediates were in accordance with the assigned structures.

The interaction of the newly synthesized compounds with [^{125}I]IMPY-labelled brain structures was analyzed at first on human postmortem cortex obtained from one patient suffering from Alzheimer's disease. The autoradiographic images were shown on Fig. 3. To avoid the brain tissue consuming technique of homogenate assays, radiotracer displacement studies were performed on brain slices and analyzed by digital autoradiography. [^{125}I]IMPY was reported to bind with high affinity to AD cortical homogenate (K_D = 5.3 nM)[21] and has been widely used as radioligand to determine the K_i values of candidate β-sheet ligands. Considering the similar chemical structure of IMPY and the newly synthesized indole derivatives, the radioligand and the test compounds are expected to interact comparably with β-sheet structures. IMPY and [^{125}I]IMPY were

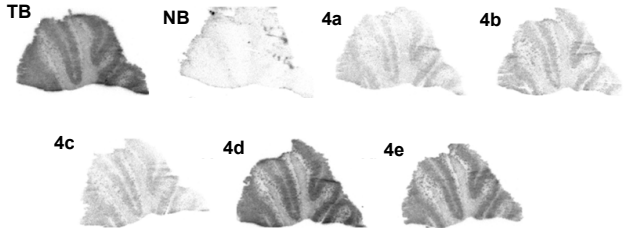


Figure 3. *In vitro* autoradiography on **4a-e** displacement with [^{125}I] IMPY-labelled AD human brain postmortem. **TB**: [^{125}I]IMPY-labelled AD human brain postmortem; **NB**: IMPY displacement with [^{125}I]IMPY-labelled AD human brain postmortem; **4a-4e**: compound **4a-e** displacement with [^{125}I]IMPY-labelled AD human brain postmortem.

Table 1. Displacement by newly synthesized indole derivatives of specific binding of [^{125}I]IMPY in human AD brain sections assessed by digital autoradiography *in vitro*

Ligand at 100 μM	Specific binding of [^{125}I]IMPY to AD brain sections
4a	10 ± 2%
4b	13 ± 3%
4c	14 ± 6%
4d	84 ± 15%
4e	47 ± 8%

All data are presented as mean values (n = 3) ±SD.

synthesized and labeled with ^{125}I according to the procedures described in the literature.[21] Autoradiographic investigation in vitro demonstrated that at 100 μM **4a**, **4b**, **4c** displaced a higher amount of specific [^{125}I]IMPY binding to AD brain tissue than **4d** and **4e** (86 to 90% *vs*. 16 to 53% displacement of specific binding, respectively; Table 1). Thus, the indole derivatives which contain only secondary amines (**4a**) or carry a single methyl substitution either at the indole-N (**4b**) or aniline-N (**4c**) possess an affinity to IMPY-labelled sites comparable to the thioflavin T itself. However, the methylation of both the aniline-N and the indole-N in **4e** and **4d**, respectively, reduced the [^{125}I]IMPY displacement efficacy significantly. Compared to fluoroethyl substitution in **4d**, the fluoropropyl substituted **4e** is assumed to show a somewhat higher affinity to IMPY-labelled structures in AD brain slices.

In summary, in this work nine indole derivatives were successfully synthesized. Five fluorine-substituted compounds were investigated regarding their affinity to human AD brain tissue in vitro. Indole derivatives **4a**, **4b**, and **4c** displayed the potential to develop ^{18}F-labeled PET tracers for imaging neuropathological hallmarks in AD brain *in vivo*.

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