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Synthesis of a [6-*Pyridinyl*-^{18}F]-labelled Fluoro Derivative of WAY-100635 as a Candidate Radioligand for Brain 5-HT$_{1A}$ Receptor Imaging with PET

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Abstract—In recent years, considerable effort has been spent on the design, synthesis and pharmacological characterization of radiofluorinated derivatives of the 5-HT$_{1A}$ receptor antagonist, WAY-100635, for the in vivo study of these receptors in human brain with PET. (*Pyridinyl*-6)-fluoro- and (*pyridinyl*-5)-fluoro-analogues of WAY-100635 (6-fluoro and 5-fluoro-WAY-100635, **5a**/**6a**) were synthesized as well as the corresponding chloro-, bromo- and nitro-derivatives as precursors for labelling (**5b–d** and **6b–d**). Comparative radiolabelling of these precursors with fluorine-18 (positron-emitting isotope, 109.8 min half-life) clearly demonstrated that only *ortho*-fluorination in this pyridine series, and not *meta*-fluorination, is of interest for the preparation of a radioligand by nucleophilic heteroaromatic substitution. 6-[^{18}F]Fluoro-WAY-100635 ([^{18}F]**5a**) can be efficiently synthesized in one step, either from the corresponding 6-bromo precursor (using conventional heating at 145 °C for 10 min) or from the corresponding 6-nitro precursor (using microwave activation at 100 W for 1 min). Typically, 15–25 mCi (0.55–0.92 GBq) of 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**, 1–2 Ci/μmol or 37–72 GBq/μmol) were obtained in 50–70 min starting from a 100 mCi (3.7 GBq) aliquot of a batch of cyclotron-produced [^{18}F]fluoride. This ^{18}F-labelled radioligand is now being evaluated in PET studies.

Introduction

The serotonergic system, with its different receptor subtypes, is one of the most important neurotransmitter system in the brain and is involved in the regulation of various physiological functions and states of mind. 5-HT$_{1A}$ receptors in particular are strongly implicated in neuropsychiatric disorders such as anxiety, depression and schizophrenia.[1] Positron Emission Tomography (PET), a high-resolution, sensitive and non-invasive imaging technique that can be used in humans, is the most advanced technology currently available for studying in vivo molecular interactions. It can play a key-role both in elucidating the involvement of these receptors in neuropsychiatric disorders,[2] in therapies with already established pharmaceuticals[3,4] or with drugs under development.[5–7]

WAY-100635 (**1**, cyclohexanecarboxylic acid {2-[4-(2-methoxy-phenyl)-piperazin-1-yl]-ethyl}-(pyridin-2-yl)-amide, Fig. 1) labelled with carbon-11, a 20.4 min half-life positron-emitter, has been established as the radioligand of choice for the study of 5-HT$_{1A}$ receptors in human brain in vivo using PET.[8–12] However, this very effective antagonist radioligand ([^{11}C]WAY-100635, [^{11}C]**1**) is rapidly metabolized and rapidly cleared from plasma[13] which can reduce the ease of applying some approaches to biomathematical analysis of the radioligand

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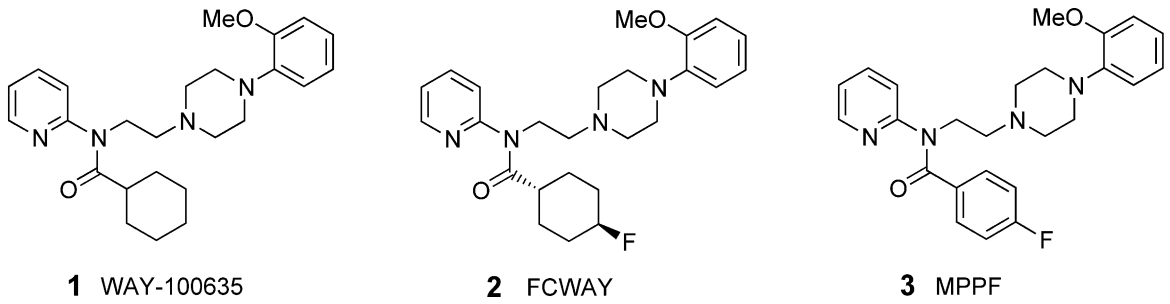


Figure 1. Chemical structures of WAY-100635 (**1**), FCWAY (**2**) and MPPF (**3**).

binding to 5-HT_{1A} receptors. Moreover, the short half-life of carbon-11 obliges the radioligand to be used local to its production. The use of longer-lived positron-emitting fluorine-18 ($t_{1/2} = 109.8$ min) has the potential to circumvent these issues.

In recent years, considerable effort has been spent on the design, synthesis and pharmacological characterization of fluorinated derivatives of WAY-100635 for radiolabelling with fluorine-18. For example, FCWAY (**2**, 4-fluoro-cyclohexanecarboxylic acid {2-[4-(2-methoxy-phenyl)-piperazin-1-yl]-ethyl}-pyridin-2-yl-amide, Fig. 1) has been labelled with fluorine-18 by nucleophilic aliphatic tosyl-to-fluoro substitution.[14,15] However, [^{18}F]FCWAY ([^{18}F]**2**) also show rapid metabolism and in particular defluorination, which eventually gives rise to problematical [^{18}F]fluoride uptake in skull.[16] Another fluorinated derivative, MPPF (**3**, 4-fluoro-*N*-{2-[4-(2-methoxy-phenyl)-piperazin-1-yl]-ethyl}-*N*-pyridin-2-yl-benzamide, Fig. 1) has been labelled with fluorine-18 by nucleophilic aromatic nitro-to-fluoro substitution.[17–23] [^{18}F]MPPF ([^{18}F]**3**) is currently under validation for human PET studies and for quantifying the endogenous ligand, serotonin, at the receptor level.[24]

Halopyridinyl derivatives of WAY-100635 (**4**, Fig. 2) have recently been described as potent 5-HT_{1A} antagonists and only minor effects on affinity or intrinsic efficacy have been shown[25] compared to the parent ligand. These halopyridinyl derivatives were also labelled with carbon-11, suggesting a promising interest in PET imaging ([^{11}C]-**4**, Fig. 2).[26] Fluoropyridinyl derivatives can be labelled with fluorine-18. Moreover, in compounds presenting a pyridine ring, nucleophilic heteroaromatic substitution with ^{18}F-labelled fluoride ion appears today as the method of choice for the highly efficient synthesis of radioligands of high specific activity for PET. However, compared to homoaromatic- and aliphatic nucleophilic radiofluorinations,[27,28] only few references can be found in the literature describing nucleophilic substitutions with [^{18}F]fluoride ion of heteroaromatic compounds such as pyridines and only reactions involving fluorination at the *ortho*-position have been intensely studied. In particular, the scope of these nucleophilic heteroaromatic fluorinations with no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F-K_{222} complex was evaluated using the synthesis of 2-[^{18}F]fluoropyridine as a model reaction.[29] The potent radioligands, *nor*-chloro[^{18}F]fluoroepibatidine ((±)-exo-2-(6-[^{18}F]fluoro-3-pyridyl)-7-azabicyclo[2.2.1]heptane)[30–36] and 2-[^{18}F]fluoro-A-85380 (2-[^{18}F]fluoro-3-[2(*S*)-2-azetidinylmethoxy]pyridine)[37–39] were recently labelled with fluorine-18 at the *ortho*-position on the pyridine ring. Heteroaromatic nucleophilic substitutions of the pyridine ring at the *meta*-position has, to our knowledge never been reported. The only example of a radiosynthesis of a *meta*-[^{18}F]fluoropyridine derivative known to us is the preparation of *N*-(2-aminoethyl)-5-[^{18}F]fluoropyridine-2-carboxamide, using a nitro-to-fluoro substitution on a chemical structure bearing a strong electron-withdrawing group *para* to the leaving group.[40]

We herein report the synthesis of 6-fluoro- and 5-fluoro-derivatives of WAY-100635 (Fig. 3), namely: *N*-(2-(1-(4-(2-methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-fluoro)-pyridinyl)cyclohexane carboxamide (**5a**, 6-fluoro-WAY-100635) and *N*-(2-(1-(4-(2-methoxyphenyl)piperazinyl)-ethyl))-*N*-(2-(5-fluoro)pyridinyl)cyclohexane carboxamide

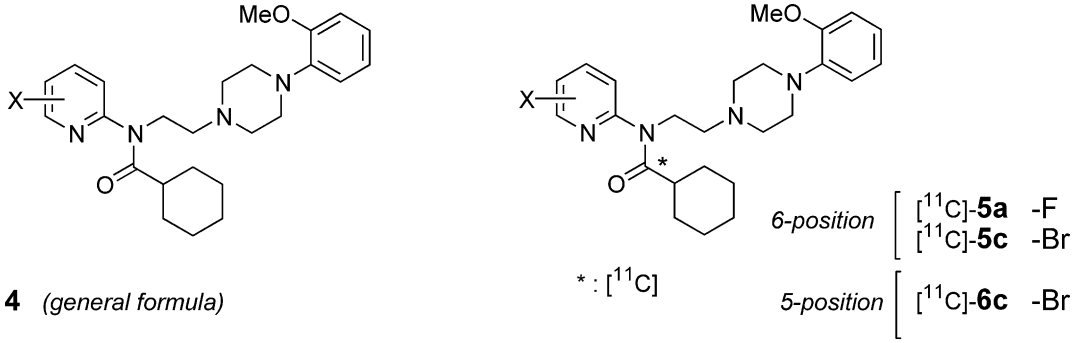


Figure 2. Chemical structures of halopyridinyl derivatives of WAY-100635 (**4**, general formula), and in particular 6-[^{11}C]fluoro-, 6-[^{11}C]bromo- and 5-[^{11}C]bromo-WAY-100635 ([^{11}C]-**5a/5c/6c**).

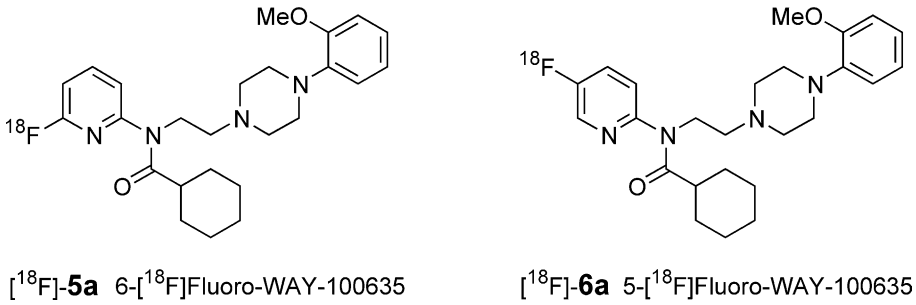


Figure 3. Chemical structures of 6-[^{18}F]fluoro- and 5-[^{18}F]fluoro-WAY-100635 ([^{18}F]-**5a/6a**).

(**6a**, 5-fluoro-WAY-100635). We also report the synthesis of the 5- and 6-chloro-, 5- and 6-bromo- and the 5- and 6-nitro- derivatives of WAY-100635 (**5b–d** and **6b–d**) as precursor for labelling. Finally, comparative radiolabelling by nucleophilic heteroaromatic substitution with fluorine-18 at the *ortho*- and *meta*-position from the corresponding precursors (**5b–d** and **6b–d**) using both conventional heating and microwave activation will be presented, leading to an efficient preparation of 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**).

Results and Discussion

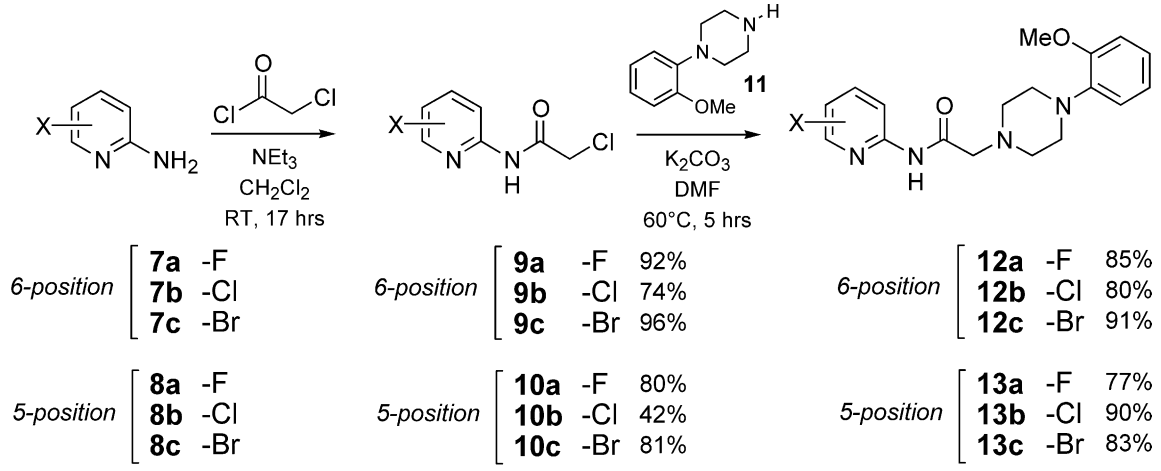
Chemistry

The synthesis of all 6- and 5-halo- derivatives of WAY-100635 (**5a–c**, **6a–c**) started from the commercially available corresponding 6- or 5-substituted 2-aminopyridines (**7a–c**, **8a–c**).

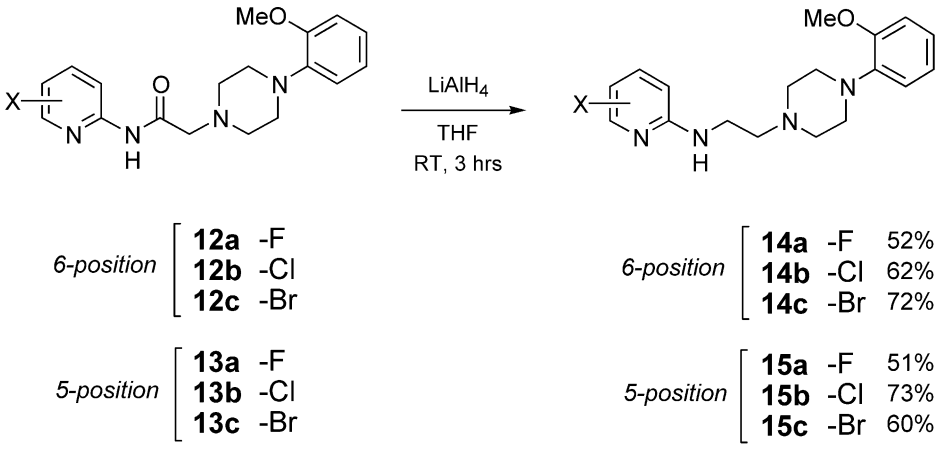
Reaction of the 6- or 5-halo-2-aminopyridines (**7a–c**/**8a–c**) with 1.5 equiv of chloroacetyl chloride in dichloromethane containing 1.5 equiv of triethylamine at room temperature for 17 h gave the corresponding *N*-pyridinyl-2-chloroacetamides **9a–c** and **10a–c** in 42–96% yield (Scheme 1). Reaction of the 2-chloroacetamides **9a–c** or **10a–c** with 1 equiv of 1-(2-methoxyphenyl)-piperazine **11** in *N*,*N*-dimethylformamide (DMF) containing 2.5 equiv of potassium carbonate at 60 °C for 5 h cleanly gave the corresponding piperazines **12a–c** and **13a–c** in 77–91% yields.

Reduction of the amide function with lithium aluminium hydride (LAH, 3 equiv) in tetrahydrofuran (THF) at room temperature gave the desired amines **14a–c** and **15a–c** in 51–73% yields (Scheme 2).

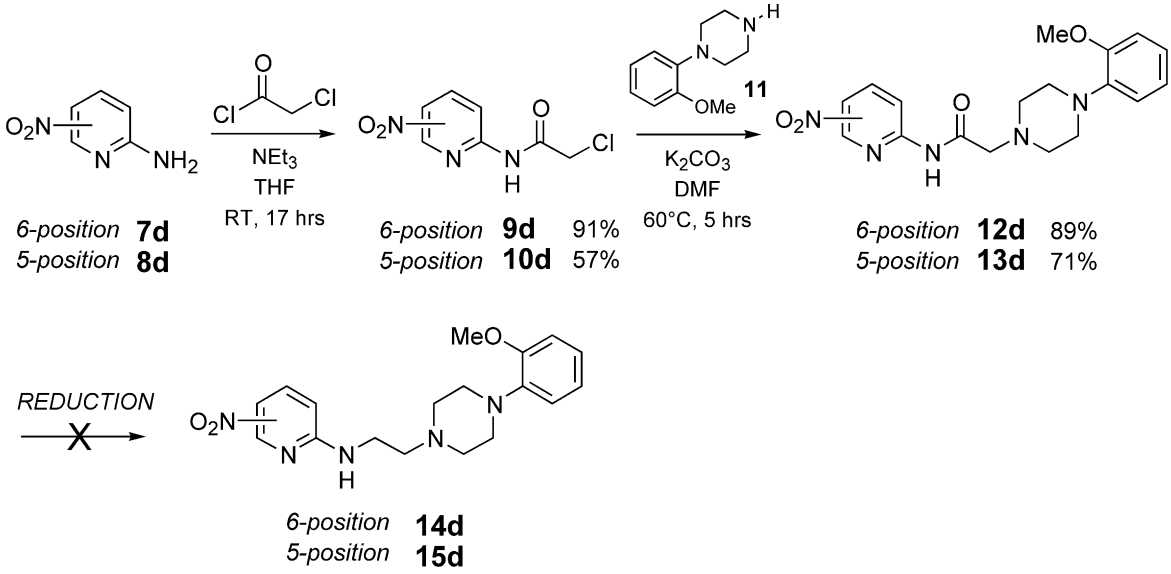
As for the corresponding 6- and 5-halo- derivatives, reaction of 6- and 5-nitro-2-aminopyridine (**7d** and **8d**) with chloroacetyl chloride in THF gave the corresponding *N*-pyridinyl-2-chloroacetamide **9d** and **10d** in 91 and 57% yields, respectively (Scheme 3). Reaction of each 2-chloroacetamides (**9d** or **10d**) with 1-(2-methoxyphenyl)piperazine **11** in DMF cleanly gave the corresponding piperazines, **12d** and **13d**, in 89 and 71% yield, respectively. However, the corresponding amines, **14d** and **15d**, could not be obtained by reduction of the amides. The use of LAH in THF at room temperature or lower temperature gave a complex mixture of compounds, without showing the desired amines **14d** and **15d**. Reduction of an amide function in the presence of an aromatic nitro function on the same chemical structure is well documented in the literature and recommends the use of borane (diborane),[41–52] borane-dimethylsulfide complex[53–55] or sodium borohydride-boron trifluoride diethyletherate,[56,57] usually in THF as solvent. Using the conditions described above, we again obtained complex mixtures and the desired amines, **14d** and **15d,** could not be isolated. No example could be



Scheme 1. Preparation of 2-[1-(4-(2-methoxyphenyl)piperazinyl]-*N*-(2-pyridinyl)acetamides **12a–c** and **13a–c**.



Scheme 2. Preparation of 1-(2-methoxyphenyl)-4-(2-(2-aminopyridinyl)-ethyl)piperazines **14a–c** and **15a–c**.



Scheme 3. Preparation of 2-[1-(4-(2-methoxyphenyl)piperazinyl]-*N*-(2-pyridinyl)acetamides **12d** and **13d**.

found in the literature where an amide function was reduced in the presence of a nitro-pyridinyl function.

In order to synthesize the amines **14d** and **15d**, 1-(2-methoxyphenyl)piperazine **11** was reacted with 5 equiv of 2-chloroethyl *p*-toluenesulfonate in acetonitrile containing 1 equiv of triethylamine at room temperature for 40 h to give the 2-chloroethylpiperazine derivative **16** in 27% yield (Scheme 4). Reaction of **16** with 5- or 6-nitro-2-aminopyridine (**7d**/**8d**) in refluxing acetonitrile containing 1.5 equiv of triethylamine for 24–48 h gave the desired amines **14d** and **15d** in 10 and 17% yield, respectively.

Reaction of the 6- and 5-substituted pyridinylamines (**14a–d**/**15a–d**) with 1.5 equiv of cyclohexanecarbonyl chloride in dichloromethane containing 1.5 equiv of triethylamine at room temperature for 48 h gave the corresponding amides (**5a–d**/**6a–d**) in 63–98% yields (Scheme 5).

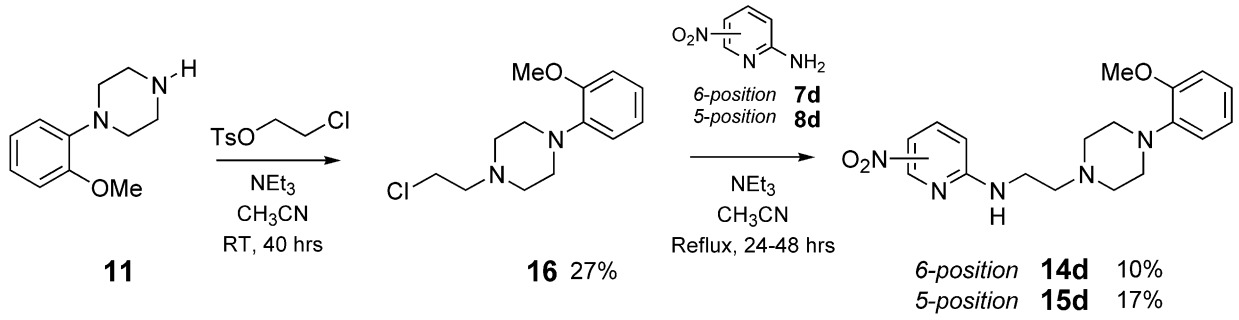
The 6- and 5-halo-derivatives were synthesized in four chemical steps starting from the commercially available corresponding 6- or 5-substituted 2-aminopyridines (**7a–c**, **8a–c**). 6-Fluoro-WAY-100635 (**5a**), 5-fluoro-WAY-100635 (**6a**) and the corresponding chloro- (**5b** and **6b**) and bromo-analogues (**5c** and **6c**) were obtained in 36, 25, 29, 22, 57 and 39% overall yield, respectively. The 6- and 5-nitro- derivatives were synthesized in three chemical steps, also using the corresponding 6- or 5-nitro-2-aminopyridines (**7d** and **8d**) and were obtained in 2 and 3% overall yields, respectively. During the preparation of this manuscript, alternative chemical syntheses of 6-fluoro-WAY-100635 (**5a**), as well as of the 5- and 6-bromo-analogues (**5c** and **6c**) were published.[25] **5a** And **5c** were obtained starting from the appropriate commercially available 2,6-dihalopyridine in two and four chemical steps, respectively (3% yield for **5a** and 26% yield for **5c**). **6c** was synthesized from 2-amino-5-bromopyridine in four chemical steps and 19% overall yield.[25]

Radiochemistry

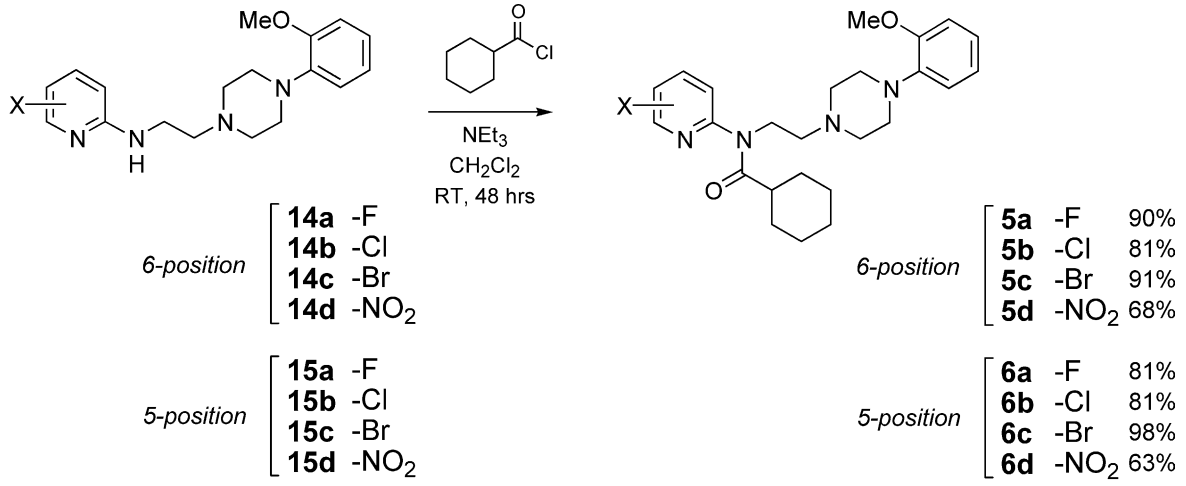
In a first step, both halo- and nitro- derivatives at the 6- and 5-position of the pyridine ring were evaluated for their effectiveness as precursors for the radiosynthesis of 6-[^{18}F]fluoro- and 5-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a/6a**) using nucleophilic heteroaromatic fluorinations (Scheme 6).

Introduction of the fluorine-18 as no-carrier-added [^{18}F]fluoride was attempted in dimethyl sulfoxide (DMSO) with the activated K[^{18}F]F-Kryptofix®222 complex[58] as the no-carrier-added radiofluorinating reactant (Kryptofix®222 (K_{222}): 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) by either conventional heating or microwave activation.

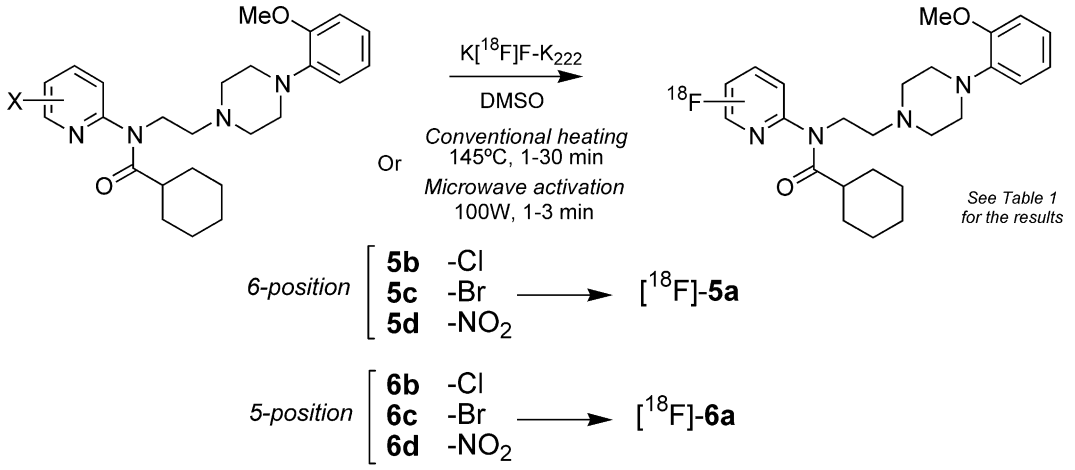
In a first set of experiments, the influence of the leaving group (Cl^-, Br^- and NO_2^-) and the reaction time were studied for both 6- and 5-substituted pyridine derivatives, **5b–d** and **6b–d**, at 145 °C. A DMSO solution (600 μL) containing 4.0–6.0 mg of the appropriate



Scheme 4. Preparation of 1-(2-methoxyphenyl)-4-(2-(2-aminopyridinyl)-ethyl)piperazines **14d** and **15d**.



Scheme 5. Preparation of *N*-(2-(1-(4-(2-methoxyphenyl)piperazinyl)ethyl))-*N*-(2-pyridinyl)cyclohexane carboxamide **5a–d** and **6a–d**.



Scheme 6. Preparation of 6-[^{18}F]fluoro- and 5-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a/6a**).

precursor for labelling (**5b–d** or **6b–d**) was transferred to 30–60 mCi of the dried K[^{18}F]F-K_{222} complex in a reaction vial (Vacutainer® tube). The tube (not sealed) was then placed in a heating block at 145 °C for 1–30 min without stirring the contents.

As shown in Table 1, the 6-chloro-, 6-bromo- and 6-nitro- derivatives (**5b–d**) were reactive under the conditions described above (conventional heating, 145 °C). Using the 6-chloro and the 6-bromo- derivatives **5b** and **5c**, the yield of 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**) increased with the reaction time up to 10 min (26 and 63% yield, respectively). High incorporation yields were observed at 3 min for the 6-nitro- derivative (**5d**) (90% yield). In each run, the remaining radioactivity at the end of the experiment was measured and 85–95% of the initial radioactivity placed in the vessel was still present. The decrease in the radiochemical yield with time was therefore not attributed to volatiles but to decomposition of the formed 6-[^{18}F]fluoropyridine derivative ([^{18}F]**5a**). Whatever the conditions used, the 5-substituted derivatives **6b–d** were completely unreactive.

In another set of experiments, the influence of the leaving group (Cl^-, Br^- and NO_2^-) and the reaction time were studied for both 5- and 6-substituted pyridine derivatives, **5b–d** and **6b–d**, using microwave activation at 100 W. A DMSO solution (600 μL) containing 4.0–6.0 mg of the appropriate precursor for labelling (**5b–d** or **6b–d**) was transferred to 30–60 mCi of the dried K[^{18}F]F-K_{222} complex in a reaction vial (Vacutainer® tube). The tube (not sealed) was then placed in a dedicated microwave oven and irradiated at 100 W for 1–3 min without stirring the contents. As shown in Table 1, the 6-chloro- and the 6-bromo- derivative (**5b** and **5c**) but especially the 6-nitro- derivative (**5d**) were reactive under the conditions described above (microwave irradiation, 100 W). Using the 6-chloro- and the 6-bromo-derivatives (**5b** and **5c**), the yield of 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**) increased with the reaction time up to 3 min (19 and 61% yield, respectively). High incorporation yields were observed at 1 min for the 6-nitro-derivative (**5d**) (93% yield). All 5-substituted derivatives (5-chloro-, 5-bromo- and 5-nitro- derivatives **6b–d**) were again unreactive.

Table 1. Yields of 6-[^{18}F]fluoro- and 5-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a/6a**) using conventional heating at 145 °C or microwave activation at 100 W: influence of the reaction time and nature of the leaving group

		Heating 145 °C						Microwaves 100 W		
Reaction time (min)		1′	3′	6′	10′	20′	30′	1′	2′	3′
5b	- Cl	1	14	18	26	28	27	6	12	19
5c	- Br	5	43	55	63	54	51	21	52	61
5d	- NO_2	79	90	83	80	70	70	93	—	—
6b–d	- X[a]	0	0	0	0	0	0	0	0	0

Conditions: 4.0–6.0 mg of precursor; K[^{18}F]F-K_{222} complex: 30–60 mCi (EOB, 1.11–2.22 GBq); Solvent: DMSO (600 μL); heating block for 1–30 min at 145 °C or microwave oven (100 W) for 1–3 min; no stirring. Indicated yields are the average of three independent runs.
[a]X:-Cl,-Br or NO_2.

In a final set of experiments, in the absence of reactivity towards nucleophilic hetero-aromatic substitution at the *meta*-position, the influence of the leaving group (Cl^-, Br^- and NO_2^-) and the reaction time and conditions were studied for the 5-substituted pyridine derivatives **6b–d** only, by conventional heating at 150–250 °C, for 1–30 min. The K[^{18}F]F-K_{222} complex was first dissolved in 600 μL of DMSO and then added to a reaction vial containing 4.0–6.0 mg of the appropriate precursor for labelling (**6b–d**). Finally, the reaction vial was tightly sealed and placed in a heating block at the desired temperature (150, 200 and 250 °C) for 1–30 min without stirring the contents. Whatever the conditions used, the 5-substituted derivatives **6b–d** were completely unreactive and the desired 5-[^{18}F]fluoro-WAY-100635 ([^{18}F]**6a**) could not be detected.

Based on these results, optimized conditions where selected for the preparation of 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**). Introduction of the fluorine-18 atom was performed in DMSO with the activated K[^{18}F]F-K_{222} complex by either conventional heating at 145 °C for 10 min using the 6-bromopyridine derivative **5c** as precursor for labelling, or by microwave activation at 100 W for 1 min using the 6-nitropyridine derivative **5d**. After Sep-Pak separation, the reaction mixture obtained from either **5c** or **5d** was purified by HPLC to give pure 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**). Typically, 15–25 mCi (0.55–0.92 GBq) of 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**, 1–2 Ci/μmol or 37–72 GBq/μmol) were easily obtained in 50–70 min starting from a 100 mCi (3.7 GBq) aliquot of a cyclotron-produced [^{18}F]fluoride production batch (15–25% non decay-corrected yield based on the starting [^{18}F]fluoride). Formulation of labelled product for iv injection was effected as follows: the HPLC solvents were removed by evaporation and the residue was redissolved in physiological saline. The solution was then filtered through a sterile 0.22 μm Millipore filter. As demonstrated by HPLC analysis, the radiopharmaceutical preparation was found to be >95% chemically and >99% radiochemically pure and was radiochemically stable for at least 120 min.

During the preparation of this manuscript, another radiochemical preparation of 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**) was presented (abstracts) at both the 48th Annual Meeting of the Society of Nuclear Medicine (Toronto, Canada)[59] and the XIVth International Symposium on Radiopharmaceutical Chemistry (Interlaken, Switzerland).[60,61] The authors used the same approach using the 6-bromopyridine derivative **5c** as precursor for labelling but with different experimental conditions and reported low and variable radiochemical yields.

Conclusion

The development of ^{18}F-labelled PET radioligands for imaging the 5-HT_{1A} receptor with PET has been an important goal in recent years. We have synthesized two fluorinated analogues of WAY-100635 (6-fluoro and 5-fluoro-WAY-100635, **5a**/**6a**) as well as the corresponding chloro-, bromo- and nitro- derivatives (**5b–d** and **6b–d**)

as precursors for labelling. Comparative radiolabelling with fluorine-18 from these precursors clearly demonstrated that only *ortho*-fluorination in this pyridine series and not *meta*-fluorination, is of interest for the preparation of radiotracer by nucleophilic heteroaromatic substitution. 6-Fluoro-WAY-100635 (**5a**) can be efficiently synthesized in one step either from the corresponding 6-bromo precursor (using conventional heating at 145 °C for 10 min) or from the corresponding 6-nitro precursor (using microwave activation at 100 W for 1 min). This ^{18}F-labelled radioligand is now being evaluated in PET studies.

Experimental

General

Chemicals, TLCs and HPLCs. 2-Amino-6-halopyridines (**7a–c**) and 2-amino-6-nitropyridine (**7d**) were purchased from ERAS-Labo, France. 2-Amino-5-fluoropyridine (**8a**) was purchased from Apollo Scientific Ltd, UK. 2-Amino-5-chloropyridine (**8b**), 2-amino-5-bromopyridine (**8c**) and 2-amino-5-nitropyridine (**8d**) as well as all other chemicals were purchased from Aldrich, Fluka or Sigma France. All chemicals were used without further purification. TLCs were run on pre-coated plates of silica gel 60F_{254} (Merck). The compounds were localized (1) when possible at 254 nm using a UV-lamp and/or (2) by iodine staining and/or (3) by dipping the TLC-plates in a 1% ethanolic ninhydrin solution (or in a 1% aqueous $KMnO_4$ solution) and heating on a hot plate. Radioactive spots were detected using a Berthold TraceMaster 20 automatic TLC linear analyser. Flash chromatography was conducted on silica gel 63–200 μm (Merck) at 0.3 bars (Ar). HPLCs (Equipment: Waters or Shimadzu systems): [HPLC A]: Equipment: system equipped with a Waters 600 Pump and Waters 600 Controller, a Shimadzu SPD10-AVP UV-multi-wavelength detector; semipreparative C-18, Zorbax® SB, Hewlett Packard (250 × 9.4 mm); porosity: 5 μm; conditions: isocratic elution with MeOH / aq 0.1 M ammonium formate/TEA:75/25/0.3 (v/v/v); flow rate: 6 mL/min; temperature: RT; absorbance detection at λ = 254 nm. [HPLC B]: Equipment: Waters system equipped with a 510 pump, a 440 UV detector or a 481/486 UV-multi-wavelength detector; semipreparative SiO_2, Zorbax® Rx-SIL, Hewlett Packard (250 × 21.3 mm); porosity: 7 μm; conditions: isocratic elution with EtOAc/$CHCl_3$/TEA:30/70/0.1 (v/v/v); flow rate: 7 mL/min; temperature: RT; absorbance detection at λ = 254 nm. [HPLC C]: Equipment: Waters Alliance 2690 equipped with a UV spectrophotometer (Photodiode Array Detector, Waters 996) and a Berthold LB509 radioactivity detector; column: analytical Symmetry-M® C-18, Waters (3.9 × 150 mm); porosity: 5 μm; conditions: isocratic elution with solvent A/solvent B:35/65 (v:v) [solvent A:H_2O containing Low-UV PIC® B7 reagent (Waters), 20 mL for 1000 mL; solvent B: H_2O/CH_3CN:50/50 (v:v) containing Low-UV PIC® B7 reagent (% by weight: methanol (18–22%), heptane sulfonic acid- sodium salts (4–6%), phosphate buffer solution (3–7%), water (65–75%), pH 3, Waters), 20 mL for 1000 mL]; flow rate: 2.0 mL/min; temperature: 30 °C; absorbance detection at λ = 220 nm.

Complementary data for the preparation and characterisation of the synthesized compounds listed below are also available in the literature. See recently published reference[25] for **5a**, **5c** and **6c**.

Spectroscopies. NMR spectra were recorded on a Bruker AMX (300 MHz) apparatus using the hydrogenated residue of the deuteriated solvents ($CDCl_3$, δ = 7.24 ppm; CD_2Cl_2, δ = 5.32 ppm; DMSO-d_6, δ = 2.50 ppm) and/or TMS as internal standards for ^{1}H NMR as well as the deuteriated solvents ($CDCl_3$, δ = 77.0 ppm; CD_2Cl_2, δ = 53.8 ppm; DMSO-d_6, δ = 39.5 ppm; CD_3OD, δ = 49.3 ppm) and/or TMS as internal standards for ^{13}C NMR. The chemical shifts are reported in ppm, downfield from TMS (s, d, t, dd, b for singlet, doublet, triplet, doublet of doublet and broad, respectively). The mass spectra (MS), DCI/NH_4^+, were measured on a Nermag R10-10 apparatus.

Radioisotope production. No-carrier-added aqueous [^{18}F]fluoride ion was produced on a CGR-MeV 520 cyclotron by irradiation of a 2 mL water target using a 17 MeV proton beam on 95% enriched [^{18}O]water by the [^{18}O(p,n)^{18}F] nuclear reaction and was transferred to the appropriate hot cell. Typical production: 550–650 mCi (20.3–24.0 GBq) of [^{18}F]F^- at the end of bombardment for a 20 μA, 30 min (36,000 μC) irradiation. A complete description of the target hardware and operation can be found in references.[35,39]

Miscellaneous. Radiosyntheses using fluorine-18, including the HPLC purifications were performed in a 7.5 cm-lead shielded cell using a computer assisted Zymate robot system (Zymark corporation, USA). Microwave activation was performed with a MicroWell 10 oven (2.45 GHz), Labwell AB, Sweden. Specific radioactivity was determined as follows: the area of the absorbance peak corresponding to the radiolabelled product was measured on the HPLC chromatogram and compared to a standard curve relating mass to absorbance.

Chemistry

General procedure: 2-chloro-*N*-(2-(halo)pyridinyl)acetamides (9a–c and 10a–c). To 20.0 mmol of the appropriate 2-amino-halopyridine (**7a–c** or **8a–c**) dissolved in 200 mL of dichloromethane, were added dropwise at room temperature, 4.20 mL of triethylamine (30.0 mmol, 1.5 equiv) and 2.39 mL of chloroacetyl chloride (30.0 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 17 h. The reaction was then stopped by addition of 10% aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The organic layers were combined, washed once with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel.

2-Chloro-*N*-(2-(6-fluoro)pyridinyl)acetamide (9a). The procedure described above was used with 2.0 g of **7a**.

Elution with CH_2Cl_2/EtOAc (90/10 to 50/50 v/v) gave 3.09 g of the desired product as a white solid (92%). R_f (Heptane/EtOAc : 50/50 v/v) : 0.45. ^1H NMR (CD_2Cl_2, 300.0K) : δ: 8.75 (b, 1H); 8.06 (d, *J*: 6 Hz, 1H); 7.88 (dd, *J*: 6 and 9 Hz, 1H); 6.75 (dd, *J*: 3 and 9 Hz, 1H); 4.23 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 165.1 [C]; 162.4 [C, d, *J*: 239 Hz]; 149.3 [C, d, *J*: 14 Hz]; 144.0 [CH, d, *J*: 8 Hz]; 110.8 [CH, d, *J*: 4 Hz]; 105.6 [CH, d, *J*: 35 Hz]; 43.4 [CH_2].

2-Chloro-*N*-(2-(6-chloro)pyridinyl)acetamide (9b). The procedure described above was used with 2.0 g of **7b**. Elution with CH_2Cl_2/EtOAc (90/10 to 50/50 v/v) gave 2.36 g of the desired product as a white solid (74%). R_f (EtOAc/Heptane: 50/50 v/v): 0.50. ^1H NMR (CD_2Cl_2, 300.0K): δ: 8.81 (b, 1H); 8.11 (d, *J*: 9.0 Hz, 1H); 7.71 (t, *J*: 9.0 Hz, 1H); 7.13 (d, *J*: 9.0 Hz, 1H); 4.22 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 165.0 [C]; 150.7 [C]; 148.5 [C]; 141.4 [CH]; 120.8 [CH]; 112.2 [CH]; 43.4 [CH_2].

2-Chloro-*N*-(2-(6-bromo)pyridinyl)acetamide (9c). The procedure described above was used with 2.0 g of **7c**. Elution with CH_2Cl_2/EtOAc (90/10 to 50/50 v/v) gave 2.76 g of the desired product as a yellow oil (96%). R_f (EtOAc/Heptane: 50/50 v/v): 0.50. ^1H NMR (CD_2Cl_2, 300.0K): δ: 8.92 (b, 1H); 8.13 (d, *J*: 9.0 Hz, 1H); 7.59 (t, *J*: 9.0 Hz, 1H); 7.27 (d, *J*: 9.0 Hz, 1H); 4.25 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 165.2 [C]; 151.0 [C]; 141.1 [CH]; 139.8 [C]; 124.7 [CH]; 112.7 [CH]; 43.4 [CH_2].

2-Chloro-*N*-(2-(5-fluoro)pyridinyl)acetamide (10a). The procedure described above was used with 1.0 g of **8a**. Elution with CH_2Cl_2/EtOAc (90/10 to 50/50 v/v) gave 1.34 g of the desired product as a white solid (80%). R_f (Heptane/EtOAc: 50/50 v/v): 0.50. ^1H NMR (CD_2Cl_2, 300.0K): δ: 8.91 (b, 1H); 8.24–8.14 (b, 2H); 7.49 (dt, *J*: 3.0 9.0 Hz, 1H); 4.21 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 164.7 [C]; 157.2 [C, d, *J*: 249 Hz]; 147.3 [C]; 136.0 [CH, d, *J*: 25 Hz]; 125.6 [CH, d, *J*: 20 Hz]; 115.1 [CH]; 43.4 [CH_2].

2-Chloro-*N*-(2-(5-chloro)pyridinyl)acetamide (10b). The procedure described above was used with 5.0 g of **8b**. Elution with CH_2Cl_2/EtOAc (90/10 to 50/50 v/v) gave 3.33 g of the desired product as a white solid (42%). R_f (Heptane/EtOAc: 60/40 v/v): 0.55. ^1H NMR (CD_2Cl_2, 300.0K): δ: 8.88 (b, 1H); 8.27 (bd, $J < 1.0$ Hz, 1H); 8.16 (d, *J*: 9.0 Hz, 1H); 7.71 (dd, *J*: 2.0 and 9.0 Hz, 1H); 4.21 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 164.9 [C]; 149.4 [C]; 147.1 [CH]; 138.5 [CH]; 127.9 [C]; 114.9 [CH]; 43.4 [CH_2].

2-Chloro-*N*-(2-(5-bromo)pyridinyl)acetamide (10c). The procedure described above was used with 1.0 g of **8c**. Elution with CH_2Cl_2/EtOAc (90/10 to 50/50 v/v) gave 1.2 g of the desired product as a yellow oil (81%). R_f (EtOAc/Heptane: 50/50 v/v): 0.55. ^1H NMR (CD_2Cl_2, 300.0K): δ: 8.80 (b, 1H); 8.37 (d, $J < 1.0$ Hz, 1H); 8.11 (d, *J*: 9.0 Hz, 1H); 7.84 (dd, *J*: 2.0 and 9 Hz, 1H); 4.20 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 179.9 [C]; 164.9 [C]; 149.4 [CH]; 141.2 [CH]; 115.8 [C]; 115.4 [CH]; 43.4 [CH_2].

General procedure: 2-chloro-*N*-(2-(nitro)pyridinyl)acetamides (9d and 10d). To 5.0 mmol of the appropriate 2-amino-nitropyridine (**7d** or **8d**) dissolved in 40 mL of THF, were added dropwise at room temperature, 1.05 mL of triethylamine (7.5 mmol, 1.5 equiv) and 0.600 mL of chloroacetyl chloride (7.50 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature overnight. The reaction was then stopped by addition of 10% aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The organic layers were combined, washed once with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel.

2-Chloro-*N*-(2-(6-nitro)pyridinyl)acetamide (9d). The procedure described above was used with 0.7 g of **7d**. Elution with CH_2Cl_2/heptane/THF (80/15/5 v/v/v) gave 0.99 g of the desired product as a yellow oil (91%). R_f (EtOAc/Heptane: 50/50 v/v): 0.50. ^1H NMR (CD_2Cl_2, 300.0K): δ: 11.48 (b, 1H); 8.47 (d, *J*: 9.0 Hz, 1H); 8.26 (t, *J*: 9.0 Hz, 1H); 8.07 (d, *J*: 9.0 Hz, 1H); 4.41 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 166.2 [C]; 154.6 [C]; 150.5 [C]; 142.9 [CH]; 119.4 [CH]; 113.3 [CH]; 43.3 [CH_2].

2-Chloro-*N*-(2-(5-nitro)pyridinyl)acetamide (10d). The procedure described above was used with 1.0 g of **8d**. Elution with CH_2Cl_2/heptane/THF (80/15/5 v/v/v) gave 0.89 g of the desired product as an orange solid (57%). R_f (EtOAc/Heptane: 50/50 v/v): 0.55. ^1H NMR (CD_2Cl_2, 300.0K): δ: 11.52 (b, 1H); 9.20 (d, *J*: 2.0 Hz, 1H); 8.65 (dd, *J*: 2.0 and 9.0 Hz, 1H); 8.27 (d, *J*: 9.0 Hz, 1H); 4.44 (s, 2H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 166.3 [C]; 155.5 [C]; 144.7 [CH]; 140.2 [C]; 134.4 [CH]; 112.7 [CH]; 43.4 [CH_2].

General procedure: 2-[1-(4-(2-methoxyphenyl)piperazinyl]-*N*-(2-pyridinyl)acetamides (12a–d and 13a–d). To 14.63 mmol of the appropriate 2-chloro-*N*-(2-pyridinyl)acetamide (**9a–d** or **10a–d**) dissolved in 20 mL of DMF was added a DMF solution (80 mL) containing 1-(2-methoxyphenyl)piperazine (**11**, 2.81 g, 14.63 mmol, 1 equiv) and anhydrous K_2CO_3 (5.05 g, 36.58 mmol, 2.5 equiv). The reaction mixture was stirred at 60 °C for 5 h. The reaction was then stopped by addition of water and the mixture was extracted with ethylacetate. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel.

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(6-fluoro)pyridinyl)acetamide (12a). The procedure described above was used with 2.76 g of **9a**. Elution with heptane/EtOAc (50/50 v/v) gave 4.29 g of the desired product as a white solid (85%). R_f (heptane/EtOAc: 50/50 v/v): 0.20. ^1H NMR (CD_2Cl_2, 300.0K): δ: 9.55 (b, 1H); 8.11 (dd, *J*: 2.1 and 6.5 Hz, 1H); 7.79 (q, *J*: 7.2 Hz, 1H); 7.03–6.82 (4H); 6.66 (dd, *J*: 1.7 and 6.7 Hz, 1H); 3.84 (s, 3H); 3.21 (s, 2H); 3.15 (b, 4H); 2.77 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 169.9 [C]; 162.8 [C, d, *J*: 238 Hz]; 153.2 [C]; 150.3 [C, d, *J*: 14 Hz]; 143.9 [CH, d, *J*: 7 Hz]; 142.0 [C]; 124.0 [C]; 123.6 [CH]; 121.7 [CH]; 119.1 [CH]; 112.3 [CH]; 104.7 [CH, d, J: 36 Hz]; 62.9 [CH_2]; 56.0 [CH_3]; 54.9 [2 × CH_2]; 51.3 [2 × CH_2].

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(6-chloro)pyridinyl)acetamide (12b). The procedure described above was used with 1.52 g of **9b**. Elution with heptane/EtOAc (50/50 v/v) gave 2.15 g of the desired product as a white solid (80%). R_f (heptane/EtOAc: 50/50 v/v): 0.25. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 9.62 (b, 1H); 8.19 (d, *J*: 6.0 Hz, 1H); 7.65 (t, *J*: 9.0 Hz, 1H); 7.03 (d, *J*: 9.0 Hz, 1H); 7.02–6.82 (4H); 3.82 (s, 3H); 3.20 (s, 2H); 3.16 (b, 4H); 2.76 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 169.6 [C]; 152.9 [C]; 151.6 [C]; 149.4 [C]; 141.7 [C]; 141.3 [CH]; 123.3 [CH]; 121.5 [CH]; 119.9 [CH]; 118.8 [CH]; 112.2 [CH]; 112.0 [CH]; 62.7 [CH_2]; 55.7 [CH_3]; 54.3 [2 × CH_2]; 51.0 [2 × CH_2].

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(6-bromo)pyridinyl)acetamide (12c). The procedure described above was used with 2.44 g of **9c**. Elution with heptane/EtOAc (50/50 v/v) gave 3.48 g of the desired product as a white solid (91%). R_f (heptane/EtOAc: 50/50 v/v): 0.25. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 9.61 (b, 1H); 8.19 (d, *J*: 9.0 Hz, 1H); 7.56 (t, *J*: 9.0 Hz, 1H); 7.21 (d, *J*: 9.0 Hz, 1H); 7.02–6.82 (4H); 3.82 (s, 3H); 3.20 (s, 2H); 3.15 (b, 4H); 2.75 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 169.0 [C]; 153.1 [C]; 152.0 [C]; 141.9 [C]; 141.2 [CH]; 140.1 [C]; 124.1 [CH]; 123.5 [CH]; 121.6 [CH]; 119.0 [CH]; 112.7 [CH]; 112.2 [CH]; 62.9 [CH_2]; 55.9 [CH_3]; 54.0 [2 × CH_2]; 51.0 [2 × CH_2].

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(6-nitro)pyridinyl)acetamide (12d). The procedure described above was used with 4.00 g of **9d**. Elution with heptane/EtOAc (50/50 v/v) gave 6.13 g of the desired product as a white solid (89%). R_f (heptane/EtOAc: 50/50 v/v): 0.20. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 9.80 (b, 1H); 8.63 (d, *J*: 9.0 Hz, 1H); 8.02 (t, *J*: 9.0 Hz, 1H); 7.92 (d, *J*: 9.0 Hz, 1H); 7.02–6.82 (4H); 3.83 (s, 3H); 3.26 (s, 2H); 3.16 (b, 4H); 2.79 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 170.1 [C]; 155.4 [C]; 152.8 [C]; 150.8 [C]; 142.2 [CH]; 141.5 [C]; 123.2 [CH]; 121.3 [CH]; 119.6 [CH]; 118.7 [CH]; 113.4 [CH]; 111.9 [CH]; 62.6 [CH_2]; 55.6 [CH_3]; 54.5 [2 × CH_2]; 52.8 [2 × CH_2].

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(5-fluoro)pyridinyl)acetamide (13a). The procedure described above was used with 1.26 g of **10a**. Elution with heptane/EtOAc (50/50 v/v) gave 1.77 g of the desired product as a clear oil (77%). R_f (heptane/EtOAc: 50/50 v/v): 0.30. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 9.60 (b, 1H); 8.25 (dd, *J*: 4.0 and 9.0 Hz, 1H); 8.14 (bd, $J < 2.0$ Hz, 1H); 7.44 (dt, *J*: 2.0 and 9.0 Hz, 1H); 7.05–6.85 (4H); 3.82 (s, 3H); 3.19 (s, 2H); 3.14 (b, 4H); 2.78 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 169.1 [C]; 156.8 [C, d, *J*: 249 Hz]; 152.9 [C]; 148.0 [C]; 141.7 [C]; 135.7 [CH, d, *J*: 26 Hz]; 125.3 [CH, d, *J*: 19 Hz]; 123.3 [CH]; 121.4 [CH]; 118.7 [CH]; 114.7 [CH]; 112.0 [CH]; 62.5 [CH_2]; 55.7 [CH_3]; 54.3 [2 × CH_2]; 51.0 [2 × CH_2].

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(5-chloro)pyridinyl)acetamide (13b). The procedure described above was used with 3.20 g of **10b**. Elution with heptane/EtOAc (50/50 v/v) gave 5.04 g of the desired product as a yellow oil (90%). R_f (heptane/EtOAc: 50/50 v/v): 0.35. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 9.66 (b, 1H); 8.30–8.15 (b, 2H); 7.67 (dd, *J*: 2.0 and 9.0 Hz, 1H); 7.05–6.85 (4H); 3.82 (s, 3H); 3.19 (s, 2H); 3.13 (b, 4H); 2.78 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 169.4 [C]; 152.8 [C]; 150.0 [C]; 147.0 [CH]; 141.7 [C]; 138.1 [CH]; 126.8 [C]; 123.2 [CH]; 121.3 [CH]; 118.6 [CH]; 114.6 [CH]; 111.9 [CH]; 62.5 [CH_2]; 55.7 [CH_3]; 54.2 [2 × CH_2]; 51.0 [2 × CH_2].

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(5-bromo)pyridinyl)acetamide (13c). The procedure described above was used with 1.51 g of **10c**. Elution with heptane/EtOAc (50/50 v/v) gave 1.37 g of the desired product as a yellow oil (83%). R_f (heptane/EtOAc: 50/50 v/v): 0.35. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 9.65 (b, 1H); 8.34 (d, *J*: 2.0 Hz, 1H); 8.18 (d, *J*: 9.0 Hz, 1H); 7.82 (dd, *J*: 2.0 and 9.0 Hz, 1H); 7.05–6.85 (4H); 3.82 (s, 3H); 3.20 (s, 2H); 3.13 (b, 4H); 2.78 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 169.5 [C]; 152.8 [C]; 150.4 [C]; 149.2 [CH]; 141.6 [C]; 140.9 [CH]; 123.2 [CH]; 121.3 [CH]; 118.6 [CH]; 115.2 [CH]; 114.7 [C]; 111.9 [CH]; 62.5 [CH_2]; 55.7 [CH_3]; 54.2 [2 × CH_2]; 51.0 [2 × CH_2].

2-[1-(4-(2-Methoxyphenyl)piperazinyl]-*N*-(2-(5-nitro)pyridinyl)acetamide (13d). The procedure described above was used with 0.89 g of **10d**. Elution with heptane/EtOAc (50/50 v/v) gave 1.10 g of the desired product as a yellow solid (71%). R_f (heptane/EtOAc: 50/50 v/v): 0.30. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 10.00 (b, 1H); 9.15 (s, 1H); 8.55–8.40 (b, 2H); 7.05–6.85 (4H); 3.84 (s, 3H); 3.28 (s, 2H); 3.17 (b, 4H); 2.82 (b, 4H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 170.2 [C]; 155.6 [C]; 152.9 [C]; 145.2 [CH]; 141.6 [C]; 141.0 [C]; 134.3 [CH]; 123.4 [CH]; 121.4 [CH]; 118.7 [CH]; 113.0 [CH]; 112.0 [CH]; 62.5 [CH_2]; 55.7 [CH_3]; 54.3 [2 × CH_2]; 51.0 [2 × CH_2].

General procedure: 1-(2-methoxyphenyl)-4-(2-(2-(halo)-aminopyridinyl)-ethyl)piperazines (14a–c and 14a–c). To 5.0 mmol of the appropriate 2-[1-(4-(2-methoxyphenyl)piperazinyl]-*N*-(2-(halo)pyridinyl)acetamide (**12a–c** or **13a–c**) dissolved in 150 mL of dry THF, was slowly added under N_2 570 mg of $LiAlH_4$ (15.0 mmol, 3 equiv). The reaction mixture was stirred at room temperature for 3 h. The reaction was then stopped by careful addition of ice and 10% aq NaOH. The mixture was stirred at room temperature for another 30 min. The precipitate was filtered off and the filtrate was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel.

1-(2-Methoxyphenyl)-4-(2-(2-(6-fluoro)aminopyridinyl)-ethyl)piperazine (14a). The procedure described above was used with 2.0 g **12a**. Elution with heptane/EtOAc (60/40 to 10/90 v/v) gave 1.00 g of the desired product as a yellow solid (52%). R_f (heptane/EtOAc: 10/90 v/v): 0.20. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.47 (t, *J*: 7.4 Hz, 1H); 7.02–6.82 (4H); 6.25 (dd, *J*: 2.4 and 7.8 Hz, 1H); 6.10 (dd, *J*: 2.3 and 8.0 Hz, 1H); 5.33 (b, 1H); 3.83 (s, 3H); 3.36 (q, *J*: 6.0 Hz, 2H); 3.07 (b, 4H); 2.66 (b, 6H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 163.8 [C, d, *J*: 234 Hz]; 158.8 [C, d, *J*: 17 Hz]; 152.8 [C]; 142.0 [C]; 141.5 [CH, d, *J*: 7 Hz]; 123.0 [CH]; 121.3 [CH]; 118.5 [CH]; 111.9 [CH]; 103.9 [CH]; 95.4 [CH, d, *J*: 37 Hz]; 57.0 [CH_2]; 55.6 [CH_3]; 53.8 [2 × CH_2]; 51.0 [2 × CH_2]; 39.3 [CH_2].

1-(2-Methoxyphenyl)-4-(2-(2-(6-chloro)aminopyridinyl)-ethyl)piperazine (14b). The procedure described above was used with 0.20 g of **12b**. Elution with heptane/EtOAc (60/40 to 10/90 v/v) gave 0.12 g of the desired product as a yellow solid (62%). R_f (heptane/EtOAc: 10/90 v/v): 0.15. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.31 (t, *J*: 9.0 Hz, 1H); 7.00–6.81 (4H); 6.97 (m, 4H); 6.51 (d, *J*: 9.0 Hz, 1H); 6.28 (d, *J*: 9.0 Hz, 1H); 5.37 (b, 1H); 3.80 (s, 3H); 3.34 (q, *J*: 6.0 Hz, 2H); 3.04 (b, 4H); 2.62 (b, 6H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 159.3 [C]; 152.8 [C]; 149.9 [C]; 142.0 [C]; 139.8 [CH]; 123.0 [CH]; 121.3 [CH]; 118.5 [CH]; 111.9 [CH]; 111.6 [CH]; 105.3 [CH]; 56.9 [CH_2]; 55.6 [CH_3]; 54.2 [2 × CH_2]; 50.9 [2 × CH_2]; 38.8 [CH_2].

1-(2-Methoxyphenyl)-4-(2-(2-(6-bromo)aminopyridinyl)-ethyl)piperazine (14c). The procedure described above was used with 2.0 g of **12c**. Elution with heptane/EtOAc (60/40 to 10/90 v/v) gave 1.38 g of the desired product as a yellow solid (72%). R_f (heptane/EtOAc: 10/90 v/v): 0.15. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.23 (t, *J*: 9.0 Hz, 1H); 7.00–6.81 (4H); 6.67 (d, *J*: 9.0 Hz, 1H); 6.33 (d, *J*: 9.0 Hz, 1H); 5.35 (b, 1H); 3.82 (s, 3H); 3.35 (q, *J*: 6.0 Hz, 2H); 3.05 (b, 4H); 2.67 (b, 6H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 159.4 [C]; 152.8 [C]; 142.0 [C]; 140.6 [C]; 139.6 [CH]; 123.0 [CH]; 121.3 [CH]; 118.5 [CH]; 115.5 [CH]; 111.9 [CH]; 105.6 [CH]; 56.9 [CH_2]; 55.6 [CH_3]; 53.8 [2 × CH_2]; 50.8 [2 × CH_2]; 38.7 [CH_2].

1-(2-Methoxyphenyl)-4-(2-(2-(5-fluoro)aminopyridinyl)-ethyl)piperazine (15a). The procedure described above was used with 1.7 g of **13a**. Elution with heptane/EtOAc (60/40 to 10/90 v/v) gave 0.85 g of the desired product as a yellow solid (51%). R_f (heptane/EtOAc: 10/90 v/v): 0.20. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.92 (d, *J*: 2 Hz, 1H); 7.17 (dt, *J*: 3.0 and 9.0 Hz, 1H); 7.05–6.85 (4H); 6.35 (dd, *J*: 5.0 and 9.0 Hz, 1H); 5.08 (b, 1H); 3.81 (s, 3H); 3.32 (bq, *J*: 5.0 Hz, 2H); 3.05 (b, 4H); 2.63 (b, 6H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 156.3 [C]; 153.7 [C, d, *J*: 239 Hz]; 152.8 [C]; 142.1 [C]; 134.7 [CH, d, *J*: 24 Hz]; 125.3 [CH, d, *J*: 20 Hz]; 123.0 [CH]; 121.3 [CH]; 118.5 [CH]; 111.9 [CH]; 107.7 [CH]; 57.2 [CH_2]; 55.6 [CH_3]; 53.6 [2 × CH_2]; 51.0 [2 × CH_2]; 39.4 [CH_2].

1-(2-Methoxyphenyl)-4-(2-(2-(5-chloro)aminopyridinyl)-ethyl)piperazine (15b). The procedure described above was used with 0.5 g of **13b**. Elution with heptane/EtOAc (60/40 to 10/90 v/v) gave 0.35 g of the desired product as a yellow solid (73%). R_f (heptane/EtOAc: 10/90 v/v): 0.20. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.99 (s, 1H); 7.34 (dd, *J*: 2.0 and 8.5 Hz, 1H); 7.05–6.85 (4H); 6.35 (d, *J*: 8.5 Hz, 1H); 5.20 (b, 1H); 3.81 (s, 3H); 3.33 (bq, *J*: 5.0 Hz, 2H); 3.05 (b, 4H); 2.63 (b, 6H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 157.7 [C]; 152.8 [C]; 146.7 [CH]; 142.0 [C]; 137.1 [CH]; 122.9 [CH]; 121.3[CH]; 119.4 [C]; 118.5 [CH]; 111.9 [CH]; 108.3 [CH]; 57.0 [CH_2]; 55.6 [CH_3]; 53.6 [2 × CH_2]; 51.0 [2 × CH_2]; 39.0 [CH_2].

1-(2-Methoxyphenyl)-4-(2-(2-(5-bromo)aminopyridinyl)-ethyl)piperazine (15c). The procedure described above was used with 1.37 g of **13c**. Elution with heptane/EtOAc (60/40 to 10/90 v/v) gave 0.79 g of the desired product as a yellow solid (60%). R_f (heptane/EtOAc: 10/90 v/v): 0.20. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 8.08 (bd, *J*: 2.0 Hz, 1H); 7.44 (dd, *J*: 2.0 and 9.0 Hz, 1H); 7.05–6.85 (4H); 6.33 (d, *J*: 9.0 Hz, 1H); 5.23 (b, 1H); 3.81 (s, 3H); 3.33 (q, *J*: 6.0 Hz, 2H); 3.05 (b, 4H); 2.65 (b, 6H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 157.9 [C]; 152.8 [C]; 148.9 [CH]; 142.0 [C]; 139.6 [CH]; 122.9 [CH]; 121.3 [CH]; 118.5 [CH]; 111.9 [CH]; 109.0 [CH]; 106.8 [C]; 57.0 [CH_2]; 55.6 [CH_3]; 53.6 [2 × CH_2]; 50.9 [2 × CH_2]; 38.9 [CH_2].

1-(2-Chloro-ethyl)-4-(2-methoxy-phenyl)-piperazine (16). To a dry acetonitrile solution (30 mL) containing 1-(2-methoxyphenyl)piperazine (**11**, 4.08 g, 21.28 mmol, 1 equiv) and triethylamine (3 mL, 21.28 mmol, 1 equiv) were added dropwise an acetonitrile solution (10 mL) containing 2-chloroethyl *p*-toluenesulfonate (25 g, 106.4 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 40 h and then concentrated. The residue was diluted with 50 mL of water and was extracted with dichloromethane. The organic layers were combined, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 1.45 g of the desired product as a yellow oil (27%). R_f (heptane/EtOAc: 50/50 v/v): 0.40. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.00–6.80 (4H); 3.82 (s, 3H); 3.62 (t, *J*: 6.0 Hz, 2H); 3.04 (b, 4H); 2.76 (t, *J*: 6.0 Hz, 2H); 2.65 (b, 4H). ^{13}C NMR ($CDCl_3$, 300.0K): δ: 152.9 [C]; 142.0 [C]; 123.1 [CH]; 121.4 [CH]; 118.6 [CH]; 111.9 [CH]; 60.3 [CH_2]; 55.7 [CH_3]; 53.9 [2 × CH_2]; 51.0 [2 × CH_2]; 41.8 [CH_2].

General procedure: 1-(2-Methoxyphenyl)-4-(2-(2-(nitro)-aminopyridinyl)-ethyl)piperazines (14d and 15d). To a solution of 2.0 mmol of the appropriate 2-amino-nitropyridine (**7d** or **8d**) in 20 mL of acetonitrile were added 510 mg of 1-(2-chloro-ethyl)-4-(2-methoxy-phenyl)-piperazine (**16**, 2.0 mmol, 1 equiv) and 0.418 mL of triethylamine (3.0 mmol, 1.5 equiv). The reaction mixture was refluxed for 24 to 48 h and then concentrated. The residue was diluted with 10 mL of water and was extracted with dichloromethane. The organic layers were combined, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel.

1-(2-Methoxyphenyl)-4-(2-(2-(6-nitro)aminopyridinyl)-ethyl)piperazine (14d). The procedure described above was used with 0.36 mg of 2-amino-6-nitropyridine (**7d**). Elution with heptane/EtOAc (50/50–10/90 v/v) gave 0.09 g of the desired product as a yellow solid (10%). R_f (heptane/EtOAc: 50/50 v/v): 0.15. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.63 (t, *J*: 8.0 Hz, 1H); 7.40 (d, *J*: 7.9 Hz, 1H); 7.00–6.81 (4H); 6.74 (d, *J*: 8.0 Hz, 1H); 5.75 (b, 1H); 3.84 (s, 3H); 3.48 (q, *J*: 6.0 Hz, 2H); 3.08 (b, 4H); 2.70 (b, 6H). ^{13}C NMR ($CDCl_3$, 300.0K): δ: 158.3 [C]; 156.6 [C]; 152.7 [C]; 141.9 [C]; 139.8 [CH]; 122.9 [CH]; 121.2 [CH]; 118.4 [CH]; 113.4 [CH]; 111.8 [CH]; 105.6 [CH]; 56.7 [CH_2]; 55.6 [CH_3]; 53.4 [2 × CH_2]; 50.8 [2 × CH_2]; 38.6 [CH_2].

1-(2-Methoxyphenyl)-4-(2-(2-(5-nitro)aminopyridinyl)-ethyl)piperazine (15d). The procedure described above

was used with 0.30 mg of 2-amino-5-nitropyridine (**8d**). Elution with heptane/EtOAc (50/50 to 10/90 v/v) gave 0.11 g of the desired product as a yellow solid (17%). R_f (heptane/EtOAc: 50/50 v/v): 0.15. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 8.97 (d, *J*: 6.0 Hz, 1H); 8.18 (td, *J*: 2.0 and 6.0 Hz, 1H); 7.05–6.85 (4H); 6.37 (d, *J*: 7.0 Hz, 1H); 6.16 (b, 1H); 3.84 (s, 3H); 3.51 (b, 2H); 3.07 (b, 4H); 2.72 (b, 6H). ^{13}C NMR ($CDCl_3$, 300.0K): δ: 161.1 [C]; 152.6 [C]; 147.1 [CH]; 141.7 [C]; 135.7 [C]; 132.7 [CH]; 122.8 [CH]; 121.1 [CH]; 118.3 [CH]; 111.7 [2 × CH]; 56.3 [CH_2]; 55.4 [CH_3]; 53.3 [2 × CH_2]; 50.8 [2 × CH_2]; 38.6 [CH_2].

General procedure: *N*-(2-(1-(4-(2-methoxyphenyl)piperazinyl)ethyl))-*N*-(2-pyridinyl)cyclohexane carboxamide (5a–d and 6a–d). To a solution of 1.0 mmol of the appropriate 1-(2-methoxyphenyl)-4-(2-(2-aminopyridinyl)-ethyl)piperazine (**14a–d** or **15a–d**) in 50 mL of dichloromethane were added dropwise cyclohexanecarbonyl chloride (0.200 mL, 1.5 mmol, 1.5 equiv) and triethylamine (0.210 mL, 1.5 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 48 h. The reaction was then stopped by addition of 10% aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The organic layers were combined, washed once with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel.

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-fluoro)pyridinyl)cyclohexane carboxamide (5a).** The procedure described above was used with 106 mg of **14a**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 127 mg of the desired product as a yellow oil (90%). R_f (heptane/EtOAc: 20/80 v/v): 0.50. Rt (HPLC A): 9.0 min. Rt (HPLC B): 9.0 min. Rt (HPLC C): 4.52 min. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.84 (q, *J*: 9.0 Hz, 1H); 7.25 (dd, *J*: 1.8 and 6.0 Hz, 1H); 7.00–6.75 (5H); 3.97 (t, *J*: 6.0 Hz, 2H); 3.79 (s, 3H); 2.96 (b, 4H); 2.60 (b, 6H); 2.41 (t, *J*: 9.0 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 177.0 [C]; 163.2 [C, d, *J*: 239 Hz]; 155.0 [C, d, *J*: 13 Hz]; 153.3 [C]; 143.5 [CH, d, *J*: 8 Hz]; 142.5 [C]; 123.5 [CH]; 121.8 [CH]; 119.5 [C]; 118.9 [CH]; 112.5 [CH]; 107.8 [CH, d, *J*: 37 Hz]; 57.2 [CH_2]; 56.1 [CH_3]; 54.1 [2 × CH_2]; 51.3 [2 × CH_2]; 45.8 [CH_2]; 43.4 [CH]; 30.6 [2 × CH_2]; 26.9 [CH_2]; 26.8 [2 × CH_2]. MS: 441 [M + H$^+$].

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-chloro)pyridinyl)cyclohexane carboxamide (5b).** The procedure described above was used with 92 mg of **14b**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 100 mg of the desired product as a yellow oil (81%). R_f (heptane/EtOAc: 20/80 v/v): 0.55. Rt (HPLC A): 12.0 min. Rt (HPLC C): 6.37 min. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.70 (t, *J*: 9.0 Hz, 1H); 7.27 (d, *J*: 9.0 Hz, 1H); 7.22 (d, *J*: 9.0 Hz, 1H); 7.02–6.82 (4H); 3.98 (t, *J*: 6.0 Hz, 2H); 3.80 (s, 3H); 2.93 (b, 4H); 2.58 (b, 6H); 2.35 (t, *J*: 9.0 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 176.7 [C]; 156.2 [C]; 152.8 [C]; 150.1 [C]; 142.0 [C]; 140.6 [CH]; 123.2 [CH]; 122.2 [CH]; 121.3 [CH]; 120.3 [CH]; 118.5 [CH]; 111.9 [CH]; 56.8 [CH_2]; 55.6 [CH_3]; 53.8 [2 × CH_2]; 50.8 [2 × CH_2]; 45.3 [CH_2]; 43.0 [CH]; 30.1 [2 × CH_2]; 26.2 [CH_2]; 26.1 [2 × CH_2]. MS: 457 [M + H$^+$]; 459 [M + H$^+$].

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-bromo)pyridinyl)cyclohexane carboxamide (5c).** The procedure described above was used with 510 mg of **14c**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 590 mg of the desired product as a yellow oil (91%). R_f (heptane/EtOAc: 20/80 v/v): 0.50. Rt (HPLC A): 14.0 min. Rt (HPLC C): 7.37 min. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 7.57 (t, *J*: 9.0 Hz, 1H); 7.35 (d, *J*: 9.0 Hz, 1H); 7.31 (d, *J*: 9.0 Hz, 1H); 7.01–6.80 (4H); 3.99 (t, *J*: 9.0 Hz, 2H); 3.77 (s, 3H); 2.93 (b, 4H); 2.59 (b, 6H); 2.40 (t, *J*: 9.0 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 176.5 [C]; 156.1 [C]; 152.6 [C]; 141.7 [C]; 140.3 [CH]; 140.2 [C]; 125.8 [CH]; 122.8 [CH]; 121.2 [CH]; 120.1 [CH]; 118.3 [CH]; 111.8 [CH]; 56.7 [CH_2]; 55.5 [CH_3]; 53.5 [2 × CH_2]; 50.5 [2 × CH_2]; 45.1 [CH_2]; 42.9 [CH]; 30.0 [2 × CH_2]; 26.3 [CH_2]; 26.2 [2 × CH_2]. MS: 501 [M + H$^+$]; 503 [M + H$^+$].

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-nitro)pyridinyl)cyclohexane carboxamide (5d).** The procedure described above was used with 88 mg of **14d**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 80 mg of the desired product as a yellow oil (68%). R_f (heptane/EtOAc: 20/80 v/v): 0.50. R_f (EtOAc): 0.6. Rt (HPLC A): 9.0 min. Rt (HPLC B): 12.5 min. Rt (HPLC C): 5.09 min. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 8.05 (b, 2H); 7.90 (dd, *J*: 1.9 and 6.4 Hz, 1H); 7.00–6.80 (4H); 4.14 (t, *J*: 6.0 Hz, 2H); 3.81 (s, 3H); 2.92 (b, 4H); 2.74 (b, 6H); 2.59 (t, *J*: 8.5 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 177.8 [C]; 155.9 [C]; 155.7 [C]; 153.2 [C]; 142.1 [C]; 141.7 [CH]; 127.0 [CH]; 123.5 [CH]; 121.7 [CH]; 118.9 [CH]; 115.1 [CH]; 112.3 [CH]; 58.6 [CH_2]; 56.1 [CH_3]; 54.2 [2 × CH_2]; 51.0 [2 × CH_2]; 45.5 [CH_2]; 43.6 [CH]; 30.6 [CH_2]; 26.6 [2 × CH_2]; 26.5 [CH_2]. MS: 468 [M + H$^+$].

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(5-fluoro)pyridinyl)cyclohexane carboxamide (6a).** The procedure described above was used with 840 mg of **15a**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 910 mg of the desired product as a yellow oil (81%). R_f (heptane/EtOAc: 20/80 v/v): 0.50. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 8.35 (bd, *J*: 3.0 Hz, 1H); 7.49 (dt, *J*: 3.0 and 9.0 Hz, 1H); 7.37 (dd, *J*: 4.0 and 9.0 Hz, 1H); 7.05–6.85 (4H); 3.90 (t, *J*: 5.0 Hz, 2H); 3.80 (s, 3H); 2.95 (b, 4H); 2.55 (b, 6H); 2.19 (t, *J*: 7.0 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 176.3 [C]; 158.4 [C, d, *J*: 254 Hz]; 152.8 [C]; 152.5 [C]; 142.0 [C]; 137.2 [CH, d, *J*: 24 Hz]; 125.4 [CH, d, *J*: 20 Hz]; 123.9 [CH]; 122.9 [CH]; 121.3 [CH]; 118.4 [CH]; 111.9 [CH]; 56.6 [CH_2]; 55.6 [CH_3]; 53.8 [2 × CH_2]; 50.9 [2 × CH_2]; 45.4 [CH_2]; 42.7 [CH]; 29.9 [2 × CH_2]; 26.0 [CH_2]; 25.9 [2 × CH_2]. MS: 441 [M + H$^+$].

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(5-chloro)pyridinyl)cyclohexane carboxamide (6b).** The procedure described above was used with 335 mg of **15b**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 355 mg of the desired product as a yellow oil (81%). R_f (heptane/EtOAc: 20/80 v/v): 0.50. ^{1}H NMR (CD_2Cl_2,

300.0K): δ: 8.43 (bd, *J*: 2.0 Hz, 1H); 7.71 (dd, *J*: 3.0 and 9.0 Hz, 1H); 7.34 (d, *J*: 8.5 Hz, 1H); 7.05–6.85 (4H); 3.95 (bt, *J*: 5.0 Hz, 2H); 3.80 (s, 3H); 2.94 (b, 4H); 2.58 (b, 6H); 2.35 (t, *J*: 8.5 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 176.4 [C]; 154.7 [C]; 152.8 [C]; 148.0 [CH]; 142.0 [C]; 138.0 [CH]; 130.0 [C]; 123.3 [CH]; 122.9 [CH]; 121.3 [CH]; 118.4 [CH]; 111.9 [CH]; 56.7 [CH_2]; 55.6 [CH_3]; 53.8 [2 × CH_2]; 50.8 [2 × CH_2]; 45.3 [CH_2]; 42.8 [CH]; 30.0 [2 × CH_2]; 29.6 [CH_2]; 26.1 [CH_2]; 26.0 [2 × CH_2]. MS: 457 [M + H$^+$]; 459 [M + H$^+$].

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(5-bromo)pyridinyl)cyclohexane carboxamide (6c).** The procedure described above was used with 738 mg of **15c**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 925 mg of the desired product as a yellow oil (98%). R_f (heptane/EtOAc: 20/80 v/v): 0.50. ^{1}H NMR (CD_2Cl_2, 300.0K): δ : 8.54 (d, *J* < 1.0 Hz, 1H); 7.85 (dd, *J*: 3.0 and 9.0 Hz, 1H); 7.27 (d, *J*: 9.0 Hz, 1H); 7.05–6.85 (4H); 3.96 (bt, *J*: 5.0 Hz, 2H); 3.80 (s, 3H); 2.94 (b, 4H); 2.59 (b, 6H); 2.35 (t, *J*: 7.5 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 176.4 [C]; 155.0 [C]; 152.8 [C]; 150.2 [CH]; 141.9 [C]; 140.8 [CH]; 123.7 [CH]; 122.9 [CH]; 121.2 [CH]; 118.4 [CH]; 118.3 [C]; 111.9 [CH]; 56.6 [CH_2]; 55.6 [CH_3]; 53.7 [2 × CH_2]; 50.7 [2 × CH_2]; 45.2 [CH_2]; 42.7 [CH]; 30.0 [2 × CH_2]; 29.6 [CH_2]; 26.1 [CH_2]; 26.0 [2 × CH_2]. MS: 501 [M + H$^+$]; 503 [M + H$^+$].

***N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(5-nitro)pyridinyl)cyclohexane carboxamide (6d).** The procedure described above was used with 114 mg of **15d**. Elution with heptane/EtOAc (80/20 to 50/50 v/v) gave 94 mg of the desired product as a yellow oil (63%). R_f (heptane/EtOAc: 20/80 v/v): 0.45. ^{1}H NMR (CD_2Cl_2, 300.0K): δ: 9.24 (bd, *J* < 1.5 Hz, 1H); 8.42 (dd, *J*: 2.0 and 6.0 Hz, 1H); 7.70 (d, *J*: 7.0 Hz, 1H); 7.05–6.85 (4H); 4.13 (t, *J*: 6.0 Hz, 2H); 3.81 (s, 3H); 2.93 (b, 4H); 2.71 (b, 6H); 2.25 (t, *J*: 8.0 Hz, 1H); 1.90–1.05 (10H). ^{13}C NMR (CD_2Cl_2, 300.0K): δ: 177.4 [C]; 159.9 [C]; 152.4 [C]; 144.2 [CH]; 141.4 [C]; 140.9 [C]; 132.5 [CH]; 122.6 [CH]; 120.9 [CH]; 119.5 [CH]; 118.0 [CH]; 111.5 [CH]; 57.0 [CH_2]; 55.2 [CH_3]; 53.5 [2 × CH_2]; 50.4 [2 × CH_2]; 44.9 [CH_2]; 43.2 [CH]; 29.8 [2 × CH_2]; 25.8 [CH_2]; 25.7 [2 × CH_2]. MS: 468 [M + H$^+$].

Radiochemistry

Preparation of the K[^{18}F]F-K_{222}-complex. In order to recover and recycle the [^{18}O]water target, the 2 mL of aqueous [^{18}F]fluoride from the target holder were passed through an anion exchange resin (Sep-Pak® Light Waters Accell™ Plus QMA Cartridge in the chloride form, washed with 5 mL 1 M aq $NaHCO_3$ and then rinsed with 50 mL of water) by He pressure (1.5–2.0 bar). He is blown through the column to extract the last traces of [^{18}O]water. See references [35,39] for more practical details. The [^{18}F]fluoride ion is then eluted from the resin using 1.0 mL of a 4.5 mg/mL aqueous K_2CO_3 solution into a Vacutainer® tube containing 12.0–15.0 mg of Kryptofix®222 (K_{222}: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane). The resulting solution was then gently concentrated to dryness at 145–150 °C under a nitrogen stream for 10 min to give no-carrier-added K[^{18}F]F-K_{222} complex as a white semi-solid residue.

If desired, the [^{18}F]fluoride ion production batch on the cartridge can also be divided into 2–12 aliquots in order to perform parallel syntheses. To do this, the [^{18}F]fluoride ion is eluted from the resin using 1.0 mL of a 4.5 mg/mL aqueous K_2CO_3 solution into an empty Vacutainer® tube. In order to distribute equally this activity over n tubes (Vacutainer® tube, n = 2–12), the quantity of K_2CO_3 was firstly adjusted to n times 4.5 mg with a 50.0 mg/mL aqueous K_2CO_3 solution and secondly, the total volume of the solution was adjusted to 2.0 mL with water. This new aqueous [^{18}F]fluoride solution was then equally distributed over the n tubes each containing 12.0–15.0 mg of Kryptofix®222 (K_{222}: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane). Finally, the volume of each fraction was adjusted to 1.0 mL with water. The resulting solutions were then independently gently concentrated to dryness at 145–150 °C under a nitrogen stream for 10 min to give no-carrier-added K[^{18}F]F-K_{222} complex as a white semi-solid residue.

6- and 5-[^{18}F]fluoropyridine derivatives: incorporation studies with K[^{18}F]F-K_{222}-complex

General procedure using conventional heating or microwave activation in a non-sealed reactor. Freshly distilled DMSO (600 μL) containing 2.0–6.0 mg of the precursor for labelling **5b–d** or **6b–d** were directly added into the Vacutainer® tube containing the dried K[^{18}F]F-K_{222} complex. The tube (not sealed) was then placed in a heating block (at 145 °C for 1–30 min) or in a dedicated microwave oven (at 100 W, for 1–3 min) without stirring the contents. The reaction vessel was then cooled using an ice-water bath and the remaining radioactivity was measured; 90–95% of the initial radioactivity placed in the vessel was still present. The resulting dark-coloured reaction mixture was then analyzed by radiochromatography. The reaction yield was calculated from the TLC-radiochromatogram and defined as the radioactivity area of the [^{18}F]fluoropyridine derivatives over total fluorine-18 radioactivity area ratio. (SiO_2-TLC, eluent: EtOAc/MeOH: 90/10 v/v, R_f: 6- or 5-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a/6a**): 0.70 and R_f: [^{18}F]fluoride ion: 0.0). Radiosynthesized 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**) co-migrated with an authentic sample of fluorine-19-synthesized **5a**; Concerning 5-[^{18}F]fluoro-WAY-100635 ([^{18}F]**6a**), no peak could be detected at the R_f of fluorine-19-synthesized **6a**.

General procedure using conventional heating in a sealed reactor. The K[^{18}F]F-K_{222} complex (Vacutainer® tube) was dissolved in 200 μL of a freshly distilled DMSO and transferred to a 5 mL pyrex® reaction vial containing 2.0–6.0 mg of the precursor for labelling (**5b–d** or **6b–d**). The evaporation tube was rinsed twice with 200 μL of DMSO which was then added to the reaction mixture. Resolubilization efficiencies were about 60–90% of the original [^{18}F]fluoride ion. The reaction vial was then tightly closed with a Teflon cap and heated in a heating block (at 150–250 °C, for 0–30 min) without stirring the

contents. The remainder of the synthesis used the same procedure as described above.

N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-[^{18}F]fluoro)pyridinyl)cyclohexane carboxamide or 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**)

Procedure using the 6-bromo derivative 5c as precursor for labelling. Freshly distilled DMSO (600 μL) containing 5.0 mg of the precursor for labelling **5c** were directly added into the Vacutainer® tube containing the dried K[^{18}F]F-K_{222} complex. The tube (not sealed) was then placed in a heating block (at 145 °C for 10 min) or in a dedicated microwave oven (at 100 W, for 3 min). The reaction vessel was then cooled using an ice-water bath. The resulting dark-coloured reaction mixture was diluted with 1 mL of water and transferred on a C18 Sep-Pak cartridge (PrepSep™ R-C18, Fisher Scientific). The tube was rinsed twice with 1 mL of water, which was also transferred and added to the diluted reaction mixture on the cartridge. The whole was then passed through the cartridge, which was then partially dried for 0.5 min by applying a nitrogen stream. At this stage, a loss of the desired 6-[^{18}F]fluoropyridine derivative [^{18}F]**5a** could not be avoided and 20–30% of the radiotracer was found in the waste. The 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**) was eluted from the cartridge with 3 mL of dichloromethane. Twice 1 mL of dichloromethane was used to wash the cartridge and to completely transfer [^{18}F]**5a** (5–10% of the total radioactivity amount engaged in the fluorination process was left on the cartridge). The mentioned dichloromethane solution was concentrated to dryness (at 60–80 °C under a gentle nitrogen stream for 4–6 min). Finally, the residue was redissolved in 1.0 mL of the HPLC solvent used for purification and the crude was injected onto HPLC. Isocratic elution [HPLC A] gave pure labelled 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**), retention time: 9.0 min.

Procedure using the 6-nitro derivative 5d as precursor for labelling. Freshly distilled DMSO (600 μL) containing 5.0 mg of the precursor for labelling **5d** were directly added into the Vacutainer® tube containing the dried K[^{18}F]F-K_{222} complex. The tube (not sealed) was then placed in a heating block (at 145 °C for 3 min) or in a dedicated microwave oven (at 100 W, for 1 min). The remainder of the preparation used the same procedure as described above except for the final HPLC purification. Isocratic elution [HPLC B] gave pure labelled 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**), retention time: 9.0 min.

Formulation and quality control. Formulation of labelled product for iv injection was effected as follows: (1) HPLC solvent removal by evaporation; (2) taking up the residue, while heating gently (45 °C), in 5 mL of physiological saline containing 10% EtOH; (3) sterile filtration on a 0.22 μm Millipore filter. As demonstrated by HPLC analysis [HPLC C], radiosynthesized 6-[^{18}F]fluoro-WAY-100635 ([^{18}F]**5a**) co-eluted with an authentic sample of fluorine-19-synthesized **5a**. The radiolabelled product was found to be >95% chemically and radiochemically pure (retention time: 4.52 min). The preparation was shown to be free of non-radioactive precursor and radiochemically stable for at least 120 min.

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