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Bioorganic & Medicinal Chemistry 12 (2004) 5505–5513
Bioorganic & Medicinal Chemistry

Synthesis and evaluation of fluorine-substituted 1*H*-pyrrolo[2,3-*b*]pyridine derivatives for dopamine D_4 receptor imaging

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Received 5 August 2004; accepted 11 August 2004
Available online 11 September 2004

Abstract—Seven fluorine-substituted 1*H*-pyrrolo[2,3-*b*]pyridine derivatives were synthesized based on a lead ligand, 3-[[4-(4-iodophenyl)piperazin-1-yl]-methyl]-1*H*-pyrrolo[2,3-*b*]pyridine (L-750,667) and evaluated as potential dopamine D_4 receptor imaging agents by positron emission tomography (PET). Binding affinities of these ligands for the dopamine D_2, D_3, and D_4 receptor subtypes were measured in vitro. Most ligands showed high and selective binding for the D_4 receptor. Ligand **7** had high affinity for the D_4 receptor, whereas ligands **1**, **2**, and **6** showed high selectivity for the D_4 receptor. Log *P* values were calculated for the ligands in this series and ligand **6** had the lowest lipophilicity. ^{18}F-labeled ligand **7** demonstrated a uniform regional brain distribution and a rapid washout in mice, probably due to nonspecific binding. Based on their in vitro binding properties and calculated log *P* values, ligand **6** appears to have the most promise for dopamine D_4 receptor imaging.
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1. Introduction

Classical neuroleptics are known to be dopamine receptor antagonists and thus their efficacies are mediated by dopamine receptors. Although most neuroleptics produce extrapyramidal side effects (EPS), the atypical neuroleptic clozapine produces fewer and milder EPS than classical neuroleptics and is shown to be effective for treatment-resistant schizophrenia patients, possibly due to its high binding affinity for the D_4 receptor relative to the D_2 receptor.[1,2] Dopamine hyperactivity in schizophrenia has been proposed because many neuroleptics used for treatment of schizophrenia actually block dopamine D_2-like receptors, including D_2, D_3, and D_4 receptor subtypes. The D_4 receptor has a distinctive distribution in the cortical and limbic regions of the brain, whereas the D_2 receptor is located in the caudate, putamen, and nucleus accumbens, and the D_3 receptor in the ventral striatum.[3]

The dopamine D_4 receptor has drawn considerable interest due to its implied role in schizophrenia.[1] The dopamine D_4 receptor level was found to be increased in the postmortem caudate-putamen tissues of schizophrenia patients in an indirect binding study, in which the receptor density determined using [^{3}H]raclopride, a D_2/D_3 receptor antagonist, was subtracted from that

Keywords: 1*H*-pyrrolo[2,3-*b*]pyridine derivatives; Dopamine D_4 receptor; Binding affinity; Log *P*.
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doi:10.1016/j.bmc.2004.08.011

of [^{3}H]nemonapride or [^{3}H]spiperone ($D_2/D_3/D_4$ receptor antagonists),[4] although this finding was not reproduced by other investigators.[5] Moreover it was suggested that high levels of D_4 mRNA are expressed in the cortical and limbic regions of the human brain. However, estimations of the D_4 mRNA levels have been inconsistent.[6]

A recent autoradiographic study using the selective D_4 receptor antagonist [^{3}H]NGD-94-1 demonstrated high radioligand binding in the hippocampus and entorhinal cortex of normal controls, and a significant increase in the entorhinal cortex of schizophrenia patients.[3,6] However, these direct studies showed no increased D_4 receptor level in the postmortem caudate-putamen tissues of normal controls or in schizophrenia patients. In addition, the associations between the D_4 receptor gene and other neuropsychiatric disorders suggest its broader involvement in neuropsychiatric disorders other than schizophrenia. Therefore, radioligands with high affinity and selectivity are required to verify the role of the D_4 receptor in schizophrenia and in other neuropsychiatric diseases.

Many dopamine D_4 receptor antagonists have been developed, such as 1*H*-pyrrolo[2,3-*b*]pyridine,[7] isoxazole,[8,9] 2-naphthonate ester,[10] benzamide,[11] chromeno[3,4-*c*]pyridine-5-one,[12] (aryloxy)alkylamine,[13] and NGD derivatives.[14,15] Some antagonists have been radiolabeled for dopamine D_4 receptor imaging, such as, ^{18}F- and ^{11}C-labeled benzamide analogs,[16–18] ^{11}C-labeled chromeno[3,4-*c*]pyridine-5-one,[19] ^{11}C-labeled SDZ GLC 756,[20] and radioiodine-labeled L-750,667;[21,22] however, no radioligand has been found that specifically binds to the D_4 receptor. Of these antagonists, L-750,667 (Fig. 1) and its 4-chloro derivative (L-745,870) have high binding affinities for cloned human D_4 receptor (K_i = 0.51 and 0.43 nM) and high selectivity relative to the D_2 (>1700 nM) and D_3 receptors (>4500 nM).[6,7] However, radioiodine-labeled L-750,667 was found to be taken up by all brain regions, and this uptake was not displaced by NGD-94-1 due to its high nonspecific binding.[21,22]

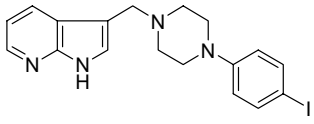


Figure 1. Structure of L-750,667.

In this study, we designed, synthesized and evaluated seven fluorine-substituted ligands for dopamine D_4 receptor imaging, in which L-750,667 was selected as a lead ligand and modified to have a fluorine substituent with less lipophilicity. Fluorine and fluoromethyl group are bioisosters of iodine that allows a bioisosteric substitution of the formers for the iodine and ^{18}F is an ideal radioisotope for the preparation of PET radiopharmaceuticals due to its relatively long half-life ($t_{1/2}$ = 109.8 min) and low positron energy. Appropriate lipophilicity is preferred to reduce nonspecific binding of the ligands.

2. Results and discussion

L-750,667 has been shown to be a highly potent and selective antagonist of the dopamine D_4 receptor.[7] However, radioiodine-labeled L-750,667 has a nonspecific regional distribution in rat brain sections and in nonhuman primates.[22] Seven less lipophilic fluorine-substituted ligands (Fig. 2) were designed based on their calculated log *P* values (Table 1). A simple bioisosteric substitution of the fluorine for the iodine gave lower lipophilicity than that of L-750,667, and an additional polar functional group such as hydroxy or nitro group to the benzene ring gave even lower log *P* values. Therefore, we synthesized the seven fluorine-substituted ligands, and then evaluated them in terms of their binding affinities for the dopamine D_2, D_3, and D_4 receptor.

A core moiety, 1*H*-pyrrolo[2,3-*b*]pyridine was introduced as either 1*H*-pyrrolo[2,3-*b*]pyridin-3-carboxaldehyde (**8**) or 3-piperazin-1-yl-methyl-1*H*-pyrrolo[2,3-*b*]-pyridine (**10**), depending on the ligands **1**–**7**. Compound **8** was synthesized by reacting 7-azaindole with phosphorus oxychloride and DMF at 80 °C for 24 h. Reductive alkylation of **8** with 1-piperazinecarboxaldehyde and the subsequent removal of *N*-formyl group under acidic condition gave **10**,[23] which was obtained in pure with a high yield by flash column chromatography using eluting solvents containing 1% triethylamine. Ligands **1**–**3** were designed based on the bioisosteric substitution of

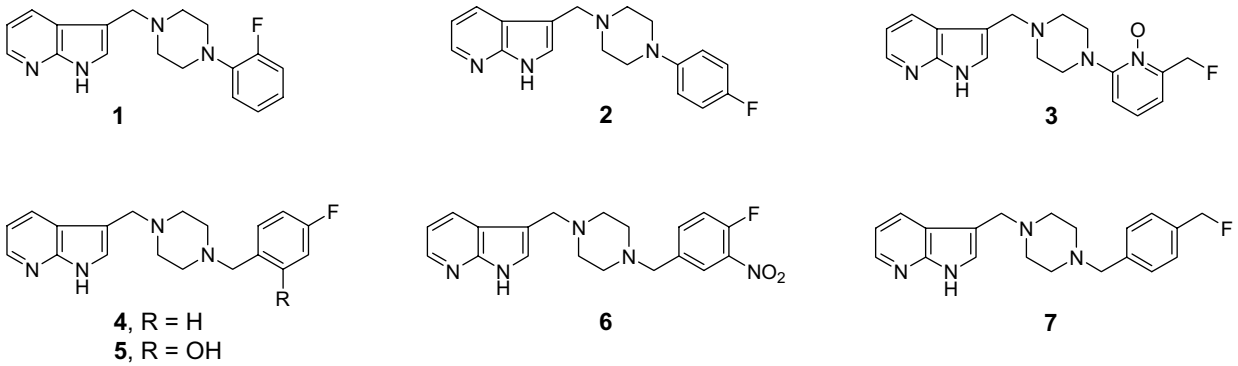
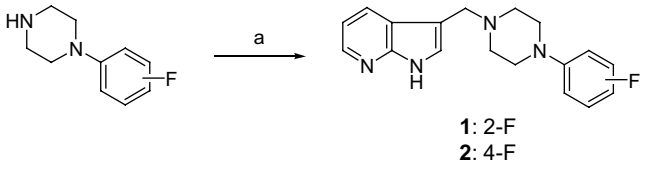


Figure 2. Structures of fluorine-substituted 1*H*-pyrrolo[2,3-*b*]pyridine derivatives.

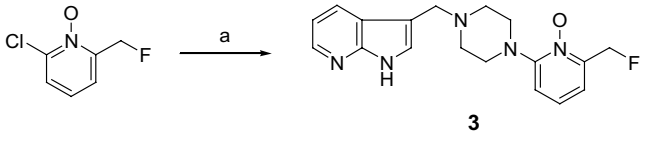
Table 1. Calculated log *P* values of 1*H*-pyrrolo[2,3-*b*]pyridine derivatives

	Ligand							
	1	**2**	**3**	**4**	**5**	**6**	**7**	Lead
Log *P*	3.14	3.59	—	3.35	2.98	2.79	3.33	4.57

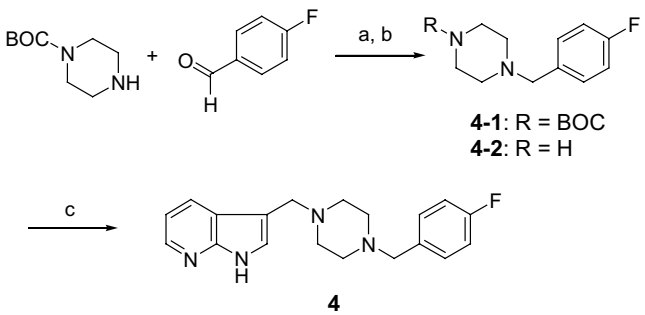
fluorine or of the fluoromethyl group for the iodine of L-750,667. An additional substitution of benzene with pyridine *N*-oxide was carried out in **3**, because the nucleophilic aromatic substitution reaction of **10** with 6-chloro-α-fluoro-2-picoline *N*-oxide is faster than that with chloropyridine or chlorobenzene, and because pyridine *N*-oxide compounds have been shown to have excellent pharmacokinetics and oral bioavailability.[24,25] A methylene linkage between **10** and a benzene moiety was added in ligands **4**–**7** with the addition of a polar functional group to the benzene ring in ligands **5** and **6**. Ligands **1**, **2**, and **4** were synthesized by the reductive alkylation of **8** with substituted piperazines in the presence of $NaBH_3CN$ and methanol (Schemes 1 and 3). Ligand **3** was prepared by a nucleophilic aromatic substitution reaction of **10** with 6-chloro-α-fluoro-2-picoline *N*-oxide (Scheme 2), and the picoline *N*-oxide was synthesized from 6-chloro-2-picoline, as described in the literature.[26] Ligands **5**–**7** were prepared from **10** by



Scheme 1. Reagents and conditions: (a) **8**, CH_3OH, $NaBH_3CN$, 80 °C, 12 h. 80–85%.



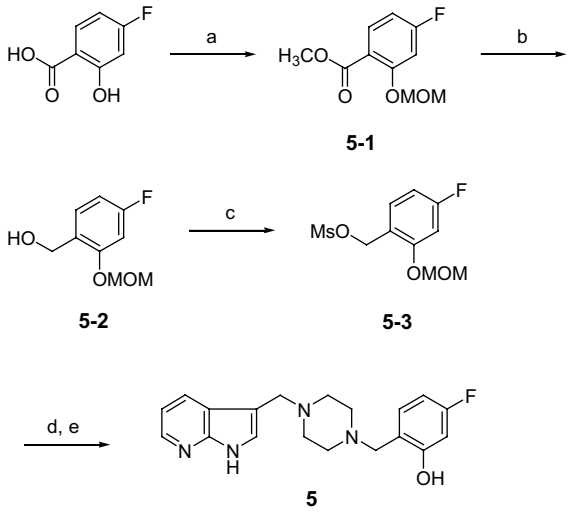
Scheme 2. Reagents and conditions: (a) **10**, DMF, isopropyl alcohol, Et_3N, 180 °C, 2 h, 14%.



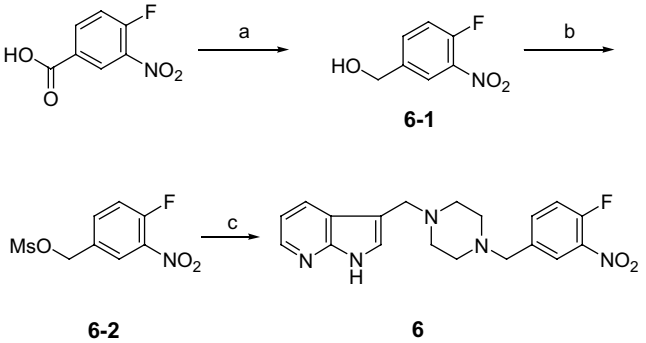
Scheme 3. Reagents and conditions: (a) $NaBH_3CN$, CH_3OH, 80 °C, 12 h, 57%; (b) CF_3COOH, CH_2Cl_2, rt, 4 h, 35%; (c) **8**, CH_3OH, $NaBH_3CN$, 80 °C, 12 h, 43%.

substitution reactions with methanesulfonate esters (Schemes 4–6).

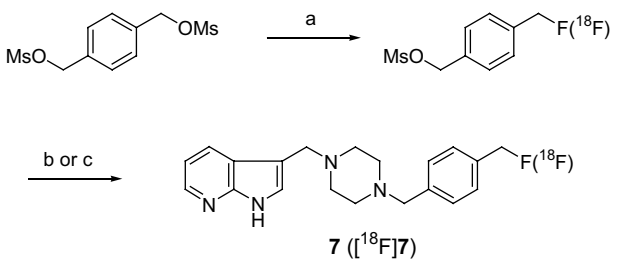
The binding affinities of all ligands to dopamine hD_{2L}, dopamine rD_3 and dopamine $hD_{4.4}$ receptors were measured, using various ligand concentrations (10^{-10}–10^{-4} M) and [^{3}H]nemonapride (Table 2).[27] Nonspecific binding was estimated using haloperidol for all receptors. Ligands **1**–**3** showed high binding affinity and selectivity for the D_4 receptor. According to Huang et al., the binding affinities and selectivities of ligands **1** and **2** were comparable to those of L-745,870 in the assays using the rat dopamine receptors and the radioligands, [^{3}H]spiperone and [^{3}H]sulpiride.[28] An additional methylene linkage between **10** and a benzene moiety lowered D_4 receptor binding affinity 5-fold, as demonstrated by ligands **2** and **4**. However, an electron-withdrawing group or a fluoromethyl group on a benzene ring as in ligands **6** and **7** significantly increased D_4 receptor binding affinity. Of the seven fluorine-substituted ligands, **7** showed highest D_4 receptor binding with excellent affinity



Scheme 4. Reagents and conditions: (a) NaH, DMF, CH_3OCH_2Cl, rt, 14 h, 64%; (b) $LiAlH_4$, THF, rt, 14 h, 62%; (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, rt, 30 min, 84%; (d) **10**, Et_3N, CH_3CN, reflux, 1 h, 64%; (e) 6 N HCl, rt, 30 min, 65%.



Scheme 5. Reagents and conditions: (a) borane, THF, rt, 1 h, 81%; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, rt, 30 min, 96%; (c) **10**, Et_3N, CH_3CN, reflux, overnight, 58%.



Scheme 6. Reagents and conditions: (a) nBu$_4$NF, rt, 1 h or nBu$_4$N [^{18}F]F, 90 °C, 5 min; (b) **10**, Et$_3$N, CH$_3$CN, reflux, 1 h, 85%; (c) **10**, Et$_3$N, CH$_3$CN, DMF, 130 °C, 15 min.

(K_i = 1.48 nM), and **1**, **2**, and **6** appeared to have high selectivity for the D_4 receptor relative to the D_2 and D_3 receptors. Recently, the preparation of [^{18}F]**4** by reductive alkylation was reported.[29]

Ligand **7** was selected for radiolabeling due to its high affinity for the D_4 receptor. The radioligand [^{18}F]**7** was prepared by reacting **10** with 4-[^{18}F]fluoromethylbenzylmethanesulfonate ester (130 °C, 15 min), which was synthesized from 1,4-benzenedimethanol bismethanesulfonate ester and nBu$_4$N[^{18}F]F (90 °C, 5 min), as described previously.[30] Use of excess amounts of **10** in this one-pot reaction increased the radiochemical yield of [^{18}F]**7**, by increasing the reaction yields with all the methanesulfonate esters including the unreacted bismethanesulfonate ester and [^{18}F]fluoromethylbenzylmethanesulfonate ester. Alkylation of **10** with the bismethanesulfonate ester prior to [^{18}F]fluorination resulted in the formation of decomposition products as well as the desired product [^{18}F]**7**. The HPLC purification of [^{18}F]**7** was carried out using 100% 0.1 M NH_4CO_2H for 5 min to remove DMF and then using a 40:60 mixture of 0.1 M NH_4CO_2H and CH_3OH. The desired fraction eluted at 28–30 min was collected for tissue distribution studies. The decay-corrected radiochemical yield of [^{18}F]**7** was 10–15% and effective specific activity was 27–30 GBq/μmol. Authenticity of [^{18}F]**7** was confirmed by co-elution with unlabeled standard **7** by HPLC. Tissue distribution studies of [^{18}F]**7** in mouse brain showed a high uptake in most brain tissues at 5 min postinjection (7–9%ID/g) but a uniform distribution with a rapid wash out in brain regions, which may have been due to nonspecific binding (Fig. 3). The radioligand suffered from severe in vivo metabolic defluorination due to increased bone uptake over time (2.05%ID/g at 5 min, 7.10%ID/g at 60 min, and 10.65%ID/g at 120 min), as shown in other ligands containing [^{18}F]fluoromethylbenzyl group.[31,32] Although ligands **1** and **2** have high specificity and selectivity for the D_4 receptor relative to the D_2 and D_3 receptors, they have similar structures and lipophilic properties to ligand **7**. Therefore, ligand **6** with high specificity and low lipophilicity appears to be suitable for D_4 receptor imaging using PET.

Table 2. Binding affinities of 1*H*-pyrrolo[2,3-*b*]pyridine derivatives to dopamine receptor subtypes

Ligand	K_i (nM ± SD)[a]		
	D_2	D_3	D_4
1	5554 ± 974	2900 ± 151	3.11 ± 0.85
2	>10,000	>10,000	11.19 ± 5.89
3	5265 ± 736	812 ± 266	5.28 ± 3.61
4	>10,000	>10,000	55.13 ± 28.36
5	>10,000	4494 ± 1699	30.85 ± 20.13
6	>10,000	3283 ± 1391	4.10 ± 1.11
7	>10,000	990 ± 487	1.48 ± 1.66
Haloperidol	12.64 ± 0.26	—	10.48 ± 4.67

[a] K_i values at dopamine hD_{2L}, rD_3, and $hD_{4.4}$ receptors are expressed as means ± SD.

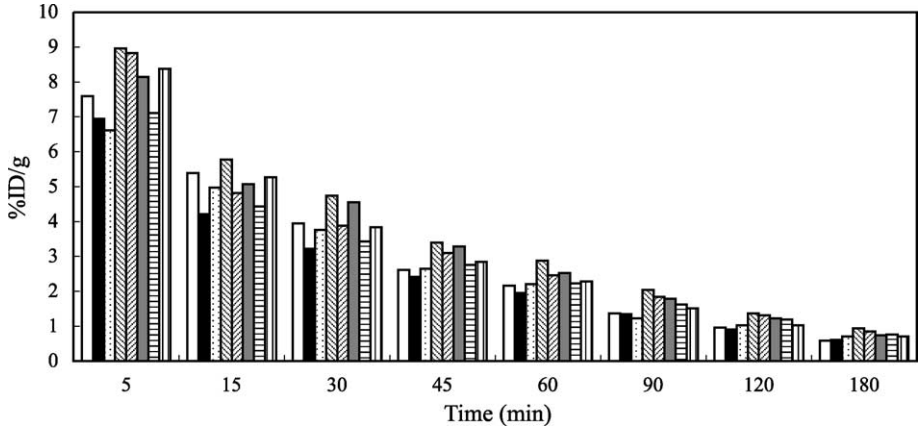


Figure 3. Tissue distribution of [^{18}F]**7** in mouse brain. Cerebellum: white solid; striatum: black solid; olfactory tubercle: dotted solid; frontal cortex: right-handed stripe; parietal cortex: left-handed stripe; hypothalamus: gray solid; hippocampus: horizontal stripe; thalamus: vertical stripe.

3. Conclusion

Seven fluorine-substituted 1*H*-pyrrolo[2,3-*b*]pyridine derivatives were synthesized and evaluated for dopamine D_4 receptor imaging using PET. Based on in vitro binding assays, these ligands showed specific and selective D_4 receptor binding relative to the D_2 and D_3 receptors. Ligand **7** demonstrated the highest affinity for the D_4 receptor, however its ^{18}F-labeled ligand underwent in vivo metabolic defluorination and showed a uniform binding in mouse brain, possibly due to nonspecific binding. Ligand **6**, thus offer a potential means of dopamine D_4 receptor imaging, due to its favorable in vitro binding properties and calculated log *P* value.

4. Experimental

4.1. Materials and methods

Solvents and reagents were purchased from the Aldrich Chemical Company (Milwaukee, WI). ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini-200 (Palo Alto, CA), a Jeol JNM-LA 300, and a JNM-GCX 400 spectrometer (Tokyo, Japan). Chemical shifts (δ) are reported as ppm downfield of internal tetramethylsilane. Electron impact (EI) mass spectra were obtained on a GC/MS QP5050A spectrometer (Shimadzu, Kyoto, Japan). Fast atom bombardment (FAB) mass spectra were recorded on a Jeol JMS-700 Mstation (Tokyo, Japan). HPLC was carried out using a Thermo Separation Products System (Fremont, CA) with a semipreparative column (Alltech Econosil C18, 10μ, 10 × 250 mm). Eluate was monitored simultaneously using a UV detector (254 nm) and a NaI(Tl) radioactivity detector. TLC was performed on Merck F_{254} silica plates and analyzed on a radio-TLC scanner (Bioscan, Washington, D.C.).

[^{3}H]nemonapride (3145 GBq/mmol) was obtained from Perkin–Elmer Life Sciences, Inc. (Boston, MA). Sf-9 membranes expressing either dopamine hD_{2L} or dopamine rD_3 receptors and CHO membranes expressing dopamine $hD_{4.4}$ receptors were purchased from BioSignal Packard Inc. (Montreal, Canada).

[^{18}F]Fluoride was produced by the ^{18}O(p,n)^{18}F reaction using a GEMS PETtrace cyclotron (Uppsala, Sweden). Radioactivity was measured in a dose calibrator (Biodex Medical Systems, Shirley, NY) and tissue radioactivity in a Wallac automatic gamma counter (Boston, MA).

4.1.1. 1*H*-Pyrrolo[2,3-*b*]pyridin-3-carboxaldehyde (8). Phosphorous oxychloride (1.28 mL, 13.70 mmol) was added to DMF (1 g, 13.70 mmol) at 0 °C and the reaction mixture was stirred for 10 min. To this mixture was added 7-azaindole (1.08 g, 9.12 mmol). The resulting solution was heated at 80 °C for 24 h, poured into ice-water and then neutralized with 4 N NaOH. The solution was then extracted with CH_2Cl_2 and washed (H_2O and brine) and then dried over Na_2SO_4. The organic layer was concentrated and purified by flash column chromatography (80:20 ethyl acetate–hexane) to provide **8** (661 mg, 50%) as a brown solid: mp >200 °C (decomposition); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.29 (dd, 1H, J = 7.8 Hz), 8.36–8.43 (m, 2H), 8.45 (d, 1H, J = 1.2 Hz), 9.91 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 115.5, 115.6, 117.4, 128.2, 137.7, 143.9, 148.4, 184.5; MS (EI) *m*/*z* 146 (M^+). Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.78; H, 4.12; N, 19.29.

4.1.2. 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl-methyl)piperazine-1-carboxaldehyde (9). To **8** (1.80 g, 12.30 mmol) in methanol (10 mL) was added 1-piperazinecarboxaldehyde (1.50 mL, 12.30 mmol). The reaction mixture was adjusted with acetic acid to pH 5 and then reacted with $NaBH_3CN$ (2.10 g, 33.20 mmol) at 60 °C for 18 h. After removing the solvent in vacuo, the residue was diluted with ethyl acetate and neutralized with 10% NaOH. Product isolation (ethyl acetate) followed by flash column chromatography (70:30 ethyl acetate–methanol) afforded **9** (2.84 g, 95%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$ + CD_3OD) δ 2.28–2.39 (m, 4H), 3.22–3.44 (m, 4H), 3.55 (s, 2H), 6.90 (q, 1H, J = 2.4 Hz), 7.09 (s, 1H), 7.79 (s, 1H), 7.91 (dd, 1H, J = 1.6 Hz), 8.04 (dd, 1H, J = 1.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$ + CD_3OD) δ 44.7, 50.9, 52.0, 108.7, 114.6, 119.9, 124.6, 127.4, 141.5, 147.6, 160.6; MS (FAB) *m*/*z* 245 $(M+H)^+$. HRMS calcd for $C_{13}H_{16}N_4O$ 245.1402, found 245.1404.

4.1.3. 3-Piperazin-1-yl-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (10). To **9** (800 mg, 3.29 mmol) in methanol (2 mL) was added 4 M H_2SO_4 (3 mL) at 0 °C. The solution was heated at 60 °C for 1 h and basified with 4 N NaOH. Product isolation (ethyl acetate) followed by flash column chromatography (70:30 ethyl acetate–methanol containing 1% Et_3N) then afforded **10** (463 mg, 65%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$ + CD_3OD) δ 2.47 (br s, 4H), 2.81–2.85 (m, 4H), 3.66 (s, 2H), 7.05 (q, 1H, J = 4.8 Hz), 7.28 (s, 1H), 8.03 (dd, 1H, J = 1.4 Hz), 8.18 (dd, 1H, J = 3.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$ + CD_3OD) δ 44.3, 52.6, 52.7, 108.5, 114.8, 120.4, 125.0, 127.5, 141.4, 147.4; MS (FAB) *m*/*z* 217 $(M+H)^+$. HRMS calcd for $C_{12}H_{16}N_4$ 217.1454, found 217.1448.

4.1.4. 3-[4-(2-Fluorophenyl)piperazin-1-yl]-1*H*-pyrrolo-[2,3-*b*]pyridine (1). To **8** (500 mg, 3.42 mmol) in methanol (8 mL) was added 1-(2-fluorophenyl)piperazine (540 μL, 3.42 mmol). The reaction mixture was adjusted with acetic acid to pH 5 and then reacted with $NaBH_3CN$ (580 mg, 9.23 mmol) at 80 °C for 12 h. After the solvent has been removed in vacuo, the residue was diluted with ethyl acetate and neutralized with 10% NaOH. Product isolation (ethyl acetate) followed by flash column chromatography (50:50 ethyl acetate–methanol) afforded **1** (509 mg, 80%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68–2.70 (m, 4H), 3.10–3.12 (m, 4H), 3.78 (s, 2H), 6.89–7.11 (m, 4H), 7.30 (dd, 1H, J = 6.0, 3.6 Hz), 8.11 (dd, 1H, J = 6.4, 1.2 Hz), 8.32 (dd, 1H, J = 3.6, 1.2 Hz), 10.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.9, 53.4, 54.1, 111.4, 116.0, 116.4, 119.2, 120.8, 122.6, 124.3, 124.6, 128.5, 140.5,

143.2, 149.2, 155.0, 157.0; MS (FAB) *m/z* 311 $(M+H)^+$. HRMS calcd for $C_{18}H_{20}FN_4$ 311.1672, found 311.1671.

4.1.5. 3-[4-(4-Fluorophenyl)piperazin-1-yl]-1*H*-pyrrolo-[2,3-*b*]pyridine (2). To **8** (300 mg, 2.05 mmol) in methanol (5 mL) was added 1-(4-fluorophenyl)piperazine (370 mg, 2.05 mmol). The reaction mixture was adjusted with acetic acid to pH 5 and then reacted with $NaBH_3CN$ (348 mg, 5.54 mmol) at 80 °C for 12 h. Product isolation (ethyl acetate) followed by flash column chromatography (50:50 ethyl acetate–methanol) afforded **2** (541 mg, 85%) as a pale yellow solid: mp 199–200 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.67–2.69 (m, 4H), 3.11–3.13 (m, 4H), 3.77 (s, 2H), 6.86–6.88 (m, 2H), 6.91–6.97 (m, 2H), 7.09 (dd, 1H, $J = 6.0$, 3.6 Hz), 7.30 (s, 1H), 8.10 (dd, 1H, $J = 6.4$, 1.2 Hz), 8.24 (dd, 1H, $J = 4.0$, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4, 53.1, 53.6, 110.4, 115,6, 115.8, 118.2, 121.0, 125.0, 128.6, 142.7, 148.1, 148.4, 156.5, 158.4; MS (FAB) *m/z* 311 $(M+H)^+$. HRMS calcd for $C_{18}H_{20}FN_4$ 311.1672, found 311.1678.

4.1.6. 2-Fluoromethyl-6-[4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl-methyl)piperazin-1yl]pyridine *N*-oxide (3). Compound **10** (138 mg, 0.64 mmol) and Et_3N (134 μL, 0.96 mmol) were added to 6-chloro-α-fluoro-2-picoline *N*-oxide (103 mg, 0.64 mmol)[26] in 0.5 mL of DMF and 0.5 mL of isopropyl alcohol in a 5 mL Reacti-vial®. The reaction mixture was then heated at 180 °C for 2 h. Product isolation (dichloromethane) followed by flash column chromatography (98:2 ethyl acetate–methanol) afforded **3** (30 mg, 14%) as a pale yellow solid: ^1H NMR (200 MHz, $CDCl_3$) δ 2.58 (t, 4H, $J = 5.0$ Hz), 3.54 (t, 4H, $J = 5.0$ Hz), 3.75 (s, 2H), 5.28 (d, 2H, $J = 47.4$ Hz), 6.54 (d, 1H, $J = 8.4$ Hz), 6.73 (d, 1H, $J = 7.4$ Hz), 7.09 (dd, 1H, $J = 8.0$, 7.8 Hz), 7.30 (s, 1H), 7.48 (t, 1H, $J = 7.9$ Hz), 8.12 (dd, 1H, $J = 7.8$, 1.5 Hz), 8.32 (dd, 1H, $J = 4.6$, 1.5 Hz), 10.79 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.50, 51.13, 52.29, 83.14 (d, $J = 168.0$ Hz), 104.43, 107.77, 107.89, 109.40, 113.93, 118.92, 122.46, 126.63, 136.39, 141.04, 147.37, 152.75, 153.18; MS (FAB) *m/z* 341 $(M+H)^+$.

4.1.7. 3-[4-(4-Fluorobenzyl)piperazin-1-yl-methyl]-1*H*-pyrrolo[2,3-*b*]pyridine (4). To **8** (125 mg, 0.86 mmol) in methanol (2 mL) was added **4-2** (167 mg, 0.86 mmol). The reaction mixture was adjusted with acetic acid to pH 5 and then reacted with $NaBH_3CN$ (145 mg, 2.32 mmol) at 80 °C for 12 h. Product isolation (ethyl acetate) followed by flash column chromatography (50:50 ethyl acetate–methanol) afforded **4** (120 mg, 43%) as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 2.41–2.49 (m, 4H), 2.49–2.58 (m, 4H), 3.45 (s, 2H), 3.71 (s, 2H), 6.95–6.98 (m, 2H), 7.07 (dd, 1H, $J = 6.0$, 3.6 Hz), 7.21–7.25 (m, 2H), 7.26 (s, 1H), 8.06 (dd, 1H, $J = 6.4$, 1.2 Hz), 8.31 (dd, 1H, $J = 3.6$, 1.2 Hz), 11.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.2, 53.9, 62.4, 111.2, 115.2, 115.3, 115.8, 120.9, 124.5, 128.4, 130.9, 134.1, 142.9, 149.3, 161.2, 163.2; MS (FAB) *m/z* 325 $(M+H)^+$. HRMS calcd for $C_{19}H_{22}FN_4$ 325.1828, found 325.1823.

4.1.8. 4-(4-Fluorobenzyl)piperazine 1-*tert*-butoxycarbonyl ester (4-1). A solution of 1-*tert*-butoxycarbonylpiperazine (820 mg, 4.38 mmol) and 4-fluorobenzaldehyde (543.6 mg, 4.38 mmol) in MeOH (5 mL) was adjusted to pH 5 with acetic acid. $NaBH_3CN$ (741.5 mg, 11.8 mmol) was then added and the reaction mixture was heated at 80 °C for 12 h. Product isolation (ethyl acetate) followed by flash column chromatography (3:1 hexane–ethyl acetate) gave a yellow oil **4-1** (728 mg, 56.5%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.34 (t, 4H, $J = 5.2$ Hz), 3.40 (t, 4H, $J = 5.2$ Hz), 3.44 (s, 2H), 6.97 (t, 2H, $J = 8.8$ Hz), 7.23 (t, 2H, $J = 5.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.24, 52.35, 52.68, 62.09, 79.50, 115.24, 114.81, 128.70, 130.49, 133.56, 159.68; MS (EI) *m/z* 294 (M^+). HRMS calcd for $C_{16}H_{23}FN_2O_2$ 294.1744, found 294.1745.

4.1.9. 1-(4-Fluorobenzyl)piperazine (4-2). Trifluoroacetic acid (1 mL) was slowly added to **4-1** (550 mg, 2.47 mmol) in CH_2Cl_2 (3 mL) and stirred at rt for 4 h. The reaction mixture was then neutralized with 1 N NaOH and extracted with CH_2Cl_2. Flash column chromatography (1:1 ethyl acetate–methanol) yielded a colorless oil **4-2** (167 mg, 34.8%): ^1H NMR (200 MHz, $CDCl_3$ + CD_3OD) δ 2.29–2.52 (m, 4H), 2.78–2.89 (m, 4H), 3.39 (s, 2H), 6.93 (t, 2H, $J = 8.8$ Hz), 7.23 (t, 2H, $J = 5.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$ + CD_3OD) δ 45.5, 53.7, 62.5, 114.6, 115.0, 130.4, 130.6, 133.6, 164.3; MS (EI) *m/z* 194 (M^+). HRMS calcd for $C_{11}H_{15}FN_2$ 194.1219, found 194.1212.

4.1.10. 3-[4-(4-Fluoro-2-hydroxybenzyl)piperazin-1-yl-methyl]-1*H*-pyrrolo[2,3-*b*]pyridine (5). Methanesulfonate ester **5-3** (0.6 g, 2.7 mmol) in CH_3CN (2 mL) was added slowly to a solution of **10** (0.3 g, 1.36 mmol) and Et_3N (0.38 mL, 2.7 mmol) in CH_3CN (20 mL) in an ice bath, and the reaction mixture was refluxed for 1 h. Product isolation (ethyl acetate) and purification by flash column chromatography (10:1 dichloromethane–methanol) afforded a colorless oil (0.33 g, 64%). To this compound (0.2 g, 0.52 mmol) in ethyl acetate (10 mL) was added 6 N HCl (0.87 mL, 5.2 mmol). After stirring at rt for 30 min, the reaction mixture was concentrated in vacuo, quenched by adding excess $NaHCO_3$ (5 mL, sat.). Product isolation (ethyl acetate) followed by flash column chromatography (12:1 dichloromethane–methanol) gave a white solid **5** (0.12 g, 65%): ^1H NMR (400 MHz, CD_3OD) δ 2.3–2.7 (m, 8H), 3.66 (s, 2H), 3.71 (s, 2H), 6.67–6.75 (m, 2H), 6.85 (dt, 1H, $J = 8.6$, 3.2 Hz), 7.09 (dd, 1H, $J = 7.8$, 4.0 Hz), 7.24 (s, 1 H), 8.06 (dd, 1H $J = 7.8$, 1.5 Hz), 8.31 (dd, 1H, $J = 4.9$, 1.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 54.2, 54.4, 54.6, 63.7, 111.4, 116.6, 116.8, 117.4, 123.2, 127.8, 130.2, 133.2, 133.3, 135.2, 144.1, 149.9, 150.1, 166.0; MS (FAB) *m/z* 341 $(M+H)^+$. HRMS calcd for $C_{19}H_{22}FN_4O$ 341.1778, found 341.1778.

4.1.11. Methyl 4-fluoro-2-(methoxymethoxy)benzoate (5-1). A slurry of NaH (0.65 g, 25.6 mmol) in DMF (5 mL) was added dropwise to 4-fluorosalicylic acid (1 g, 6.4 mmol) in DMF (5 mL) in an ice bath. The reaction mixture was cooled to 0 °C and methoxymethyl chloride (1.95 mL, 25.62 mmol) was slowly added. After stirring at rt for 14 h, the mixture was filtered, and the filtrate was poured into NH_4Cl (sat.). Product isolation (ethyl

acetate) followed by flash column chromatography (5:1 hexane–ethyl acetate) yielded a colorless oil **5-1** (1.36 g, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 3H), 3.90 (s, 3H), 5.20 (s, 2H), 7.10–7.20 (m, 2H), 7.48 (dd, 1H, J = 8.8, 2.9 Hz); MS (EI) m/z 214 (M^+). HRMS calcd for $C_{10}H_{11}FO_4$ 214.0641, found 214.0647.

4.1.12. [4-Fluoro-2-(methoxymethoxy)phenyl]methanol (5-2). Compound **5-1** (1.4 g, 5.7 mmol) in THF (5 mL) was added to a slurry of $LiAlH_4$ (0.23 g, 5.7 mmol) in THF (20 mL) in an ice bath. After stirring at rt for 14 h, the reaction mixture was filtered and poured into NH_4Cl (sat.). Product isolation (ethyl acetate) followed by flash column chromatography (3:1 hexane–ethyl acetate) afforded a colorless oil **5-2** (0.5 g, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (br s, 1H), 3.46 (s, 3H), 4.65 (s, 2H), 5.14 (s, 2H), 6.89 (dt, 1H, J = 7.8, 3.0 Hz), 7.01 (dd, 1H, J = 9.0, 4.5 Hz), 7.07 (dd, 1H, J = 9.3, 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 60.8, 95.2, 132.0, 132.1, 150.80, 150.82, 156.26, 159.44; MS (EI) m/z 186 (M^+). HRMS calcd for $C_8H_7FO_2$ $(M-MeOH)^+$ 154.0430, found 154.0428.

4.1.13. 4-Fluoro-2-(methoxymethoxy)benzyl methanesulfonate ester (5-3). Methanesulfonyl chloride (0.33 mL, 4.24 mmol) was slowly added to a solution of the alcohol **5-2** (0.5 g, 3.53 mmol) and Et_3N (0.74 mL, 5.3 mmol) in CH_2Cl_2 (15 mL) in an ice bath. After stirring at rt for 30 min, the reaction mixture was treated with NH_4Cl (20 mL, sat.). Product isolation (ethyl acetate) followed by flash column chromatography (3:1 hexane–ethyl acetate) yielded a colorless oil **5-3** (0.66 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 3H), 3.49 (s, 3H), 5.19 (s, 2H), 5.28 (s, 2H), 6.99–7.06 (m, 1H), 7.09–7.15 (m, 2H); MS (FAB) m/z 265 $(M+H)^+$. HRMS calcd for $C_{10}H_{14}FO_5S$ 265.0628, found 265.0637.

4.1.14. 3-[4-(4-Fluoro-3-nitrobenzyl)piperazin-1-yl-methyl]-1*H*-pyrrolo[2,3-*b*]pyridine (6). The methanesulfonate ester **6-2** (1 g, 4.0 mmol) in CH_3CN (3 mL) was slowly added to a solution of **10** (0.44 g, 2.0 mmol) and Et_3N (0.56 mL, 4.0 mmol) in CH_3CN (30 mL) in an ice bath. The reaction mixture was refluxed overnight. Product isolation (ethyl acetate) followed by flash column chromatography (5:4:1 hexane–dichloromethane–methanol) afforded a yellow solid **6** (0.43 g, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (br s, 4H), 2.57 (br s, 4H), 3.49 (s, 2H), 3.52 (s, 2H), 7.09 (dd, 1H, J = 6.4, 4.0 Hz), 7.21 (dd, 1H, J = 8.8, 7.0 Hz), 7.26 (s, 1H), 7.57 (m, 1H), 8.01 (dd, 1H, J = 6.0, 1.6 Hz), 8.06 (dd, 1H, J = 6.0, 0.8 Hz), 8.30 (d, 1H, J = 3.2 Hz), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 53.7, 61.4, 116.1, 118.3, 118.4, 120.7, 124.5, 126.2, 128.3, 135.9, 137.6, 143.3, 149.0, 153.7, 155.8; MS (FAB) m/z 370 $(M+H)^+$. HRMS calcd for $C_{19}H_{21}FN_5O_2$ 370.1679, found 370.1680.

4.1.15. (4-Fluoro-3-nitrophenyl)methanol (6-1). Borane (1 M in THF, 64 mL, 64 mmol) was added dropwise to 4-fluoro-3-nitrobenzoic acid (5 g, 32 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 1 h. Product isolation (ethyl acetate) followed by flash column chromatography (2:1 hexane–ethyl acetate) gave a colorless oil **6-1** (4.3 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 2H), 7.28 (dd, 1H, J = 10.7, 8.6 Hz), 7.61–7.66 (m, 1H), 8.06 (dd, 1H, J = 7.1, 2.2 Hz); MS (EI) m/z 171 (M^+). HRMS calcd for $C_7H_6FNO_3$ 171.0332, found 171.0317.

4.1.16. 4-Fluoro-3-nitrobenzylmethanesulfonate ester (6-2). Methanesulfonyl chloride (2.5 mL, 31.6 mmol) was slowly added to a solution of **6-1** (3.6 g, 21.1 mmol) and Et_3N (5.9 mL, 42.1 mmol) in CH_2Cl_2 (60 mL) in an ice bath. After 30 min, the reaction mixture was treated with NH_4Cl (60 mL, sat.). Product isolation (ethyl acetate) followed by flash column chromatography (2:1 hexane–ethyl acetate) afforded a white solid **6-2** (5.04 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3H), 5.27 (s, 2H), 7.36 (dd, 1H, J = 10, 9.03 Hz), 7.7–7.8 (m, 1H), 8.13 (dd, 1H, J = 6.81, 2.19 Hz); MS (EI) m/z 249 (M^+). HRMS calcd for $C_8H_8FNO_5S$ 249.0107, found 249.0111.

4.1.17. 3-[4-(4-Fluoromethylbenzyl)piperazin-1-yl-methyl]-1*H*-pyrrolo[2,3-*b*]pyridine (7). 4-Fluoromethylbenzylmethanesulfonate ester (30 mg, 0.14 mmol)[30] and Et_3N (29 μL, 0.21 mmol) were added to **10** (30 mg, 0.14 mmol) in CH_3CN (3 mL). The reaction mixture was refluxed for 1 h. Product isolation (chloroform) followed by flash column chromatography (50:50 ethyl acetate–methanol) afforded **7** (40 mg, 85%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38–2.51 (m, 4H), 2.51–2.58 (m, 4H), 3.51 (s, 2H), 3.72 (s, 2H), 3.78 (s, 2H), 6.89–7.09 (m, 5H), 7.32 (s, 1H), 8.06 (dd, 1H, J = 6.0, 1.2 Hz), 8.30 (dd, 1H, J = 4.0, 1.2 Hz, J = 4.0 Hz), 9.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.2, 53.9, 62.9, 84.7, 111.5, 115.9, 116.3, 120.7, 124.3, 127.8, 128.4, 129.6, 135.1, 143.2, 149.2, 155.0, 157.0; MS (FAB) m/z 339 $(M+H)^+$. HRMS calcd for $C_{20}H_{24}FN_4$ 339.1985, found 339.1982.

4.1.18. 3-[4-(4-[^{18}F]Fluoromethylbenzyl)piperazin-1-ylmethyl]-1*H*-pyrrolo[2,3-*b*]pyridine ([^{18}F]7). 4-[^{18}F]Fluoromethylbenzylmethanesulfonate ester was synthesized by reacting 1,4-benzenedimethanol bismethanesulfonate ester (2 mg, 6.8 μmol) and nBu$_4$N[^{18}F]F (90 °C, 5 min), as described previously.[30] The progress of the reaction was monitored by radio-TLC. To the mixture were added **10** (5 mg, 32.1 μmol), Et_3N (4.6 μL, 32.5 μmol), CH_3CN (150 μL), and DMF (50 μL). The reaction mixture was heated at 130 °C for 15 min and then passed through a short plug filled with 0.5 cm silica gel and 0.5 cm Na_2SO_4 using a 9:1 mixture of CH_2Cl_2 and methanol. The eluate was concentrated under a stream of N_2 at 50 °C (water bath) and redissolved in 1 mL of a 70:30 mixture of 0.1 M NH_4CO_2H and CH_3OH. [^{18}F]**7** was purified on a HPLC column eluted with 100% 0.1 M NH_4CO_2H for 5 min, and then a 40:60 mixture of 0.1 M NH_4CO_2H and CH_3OH, at 4 mL/min. The desired fraction eluted at 28–30 min was collected for tissue distribution studies. Effective specific activity of [^{18}F]**7** was determined by using a standard curve obtained from **7** with different concentrations injected on HPLC versus UV absorbance at 254 nm. Another aliquot of [^{18}F]**7** was coinjected with unlabeled **7** into HPLC to confirm its identity.

4.2. Log *P* determinations

Log *P* values were calculated using the CLOPG program 3.05 implemented in Sybyl 6.5.

4.3. In vitro binding assay

4.3.1. Inhibition of [^{3}H]nemonapride binding to dopamine hD_{2L}, dopamine rD_3 and dopamine $hD_{4.4}$ receptors by various drugs. Binding assays were performed using a modification of a method previously described by Hidaka et al.[27] Briefly, on the day of the experiment, frozen membranes (Sf-9-hD_{2L}, Sf-9-rD_3 or CHO-$hD_{4.4}$) were thawed on ice and homogenized in 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1.5 mM $CaCl_2$, and 5 mM EDTA. The membranes were suspended to final concentrations of 40, 24 or 40 μg protein/tube for dopamine hD_{2L}, rD_3, and $hD_{4.4}$ receptors, respectively. Protein concentrations were determined by using the method of Lowry et al. with a bovine serum albumin standard.[33]

To determine hD_{2L}, rD_3 and $hD_{4.4}$ binding, each sample was incubated for 60 min at 25 °C with various concentrations of competing ligands (10^{-10}–10^{-4} M) and radioligand (20, 50 or 200 pM [^{3}H]nemonapride) in 0.5, 0.5, or 2 mL of 50 mM Tris–HCl buffer (pH 7.4), respectively, containing 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1.5 mM $CaCl_2$, and 5 mM EDTA. Nonspecific binding was estimated in the presence of 100 μM haloperidol for all receptors. The reaction was terminated by rapid filtration through Whatman GF/B filters presoaked in ice-cold 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl. Filters were rinsed four times with 4 mL of the washing buffer containing 50 mM Tris–HCl and 120 mM NaCl (pH 7.4). Radioactivity bound to the filter was measured using a liquid scintillation counter (Tricarb 2500, Packard, Meriden, CT) and 8 mL of scintillation fluid (ACS II, Amersham).

Binding data were analyzed using the LIGAND curve-fitting computer program (Elsevier-Biosoft, Cambridge, UK). IC_{50} values were derived from the calculated curves and converted to K_i values as described previously.[34] To calculate K_i we used the K_D value for [^{3}H] nemonapride as determined by Hidaka et al.[27]

4.4. Tissue distribution studies

Radioligand [^{18}F]**7** collected from HPLC was concentrated, redissolved in ethanol, and diluted with saline to give a final solution of 10% ethanol in saline. Male ICR mice (25–30 g, 4 mice per time point) were injected with the radioligand (2.5 MBq) in 0.2 mL of 10% ethanol–saline via a tail vein. At the indicated time points (5, 15, 30, 45, 60, 90, 120 and 180 min), the mice were sacrificed by cervical dislocation. Samples of bone and brain tissue (cerebellum, striatum, olfactory tubercle, frontal cortex, parietal cortex, hypothalamus, hippocampus, and thalamus) were removed, weighed, and counted. The data obtained are expressed as percent injected dose per gram of tissue (%ID/g).

Acknowledgements

We are grateful to Mr. S. H. Hwang for performing the tissue distribution studies. This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (02-PJ3-PG6-EV06-0002) (B.T.K.) and by a grant from National Research Laboratory Program, Korea (D.Y.C.).

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