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A Series of ^{18}F-Labelled Pyridinylphenyl Amides as Subtype-Selective Radioligands for the Dopamine D3 Receptor

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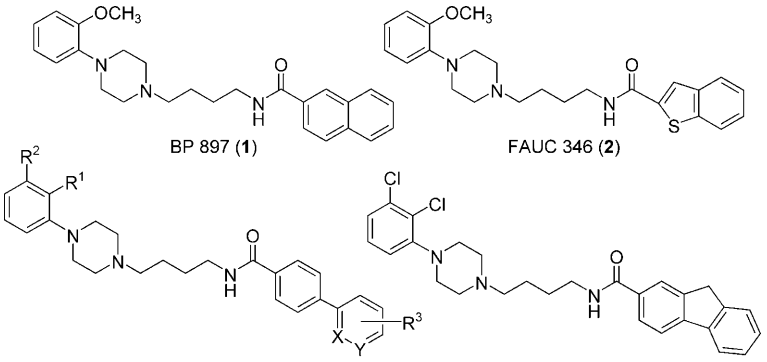
Synthesis, biological activity, and structure–selectivity relationship (SSR) studies of a novel series of potential dopamine D3 receptor radioligands as imaging agents for positron emission tomography (PET) are reported. Considering a structurally diverse library of D3 ligands, SSR studies were performed for a new series of fluorinated pyridinylphenyl amides using CoMFA and CoMSIA methods. The in vitro D3 affinities of the predicted series of biphenyl amide ligands **9a**–**d** revealed single-digit to sub-nanomolar potencies (K_i = 0.52–1.6 nM), displaying excellent D3 selectivity over the D2 subtype of 110- to 210-fold for the test compounds **9a**–**c**. Radiofluorination by nucleophilic substitution of Br or NO_2 by ^{18}F led to radiochemical yields of 66–92% for [^{18}F]**9a**–**d**. However, the specific activities of [^{18}F]**9b** and [^{18}F]**9d** were insufficient, rendering their use for in vivo studies impossible. Biodistribution studies of [^{18}F]**9a** and [^{18}F]**9c** using rat brain autoradiography revealed accumulation in the ventricles, thus indicating insufficient biokinetic properties of [^{18}F]**9a** and [^{18}F]**9c** for D3 receptor imaging in vivo.

Introduction

Dopaminergic neurotransmission plays an important role in various physiological processes. Correspondingly, it is implicated in the pathogenesis of a variety of diseases including extrapyramidal movement disorders such as Parkinson's disease and psychiatric illnesses such as schizophrenia or drug addiction.[1–3]

Dopamine receptors can be differentiated into the five subtypes D1–D5. Among these, the D2 subtype has received most attention owing to its essential role in the nigrostriatal axis. However, knowledge of the physiological and pathophysiological roles of the other subtypes is rapidly evolving. In particular, research has focused on the D3 subtype, as disturbances of its expression and/or activity seem to play a role in emotional functions associated with reward, behavioural reinforcement, and craving.[4,5] The D3 receptor is a therapeutic target for a variety of diseases including schizophrenia, depression, and Parkinson's disease.[6–8] In rats, the D3 receptor is expressed at high density in the granule cells of the islands of Calleja and in the olfactory bulb; moderate density is observed in the nucleus accumbens.[9–14] Selective D3 receptor partial agonists and antagonists have been investigated as potential drug abuse therapeutic agents,[15,16] as nonselective dopaminergic ligands appeared to induce unwanted side effects.

In the past few years, a variety of structural analogues of D3 receptor ligands have been developed to improve the D3 receptor affinity, while simultaneously increasing their D3 selectivity over the interfering D2 subtype.[3,17–21] Most of these studies were based on D3-selective lead compounds such as BP 897 (**1**), FAUC 346 (**2**), CJB 090 (**3a**), or NGB 2904 (**4**).[6,22–24] In 1999, BP 897 received great attention as it was first reported to be effective in the treatment of cocaine abuse.[6] Compared to the partial agonist BP 897 (**1**), FAUC 346 (**2**) differs by a ben-



3a: R^1=Cl, R^2=Cl, R^3=6-H, X=N, Y=CH (CJB 090)
3b: R^1=MeO, R^2=H, R^3=6-F, X=CH, Y=N
3c: R^1=MeO, R^2=H, R^3=6-F, X=N, Y=CH
3d: R^1=Cl, R^2=H, R^3=6-H, X=CH, Y=CH

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zothiophene ring system instead of the naphthyl moiety. Notably, FAUC 365, the 2,3-dichlorophenylpiperazinyl analogue of **2**, was described as a D3 antagonist with a 7200-fold selectivity over the D2 receptor.[22] Furthermore, the aryl amide functional group also revealed increased D3 selectivity when extended to a diaryl ring system as reported for CJB 090 (**3a**) and **3d**, representing less lipophilic analogues of the first-generation D3 antagonist NGB 2904 (**4**).[17,25]

D3 receptor subtype selectivity, optimal affinity, and decreased lipophilicity are some of the most important prerequisites for a successful D3 radioligand suitable for in vivo imaging applications. Positron emission tomography (PET) has emerged as a highly sensitive imaging method, which would allow new insight into the role of the D3 receptor subtype in the pathophysiology of various psychiatric diseases. However, the lack of bioavailable D3-selective radioligands for PET, which exclude cross talk with the strongly related subtypes D2 and D4, thus far hampers the noninvasive investigation of the D3 receptor by PET.

To overcome this drawback, FAUC 346 (**2**) has been labelled with the positron emitters carbon-11 and fluorine-18.[26,27] The ^{11}C-labelled candidate has been studied in vivo and revealed specific uptake in the rat brain, however, the regional brain distribution has not yet been determined. Despite the promising results in the rat model, ^{11}C-labelled FAUC 346 failed as a suitable PET radioligand for imaging of D3 receptors in baboon, as the intravenous injection of BP 897 did not affect the brain uptake of the radioligand.[26] Furthermore, the ^{11}C-labelled imidazo[2,1-*b*]thiazolylpiperazine derivative RGH 1756 also indicated an insufficiently low signal for specific D3 binding in vivo, possibly due to the presence of competing endogenous dopamine.[28] Recently, the naphthoxazine [^{11}C](+)-PHNO, a D2/D3 agonist radioligand, has been discovered to act as a D3 receptor preferring radioligand in vivo, as indicated by its specific binding in the globus pallidus, thereby reflecting the D3 receptor distribution more accurately than the nonselective D2/D3 radioligand [^{11}C]raclopride.[29–32] However, the ^{18}F-labelled derivative of PHNO did not show specific binding in D3-rich brain areas in vivo.[33] In summary, it is tempting to speculate that at least some of the D3 radioligand candidates probably failed because of their high lipophilicity resulting in significant nonspecific binding when employed in vivo. Another reason for the failure of partial agonist radioligands could be an insufficient D3 receptor affinity preventing efficient competition with the endogenous agonist dopamine.

Moreover, the clearance of promising D3-selective radioligands, such as [^{11}C](+)-PHNO, in distinct brain regions is relatively slow.[32] Therefore, a radioligand with a longer half-life than C-11 (20 min) would provide a favourable adjustment of biokinetics and physical half-life of the tracer. The availability of a suitable ^{18}F-labelled D3 radioligand with the half-life of 110 min would facilitate prolonged PET scanning times in the clinical setting and would also provide the option to distribute the radioligand within longer distances for external clinical application.

Based on our work on SAR studies guiding the development of D3-selective lead compounds,[3,34,35] we recently reported two ^{18}F-substituted pyridinylphenyl amides (**3b,c**) as analogues of the lead compound CJB 090, that displayed high affinities at the D3 receptor [K_i = 0.37 nM (**3c**) and K_i = 0.45 nM (**3b**)], while having moderate affinity to D2 [K_i = 16 nM (**3c**) and K_i = 12 nM (**3b**)].[35] In the present work we extended this series of compounds and evaluated the D3 binding specificity of their ^{18}F-labelled versions in vivo. We describe the influence of structural changes on a focused library of fluorinated pyridinylbenzamides that were predicted for adequate D3 selectivities and affinities by using CoMFA and CoMSIA methods. In this study, we changed the substitution pattern of the phenylpiperazinyl moiety introducing the 2-chloro and 3-chloro-2-methoxy substitution pattern in the phenylpiperazinyl group and varied the position of the fluorine substituent at the pyridinyl moiety. Furthermore, the predicted D3 selectivities of the new series of compounds **9a–d** were compared with experimental data derived from in vitro binding studies using dopamine receptor subtype-expressing Chinese hamster ovary cells (CHO). Herein we report the syntheses of the radioligands [^{18}F]**9a–d**, their unlabelled reference compounds **9a–d** and the appropriate bromo or nitro precursors **10a–d** for ^{18}F-fluorination. After selection of promising radioligand candidates ([^{18}F]**9a** and [^{18}F]**9c**), their in vivo binding behaviour was assessed by rat brain autoradiography.

Results and Discussion

Prediction of D3-selective PET tracers

In our previous work, we successfully established CoMFA and CoMSIA models which allowed us a precise prediction of D3 affinity and selectivity over both congeners $D2_{long}$ and D4.[35,36] On this basis, the selectivities of the proposed structures **9a–d** were calculated. The results are listed in Table 1, indicating pK_i differences expressed as $\Delta\log(K_i(D3)/K_i(D2_{long}))$ and $\Delta\log(K_i(D3)/K_i(D4))$ values. Employing the CoMFA and CoMSIA models, the compounds **9a–c** were predicted to have high D3 subtype selectivity, as determined by the deviation of theoretical from experimental values (Table 1).

Chemistry

Following the synthetic strategy that has been proven to be efficient and reliable in our previous studies,[18,37] we achieved

Table 1. Experimental and predicted selectivities of compounds **9a–d**.

Compd	D_3/D_2 (exp.)[a]	$\Delta D_3/D_2$[b]		D_3/D_4 (exp.)[a]	$\Delta D_3/D_4$[b]	
		CoMFA	CoMSIA		CoMFA	CoMSIA
9a	2.32	−0.02	0.21	2.47	0.39	−0.39
9b	2.07	−0.53	−0.20	2.56	0.23	−0.20
9c	2.05	−0.42	−0.01	2.05	0.12	−0.07
9d	1.68	−0.95	−0.30	2.20	−0.03	−0.02

[a] Expressed as pK_i differences (see also Table 2). [b] $\Delta(D_3/D_2)$ and $\Delta(D_3/D_4)$ are defined as the difference between experimental and calculated selectivities; the calculated selectivities are expressed as $-\log(K_i(D3)/K_i(D2_{long}))$ and $-\log(K_i(D3)/K_i(D4))$, respectively.

the series of target ligands as shown in Scheme 1. Starting from commercially available 2-chlorophenylpiperazine (**6a**) and 3-chloro-2-methoxyphenylpiperazine (**6b**), which was synthesised by nucleophilic displacement of 1,3-dichloro-2-methoxybenzene (**5**) with piperazine,[38] the nitriles **7a**,**b** were obtained in good yields by alkylation with 4-bromobutyronitrile. Reduction of the resulting arylpiperazinylbutyronitriles **7a**,**b** with $LiAlH_4$ proceeded in good yield to provide 4-[4-(2-chlorophenyl)piperazin-1-yl]butyl-1-amine (**8a**) and 4-[4-(3-chloro-2-methoxyphenyl)piperazin-1-yl]butyl-1-amine (**8b**), respectively. Finally, the compounds of interest were prepared by dicyclohexylcarbodiimide (DCC) coupling of the amines **8a**, **b** with the appropriate fluoropyridinylbenzoic acids, providing the amides **9a**–**d** in yields of 43–72%. The precursors **10a**–**d** were prepared using the same course of synthesis, by coupling of **8a**, **b** with the appropriate bromo and nitropyridinylbenzoic acids to give the amides **10a**–**d** in yields of 52–79%.

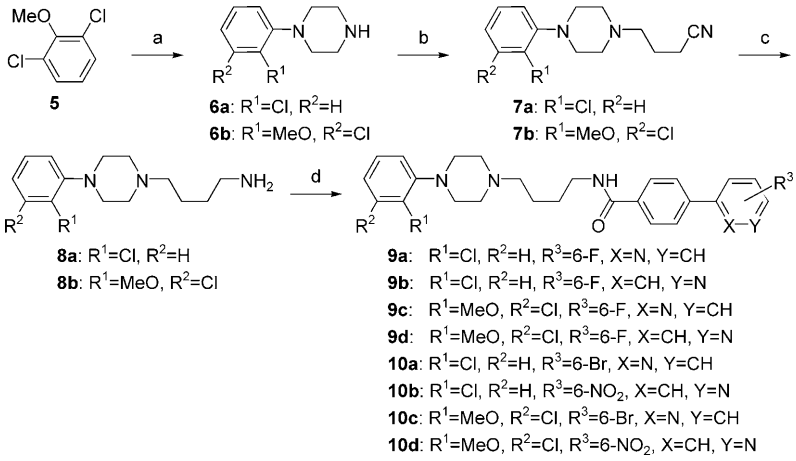
pressed in CHO cells and the radioligand [^{3}H]spiperone.[39–42] Furthermore, affinities to the serotonin receptors 5-HT_{1A}, 5-HT_2, and the adrenergic α1 receptor were determined using porcine cortical membranes and the selective radioligands [^{3}H]WAY 100635, [^{3}H]ketanserin and [^{3}H]prazosin, respectively.[43]

As displayed in Table 2, all test compounds (**9a**–**d**) showed excellent D3 binding with K_i values in the single-digit or even sub-nanomolar range. Depending on the substitution pattern at the phenylpiperazine moiety, the 3-chloro-2-methoxy substituted analogues **9c**, **d** show K_i values of 1.6 and 1.4 nM, respectively, whereas the 2-chlorophenylpiperazinyl derivatives **9a**, **b** bind to the D3 receptor with sub-nanomolar K_i values of 0.58 and 0.52 nM, respectively. In terms of subtype selectivity expressed as K_i(D3)/K_i($D2_{long}$), compounds **9a**–**c** demonstrated high D3 selectivity of 110- to 210-fold over D2 (Table 2). This observation could be ascribed to the variation of the substitution pattern at the pyridinyl moiety, revealing an influence on D2 receptor recognition. The 6-fluoropyridin-2-yl benzamide substitution in **9a** and **9c** decreased the affinity to the D2 receptor by two to threefold, thereby resulting in an increased D3 subtype selectivity when compared with their corresponding structural isomers **9b** and **9d**, respectively (Table 2). These results indicate that the structural modifications successfully induced decreased D2 affinity and therefore could be used to obtain ligands with improved D3 subtype selectivity.

Table 2. Binding affinities of the fluorinated compounds **9a**–**d** to the human dopamine receptor subtypes $D2_{long}$, $D2_{short}$, D3, and D4, the porcine D1, and the porcine 5-HT_{1A}, 5-HT_2, and α1 receptors.

Compd	K_i [nM][a]							
	[^{3}H]SCH 23390	[^{3}H]spiperone[b]				[^{3}H]WAY 100635	[^{3}H]ketanserin	[^{3}H]prazosin
	D1	$D2_{long}$	$D2_{short}$	D3	D4.4	5-HT_{1A}	5-HT_2	α_1
9a	270[c]	120[c]	42	0.58[d]	170	160	230	8.0
9b	340	61	22	0.52[d]	190	140	170	4.8
9c	2400	180	62	1.6	180	270	180	44
9d	15000[c]	67	32	1.4	220	270	93	21

[a] Values reflect the means of two or three experiments, each done in triplicate; SD < 35%. [b] $D2_{long}$ and $D2_{short}$ are two isoforms of the D2 receptor. [c] SD > 35% and < 50%. [d] SEM < 20%.



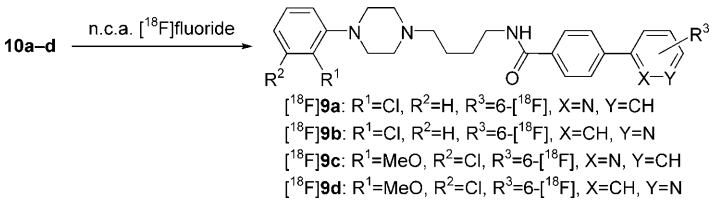
Scheme 1. Synthesis of **9a**–**d** and **10a**–**d**. Reagents and conditions: a) piperazine, toluene, $Pd(OAc)_2$, (*o*-biphenyl)P(*t*Bu)$_2$, NaO*t*Bu, 80 °C, 21 h (see ref. [38]); b) 4-bromobutyronitrile, DMF, 100 °C, 5 h (see ref. [18]); c) $LiAlH_4$, THF, 0 °C→reflux, 5 h; d) 4-(6-bromopyridin-2-yl)benzoic acid or 4-(6-nitropyridin-3-yl)benzoic acid or 4-(6-fluoropyridin-2-yl)benzoic acid or 4-(6-fluoropyridin-3-yl)benzoic acid, DCC, DMAP, CH_2Cl_2, room temperature, overnight.

Receptor binding experiments and data analysis

Radioligand displacement experiments were conducted to evaluate the binding profiles of the fluorinated ligands **9a**–**d**. Receptor binding to the dopamine D1 receptor was measured using membrane preparations from porcine striatum and the subtype-selective radioligand [^{3}H]SCH 23390.[39] Binding experiments with the human subtypes $D2_{long}$, $D2_{short}$, D3, and D4.4 were performed employing the cloned receptors stably ex-

Radiochemistry

The introduction of fluorine-18 via nucleophilic aromatic substitution was performed by exchanging bromine or a nitro group at the pyridinyl benzamide site, following the reaction conditions described previously.[35] The radiosyntheses of [^{18}F]**9a**–**d** are shown in Scheme 2. The nitro precursors **10b**, **d** and the bromo precursors **10a**, **c** were synthesised as depicted in Scheme 1. The radiofluorination of the nitro and bromo precursor (8 μmol) was performed at 140 °C in DMF as solvent for a reaction time of 30 min. The radiolabelled product was ana-



Scheme 2. Nucleophilic aromatic substitution: DMF (500 μL), precursor **10a–d** (8 μmol), 140 °C, n.c.a.[^{18}F]fluoride (50–70 MBq), PTC: Kryptofix 2.2.2, K_2CO_3; $t = 30$ min.

lysed by gradient reversed-phase radio-HPLC. The radiochemical identities of [^{18}F]**9a–d** were verified by co-elution of the radioactive peak with the respective reference compound **9a–d**. The k' values of the reference fluoro compounds are listed in Table 3. The radiochemical yields (RCY) of the ^{18}F-labelled compounds [^{18}F]**9a–d** ranged between 66 and 92%. No significant differences in the RCY were identified by varying the substitution pattern of the arylpiperazine. By changing the leaving group from nitro to bromo, a decreased RCY of more than 25% was observed, most likely attributable to the high Hammett constant of the nitro group,[44] indicating that nitro is a more suitable leaving group for aromatic substitution than bromine. However, the separation of the nitro precursors **10b** and **10d** from the respective ^{18}F-labelled radioligands, [^{18}F]**9b** and [^{18}F]**9d**, by HPLC turned out to be challenging. As a result we were unable to obtain [^{18}F]**9b** and [^{18}F]**9d** with high specific activity, rendering the use of [^{18}F]**9b** and [^{18}F]**9d** for further in vivo studies impossible.

Table 3. Radiochemical yields (RCY) using the precursor compounds **10a–d** and k' values of the corresponding radioligands [^{18}F]**9a–d** and analytical data for [^{18}F]**9a–d**.

Precursor	Leaving group	RCY [%][a]	k' [min][b]	Clog$P$[c]	log$D_{7.4}$
10a	Br	67 ± 4, [^{18}F]**9a**	2.43, [^{18}F]**9a**	4.60	2.88
10b	NO_2	92 ± 2, [^{18}F]**9b**	2.28, [^{18}F]**9b**	4.39	1.91
10c	Br	66 ± 5, [^{18}F]**9c**	2.55, [^{18}F]**9c**	4.20	2.45
10d	NO_2	90 ± 2, [^{18}F]**9d**	2.40, [^{18}F]**9d**	3.99	1.77

[a] 500 μL DMF, 8 μmol precursor, n.c.a.[^{18}F]fluoride (50–70 MBq), Kryptofix 2.2.2, K_2CO_3, 30 min, 140 °C. [b] k' values from HPLC System A. [c] Clog$P$ calculated by the software Clog$P$ (BioByte Corp.).

As **9a** and **9c** showed favourable selectivity for the D3 subtype and excellent sub-nanomolar D3 affinity, we decided to perform further in vitro and a comparative in vivo experiment with the ^{18}F-labelled radioligands [^{18}F]**9a** and [^{18}F]**9c**. For these studies, [^{18}F]**9a** and [^{18}F]**9c** were isolated by semipreparative HPLC and solid-phase extraction methods that allowed formulation of each radioligand in an injectable solution.

Lipophilicity and stability in human serum

The lipophilicity of radioligands plays an important role for adequate brain uptake, the distribution of the tracer, and its metabolism and elimination.[45] As a measure of lipophilicity, the log$P$ value is defined by the octanol/water partition coefficient, that is, the ratio of the concentration of the test compounds in the octanol phase and in water at neutral pH. The lipophilicities of **9a–d** were calculated using the software Clog$P$ (Table 3). The experimental octanol/buffer partition coefficient (log$D_{7.4}$; measured with PBS as aqueous phase, pH 7.4) of [^{18}F]**9a–d** were experimentally determined to range between 1.77 and 2.88 (Table 3), suggesting an adequate penetration of the blood–brain-barrier for further in vivo use. The calculated log$P$ value (Clog$P$) and log$D_{7.4}$ differ significantly, most likely due to the presence of the partly protonated piperazine at pH 7.4. Moreover, we proved the stability of [^{18}F]**9a** against metabolism by serum enzymes. Incubation in human serum and HPLC analysis showed the excellent stability of [^{18}F]**9a** (Figure 1).

In vivo experiments using rat brain autoradiography

The regional brain distribution of [^{18}F]**9a** and [^{18}F]**9c**, respectively, was determined by ex vivo autoradiography of rat brain slices after intravenous injection of the tracer into the tail vein of isofluorane-anaesthetised rats alone and in combination with the D3-selective ligand BP 897 (1 mg kg^{-1}), to test for specific receptor binding. Rats were sacrificed by decapitation 60 min post-injection. In Figure 2 the autoradiography and histology of the rat brain slices of [^{18}F]**9a** and [^{18}F]**9c** are shown. Stanwood et al. previously described the regional distribution of the D3 receptor in the rat brain by quantitative autoradiography using [^{125}I]7-OH-PIPAT.[46] These authors showed that D3 receptors in the rat brain are located

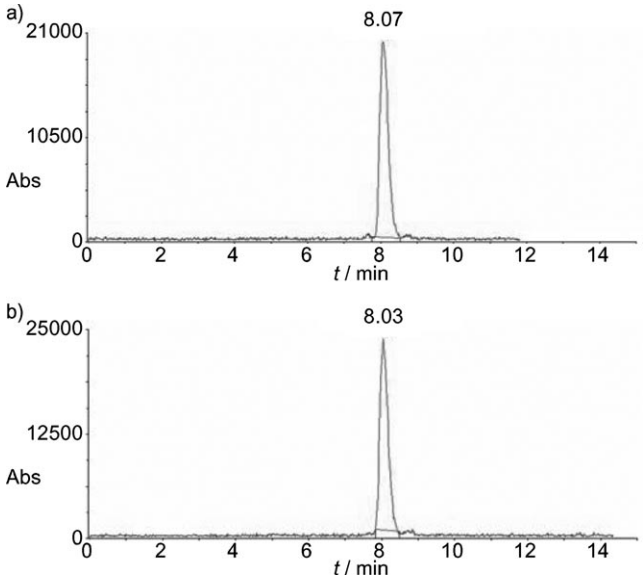


Figure 1. Determination of stability of [^{18}F]**9a** after incubation in human serum for 60 min at 37 °C. HPLC analysis of a) treated [^{18}F]**9a** in comparison with that of b) pure [^{18}F]**9a** (HPLC conditions: see Experimental Section).

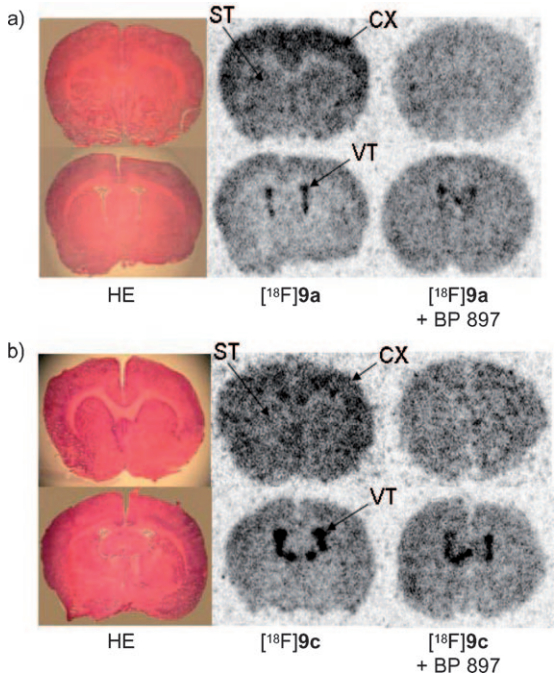


Figure 2. Effects of a) [^{18}F]**9a** and b) [^{18}F]**9c**. Left columns: haematoxylin/eosin (HE) staining and rat brain autoradiography obtained from representative striatal slices and slices containing the brain ventricles (ST = striatum, CX = cortex, VT = ventricle). Center columns: autoradiography of rat brain slices 60 min after intravenous injection of [^{18}F]**9a** (10.4 MBq) or [^{18}F]**9c** (7.3 MBq). Right columns: corresponding rat brain slices obtained from animals co-injected with BP 897 (1 mg kg^{-1}) and [^{18}F]**9a** (13.9 MBq) or [^{18}F]**9c** (6.1 MBq).

in the nucleus accumbens, the islands of Calleja, the ventral pallidum and, to a lower extent, the caudate putamen (striatum). In comparison, our results show that we could detect a low specific uptake of [^{18}F]**9a** and [^{18}F]**9c** in the striatum (Figure 2), however, a specific signal in other D3 receptor reference regions was not visible. Besides low striatal binding, [^{18}F]**9a** and [^{18}F]**9c** specifically accumulated in the cortex. Moreover, our experiments show a significant nonspecific accumulation of both radioligands in the ventricles, the ependyma cells or plexus tissue (Figure 2). This finding could be due to rapid and specific transport of [^{18}F]**9a** and [^{18}F]**9c** into these tissue compartments, most likely mediated by transporters, such as polyamine transporters, that could be capable of specifically recognising the diaryl amides under investigation. Further studies are necessary to characterise this phenomenon in more detail.

Conclusions

Compounds **9a–d** were identified as a new series of fluoro-substituted diaryl amides derived from **3b,c** with substantial D3 receptor affinity. The SAR established the importance of the arylpiperazine moiety. Changing the substitution pattern on the arylpiperazine did not influence the binding affinity to the D3 receptor, whereas it decreased the affinity for D2 receptors. Compounds **9a–c** had a favourable in vitro binding profile indicated by high affinity to the D3 receptor and superior selectivity for D3 over D2. In vivo studies with [^{18}F]**9a** and [^{18}F]**9c** using rat brain autoradiography did not reveal an intracerebral distribution of the radioligand in accordance with the known distribution of the D3 receptor within this species. Besides a low signal of specific binding in cortical and striatal brain areas, no specific uptake was observed in the known D3 receptor-rich reference regions. Instead, we observed a significant accumulation of [^{18}F]**9a** and [^{18}F]**9c** within the brain ventricles, suggesting biological properties for these radioligands such as binding to interfering receptors or proteins in ventricular compartments, that impedes specific binding in D3 receptor-rich areas for in vivo imaging applications.

Experimental Section

General

Commercial reagents were used as received without additional purification. [^{18}F]Fluoride was supplied by PET Net GmbH (Erlangen, Germany). Purifications of experimental compounds were performed by column chromatography using silica gel 60. Radio HPLC analysis of [^{18}F]**9a–d** was performed on a Hewlett Packard (HP 1100) with a quaternary pump and variable wavelength detector (HP 1100) and the radiodetector D505TR (Canberra Packard).

System A: (analysis of [^{18}F]**9a–d**): Chromolith RP18, 100×4.6 mm column, eluted with CH_3CN/H_2O (0.1% TFA), 10:90 (*v*/*v*) to 100% CH_3CN (0.1% TFA) over 5 min, flow rate: 4.0 mL min^{-1}.

System B: (preparative separation of [^{18}F]**9a**): Kromasil C_8, 125×8 mm, 5 μm column, eluted with CH_3CN/H_2O (0.1% TFA), 40:60 (*v*/*v*), flow rate: 4.0 mL min^{-1}.

^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker AM 360 or a Bruker Avance spectrometer in solution. Proton chemical shifts (δ) are reported in parts per million (ppm) downfield from $(CH_3)_4Si$ (0.00 ppm) as an internal standard. Chemical shifts for ^{13}C NMR spectra are reported as δ values relative to the deuterium triplet signal of the solvent ($CDCl_3$, 77.5 ppm). HR-EIMS were run on a Finnigan MAT TSQ 70 instrument using peak matching ($M/\Delta M$ = 10000).

Chemistry

In previous studies, we have described the synthesis and analytical data of biarylcarboxylic acids using Suzuki coupling, starting from 4-carboxybenzene boronic acid with the corresponding bromo-substituted pyridine derivatives, in 43–67% yields.[35] The synthesis and analytical data of 4-[4-(2-chlorophenyl)piperazin-1-yl]butyl-1-amine (**8a**) and 4-[4-(3-chloro-2-methoxyphenyl)piperazin-1-yl)butyl-1-amine (**8b**) have been described previously.[43,47] In brief, the *N*-phenylpiperazines **6a**, **b** were converted into the alkylnitrile derivatives **7a**,**b** by alkylation with 4-bromobutyronitrile and subsequent reduction with $LiAlH_4$ in THF affording the primary amines **8a**,**b** in very good yield.

General procedure for synthesis of compounds 9a–d and 10a–d

N,*N*-dimethylpyridine-4-amine (DMAP, 1.3 equiv), dicyclohexylcarbodiimide (DCC, 1.3 equiv), and the corresponding carboxylic acids (1 equiv) were added to a solution of 4-[4-(2-chlorophenyl)piperazin-1-yl]butan-1-amine (**8a**, 1 equiv) or 4-[4-(3-chloro-2-methoxy-

phenyl)piperazin-1-yl]butyl-1-amine (**8b**, 1 equiv) in dry CH_2Cl_2 (15 mL) under Ar atmosphere. The mixture was stirred at room temperature overnight. After filtration of the precipitate, the remaining solution was washed with H_2O (2×20 mL) and brine (20 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure to get a residue of crude product. Subsequent column chromatography (CH_2Cl_2/MeOH; 9:1) gave each compound **9a–d**, **10a–d** in yields of 43–79%.

***N*-[4-[4-(2-Chlorophenyl)piperazin-1-yl]butyl]-4-(6-fluoropyridin-2-yl)benzamide (9a).** Compound **9a** was prepared by coupling of 4-[4-(2-chlorophenyl)piperazin-1-yl]butyl-1-amine (**8a**) and 4-(6-fluoropyridin-2-yl)benzoic acid according to the general procedure. Yield: 72%; ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.49–1.55 (m, 2H), 1.59 (td, J = 13.7, 6.7 Hz, 2H), 2.27–2.37 (m, 2H), 2.49 (s, 4H), 2.85 (d, J = 57.53 Hz, 4H), 3.37 (dd, J = 12.4, 6.7 Hz, 2H), 6.76 (dd, J = 8.1, 2.7 Hz, 1H), 6.79–6.87 (m, 2H), 7.01–7.07 (m, 1H), 7.21 (dd, J = 7.9, 1.5 Hz, 1H), 7.26 (q, J = 5.6 Hz, 1H), 7.49 (dd, J = 7.5, 2.1 Hz, 1H), 7.67–7.73 (m, 1H), 7.75–7.79 (m, 2H), 7.87–7.93 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 24.24, 27.28, 39.86, 50.73, 53.08, 57.86, 108.09, 108.34, 117.49, 120.14, 123.47, 126.78, 127.35, 128.47, 130.38, 135.63, 139.76, 141.66, 141.71, 148.94, 154.70, 154.79, 162.37, 163.95, 167.13 ppm; HRMS calcd for $C_{26}H_{28}ClFN_4O$ [M^+]: 466.1936, found: 466.1936.

***N*-[4-[4-(2-Chlorophenyl)piperazin-1-yl]butyl]-4-(6-fluoropyridin-3-yl)benzamide (9b).** Compound **9b** was prepared from 4-[4-(2-chlorophenyl)piperazin-1-yl]butyl-1-amine (**8a**) and 4-(6-fluoropyridin-3-yl)benzoic acid according to the general procedure. Yield: 47%; ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.67 (ddd, J = 10.5, 9.2, 4.1 Hz, 2H), 1.70–1.76 (m, 2H), 2.48 (t, J = 7.1 Hz, 2H), 2.64 (s, 4H), 3.03 (s, 4H), 3.51 (dd, J = 12.3, 6.6 Hz, 2H), 6.95 (dd, J = 3.0, 1.6 Hz, 1H), 6.96 (dd, J = 3.6, 1.4 Hz, 1H), 7.01 (dd, J = 8.5, 2.5 Hz, 1H), 7.17 (ddd, J = 8.0, 7.4, 1.5 Hz, 2H), 7.31–7.34 (m, 1H), 7.54–7.58 (m, 2H), 7.88–7.92 (m, 2H), 7.95 (ddd, J = 8.4, 7.6, 2.6 Hz, 1H), 8.39 ppm (d, J = 2.62 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 24.28, 27.34, 39.94, 50.84, 53.19, 57.92, 109.42, 109.67, 120.12, 123.59, 126.92, 127.42, 127.82, 128.59, 130.49, 133.65, 134.57, 139.25, 139.61, 139.66, 145.72, 145.81, 148.95, 162.46, 164.06, 166.98 ppm; HRMS calcd for $C_{26}H_{28}ClFN_4O$ [M^+]: 466.1936, found: 466.1936.

***N*-[4-[4-(3-Chloro-2-methoxyphenyl)piperazin-1-yl]butyl]-4-(6-fluoropyridin-2-yl)benzamide (9c).** Compound **9c** was prepared from 4-[4-(3-chloro-2-methoxyphenyl)piperazin-1-yl]butyl-1-amine (**8b**) and 4-(6-fluoropyridin-2-yl)benzoic acid according to the general procedure. Yield: 69%; ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.62–1.68 (m, 2H), 1.69–1.74 (m, 2H), 2.45 (dd, J = 16.3, 9.3 Hz, 2H), 2.58 (s, 4H), 3.08 (s, 4H), 3.50 (dd, J = 12.3, 6.7 Hz, 2H), 3.82–3.86 (m, 3H), 6.70–6.76 (m, 1H), 6.87–6.93 (m, 2H), 6.97 (dt, J = 8.0, 2.1 Hz, 1H), 7.03 (t, J = 5.4 Hz, 1H), 7.62 (dd, J = 7.5, 2.1 Hz, 1H), 7.83–7.87 (m, 3H), 8.02–8.03 (m, 1H), 8.03–8.05 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 24.41, 27.39, 40.00, 50.00, 53.64, 58.02, 58.89, 108.26, 108.51, 117.00, 117.59, 123.15, 124.53, 126.92, 127.44, 128.60, 135.75, 141.74, 141.79, 146.47, 148.55, 154.87, 154.96, 162.53, 164.11, 167.19 ppm; HRMS calcd for $C_{27}H_{30}ClFN_4O_2$ [M^+]: 496.2041, found: 496.2041.

***N*-[4-[4-(3-Chloro-2-methoxyphenyl)piperazin-1-yl]butyl]-4-(6-fluoropyridin-3-yl)benzamide (9d).** Compound **9d** was prepared from 4-[4-(3-chloro-2-methoxyphenyl)piperazin-1-yl]butyl-1-amine (**8b**) and 4-(6-fluoropyridin-3-yl)benzoic acid according to the general procedure. Yield: 43%; ^{1}H NMR (360 MHz, $CDCl_3$) δ = 1.64–1.76 (m, 4H), 2.43–2.51 (m, 2H), 2.62 (s, 4H), 3.10 (s, 4H), 3.52 (dd, J = 12.2, 6.5 Hz, 2H), 3.83 (d, J = 20.0 Hz, 3H), 6.74 (dd, J = 8.1, 1.4 Hz, 1H), 6.87–6.94 (m, 2H), 7.01 (ddd, J = 9.5, 8.3, 2.14 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.92–7.98 (m, 1H), 8.41 ppm (d, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 24.36, 27.41, 39.99, 49.98, 53.67, 58.03, 58.95, 109.51, 109.75, 116.93, 123.30, 124.56, 127.08, 127.83, 128.73, 134.62, 139.46, 139.70, 139.75, 145.85, 145.95, 146.45, 148.60, 162.59, 167.06 ppm; HRMS calcd for $C_{27}H_{30}ClFN_4O_2$ [M^+]: 496.2041, found: 496.2042.

***N*-[4-[4-(2-Chlorophenyl)piperazin-1-yl]butyl]-4-(6-bromopyridin-2-yl)-benzamide (10a).** Compound **10a** was prepared from 4-[4-(2-chlorophenyl)piperazin-1-yl]butyl-1-amine (**8a**) and 4-(6-bromopyridin-2-yl)benzoic acid according to the general procedure. Yield: 79%: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.57–1.74 (m, 4H), 2.43 (t, J = 6.9 Hz, 2H), 2.60 (s, 4H), 3.01 (s, 4H), 3.40–3.52 (m, 2H), 6.89–6.97 (m, 2H), 7.12–7.19 (m, 1H), 7.29–7.35 (m, 2H), 7.37–7.42 (m, 1H), 7.52–7.58 (m, 1H), 7.63 (dd, J = 7.7, 0.9 Hz, 1H), 7.82–7.88 (m, 2H), 7.95–8.01 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 24.13, 27.22, 39.84, 50.74, 53.09, 57.79, 119.08, 120.13, 123.45, 126.73, 126.74, 127.38, 127.39, 128.42, 130.34, 135.58, 138.95, 139.78, 142.00, 148.87, 156.95, 167.15 ppm; HRMS calcd for $C_{26}H_{28}BrClN_4O$ [M^+]: 526.1135, found: 526.1135.

***N*-[4-[4-(2-Chlorophenyl)piperazin-1-yl]butyl]-4-(6-nitropyridin-3-yl)-benzamide (10b).** Compound **10b** was prepared from 4-[4-(2-chlorophenyl)piperazin-1-yl]butyl-1-amine (**8a**) and 4-(6-nitropyridin-3-yl)benzoic acid according to the general procedure. Yield: 54%: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.61–1.79 (m, 4H), 2.50 (t, J = 6.9 Hz, 2H), 2.65 (s, 4H), 3.04 (s, 4H), 3.46–3.58 (m, 2H), 6.91–6.99 (m, 2H), 7.07 (t, J = 5.4 Hz, 1H), 7.13–7.21 (m, 1H), 7.28–7.36 (m, 1H), 7.66–7.72 (m, 2H), 7.93–7.99 (m, 2H), 8.16–8.22 (m, 1H), 8.33 (td, J = 3.0, 1.5 Hz, 1H), 8.79–8.83 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 24.27, 27.34, 40.02, 50.86, 53.23, 57.89, 118.14, 120.12, 123.63, 127.45, 127.51, 128.12, 128.60, 130.53, 135.97, 137.82, 137.84, 141.18, 147.04, 148.96, 155.84, 166.62 ppm; HRMS calcd for $C_{26}H_{28}ClN_5O_4$ [M^+]: 493.1881, found: 493.1881.

***N*-[4-[4-(3-Chloro-2-methoxyphenyl)piperazin-1-yl]butyl]-4-(6-bromopyridin-2-yl)-benzamide (10c).** Compound **10c** was prepared from 4-[4-(3-chloro-2-methoxyphenyl)piperazin-1-yl]butyl-1-amine (**8b**) and 4-(6-bromopyridin-2-yl)benzoic acid according to the general procedure. Yield: 65%: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.58–1.77 (m, 4H), 2.45 (t, J = 6.9 Hz, 2H), 2.59 (s, 4H), 3.08 (s, 4H), 3.40–3.54 (m, 2H), 3.84 (t sext., J = 6.6, 5.0 Hz, 3H), 6.74 (dd, J = 8.0, 1.6 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H), 6.95–7.00 (m, 1H), 7.09 (t, J = 5.4 Hz, 1H), 7.43 (dd, J = 7.7, 0.9 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.67 (dd, J = 7.7, 0.9 Hz, 1H), 7.81–7.89 (m, 2H), 7.98–8.05 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 24.26, 27.32, 39.93, 49.91, 53.56, 57.94, 58.86, 116.97, 119.18, 123.12, 124.51, 126.87, 126.90, 127.42, 128.54, 135.71, 139.02, 139.99, 142.15, 146.39, 148.50, 157.12, 167.21 ppm; HRMS calcd for $C_{27}H_{30}BrClN_4O_2$ [M^+]: 556.1241, found: 556.1240.

***N*-[4-[4-(3-Chloro-2-methoxyphenyl)piperazin-1-yl]butyl]-4-(6-nitropyridin-3-yl)-benzamide (10d).** Compound **10d** was prepared from 4-[4-(3-chloro-2-methoxyphenyl)piperazin-1-yl]butyl-1-amine (**8b**) and 4-(6-nitropyridin-3-yl)benzoic acid according to the general procedure. Yield: 52%: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.59–1.81 (m, 4H), 2.48 (t, J = 6.8 Hz, 2H), 2.62 (s, 4H), 3.10 (s, 4H), 3.53 (q, J = 6.4 Hz, 2H), 3.84 (d, J = 4.6 Hz, 3H), 6.74 (dd, J = 8.0, 1.6 Hz, 1H), 6.87–7.02 (m, 3H), 7.65–7.73 (m, 2H), 7.90–7.98 (m, 2H), 8.18 (dd, J = 8.4, 2.4 Hz, 1H), 8.35 (dd, J = 8.4, 0.7 Hz, 1H), 8.83 ppm (dd, J = 2.3, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 24.32, 27.36, 40.04, 49.98, 53.66, 57.97, 58.94, 116.88, 118.19, 123.29, 124.54, 127.60, 128.14, 128.72, 136.00, 137.90, 137.94, 141.24, 146.41, 147.12, 148.59, 155.93, 166.74 ppm; HRMS calcd for $C_{27}H_{30}ClN_5O_4$ [M^+]: 523.1986, found: 523.1986.

Radiochemistry

No-carrier-added aqueous [^{18}F]fluoride ion was produced in a RDS 111 cyclotron (PET Net GmbH, Erlangen, Germany) by irradiation of enriched [^{18}O]H_2O via the $^{18}O(p,n)^{18}F$ nuclear reaction. The [^{18}F]fluoride ions were transferred on a QMA cartridge (Waters). Elution of [^{18}F]fluoride from the cartridge was performed using an aqueous solution of Kryptofix 2.2.2 (10 mg) and potassium carbonate stock solution (13 μL, 1 M) in CH_3CN/H_2O (4:1). The solvent was evaporated under a stream of Ar at 80 °C and the azeotropic drying step was repeated twice using 500 μL CH_3CN. The syntheses of [^{18}F]**9a**–**d** were performed by nucleophilic fluorination under the reaction conditions indicated in Table 3, following the previously described experiments.[35]

*Preparation and isolation of [^{18}F]**9a** and [^{18}F]**9c**:* After synthesis of [^{18}F]**9a** or [^{18}F]**9c** via nucleophilic fluorination of **10a** or **10c** with [^{18}F]fluoride, the reaction mixtures were cooled and then diluted with 20 mL H_2O. The resulting suspensions were transferred on a RP18 cartridge (300 mg, Sep-Pak, Waters). After drying, the cartridge was eluted with CH_3CN (2.5 mL). For isolation of [^{18}F]**9a** or [^{18}F]**9c**, this solution was fractionated by semipreparative HPLC (System B). The product fractions were diluted with H_2O (20 mL), concentrated by solid-phase extraction (Lichrosorb-RP18 cartridge, 100 mg, Merck), and eluted from the cartridge with EtOH (1 mL). After evaporation of the solvent, [^{18}F]**9a** or [^{18}F]**9c** were redissolved as appropriate for further experimental use.

Octanol buffer partition coefficient

After preparative isolation by HPLC or SPE, each radioligand ([^{18}F]**9a**–**d**, ~10 kBq) was dissolved in PBS and transferred into a two-layer system of octanol (500 μL) and PBS (pH 7.4, 500 μL). The tube was vortexed for 2 min and then centrifuged. Three samples of each phase were collected in separate tubes. Each experiment was performed in triplicate. The radioactivity of each tube was measured in a γ counter (Wallac, Packard) and the distribution coefficient ($\log D_{7.4}$) was calculated as the mean value with a standard deviation of $<12\%$ in three independent experiments.

Determination of tracer stability in human serum

An aliquot of [^{18}F]**9a** in PBS (50 μL) was added to human serum (200 μL) and incubated for 60 min at 37 °C. An aliquot (25 μL) was taken and diluted in CH_3OH/CH_2Cl_2 (1:1, 100 μL). The samples were centrifuged, and the supernatant was analysed by radio-HPLC (Kromasil C_8, 250×4.6, 40–100% CH_3CN (0.1% TFA) within 50 min, 1.5 mL min^{-1}) and compared with the HPLC chromatogram of the intact reference solution of [^{18}F]**9a**.

Animal studies and autoradiography

All animal experiments were performed in compliance with the protocols approved by the local Animal Protection Authorities (Regierung Mittelfranken, Germany, No. 54-2531.31-28/06). Sprague Dawley rats were obtained from Charles River (250–300 g body weight) and were kept under standard conditions (12 h light/dark) with food and water available ad libitum.

Each radioligand and BP 897 were formulated in PBS/acetate buffer (pH 4.5) containing PEG-400 (6%) and EtOH (5%). Rats were injected with 6–14 MBq [^{18}F]**9a** or [^{18}F]**9c**, respectively, with or without BP 897 (1 mg kg^{-1}) via the tail vein under anaesthesia with isoflurane. The brains were quickly removed and frozen immediately in cold hexane (−50 °C). Brain slices (20 μm) were prepared on a cryostat microtome (HM550, Microm) and thaw-mounted on glass slides (Histobond). The slides were placed on a phosphor imaging screen (Kodak K-screen, Biorad) and measured overnight. The screen was analysed by a Fluor-S Multilmager using the software Quantity One (version 4.6.3; Bio-Rad Laboratories). For histological analyses, the slices were counter-stained with haematoxylin and eosin (HE) following standard procedures. Histological images were obtained by a digital camera equipped to an Olympus light microscope.

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Keywords: autoradiography · D3 receptors · dopamine · positron emission tomography · QSAR

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