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Synthesis and evaluation of ^{18}F-labeled dopamine D3 receptor ligands as potential PET imaging agents

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Abstract—A series of fluoro substituted aryl carboxamides was synthesized revealing high affinity for the dopamine D3 receptor. In contrast to 2-methoxy substitution, a 2,3-dichloro substitution pattern at the phenylpiperazine moiety induces a 10-fold increase of D3 affinity which is expressed by K_i values of 0.53, 1.1, and 9.0 nM for **8b**, **8d**, and **8f**. Applying aromatic ^{18}F-for-Br(Cl) substitution, high radiochemical yields between 76–82% were obtained for [^{18}**F**]**8c–f**. The most promising ligand, [^{18}**F**]**8d**, was used as imaging agent of the D3 receptor in vitro. However, due to the lack of specific binding, further studies should aim at the development of radioligands with improved D3 receptor selectivity.

The dopamine D2-like receptors are involved in numerous physiological processes and are supposed to be key players in disorders such as schizophrenia, Parkinson's disease, and cocaine addiction.[1–3] This is also illustrated by the high affinity of antipsychotic drugs, such as haloperidol (**1**), to the D2-like receptors (Fig. 1).

The D2-like receptor family comprises of D2, D3, and D4 receptors. The dopamine D3 receptor was identified and cloned by Sokoloff et al.,[4] and is mainly found in the mesocorticolimbic system, whereas the D2 subtype is accumulated in the striatum.[5,6] The physiological role of the D3 receptor is as yet unclear. However, the location of this receptor subtype in brain regions implicated in emotion and cognition makes it an attractive candidate for research aimed at elucidating the pathogenesis of the above-mentioned psychiatric diseases.[7–9] To validate this hypothesis, the synthesis of potent and selective D3 receptor ligands represents an important goal. Recently, various series of arylpiperazines with high affinity and selectivity for the D3 receptor were characterized.[10–14] These include BP 897 (**2**), which acts as a partial agonist with a D2/D3 suptype selectivity of 66-fold.[2]

As part of our drug discovery and SAR investigations on selective dopamine D3 receptor ligands, we developed the superpotent benzothiophene derivate FAUC 365 (**3**), displaying a neutral antagonistic behavior and a 7200-fold selectivity over the D2 subtype.[15] Furthermore, we synthesized radioiodinated derivatives of FAUC365 for non-invasive single-photon emission tomography (SPET).[16] The development of specific and potent radioligands as positron emission tomography (PET) tracers for D3 receptors is an important step to investigate the role of this receptor subtype in the pathophysiology of numerous diseases.

Based on the results of Murray et al.,[17] we chose the 4-bromophenyl carboxamide **4** as an interesting lead compound for the development of ^{18}F-labeled PET tracers. Recently, this potent D3 receptor ligand (pK_i 9.3) was radioiodinated to allow its application as a SPET tracer.[18]

This paper reports the synthesis and in vitro evaluation of a series of fluoro substituted analogs of **4**, representing our target compounds for the radiosynthesis of ^{18}F-labeled tracers potentially suitable for PET imaging. Herein, we prepared a series of respective haloaryl

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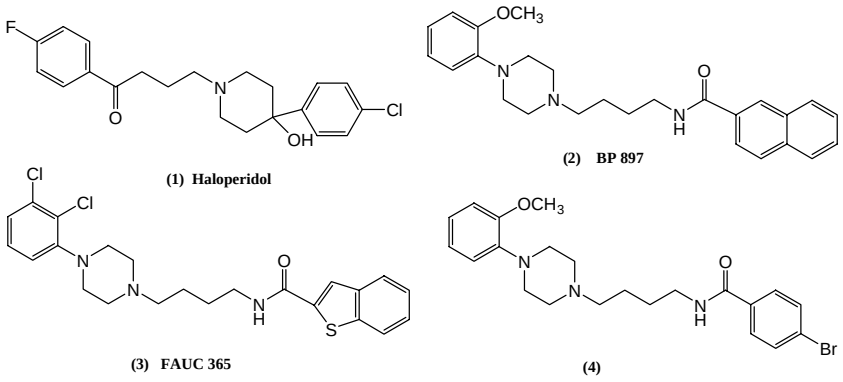


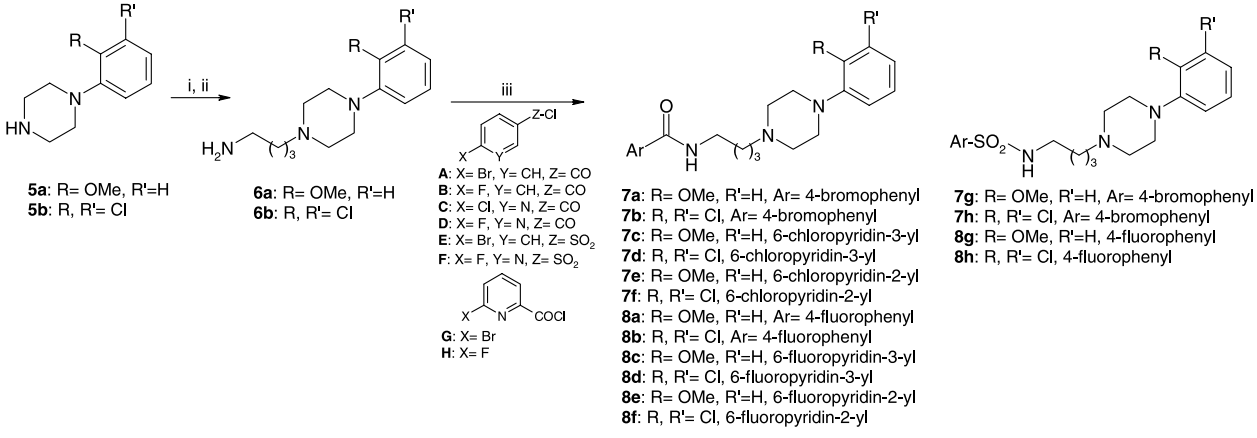
Figure 1. Potent dopamine D3 receptor ligands.

carboxamides and assessed their suitability in ^{18}F-for-Br and ^{18}F-for-Cl nucleophilic substitution.

The syntheses of the series of compounds are shown in Scheme 1. The commercially available *N*-phenylpiperazines **5a**,**b** were converted to the respective aminobutyl derivatives by alkylation with 4-bromobutyronitrile and subsequent reduction with $LiAlH_4$ in THF affording the primary amines **6a**,**b** in more than 60% overall yield. Acylation of **6a**,**b** with 4-bromobenzoyl chloride, 6-chloronicotinoyl chloride, 6-bromopicolinic acid chloride, or 4-bromobenzenesulfonyl chloride in CH_2Cl_2 in the presence of triethylamine afforded the respective amides **7a**–**h** (53–82% yield) bearing leaving groups (chloride or bromide) for the nucleophilic substitution with [^{18}F]fluoride.[19] Condensation of the amines **6a**,**b** with the appropriate fluorobenzoic acid chlorides gave the corresponding amides **8a**–**h** in yields of 43–64%.[20] These compounds were subjected, after identification[21], to receptor binding studies, as described below to determine the pharmacological potency of the aspired radiolabeled analogs.

The radiosynthetic approach and results of radiochemical yields (RCYs) for the aromatic substitution of **7a**–**h** with no-carrier-added (n.c.a.) [^{18}F]fluoride are given in Table 1 and Scheme 2. Alternative solvents (DMF or acetonitrile) were examined, but the best results were obtained employing the reaction conditions described in Scheme 2. The RCYs of radiofluorinated nicotinamides ([^{18}**F**]**8c**,**d**) and picolinamides ([^{18}**F**]**8e**,**f**) were about 76–82%. Significant differences in radiochemical yields between both heteroaromatic systems could not be observed. The RCYs were not significantly influenced by the substitution pattern (2-methoxy or 2,3-dichloro) of the *N*-phenylpiperazinyl moiety of the molecules. The nucleophilic aromatic substitution with (n.c.a.) [^{18}F]fluoride requires aromatic activation in ortho- or para position. This is usually realized by electronic withdrawal groups, such as carboxamides and sulfonamides in *para* position or *ortho* halogen-substituted pyridines.[22] The radiolabeled compounds ([^{18}**F**]**8c-f**) could be obtained in sufficiently high yield to investigate the tracer behavior in vivo and in vitro for further studies. In strong contrast to these results, apparently low or negligible RCYs of the benzamide and benzenesulfonamide derivatives [^{18}**F**]**8a**,**b** and [^{18}**F**]**8g**,**h**, respectively, were obtained.

Radioligand binding assays were employed to investigate the affinity and selectivity of the target compounds **8a**–**h** to the different subtypes of dopamine receptors and to the related biogenic amine receptors 5-HT1$_A$, 5-HT2, and α1. Binding affinities at the human dopamine

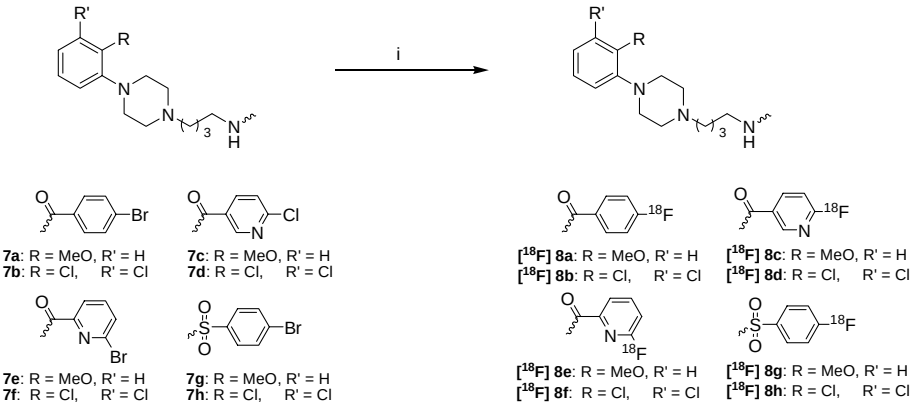


Scheme 1. Reagents and conditions: (i) 4-bromobutyronitrile, DMF, 100 °C, 5 h[16]; (ii) $LiAlH_4$, THF, 0 °C—reflux, 5 h[16]; (iii) acid chlorides **A**–**H**, CH_2Cl_2, NEt_3, rt (43–82%).

Table 1. Radiochemical yields (RCY) [%] of the radiofluorinated compounds [^{18}**F**]**8a–h** (500 μL DMSO, 140 °C, n.c.a. [^{18}F]fluoride (20-100 MBq), Kryptofix®2.2.2. K_2CO_3, t = 20 min)

Compound	R	R′	Amide	Ar	Leaving group	RCY [%] of [^{18}**F**]**8a–h**	Log$P$[a] of **8a–h**
8a	CH_3O	H	Carboxamide	4-Fluorophenyl	Br	2 ± 2	3.63
8b	Cl	Cl	Carboxamide	4-Fluorophenyl	Br	3 ± 2	5.27
8c	CH_3O	H	Carboxamide	6-Fluoropyridin-3-yl	Cl	81 ± 5	2.76
8d	Cl	Cl	Carboxamide	6-Fluoropyridin-3-yl	Cl	82 ± 4	4.39
8e	CH_3O	H	Carboxamide	6-Fluoropyridin-2-yl	Br	76 ± 6	3.11
8f	Cl	Cl	Carboxamide	6-Fluoropyridin-2-yl	Br	78 ± 5	4.74
8g	CH_3O	H	Sulfonamide	4-Fluorophenyl	Br	0	3.79
8h	Cl	Cl	Sulfonamide	4-Fluorophenyl	Br	0	5.43

[a] Calculated value using the program $C\log P$; $\log P$ of the reference FAUC365 was 5.34.



Scheme 2. Radiosyntheses of [^{18}**F**]**8a–h** starting from the precursors **7a–h**; reagents and conditions: (i) n.c.a. [^{18}F]fluoride, phase transfer catalyst (Kryptofix®2.2.2.), K_2CO_3, DMSO, 140 °C, 20 min.

receptor subtypes $D2_{long}$, $D2_{short}$,[23] D3,[24] and D4.4[25] were measured using membranes of CHO cells stably expressing these receptors and the radioligand [^{3}H]spiperone, as described previously.[26] D1 receptor affinities were determined utilizing porcine striatal membranes and the D1 selective radioligand [^{3}H]SCH 23390.[26] Binding properties to the serotoninergic receptors 5-$HT1_A$ and 5-HT2, and to the adrenergic α1 receptor were evaluated utilizing porcine cortical membranes and the selective radioligands [^{3}H]8-OH-DPAT, [^{3}H]ketanserin, and [^{3}H]prazosin, respectively. The results of the binding experiments listed in Table 2 reveal only weak affinity to the D1 receptor and a preferred binding to the receptors of the D2 family. While the benzamide derivatives **8a–f** show a clear binding preference to the D3 receptor in a low nanomolar range, high affinities to the D4 receptor were determined for both benzensulfonamides **8g** and **8h** with K_i values of 9.9 and 17 nM, respectively. A privileged aromatic scaffold is the *para* substituted benzamide substructure of the compounds **8a**,**b** and the *aza* analoges of **8c**,**d** recognizing the D3 receptor in low nanomolar or even subnanomolar concentrations (K_i of **8b**[27] for D3 = 0.53 nM). Looking at the influence of the phenylpiperazine moiety, the 2,3-dichloro substitution, when compared to the 2-methoxy derivatives, induces a 10-fold increase in D3 affinity, which is expressed by K_i values of 0.53, 1.1, and 9.0 nM for **8b**, **8d**, and **8f** and 4.3, 14, and 86 nM for the appropriate 2-methoxy derivatives **8a**, **8c**, and **8e**, respectively. Additionally, the 2,3-dichloro substitution pattern also improves selectivity of D3 binding against D4 with the factor of 10 when the selectivity ratios rise from 7.9 to 83 (**8a**,**b**), 9.2 to 91 (**8c**,**d**), and from 0.88 to 11 (**8e**,**f**). However, all the developed fluorinated compounds showed a lesser D3 selectivity as reference compound FAUC365.

All test compounds showed good affinity (15–120 nM) to the serotonin receptor 5-$HT1_A$, but less binding to the 5-HT2 subtype (84–3700 nM) when the affinity to this receptor was strongly inferred by substituents of the phenylpiperazine moiety. The 2-methoxy derivatives show K_i values only in the micromolar range, whereas the 2,3-dichloro substitution induces an improved binding, indicated by an increase of affinity up to 45-fold (for **8c**/**8d**). Interestingly, for all compounds binding affinities to the α1 receptor were determined with low nanomolar K_i values when the benzenesulfonamide **8g** showed best binding with 3.9 nM.

The most promising radioligand [^{18}**F**]**8d** was used for preliminary in vitro studies. [^{18}**F**]**8d** is structurally related to **8b** and also revealed a similar D3 receptor affinity (ca. 1 nM), but significantly higher RCYs were obtained in the case of [^{18}**F**]**8d**, so this radioligand was chosen for initial receptor autoradiography studies on rat brain slices. D3 receptor binding was conducted as described in the literature.[28] The results of this initial study could not reveal a typical D3 receptor distribution, such as increased binding in the brain area of the nucleus accumbens. The rat brain slices incubated with [^{18}**F**]**8d** showed a homogeneous distribution and high nonspecific

Table 2. Binding affinities of the fluorinated target compounds **8a–h** to the human dopamine receptor subtypes $D2_{long}$, $D2_{short}$, D3, D4, and the porcine D1 receptor, as well as the porcine 5-$HT1_A$, 5-HT2 and α1 receptors (2–4 experiments each performed in triplicate)

Compound	K_i values (nM)									
	[^{3}H]spiperone				D3 selectivity within the D2 family	[^{3}H]SCH 23990	[^{3}H]8-OH-DPAT	[^{3}H]ketanserin	[^{3}H]prazosin
	$D2_{long}$	$D2_{short}$	D3	D4.4	$D2_{long}$/D3–$D2_{short}$/D3–D4/D3	D1	5-$HT1_A$	5-HT2	α1
8a	98	140	4.3	34	23–32–7.9	2700	15	2300	7.4
8b	17	18	0.53	44	32–34–83	920	60	230	17
8c	160	240	14	130	11–17–9.2	6300	22	3700	12
8d	21	29	1.1	100	19–26–91	1300	28	84	16
8e	260	400	86	76	3.0–4.7–0.88	4100	24	3200	5.8
8f	44	57	9.0	97	4.9–6.3–11	910	30	240	13
8g	72	120	210	9.9	0.34–0.57–0.047	3500	51	3500	3.9
8h	39	49	16	17	2.4–3.1–1.1	1800	120	830	14
FAUC365	3600	2600	0.5	340	7200–5200–680	8800	360	3000	370

binding, indicating that this ligand may not be a useful candidate for PET imaging studies. This result is also in accordance with a recently published report of Tu et al. describing a C-11-labeled benzamide.[29]

In summary, we reported the syntheses, binding affinities, ^{18}F-radiosyntheses, and in vitro studies of selective dopamine D3 receptor ligands. The compounds **8b** and **8d** were characterized with good affinities to the D3 receptor. Applying aromatic ^{18}F-for-Br(Cl) substitution, the obtained radiochemical yields of [^{18}**F**]**8c–f** were sufficiently high. The most promising nicotinamide derivative [^{18}**F**]**8d** was characterized by an initial in vitro study indicating undesirable pharmacologic properties. Thus, future efforts in our laboratory aim at the development of radioligands with improved D3 receptor selectivity.

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19. General procedure for nucleophilic substitution with n.c.a. [^{18}F]fluoride on aromatics: [^{18}F]Fluoride was produced by the ^{18}O(p,n)^{18}F reaction using a RDS 111 cyclotron (CTI) at PET Net GmbH (Erlangen, Germany). A QMA-cardridge with [^{18}F]fluoride (20–100 MBq) was eluted with a solution of 15 mg Kryptofix 2.2.2.®/15 μL of 1 N potassium carbonate stock solution in 1 mL acetonitrile/water (8:2). The solvent was evaporated under a stream of argon at 80 °C and the azeotropic drying step was repeated two times using 500 μL acetonitrile. The dry residue was resolubilized with a solution of 10–20 μmol precursor **7a**–**e** in 500 μL dry DMSO. The solution was heated to 140 °C for 20 min. Samples of the solution (25 μL) were isolated in periods of 2, 5, 10, 20, and 30 min. These samples were used for determination of radiochemical yields by reversed-phase HPLC. The identification of radiofluorinated compounds [^{18}**F**]**8a**–**h** was performed by gradient reversed-phase radio HPLC (RP 18 Select B5 column (250 × 4 mm)) eluted with acetonitrile/water (20/80 to 70/30 v/v, 0.1% TFA, 1 mL/min) using the UV absorbance at 254 nm of standard compounds **8a**–**h** as a reference signal. Analytical HPLC was performed on the following system: HPLC Hewlett Packard (HP 1100) with a quaternary pump and variable wavelength detector (HP 1100) connected to a radio-HPLC detector D505TR (Canberra Packard). Computer analysis of the HPLC data was performed using FLO-One software (Canberra Packard). Electronic autoradiography (InstantImager™, Canberra Packard) was used to analyze radio-TLC data.
20. To a solution of **6a**,**b** (0.5 mmol) and triethylamine (1 mmol) in CH_2Cl_2 (10 mL) was added the appropriate fluoro substituted benzoic acid chloride or sulfonic acid chloride (1.1 equiv) at room temperature. The mixture was stirred at room temperature overnight. After the addition of aqueous $NaHCO_3$ solution, the mixture was stirred for 5 min and the organic layer was separated. The organic phase was dried (Na_2SO_4), filtered, and concentrated. Product isolation was followed by column chromatography on silica gel (CH_2Cl_2/methanol 95/5) to give **8a**–**h** (43–64% yield).
21. ^{1}H NMR (DMSO-d_6, 300,18 MHz), ^{19}F NMR (DMSO-d_6, 282,41 MHz), **8a**: ^{1}H NMR δ (ppm): 1.52 (m, 4H), 2.36 (m, 2H), 2.49 (m, 4H), 2.94 (m, 4H), 3.25 (m, 2H), 3.74 (s, 3H), 6.82–6.87 (m, 4H), 7.2–7.25 (m, 2H), 7.83–7.88 (dd, 2H), 8.37 (t, 1H), ^{19}F NMR δ (ppm): −110.423, **8b**: ^{1}H NMR δ (ppm): 1.53 (m, 4H), 2.36 (m, 2H), 2.52 (m, 4H), 2.96 (m, 4H), 3.26 (m, 2H), 7.09 (dd, 1H), 7.23–7.26 (m, 4H), 7.84–7.89 (dd, 2H), 8.37 (t, 1H), ^{19}F NMR δ (ppm): −110.428, **8c**: ^{1}H NMR δ (ppm): 1.7 (m, 4H), 2.5 (m, 2H), 2.65 (m, 4H), 3.05 (m, 4H), 3.5 (m, 2H), 3.85 (s, 3H), 6.8–6.9 (m, 3H), 7.0 (dd, 2H), 7.1 (t, 1H), 8.2 (t, 1H) 8.6 (s, 1H), **8d**: ^{1}H NMR δ (ppm): 1.7 (m, 4H), 2.5 (m, 2H), 2.55–2.7 (m, 4H), 2.95–3.1 (m, 4H), 3.5 (m, 2H), 6.9 (m, 2H), 7.0 (m, 1H), 7.15 (dd, 2H), 8.2 (t, 1H), 8.6 (s, 1H), **8e**: ^{1}H NMR δ (ppm): 1.48 (m, 2H), 1.54 (m, 2H), 2.34 (m, 2H), 2.48 (m, 4H), 2.94 (m, 4H), 3.29 (dd, 2H), 3.74 (s, 3H), 6.82–6.87 (m, 4H), 7.35 (m, 1H), 7.92 (m, 1H), 8.12 (dd, 1H), 8.6 (t, 1H). ^{19}F NMR δ (ppm): −68.636, **8f**: ^{1}H NMR δ (ppm): 1.48 (m, 2H), 1.56 (m, 2H), 2.37 (m, 2H), 2.53 (m, 4H), 2.97 (m, 4H), 3.29 (dd, 2H), 7.09 (m, 1H), 7.23 (m, 2H), 7.36 (m, 1H), 7.93 (m, 1H), 8.12 (dd, 1H), 8.6 (t, 1H), ^{19}F NMR δ (ppm): −68.634, **8g**: ^{1}H NMR δ (ppm): 1.38 (m, 4H), 2.23 (m, 2H), 2.43 (m, 4H), 2.76 (m, 2H), 2.91 (m, 4H), 3.74 (s, 3H), 6.82–6.88 (m, 4H), 7.38 (m, 2H), 7.59 (t, 1H), 7.8 (dd, 2H), ^{19}F NMR δ (ppm): −107.845, **8h**: ^{1}H NMR δ (ppm): 1.39 (m, 4H), 2.25 (m, 2H), 2.46 (m, 4H), 2.77 (m, 2H), 2.93 (m, 4H), 7.1 (dd, 1H), 7.24 (m, 2H), 7.38 (m, 2H), 7.58 (t, 1H), 7.81 (m, 2H), ^{19}F NMR δ (ppm): −107.808.
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