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Synthesis, biological evaluation and radiolabelling by ^{18}F-fluoroarylation of a dopamine D_3-selective ligand as prospective imaging probe for PET

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ABSTRACT

Radical ^{18}F-fluoroarylation with fluorine-18-labelled arenediazonium chlorides has been successfully applied to the radiochemical synthesis of the dopamine D_3-selective ligand SH 317 ([^{18}F]**8**). SH 317 has been evaluated as a new PET ligand candidate by in vivo experiments.

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Over the past decades, positron emission tomography (PET) has gained more and more clinical importance as a powerful and highly sensitive non-invasive method for imaging and quantification of physiological and pathophysiological processes in vivo. Due to its properties, that is, its broad availability, its low positron energy (E_{max} = 635 keV) and manageable half-life ($t_{1/2}$ = 109.7 min), no-carrier-added (n.c.a.) fluorine-18 has become the most commonly used PET isotope.[1] Nevertheless, chemical synthesis including the incorporation of fluorine-18 into target molecules in acceptable overall reaction times of <2 h, often represents a major difficulty in the development of new radiopharmaceuticals.[2]

For this existing synthetic challenge, the application of radical ^{18}F-chemistry represents an alternative approach which has so far only marginally been exploited. As we have shown recently, short reaction times can be achieved when ^{18}F-fluoroarylation reactions are employed for radiochemical labelling.[3] Starting from [^{18}F]fluoro-substituted arenediazonium salts,[4,5] radioligands for a variety of receptors in the central nervous system containing a deactivated 4-[^{18}F]fluorophenyl group could be accessible by applying the radical ^{18}F-fluoroarylation strategy.

Among the dopamine receptors, which can be differentiated into five subtypes, D_1–D_5, the D_2 subtype has been the most interesting target for a long time. Recent research has also focussed on the D_3 subtype, since a variety of diseases such as schizophrenia, depression, Parkinson's disease and also drug addiction have been related to disturbances of its expression and/or activity.[6] With respect to an in vivo investigation of the dopamine D_3 receptor by PET, only a few carbon-11 and fluorine-18-labelled compounds have been evaluated so far (Fig. 1).

Recently, the D_3/D_2 radioligand [^{11}C](+)-PHNO (**4a**) has been successfully used for studying D_3 receptor occupancy in vivo by PET when the selective D_3 antagonist SB-277011 was applied to dissect the signal attributable to D_3 receptors.[10] Since insufficient selectivity for D_3 over D_2 receptors or undesirable biokinetic properties have hindered the PET application of these promising ligands so far, the development of a dopamine D_3-selective ligand suitable for PET imaging applications remains challenging.

Continuing our efforts on the development of subtype selective dopamine receptor radioligands for PET imaging studies,[13,15] we herein report on the application of the radical ^{18}F-fluoroarylation methodology for the radiosynthesis of a dopamine D_3-selective ligand. For our studies, we selected cinnamoyl carboxamide **8**, a fluorinated derivative of ST 168 (**7**), as lead compound (Fig. 2), due to its sub-nanomolar D_3 affinity and adequate subtype selectivity that has been described previously.[16,17] Structurally comparable carboxamides have recently shown high D_3 receptor affinities combined with remarkable selectivity over the dopamine D_2 receptor subtype ($K_i(D_3)/K_i(D_2)$) (Table 1).[17]

We aimed at the radiosynthesis of ^{18}F-labelled SH 317 ([^{18}F]**8**) since its cinnamoyl amide substructure could probably be assembled in the final synthetic step by radical fluoroarylation. In this manuscript, we report on the synthesis and ^{18}F-radiosynthesis,

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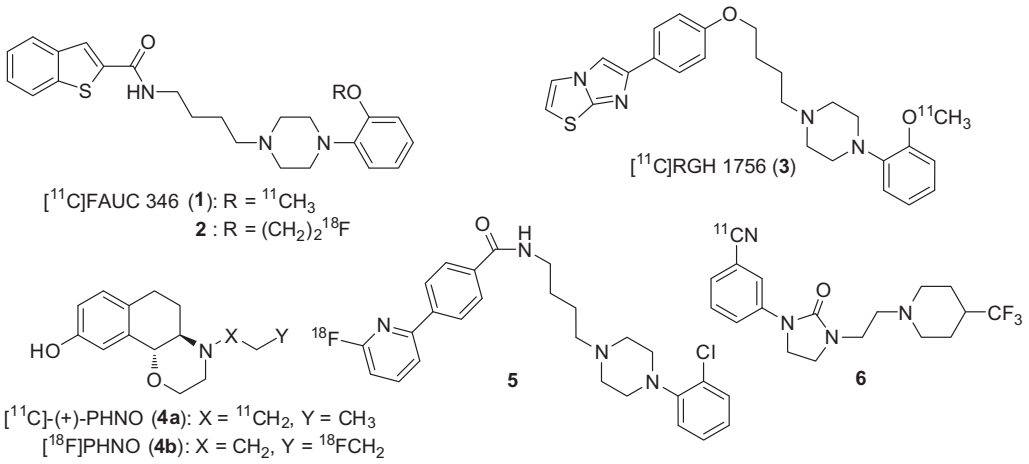


Figure 1. Carbon-11 and fluorine-18-labelled dopamine D_3 receptor ligands [^{11}C]FAUC 346 (**1**),[7] fluorine-18-labelled derivative of FAUC 346 **2**,[8] [^{11}C]RGH 1756 (**3**),[9] [^{11}C](+)-PHNO (**4a**),[10] naphthoxazine derivative **4b**,[11] CBJ 090 biaryl amide derivative **5**[12,13] and imidazolidinone **6**.[14]

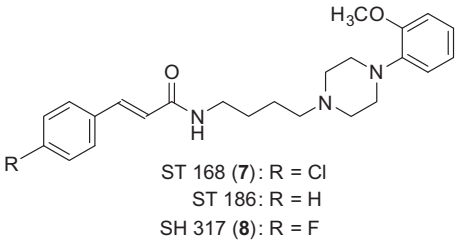
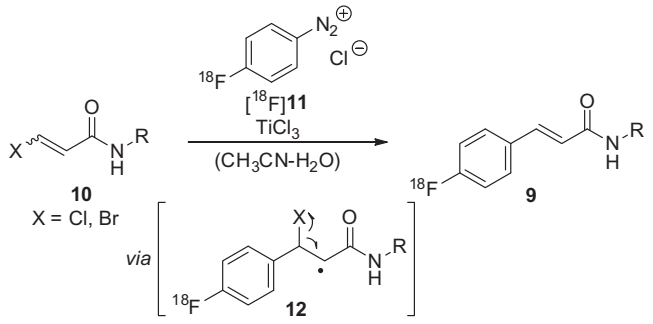


Figure 2. ST 168 (**7**) and radioligand SH 317 (**8**).

the biological evaluation and in vivo properties of ^{18}F-labelled SH 317 ([^{18}F]**8**).

In general, [^{18}F]fluorinated cinnamoyl amides **9** could be obtained in a radical fluoroarylation reaction starting from β-halogenated acrylic amides **10** that were treated with fluorine-18-labelled arenediazonium chlorides [^{18}F]**11** in the presence of the reductant titanium(III)-chloride as described previously (Scheme 1).[18–20] This reaction proceeds in a radical addition–elimination sequence via intermediate **12**. Since radical arylations are in general insensitive to non-protected functional groups such as amines, carboxylic acids or alcohols, they are well-suited for ^{18}F-labelling applications when mild and aqueous reaction conditions are needed. Moreover, radical arylation reactions proceed rapidly and the application of ^{18}F-labelled arenediazonium chloride (**11**) could therefore allow easy access to radioligands containing the metabolically stable [^{18}F]fluorophenyl moiety.



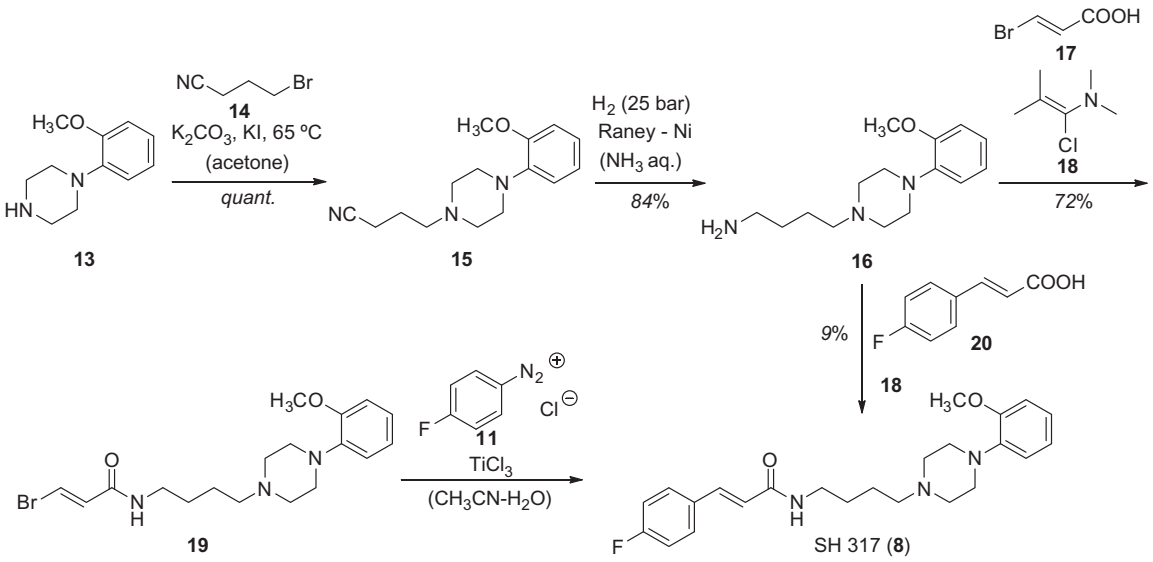
Scheme 1. Radiochemical synthesis of cinnamoyl amides **9** by radical fluoroarylation.

The synthesis of precursor **19** started from commercially available *N*-(2-methoxyphenyl)-piperazine (**13**) (Scheme 2). Alkylation of **13** with 4-bromobutyronitrile (**14**) gave **15** which was reduced to amine **16** under hydrogen (25 bar) in the presence of Raney nickel as catalyst.[17] Coupling of amine **16** with (*E*)-β-bromoacrylic acid (**17**) using chlorovinylamine **18** as activating reagent furnished the labelling precursor **19**.[21] The fluorinated, non-radioactive D_3 ligand SH 317 (**8**) was accessible via radical fluoroarylation with diazonium salt **11** or by coupling of amine **16** with (*E*)-3-(4-fluorophenyl)acrylic acid (**20**) in the presence of the activating agent **18**. The alternative synthetic route to **8** via **20** was

Table 1
Receptor binding data for compound **8** at the human dopamine receptors D_{2long}, D_{2short}, D_3 and D_4 and the porcine receptors D_1, 5-HT_{1A}, 5-HT_2 and α_1 in comparison to previously reported ligands

Compound	K_i values ± SD[a] (nM)								Ratio[g] D_2/D_3
	D_1[b]	D_{2long}[c]	D_{2short}[c]	D_3[c]	$D_{4.4}$[c]	5-HT_{1A}[d]	5-HT_2[e]	α_1[f]	
SH 317 (**8**)	1100 ± 170	27 ± 8.5 20.7 ± 0.8[16]	21 ± 0.71	0.34 ± 0.049 0.69 ± 0.11[16]	43 ± 3.5	28 ± 1.4	330 ± 160	5.2 ± 1.4	79 (62) 30[16]
ST 168 (**7**)[16]	–	22.6 ± 1.0	–	0.44 ± 0.09	–	–	–	–	51
ST 186[16]	–	13.54 ± 1.2	–	0.33 ± 0.1	–	–	–	–	41
6[13]	270	120	42	0.51	170	160	230	8.0	235 (82)

[a] K_i-Values (nM) are mean values of two independent experiments each done in triplicate.
[b] [^{3}H]SCH 23990.
[c] [^{3}H]spiperone.
[d] [^{3}H]WAY600135.
[e] [^{3}H]ketanserin.
[f] [^{3}H]prazosin.
[g] Ratio of $K_i(D_{2long})/K_i(D_3)$ and $K_i(D_{2short})/K_i(D_3)$ in parentheses.



Scheme 2. Synthesis of the labelling precursor **19** and SH 317 (**8**).

chosen since the radical pathway via **11** usually requires the olefinic substrate **19** in large excess to be efficient.[3a,22] Since a large amount of unreacted **20** was recovered from reaction mixture containing **16** and **17**, the activating agent **18** appears to be by far not as effective for cinnamic acid **20** as for acrylic acid **17**.[23] Notably, no *E*/*Z* isomerization was observed when ligand SH 317 (**8**) was stirred over 10 days in phosphate buffer (pH 7), confirming the conformational stability of **8**.

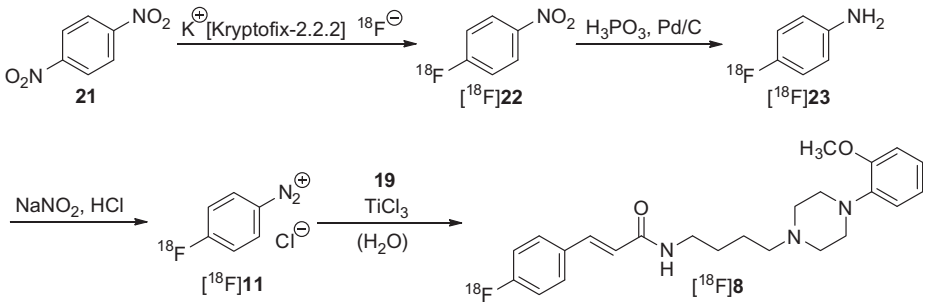
To evaluate the binding properties of the fluorinated test compound, competition binding experiments were done using the human dopamine receptors D_{2long}, D_{2short},[24] D_3[25] and $D_{4.4}$[26] stably expressed in CHO cells. Binding affinities to porcine D_1, the serotonin receptors 5-HT_{1A} and 5-HT_2 and the α_1 adrenoreceptor were also determined.[27] Table 1 displays binding affinities of SH 317 (**8**) in comparison with previously reported data, ST 168 (**7**) and ST 186[16] as well as the previously studied pyridinylphenyl carboxamide **6**.[13] The experiments indicated an excellent sub-nanomolar affinity of test compound **8** for the D_3 receptor (K_i = 0.34 nM) together with a good D_3/D_2 selectivity (>60-fold) which is in good agreement with the previously reported data.[16] Compound **8** also revealed an acceptable α_1 binding affinity, being one magnitude lower than its D_3 affinity (Table 1). However, considering the relatively low D_3 receptor density in the rat striatum (68 fmol/mg),[28] where it is co-localised with the predominating D_2 subtype (143 fmol/mg),[28] the selective recognition of D_3 receptors by **8** might be problematic. In comparison with the D_3-preferring radioligand [^{11}C]-(+)-PHNO that has K_i values of 0.16 nM at D_3 and 8.5 nM at D_2 receptors,[29] compound **8** showed a similar binding profile (Table 1). As [^{11}C]-(+)-PHNO reached an in vivo binding potential (B_{max}/K_d) of 3–4,[30] and has been successfully used for studying D_3 receptor occupancy in vivo by PET recently,[10a] we assumed that ligand [^{18}F]**8** could also be suitable for in vivo PET imaging of D_3 receptors, especially of those in extrastriatal regions.

However, the affinity ratio (D_2/D_3) and therefore the binding potential of a radioligand for each receptor subtype may differ significantly between the in vitro and in vivo situation, due to differences in the level (and density) of active states of G-protein-coupled receptors in the system. Importantly, this is most relevant for agonist ligands, which preferentially bind to the active GPCR conformation (high-affinity state), whereas antagonists display equal affinity for the active and inactive state. Therefore, we studied the intrinsic activity of **8** by measuring the [^{3}H]thymidine incorporation into growing CHO cells stably expressing the dopamine D_3 and the D_{2long} receptors,[31] respectively, when for both subtypes a neutral antagonism was determined compared to the reference quinpirole. This result is not in agreement with the published data for the chloro derivative **7** at the D_3 receptor that has been described as a partial agonist in a mitogenesis assay using NG 108-15 cells,[16] and may be explained by the structural modifications or, more likely, the use of different cell systems.[32]

The promising in vitro binding characteristics of **8**, especially its sub-nanomolar D_3 affinity, prompted us to perform ex vivo rat brain autoradiography studies with the ^{18}F-labelled radioligand.

The radiochemical synthesis of [^{18}F]**8** started from 1,4-dinitrobenzene (**21**), following the previously described procedures[3,5] with modifications (Scheme 3). Applying a modified cryptate system by the use of K_2CO_3/KH_2PO_4 and reducing the concentration of **21** to 50 mM for the nucleophilic ^{18}F-fluorination of **21** in the first reaction step, we obtained an improved radiochemical yield (RCY) of 90–95% for [^{18}F]**22** (see Supplementary data). Former studies reported an RCY of only 50–80% employing the commonly used cryptate–carbonate system.[3,5] [^{18}F]**22** was further reduced to aniline [^{18}F]**23** which was isolated by solid phase extraction on a silica gel cartridge. Diazotization furnished the [^{18}F]fluorophenyl diazonium chloride [^{18}F]**11** which was subsequently applied to the radical ^{18}F-arylation reaction with labelling precursor **19** in the presence of titanium(III) chloride in an aqueous solution at room temperature. The radiochemical yield of [^{18}F]**8** was 17–32% after 10 min, as determined by radio-HPLC of a sample withdrawn from the reaction mixture. We did not observe any influence on the RCY by varying the reaction temperature (0–80 °C) or the amount of **19** (up to 70 μmol). However, a significant amount of up to 30% of the byproduct [^{18}F]fluorobenzene was observed. The ^{18}F-arylation of **19** in the final step of the synthesis proceeded quickly, leading to an overall decay-uncorrected RCY of 1–3% in a total synthesis time of about 100 min starting from [^{18}F]fluoride (see Supplementary data). Including the final HPLC purification and formulation, this procedure provided [^{18}F]**8** in sufficient amounts (10–15 MBq) to perform further in vitro and in vivo studies.

To assess the lipophilicity of [^{18}F]**8** as a measure of blood–brain barrier (BBB) permeability, we determined the log $D_{7.4}$ value by extraction of the radioligand in *n*-octanol–phosphate buffered saline (pH 7.4, 1:1). [^{18}F]**8** revealed a log $D_{7.4}$ value of 2.07 ± 0.24 (n = 7), suggesting sufficient brain uptake of [^{18}F]**8** when applied in vivo.



Scheme 3. Radiochemical synthesis of [^{18}F]**8**.

Moreover, we performed preliminary CNS biodistribution studies with [^{18}F]**8** using brain autoradiography after intravenous injection of the radiotracer in Sprague–Dawley rats.[33] The regional brain distribution of [^{18}F]**8** was compared with the results obtained from animals that were injected with a combination of [^{18}F]**8** and the D_3-selective ligand BP 897 to test for specific receptor binding of [^{18}F]**8** in vivo. The dose of BP 897 (1 mg/kg) was chosen since it is known that D_3 and D_2 receptors are saturated at doses >0.5 mg/kg.[6a] Rats were sacrificed by decapitation at 45 min post injection (p.i.). The ex vivo autoradiography and histology of the rat brain slices of control and co-injected animals are shown in Figure 3.

The regional distribution of the D_3 receptor in the rat brain has been determined by quantitative in vitro autoradiography in previous studies, indicating the nucleus accumbens, the islands of Calleja, the ventral pallidum, the caudate–putamen (striatum) and cortex as D_3 receptor-positive brain regions.[28,34] In our experiments, we detected specific uptake of [^{18}F]**8** mainly in the striatum and cortex (Fig. 3), as determined by integration of regions of interest (ROI) and comparison with BP 897-co-injected animals, which revealed a reduced tracer uptake of about 90% in striatal and cortical regions (see Supplementary data). However, specific binding of [^{18}F]**8** in other D_3 receptor reference regions, such as the nucleus accumbens or the islands of Calleja, was not visualised. Instead, we observed a high accumulation of [^{18}F]**8** in the brain ventricles with ratios of VT/ST = 3.7 ± 0.8 (n = 6) and VT/CX = 2.1 ± 0.2 (n = 6) (Fig. 3). In BP 897-co-injected animals the ventricular uptake of [^{18}F]**8** was reduced by 50%. It is tempting to speculate that the uptake of [^{18}F]**8** in the brain ventricles could be ascribed to binding to the ependymal cell layer or could be due to the occurrence of radioactive metabolites from [^{18}F]**8**. However, similar cinnamoyl amides have been reported to be stable in vivo,[35] and the uptake of [^{18}F]**8** into the brain ventricles confirmed our studies on ^{18}F-labelled pyridinylphenyl amides, that also significantly accumulated in the brain ventricles.[13] Interestingly, the expression of D_3 receptors on the ependymal cell layer that covers the brain ventricles had been demonstrated by Tomé et al. using immunocytochemistry.[36] The determination of the biokinetics of [^{18}F]**8** and its transport and binding to the ventricular compartment need elucidation by further in vivo experiments.

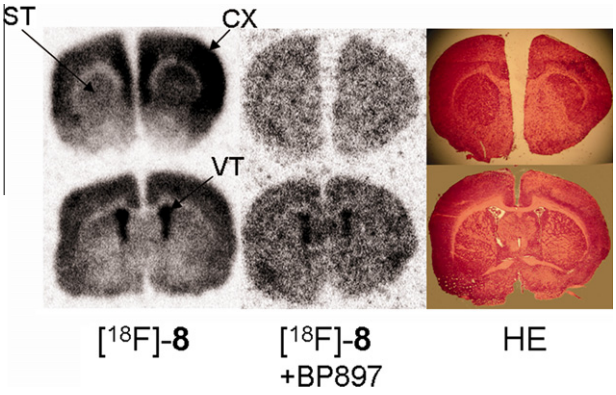


Figure 3. Rat brain autoradiography and haematoxylin/eosin (HE) staining obtained from representative striatal slices and slices containing the brain ventricles (ST = striatum, CX = cortex, VT = ventricle). The experimental procedures have been described in detail previously.[13] Left column: autoradiography of rat brain slices 45 min after administration of [^{18}F]**8** (8.5 MBq). Centre column: rat brain slices obtained from animals co-injected with BP 897 (1 mg/kg) and [^{18}F]**8** (9.3 MBq).

In summary, the three step synthesis of diazonium salt [^{18}F]**11** could be improved within this study and the radical ^{18}F-fluoroarylation method has been successfully applied to the radiochemical synthesis of the dopamine D_3-selective ligand SH 317 ([^{18}F]**8**). In comparison with previously reported arylations of styrene derivatives,[3a] low yields were obtained when applying the fluoroarylation strategy to acrylic amides. Acrylic amides are therefore probably not ideal substrates for labelling techniques based on free aryl radicals. Nevertheless, the ^{18}F-arylation strategy provided sufficient yield of a new PET ligand candidate and allowed its evaluation by in vivo experiments.

Since radiochemical ^{18}F-labelling by radical reactions enables the introduction of the fluorophenyl moiety into a variety of radiopharmaceuticals for PET when established methods are incapable, we are currently working on alternative sources for ^{18}F-fluorinated aryl radicals to facilitate the overall radiochemical yield of this strategy.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.09.142.

References and notes

1. (a) Phelps, M. E. *J. Nucl. Med.* **2000**, *41*, 661; (b) Le Bars, D. *J. Fluorine Chem.* **2006**, *127*, 1488; (c) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501; (d) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, 2853.
2. For recent synthetic developments, see: (a) Lemaire, C. F.; Aerts, J. J.; Voccia, S.; Libert, L. C.; Mercier, F.; Goblet, D.; Plenevaux, A. R.; Luxen, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3161; (b) Maschauer, S.; Einsiedel, J.; Haubner, R.; Hocke, C.; Ocker, M.; Hübner, H.; Kuwert, T.; Gmeiner, P.; Prante, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 976; (c) Bejot, R.; Fowler, T.; Carroll, L.; Boldon, S.; Moore, J. E.; Declerck, J.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 586.
3. (a) Hultsch, C.; Blank, O.; Wester, H.-J.; Heinrich, M. R. *Tetrahedron Lett.* **2008**, *49*, 1881; (b) Höfling, S. B.; Hultsch, C.; Wester, H.-J.; Heinrich, M. R. *Tetrahedron* **2008**, *64*, 11846.

4. For the first synthesis of [^{18}F]fluoro-substituted arenediazonium salts, see: Feliu, A. J. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 1245.
5. For an application of [^{18}F]fluoro-substituted azosulfides, see: Patt, J. T.; Patt, M. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 1229.
6. (a) Pilla, M.; Perachon, S.; Sautel, F.; Garrido, F.; Mann, A.; Wermuth, C. G.; Schwartz, J. C.; Everitt, B. J.; Sokoloff, P. *Nature* **1999**, *400*, 371; (b) Sokoloff, P.; Diaz, J.; Le Foll, B.; Guillin, O.; Leriche, L.; Bezard, E.; Gross, C. *CNS Neurol. Disord. Drug Targets* **2006**, *5*, 25; (c) Joyce, J. N. *Pharmacol. Ther.* **2001**, *90*, 231; (d) Boeckler, F.; Gmeiner, P. *Biochim. Biophys. Acta* **2007**, *1768*, 871.
7. Kuhnast, B.; Valette, H.; Besret, L.; Demphel, S.; Coulon, C.; Ottaviani, M.; Guillermier, M.; Bottlaender, M.; Dolle, F. *Nucl. Med. Biol.* **2006**, *33*, 785.
8. Hocke, C.; Prante, O.; Salama, I.; Hübner, H.; Löber, S.; Kuwert, T.; Gmeiner, P. *ChemMedChem* **2008**, *3*, 788.
9. Sovago, J.; Farde, L.; Halldin, C.; Langer, O.; Laszlovszky, I.; Kiss, B.; Gulyas, B. *Neurochem. Int.* **2004**, *45*, 609.
10. (a) Rabiner, E. A.; Slifstein, M.; Nobrega, J.; Plisson, C.; Huiban, M.; Raymond, R.; Diwan, M.; Wilson, A. A.; McCormick, P.; Gentile, G.; Gunn, R. N.; Laruelle, M. A. *Synapse* **2009**, *63*, 782; (b) Wilson, A. A.; McCormick, P.; Kapur, S.; Willeit, M.; Garcia, A.; Hussey, D.; Houle, S.; Seeman, P.; Ginovart, N. *J. Med. Chem.* **2005**, *48*, 4153; (c) Ginovart, N.; Galineau, L.; Willeit, M.; Mizrahi, R.; Bloomfield, P. M.; Seeman, P.; Houle, S.; Kapur, S.; Wilson, A. A. *J. Neurochem.* **2006**, *97*, 1089; (d) Narendran, R.; Slifstein, M.; Guillin, O.; Hwang, Y. Y.; Hwang, D. R.; Scher, E.; Reeder, S.; Rabiner, E.; Laruelle, M. *Synapse* **2006**, *60*, 485.
11. Vasdev, N.; Seeman, P.; Garcia, A.; Stableford, W. T.; Nobrega, J. N.; Houle, S.; Wilson, A. A. *Nucl. Med. Biol.* **2007**, *34*, 195.
12. Bettinetti, L.; Löber, S.; Hübner, H.; Gmeiner, P. *J. Comb. Chem.* **2005**, *7*, 309.
13. Hocke, C.; Maschauer, S.; Hübner, H.; Löber, S.; Utz, W.; Kuwert, T.; Gmeiner, P.; Prante, O. *ChemMedChem* **2010**, *5*, 941.
14. Bennacef, I.; Salinas, C. A.; Bonasera, T. A.; Gunn, R. N.; Audrain, H.; Jakobsen, S.; Nabulsi, N.; Weinzimmer, D.; Carson, R. E.; Huang, Y.; Holmes, I.; Micheli, F.; Heidbreder, C.; Gentile, G.; Rossi, T.; Laruelle, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5056.
15. (a) Prante, O.; Tietze, R.; Hocke, C.; Löber, S.; Hübner, H.; Kuwert, T.; Gmeiner, P. *J. Med. Chem.* **2008**, *51*, 1800; (b) Tietze, R.; Löber, S.; Hübner, H.; Gmeiner, P.; Kuwert, T.; Prante, O. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 983.
16. Hackling, A.; Ghosh, R.; Perachon, S.; Mann, A.; Höltje, H.-D.; Wermuth, C. G.; Schwartz, J.-C.; Sippl, W.; Sokoloff, P.; Stark, H. *J. Med. Chem.* **2003**, *46*, 3883.
17. Saur, O.; Hackling, A.; Perachon, S.; Schwartz, J.-C.; Sokoloff, P.; Stark, H. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 178.
18. For the generation of aryl radicals from arenediazonium salts, see: Galli, C. *Chem. Rev.* **1988**, *88*, 765.
19. For a review on aryl radicals in olefin functionalizations, see: Heinrich, M. R. *Chem. Eur. J.* **2009**, *15*, 820.
20. Grishchuk, B. D.; Gorbovoi, P. M.; Kudrik, E. Y.; Ganushchak, N. I. *Russ. J. Gen. Chem.* **1993**, *63*, 1620.
21. Wessig, P.; Wettstein, P.; Giese, B.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1994**, *77*, 829.
22. The synthesis of **8** was also carried out using **19** and **11** as reactants. We are unable to report an exact yield for this reaction since **8** could not be separated from unreacted **19** by column chromatography.
23. Several activating agents and conditions were examined for the synthesis of cinnamic amide **8** from amine **16** and acid **20**. Among DCC–DMAP, oxalyl chloride and EDC–DMAP, the described procedure (Ref. 20) was the only method to produce **8** in quantities useful for characterisation and analysis.
24. Hayes, G.; Biden, T. J.; Selbie, L. A.; Shine, J. *Mol. Endocrinol.* **1992**, *6*, 920.
25. Sokoloff, P.; Andrieux, M.; Besançon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. *Eur. J. Pharmacol.* **1992**, *225*, 331.
26. Asghari, V.; Sanyal, S.; Buchwaldt, S.; Paterson, A.; Jovanovic, V.; Van Tol, H. H. M. *J. Neurochem.* **1995**, *65*, 1157.
27. Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.
28. Xu, J.; Hassanzadeh, B.; Chu, W.; Tu, Z.; Jones, L. A.; Luedtke, R. R.; Perlmutter, J. S.; Mintun, M. A.; Mach, R. H. *Synapse* **2010**, *64*, 449.
29. Freedman, S. B.; Patel, S.; Marwood, R.; Emms, F.; Seabrook, G. R.; Knowles, M. R., et al *J. Pharmacol. Exp. Ther.* **1994**, *268*, 417.
30. Willeit, M.; Ginovart, N.; Kapur, S.; Houle, S.; Hussey, D.; Seeman, P.; Wilson, A. A. *Biol. Psychiatry* **2006**, *59*, 389.
31. Huber, D.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2009**, *52*, 6860.
32. Newman, A. H.; Grundt, P.; Nader, M. A. *J. Med. Chem.* **2005**, *48*, 3663.
33. 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).
34. Stanwood, G. D.; Artymyshyn, R. P.; Kung, M. P.; Kung, H. F.; Lucki, I.; McGonigle, P. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 1223.
35. Austin, N. E.; Avenell, K. Y.; Boyfield, I.; Branch, C. L.; Hadley, M. S.; Jeffrey, P.; Johnson, C. N.; Macdonald, G. J.; Nash, D. J.; Riley, G. J.; Smith, A. B.; Stemp, G.; Thewlis, K. M.; Vong, A. K. K.; Wood, M. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 685.
36. Tomé, M.; Moreira, E.; Pérez-Fígares, J.-M.; Jiménez, A. J. *J. Neural. Transm.* **2007**, *114*, 983.