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Discovery of a dopamine D4 selective PET ligand candidate taking advantage of a click chemistry based REM linker

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Abstract—Employing D4 selective azaindoles as lead compounds, a focused library of the carbocyclic arene bioisosteres **1** was synthesized when we took advantage of the click chemistry derived triazolylmethyl acrylate resin **2**. Ligand binding assays on monoaminergic GPCRs led to SARs that indicated further lead structure optimizations when the attachment of alkoxy substituents provided both an improvement of the biological properties and the opportunity to introduce ^{18}F as a radioisotope. Finally, radiosynthesis resulted in formation of the radioligand [^{18}F]**7h** that showed optimal log $D_{7.4}$ of 2.8 and was determined to be highly stable in human serum. Thus, [^{18}F]**7h** represents a promising dopamine D4 selective radioligand for positron emission tomography (PET).

The dopamine D4 receptor has attracted considerable attention as a pharmacological target for the treatment of schizophrenia, Parkinson's disease, depression, and attention deficit hyperactivity disorder (ADHD).[1] Ongoing efforts have been made to generate selective ligands revealing high D4 affinity. Thus, an *N*-arylpiperazine framework proved to be a privileged structural unit,[2] when the second nitrogen atom of the piperazine moiety is preferably attached to a benzylic CH_2 position of a fused heteroarene moiety (Chart 1). Among the bioisosteric elements investigated, azaindole derivatives including the partial agonists L-745,870,[3,4] FAUC 113,[5] ABT-724,[6] PIP3EA[7] and the neutral antagonist FAUC 213[8,9] revealed superior D4 recognition and selectivity. We were intrigued by the question whether a bioisosteric replacement of the azaindole regioisomers by benzene derived carbocyclic analogs could be performed facilitating a regiocontrolled attachment of a wide range of substituents. As a part of our ongoing investigations on the discovery of subtype specific dopaminergic PET candidates,[10–13] we herein describe a two-step procedure involving a click chemistry promoted approach to a focused chemical library and further careful lead optimization facilitating a fine tuning of both selectivity profiles and lipophilicity resulting in the development of the PET ligand [^{18}F]**7h**.

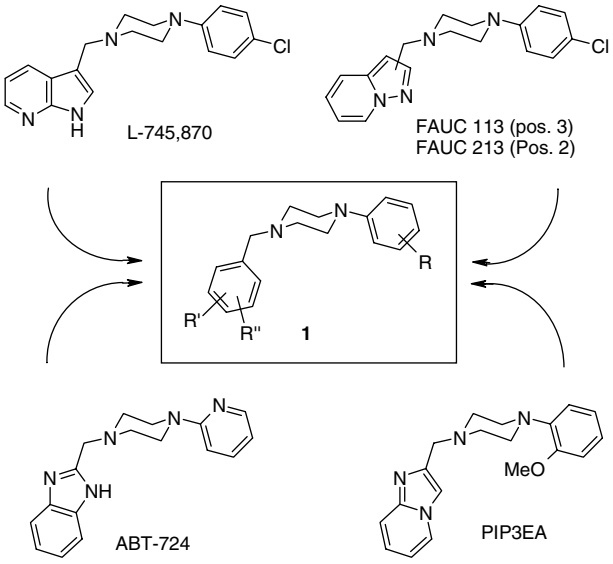

Chart 1. Structures of D4 selective lead and target compounds.

Keywords: D2-like dopamine receptors; Click chemistry; SPOS; Positron emission tomography; PET; F-18.
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'Click resins' enable solid phase supported reactions to work under nearly perfect conditions fulfilling the requirements of click chemistry. Utilizing the triazolylmethyl acrylate (TMA) linker **2**,[14] which is readily available from azidomethyl substituted polystyrene and propargyl acrylate via copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), a regenerative Michael acceptor (REM) strategy[15–17] was envisaged for a parallel synthesis of bioactive tertiary amines of type **1**. In detail, the resin bound Michael acceptor **2** was treated with the phenylpiperazines A1-6 to give the intermediates **3a–f** (Scheme 1). *N*-alkylation with the benzyl bromides B1-3 followed by *Hofmann* elimination of the resulting ammonium ions **4a–r** gave final products **1a–r**.[18] For all solid phase organic synthesis (SPOS) products investigated, the yields were satisfying and comparable to those described for REM-based strategies (Table 1). LCMS analysis of the unpurified final products **1a–r** employing reversed phase chromatography in combination with UV (254 nm) and APCI-ion trap detection indicated an excellent average purity of 95%.

The selection of 'D4-like' building blocks for the parallel synthesis was based on previous SAR studies indicating that chloro and methoxy groups lead to an increase of receptor affinity. Taking into account screening data of our existing in-house library revealing only poor D4 binding for *N*-benzyl-(4-chlorophenyl)piperazine (K_i = 250 nM), H-bond accepting benzyl substituents should be considered simulating the electronegative nitrogen units of the heteroarene based lead compounds. This type of functionalization was also expected to increase solubility and prevent from putatively high unspecific, lipophilicity induced membrane binding. Dopamine receptor screening of the test compounds **1a–r** was performed without further purifications when their ability to bind to the cloned human $D2_{long}$, $D2_{short}$,[19] D3,[20] and D4[21] dopamine receptors, and the porcine D1 subtypes was evaluated in vitro.[22] This was performed in a screening system by measuring the displacement of the radioligands [^{3}H]spiperone for D2, D3, D4 and [^{3}H]SCH23390 for D1 receptors using 10 μM, 100 nM, and 1 nM concentrations of the test compounds. The results in Table 1 depicting the displacement data at a final concentration of 100 nM indicate D4 receptor preference for most test compounds. Comparison of unpolar arenes with the derivatives bearing H-bond accepting groups confirmed our anticipation that a bioisosteric replacement of the azaindole moiety requires an electronegative congener that could be represented by a methoxy or cyano unit. Combining this pharmacophoric portion with 3,4-dichloro- or 2-methoxyphenylpiperazines via a common methylene linker led to the most promising D4 ligands **1d**,**e** and **1j**, respectively.

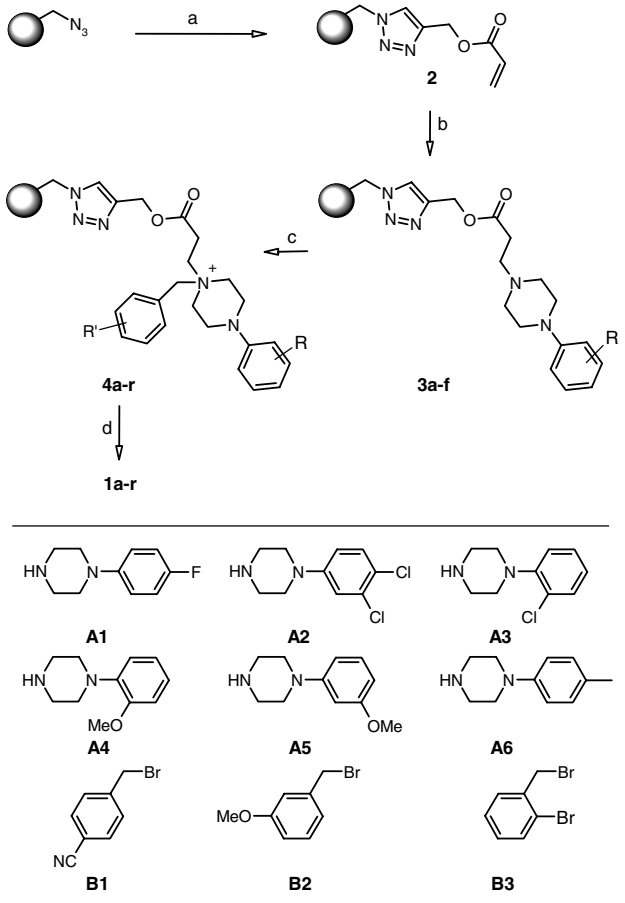
Aiming at the design of ^{18}F-labeled analogs derived from these lead compounds, our strategy was based on the formal structural exchange of methoxy groups by 2-fluoroethoxy moieties. Thus, the D4 ligand **1e** represents a 'starting point' for further careful lead optimization by introducing additional methoxy substituent at the benzyl system and, thus, optimizing lipophilicity, while simultaneously varying the position of a fluoroethoxy substituent. Furthermore, we chose 2-methoxyphenylpiperazine (A4) and the A2 derived analog 4-chlorophenylpiperazine, which has been successfully validated as a capable recognition element in vivo,[9] as promising scaffolds in the syntheses of a new series of test compounds (Scheme 2).

The benzaldehyde derivatives **5a–5d**, bearing a free hydroxyl group in the *para*-position (**5a** (vaniline), **5b**), in *meta*-position (**5c**), and in *ortho*-position (**5d**), respec-

Table 1. Purities,[a] yields, and screening data for dopaminergic affinities[b] of benzylpiperazines **1a–r**

Compound	Building blocks	Purity (%)	Yield (%)	$D2_{long}$	D3	D4
1a	A1B1	90	53	0	15	47
1b	A1B2	95	65	2	0	18
1c	A1B3	99	74	1	1	4
1d	A2B1	99	82	0	0	91
1e	A2B2	99	59	9	2	92
1f	A2B3	98	58	10	14	0
1g	A3B1	96	64	2	2	73
1h	A3B2	99	64	4	13	55
1i	A3B3	98	45	0	4	9
1j	A4B1	99	76	4	5	82
1k	A4B2	96	86	6	39	26
1l	A4B3	99	82	9	21	44
1m	A5B1	99	83	2	6	69
1n	A5B2	86	84	0	9	46
1o	A5B3	99	63	2	0	4
1p	A6B1	92	36	0	4	59
1q	A6B2	97	88	6	39	45
1r	A6B3	91	43	6	16	7
Color code						
Displacement (%)		<20	20–39	40–59	60–79	80–100

[a] Determined by LCMS analyses at 254 nm.
[b] Relative displacement of radioligand at a concentration of the test compound of 100 nM determined as triplicate.

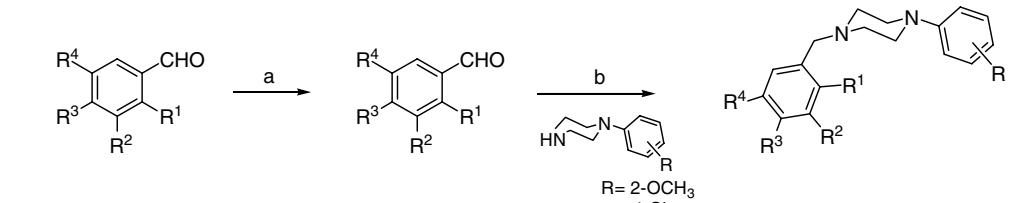


Scheme 1. Reagents and conditions: (a) propargyl acrylate, Cu(I)I, DMF, THF, DIPEA, 35 °C, 10 h (Ref. 14); (b) **A1-6**, NMP, rt, 36 h; (c) **B1-3**, DMSO, rt, 16 h; (d) TEA, DMF, rt, 4 h.

tively, were converted to the corresponding fluoroethyl ethers **6a**–**6d** by alkylation with 2-fluoroethyl tosylate in the presence of tetrabutylammonium hydroxide, following a procedure described by Wilson and coworkers.[23] Subsequent reductive amination of **6a**–**6d** with commercially available 4-chloro- or 2-methoxyphenylpiperazine using $Na(OAc)_3BH$ readily afforded a series of 8 target benzyl compounds (**7a**–**7h**) in 30–80% yield.[24]

After purification by chromatography, LCMS analysis, and identification,[25] the target compounds **7a**–**h** were subjected to receptor binding studies to determine the affinity and selectivity profile with respect to the different subtypes of dopamine receptors, as described above. In addition, binding properties to the related serotonin receptors 5-HT_{1A} and 5-HT_2, and to the adrenergic α_1 receptor were measured using porcine cortical membranes and the selective radioligands [^{3}H]8-OH-DPAT or [^{3}H]WAY600135, [^{3}H]ketanserin, and [^{3}H]prazosin, respectively. For comparison, the affinity constant (K_i) values of a reference compound (FAUC 213) determined under the same assay conditions are included in Table 2.

All test compounds revealed weak affinity to the D1 receptor, while **7a**–**d** and **7h** preferentially bind to the D4 receptors in the low nanomolar range (1.3–3.7 nM; Table 2). The 2-methoxyphenyl moiety (**7a**–**d**) is beneficial for high D4 receptor affinity, while some of the corresponding derivatives bearing a 4-chlorophenyl substituent (**7e**–**g**) revealed decreased D4 affinities. When comparing **7a**–**7d** among each other, variation of the fluoroethoxy substitution pattern and introduction of additional methoxy groups have only marginal effects on the binding profile, resulting in good D4 affinities, but relatively low D4/D2 subtype selectivities of only about 30-170. Contrary to the series **7a**–**d**, in the case of **7e**–**h** the D2 and D4 binding was significantly influenced by the substitution pattern of the benzyl scaffold (Table 2). In fact, the introduction of a methoxy group in *meta*-position led to a markedly increased D4/D2 subtype-selectivity (**7e**: 1750) accompanied by only weak differences in D4 affinity (cf. **7e** vs **7f**). While a fluoroethoxy substitution in *meta*-position turned out to be less suitable, which is due to decreased D4 affinity (**7g**, Table 2), the introduction of additional methoxy groups and simultaneously maintaining the fluoroethoxy group in the *ortho*-position turned out to be benefi-



5a: R^1= H, R^2= OCH_3, R^3= OH, R^4= H

5b: R^1= H, R^2= H, R^3= OH, R^4= H

5c: R^1= H, R^2= OH, R^3= H, R^4= H

5d: R^1= OH, R^2= H, R^3= OCH_3, R^4= OCH_3

6a: R^1= H, R^2= OCH_3, R^3= $O(CH_2)_2F$, R^4= H

6b: R^1= H, R^2= H, R^3= $O(CH_2)_2F$, R^4= H

6c: R^1= H, R^2= $O(CH_2)_2F$, R^3= H, R^4= H

6d: R^1= $O(CH_2)_2F$, R^2= H, R^3= OCH_3, R^4= OCH_3

7a: R= 2-OCH_3, R^1= H, R^2= OCH_3, R^3= $O(CH_2)_2F$, R^4= H

7b: R= 2-OCH_3, R^1= H, R^2= H, R^3= $O(CH_2)_2F$, R^4= H

7c: R= 2-OCH_3, R^1= H, R^2= $O(CH_2)_2F$, R^3= H, R^4= H

7d: R= 2-OCH_3, R^1= $O(CH_2)_2F$, R^2= H, R^3= OCH_3, R^4= OCH_3

7e: R= 4-Cl, R^1= H, R^2= OCH_3, R^3= $O(CH_2)_2F$, R^4= H

7f: R= 4-Cl, R^1= H, R^2= H, R^3= $O(CH_2)_2F$, R^4= H

7g: R= 4-Cl, R^1= H, R^2= $O(CH_2)_2F$, R^3= H, R^4= H

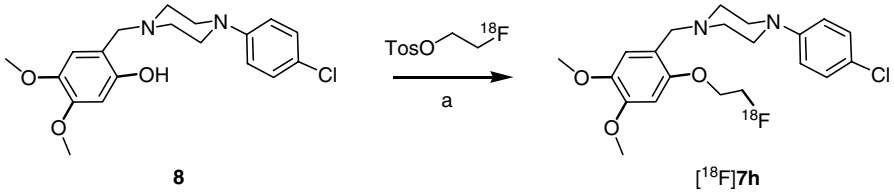
7h: R= 4-Cl, R^1= $O(CH_2)_2F$, R^2= H, R^3= OCH_3, R^4= OCH_3

Scheme 2. Reagents and conditions: (a) 2-fluoroethyl tosylate, $N(Bu)_4OH$, DMF, rt, 24 h; (b) $Na(OAc)_3BH$ (4–5 equiv), CH_2Cl_2, rt, 16 h.

Table 2. Receptor binding data of **7a**–**7h** at human $D2_{long}$, D3, and D4.4 receptors as well as porcine D1, 5-HT_{1A}, 5-HT_2, and α_1 receptors[a]

Compound	pD1	$hD2_{long}$	hD3	hD4.4	p5-HT_{1A}	p5-HT_2	pα_1	*C*log*P*[b]
7a	5400	310	1100	1.8	100	2100	21	3.3
7b	3400	120	77	3.7	120	5400	47	3.5
7c	5200	57	270	1.6	32	1900	36	3.5
7d	6800	94	330	1.3	100	280	13	3.2
7e	5700	21,000	4900	12	18,000	850	18	4.1
7f	1400	1100	1100	50	5200	1800	160	4.4
7g	5100	590	1100	82	3300	980	190	4.4
7h	3500	760	3900	1.7	2800	100	4.4	4.1
FAUC 213	5500	3400	5300	2.2	1700	900	270	3.5

[a] K_i values in nM are based on the means of 2–4 experiments each done in triplicate.
[b] Calculated value using the software *C*log*P* (Biobyte Corp.).



Scheme 3. Reagent and condition: (a) NBu_4OH, DMF, 110 °C, 3 min.

cial as indicated by K_i values in the low nanomolar range for D4 (**7d** and **7h**). **7h** showed an adequate balance between D4 affinity (1.7 nM) and exceptional D4 subtype selectivities (D4/D2 = 450, D4/D3 = 2300, Table 2).

In order to assess the lipophilicity of the test compounds as a measure of blood brain barrier permeability, we calculated log*P* values (Table 2). Within the series of 2-methoxyphenyl derivatives (**7a**–**7d**) *C*log*P* values were 3.2–3.5, being consistent with FAUC 213 as a reference, whereas the 4-chlorophenyl derivatives (**7e**–**7h**) revealed higher lipophilicity with *C*log*P* of 4.1–4.4. Noteworthy, within each series of test compounds, the presence of additional methoxy groups in the benzyl moeity (**7d**, **7h**) clearly reduced lipophilicity to a minimum (Table 2). This effect could help to adequately meet the prerequisites for optimal brain uptake, since radiotracer uptake into the brain is a function of log*P* that peaks between log*P* of 2 and 3.[26]

As a proof of concept and due to the promising high D4 receptor affinity and distinct D4 receptor subtype-selectivity of **7h**, we aimed at the radiosynthesis of the corresponding ^{18}F-labeled analog. Employing ^{18}F-fluoroalkylation by means of [^{18}F]fluoroethyl tosylate[11] as one of the most commonly used ^{18}F-labeled prosthetic groups,[27] we prepared the 2-hydroxybenzyl derivative **8** as a suitable precursor following the general procedure for reductive amination starting from **5d**.[24] The intermediate **8** was reacted with tetrabutylammonium hydroxide in DMF at 110°C to form the *ortho*-phenoxide in situ before addition of [^{18}F]fluoroethyl tosylate (Scheme 3).[28] The decay-corrected radiochemical yield of [^{18}F]**7h** was 92 ± 4% after 3 min as determined by radio-HPLC. The D4 ligand **7h** served as authentic reference in analytical radio-HPLC to confirm chemical identity of [^{18}F]**7h**. [^{18}F]**7h** was isolated by semipreparative RP-HPLC followed by solid phase extraction (Sep-Pak C-18).

The resulting buffered solution (PBS) of [^{18}F]**7h** was used to determine experimental log$D_{7.4}$ values (extraction in octanol/PBS)[29] and for studying the metabolic stability in human serum. [^{18}F]**7h** revealed a log$D_{7.4}$ value of 2.8 ± 0.2 (n = 6), due to the presence of the partly protonated piperazine at physiological pH. In addition to the hydrophilic influence of additional methoxy groups, the resulting lipophilicity excellently complied with an optimum. Moreover, [^{18}F]**7h** was determined to be highly stable in human serum (>95%, 90 min), as analyzed by radio-HPLC. These in vitro parameters suggest advantageous characteristics for in vivo use, such as adequate blood-brain-barrier penetration combined with high metabolic stability in the blood. This assumption has to be confirmed by further biodistributional studies.

In conclusion, a click chemistry promoted SPOS approach allowed rapid access to a focused chemical library when further lead optimization resulted in the discovery of a series of potential D4 PET ligands. As exemplified by the ^{18}F-radiosynthesis of [^{18}F]**7h**, the use of modern SPOS techniques followed by careful lead optimization considering the structural requirements for ^{18}F-labeling can facilitate the development of D4 selective PET ligands.

Acknowledgments

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Shine (The Garvan Institute of Medical Research, Sydney), and late Dr. H.H.M. Van Tol (Clarke Institute of Psychiatry, Toronto) for providing D3, D4.4, and D2 receptor expressing cell lines. This research was supported by a grant of the Deutsche Forschungsgemeinschaft (PR 677/2-2).

References and notes

1. Todd, R. D.; O'Malley, K. L. *TIPS* **2001**, *22*, 55.
2. Klabunde, T.; Hessler, G. *Chem. Bio. Chem.* **2002**, *3*, 928.
3. Kulagowski, J. J.; Broughton, H. B.; Curtis, N. R.; Mawer, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedman, S. B.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1941.
4. Gazi, L.; Bobirnac, I.; Danzeisen, M.; Schüpbach, E.; Langenegger, D.; Sommer, B.; Hoyer, D.; Tricklebank, M.; Schoeffter, P. *Br. J. Pharmacol.* **1999**, *128*, 613.
5. Löber, S.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97.
6. Cowart, M.; Latshaw, S. P.; Bhatia, P.; Daanen, J. F.; Rohde, J.; Nelson, S. L.; Patel, M.; Kolasa, T.; Nakane, M.; Uchic, M. E.; Miller, L. N.; Terranova, M. A.; Chang, R.; Donnelly-Roberts, D. L.; Namovic, M. T.; Hollingsworth, P. R.; Martino, B. R.; Lynch, J. J., III; Sullivan, J. P.; Hsieh, G. C.; Moreland, R. B.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2004**, *47*, 3853.
7. Enguehard-Gueiffier, C.; Hübner, H.; El Hakmaoui, A.; Allouchi, H.; Gmeiner, P.; Argiolas, A.; Melis, M. R.; Gueiffier, A. *J. Med. Chem.* **2006**, *49*, 3938.
8. Löber, S.; Hübner, H.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2001**, *44*, 2691.
9. Boeckler, F.; Russig, H.; Zhang, W.; Löber, S.; Hübner, H.; Ferger, B.; Gmeiner, P.; Feldon, J. *Psychopharmacology* **2004**, *175*, 7.
10. Salama, I.; Hocke, C.; Utz, W.; Prante, O.; Boeckler, F.; Hübner, H.; Kuwert, T.; Gmeiner, P. *J. Med. Chem.* **2007**, *50*, 489.
11. Tietze, R.; Hocke, C.; Löber, S.; Hübner, H.; Kuwert, T.; Gmeiner, P.; Prante, O. *J. Labelled Compd. Radiopharm.* **2006**, *49*, 55.
12. Hocke, C.; Prante, O.; Löber, S.; Hübner, H.; Gmeiner, P.; Kuwert, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4819.
13. Hocke, C.; Prante, O.; Löber, S.; Hübner, H.; Gmeiner, P.; Kuwert, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3963.
14. Löber, S.; Gmeiner, P. *Tetrahedron* **2004**, *60*, 8699.
15. Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1997**, *38*, 3209.
16. Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288.
17. Kroll, F. E. K.; Morphy, J. R.; Rees, D.; Gani, D. *Tetrahedron Lett.* **1997**, *38*, 8573.
18. General procedure: TMA resin (**2**) (300 mg, 1,63 mmol/g) was agitated with a arylpiperazine (A1-6, 10 equiv) in NMP (6 ml) for 36 h at ambient temperature. The suspension was filtered through the vessel frit and the resin was rinsed alternately with MeOH (5×10 mL), CH_2Cl_2 (5×10 mL), and pyridine (5×10 mL). Subsequent washing with DMSO (2×10 mL) was followed by the addition of a solution of a benzyl bromide (B1-3, 5 equiv) in DMSO (6 mL) and agitation for 16 h at ambient temperature. After filtration of the solvent the resin was washed with MeOH (3×10 mL) and CH_2Cl_2 (10×5 mL), and TEA (0.6 mL, 14 mmol) in DMF (6 mL) was added. Stirring at ambient temperature for 6 h was followed by filtration of the solvent, whereas the resin was washed with DMF (10 mL) and CH_2Cl_2 (3×10 mL). After evaporation of the solvent the resulting residue was dissolved in CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$. Evaporation of the solvent afforded the desired benzylpiperazines **1a**–**r** in 36–86 % yield.
19. Hayes, G.; Biden, T. J.; Selbie, L. A.; Shine, J. *Mol. Endocrinol.* **1992**, *6*, 920.
20. Sokoloff, P.; Andrieux, M.; Besancon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. *Eur. J. Pharmacol.* **1992**, *225*, 331.
21. Asghari, V.; Sanyal, S.; Buchwaldt, S.; Paterson, A.; Jovanovic, V.; Van Tol, H. H. M. *J. Neurochem.* **1995**, *65*, 1157.
22. Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.
23. Wilson, A. A.; DaSilva, J. N.; Houle, S. *Nucl. Med. Biol.* **1996**, *23*, 487.
24. General procedure: **6a**–**6d** or **5d** (0.7 mmol, 1 equiv) and 1-(2-methoxyphenyl)piperazine or 1-(4-chlorophenyl)piperazine (1.3 equiv), respectively, were dissolved in 20 mL dry CH_2Cl_2. $Na(OAc)_3BH$ (4–5 equiv) was added to the suspension in one portion. The mixture was stirred overnight at room temperature. The reaction was quenched by adding 30 mL saturated $NaHCO_3$. The product was extracted with ethyl acetate (3×20 mL) and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica gel chromatography using CH_2Cl_2/MeOH (95:5). **7a**–**7h** and **8** were obtained in 30–80% yield.
25. **7a**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.66 (brs, 4H), 3.11 (brs, 4H), 3.54 (s, 2H), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.22–4.32 (dt, 2H), 4.69–4.85 (dt, 2H), 6.84–7.01 (m, 7H). LC-MS (APCI): *m/z* 375.1 $[M+H]^+$. **7b**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.67 (brs, 4H), 3.10 (brs, 4H), 3.55 (s, 2H), 3.86 (s, 3H, OCH_3), 4.17–4.27 (dt, 2H), 4.68–4.84 (dt, 2H), 6.84–7.00 (m, 5H), 7.29 (d, 2H). LC-MS (APCI): *m/z* 345.0 $[M+H]^+$. **7c**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.68 (brs, 4H), 3.11 (brs, 4H), 3.58 (s, 2H), 3.86 (s, 3H, OCH_3), 4.19–4.29 (dt, 2H), 4.68–4.84 (dt, 2H), 6.83–7.01 (m, 6H), 7.23–7.31 (m, 2H). LC-MS (APCI): *m/z* 345.1 $[M+H]^+$. **7d**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.72 (s, 4H), 3.10 (s, 4H), 3.63 (s, 2H), 3.85 (s, 3H, OCH_3), 3.87 (brs, 6H, $2 \times OCH_3$), 4.16–4.26 (dt, 2H), 4.65–4.81 (dt, 2H), 6.54 (s, 1H), 6.83–7.01 (m, 5H). LC-MS (APCI): *m/z* 405.2 $[M+H]^+$. **7e**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.63 (brs, 4H), 3.21 (brs, 4H), 3.55 (s, 2H), 3.90 (s, 3H, OCH_3), 4.23–4.33 (dt, 2H), 4.70–4.86(dt, 2H), 6.84 (d, 2H), 6.86–6.90 (m, 2H), 7.21 (d, 2H), 7.27(s, 1H). LC-MS (APCI): *m/z* 379.2 $[M+H]^+$. **7f**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.60 (brs, 4H), 3.16 (brs, 4H), 3.52 (s, 2H), 4.15–4.25 (dt, 2H), 4.66-4.81 (dt, 2H), 6.80 (d, 2H), 6.88 (d, 2H), 7.17 (d, 2H), 7.27 (d, 2H). LC-MS (APCI): *m/z* 349.2 $[M+H]^+$. **7g**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.68 (brs, 4H), 3.24 (brs, 4H), 3.63 (s, 2H), 4.22–4.31 (dt, 2H), 4.69–4.85 (dt, 2H), 6.84 (d, 2H) 6.86–6.92 (m, 1H), 6.99 (d, 1H) 7.21 (d, 2H), 7.25 (m, 2H). LC-MS (APCI): *m/z* 349.5 $[M+H]^+$. **7h**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.68 (brs, 4H), 3.19 (brs, 4H), 3.64 (s, 2H), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.17–4.27 (dt, 2H), 4.66–4.82 (dt, 2H), 6.55 (s, 1H), 6.83 (d, 2H), 7.20 (d, 2H), 7.27 (s, 1H). LC-MS (APCI): *m/z* 409.2 $[M+H]^+$. **8**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 2.72 (brs, 4H), 3.21 (brs, 4H), 3.70 (s, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 6.46 (s, 1H), 6.53 (s, 1H), 6.84 (d, 2H), 7.21 (d, 2H). LC-MS (APCI): *m/z* 363.1 $[M+H]^+$.
26. Waterhouse, R. N. *Mol. Imaging Biol.* **2003**, *5*, 376.
27. For a recent review, see: Schirrmacher, R.; Wängler, C.; Schirrmacher, E. *Mini-Rev. Org. Chem.* **2007**, *4*, 317.
28. An aqueous solution (1 mL, CH_3CN/H_2O, 8:2) containing K_2CO_3 (15 μmol), Kryptofix 2.2.2 (15 mg), and no-carrier-added [^{18}F]fluoride (0.5–1.0 GBq, PET Net GmbH,

Erlangen) was azeotropicaly dried at 85 °C. As described previously,[11] 4.5 mg (12 μmol) bistosyloxyethane in 0.5 mL anhydrous acetonitrile was added and the mixture was stirred for 3 min at 90 °C. After semipreparative HPLC (Lichrosorb RP18, 125 × 8 mm, 4 mL/min, 40% acetonitrile in water), [^{18}F]fluoroethyl tosylate was obtained in a decay-uncorrected radiochemical yield of about 60%, a molar radioactivity of >330 GBq/μmol and a radiochemical purity of at least 98%. Subsequently, 750 μL of a solution of [^{18}F]fluoroethyl tosylate in dry DMF (0.3–0.6 GBq) was added to a preincubated solution of **8** (2.8 mg, 7.7 μmol) in 250 μL dry DMF and 20 μL of 1.4 M tetrabutylammonium hydroxide in dry MeOH (3 min, 110°C). The radiochemical yield of [^{18}F]**7h** was 92 ± 4% after 3 min (n = 3; radio-TLC, R_f = 0.44; radio-HPLC, Lichrosorb RP-18, 250 × 4.6 mm, 1 mL/min, 25–100% acetonitrile in water (0.1% TFA) in 30 min): t_R = 14.1 min). [^{18}F]**7h** was manually purified by semipreparative HPLC (Kromasil C-8, 125 × 8 mm, 4 mL/min, 37.5% acetonitrile in water (0.1% TFA), t_R([^{18}F]**7h**) = 5.7 min, t_R(**8**) = 3.1–4.5 min) followed by SPE (C-18, 100 mg, Merck).

29. Prante, O.; Hocke, C.; Löber, S.; Hübner, H.; Gmeiner, P.; Kuwert, T. *Nuklearmedizin* **2006**, *45*, 41.