Bioorganic & Medicinal Chemistry Letters 24 (2014) 5399–5403

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Synthesis and evaluation of fluoro substituted pyridinylcarboxamides and their phenylazo analogues for potential dopamine D3 receptor PET imaging

Natascha Nebel [a], Simone Maschauer [a], Amelie L. Bartuschat [b], Stefanie K. Fehler [b], Harald Hübner [b], Peter Gmeiner [b], Torsten Kuwert [a], Markus R. Heinrich [b], Olaf Prante [a,*], Carsten Hocke [a]

[a] Department of Nuclear Medicine, Molecular Imaging and Radiochemistry, Friedrich Alexander University, Schwabachanlage 6, D-91054 Erlangen, Germany
[b] Department of Chemistry and Pharmacy, Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, Schuhstrasse 19, D-91052 Erlangen, Germany

ARTICLE INFO

*Article history:*
Received 20 August 2014
Revised 9 October 2014
Accepted 14 October 2014
Available online 22 October 2014

*Keywords:*
Fluoroarylation
Azoester
Fluorine
PET
Dopamine
D3 receptor

ABSTRACT

A series of fluoro substituted pyridinylcarboxamides and their phenylazo analogues with high affinity and selectivity for the dopamine D3 receptor was synthesized by the use of 6-fluoropyridine-3-carbonyl chloride (**1**) and fluorophenylazocarboxylic ester (**2**). Several of these compounds (**9a–e** and **10a–h**) have been evaluated in vitro, among which **9b**, **10a**, **10c** and **10d** proved to have at least single-digit nanomolar affinity for D3. They also exhibit considerable selectivity over the other dopamine receptor subtypes and noteworthy selectivity over the structurally related serotonin receptor subtypes 5-$HT_{1A}$ and 5-$HT_2$, offering potential radiotracers for positron emission tomography.



The receptors of the dopaminergic neurotransmission system belong to the family of transmembrane G-protein-coupled receptors (GPCRs).[1,2] These dopamine receptors are widely distributed in the central nervous system (CNS), and are also found in peripheral tissues. Five subtypes of dopamine receptors are known, comprising two main classes according to their pharmacological properties: activation of D1-like receptors, which include D1 and D5 receptors, stimulates adenylyl cyclase, whereas activation of D2-like receptors (D2–D4) receptors has an inhibitory action on adenylyl cyclase.[3]

The several dopamine receptors have long been important targets for the development of pharmacotherapeutic agents for treating CNS disorders, notably Parkinson's disease, schizophrenia, depression and drug addiction.[4–7] However, relatively few pharmaceuticals have complete selectivity between D2 and D3 receptor subtypes. The predominant distribution of D3 receptors in the nucleus accumbens suggests a particular role of these receptors in the action of drugs of abuse,[8,9] and altered density of these receptors may underlie habituation and dependence on psychostimulants.[10] In addition, D3-selective antagonists might afford antipsychotic activity with less incidence of extrapyramidal motor symptoms,[11] as typically occurs due to blockade of D2 receptors in the dorsal striatum. A large number of dopamine D3-selective ligands have been synthesized as candidates for therapeutics.[12–22]

In a search to identify an agent for selective imaging of D3 receptors in the human brain using positron emission tomography (PET), the most prominent progress has been achieved by the discovery of the naphthoxazine **[$^{11}$C](+)-PHNO** (Fig. 1), a D2/D3 agonist radioligand, that preferentially binds to the D3 subtype in vivo.[23,24] An interesting finding was made by the in vivo characterization of the D3-selective [$^{18}$F]fluoroethoxy substituted thienyl benzamide **[$^{18}$F]LS-3-134** (Fig. 1). The study revealed significant competition between endogenous dopamine and the D3 selective radioligand for the available fraction of D3 receptors in vivo, resulting in a markedly diminished PET signal.[25]

Lead compounds **BP897** and **FAUC346** (Fig. 1), have high affinity to the dopamine D3 receptor, and considerable selectivity over the other subtypes.[12,26] In addition to high affinity and selectivity, favorable properties of candidate PET tracers derived from these lead compounds are their high specific activity, an absence of pharmacologically active radiolabelled metabolites, and appropriate lipophilicity.[27] However, in our experience, D3 ligands of this structural class also tend to bind to serotonin 5-$HT_{1A}$ receptors in brain tissue.[28,29] In our endeavor to synthesize $^{18}$F-labeled D3 receptor ligands suitable for PET studies, we further investigated structure–activity relationships (SARs), based upon two early

* Corresponding author. Tel.: +49 9131 8544440; fax: +49 9131 8534440.
*E-mail address:* olaf.prante@uk-erlangen.de (O. Prante).

http://dx.doi.org/10.1016/j.bmcl.2014.10.043
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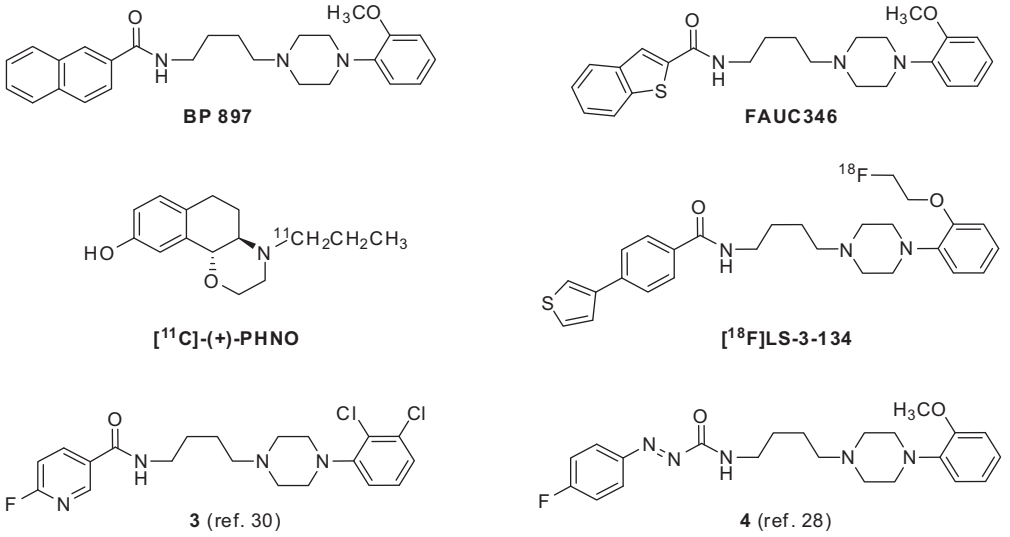



**Figure 1.** Structures of D3 ligand lead compounds.

$^{18}$F-labeled lead series derivatives of the pyridinylcarboxamide **3**[18,30] and phenylazocarboxamide **4**[28] (Fig. 1). These newly developed $^{18}$F-labeled tracers needed further optimization, since interfering binding to 5-$HT_{1A}$ receptors was observed and the lipophilicity of these candidates needed to be improved.

Compound **3** showed a high octanol/water partition coefficient (log*P*) of 4.39, which is predictive of permeability to the blood–brain barrier (BBB). However, log*P* values in the range 2–3.5 are considered optimal; within a class of structurally related compounds, higher log*P* values generally impart higher non-specific binding, and less signal-to-noise in PET recordings.[31] This is particularly an issue for detecting receptors of rather low abundance, such as the D3 site. The calculated log*P* of the compound **4** was similar (4.55) (Fig. 1).

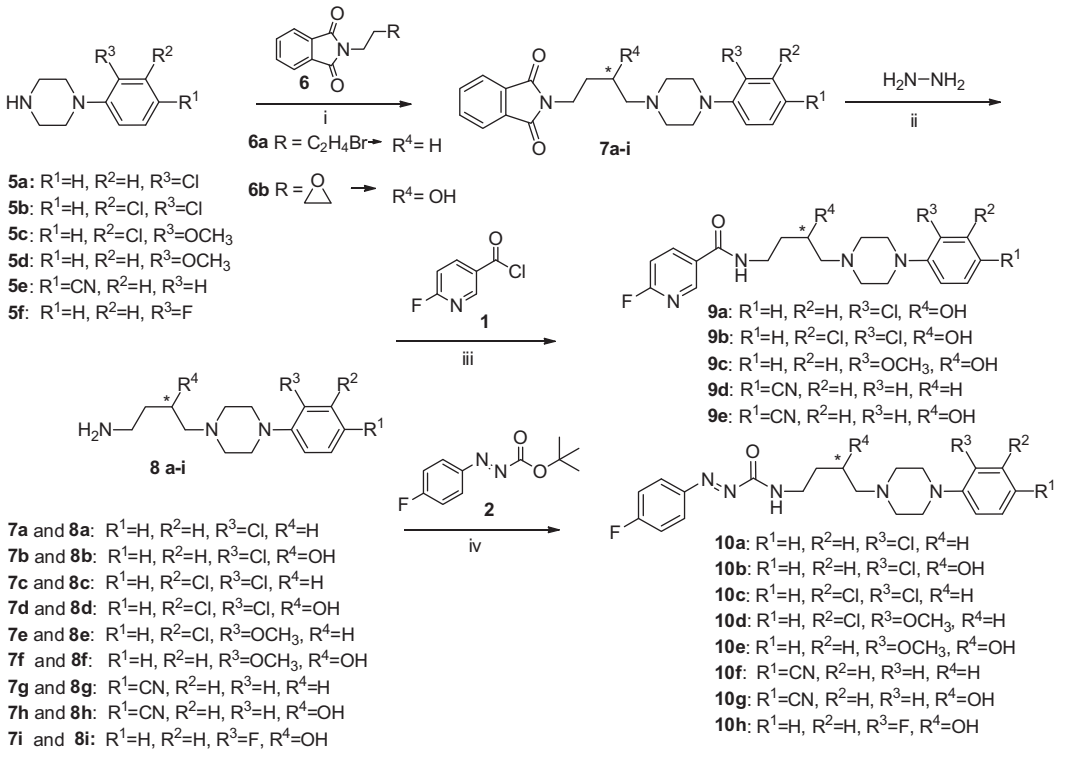
Previous studies by other groups have shown that hydroxylation of the alkyl chain lowers the log*P* value, whilst retaining high affinity, and in some cases even increasing D3 selectivity.[15] Thus, we predicted that the lipophilicity of lead compounds **3** and **4** should be significantly reduced by the introduction of a C-3 hydroxyl group. The aspect of further SAR studies with lead compound **4** despite its high log*P* value is the observation that the aromatic nucleus of phenylazocarboxylic esters is highly activated for nucleophilic aromatic substitution, and subsequent reactions based at the carbonyl group are also easily obtained. These are favorable attributes for very efficient $^{18}$F-labeling.[28,32,33]

We now report further SAR developments on pyridinylcarboxamide **3** and phenylazocarboxamide **4** with the intention to generate a high affinity and highly selective D3 receptor ligand. In addition, the lipophilicity of a series of compounds was reduced by introducing a hydroxyl group at the butyl spacer in both classes of lead compounds. Moreover, we varied the substituents at the aromatic ring of our new series of compounds for three reasons: First, our previous studies on the influence of the 2,3-dichloro substituent[34] and the 2-chloro or mixed chloro and methoxy substituents[17] at the phenylpiperazinyl moiety of structurally related derivatives revealed a significant influence on D3 affinity and beneficial D3 subtype selectivity. Second, the introduction of a methoxy substituent could be most suitable to further improve the hydrophilicity of candidate ligands,[35,36] and third, the introduction of the para-cyano substituent was envisaged, since this substitution pattern has been previously reported for a D3 antagonist ligand.[37]

We demonstrate the synthesis of several new fluorinated D3 receptor ligands with potential as PET tracers. The synthesis of the new derivatives is outlined in Scheme 1 and followed previously published synthetic routes.[12,15,18,28,38]

The primary amines **8a**, **8c**, **8e** and **8g** were obtained starting from the commercially available substituted phenylpiperazine by N-alkylation with 4-bromobutylphthalimide (**6a**) and subsequent hydrazinolysis in yields of 53–66% (Scheme 1).[12] Compound **9d** was synthesized by coupling of 6-fluoropyridine-3-carbonyl chloride (**1**) with the aminobutyl-substituted phenylpiperazine **8g** in a yield of 45%.[18] The synthesis of the hydroxylated pyridinylcarboxamides **9a**, **9b**, **9c** and **9e** and phenylazocarboxamides **10b**, **10e**, **10g** and **10h** are also illustrated in Scheme 1. 2-(2-Bromoethyl)oxirane, which is synthesized from commercially available 4-bromo-1-butene and mCPBA, was reacted with potassium phthalimide to form the 2-(2-(oxirane-2-yl)-ethyl)isoindoline-1,3-dione **6b**.[15,39] The conformationally strained epoxides react cleanly with amines **5a**, **5b**, **5d–f** to yield amino alcohols **7b**, **7d**, **7f**, **7h** and **7i** when the ring opening occurs in a regioselective manner at the least substituted side of the oxirane. This is the case for all of the phenylpiperazines, leading to racemic mixtures of products in high yields (86–93%). The hydroxybutylamines **8b**, **8d**, **8f**, **8h**, **8i** were obtained after treatment of **7b**, **7d**, **7f**, **7h**, **7i** with hydrazine in markedly varying yields (36–70%).[15] In the final coupling step, **8b**, **8f**, **8h**, **8i**, as well as unhydroxylated compounds **8a**, **8c**, **8e** and **8g** were then reacted with *tert*-butyl 2-(4-fluorophenyl)azocarboxylate (**2**) in the presence of $K_2CO_3$ in an nucleophilic substitution to afford **10a–h** in low yields (10–45%).[28] The synthesis of the respective desired hydroxylated pyridinylcarboxamide derivatives **9a–c** and **9e** was accomplished by N-acylation of **8b**, **8d**, **8f** and **8h** with 6-fluoropyridine-3-carbonyl chloride **6a** in yields of 43–64%.[15,18]

The lipophilicity calculations of the compounds **9a–e** and **10a–h** were performed using the software ChemDraw Ultra (CambridgeSoft, Perkin Elmer). The range of calculated log*P* (*c*log*P*) values of the compounds **9a–e** and **10a–h** were between 2.05 and 6.18 (Table 1). The introduction of the hydroxyl group at the butyl spacer ($R^4$) of lead compound **4** (*c*log*P* 4.55) lowered the log*P* value by 0.82 units as demonstrated by the c log*P* of compound **10e** (*c*log*P* 3.73, Table 1). The same effect was found by comparing compounds **10a** with **10b**, and **10f** with **10g** (decreased *c*log*P* by 0.86 units). In the case of structures of class **9**, the difference in *c*log*P* units induced by the hydroxyl group was 0.63, as seen in the comparisons of lead compound **3** with **9b**, and **9d** with **9e**. Thus, introduction of a hydroxyl function in the alkyl linking chain consistently lowers lipophilicity. Varying the substitution pattern




**Scheme 1.** Reaction scheme for the syntheses of pyridinyl- and phenylazocarboxamides. Reagents and conditions: 1. $R^4$ = H (i) $K_2CO_3$, DMF, 80 °C, 24 h. (ii) Hydrazine, EtOH, reflux, 24 h. (iii) Triethylamine, $CH_2Cl_2$, rt, 24 h. (iv) $K_2CO_3$, EtOAc, rt, 72 h. 2. $R^4$ = OH (i) 2-PrOH, 100 °C, 20 min, microwave. (ii) Hydrazine, EtOH, 100 °C, 20 min, microwave. (iii) Triethylamine, $CH_2Cl_2$, rt, 24 h. (iv) $K_2CO_3$, EtOAc, rt, 72 h.

**Table 1**
Binding affinities of new fluorinated ligands **9a–e**, **10a–h** and reference compounds **3** and **4** to the human dopamine receptor subtypes $D2_{long}$, $D2_{short}$, D3, D4, D1 and D5 receptors, as well as the porcine 5-$HT_{1A}$, the human 5-$HT_2$ and the porcine α1 receptors

| Compd | $K_i$ values (nM)[a] | | | | | | | | | *c*log*P*[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| | [$^3$H]spiperone | | | | [$^3$H]SCH 23990 | | [$^3$H]WAY 600135 | [$^3$H]ketanserin | [$^3$H]prazosin | |
| | $D2_{long}$ | $D2_{short}$ | D3 | D4.4 | D1 | D5 | 5-$HT_{1A}$ | 5-$HT_2$ | α1 | |
| **9a** | 390 | 300 | 27 | 1700 | 3000 | 17,000 | 57 | 510 | 27 | 3.10 |
| **9b** | 90 | 43 | 1.9 | 290 | 6650 | >60,000 | 5 | 12 | 98 | 3.77 |
| **9c** | 1100 | 530 | 400 | 680 | >70,000 | >60,000 | 62 | 3700 | 100 | 2.16 |
| **9d** | 2300 | 1500 | 550 | 880 | 5000 | >70,000 | 1200 | 900 | 740 | 2.68 |
| **9e** | 40,000 | 40,000 | 740 | 12,000 | >85,000 | >100,000 | 1700 | 10,000 | 2800 | 2.05 |
| **10a** | 49 | 20 | 1.8 | 55 | 620 | 3500 | 11 | 190 | 5.8 | 5.53 |
| **10b** | 140 | 140 | 14 | 1000 | 1900 | 11,000 | 100 | 590 | 51 | 4.67 |
| **10c** | 8.6 | 5 | 0.39 | 39 | 570 | 2900 | 12 | 7.4 | 15 | 6.18 |
| **10d** | 34 | 27 | 3.8 | 67 | 2000 | 17,000 | 16 | 19 | 18 | 5.18 |
| **10e** | 420 | 360 | 52 | 800 | >60,000 | >70,000 | 68 | 2300 | 66 | 3.73 |
| **10f** | 16,000 | 8800 | 1100 | 6000 | 19,000 | >100,000 | 6100 | 2500 | 1800 | 4.48 |
| **10g** | 3600 | 2500 | 970 | 9700 | >70,000 | >65,000 | 1900 | 2700 | 2900 | 3.62 |
| **10h** | 300 | 220 | 67 | 1800 | 3800 | 33,000 | 320 | 1100 | 140 | 4.10 |
| **3**[b] | 21 | 29[b] | 1.1 | 100 | 1300 | nd | 28 | 84 | 16 | 4.39 |
| **4**[c] | 38 | 36 | 3.5 | 94 | nd | nd | 6.4 | 43 | 5.2 | 4.55 |

nd: Not determined;
[a] $K_i$ values are the mean values of 2–6 experiments each done in triplicate.
[b] Data from Ref. [18].
[c] $K_i$ values from Ref. [28].
[d] *c*log*P* values were calculated using the software ChemDraw Ultra 13.0 (CambridgeSoft, Perkin Elmer).

on the aromatic system by adding the methoxy substitution in 2-position or the cyano substitution served to reduce lipophilicity (Table 1: **9c**, **10e**). In the case of compound **9a**, by avoiding the chlorine substituent at $R^2$ (Scheme 1), and through introduction of the hydroxyl function, a further lowering of the *c*log*P* value to reach 3.1 was possible. However, it turned out that increased hydrophilicity of the candidate ligands **9a**, **9c–e** compromised the high affinity at D3 receptors, while only the hydroxyl analogue **9b**, derived from lead compound **3**, indicated a moderately increased hydrophilicity (*c*log*P* 3.77) and retained single-digit nanomolar affinity to D3 receptors (Table 1).

To determine the affinity and selectivity of the target compounds **9a–e** and **10a–h**, we used a battery of ligand binding assays for the subtypes of dopamine receptors, and also some related biogenic amine receptors, i.e. serotonin 5-$HT_{1A}$, and 5-$HT_2$, and the $\alpha_1$ adrenergic subtype.[40] Binding to the dopamine receptors

of the D2 family was measured with membranes of CHO cells stably expressing human dopamine receptors or with homogenates from HEK 293 cells transiently transfected with D1 or D5. The D1 and D5 were measured using the radioligand [$^3$H]SCH 23390, and the $D2_{long}$, $D2_{short}$, D3 and D4.4 subtypes were measured with [$^3$H]spiperone. The human serotonergic 5-$HT_{2A}$ receptor expressed in membranes of HEK 293 cells was detected with [$^3$H]ketanserin. Binding properties to the serotoninergic receptor 5-$HT_{1A}$ and the adrenergic receptor $\alpha_1$ were evaluated with porcine cortical membranes and the selective radioligands [$^3$H]WAY600135 and [$^3$H]prazosin.

One focus of our study was the modification of the substituent at the phenyl ring of our lead compound **4** with and without the inclusion of a hydroxyl group in the alkyl chain. The highest affinity for the D3 receptor was found with the 2,3-dichloro derivative **10c** (0.39 nM), which had good selectivity over 5-$HT_{1A}$ (31-fold), compared to only 1.8-fold for compound **4**. Compounds **10a**, **10b** and **10d** had affinities of 1.8, 14 and 3.8 nM to the D3 subtype, respectively. These compounds showed slight improvements in terms of selectivity for D3 compared to analogue **4**, with 4–7 fold higher D3 selectivity over 5-$HT_{1A}$ sites. We were disappointed by the outcome of compounds **9d**, **9e** and **10f**, **10g**; these para-substituted cyano compounds all showed a significant loss of affinity to the D3 receptor, with $K_i$ values in the range of 550–1100 nM. Compared with the lead compound **4** (Fig. 1), its analogue **10e** suffered a 15-fold loss of D3 affinity through hydroxylation. A similar effect was observed in the case of the 2-fluoro substituted derivative **10h**.

With respect to the pyridinylcarboxamides **9a**–**e**, the chloro analogues **9a** and **9b** showed higher affinity at D3 receptors compared to the methoxy-substituted analogue **9c**; a similar finding was previously reported for this class of compounds.[18] However, none of the new pyridinylcarboxamide analogues displayed improved D3 affinity or D3-versus-5-$HT_{1A}$ selectivity more suitable than that of the lead compound **3**. In particular, only pyridinylcarboxamide **9b** showed a similar high affinity for the D3 receptor (1.9 nM) as did lead structure **3**.

Our results on the receptor binding data of the pyridinylcarboxamides **9** and phenylazocarboxamides **10** generally confirmed our previous SAR study on the substitution pattern at the phenylpiperazine fragment,[12,17,18] suggesting that the 2,3-chloro-substitution is preferred for high D3 affinity. When comparing derivatives of the series of pyridinylcarboxamides **9** with the corresponding phenylazocarboxamides of type **10** (e.g., **9a**/**10b** or **3**/**10c** or **9c**/**10e**), we conclude that the binding profile was very similar, confirming that the phenylazocarboxamides could be used as bioisosteres for phenylcarboxamides in their binding to D3 receptors. Interestingly, the series of phenylazocarboxamides tended to show a slightly increased D3-over-5-$HT_{1A}$ selectivity (Table 1).

The corresponding $^{18}$F-labeled compounds of **9a**–**e** could be achieved by direct $^{18}$F-for-Br aromatic nucleophilic substitution, following a previously described procedure.[18] Recently, we have successfully developed a highly efficient two-stage process of $^{18}$F-labeling, applying the trimethylammonium triflate of the para-substituted phenylazocarboxylic ester as a precursor amenable to $^{18}$F-labeling.[28] The resulting reactive 4-[$^{18}$F]fluorophenylazocarboxylate intermediate reacts with primary amines via amidation and yielded the $^{18}$F-labeled lead compound **4**.[28] Very recently, we further optimized the $^{18}$F-labeling reaction between primary amines and $^{18}$F-labeled phenylazocarboxamides and demonstrated that this $^{18}$F-labeling reaction was transferable onto the synthesis of the hydroxylated analogues of the phenylazocarboxamides, offering a synthesis strategy for $^{18}$F-labeled compounds **10a**–**h**. However, the radiosyntheses of $^{18}$F-labeled compounds was beyond the scope of the current study; the detailed results on the optimization of the $^{18}$F-chemistry will be published elsewhere.

The present study involved the synthesis of novel ligands for dopamine D3 receptors, with an aim to attain optimal properties for PET studies *in vivo*, with respect to affinity, selectivity, and lipophilicity. We find that incorporation of the hydroxyl substituent in the alkyl chain has a significant effect of reducing lipophilicity in all the derivatives. By changing the substitution pattern on the phenyl ring, we identified some derivatives with at least single-digit nanomolar affinity for the D3 receptor, comprising **9b**, **10a**, **10c** and **10d**. Moreover, **10a**, **10c** and **10d** also revealed improved D3-over-5-$HT_{1A}$ and D3-over-$\alpha$1 selectivity in comparison with lead compound **4**. The reduction in lipophilicity through addition of the hydroxyl function together with the preferred 2,3-dichloro substitution at the phenylpiperazinyl moiety turned out to be a promising strategy without unfavorable effects on D3 receptor affinity, which points towards structures suitable for investigation by PET.

## Acknowledgments

The authors thank Katharina Zhuravlova for experimental help. We note professional editing of the manuscript by Inglewood Biomedical Editing. This work was supported by the Deutsche Forschungsgemeinschaft (DFG; PR 677/3-2, HE 5413/3-1). This study is part of the Neurotrition Project, which is supported by the Emerging Fields Initiative of the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU).

## Supplementary data

Supplementary data (detailed experimental procedures and data for the synthesis and the pharmacological investigations) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.10.043.

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