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

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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

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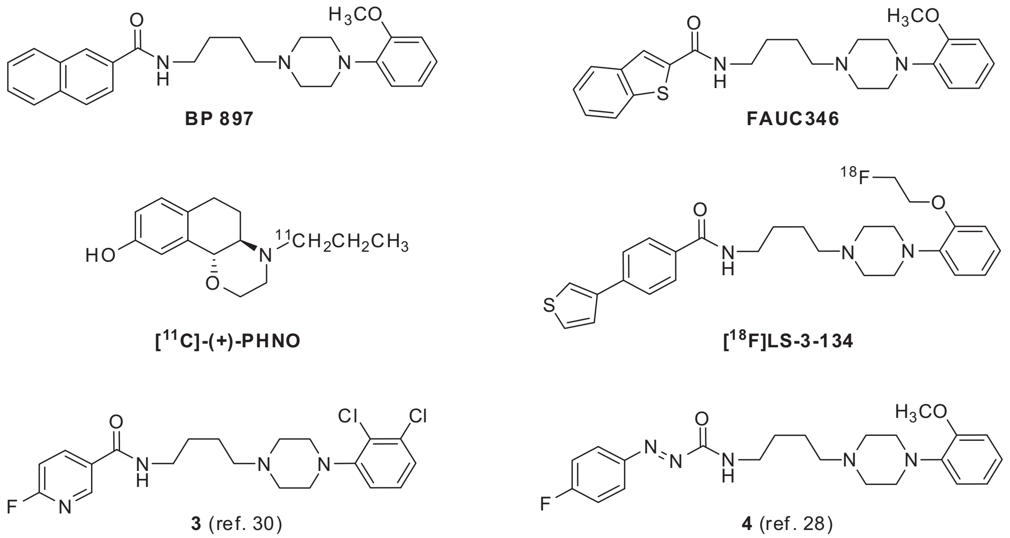

Figure 1. Structures of D3 ligand lead compounds.

^{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