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Dopamine D_3 receptor antagonists: The quest for a potentially selective PET ligand. Part one: Lead identification

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ABSTRACT

The synthesis and SAR of a new series of potent and selective dopamine D_3 receptor antagonists is reported.

Following the isolation and characterization of the cDNA for the dopamine (DA) D_3 receptor,[1] a number of DA D_3 receptor antagonists both selective and non selective have been reported from industrial and academic groups. Detailed reviews on this topic are available.[2] Growing evidence suggests that selective antagonists at the DA D_3 receptor can reduce the reinforcing efficacy of drugs of abuse, significantly improve drug-induced learning deficits without altering the normal learning process in non-impaired rats, and show efficacy in animal models of schizophrenia.[2a] GSK has had a long-standing interest in this field and have actively contributed with the discovery of selective DA D_3 receptor antagonists.[3–12] A number of recently disclosed molecules are reported in Figure 1.

The proof of efficacy of a DA D_3 receptor antagonist for the treatment of neuropsychiatric indications will be confirmed ultimately from clinical trials. As such, the availability of a selective ligand to visualize the DA D_3 receptor and to provide information about the receptor occupancy in the human brain is critical. The recently disclosed compound [^{11}C]PHNO, an agonist at DA D_2-like receptors, may offer potential as such a discovery medicine tool. Encouraging Positron Emission Tomography (PET) studies in cats and humans with [^{11}C]PHNO revealed an atypical distribution compared to radiolabeled D_2-like antagonists (such as [^{11}C]raclopride) or other D_2-like agonists (such as [^{11}C]NPA) suggesting that the D_3 receptor contribution to [^{11}C]PHNO signal is higher than that of [^{11}C]raclopride.[13,14]

Although results generated using the agonist [^{11}C]PHNO show great potential, the discovery and development of a selective DA D_3 receptor antagonist as a PET ligand remains an interesting target for experimental medicine studies.

The optimization of a specific PET ligand, requires a focus on different physico-chemical parameters to those normally used in the identification of a potential clinical drug candidate. Our efforts towards the identification of a selective DA D_3 PET ligand and initial evaluation studies will be described in this Letter.

In order to identify an appropriate molecule, each new chemical entity (NCE) prepared in this study was evaluated for its agonistic versus antagonistic properties using a functional GTPγS assay expressing the human DA D_3 receptor;[5] all the compounds reported in the present work proved to be antagonists at the DA D_3 receptor. Their affinity is reported as functional pK_i (fpK_i) in the following tables.

Criteria for lead identification within the investigations for a PET ligand included a minimum of 30-fold selectivity versus DA D_2 (functional assays), and a 10-fold selectivity versus the hERG ion channel (Dofetilide binding assay).[5] Furthermore, selected derivatives were tested for brain penetration, free fraction in tissue, and plasma protein binding.

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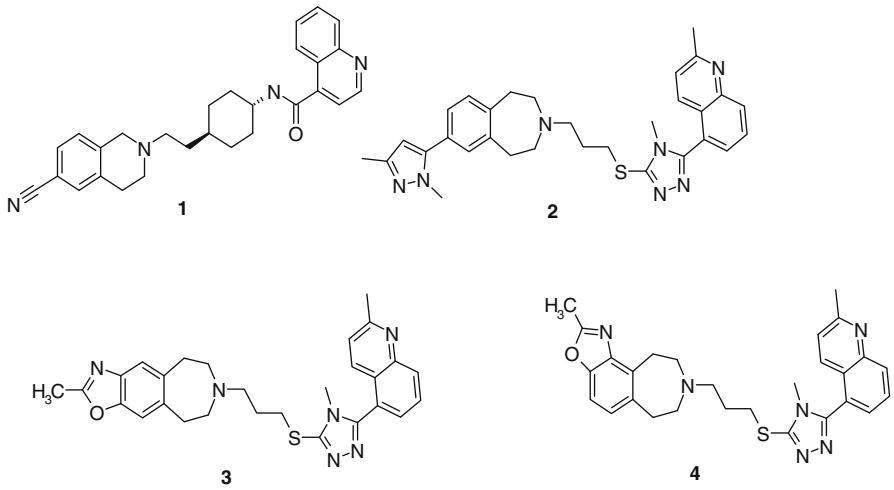


Figure 1. GSK selective DA D_3 receptor antagonists.

The ideal profile for a potential PET ligand is a structure endowed with high potency at the target receptor, high selectivity, low lipophilicity, and low plasma protein binding. Accordingly, it was decided to attempt to optimize a hit molecule from our internal screening collection with appropriate potency and developability but poor initial selectivity (D_3 vs D_2), namely the phenyl-3-[2-(diethylamino)ethyl]-2-imidazolidinone (**5**) (Table 1).

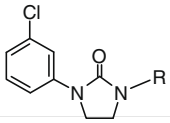
This molecule had a 10-fold selectivity versus D_2 receptor, but more than a 100-fold selectivity versus the hERG channel.

As this new template showed a potentially different binding mode in the receptor model[5] compared to previously explored templates, it was decided to keep the 3-Cl phenyl group fixed and to explore the right hand side with different side chains to build an initial understanding of SAR for the series. In particular, different aliphatic and aromatic substituents were chosen to potentially probe some lipophilic/aromatic interactions within the above mentioned receptor model.

The introduction of a substituted pyrrolidine moiety (**6**) led to a decrease in the desired affinity at the D_3 receptor and a decrease in selectivity versus the D_2 receptor.

Further exploration was initiated (**15**–**24**) with the hope that the introduction of a second aromatic ring would lead to improved potency and selectivity. As clearly seen by the tabulated results, this goal was not achieved with the exception of derivative **23** for which nanomolar affinity at the D_3 receptor was met. Unfortunately, the above mentioned selectivity criterion was not achieved.

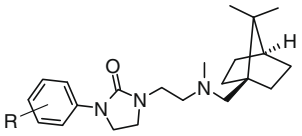
Table 1
hERG and affinity results



Entry	R	D_3 fpKi	D_2 fpKi	hERG pIC_{50}
1	N.A.	8.4	6.4	5.7
2	N.A.	8.8	6.5	5.7
3	N.A.	7.2	<5.6	<5.0
4	N.A.	7.2	<6.2	5.6
5	2-(Diethylamino)ethyl	8.6	7.6	5.5
6	(2*S*)-2-[(Methyloxy)methyl]-1-pyrrolidinyl	7.1	7.1	5.3
7	2-[(1*S*,5*R*)-1,3,3-Trimethyl-6-azabicyclo[3.2.1]oct-6-yl]ethyl	7.9	7.0	5.9
8	2-[(1*R*,4*S*)-2-Azabicyclo[2.2.1]hept-2-yl]ethyl	8.6	8.4	4.9
9	2-{(1*R*,5*S*)-8-[(Methyloxy)methyl]-3-azabicyclo[3.2.1]oct-3-yl}ethyl	6.8	6.5	6.0
10	2-[(1*R*,5*S*)-1-Methyl-3-phenyl-6-azabicyclo[3.2.1]oct-6-yl]ethyl	7.7	7.8	7.2
11	2-[(1*S*,5*S*)-3-Azabicyclo[3.2.2]non-3-yl]ethyl	8.5	7.6	6.4
12	2-[(1*S*,5*R*)-1,8,8-Trimethyl-3-azabicyclo[3.2.1]oct-3-yl	7.8	7.5	5.9
13	2-[(1*R*,10*S*)-11-Azatricyclo[8.2.2.03,8]tetradeca-3,5,7-trien-11-yl]ethyl	8.6	7.6	7.2
14	2-[(1*R*,5*S*)-8-Azabicyclo[3.2.1]oct-8-yl]ethyl	8.9	8.3	5.8
15	2-{3-[3-(Methyloxy)phenyl]-1-piperidinyl}ethyl	6.2	7.6	6.7
16	2-{3-[(Phenylmethyl)oxy]-1-piperidinyl}ethyl	7.0	7.1	7.1
17	2-[4-(4-Chlorophenyl)-1-piperidinyl]ethyl	7.3	6.6	8.1
18	2-(Methyl{2-[3-(methyloxy)phenyl]ethyl}amino)ethyl	6.9	7.3	6.2
19	2-[3,4-Bis(methyloxy)phenyl]ethyl}(methyl)amino]ethyl	6.9	7.0	5.6
20	2-[4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-1-piperidinyl]ethyl	6.8	6.3	6.6
21	2-[(1-Benzothien-2-ylmethyl)(methyl)amino]ethyl	7.5	7.3	5.8
22	2-{Methyl[(3-methyl-5-isoxazolyl)methyl]amino}ethyl	6.9	6.8	4.3
23	2-(4,6,7,8-Tetrahydro-5*H*-thieno[3,2-c]azepin-5-yl)ethyl	9.2	8.5	6.1
24	2-[(1*S*,7*R*)-10,10-Dimethyl-4-azatricyclo[5.2.1.01,5]dec-4-yl]ethyl	7.6	6.5	6.1
25	2-(1,3-Dihydro-2*H*-isoindol-2-yl)ethyl	8.6	7.0	5.5

SEM for D_3 GTPγS, and HERG data sets is ±0.1; SEM for the D_2 GTPγS data is ±0.2. N.A. = Not applicable.

Table 2
hERG and affinity results



Entry	R	D_3 fpKi	D_2 fpKi	hERG pIC_{50}
26	3-Cl	8.2	6.9	5.5
27	3-CF_3	8.8	7.7	5.2
28	4-Me	7.6	6.0	5.6
29	3-OMe	8.3	6.9	5.7
30	3-Me	7.7	6.6	5.8
31	H	8.0	6.7	5.4
32	4-F	7.4	6.2	5.5
33	3,4-Dioxolanyl	7.3	5.8	5.2

SEM for D_3 GTPγS, and HERG data sets is ±0.1. SEM for the D_2 GTPγS data is ±0.2.

Differently to the above strategy, in this series the introduction of an aromatic moiety spaced by one carbon atom from the basic nitrogen (**25**) showed improved potency and selectivity, leading to a template endowed with a 40-fold selectivity over the DA D_2 receptor and a more than 100-fold selectivity with respect to the hERG channel.

A similar result was achieved using {[(1*R*,4*R*)-7,7-dimethylbicyclo[2.2.1]hept-1-yl]methyl}methylamine to give molecules in which again the ring system is spaced by one carbon atom from the basic nitrogen. This approach led to **26** (Table 2) which displays a 20-fold selectivity over D_2 and high selectivity over hERG.

Keeping the amine moiety fixed the role of the substitution pattern on the left hand side aryl group in this series was further explored (**27–33**).

The introduction of an electron withdrawing group with no mesomeric effect like the $-CF_3$ group (**27**) produced an increase in potency at both D_3 and D_2 receptors, whereas a substituent with electron withdrawing properties, but a strong mesomeric effect ($-OCH_3$, **29**) gave similar results to the 3-chloro substituted derivative (**26**) or to the un-substituted system (**31**). The introduction of a 'neutral' substituent with no electro donating properties ($-CH_3$, **30** and **28**) showed no major impact. Finally, the 4-F substituent and the dioxolane group (**32** and **33**, respectively) were poorly tolerated with a drop in D_3 potency.

This initial exploratory work led us to conclude that compound **25** (moderate selectivity vs D_2 and simple chemical structure) appears to be the best candidate for a further lead optimization program of a PET ligand. Accordingly, additional selectivity tests were performed before investing further resources in the exploration of this template. The compound was tested at 1 μM at Cerep[15] showing good selectivity (<50% binding) over a panel of 60 receptors, including H1, the muscarinic family, and the 5-HT family with the exception of the 5-HT_{2A} receptor where the compound showed a functional $pK_i = 6.2$.

Further in house testing at more than 100 receptors revealed a very clean profile for such a simple molecule, the only additional activity identified was at the DA D_4 receptor with a $pK_i = 6.8$.

As **25** represented the starting point for optimization of a potential PET ligand, for which the pharmaco-kinetic properties are crucial, the molecule was profiled in vitro.

When assayed for intrinsic clearance in human and rat liver microsomes,[5] **25** showed values of 8.9 and 36.9 (ml/min/kg), respectively. These data suggest the potential for quick metabolism from the body, another positive characteristic for a PET ligand.

The promising results of the PET ligand lead identification phase encouraged us to further proceed toward the lead optimization phase that will be described in Part two.

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