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Improving selectivity of dopamine D3 receptor ligands

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ABSTRACT

The seminal human dopamine D3 receptor (hD3R) ligand BP 897 has shown interesting properties during clinical trials. However, its lack of selectivity towards human adrenergic receptor impedes further development. Two approaches were followed to increase hD3R selectivity. The lead optimisation succeeded, we disclose here ligands with subnanomolar potency for D3R, combined with a good selectivity for the closely related human dopamine D2 and human adrenergic alpha-1 receptors.

Since its discovery in 1990,[1] the dopamine D3 receptor (D3R) has been widely studied. Its localisation in the limbic area of the brain[2] as well as the early investigations with agonists[3] or antagonists[4] led to the hypothesis that the therapeutic use of such compounds should be directed towards drug abuse.[5] More recent studies have shown that therapeutic potential uses could lie in other neurological and neuropsychiatric disorders.[6]

BP 897[4] (Fig. 1) is the first representative of potent selective partial agonists identified for this receptor. It has represented a prototype for further analogues by many groups. However, contrary to preliminary evaluation on rat adrenergic alpha-1 receptor, selectivity towards human adrenergic alpha-1 receptor proved to be insufficient and led to side effects (orthostatic hypotension) in clinical trials.

It was thus decided to improve selectivity towards human adrenergic alpha-1 receptor (hα1R), while keeping the selectivity towards the structurally close human dopamine D2 receptor (hD2R). A good affinity for the human dopamine D3 receptor (hD3R) along with partial agonist activity was also required.[7]

Some of the well known hα1R ligands are described in Figure 2.

The common ortho-methoxyphenylpiperazine present in these structures as well as in BP 897 could be responsible for the hα1R affinity. The first approach was thus to systematically investigate the influence of the substitution of this aromatic ring onto the selectivity. A first set of compounds was thus prepared according to the following synthetic scheme:[8]

Substitution on the ortho position with electron donating (**3a**, **3b**, **3c**) or electron withdrawing (**3d**, **3e**), lipophilic (**3b**, **3d**, **3e**) or hydrophilic (**3c**) substituent did not alter the affinity for the hα1R (Table 1). All these compounds (**3a**–**3e**) displayed an affinity constant in the ten nanomolar range while retaining a strong binding to hD3R. The only exception was the hydrophilic hydroxy (**3c**) which is twenty fold less potent on hD3R (see Scheme 1).

meta (**3f**) or *para* (**3g**) substitution with a chlorine atom slightly diminished the binding to hα1R, but *para*-substitution (**3g**) seemed to be more detrimental for hD3R. Molecular modelling indicated that the *para* substituent of the phenyl impedes its localisation in the hydrophobic pocket. Steric hindrance was thus supposed to be responsible for this decrease of affinity and further investigation of the *para* position was abandoned (see Table 2).

Disubstitution on both ortho and *meta* position with chlorine is known to give potent hD3R ligands. This observation was transposed here and gave a potent compound with a good selectivity for hD2R. Interestingly, disubstitution with either electron with-

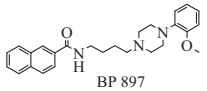

Figure 1. Structure of BP 897.

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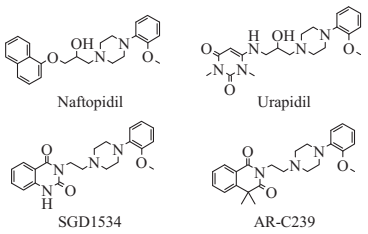
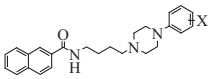


Figure 2. Structure of known hα1R ligands.

Table 1
Binding and selectivity ratio of compounds **3a-k** at human dopamine D2 and D3 receptors and human adrenergic α1 receptor



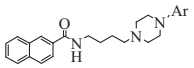
Entry	X	K_i (nM)			Ratio	
		D2	D3	α1	D2/D3	α1/D3
3a	o-OMe	186	0.67	9.15	280	14
3b	o-Me	404	0.73	29.9	550	41
3c	o-OH	5031	12.7	46.7	400	3.7
3d	o-F	310	1.23	38.5	250	31
3e	o-Cl	238	0.7	29.9	340	43
3f	m-Cl	3323	4.7	50.2	700	11
3g	p-Cl	12143	10.4	166	1170	16
3h	o,m-Cl_2	1149	1.08	104	1100	96
3i	o,m-Me_2	302	1.33	230	230	170
3j	m-CF_3	1553	1.1	283	1400	260
3k	m-OH	373	0.2	1525	1900	7600

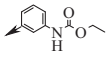
drawing chlorine (**3h**) or electron donating methyl (**3i**) gave nearly the same result for hα1R. This selectivity profile of the ligands was improved, but it was still not sufficient for a drug candidate (see Fig. 3).

Further investigation of the *meta* position revealed that lipophilic electron withdrawing CF_3 (**3j**) or hydrophilic slightly electron withdrawing hydroxy (**3k**) was detrimental to hα1R binding. Chloro (**3f**) has similar electronic and hydrophobic properties as compared to CF_3, but is less detrimental to hα1R binding. The effects are probably multi parametric: both steric hindrance (for **3j** CF_3) and hydrophilicity (for **3k** hydroxy) may be key parameters. Both of these last compounds (**3j** and **3k**) retained a nanomolar affinity for hD3R, with a special enhancement for the hydroxy substituent (**3k**). Molecular modelling suggested that a hydrogen bond with Ser192 and/or Ser196 could be responsible for this gain. This last compound displayed a suitable selectivity but phenol moiety usually displays metabolic liabilities. Furthermore, both compounds interact with hERG channel giving 51% (**3j**) and 30% (**3k**) inhibition of dofetilide binding when tested at 1 μM. Not surprisingly, affinity for hERG channel correlates with lipophilicity.

Every compound in the naphthylamide series displaying a K_i for hD3R below 2 nM was found to be a partial agonist[1] with an intrinsic activity of 0.5–0.7. The arylpiperazine part of the molecule does not seem to be involved in the modulation of the agonism.

Table 2
Binding and selectivity ratio of compounds **3a–k** at human dopamine D2 and D3 receptors and human adrenergic α1 receptor



Entry	Ar	K_i (nM)			Ratio	
		D2	D3	α1	D2/D3	α1/D3
3k		373	0.2	1525	1900	7600
3l		95	1.3	19	73	15
3m		52	0.5	211	100	420
3n		131	3.5	158	37	45
3o		55	1.6	160	34	100
3p		911	3.9	1030	234	264

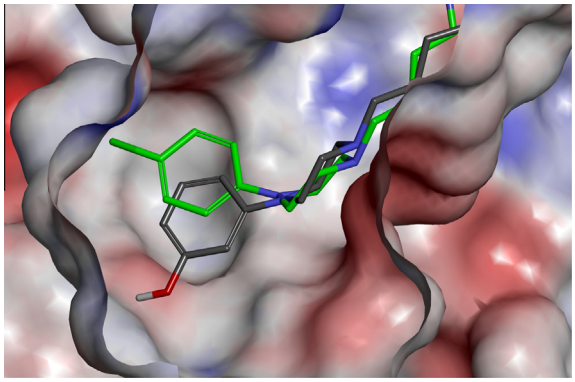
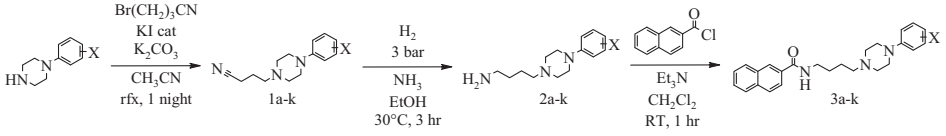


Figure 3. Putative binding mode of ligands in the D3R.[9] Compound **3g** (carbon atoms in green) and compound **3k** (carbon atoms in grey) are superimposed in the D3R binding site.[10] Due to steric limitations and the lack of hydrogen bond, the centroid of the chlorophenyl is 1.5 Å above that of hydroxyphenyl.

Bioisosteric replacement of the phenol[11] with indole (**3l**), indolinone (**3m**), and benzimidazolone (**3n**) was thus investigated. Good affinity for human D3 receptor was retained whereas selectivity was decreased for both hD2R and hα1R. Making the hypothesis that selectivity could also rely on the absence of substituent on the ortho position, other H donating groups were introduced in the *meta* position: methylsulfonamide[12] (**3o**) and ethyl carbamate (**3p**). None of these retained the selectivity of the *meta*-hydroxyphenyl (**3k**).

Another approach to address the lack of selectivity was to systematically investigate the left hand part of the molecule. The chemical tractability of the amino precursor (**2a**) allowed diverse condensations, as depicted in Scheme 2.



Scheme 1. Synthesis of naphthamide derivatives.