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BMCL Digest

Synthesis and evaluation of amides surrogates of dopamine D3 receptor ligands

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ABSTRACT

Isosteric replacement of the amide function and modulation of the arylpiperazine moiety of known dopamine D3 receptor ligands led to potent and selective compounds. Enhanced bioavailability and preferential brain distribution make compound **6c** a good candidate for pharmacological and clinical evaluation.

Since its discovery in 1990,[1] the dopamine D3 receptor (D3R) has been widely studied. Its localization in the limbic area of the brain[2] as well as the early investigations with agonists[3] or antagonists[4] led to the current view that the therapeutic use of such compounds should be directed toward drug abuse. More recent studies have shown that therapeutic potential uses could lie in other neurological and neuropsychiatric disorders.[5] Hence, there are at least two new chemical entities currently in phase I development: ABT-614 and GSK618334, planned to be used for alcoholism, compulsive disorder and substance abuse.

BP 897[4] (Fig. 1) is the first representative of potent selective antagonists or partial agonists for this receptor. It has represented a prototype for further analogs by many groups. The structural modifications addressed all parts of the molecule: modification of the naphthyl part, homologation, and rigidification of the linker, substitution of the arylpiperazine and its replacement with other heterocycles.

Modification of the aromatic amide has mainly focused toward its replacement with other polyaromatics such as fluorene in NGB2904[6] and biphenyl in GR103691,[7] or heteroaromatics like benzothiophene in FAUC346[8] or benzofurane in A[9] and, even, large ferrocenyl derivatives.[10] Aromatic amides bearing an *ortho*-methoxyphenylpiperazine have been found to be generally partial agonists.[11] Such substitution however is also linked to strong affinity for adrenergic α1 receptor (α1R), which represents a serious drawback for clinical candidates.

Isosteric replacement of the aromatic amide with pyrimidone (A-690344)[12] or incorporation into a benzodiazepinedione (A-706149)[13] or a benzolactam[14] has been reported (Fig. 2), but the effect of these substitutions on α1R affinity was not reported.

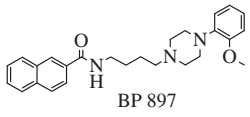

Figure 1. Structure of BP 897.

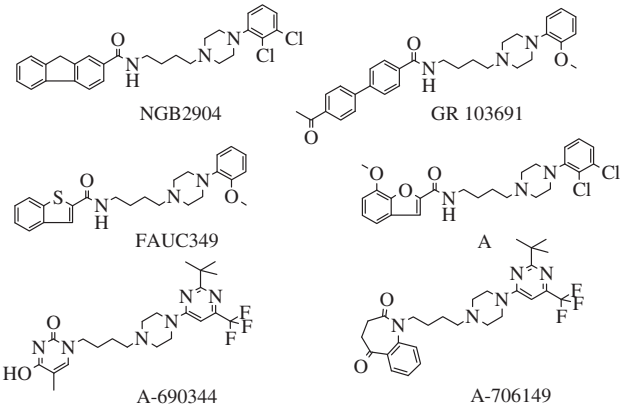

Figure 2. Structure of D3R ligands derived from BP 897.

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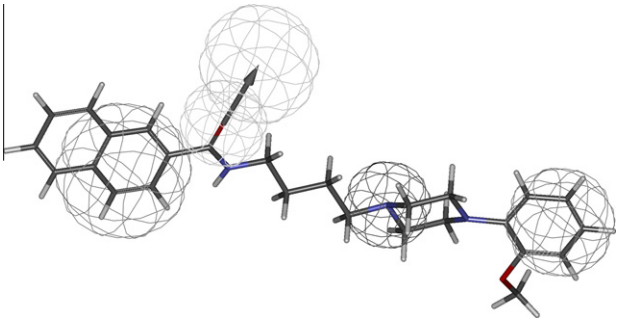


Figure 3. Parmacophore representation of D3 receptor ligands. Grey spheres represent lipophilic groups, black sphere is for positive ionisable function, and the vector symbolizes the hydrogen bond acceptor.

The current pharmacophore[15] for D3 ligands is depicted in Figure 3 with BP 897.

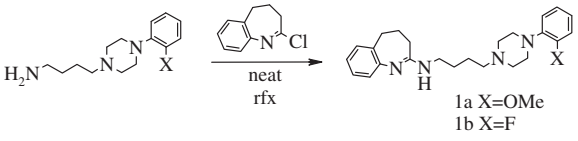
As its congeners, BP 897 has a potent activity toward human α1R (K_i = 9 nM). Thus we tackled this aspect of D3R ligands, while maintaining selectivity versus D2 receptor. Rigidification is a well-known strategy to improve selectivity, but it was shown detrimental for D3R affinity when applied to the linker.[15a] We thus turned toward incorporating the hydrogen bond acceptor and the aromatic moiety into an heterocycle. The rotatable bond between naphthyl and carbonyl thus disappears. Moreover, rigidification can improve bioavailability and suppression of the hydrophile amide bond should be beneficial to brain permeation.

A first set of compounds was synthesized with a benzo[*f*]azepine as replacement of the naphthamide part of BP 897. For comparison purpose, we prepared compounds bearing the same chain as BP 897 and a fluoro-substituted analog as fluorine is supposed to be able to get involved in hydrogen bonding.

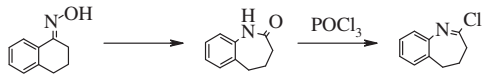
The compounds were prepared by reacting 2-chlorobenzo[*f*]azepine with 4-arylpiperazinebutanamines (Scheme 1).

Starting 2-chlorobenzo[*f*]azepine was prepared in two steps from tetralone oxime: Beckman rearrangement and chlorination with phosphoryl chloride (Scheme 2).

The 4-arylpiperazinebutanamines were prepared by reacting the corresponding substituted arylpiperazine with 4-bromobutyronitrile and reducing the nitrile with Raney nickel (Scheme 3).



Scheme 1. Synthesis of 4-(4-arylpiperazinyl)butylaminoheterocycles.



Scheme 2. Synthesis of 2-chlorobenzo[*f*]azepine.

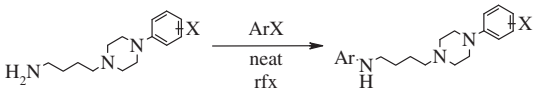
These first two compounds showed a modest affinity for D3 receptor[16] (**1a** 19 nM, **1b** 52 nM) with a 20-fold selectivity over D2 receptor. Although, their D3R affinity is clearly not sufficient, the initial isosteric replacement was shown to be valid. We thus turned toward other ring size incorporating the amidine ring.

A second set of compounds was synthesized with pyridine as heteroaromatics. Substituents on the arylpiperazine were *ortho*-methoxy (as in BP 897, GR103691, and FAUC349), *ortho*,*meta*-dichloro (as in NGB2904 and benzofurane A). We also added *meta*-trifluoromethyl (strong electrowithdrawing substituent) and *ortho*-fluoro (methoxy surrogate) as further variations.

Synthesis was achieved by condensing 2-chloropyridine derivative onto appropriate 4-(4-arylpiperazinyl)butylamines (scheme 4).[17]

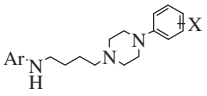
Binding experiments (see Table 1) showed that substitutions with methoxy (**2a**) or dichloro (**2b**) lead to potent ligands with subnanomolar affinity at dopamine D3 receptor. Modulation of D2 receptor recognition was observed, but selectivity for α1 was not reached. Replacement of *ortho*-methoxy by *ortho*-fluoro (**2d**) did not improve this last parameter. Further replacement with methyl (**2e**–**f**) showed that hydrogen or halogen bonding is not implicated in adrenergic activity as it is for D3R. Methylated compound cannot build hydrogen bond, but showed an improvement in the α1R binding. Interestingly, *meta*-trifluoromethylation (**2c**) strongly diminished binding to α1 receptor, though affinity for D3R was insufficient.

We then turned toward extending the aromatic part of the pyridine. This approach led to quinoleine (**3a**–**c**) or isoquinoleine

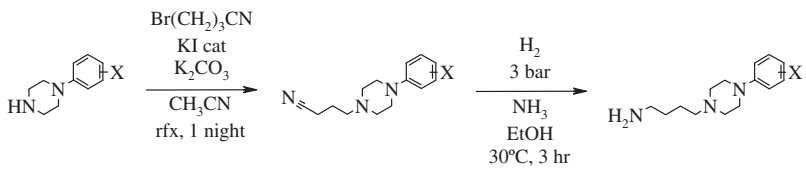


Scheme 4. Synthesis of 4-(4-arylpiperazinyl)butylaminoheterocycles.

Table 1
Binding and selectivity ratio of compounds **2**–**4 a**–**f** at dopamine D2 and D3 receptors and adrenergic α1 receptor



Entry	Ar	X	K_i (nM)			Ratio	
			D2	D3	α1	D2/D3	α1/D3
2a	2-Pyridyl	2-OMe	198	0.8	23	247	29
2b	2-Pyridyl	2,3-Cl_2	25	0.4	33	62	84
2c	2-Pyridyl	3-CF_3	198	17	593	12	35
2d	2-Pyridyl	2-F	133	11	17	12	1.5
2e	2-Pyridyl	2-Me	383	32	14	12	0.4
2f	2-Pyridyl	2,3-Me_2	207	12	40	17	3
3a	2-Quinolyl	2-OMe	15	5.6	6.0	2.6	1.1
3b	2-Quinolyl	2,3-Cl_2	23	0.6	46	39	77
3c	2-Quinolyl	3-CF_3	53	1.6	12	33	7.5
4a	1-Isoquinolyl	2-OMe	70	1.0	6.0	70	6.3
4b	1-Isoquinolyl	2,3-Cl_2	19	3.1	60	6.2	19
4c	1-Isoquinolyl	3-CF_3	58	1.0	68	58	68



Scheme 3. Synthesis of 4-(4-arylpiperazinyl)butylamines.

(**4a–c**), these bicyclic aromatics being reminiscent of the naphthyl part of BP 897. Here again, *ortho*-methoxylated derivatives (**3a** and **4a**) showed adrenergic affinity. Extension of the heteroaromatic part allowed wider substitution onto the arylpiperazine as products substituted with *meta*-trifluoromethyl (**3c** and **4c**) displayed nanomolar affinity. Unfortunately, all these compounds were less selective toward D2R and α1R.

The precise location of the aromatic part is thought to be a key factor for both D2R and D3R recognition.[15a] Therefore this parameter had to be investigated in order to get a good selectivity for D3R over D2R. We thus turned toward compounds in which the extension of the aromatic part is realized through a phenyl substituent appended onto the pyridine.

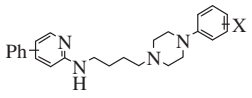
These compounds were synthesized using the same strategy as for pyridine derivatives. Pyridine bearing a phenyl in position 5 showed subnanomolar affinity for dopamine D3 receptor (Table 2). Interestingly, selectivity over D2R and α1R was improved, but only in a sufficient manner for the *meta*-trifluoromethylated arylpiperazine. Further improvement was reached when phenyl was located on position 4.

Isosteric replacement of the pyridine nucleus with oxazole and thiazole has also been investigated leading to compounds **7** and **8**. Interestingly, selectivity over dopamine D2 receptor is retained regardless the observed decrease of affinity for dopamine D3 receptor (Table 3).

Compound **6c** was shown to be a potent and selective dopamine D3R ligand. Furthermore, this compound showed no strong interaction with human cytochromes. The bioavailability and distribution of this compound were further investigated in mice (Fig. 4) and rat (Fig. 5). Absolute bioavailability was rather satisfactory (0.40 in mice and 0.65 in rat). Compared to other investigated organs, brain exposure was particularly high (Fig. 6). This is clearly a major advantage for this CNS-oriented class of molecules.

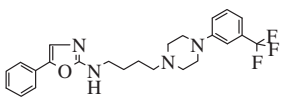
Rigidification of the amide part of BP 897 by incorporation into a heterocycle has led to a new scaffold. Further optimization of the aromatic part together with the modulation of the substitution onto the arylpiperazine led to potent and selective compounds. As expected, the overall reduction in aqueous solubility of the molecules had enhanced both bioavailability and brain permeation. The optimized compound **6c** is a very potent D3 ligand which set-

Table 2
Binding and selectivity ratio of compounds **5** and **6 a–c** at dopamine D2, dopamine D3 and adrenergic α1 receptors

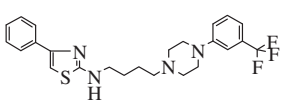


Entry	Ar	X	K_i (nM)			Ratio	
			D2	D3	α1	D2/D3	α1/D3
5a	5-Phenyl	2-F	122	2.5	10	49	4
5b	5-Phenyl	2,3-Cl_2	41	0.59	21	69	35
5c	5-Phenyl	3-CF_3	143	1.1	227	130	207
6a	4-Phenyl	2-F	309	1.5	9	206	6
6b	4-Phenyl	2,3-Cl_2	184	0.55	58	334	106
6c	4-Phenyl	3-CF_3	194	0.76	119	256	157

Table 3
Binding and selectivity ratio of compounds **7** and **8** at dopamine D2, dopamine D3 and adrenergic α1 receptors



7



8

Entry	K_i (nM)			Ratio	
	D2	D3	α1	D2/D3	α1/D3
7	2322	9.6	272	242	28
8	2431	13	72	183	5.4

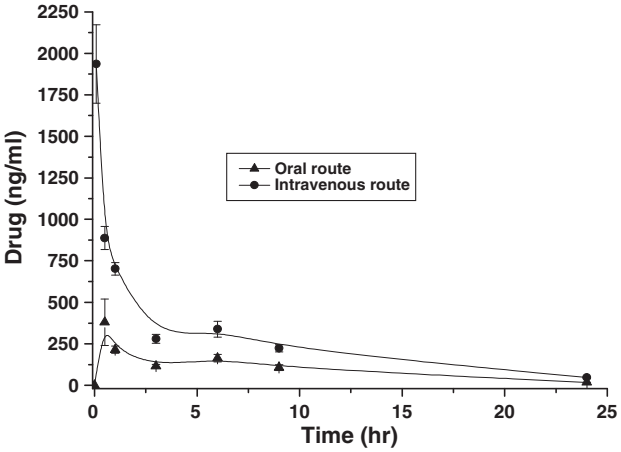


Figure 4. Absolute bioavailability of **6c** in mice plasma administered at 10 mg/kg dose po and iv.

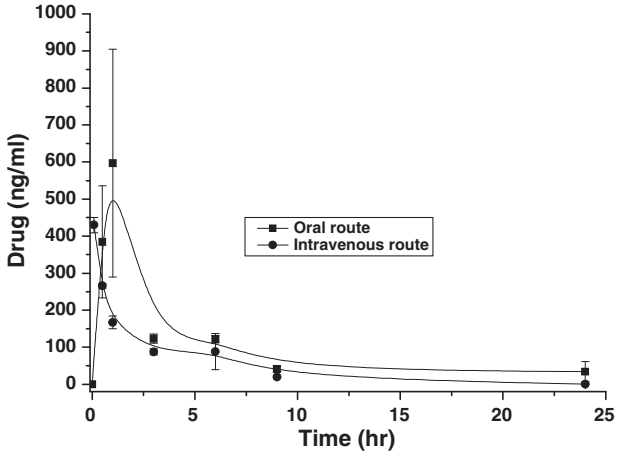


Figure 5. Absolute bioavailability of **6c** in rat plasma administered at 10 mg/kg dose po and 3 mg/kg iv.

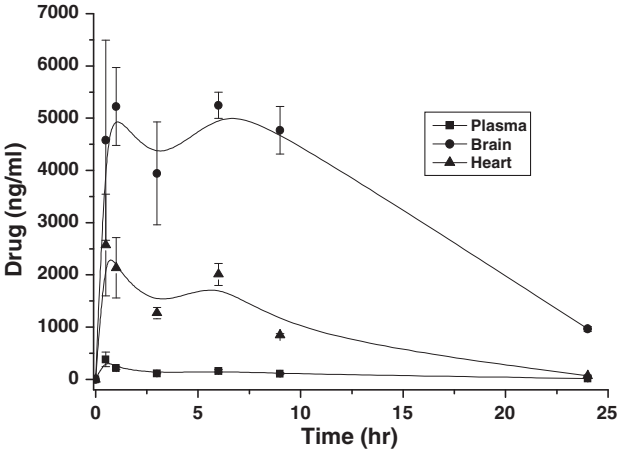


Figure 6. Tissue distribution of **6c** in mice administered at 10 mg/kg po.

tled D2R and α1R selectivity (K_i ratio of 250 and 150, respectively). It represents thus a good candidate for further pharmacological and clinical investigations.

Acknowledgments

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References and notes

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16. *Determination of dopamine receptor subtype and adrenergic α1 receptor binding:* Biochemical assays for the human D3 and human D2S dopamine receptors were performed as described previously with slight modifications.[15a] Briefly, for the D3 receptor, binding was performed with [^{3}H] spiperone using 5 μg of membrane suspension (prepared from stable human D3 transfected CHO cell line). Binding of the D2S receptor was performed with [^{3}H] spiperone using 10 μg of membrane suspension (prepared from stable human D2S transfected HEK293 cell line). For the human adrenergic α1 receptor, binding was achieved with [^{3}H] prazosin using 5 μg of membrane suspension (prepared from stable human hADRA1A transfected cell line). All assays were performed at least in duplicate. Mean values are given.
17. *Step A:* preparation of 4-[4-(3-trifluoromethylphenyl)piperazin-1-yl]butyronitrile. A mixture of 12.02 g (52 mmol) of 1-(3-trifluoromethylphenyl) piperazine, 7.9 g (57 mmol) of potassium carbonate, 8.5 g (57 mmol) of 4-bromobutyronitrile and 120 mL of acetonitrile was refluxed overnight. The reaction medium was concentrated, taken up with ethyl acetate and washed with water. After separation of the aqueous phase, the organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. In this manner, 15 g (97%) of 4-[4-(3-trifluoromethylphenyl)piperazin-1-yl]butyronitrile were obtained as a viscous oil which was used without any further purification.
Step B: preparation of 4-[4-(3-trifluoromethylphenyl)piperazin-1-yl]butylamine. Approximately 1 g of Raney nickel washed beforehand with ethanol was added to a solution of 15 g (37.4 mmol) of 4-[4-(3-trifluorophenyl) piperazin-1-yl]butyronitrile obtained previously, in a mixture of 100 mL of an aqueous solution of concentrated ammonia and 100 mL of an approx. 8 N solution of ammoniacal ethanol. The suspension was hydrogenated overnight under 3 bar of hydrogen at 30 °C. The mixture was filtered on Celite, rinsed with ethanol and concentrated under a vacuum. The oily residue was taken up with 50 mL of ethanol and concentrated. This operation was repeated once to afford 14 g (92%) de 4-[4-(3-trifluorophenyl)piperazin-1-yl]butylamine as a viscous oil which was used without any further purification.
Step C: preparation of 2-{4-[4-(3-trifluoromethylphenyl)piperazin-1-yl]butyl} amino-4-phenylpyridine. In a test tube, 0.38 g (2.0 mmol) of 2-chloro-4-phenylpyridine, 0.6 g (2.0 mmol) of 4-[4-(3-trifluoromethylphenyl)piperazin-1-yl]butylamine and a spatula tipful of 4-dimethylaminopyridine were heated to approximately 300–350 °C for 3 min. The mixture was diluted with ethyl acetate and chromatographed on silica gel (eluent: dichloromethane/ethanol 90:10). The product crystallized upon concentration of collected fractions. Trituration in diethyl oxide, filtration and drying gave 80 mg of 2-{4-[4-(3-trifluoromethylphenyl)piperazin-1-yl]butyl}amino-4-phenylpyridine as a white solid melting at 120 °C (tube).
1H NMR ($CDCl_3$): 8.1 (doublet, 1H); 7.65–7.55 (unresolved peaks, 2H); 7.5–7.25 (unresolved peaks, 4H); 7.2–7.0 (unresolved peaks, 3H); 6.8 (doublet, 1H); 6.55 (singlet, 1H); 4.8 (wide triplet, 1H); 3.35 (multiplet, 2H); 3.35–3.15 (unresolved peaks, 4H); 2.7–2.55 (unresolved peaks, 4H); 2.45 (triplet, 2H); 1.85–1.65 (unresolved peaks, 4H).