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Novel morpholine scaffolds as selective dopamine (DA) D3 receptor antagonists

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ABSTRACT

A new series of morpholine derivatives has been identified as selective DA D3 receptor antagonists; their in vitro profile and pharmacokinetic data are provided.

A growing number of studies have demonstrated a close association between the dopamine (DA) D3 receptor and drug addiction, which suggested that selective DA D3 receptor antagonists may be effective in reducing drug-induced incentive motivation, attenuating drug's rewarding efficacy, and reducing reinstatement of drug-seeking behavior.[1,2] Selective DA D3 receptor antagonists have been recently discovered, some with benzoazepine and [3.1.0] templates,[3,4] others with piperazine and alternative scaffolds.[5,6] The original pharmacophore model reported by Stark in 2002[7] involving the presence of a key basic moiety within the different templates used is still valid in its basic assumptions. Since then, additional evidence has been generated including X-ray structures and molecular modeling simulations.[8,9] A few examples of these templates are reported in Figure 1.

Several approaches can be used for the identification of an appropriate basic moiety that interacts with Asp$^{3.32}$ in the recently described[8] orthosteric binding site that endows the molecule with an appropriate 'anchor point' that directs the remaining part of the molecule to interact at a secondary site that is unique to D3R allowing for selectivity versus the DA D2 receptor. A combination of these approaches has been recently used[9] by exploiting the DA D3 receptor crystal structure to guide the drug design process.

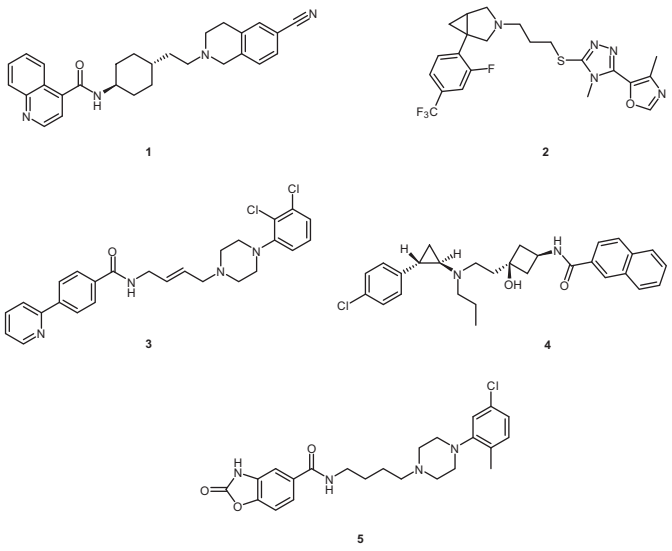

Figure 1. A few selective DA D_3 receptor antagonists. SB-277011 (**1**), GSK598809A (**2**), PG01037 (**3**), CJ-1882 (**4**), YQA14 (**5**).

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Although both affinity and selectivity are on the critical path of the drug discovery process, the overall 'developability' profile[10] of the molecule is also essential to ensure the progression of the compound toward clinical development.

This Letter describes a joint medicinal and computational chemistry 'scaffold hopping' strategy (with respect to the classical piperidines and to the azabicyclo[3.1.0]-hexanes series) that resulted in the identification of a variety of basic moieties. Specifically, a morpholine scaffold is described together with its pharmacokinetic (PK) profile.[11,12] The general structure of the newly identified DA D3 receptor antagonists is reported in Figure 2.

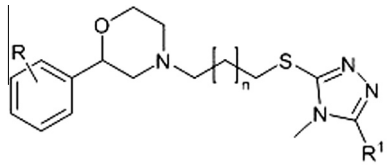

Figure 2. The general structure of the newly reported DA D3 receptor antagonist.

Biological results are reported in Tables 1–3 where **R**, **R1** and **n** refer to the general structure reported in Figure 2. Experimental details and further references for these assays can be found in Ref. 2–4.

All the compounds were prepared in agreement with Schemes 1 and 2.

All the data were compared to the affinity of SB-277011 (**1**, Fig. 1), which is one of the prototypical DA D3 receptor antagonists. The screening cascade consisted of binding affinity at the DA D3 and D2 receptors, potency of the compounds at inhibiting the human ERG potassium channel (hERG) tail current as well as

Table 1
Affinity results for the selected derivatives[a]

Entry	R	R1	n	Sterochem.	DA D3 pK_i	DA D3 GTPγS fpK_i	DA D2 pK_i	hERG fpK_i
1	N.A.	N.A.	N.A.	s.e.	8.2	8.4	6.3	6.2
6	*p*-F	4-Methyl-1,3-oxazol-5-yl	1	rac.	6.4	N.T.	<5.0	N.T.
7	*p*-F	4-Methyl-1,3-oxazol-5-yl	1	s.e.	6.6	N.T.	<5.0	5.5
8	*p*-CF_3	4-Methyl-1,3-oxazol-5-yl	1	rac.	6.9	N.T.	N.T.	N.T.
9	*p*-CF_3	4-Methyl-1,3-oxazol-5-yl	1	s.e.	7.3	7.6	4.9	5.5
10	*p*-CF_3	4-Methyl-1,3-oxazol-5-yl	2	rac.	7.1	7.6	<5.0	N.T.
11	*p*-CF_3	4-Methyl-1,3-oxazol-5-yl	2	s.e.	7.1	7.8	<5.0	5.6
12	2-F,4-CF_3	4-Methyl-1,3-oxazol-5-yl	1	rac.	6.7	N.T.	5.0	N.T.
13	*p*-CH_3	4-Methyl-1,3-oxazol-5-yl	1	rac.	6.3	N.T.	N.T.	N.T.
14	*p*-Br	4-Methyl-1,3-oxazol-5-yl	1	rac.	6.7	N.T.	4.8	N.T.
15	*p*-CF_3	Thiophen-3-yl	1	rac.	7.0	N.T.	5.1	N.T.
16	*p*-CF_3	1,3-Thiazol-2-yl	1	rac.	6.6	N.T.	5.1	N.T.
17	*p*-CF_3	1-Methyl-1*H*-pyrazol-5-yl	1	rac.	6.2	N.T.	<5.0	N.T.
18	*p*-CF_3	1-Methyl-1*H*-pyrrol-2-yl	1	rac.	6.9	N.T.	5.2	N.T.

[a] N.A. = not applicable; N.T. = not tested. Affinity results: SEM for the data sets is ±0.1. rac = racemate; s.e. = single enantiomer.

Table 2
Affinity results for the selected derivatives[a]

Entry	R	R1	n	Sterochem.	DA D3 pK_i	DA D3 GTPγS fpK_i	DA D2 pK_i	hERG fpK_i
19	*p*-CF_3	CyH	1	rac.	7.4	7.7	5.1	N.T.
20	*p*-CF_3	4-Py	1	rac.	7.0	N.T.	4.9	N.T.
21	*p*-CF_3	3-Py	1	rac.	6.6	N.T.	4.8	N.T.
22	*p*-CF_3	2-Pyrazine	1	rac.	6.8	N.T.	5.0	N.T.
23	*p*-CF_3	5-Pyridine-2-carboxamide	1	rac.	7.5	7.8	4.6	5.7
24	*p*-CF_3	5-Pyridine-3-carboxamide	1	rac.	7.0	N.T.	4.8	N.T.
25	*p*-CF_3	4-Benzeneamide	1	rac.	7.5	7.7	5.0	5.3
26	*p*-CF_3	4-Benzeneamide	1	s.e.	7.8	8.2	4.9	5.2
27	*p*-CF_3	3-Benzeneamide	1	rac.	6.5	N.T.	4.8	N.T.
28	*p*-CF_3	4-Phenylethan-1-one	1	rac.	7.2	7.7	4.7	N.T.
29	*p*-CF_3	4-Benzene-1-sulfonamide	1	rac.	6.9	N.T.	<4.5	N.T.
30	*p*-CF_3	4-Benzonitrile	1	rac.	7.0	N.T.	5.0	N.T.
31	2-F,4-CF_3	4-Benzeneamide	1	rac.	7.2	7.4	4.8	N.T.

[a] N.A. = not applicable; N.T. = not tested. Affinity results: SEM for the data sets is ±0.1. rac = racemate; s.e. = single enantiomer.

Table 3
Affinity results for the selected derivatives[a]

Entry	R	R1	n	Sterochem.	DA D3 pK_i	DA D3 GTPγS fpK_i	DA D2 pK_i	hERG fpK_i
32	*p*-CF_3	4-(1,3-Oxazol-2-yl)phenyl	1	rac.	8.3	8.0	5.8	6.0
33	*p*-CF_3	4-(1,3-Oxazol-2-yl)phenyl	1	s.e.#1	6.4	N.T.	4.8	N.T.
34	*p*-CF_3	4-(1,3-Oxazol-2-yl)phenyl	1	s.e.#2	8.2	8.5	5.3	5.9
35	*p*-CF_3	1,2,4-Triazol-4-yl)phenyl	1	rac.	6.9	N.T.	5.0	N.T.
36	*p*-CF_3	4-(1,3,4-Oxadiazol-2-yl)phenyl	1	rac.	7.8	7.9	4.9	N.T.
37	*p*-CF_3	4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl	1	rac.	7.6	8.0	<5.0	N.T.
38	*p*-CH_3	4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl	1	rac.	7.1	7.8	4.6	6.0

[a] N.A. = not applicable; N.T. = not tested. Affinity results: SEM for the data sets is ±0.1. rac = racemate; s.e. = single enantiomer.