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SAR of the arylpiperazine moiety of obeline somatostatin sst_1 receptor antagonists

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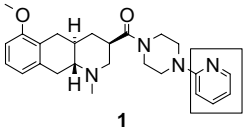
Abstract—The SAR of over 50 derivatives of octahydrobenzo[*g*]quinoline (obeline)-type somatostatin sst_1 receptor antagonist **1** is presented, focusing on the modification of its arylpiperazine moiety. Sst_1 affinities in this series cover a range of five orders of magnitude with the best derivatives displaying subnanomolar sst_1 affinities and >10,000-fold selectivities over the sst_2 receptor subtype as well as promising pharmacokinetic properties.

The initial structure–activity relationship of highly active, non-peptidic, obeline-type somatostatin sst_1 receptor antagonists and their in vitro pharmacological profile is presented in the preceding paper.[1] The focus of our medicinal chemistry derivatization program was on the arylpiperazine moiety of lead molecule **1** (example **2a** in Ref. 1) with the goal to raise the sst_1 receptor affinities to a subnanomolar level while improving on selectivities toward the somatostatin sst_2 receptor (a detailed rationale is given in the preceding paper[1]) without compromising on the favorable drug-like properties of **1** (no 'rule-of-5' violations, *c*log*P* 3.4, molecular weight 421, PSA 49 Å^2). From our earlier work on structurally related somatostatin ligands[2] it was anticipated that an efficient fine-tuning of somatostatin receptor binding properties is achievable by introducing structurally and electronically diverse aryl piperazine moieties. In a second step, additional criteria (e.g., in vitro or in vivo ADME properties) served for selection among a subset of highly active and selective compounds.



1

Representative examples for the derivatization of the arylpiperazine moiety in **1** are shown in Tables 1–3. As in the preceding paper,[1] radioligand binding data to rat somatostatin sst_1 and sst_2 receptors are given. The assay is performed in rat cortex membranes using [^{125}I]SRIF-14 in the presence of 120 mM NaCl.[3] The synthesis of all compounds listed in Tables 1–3 is outlined in Supporting Information.

The optimization program started by replacement of the 2-pyridyl moiety in **1** (pK_d sst_1 = 7.76, selectivity over sst_2 ca. 600-fold) with other heteroaryl moieties: while the regioisomeric 4-pyridyl compound and the corresponding pyridazine and pyrimidine derivatives were considerably less active and selective (Table 1, entries **2**–**4**), introduction of a 4-cyano substituent gave a clear gain in sst_1 affinity (entry **5**, pK_d sst_1 = 8.45); other substituents in 3-, 4- or 6-position were however less favorable (entries **6**–**8**). Going from the 2-pyridine to a 2-pyridone moiety led to an improved affinity, with the *N*-methyl derivative **10** showing a superior profile (pK_d sst_1 = 8.74, selectivity over sst_2 > 6000-fold) over the

Keywords: Somatostatin sst_1 receptor antagonist; Octahydro[*g*]quinoline (obeline).
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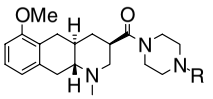
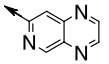
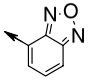
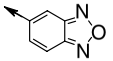
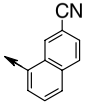
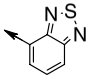
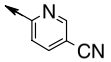
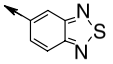
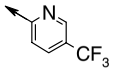
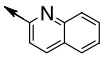
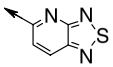
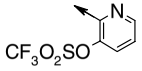
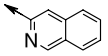
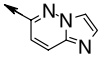
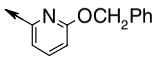
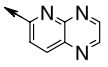
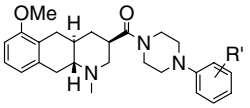
Table 1. Binding affinities of octahydrobenzo[*g*]quinoline derivatives **1**–**23** (arylpiperazines, not phenylpiperazines) to rat sst_1 and sst_2 receptors



Compound	R	pK_d r sst_1[a]	pK_d r sst_2[a]	Compound	R	pK_d r sst_1[a]	pK_d r sst_2[a]	Compound	R	pK_d r sst_1[a]	pK_d r sst_2[a]
1		7.76 ± 0.12	4.99 ± 0.06	**9**		8.12 ± 0.09	4.93 ± 0.11	**17**		6.45 ± 0.16	5.15 ± 0.01
2		5.73 ± 0.02	4.75 ± 0.06	**10**		8.74 ± 0.02	4.96 ± 0.11	**18**		8.44 ± 0.06	5.14 ± 0.08
3		7.28 ± 0.10	4.60 ± 0.03	**11**		7.06 ± 0.04	5.26 ± 0.02	**19**		8.77 ± 0.09	5.46 ± 0.17
4		6.33 ± 0.04	4.56 ± 0.06	**12**		8.06 ± 0.04	5.28 ± 0.09	**20**		8.56 ± 0.05	5.00 ± 0.04
5		8.45 ± 0.18	4.99 ± 0.13	**13**		6.16 ± 0.07	5.28 ± 0.06	**21**		7.97 ± 0.04	5.37 ± 0.01
6		6.98 ± 0.07	4.70 ± 0.14	**14**		7.58 ± 0.03	5.68 ± 0.04	**22**		8.91 ± 0.05	5.24 ± 0.03
7		6.25 ± 0.12	4.93 ± 0.15	**15**		6.54 ± 0.12	5.26 ± 0.05	**23**		7.06 ± 0.03	4.68 ± 0.03
8		6.98 ± 0.03	5.18 ± 0.14	**16**		8.24 ± 0.05	4.85 ± 0.03				

[a] Mean ± SEM. Number of experiments: $n = 3$–5.

Table 2. Binding affinities of octahydrobenzo[*g*]quinoline derivatives **24–46** (phenylpiperazines) to rat sst_1 and sst_2 receptors



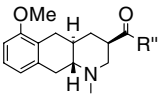
Compound	R′	pK_d r sst_1[a]	pK_d r sst_2[a]
24	2-F	7.75 ± 0.11	4.73 ± 0.04
25	3-F	8.48 ± 0.05	4.67 ± 0.06
26	4-F	8.47 ± 0.05	4.58 ± 0.10
27	2-CN	8.70 ± 0.19	5.13 ± 0.01
28	4-CN	8.09 ± 0.05	5.00 ± 0.11
29	2-NO_2	8.89 ± 0.11	4.96 ± 0.03
30	3-NO_2	8.88 ± 0.02	5.17 ± 0.06
31	4-NO_2	9.15 ± 0.31	5.11 ± 0.01
32	3-CF_3	7.63 ± 0.07	4.88 ± 0.10
33	4-CF_3	6.56 ± 0.03	5.29 ± 0.12
34	4-OH	6.20 ± 0.04	4.61 ± 0.05
35	4-COMe	6.82 ± 0.01	5.06 ± 0.02
36	4-CO_2Me	6.79 ± 0.12	4.83 ± 0.12
37	4-$CONH_2$	5.82 ± 0.11	4.78 ± 0.03
38	4-$CONEt_2$	5.77 ± 0.13	4.70 ± 0.05
39	4-CO_2Na	4.09 ± 0.17	3.60 ± 0.26
40	4-SO_2Me	6.20 ± 0.02	5.06 ± 0.03
41	4-SO_2NH_2	6.23 ± 0.17	5.04 ± 0.10
42	3,4-F_2	9.13 ± 0.04	4.78 ± 0.06
43	2-CN-3-F	8.55 ± 0.06	4.78 ± 0.03
44	2-CN-4-NO_2	8.49 ± 0.08	5.36 ± 0.05
45	2-NO_2-4-CF_3	6.96 ± 0.04	5.31 ± 0.07
46	2-SO_2Me-4-NO_2	8.76 ± 0.06	5.28 ± 0.08

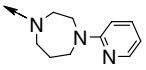
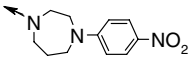
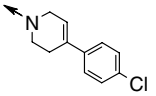
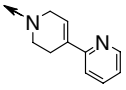
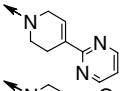
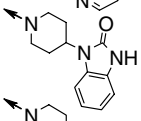
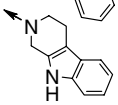
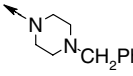
[a] Mean ± SEM. Number of experiments: $n = 3–6$.

parent pyridone **9** (pK_d sst_1 = 8.12, selectivity over sst_2 1550-fold). The introduction of annelated six-membered rings (entries **11–17**) revealed the narrow SAR within this series: for example, isomeric pyridopyrazines **16** and **17** that differ only by the position of one nitrogen atom show a difference in sst_1 affinity by nearly two orders of magnitude (pK_d sst_1 = 8.24 for **16** vs 6.45 for **17**). Among the benzoxadiazole and benzothiadiazole derivatives (entries **18–22**) compound **22** displays highest affinity and selectivity (pK_d sst_1 = 8.91, selectivity over sst_2 > 4600-fold). The corresponding imidazopyridazine derivative **23**, however, proved less promising (pK_d sst_1 = 7.06).

Substituted *phenyl*piperazines are given in Table 2. While a fluorine atom was best tolerated in the 3-or 4-position, not in the 2-position (entries **24–26**) and a cyano group in the 2-position (entries **27** and **28**), introduction of a nitro group in all positions resulted in highly active derivatives (entries **29–31**) with the 4-nitro derivative **31** being one of the best compounds of the whole series (pK_d sst_1 = 9.15, selectivity over sst_2 > 10,000-fold). The detailed in vitro profile of this compound is published elsewhere.[1,4] Less favorable is a CF_3 group (in 3- or 4-position, entries **32** and **33**) or a 4-hydroxy, -carbonyl, -carboxyl, -sulfonyl or -sulfonamide substitution (**34–41**). Among the disubstituted phenyl derivatives (**42–46**), the 3,4-difluoro derivative **42** showed affinity and selectivity comparable to **31** (pK_d sst_1 = 9.13, selectivity over sst_2 > 22,000-fold).

Table 3. Binding affinities of octahydrobenzo[*g*]quinoline derivatives **47–55** (cyclic tertiary amides, not piperazine derivatives) to rat sst_1 and sst_2 receptors



Compound	R″	pK_d r sst_1[a]	pK_d r sst_2[a]
47		6.68 ± 0.04	4.46 ± 0.39
48		6.58 ± 0.07	4.65 ± 0.23
49		7.09 ± 0.06	5.60 ± 0.04
50		7.52 ± 0.05	5.63 ± 0.04
51		6.31 ± 0.03	5.62 ± 0.06
52		6.31 ± 0.01	5.69 ± 0.03
53		7.15 ± 0.04	5.21 ± 0.00
54		6.34 ± 0.04	5.04 ± 0.08
55		4.98 ± 0.04	4.36 ± 0.10

[a] Mean ± SEM. Number of experiments: $n = 2–4$.

Derivatives that replace the arylpiperazine moiety by other cyclic secondary amines are given in Table 3. The piperazine ring itself was replaced by a homopiperazine (entries **47** and **48**) or a tetrahydropyridine ring (entries **49–51**). The arylpiperazine moiety was substituted by 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (entry **52**), a popular moiety in the field of peptidic and non-peptidic sst receptor ligands,[5,6] β-carboline (entry **53**), benzylpiperazine (entry **54**) or unsubstituted piperazine (entry **55**). All these derivatizations led to a dramatic loss in affinity and selectivity and were not followed up any further.

Attempts to develop a QSAR understanding of these results based on different molecular descriptors (dipole moments, volumes, surfaces areas, hydrophilicities, frontier orbital energies, etc., alone or in combinations) and using pertinent methods[7] were not successful so far. A possible explanation could be that these compounds bind to different parts of the receptor in varying orientations and receptor conformations in spite of their rather high structural analogy, a fact that cannot be further elaborated in absence of structural information on the somatostatin sst_1 receptor.

The derivatives in Tables 1–3 have calculated molecular properties that are in line with oral bioavailability according to the 'rule of 5'. Indeed, compounds **21**, **22**, and **42** show good absorption and brain penetration in mice (brain plasma ratios of 4.8, 1.8 and 7.5, respectively, 1 h after 10 mg/kg oral administration). Compound **31** was analyzed in more detail in rats: it shows an oral bioavailability of ca. 35% and a moderate clearance rate and tissue distribution (CL ca. 5 ml/min, V_{ss} 3–6 l/kg). Brain plasma ratios are 10–15 (90 min after oral administration of 10, 30, and 100 mg/kg); at doses of 1–10 mg/kg po, concentrations in the rat brain are sufficient to fully occupy sst_1 receptors for at least 4 h. Details as well as pharmacological in vivo data will be published elsewhere in due course.

In conclusion, we have established the SAR of the arylpiperazine moiety of obeline-type somatostatin sst_1 receptor antagonist **1**, leading to compounds with subnanomolar sst_1 affinities, >10,000-fold selectivities over the sst_2 receptor subtype and promising initial PK properties.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.04.078.

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