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Bioorganic & Medicinal Chemistry Letters 17 (2007) 3983–3987
Bioorganic & Medicinal Chemistry Letters

Identification and SAR of potent and selective non-peptide obeline somatostatin sst_1 receptor antagonists

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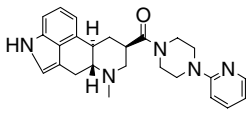
Received 26 March 2007; revised 24 April 2007; accepted 25 April 2007
Available online 29 April 2007

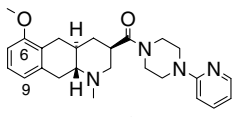
Abstract—A novel class of non-peptide somatostatin receptor ligands bearing the octahydrobenzo[*g*]quinoline (obeline) structural element has been identified. SAR studies have been performed that led to the discovery of derivatives with high affinity (pK_d r $sst_1 \geqslant 9$) and selectivity ($\geqslant$150-fold for h sst_1 over h sst_2–h sst_5) for somatostatin receptor subtype sst_1. In a functional assay, the compounds act as antagonists at human recombinant sst_1 receptors.

Somatostatin (somatotropin-release-inhibiting factor, SRIF) is a widely distributed peptide hormone/neurotransmitter[1] that occurs in two biologically active forms, a tetradecapeptide $SRIF_{14}$ and a 28-amino acid peptide $SRIF_{28}$. Multiple biological effects have been attributed to SRIF, in the periphery[2–4] as well as in the CNS.[5–10] To date, five somatostatin receptor subtypes (sst_1 to sst_5) have been cloned and characterized, all belonging to the G-protein-coupled receptor superfamily.[11–13] So far, only sst_2 and sst_5 receptors have been clearly linked to specific physiological functions,[14,15] whereas the role of the sst_1 receptor is still not fully understood.[16–19] In order to further elucidate the function of the different SRIF receptor subtypes and to evaluate the potential of somatostatin receptor ligands as therapeutic agents, there is a need for non-peptidic, metabolically stable, potent, and subtype selective SRIF receptor agonists and antagonists.[20] The first non-peptidic structures with micromolar affinity for SRIF receptors used sugar or benzodiazepine cores to align the crucial functionalities of the Phe, Trp, and Lys side-chains appropriately.[21–24] In the meantime, more selective non-peptidic agonists with nanomolar affinity for each of the five receptor subtypes have been published.[25–30] The only non-peptidic and potent antagonists reported so far are sst_2 selective analogs of the dipeptide D-Trp-Lys[31] and sst_3 selective D-Trp derived imidazoles.[32,33] Herein and in the following paper,[34] we present the identification and optimization of a novel class of non-peptidic somatostatin sst_1 receptor antagonists.

As a starting point we chose the screening hit **1**, an ergoline[35] derivative which already showed appreciable affinity for the rat sst_1 receptor ($pK_d = 7.85$) and good selectivity over r sst_2 ($pK_d = 4.75$).[36] By applying a well-known bioisosterism,[37] the ergoline part of **1** could be replaced with an octahydrobenzo[*g*]quinoline (obeline) moiety. The resulting derivative **2a** indeed had comparable affinity for the rat sst_1 receptor ($pK_d = 7.76$) and retained selectivity over sst_2 ($pK_d = 4.99$). The octahydrobenzo[*g*]quinoline derivative **2a** was therefore selected as lead for an extensive derivatization program with the goal to identify potent and selective sst_1 receptor ligands.



1



2a

In this paper, we present the structure–activity relationship that was explored for the positions 6 and 9 of the octahydrobenzo[*g*]quinoline ring system. In the following paper,[34] our derivatization efforts at the aryl piperazine moiety of **2a** will be discussed. For the SAR studies

Keywords: Somatostatin sst_1 receptor antagonists; Octahydrobenzo[g]quinolines (obelines).
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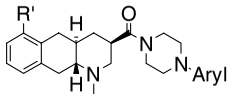
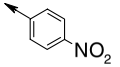
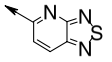
doi:10.1016/j.bmcl.2007.04.086

Table 1. Binding affinities of octahydrobenzo[*g*]quinoline derivatives to rat sst_1 and sst_2 receptors (variations at position 6)

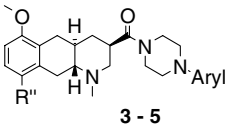


2 - 4

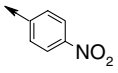
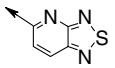
R′	Aryl = 			Aryl = 			Aryl = 		
	Compound	pK_d r sst_1[a]	pK_d r sst_2[a]	Compound	pK_d r sst_1[a]	pK_d r sst_2[a]	Compound	pK_d r sst_1[a]	pK_d r sst_2[a]
–OMe	**2a**	7.76 ± 0.12	4.99 ± 0.06	**3a**	9.15 ± 0.31	5.11 ± 0.01	**4a**	8.91 ± 0.05	5.24 ± 0.03
–O*i*-Pr				**3b**	9.09 ± 0.06	5.24 ± 0.05			
–OBn							**4c**	8.92 ± 0.10	5.32 ± 0.02
–OH				**3d**	7.73 ± 0.02	5.11 ± 0.14			
–OCO*t*-Bu				**3e**	7.60 ± 0.03	4.78 ± 0.17			
–OCO_2*t*-Bu				**3f**	8.32 ± 0.01	4.81 ± 0.25			
–OSO_2Me				**3g**	9.39 ± 0.03	5.43 ± 0.09	**4g**	9.67 ± 0.07	5.29 ± 0.06
–OSO_2*p*-Tol							**4h**	9.24 ± 0.10	5.72 ± 0.05
–OSO_2CF_3	**2i**	8.85 ± 0.11	4.96 ± 0.01	**3i**	8.81 ± 0.03	5.45 ± 0.06	**4i**	9.40 ± 0.06	5.41 ± 0.02
–H	**2j**	6.80 ± 0.07	4.49 ± 0.08						
–CN				**3k**	7.80 ± 0.04	5.14 ± 0.06			
–COMe				**3l**	8.22 ± 0.18	5.14 ± 0.13			

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

Table 2. Binding affinities of octahydrobenzo[*g*]quinoline derivatives to rat sst_1 and sst_2 receptors (variations at position 9)

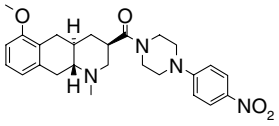


3 - 5

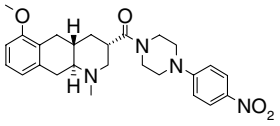
R″	Aryl = 			Aryl = 	
	Compound	pK_d r sst_1[a]	pK_d r sst_2[a]	Compound	pK_d r sst_1[a]	pK_d r sst_2[a]
–H	**3a**	9.15 ± 0.31	5.11 ± 0.01	**4a**	8.91 ± 0.05	5.24 ± 0.03
–Cl	**3m**	8.45 ± 0.11	4.86 ± 0.07			
–Br	**3n**	8.34 ± 0.04	5.04 ± 0.10	**4n**	8.92 ± 0.11	5.20 ± 0.12
–SMe	**3o**	8.10 ± 0.02	5.00 ± 0.13			
–CHO				**4p**	9.08 ± 0.02	5.00 ± 0.03
–COMe				**4q**	7.46 ± 0.08	5.54 ± 0.03

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

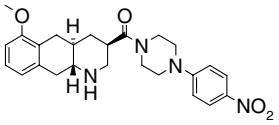
Table 3. Compounds **3a**, ent-**3a** and **6**: comparison of physicochemical parameters and affinities for different somatostatin receptor subtypes



3a



ent-3a



6

Compound	$[\alpha]_D^{20}$[b]	Mp[c]	pK_d[a]						
			r sst1	r sst2	h sst1	h sst2	h sst3	h sst4	h sst5
3a	−128.7 °	267–271 °	9.15 ± 0.31	5.11 ± 0.01	7.99 ± 0.04	4.44 ± 0.03	5.06 ± 0.03	4.82 ± 0.07	5.75 ± 0.02
ent-**3a**	+135.3 °	254 °	5.88 ± 0.10	4.83 ± 0.08	nd	nd	nd	nd	nd
6	−115 °	224–226 °	6.33 ± 0.04	5.41 ± 0.05	nd	nd	nd	nd	nd

[a] Means ± SEM. Number of experiments: $n = 3–6$.
[b] Of free base (DMF, $c = 0.5$).
[c] Of HCl salt.

presented herein, the most promising aryl piperazine moieties identified[34] were used ((4-nitro-phenyl)-piperazine in compounds **3** and [1,2,5]thiadiazolo[3,4b]pyridine-5-piperazine in compounds **4**, see Tables 1 and 2). Affinities to the sst_1 as well as the sst_2 receptors were determined in a radioligand binding assay performed in rat cortex membranes using [^{125}I]SRIF-14 in the presence of 120 mM NaCl.[36]

SAR in position 6 (Table 1).[38] An increase in size of the *O*-alkyl substituent from methyl to *i*-propyl (**3b**) as well as benzyl (**4c**) retained potency of the corresponding methyl derivatives (**3a** and **4a**, respectively). The free phenol (**3d**), on the other hand, had reduced sst_1 affinity, as did the *t*-butyl ester **3e** and the *t*-butyl carbonate derivative **3f**. Sulfonic acid esters of the phenol moiety, on the other hand, substantially increased affinity at the sst_1 receptor in several cases, without compromising selectivity over sst_2, and led to some of the most active derivatives identified in this series, e.g., **3g** (pK_d = 9.39), **4g** (pK_d = 9.67) or **4i** (pK_d = 9.40). Replacement of the 6-OMe group with a hydrogen atom (**2j**), a nitrile (**3k**) or an acetyl group (**3l**) are all detrimental to sst_1 affinity.

SAR in position 9 (Table 2).[38] Halogenation of the octahydrobenzo[*g*]quinoline ring system did not have dramatic effects either on sst_1 affinity or on selectivity over sst_2 receptors: The 9-bromo derivative **4n** retained the sst_1 affinity of the non-halogenated analog **4a**, while in the 4-nitrophenyl-piperazine series, halogenation led to reduced affinity (**3m** and **3n**). Introduction of a thiomethyl substituent was detrimental to affinity (**3o**). Formylation was tolerated (**4p**), while acetylation decreased sst_1 affinity by a factor of 30 (**4q**).

An alkyl substituent in position 1 seems to be essential: demethylation of **3a** to **6** led to a compound with 70-fold lower affinity for the rat sst_1 receptor (pK_d = 6.33, Table 3). The enantiomer of **3a** was prepared[38] and found to be less potent at the rat sst_1 receptor by a factor of 200 (Table 3).

Compound **3a**, as a typical representative of this class of compounds, was tested for its binding affinity to the human recombinant somatostatin receptors h sst_1–h sst_5.[39] This compound displayed a pK_d of 7.99 for h sst_1, and pK_ds <5.8 for h sst_2–h sst_5 (Table 3), and is therefore

highly selective for sst_1 over the other four subtypes. In extensive radioligand binding studies, **3a** showed low affinities for a panel of 40 neurotransmitter and monoamine receptors, with the exception of the human dopamine D4 receptor ($pK_d = 8.30$), 5-HT_{1D} ($pK_d = 6.95$) and β1-adrenoceptors ($pK_d = 6.65$).[39]

In a functional assay, **3a** acted as an antagonist at human recombinant sst_1 receptors. It blocked SRIF-14 induced inhibition of forskolin-stimulated adenylate cyclase activity with a pK_b of 7.50. The compound was devoid of intrinsic activity. Compound **3a** also acted as an antagonist in other sst_1 receptor assays, e.g. inhibition of somatostatin stimulated GTPγS binding or in reporter gene assays (somatostatin induced luciferase gene expression) with similar potency.[39]

In conclusion, we identified novel octahydrobenzo[*g*]-quinoline derivatives that are highly potent and selective antagonists at the somatostatin sst_1 receptor. Further studies concerning PK properties of these compounds and their evaluation in different in vivo animal models will be published elsewhere in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.04.086.

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38. All compounds listed in Tables 1–3 were prepared according to procedures given as Supporting information.

39. Hoyer, D.; Nunn, C.; Hannon, J.; Schoeffter, P.; Feuerbach, D.; Schuepbach, E.; Langenegger, D.; Bouhelal, R.; Hurth, K.; Neumann, P.; Troxler, T.; Pfaeffli, P. *Neurosci. Lett.* **2004**, *361*, 132, On average, when tested as free base or various salts, and under different incubation conditions, **3a** had a pK_d of 8.60 for the native rat brain cortex sst1 receptor. The data in Tables 1–3 apply to the free base.