Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 799–802

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptors. Part 3: 7-Methoxy-1-hydroxy-1-substituted Tetraline Derivatives

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Received 21 November 2001; accepted 27 December 2001

Abstract—As a part of our continuing research on NPY-Y5 receptor antagonists in the series of novel 6-methoxybenzo[*a*]cycloheptene derivatives, we discovered a novel skeleton, 7-methoxy-1-hydroxytetraline **7** which had been used as an intermediate, to be more suitable for increasing potencies leading to compound **3** (**FR230481**). Additionally, we discovered that the naphthalenesulfonamide moiety which was thought to be an essential pharmacophore could be replaced by the 5-chlorobenzothiazolin-3-acetic acid moiety to lead to potent compound **4** (**FR233118**). The structure–activity relationships on compounds **3**, **4** and their related derivatives are described. Unfortunately, although compounds **3** and **4** had very high affinities for Y5 receptors, their poor permeabilities to brain were shown by exo-vivo binding assays when orally administered.

Neuropeptide Y (NPY) is a 36 amino acid peptide that was first isolated from porcine brain[1] and is said to have a relation to food intake.[2–4] A strong association between obesity and non-insulin dependent diabetes mellitus (NIDDM) has been claimed, and more than 80% of NIDDM patients are known to be clinically obese.[5] It has been reported that chronic injection of NPY in rats lead to severe overeating leading to the development of obesity.[4] The Y1 and/or Y5 receptor subtypes amongst the already cloned five different subtypes are activated according to centrally-mediated NPY-induced feeding responses.[6–9] Furthermore, it has been reported that compounds which antagonize the Y5 receptor (e.g., **CGP71683A**[10] or compound **1**) are significantly effective in reducing food intake in *ob*/*ob* mice and Zucker obese rat models.[11] Consequently, we attempted to discover a novel compound that possesses Y5 receptor antagonistic activity for the treatment of obesity and eating disorders (Fig. 1).

We reported in a previous paper[12] that novel 8-methoxybenzo[*a*]cycloheptene derivative **2** (**FR226928**), was a potent Y5 receptor antagonist. We have continued our search for improved derivatives because of dissatisfaction from the viewpoint of potency and brain permeability. We succeeded in discovering **3** (**FR230481**), and **4** (**FR233118**), which showed increased activity (about 20-fold relative to 2) (Fig. 2). This letter describes the synthesis and structure–activity relationships of these analogues.

We discovered **3** using serendipity, by employing a novel skeleton, 7-methoxy-1-aminomethyl-1-hydroxytetraline **7**, which was used as an intermediate in the preparation of **2** described previously.[12] **7** was easily condensed with **8**, prepared by general methods, by reductive amination reactions in the presence of sodium borotriacetoxyhydride and a catalytic amount of acetic acid in methylene chloride, as shown in Scheme 1.

Surprisingly, compound **3** exhibited very potent affinity for the Y5 receptor, hence we next prepared related compounds with larger and smaller rings than a tetraline ring (**3a** and **3b**), modified length of spacer (**3c**) and

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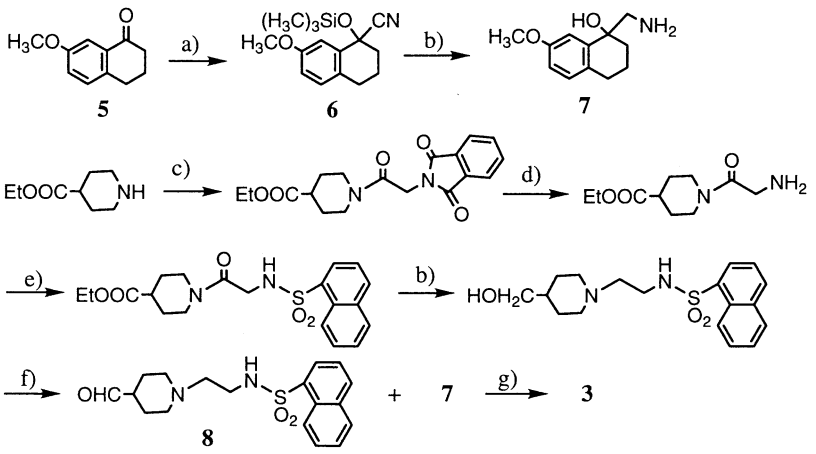
0960-894X/02/$ - see front matter
PII: S0960-894X(02)00018-5



Scheme 1. Reagents and conditions: (a) $(CH_3)_3SiCN$, cat $Zn1_2$; (b) $LiAlH_4$ (c) phthalimide-*N*-acetic acid, HOBT, WSC; (d) hydrazine hydrate; (e) α-naphthalenesulfonyl chloride, Et_3N; (f) MnO_2; (g) $NaBH(OAc)_3$.

exchanged the naphthalenesulfonamide into various substituted phenyl sulfonamides (**3d** and **3e**). These analogues were synthesized according to similar methods to that carried out in the preparation of **3**, and are summarized in Table 1 accompanied by the IC_{50} values for human Y5 receptor binding.

The tetraline ring was found to be the most suitable ring in this series. Both the ring-enlarged **3a** and ring-contracted **3b** showed only about one hundredth the potency when compared with **3**. When comparing **3c** with **3**, it was found that there is also a proper spacer length in this series, and $n=1$ is more suitable than $n=2$. The naphthalene ring of compound **3** was found to be the most suitable, because compounds **3d** and **3e** containing the substituted phenyl ring instead of the naphthalene ring were decreased in their affinities to one twentieth when compared with **3**.

Compound **9** (Fig. 3) was discovered by screening of our in-house chemical library as a comparable potent ($IC_{50}=53$ nM) NPY-Y5 receptor antagonist. We have prepared many kinds of derivatives developed from its novel and unique structure by parallel synthesis technique in a previously reported paper.[13] We considered that a part of this structure, 5-chloro-2-oxobenzothia-

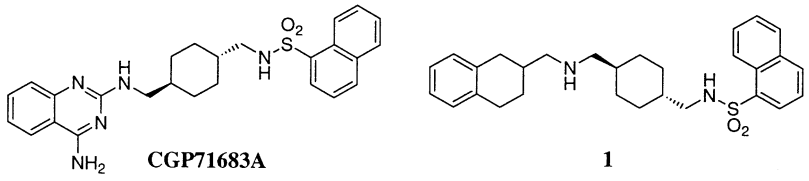


Figure 1.

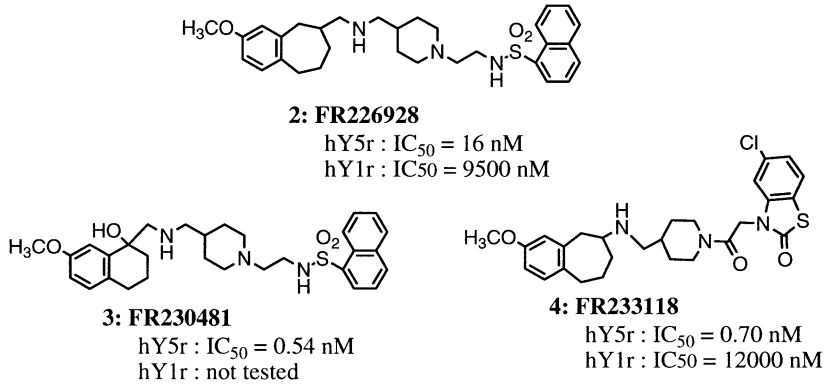


Figure 2.

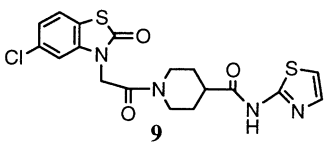


Figure 3.

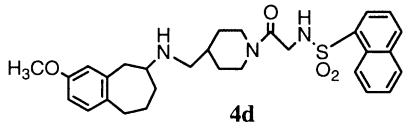
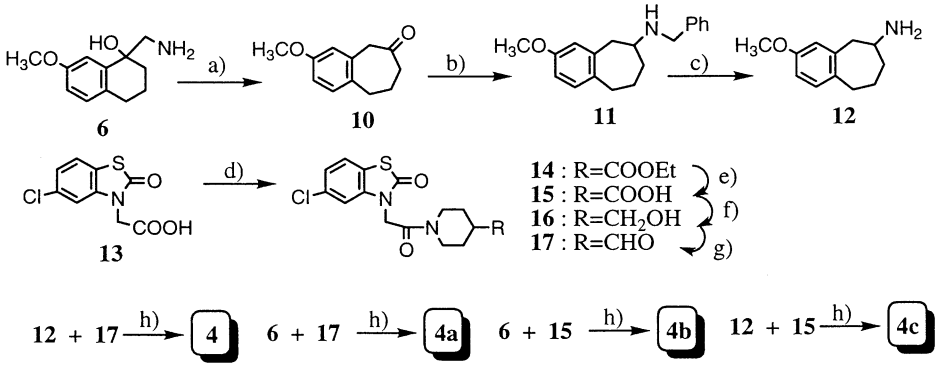


Figure 4.



Scheme 2. Reagents and conditions: (a) $NaNO_2$; (b) $PhCH_2NH_2$, $NaBH(OAc)_3$; (c) H_2, Pd/C; (d) ethyl isonipecotate, WSC HCI, HOBT, Et_3N; (e) aq NaOH; (f) BH_3 Me_2S; (g) MnO_2; (h) $NaBH(OAc)_3$.

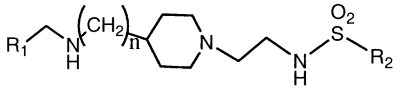
zoline, could be used instead of naphthalene moiety of compound **3**.

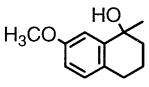
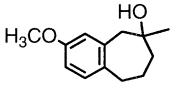
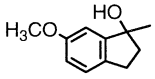
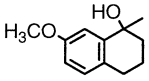
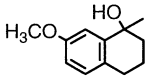
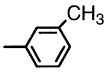
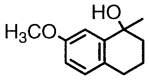
Compound **4** and its related compounds (**4a**–**4c**) were prepared as shown in Scheme 2.

The intermediate amine **12** was obtained by hydrogenolysis of compound **11**, prepared by reductive amination with benzylamine of ketone **10**, which was prepared by diazotization of compound **6** with sodium nitrite followed by ring expansion reaction. The intermediate carboxylic acid **15** was obtained by alkali hydrolysis of amidated product **14** with ethyl isonipecotinate, and the aldehyde **17** was prepared by manganese oxidation of alcohol **16**, which was obtained by reduction of **15** with borane dimethylsulfide, respectively. The structures and the evaluation results of these compounds are summarized in Table 2.

It was found that all of these compounds were as potent as compound **3**, that is to say that the 5-chloro-2-oxobenzothiazolin-3-acetic acid moiety could be used as a bioisoster of a naphthalene alkylsulfonamide group in this series. Compound **4** showed not only about 20-fold potency for Y5 receptors than compound **2**, but also high selectivity for Y5 over Y1 receptors as shown in Figure 2. It was very interesting that **4b** and **4c** showed high affinities for Y5 receptors although they have no basic part in their structure, in contrast to compound **3**. Nevertheless, **4b** and **4c** had been dramatically decreased in their water solubilities due to the two

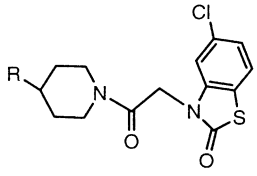
Table 1. Y5 receptor affinities of compounds **3** and **3a**–**e**

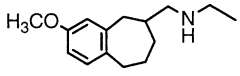
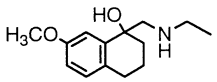
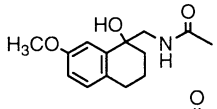
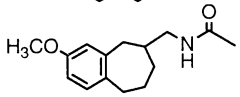


Compd[a]	R_1	n	R_2	IC_{50} (nM)[b]
3		1		0.54
3a		1		56
3b		1		66
3c		2		24
3d		1		13
3e		1		11

[a]Compound is a racemic mixture.
[b]Concentration of compound that inhibited 50% of total specific binding of 125 I-PYY as a ligand to the human NPY-Y5 receptors; obtained from mean value of twice experiments at each concentration (10^{-6} – 10^{-10} M).

Table 2. Evaluation results on binding affinities for NPY Y5 receptor of **4** and **4a**–**c**



Compd[a]	R	IC_{50} (nM)[b]
4		0.7
4a		28
4b		1.0
4c		1.2

[a]Compound is a racemic mixture.
[b]Concentration of compound that inhibited 50% of total specific binding of 125 I-PYY as a ligand to the human NPY-Y5 receptors; obtained from mean value of twice experiments at each concentration (10^{-6} – 10^{-10} M).

amides moieties. Accordingly, we tried again to introduce a naphthalenesulfonamide group into compound **4**. We designed **4d**, as shown in Figure 4, in which the basicity of the piperidine ring was removed by amide formation and the other basic amine was left untouched in order to be able to form a salt. **4d** exhibited potent affinity (3.7 nM) for NPY Y5 receptors as was expected.

Unfortunately, although the compounds described in this paper possessed potent affinities for NPY Y5 receptors, their poor permeabilities to brain were shown by exo-vivo binding assays when orally administered at 100 mg/kg to rats.

Summary

As a part of our continuing research on NPY-Y5 receptor antagonists in the series of novel 8-methoxybenzo[*a*]cycloheptene derivatives, we discovered a novel skeleton, 7-methoxy-1-hydroxytetraline **7** which had been used as an intermediate, to be more suitable for increasing potencies leading to compound **3** (**FR230481**). This compound showed 30-fold more potent affinity for Y5 receptors when compared with **2** (**FR226928**), the most potent compound in the previously reported series.[12] Additionally, we discovered that the naphthalenesulfonamide moiety which was thought to be an essential pharmacophore could be replaced by the 5- chlorobenzothiazolin-3-acetic acid moiety to lead to compound **4** (**FR233118**) exhibiting about 20-fold more potent activity than **2**.

Unfortunately, although compounds **3** and **4** had very high affinities for Y5 receptors, their poor permeabilities to brain were shown by exo-vivo binding assays when orally administered at 100 mg/kg to rats, and we are continuing our search for improved compounds.

Acknowledgements

We would like to thank Dr. D. Barrett for helpful discussions and critical reading of the manuscript.

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