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Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptors. Part 2: Substituted Benzo[*a*]cycloheptene Derivatives

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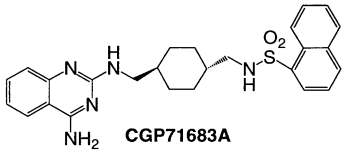
Abstract—Novel benzo[*a*]cycloheptene derivatives were prepared for the purpose of searching new neuropeptide Y-Y5 (NPY-Y5) receptor antagonists. The structure–activity relationships are described and compound **2o (FR226928)** showed the most potent affinity for Y5 receptor of all we prepared and was found to have higher potency and better selectivity for Y5 over Y1 receptor affinities when compared with the known lead compound **1**.

Obesity is now a major health problem in advanced nations and even mild obesity enhances the risk of premature death, hypertension, diabetes mellitus, hyperlipidaemia, atherosclerosis, coronary heart disease, arthritis, sleep apnea and certain types of cancer.[1,2] 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.[3]

Neuropeptide Y (NPY) is a 36 amino acid peptide that was first isolated from porcine brain[4] and is found abundantly in the central and peripheral nervous system.[5,6] NPY is said to have a relation to a number of physiological responses, such as food intake,[7–9] blood pressure regulation,[10,11] hormone secretion,[12] sexual behavior,[13] and circadian rhythm[10] and is implicated in the pathophysiology of several disorders. It has been reported that chronic injection of NPY in rats lead to severe overeating leading to the development of obesity.[9] There are at least five different NPY receptor subtypes (Y1, Y2, Y4, Y5 and Y6), which are recognized as members of the superfamily of G-protein coupled receptors. The existence of a Y3 subtype receptor has been supported by substantial pharmacological evidence but it has not yet been cloned. The Y1 and/or Y5 receptor subtypes are activated according to centrally-mediated NPY-induced feeding responses.[14–17] It has been reported that compounds which antagonize the Y5 receptor, for example, **CGP71683A**,[18] are significantly effective in reducing food intake in *ob*/*ob* mice and Zucker obese rat models.[19] Furthermore, potent compounds, which contain α- or β-naphthalenesulfonamide as a substructure (e.g., **1**) were disclosed recently (Fig. 1).[20]

Consequently, we attempted to discover a novel compound that possesses Y5 receptor antagonistic activity



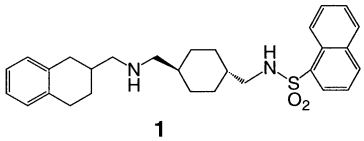


Figure 1.

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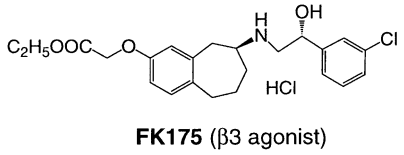
by using these lead compounds for the treatment of obesity and eating disorders. We speculated that the naphthalenesulfonamide moiety was essential for affinity to the Y5 receptor and the *trans*-cyclohexyl group was exchangable into a piperizine ring. Instead of the aminoquinazoline and the tetralin nuclei, we selected a substituted benzo[*a*]cycloheptene ring as a key pharmacophore, because it is also used in β3-adrenoceptor agonists and is present in **FK175**, a candidate discovered in another research team,[21] in an attempt to identify a compound with dual character as an NPY-Y5 receptor antagonist and a β3-adrenoceptor agonist.



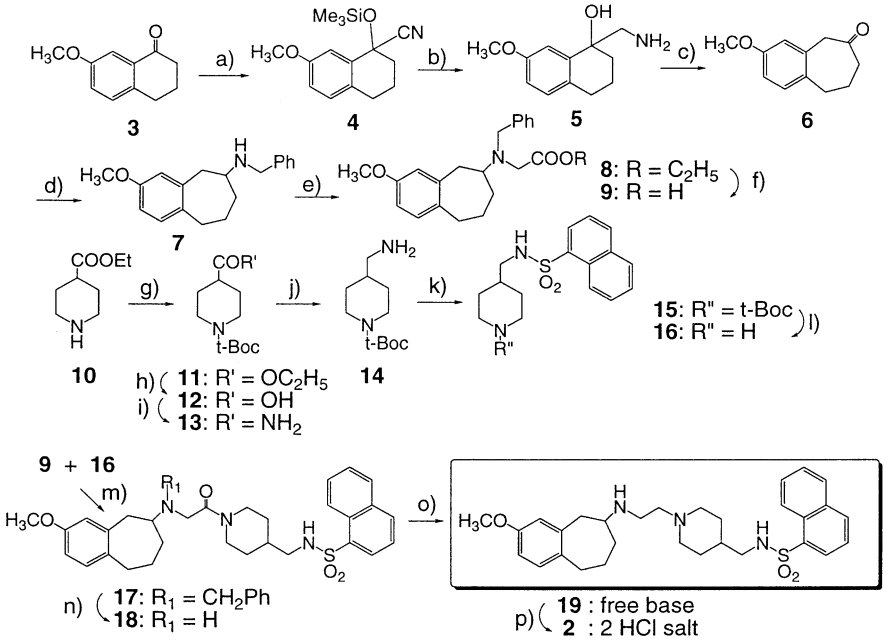
FK175 (β3 agonist)

Figure 2.

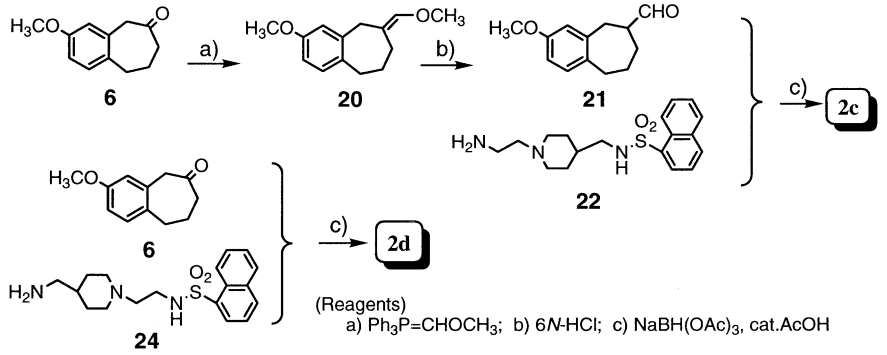
This paper describes the synthesis of novel benzo[*a*]-cycloheptene derivatives as NPY-Y5 receptor antagonists and their structure–activity relationships (Fig. 2).

Initially, we prepared racemic compound **2** by the route shown in Scheme 1. Compound **2** showed a moderate affinity for Y5 receptors ($IC_{50} = 7.4 \times 10^{-7}$ M) and poor affinity for Y1 receptors ($IC_{50} = 1.9 \times 10^{-5}$ M). This prompted us to synthesize other related compounds to obtain more potent and selective derivatives.

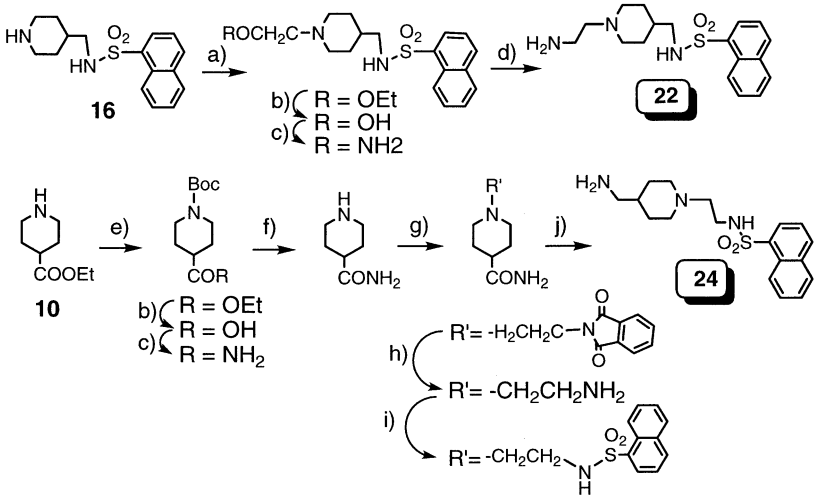
We first exchanged the position of the methoxy group on the benzo[*a*]cycloheptene ring, the alkyl spacer length and the binding positions to the piperidine ring. Compounds **2a** and **2b** were prepared according to similar methods to that carried out in the preparation of **2**. **2c** and **2d** were obtained by reductive amination of aldehyde **21** and ketone **6**, as shown in Scheme 2, with the respective amines **22** and **24**, which were prepared by general methods as shown in Scheme 3. They are



Scheme 1. Reagents and conditions: (a) Me_3SiCN, cat ZnI_2; (b) $LiAlH_4$; (c) aq $NaNO_2$; (d) $C_6H_5CH_2NH_2$, $NaBH(OAc)_3$; (e) $BrCH_2CO_2Et$, K_2CO_3; (f) aq NaOH; (g) Boc_2O, Et_3N; (h) aq NaOH; (i) CICOO-*i*-Bu, *N*-methylmorpholine; aq NH_3; (j) $LiAlH_4$; (k) α-naph-SO_2Cl, Et_3N; (l) 4*N*-HCl-AcOET; (m) WSC, HOBT; (n) $HCOONH_4$, Pd/C; (o) $LiAlH_4$; (p) 4*N*-HCl–AcOEt.

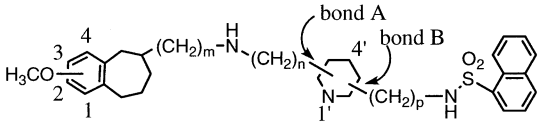


Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHOCH_3$; (b) 6*N*-HCl; (c) $NaBH(OAc)_3$, cat AcOH.



Scheme 3. Reagents and conditions: (a) $BrCH_2CO_2Et$, Et_3N; (b) aq NaOHl; (c) ClCOO-*i*-Bu, *N*-methylmorpholine; aq NH_3; (d) $LiAlH_4$; (e) Boc_2O, Et_3N; (f) 4*N*-HCl-AcOEt; (g) *N*-bromoethylphthalimide, Et_3N; (h) $NH_2NH_2\ H_2O$; (i) naphthalenesulfonyl chloride, Et_3N; (j) $LiAlH_4$.

Table 1. Y5 and Y1 receptor affinities of compounds **2** and **2a–d**



Compd[a]	Position of $-OCH_3$	*m*	*n*	Bond A to piperidine	Bond B to piperidine	*p*	Binding affinity (IC_{50})	
							Y5[b]	Y1[c]
1[d]							3.8×10^{-8} M	1.3×10^{-6} M
2	3	0	2	1′	4′	1	7.4×10^{-7} M	1.9×10^{-5} M
2a	2	0	2	1′	4′	1	1.0×10^{-6} M	—
2b	1	0	2	1′	4′	1	$>1.0\times10^{-6}$ M	—
2c	3	1	2	1′	4′	1	5.4×10^{-7} M	2.8×10^{-6} M
2d	3	0	1	4′	1′	2	4.5×10^{-8} M	1.4×10^{-5} M

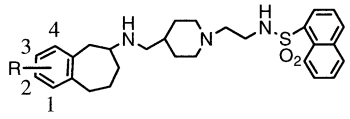
[a]Compound is a racemic mixture.
[b]Concentration of compound that inhibited 50% of total specific binding of ^{125}I-PYY as a ligand to human NPY-Y5 receptors.
[c]Concentration of compound that inhibited 50% of total specific binding of ^{125}I-PYY to human NPY-Y1 receptors.
[d]Lead compound **1**.

summarized in Table 1 accompanied by the biological evaluation results of them and the lead compound **1**.

The best position for the methoxy moiety was found to be the 3-position of the benzo[*a*]cycloheptene ring, and the optimum length of spacer, that is, $m+n+p$, was found to be 3. Furthermore, it is also found that compound **2d**, whose bond-A binds to the 4′-position of piperidine ring, was more potent than the other compounds. We next changed the methoxy group of **2d** into other kinds of substituents leaving other parts of the structure unchanged. These compounds were synthesized according to similar methods to that carried out in the preparation of **2d** and are summarized in Table 2.

The kind of 3-substituents was found not to be so important for increasing the potencies and **2d** showed the most potent affinity in this series. Next, we changed the alkyl spacer length between the benzo[*a*]cycloheptene and piperidine rings. The evaluation results are summarized in Table 3.

Table 2. Substituent effects on Y5 and Y1 receptor affinities



Compd[a]	R	Binding affinity (IC_{50})	
		Y5[b]	Y1[c]
2d	3-OCH_3	4.5×10^{-8} M	1.4×10^{-5} M
2e	H	2.1×10^{-7} M	—
2f	2,3-di-OCH_3	6.8×10^{-8} M	1.7×10^{-5} M
2g	3-Cl	8.5×10^{-8} M	8.5×10^{-6} M
2h	3-CH_3	7.2×10^{-8} M	1.8×10^{-5} M
2i	3-NO_2	7.9×10^{-8} M	1.5×10^{-5} M
2j	3-NH_2	5.2×10^{-8} M	—
2k	3-$OCH_2CO_2C_2H_5$	6.8×10^{-7} M	—
2l	3-OCH_2CO_2H	25.7% (at 10^{-6} M)	—

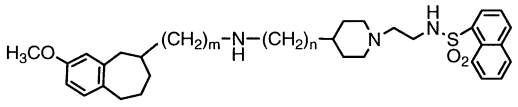
[a]Compound is a racemic mixture.
[b]Concentration of compound that inhibited 50% of total specific binding of ^{125}I-PYY as a ligand to human NPY-Y5 receptors.
[c]Concentration of compound that inhibited 50% of total specific binding of ^{125}I-PYY to human NPY-Y1 receptors.

As shown in Table 3, the order of potency as Y5 receptor antagonists was **2o** > **2n** > **2d** > **2m**, though we consider there is no significant difference in terms of pharmacological effect.

Considering the above results, we next synthesized related compounds by changing the piperidine part into other aliphatic heterocyclic rings. We selected an azetidine ring instead of piperidine because of its easy availability and lack of an asymmetric carbon. *N*-[2-(3-Aminomethylazetidin-1-yl)ethyl]-1-naphthalenesulfonamide was synthesized by similar methods to that carried out in the preparation of piperidine derivative **24**. The structures and evaluation results are summarized in Table 4.

It was found that an azetidine ring had a similar effect to that of the piperidine ring, but was slightly weaker. When the piperidine ring was replaced by azetidine, the 3-methoxy moiety was also more suitable as a substituent on the benzo[*a*]cycloheptene ring compared to 3,4-di-methoxy, 3-chloro- and 3-methyl groups.

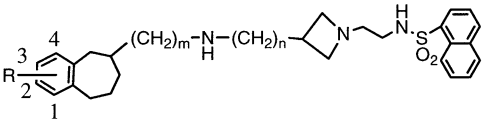
Table 3. Effects of the spacer alkyl length



Compd[a]	*m*	*n*	Binding affinity (IC_{50})	
			Y5[b]	Y1[c]
2d	0	1	4.5×10^{-8} M	1.4×10^{-5} M
2m	0	0	6.6×10^{-8} M	3.5×10^{-5} M
2n	1	0	3.9×10^{-8} M	2.9×10^{-5} M
2o	1	1	1.6×10^{-8} M	9.6×10^{-6} M
1[d]			3.8×10^{-8} M	1.3×10^{-6} M

[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 human NPY-Y5 receptors.
[c]Concentration of compound that inhibited 50% of total specific binding of ^{125}I-PYY to human NPY-Y1 receptors.
[d]Lead compound **1**.

Table 4. Effect of azetidine in place of piperidine ring



Compd[a]	R	*m*	*n*	Binding affinity (IC_{50})	
				Y5[b]	Y1[c]
2p	3-OCH_3	1	1	8.6×10^{-8} M	2.2×10^{-5} M
2r	3,4-di-OCH_3	0	1	1.4×10^{-7} M	—
2s	3-Cl	0	1	3.1×10^{-7} M	—
2t	3-CH_3	0	1	1.9×10^{-7} M	—
1[d]				3.8×10^{-8} M	1.3×10^{-6} M

[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 human NPY-Y5 receptors.
[c]Concentration of compound that inhibited 50% of total specific binding of ^{125}I-PYY to human NPY-Y1 receptors.
[d]Lead compound **1**.

Summary

We synthesized many novel substituted benzo[*a*]cycloheptene derivatives based on the idea that lead compound **1** as an NPY-Y5 antagonist might lead to an ideal anti-obesity drug if it possessed the β3-adrenoceptor agonistic character of **FK175**, which contains a benzo[*a*]cycloheptene ring in its structure. Compound **2o** (**FR226928**) showed the most potent affinity ($IC_{50} = 1.6\times10^{-8}$ M) for the NPY-Y5 receptor of all compounds we prepared, and it was found to have higher potency and better selectivity for Y5 over Y1 receptor affinities than the lead compound **1**. Nevertheless, it was not enough from the viewpoint of potency and brain permeability. This derivative is undergoing further biological evaluation to determine whether the β3-adrenoceptor agonistic character is present in addition to its NPY-Y5 antagonistic activity or not. We are continuing our search for improved derivatives.

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