Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1009–1011

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Novel Potent Antagonists of Human Neuropeptide Y-Y5 Receptor. Part 4: Tetrahydrodiazabenzazulene Derivatives

Yoshinari Satoh,[a,*] Chie Hatori[b] and Harunobu Ito[b]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

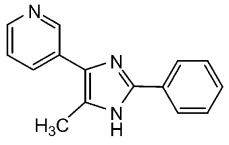
[b]*Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 5-2-3 Tohkohdai, Tsukuba 300-2698, Japan*

Received 19 December 2001; accepted 1 February 2002

Abstract—Novel tetrahydrodiazabenzazulene derivatives, designed from the lead compound **1** discovered by screening of our in-house chemical library, were prepared and found to be potent neuropeptide Y-Y5 (NPY-Y5) receptor antagonists. The structure–activity relationships are described. Compounds **7** (**FR240662**) and **16** (**FR252384**) were especially attractive owing to their high affinities for the NPY-Y5 receptors, oral absorption and permeability to brain.

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] We have already reported some attempts to provide potent and novel chemical entities, 2-oxobenzothiazolin-3-acetic acid derivatives,[5] benzo[*a*]cycloheptene derivatives[6] and tetraline derivatives,[7] as NPY-Y5 receptor antagonists for the treatment of obesity and eating disorders. Unfortunately, the compounds described were so far showed little absorption and permeability to brain by oral administration.

By screening of our in-house chemical library in our Exploratory Research Laboratories, 2-phenyl-4-(3-pyridyl)-5-methylimidazole (**1**, **FR79620**) was found to have an interesting profile as a new lead compound in the search for a novel NPY-Y5 receptor antagonist, that is it showed an IC_{50} value of binding inhibition of ^{125}I-PYY on human NPY-Y5 receptors of 4.27×10^{-7} M. It also showed a dose dependent decrease of food intake and body weight by continuous po administration of 10, 30 and 100 mg/kg for 4 days (b.i.d.) to SD rats: It was also found to decrease food intake and body weight of *db*/*db* mice by continuous po administration of 100 mg/kg for 4 days (b.i.d.) and possess good oral absorption and permeability to brain (Fig. 1).



1 : FR79620

Figure 1.

The distinctive structural features of this compound were considered as follows: (i) the molecular weight (=235) is small enough to be well absorbed by po administration; (ii) the existence of a basic nitrogen containing heterocyclic moieties such as pyridyl and imidazolyl is related to some extent to its solubility in water, oral absorption and permeability to brain; (iii) the compact molecular shape is also connected to good oral absorption and permeability to brain.

We designed a new chemical entity **2** after consideration of these features by a ring closure with trimethylene moiety between the methyl group and the pyridine ring of compound **1**, as shown in Figure 2. Furthermore, we used a methoxy substituted phenyl ring instead of pyridine ring as compound **3** in Figure 2 because the starting material 7-methoxy-1-tetralone was easily available and we expected the electron donating methoxy moiety to show a similar effect to the nitrogen atom of pyridine. The ring closure with trimethylene bond formation was owing to our thought that the phenyl and the imidazolyl rings are not coplaner as similar to the pyridyl and the imidazolyl rings of compound **1**.

*Corresponding author. Tel.: +81-6-6390-1376; fax: +81-6-6304-5435; e-mail: yoshinari_satoh@po.fujisawa.co.jp

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00090-2

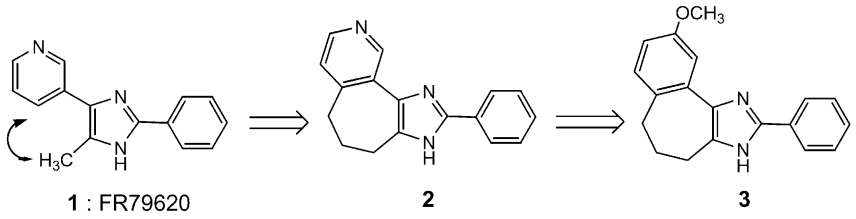
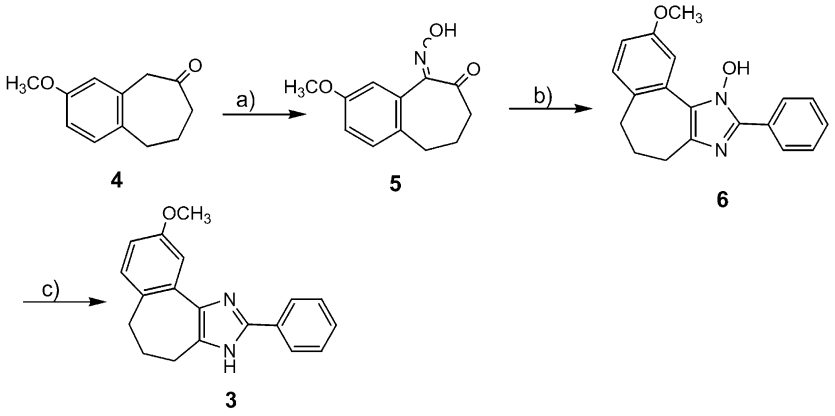


Figure 2.



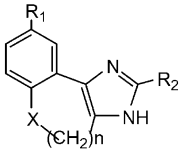
Scheme 1. Reagents and conditions: (a) *i*-Amyl-ONO/aq HCl–THF; (b) Ph-CHO, NH_4OAc; (c) PCl_3/DMF, or H_2/Pd–C, or $HCOONH_4$ Pd–C.

Compound **3** was prepared as shown in Scheme 1. The starting material 8-methoxy-2-oxobenzo[*a*]cycloheptene **4** was reported in the previous paper,[6] and was oximated with *i*-amylnitrite in an acidic medium to afford oximeketone **5** followed by ring closure with benzaldehyde and ammonium acetate to give 1-hydroxy-2-phenyltetrahydrodiazabenzazulene **6** in high yield. The dehydroxylation was performed by reduction with phosphorus trichloride or hydrogenation with 10% palladium on carbon leading to **3**.

Fortunately, the firstly prepared compound **3** showed about 20-fold improved affinities for both human and rat NPY-Y5 receptors, when compared with the lead **1**, **FR79620**. This prompted us to search for related compounds. We planned first of all to prepare a compound in which we would exchange the phenyl ring at the 2-position of the imidazole nucleus into a pyridine ring (**7**) in order to confer similar water solubility to the lead **1**. Next, an electron donating methoxy group was exchanged by a neutral hydrogen and an electron-withdrawing chlorine (**8** and **9**). These compounds showed the same or higher affinities when compared with compound **3**. Compounds **10**, **11** and **12** were found to have lower affinities than compound **3**, except that **12** showed comparable affinity. They were prepared by similar methods to that carried out in the preparation of **3**, and their chemical structures and biological evaluation results are summarized in Table 1.

We concluded that a pyridine ring was suitable for a substituent at the 2-position of tetrahydrodiazabenzazulene when considering the oral absorption and permeability of the brain owing to its hydrophobicity and basicity. Furthermore, we thought that there was little possibility of potentiating the affinities for binding

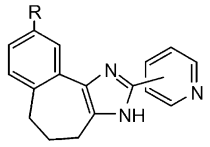
Table 1. Chemical structures and Y5 receptor affinities of compounds **3**, **7**–**12**



Compd	R_1	X	*n*	R_2	IC_{50} (M)[a]
3	$-OCH_3$	$-CH_2-$	2		2.5×10^{-8}
7	$-OCH_3$	$-CH_2-$	2		1.3×10^{-8}
8	–H	$-CH_2-$	2		5.8×10^{-9}
9	–Cl	$-CH_2-$	2		1.7×10^{-9}
10	–H	–O–	2		6.1×10^{-6}
11	–H	$-CH_2-$	2		5.7×10^{-7}
12	$-OCH_3$	$-CH_2-$	1		5.2×10^{-8}

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

Table 2. Chemical structures and Y5 receptor affinities of compounds **7**, **13**–**23**



Compd	R	Bonding position of pyridine ring	IC_{50} (M)[a]
13	$-OCH_3$	2-	1.1×10^{-7}
14	$-OCH_3$	3-	6.3×10^{-9}
7	$-OCH_3$	4-	1.3×10^{-8}
15	$-CH_3$	2-	3.2×10^{-8}
16	$-CH_3$	3-	2.3×10^{-9}
17	$-CH_3$	4-	6.4×10^{-9}
18	–H	2-	1.1×10^{-7}
19	–H	3-	7.3×10^{-9}
20	–H	4-	2.0×10^{-8}
21	–F	2-	4.6×10^{-8}
22	–F	3-	6.4×10^{-9}
23	–F	4-	1.3×10^{-8}

[a]See footnote to Table 1.

by changing the ring-closing bond from a trimethylene moiety when comparing compound **10** with **8** and compound **12** with **3** as shown in Table 1. Although there was a tendency for phenyl substituents to increase affinities by increasing the electron withdrawing properties, further investigation was necessary.

We next investigated the combination between 9-substituents and the bonding position of the pyridine ring at the 2-position of tetrahydrodiazabenzoazulene. We selected $-OCH_3$, $-CH_3$, –H and –F moieties as the substituents at the 9-position and 2-, 3- and 4-pyridyl groups as the substituent at the 2-position. 7-Fluoro-1-tetralone was prepared from 3-(4-fluorobenzoyl)-propionic acid by Wolff–Kishner reduction followed by ring closure with polyphosphoric acid and other substituted 1-tetralones where commercially available. The starting materials, 8-substituted benzo[*a*]cyclohepten-2-ones, were synthesized by similar procedures to that described in a previous paper[6] and the target compounds were obtained by similar methods to that carried out in the preparation of compound **3**.

The chemical structures and biological evaluation results of the obtained compounds **13**–**23** are summarized in Table 2 accompanied with those of compound **7**.

Considering the evaluation results shown in Table 2, it was found that the electronic effect of the substituent (R) was not so important to increase the affinity for NPY-Y5 receptors, but the bonding positions of the pyridine ring at the 2-position of the imidazole nucleus related closely to their potencies. Thus, the affinities for receptor binding of the compounds possessing an electron donating methoxy or methyl group were as potent as the affinities of compounds substituted by the neutral hydrogen or the electron withdrawing fluorine when compared in a series. However, the compounds substituted by a 3-pyridyl moiety at the 2-position were found to be several or 10-fold more potent than compounds substituted by 2- or 4-pyridyl groups in all series. Compound **16** showed the most potent affinities for the NPY-Y5 receptors of all compounds we prepared.

Compounds **7** (**FR240662**) and **16** (**FR252384**) were investigated in more detail by administration orally to Zucker fatty rats for development as an anti-obesity drug. Unfortunately, we have obtained some biological data suggesting that there is little relation between the NPY-Y5 receptor activation and food intake in spite of enough concentrations to show activities of unchanged compounds **7** and **16** in both plasma and brain. These detailed evaluation results, such as selectivity for Y5 receptors over Y1 receptors, functional assay results by c-AMP production induced by forskoline in human Y5 receptors, effects on food intake and body weight in both SD rats and Zucker fatty rats, effects on plasma glucose, insulin and triacylglycerol levels, effects on GOT and GPT and so on, will be disclosed elsewhere in the near future.

Summary

We prepared novel tetrahydrodiazabenzazulene derivatives and found that some of them showed potent NPY-Y5 receptor antagonistic activities. Compounds **7** (**FR240662**) and **16** (**FR252384**) were especially attractive owing to their high affinities for the NPY-Y5 receptors, oral absorption and permeability to brain.

Acknowledgements

The authors would like to acknowledge Dr. D. Barrett for helpful discussions and critical reading of the manuscript.

References and Notes

1. Tatemoto, K.; Carlquist, M.; Mutt, V. *Nature* **1982**, *296*, 651.
2. Stanley, B. G.; Leibowitz, S. F. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3940.
3. Kalra, S. P.; Dube, M. G.; Fournier, A.; Kalra, P. S. *Physiol. Behav.* **1992**, *50*, 5.
4. Beck, B.; Stricker-Krongrad, A.; Nicolas, J.-P.; Burlet, C. *Int. J. Obesity* **1991**, *16*, 295.
5. Tabuchi, S.; Itani, H.; Sakata, Y.; Oohashi, H.; Satoh, Y.; *Bioorg. Med. Chem. Lett.*, submitted for publication.
6. Itani, H.; Ito, H.; Sakata, Y.; Hatakeyama, Y.; Oohashi, H.; Satoh, Y.; *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 757.
7. Itani, H.; Ito, H.; Sakata, Y.; Hatakeyama, Y.; Oohashi, H.; Satoh, Y.; *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 799.