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STRUCTURE–ACTIVITY RELATIONSHIP OF A SERIES OF DIAMINOALKYL SUBSTITUTED BENZIMIDAZOLE AS NEUROPEPTIDE Y Y1 RECEPTOR ANTAGONISTS

Hamideh Zarrinmayeh,* Dennis M. Zimmerman, Buddy E. Cantrell, Douglas A. Schober, Robert F. Bruns, Susan L. Gackenheimer, Paul L. Ornstein, Philip A. Hipskind, Thomas C. Britton, and Donald R. Gehlert

Eli Lilly and Company, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, U.S.A

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Abstract: A series of benzimidazoles (**4**) was synthesized and evaluated in vitro as potent and selective NPY Y1 receptor antagonists. Substitution of the piperidine nitrogen of **4** with appropriate R groups resulted in compounds with more than 80-fold higher affinity at the Y1 receptor compared to the parent compound **5** (R = H). The most potent benzimidazole in this series was **21** (K_i = 0.052 nM).

Neuropeptide Y (NPY) is a 36 amino acid peptide found and isolated in 1982.[1] Besides its high concentration in the central nervous system,[2] NPY is also widely distributed throughout the peripheral nervous system.[3] NPY is involved in a broad spectrum of brain functions, including food intake,[4] blood pressure regulation,[5] hormone secretion,[6] sexual behavior,[7] and circadian rhythm.[5] Specifically NPY's role in feeding disorders has been focus of the recent research in this field. Chronic injection of NPY in rats produces profound overeating, particularly of carbohydrate and fat that leads to the development of obesity.[8] NPY mediates its biological effects through a portfolio of G-protein coupled receptors. The receptor mediating the effects of NPY on food intake remains a controversial topic. While several investigators have suggested the Y1 receptor mediates this response,[9] the more recently discovered Y5 receptor has emerged as a promising candidate.[10–12]

Previously discovered NPY Y1 receptor antagonists include BIBP3226,[13] SR120819A,[14] and PD160170.[15] Although these antagonists have been useful as pharmacological tools, particularly BIBP3226, there is still a need for more potent and selective antagonists. Recently, we have disclosed the structure–activity relationship of the two novel series of the NPY Y1 receptor antagonists; represented by the indole **1**[16] and the benzimidazoles **2** and **3**.[17,18] Within the benzimidazole series Y1 antagonists, we have shown that the activity was enhanced with two appropriately positioned aminoalkyl groups such as piperidinylalkyl functionalities at either N1 (**2**) or N1 and C4 positions (**3**). These two compounds represent the most potent benzimidazole analogues reported in our previous work. The goal of this work was to rationally combine these previous discoveries to provide antagonists with even higher potency and better selectivity at the Y1 receptor.

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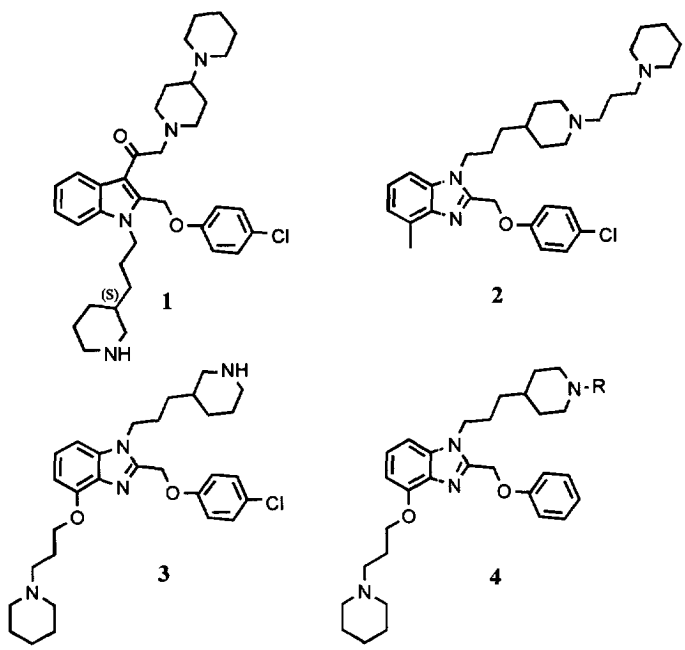
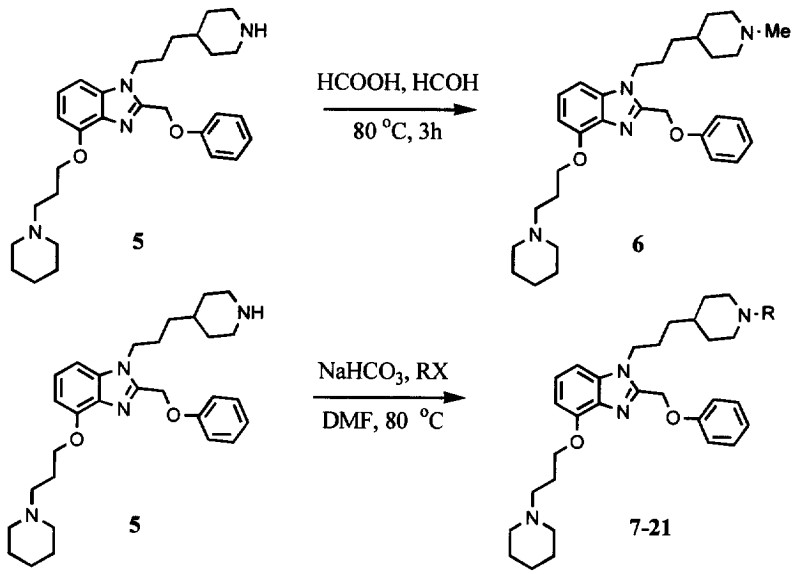


In this work, our SAR studies were extended in the benzimidazole series through substitution of the piperidine nitrogen of compound **4**. The binding affinities of these new compounds were determined by measuring their ability to displace [^{125}I]-peptide YY binding to cloned human Y1 receptors expressed in AV-12 cells.[18] To evaluate selectivity, some selected analogs were assessed for their ability to inhibit [^{125}I]-peptide YY binding to NPY Y2, Y4 and Y5 expressed in CHO cells. In vitro functional activity of selected compounds was determined by their ability to antagonize 1 nM NPY's inhibition of forskolin-stimulated cyclic AMP accumulation in SK-N-MC cells.

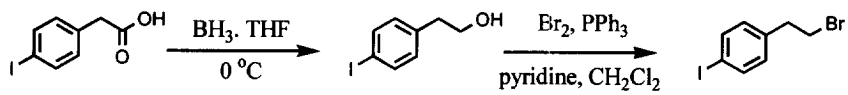
Chemistry

Synthesis of the benzimidazoles **2**, **3**, and **5** have been reported previously.[17,18] As shown in Scheme 1, compound **6** was prepared by heating benzimidazole **5** with 96% formic acid and 37% formaldehyde for 3 h. Alkylation of **5** under standard condition ($NaHCO_3$, DMF, alkyl halide (bromide or chloride), 80 °C) gave products **7**–**21** as shown in Scheme 1. In many cases alkyl bromides were commercially available or they were prepared from a commercially available starting materials. For example *p*-iodophenylethylbromide was prepared from the reduction of the *p*-iodophenylacetic acid with borane (BH_3, THF, 0 °C) and subsequent bromination of the alcohol (Br_2, PPh_3, Pyridine, CH_2Cl_2), Scheme 2.

Scheme 1



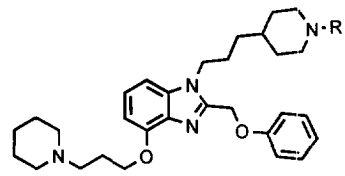
Scheme 2



Pharmacology

The binding affinity data for the new compounds is presented in Table 1. Compounds with diverse R groups were prepared in order to understand their nature of binding to the Y1 receptor and also to utilize this information for preparing more potent antagonists. Replacement of hydrogen with methyl, *i*-propyl or propenyl groups produced a small increase in Y1 receptor affinity. Higher increases in affinity were found through substitution with larger alkyl groups such as *i*-butyl , methylcyclohexyl and ethylcyclohexyl (compounds **9–13**). Incorporation of another polar moiety such as piperidine as well as elongation of the tether also increased the binding affinity (**14** compared to **5**). Interestingly phenylethyl (**15**) or phenylpropyl (**16**) substitution on the nitrogen resulted in compounds with very high affinity. Comparison of the binding affinities of **14**, **15**, and **16** suggest the discovery of a new binding pocket in the Y1 receptor that is sensitive to both hydrophobic and hydrophilic functionalities. We further characterized binding to this pocket through incorporation of the carbonyl group in the alkylaryl substituent (**18** and **19**). Compounds **18** and **19** bound with very high affinities. A further break-through occurred with *p*-iodophenylethyl substitution which gave compound **21** with binding affinity of 0.052 nM. Compound **21** is the highest affinity Y1 receptor antagonist discovered to date.

Table 1. In vitro binding affinities of substituted benzimidazoles **5–21** at the NPY receptor in AV-12 cell line.



5 - 21

Compounds	R	NPY-Receptor Binding K_i (nM) ± SEM
1	-	0.75 ± 0.02
2	-	4.5 ± 0.1
3	-	1.7 ± 0.03
5	H	4.5 ± 0.045
6	CH_3	1.62 ± 0.03
7	$CH(CH_3)_2$	1.61 ± 0.34
8	$CH_2CH{=}CH_2$	1.63 ± 0.00
9	$CH_2CH(CH_3)_2$	0.829 ± 0.033
10	$CH_2CH_2CH{=}CH_2$	0.707 ± 0.021
11	$CH_2CH_2CH(CH_3)_2$	0.290 ± 0.005
12	$CH_2(CH_2)_6$	0.393 ± 0.036
13	$CH_2CH_2(CH_2)_6$	0.285 ± 0.004
14	$CH_2CH_2CH_2N(CH_2)_5$	0.106 ± 0.564
15	CH_2CH_2Ph	0.191 ± 0.005
16	$CH_2CH_2CH_2Ph$	0.361 ± 0.01
17	$CH_2CH{=}CHPh$	0.183 ± 0.008
18	CH_2CH_2COPh	0.112 ± 0.02
19	$CH_2CH_2CH_2COPh$	0.132 ± 0.00
20	CH_2CH_2Ph-OH	0.313 ± 0.001
21	CH_2CH_2Ph-I	0.052 ± 0.005

Antagonist activity (K_i) of selected compounds such as **13, 14, 16,** and **21** was measured to be respectively 5.2, 0.564, 3.4, and 6.00 nM in adenylate cyclase assays using SK-N-MC cell line. Selected Y1 antagonists including **21** were tested for affinity to human Y2, Y4, and Y5 receptors expressed in CHO cells. These compounds showed less than 50% inhibition of the binding of peptide YY at the concentration of 1 μM at these receptors.[18]

In summary, herein we have reported a new class of NPY antagonists with high affinity and selectivity at the NPY Y1 receptor. The most potent compound in this series is benzimidazole **21** with K_i = 0.052 nM. This compound is the most potent NPY Y1 antagonist discovered to date.

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