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STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF 1-SUBSTITUTED-4-METHYLBENZIMIDAZOLE NEUROPEPTIDE Y-1 RECEPTOR ANTAGONISTS

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Abstract: The characterization of a novel series of NPY-1 receptor antagonists derived from the 4-methylbenzimidazole **4** is described. Appropriate substitution on the piperidyl nitrogen of **4** led to systematic increases in Y-1 receptor affinity, to approximately 50-fold, and to the discovery of the importance of a second basic substituent.

Neuropeptide Y (NPY) is a 36 amino acid peptide abundantly expressed in the periphery and the central nervous system.[1,2] It is known to be involved in a number of physiological responses and implicated in the pathophysiology of several disorders. A number of receptors with high affinity for NPY have been characterized by pharmacological and molecular cloning techniques;[3] however, their specific involvement in NPY mediated pharmacology remains to be fully characterized. To accomplish this goal, specific NPY antagonists with appropriate pharmacodynamic properties will need to be discovered.

Accordingly, we sought to discover selective NPY-1 receptor antagonists. Evidence has shown NPY-1 receptor involvement in cardiovascular function[4] and food intake,[5,6] which suggests important therapeutic potential for NPY-1 receptor antagonists. Previously discovered NPY-1 antagonists include BIBP3226,[7] SR120819A,[8] and PD160170;[9] however, the need for other selective NPY-1 antagonists still exists. Recently, our group has disclosed the structure-activity relationships (SAR) of two novel series of NPY-1 antagonists that contain indole[10] and benzimidazole[11] based platforms (e.g., **1** and **2**).

In this work, we sought to extend the SAR of the benzimidazole series. Previous studies identified a marked effect on activity through substitution at the 4 position of the benzimidazole ring with alkyl and alkyloxy substituents. Maximum enhancement of activity was found with the 4-(piperdyl)-propyloxy substituent. Compound **2** was the most potent benzimidazole NPY-1 antagonist identified ($K_i = 0.002$ μM).

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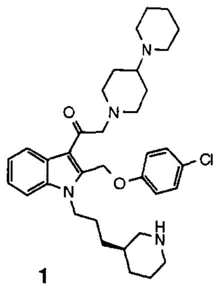

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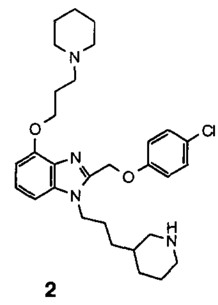

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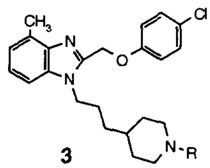

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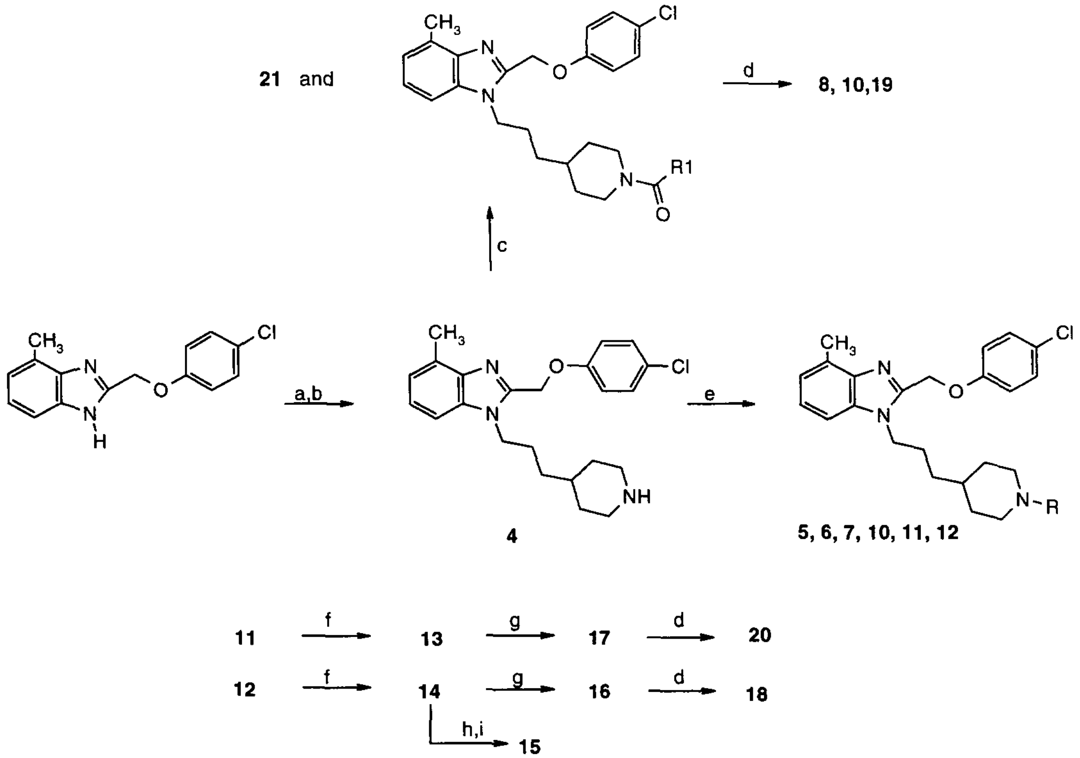
However, substitution of methyl for hydrogen at the 4 position produced a significant, ten-fold increase in receptor affinity. This finding appeared important and we chose to further explore it. In this paper we describe the synthesis and characterization of a series of 4-methyl-benzimidazoles **3** with varying substitution of the piperidyl nitrogen. Compounds synthesized are identified in table 1. The synthesis of the 4-methylbenzimidazole **4** was previously reported[11] and the subsequent transformations of it, summarized in the synthetic scheme, were well precedented. Alkylation of **4** was achieved using sodium hydride in DMF in greater than 90% yield. The Boc protected derivatives were purified using silica gel column chromatography. Alkylation or acylation (followed by reduction of the intermediate amides) of **4** afforded the nitrogen substituted derivatives.

Table 1. Binding affinities of substituted benzimidazoles (3) at cloned NPY-1 receptors expressed in AV-12 cells.

Compound	R	NPY-Receptor Binding Ki (μM)[a]	Compound	R	NPY-Receptor Binding Ki (μM)[a]
4	H	0.335 ± 0.009	14	$(CH_2)_3CO_2H$	1.63 ± 0.04
5	CH_3	0.052 ± 0.001	15	$(CH_2)_3CONH_2$	0.088 ± 0.002
6	$(CH_2)_2CH_3$	0.029 ± 0.0002	16	$(CH_2)_3CON(CH_2)_5$	0.021 ± 0.01
7	$(CH_2)_2CH(CH_3)_2$	0.011 ± 0.003	17	$CH_2CON(CH_2)_5$	0.136 ± 0.018
8	CH_2Ph	0.109 ± 0.0	18	$(CH_2)_4N(CH_2)_5$	0.0057 ± 0.0009
9	CH_2CH_2Ph	0.029 ± 0.003	19	$(CH_2)_3N(CH_2)_5$	0.0045 ± 0.0001
10	$(CH_2)_3Ph$	0.057 ± 0.002	20	$(CH_2)_2N(CH_2)_5$	0.037 ± 0.001
11	$CH_2CO_2CH_2CH_3$	0.427 ± 0.073	21	$(CH_2)_4N(CH_2)_5$	0.052 ± 0.001
12	$(CH_2)_3CO_2CH_2CH_3$	0.029 ± 0.002	22	$CO(CH_2)_2N(CH_2)_5$	0.260 ± 0.018
13	CH_2CO_2H	2.19 ± 0.21			

[a] Hill coefficient values for these compounds ranged from 0.7 to 1.05

As shown in Table 1, appropriate substitution of the amine of **3** led to the discovery of compounds with increased affinity for the NPY-1 receptor. The two most potent compounds identified were analogs **18** and **19** (K_i = 0.0057 and 0.0045 μM, respectively), which represents a greater than 50-fold increase in affinity over hydrogen substitution.



Reagents. (a) NaH, $BrCH_2CH_2CH_2$-$(CH_2)_5$N-BOC, 80 °C., DMF, 6 h; (b) TFA, CH_2Cl_2; (c) R_1CO_2H, DCC, HOBt, DMF, rt; (d) BH_3·THF, 0 °C → rt ; (e) R-X (Br or I), $NaHCO_3$, DMF, 70-100 °C; (f) LiOH, THF, MeOH, H_20,rt; (g) $HN(CH_2)_5$, HOBt, DCC, rt; (h) $(COCl)_2$, CH_2Cl_2, DMF, rt; (i) NH_4OH, rt .

Some significant SAR trends were observed in this study. Two important binding regions distal and proximal to the benzimidazole nucleus were characterized. In both, a basic amine was required for maximum affinity; however, other hydrophilic groups (e.g., **12** and **16**) and lipophilic groups (e.g., **6** and **9**) were also well tolerated in the distill binding region. Substitution of a carboxcyclic acid in the distal region caused a marked loss of receptor affinity. Evaluation of **19** in two in vitro functional assays showed that **19** was an NPY-1 receptor antagonist. Compound **19** reversed NPY induced inhibition of forskilin-stimulated cAMP (K_i = 0.046 μM) and inhibited NPY-induced intracellular Ca^{+2} mobilization[12] (K_i = 0.026 μM) in SK-N-MC cells.[13,14]

In summary, functionalization on nitrogen of the benzimidazole **4** resulted in a marked increase in NPY-1 receptor affinity. These 4-methyl substituted benzimidazoles represent another class of highly potent NPY-1 receptor antagonists available for molecular modeling and pharmacological studies. Compounds **18** and **19**, the most potent compounds identified, possessed two basic amines which might suggest similarities in their binding

and the binding of Arg **32** and Arg **34** of NPY for the NPY-1 receptor.[15] At this time, there is insufficient information to determine if the two basic amines of compounds in this series (e.g., **18** and **19**) and **2** bind to the same recognition sites on the NPY-1 receptor.

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