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Dihydropyridine Neuropeptide Y Y_1 Receptor Antagonists

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Abstract—Dihydropyridine **5a** was found to be an inhibitor of neuropeptide Y_1 binding in a high throughput ^{125}I-PYY screening assay. Structure–activity studies around certain portions of the dihydropyridine chemotype identified BMS-193885 (**6e**) as a potent and selective Y_1 receptor antagonist. In a forskolin-stimulated *c*-AMP production assay using CHO cells expressing the human Y_1 receptor, **6e** demonstrated full functional antagonism ($K_b = 4.5$ nM). Compound **6e** inhibited NPY-induced feeding in satiated rats when dosed at 3.0 and 10.0 mg/kg (ip), and also decreased spontaneous overnight food consumption in rats at doses of 10 and 20 mg/kg (ip).

Neuropeptide Y (NPY) is a 36-amino acid peptide, which was first isolated in 1982 from porcine brain.[1] The peptide is a member of a larger peptide family which also includes peptide YY (PYY), pancreatic peptide (PP), and a non-mammalian fish pancreatic peptide (PY).[2] NPY is very highly conserved in a wide variety of animal, reptile, and fish species and is found in many central and peripheral sympathetic neurons. It is the most abundant peptide observed in mammalian brain and has long been implicated in the regulation of feeding behavior and energy homeostasis.[3–5] To date, NPY remains the most potent orexigenic agent known.

Currently six different NPY receptor subtypes have been identified (Y_1, Y_2, Y_4, Y_5, and Y_6).[6,7] Although recent evidence suggests the Y_5 receptor is most closely associated pharmacologically with the "feeding receptor", it is generally believed that both Y_1 and Y_5 receptors are involved in the feeding response to NPY.[8] Over the past several years a number of specific and selective, small molecule Y_1 and Y_5 receptor antagonists have been studied and their inhibitory effects on feeding described (Fig. 1).[9–11] With respect to the involvement of Y_1 receptor antagonists in feeding, BIBP 3226 was the first potent, non-peptidic agent reported with inhibitory activity on feeding, although the effect remains controversial.[12,13] More recently, several new Y_1 antagonists (LY357897 and J-104870) have appeared which have reported inhibitory effects on feeding in rodents and support the involvement of the Y_1 receptor on food intake.[14,15]

In-house high throughput screening efforts resulted in the identification of the dihydropyridine derivative **5a** (BMY-20429). The compound was found to be an inhibitor of NPY Y_1 binding ($K_i = 109$ nM) and subsequently shown to be a competitive Y_1 receptor antagonist. A synthetic program was initiated to more fully examine structure–activity relationships around certain portions of the dihydropyridine chemotype. This communication will describe some of our structure–activity efforts around the C-3 ester and terminal amine portions of the molecule.

The synthesis of C-3 modified dihydropyridines **5** and **6** incorporating either piperazine or piperidine ring functionality on the terminal side chain is shown in Scheme 1. Reduction of the nitrophenyl substituted dihydropyridines **1** furnished the aniline derivatives **2** that were subsequently converted to the respective isocyanates **3** by either one of two methods. The first method employed conditions described by Alper (conversion of **2** to an intermediate methyl urethane derivative followed by treatment with *B*-chlorocatecholborane).[16] Alternatively, careful treat-

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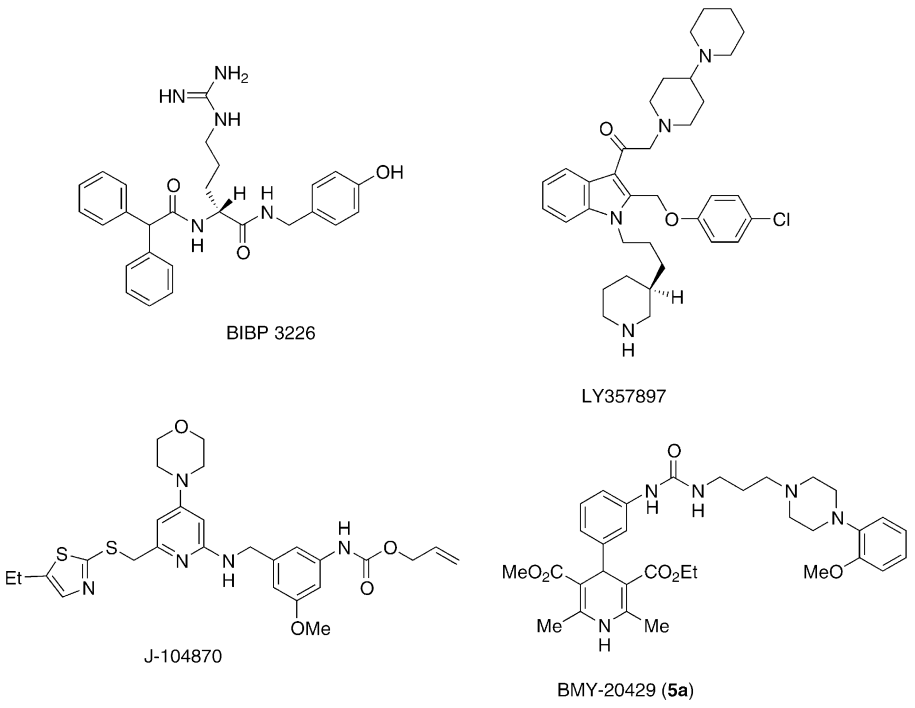
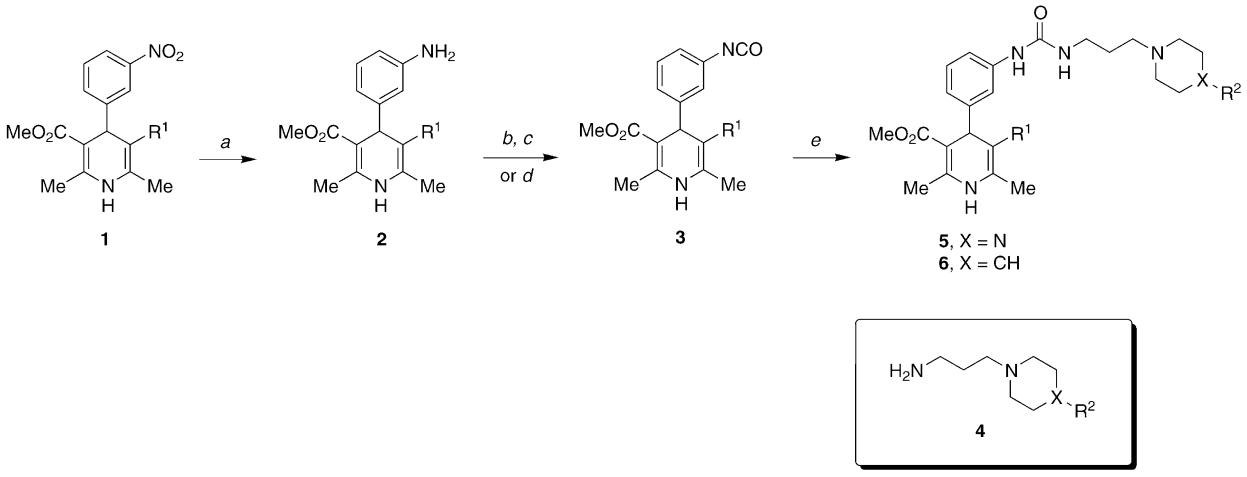


Figure 1. Y_1 Receptor antagonists.



Scheme 1. Synthesis of dihydropyridines **5** and **6**. (a) Fe, NH_4Cl, MeOH; (b) $ClCO_2Me$, pyridine, CH_2Cl_2; (c) *B*-chlorocatecholamine, Et_3N, THF; (d) $COCl_2$, THF; (e) **4**, CH_2Cl_2.

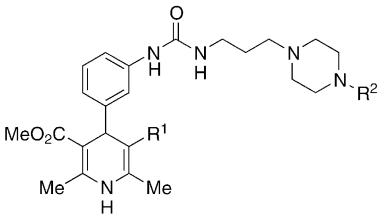
ment of **2** with excess phosgene in THF directly furnished the respective isocyanates. These were then condensed with the appropriate *N*-aminopropylpiperazine or piperidine intermediates **4**[17] to afford the respective dihydropyridine urea derivatives **5** and **6**.

Dihydropyridines **5** and **6** were examined in a competition binding affinity assay using ^{125}I-PYY as the radioligand in SK-N-MC cell membranes which endogenously express the human Y_1 receptor.[18] The results are summarized in Tables 1 and 2 for the piperazine and piperidine containing dihydropyridines **5a**–**5n** and **6a**–**6i**, respectively. For the piperazine containing derivatives **5**, substitution at the *C*-3 ester position on the dihydropyridine ring had a profound effect on Y_1 binding affinity. In comparison to the initial lead ester BMY-20429 (**5a**, $R^1 = CO_2Et$), larger substituents (**5c**, $R^1 = CO_2n$-Bu and **5d**, $R^1 = CO_2t$-Bu) dramatically reduced binding affinity. In contrast, substitution at the *C*-3 position with a smaller methyl substituent (**5b**, $R^1 = CO_2Me$) considerably enhanced binding potency ($K_i = 12$ nM). The small cyano substituent in **5e** ($R^1 = CN$) was less potent than **5a**, suggesting the ester group contributes to binding. Interestingly, it should be noted that conversion of the asymmetric methyl ethyl ester derivative **5a** to the symmetrical bis methyl ester congener **5b** not only enhanced Y_1 binding potency but also rendered the *C*-4 position of the dihydropyridine ring achiral.[19]

Aryl substitution at the *N*-4 position of the piperazine ring had a less pronounced effect on binding potency except for *p*-phenyl substituents. Rank ordering of the

binding affinities for the five Topliss derivatives **5f** (R^2 = Ph), **5j** (R^2 = 3,4-Cl_2Ph), **5k** (R^2 = 4-ClPh), **5l** (R^2 = 4-MePh), and **5m** (R^2 = 4-MeOPh) suggests a detrimental steric interaction (E_4) at the *para* position.[22] *Ortho* and *meta* substituents were well tolerated and in some cases enhanced binding potency relative to the initial lead **5a** (e.g., **5i**, R^2 = 3-HOPh). The simple piperazine **5n** showed considerably less binding affinity, suggesting substitution at *N*-4 is important for recognition.

Table 1. Y_1 Binding affinities for piperazine containing dihydropyridines **5a**–**5n**

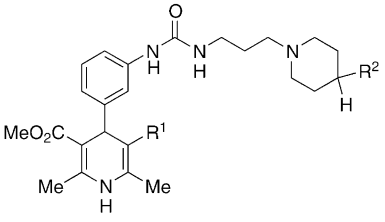


5

Compd[a,b]	R^1	R^2	Y_1 (K_i, nM)[c]
5a	CO_2Et	2-MeOPh	105
5b	CO_2Me	2-MeOPh	12
5c	CO_2n-Bu	2-MeOPh	995
5d	CO_2t-Bu	2-MeOPh	1162
5e	CN	2-MeOPh	684
5f	CO_2Et	Ph	66
5g	CO_2Et	2-MePh	96
5h	CO_2Et	2-HOPh	108
5i	CO_2Et	3-HOPh	37
5j	CO_2Et	3,4-Cl_2Ph	677
5k	CO_2Et	4-ClPh	322
5l	CO_2Et	4-MePh	503
5m	CO_2Et	4-MeOPh	405
5n	CO_2Me	H	>1000

[a]Standard reference agent BIBP 3226 displayed K_i of 14.9 nM in this Y_1 binding assay.
[b]Dihydropyridines **5a** and **5c**–**5m** are racemic mixtures.
[c]^{125}I-PYY binding in SK-N-MC cell membranes. The K_i's were obtained from a single experiment (n = 1) with each point being run in duplicate.

Table 2. Y_1 Binding affinities for piperidine containing dihydropyridines **6a**–**6i**



6

Compd[a]	R^1	R^2	Y_1 (K_i, nM)[b]
6a	CO_2Et	Ph	89
6b	CO_2Me	Ph	10
6c	CO_2Me	2-MeOPh	4.1
6d	CO_2Me	3-HOPh	2.7
6e	CO_2Me	3-MeOPh	3.3
6f	CO_2Me	3-PhPh	188
6g	CO_2Me	CH_2Ph	84
6h	CO_2Me	*c*-Hexyl	9.5
6i	CO_2Me	H	523

[a]Dihydropyridine **6a** is a racemic mixture.
[b]See footnote c in Table 1.

The piperidine derivatives listed in Table 2 displayed Y_1 binding potencies in the same range as the piperazines. Similarly, bis methyl ester substitution enhanced binding affinity relative to the asymmetric ethyl methyl ester derivative (**6a**, $R^1 = CO_2Et$ vs **6b**, $R^1 = CO_2Me$). Substitutions at the *C*-4 position on the piperidine ring with either aryl (**6c**, R^2 = 2-MeOPh, **6d**, R^2 = 3-HOPh, and **6e**, R^2 = 3-MeOPh) or alkyl (**6h**, R^2 = *c*-hexyl) substituents were well tolerated; however, the simple, unsubstituted piperidine **6i** (R^2 = H) was inactive in the assay, reflecting similar steric and/or lipophilic demands as the piperazines at this position.

The piperidine containing dihydropyridine derivative **6e** was selected for further investigation. Scatchard analysis of **6e** on the effect of ^{125}I-PYY binding in SK-N-MC cell membranes suggests the binding inhibition is competitive [**6e** at 10 nM concentration reduced PYY binding affinity (K_d of 0.65 vs 0.35 nM) without affecting its binding capacity (B_{max} of 0.16 vs 0.16 pmol/mg protein)].[23] Functional studies in CHO cells expressing the human Y_1 receptor found that **6e** antagonized the NPY-mediated inhibition of forskolin-stimulated *c*-AMP accumulation in a competitive manner (K_b = 4.5 nM), indicating the compound is a full functional antagonist.[24] In other competition binding experiments, **6e** showed no affinity for other cloned human NPY receptor subtypes (Y_2, Y_4, and Y_5, K_i's >1000 nM).

The compound was further examined in several animal models of feeding to assess its ability to inhibit food intake. Administration of **6e**, at doses of 10 and 30 mg/kg (ip), antagonized the increase in food consumption induced by icv infusion of 10 μg of NPY by 33±13% and 57±11%, respectively, in satiated rats.[25] There was no effect of **6e** administered alone on food consumption when dosed at 10 mg/kg (ip). Additionally, administration of **6e** at 10 and 20 mg/kg (ip) decreased spontaneous nocturnal food intake in rats 29±6% and 54±11%, respectively, relative to vehicle treated controls.[15]

In summary, dihydropyridine **6e** (BMS-193885) is a potent, selective, and competitive Y_1 receptor antagonist with the ability to inhibit NPY-induced and spontaneous overnight feeding in rats. The dihydropyridine chemotype as depicted by **5** and **6** represents another novel class of selective Y_1 receptor antagonists with demonstrated anti-orexigenic properties. The compound provides an additional example of the potential utility of Y_1 antagonists for the treatment of hyperphagia and obesity. More detailed examples of **6e** and related compounds will be reported in the future.

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