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Isosteric *N*-arylpiperazine replacements in a series of dihydropyridine NPY_1 receptor antagonists

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Abstract—4-Amino-*N*-arylpiperidines serve as effective bioisosteres for *N*-arylpiperazines in the series of dihydropyridine NPY_1 receptor antagonists. These were prepared by a $ZnCl_2$-mediated reductive amination reaction between elaborated primary amines, **2** or **5**, and 4-arylpiperidones.

1. Introduction

Neuropeptide Y (NPY), a 36-amino acid, single-chain polypeptide, is one of the most abundant neurotransmitters in the central nervous system. Because of its abundance, homology across the species, and ubiquitous presence in the central nervous system, it has been implicated in a variety of physiological processes and behaviors, such as feeding, energy homeostasis, cardiovascular regulation, anxiety, seizures, memory, circadian rhythms, and sexual functions.[1]

With regard to feeding, NPY is the most potent orexigenic agent known. Central administration of NPY greatly increases food intake in a variety of animal species.[1,2] There are six known NPY receptors, of which five have been cloned (Y_1, Y_2, Y_4, Y_5, and y_6). Among them both Y_1 and Y_5 receptors are thought to be involved in the regulation of feeding and energy homeostasis.[1,2] Both Y_1 and Y_5 receptor antagonists have been shown to reduce food intake in rodents, although the effect of Y_5 receptor antagonists is not quite clear, and therefore they both may have potential utility in the treatment of obesity.[1,2]

A number of small molecule Y_1 receptor antagonists have been described over the last several years (Fig. 1).[1–3] Some of them (e.g., LY357879 and J-104870) are very potent Y_1 antagonists, which have reported inhibitory effects on feeding in rodents and clearly support the involvement of the Y_1 receptor on food intake.[2c,d]

In a previous publication, we disclosed the synthesis of 1,4-dihydropyridine-derived Y_1 receptor antagonist containing *N*-arylpiperazine functionality.[3a] Two of the representative *N*-arylpiperazines in the series, BMS-189323 (urea)[3a] and BMS-245782 (cyanoguanidine)[3b,c,4] (Fig. 1), display Y_1 receptor binding affinities IC_{50} of 12 nM and 39 nM, respectively. We were interested in modifying the right-side arylpiperazine portion of the urea and cyanoguanidine chemotypes and determining whether the piperazine was required for affinity, as shown in Figure 2. In this regard, a recent patent application from Merck has demonstrated that the 4-amino-*N*-arylpiperidine moiety can serve as a bioisotere for *N*-arylpiperazine.[5] This paper will document our synthetic and structure–activity efforts around the 4-amino-*N*-arylpiperidine moiety as a replacement for *N*-arylpiperazine in our chemotype series.

2. Chemistry

As shown in Scheme 1, both cyanoguanidine and urea intermediates, **2** and **5**, were prepared from known

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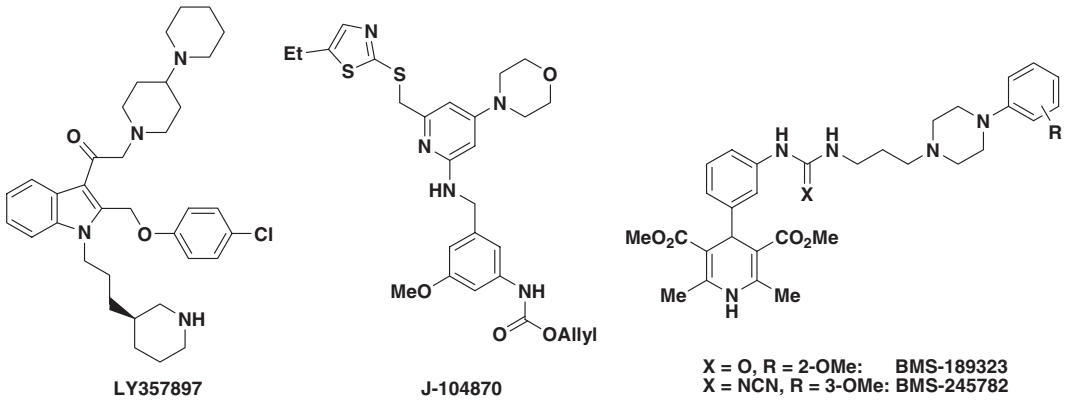


Figure 1. Y_1 Receptor antagonists.

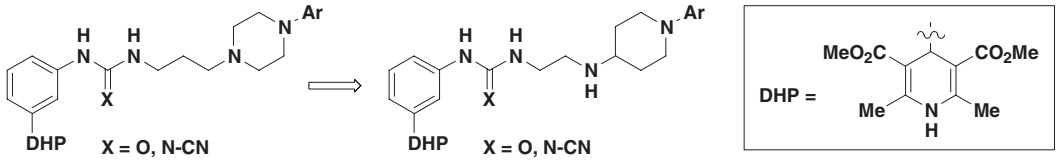
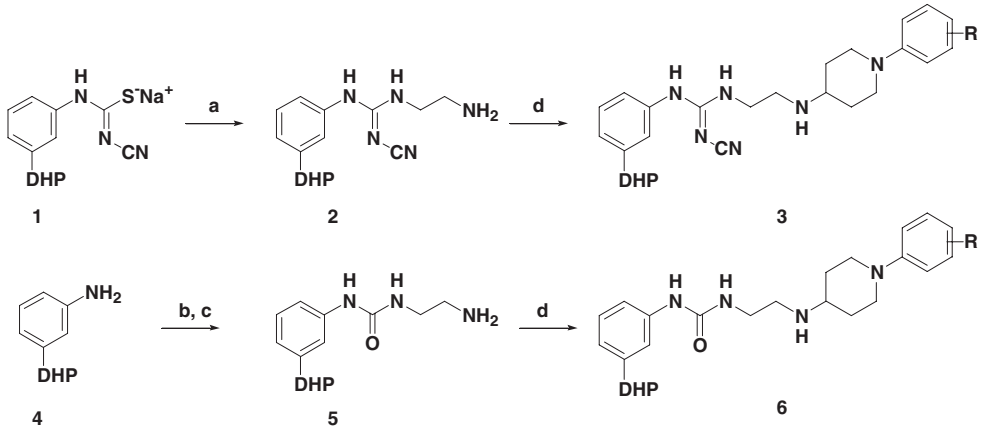


Figure 2. 4-Aminopiperidine as a bioisostere of piperazine.



Scheme 1. Reagents and conditions: (a) ethylene diamine (8 equiv), $HgCl_2$ (2.0 equiv), THF, rt, 3 h, 58%; (b) phenyl chloroformate (1.05 equiv), pyridine; (c) ethylene diamine (10 equiv), CH_3CN, 93% (two steps); (d) 4-arylpiperidone (1.0 equiv), amine (**2** or **5**, 1.02 equiv), $NaBH_3CN$ (0.5 equiv), $ZnCl_2$ (0.5 equiv), MeOH, rt, 20 min.

intermediates, **1** and **4** respectively.[3] Treatment of **1** with excess ethylene diamine provided **2** in good yield and offered almost none of the bis-functionalized product. For the synthesis of **5**, aniline **4** was treated with phenyl chloroformate followed by treatment of the crude intermediate with excess ethylene diamine to provide the product in excellent yield after purification by silica gel chromatography.

With **2** and **5** readily available, we intended to prepare the series of aminopiperidines via reductive amination with various 4-arylpiperidones. However, simple protic acid promoted reductive amination of **2** with 4-arylpiperidones using $NaBH_3CN$ gave either intractable mixtures or low isolated yields (**3c** and **3d**, Table 1), even when excess amines were used.

Use of the Mattson procedure in which $Ti(O^iPr)_4$ was utilized in place of protic acid afforded good yields of 4-aminopiperidines through a proposed chelated aminal intermediate with subsequent $NaBH_3CN$ reduction.[6] However, the stepwise reaction proved to be very moisture sensitive and somewhat tedious, especially for our desired parallel synthesis conditions.

We next employed $ZnCl_2$, which is less hygroscopic, as the Lewis acid in promoting the reductive aminations. Instead of stepwise reaction, the reduction by $NaBH_3CN$ took place in a one-pot procedure. The procedure afforded high yields of desired secondary amine products without formation of tertiary amines. Furthermore, it was found that $ZnCl_2$ could be employed in catalytic amounts. Additionally, the reaction was very fast

Table 1. Reaction yields and Y_1 receptor binding data for the cyanoguanidine series of compounds **3a–j**

Compds[a]	R	Reductive amination Yields[b] (%)	Y_1 IC_{50}, nM[c]
3a	H	– (66)	10
3b	2-NO_2	90	4
3c	2-CH_3	70 (0)	4
3d	2-CF_3	– (31)	14
3e	2-CN	85	3
3f	2-OCH_3	84	4
3g	2-OCF_3	82	28
3h	2-OH	82	5
3i	3-Cl	87	8
3j	2-SCH_3	86	3

[a] The geometry of the cyanoguanidine group is not known.
[b] Purified yields based on starting piperidone. Some yields with protic acid reaction conditions are listed in the parenthesis. All compounds are fully characterized by ^{1}H NMR, ^{13}C NMR, LCMS, and elemental analysis.
[c] ^{125}I-PYY binding to membranes of SK-N-MC cells expressing the human Y_1 receptors (average of at least two duplicated experiments).

Table 2. Reaction yields and Y_1 receptor binding data for the urea series of compounds **6a–j**

Compds	R	Reductive amination Yields[a] (%)	Y_1 IC_{50}, nM[b]
6a	H	79	2
6b	2-NO_2	81	2
6c	2-CH_3	80	4
6d	2-CF_3	74	31
6e	2-CN	84	3
6f	2-OCH_3	82	2
6g	2-OCF_3	85	25
6h	2-OH	85	6
6i	3-Cl	74	8
6j	2-SCH_3	85	5

[a] Purified yields based on starting piperidone. All compounds are fully characterized by ^{1}H NMR, ^{13}C NMR, LCMS, and elemental analysis.
[b] See footnote c in Table 1.

and not very sensitive to moisture, which made it amendable for use in parallel synthesis. Although this method has been reported earlier by Kim et al.,[7] it has not been widely used. Thus, we were able to utilize high throughput techniques to obtain our final products (**3** and **6**) in good yields using this very simple reductive amination process (Scheme 1, Tables 1 and 2).[8]

3. Results and discussion

All of the final products, **3a–j** and **6a–j**, were examined in a Y_1 receptor binding assay as previously described.[3] The binding results are shown in Tables 1 and 2 for the cyanoguanidine and urea series, respectively.

The dihydropyridine chemotype represents one of the most potent Y_1 receptor antagonists reported to date.[3] In the new series **3** and **6**, the 4-aminopiperidine moiety appears to effectively function as piperazine replacement with both cyanoguanidine and urea analogs. With respect to the *N*-aryl piperidines, substitution at both *ortho* and *meta* positions of the phenyl ring is well tolerated for the binding, as has been shown earlier in the urea series. Fluorine containing substituents (**3d**, **3g**, **6d** and **6g**) were somewhat less potent than other types of substitution. However, the electronic nature of the substituents did not appear to influence the binding results. Both electron-withdrawing (nitro- or cyano-) and electron-donating (methoxy- or hydroxy-) substituents gave very potent receptor binding in both cyanoguanidine and urea series.

The Y_1 receptor potencies of **3** and **6** also track well with the piperazine series reported earlier.[3] For example, the corresponding piperazine analogs of **3a** (R = H) and **6f** (R = 2-OMe) have Y_1 binding affinities (IC_{50}'s) of 13 nM[3b,4] and 12 nM (BMS-189323),[3a] respectively. The binding results show that 4-amino piperidines effectively serve as bioisosteres for piperazines in this series of Y_1 receptor ligands. To further test the functional antagonism of the piperazine series, an apparent K_b determination had been carried out by measuring the inhibition of the forskolin-stimulated cAMP production inhibited by NPY by compounds **3f** and **6f**[3]. These compounds are full functional antagonists of the Y_1 receptor (**3f**: K_i = 3.6 nM, K_b = 9.4 nM; **6f**: K_i = 1.9 nM, K_b = 20 nM).

4. Conclusion

A series of *N*-arylpiperidine derivatives were prepared by reductive amination with $ZnCl_2$ in a parallel fashion. The potency of these compounds demonstrates that the 4-aminopiperidine group can serve as an effective piperazine replacement in our series of NPY receptor antagonists and supports earlier results by Patane et al.[5] These highly potent small molecule Y_1 receptor antagonists will be useful in further evaluating the role of NPY in the regulation of energy homeostasis.

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8. Typical procedure for the synthesis of aminopiperidines: To a mixture of the starting amine (**2** or **5**, 1.05 equiv), 4-arylpiperidone (1.0 equiv), $NaBH_3CN$ (0.5 equiv) in MeOH (0.1 M with regard to the amine) was added $ZnCl_2$ (0.5 equiv) in one portion. The mixture was stirred at room temperature for 20 min. MeOH was then evaporated and the residue was partitioned between 1 N NaOH and CH_2Cl_2. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue purified by flash column chromatography to afford **3** or **6**. Analytical data for representative compounds **3j**: IR (KBr): 3300, 2946, 2170, 1686, 1606, 1582,1566, 1433, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25–6.95 (m, 8H), 6.50–6.42 (br, 1H), 6.14–6.03 (br, 1H), 4.98 (s, 1H), 3.63 (s, 6H), 3.40–3.31 (m, 2H), 3.26–3.14 (m, 2H), 2.90–2.83 (m, 2H), 2.69–2.51 (m, 3H), 2.39 (s, 3H), 2.32 (s, 6H), 2.04–1.92 (m, 2H), 1.91–1.62 (br, 2H), 1.59–1.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.1, 159.5, 149.7, 149.4, 145.1, 134.9, 129.0 (CH), 124.9 (CH), 124.5 (CH), 124.1 (CH), 119.7 (CH), 118.5, 103.2, 55.1 (CH), 51.22 (CH_3), 51.18 (CH_2), 39.4 (CH), 33.3 (CH_2), 27.7 (CH_2), 19.5 (CH_3), 14.4 (CH_3); MS: [M+H] = 632; Elemental analysis calcd for $C_{33}H_{41}N_7O_4S_1 \cdot 0.30CH_2Cl_2$: C, 60.85; H, 6.38; N, 14.92. Found: C, 60.90; H, 6.64; N, 14.90. **6b**: IR (KBr): 3346, 2947, 1683, 1490, 1217, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75 (dd, J = 1.7 and 8.2 Hz, 1H), 7.44 (dt, J = 1.7 and 7.8 Hz, 1H), 7.23–7.16 (m, 2H), 7.14–7.08 (m, 2H), 7.04–6.93 (m, 2H), 6.53 (s, 1H), 5.65 (t, J = 5.3 Hz, 1H), 4.98 (s, 1H), 3.62 (s, 6H), 3.31–3.17 (m, 4H), 2.84–2.71 (m, 4H), 2.63–2.49 (m, 1H), 2.25 (s, 6H), 1.94–1.60 (br, 4H), 1.55–1.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.5, 156.9, 148.8, 146.6, 145.2, 143.0, 139.2, 133.8 (CH), 128.9 (CH), 126.2 (CH), 122.9 (CH), 121.4 (CH), 121.3 (CH), 119.6 (CH), 118.4 (CH), 103.4, 54.5 (CH), 51.2 (CH_3), 51.1 (CH_2), 46.7 (CH_2), 41.0 (CH_2), 39.4 (CH), 32.9 (CH_2), 19.4 (CH_3); MS: [M+H] = 607; Elemental analysis calcd for $C_{31}H_{38}N_6O_7 \cdot 0.25CH_2Cl_2$: C, 59.78; H, 6.18; N, 13.38. Found: C, 59.75; H, 6.28; N, 13.45.