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N-Acylated α-(3-Pyridylmethyl)-β-Aminotetralin Antagonists of the Human Neuropeptide Y Y5 Receptor

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Abstract—α-(3-Pyridylmethyl)-β-aminotetralins were acylated with amino-piperidinyl and-pyrrolidinyl acetic acids, and with (aminomethyl)cyclohexanecarboxylic acid. Reaction with acyl chlorides, chloroformates, and isocyanates gave amides **8e**, carbamates **9**, and ureas **10**, which bound to the Y5 receptor with nanomolar affinity. Congeners **11a** and **11d** containing a terminal benzimidazolone group were shown to be functional Y5 antagonists.

Neuropeptide Y (NPY) is a 36 amino acid protein found abundantly in the central nervous system that robustly stimulates feeding.[1–4] A family of NPY receptor subtypes[5–14] that belongs to the superfamily of G-protein coupled receptors is known. Activation of the Y1 and Y5 receptor subtypes appears to be responsible for centrally-mediated NPY-induced feeding responses.[13,15–17] Since compounds that antagonize the Y5 receptor can reduce food intake in animal models of feeding,[18] there has been an impetus to discover and develop small molecule Y5 antagonists as a therapeutic strategy for the treatment of human obesity.[19] We have recently disclosed two novel series of sulfonamide-based Y5 antagonists (exemplified by compounds **1**–**2**; Fig. 1) that originated from a micromolar lead.[20,21] Herein we report on a novel series of *N*-acylated α-(3-pyridinylmethyl)-β-aminotetralins that bind to the human Y5 receptor with nanomolar affinity. A salient feature of this work is the replacement of the terminal sulfonamide group that was indispensable for binding affinity in our earlier work. As described below, appropriately positioned amide, carbamate, and benzimidazolone groups can serve as sulfonamide surrogates and afford potent and structurally diverse congeners that act as functional antagonists of the Y5 receptor.

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Chemistry

Condensation of β-tetralones **3** with 3-pyridine carboxaldehyde in the presence of piperidine followed by reductive amination gave *cis*-α-(3-pyridinylmethyl)-β-aminotetralins **5**. Subsequent coupling with *N*-Boc-protected-aminopiperidinyl and -pyrrolidinyl acetic acids afforded the amide adducts **6**, which were treated with acid to liberate the terminal amine moiety thus giving **7** (Scheme 1). At this stage, we chose to explore groups other than the sulfonamide functionality present in our earlier work. In simple terms, we chose to replace the sulfonyl center with a carbonyl group and to introduce heteroatoms adjacent to this center thus giving amido **8**, carbamoyl **9**, and ureido **10** congeners. The chemistry required was straightforward as key intermediate **7** underwent acylation, carbamoylation or urea formation upon reaction with acyl halides, chloroformates and isocyanates, respectively (Scheme 2). Coupling of **5** with [4-(2-keto-1-benzimidazolinyl)piperidinyl]acetic acid yielded analogues containing a benzimidazolone terminus **11**.

Results

Compounds **8**–**11** were evaluated for binding affinity to the human neuropeptide Y Y5 receptor using a stably-transfected HEK293 cell line and measuring competitive inhibition of binding of ^{125}I-PYY (Table 1). The linking

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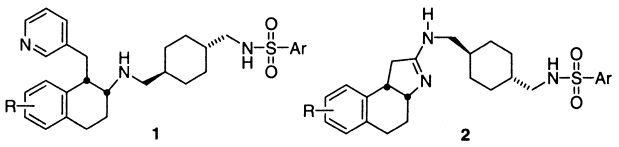
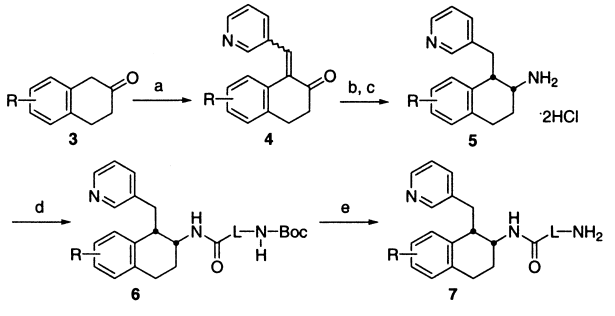
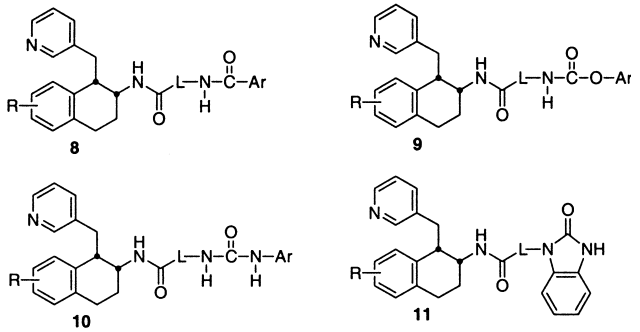


Figure 1. α-Substituted *N*-(sulfonamido)alkyl-β-aminotetralins **1** and *N*-(sulfonamido)alkyl[tetrahydo-1*H*-benzo[*e*]indol-2-yl]amines **2**.



(a) 3-Pyr-CHO (1.1 equiv), cat. piperidine (0.1 equiv)/PhH reflux (-H_2O);
(b) Na(BH_3)CN (5 equiv), NH_4OAc (10 equiv) / MeOH; (c) HCl;
(d) HOOC-L-NH-*t*-Boc (1.0 equiv), HBTU (1.1 equiv), DIEA / DMF;
(e) TFA, trace H_2O/CH_2Cl_2-MeOH.

Scheme 1. Synthesis and acylation of *cis*-α-(3-pyridinylmethyl)-β-aminotetralins.

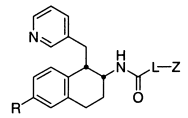


(a) compound **7** (1.0 equiv), ArC(O)Cl (1.0 equiv), DIEA / CH_3CN;
(b) compound **7** (1.0 equiv), ArOC(O)Cl (1.0 equiv), DIEA / CH_3CN;
(c) compound **7** (1.0 equiv), Ar-N=C=O (1.0 equiv), DIEA / CH_3CN;
(d) compound **5** (1.0 equiv), [4-(2-keto-1-benzimidazolinyl)piperidinyl] acetic acid (1.1 equiv), HBTU (1.1 equiv)/DMF;
(e) HCl / MeOH.

Scheme 2. *N*-Acylated *cis*-α-(3-pyridylmethyl)-β-aminotetralin amides **8**, carbamates **9**, ureas **10** prepared from **7** and benzimidazolones **11** prepared from **5**.

group (L) did not influence binding affinity appreciably although compounds that contained a piperidinyl- or pyrrolidinyl-derived tether had improved aqueous solubility compared to compounds that had a methylcyclohexyl scaffold (**8a**–**b**, **9a**–**b**, and **10a**). However, the terminal functionality (Z) did influence binding considerably; compounds lacking this structural feature, such as precursor **7**, were routinely inactive (>1 μM). In contrast, compounds containing an amide (**8a**–**e**) or carbamate (**9a**–**g**) terminus typically gave IC_{50} values in the 20–40 nM range and were nearly an order of magnitude more potent than urea analogues (**10a**–**c**). Most interestingly, the benzimidazolone group, an isomeric variation of

Table 1. Neuropeptide Y Y5 receptor binding affinity[a] of *N*-substituted α-(3-pyridinylmethyl)-β-aminotetralins[b] **8a**–**d**



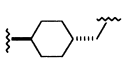
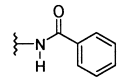
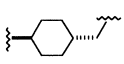
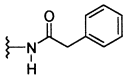
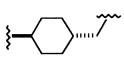
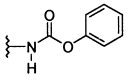
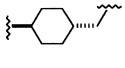
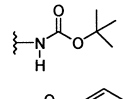
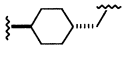
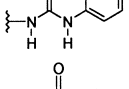
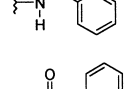
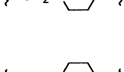
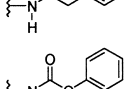
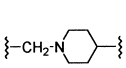
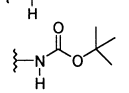
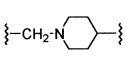
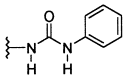
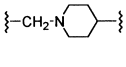
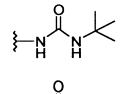
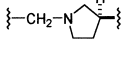
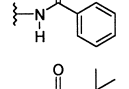
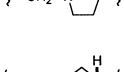
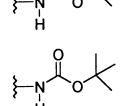
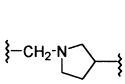
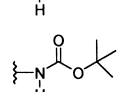
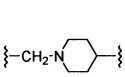
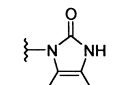
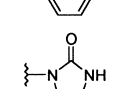
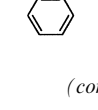
	R	L	Z	Y5 IC_{50} (nM)
8a	F			39 ± 4 ($n=3$)
8b	F			114 ± 74 ($n=3$)
9a	F			31 ± 9 ($n=4$)
9b	F			16 ± 4 ($n=4$)
10a	F			170 ± 95 ($n=4$)
8c	F			28 ± 9 ($n=3$)
8d	F			36 ± 11 ($n=4$)
9c	F			52 ± 29 ($n=3$)
9d	F			37 ± 17 ($n=3$)
10b	F			236 ± 84 ($n=3$)
10c	F			140 ± 53 ($n=3$)
8e	F			26 ± 16 ($n=5$)
9e	F			17 ± 11 ($n=3$)
9f	F			30 ± 15 ($n=3$)
9g	F			45 ± 30 ($n=3$)
11a	F			25 ± 7 ($n=3$)
11b	H			22 ± 13 ($n=3$)

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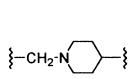
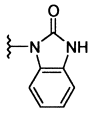
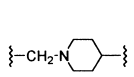
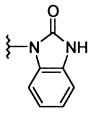
Table 1 (*continued*)

	R	L	Z	Y5 IC_{50} (nM)
11c	OCH_3			75 ± 57 ($n=3$)
11d	OH			6 ± 4 ($n=4$)

[a]IC_{50} data are given as mean values with standard deviation; numbers of determinations are given in parentheses.
[b]All compounds are racemates with the exception of compounds **8e**, **9e** and **9f**, which are sets of diastereomers (chiral center of known configuration is shown in L column).

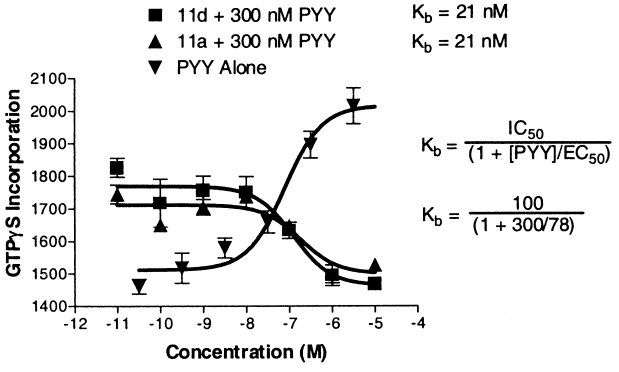


Figure 2. Antagonist potency of compounds **11a** and **11d**. K_b values were determined by inhibition of peptide YY (PYY)-induced incorporation of ^{35}S-GTPγS into membranes prepared from NPY5 receptor expressing cells. The EC_{50} for PYY-induced ^{35}S-GTPγS incorporation was 78 nM. IC_{50} values for compounds **11d** and **11a** (100 nM each) were determined in the presence of 300 nM PYY and converted to K_b values according to the equation of Cheng and Prusoff.[22] Error bars represent the standard error from quadruplicate samples.

phenylureido, was an exceptional replacement affording compounds **11a**–**d**, which had low nanomolar affinity for the Y5 receptor.

Compounds **11a** and **11d** did not stimulate binding of labeled GTPγS in a Bowes melanoma cell line transfected with the human Y5 receptor, but in the presence of PYY, were able to inhibit incorporation of ^{35}S label, thus demonstrating that these compounds behave as functional antagonists of the Y5 receptor (Fig. 2).

Conclusion

N-Acylated α-(3-pyridylmethyl)-aminotetralins that contain an appropriately positioned amide, carbamate or benzimidazolone group are nanomolar neuropeptide Y Y5 receptor antagonists.

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References and Notes

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