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Differentially Functionalized Diamines as Novel Ligands for the NPY_2 Receptor

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Abstract—The synthesis of novel ligands for the NPY_2 receptor using solid phase split pool methodology is described. One of the analogues, diamine **16**, was found to be a potent NPY_2 binder.

Neuropeptide Y (NPY) is a 36 amino acid peptide that is widely distributed in the central nervous system. This neuropeptide activates a family of 6 NPY receptors, 5 of which have been cloned.[1] The Y_2 receptor is the predominant NPY receptor in the brain and can also be found in the periphery (i.e., the intestine, kidneys, sexual organs, etc.). The Y_2 receptor has been implicated in a variety of physiological functions, such as kidney functions,[2] bone formation,[3] gastrointestinal motility, food intake, regulation of glucose and cholesterol homeostasis in type 2 diabetes, cardiovascular regulation, neuronal excitability,[4] anxiety,[5] learning and memory, pain,[6] and migraine.[7] Identification of novel Y_2 receptor ligands is necessary for the elucidation of the physiological role of the Y_2 receptor. Our early search for a novel ligand for the NPY_2 receptor, via high-throughput screening, lead to diamine **10**. Its structural simplicity and suitability for combinatorial synthesis made these diamines attractive hits. The present paper describes the synthesis of acylated diamines and their affinity for binding to the NPY_2 receptor. Uriac employed a solid phase approach to the synthesis of nonsymmetrical polyamines.[8] After due consideration, we chose as our starting point the polymer bound acyl imidazole as described by Hauske[9] (Scheme 1). Wang[10] resin **1** was treated with carbonyldiimidazole (CDI) to give the activated resin **2**. Displacement of the imidazole with an amino alcohol at 60 °C followed by oxidation yielded yielded resin bound aldehyde **3**.[11] Reductive amination with substituted anilines gave amino carbamate **4**. Acylation of polymer bound diamine **4** with various acid chlorides afforded intermediate **5**. Intermediate **5** could then be cleaved from solid support by trifluoroacetic acid. Post cleavage reductive amination yielded the tertiary amines **6**. Yields for the synthesis, including the post-solid support reductive amination step, averaged 30%.

Initial SAR[12] (vide infra) lead to the need to further examine diversity at R2. Thus, *ortho*-iodo resin **7** was treated with various aryl zinc bromides to afford coupled intermediate **8** using standard conditions as shown in Scheme 2.[12] Resin cleavage and reductive amination afforded tertiary amines **9**.

The first area of interest was the replacement of the cinnamic acid moiety at R1, which was thought to be a potential metabolic liability (Table 1).

Both the benzothiophene (compound **12**) and the *trans*-cyclopropyl phenyl group (compound **11**) proved to be good cinnamic acid surrogates. Gratifyingly, the benzothiophene group also increased potency by one order of magnitude. It is worthy of mention that other cinnamic acid surrogates such as the benzofuran, (compound **13**) were employed, but the resulting analogues showed poor binding affinity.

Next, we focused our attention on the length of the diamine linker R2 (Table 2).

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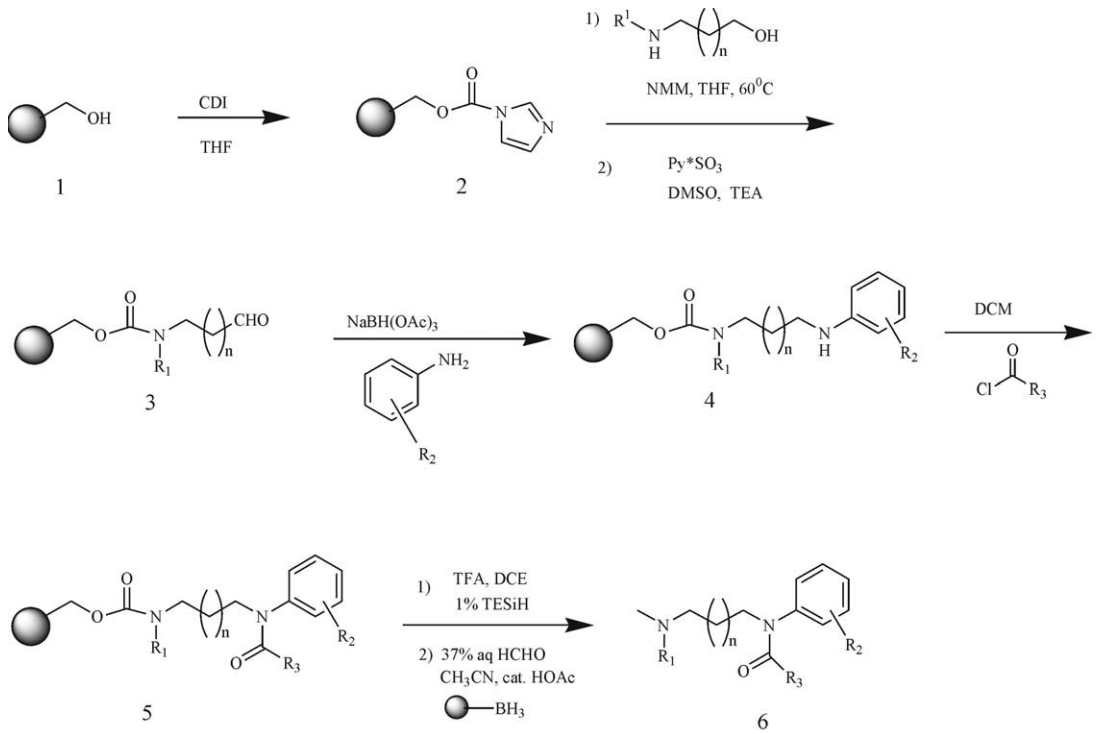
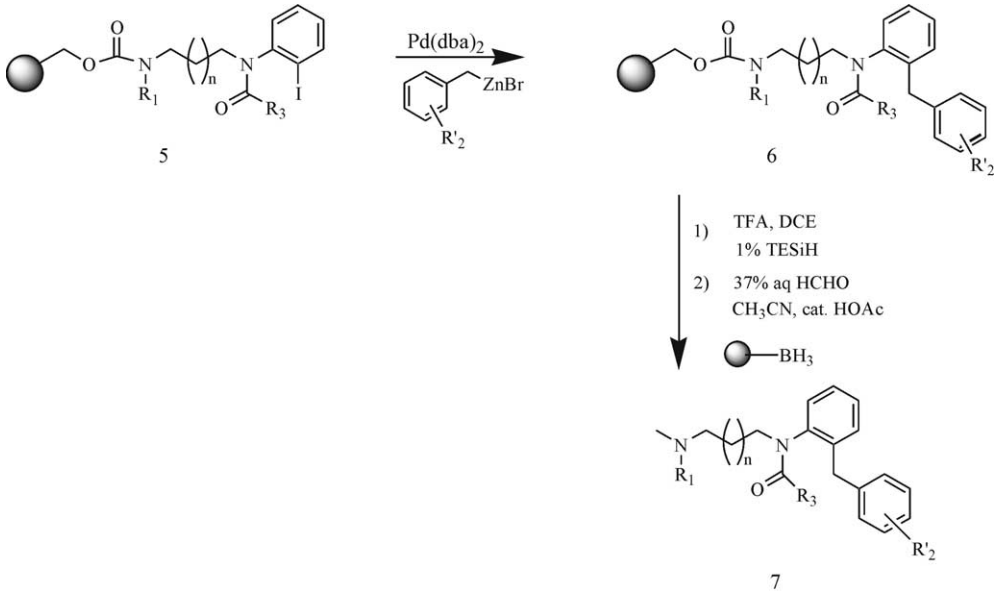


Scheme 1. Solid phase diamine synthesis.



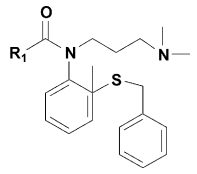
Scheme 2. Negishi cross-coupling on solid support.

Two, three, and four carbon linked diamines were synthesized, with the best potency arising from the three carbon spacer (compound **16**). Other linkers, including linkers cyclized on the terminal amine, failed to generate stronger binding potencies. Lastly, we searched for a suitable replacement for the 2-benzylsulfanyl aniline because sulfur was viewed as a potential oxidative liability. We examined a wide range of commercially available and structurally diverse anilines (Table 3).

Testing of numerous analogues quickly revealed the importance of the aniline substitution pattern at R3. Those compounds containing *meta* and *para* substitution failed to show Y_2 receptor binding activity. This left us to analogue at only the *ortho* position on the aniline ring. Formation of carbon-carbon bonds at the *ortho* position, by employing Negishi couplings,[13] led to analogue **21**, the most potent compound in the series.

In summary, functionalized diamines were efficiently synthesized and shown to be ligands for the NPY_2 receptor. This work illustrates for the first time that a small molecule is capable of displacing NPY and binding to the NPY_2 receptor. In vivo biological studies of

Table 1.



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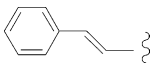
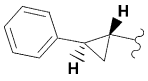
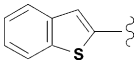
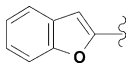
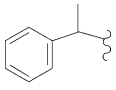
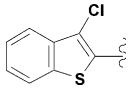
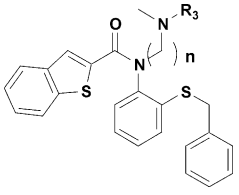
10		10,000
11		3700
12		1000
13		> 10,000
14		1000
15		> 10,000

Table 2.



Compd	*n*	R_3	IC_{50} (nM)
16	2	Me	> 10,000
17	3	Me	1000
18	4	Me	> 10,000
19	3	H	> 10,000

these compounds will be the subject of a future communication.

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12. Test compounds in five concentrations (0.001, 0.01, 0.1, 1 and 10 μM) were assayed in Laboratory Automation System (Biomek 2000 from Beckman). Experiments were carried out in the following buffer: 50 mM Tris pH7.4, 1 mM MgCl, 2.5 mM $CaCl_2$, 145 mM NaCl, 0.1% BSA, 10 μg/mL Leupeptin and 10 μg/mL Aprotinin. The assay was conducted as follows: each reaction consisted of 25 μL compound, 25 μL [^{125}I]PYY (0.05 nM final conc., NEN Du-Pont) and 200 μL SMS-KAN cell membranes endogenously expressing NPY Y_2 receptor (8 μg/reaction). After incubating at 25 °C for 1 h, assay plates were filtered through 1% PEI pre-soaked (> 2 h) GF/C filters and then washed with ice cold Tris buffer (50mM pH7.4) 5×1 mL. The samples were put in sample plate and 200 μL Opti-Phase 'SuperMix' (Wallac) was added to each well. The samples were soaked for 10 h before counting in 1450 Microbeta Plus Liquid Scintillation Counter (Wallac). $IC_{50's}$ were determined by non-linear regression using Excel Fit program.
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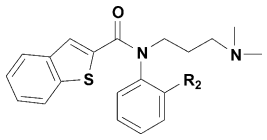
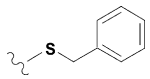
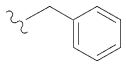
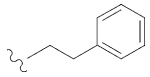
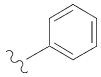
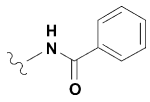
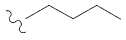
Table 3.



Compd	R_2	1000
20		450
21		> 10,000
22		> 10,000
23		> 10,000
24		> 10,000
25		2200