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# Novel non-peptidic neuropeptide Y $Y_2$ receptor antagonists

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**Abstract**—Through SAR studies of a piperidinylindoline cinnamide HTS lead, the first potent, non-peptide, low molecular weight selective Neuropeptide Y $Y_2$ (NPY $Y_2$) antagonists have been synthesized. The SAR studies around the piperidinyl, the indolinyl, and the cinnamyl moieties are discussed.


Neuropeptide Y (NPY) is a 36 amino acid C-amidated peptide, which is highly expressed in both the central and peripheral systems.[1] The high abundance of NPY in the brain and its localization suggests the involvement of NPY in a variety of physiological processes such as anxiety, food intake, water consumption, circadian rhythms, hormone release, learning and memory.[1] Pharmacological and molecular biological studies on NPY identified five NPY receptors ($Y_1$, $Y_2$, $Y_4$, $Y_5$ and $Y_6$).[2,3] While most medicinal chemistry efforts have focused on the $Y_1$ and $Y_5$ receptors, we chose to develop small molecule modulators of the $Y_2$ receptor.[4] The $Y_2$ receptor is found in several areas of the brain including the septum, hypothalamus, hippocampus, substantia nigra and cerebellum.[1] Recently this receptor has gained considerable interest because of its possible role in the regulation of food intake[5–7] and bone formation.[8,9]

Previous work in the discovery of NPY $Y_2$ ligands includes the research of Grouzmann and co-workers. They described a peptide-based ligand, T4-[NPY 33-36]$_4$, which showed considerable affinity ($IC_{50} = 67$ nM) for the NPY $Y_2$ receptor.[10] Also, Doods and co-workers reported on BIIE0246, which also binds to the NPY $Y_2$ receptor with good affinity ($IC_{50} = 3.3$ nM).[11] However, the therapeutic potential of these compounds may be limited due to their peptidic nature and high molecular weight.

Following the set-up and validation of a neuropeptide Y $Y_2$ receptor binding assay,[12] high throughput screening of our corporate compound collection was undertaken. A series of small molecule $Y_2$ ligands, exemplified by piperidinylindoline cinnamide JNJ-2765074 (**1**), ($IC_{50} = 4$ μM) were identified and a medicinal chemistry program was initiated to evaluate the SAR for these $Y_2$ ligands.

The piperidinylindoline cinnamide can be dissected into three readily prepared fragments and the general synthetic method for the preparation of analogues is shown in Scheme 1.[13] We found it necessary to initially couple the indoline portion (**3**) with the piperidone moiety (**2**), followed by attachment to the cinnamide residue (**5**). Attempts to prepare our analogues by combining the indole (**3**) with the cinnamide portion (**5**), followed by coupling to the piperidinyl moiety (**2**) were unsuccessful.

The role of the acetyl substituted indoline ring was investigated initially, as shown in Table 1, and it was determined that *N*-1 substituted analogues such as formyl analogue **8**,[14] acetyl acetate compound **9**, glyoxylate **10**, and *N*-methyl substituted indoline **11** retained binding activity that was comparable to the lead. All other analogues including unsubstituted indoline **12**, and the methylsulfonyl **13** and the trifluoromethyl acetyl **14**

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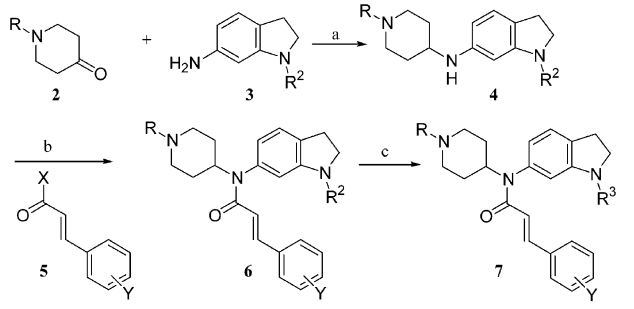
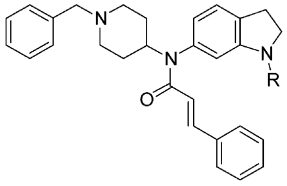
analogues displayed greatly decreased activity at the $Y_2$ receptor.

Major structural modifications to the indoline portion of the molecule were also made, as shown in Table 2. These compounds were found to be significantly less active than the *N*-acetylindoline lead (**1**). The 7-(*N*-acetyl-tetrahydroquinolinyl) compound **15** retained modest activity as shown in Table 2. However, the 6-(2-oxoindoline) **16**[16] and the 6-(*N*-acetyl-indolyl) **17**[17] showed little binding at the NPY $Y_2$ receptor.



**Scheme 1.** General preparation of piperidinylindoline cinnamide analogues. (a) 1.0 equiv ketone **2**, 1.2 equiv amine **3**, $Na(OAc)_3BH$ (1.6 equiv), DCE or DCM; (b) (i) **5** (X=OH, 1.5 equiv), $(COCl)_2$ (1.8 equiv), DMF (cat.), DCM, 0 °C–rt; (ii) amine **4** (1 equiv), $Et_3N$ (2 equiv), DCM; (c) when $R^2 = H$, (i) $R^3CO_2H$, DCC, DCM or (ii) $R^3COCl$ or $R^3SO_2Cl$, $Et_3N$, DCM.

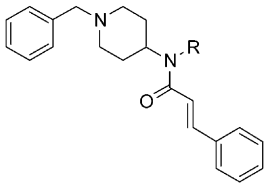
**Table 1.** *N*-1 Substituted indole analogues and their affinity at the NPY $Y_2$ receptor



| No. | R = | Binding affinity[15] $IC_{50}$, μM |
|---|---|---|
| **1** | $COCH_3$ | 4±0.6 |
| **8** | CHO | 3.5±0.4 |
| **9** | $CO(CH_2)COCH_3$ | 4.8±0.5 |
| **10** | $CO(CO)OCH_2CH_3$ | 4.8±0.4 |
| **11** | $CH_3$ | 5.3±0.3 |
| **12** | H | 22±1 |
| **13** | $SO_2CH_3$ | 15[a] |
| **14** | $COCF_3$ | 30 |

[a] $n = 1$ for this compound.

**Table 2.** Indoline replacement analogues and their affinity at the NPY $Y_2$ receptor



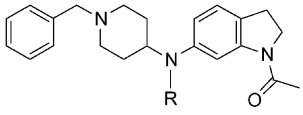
| No. | R = | Binding affinity[15] $IC_{50}$, μM |
|---|---|---|
| **15** | 7-(*N*-Acetyl-tetrahydroquinolinyl) | 10[a] |
| **16** | 6-(2-oxoindoline) | 30[a] |
| **17** | 6-(*N*-acetyl-indolyl) | 30 |

[a] $n = 1$ for this compound.

Since all modifications to the indoline led to a decrease in binding affinity, chemistry efforts were directed towards the cinnamide portion of lead **1**, as shown in Table 3. Early work demonstrated that the olefin was essential for activity as seen in saturated analogue **18**, although cyclopropyl substituted compound **19** showed modest binding affinity ($IC_{50} = 11$ μM). The cinnamide carbonyl was also found to be a critical component to maintain affinity for the NPY $Y_2$ receptor. When removed (**20**), or replaced with a sulfone (**21**), the resulting molecules exhibited minimal activity. Acetylene linked compound **22** was found to have modest affinity while the (*Z*)-olefin isomer **23**, prepared through a modification of the Horner–Wadsworth–Emmons reaction,[18] showed 5-fold less affinity than the (*E*)-isomer (**1**). In contrast, analogue **24**, which contains an additional olefin, displayed activity comparable to the lead (**1**).

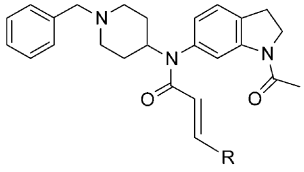
Replacements for the phenyl moiety of the cinnamide were then studied, as shown in Table 4. Acrylamide **25** possessed minimal binding affinity, whereas the 3-thiophenyl analogue **26** was approximately equipotent

**Table 3.** Initial SAR of the cinnamide portion



| No. | R = | Binding affinity[15] $IC_{50}$, μM |
|---|---|---|
| **18** | $CO(CH_2CH_2)C_6H_5$ | 18±1 |
| **19** | *anti*-CO ($C_3H_4$) $C_6H_5$ | 11±1 |
| **20** | $CH_2CH=CHC_6H_5$ | 30 |
| **21** | (*E*)-$SO_2$-$CH=CHC_6H_5$ | 30 |
| **22** | $COC{\equiv}CC_6H_5$ | 9.2±0.5 |
| **23** | (*Z*)-$COCH=CHC_6H_5$ | 22±1.0 |
| **24** | (*E,E*)-$CO(CH=CH)_2C_6H_5$ | 2.8±0.09 |

**Table 4.** Representative olefin analogues and their binding affinity to the NPY $Y_2$ receptor



| No. | R = | Binding affinity[15] $IC_{50}$, μM |
|---|---|---|
| **25** | H | 30 |
| **26** | 3-Thiophenyl | 3.2±0.2 |
| **27** | 2-Pyridyl | 30 |
| **28** | 3-Pyridyl | 30 |
| **29** | 4-Pyridyl | 12[a] |
| **30** | 4-Pyridyl-*N*-oxide | 30 |
| **31** | 2-(Imidazolyl) | 17[a] |

[a] $n = 1$ for this compound.

to lead **1**. This portion of the molecule also appeared to be sensitive to subtle changes in electronics, which were exemplified by significant differences in activity for compounds bearing the 2-pyridyl (**27**), 3-pyridyl (**28**) and 4-pyridyl (**29**) substitution. The 2- and 3-pyridyl analogues retain only minimal activity at the NPY $Y_2$ receptor, while the 4-pyridyl binds modestly with $IC_{50} = 12$ μM. Oxidation of analogue **29** provided the 4-pyridyl-*N*-oxide analogue **30**, which was inactive. Slight activity was also seen in the compound with 2-imidazolyl substitution as shown in analogue **31**.

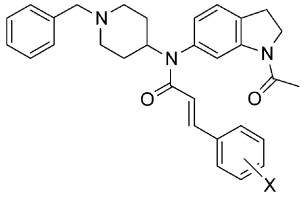
Substitution on the benzene ring of the cinnamide moiety was explored next and several general trends emerged, as shown in Table 5. Substitution in the 3-position was preferred, with slightly lower affinity seen when the same substituent was in the 4-position, as demonstrated by compounds **32** (3-Cl, $IC_{50} = 3.0$ μM) and **33** (4-Cl, $IC_{50} = 3.6$ μM). However, the $CF_3$ substituted compounds did not follow this general trend as seen in compounds **34**–**36**. The receptor was tolerant of both electron donating ($CH_3$) and electron withdrawing ($NO_2$) substituents in the 3-position, as seen in the comparable activities of compounds **37**–**41**. However, the 3-$SOCF_3$ analogue **42** showed slightly lower affinity for the $Y_2$ receptor at $IC_{50} = 5.8$ μM. The 3,5-difluoro (**43**) and the 3,5-dimethyl (**44**) substituted compounds displayed comparable activity at $IC_{50} = 2.5$ μM and 3.9 μM, respectively. In contrast, the 3,5-dichloro (**45**) analogue showed only minimal activity at the NPY $Y_2$ receptor at $IC_{50} = 30$ μM.

Initial exploration of the *N*-benzylpiperidine portion of the lead compound **1** began by varying the length and nature of the linker connecting the phenyl group to the piperidine nitrogen, as shown in Table 6. Replacing the benzyl moiety with a benzoate (**46**) led to a significant loss in affinity suggesting the need for a basic amine. The length of the linker also significantly affected binding. Phenethyl analogue **47** also showed a decrease in activity whereas the phenpropyl analogue **48** displayed a slight increase in binding affinity. Replacing the phenyl group with a cyclohexyl group (**49**) improved activity and when the linker was also extended (**50**) an additional increase in affinity ($IC_{50} = 0.6$ μM) was observed. The cyclopentyl ethyl group in this position (**51**) provided a compound with comparable activity.

Several structural modifications were made to the substituted piperidine moiety and all resulted in compounds with significantly reduced affinity at the NPY $Y_2$ receptor as seen in Figure 1.

Lastly we combined the best modifications from the piperidine portion of lead **1**, namely the cyclopentylethyl and the cyclohexylethyl groups, with those from the cinnamide work, the 4-Cl, 3-CN or 3-$NO_2$, to prepare the compounds shown in Table 7. In the initial SAR studies, it was determined that the *N*-acyl-6-indolinyl substituent was optimal for receptor binding. Thus this section of the molecule was left unchanged. Cinnamide substitution did not significantly alter the binding affinity of the cyclohexylethyl analogues **56** or **57**.

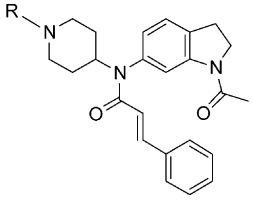
**Table 5.** Representative cinnamide analogues and their binding affinity to the NPY $Y_2$ receptor



| No. | X = | Binding affinity[15] $IC_{50}$, μM |
|---|---|---|
| **32** | 3-Cl | 3.0 ± 0.3 |
| **33** | 4-Cl | 3.6[a] |
| **34** | 4-$CF_3$ | 2.8 ± 0.2 |
| **35** | 3-$CF_3$ | 8.9 ± 1.0 |
| **36** | 2-$CF_3$ | 30[a] |
| **37** | 3-Br | 3.3 ± 0.5 |
| **38** | 3-F | 3.6 ± 0.4 |
| **39** | 3-$CH_3$ | 1.4 ± 0.2 |
| **40** | 3-$NO_2$ | 1.9 ± 0.3 |
| **41** | 3-CN | 1.0 ± 0.8 |
| **42** | 3-$SOCF_3$ | 5.8 ± 0.3 |
| **43** | 3,5-Difluoro | 2.5 ± 0.2 |
| **44** | 3,5-di$CH_3$ | 3.9 ± 0.2 |
| **45** | 3,5-diCl | 30[a] |

[a] $n = 1$ for this compound.

**Table 6.** Representative piperidine substituted analogues and their binding affinity to the NPY $Y_2$ receptor



| No. | R = | Binding affinity[15] $IC_{50}$, μM |
|---|---|---|
| **46** | $C_6H_5CO$ | 29 ± 1 |
| **47** | $C_6H_5(CH_2)_2$ | 26 ± 3 |
| **48** | $C_6H_5(CH_2)_3$ | 2.3 ± 0.3 |
| **49** | $C_6H_{11}CH_2$ | 1.1 ± 0.08 |
| **50** | $C_6H_{11}(CH_2)_2$ | 0.6 ± 0.04 |
| **51** | $C_5H_9(CH_2)_2$ | 0.8 ± 0.02 |

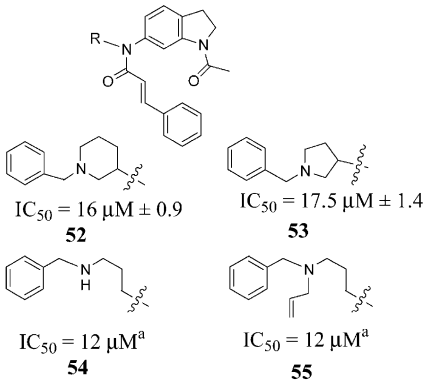
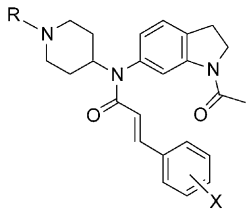



**Figure 1.** Structurally modified piperidine analogues:[15] [a] $n = 1$ for this compound.

**Table 7.** Representative combination analogues and their binding affinity to the NPY $Y_2$ receptor



| No. | R = | X = | Binding affinity[15] $IC_{50}$, μM |
|---|---|---|---|
| **56** | $C_6H_{11}(CH_2)_2$ | 4-Cl | 1.1 ± 0.1 |
| **57** | $C_6H_{11}(CH_2)_2$ | 3-$NO_2$ | 0.5 ± 0.09 |
| **58** | $C_5H_9(CH_2)_2$ | 4-Cl | 1.1 ± 0.1 |
| **59** | $C_5H_9(CH_2)_2$ | 3-$NO_2$ | 0.35 ± 0.05 |
| **60** | $C_5H_9(CH_2)_2$ | 3-CN | 0.1 ± 0.01 |

Conversely, the cyclopentylethyl analogues **58**–**60** displayed a wide range of activities. No change in activity was seen with the 4-Cl cinnamide **58** and a slight increase in activity was observed in the 3-$NO_2$ cinnamide substituted analogue, **59**. However, the 3-CN cinnamide analogue (**60**) showed a marked increase in binding activity at $IC_{50} = 0.1$ μM. Through combining the optimal substitution on the indoline, the cinnamide and the piperidine, we prepared the most potent analogue, **60**.

A detailed biological evaluation of compound **60**, also known as JNJ-5207787, was undertaken due to its high affinity for the NPY $Y_2$ receptor. JNJ-5207787 was demonstrated to be an antagonist via inhibition of PYY-stimulated [$^{35}$S]GTPγS binding ($pIC_{50}$ corr = 7.2 ± 0.12).[12] This compound was also found to be >100-fold selective versus human $Y_1$, $Y_4$ and $Y_5$ receptors as evaluated by radioligand binding.[12] In addition, JNJ-5207787 was found to be selective against a wide variety of receptors and enzymes (inhibition <50% at 1 μM).

In conclusion, through an HTS effort a series of indolylpiperidines, exemplified by **1** were identified as potential NPY $Y_2$ ligands. Through a medicinal chemistry program, we prepared compounds with 40-fold higher affinity for the receptor (**60**, JNJ-5207787, $IC_{50} = 0.1$ μM). Further biological evaluation of this compound determined that it behaved as a selective NPY $Y_2$ antagonist. Thus, we have identified the first small molecule NPY $Y_2$ antagonist.[19]

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