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Aminopyrazoles with High Affinity for the Human Neuropeptide Y5 Receptor

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Abstract—1,3-Disubstituted-5-aminopyrazoles were prepared based on a lead compound found through high-throughput screening of our corporate compound library in an assay measuring affinity for the human neuropeptide Y5 receptor. The target compounds were prepared by cyclization of α-cyanoketones with appropriate hydrazines, followed by reduction and coupling to various sulfonamido-carboxylic acids. Several of these arylpyrazoles (e.g., **19** and **45**) displayed high affinity for the human NPY Y5 receptor (<20 nM IC_{50}s).

Neuropeptide Y (NPY) is a 36-amino acid C-amidated peptide, which is a member of the pancreatic polypeptide family.[1] It is highly expressed in several regions of the brain and is released into the circulation from neuronal stores in times of stress. In the CNS, NPY has been implicated in obesity and feeding,[2,3] as NPY is a powerful stimulant of food intake when administered directly into the hypothalamus. Recent discoveries have revealed six G-protein coupled receptors that bind with high affinity to NPY and related peptides such as peptide YY, pancreatic polypeptide and truncated NPY analogues.[4–13] The most likely receptor subtypes responsible for centrally-mediated NPY-induced feeding responses are NPY Y1 and NPY Y5.[12,14–16] Antagonists at the NPY Y5 receptor have been shown to be effective in reducing food intake in various animal models of feeding.[17] Consequently, NPY Y5 receptor antagonists may provide new treatments for obesity and other eating disorders.[18]

NPY Y5 antagonists that have been reported in the literature encompass many diverse structural types (Fig. 1). The first NPY Y5-selective antagonists appeared in mid-1997.[19,20] Quinazoline sulfonamide **1** was found to have low nanomolar affinity at the Y5 receptor. Other sulfonamides bearing a β-aminotetralin substructure, typified by **2**, are also potent NPY Y5 antagonists.[21–23] One of the most potent NPY Y5 antagonists is amide derivative **3**, reported to have an IC_{50} value of 0.47 nM at the Y5 receptor.[24] Aminopyrazoles **4** and **5** have both been shown to have low nanomolar affinity for the Y5

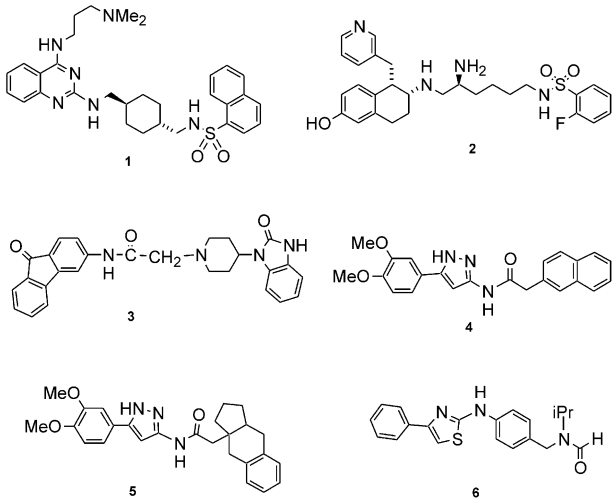

Figure 1. Non-peptide NPY 5 receptor antagonists.

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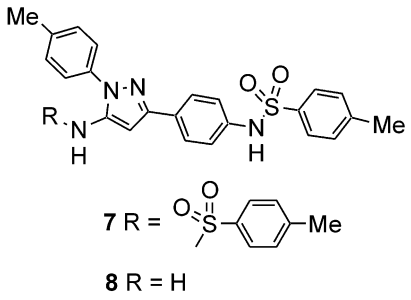


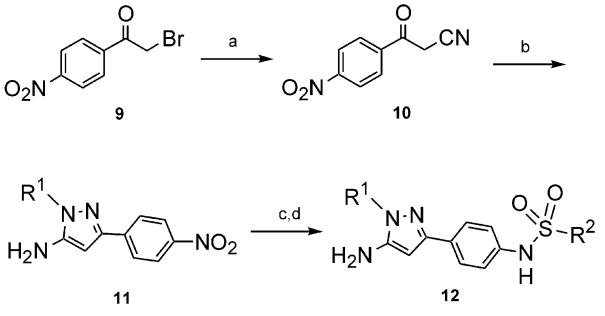
Figure 2. Aminopyrazole lead structures from HTS.

receptor.[25,26] Aminothiazole **6** has also been described as an NPY Y5 antagonist.[27]

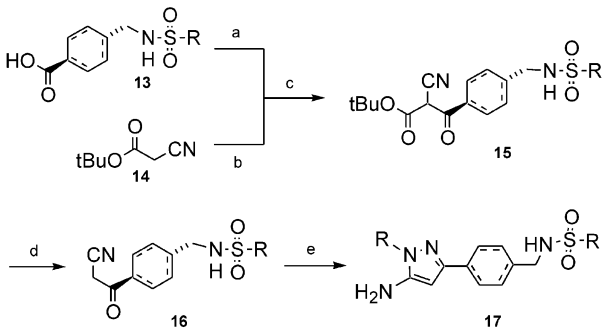
Screening of our corporate compound library identified aminopyrazole bis-sulfonamide **7** (Fig. 2), obtained through a compound aquisition program, as having nanomolar binding affinity for the human Y5 receptor. Structural characterization of the sample revealed, unexpectedly, that it was a 1:1 mixture of two compounds, which were found to bis-sulfonamide **7** and aminopyrazole **8**. Evaluation of the individual components of the mixture revealed that all of the original activity resided in aminopyrazole **8**, having a 40 nM IC_{50}. The bis-sulfonamide **7** was inactive with a 6 μM IC_{50}. An intensive effort to develop structure–activity relationships (SARs) based on aminopyrazole lead **8** was then undertaken.

The target aminopyrazoles were synthesized in four steps from commercially available 2-bromo-4′-nitroacetophenone **9** (Scheme 1). This compound was reacted with NaCN in aqueous ethanol at 0 °C to provide 2-cyano-4′nitroacetophenone **10**. Formation of the pyrazole core stucture was effected by cyclization of the α-cyanoketone with an arylhydrazine in the presence of triethylamine in refluxing ethanol, which yielded pyrazole **11**. The nitro group was then reduced to an amine under hydrogenation conditions and the amine was coupled to an aryl sulfonyl chloride to afford desired aminopyrazoles **12** in excellent yields.

Alternatively, aminopyrazoles that contained a cyclohexylmethyl- or phenylmethyl-sulfonamido group were prepared as illustrated in Scheme 2. These compounds were designed because the cyclohexylmethylsulfonamido group had previously been shown to be present in high-affinity NPY Y5 ligands.[19–21] The mixed anhydride of the *trans*-cyclohexyl acid **13** was reacted with the anion of *t*-butyl cyanoacetate **14** to yield cyclohexyl β-ketoester **15**. The *t*-butyloxycarbonyl group was removed by treatment with TFA. The pyrazoles were formed by reacting α-cyano ketone **16** with a substituted hydrazine in the presence of Et_3N in ethanol at reflux to provide the cyclohexylmethyl pyrazoles **17** in fair to moderate yields. The analogous phenylmethyl sulfonamido compounds were prepared in the same manner starting with the corresponding benzoic acid **13**.



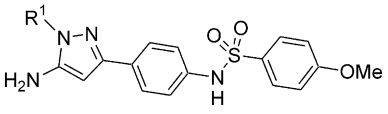
Scheme 1. Reagents: (a) NaCN, H_2O, EtOH, 0 °C; (b) R^1NHNH_2, Et_3N, EtOH, reflux; (c) H_2, 10% Pd–C, EtOAc, 30 psig; (d) R^2SO_2Cl, K_2CO_3, THF, H_2O.



Scheme 2. Reagents: (a) isobutylchloroformate, Et_3N, DCE; (b) NaH, THF; (c) 14 h; (d) TFA, DCE; (e) arylhydrazine hydrochloride, Et_3N, EtOH, reflux.

The aminopyrazole sulfonamides 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). Table 1 illustrates aminopyrazole sulfonamides in which the substituent on the pyrazole ring (R^1) was varied to develop an SAR profile. The parent *N*-phenyl derivative **18** had a 100 nM IC_{50} for the human NPY Y5 receptor. In general, when the R^1 group was a *substituted* phenyl the compounds were found to be the more potent NPY ligands. In particular, the best affinity was found when R^1 was 4-methylphenyl (**19**), for which a 15 nM IC_{50} was observed.[28] 3-Substitution on the phenyl ring resulted in a slight loss of

Table 1. Human NPY Y5 receptor binding affinity of aminopyrazoles with R^1 variation[a]



Compd	R^1	Y5 IC_{50} (nM)
18	Phenyl	100
19	4-Methylphenyl	15
20	3-Methylphenyl	37
21	3-(Dimethylamino)phenyl	30
22	3,5-(Bistrifluoromethyl)phenyl	>1000
23	4-Fluorophenyl	37
24	1-Naphthyl	48
25	2-Pyridyl	436
26	4-Trifluoromethyl-2-pyridyl	>1000
27	4-Trifluoromethyl-2-pyrazine	709

[a]HEK 293 cells were stably transfected with the human NPY Y5 cDNA, and the receptor affinity was determined as described in ref 21.

activity versus 4-substitution (**19** vs **20**). Compounds with nitrogens that could be protonated were of interest to us because they could perhaps increase aqueous solubility. Therefore, it was gratifying that dimethylamino compound **21** had a 30 nM IC_{50} at the human NPY Y5 receptor. Surprisingly, the 3,5-bis(trifluoromethyl)phenyl congener (**22**) was devoid of activity at a concentration of 1 μM. 4-Fluorophenyl and 1-naphthyl derivatives **23** and **24** demonstrated good receptor affinity with 37 and 48 nM IC_{50}s, respectively. Heteroaryls **25**, **26**, and **27** had greatly diminished activity.

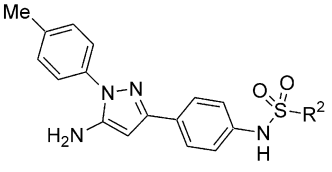
Variations were also made to the sulfonamide substituent (R^2, Table 2). For this analysis, the R^1 group was held constant at 4-MePh because of the potent receptor affinity of **19**. In general, phenyl (**28**) and 4-substituted phenyls (**19** and **29**–**35**) provided the best affinity for the NPY Y5 receptor. Electon-donating substituents 4-Me (**29**) and 4-MeO (**19**) displayed 40 and 15 nM IC_{50}s for the NPY Y5 receptor, respectively. Electron-withdrawing groups in the 4-position were also tolerated, such as with 4-CF_3Ph **30**, 4-(CF_3O)Ph **31**, 4-FPh **32** (29 nM IC_{50}), and 4-NO_2Ph **33**. The 4-NH_2Ph congener **34,** obtained by reduction of **33**, was equipotent to **33**, indicating a broad tolerance for substitution in this position. 4-(Me_2N)Ph **35** was less active with a 162 nM IC_{50}. Direct comparison of 4- and 3-substitution revealed a loss of activity when moving an amino group to the 3-position (viz. **36** vs **34**), whereas the 3-(Me_2N)Ph analogue (**37**) was nearly equivalent in activity to 4-substituted **35**. Compounds **38** and **39** with 2-substitution showed moderate activity. Incorporation of bicyclic quinoline and naphthyl groups (**40** and **41**) abolished the receptor affinity.

The sulfonamide N–H in **19** appears to be crucial for activity because *N*-methyl **42** was inactive (>1 μM IC_{50}; Fig. 3). In addition, the 1,4-orientation of the pyrazole and the sulfonamide on the middle phenyl ring is also necessary for activity. When the groups were transposed into a 1,3-orientation (**43**), affinity for the NPY Y5 receptor was lost (>1 μM IC_{50}). Methylation of the amino group attached to the pyrazole ring of **35** provided **44**, which resulted in a 3-fold decrease in activity (487 nM IC_{50}).

When a cyclohexylmethyl group replaced the phenyl ring, resultant compounds **45** and **46** were slightly better or similar in activity when compared with phenyl derivative **19**. The 2-NO_2 and 2-NH_2 substitution on R^3 was selected for these compounds because of literature precedent with compounds of type **2**.[21] Phenyl methyl linker congener **47** had an IC_{50} of 114 nM. Replacement of the sulfonamido group with either an amide (**48**) or a reverse amide (**49**) resulted in a loss of activity, indicating that the sulfonamide is critical for activity here as it is for some of the other NPY Y5 chemical series, as seen for **1** and **2** previously (Table 3).

Several of the aminopyrazole sulfonamides we report here show high affinity for the human neuropeptide Y5 receptor. This series contains an arylpyrazole and an arylsulfonamide that are connected via a suitable linker. For example, among the most active compounds are those in which there is a substituted phenyl pyrazole on one side and a 4-substituted phenyl sulfonamide on the other with a 1,4-phenyl linker in the middle (viz. **19**, **21**, **23**, and **28**). Additionally, derivatives with a (cyclohexyl)methylamino spacer (viz. **45** and **46**) have significant activity, with **45** exhibiting a 10 nM IC_{50} at the human NPY Y5 receptor. These compounds may be useful for the treatment of human feeding disorders and obesity, especially if a compound with favorable pharmacokinetic properties can be obtained with this level of in vitro affinity.

Table 2. Human NPY Y5 receptor binding affinity of aminopyrazoles with R^2 modifications



Compd	R^2	Y5 IC_{50} (nM)
28	Phenyl	25
29	4-Methylphenyl	40
19	4-Methoxyphenyl	15
30	4-Trifluoromethyl	63
31	4-(Trifluoromethoxy)phenyl	67
32	4-Fluorophenyl	29
33	4-Nitrophenyl	79
34	4-Aminophenyl	74
35	4-(Dimethylamino)phenyl	162
36	3-Aminophenyl	303
37	3-(Dimethylamino)phenyl	145
38	2-Nitrophenyl	178
39	2-Aminophenyl	229
40	8-Quinolinyl	>1000
41	1-Naphthyl	>1000

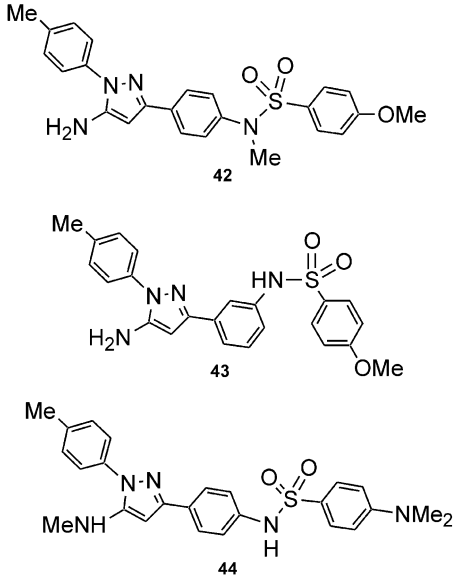
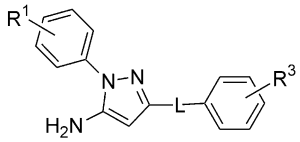
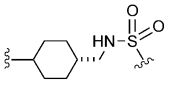
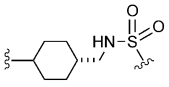
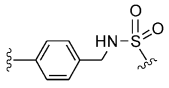
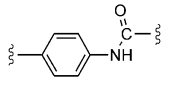
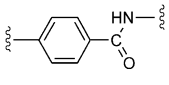


Figure 3. Variably substituted pyrazole derivatives.

Table 3. NPY Y5 receptor binding affinity of aminopyrazoles with variation of the middle linker portion



Compd	R^1	L	R^3	Y5 IC_{50} (nM)
45	3-CF_3		2-NO_2	10
46	3-CF_3		2-NH_2	20
47	3-CF_3		H	114
48	4-Me		4-MeO	>3000
49	4-Me		4-Me	>3000

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28. Compound **19** was inactive at the human neuropeptide NPY-1 and NPY-2 receptors: <10% specific binding at 10^{-5} M.