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Design, syntheses, and structure–activity relationships of novel NPY Y5 receptor antagonists: 2-{3-Oxospiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl}benzimidazole derivatives

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ABSTRACT

Design, syntheses, and structure–activity relationships of a novel class of 2-{3-oxospiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl}benzimidazole NPY Y5 receptor antagonists are described. The benzimidazole structures were newly designed based on the urea linkage of our prototype Y5 receptor antagonists (**2** and **3**). By optimizing substituents on the benzimidazole core part of the lead compound **5a**, we were able to develop a potent, orally available, and brain-penetrable Y5 selective antagonist (**5k**).

Obesity is a serious and growing public health problem in the world, and is associated with significant morbidity. Obesity-related comorbidities include type 2 diabetes, hypertension, and cardiovascular diseases. Although several drugs are clinically used, ideal treatments for obesity are strenuously pursued, especially in terms of safety.

Neuropeptide Y (NPY) is a highly conserved 36-amino acid peptide with potent, centrally mediated orexigenic effects.[1] NPY is a member of the peptide family that also includes peptide YY (PYY) and pancreatic polypeptide (PP). Chronic administration of NPY into the brain in female rats results in hyperphagia and body weight gain.[2] Concentrations of NPY and its messenger RNA (mRNA) in the hypothalamus are markedly increased during food deprivation and in some rodent genetic models of obesity.[3] These data suggest that NPY is one of the major regulators of physiological feeding behaviors.

Presently, 5 distinct types of G protein-coupled NPY receptors subtypes, Y1, Y2, Y4, Y5, and Y6, have been cloned thus far.[4] Of these, the Y5 receptor subtype is thought to be responsible for centrally mediated NPY-induced feeding responses.[5] Moreover, we have found that the Y5 receptor subtype is involved in the regulation and development of diet-induced obesity in rodents.[6] Taken together, the data suggest that antagonism of the Y5 receptor would be a beneficial treatment of obesity. Indeed, a recent 52 week clinical trial, a significant weight loss was observed with the administration of the selective Y5 antagonist.[7] To date, a number of potent Y5 receptor antagonists,[8] each with distinct structure classes that include sulfonamide,[8a,8b] pyrrolo[3,2-d]pyrimidine,[8c] carbazole,[8e] imidazolylpyridine,[8g] and imidazolone[8i] classes have been reported.

In the course of our program, which was aimed at developing orally bioavailable Y5 receptor antagonists for the treatment of obesity, we have been pursuing potent and selective Y5 antagonist leads.[8f,8j] In particular, identification of 2-methanesulfonamidephenylpiperazine derivative (**1**) was important because it gave us a structural insight into further design of other novel Y5 antagonist lead structures.[9,10] Based on the structure of **1**, prototype Y5 antagonist leads (**2** and **3**) were identified by connecting a 2-methylsulfonyl-3-spiro(indolin-3,4′-piperidine) **11**[9] or 3-oxospiro[isobenzofuran-1(3*H*),4′-piperidine] **17**[10] part with a substituted aniline moiety through a urea bond. In the light of the phenylurea sub-structure in **2** and **3**, we further designed fused ring systems such as benzimidazole and benzothiazole, which were directly attached to the above-mentioned spiropiperidines or the corresponding cyclohexane moiety (Fig. 1). The syntheses and in vitro evaluation led to the identification of novel Y5 lead structures, 2-[3-oxospiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl]benzimidazole

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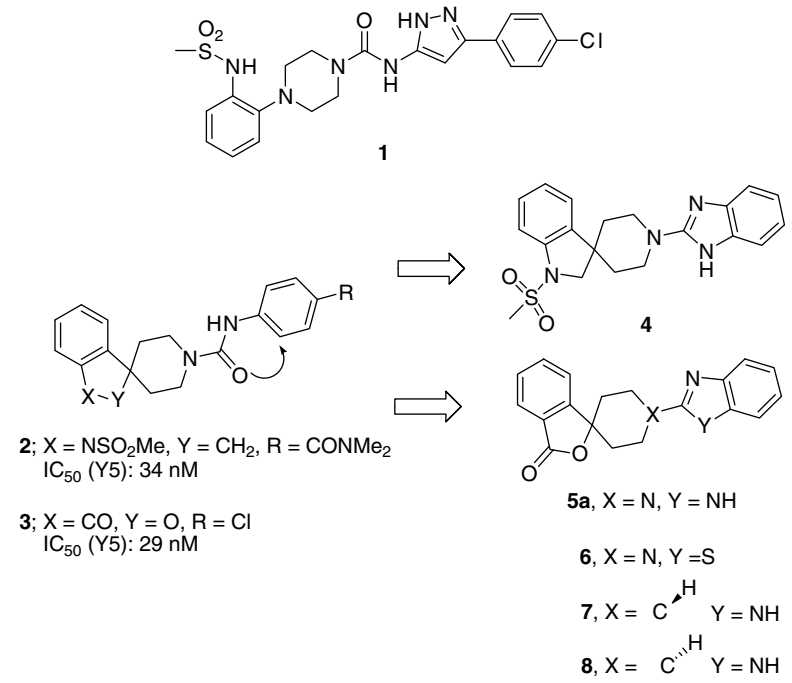


Figure 1. Design of benzimidazole and related templates.

(**5a**) and the corresponding cyclohexan-4-ylbenzimidazole (**7**). Although their affinity for the Y5 receptor subtype was moderate, their structural uniqueness prompted us to further derivatize these leads.

In this letter, we describe the syntheses and structure–activity relationships (SARs) of 2-[3-oxospiro[isobenzofuran-1(*3H*),4′-piperidin]-1′-yl]benzimidazole derivatives.[11] In addition, the SARs of 2-[3-oxospiro[isobenzofuran-1(*3H*),1′-cyclohexan]-4′-yl]benzimidazole derivatives (**7**) will be described.

General synthetic methods of the benzimidazole derivatives (**5a–5z**, **5aa–5gg**) are summarized in Scheme 1. Basically, these benzimidazoles can be prepared through the coupling of spiropiperidine **11** and 2-chlorobenzimidazoles **15**.[12] The spiropiperidine, 3-oxospiro[isobenzofuran-1(3*H*),4′-piperidine] **11**,[10b] was prepared from 2-bromobenzoic acid **9** as follows. Nucleophilic addition reaction of the dianion, generated from **9** and *n*-BuLi, to *N*-benzyl-4-piperidone and a subsequent acidic treatment of the reaction mixture afforded **10** in a 45% yield. Catalytic hydrogenation of **10** in the presence of 20% palladium hydroxide on carbon under an acidic condition (4 N HCl in EtOAc) gave **11** as a hydrochloride salt in 85% yield.

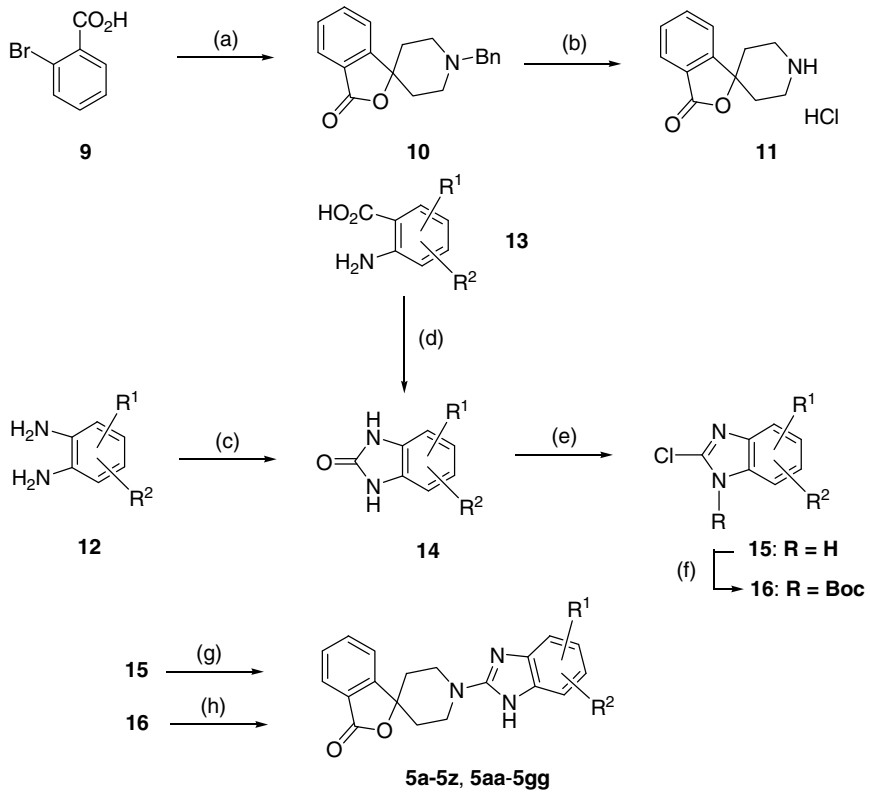
Syntheses of the 2-chlorobenzimidazoles **15** were carried out from commercially available substituted phenylenediamines **12** or substituted anthranilic acids **13**. Phenylenediamines **12** were treated with 1,1′-carbonyldiimidazole to give benzimidazol-2-ones **14**. Chlorination of **14** through treatment with $POCl_3$ at 110 °C resulted in 40–70% yields of 2-chlorobenzimidazoles **15**. On the other hand, anthranilic acids **13** were treated with diphenylphosphoryl azide to produce good yields of **14**, which were converted to **15** by treatment with $POCl_3$. Under basic conditions (K_2CO_3, Na_2CO_3, or Cs_2CO_3) at 100–150 °C coupling of **11** with **15** produced the desired benzimidazole derivatives (**5a–5z**, **5aa–5gg**) with 30–70% yields. When *N*-Boc-protected 2-chlorobenzimidazoles **16** were used in place of **15**, the coupling reaction proceeded at a lower temperature (80–90 °C) with 30–50% yields.

Syntheses of the other derivatives (**4**, **6**–**8**, **18**, **19**) are summarized in Scheme 2. Basically, the derivatives (**4**, **6**, **18**, and **19**) were prepared in a similar manner as described for the preparation of **5a**. As for the synthesis of **7** and **8**, condensation of the carboxylic acid **20**[10] and phenylenediamine (WSC, Py, rt) along with the subsequent intramolecular cyclization of the resulting amide ($TsOH{\cdot}H_2O$, xylene, reflux, 6 h) afforded a mixture of **7** and **8** (ratio = 6.5:1) with a 65% yield.[13] Separation of the mixture was easily achieved through the use of silica gel column chromatography (1–5% MeOH–$CHCl_3$).

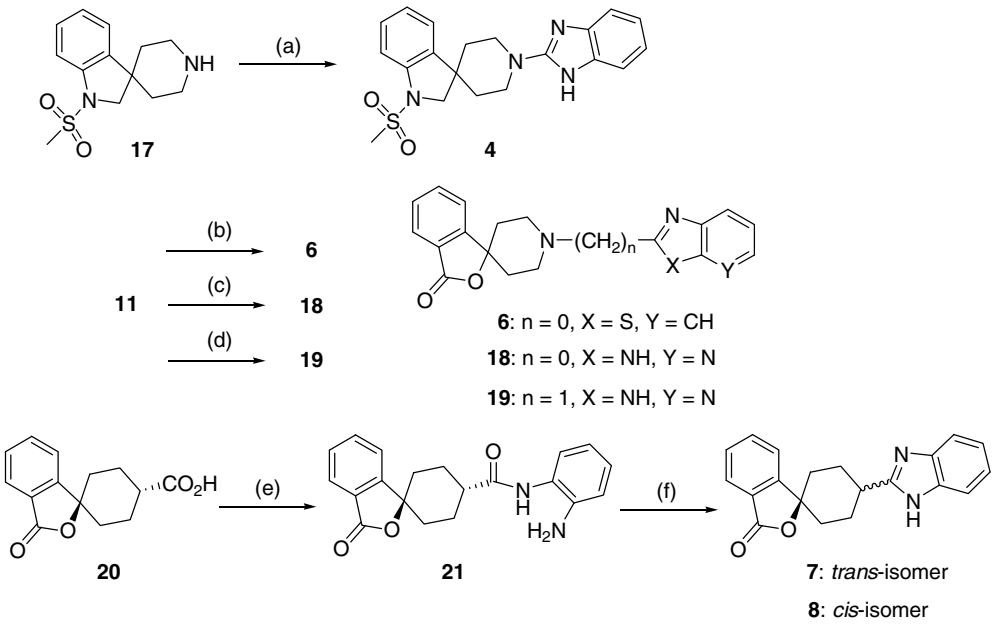
Compounds were tested in an initial screen for the binding affinity against human NPY Y5 receptor subtype (Y5) in transfected LMtk- cells.[5b] Subsequently, selected compounds were examined for their subtype selectivity over the other NPY receptors (Y1, Y2, and Y4) and their Y5 antagonist activity (Ca^{2+} flux).[5b]

As described above, derivatives bearing the 2-(substituted piperidin-1-yl)benzimidazoles (**4**, **5a**), benzothiazole (**6**), imidazo[4,5-*b*]pyridine (**18**), 2-(substituted piperidin-1-ylmethyl)benzimidazole (**19**), *trans*-2-(substituted cyclohexyl)benzimidazole (**7**) and the corresponding *cis*-isomer (**8**) were evaluated in the Y5 receptor binding assay (Table 1). Among these, **5a** and **7** had moderate Y5 binding affinity (IC_{50}: 100–200 nM), while the others exhibited IC_{50} values of more than 1000 nM. Based on these results, we firstly focused on developing SARs of **5a** as a novel Y5 lead.

We hypothesized that incorporation of substituents into the phenyl ring of the benzimidazole core part would be an effective way to enhance the Y5 affinity based on the superimposition of the entire structures of **1** and **5a**. Therefore, as a first step we focused on the optimization of the incorporation of substituents into the benzimidazole core part. To examine the effects of mono-substitution at the 4- or 5-position of the benzimidazole ring on the Y5 binding affinity (Table 2), various substituents, such as a fluorine atom, methyl, trifluoromethyl, and phenyl groups, were introduced. Generally, incorporation of a substituent into the 4- or 5-position was tolerated in the Y5 binding affinity, with the 5-substitution resulting in a greater improvement as compared to the corresponding 4-substitution. In particular, the 5-chloro- (**5i**), 5-trifluoromethyl- (**5k**), and 5-phenyl- (**5m**) benzimidazoles had single digit nanomolar binding affinities (IC_{50}: **5i** = 6.6 nM, **5k** = 3.5 nM, **5m** = 2.4 nM) for the Y5 receptor and achieved approximately a 20- to 60-fold improvement, as compared with



Scheme 1. Syntheses of benzimidazole derivatives (**5a**–**5z**, **5aa**–**5gg**). Reagents and conditions: (a) 1—*n*-BuLi, *N*-benzyl-4-piperidone, THF, −70 °C; 2—concd HCl, H_2O, reflux; (b) 20% $Pd(OH)_2$, H_2, 4 N HCl in EtOAc–MeOH, rt; (c) CDI, DMF, 80 °C; (d) $(PhO)_2P(O)N_3$, NEt_3, THF, 80 °C; (e) $POCl_3$, *N*,*N*-dimethylaniline, 110 °C; (f) DIBOC, DMAP, $CHCl_3$, rt; (g) **11**, Cs_2CO_3, DMF,150 °C; (h) **11**, Cs_2CO_3, DMF, 80 °C, then TFA, rt.

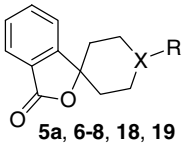


Scheme 2. Synthesis of the other derivatives (**4**, **6**–**8**, **18**, **19**). Reagents and conditions: (a) Na_2CO_3, 2-chlorobenzimidazole, DMF, 100 °C; (b) Cs_2CO_3, 2-chlorobenzothiazole, dioxane, 80 °C; (c) K_2CO_3, 2-chloromethylbenzimidazole, DMF, 100 °C; (c) Na_2CO_3, *N*-Boc-2-chloroimidazo(4,5-*b*)pyridine, dioxane, 90 °C; (e) WSC, phenylenediamine, Py, rt; (f) TsOH·monohydrate (0.2 equiv), xylene, reflux.

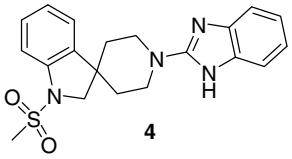
the original lead **5a**. These results suggested that a hydrophobic substituent at the 5-position significantly contributed to the enhancement noted in the Y5 binding affinity. Therefore, further derivatization was focused on the substitutions at the 5-position.

Introduction of an ester group such as methyl ester (**5q**) or ethyl ester (**5r**) in place of the hydrophobic substituents retained the Y5 binding affinity, while introduction of more hydrophilic substituent such as a carbamoyl (**5t**), dimethylcarbamoyl (**5v**), methanesulfonamide (**5y**), or methanelsulfonyl (**5z**) resulted in significant decreases in the Y5 binding. These SARs suggested that the Y5 potency would be influenced by steric factors rather than electronic nature of the substituents on the benzimidazole core ring.

Table 1
Binding affinity of benzimidazole and related compounds to the Y5 receptor



5a, **6-8**, **18**, **19**



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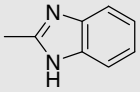
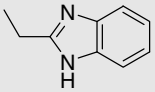
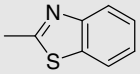
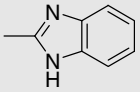
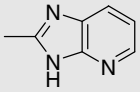
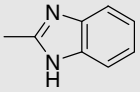
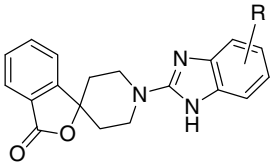
Compound	X	R	Y5 (IC_{50}, nM)[a]	Compound	X	R	Y5 (IC_{50}, nM)[a]
4			>1000				
5a	N		140	**19**	N		4900
6	N		>10,000	**7**	 (*trans*-isomer)		91
18	N		1600	**8**	 (*cis*-isomer)		1400

[a] Values are the mean of two or more independent assays (Ref. 14).

Table 2
The binding affinity of benzimidazole derivatives (**5a**–**5z**) to the Y5 receptor



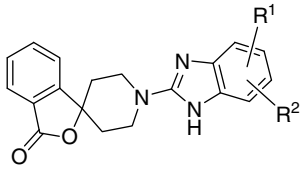
Compound	R	Y5 (IC_{50}, nM)[a]	Compound	R	Y5 (IC_{50}, nM)[a]
5a	H	140	**5n**	5-Bromo	10
5b	4-Fluoro	500	**5o**	5-Nitro	10
5c	5-Fluoro	28	**5p**	5-Cyano	19
5d	4-Methyl	74	**5q**	5-*iso*-Butyl	1.8
5e	5-Methyl	36	**5r**	5-Methoxycarbonyl	2.7
5f	4-Methoxy	250	**5s**	5-Ethoxycarbonyl	2.0
5g	5-Methoxy	37	**5t**	5-Carbamoyl	110
5h	4-Chloro	51	**5u**	5-*N*-Methylcarbamoyl	20
5i	5-Chloro	6.6	**5v**	5-*N*,*N*-Dimethylcarbamoyl	58
5j	4-Trifluoromethyl	83	**5w**	5-Carboxy	>1000
5k	5-Trifluoromethyl	3.5	**5x**	5-Acetylamino	130
5l	4-Phenyl	17	**5y**	5-Methanesulfonylamino	56
5m	5-Phenyl	2.4	**5z**	5-Methanesulfonyl	85

[a] Values are the mean of two or more independent assays (Ref. 14).

Di-substituted benzimidazole derivatives were prepared and assessed in the Y5 binding assay (Table 3). Generally, these di-substituted benzimidazoles (**5aa**–**5ee**) were more potent than the corresponding mono-substituted compounds. For example, the 5,6-dichlorobenzimidazole **5bb** (IC_{50}: 1.6 nM) was approximately 4-fold more potent than the 5-chlorobenzimidazole **5i** (IC_{50}: 6.6 nM). Furthermore, comparison of the Y5 affinity of 4,6-dichlorobenzimidazole **5aa** with that of the 5,6-dichlorobenzimidazole **5bb** suggested that the 5,6-disubstitution was more likely to have higher affinity than the 4,6-disubstitution. Among the di-substituted benzimidazoles, **5bb** showed the best binding affinity for the Y5 receptor.

Further characterization of the representative benzimidazole derivatives (**5i**, **5k**, **5m**, **5r**, **5bb**) was conducted (Table 4). These compounds had more than 1000-fold subtype selectivity over the other NPY receptors (Y1, Y2, Y4) in addition to having potent antagonist activity, as demonstrated via the inhibition of the NPY-induced [Ca^{2+}] increases in LMtk- cells that expressed the Y5 receptor. To examine the oral absorption in rats, these compounds were orally administered at 10 mg/kg, and then the plasma levels were measured at 2 and 4 h after the administration. Of the compounds administered, two derivatives (**5i** and **5k**) showed high plasma exposures (>10 μM) even at 4 h after the administration, suggesting that these derivatives were long lasting Y5 antagonists with excellent oral absorption in rats. The plasma levels of **5i** and **5k** at 4 h were higher than those at 2 h, which was more than likely due to low hepatic clearance and slow intestinal absorption.[15] In contrast, the derivative **2r** showed the lower plasma level (0.1 μM) at 4 h after the oral administration. This was probably due to the high hepatic clearance that is often observed in rats.[15]

Table 3
The binding affinity of benzimidazole derivatives (**5aa**–**5gg**) to the Y5 receptor



Compound	R^1, R^2	Y5 (IC_{50}, nM)[a]
5i	5-Chloro	6.6
5aa	4,6-Dichloro	5.7
5bb	5,6-Dichloro	1.6
5cc	5,6-Dimethyl	9.2
5dd	5,6-Difluoro	4.8
5ee	5-Chloro-6-fluoro	6.7
5ff	5,6-Methylenedioxy	9.3
5gg	5,6-Difluoromethylenedioxy	2.2

[a] Values were the mean of two or more independent assays (Ref. 14).

Table 4
Biological properties of the representative compounds

Compound	Y5	Y1	Y2	Y4	Y5[a]	Rat plasma levels[c] (μM)		*B*/*P*[d]
	IC_{50}[b] (nM)				IC_{50}[b] (nM)	2 h	4 h	Ratio
5i	6.6	>10,000	>10,000	>10,000	1.2	27.8	25.6	—
5k	3.5	>10,000	>10,000	>10,000	6.4	15.3	17.5	0.31
5m	2.4	>10,000	>10,000	>10,000	1.8	1.8	1.3	0.35
5r	2.7	>10,000	>10,000	>10,000	1.5	3.2	0.1	0.08
5bb	1.6	>10,000	>10,000	>10,000	1.4	2.9	4.6	—

[a] Antagonist activity was determined by the amount of inhibition of NPY-induced [Ca^{2+}] increase in LMtk- cells expressing the human Y5 receptor.
[b] Values are the mean of two or more independent assays.
[c] Compounds (10 mg/kg) were orally administered to rats (n = 3), and the plasma levels were measured at 2 and 4 h.
[d] Compounds (10 mg/kg) were orally administered to rats (n = 3), and the plasma and brain levels were measured at 2 h. *B*/*P* means the ratio of the brain level (nmol/g) to plasma level (μM) of the compounds.

The brain penetration (*B*/*P*) of the compounds (**5k**, **5m**, and **5r**) was examined in rats. The results suggested that the lipophilic compounds (**5k** and **5m**) had moderate brain penetration (*B*/*P* = ~0.3), while the brain penetrability of the hydrophilic compound **5r** was poor (*B*/*P* = ~0.08). Since we found that **5k** showed excellent brain exposure in rats, we evaluated the in vivo efficacy of **5k** on D-Trp^{34} NPY-induced food intake in rats. Oral administration of **5k** (10 mg/kg) significantly suppressed intracerebroventricular (ICV) injected D-Trp^{34}NPY-induced food intake in rats.[16,17]

In conclusion, we designed and synthesized the novel 2-[3-oxospiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl]benzimidazole structure (**5a**) along with other related compounds (**4**, **6**–**8**, **18**, **19**), based on the urea linkage of the prototype Y5 antagonists (**2** and **3**), resulting in the identification of **5a** and **7** as novel Y5 antagonist leads. The SAR studies on **5a** along with the subsequent characterization of the selected compounds revealed that **5k** was a potent, orally available, and brain-penetrable Y5 selective antagonist.

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