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Design, Synthesis and SAR of a Series of 2-Substituted 4-Amino-quinazoline Neuropeptide Y Y_5 Receptor Antagonists

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Abstract—The design of a novel series of NPY-Y_5 receptor antagonists is described. Key elements for the design were the identification of weak Y_5 hits from a Y_1 program, results from a combinatorial approach and database mining. This led to the discovery of the quinazoline **4** and the aryl-sulphonamide moiety as major components of the pharmacophore for Y_5 affinity. The synthesis and SAR towards CGP71683A is described. © 2000 Elsevier Science Ltd. All rights reserved.

Neuropeptide Y (NPY), a 36 amino acid peptide, has been the focus of much attention since its discovery as the most abundant peptide in the mammalian brain.[1] It is present in a highly conserved manner across species and is involved in a number of physiological responses and implicated in the pathophysiology of several disorders. Within the hypothalamus, NPY is intimately involved in the regulation of several aspects of neuroendocrine function and behavior, in particular food intake.[2] At least six receptor-subtypes have been characterized to date by pharmacological and molecular cloning techniques.[3,4] However, their specific involvement in NPY mediated food intake regulation remains to be fully validated.

Recently, the hypothetical "feeding" receptor, named Y_5, was cloned and expressed by Synaptic Pharmaceutical Corporation.[5] In collaboration with Novartis, evidence was generated indicating that the NPY-Y_5 receptor is the primary mediator of NPY-induced feeding.[6,7] However, other investigators made the observation that the NPY-Y_1 receptor is also involved in the control of NPY-induced food intake.[8–10] Our findings, however, indicate that the Y_5-subtype shows more robust evidence for an involvement in the regulation of food intake.[12] Antagonists for the NPY-Y_5-subtype are, therefore, required and targeted.

Herein, we disclose a novel series of potent and selective NPY-Y_5 antagonists that demonstrate that the Y_5-subtype plays a major role in mediating food intake induced by NPY.

We used an integrated approach of selected screening and combinatorial chemistry to identify Y_5-subtype selective compounds. Exploitation of weak Y_5 hits from a previous Y_1 program and exploration of the internal compound library by Y_5 pharmacophore models generated with Catalyst®, revealed the 2-substituted 4-aminoquinazolines **1**–**3** with sub-micromolar affinity and some selectivity towards the Y_5-subtype.

In parallel to the optimization of the quinazoline scaffold **4** by traditional methodology, a small biased combinatorial library was prepared in solution[12] and on solid support,[13] based on the weak Y_5 hit **5**, containing at least two distal hydrophobic moieties namely a basic nitrogen containing scaffold and an H-bond acceptor functionality. These efforts resulted in the identification of compounds **6** and **7** (SNAP6608A),

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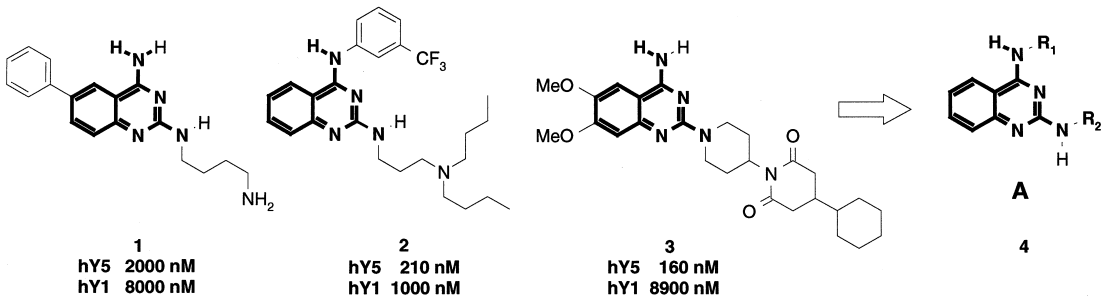


and suggested that the naphthylsulfonamide moiety might be an important part of the Y_5 pharmacophore.

Linking this moiety by a semi-rigid spacer to the heteroaryl fragment **A** led to the preparation of sulfonamide-tethered 2,4-diamino-quinazolines and ultimately to **8** (CGP71 683A), a potent and selective antagonist of the Y_5 subtype.

Chemistry

The synthesis of the quinazoline-sulfonamide derivatives is outlined in Scheme 1. Starting from 2,4-dichloroquinazoline **9**, sequential amination with the corresponding amine for the 4-position, followed by the amine for the 2-position led to compounds **11a**–**j**. The amine intermediate **15a** was obtained from *trans*-4-aminomethyl-cyclohexyl-carboxylic acid (**14**) by sulfonylation with 1-naphthylsulfonylchloride, amide formation via the mixed anhydride with ammonia followed by reduction of the amide group with BH_3-THF. Standard procedures were applied for the one carbon contraction and extension of the semi-rigid spacer starting from the same precursor **14**.

Results and Discussion

On the basis of the low molecular weight quinazoline hits **1**–**3**, a series of substituted 2,4-diamino quinazolines were synthesized using traditional medicinal chemistry and applying the decision tree by Topliss[14] (**11a**–**e**) followed by a Hansch analysis[15] for the optimization of the 2-arylamino substituent. High binding affinity is predicted for compounds bearing substituents that possess a large π- and σ-value like *p*-NEt_2 in **11g** of Table 1. At this point in time the results of the combinatorial effort became available suggesting that an aryl-sulphonamide moiety as encountered in **6** and **7** is an important component of the pharmacophore for Y_5 affinity. Therefore, we explored the effect of H-bonding acceptor headgroups at the 2-aryl- and 2-cyclohexyl-moieties. Substitution of the methyl group of **11b** ($IC_{50} = 200$ nM) in the *para*-position by attachment of a sulfonamide (**11h**) or sulfone (**11i**) moiety improved affinity >100-fold to the sub-nanomolar range, whereas other H-bond acceptors (e.g., $P(O)(OEt)_2$ **11j**) were less optimal. In the cyclohexyl series compounds **12f** and **12g** possessing a sulfonamide moiety in which the sulfonyl and NH had been reversed as compared to compound **11h** showed

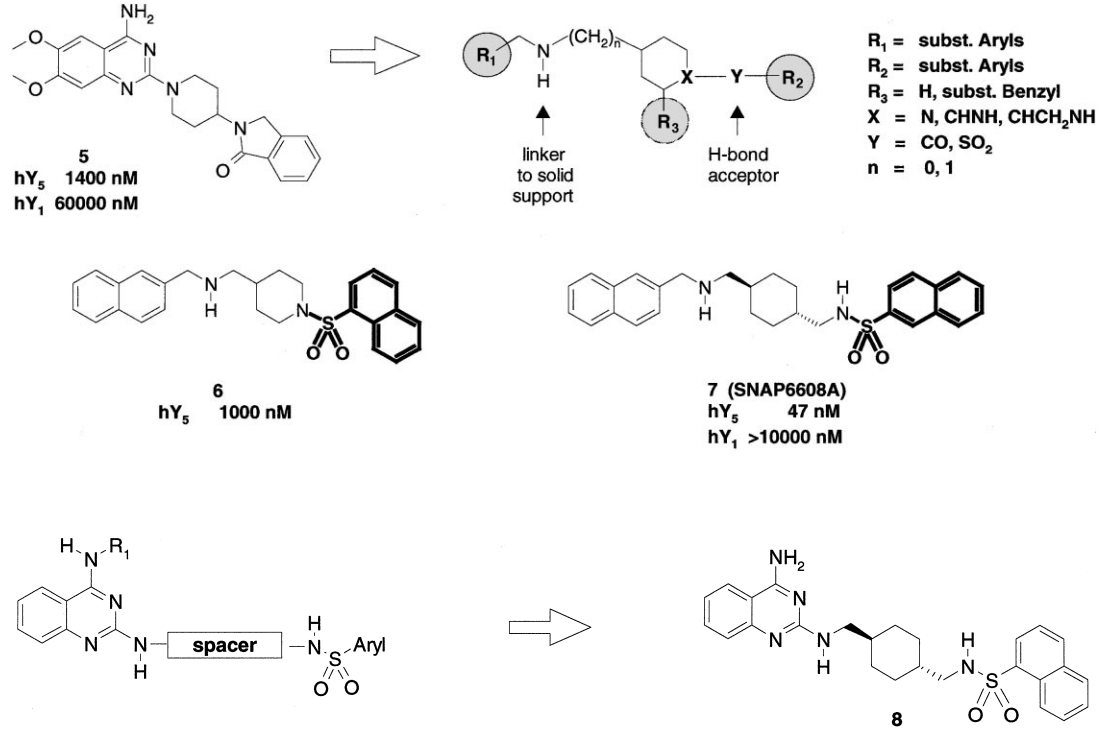
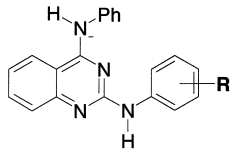
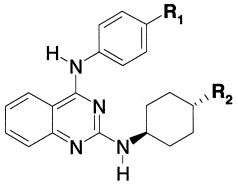


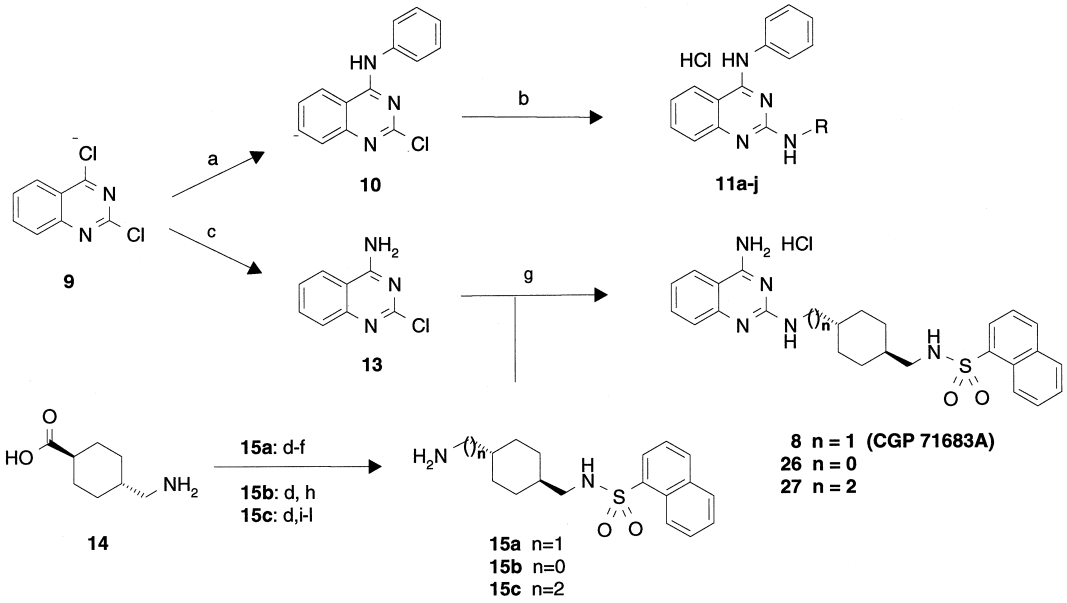
Table 1.





Compound	R	IC_{50} (nM)[a]	Compound	R_1	R_2	IC_{50} (nM)[a]
11a	3,4-Cl_2	270	**12a**	Cl	$CH_2NHCOMe$	390
11b	4-Me	200	**12b**	Cl	$CH_2NHCOPh$	310
11c	4-Cl	100	**12c**	Cl	CH_2NHMe	510
11d	H	80	**12d**	Cl	$CH_2N(Me)COPh$	250
11e	4-MeO	33	**12e**	Cl	$CH_2N(Me)COMe$	58
11f	4-C_6H_{11}	20 (2)[b]	**12f**	H	$CH_2NHSO_2Ph(4\text{-}Me)$	4
11g	4-NEt_2	4 (2)[b]	**12g**	H	CH_2NHSO_2Me	2
11h	4-$CH_2SO_2NMe_2$	0.9	**12h**	H	H	50
11i	4-CH_2SO_2Et	0.6	**12i**	H	OCOMe	6
11j	4-$CH_2P(O)(EtO)_2$	33	**12j**	H	OCOPh	400

[a]Binding affinities to Y_5-receptor subtype stable expressed in LM(tk-) cells ($n = 3$–6), values determined at Novartis Pharma AG.
[b]Predicted IC_{50} value by the Hantsch equation: $-\log(IC_{50}) = 0.18\ \pi^2 - 1.65\sigma + 0.01\ Es + 1.00$.



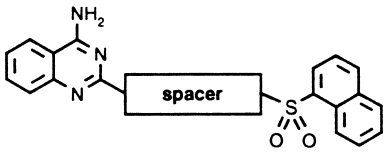
Scheme 1. Reagents and conditions: (a) Ph-NH_2, DIPEA, iPrOH, reflux, 97%; (b) R-NH_2, isopentanol, 155 °C; 48%; (c) NH_3, MeOH, rt, 100%; (d) (1-$C_{10}H_8$)SO_2Cl, 1 N NaOH, rt, 80%; (e) (i) $ClCO_2Et$, Et_3N, THF; (ii) aq NH_3, 90%, (f) BH_3-THF, THF, reflux, 90%; (g) (i) isopentanol, 120 °C, (ii) 4N HCl/dioxane, CH_2Cl_2, 58–73%; (h) (i) $ClCO_2Et$, Et_3N, THF, (ii) NaN_3, H_2O, (iii) toluene, reflux, (iv) aq 4N HCl, reflux, 68%; (i) $LiAlH_4$, THF, reflux, 80%; (j) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 90%; (k) NaCN, DMF, 50 °C, 99%; (l) H_2, Ra-Ni, NH_3-MeOH, rt, 89%.

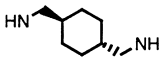
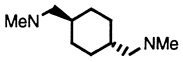
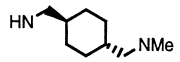
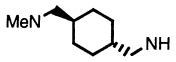
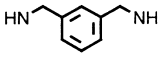
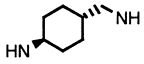
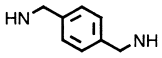
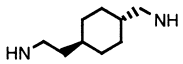
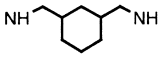
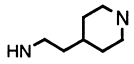
equally high affinities. The aryl-substituted sulfonamide **12f** showed a somewhat weaker affinity compared to the methyl analogue **12g**. These results suggest that the presence of the sulfonyl group or an equally well positioned carbonyl group as in analogue **12i** are important for receptor binding possibly through H-bonding to H398 identified by site-directed mutagenesis.[16]

A more detailed exploration of the distance requirements to link the two pharmacophoric elements 2,4-diamino-quinazoline **4** and the sulfonamide moiety together, is depicted in Table 2. Compounds **16**–**18** illustrate that long linear spacers are superior to short restricted ones (**19**–**21**) and semi-rigid spacers of variable length (**8**, **26**, **27**) are optimal. *N*-Methylation as in **23**–**25** resulted in a drastic drop in affinity indicating that the NH function might act as an H-bond donor.

The superimposition of the low-energy conformations of **11h** (phenyl spacer), **12g** (cyclohexyl spacer) and **8** (methyl-cyclohexyl spacer) is shown in Figure 1. The good overlap of the equally potent compounds point to a common pharmacophore: the hydrophobic element and the H-bond donor/acceptor principle of the quinazoline, the H-bond acceptor of the sulfonamide moiety and the hydrophobic element of the spacer. In the phenyl- and the cyclohexyl-spacer series, an additional hydrophobic pocket is occupied by the 4-phenylamino-

Table 2. SAR of the spacer



Compound	Spacer	IC_{50} (nM)[a]	Compound	Spacer	IC_{50} (nM)[a]
16	HN-$(CH_2)_6$-NH	28	**8** CGP71683A		2.9
17	HN-$(CH_2)_7$-NH	44	**23**		710
18	HN-$(CH_2)_8$-NH	46	**24**		110
19[b]		4900	**25**		16
20		380	**26**		2.7
21		290	**27**		2.9
22[c]		38	**28**		51

[a]Binding affinities to Y_5-receptor subtype stable expressed in LM(tk-) cells ($n = 3$–6), values determined at Novartis Pharma AG.
[b]Racemic.
[c]Racemic *cis*/*trans* ratio = 4:1.

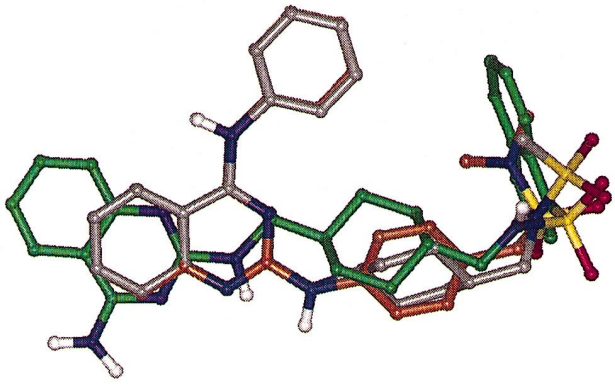


Figure 1. Superimposition of **11h** (in silver), **12g** (in gold) and **8** (CGP71683A, in green).

substituent, whereas in the methyl-cyclohexyl spacer series, this pocket is not used and a different pair of nitrogen atoms of the quinazoline moiety make up the H-bond donor/acceptor principle.

The loss of hydrophobic interaction is probably compensated by the additional hydrophobic substituent attached at the sulfonamide.

The best compounds of these series were selected for in vivo studies and tested in the rat food deprivation model.[11] Compound **8** was selected for further concept validation studies based upon its activity and Y-type selectivity (hY_5, rY_5, [IC_{50}±SEM; nM] 2.9±0.16, 1.4±0.09 and hY_1, hY_2, hY_4 [IC_{50}±SEM; nM] 8370±530, 1890±260, 5740±230). Furthermore, **8** was active in the following functional assays:[11] the NPY-induced intracellular Ca^{2+} mobilization ($K_b = 5.8 \pm 1.2$ nM) and in an assay of the reversal of NPY-induced inhibition of forskolin stimulated cAMP production ($K_b = 1.9 \pm 0.6$ nM) in LM(tk-) cells.

In summary, key pharmacophoric elements of hits identified by screening of biased libraries prepared in solution and on solid support and 3-D-database mining were combined and optimized. This resulted in the design of **8** (CGP71683A), the first selective, nanomolar Y_5 antagonist. This new compound helped to elucidate the Y_5-subtype involvement in mediating food intake induced by NPY.[11]

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