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Discovery and SAR of potent, orally available and brain-penetrable 5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen- and 4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen derivatives as neuropeptide Y Y5 receptor antagonists

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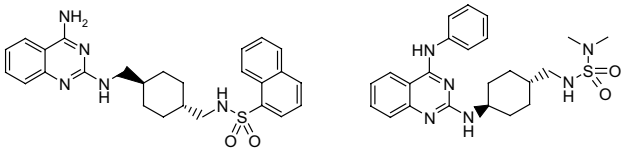
Abstract—Combination of structural elements from a potent Y5 antagonist (**2**) with thiazole fragments that exhibit weak Y5 affinities followed by lead optimisation led to the discovery of (5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-yl-methyl-amino and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amino derivatives. Both classes of compounds are capable of delivering potent and selective orally and centrally bioavailable NPY Y5 receptor antagonists.

1. Introduction

Neuropeptide Y (NPY) is a 36 amino acid peptide neurotransmitter widely expressed in both the peripheral and central nervous system.[1] Cloned receptors for NPY and related family members peptide YY and pancreatic polypeptide are classified as Y-type receptors (Y1, Y2, Y4 and Y5; note there is also a Y6 receptor gene that is absent in the rat and a pseudogene in human). NPY is considered to regulate a variety of physiological processes, including vasoconstriction, nasal congestion, blood pressure, intestinal motility, anxiety, depression, pain, feeding, reproductive endocrinology, neuronal excitability and memory retention.[2] As such, receptor specific ligands modulating NPY receptor signalling may have therapeutic value.

In this report, we describe the discovery and SAR of 5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine derivatives as potent and selective orally bioavailable and brain penetrable Y5 antagonists, which may ultimately be valuable in several therapeutic areas including obesity.[3]

Previously, we reported the discovery of potent and selective Y5 antagonists **1** (CGP71683A) and **2**. Despite potent Y5 antagonistic properties these compounds exhibited only little absorption and permeability to the brain after oral administration (Fig. 1).



1 (CGP71683A) hY5 IC50: **3 nM** **2** hY5 IC50: **2 nM**

Figure 1.

Keywords: NPY Y5 antagonists; Neuropetide Y receptors.
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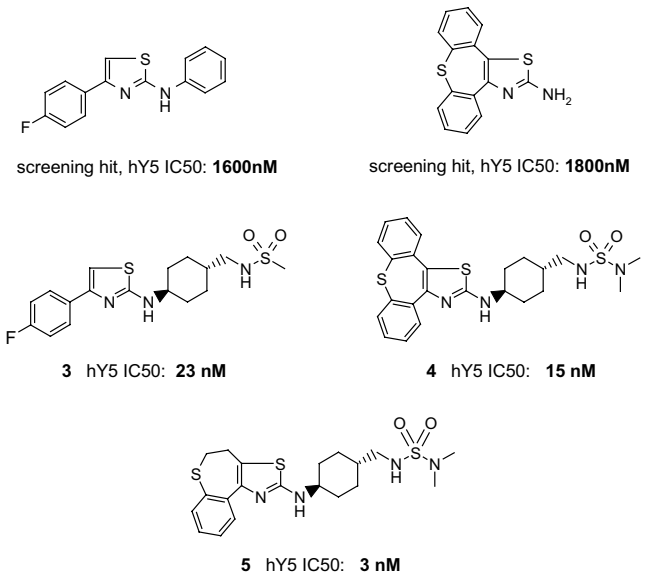


Figure 2. Binding affinities[4] of screening hits and thiazole variations.

We suspected that replacement of the quinazoline and sulfamyl residues might lead us to discover structurally novel series of compounds that possess more favourable pharmacokinetic properties. From screening in-house compound collections thiazole derivatives were obtained as weakly active Y5 antagonists (Fig. 2).

Structural variations at the thiazole scaffolds and combination with the cyclohexylmethyl–sulfamyl residue that is present in compound **2**, led to the identification of the 4-phenyl-thiazol-2-ylamino, the 1,8-dithia-3-aza-dibenzo[*e*,*h*]azulen-2-ylamino and the 4,5-dihydro-3,6-dithia-1-aza-benzo[*e*]azulen-2-ylamino derivatives **3**, **4** and **5**, respectively, as potent Y5 antagonists.

It appears that formal removal of one of the phenyl groups from the ring system of **4** is responsible for the 5-fold increase in Y5 receptor affinity of the resulting 'tricyclic thiazole' (5,6-dihydro-4*H*-3-thia-1-aza-benzo-[*e*]azulene)derivative **5**. Consequently **5** was chosen as a lead compound for further optimisation work. Structural modifications aiming at the elimination of the sulfur in the seven-membered ring and at the replacement of the sulfamyl residue, both potential metabolic weak points, led to the identification of the following tricyclic thiazole derivatives: (4-amino-cyclohexylmethyl)-(5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-amines (**A**), (5,6-dihydro-4*H*-3-thia-1-aza-benzo-[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amines (**B**) and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amines (**C**) as potent, highly selective and orally bioavailable brain-penetrable Y5 antagonists (Fig. 3).

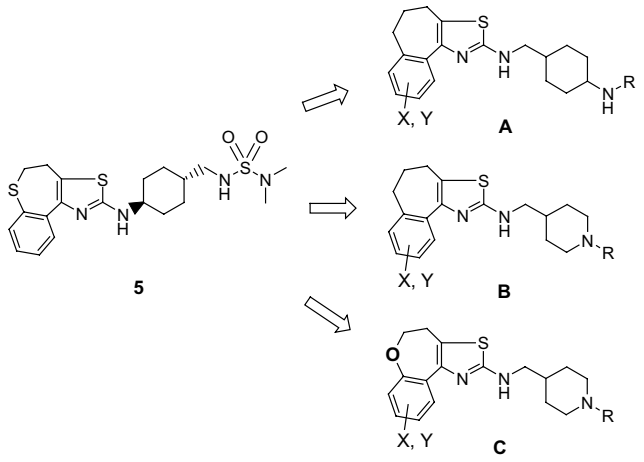
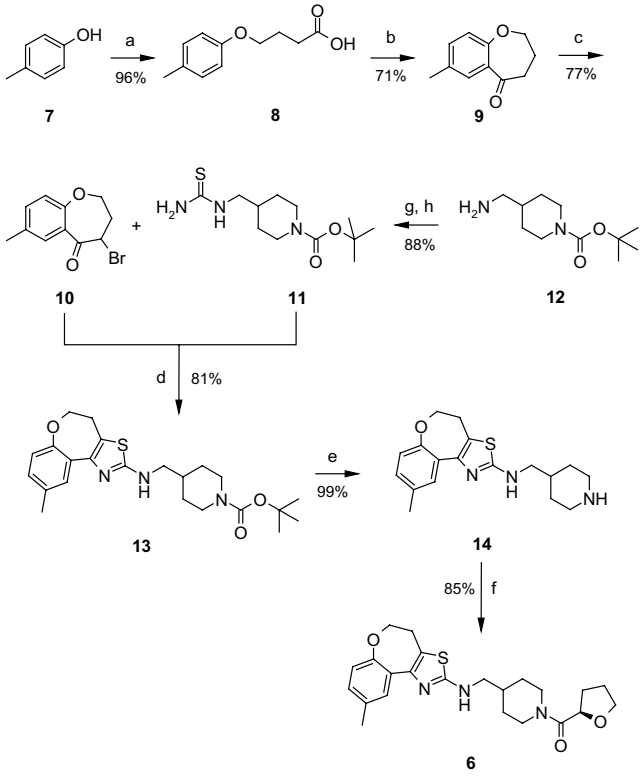


Figure 3. Tricyclic thiazole derivatives.

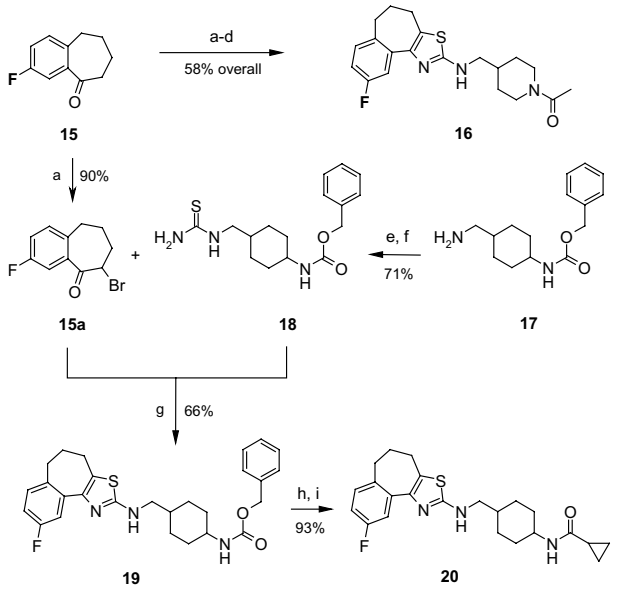
2. Chemistry

The syntheses of the tricyclic thiazole derivatives **6** (Scheme 1) **16** and **20** (Scheme 2) are illustrative for the preparation of all the various thiazole amides.



Scheme 1. Reagents and conditions: (a) NaOMe, γ-butyrolactone, 1,2-dichlorobenzene, EtOH, 150 °C; (b) PPA, 110 °C; (c) Br_2, Et_2O, 25 °C; (d) DIPEA, EtOH, reflux; (e) TFA, CH_2Cl_2, 25 °C; (f) (*R*)-(+)-tetrahydro-2-furoic acid, EDC, pyridine, CH_2Cl_2, 25 °C; (g) PhCONCS, THF, reflux; (h) K_2CO_3, MeOH/H_2O 3:1, reflux.

Compound **6** was prepared starting from *p*-cresol. Alkylation of the oxygen with γ-butyrolactone followed by cyclisation in the presence of polyphosphoric acid led to benzo[*e*]oxepinone **9**. Bromination of this compound and subsequent reaction of the resulting bromide **10** with the thiourea derivative **11** yielded the tricyclic thiazole derivative **13**. Boc deprotection followed by acylation of the piperidine nitrogen led to the final product {4-[(9-methyl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]-azulen-2-ylamino)-methyl]piperidin-1-yl}-((*R*)-tetrahydro-



Scheme 2. Reagents and conditions: (a) Br_2, AcOH, 25 °C; (b) **11**, DIPEA, EtOH, reflux; (c) 5 N HCl in *i*PrOH, 25 °C; (d) acetyl chloride, NEt_3, CH_2Cl_2, 0–25 °C; (e) PhCONCS, THF, reflux; (f) K_2CO_3, MeOH/H_2O 3:1, reflux; (g) DIPEA, EtOH, reflux; (h) TMS–I, acetonitrile, 0–25 °C; (i) cyclopropane carboxylic acid chloride, NEt_3, CH_2Cl_2, 0–25 °C.

furan-2-yl)-methanone **6**. Thiourea derivative **11** was prepared in two steps from the aminomethyl-piperidine derivative **12** and phenylisocyanate as described in Scheme 1.

Starting from the commercially available benzosuberone derivative **15**, **16** (1-{4-[(9-fluoro-5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-ylamino)-methyl]-piperidin-1-yl}-ethanone) was prepared using the same reaction sequence as described for the preparation of **6**. Also the preparation of aminocyclohexyl derivatives such as **20** was carried out using the same reaction sequence as described for the preparation of **6** and **16**. However, instead of using thiourea derivative **11** (4-thioureidomethyl-cyclohexyl)-carbamic acid benzyl ester **18** was used (Scheme 2).

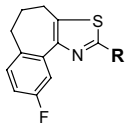
3. Results and discussion

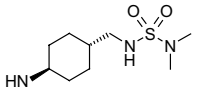
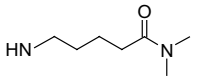
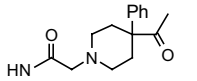
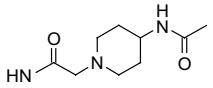
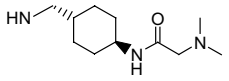
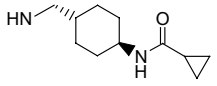
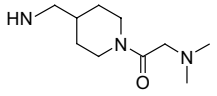
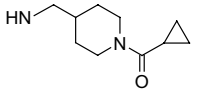
In an attempt to identify a replacement residue for the sulfamyl–cyclohexyl moiety in **5** a variety of selected residues were attached to the tricyclic thiazole part. Selected residues consist of a carbon linker with an amidic H-bonding acceptor functionality instead of the undesired sulfonamide (or sulfamyl acceptor group).

As can be seen from the Y5 receptor binding data shown in Table 1 compounds with either 4-amino-cyclohexyl-amide or even better 4-aminomethyl-piperidine-amide moieties display Y5 receptor affinities that are as potent as the sulfamyl derivative **5**.

In order to further explore the potential of the 4-amino-cyclohexyl-amide and of the 4-aminomethyl-piperidine-amide series we prepared additional derivatives. A variety of acyl residues were chosen in view of producing final compounds that should possess drug like properties ($c\log P < 5$, $MW < 500$, $PSA < 100$ Å, $SumCa < 10$).

Table 1. In vitro binding affinities[4] of tricyclic thiazole derivatives to hY5 receptors



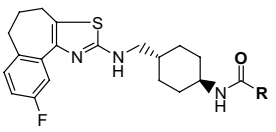
Compound #	R	HY5 binding IC_{50} (nM)[a]
5		3
21		25
22		15
23		78
24		81
25		6
26		4
27		2

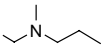
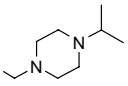
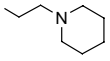
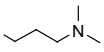
[a] Values are means of three experiments.

The results are summarised in Table 2. As can be seen from the Y5 receptor affinities it appears that in general lipophilic amide substituents at the cyclohexyl-amino group are well tolerated and lead to potent Y5 antagonists. An increase in water solubility and a decrease of the lipophilicity was achieved by the introduction of additional heteroatoms, that is, nitrogen. However, the resulting compounds exhibit a significantly lowered binding affinity to the Y5 receptor as exemplified by **35**–**38**.

A different picture is observed in the 4-aminomethyl-piperidine-amide series. As shown in Table 3 a much larger variety of amide substituents at the piperidine

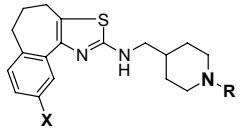
Table 2. In vitro binding affinities[4] of compounds to hY5 receptor



Compound #	R	hY5 binding IC_{50} (nM)[a]
29	–OMe	2
30	–*n*Bu	6
20		6
31		6
32		15
33	NH-CO-R = 	5
34		6
35		29
36		210
37		150
38		290

[a] Values are means of three experiments.

Table 3. In vitro binding affinities[4] of tricyclic thiazoles to hY5 receptors



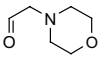
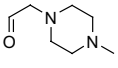
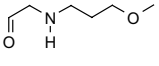
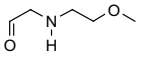
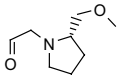
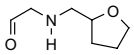
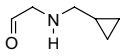
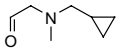
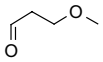
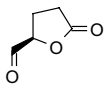
Compound #	X	R	hY5 binding-IC_{50} (nM)[a]
39	H		6
40	Cl		7
41	F		4
42	F		2
43	F		24
44	F		15
45	F		2

Table 3 (*continued*)

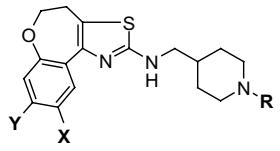
Compound #	X	R	hY5 binding-IC_{50} (nM)[a]
46	F		3
47	F		6
48	F		6
49	F		3
16	F		2
50	F		2
51	F		20
52	F		4
53	F		2
54	F		2
55	F		4
56	F		1
57	F		2
58	F		2

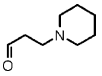
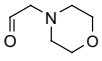
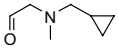
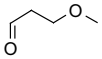
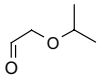
[a] Values are means of three experiments.

nitrogen is tolerated. In contrast to the 4-amino-cyclohexyl-amide series nonpolar as well as amide substituents with additional polar (nitrogen or oxygen) functionalities are tolerated and compounds with highly potent Y5 receptor affinities are obtained from the 4-aminomethyl-piperidine-amide series. Replacement of the fluoro substituent at the phenyl ring of **41** with either hydrogen or chlorine leads to equipotent compounds **39** and **40**.

In an attempt to further decrease the lipophilicity and to increase water solubility of the resulting compounds an oxygen atom was introduced into the seven-membered ring. When compared to the carbocycle analogues this alteration unfortunately led to a more or less pronounced decrease in potency of the resulting compounds depending on the amide residue and on the substituent(s) on the phenyl ring of the tricyclic thiazole part. As can be seen from the data in Table 4, surprisingly in selected cases only, that is, compounds **79** and **81**, the tetrahydrofuran substituted analogues are as potent as the corresponding carbocycle analogues (**57**, **58**). The influence of a variety of substituents on the phenyl ring of the thiazole on receptor affinity of the resulting compounds is also shown in Table 4. Methyl (e.g., **69**) appears to be a good replacement for the fluoro substituent (**68**) producing even more potent compounds in some cases, whereas a methoxy group (**67**) leads to a slight reduction in the Y5 affinity of the corresponding compound. Introduction of a second halogen substituent is not very well tolerated and leads to a significant loss of binding affinity of the resulting

Table 4. In vitro binding affinities[4] of oxygen containing tricyclic thiazoles to hY5 receptor



Compound #	X	Y	R	hY5 binding IC_{50} (nM)[a]
59	F	H		71
60	OMe	H		2460
61	F	H		41
62	F	H		18
63	Me	H		25
64	F	H		69
65	F	F		38
66	Cl	F		20
67	OMe	H		17
68	F	H		7
69	Me	H		7
70	Me	H		5
71	Cl	F		13
72	F	Cl		99
73	F	F		40
74	F	H		37
75	F	H		22
76	F	H		28
77	Me	H		18
78	Me	H		21
79	F	H		19
80	Me	H		17
81	F	H		5
6	Me	H		5

[a] Values are means of three experiments.

Table 5. In vitro binding affinities[4] to Y receptors and Y5 antagonistic properties of (5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine derivatives

#	hY5 IC_{50} (nM)[a]	hY5 $[Ca^{2+}]_i$ response IC_{50} (nM)[a]	rY5 IC_{50} (nM)[a]	hY1 IC_{50} (μM)[a]	hY2 IC_{50} (μM)[a]	hY4 IC_{50} (μM)[a]
16	2	254	ND	>30	>30	>30
68	7	100	6	>30	>30	>30
70	5	61	ND	>30	>30	>30
6	5	40	2.9	>30	>30	>30

[a] Values are means of three experiments.

Table 6. Concentrations of (5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine derivatives in rat plasma and hypothalamus after oral dosing at 30 mg/kg p.o.[5]

#	2 h Plasma (μg/mL)	6 h Plasma (μg/mL)	2 h Hypothalamus (μg/g)	6 h Hypothalamus (μg/g)
41	0.24	0.13	1.17	0.62
16	0.95	0.07	3.70	0.29
56	0.54	0.14	1.22	0.44
57	1.60	0.32	6.69	1.33
58	0.32	0.22	0.86	0.67
68	0.74	0.07	2.23	0.26
70	0.84	0.33	2.42	0.88
79	0.93	0.14	5.48	0.64
81	0.97	0.39	2.44	1.08
6	0.87	0.26	1.46	0.40

compounds as can be observed in derivatives **65**, **66** and **71**–**73**, which exhibit 3–20-fold less potent Y5 receptor affinities in comparison to the mono halogenated compound **68**.

The data of the exemplified compounds given in Table 5 show, that these are functional Y5 antagonists[4] and in addition are very selective for the Y5 receptor as no appreciable affinity to human Y1, Y2 or Y4 receptors can be observed. Also, selected members of this tricyclic thiazole class of Y5 antagonists (**6**, **68** and **76**) did not have any significant activity at over 30 receptors and ion channels (<50% inhibition at 1 μM).

In order to assess the potential of the (5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amine classes as orally active and brain penetrable NPY Y5 antagonists, plasma and hypothalamus concentrations at 2 and 6 h after oral administration of a 30 mg/kg dose to rats were determined.[5] The results are summarised in Table 6. The data shows that after oral administration both, the (5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amino derivatives and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amino derivatives, appear to be well absorbed and reach moderate to high plasma levels and high to very high hypothalamus levels 2 h after administration. 6 h after administration both plasma and hypothalamus levels decreased by a factor of 2–4 in the case of compounds **41**, **56**–**58**, **70**, **79**, **81** and **6**. An apparently higher clearance can be observed for compounds **16** and **68**. Several compounds, that is, **70** with 2 h and 6 h hypothalamus levels of 2.42 and 0.88 μg/g, respectively, clearly demonstrate that the tricyclic thiazole series of Y5 antagonists is capable of delivering potent and selective orally and centrally bioavailable compounds.

In addition, protein binding data[6] obtained from compound **6** (3.6% free, rat) indicates that this compound is suitable for in vivo studies. Compound **6** was taken into further pharmacological evaluation and orally administered **6** (30 mg/kg) was actually shown to completely inhibit feeding induced by a selective NPY5 agonist (i.c.v.) in rats. However, similar to the negative results previously reported,[3n,q] **6** (30 mg/kg, p.o.) also did not reduce free- or fasting-induced feeding in rats.[7]

4. Summary

We have shown that initial combination of structural elements from a potent Y5 antagonist (**2**) with thiazole fragments that exhibit weak Y5 affinities followed by lead optimisation led to the discovery of (5,6-dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amino and (4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen-2-yl)-piperidin-4-ylmethyl-amino derivatives. Both classes of compounds are capable of delivering potent and selective orally and centrally available NPY Y5 receptor antagonists. Despite an attractive pharmacokinetic profile, and inhibition of Y5 receptor agonist mediated feeding in rats following oral administration, compounds such as **6** did not reduce free- or fasting-induced feeding in rats, which indicates that the Y5 receptor alone has no significant role in feeding in these models.

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