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5-(2′-Pyridyl)-2-aminothiazoles: Alkyl amino sulfonamides and sulfamides as potent NPY_5 antagonists

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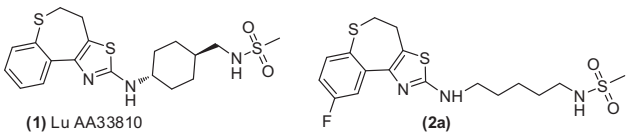
ABSTRACT

Synthesis, SAR and physico-chemical properties of an alkyl aminothiazole series **8** and **16** are described. 2-Pyridylaminothiazole based compounds such as **8c** and **16a** exhibit high affinity at the NPY_5 receptor with desirable *c*Log*P*s and solubilities. However, they also suffer from high in vitro and in vivo clearance. Compound **16a** partially inhibits the feeding behavior elicited by i.c.v. injection of the selective NPY_5 agonist [cPP^{1-7}, NPY^{19-23}, Ala^{31}, Aib^{32}, Gln^{34}]-human pancreatic polypeptide polypeptide (cPP).

Neuropeptide Y (NPY) is widely distributed throughout the central and peripheral nervous systems[1] and modulates numerous physiological processes (e.g., appetite,[2–4] metabolism and mood).[5] The stimulation of feeding behavior by NPY is linked to activation of hypothalamic NPY_5 receptors.[6,7] NPY_5 receptors are widely distributed in the limbic region[8a] and along the hypothalamus-pituitary-adrenal gland (HPA) axis.[8b] Recently two NPY_5 antagonists from Merck and Shionogi, MK-0577[9a] and Velneperit,[9b] respectively, have advanced to human clinical trials where both compounds reportedly decreased body weight relative to placebo. Limbic Y5 receptor expression potentially makes the target of interest for mood disorders. The NPY_5 antagonists Lu AA33810 and L-152804 have been shown to be efficacious in preclinical models of depression[10a] and addiction,[10b] respectively.

Recently we reported compound Lu AA33810, **1** as a highly potent and selective NPY_5 antagonist which exerts anxiolytic and anti-depressant like effects in rat behavioral models.[10a,c] However, this compound suffers from poor solubility hampering further development. In an attempt to improve the solubility we investigated modifications of the cycloalkyl linker and aryl groups of this scaffold. Here we report that linear alkylamino thiazole derived compounds are equipotent NPY_5 antagonists with improved *c*Log*P* and solubility properties. Detailed SAR studies and synthesis of linear alkyl aminothiazoles (**8** and **16**) are discussed.

Compound **1**, Lu AA33810 exhibits high affinity at the NPY_5 receptor with K_i 1.5 nM. While its *c*Log*P* is in the desirable range for a CNS drug (*c*Log*P* = 4.32), it suffers from unacceptably low solubility (0.04 μg/mL at pH 7.4, Fig. 1).[10c] The compound is highly brain permeable despite its poor solubility. We hypothesized that the poor solubility could arise due to the rigid nature of the tricyclic dihydrobenzo[2,3]thiepino[4,5-*d*]thiazole and the cyclohexyl linker. Recently we reported that the cyclohexyl linker could be replaced with a linear alkyl chain of four to six carbon atoms without losing targeted affinity.[10c] For example, the dihydrobenzo[2,3]thiepino[4,5-*d*]thiazole analog with a pentylamine linker, compound **2a** (K_i = 1.7 nM), is equipotent like Lu AA33810. However the solubility remains low. We anticipated that we could



(1) Lu AA33810
hNPY5 K_i 1.5 nM
cLogP 4.32
Solubility 0.04 μg/mL

(2a)
hNPY5 K_i 1.7 nM
cLogP 4.03
Solubility 1.40 μg/mL

Figure 1. Tricyclic NPY_5 antagonists.

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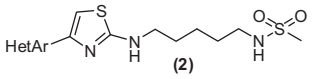
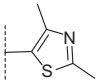
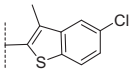
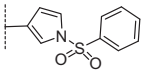
Table 1
SAR of heteroaryl modification of compound **2** analogs

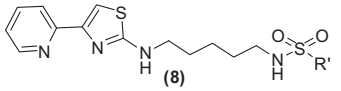


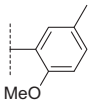
Compound	HetAr	hNPY5 K_i[a] (nM)	Solubility[b] (μg/mL)	*c*Log*P*
2b		530	>240	1.98
2c		170	1.2	3.05
2d		80	1.7	2.84
2e		150	1.1	1.97
2f		4300	ND	1.80
2g		360	5.5	5.36
2h		740	1.6	3.40

[a] For a description of the binding assay (K_i) see Refs. 11,12 and 13. The K_i value is reported as average of $n \geqslant 3$ determinations. $hNPY_5$ = human cloned NPY_5 receptor. ND = Not determined.
[b] The solubility (μg/mL) was measured from solid sample.

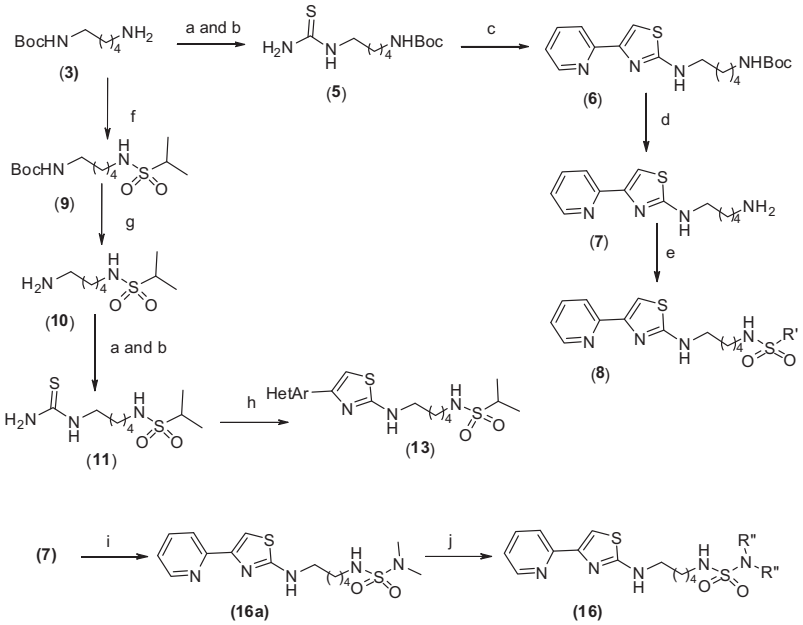
improve the solubility by opening the dihydrobenzo[2,3]thiepine ring and maintain NPY_5 potency by appropriate modification of the aryl rings and sulfonamide. In our first approach, the dihydrobenzo[2,3]thiepine moiety of compound **2a** was replaced with several heterocycles while keeping the methane sulfonamide moiety constant (Table 1). The study resulted in compounds **2b–2h** with low to moderate potency at the NPY_5 receptor. The pyridyl analog **2b** stood out as having dramatically improved solubility and

Table 2
The in vitro NPY5 affinity and solubility profiles of compound **8** analogs



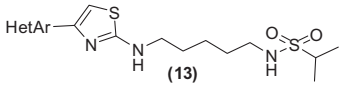
Compound	R^1 hNPY5 K_i[a] (nM)	Solubility[b] (μg/mL)	Compound
2b	Me	530	>240
8a	CF_3	109	2.6
8b	Et	150	ND
8c	*i*-Pr	12	233
8d	*c*-Pr	45	95
8e	*s*-Bu	49	15
8f	*c*-PenCH_2	250	ND
8g	*c*-Hex	110	1.6
8h	4-Piperidine	2700	>240
8i	*N*-Cbz-4-Piperidine	240	2.1
8j		8.0	5.1
8k		1.9	10.0
8l		31	4.40
8m		1122	ND
8n		159	413
8o		19	26
8p		3.4	74.0

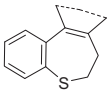
[a] For the binding assay description, see Refs. 11,12 and 13.
[b] The solubility measurements, see footnote in Table 1. ND = Not determined.



Scheme 1. Reagents and conditions: (a) BzNCS, THF, rt, 90%; (b) K_2CO_3, MeOH–H_2O, 83%; (c) 2-PyCOCH$_2$Br (**12a**), Et_3N, EtOH, reflux, 70%; (d) 10%TFA in DCM, rt, quant.; (e) R′SO_2Cl, DCM, Et_3N, rt, 45–80%; (f) *i*-PrSO_2Cl, DCM, Et_3N, rt, 90%; (g) 4 M HCl, DCM, rt, 88%; (h) HetArCOCH$_2$Br or HetArCOCH$_2$Cl (**12b–12f**), Et_3N, EtOH, reflux, 70–94%; (i) Me_2NSO_2Cl, DCM, Et_3N, rt, 45–65% and (j) R″R″NH, dioxane, 24 h, heat, sealed tube, 30–50%.

Table 3
SAR of sulfonamide analogs and its NPY5 affinity, solubility and in vitro metabolic clearance data



Compound	HetAr	hNPY5 K_i[a] (nM)	Solubility[b] (μg/mL)	hCl_{int}[c] (L/min)	rCl_{int}[c] (mL/min)
8c		12	233	2.2	72.0
13a		515	207	ND	ND
13b		1851	341	ND	ND
13c		3.7	30	5.4	87.0
13d		34	0.1	ND	ND
13e		2.0	0.1	ND	ND

[a] For the binding assay description, see footnote in Table 1.
[b] The solubility measurements, see footnote in Table 1.
[c] The hCl_{int} and rCl_{int} are human (L/min) and rat (mL/min) intrinsic clearances, respectively, and the clearances were determined according to Obach et al.[14] The rat and human maximum liver blood flow corresponds to 20 mL/min and 1.5 L/min,

*c*Log*P*. We therefore chose analog **2b** for further optimization to improve NPY_5 affinity and its physico-chemical properties.

Compounds **8a–8p**, **13a–13d** and **16a–16g** were prepared according to the reactions depicted in Scheme 1. The thiourea intermediates **5** and **11** were synthesized from commercially available *N*-Boc protected 1,5-diaminopentane **3** as shown in Scheme 1.[13] The key intermediate *N*-Boc-aminopentyl thiourea **5** was prepared by treatment of mono *N*-Boc protected diaminopentane with benzoyl isothiocyanate in THF to afford *N*-benzoyl thiourea **4** (90%) which was hydrolyzed to give **5** (83%). Coupling of thiourea **5** with (α-bromoacetyl)-2-pyridine (**12a**) afforded *N*-Boc aminopentylaminothiazole **6** which upon deprotection gave amine **7** as its TFA salt. Treatment of amine **7** with alkyl, aryl and heteroaryl sulfonyl chlorides afforded the sulfonamide analogs **8a–8p** in good yield.

Alternatively, the thiourea intermediate **11** was synthesized in a sequence of four steps. The mono protected *N*-Boc diaminopentane (**3**) was treated with isopropyl sulfonyl chloride in the presence of Et_3N to afford the sulfonamide analog **9** (90%), which upon deprotection using 4 M HCl afforded the amine **10** (88%) as its HCl salt. The amine **10** was readily converted into the *N*-(isopropylsulfonamido)pentyl thiourea (**11**, 92%) by following the above sequence as for the intermediate **5**. The α-haloketones **12a–12f** were prepared by bromination of the corresponding ketones or prepared from the corresponding carboxylic acid in a three steps sequence (scheme not-shown). Heteroaryl carboxylic acids were converted into their acid chlorides by reaction with oxalyl chloride in CH_2Cl_2. Treatment of acid chlorides with 1 M $TMSCHN_2$ afforded the corresponding α-diazoketones which upon treatment with HBr or HCl afforded the desired α-haloketones.[13] Condensation of the heteroaryl α-haloketones **12b–12f** and (*N*-isopropylsulfonamido) pentylthiourea (**11**) in the presence of base under refluxing conditions in ethanol afforded isopropyl sulfonamide analogs **13a–13e** in good yield.

Replacement of the methyl moiety in compound **2b** by a CF_3 group **8a** led to a modest improvement in NPY_5 affinity but with

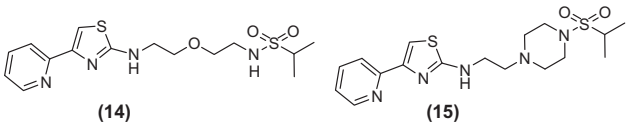


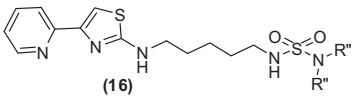
Figure 2. Heteroatom substituted linkers.

Table 4
SAR of Heteroatom substituted linker analogs data

Compound	hNPY5 K_i[a] (nM)	Solubility[b] (μg/mL)	*c*Log*P*	hCl_{int}[c] (L/min)
14	290	>1000	2.21	1.1
15	5000	480	2.93	ND

[a] For the binding assay description, see footnote in Table 1.
[b] The solubility measurements, see footnote in Table 1.
[c] The hCl_{int} refers to human (L/min) intrinsic clearance (see footnote in Table 3).
ND = Not determined.

Table 5
SAR of sulfamide analogs and its NPY5 affinity, solubility and in vitro metabolic clearance data



Compound	R″$_2$N	hNPY5 K_i[a] (nM)	Solubility[b] (μg/mL)	$hhCl_{int}$[c] ((L/min)	rCl_{int}[c] (mL/min)
16a	Me_2N	7.6	690	1.8	110
16b	NH_2	803	ND	ND	ND
16c	Et_2N	1.8	63	27	290
16d	Morpholino	38	790	2.9	44.0
16e	2,6-Dimethyl morpholino	75	55	11	74.0
16f	*N*-Me piperazino	170	1000	2.5	120.0
16g	$(MeOCH_2CH_2)_2N$	60	530	16	150.0

[a] For the binding assay description see footnote in Table 1.
[b] The solubility measurements see footnote in Table 1.
[c] The hCl_{int} and rCl_{int} are human (L/min) and rat (mL/min) intrinsic clearances, respectively (see footnote in Table 3). ND = Not determined.

a dramatic reduction in solubility. Systematically increasing the steric bulk of the alkylsulfonamide from methyl to cyclohexyl indicated that isopropyl **8c** is the optimal size for NPY_5 affinity (Table 2). We were gratified to find that the isopropyl sulfonamide retained good solubility. Various substituted aryl and heteroaryl sulfonamides were also tolerated (**8j**, **8k**, **8l**, **8o** and **8p**). Compound **8p** was found to be equipotent with the isopropyl sulfonamide analog **8c** however, it was limited by high human in vitro clearance (hCl_{int} = 27 L/min).

Keeping the isopropyl sulfonamide constant we next turned our attention to optimizing the heteroaryl group at the C-5 position of the thiazole ring (Table 3). Replacement of the 2-pyridyl moiety by a 3-pyridyl or substituted 2-pyrazinyl or dimethyl thiazole moiety led to a dramatic loss of NPY_5 affinity (**13a, 13b** and **13d**). On the other hand, replacement of the 2-pyridyl moiety with a 3-thienyl or dihydrobenzo[2,3]thiepine moiety improved the NPY_5 affinity (**13c** and **13e**). These analogs however, suffered from a disappointing loss in solubility.

Modification of the linear alkyl linker by heteroatom substitution such as compounds **14** and **15** depicted above (Fig. 2, Table 4) improved the solubility but diminished NPY_5 affinity.

Replacement of the sulfonamide with various sulfamides was also investigated. Compounds **16a** and **16c** were synthesized by

Table 6
Summary of data for selected compounds data[15]

Compound	NPY_5 K_i[a] (nM)	*c*Log*P*	Sol[b] (μg/mL)	hCl_{int}[c] (L/min)	rCl_{int}[c] (mL/min)	CL_p[d] (L/h/kg)	V_{ss}[e] (L/kg)	%*F*[f]
8c	12	2.82	233	2.2	72	23	22	49
16a	7.6	1.84	690	1.8	110	8.4	47	26
1	1.4	4.32	0.04	2.5	40	1.1	3.3	92

[a] For the binding assay description see footnote in Table 1.
[b] The solubility (Sol) measurements see footnote in Table 1.
[c] The hCl_{int} and rCl_{int} are human (L/min) and rat (mL/min) intrinsic clearances, respectively (see footnote in Table 3).
[d] CL_p = plasma clearance (L/h/kg).
[e] V_{ss} = volume of distribution at steady state (L/kg).
[f] %*F* = absolute oral bioavailability in rats.

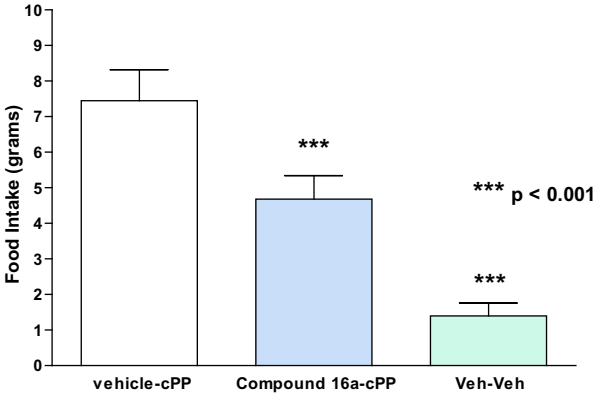


Figure 3. Effect of compound **16a** on 1 h food intake in response to cPP.[16] Male Sprague Dawley rats received 0.6 nmol of cPP 1 h after administration of compound **16a** (3 mg/kg, po) in 20% cyclodextrin vehicle or vehicle alone. Results are presented as mean 1 h food intake (g) ±SEM from 8 to 10 animals per group. Data for each time point were expressed as food intake in grams relative to the vehicle + cPP group and analyzed with one-way analysis of variance. The Newman–Keuls test was used for post-hoc analysis.

treatment of TFA salt of the amine **7** with the corresponding dialkylaminosulfonyl chlorides as outlined in Scheme 1. On the other hand, compounds **16d–16g** were synthesized in moderate yields by heating compound **16a** and the respective amines in dioxane in a sealed tube.

Both the dimethyl **16a** and diethyl sulfamide **16c** analogs were potent at the NPY_5 receptor with significant improvements in solubility. The dimethyl sulfamide **16a** had comparable in vitro clearance with **8c** while the diethyl analog **16c** had much higher in vitro clearance presumably due to its higher lipophilicity (Table 5). Removal of the alkyl substitution **16b** or making it larger (**16d–16g**) reduced the NPY_5 affinity akin to bulkier sulfonamide analogs (**8g–8j**).

Compounds **8c** and **16a** were chosen for evaluation in rat pharmacokinetic studies (Table 6). Both analogs exhibited much higher clearance (Cl_p = 23 and 8.4 L/h/kg) than compound **1** with modest bioavailabilities (*F* = 49% and 26%). Compound **16a** was selected for further profiling over **8c** because of its high solubility. Profiling of compound **16a** revealed that the compound is selective among NPY subtypes and did not display cross-reactivity when tested against an in-house panel of 18 recombinant GPCR targets. Compound **16a** is a weak inhibitor of Cytochrome P450 CYP1A2, CYP2C9, CYP2C19 and CYP3A4 (IC_{50} >7 μM), but exhibits sub micromolar inhibition of CYP2D6 (IC_{50} = 950 nM). In rats, compound **16a** exhibits low exposure in the brain after 10 mg/kg, po dosing at 4 h (brain = 12 ng/g; plasma = 24 ng/mL). Compound **16a** partially blocked the increase in food intake elicited by intracerebrovascular (i.c.v.) administration of the NPY_5 agonist [cPP^{1-7},NPY^{19-23},Ala^{31},Aib^{32},Gln^{34}]-human pancreatic polypeptide polypeptide (cPP) at a dose of 3 mg/kg, po (~37% reduction, Fig. 3) similar to that of compound **1**.[10a,c] Pharmacokinetic analysis of satellite animals from this study indicated that brain and plasma levels at this dose at the time of the experiment are 4 ng/g and 12 ng/mL, respectively (po dose). The lowest estimated free brain level (~1.2 nM, rat f_u 3.7%, rat free fraction from brain homogenate) corresponding with efficacy is consistent with the rat Y5 potency (K_i = 5.4 nM).

In summary, we have shown that opening the dihydrobenzo[2,3]thiepine and cyclohexyl rings of compound **1** and re-optimization of the aryl and sulfonamide regions resulted in compounds with moderate to high affinity for the NPY_5 receptor. In general, the 2-pyridyl moiety is preferred over other heterocycles. Sulfonamide **8c** and sulfamide **16a** analogs were identified as potent NPY_5 antagonists with low *c*Log*P* and improved solubility. However, the high in vivo clearance remains an issue for compounds of this type. Further optimization of 2-pyridyl thiazole analogs are in progress and will be reported in due course.

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15. The animals ($n = 2$) were dosed at 1 and 2 mg/kg iv and po, respectively, in a crossover manner following a 24 h washout period. Both jugular and carotid artery cannulated Sprague Dawley male rats with averaged body weight of 200–250 g were dosed with compounds **8c** and **16a** dissolved in 20% beta cyclodextrin, pH adjusted using methane sulfonic acid to afford a solution. The serial blood samples consist of 12 time points were collected over a 24 h post dose using an automated blood sampling device (Dilab, Lund, Sweden). The plasma were afforded by centrifugation of blood samples and the plasma concentrations were measured using an Agilent 1100 HPLC (Agilent Technologies, Palo Alto, CA) and a TSQ Quantum MS spectrometry (ThermoFinnigan, San Jose, CA) with quantitative analysis performed using Xcalibur software. The PK parameters were determined performing non-compartmental analysis of plasma concentration-time profile using WinNonlin 5.2 Software (Pharsight, Cary, NC)
16. Rats were obtained from Charles River Labs (Kingston, NY) with cannulae implanted into the lateral cerebral ventricle. Male Sprague Dawley rats received 0.6 nmol of cPP (in 0.9% saline vehicle) 1 h after administration of compound **16a** (3 mg/kg po) in 20% cyclodextrin vehicle or vehicle alone. A third group of rats received two vehicle injections (0.9% saline i.c.v. 1 h after 20% cyclodextrin po). Results are presented as mean 1-h food intake (g) ± SEM from 8 to 10 animals per group. To assess statistical significance, data for each time point were expressed as food intake in grams relative to the vehicle + cPP group and analyzed with one-way analysis of variance. The Newman-Keuls test was used for post-hoc analysis. Brain and plasma samples were obtained from a satellite group of animals ($n = 2$ per dose).