DOI: 10.1002/cmdc.201100248

Acetamide Scanning around Bicyclic Thiazoles: SAR at the H_3 Receptor

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The third histamine receptor (H_3R) is expressed mainly in the central nervous system (CNS) and regulates the release of numerous other neurotransmitters. It is highly interesting as a target for the control of CNS disorders such as excessive daytime sleepiness and cognitive disorders such as Alzheimer's disease.[1] In our medicinal chemistry investigations around this receptor, we have identified nanomolar-affinity ligands based on a phenyloxazole scaffold (Figure 1).[2] We noticed that affinity increased between isomers **I** and **II**. Starting from thiazole **III**, we embarked on a systematic comparison of rigid bicyclic thiazoles bearing the *N*-acetyl side chain in all orientations in an attempt to identify the isomer with the best properties. This isomer was then used to further explore the structure–activity relationships (SAR).

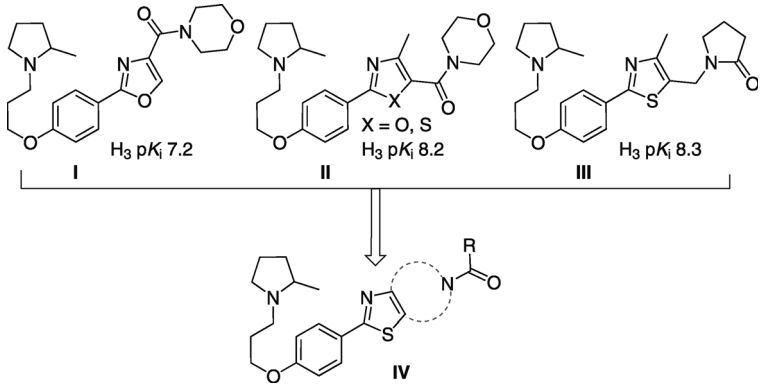
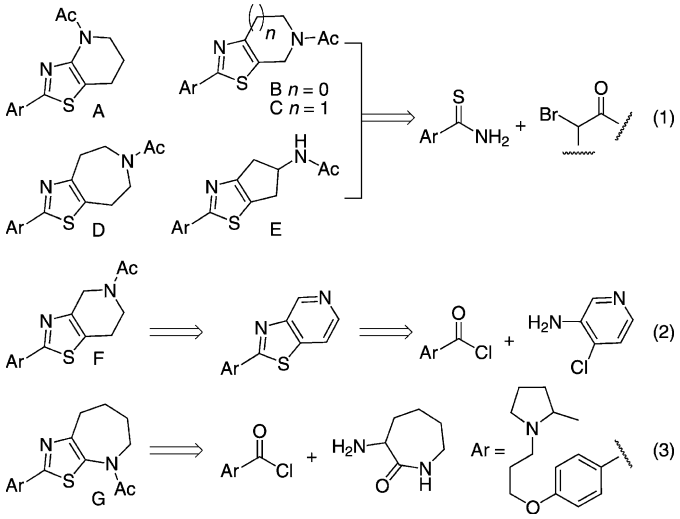


Figure 1. Nanomolar-affinity H_3R ligands **I**, **II**, and **III** based on a phenyloxazole scaffold.

Our primary strategy to prepare these heterocycles relies on the Hantzsch condensation of an α-bromocarbonyl compound with a thiobenzamide [Scheme 1, Eq. (1)].[3] This strategy has been applied for the synthesis of thiazolotetrahydropyridines A and C, thiazolopyrroline B, thiazoloazepine D, and thiazolocyclopentanes E. Although this methodology is well established for the synthesis of most thiazoles, there are only two reports of its application to α-bromoimides, and this only with the more reactive thioureas.[4] We also developed a novel access to N-unsubstituted thiazolo[4,5-*c*]piperidine F by reduction of the corresponding pyridine in the presence of acetyl chloride and sodium borohydride [Scheme 1, Eq. (2)]. This procedure greatly simplifies the conventional procedure,[5] which relies on reduction of an *N*-methylpyridinium group, leaving a piperidine nitrogen, which is difficult to functionalize. For thiazolo[5,4-*b*]azepine G, it was more expeditious to perform the cyclocondensation in two steps by first forming an amide with α-aminocaprolactam followed by a cyclization mediated by Lawesson's reagent [Scheme 1, Eq. (3)].[6]

Thiobenzamide **3**, required for the Hantzsch condensation, was obtained by alkylation of commercially available 4-hydroxybenzamide with 3-chloro-1-bromopropane, followed by thionation with Lawesson's reagent (Scheme 2). Displacement of the terminal chloride finally gave **4**.[7]

5-Acetamidocyclopentathiazole **16** was obtained from bromoketo ester **10** obtained from cyclopentene **7**, itself resulting from the condensation of 1,4-dichlorobutene and dimethyl malonate (Scheme 3). Hydrobromination of **8** and oxidation of **9** occurred smoothly, as well as the subsequent Curtius rearrangement of **12**. The use of this rearrangement to introduce the amino group was particularly useful to introduce the required amine, as 2-bromocyclopentane-1,4-dione would not lend itself to the Hantzsch condensation.



Scheme 1. Heterocyclic systems studied herein and their retrosynthetic analysis.

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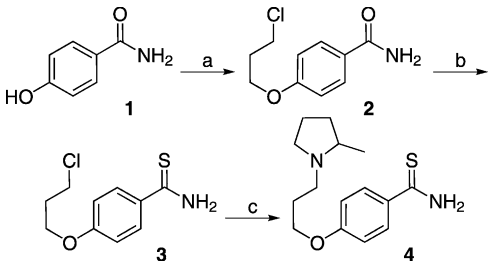
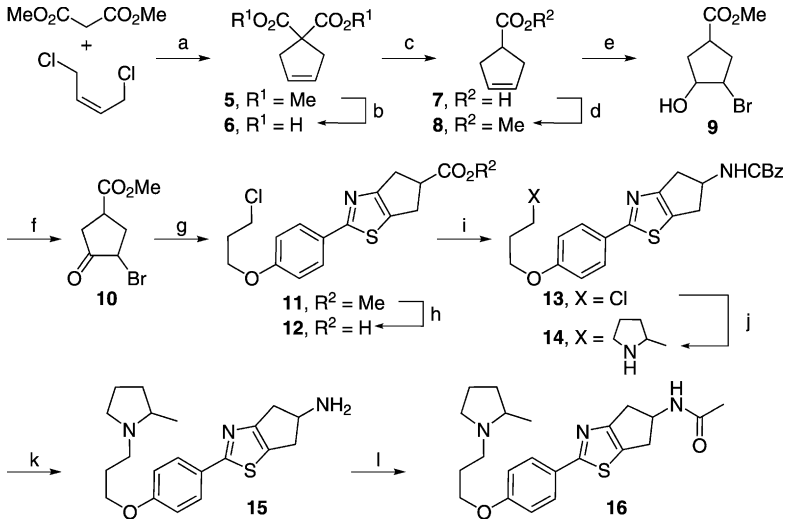


Scheme 2. *Reagents and conditions*: a) $Br(CH_2)_3Cl$, K_2CO_3, MeCOEt, reflux, 24 h (95%); b) Lawesson's reagent, $CHCl_3$, 22 °C, 12 h, (88%); c) 2-methylpyrrolidine, K_2CO_3, NaI (cat.), CH_3CN, 90 °C, 20 h (50%).



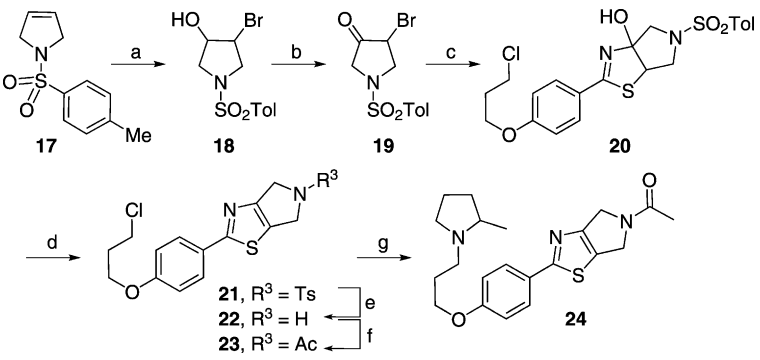
Scheme 3. *Reagents and conditions*: a) LiH, DMF, 20 °C, 64 h, (86%); b) KOH, EtOH/H_2O, reflux, 1 h, (67%); c) 180 °C, neat, 1 h, (93%); d) $SOCl_2$, MeOH, −70→0 °C, 1 h, (65%); e) NBS, $CaCO_3$, CH_3CN/H_2O, 20 °C, 4 h, (90%); f) Dess–Martin, CH_2Cl_2, 20 °C, 48 h, (83%); g) **3**, EtOH, reflux, 12 h, (90%); h) LiOH, THF/H_2O, 20 °C, 12 h, (93%); i) DPPA, Et_3N, PhMe, 20 °C, 12 h, then BnOH, reflux, 24 h, (90%); j) 2-methylpyrrolidine, K_2CO_3, NaI, CH_3CN, 90 °C, 1 h, (37%); k) 5 N aq. HCl, reflux, 1.5 h, (100%); l) AcCl, Et_3N, CH_2Cl_2, 20 °C, 2.5 h, (51%).

Thiazolopyrroline **24** proved more difficult to obtain. Using the same approach as above, we tried to condense the required N-acetylated cyclic bromoketone, but this one seemed to be particularly elusive. Only *para*-toluenesulfonyl-protected pyrroline **17** was amenable to the synthesis of the required α-bromoketone (Scheme 4). In this particular case, water elimination did not occur spontaneously during the cyclization reaction. Fortunately, it was possible to eliminate the hydroxy group of **20** in the form of the methanesulfonate ester. Toluenesulfonyl deprotection from **21** had to occur under ambient conditions, as higher temperatures destroyed this fragile bicycle. Finally acetylation of the secondary amine delivered the required compound **24**. This is the first reported synthesis of this particular bicycle using a Hantzsch condensation strategy.[8]

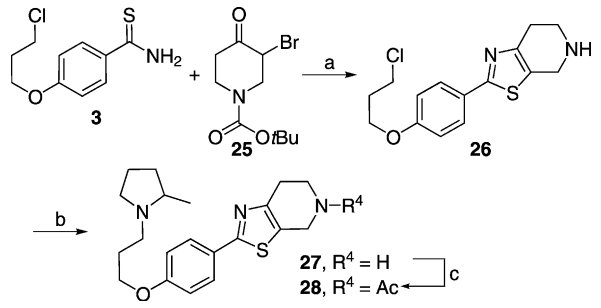
Thiazolo[5,4-*c*]piperidine **28** was the most straightforward to obtain. It was easily formed by condensation of thioamide **3** with *tert*-butoxycarbonyl (Boc)-protected 3-bromo-4-piperidone **25** with in situ deprotection of the secondary amine. Installation of 2-methylpyrrolidine followed by acetylation of the piperidine afforded the desired product in good yield (Scheme 5).

The isomeric thiazolo[4,5-*c*]piperidine **36** could not be made in the same fashion, as bromination of protected 3-piperidones remained unsuccessful. For this substitution pattern, we relied on the reduction of the corresponding thiazolopyridine **31** (Scheme 6). It could be obtained from the cyclization of 3-amino-4-chlorobenzamide **30** in the presence of Lawesson's reagent.[9] Reduction of the pyridine ring was not straightforward. It had been first envisaged to reduce methylpyridinium **32** into piperidine **33** and demethylate the piperidine afterward. Although the reduction works, we have remained unsuccessful in our demethylation attempts. We finally found that intermediate activation of the pyridine through a putative acyl–pyridinium species allowed hydride-mediated reduction of the ring system. It was later found on a similar system that the pyridine ring could be efficiently reduced with Adam's catalyst[10] under hydrogen (50 bar).

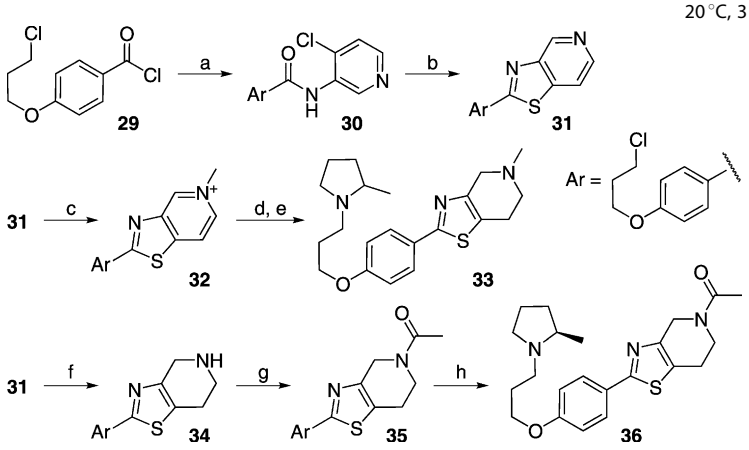
We used a similar approach to obtain the isomeric [5,4-*b*] ring system, but all attempts were unsuccessful. In view of the low stability of this system, we switched to the larger homologue to obtain the required isomer. It was obtained through the cyclization of bis-amide **38** with Lawesson's reagent (Scheme 7). The resulting bicycle **39** slowly degraded upon storage. It could only be kept as its hydrochloride salt. Fortunately, the corresponding amide **40** also showed reasonable stability. Debenzylation, followed by installation of the usual aminopropoxy chain, took place uneventfully to yield **43**.



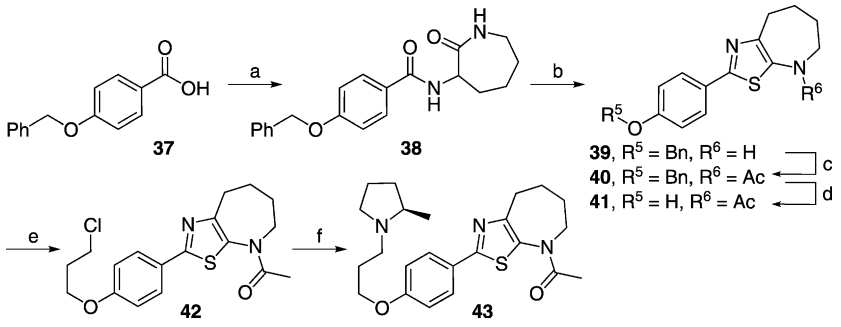
Scheme 4. *Reagents and conditions*: a) NBS, DMSO/H_2O/CH_3CN, 20 °C, 2 h, (100%); b) Dess–Martin, CH_2Cl_2, 20 °C, 2 h; c) **3**, DMF, 60 °C, 2 h (83%); d) MsCl, Et_3N, CH_2Cl_2, 20 °C, 12 h, (92%); e) *p*-HOPhCO$_2$H, HBr/AcOH, 20 °C, 5 days (9%); f) AcCl, Et_3N, CH_2Cl_2, 20 °C, 2 h, (55%); g) 2-methylpyrrolidine, CH_3CN, 100 °C, 6 h, (33%).



Scheme 5. *Reagents and conditions*: a) *i*PrOH, 90 °C, 1 h, (81%); b) 2-methylpyrrolidine, CH_3CN, NaI, 90 °C, 24 h, (45%); c) AcCl, DMAP, CH_2Cl_2, 20 °C, 2 h, (59%).

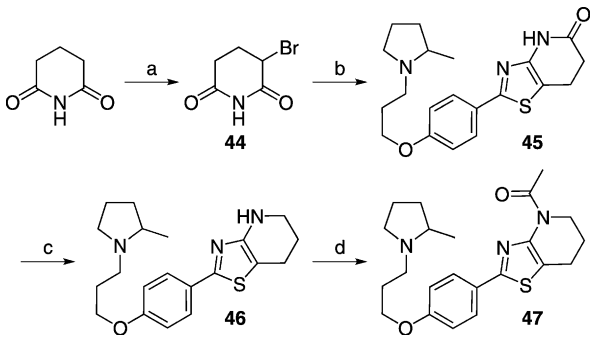


Scheme 6. *Reagents and conditions*: a) NaH, 3-amino-4-chloropyridine, THF, 80 °C, 8 h (38%); b) Lawesson's reagent, PhMe, 110 °C, 4 h (51%); c) MeI, DMF, 80 °C, 4 h (100%); d) $NaBH_4$, MeOH, 20 °C, 1 h (26%); e) 2-methylpyrrolidine, K_2CO_3, CH_3CN, 90 °C, 20 h (71%); f) AcCl, $NaBH_4$, THF, −40 °C, 1 h (31%); g) AcCl, Et_3N, CH_2Cl_2, 20 °C, 3 h (75%); h) (*R*)-2-methylpyrrolidine, K_2CO_3, NaI, CH_3CN, 80 °C, 20 h (32%).



Scheme 7. *Reagents and conditions*: a) $(COCl)_2$, CH_2Cl_2 then α-aminocaprolactam, Et_3N, CH_2Cl_2, 20 °C, 1 h, (80%); b) Lawesson's reagent, pyridine, 100 °C, 20 h, (23%); c) AcCl, Et_3N, CH_2Cl_2, 20 °C, 2 h, (64%); d) BBr_3 (5 equiv), CH_2Cl_2, 20 °C, 12 h (79%); e) K_2CO_3, $Br(CH_2)_3Cl$, MeCOEt, reflux, 20 h, (100%); f) (*R*)-2-methylpyrrolidine, NaI, CH_3CN, 80 °C, 1 h, (56%).

The [4,5-*b*] ring system **47** was prepared analogously to the Hantzsch conditions, with α-bromoglutarimide in the role of the starting α-bromocarbonyl compound (Scheme 8).[11] Bromination of glutarimide was difficult to perform reproducibly, and the bromoimide was used immediately in the cyclization reaction. Reduction of lactam **45** followed by acetylation finally yielded the target compound.



Scheme 8. *Reagents and conditions*: a) TCE, Br_2, 110 °C, 2 h, (43%); b) **4**, DMF, 90 °C, 12 h (56%); c) BH_3·DMS, THF, 20 °C, 12 h, (52%); d) AcCl, Et_3N, CH_2Cl_2, 20 °C, 3 h, (71%).

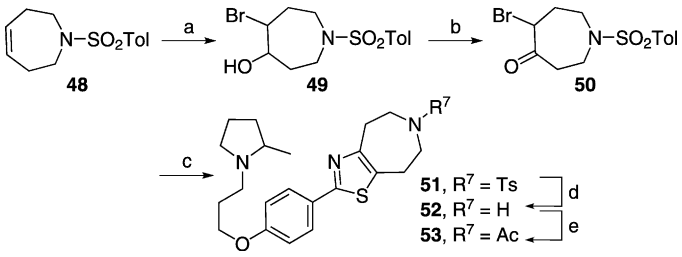
The symmetrical thiazoloazepane **53** is prepared by a route reminiscent of our work on thiazolocyclopentane **16** (Scheme 9). The required bromoketone **50** is obtained by hydrobromination of **48** followed by oxidation. In contrast to its equivalent **21** in the [5.5] series, the acid-mediated detosylation of **51** worked smoothly at higher temperatures, highlighting the increased stability of thiazoloazepanes.

The compounds thus obtained were tested against H_3R and profiled against their drug-like in vitro properties (Table 1). The comparison of **16** and **24** highlights the very small difference in binding affinity of exo- versus endocyclic amides. This result oriented our synthesis toward endocyclic amides, as they have a lower hydrogen bond count and are thus likely to show facilitated brain penetration. This also removes one stereogenic atom and simplifies the chemistry.

To our surprise, variation of the amide position did not significantly influence the binding affinity of those compounds toward H_3R. The only visible trend is that acetamides **36** and **47**, placed closer to the nitrogen atom of the thiazole, tend to have lower affinities.

Among the endocyclic amines, interaction with the hERG channel occurred at micromolar levels, with the exception of **36**, which required >10 μM concentrations to interact. However, this comes at the expense of membrane permeation, and the overall selectivity of H_3R versus hERG was not increased relative to **28**. All compounds showed favorable log*D* values, with low in vitro metabolic clearance and good in vitro intestinal permeability.

Overall, compound **28** offered the best potential for further investigations. It is more potent (even slightly so) than **36**, **47**, and **53**, has better properties than equipotent **16** and **43**, and offers an easier synthetic access than **24**. Independent synthe-

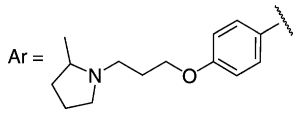
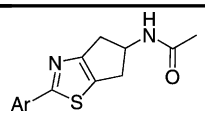
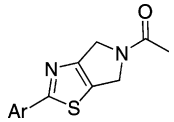
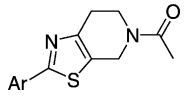
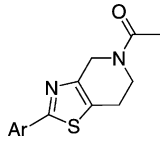
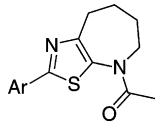
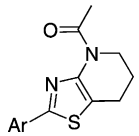
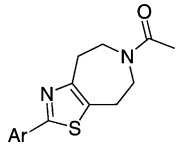


Scheme 9. *Reagents and conditions*: a) NBS, DMSO/H_2O, 20 °C, 60 h, (100%); b) Dess–Martin, CH_2Cl_2, 20 °C, 20 h, (75%); c) **4**, EtOH, 65 °C, 65 h, (74%); d) HBr, PhOMe, 100 °C, 48 h, (81%); e) AcCl, Et_3N, CH_2Cl_2, 20 °C, 1 h, (55%).

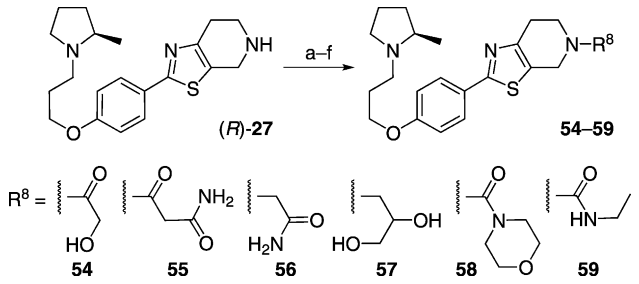
sis of the two enantiomers confirmed that the *R* isomer offers superior affinity toward H_3R, as was already the case in the monocyclic thiazoles and oxazoles.[2] This isomer was used to further explore the SAR, with a focus on polar substituents to decrease hERG affinity. A series of thiazolopiperidines with polar side chains was thus prepared by starting from intermediate (*R*)-**27** (Scheme 10).

As is apparent from Table 2, introduction of polar substituents on the fused thiazole ring is compatible with H_3R affinity. For compounds **55** and **57**, the slight increase in polarity allowed a decrease in hERG affinity. However, this was not the case with the other examples. This can be attributed to the extensive aromatic surface of those compounds, which, in combi-

Table 1. In vitro properties of tested compounds.[a]

Compd	Ar = 	H_3 K_i [nM][b]	hERG IC_{50} [μM][c]	log *D*[d]	*S* [mg mL^{-1}][e]	CL_{int} (H/R)[f]	Papps [nm s^{-1}][g]
16		2.0 ± 0.9		1.5	0.4		
24		1.6 ± 0.6		1.1	> 1.5	1/4	118
28		2.0 ± 0.6 (*R*) 1.00 ± 0.4 (*S*) 10.0 ± 0.8	6.3	1.3	1.3	1/1	216
36		(*R*) 5.0 ± 0.2	15.8	1.5	> 1.4	1/5	60
43		(*R*) 1.6	5.0	2.0	1.4	8/27	153
47		5.0		2.2	1.4		
53		4.0 ± 0.5	5.0	1.4	1.3	1/4	112

[a] Unless otherwise indicated, the data reported refer to racemates. [b] H_3R binding affinities were assessed by displacement of [^{3}H]*N*-α-methylhistamine in CHO cell membranes expressing human H_3 receptors; K_d [^{3}H]*N*-α-methylhistamine: 0.4 nM; assay concentration: 0.2 nM; pK_i thioperamide: 6.82 ± 0.13 ($n > 75$); results are the mean of two to six experiments, and when only two experiments were done, the two measurements were within 0.2 log units. [c] hERG assay was performed on HEK293 cells transfected with the hERG potassium channel. Cells were incubated for 5 min with test compound at 0.1, 1, 10 and 30 μM in water with up to 0.3% DMSO ($n = 3$ per cell per concentration). The potassium current was recorded while stimulating the cells every 15 s. [d] Log *D* at pH 7.4 was measured by sonicating a solution of compound in PBS-saturated octanol with the same volume of water. The concentration of product in both phases was determined by HPLC. [e] Water solubility at pH 7.4, 20 °C. [f] Human (H) and rat (R) intrinsic metabolic clearance measured from parent drug disappearance following incubation with liver microsomes [μL min^{-1} (mg protein)$^{-1}$]. [g] Apical-to-basolateral permeability in Caco-2 cell assay.



Scheme 10. *Reagents and conditions*: a) $HOCH_2CO_2H$, HOBt, EDCI, DMAP, CH_2Cl_2, 20 °C, 2 h, (52%, **54**); b) 1. $ClC(O)CH_2CO_2Me$, Et_3N, CH_2Cl_2, 2 h, 2. NH_3, MeOH, 90 °C, 20 h (14% over two steps, **55**); c) $BrCH_2C(O)NH_2$, K_2CO_3, NaI, CH_3CN, 80 °C, 20 h (32%, **56**); e) $ClCH_2CH(OH)CH_2OH$, (58%, **57**); f) triphosgene, CH_2Cl_2, 0 °C, 1 h, then morpholine, Et_3N, 0–20 °C, 12 h, (48%, **58**); f) EtNCO, CH_2Cl_2, 20 °C, 12 h, (62%, **59**).

nation with the basic site, matches quite well with the hERG pharmacophore.[12]

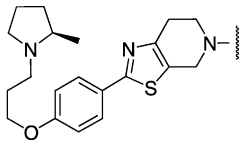
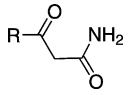
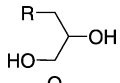
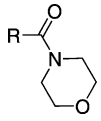
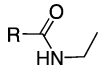
While some of these derivatives have significantly decreased hERG affinities, all the compounds with polar side chains have lower membrane permeability than **28**. Because none of the new derivatives could improve over (*R*)-**28**, which still displays the best overall characteristics, it was thus further profiled in vitro and in vivo.

The inverse agonistic profile of (*R*)-**28** was confirmed in a GTPγS assay ($pEC_{50} = 9.2$; thioperamide $pEC_{50} = 7.0$) and in assays with electrically stimulated guinea pig myenteric plexus ($pA_2 = 9.4$). For comparison, thioperamide had a pA_2 value of 7.6 in the same assay. Compound (*R*)-**28** had greater than 100-fold selectivity toward 50 targets of the CEREP receptogram, and there were no detectable interactions with major cytochrome P450 isoforms (inhibitory concentrations > 10 μM).

The in vivo pharmacokinetic (PK) profile of (*R*)-**28** in rat was consistent with its physicochemical and in vitro DMPK properties (Table 3). The compound shows excellent oral bioavailability coupled with a reasonable elimination rate ($t_{1/2} = 3.4$ h; total plasma clearance: $CL = 24\ mL\,min^{-1}\,kg$). Notably, its volume of distribution (V_{ss}) is $5.85\ L\,kg^{-1}$, which is acceptable for a basic compound. In addition, in vitro plasma protein binding was found to be low (~70%), irrespective of the species.

Ex vivo binding experiments were performed in rats. Binding of radiolabeled thioperamide was measured on rat cortex homogenates 1 h after oral (p.o.) administration of (*R*)-**28**. The observed EC_{50} value of 26 nM confirmed that the compound

Table 2. In vitro properties of thiazolo[5,4-*c*]piperidines.

Compd[a]	R = 	H_3 K_i [nM][b]	hERG IC_{50} [μM][c]	log *D*[d]	*S* [mg mL^{-1}][e]	CL_{int} (H/R)[f]	Papps [nm s^{-1}][g]
(*R*)-**28**		1.0 ± 0.4	6.3	1.3	1.3	1/1	216
54		1.2 ± 0.7	10.0	0.9	1.4	1/4	75
55		1.2 ± 0.7	> 100	0.5	1.4		NT
56		2.0	6.3	0.91	0.7	1/5	17
57		0.8 ± 0.6	> 100	0.61	1.4	2/8	17
58		2.0	6.3	1.6	0.6	5/8	32
59		5.0 ± 0.5	6.3	2.0	0.8	1/7	59

[a] All compounds are enantiomerically pure (*R*) at the pyrrolidine; compound **57** is a diastereomeric mixture of epimers at the hydroxy group. [b] H_3R binding affinities were assessed by displacement of [^{3}H]*N*-α-methylhistamine in CHO cell membranes expressing human H_3 receptors; K_d [^{3}H]*N*-α-methylhistamine: 0.4 nM; assay concentration: 0.2 nM; pK_i thioperamide: 6.82 ± 0.13 ($n > 75$); results are the mean of two to six experiments, and when only two experiments were done, the two measurements were within 0.2 log units. [c] hERG assay was performed on HEK293 cells transfected with the hERG potassium channel. Cells were incubated for 5 min with test compound at 0.1, 1, 10 and 30 μM in water with up to 0.3% DMSO ($n = 3$ per cell per concentration). The potassium current was recorded while stimulating the cells every 15 s. [d] Log *D* at pH 7.4 was measured by sonicating a solution of compound in PBS-saturated octanol with the same volume of water. The concentration of product in both phases was determined by HPLC. [e] Water solubility at pH 7.4, 20 °C. [f] Human (H) and rat (R) intrinsic metabolic clearance measured from parent drug disappearance following incubation with liver microsomes [μL min^{-1}(mg protein)$^{-1}$]. [g] Apical-to-basolateral permeability in Caco-2 cell assay; NT: not tested.

Table 3. In vivo PK data for (*R*)-**28**.[a]

Parameter	Value	Parameter	Value
DNC [ng mL^{-1}][b]	80	V_{ss} [L kg^{-1}][d]	5.85
CL [mL min^{-1} kg^{-1}][c]	24	$t_{1/2}$ [h][e]	3.4
		F [%][f]	100

[a] Parameters obtained after single p.o. and i.v. dosing at 6 and 1 mg kg^{-1} to male and female Wistar rats ($n=2$ per gender); data are reported as males and females combined, as no gender effect could be observed. All experiments were approved by the local ethics committee for animal experimentation according to Belgian law. [b] Dose-normalized maximum concentration C_{max} after p.o. administration. [c] Total plasma clearance. [d] Volume of distribution. [e] Half-life. [f] Oral bioavailability.

could successfully occupy brain H_3R at sub-micromolar concentrations (Figure 2).

Finally, the promnesiant effect of (*R*)-**28** was evaluated after intraperitoneal (i.p.) administration in a two-trial object recognition test[13] in adult C57 black male mice. Scopolamine (0.3 mg kg^{-1}, i.p.) was used to induce recognition memory deficits.[14] Mice were submitted to a habituation session the day before the object recognition test, during which they were allowed to freely explore the arena in the presence of two objects. On the experimental day, mice were submitted to two trials. During the first trial (T1), mice were placed in an arena containing two identical objects, and the time required to complete 20 s of object exploration was determined with a 12 min cutoff time. In the retention trial or trial two (T2), performed 1 h later, one of the two objects had been replaced by a novel object, and the amount of time spent to explore each object was determined for 5 min. The results are expressed as the exploration difference (N−F), which is time spent exploring the novel object minus time spent exploring the familiar object. Compound (*R*)-**28**, thioperamide (positive control) or vehicle (1% methylcellulose/5% DMSO in pure water) were administered 40 min before T1, and scopolamine was administered 30 min before T1.

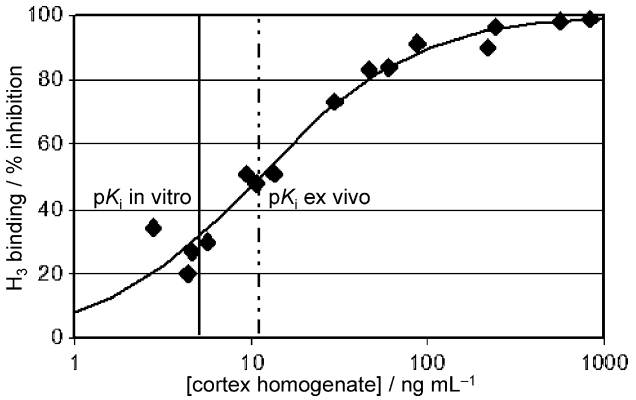


Figure 2. Ex vivo binding of (*R*)-**28** (◆). The binding of [^{3}H]thioperamide was measured on rat cortex homogenate 1 h after p.o. administration of (*R*)-**28**.

The results (Figure 3) indicate that treatment with scopolamine alone (vehicle group) prevents preferential exploration of the novel object during the retention trial, such that the exploration difference is close to zero, indicating that mice spend nearly the same amount of time exploring the familiar and novel objects during the retention trial (N−F = −1). Compound (*R*)-**28** at doses of 2.3–10 μmol kg^{-1}, is able to significantly prevent scopolamine-induced amnesia. This is indicated by the fact that mice spend more time exploring the novel object than the familiar one. The prototypical H_3R antagonist thioperamide, used as a positive control, is also shown to prevent scopolamine-induced deficit (0.5 mg kg^{-1}). Compound (*R*)-**28** does not alter locomotor activity (data not shown).

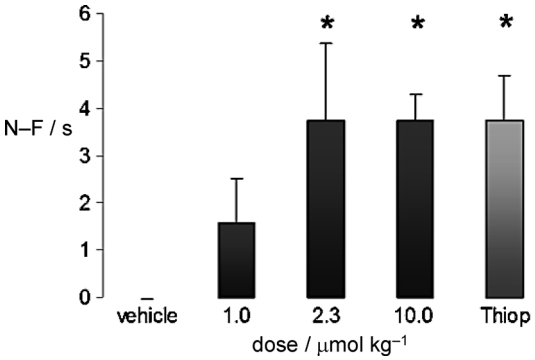


Figure 3. Promnesiant effect of (*R*)-**28** in the two-trial object recognition test in mice using scopolamine to induce recognition memory deficit. Results are expressed as the exploration difference (mean ± SEM) between novel and familiar objects during the retention trial. All groups received scopolamine (0.3 mg kg^{-1} i.p.) 30 min before the acquisition trial; drugs were administered i.p. 40 min before acquisition trial. Vehicle was 1% methylcellulose/5% DMSO in water; Thiop = thioperamide (1.2 μmol kg^{-1}). Statistical analysis was carried out by one-way ANOVA followed by Dunnett's post hoc comparison versus vehicle; statistical significance was set at $^*p<0.05$, $n=8$–9 subjects per group.

In conclusion, we have identified several novel rigidified phenylthiazoles bearing an *N*-acetamide that interact with H_3R at nanomolar-level affinities. More polar derivatives retained good affinities toward H_3R and showed lower hERG affinities, but this came at the expense of decreased permeation. Compound (*R*)-**28** showed good in vivo PK properties and activity in the novel object recognition paradigm, supporting the therapeutic potential for this compound in cognitive disorders.

Acknowledgements

The authors thank Mr. A. Safronov and Mr. M. Yakovlev (ChemBridge Corp.) for their skillful syntheses; Dr. L. Quéré, Ms. G. Longfils, and Ms. L. Ellens for lipophilicity and solubility measurements; Ms. V. Pinilla for chromatographic purifications; Dr. R. Dieden, Dr. B. Mathieu, Mr. A. Fauconnier, Mr. J. Claessens, Ms. A. Descamps, and Ms. C. Derwa for analytical assistance; Mr. P. Collart for in vitro PK measurements; and Dr. D. Harding for cardiac safety assessment. Dr. V. Bertaina-Anglade, E. Enjuanes, and Dr. C. Drieu la Rochelle (Biotrial) are greatly acknowledged for the testing of compounds in the two-trial object recognition model. The authors are most grateful to Dr. C. Audouin and Dr. C. Géni-

cot for their valuable comments in the preparation of this manuscript.

Keywords: bicyclic thiazoles · cognitive disorders · drug-like properties · histamine H_3 receptor · structure–activity relationships

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Received: May 18, 2011
Revised: June 16, 2011
Published online on July 14, 2011

