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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Non-imidazole histamine H_3 ligands: part V. synthesis and preliminary pharmacological investigation of 1-[2-thiazol-4-yl- and 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives

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Abstract Series of 1-[2-thiazol-4-yl-(2-aminoethyl)]- and 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives have been prepared and in vitro tested as H_3-receptor antagonists (the electrically evoked contraction of the guinea-pig jejunum). It appeared that by comparison of homologous pairs, the 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazines (**3a**,**b** and **4a**–**d**) have much higher potency than their analogous 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazines (**2a**–**k**). Based on the obtained results, we observed the 5-position of 2-methyl-2-R-aminoethyl substituents in the thiazole ring is favourable for histamine H_3 receptor antagonist activity, whereas its presence in position 4 leads, almost in each case, to strong decrease of activity.

Keywords Histamine H_3-receptor · H_3-antagonists · 1-[2-thiazol-4-yl-(2-aminoethyl)]- and 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives

Introduction

Histamine plays a variety of physiological roles in the central nervous system (CNS) and peripheral tissues through the four known G protein-coupled receptors, H_1, H_2, H_3 and H_4 (Hough, 2001). H_1 and H_2 receptor antagonists are well-known therapeutic agents and are in use for the treatment of allergic disease (Leurs *et al*., 2002) and peptic ulcer (Brimblecombe *et al*., 1978), respectively. The newly discovered H_4 receptor seems to have a role in regulating inflammatory responses (Thurmond *et al*., 2004). The histamine H_3 receptor, which was discovered in 1983 by Arrang and co-workers (Arrang *et al*., 1983), mainly located in the CNS, is a presynaptic autoreceptor that does not only modulate the production and the release of histamine from histaminergic neurons (Arrang *et al*., 1987) but also regulates the release of other neurotransmitters like acetylocholine (Clapham and Kilpatrick, 1992; Yokatoni *et al*., 2000), dopamine (Schlicker *et al*., 1993), norepinephrine (Schlicker *et al*., 1990), serotonin (Schlicker *et al*., 1988) and glutamate (Brown and Reymann, 1996) in both the CNS and peripheral nervous system. Enhancement of neurotransmitter release by histamine H_3 receptor antagonist shows a clinical approach to the treatment of several CNS disorders (Esbenshade *et al*., 2006; Cemkov *et al*., 2009), including attention deficit hyperactivity disorder (Quades, 1987), sleep disorders (Monti, 1993), epilepsy (Vahora *et al*., 2001) and schizophrenia (Velligan and Miller, 1999). Pharmacological data also suggest a potential role for H_3 antagonists in the control of feeding, appetite, and support the role of H_3 receptor in obesity (Hancock, 2003; Hancock *et al*., 2004).

Early generation of H_3 receptor ligands were based on structures containing the imidazole moiety, many of which have found utility as pharmacological tools (Stark *et al*., 1996; Van der Goot and Timmerman, 2000). However, antagonist carrying on the imidazole heterocycle is the potential issue for drug–drug interactions through inhibition of hepatic cytochrome P_{450} enzymes and poor CNS penetration (Lin and Lu, 1998; Zhang *et al*., 2005). For these reasons, and after the successful cloning of the human histamine H_3 receptor by Lovenberg (Lovenberg *et al*., 1999), efforts have been directed towards the discovery of H_3 antagonists without an imidazole moiety as these compounds may offer improvements in binding affinity, CNS penetration, and reduced potential for cytochrome P_{450}

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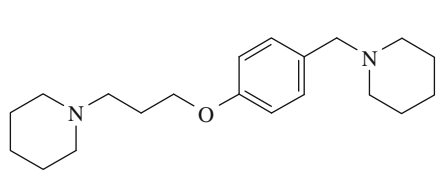
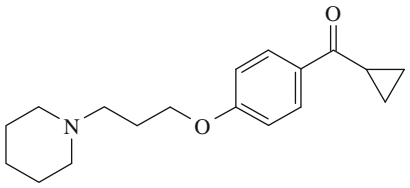
enzymes inhibition (Cowart *et al*., 2004). A number of non-imidazole antagonists have since been reported (Ganellin *et al*., 1998; Celanire *et al*., 2005). Representative examples of non-imidazole H_3 antagonists included among others were JNJ-5207852 (hH_3RK_i = 0.6 nM) (Apodaca *et al*., 2003), UCL 2190 (rH_3RK_i = 4 nM) (Meier *et al*., 2001) and ABT-239 (hH_3RK_i = 0.45 nM) (Cowart *et al*., 2002) (Chart 1).

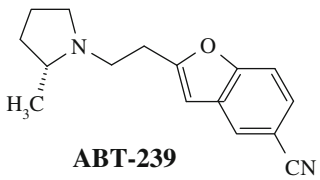
Previously, our laboratory has described several non-imidazole piperazine-based histamine H_3 antagonists, consisting of 1-(2-thiazolobenzo)-, 1-(2-thiazolopyridine)- and 1-[2-thiazol-5-yl-(2-aminoethyl)] moieties with moderate to pronounced affinity for the receptor (Walczyński *et al*., 1999, 2005; Frymarkiewicz and Walczynski, 2009). The SAR of 1-[(2-thiazolobenzo)-4-*n*-propyl]piperazines and 1-[(2-thiazolopyridine)-4-*n*-propyl]piperazines series, showed no significant



JNJ-5207852



UCL2190



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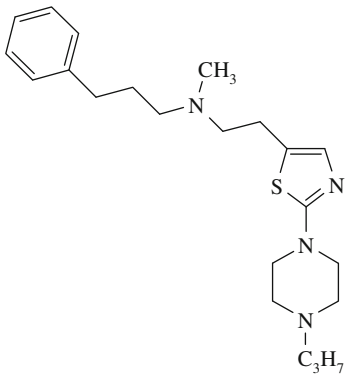

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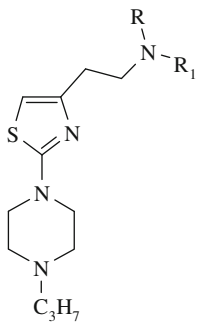
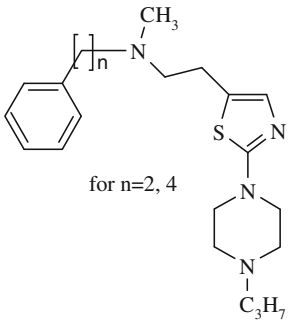
The target molecules of this study

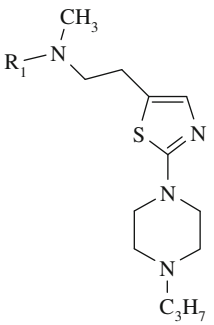


2a-k

where R=CH_3 and R_1=H
or R=CH_3 and R_1=CH_3; C_3H_7
or R=CH_3 and R_1=$(CH_2)_n$-C_6H_5 for n=1-5
or R=CH_3 and R_1=COR_2
where R_2=CH_3; C_6H_5;4-$CH_3C_6H_4$;
4-Cl-C_6H_4; 4-$O_2NC_6H_4$



3a,b

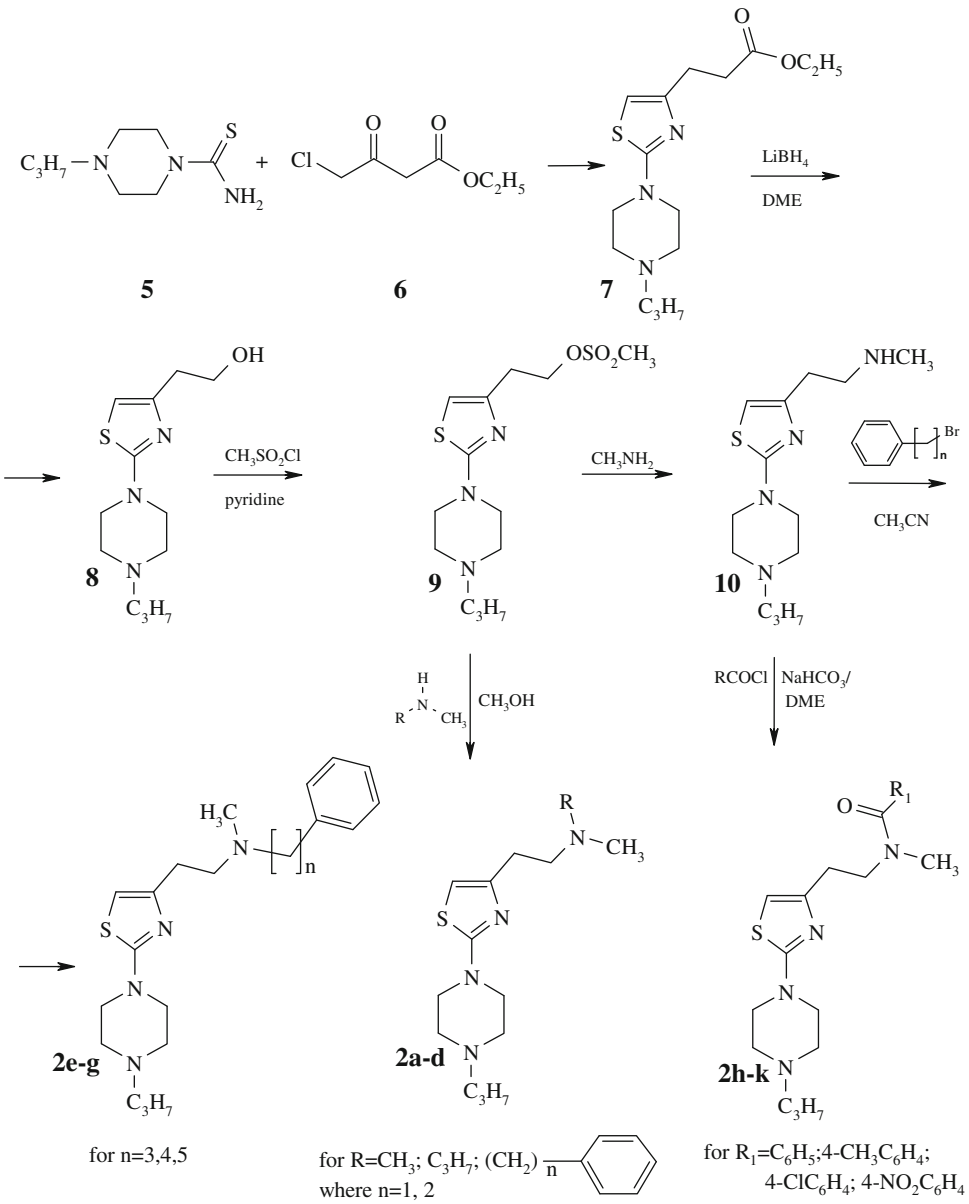


4a-d

where R_1=COR_2
and
R_2=C_6H_5;4-$CH_3C_6H_4$;
4-Cl-C_6H_4; 4-$O_2NC_6H_4$

Chart 1 Representative non-imidazole H_3-histamine receptor antagonists and the target molecules of this study

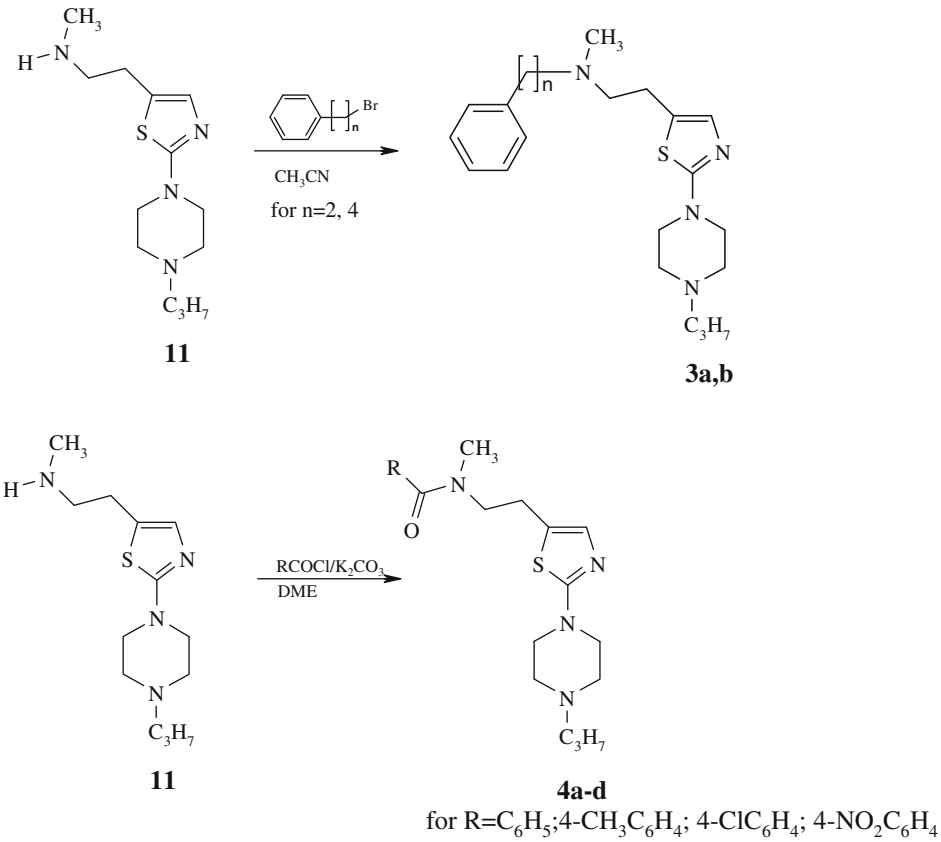
Scheme 1 Synthesis of 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazines **2a–k**



difference in H_3 activities (Walczyński *et al*., 1999, 2005). These results prompted us to replace the benzo ring by 2-methyl-2-alkylaminoethyl amide, 2-methyl-2-alkylaminoethyl and 2-methyl-2-phenylalkylaminoethyl chains at position 5 of 1-(2-thiazol-5-yl)-4-*n*-propylpiperazine moiety. The highest affinity for these series has been seen in the compound with the *N*-methyl-*N*-phenylpropylamino substituent **1** (Chart 1; $pA_2 = 8.27$; electric field stimulation assay on guinea-pig jejunum) and with slightly lower potencies for compounds carrying on *N*-methyl-*N*-benzylamino and *N*,*N*-dimethylamino substituents with $pA_2 = 7.75$ and 7.78, respectively (Frymarkiewicz and Walczynski, 2009).

In continuation of our earlier work, we studied the influence, on H_3-receptor antagonistic activity, of the introduction of 2-CH_3-2-R-aminoethyl-substitution at position 4 of the thiazole ring. Therefore, the series of 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazines **2a–k** (Chart 1), bearing the substituents showing the highest affinity in previously described 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazines (Frymarkiewicz and Walczynski, 2009), was prepared and pharmacologically evaluated (electric field stimulation assay on guinea-pig jejunum). In addition, with the aim of the complement 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazines series, 1-[2-thiazol-5-yl-(2-methyl-2-phenylethyl)]- **3a**, 1-[2-thiazol-5-yl-(2-methyl-2-phenylbutylaminoethyl)]-4-*n*-propylpiperazine **3b** and 1-[2-thiazol-5-yl-(2-methyl-2-phenylcarbonylaminoethyl)]-4-*n*-propylpiperazine amides **4a–d** (Chart 1) were synthesized.

In this study, we report on synthesis and preliminary pharmacological investigation of new 1-[2-thiazol-5-yl-



Scheme 2 Synthesis of 1-[2-thiazol-5-yl-(2-methyl-2-phenylalkylaminoethyl)]-4-*n*-propyl- piperazines 3**a**, **b** and 1-[2-thiazol-5-yl-(2-methyl-2-phenylcarbonylaminoethyl)]-4-*n*-propyl- piperazine amides **4a–d**

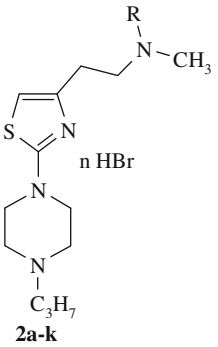
(2-aminoethyl)]-4-*n*-propylpiperazine derivatives **2** and 1-[2-thiazol-5-yl-(2-methyl-2-phenylethyl-, 1-[2-thiazol-5-yl-(2-methyl-2-phenylbutylaminoethyl)]-4-*n*-propylpiperazines **3** and 1-[2-thiazol-5-yl-(2-methyl-2-phenylcarbonylaminoethyl)]-4-*n*-propylpiperazine amides **4**.

Chemistry

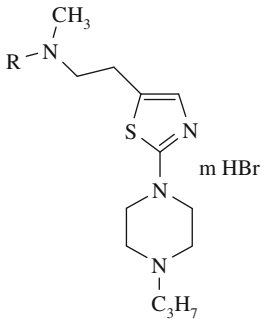
The general synthetic procedure used in this study is illustrated in Schemes 1 and 2. 1-[2-Thiazol-4-yl-(2-methylaminoethyl)]-4-*n*-propylpiperazine **10** (Scheme 1) was prepared from compound **5** by four-step synthesis including cyclization reaction of 1-(4-*n*-propyl)piperazine thioamide **5** with ethyl 4-chloroacetoacetate **6** to 1-[2-thiazol-4-yl-(2-methoxycarbonylethyl)]-4-*n*-propylpiperazine **7**, reduction with $LiAlH_4$ in dry ethyl ether to 1-[2-thiazol-4-yl-(2-hydroxyethyl)]-4-*n*-propylpiperazine **8**, mesylation with methanesulfonyl chloride in dry pyridine to 1-[2-thiazol-4-yl-(2-mesyloxyethyl)]-4-*n*-propylpiperazine **9** and finally through nucleophilic displacement of the mesyloxy group by methylamine in methanol to 1-[2-thiazol-4-yl-(2-methylaminoethyl)]-4-*n*-propylpiperazine **10**. 1-[2-Thiazol-4-yl-(2-methy-2-alkylaminoethyl)]-4-*n*-propylpiperazines **2a**,**b** and 1-[2-thiazol-4-yl-(2-methy-2-phenylalkylaminoethyl)]-4-*n*-propylpiperazines **2c**,**d** were prepared from 1-[2-thiazol-4-yl-(2-mesyloxyethyl)]-4-*n*-propylpiperazine **9** through nucleophilic substitution of the mesyloxy group by an appropriate secondary amine in methanol. Compounds **2e–g**, 1-[2-thiazol-4-yl-(2-methyl-2-phenylalkylaminoethyl)]-4-*n*-propylpiperazine, were obtained from 1-[2-thiazol-4-y l-(2-methylaminoethyl)]-4-*n*-propylpiperazine **10** by alkylation with the corresponding primary phenyloalkyl halides in acetonitrile followed by purification with column chromatography. [2-Thiazol-4-yl-(2-metyl-2-phenylcarbonylaminoethyl)]-4-*n*-propylpiperazine amides **2h–k** were obtained by standard methods. Compound **10** was acetylated with an appropriate acid chloride in the presence of $NaHCO_3$ in DME, followed by purification with column chromatography.

Compounds **3a**, **b**, 1-[2-thiazol-5-yl-(2-methyl-2-phenylalkylaminoethyl)]-4-*n*-propylpiperazine (Scheme 2), were synthesized from compound **11** by alkylation with the corresponding primary phenylalkyl halides in acetonitrile followed by purification with column chromatography. Amides **4a–d** were obtained by acetylation of 1-[2-thiazol-5-yl-(2-methylaminoethyl)]-4-*n*-propylpiperazine **11** (Scheme 2) with an

Table 1 H_3 antagonistic activity of 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazines **2a–k** and their homologous series 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazines **3a**,**b** and **4a–d** as tested on the guinea-pig jejunum



2a-k



3a,b and **4a-d**

R	Cpd.	*n*	pA_2 (sem) H_3	*N* (caviae)	Cpd.	*m*	pA_2 (sem) H_3	*N* (caviae)
CH_3–	**2a**	3	6.76 (014)	9 (3)	*	3	7.78 (0.03)	21 (6)
C_3H_7–	**2b**	3	6.92 (0.10)	9 (3)	*	3	7.53 (0.05)	18 (5)
Ph–CH_2–	**2c**	3	7.12 (0.18)	9 (3)	*	3	7.76 (0.06)	18 (5)
Ph–$(CH_2)_2$–	**2d**	3	6.81 (0.15)	9 (3)	**3a**	3	7.61 (0.06)	9 (3)
Ph–$(CH_2)_3$–	**2e**	3	6.61 (0.11)	9 (3)	*	3	8.27 (0.05)	20 (6)
Ph–$(CH_2)_4$–	**2f**	3	6.72 (0.11)	9 (3)	**3b**	3	7.80 (0.03)	9 (3)
Ph–$(CH_2)_5$–	**2g**	3	6.69 (0.05)	9 (3)	*	3	7.25 (0.04)	11 (5)
Ph–CO–	**2h**	2	5.65 (0.00)	6 (2)	**4a**	2	7.45 (0.01)	9 (3)
p-CH_3–Ph–CO–	**2i**	2	5.80 (0.10)	9 (3)	**4b**	2	7.61 (0.16)	9 (3)
p-Cl–Ph–CO–	**2j**	2	6.23 (0.11)	9 (3)	**4c**	2	7.73 (0.11)	9 (3)
p-NO_2–Ph–CO–	**2k**	2	6.03 (0.02)	9 (3)	**4d**	2	7.76 (0.02)	9 (3)

Thioperamide—pA_2 H_3 = 8.43, (sem) (0.07); *N* (caviae)—18 (6)

H_3 antagonistic activity of all compounds marked with asterisk was described in previous paper (Frymarkiewicz and Walczynski, 2009)

sem standard error of the mean, *N* number of different animal preparation; *cavie* number of animals; *m* and *n* number of HBr

appropriate acid chloride with the presence of K_2CO_3 in DME, followed by purification with column chromatography.

All free bases were dissolved in small amount of *n*-propanol and treated with methanolic HBr. The hydrobromides crystallized as white solid.

The 1-(4-*n*-propyl)piperazine thioamide (**5**) was directly obtained by the reaction of the 1-*n*-propylpiperazine dihydrobromide with potassium thiocyanate in aqueous solution (Frymarkiewicz and Walczynski, 2009).

The 5-phenylpentyl bromide was obtained according to Collins (Collins and Davis, 1961). The 5-phenyl-1-pentanol was converted into the bromide by treatment with 50 % aqueous hydrobromic acid and concentrated sulphuric acid.

The ethyl 4-chloroacetoacetate, 1-*n*-propylpiperazine dihydrobromide, benzyl bromide, 1-bromo-3-phenylpropane, 1-bromo-4-phenylbutane 5-phenyl-1-pentanol, dimethylamine solution in methanol, *N*-methylpropylamine, *N*-benzylmethylamine, *N*-methyl-2-phenethylamine, benzoyl chloride, *p*-toluoyl chloride, 4-chlorobenzoyl chloride and 4-nitrobenzoyl chloride were all purchased from commercial sources.

Results and discussion

The compounds were in vitro tested as H_3 receptor antagonists—the electrically evoked contraction of the guinea-pig jejunum.

The presented series of 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazines (**2a–k**) and their analogous 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine (**3a**,**b** and **4a–d**) derivatives possess weak to pronounced H_3-receptor antagonist potency (Table 1).

The introduction of 2-methyl-2-R-aminoethyl-substituents at position 4 of the thiazole ring led to the derivatives **2a**, **b**, **d–k** having, independent of the sort of substituent, weak activity, except for derivative **2c** showing moderate affinity with $pA_2 = 7.12$.

It appeared that by comparison of homologous pairs,the 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazines (**3a**,**b** and **4a–d**) have much higher potency than their analogous 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazines (**2a–k**). The differences are observed inside of each series. In the case of 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazines,

elongation of alkyl chain from one to three methylene groups results in an increase of potency for **2a** $pA_2 = 6.76$ and **2b** $pA_2 = 6.96$, this is in opposition to the 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives where the 1-[2-thiazol-5-yl-(2-*N*,*N*-dimethylaminoethyl)]-4-*n*-propylpiperazine shows slightly higher potency than its *N*-methyl-*N*-propyl analogue ($pA_2 = 7.78$; $pA_2 = 7.53$, respectively).

In the 2-methyl-*2*-phenylalkyl derivatives of 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazine (**2c**–**g**), there is no significant difference in affinity. Elongation of alkyl chain from one to five methylene groups does not influence antagonistic activity (pA_2 ranging from 6.81 for compound **2d** to 6.69 for compound **2g**). In the analogues series, there is no significant difference in affinity among the methyl and ethyl derivatives ($pA_2 = 7.76$ and 7.61 for compound **3a**). A further elongation in the alkyl chain length to 3 methylene groups results in an increase of antagonistic activity, reaching the maximum for 1-[2-thiazol-5-yl-(2-methyl-2-phenylpropylaminoethyl)]-4-*n*-propylpiperazine ($pA_2 = 8.27$); activity decreases on further lengthening up to 5 methylene groups ($pA_2 = 7.80$ for compound **3b** and 7.25 for 1-[2-thiazol-5-yl-(2-phenylpentylmethylaminoethyl)]-4-*n*-propylpiperazine). Replacement of hydrogen by *p*-benzoyl substituent at the end of *N*-methyl group leads to the compounds **2h**–**k** (pA_2 from 5.65 to 6.23) and their analogues **4a**–**d** (pA_2 from 7.45 to 7.76). By comparison of homologous pairs, the 1-[2-thiazol-5-yl-(2-methyl-2-phenylcarbonylaminoethyl)]-4-*n*-propylpiperazineamides **4a**–**d** have much higher potency than their analogous 1-[2-thiazol-4-yl-(2-methyl-2-phenylcarbonylaminoethyl)]-4-*n*-propylpiperazine amides **2h**–**k**. In both series, a slightly higher activity is observed for compounds carrying on electron-withdrawing substituent at *para*-position in the benzene ring.

Summarizing, 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazines display a higher activity than their 1-[2-thiazol-4-yl-(2-aminoethyl)]-4-*n*-propylpiperazine analogues. We observe that the position 5 of 2-methyl-2-R-aminoethyl-substituents in the thiazole ring is favourable for histamine H_3 receptor antagonist activity, whereas its presence in position 4 leads, almost in each case, to strong decrease of activity.

The highest potency for both homologous series is seen in the compound with the 2-methyl-2-phenylpropylaminoethyl substituent ($pA_2 = 8.27$) and with slightly lower potencies for compounds carrying on 2,2-dimethylaminoethyl, 2-methyl-2-(4-chlorophenyl)carbonylaminoethyl and 2-methyl-2-(4-nitrophenyl)-carbonylaminoethyl substituents ($pA_2 = 7.78$; $pA_2 = 7.73$ and $pA_2 = 7.76$, respectively).

Experimental protocols

General Methods. All melting points (mp) were measured in open capillaries on an electrothermal apparatus and are uncorrected. For all compounds, ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer. Chemical shifts are expressed in ppm downfield from internal TMS as reference. ^{1}H NMR data are reported in order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; * exchangeable by D_2O) number of protons, and approximate coupling constant in Hertz. ^{13}C NMR spectra were recorded on Bruker Avance III 600 MHz spectrometer. Elemental analysis (C, H, N) for all compounds were measured on Perkin Elmer Series II CHNS/O Analyzer 2400 and are within ±0.4 % of the theoretical values. TLC was performed on silica gel 60 F_{254} plates (Merck). Flash column chromatography was carried out using silica gel 60 Å 50 μm (J. T. Baker B. V.), employing the same eluent as was indicated by TLC.

Chemistry

The synthesis of 1-[2-thiazol-4-yl-(2-methoxycarbonylethyl)]-4-n-propylpiperazine (7)

The 1-(4-*n*-propyl)piperazine thioamide (**5**) (0.032 mol) was added to a solution of ethyl 4-chloroacetoacetate (**6**) (0.032 mol) in 70 mL of *n*-propanol. The reaction mixture was heated at 90 °C for 6 h. After cooling, the solvent was removed in vacuo. The hydrochloride product was obtained as brown solid. The free base was obtained as follows: the hydrochloride of the 1-[2-thiazol-4-yl-(2-methoxycarbonylethyl)]-4-*n*-propylpiperazine (**7**) was mixed with saturated aqueous sodium bicarbonate solution for 1 h at room temperature and then water layer was extracted with dichloromethane (2 × 30 mL). The organic extracts were washed with water (3 × 30 mL), dried (Na_2SO_4), filtered and evaporated to give compound **7** as a sticky oil: The free base was dissolved in small amount of *n*-propanol and treated with methanolic HBr. The dihydrobromide crystallized as white solid.

7. $C_{14}H_{23}N_3O_2S$ ($M = 297$); yield 82.6 %; sticky oil; ^{1}H NMR ($CDCl_3$) δ: 0.89–0.95 (t, 3H, $CH_2\underline{CH_3}$ J = 7.5 Hz); 1.25–1.29(t, 3H, $\underline{CH_3}CH_2O$–) 1.48–1.60 (m, 2H, –$CH_2\underline{CH_2}CH_3$); *2*.33–2.38 (m, 2H, –CH_3CH_2 $\underline{CH_2}$–); 2.52–2.56 (m, 4H $CH_2\underline{CH_2}N$); 3.46–3.50 (m, 4H, –$CH_2\underline{CH_2}N$); 3.60 (s, 2H, $\underline{CH_2}CO$–) 4.14–4.22(q, 2H $\underline{CH_2}O$, J = 7.2 Hz) 6,39 (s, 1H, $\underline{H}_{thiazole}$); TLC (methylene chloride:methanol 19:1) $R_f = 0.21$

Elemental analysis for dihydrobromide $C_{14}H_{25}Br_2N_3O_2$ S (459.26)

	C	H	N
Calculated	36.61 %	5.49 %	9.15 %
Found	36.25 %	5.38 %	9.18 %

$mp_{dihydrobromide}$ 220–222 °C

*The synthesis of 1-[2-thiazol-4-yl-(2-hydroxyethyl)]-4-n-propylpiperazine (**8**)*

To a solution of the 1-[2-thiazol-4-yl-(2-methoxycarbonylethyl)]-4-*n*-propylpiperazine (**7**) (0.032 mol) in 110 mL of DME at 55 °C, $LiBH_4$ (0.055 mol) was added. The mixture was stirred at 70 °C for 24 h. The solvent was evaporated and remaining material was dissolved in 60 mL of methanol and was heated at 70 °C for 24 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel. The title products were obtained as sticky oil. The free base was dissolved in small amount of *n*-propanol and treated with methanolic HBr. The dihydrobromide crystallized as white solid.

8. $C_{12}H_{21}N_3OS$ ($M = 256$); yield 75.0 %.; ^1H NMR ($CDCl_3$) δ: 0.89–0.95 (t, 3H, $CH_2\underline{CH_3}$ J = 7.5 Hz); 1.51–1.60 (m, 2H, $-CH_2\underline{CH_2}$ CH_3); 2.33–2.38 (m, 2H, $-CH_3CH_2$ $\underline{CH_2}-$); 2.52–2.56 (m, 4H $CH_2\underline{CH_2}N$); 2.75–2.78 (t, 2H, CH_2-thiazole J = 5.7 Hz); 3.45–3.49 (m, 4H, $-CH_2\underline{CH_2}N$); 3.84–3.87 (t, 2H $\underline{CH_2}OH$, J = 5.7 Hz) 4.01 (s* br, H, O<u>H</u>–) 6.20 (s, 1H, $\underline{H}_{thiazole}$); TLC (methylen chloride:methanol 10:1) $R_f = 0.27$.

Elemental analysis for dihydrobromide $C_{12}H_{21}N_3OSx2HBr$ (M = 417,22)

	C	H	N
Calculated	34.54 %	5.56 %	10.07 %
Found	34.30 %	5.52 %	10.07 %

$mp_{dihydrobromide}$ 244–246 °C

*The synthesis of 1-[2-thiazol-4-yl-(2-mesyloxyethyl)]-4-n-propylpiperazine (**9**)*

To a cooled solution of the 1-[2-thiazol-4-yl-(2-hydroxyethyl)]-4-*n*-propylpiperazine (**8**) (0.009 mol) in 10 mL of dry pyridine, while stirring, methanesulfonyl chloride (0.009 mol) was added dropwise. The mixture was stirred at room temperature for 0.5 h. Then, reaction mixture was poured out in ice-cold water (40 mL) and extracted with ethyl ether (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to give compound **9** as a sticky yellow oil. The crude compound **9** was used in the next step without further purification.

9. $C_{13}H_{23}N_3O_3S_2$ ($M = 333$); yield 58.1 %; ^1H NMR ($CDCl_3$) δ: 0.90–0.95 (t, 3H, $CH_2\underline{CH_3}$ J = 7.4 Hz); 1.48–1.60 (m, 2H, $-CH_2\underline{CH_2}$ CH_3); 2.33–2.38 (m, 2H, $-CH_3CH_2$ $\underline{CH_2}-$); 2.52–2.56 (m, 4H $CH_2\underline{CH_2}N$); 2.92 (s, 3H, $\underline{CH_3}SO_3$) 2.96–3.02 (t, 2H, CH_2-$_{thiazole}$ J = 6.6 Hz); 3.45–3.48 (m, 4H, $-CH_2\underline{CH_2}N$); 4.49–4.52 (t, 2H $\underline{CH_3}SO_3\underline{CH_2}$, J = 6.6 Hz) 6,29 (s, 1H, $\underline{H}_{thiazole}$); TLC (methylen chloride:methanol 10:1) $R_f = 0.44$.

*The synthesis of 1-[2-thiazol-4-yl-(2-methylaminoethyl)]-4-n-propylpiperazine (**10**)*

The crude 1-[2-thiazol-4-yl-(2-mesyloxyethyl)]-4-*n*-propylpiperazine **9** (0.008 mol) was dissolved in 30 mL of 40 % solution methylamine in methanol. The mixture was stirred at room temperature for 24 h. Then, organic solvent was evaporated, and residue was dissolved in DME (40 mL), alkalized with solid $NaHCO_3$ (0.001 mol) and stirred for 1 h. The mixture was filtered and DME was evaporated to give compound **2** as a yellowish sticky oil. The free base was dissolved in small amount of *n*-propanol and treated with methanolic HBr. The treehydrobromide crystallized as white solid.

2. $C_{13}H_{24}N_4S$ ($M = 268$); yield 68.9 %; ^1H NMR ($CDCl_3$) δ: 0.90–0.95 (t, 3H, $CH_2\underline{CH_3}$ J = 7.5 Hz); 1.50–1.60 (m, 2H, $-\underline{CH_2}$ CH_3); 2.01 (s* br, 1H, N<u>H</u>); 2.32–2.37 (m, 2H, $-CH_3CH_2$ $\underline{CH_2}-$); 2.45 (s, 3H $-\underline{CH_3}$); 2.52–2.56; (m, 4H $CH_2\underline{CH_2}N$); 2.73–2.77 (t, 2H, $\underline{CH_2}$-$_{thiazole}$, J = 6.6 Hz); 2.86–2.91 (t, 2H, $\underline{CH_2}N$ J = 6.6 Hz) 3.45–3.48 (m, 4H, $CH_2\underline{CH_2}N$); 6.19 (s, 1H, $\underline{H}_{thiazole}$); TLC (chloroform metanol concentrated ammonium hydroxide 60:10:1) $R_f = 0.10$.

Elemental analysis for treehydrobromide $C_{13}H_{27}N_4$ Br_3S (511,20)

	C	H	N
Calculated	30.54 %	5.32 %	10.96 %
Found	30.61 %	5.23 %	10.97 %

$mp_{treehydrobromide}$ 226–228 °C

*General method for the preparation of 1-[2-thiazol-4-yl-(2-alkylmethylaminoethyl)] (**2a**,**b**) and 1-[2-thiazol-4-yl-(2-phenylalkylmethylaminoethyl)] 4-n-propylpiperazines (**2c**,**d**)*

To a solution of 1-[2-thiazol-4-yl-(2-mesyloxyethyl)]-4-*n*-propylpiperazine (**9**) (0.002 mol) in 5.0 mL of methanol, the corresponding amine (0.004 mol) was added (in case of the compound **2a**—33 % solution dimethylamine in methanol was used). The mixture was stirred at 50 °C for 6–10 h. (monitored by TLC). After the completion of reaction, the solvent was evaporated and the residue was alkalized with saturated aqueous $NaHCO_3$ solution (15 mL) and stirred for 0.5 h. Then, the mixture was extracted with ethyl ether (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography on silica gel. The

title products were obtained as sticky oil. The free base was dissolved in small amount of *n*-propanol and treated with methanolic HBr. The hydrobromide crystallized as white solid to give compounds **2a**–**d**.

2a. $C_{14}H_{26}N_4S$ ($M = 282$); yield 64.0 %.; ^{1}H NMR ($CDCl_3$) δ: 0.89–0.94 (t, 3H, –$CH_2\underline{CH_3}$ J = 7.2 Hz); 1.47–1.57 (m, 2H, –$CH_2\underline{CH_2}CH_3$); 2.74 (s, 3H, –NCH_3); 2.31–2.36 (m, 2H, –$CH_3CH_2\underline{CH_2}$–); 2.51–2.54 (m, 4H $\underline{CH_2CH_2}$N); 2.58–2.64 (m, 2H, $\underline{CH_2}$N)); 2.72–2.75 (m, 2H CH_2-thiazole) 3.45–3.48 (m, 4H, –$\underline{CH_2CH_2}$N 6.29 (s, 1H, $\underline{H}_{thiazole}$); TLC (chloroform:methanol:concentrated ammonium hydroxide 40:10:1) $R_f = 0.19$. $mp_{threehydrobromide}$ 242–244 °C.

IR (for dihydrobromide; KBr) cm^{-1}: 3446, 3052, 2962, 2914, 2660, 2587, 2520, 2467, 1613, 1592, 1470, 1432, 1287, 1168, 1133, 997, 969, 813, 662.

Elemental analysis for dihydrobromide $C_{14}H_{29}Br_3N_3S$ (525,22)

	C	H	N
Calculated	33.01 %	5.57 %	10.67 %
Found	32.70 %	5.67 %	10.62 %

$mp_{threehydrobromide}$ 242–244 °C

2b. $C_{16}H_{30}N_4S$ ($M = 310$); yield 68.0 %.; ^{1}H NMR ($CDCl_3$) δ: 0.87–0.95 (m 6H, –$CH_2\underline{CH_3}$); 1.47–1.60 (m, 4H, –$CH_2\underline{CH_2}$ CH_3); 2.32 (s, 3H, –$N\underline{CH_3}$); 2.34–2.43 (m, 4H, –CH_3CH_2 $\underline{CH_2}$–); 2.52–2.55 (m, 4H $CH_2\underline{CH_2}$N); 2.76 (s, 4H –$N\underline{CH_2CH_2}_{thiazole}$); 3.45–3.48 (m, 4H, –$CH_2\underline{CH_2}$N); 6.29 (s, 1H, $\underline{H}_{thiazole}$); TLC (chloroform:methanol:concentrated ammonium hydroxide 40:10:1) $R_f = 0.25$.

IR (for treehydrobromide; KBr) cm^{-1}: 3428, 3073, 2963, 2923, 2708, 2655, 2581, 2527, 2469, 1611, 1591, 1459, 1426,1356, 1289, 1239, 1181, 1133, 1099, 1055, 1028, 967, 898, 808, 760, 721, 638, 548.

Elemental analysis for treehydrobromide $C_{16}H_{33}Br_3N_4S$ (553.27)

	C	H	N
Calculated	34.73 %	6.01 %	10.13 %
Found	34.71 %	6.07 %	10.13 %

$mp_{threehydrobromide}$ 242–244 °C

2c. $C_{20}H_{30}N_4S$ ($M = 359$); yield 41.0 %; ^{1}H NMR ($CDCl_3$) δ: 0.81–0.86 (t 3H, –$CH_2\underline{CH_3}$ J = 7.4 Hz); 1.38–1.51 (m, 2H, –$CH_2\underline{CH_2}$ CH_3); 2.16 (s, 3H, –$N\underline{CH_3}$); 2.22–2.28 (m, 4H, –CH_3CH_2 $\underline{CH_2}$–); 2.36–2.45 (m, 4H $CH_2\underline{CH_2}$N); 2.63–2.76 (m, 4H –$N\underline{CH_2CH_2}$-thiazole); 3.35–3.44 (m, 4H, –$\underline{CH_2CH_2}$N) 3.46 (s, 2H, CH_2Ph) 6.29 (s, 1H, $\underline{H}_{thiazole}$); 7.11–7.26 (m,5H,–$\underline{H}_{arom}$); TLC (chlorek metylenu:metanol 10:1) $R_f = 0.23$.

IR (for treehydrobromide; KBr) cm^{-1}: 3435, 3071, 2963, 2918, 2702, 2653, 2579, 2459, 1615, 1429, 1287, 1185, 1097, 1056, 969, 751, 699.

Elemental analysis for treehydrobromide $C_{20}H_{33}Br_3N_4S$ (601.31)

	C	H	N
Calculated	39.95 %	5.53 %	9.32 %
Found	39.57 %	5.47 %	9.19 %

$mp_{threehydrobromide}$ 232–234 °C

2d. $C_{21}H_{32}N_4S$ ($M = 373$); yield 16.9 %; ^{1}H NMR ($CDCl_3$) δ: 0.89–0.94 (t 3H, –$CH_2\underline{CH_3}$ J = 7.3 Hz); 1.47–1.59 (m, 2H, –$CH_2\underline{CH_2}$ CH_3); 2.32–2.34 (m, 2H, –CH_3CH_2 $\underline{CH_2}$–); 2.36 (s, 3H, –$N\underline{CH_3}$); 2.52–2.59 (m, 4H $CH_2\underline{CH_2}$N); 2.64–2.70 (m, 2H –$N\underline{CH_2CH_2}$-thiazole); 2.70–2.85 (m, 6H, –$\underline{CH_2}$–thiazole –$\underline{CH_2CH_2}$Ph,); 3.45–3.54 (m, 4H, –$CH_2\underline{CH_2}$N); 6.16 (s, 1H, $\underline{H}_{thiazole}$); 7.18–7.30 (m, 5H, H_{arom}); (TLC (chloroform:metanol:amoniak 60:10:1) $R_f = 0.55$.

IR (for treehydrobromide; KBr) cm^{-1}: 3430, 3071, 2962, 2928, 2702, 2653, 2577, 2458, 1613, 1594, 1456, 1411, 1357, 1289, 1181, 1098, 1055, 968, 807, 751, 698.

Elemental analysis for treehydrobromide $C_{21}H_{35}Br_3N_4S$ (615.32)

	C	H	N
Calculated	40.72 %	5.70 %	9.05 %
Found	40.57 %	5.37 %	9.02 %

$mp_{threehydrobromide}$ 216–218 °C

*General method for the preparation of 1-[2-thiazol-4-yl-(2-phenylalkylmethylaminoethyl)] 4-n-propylpiperazines (**2e**–**g**) and 1-[2-thiazol-5-yl-(2-phenylalkylmethylaminoethyl)] 4-n-propylpiperazines (**3a**,**b**)*

To a solution of 1-[2-thiazol-4-yl-(2-methylaminoethyl)]-4-n-propylpiperazine (**10**) (0.002 mol) or 1-[2-thiazol-5-yl-(2-methylaminoethyl)]-4-n-propylpiperazine (**11**) (0.002 mol) with the presence of K_2CO_3 (0.003 mol) in 5.0 mL of acetonitrile, the corresponding phenylalkyl bromide (0.002 mol) was added. The mixture was stirred at room temperature for 6–10 h (monitored by TLC). Then, inorganic salt was filtered off and solvent was evaporated. The residue was purified by column chromatography on silica gel. The title products were

obtained as sticky oil. The free base was dissolved in small amount of n-propanol and treated with methanolic HBr. The hydrobromide crystallized as white solid to give compounds **2e–g** and **3a**,**b**, respectively.

2e. $C_{22}H_{34}N_4S$ ($M = 387$); yield 39.8 %; ^{1}H NMR ($CDCl_3$) δ: 0.91–0.96 (t 3H, –CH_2<u>CH_3</u> J = 7.3 Hz); 1.49–1.62 (m, 2H, –CH_2<u>CH_2</u> CH_3); 1.76–1.86 (m, 2H, –CH_2<u>CH_2</u> CH_2); 2.29 (s, 3H, –N<u>CH_3</u>); 2.33–2.38 (m, 2H, –CH_3CH_2 <u>CH_2</u>–); 2.43–2.48 (t, 2H, –N<u>CH_2</u>CH_2 CH_2, J = 7.5 Hz); 2.51–2.63 (m, 6H, –CH_2CH_2N, <u>CH_2</u>Ph,); 2.71(s, 4H, –CH_2-thiazole <u>CH_2CH_2</u>N); 3.42–3.45 (m, 4H, –CH_2<u>CH_2</u>N); 6.34 (s, 1H, <u>H</u>$_{thiazole}$); 7.12–7.28 (m,5H,–<u>H</u>$_{arom}$); TLC (chloroform:metanol:amoniak 60:10:1) $R_f = 0.46$.

IR (for threehydrobromide; KBr) cm^{-1}: 3428, 3075, 2962, 2922, 2649, 2577, 2519, 2458, 2363, 1620, 1453, 1430, 1403, 1286, 1240, 1185, 1134, 1033, 967, 808, 753, 700.

Elemental analysis for threehydrobromide $C_{22}H_{37}Br_3N_4S$ (629.7)

	C	H	N
Calculated	41.98 %	5.93 %	8.90 %
Found	41.93 %	5.96 %	8.88 %

$mp_{threehydrobromide}$ 220–222 °C

2f. $C_{23}H_{36}N_4S$ ($M = 401$); yield 40.5 %; ^{1}H NMR ($CDCl_3$) δ: 0.90–0.94 (t 3H, –CH_2<u>CH_3</u> J = 7.3 Hz); 1.47–1.67 (m, 6H, –CH_2<u>CH_2</u> CH_3, <u>CH_2</u>CH_2N; <u>CH_2</u> CH_2Ph); 2.27 (s, 3H, –N<u>CH_3</u>); 2.32–2.44 (m, 4H, –CH_3CH_2 <u>CH_2</u>, N<u>CH_2</u>CH_2 CH_2–); 2.41–2.49 (m, 4H CH_2<u>CH_2</u>N); 2.59–2.64 (t, 2H, CH_2Ph J = 7.2 Hz); 2.72 (s, 4H, –thiazole <u>CH_2CH_2</u>N); 3.42–3.48 (m, 4H, –CH_2<u>CH_2</u>N); 6.16 (s, 1H, <u>H</u>$_{thiazole}$); 7.16–7.29 (m,5H,–<u>H</u>$_{arom}$); TLC (chloroform:metanol:amoniak 60:10:1) $R_f = 0.49$.

IR (for threehydrobromide; KBr) cm^{-1}: 3523, 3422, 3067, 2965, 2938, 2705, 2655, 2582, 2529, 2469, 1613, 1592, 1457, 1413, 1357, 1289, 1182, 1097, 1029, 969, 809, 748, 705, 669, 550.

Elemental analysis for threehydrobromide $C_{23}H_{39}Br_3N_4S$ (643.7)

	C	H	N
Calculated	42.93 %	6.11 %	8.71 %
Found	42.73 %	6.27 %	8.67 %

$mp_{threehydrobromide}$ 217–219 °C

2g. $C_{24}H_{38}N_4S$ ($M = 415$); yield 66.8 %; ^{1}H NMR ($CDCl_3$) δ: 0.88–0.93 (t 3H, –CH_2<u>CH_3</u> J = 7.3 Hz); 1.27–1.37 (m, 2H, $(CH_2)_2$<u>CH_2</u>$(CH_2)_2$); 1.45–1.65 (m, 6H, –CH_2<u>CH_2</u> CH_3, <u>CH_2</u>CH_2N); 2.30–2.35 (m, CH_3CH_2<u>CH_2</u>–N<u>CH_3</u>); 2.41–2.52 (m, 6H, CH_2<u>CH_2</u>N <u>CH_2</u>CH_2Ph 2.56–2.61 (t, 2H –<u>CH_2</u>Ph 2,76 (s, 4H, thiazole <u>CH_2CH_2</u>N); 3.39–3.46 (m, 4H, –CH_2<u>CH_2</u>N) 6.17 (s, 1H, <u>H</u>$_{thiazole}$); 7.12–7.28 (m,5H,–<u>H</u>$_{arom}$); TLC (chloroform:metanol:amoniak 60:10:1) $R_f = 0.51$.

IR (for threehydrobromide; KBr) cm^{-1}: 3427, 3305, 3077, 2937, 2876, 2653, 2580, 2458, 1616, 1597, 1434, 1286, 1185, 1096, 967, 807, 756, 701, 528.

Elemental analysis for threehydrobromide $C_{24}H_{41}Br_3N_4S$ ($M = 657.40$)

	C	H	N
Calculated	43.84 %	6.29 %	8.52 %
Found	43.75 %	6.32 %	8.55 %

$mp_{threehydrobromide}$ 214–216 °C

3a. $C_{21}H_{32}N_4S$ ($M = 372.56$); yield 48.0 %; ^{1}H NMR ($CDCl_3$) δ: 0.90–0.92 (t 3H. –CH_2<u>CH_3</u> J = 7.2 Hz); 1.50–1.56 (m, 2H, –<u>CH_2</u>CH_3); 2.32–2.34 (m, 2H CH_3CH_2<u>CH_2</u>N); 2.35 (s, 3H <u>CH_3</u>N); 2.52–2.53 (m, 4H –CH_2<u>CH_2</u>N); 2.62–2.67 (m, 4H <u>CH_2</u>Ph <u>CH_2</u>N) 2.77–2.82 (m, 2H –<u>CH_2</u>N –<u>CH_2</u>-tiazol); 3.43–3.45 (m 4H –CH_2<u>CH_2</u>N); 6.87 (s 1H <u>H</u>$_{thiazole}$); 7.16–7.28 (m 5H $H_{arom.}$); TLC (chloroform:methanol 9:1) $R_f = 0.23$.

IR (for threehydrobromide; KBr) cm^{-1}: 3507, 3451, 3052, 2959, 2915, 2695, 2583, 2526, 1578, 1430, 1409, 1309, 1291, 1243, 1188, 1161, 1093, 1033, 964, 810, 756, 728, 703, 623, 544, 510.

Elemental analysis for threehydrobromide $C_{21}H_{35}Br_3N_4S$ ($M = 615.34$)

	C	H	N
Calculated	40.99 %	5.73 %	9.11 %
Found	40.92 %	5.51 %	9.16 %

$mp_{threehydrobromide}$ 204–206 °C

3b. $C_{23}H_{36}N_4S$ ($M = 400.62$) yield 61.0 %; ^{1}H NMR ($CDCl_3$) δ: 0.91–0.93 (t, 3H. –CH_2<u>CH_3</u> J = 7.2 Hz); 1.49–1.56 (m, 4H –<u>$CH_2CH_2CH_2$</u>N); 1.62–1.67 (m, 2H <u>CH_2</u>CH_3); 2.23 (s, 3H <u>CH_3</u>N); 2.32–2.34 (m, 2H CH_3CH_2<u>CH_2</u>N); 2.38–2.40 (t, 2H J = 7.2 Hz <u>CH_2</u>N); 2.50–2.55 (m, 6H –CH_2<u>CH_2</u>N –<u>CH_2</u>Ph); 2.61–2.63 (t, 2H J = 7.2 Hz <u>CH_2</u>N); 2.77–2.79(t, 2H J = 7.2 Hz <u>CH_2</u>-tiazol); 3.42–3.43 (m, 4H –CH_2<u>CH_2</u>N); 6.87 (s, 1H <u>H</u>$_{thiazole}$); 7.15–7.26 (m 5H $H_{arom.}$); TLC (chloroform: methanol 9:1) $R_f = 0.14$.

IR (for threehydrobromide; KBr) cm^{-1}: 3471, 3399, 3052, 2938, 2639, 2597, 2473, 1627, 1498, 1434, 1291, 1193, 1027, 964, 846, 752, 722, 597.

Elemental analysis for threehydrobromide $C_{23}H_{39}Br_3N_4S$ ($M = 643.39$)

	C	H	N
Calculated	42.93 %	6.11 %	8.71 %
Found	42.87 %	6.14 %	8.78 %

$mp_{threehydrobromide}$ 260–262 °C

*General method for the preparation of 1-[2-thiazol-4-yl-(2-methyl-2-phenylcarbonylaminoethyl)]-4-n-propylpiperazine amides **2h–k** and 1-[2-thiazol-5-yl-(2-methyl-2-phenylcarbonylaminoethyl)]-4-n-propylpiperazine amides **4a–d***

To a solution of 1-[2-thiazol-4-yl-(2-methylaminoethyl)]-4-n-propylpiperazine (**2**) or 1-[2-thiazol-5-yl-(2-methylaminoethyl)]-4-n-propylpiperazine (**11**) (0.001 mol) in 10 mL of DME, the corresponding acid chloride (0.001 mol) was added. After 15 min, $NaHCO_3$ (0.001 mol) was added and the mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was suspended with H_2O (30 mL) and extracted with chloroform (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography on silica gel. The title products were obtained as sticky oil. The free base was dissolved in small amount of n-propanol and treated with methanolic HBr. The hydrobromide crystallized as white solid to give compounds **2h–k** and **4a–d**, respectively. Because ^{1}H NMR data for compounds **2h–k** and **4a–d** have been illegible. ^{13}C NMR data are presented for these derivatives.

2h. $C_{20}H_{28}N_4OS$ ($M = 372$); yield 82.9 %; (δ in ppm; $CDCl_3$, 600 MHz); 171.67; 161.18; 159.80; 137.06; 129.94; 128.00; 127.15; 122.37; 59.28; 52.05; 45.42; 43.59; 33.16; 27.08; 20.46; 13.29;. TLC (dichloromethane: methanol: 10:1) $R_f = 0{,}36$.

IR (for dihydrobromide; KBr) cm^{-1}: 3399, 3104, 3077, 2974, 2919, 2793, 2919, 2793, 2703, 2664, 2576, 2465, 1599, 1501, 1439, 1406, 1275, 1218, 1187, 1122, 1072, 1029, 998, 967, 841, 798, 723, 637, 566, 463.

MS *m/z* (relative intensity) 372 (M^+, 17), 274 (66), 261 (13), 152 (17), 139 (41), 126 (24), 111 (17), 105 (100), 77 (33).

Elemental analysis for dihydrobromide $C_{20}H_{30}Br_2N_4OS$ ($M = 534.37$)

	C	H	N
Calculated	44.91 %	5.28 %	10.48 %
Found	45.00 %	5.47 %	10.58 %

$mp_{dihydrobromide}$ 227–228 °C

2i. $C_{21}H_{30}N_4OS$ ($M = 386$); yield 71.9 %; (δ in ppm; $CDCl_3$, 600 MHz); 171.53; 161.18; 159.80; 139.83; 133.26; 128.69; 126.73; 121.78; 60.08; 52.05; 46.07; 44.05; 33.09; 28.34; 21.50; 20.46; 13.29;.TLC (dichloromethane: methanol: 10:1) $R_f = 0.28$.

IR (for dihydrobromide; KBr) cm^{-1}: 3431, 3102, 3000, 2926, 2768, 2569, 2514, 2462, 1597, 1478, 1455, 1406, 1362, 1291, 1276, 1184, 1122, 1075, 998, 967, 834, 786, 715, 640, 565, 476.

MS *m/z* (relative intensity) 386 (M^+, 12), 288 (43), 152 (13), 139 (22), 126 (15), 119 (100) 111 (14), 98 (20), 91 (30).

Elemental analysis for dihydrobromide $C_{21}H_{30}Br_2N_4OS$ ($M = 547.8$)

	C	H	N
Calculated	46.00 %	5.88 %	10.22 %
Found	45.91 %	5.94 %	10.16 %

$mp_{dihydrobromide}$ 210–212 °C

2j. $C_{20}H_{27}ClN_4OS$ ($M = 407$); yield 49,5 %; (δ in ppm; $CDCl_3$, 600 MHz); 171.86; 161.34; 159.80; 136.81; 132.00; 129.73; 127.53; 121.78; 59.73; 51.27; 46.95; 43.56; 31.33; 27.54; 20.46; 13.29; TLC (dichloromethane: methanol: 10:1) $R_f = 0.38$.

IR (for dihydrobromide; KBr) cm^{-1}: 3101, 3072, 2967, 2928, 2759, 2706, 2574, 2463, 1617, 1596, 1441, 1408, 1291, 1215, 1186, 1122, 1093, 1073, 1014, 965, 915, 845, 786, 757, 691, 670, 639, 553, 474.

MS *m/z* (relative intensity) 406 (M^+, 10), 308 (37), 152 (15), 141 (23), 139 (100), 126 (19), 111 (18), 98 (25).

Elemental analysis for dihydrobromide $C_{20}H_{29}Br_2ClN_4OS$ ($M = 568.81$)

	C	H	N
Calculated	42.22 %	5.14 %	9.85 %
Found	42.33 %	5.01 %	9.98 %

$mp_{dihydrobromide}$ 221–223 °C

2k. $C_{20}H_{27}N_5O_3S$ ($M = 417$); yield 75,5 % (δ in ppm; $CDCl_3$, 600 MHz); 171.98; 161.57; 159.87 148.38; 143.12; 127.64; 123.71; 121.87; 55.24; 45.42; 43.81; 33.25; 27.89; 20.53; 13.32; TLC (dichloromethane: methanol: 10:1) $R_f = 0.43$.

IR (for dihydrobromide; KBr) cm^{-1}: 3430, 3102, 1620, 1597, 1522, 1439, 1410, 1352, 1290, 1179, 1073, 1031, 965, 869, 851, 747, 723, 639, 558, 457.

MS *m/z* (relative intensity) 417 (M^+, 22), 319 (100), 208 (21), 152 (32), 139 (75), 126 (26), 120 (26), 111(31), 104(31), 98 (64).

Elemental analysis for dihydrobromide $C_{20}H_{29}Br_2N_5O_3S$ ($M = 579.37$)

	C	H	N
Calculated	41.46 %	5.05 %	12.09 %
Found	41.45 %	5.07 %	12.05 %

$mp_{dihydrobromide}$ 195–197 °C

4a. $C_{15}H_{29}Br_3N_4OS$ ($M = 372$); yield 80,1 %; (δ in ppm; $CDCl_3$, 600 MHz); 172.87; 159.28; 138.48; 131.10; 130.04; 128.00; 126.46; 120.54; 56.47; 51.26; 45.44; 39.64; 32.76; 26.28; 20.49; 13.29;.TLC (dichloromethane:methanol: 19:1) $R_f = 0.32$.

IR (for dihydrobromide monohydrate; KBr) cm^{-1}: 3509, 3436, 3046, 2971, 2923, 2681, 2586, 2522, 2464, 2084, 1629, 1607, 1575, 1443, 1402, 1360, 1294, 1221, 1098, 1075, 1023, 969, 794, 743, 714, 631, 546.

MS *m/z* (relative intensity) 372 (M^+, 24), 274 (40), 237 (60), 224 (100), 152 (21), 139 (30), 112 (20), 105 (64), 98 (34), 77 (34).

Elemental analysis for dihydrobromide monohydrate $C_{20}H_{30}Br_2N_4OS$ H_2O ($M = 552.39$)

	C	H	N
Calculated	43.48 %	5.84 %	10.14 %
Found	43.73 %	5.74 %	10.20 %

$mp_{dihydrobromide}$ 224–226 °C

4b. $C_{21}H_{30}N_4OS$ ($M = 387$) yield 79,2 %; (δ in ppm; $CDCl_3$, 600 MHz); 172.67; 159.80; 140.06; 138.48; 128.32; 125.97; 120.45; 56.39; 51.34; 45.42; 39.75; 32.84; 26.16; 21.50; 20.46; 13.29; TLC (dichloromethane: methanol: concentrated ammonium hydroxide 89:10:1) $R_f = 0.51$.

IR (for dihydrobromide; KBr) cm^{-1}: 3430, 3079, 2967, 2920, 2637, 2564, 2452, 1611, 1479, 1437,1400, 1285, 1270, 1199, 1068, 1039, 968, 925, 873, 839, 757, 726, 583, 508.

MS *m/z* (relative intensity) 386 (M^+, 20), 288 (27), 237 (80), 224 (95), 152 (25), 139 (28), 119 (100)112 (31), 111 (45), 98 (39), 91 (36).

Elemental analysis for dihydrobromide $C_{20}H_{30}Br_2N_4OS$ ($M = 534.37$)

Calculated	45.99 %	5.88 %	10.22 %
Found	45.92 %	5.91 %	10.16 %

$mp_{dihydrobromide}$ 196–198 °C

4c. $C_{20}H_{27}ClN_4OS$ ($M = 407$) yield 78,3 %; (δ in ppm; $CDCl_3$, 600 MHz); 172.87; 159.28; 138.53; 136.18 129.26; 128.96; 127.53; 120.00; 56.39; 51.23; 45.57; 39.61; 32.82; 26.25; 20.52; 13.30; TLC (dichloromethane: methanol: concentrated ammonium hydroxide 89:10:1) $R_f = 0.74$

IR (for dihydrobromide; KBr) cm^{-1}: 3522, 3422, 3034, 2988; 2938, 2896, 2656, 2569, 2458, 1622, 1430, 1399, 1339, 1291, 1257, 1174, 1089, 1039, 968, 832, 793, 758, 728, 682, 600, 552, 480.

MS *m/z* (relative intensity) 406 (M^+, 18), 288 (27), 308 (28), 237 (34), 224 (100), 152 (64), 141 (21), 139 (92), 112 (31), 111 (43), 98 (45).

Elemental analysis for dihydrobromide $C_{20}H_{29}Br_2ClN_4OS$ ($M = 568.81$)

Calculated	42.22 %	5.14 %	9.85 %
Found	42.41 %	5.22 %	9.61 %

$mp_{dihydrobromide}$ 206–208 °C

4d. $C_{20}H_{27}N_5O_3S$ ($M = 417$) yield 83.0 %; (^{13}C δ in ppm; $CDCl_3$, 600 MHz); 172.98; 159.67; 148.27; 140.43; 138.48; 126.87; 123.71; 120.51; 56.42; 51.56; 45.48; 39.81; 32.76; 26.22; 20.51; 13.32; TLC (dichloromethane: methanol: 10:1) $R_f = 0.43$.

IR (for dihydrobromide monohydrate; KBr) cm^{-1}: 3451, 3039, 2968, 2934, 2903, 2784, 2696, 2601, 2515, 2457, 1625, 1599, 1524, 1445, 1429, 1404, 1353, 1290, 1260, 1176, 1095, 1033, 1009, 968, 870, 742, 725.

MS *m/z* (relative intensity) 417 (M^+, 26), 319 (55), 237 (20), 224 (100), 152 (27), 150 (39) 141 (21), 139 (34),120 (25), 112 (29), 111 (68), 98 (88).

Elemental analysis for dihydrobromide monohydrate $C_{20}H_{29}Br_2N_5O_3S$ H_2O ($M = 597.39$)

Calculated	40.20 %	5.23 %	11.72 %
Found	40.46 %	5.03 %	11.77 %

$mp_{dihydrobromide}$ 195–197 °C

Pharmacology

All compounds were tested for H_3 antagonistic effects in vitro on the guinea-pig jejunum using standard methods (Vollinga *et al*., 1992).

Male guinea pigs weighing 300–400 g were killed by a blow on the head. A portion of the small intestine, 20–50 cm proximal to the ileocaecal valve (jejunum), was removed and placed in Krebs buffer (composition (mM) NaCl 118; KCl 5.6; $MgSO_4$ 1.18; $CaCl_2$ 2.5; NaH_2PO_4 1.28; $NaHCO_3$ 25; glucose 5.5 and indomethacin (1×10^{-6} mol/L)). Whole jejunum segments (2 cm) were prepared and mounted between two platinum electrodes (4 mm apart) in 20 mL Krebs buffer, continuously gassed with 95 % O_2:5 % CO_2 and maintained at 37 °C. Contractions were recorded isotonically under 1.0 g tension with Hugo Sachs Hebel–Messvorsatz (Tl-2)/HF-modem

(Hugo Sachs Electronik, Hugstetten, Germany) connected to a pen recorder. After equilibration for 1 h with every 10 min washings, the muscle segments were stimulated maximally between 15 and 20 V and continuously at a frequency of 0.1 Hz and a duration of 0.5 ms, with rectangular-wave electrical pulses, delivered by a Grass Stimulator S-88 (Grass Instruments Co., Quincy, USA). After 30 min of stimulation, 5 min before adding (R)-α-methylhistamine, pyrilamine (1×10^{-5} mol/L concentration in organ bath) was added, and then cumulative concentration–response curves (half-log increments) of (R)-α-methylhistamine, H_3-agonist were recorded until no further change in response was found. Five minutes before adding the tested compounds, the pyrilamine (1×10^{-5} mol/L concentration in organ bath) was added, and after 20 min cumulative concentration–response curves (half-log increments) of (R)-α-methylhistamine, H_3-agonist, were recorded until no further change in response was found. Statistical analysis was carried out with the Students' t test. In all tests, $p < 0.05$ was considered statistically significant. The potency of an antagonist is expressed by its pA_2 value calculated from the Schild (Arunlakshana and Schild, 1959) regression analysis where at least three concentrations were used. The pA_2 values were compared with the potency of thioperamide.

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