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Original article

Non-imidazole histamine H_3 ligands, Part IV: SAR of 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives

Anna Frymarkiewicz, Krzysztof Walczyński*

Department of Synthesis and Technology of Drugs, Medical University, Muszyńskiego Street 1, 90-145 Łódź, Poland

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Dedicated to Professor Henk Timmerman on the occasion of his 70th birthday.

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H_3-Antagonists
1-[2-Thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives

ABSTRACT

A series of 1-[[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propyl]piperazine 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-methyl-2-phenyl-alkylaminoethyl)]-4-*n*-propyl]piperazine derivatives (**4c1**–**4c3**) have slightly higher activity than their 1-[2-thiazol-5-yl-(2-methyl-2-alkylaminoethyl)]-4-*n*-propylpiperazine analogues (**4b1**–**4b3**). In the 2-methylalkylamide series (**4a1**–**4a3**) a somewhat lower activity was observed. The most potent compound of the series is the 1-[2-thiazol-5-yl-(2-methyl-2-phenylpropylaminoethyl)]-4-*n*-propylpiperazine (**4c2**) with $pA_2 = 8.27$ (its alkyl analogue (**4b2**) showed $pA_2 = 7.53$ and the corresponding amide (**4a2**) displayed $pA_2 = 7.36$).
Selected compounds (**4b1**, **4b2**, **4c1** and **4c2**) were also tested (in vitro) for H_1 antagonistic effects in vitro applying standard methods (guinea pig ileum). None showed any H_1 antagonistic activity ($pA_2 < 4$).

1. Introduction

The third histamine receptor was discovered in 1983 by Arrang and co-workers [1]. This receptor subtype confirmed the function of histamine as a neurotransmitter. The H_3-receptor mediates the inhibition of synthesis and release of histamine from histaminergic neurons via a negative feedback loop [2,3] but also exerts modulatory effects on the other neurotransmitter systems, e.g. the cholinergic [4,5], dopaminergic [6], noradrenergic [7], and serotoninergic [8], glutamatergic [9] and peptidergic [10] systems in both the central and peripheral nervous systems.

The cloning of rodent and especially human H_3 receptors and the identification of different isoforms in rodents as well as in man has opened a new chapter in the understanding of the role of the third histamine receptor subtype [11–17].

Attempts to identify selective ligands for the H_3 receptor have resulted in the identification of several potent and selective H_3 ligands, both agonists and antagonists/inverse agonists. Most of the initial approaches have focused on structural modification of the endogenous ligand, histamine, and have resulted in a series of very potent imidazole-containing H_3 antagonists (inverse agonists) [18,19], for example, thioperamide [20], clobenpropit [21], GT-2331 – Pereceptin [22] or proxyfan [23] (Chart 1). As imidazole-derived ligands have an inhibitory effect of cytochrome P450 enzymes, caused by imidazole nitrogen complexation to heme iron in the active site of the enzyme [24] and leading to drug–drug interactions and moreover show pharmacokinetic constraints. The development of potent non-imidazole H_3 receptor compounds became attractive for the search for potential medicines.

A number of non-imidazole antagonists have since been reported. A successful approach was the replacement of the imidazole moiety by a pyrollidine group [25]; (UCL 1972; Chart 1) or piperazine and several other amines [26,27]. One of the most potent non-imidazole histamine H_3 receptor antagonists, reported so far is compound I, shown in Chart 1; this derivative possesses, also a strong inhibitory activity on the main histamine metabolising enzyme, histamine *N*-methyltransferase [28].

Previously we reported the synthesis and biological evaluation of 1-[(2-benzothiazole)-4-substituted]piperazine derivatives as non-imidazole histamine H_3-receptor antagonists [29,30]. We showed that the most potent compounds (in vitro screening) at the model are the *n*-propyl-, *i*-propyl- and allylbenzothiazole derivatives (2; Chart 1) with $pA_2 = 7.16$; 7.21; 7.10, respectively. These results suggested that for optimal size in the alkyl homologues series the substituent should consist of three carbon atoms, independent of the presence or the absence of a double bond. In the next step we studied the influence, on H_3-receptor antagonistic activity, of the introduction of an additional nitrogen

* Corresponding author. Tel.: +48 42 6779196; fax: +48 42 6779159.
E-mail address: kwalczynski@pharm.am.lodz.pl (K. Walczyński).

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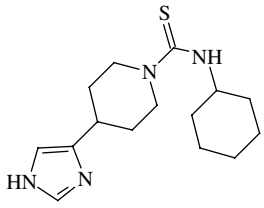
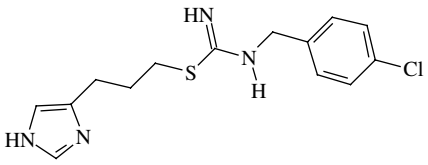
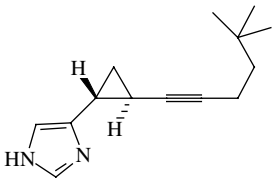
Imidazole-containing H_3-receptor antagonists



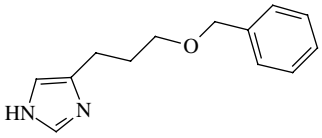
Thioperamide



Clobenpropit

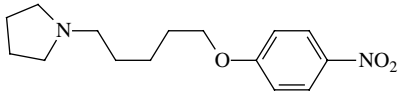


GT-2331

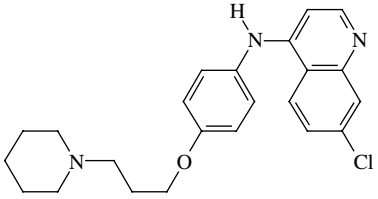


Proxyfan

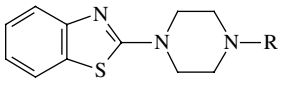
Non-imidazole his tamine H_3-receptor antagonists



UCL1972

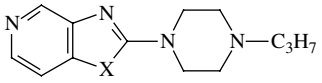


1



2

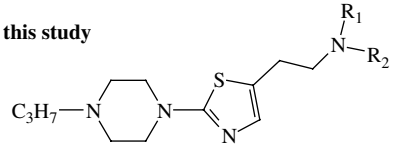
where R = C_3H_7, or  ; or $-CH_2CH=CH_2$



3

where X=N or O

The target molecules of this study



4

Chart 1. Structures of some known histamine H_3-receptor antagonists and the target molecules of this study.

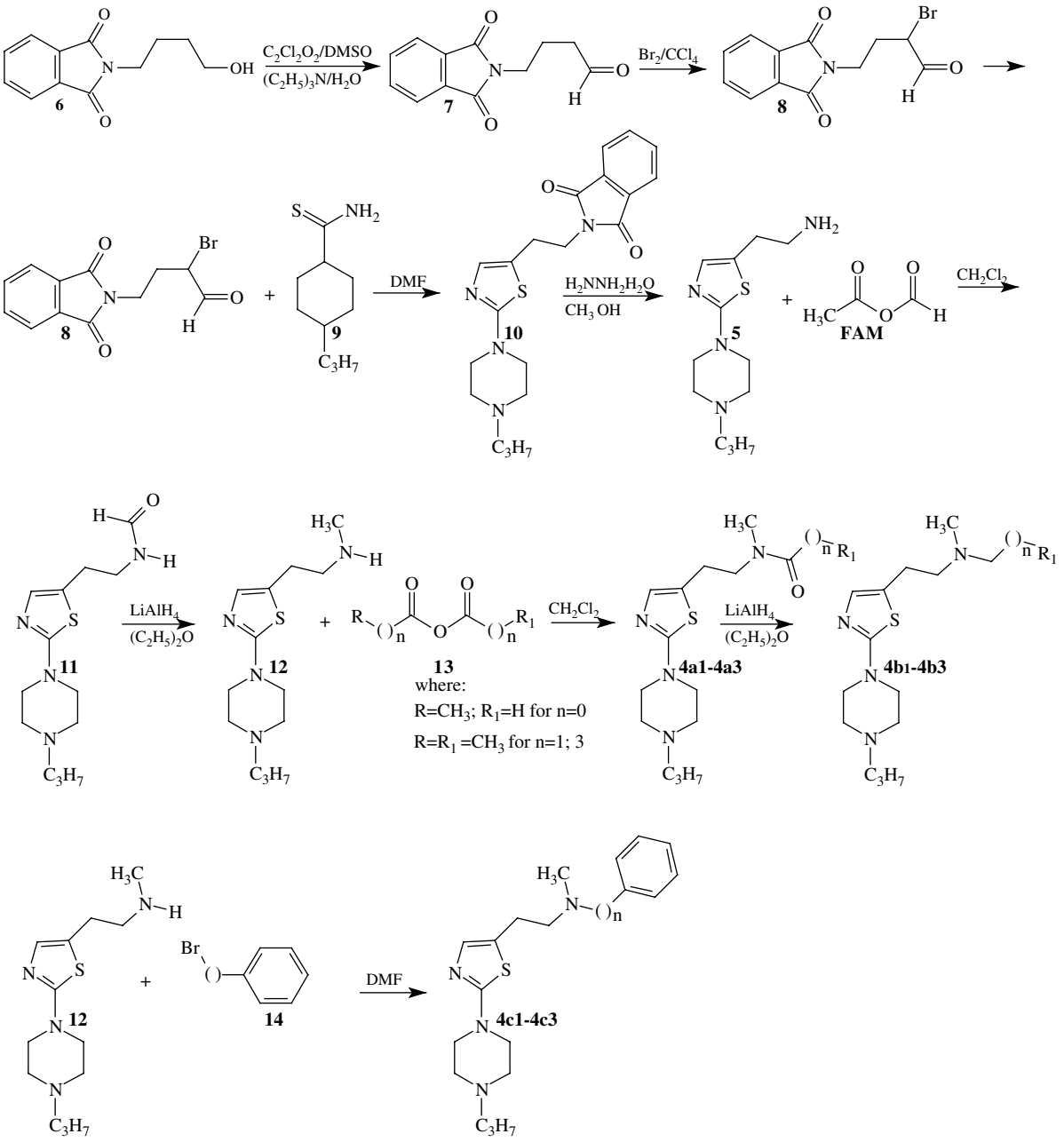
at various positions in the benzo ring and replacement of the sulphur atom by oxygen in the thiazole ring, keeping 1-*n*-propylpiperazine moiety present [31]. It appeared that in pairs of homologues the thiazolo derivatives have slightly higher activity than their oxazolo analogues. The most potent compound of the series is the 1-(2-thiazolo[5,4-c]pyridine)-4-*n*-propylpiperazine (3; Chart 1) with $pA_2 = 7.25$ (its oxazole analogue showed $pA_2 = 6.9$).

The SAR of both the series, e.g. 1-[(2-thiazolobenzo)-4-*n*-propyl]piperazines and 1-[(2-thiazolopyridine)-4-*n*-propyl]piperazines, showed no significant difference in H_3 activities. These results prompted us to replace the benzo ring by 2-methyl-2-alkylaminoethyl amide-, 2-methyl-2-alkylaminoethyl- and 2-methyl-2-phenylalkylaminoethyl- chain at position 5 of 1-(2-thiazol-5-yl)-4-*n*-propylpiperazine moiety. We have therefore prepared series of 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives and determined the H_3 antagonist activity of these compounds (in vitro tests; guinea pig jejunum) [32]. In this series we varied the length of the alkyl spacer from one to five methylene groups and additionally replaced the alkyl chain by phenylalkyl substituents. We also study the influence of the replacement of alkyl chain by the corresponding amides on H_3-receptor antagonist activity.

In the present study we report the synthesis and the preliminary pharmacological evaluation of new 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives.

2. Chemistry

The general synthetic procedure used in this study is illustrated in Scheme 1. The central building block of all title compounds was 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine (**5**). The phthalimidobutanol (**6**) was prepared form 4-aminobutanol and phthalic anhydride to yield 91% of the desired compound [33]. The 4-phthalimidobutyraldehyde (**7**) was obtained from 4-phthalimidobutanol (**6**) by reaction with oxalyl chloride/dimethyl sulfoxide, followed by proton abstraction with triethylamine and hydrolyses to the corresponding aldehyde. Bromination of the aldehyde was performed in carbon tetrachloride and after identification with NMR, the crude 2-bromo-4-phtalimidobutanal (**8**) [33] was used in the cyclization reaction (Scheme 1). 1-[2-Thiazol-5-yl-(2-phtalimidoethyl)]-4-*n*-propylpiperazine (**10**) was obtained by reaction of the 1-(4-*n*-propyl)piperazine thioamide (**9**) and 2-bromo-4-phtalimidobutanal (**8**) in anhydrous DMF under N_2 atmosphere, after purification by column chromatography. Subsequent hydrazinolysis, basification with sodium hydroxide and extraction with chloroform led to the pure amine (**5**), after separation by column chromatography. 1-[2-Thiazol-5-yl-(2-methyl-aminoethyl)]-4-*n*-propylpiperazine (**12**) was prepared from compound **5** by two step synthesis including formylation with formic acid–acetic anhydride (FAM) to compound **11** and finally reduction with $LiAlH_4$ in dry ethyl ether. 1-[2-Thiazol-5-yl-(2-metyl-2-alkylaminoethyl)]-4-*n*-propylpiperazines (**4b1**–**4b3**) were obtained by standard methods. Compound **12** was acetylated with an appropriate acid anhydride and next, obtained amides **4a1**–**4a3**



Scheme 1. The synthesis of 1-[2-[thiazol-5-yl-(2-methyl-2-alkylcarbonylaminoethyl)]-4-*n*-propyl]piperazine amides, 1-[2-thiazol-[5-(2-methyl-2-alkyl- and 2-methyl-2-phenyl-alkylaminoethyl)]-4-*n*-propyl]piperazines.

were reduced with $LiAlH_4$ in dry ethyl ether followed by purification with column chromatography.

1-[2-Thiazol-5-yl-(2-methyl-2-phenylalkylaminoethyl)]-4-*n*-propylpiperazine (**4c1**–**4c3**) were synthesized from compound **12** by alkylation with the corresponding primary phenyloalkyl halides with the presence of K_2CO_3 in DMF followed by purification with column chromatography. All free bases were treated with methanolic HBr and hydrobromides were precipitated with dry diethyl ether.

The 1-(4-*n*-propyl)piperazine thioamide (**9**) was directly obtained by the reaction of the 1-*n*-propylpiperazine dihydrobromide with potassium thiocyanate in aqueous solution.

The formic acid–acetic anhydride (FAM) was obtained according to Van Es and Stewens [34] by the action of formic acid on acetic anhydride. The 5-phenylpentyl bromide was obtained according to Collins and Davis [35]. The 5-phenyl-1-pentanol was converted into the bromide by treatment with 50% aqueous hydrobromic acid and concentrated sulphuric acid.

The 4-aminobutanol, phthalic anhydride, oxalyl chloride, 1-*n*-propylpiperazine dihydrobromide, propionic anhydride, pentanoic anhydride, benzyl bromide, 1-bromo-3-phenylpropane, 5-phenyl-1-pentanol, acetyl chloride, benzoyl chloride were all purchased from commercial sources.

3. Results and discussion

The presented series of 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine derivatives all possess, moderate to pronounced H_3-receptor antagonist potency (Table 1).

While there is no significant difference in activity among the primary amine (**5**) with $pA_2 = 7.19$ and methyl derivative (**12**) with $pA_2 = 7.20$, elongation of the second alkyl chain length from one to five methylene groups (**4b1**–**4b3**) results in a decrease of antagonist activity reaching the minimum for compound (**4b3**) ($pA_2 = 7.05$).

Replacement of the methylalkylamine substituents by the corresponding methylalkylamide groups leads to the compound (**4a1**–**4a3**), having a somewhat lower activity (almost on the same level, independent of the length of alkyl chain), than their alkyl analogues.

Replacement of hydrogen by a phenyl group at the end of *N*-alkyl chain leads to compounds (**4c1**–**4c3**) with $pA_2 = 7.76$; $pA_2 = 8.27$; $pA_2 = 7.25$, respectively. This is in opposition to the methylalkylamine series (**4b1**–**4b3**), where the elongation of the alkyl chain leads to decrease of potency. Replacement of hydrogen in the HN-methyl group by a benzyl and phenylpropyl group results in an increase of potency, reaching the maximum for compound (**4c2**) ($pA_2 = 8.27$), a further increase in the alkyl chain length to five methylene groups results in a decrease of potency for compound (**4c3**) ($pA_2 = 7.25$).

The highest potency for third homologous series is seen in the compound with the *N*-methyl-*N*-phenylpropylamino- substituent (**4c2**) ($pA_2 = 8.27$) and with slightly lower potencies for compounds **4c1** ($pA_2 = 7.75$) and **4b1** ($pA_2 = 7.78$) carrying *N*-methyl-*N*-benzylamino- and *N*,*N*-dimethylamino- substituents, respectively.

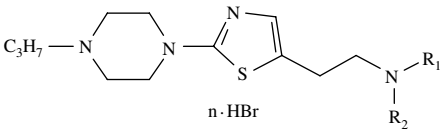
Compounds **4c2**, **4c1** and **4b1** may be interesting subjects for further investigation and development.

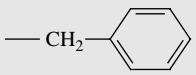
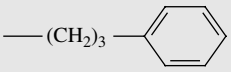
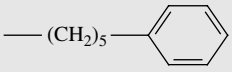
Additionally, selected compounds (**4b1**, **4b2**, **4c1** and **4c2**) were also tested for H_1 antagonistic effects in vitro, following standard methods, using the guinea pig ileum. None shows any H_1 antagonistic activity ($pA_2 < 4$; for pyrilamine $pA_2 = 8{,}96$).

4. Experimental protocols

General methods. All melting points (mp) were measured in open capillaries on an electrothermal apparatus and are uncorrected. For all compounds ^1H NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer. Chemical shifts are expressed in ppm downfield from internal TMS as reference. ^1H

Table 1
H_3 antagonistic activity of compounds **4a1**–**4a3**, **4b1**–**4b3**, **4c1**–**4c3**, **5**, **11** and **12** as tested on the in vitro test system on the guinea pig jejunum.



Compound	R_1	R_2	*n*	pA_2 (sem) H_3	N (*caviae*)
5	–H	–H	**3**	**7.19** (0.06)	**11** (3)
11	–CHO	–H	**2**	**6.93** (0.03)	**12** (4)
12	$-CH_3$	–H	**3**	**7.20** (0.02)	**18** (6)
4a1	$-CH_3$	–CHO	**2**	**7.26** (0.07)	**10** (3)
4a2	$-CH_3$	$-COCH_2CH_3$	**3**	**7.36** (0.04)	**12** (4)
4a3	$-CH_3$	$-CO(CH_2)_3CH_3$	**3**	**7.02** (0.03)	**12** (4)
4b1	$-CH_3$	$-CH_3$	**3**	**7.78** (0.03)	**21** (6)
4b2	$-CH_3$	$-CH_2CH_2CH_3$	**3**	**7.53** (0.05)	**18** (5)
4b3	$-CH_3$	$-CH_2(CH_2)_3CH_3$	**3**	**7.05** (0.07)	**20** (6)
4c1	$-CH_3$		**3**	**7.76** (0.06)	**18** (5)
4c2	$-CH_3$		**3**	**8.27** (0.05)	**20** (6)
4c3	CH_3		**3**	**7.25** (0.04)	**11** (5)
Thioperamide				**9.06** (0.07)	**18** (6)

sem – standard error of the mean; *N* – number of different animal preparation; *cavie* – number of animals; *n* – number of HBr.

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. Elemental analysis (C, H, N) for all compounds were measured on Heraeus EA 415-0 and are within ±0.4% of the theoretical values. TLC was performed on silica gel PF_{254} plates (Merck). Flash column chromatography was carried out using silica gel 30–60 μm (J.T. Baker B.V.), employing the same eluent as was indicated by TLC.

4.1. Chemistry

4.1.1. The synthesis of 1-[2-thiazol-5-yl-(2-phtalimidoethyl)]-4-n-propylpiperazine (**10**)

To a solution of 2-bromo-4-phthalimidobutanal (**8**) (0.2 mol) in 250.0 mL of anhydrous DMF was added under a N_2 atmosphere while stirring a solution of the 1-(4-*n*-propyl)piperazine thioamide (**9**) (0.2 mol) in 250.0 mL of anhydrous DMF, and the reaction mixture was heated at 120 °C for 3.0 h. After cooling, the solvent was removed in vacuo, the residue stirred with 1250.0 mL of anhydrous EtOH and cooled to 5 °C, the precipitate filtered off and washed with ether. The hydrobromide product was obtained as brown solid. The free base was obtained as follows: the hydrobromide of the phthalimide was mixed with saturated aqueous potassium carbonate solution overnight at room temperature. The solid was filtered, washed with water, ether and air dried to leave a light brown solid. The crude phthalimide (**10**) was recrystallised from acetone to give the pure product as colourless crystals.

Compound ***10***: $C_{20}H_{24}N_4O_2S$ ($M = 384$); yield 70.6%; mp 238–240 °C; ^{1}H NMR ($CDCl_3$): $\delta = 0.90$–0.94 (t, 3H, –C<u>H</u>$_3$, $J = 7.5$ Hz); $\delta = 1.48$–1.52 (m, 2H, –C<u>H</u>$_2$–); $\delta = 2.31$–2.36 (t, 2H, –C<u>H</u>$_2$–, $J = 7.5$); $\delta = 2.48$–2.54 (m, 4H, –C<u>H</u>$_2$–;–C<u>H</u>$_2$–); $\delta = 3.07$–3.13 (t, 2H, –C<u>H</u>$_2$–, $J = 6.9$); $\delta = 3.42$–3.47 (m, 4H, –C<u>H</u>$_2$–; –C<u>H</u>$_2$–); $\delta = 3.86$–3.91 (t, 2H, –C<u>H</u>$_2$–, $J = 7.5$); $\delta = 6.9$ (s, 1H, thiazole); $\delta = 7.68$–7.74 (m, 2H); $\delta = 7.81$–7.87 (m, 2H); TLC (dichloromethane:methanol, 19:2) $R_f = 0.69$.

4.1.2. The synthesis of 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-n-propylpiperazine (**5**)

The 1-[2-thiazol-5-yl-(2-phtalimidoethyl)]-4-*n*-propylpiperazine (**10**) (0.14 mol) was added to a solution of hydrazine monohydrate in methanol (280.0 mL, 1.0 M), and the reaction mixture was heated for 0.5 h until it became homogeneous. The reaction mixture was then stirred at room temperature for another 2 h. Concentration in vacuo provided a white sticky semi-solid, which was purified by column chromatography on silicagel. The title products were obtained as sticky oil. The free base was treated with methanolic HBr and hydrobromide was precipitated with dry diethyl ether.

$C_{12}H_{22}N_4S$ ($M = 254$); yield 73.0%; ^{1}H NMR ($CDCl_3$): $\delta = 0.90$–0.94 (t, 3H, –C<u>H</u>$_3$, $J = 7.5$ Hz); $\delta = 1.52$–5.6 (m, 2H, –C<u>H</u>$_2$–); $\delta = 1.67$ (s*, 2H, –N<u>H</u>$_2$); $\delta = 2.32$–2.37 (t, 2H, –C<u>H</u>$_2$–, $J = 7.5$); $\delta = 2.52$–2.56 (m, 4H, –C<u>H</u>$_2$–; –C<u>H</u>$_2$); $\delta = 2.75$–2.80 (t, 2H, –C<u>H</u>$_2$–, $J = 6.6$); $\delta = 2.90$–2.96 (t, 2H, –C<u>H</u>$_2$–, $J = 6.6$); $\delta = 3.43$–3.48 (m, 4H, –C<u>H</u>$_2$–; –C<u>H</u>$_2$–); $\delta = 6.88$ (s, 1H, thiazole); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 89:10:1) $R_f = 0.44$; $mp_{threehydrobromide} = 254$–$256$ °C.

Elemental analysis for threehydrobromide $C_{12}H_{25}Br_3N_4S$ ($M = 497.17$).

	C (%)	H (%)	N (%)
Calculated	28.99	5.07	11.27
Found	28.93	5.02	11.34

4.1.3. The synthesis of 1-[2-thiazol-5-yl-(2-formylaminoethyl)]-4-n-propylpiperazine (**11**)

To a solution of 1-[2-thiazol-5-yl-(2-aminoethyl)]-4-*n*-propylpiperazine (**5**) (0.1 mol) in 200.0 mL of anhydrous dichloromethane was added FAM (30 mL). The mixture was stirred at room temperature for 1 h. Then, water (50.0 mL) and ethyl acetate (50.0 mL) was added and the mixture was neutralized with K_2CO_3 and water layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to give compound **11** as a sticky semi-solid, which was crystallized from mixture *n*-hexane:ethyl acetate (8:1) to give the pure product as light yellow crystals. The free base was treated with methanolic HBr and hydrobromide was precipitated with dry diethyl ether.

Compound ***11***: $C_{13}H_{22}N_4SO$ ($M = 282$); yield 86.0%; mp 76–78 °C; ^{1}H NMR ($CDCl_3$): $\delta = 0.90$–0.95 (t, 3H, –C<u>H</u>$_3$, $J = 7.5$ Hz); $\delta = 1.52$–156 (m, 2H, –C<u>H</u>$_2$–); $\delta = 2.29$–2.34 (t, 2H, –C<u>H</u>$_2$–, $J = 7.5$); $\delta = 2.48$–2.54 (m, 4H, –C<u>H</u>$_2$–; –C<u>H</u>$_2$–); $\delta = 2.86$–2.92 (t, 2H, –C<u>H</u>$_2$–, $J = 6.6$); $\delta = 3.39$–3.49 (m, 4H, –C<u>H</u>$_2$–C<u>H</u>$_2$–); $\delta = 5.82$ (s*, 1H, –N<u>H</u>–); $\delta = 6.88$ (s, 1H, thiazole); $\delta = 8.16$ (s, 1H, –C<u>H</u>O); TLC (methylene chloride:methanol, 9:1) $R_f = 0.29$; $mp_{dihydrobromide} = 213$–$215$ °C.

Elemental analysis for dihydrobromide $C_{13}H_{25}Br_3N_4OS$ ($M = 444.18$).

	C (%)	H (%)	N (%)
Calculated	35.15	5.45	12.61
Found	35.0 6	5.47	12.36

4.1.4. The synthesis of 1-[2-thiazol-5-yl-(2-methylaminoethyl)]-4-n-propylpiperazine (**12**)

To a solution of 1-[2-thiazol-5-yl-(2-formylaminoethyl)]-4-*n*-propylpiperazine (**11**) (0.08 mol) in 240 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.31 mol). The mixture was stirred at room temperature for 1 h, and quenched by dropwise addition of water (13 mL), 10% of NaOH solution (13 mL), and water (13 mL). The suspension was stirred for 30 min, and filtered. The filter cake was washed twice with ether (50 mL each time). The combined organic extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the remaining material was purified by column chromatography on silicagel. The title products were obtained as sticky oil. The free base was treated with methanolic HBr and hydrobromide was precipitated with dry diethyl ether.

Compound ***12***: $C_{13}H_{24}N_4S$ ($M = 268$); yield 85%; ^{1}H NMR ($CDCl_3$): $\delta = 0.89$–0.94 (t, 3H, –C<u>H</u>$_3$, $J = 7.5$ Hz); $\delta = 1.49$–1.54 (m, 2H, –C<u>H</u>$_2$–); $\delta = 2.25$ (s*, 1H, –N<u>H</u>–); $\delta = 2.30$–2.37 (m, 2H, –C<u>H</u>$_2$–); $\delta = 2.45$ (s, 3H, –C<u>H</u>$_3$); $\delta = 2.50$–2.54 (m, 4H, –C<u>H</u>$_2$–; –C<u>H</u>$_2$–); $\delta = 2.77$–2.89 (m, 4H, –C<u>H</u>$_2$–C<u>H</u>$_2$–); $\delta = 3.44$–3.49 (m, 4H, –C<u>H</u>$_2$–; –C<u>H</u>$_2$–); $\delta = 6.88$ (s, 1H, thiazole); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 89:10:1) $R_f = 0.4$; $mp_{threehydrobromide} = 197$–199 °C.

Elemental analysis for threehydrobromide $C_{13}H_{27}Br_3N_4S$ ($M = 511.19$).

	C (%)	H (%)	N (%)
Calculated	30.66	4.91	11.01
Found	30.55	5.32	10.96

4.1.5. General method for the preparation of 1-[2-thiazol-5-yl-(2-methyl-2-alkylcarbonylaminoethyl)]-4-n-propylpiperazine amides (**4a1–4a3**)

To a solution of 1-[2-thiazol-5-yl-(2-methylaminoethyl)]-4-*n*-propylpiperazine (**12**) (0.001 mol) in 15.0 mL of anhydrous dichloromethane was added the corresponding acid anhydride (0.0015 mol). The mixture was stirred at room temperature for 2–3 h. Then, water (25.0 mL) and ethyl acetate (50.0 mL) was added

and the mixture was neutralized with K_2CO_3 and water layer was extracted with dichlorometane (2 × 15 mL). The combined organic extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to give compounds **4a1**–**4a3** as a sticky semi-solid. In each case, the crude product was purified by column chromatography. The free base was treated with methanolic HBr and hydrobromide was precipitated with dry diethyl ether.

Compound ***4a1***: $C_{14}H_{24}N_4OS$ ($M = 296$); yield 90.57%; ^{1}H NMR ($CDCl_3$): $\delta = 0.91$–0.96 (t, 3H, $\underline{CH_3}$–CH_2–CH_2–, $J = 7.5$ Hz); $\delta = 1.47$–1.59 (m, 2H, CH_3–$\underline{CH_2}$–CH_2–); $\delta = 2.32$–2.37 (m, 2H, CH_3–CH_2–$\underline{CH_2}$–); $\delta = 2.52$–2.55 (m, 4H, –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 2.88$–2.93 (m, 5H, $\underline{CH_3}$–N; –$\underline{CH_2}$–), $\delta = 3.48$–3.56 (m, 6H, –$\underline{CH_2}$–; –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 6{,}89$ (s, 1H, thiazole); $\delta = 7.99$ (s, 1H, $\underline{CH}$O); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 139:10:1) $R_f = 0.42$; $mp_{direehydrobromide} = 207$–$209$ °C.

Elemental analysis for dihydrobromide $C_{14}H_{26}Br_2N_4OS$ ($M = 457.8$).

	C (%)	H (%)	N (%)
Calculated	36.70	5.68	12.23
Found	36.45	5.39	11.92

Compound ***4a2***: $C_{16}H_{28}N_4OS$ ($M = 324$); yield 79.14%; ^{1}H NMR ($CDCl_3$): $\delta = 0.92$–0.98 (t, 3H, $\underline{CH_3}$–CH_2–CH_2–, $J = 7.5$ Hz); $\delta = 1.08$–1.18 (m, 2H, CH_3–$\underline{CH_2}$–CH_2–); $\delta = 1.51$–1.56 (m, 2H, CH_3–CH_2–$\underline{CH_2}$–); $\delta = 2.22$–2.27 (m, 2H, –$\underline{CH_2}$–); $\delta = 2.29$–$2{,}40$ (m, 3H, = N–$\underline{CH_3}$); $\delta = 2.50$–2.58 (m, 4H, –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 2.87$–2.95 (m, 5H, $\underline{CH_3}$–$\underline{CH_2}$–CO–); $\delta = 3.45$–3.51 (m, 4H, –$\underline{CH_2}$–; –$\underline{CH_2}$–), $\delta = 3.48$–3.56 (m, 2H, –$\underline{CH_2}$–); $\delta = 6.88$ (s, 1H, thiazole); $mp_{threehydrobromide} = 205$–$207$ °C.

Elemental analysis for threehydrobromide $C_{16}H_{31}Br_3N_4OS$ ($M = 567.26$).

	C (%)	H (%)	N (%)
Calculated	33.88	5.51	9.88
Found	34.01	5.32	9.84

Compound ***4a3***: $C_{18}H_{32}N_4OS$ ($M = 352$); yield 63.78%; ^{1}H NMR ($CDCl_3$): $\delta = 0.87$–0.95 (m, 6H, ($\underline{CH_3}$–)$_2$); $\delta = 1.24$–1.42 (m, 2H, –$\underline{CH_2}$–); $\delta = 1.47$–1.66 (m, 4H, –$\underline{CH_2}$–$\underline{CH_2}$–); $\delta = 2.20$–2.28 (t, 2H, –$\underline{CH_2}$–, $J = 7{,}5$ Hz,); $\delta = 2.31$–2.39 (m, 4H, –$\underline{CH_2}$–$\underline{CH_2}$–); $\delta = 2.50$–2.55 (m, 4H, –$\underline{CH_2}$–; $\underline{CH_2}$–); $\delta = 2.86$–2.91 (m, 2H, –$\underline{CH_2}$–); $\delta = 2.95$ (s, 3H, = N–$\underline{CH_3}$); $\delta = 3.43$–3.46 (m, 4H, $\underline{CH_2}$–; –$\underline{CH_2}$–), $\delta = 3.50$–3.56 (m, 2H, –$\underline{CH_2}$–); $\delta = 6.88$ (s, 1H, thiazole); $mp_{threehydrobromide} = 176$–$178$ °C.

Elemental analysis for threehydrobromide $C_{18}H_{35}Br_3N_4OS$ ($M = 595.31$).

	C (%)	H (%)	N (%)
Calculated	36.31	5.92	9.41
Found	36.75	6.18	9.62

*4.1.6. General method for the preparation of 1-[2-thiazol-5-yl-(2-methyl-2-alkylaminoethyl)]-4-*n*-propylpiperazines (**4b1**–**4b3**)*

To a solution of the appropriate 1-[2-thiazol-5-yl-(2-methyl-2-alkylcarbonylaminoethyl)]-4-*n*-propylpiperazine amide (**4a1**–**4a3**) (0.0005 mol) in 15.0 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.002 mol). The mixture was stirred at room temperature for 1 h, and quenched by dropwise addition of water (1.0 mL), 10% of NaOH solution (1.0 mL), and water (1.0 mL). The suspension was stirred for 30 min, and filtered. The filter cake was washed twice with ether (10 mL each time). The combined organic extracts were washed with water (3 × 15.0 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and remaining material was purified by column chromatography on silicagel. The title products were obtained as sticky oil. The free base was treated with methanolic HBr and hydrobromide was precipitated with dry diethyl ether.

Compound ***4b1***: $C_{14}H_{26}N_4S$ ($M = 282$); yield 94.0%; ^{1}H NMR ($CDCl_3$): $\delta = 0.92$–0.97 (t, 3H, $\underline{CH_3}$–CH_2–CH_2–, $J = 7.5$ Hz,); $\delta = 1.53$–1.58 (m, 2H, CH_3–$\underline{CH_2}$–CH_2–); $\delta = 2.270$ (s, 6H, (CH_3–)$_2$N–); $\delta = 2.34$–2.40 (t, 2H, CH_3–CH_2–$\underline{CH_2}$–, $J = 7.5$,); $\delta = 2.47$–2.59 (m, 6H, –$\underline{CH_2}$–; –$\underline{CH_2}$–CH_2–), $\delta = 2.80$–2.87 (m, 2H, –CH_2–); $\delta = 3.45$–3.52 (m, 4H, –$\underline{CH_2}$–$\underline{CH_2}$–); $\delta = 6.88$ (s, 1H, thiazole); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 89:10:1) $R_f = 0.62$; $mp_{threehydrobromide} = 302$–$304$ °C.

Elemental analysis for threehydrobromide $C_{14}H_{29}Br_3N_4S$ ($M = 525.22$).

	C (%)	H (%)	N (%)
Calculated	32.02	5.57	10.67
Found	32.03	5.34	10.85

Compound ***4b2***: $C_{16}H_{30}N_4S$ ($M = 310$); yield 66.5%; ^{1}H NMR ($CDCl_3$): $\delta = 0.91$–0.99 (m, 6H, (–$\underline{CH_3}$)$_2$); $\delta = 1.26$–1.60 (m, 4H, –$\underline{CH_2}$–CH_2–); $\delta = 2.25$ (s, 3H, = N–$\underline{CH_3}$); $\delta = 2.31$–2.36 (m, 4H, –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 2.51$–2.58 (m, 6H, –$\underline{CH_2}$–; –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 2.79$–2.82 (m, 2H, –$\underline{CH_2}$–); $\delta = 3.44$–3.49 (m, 4H, –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 6.87$ (s, 1H, thiazole); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 89:10:1) $R_f = 0.57$; $mp_{threehydrobromide} = 270$–$272$ °C.

Elemental analysis for threehydrobromide $C_{14}H_{33}Br_3N_4S$ ($M = 553.26$).

	C (%)	H (%)	N (%)
Calculated	34.73	6.01	10.13
Found	34.79	6.11	10.13

Compound ***4b3***: $C_{18}H_{34}N_4S$ ($M = 338$); yield 62.3%; ^{1}H NMR ($CDCl_3$): $\delta = 0.87$–0.95 (m, 6H, –(CH_3)$_2$); $\delta = 1.23$–1.36 (m, 4H, –$\underline{CH_2}$–$\underline{CH_2}$–); $\delta = 1.47$–1.66 (m, 4H, –$\underline{CH_2}$–$\underline{CH_2}$–); $\delta = 2.27$ (s, 3H, CH_3–); $\delta = 2.32$–2.39 (m, 4H, –$\underline{CH_2}$–$\underline{CH_2}$–); $\delta = 2.52$–2.58 (m, 6H, –$\underline{CH_2}$–; –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 2.77$–2.83 (m, 2H, –$\underline{CH_2}$–); $\delta = 3.43$–3.46 (m, 4H, $\underline{CH_2}$–; –$\underline{CH_2}$–) $\delta = 6.87$ (s, 1H, thiazole); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 139:10:1) $R_f = 0{,}57$; $mp_{threehydrobromide} = 285$–$287$ °C.

Elemental analysis for threehydrobromide $C_{18}H_{37}Br_3N_4S$ ($M = 581.31$).

	C (%)	H (%)	N (%)
Calculated	37.19	6.40	9.63
Found	37.17	6.65	9.59

*4.1.7. General method for the preparation of 1-[2-thiazol-5-yl-(2-methyl-2-phenylalkylaminoethyl)]-4-*n*-propylpiperazines (**4c1**–**4c3**)*

To a solution of 1-[2-thiazol-5-yl-(2-methylaminoethyl)]-4-*n*-propyl]piperazine (**12**) (0.00075 mol) with the presence of potassium carbonate (0.003 mol) in 20.0 mL of anhydrous DMF was added corresponding phenylalkyl halide (0.0008 mol). The reaction mixture was stirred for 2 h at room temperature in the case of compounds **4c1**, **4c2** and heated at 60 °C for 24 h in the case of compounds **4c3**. The solvent was evaporated and 25 mL of water was added to the residue and the mixture was extracted with dichloromethane (3 × 25 mL). The water layer was discarded and the solvent was dried and evaporated to give the crude product which was purified by column chromatography. The title products were obtained as sticky oil. The free base was treated with methanolic HBr and hydrobromide was precipitated with dry diethyl ether.

Compound ***4c1***: $C_{20}H_{30}N_4S$ ($M = 358$); yield 82%; ^{1}H NMR ($CDCl_3$): $\delta = 0.90$–0.97 (t, 3H, –$\underline{CH_3}$, $J = 7.5$ Hz); $\delta = 1.48$–1.53 (m, 2H, –$\underline{CH_2}$–); $\delta = 2.23$ (s, 3H, =N–$\underline{CH_3}$); $\delta = 2.35$–2.42 (t, 2H, –$\underline{CH_2}$–, $J = 7.5$); $\delta = 2.53$–2.60 (m, 4H, –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 2.60$–2.65 (t, 2H, –$\underline{CH_2}$–, $J = 7.2$); $\delta = 2.83$–2.89 (t, 2H, –$\underline{CH_2}$–, $J = 7.2$); $\delta = 3.43$–3.49 (m, 4H, –$\underline{CH_2}$–; –$\underline{CH_2}$–); $\delta = 6.54$ (s, 2H, –$\underline{CH_2}$–); $\delta = 6.88$ (s, 1H,

thiazole); $\delta = 7.21–7.34$ (m, 5H); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 89:10:1) $R_f = 0.36$. $mp_{treehydrobromide} = 256\text{-}258\ ^\circ C$.

Elemental analysis for threehydrobromide $C_{20}H_{33}Br_3N_4S$ ($M = 601.31$).

	C (%)	H (%)	N (%)
Calculated	39.95	5.53	9.32
Found	39.67	5.51	9.36

Compound ***4c2***: $C_{22}H_{34}N_4S$ ($M = 386$); yield 74%; ^1H NMR ($CDCl_3$): $\delta = 0.89–0.93$ (t, 3H, $-CH_3$, $J = 7.5$ Hz); $\delta = 1.48–1.53$ (m, 2H, $-CH_2-$); $\delta = 1.78–1.83$ (m, 2H, $-CH_2-$); $\delta = 2.26$ (s, 3H, $-CH_3$); $\delta = 2.29–2.34$ (m, 2H, $-CH_2-$); $\delta = 2.40–2.45$ (tm, 2H, $-CH_2-$); $\delta = 2.51–2.66$ (m, 6H, $-CH_2-$; $-CH_2-$; $-CH_2-$); $\delta = 2.76–2.81$ (m, 2H, $-CH_2-$); $\delta = 3.41–3.47$ (m, 4H, $-CH_2-$; $-CH_2-$); $\delta = 6.88$ (s, 1H, thiazole); $\delta = 7.17–7.25$ (m, 3H); $\delta = 7.26–7.30$ (m, 2H); TLC (hexane:acetone:triethylamine, 100:100:2) $R_f = 0.46$. $mp_{treehydrobromide} = 256–258\ ^\circ C$.

Elemental analysis for threehydrobromide $C_{22}H_{36}Br_3N_4S$ ($M = 629.37$).

	C (%)	H (%)	N (%)
Calculated	41.99	5.93	8.90
Found	41.68	5.85	8.97

Compound ***4c3***: $C_{24}H_{38}N_4S$ ($M = 414$); yield 46%; ^1H NMR ($CDCl_3$): $\delta = 0.90–0.97$ (t, 3H, $-CH_3$, $J = 7.5$ Hz); $\delta = 1.31–1.39$ (m, 2H, $-CH_2-$); $\delta = 1.66–1.68$ (m, 4H, $-CH_2-$; $-CH_2-$); $\delta = 2.26$ (s, 3H, $-CH_3$); $\delta = 2.31–2.39$ (m, 4H, $-CH_2-CH_2-$); $\delta = 2.51–2.63$ (m, 6H, $-CH_2-$; CH_2-; $-CH_2-$); $\delta = 2.78–2.84$ (t, 2H, $-CH_2-$, $J = 7.5$); $\delta = 3.42–3.47$ (m, 8H, $-CH_2-CH_2-$; $-CH_2-CH_2-$); $\delta = 6.88$ (s, 1H, thiazole); $\delta = 7.15–7.18$ (m, 3H); $\delta = 7.24–7.29$ (m, 2H); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 89:10:1) $R_f = 0.36$; $mp_{threehydrobromide} = 275–278\ ^\circ C$.

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

	C (%)	H (%)	N (%)
Calculated	43.85	6.29	8.52
Found	43.49	6.50	8.51

4.1.8. The synthesis of 1-(4-n-propyl)piperazine thioamide (**9**)

To a solution of 1-*n*-propylpiperazine dihydrobromide (0.043 mol) in 5.0 mL of water while stirring a solution of potassium thiocyanate (0.17 mol) in 13.0 mL of water was added, and the reaction mixture was heated at 70 °C for 24.0 h. After cooling, the solution was alkalized with KOH (pH = 14) and extracted with CH_2Cl_2 (5 × 30 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and the residue was crystallized twice from isopropanol.

$C_8H_{17}N_3S$ ($M = 187$); yield 43.0%; ^1H NMR ($CDCl_3$): $\delta = 0.85–0.92$ (t, 3H, $J = 7.5$ Hz, $-CH_3$); $\delta = 1.45–1.54$ (m, 2H, $-CH_2-CH_3$); $\delta = 2.21–2.37$ (m, 2H, $-CH_2-$); 2.40–2.53 (m, 4H, $-CH_2-$; $-CH_2$); $\delta = 3.73–3.87$ (m, 4H, $-CH_2-$; $-CH_2$); 5.72 (s*, 2H, $-NH_2$); TLC (methylene chloride:methanol:concentrated ammonium hydroxide, 89:10:1) $R_f = 0.76$; mp = 158–160 °C.

4.2. Pharmacology

All compounds were tested for H_3 antagonistic effects in vitro on the guinea pig jejunum [32] using standard methods.

Male guinea pigs weighing 300–400 g were sacrificed 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 washings every 10 min, 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 test $p < 0.05$ was considered statistically significant. The potency of an antagonist is expressed by its pA_2 value, calculated from the Schild [36] regression analysis where at least three concentrations were used. The pA_2 values were compared with the potency of thioperamide.

4.2.1. H_1 antagonistic activity for **4b1**, **4b2**, **4c1** and **4c2** compounds

Selected compounds were tested for H_1 antagonistic effects in vitro, following standard methods, using the guinea pig ileum [36].

Male guinea pigs weighing 300–400 g were sacrificed by a blow on the head. The ileum was excised and placed in phosphate buffer at room temperature (pH 7.4) containing (mM) NaCl (136.9); KCl (2.68); $NaHPO_4$ (7.19). After flushing the intraluminal contents, segments of about 2 cm long were cut and mounted for isotonic contractions in water jacketed 20 mL organ baths filled with oxygenated (O_2:CO_2 = 95:5, v/v) Krebs buffer containing (mM) NaCl (117.5); 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) at 37 °C under a constant load of 0.5 g. After a 30 min equilibration period with washings every 10 min, a submaximal priming dose of histamine (1 μM) was given and washed out (standard washing procedure: 3 changes of buffer during 30 min). After washing out, the antagonistic activity of given compounds was measured by recording a concentration response curve (CRC) for histamine in the presence of the testing compounds (**4b1**, **4b2**, **4c1** and **4c2**) which was added 5 min before histamine. This procedure was repeated with higher concentrations of the compounds. The antagonism was of a competitive nature causing a parallel shift of the CRC. The pA_2 values were calculated according to Arunlakshana and Schild [36]. The pA_2 values were compared with the potency of pyrilamine.

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