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Histamine H_1 receptor ligands Part II. Synthesis and in vitro pharmacology of 2-[2-(phenylamino)thiazol-4-yl]ethanamine and 2-(2-benzhydrylthiazol-4-yl)ethanamine derivatives

Krzysztof Walczyński [a,*], Roman Guryn [a], Obbe P. Zuiderveld [b], Ming-Qiang Zhang [b,1], Henk Timmerman [b]

[a] *Department of Synthesis and Technology of Drugs, Medical Academy, Muszyńskiego Street 1, 90-145 Łódz, Poland*
[b] *Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands*

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Abstract

New 2-[2-(phenylamino)thiazol-4-yl]ethanamine and 2-(2-benzhydrylthiazol-4-yl)ethanamine derivatives were prepared and tested in vitro as H_1 receptor antagonists. The compounds with 2-phenylamino substitution with *meta*-halide substituents at the phenyl ring, showed weak H_1-antagonistic activity (pA_2: 4.62–5.04) and this activity was completely lost in the case of *meta*-methyl substituent ($pA_2 < 4$). When the phenylamino group was replaced by benzhydryl groups of classic antihistamines, the resulting compounds exhibited slightly improved H_1-antagonistic activity (at the *meta*-position pA_2: 6.38–6.15; at the *para*-position pA_2: 6.04–5.87). © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Histamine H_1-receptor; H_1-antagonists; 2-[2-(Phenylamino)thiazol-4-yl]ethanamines; 2-(2-Benzhydrylthiazol-4-yl)ethanamines

1. Introduction

It is more than 60 years since the discovery of the first histamine H_1-receptor antagonists. Many different structural classes of compounds are now known to show high antagonist potency at this receptor. The therapeutic potential for antihistaminic drugs has increased due to the discovery of several new antihistaminic compounds, which are non-sedating. Some of these new compounds (cetirizine [1], loratadine [2], etc.) are widely and successfully used against histamine-mediated allergic responses (rhinitis, urticaria). It has been demonstrated that some modern H_1-antagonists, i.e. cetirizine and loratadine, have a remarkable specificity for H_1-receptors, whereas most classical H_1-antagonists are less selective and interact with many other receptors (i.e. adrenergic, serotonergic and cholinergic receptors) [3]. Generally, in attempting to identify histamine H_1-receptor antagonists with potentially greater clinical efficacy than earlier compounds, two approaches have been adopted. In one approach, attempts have been made to identify compounds combining H_1-receptor antagonism with additional and potentially beneficial properties [4–6]. The second approach has been made to antihistamines, which do not easily penetrate the CNS, in the hope of limiting side effects such as sedation and most recently arrhythmia.

These subjects have been extensively reviewed, including some detailed accounts of structure–activity relationships [7–11].

Previously we reported the synthesis and biological evaluation of 2-(2-phenylthiazol-4-yl)ethanamines and 2-(2-benzylthiazol-4-yl)ethanamines as histamine H_1-receptor ligands [12]. The compounds with 2-phenyl substitution showed H_1-agonistic activity. When the phenyl group was replaced by a benzyl group, the resulting compounds all exhibited weak H_1-antagonistic activity. These results prompted us to investigate a series of

* Corresponding author. Tel.: +48-42-78 3628; fax: +48-42-78 4796.

[1] Present address: Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH Scotland, UK.

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2-[2-(phenylamino)thiazol-4-yl]ethanamines and 2-(2-benzhydrylthiazol-4-yl)ethanamines, with the aim of explaining the influence of breaking the conjugation between phenyl and thiazole ring-systems on activity of 2-substituted-thiazoles. Since many classic H_1-antagonists carry the characteristic benzhydryl group which constitutes, together with the tertiary amine, the pharmacophore of histamine H_1-antagonists, we also investigated the influence of substituents in the second phenyl ring on antagonistic activity in comparison with a series of 2-(2-benzylthiazol-4-yl)ethanamines.

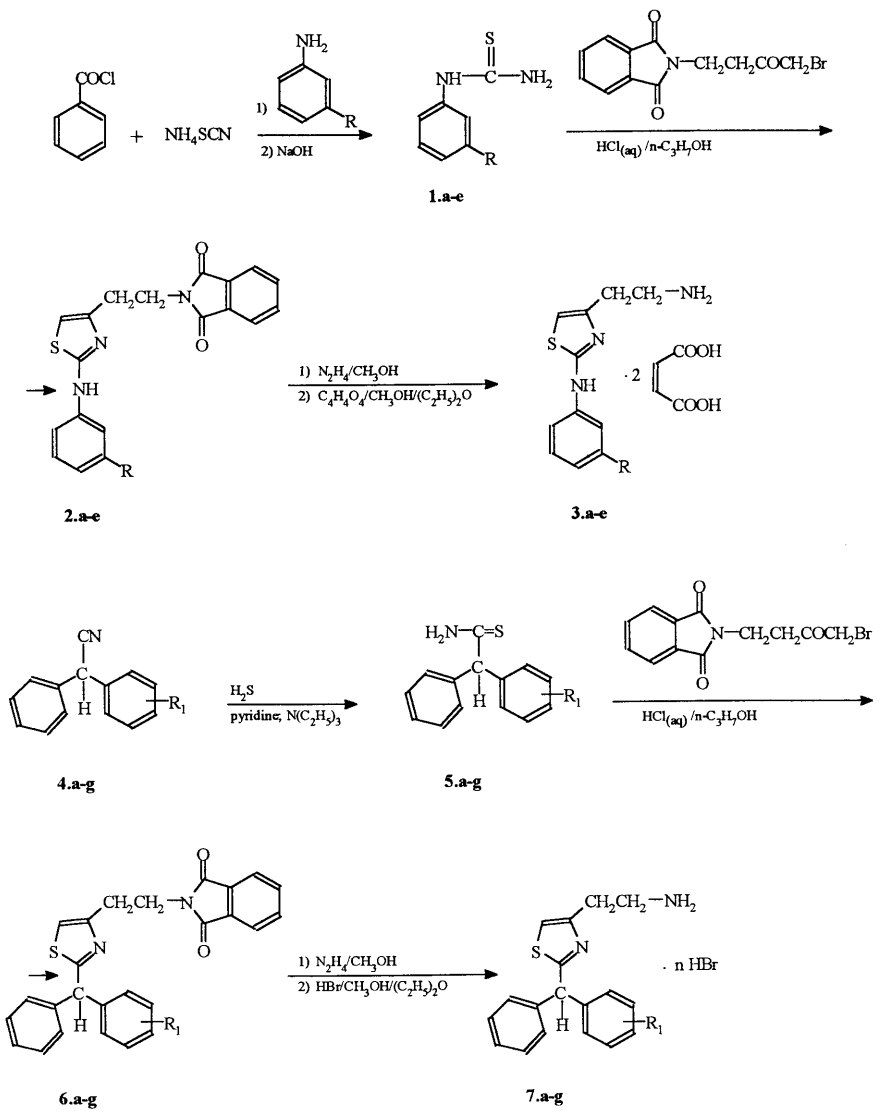
2. Chemistry

All 2-substituted-thiazol-4-ylethanamine derivatives were prepared using well established pathways (Scheme 1). The 3-substituted-anilines, and the 3- and 4-substituted-phenylacetonitriles were purchased from commercial sources.

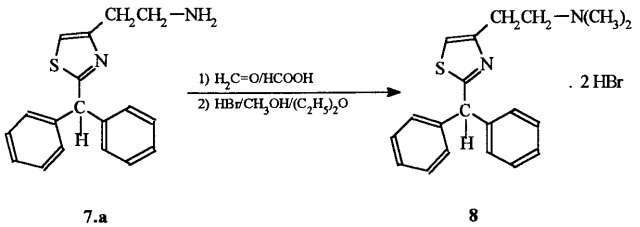
The appropriate phenylthioureas (**1a**–**e**) were obtained according to Frank and Smith [13] by the action of benzoyl isothiocyanate on 3-substituted aniline and alkaline hydrolysis of obtained 1-benzoyl-2-(3-substituted-phenyl)thiourea.

The appropriate α,α-diphenylacetonitriles (**4a**–**g**) were directly obtained according to Robb and Schultz [14] by the reaction of the crude α-bromo-α-phenylacetonitrile (obtained by the reaction of the 3- or 4-substituted-benzylnitrile with bromine) with benzene in the presence of anhydrous aluminum trichloride.

The appropriate benzhydrylthioamides (**5a**–**g**) were prepared according to Fairfull et al. [15] by the reaction of the nitrile with hydrogen sulfide in pyridine in the presence of triethylamine.

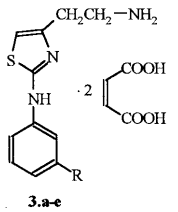


Scheme 1. Synthesis of 2-[2-(phenylamino)thiazol-4-yl] ethanamines (**3a**–**e**) and 2-(2-benzhydrylthiazol-4-yl)ethanamines (**7a**–**g**).



Scheme 2. Synthesis of *N*,*N*-dimethyl-2-(2-benzhydrylthiazol-4-yl)ethanamine (**8**).

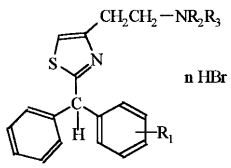
Table 1
Structures and results of the pharmacological screening on the isolated guinea-pig ileum for 2-[2-(phenylamino)thiazol-4-yl] ethanamines



3.a-e

Comp.	R	$pA_2 \pm sem(n)$
3a	H	$4.44 \pm 0.08(9)$
3b	F	$4.62 \pm 0.14(9)$
3c	Cl	$4.61 \pm 0.19(6)$
3d	Br	$5.04 \pm 0.07(6)$
3e	CH_3	$<4(9)$
Temelastine		$9.63 \pm 0.07(11)$

Table 2
Structures and results of the pharmacological screening on the isolated guinea-pig ileum for 2-(2-benzhydrylthiazol-4-yl)ethanamines



7.a-g and 8

Comp.	3-R_1	4-R_1	R_2,R_3	$pA_2 \pm sem(n)$
7a	H	H	H,H	$5.88 \pm 0.11(7)$
7b	F	H	H,H	$6.15 \pm 0.15(7)$
7c	Cl	H	H,H	$6.38 \pm 0.15(6)$
7d	Br	H	H,H	$6.16 \pm 0.16(5)$
7e	H	F	H,H	$5.99 \pm 0.18(7)$
7f	H	Cl	H,H	$6.04 \pm 0.13(6)$
7g	H	Br	H,H	$5.87 \pm 0.12(6)$
8	H	H	CH_3,CH_3	$5.98 \pm 0.14(6)$
Temelastine				$9.63 \pm 0.07(11)$

2-[2-(Phenylamino)thiazol-4-yl]ethyl-4-phthalimides (**2a**–**e**) and 2-(2-benzhydrylthiazol-4-yl)ethyl-4-phthalimides (**6a**–**g**) were obtained by reaction of the corresponding thioamide with 1-bromo-4-phthalimidobutanone-2 [16] in *n*-propanol in the presence of concentrated hydrochloric acid. All phthalimide derivatives were purified by column chromatography.

2-[2-(Phenylamino)thiazol-4-yl]ethanamines (**3a**–**e**) and 2-(2-benzhydrylthiazol-4-yl)ethanamines (**7a**–**g**) were obtained after hydrazinolysis of the corresponding phthalimides, followed by purification by column chromatography.

N,*N*-Dimethyl-2-(2-benzhydrylthiazol-4-yl)ethanamine (**8**) was prepared by reaction of the 2-(2-benzhydrylthiazol-4-yl)ethanamine (**7a**) with formaldehyde in formic acid (Scheme 2). The crude product was purified by column chromatography.

3. Pharmacology

The histaminergic H_1 antagonism of the compounds was established on isolated guinea pig ileum by conventional methods; the pA_2 values were compared with the potency of temelastine (Tables 1 and 2) [17].

4. Results and discussion

2-[2-(Phenylamino)thiazol-4-yl]ethanamines (**3a**–**e**), 2-(2-benzhydrylthiazol-4-yl)ethanamines (**7a**–**g**) and *N*,*N*-dimethyl-2-(2-benzhydrylthiazol-4-yl)ethanamine (**8**) were tested for histamine H_1-receptor activity in vitro on isolated guinea pig ileum as described in the Section 5.

The data reported in Table 1 show that the phenylamine group attached at position 2 in 4-thiazolethanamine yields weak H_1-antagonists (**3a**–**d**); in the case of the 3-methyl analogue **3e** the H_1-activity was completely lost.

All 2-(2-benzhydrylthiazol-4-yl)ethanamines and *N*,*N*-dimethyl-2-(2-benzhydrylthiazol-4-yl)ethanamine (**7a**–**g** and **8**) showed weak H_1-antagonistic activity (Table 2). The antagonistic activities of the present series with the benzhydryl group substituted at position C2 of the thiazole ring **7a**–**g** are comparable with the activities of the corresponding 2-(benzhydryl)histamines [18]. No definite structure–activity relationships can be drawn from the present series as the influence of a substituent in the benzhydryl group is only seen for *meta* substituents; the activity of **7b**–**d** is slightly higher than that of the unsubstituted compound **7a**, whereas in the classical diphenhydramines type of compounds only *para* substitution increases the H_1 activity. We conclude therefore that the benzhydryl groups play a different role in both classes.

The same conclusion can be reached by comparing the activity of the present benzhydryl compounds with these of the corresponding benzyl analogues, the latter showing a somewhat lighter antagonistic activity, whereas in the classic compounds the benzene analogs have almost completely lost the H_1 blocking properties.

5. Experimental

5.1. Chemistry

All melting points (m.p.) were taken in open capillaries on an electrothermal apparatus and are uncorrected. For all compounds ^{1}H NMR spectra were recorded on a Varian EM 360 (60 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from the internal standard TMS. ^{1}H NMR data are reported in the order: multiplicity (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 $\pm 0.4\%$ of the theoretical values. TLC was performed on silica gel PF_{254} plates (Merck). Column chromatography was carried out using silica gel 30–60 μm (J.T. Baker), employing the same eluent as was indicated by TLC.

5.2. General method for the preparation of α,α-diphenylacetonitriles — 4a–g

An appropriate phenylacetonitrile solution (0.35 mol) in benzene was placed in a flask equipped with a dropping funnel and an efficient stirrer, and heated to 110°C. Bromine (0.39 mol) was added over a period of 1 h (during the addition and for 15 min thereafter the temperature of the liquid was maintained at 105–110°C). The resulting benzene solution of the corresponding α-bromo-α-phenylacetonitrile was added in small portions to the boiling mixture, containing powdered anhydrous aluminum trichloride (0.35 mol) in 130.0 ml of dry benzene, over a period of 2 h. After the addition was complete, the reaction mixture was refluxed for an additional 1 h period. The flask was then cooled, and the mixture was poured into a stirred mixture of 350 g of crushed ice and 35 ml of concentrated hydrochloric acid. The benzene layer was separated. The aqueous layer was extracted with 200 ml of ether in two equal portions. The ether and benzene solutions were combined and washed successively with water, saturated sodium bicarbonate solution and water. The organic layer was dried over 50 g of anhydrous sodium sulfate. The drying agent was separated from the solution, and the solvents were removed by heating on a steam bath. The residue was distilled under reduced pressure. The solid was then recrystallized from isopropyl alcohol. **4a**. $C_{14}H_{11}N$ (193); b.p.: 122–125°C/1–2 mmHg. M.p.: 74–75°C [16]. M.p.: 71–73°C. Yield: 76%. **4b**. $C_{14}H_{10}FN$ (211). ^{1}H NMR ($CDCl_3$–TMS) (δ): 5.1 (s, 1H, CH); 7.40 (m, 9H, arom.). B.p.: 143–147°C/0.3 mmHg. Sticky oil. Yield: 71%. **4c**. $C_{14}H_{10}ClN$ (227.5). B.p.: 163–166°C/0.1 mmHg. M.p.: 50.5–52.5°C. Yield: 67%. **4d**. $C_{14}H_{10}BrN$ (271.9). B.p.: 160–164°C/0.2 mmHg. M.p.: 76–78°C. Yield: 63%. **4e**. $C_{14}H_{10}FN$ (211). B.p.: 140–146°C/0.3 mmHg. M.p.: 43–44°C. Yield: 65%. **4f**. $C_{14}H_{10}ClN$ (227.5). ^{1}H NMR ($CDCl_3$–TMS) (δ): 5.15 (s, 1H, CH); 7.4 (m, 9H, arom.). B.p.: 154–157°C/0.3 mmHg. M.p.: 74–75°C. Yield: 79%. **4g**. $C_{14}H_{10}BrN$ (271.9). B.p.: 166–168°C/0.1 mmHg. M.p.: 80.5–81°C. Yield: 70%.

5.3. General method for the preparation of thioureas — 1a–e

Benzoyl chloride (0.1 mol) was added dropwise to a solution of ammonium thiocyanate (0.11 mol) in 50 ml of dry acetone. After the addition was complete, the mixture was refluxed for 5 min. A solution of the appropriate aniline (0.1 mol) in 25 ml of dry acetone was then added at such a rate that the solution refluxed gently. The mixture was poured into 750 ml of water, and the resulting precipitate was separated by filtration. The crystals were treated for 5 min with a boiling solution of 15 g of sodium hydroxide in 135 ml of water. The solution was acidified with concentrated hydrochloric acid and then made slightly basic with ammonium hydroxide. The solid was collected, washed with water, and recrystallized from toluene. **1a**. $C_7H_8N_2S$ (152). M.p.: 152.5–153°C [12]. M.p.:: 152–154°C. Yield: 75%. **1b**. $C_7H_7FN_2S$ (170). M.p.: 115–117.5°C. Yield: 70%. **1c**. $C_7H_7ClN_2S$ (186.5). M.p.: 139–140.5°C. Yield: 71%. **1d**. $C_7H_7BrN_2S$ (230.9). M.p.: 154–155°C. Yield: 73%. **1e**. $C_8H_{10}N_2S$ (166). ^{1}H NMR (DMSO-d_6) (δ): 2.3 (s, 3H, CH_3); 6.8–7.2 (m, 4H, arom.); 7.35 (s*, 2H, NH_2); 9.9 (s*, 1H, NH). M.p.: 100–102.5°C. Yield: 65%.

5.4. General method for the preparation of benzhydrylthioamides — 5a–g

The appropriate nitrile (0.1 mol) was dissolved in at least an equal weight of dry pyridine and triethylamine (0.1 mol) was added. Dry hydrogen sulfide was passed through the solution in a steady stream for 12 h at room temperature (r.t.). The mixture was poured into a stirred solution of 1500 ml of water and 100 ml of concentrated hydrochloric acid, and the thioamide collected by filtration. All thioamides were crystallized from ethanol. TLC (9:1 chloroform–ethyl acetate). **5a**. $C_{14}H_{13}N_2S$ (241). M.p.: 146–148°C. Yield: 95%. TLC ($R_f = 0.57$). **5b**. $C_{14}H_{12}FN_2S$ (259). M.p.: 119–120.5°C.

Yield: 56%. TLC ($R_f = 0.51$). **5c**. $C_{14}H_{12}ClN_2S$ (275.5). M.p.: 120–121°C. Yield: 91%. TLC ($R_f = 0.53$). **5d**. $C_{14}H_{12}BrN_2S$ (319.9). ^1H NMR ($CDCl_3$–TMS) (δ): 5.65 (s, 1H, CH); 6.95 (s*, 2H, NH_2); 7.3 (m, 9H, arom.). M.p.: 113–115°C. Yield: 58%. TLC ($R_f = 0.58$). **5e**. $C_{14}H_{12}FN_2S$ (259). M.p.: 127–129°C. Yield: 68%. TLC ($R_f = 0.50$). **5f**. $C_{14}H_{12}ClN_2S$ (275.5). M.p.: 167–168°C. Yield: 58%. TLC ($R_f = 0.50$). **5g**. $C_{14}H_{12}BrN_2S$ (319.9). M.p.: 173–174°C. Yield: 84%. TLC ($R_f = 0.49$).

5.5. General method for the preparation of phthalimides — 2a–e and 6a–g

1-Bromo-4-phthalimido-2-butanone (0.01 mol) and the appropriate thiourea or thioamide (0.02 mol) were mixed with *n*-propanol (50.0 ml) and concentrated hydrochloric acid (5.0 ml), and the reaction mixture was heated to reflux for 2 h. After cooling, the precipitate was filtered off and washed with *n*-propanol and ether. After air drying, the product was obtained as yellowish hydrochloride.

The free base, in each case, was obtained as follows: the salt of an appropriate phthalimide was treated with saturated aqueous potassium carbonate solution overnight at r.t. The solid was filtered, washed with water, ether and air dried to leave a white or light brown product. All phthalimide derivatives were purified by column chromatography on silica gel (eluent: 9:1 chloroform–ethyl acetate) for 2-[2-(phenylamino)thiazol-4-yl]ethyl-4-phthalimides and 95:5 dichloromethane–ethyl acetate for 2-(2-benzhydrylthiazol-4-yl)ethyl-4-phthalimides). **2a**. $C_{19}H_{15}N_3O_2S$ (349). M.p.: 162–165°C. Yield: 62%. TLC ($R_f = 0.39$). **2b**. $C_{19}H_{14}FN_3O_2S$ (367). M.p.: 142.5–144.5°C. Yield: 44.5%. TLC ($R_f = 0.36$). **2c**. $C_{19}H_{14}ClN_3O_2S$ (383.5). ^1H NMR ($CDCl_3$–TMS) (δ): 3.0 (t, $J = 7$ Hz, 2H, CH_2); 4.05 (t, $J = 7$ Hz, 2H, CH_2); 6.35 (s, $H_{thiazole}$); 7.05 (m, 1H, arom.); 7.4 (m, 3H, arom); 7.7 (m, 4H, arom.); 7.9 (s*, 1H, NH). M.p.: 148–150°C. Yield: 36.5%. TLC ($R_f = 0.12$). **2d**. $C_{19}H_{14}BrN_3O_2S$ (427.9). M.p.: 167–168°C. Yield: 31%. TLC ($R_f = 0.66$). **2e**. $C_{20}H_{17}N_3O_2S$ (363). M.p.: 126.5–128.5°C. Yield: 74.0%. TLC ($R_f = 0.10$). **6a**. $C_{26}H_{20}N_2O_2S$ (424). M.p.: 110–111°C. Yield: 67%. TLC ($R_f = 0.46$). **6b**. $C_{26}H_{19}FN_2O_2S$ (442). Sticky oil. Yield: 86%. TLC ($R_f = 0.46$). **6c**. $C_{26}H_{19}ClN_2O_2S$ (458.5). Sticky oil. Yield: 70%. TLC ($R_f = 0.47$). **6d**. $C_{26}H_{19}BrN_2O_2S$ (502.9). ^1H NMR ($CDCl_3$–TMS) (δ): 3.05 (t, $J = 7$ Hz, 2H, CH_2); 4.1 (t, $J = 7$ Hz, 2H, CH_2); 5.75 (s, 1H, CH); 6.9 (s, 1H, $H_{thiazole}$ 7.5 (m, 9H, arom.); 8.0 (m, 4H, arom.). Sticky oil. Yield: 60%. TLC ($R_f = 0.40$). **6e**. $C_{26}H_{19}FN_2O_2S$ (442). Sticky oil. Yield: 65%. TLC ($R_f = 0.47$). **6f**. $C_{26}H_{19}ClN_2O_2S$ (458.5). Sticky oil. Yield: 59%. TLC ($R_f = 0.51$). **6g**. $C_{26}H_{19}BrN_2O_2S$ (502.9). Sticky oil. Yield: 60%. TLC ($R_f = 0.47$).

5.6. General methods for the preparation of the thiazoles 3a–e and 7a–g

The appropriate 2-[2-(phenylamino)thiazol-4-yl]ethyl-4-phthalimide or 2-(2-benzhydryl-thiazol-4-yl)ethyl-4-phthalimide (0.0025 mol) was added to a solution of hydrazine in methanol (50.0 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 r.t. for another 2 h. Concentration in vacuum provided a white sticky semi-solid, which was purified by column chromatography (eluent: 88:20:2 chloroform–methanol–concentrated ammonium hydroxide). The title products were obtained as a sticky oils. **3a**. $C_{11}H_{13}N_3S$ (219). Yield: 34%. TLC ($R_f = 0.30$). $C_{11}H_{13}N_3S{\cdot}2C_4H_4O_4$ (451). M.p.: 146–147.5°C. **3b**. $C_{11}H_{12}FN_3S$ (237). Yield: 32%. ^1H NMR ($CDCl_3$–TMS) (δ): 2.7 (t, $J = 6$ Hz, 2H, CH_2); 3.1 (t, $J = 6$ Hz, 2H, CH_2); 4.1 (s*, 2H, NH_2); 6.3 (s, 1H, $H_{thiazole}$); 6.8 (m, 1H, arom.); 7.2 (m, 3H, arom.); 7.45 (s*, 1H, NH). TLC ($R_f = 0.61$). $C_{11}H_{12}FN_3S{\cdot}2C_4H_4O_4$ (469). M.p.: 153–154.5°C. **3c**. $C_{11}H_{12}ClN_3S$ (253.5). Yield: 31%. TLC ($R_f = 0.18$). $C_{11}H_{12}ClN_3S{\cdot}2C_4H_4O_4$ (485.5). M.p.: 151–153°C. **3d**. $C_{11}H_{12}BrN_3S$ (297.9). Yield: 28%. TLC ($R_f = 0.24$). $C_{11}H_{12}BrN_3S{\cdot}2C_4H_4O_4$ (530). M.p.: 162–163°C. **3e**. $C_{12}H_{15}N_3S$ (233). Yield: 67%. TLC ($R_f = 0.43$) $C_{12}H_{15}N_3S{\cdot}2C_4H_4O_4$ (465). M.p.: 146–147°C.

All free bases were treated with methanolic maleic acid and maleic acid salts were precipitated with dry diethyl ether. **7a**. $C_{18}H_{18}N_2S$ (294). Yield: 72%. TLC ($R_f = 0.14$). $C_{18}H_{18}N_2S{\cdot}2HBr$ (455.8). M.p.: 209–211°C. **7b**. $C_{18}H_{17}FN_2S$ (312). Yield: 43%. ^1H NMR ($CDCl_3$–TMS) (δ): 1.75 (s*, 2H, NH_2); 3.0 (m, 4H, $2CH_2$); 5.8 (s, 1H, CH); 6.9 (s, 1H, $H_{thiazole}$); 7.3 (m, 9H, arom.). TLC ($R_f = 0.22$). $C_{18}H_{17}FN_2S{\cdot}HBr$ (393.3). M.p.: 192–193°C. **7c**. $C_{18}H_{17}ClN_2S$ (328.5). Yield: 52%. TLC ($R_f = 0.26$). $C_{18}H_{17}ClN_2S{\cdot}HBr$ (409.78). M.p.: 198–200°C. **7d**. $C_{18}H_{17}BrN_2S$ (372.9). Yield: 73%. TLC ($R_f = 0.22$). $C_{18}H_{17}BrN_2S{\cdot}HBr$ (454.2). M.p.: 144–146°C. **7e**. $C_{18}H_{17}FN_2S$ (312). Yield: 72%. TLC ($R_f = 0.27$). $C_{18}H_{17}FN_2S{\cdot}HBr$ (393.3). M.p.: 179–181°C. **7f**. $C_{18}H_{17}ClN_2S$ (328.5). Yield: 83%. TLC ($R_f = 0.22$). $C_{18}H_{17}ClN_2S{\cdot}2HBr$ (490.7). M.p.: 204–206°C. **7g** $C_{18}H_{17}BrN_2S$ (372.9). Yield: 85%. TLC ($R_f = 0.22$). $C_{18}H_{17}BrN_2S{\cdot}HBr$ (454.2). M.p.: 188–189°C.

All free bases were treated with methanolic HBr and hydrobromides were precipitated with dry diethyl ether.

5.7. N,N-Dimethyl-2-(2-benzhydrylthiazol-4-yl)-ethanamine (8)

2-(2-Benzhydrylthiazol-4-yl)ethanamine (1.40 g, 0.005 mol) was dissolved in 100% formic acid (11.5 g) and 36% formaldehyde (0.9 g) was added. The mixture was heated for 10 h at 100–105°C. After cooling the mix

ture was alkalinized with sodium hydroxide to pH 12 and extracted with diethyl ether (3×50.0 ml). The crude product, was purified by column chromatography on silica gel (eluent: 90:10:1 chloroform–methanol–concentrated ammonium hydroxide). **8**. $C_{20}H_{22}N_2S$ (322). Yield: 47%. ^1H NMR ($CDCl_3$–TMS) (δ): 2.3 (s, 6H, $2CH_3$); 2.75 (t, $J = 6$ Hz, 2H, CH_2); 2.95 (t, $J = 6$ Hz, 2H, CH_2); 5.9 (s, 1H, CH); 6.6 (s, 1H, $H_{thiazole}$); 7.4 (m, 10H, arom.). TLC ($R_f = 0.24$). $C_{20}H_{22}N_2S \cdot 2HBr$ (484.3). M.p.: 244–246°C.

5.8. Pharmacology

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 r.t. (pH 7.4) containing NaCl (136.9 mM); KCl (2.68 mM); $NaHPO_4$ (7.19 mM). After flushing the intraluminal contents, segments about 2 cm were cut and mounted for isotonic contractions in water jacked 20 ml organ baths filled with oxygenated (95:5 O_2–CO_2, v/v) Krebs buffer containing NaCl (117.5 mM); KCl (5.6 mM); $MgSO_4$ (1.18 mM); $CaCl_2$ (2.5 mM); NaH_2PO_4 (1.28 mM); $NaHCO_3$ (25 mM); glucose (5.5 mM) at 37°C under a constant load of 0.5 g. After a 30 min equilibration period with washing 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, the antagonistic activity of the compound was measured by recording a concentration response curve (CRC) for histamine in the presence of the testing compounds (**3a**–**e**, **7a**–**h** and **8**) which were added 5 min before histamine. This procedure was repeated with higher concentration of the compounds. The antagonism was of a competitive nature causing a parallel shift in the CRC. The pA_2 values and slopes were determined according to Arunlakshana and Schild [17].

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