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Original article

Non-imidazole histamine H_3 ligands. Part III. New 4-*n*-propylpiperazines as non-imidazole histamine H_3-antagonists

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Abstract

In search for a new lead of non-imidazole histamine H_3-receptor antagonists, a series of 1[(2-thiazolopyridine)-4-*n*-propyl]piperazines, the analogous 1-[(2-oxazolopyridine)-4-*n*propyl]piperazines, 1-[(2-benzothiazole)-4-*n*-propyl]piperazine and 1-[(2-benzooxazole)4-*n*-propyl]-piperazine were 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 thiazolo derivatives have slightly higher activity than their oxazolo analogues. The most potent compound of these series is the 1-(2-thiazolo[4,5-c]pyridine)-4-*n*-propylpiperazine (**3c**) with pA_2 = 7.25 (its oxazole analogue (**4g**) showed pA_2 = 6.9). The structure–activity relationships for compounds with various positions of the nitrogen in the benzene ring for the thiazoles compared with oxazoles are discussed.

Keywords: Histamine H_3-receptor; H_3-antagonists; 1-[(2-Thiazolopyridine)-4-*n*-propyl]piperazines; 1[(2-Oxazolopyridine)-4-*n*-propyl]piperazines; 1-[(2-Benzothiazole)-4-*n*-propyl]piperazine; 1-[(2-Benzooxazole)-4-*n*-propyl]piperazine

1. Introduction

Histamine H_3-receptors have been shown to be inhibitory presynaptic autoreceptors, which modulate the synthesis [1] and release [2] of histamine at histaminergic neurons in the central nervous system (CNS). The H_3-receptors also occur as heteroreceptors on nonhistaminergic, as serotoninergic [3], cholinergic [4], noradrenergic [5] and dopaminergic [6] neurons. After several efforts made by various laboratories to clone the H_3-receptor, Lovenberg et al. [7] cloned and identified the human histamine H_3-receptor. When Drutel et al. [8] identified the cDNAs of three functional rat H_3-receptor isoforms (H_{3A}, H_{3B}, and H_{3C}) and one non-functional truncated H_3-receptor (H_{3T}), it became clear that a new chapter in the understanding of the role of the third histamine receptor subtype has been opened [9].

Actually it has become evident that the H_3-receptor is the part of a general regulatory system, which may serve as the target for the design of new therapeutics. However, histamine H_3-receptors antagonists have not been introduced into therapy yet, but potential therapeutic applications have been proposed, e.g. memory and learning deficits [10–12], epilepsy [13,14], Alzheimer's disease [15,16], and attention-deficit hyperactivity disorder [17].

Since the discovery of thioperamide (K_i = 4.3 nM) [18] (Chart 1), the prototype of H_3-antagonist, many potent ligands carrying an imidazole moiety have been described [19–24] among others, potent and selective antagonists with high in vitro and in vivo activity **FUB 470** [25] and **ciproxifan** [26] (Chart 1). The most representative compound of this group is **GT 2331** (K_i = 0.12 nM) [27] (Chart 1); the first histamine H_3-antagonist to be taken into human clinical trials. Because of the presence of the imidazole nucleus in most active ligands, these compounds may show poor blood–brain barrier (BBB) penetration [28], but not always. In this light, for potential therapeutic use, the design of histamine H_3-receptor ligands devoid of an imidazole ring is desirable. Early attempts to replace the imidazole moiety in existing H_3-receptor ligands with other nitrogen containing heterocycles have met with

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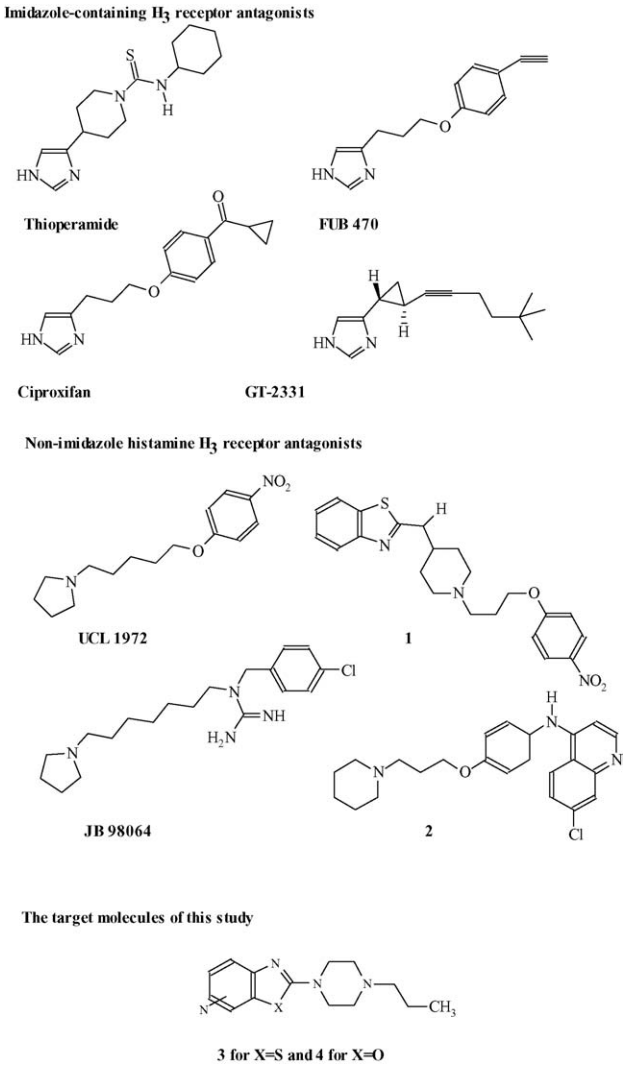


Chart 1. Structures of some known histamine H_3-receptor antagonists and the target molecules of this study.

limited success [29–31]. One of the first successful replacements of the imidazole ring of a known compound was reported by Ganellin et al. [32] **UCL 1972** (K_i = 39 nM; ED50 = 1.1 mg/kg) (Chart 1). Based on the structure of the histamine H_3-receptors, weak active sabeluzole (antagonist), and dimaprit as potential leads led to the discovery of the active benzothiazole (**1**) (pA_2 = 7.67; pK_i = 8.2) [33], and **JB 98064** (pK_B = 8.38; pK_i = 8.7) [34] (Chart 1), respectively. Only very recently several groups have described series of potent non-imidazole based histamine H_3-antagonists. Thus these groups have used such nuclei as pyrrolidine [35] and piperidine linked with substituted: fluorenes [36], 2-phenylimidazopyridines [37], aminoquinolines [38] and 4-(phenoxymethyl)benzyles [39] moieties. Compound (**2**) (K_i = 0.086 nM) [38] (Chart 1) is one of the most potent non-imidazole histamine H_3-receptor antagonists, reported so far, possessing also a strong inhibitory activity on the main histamine metabolising enzyme, histamine *N*-methyltransferase.

Previously we reported the synthesis and biological evaluation of 1-[(2-benzothiazole)-4substituted]piperazine derivatives as non-imidazole histamine H_3-receptor antagonists [40,41]. It was shown that the most potent compounds under in vitro screening conditions were the *n*-propyl-, *iso*-propyl- and allylbenzothiazole derivatives. These results suggested that for optimal size in the alkyl homologues series, the substituent should consist of three carbon atoms independently on a presence or an absence of a double bond.

In the continuation of our earlier work, in search for the new lead of non-imidazole histamine H_3-receptor antagonist, we have studied the influence on H_3-receptor antagonistic activity; of the introduction of an additional nitrogen at various positions in the benzene ring and replacement of the sulphur atom by oxygen in the thiazole ring, keeping 1-*n*-propylpiperazine moiety present. Therefore, the series of 1-[(2thiazolopyridine)-4-*n*-propyl]piperazines (**3**) (Chart 1) and the analogous 1-[(2-oxazolopyridine)-4-*n*-propyl] piperazines (**4**) (Chart 1) were synthesised and their activities were pharmacologically determined.

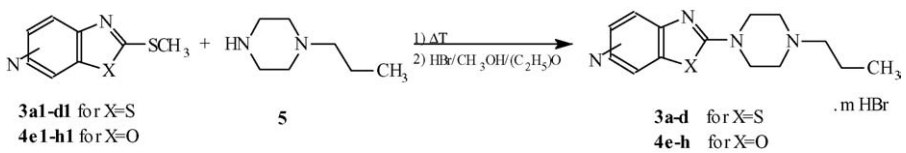
2. Chemistry

The general synthetic procedure used in this study is illustrated in Scheme 1. The series of 1-[(2-thiazolopyridine)-4-*n*-propyl]piperazines (**3a**–**d**) (Table 1) and the analogous 1-[(2oxazolopyridine)-4-*n*-propyl]piperazines (**4e**–**h**) (Table 1) were prepared from the appropriate 2-(methylthio)thiazolo- (**3a1**–**d1**) or 2-(methylthio)oxazolepyridines (**4e1**–**h1**) by nucleophilic substitution of the methylthio group by 1-*n*-propylpiperazine (**5**).

The crude products were purified with column chromatography. All free bases were treated with methanolic HBr and the corresponding hydrobromides were precipitated with dry diethyl ether.

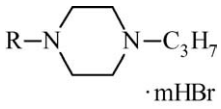
The appropriate 2-(methylthio)thiazolo- (**3a1**–**d1**) and 2-(methylthio)oxazolopyridines (**4e1**–**h1**) were synthesised according to known methods [42–45] as shown in Schemes 2, 3, respectively. The 2-(methylthio)thiazolopyridines (**3a1**–**d1**) were obtained by subsequent treatment of sodium salts of (**a2**, **b3**, **c2**, **d3**) with methyl iodide in C_2H_5OH.

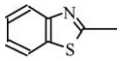
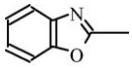
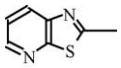
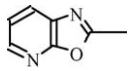
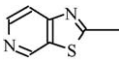
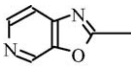
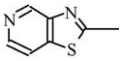
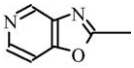
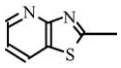
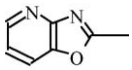
The thiazolopyridine-2-thiones (**a2**, **c2**) were obtained according to **Procedure A** (Scheme 2). Thus, 2-chloro-3-



Scheme 1. Synthesis of 1-[(2-thiazolopyridine)-4-*n*-propyl]piperazines (**3a**–**d**) and the analogous 1-[(2-oxazolopyridine)-4-*n*-propyl]piperazines (**4e**–**h**).

Table 1
Histamine H_3-receptor antagonistic activity of compounds (**3a–d**), (**4e–h**), (**9**) and (**10**) as tested on the in vitro test system on the guinea-pig jejunum



Compound	m	R	pA_2 (S.E.M.) H_3	*N* (*caviae*)	Compound	m	R	pA_2 (S.E.M.) H_3	*N* (*caviae*)
9	**2**		7.17 (0.06)	11 (5)	**10**	**2**		6.95 (0.04)	22 (4)
3a	**2**		7.08 (0.03)	21 (4)	**4e**	**2**		6.63 (0.13)	15 (4)
3b	**3**		6.98 (0.02)	18 (2)	**4f**	**2**		6.64 (0.03)	30 (3)
3c	**2**		7.25 (0.07)	20 (4)	**4g**	**2**		6.90 (0.07)	20 (4)
3d	**2**		5.98 (0.07)	18 (2)	**4h**	**2**		5.42 (0.05)	43 (3)

S.E.M. – Standard error of the mean. N – Number of different animal preparations. Caviae – Number of animals.

nitropyridine (**a1**) or 4-chloro-3-nitropyridine (**c1**) was converted to the corresponding thiazolopyridine-2-thiones (**a2**) [42], (**c2**) [43]) by treatment with H_2S in a water solution of sodium hydroxide in the presence of sodium sulphide and carbon disulphide. The thiazolopyridine-2-thiones (**b3**) [44] and (**d3**) [45] (**Procedure B**; Scheme 2) were obtained as follows: firstly the treatment of doubly lithiated 4-(**b1**) [44] or 2(pivaloyloamino)pyridine (**d1**) [45]—synthesised by the reaction of 4- or 2-aminopyridine with pivaloyl chloride in dry dichloromethane in the presence of triethylamine—with tetraisopropylothiuram disulphide (TITD) [44] led to (**b2**) or (**d2**). Subsequent hydrolysis of (**b2**) or (**d2**) in 20% ethanolic sodium hydroxide solution gave the 2-mercaptothiazolopyridines (**b3**) [44] or (**d3**) [**45**]).

The 2-(methylthio)oxazolopyridines [46] (**4e1–h1**; Scheme 3) were obtained by subsequent treatment of (**e2–h2**) with methyl iodide in DMF in the presence of K_2CO_3. The 2-thiooxazolopyridines [46] (**f2–h2**) were obtained by cyclisation reaction of the appropriate aminohydroxypyridines (**f1–h1**) with potassium ethyl xanthate in refluxing ethanol. The 2-thiooxazolo[5,4-b]pyridine (**e2**) [46] (Scheme 3) was obtained by treatment of 3-aminohydroxypyridine (**e1**) with thiophosgene in THF under N_2.

2-Amino-3-hydroxypyridine (**h1**) is commercially available, while 3-amino-4-hydroxypyridine (**g1**) [47] and 3-amino-2-hydroxypyridine (**e1**) [48] are easily obtained via hydrogenation of the corresponding nitro derivatives. The synthesis of 4-amino-3-hydroxypyridine (**f1**) [46] is schematically shown in Scheme 4. To the 4(pivaloyloamino)pyridine (**b1**), after *ortho* lithiation with *n*-BuLi, was introduced the hydroxyl group, using the reactive electrophile trimethyl borate ($B(OCH_3)_3$), what resulted in 3-hydroxy-4-(pivaloyloamino)pyridine (**6**). Cleavage of the pivaloyl group with 10% HCl led to the desired pyridinol (**f1**) in good yield.

The 1-[(2-benzothiazole)-4-*n*-propyl]piperazine (**9**) [41] and 1-[(2-benzooxazole)-4-*n*propyl]piperazine (**10**) were prepared using well established pathways (Scheme 5), from 2-chlorobenzothiazole (**7**) or 2-chlorobenzooxazole (**8**) through nucleophilic substitution of the chlorine atom by 1-*n*-propylpiperazine (**5**). The crude products were purified with column chromatography. Free bases were treated with methanolic HBr and the corresponding hydrobromides were precipitated with dry diethyl ether.

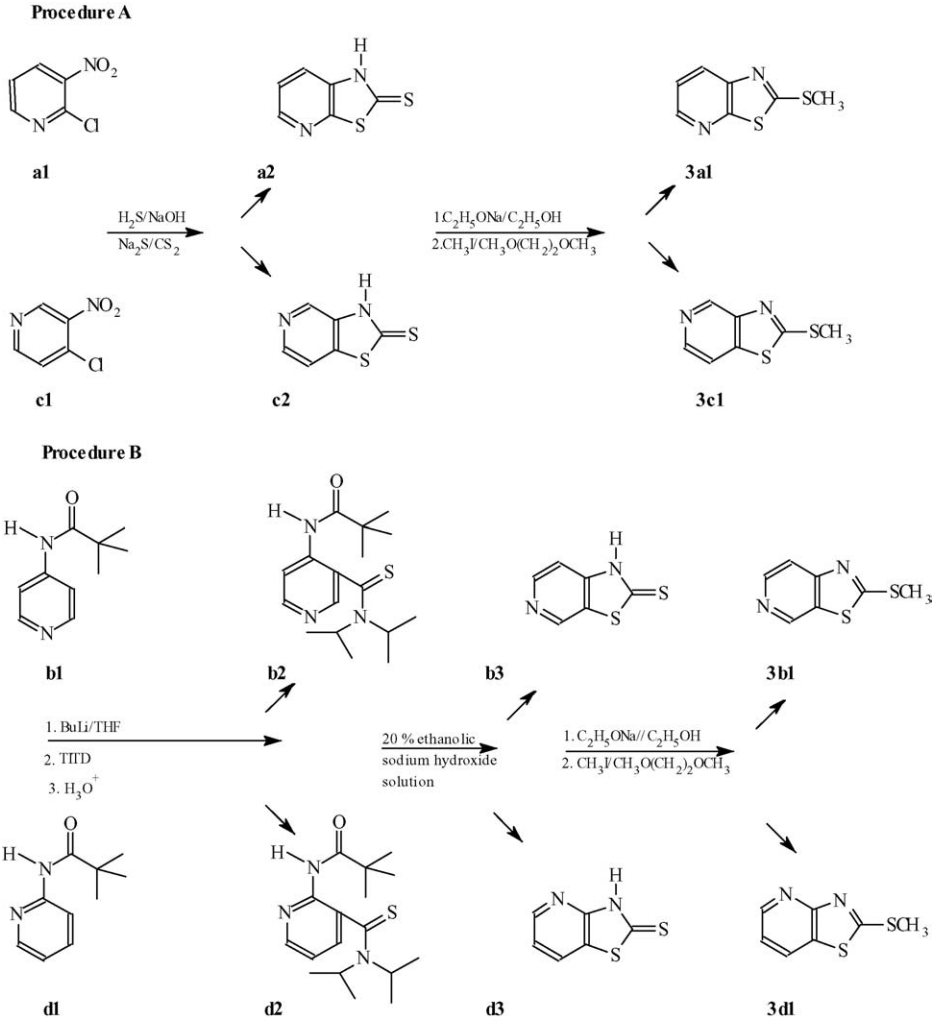
The TITD [44] was prepared by the reaction of diisopropylamine with carbon disulphide in aqueous sodium hydroxide solution in the presence of potassium ferricyanide.

3. Pharmacology

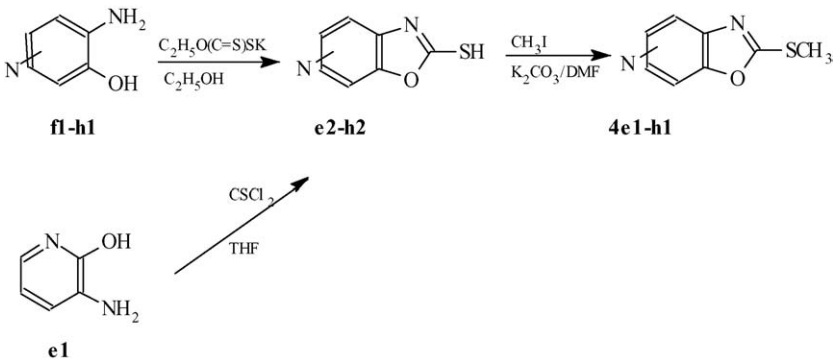
All target compounds were tested for H_3-antagonistic effects in vitro, following standard methods, using the electrically contracting guinea-pig jejunum [49]. The potency is expressed by its pA_2 value, calculated according to Arunlakshana and Schild [50] regression analysis, in all cases at least three concentrations were used.

4. Results and discussion

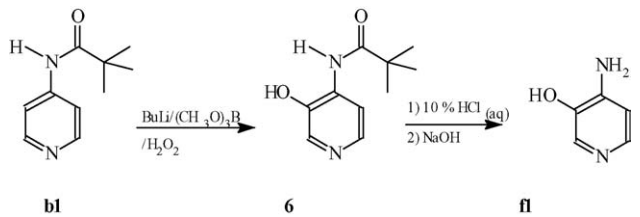
The presented series of 1-[(2-thiazolopyridine)-4-*n*-propyl]piperazines (**3**), 1-[(2-thiazolobenzo)-4-*n*-propyl]pipe-



Scheme 2. The synthesis of 2-methylthiothiazolopyridines (**3a1**–**d1**).



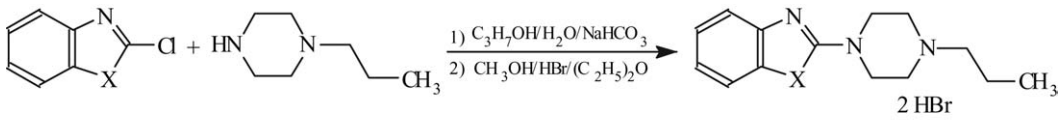
Scheme 3. The synthesis of 2-methylthiooxazolopyridines (**4e1**–**h1**).



Scheme 4. The synthesis of 4-amino-3-hydroxypyridine (**f1**).

razine (**9**) and their analogous 1-[(2-oxazolopyridine)-4-*n*-propyl]piperazines (**4**), 1-[(2-oxazolobenzo)-4-*n*-propyl]-piperazine (**10**) possess moderate to pronounced H_3-receptor antagonist activity (Table 1).

It appeared that by comparison of homologous pairs, the 1-[(2-thiazolopyridine)-4-*n*-propyl]piperazines (**3**) have slightly higher activity than their corresponding 1-[(2-oxazolopyridine)-4-*n*-propyl]piperazine analogues (**4**). The



7 for X=S
8 for X=O

5

9 for X=S
10 for X=O

Scheme 5. The synthesis of 1-[(2-thiazolobenzo)-4-*n*-propyl]piperazine (**9**) and 1-[(2oxazolbenzo)-4-*n*-propyl]piperazine (**10**).

same can be observed for compounds (**9**) and (**10**). Benzothiazole derivative (**9**; pA_2 = 7.17) has slightly higher activity than its benzooxazole analogue (**10**; pA_2 = 6.95).

In the case of thiazole series (**3a–d**; **9**), the introduction of additional nitrogen at various positions in the benzene ring, lead to compound (**3c**; pA_2 = 7.25), containing nitrogen in 5-position in benzene ring with slightly higher affinity and to compound (**3a**; pA_2 = 7.08), containing nitrogen in 7-position in benzene ring with slightly lower affinity compared to the benzene derivative (**9**). Compounds (**3b**) containing nitrogen in 6- and, particularly (**3d**) containing nitrogen in 4-position in benzene ring, have a somewhat lower activity.

Exchange of sulphur by oxygen in thiazole ring results in a series of compounds (**4e–4h**) with a slightly lower activity compared to the benzo derivative (**10**). In this series, similar results were observed, as in the thiazole one; the most potent compound is 1-[(2oxazolo[4,5-c]pyridine)-4-*n*-propy]]piperazine (**4g**; pA_2 = 6.9), containing nitrogen in 5-position in benzene ring and again the lowest activity has been showed by 1-[(2oxazolo[4,5-b]pyridine)-4-*n*-propyl]piperazine (**4h**; pA_2 = 5.42), compound containing nitrogen in 4-position in benzene ring. Because the lowest activities of both series are presented by compound (**4h**) and its thiazole analogue (**3d**), we concluded that the 4-position of nitrogen in benzene ring is unfavourable for blocking histamine H_3-receptors.

Clearly, thiazoles (**3a–d**; **9**) display a higher activity than their oxazole (**4e–4h**; **10**) analogues. We observe, that the 5- or possibly 7-position of nitrogen in the benzene ring (**3c**) or (**3a**) is favourable for histamine H_3-receptor antagonist activity, whereas its presence in position-4 (**3d**, **4h**) leads to a strong decrease of activity. These results show that the 5- or possibly also 7-position for nitrogen in the benzene ring for thiazole series leads to moderate pronounced histamine H_3-receptor affinity.

Based on the obtained results, the 1-(2-thiazolo[4,5-c]pyridine)-4-*n*-propylpiperazine (**3c**) was chosen as a new lead for non-imidazole histamine H_3-receptor antagonists.

5. Experimental protocols

General methods. All melting points (m.p.) 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. Elemental analyses (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), using the following eluting mixtures: (a) methylene chloride/methanol: 19:1; (b) methylene chloride/methanol: 9:1; (c) methylene chloride/ethyl acetate: 9:1. 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.

The 2-chloro-3-nitropyridine, 4-chloro-3-nitropyridine, 4-aminopyridine, 2-aminopyridine, 2-amino-3-hydroxypyridine, 3-nitro-4-hydroxypyridine, 3-nitro-2-hydroxypyridine, pivaloyl chloride, potassium ethyl xanthate, 1-*n*-propylpiperazine, 2-chlorobenzothiazole, 2-chlorobenzooxazole were all purchased from commercial sources.

5.1. Chemistry

5.1.1. General method for the preparation of thiazolo[5,4-b]- [42] and thiazolo[4,5-c]pyridine-2-thiones [43]—(*a2*) and (*c2*)

A solution of sodium hydroxide (6 g, 0.45 mol) in 32 ml of water was saturated with hydrogen sulphide. To this hot solution 2-chloro-3-nitropyridine (**a1**) or 4-chloro-3niropyridine (**c1**) (8 g, 0.05 mol) was added and the reaction mixture was heated under reflux for 5 min. To the boiling solution sodium sulphide nonahydrate (24 g, 0.1 mol) was added portion wise and hydrogen sulphide was bubbled into the boiling reaction mixture for 2.5 h. Thereafter, the reaction mixture was treated with aqueous sodium hydroxide (2.8 g, 0.07 mol in 12 ml of water), saturated with hydrogen sulphide, and finally, after cooling to room temperature, carbon disulphide (17 g, 22 ml, 0.23 mol) was added. The reaction mixture was stirred at 45 °C for 3 h and then 5 h at 110 °C, cooled and neutralised with acetic acid. The separated product was filtered, dissolved in aqueous ammonia, charcoaled and filtered. The filtrate was acidified with acetic acid, the product was filtered off and washed with small amount of cold ethanol.

a2. $C_6H_4N_2S_2$ (167.98); Yield 52% (Ref. [42] 97%); m.p. > 290 °C (Ref. [42] >290 °C); ^{1}H NMR (δ in ppm; DMSO-d_6): 14.3 (br*, 1H, NH); 8.45–8.35 (dd, $1H_{(6)}$; J = 4.8, 1.6 Hz); 8.2–8.15 (dd, $1H_{(4)}$; J = 8, 1.6 Hz); 7.45–7.35 (dd, $1H_{(5)}$; J = 8, 4.8 Hz). $TLC_{(a)}$ R_f = 0.34.

c2. $C_6H_4N_2S_2$ (167.98); Yield 46% (Ref. [44] 66%); m.p. > 300 °C (Ref. [42] >300 °C); ^{1}H NMR (δ in ppm; DMSO-d_6):

14.25 (br*, 1H, NH); 8.8–8.7 (d, $1H_{(4)}$; $J = 0.8$ Hz); 8.55–8.5 (d, $1H_{(6)}$; $J = 6$ Hz); 7.35–7.3 (dd, $1H_{(7)}$; $J = 6, 0.8$ Hz). $TLC_{(b)}$ $R_f = 0.08$.

*5.1.2. General method for the preparation of thiazolo[5,4-c]- [44] and thiazolo[4,5-b]pyridine-2-thiones [45]—(**b3**) and (**d3**)*

*5.1.2.1. Pivaloylaminopyridines—(**b1**) and (**d1**).* To a solution of 4-aminopyridine or 2-aminopyridine (19.2 g, 0.2 mol) and triethylamine (37 ml, 0.27 mol) in dichloromethane (100 ml) at 0 °C was cautiously added a solution of pivaloyl-(trimethylacetyl) chloride (28.8 ml, 0.23 mol) in dichloromethane (30 ml). The mixture was stirred in an ice bath for 1 h and then allowed to warm to room temperature and stirred overnight. Cold water (50 ml) was added and the organic layer was washed with saturated $NaHCO_3$ water solution (2 × 100 ml). After drying ($MgSO_4$) and evaporation of the solvent, the crude brown product of 4-(pivaloylamino)pyridine (**b1**) was recrystallised from dichloromethane/hexane and 2-(pivaloylamino)pyridine (**d1**) from ethyl acetate/hexane to give the pure product as colourless crystals, 28.5 g (85.0%) with m.p. 133–135 °C (Ref. [44] 133–135 °C) and 30 g (90.0%) with m.p. 71–73 °C (Ref. [45] 72–73 °C), respectively.

*5.1.2.2. 3-(*N,N*-Disopropyldithiocarbamato)-4- and 3-(*N,N*-disopropyldithiocarbamato)2-pivaloylamino)pyridines—(**b2**) and (**d2**).* To a solution of 4- (**b1**) or 2-(pivaloylamino)pyridine (**d1**) (13.3 g, 0.075 mol) in dry THF (120 ml) at –78 °C, *n*-butyllithium (63 ml, 2.5 M in hexane, 0.157 mol) was added. The mixture was then allowed to warm rapidly to 0 °C and stirred at this temperature for 2.5 h. The reaction mixture was cooled to –78 °C and solution of TITD (26.35 g, 0.075 mol) in THF (100 ml) was slowly added. The mixture was then allowed to warm up and when it had just become clear, water (120 ml) and ether (120 ml) were added. The organic layer was separated, washed with water (2 × 150 ml), dried (Na_2SO_4) and evaporated. The crude products (**b2**) and (**d2**) were recrystallised from ethyl acetate, 17.6 g (73.2%) with m.p. 118–119 °C (Ref. [44] 118–119 °C) and 16.6 g (69.0%) with m.p. 129.5–131 °C (Ref. [45] 130–131 °C), respectively.

*5.1.2.3. Thiazolo[5,4-c]- [44] and thiazolo[4,5-b]pyridine-2-thiones [45]—(**b3**) and (**d3**).* A suspension of 3-(N,N-disopropyldithiocarbamato)-4- (**b2**) or 2-(pivaloylamino)-pyridine (**d2**) (10 g, 0.0282 mol) in 20% ethanolic sodium hydroxide (200 ml) was refluxed for 4 h. The mixture was cooled and acidified with acetic acid to give a colourless solid which was filtered and washed with water. Drying gave solid (**b3**) and (**d3**).

b3. $C_6H_4N_2S_2$ (167.98); Yield 46% (Ref. [44] 66%); m.p. >290 °C (Ref. [44] >275 °C); ^1H NMR (δ in ppm; DMSO-d_6): 14.25 (br*, 1H, NH); 8.8 (s, $1H_{(7)}$); 8.55–8.5 (d, $1H_{(5)}$; $J = 6$ Hz); 7.35–8.3 (dd, $1H_{(4)}$; $J = 6$ Hz); $TLC_{(b)}$ $R_f = 0.18$.

d3. $C_6H_4N_2S_2$ (167.98); Yield 75% (Ref. [45] 85%); m.p. >300 °C (Ref. [45] >300 °C); ^1H NMR (δ in ppm; DMSO-d_6): 14.35 (br*, 1H, NH); 8.4–8.3 (dd, $1H_{(5)}$; $J = 5.0, 1.6$ Hz); 8.1–8.2 (dd, $1H_{(7)}$; $J = 7.9, 5$ Hz); 7.3–7.2 (dd, $1H_{(6)}$; $J = 5.0, 1.6$ Hz); $TLC_{(a)}$ $R_f = 0.41$.

*5.1.3. General method for the preparation of 2-thiooxazolopyridines [46]—(**f2**–**h2**)*

To a solution of the corresponding aminohydroxypyridines (**f1**–**h1**) (11 g, 0.1 mol) in ethanol (225 ml) was added potassium ethyl xanthate (32 g, 0.2 mol) in one portion. This heterogeneous mixture was then heated to reflux with stirring under an atmosphere of N_2 for 18 h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved with water and acidified to pH 5 with acetic acid. The resulting precipitate was filtered, washed with water (3 × 50 ml) and dried under reduced pressure to give 2-thiooxazolopyridines (**f2**–**h2**) as yellow–brown solids.

f2. $C_6H_4N_2SO$ (M = 148.98); Yield 79% (Ref. [46] 83%); m.p. >290 °C; ^1H NMR (δ in ppm; DMSO-d_6): 8.65 (s, $1H_{(7)}$); 8.35–8.3 (d, $1H_{(5)}$; $J = 6.1$ Hz); 7.4–7.35 (d, $1H_{(4)}$, $J = 6.1$); $TLC_{(b)}$ $R_f = 0.26$.

g2. $C_6H_4N_2SO$ (M = 148.98); Yield 50% (Ref. [46] 52%); m.p. >290 °C; ^1H NMR (δ in ppm; DMSO-d_6): 8.55 (s, $1H_{(4)}$); 8.35–8.3 (d, $1H_{(6)}$; $J = 5.9$ Hz); 7.5–7.45 (d, $1H_{(7)}$; $J = 5.9$); $TLC_{(b)}$ $R_f = 0.11$.

h2. $C_6H_4N_2SO$ (M = 148.98); Yield 66% (Ref. [46] 73%); m.p. >290 °C; ^1H NMR (δ in ppm; CD_3OD): 8.25–8.2 (dd, $1H_{(5)}$; $J = 5.2, 1.2$ Hz); 7.7–7.6 (dd, $1H_{(7)}$; $J = 8.1, 1.2$ Hz); 7.2–7.25 (dd, $1H_{(6)}$; $J = 8.1, 5.2$ Hz); $TLC_{(a)}$ $R_f = 0.11$.

*5.1.3.1. The synthesis of 2-thiooxazolo[5,4-b]pyridine [46]—(**e2**).* To a solution of 3-amino-2-hydroxypyridine (**e1**) (7.86 g, 0.0714 mol) in anhydrous THF (220 ml) with stirring under N_2, was added thiophosgene (6.5 ml, 0.0875 mol). This homogeneous mixture was stirred at room temperature for 1 h, adjusted to pH 5 with 10 N NaOH, and evaporated in vacuo. The residue was diluted with water, and the precipitate was filtered, washed with H_2O (3 × 25 ml), and dried under vacuum to give (**e2**) as an orange–yellow solid.

e2. $C_6H_4N_2SO$ (M = 148.98); Yield 63% (Ref. [46] 70%); m.p. >290 °C; ^1H NMR (δ in ppm; $CDCl_3$): 7.45–7.4 (dd, $1H_{(6)}$; $J = 6.5, 1.9$ Hz); 7.35–7.3 (dd, $1H_{(4)}$; $J = 7.2, 1.9$ Hz); 6.35–6.3 (dd, $1H_{(5)}$; $J = 7.2, 6.5$ Hz); $TLC_{(a)}$ $R_f = 0.52$.

*5.1.4. General method for the preparation of 2-(methylthio)thiazolopyridines—(**3a1**–**3d1**)*

The corresponding thione (**a2**), (**c2**), (**b3**) or (**d3**) (1.68 g, 0.01 mol) was dissolved in ethanolic sodium ethylate (prepared from 0.23 g sodium (0.01 mol) in 50 ml of absolute ethanol) and the solution was evaporated to dryness. The residue was dissolved in 1,2-dimethoxyethan (75 ml) and methyl iodide (1.76 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 10 min, the solvent was evaporated, water (25 ml) was added and the separated product was filtered off. In each case, the crude product was purified by

column chromatography. All compounds were crystallised from *n*-hexane.

3a1. $C_7H_7N_2S_2$ (M = 182.98); Yield 65% (Ref. [42] 70%); m.p. 87–88 °C (Ref. [42] 88.5 °C); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.3–8.25 (dd, $1H_{(6)}$; J = 4.8, 1.6 Hz); 8.0–7.9 (dd, $1H_{(4)}$; J = 8.0, 1.6 Hz); 7.25–7.15 (dd, $1H_{(5)}$; J = 8.0, 4.8 Hz); 2.75 (s, 3H); $TLC_{(c)}$ R_f = 0.33.

3b1. $C_7H_7N_2S_2$ (M = 182.98); Yield 48%; m.p. 84–86 °C; ^{1}H NMR (δ in ppm; $CDCl_3$): 9.05–9 (d, $1H_{(7)}$; J = 0.8); 8.65–8.6 (d, $1H_{(5)}$; J = 5.5 Hz); 7.65–7.6 (dd, $1H_{(4)}$; J = 5.5, 0.8 Hz); 2.8 (s, 3H); $TLC_{(c)}$ R_f = 0.12.

3c1. $C_7H_7N_2S_2$ (M = 182.98); Yield 40% (Ref. [43] 41%); m.p. 83–85 °C (Ref. [43] 85 °C); ^{1}H NMR (δ in ppm; $CDCl_3$): 9.2–9.1 (d, $1H_{(4)}$; J = 0.8 Hz); 8.5–8.4 (d, $1H_{(6)}$; J = 5 Hz); 8.28.1 (dd, $1H_{(7)}$; J = 5.0, 0.8 Hz); 2.8 (s, 3H); $TLC_{(c)}$ R_f = 0.09.

3d1. $C_7H_7N_2S_2$ (M = 182.98); Yield 56%; m.p. 74–76 °C; ^{1}H NMR (δ in ppm; $CDCl_3$): 8.65–8.6 (dd, $1H_{(5)}$; J = 4.8, 1.6 Hz); 8.15–8.1 (dd, $1H_{(7)}$; J = 7.9, 1.6 Hz); 7.25–7.2 (dd, $1H_{(6)}$; J = 7.9, 4.8 Hz); 2.85 (s, 3H); $TLC_{(c)}$ R_f = 0.26.

*5.1.5. General method for the preparation of 2-(methylthio)oxazolopyridines—(**4e1–4h1**)*

To a cooled solution of the corresponding 2-thiooxazolopyridines (**e2–h2**) (1 g, 0.0066 mol) in anhydrous DMF (20 ml) with stirring under N_2 was added potassium carbonate (1 g, 0.01 mol) followed by iodomethane (0.5 ml, 0.008 mol). The reaction mixture was stirred for 1 h, diluted with water, and extracted with ethyl acetate (4 × 25 ml). The combined organic extracts were washed with water (3 × 25 ml), dried (Na_2SO_4), filtered, and evaporated to give 2-(methylthio)oxazolopyridines (**4e1–4h1**) as tan solids. In each case, the crude product was purified by column chromatography. All compounds were crystallised from isopropyl ether.

4e1. $C_7H_7N_2SO$ (M = 163.98); Yield 76% (Ref. [46] 93%); m.p. 80–81 °C (Ref. [46] 81 °C); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.2–8.15 (dd, $1H_{(6)}$; J = 5.0, 1.5 Hz); 7.9–7.8 (dd, $1H_{(4)}$; J = 7.8, 1.5 Hz); 7.3–7.2 (dd, $1H_{(5)}$; J = 7.8, 5 Hz); 2.75 (s, 3H); $TLC_{(a)}$ R_f = 0.66.

4f1. $C_7H_7N_2SO$ (M = 163.98); Yield 73% (Ref. [46] 83%); m.p. 80–81 °C (Ref. [46] 81 °C); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.8 (s, $1H_{(7)}$); 8.55–8.5 (d, $1H_{(5)}$; J = 5.3 Hz); 7.45–7.4 (d, $1H_{(4)}$, J = 5.3 Hz); 2.75 (s, 3H); $TLC_{(a)}$ R_f = 0.42.

4g1. $C_7H_7N_2SO$ (M = 163.98); Yield 82% (Ref. [46] 83%); m.p. 82–83 °C (Ref. [46] 82–83 °C); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.95–8.90 (d, $1H_{(4)}$; J = 0.9 Hz); 8.5–8.45 (d, $1H_{(6)}$; J = 5.5 Hz); 7.45–7.4 (dd, $1H_{(7)}$; J = 5.5, 0.9 Hz); 2.75 (s, 3H); $TLC_{(a)}$ R_f = 0.37.

4h1. $C_7H_7N_2SO$ (M = 163.98); Yield 75% (Ref. [46] 91%); m.p. 62–63 °C (Ref. [46] 63 °C); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.5–8.4 (dd, $1H_{(5)}$; J = 5.0, 1.4 Hz); 7.7–7.6 (dd, $1H_{(7)}$; J = 8.1, 1.4 Hz); 7.2–7.15 (dd, $1H_{(6)}$; J = 8.0, 5 Hz); 2.8 (s, 3H); $TLC_{(a)}$ R_f = 0.51.

*5.1.6. General method for the preparation of 1-[(2-thiazolopyridine)-4-npropyl]piperazines—(**3a–d**)*

The appropriate methylthio derivative (**3a1–d1**) (0.87 g, 0.005 mol) was treated with few drops of ethanol and 1-*n*-propylpiperazine (**5**) (1.28 g, 0.01 mol) and the reaction mixture was heated at 60 °C for 45–120 min. After cooling, water (25 ml) and dichloromethane (25 ml) were added and organic layer was separated, dried (Na_2SO_4) and evaporated to give the crude product which was purified by column chromatography.

3a. $C_{13}H_{18}N_4S$ (M = 294.00); Yield 63%; m.p. 93–95 °C (for free base) and 277–276 °C (for dihydrobromide); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.3–8.25 (dd, $1H_{(6)}$; J = 4.8, 1.6 Hz); 8.0–7.9 (dd, $1H_{(4)}$; J = 8.0, 1.6 Hz); 7.15–7.25 (dd, $1H_{(5)}$; J = 8.0, 4.8 Hz); 3.80–3.70 (m, $4H_{\text{“piperazine”}}$); 2.70–2.60 (m, $4H_{\text{“piperazine”}}$); 2.45–2.30 (t, 2H, J = 7.5 Hz); 1.60–1.45 (m, 2H); 1.00–0.85 (t, 3H; J = 7.3 Hz); $TLC_{(b)}$ R_f = 0.39.

3b. $C_{13}H_{18}N_4S$ (M = 294.00); Yield 48%; m.p. 96–98 °C (for free base) and >300 °C (for trihydrobromide); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.75 (d, $1H_{(7)}$; J = 0.6); 8.42–8.38 (d, $1H_{(5)}$; J = 5.5 Hz); 7.65–7.6 (dd, $1H_{(4)}$; J = 5.5, 0.6 Hz); 3.74–3.70 (m, $4H_{\text{“piperazine”}}$); 2.60–2.40 (m, $4H_{\text{“piperazine”}}$); 2.37–2.35 (t, 2H, J = 7.7 Hz); 1.58–1.51 (m, 2H); 0.96–0.91 (t, 3H; J = 7.3 Hz); $TLC_{(b)}$ R_f = 0.46.

3c. $C_{13}H_{18}N_4S$ (M = 294.00); Yield 40%; m.p. 101–102 °C (for free base) and 252–253 °C (for dihydrobromide); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.8 (s, $1H_{(4)}$); 8.25–8 (d, $1H_{(6)}$; J = 5.5 Hz); 7.55–7.5 (d, $1H_{(7)}$; J = 5.5 Hz); 3.74–3.70 (m, $4H_{\text{“piperazine”}}$); 2.60–2.40 (m, $4H_{\text{“piperazine”}}$); 2.37–2.35 (t, 2H, J = 7.7 Hz); 1.58–1.51 (m, 2H); 0.96–0.91 (t, 3H; J = 7.3 Hz); $TLC_{(b)}$ R_f = 0.44.

3d. $C_{13}H_{18}N_4S$ (M = 294.00); Yield 56%; m.p. 86–87 °C (for free base) and 280–282 °C (for dihydrobromide); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.3–8.25 (dd, $1H_{(5)}$; J = 5.0, 1.8 Hz); 8.0–7.9 (dd, $1H_{(7)}$; J = 7.8, 1.8 Hz); 7.15–7.25 (dd, $1H_{(6)}$; J = 7.8, 5 Hz); 3.80–3.70 (m, $4H_{\text{“piperazine”}}$); 2.70–2.60 (m, $4H_{\text{“piperazine”}}$); 2.45–2.30 (t, 2H, J = 7.5 Hz); 1.60–1.45 (m, 2H); 1.00–0.85 (t, 3H; J = 7.3 Hz); $TLC_{(b)}$ R_f = 0.56.

*5.1.7. General method for the preparation of 1-[(2-oxazolo)-4-*n*-propyl]piperazines—(**4eh**)*

A mixture of the appropriate 2-(methylthio)oxazolopyridine (**4e1–4h1**) (1 g, 0.006 mol) and 1-*n*-propylpiperazine (**5**) (1.54 g, 0.012 mol) was heated to 85 °C for 45 min and cooled to room temperature. The residue was purified by column chromatography.

4e. $C_{13}H_{18}N_4O$ (278.00); Yield 90%; m.p. 82–83 °C (for free base) and 259–260 °C (for dihydrobromide); ^{1}H NMR (δ in ppm; $CDCl_3$): 7.95–7.90 (dd, $1H_{(6)}$; J = 5.1, 1.6 Hz); 7.607.50 (dd, $1H_{(4)}$; J = 7.7, 1.6 Hz); 7.15–7.25 (dd, $1H_{(5)}$; J = 5.1, 7.7 Hz); 3.80–3.70 (m, $4H_{\text{“piperazine”}}$); 2.60–2.50 (m, $4H_{\text{“piperazine”}}$); 2.40–2.30 (t, 2H, J = 7.5 Hz); 1.60–1.50 (m, 2H); 1.00–0.85 (t, 3H; J = 7.3 Hz); $TLC_{(a)}$ R_f = 0.43.

4f. $C_{13}H_{18}N_4O$ (278.00); Yield 78%; m.p. 79–80 °C (for free base) and 259–262 °C (for dihydrobromide); ^{1}H NMR (δ in ppm; $CDCl_3$): 8.50 (d, $1H_{(7)}$; J = 1 Hz); 8.35–8.30 (d,

$1H_{(5)}$; J = 5.3 Hz); 7.25–7.20 (dd, $1H_{(4)}$; J = 5.3, 1 Hz); 3.80–3.75 (m, $4H_{\text{"piperazine"}}$); 2.60–2.55 (m, $4H_{\text{"piperazine"}}$); 2.40–2.35 (t, 2H, J = 7.5 Hz); 1.60–1.50 (m, 2H); 0.96–0.91 (t, 3H; J = 7.3 Hz); $TLC_{(a)}$ R_f = 0.35.

4g. $C_{13}H_{18}N_4O$ (278.00); Yield 76%; m.p. 86–87 °C (for free base) and >300 °C (for dihydrobromide); ^1H NMR (δ in ppm; $CDCl_3$): 8.65 (d, $1H_{(4)}$; J = 1.0); 8.30–8.25 (d, $1H_{(6)}$; J = 5.5 Hz); 7.25–7.20 (dd, $1H_{(7)}$; J = 5.5, 1 Hz); 3.80–3.75 (m, $4H_{\text{"piperazine"}}$); 2.65–2.55 (m, $4H_{\text{"piperazine"}}$); 2.40–2.35 (t, 2H, J = 7.7 Hz); 1.65–1.55 (m, 2H); 0.96–0.91 (t, 3H; J = 7.3 Hz); $TLC_{(a)}$ R_f = 0.33.

4h. $C_{13}H_{18}N_4O$ (278.00); Yield 90%; m.p. 76–78 °C (for free base) and >300 °C (for dihydrobromide); ^1H NMR (δ in ppm; $CDCl_3$): 8.25–8.00 (dd, $1H_{(5)}$; J = 5.1, 1.5 Hz); 7.457.40 (dd, $1H_{(7)}$; J = 8.0, 1.5 Hz); 7.25–7.2 (dd, $1H_{(6)}$; J = 8.0, 5.1 Hz); 3.80–3.70 (m, $4H_{\text{"piperazine"}}$); 2.35–2.30 (m, $4H_{\text{"piperazine"}}$); 2.20–2.15 (t, 2H, J = 7.7 Hz); 1.50–1.45 (m, 2H); 0.96–0.91 (t, 3H; J = 7.3 Hz); $TLC_{(a)}$ R_f = 0.40.

*5.1.8. General method for the preparation of 1-[(2-thiazolobenzo)-4-*n*-propyl]piperazine (**9**) and 1-[(2-oxazolobenzo)-4-*n*-propyl]piperazine (**10**)*

To a refluxing mixture of the 1-*n*-propylpiperazine (**5**) (1.28 g, 0.01 mol) and sodium bicarbonate (1.68, 0.02 mol) in 70 ml of 80% 2-PrOH a solution of 2-chlorobenzothiazole (**7**) (0.85 g, 0.005) or 2-chlorobenzooxazole (**8**) (0.77 g, 0.005 mol) in 4 ml of 2-PrOH was added dropwise. The mixture was refluxed 24 h. The solvent was evaporated under reduced pressure, and the sticky oil residue was suspended in 100 ml of water. After stirring for 1 h, the mixture was extracted with CH_2Cl_2, and the solvent was removed in vacuo. The products (**9**) and (**10**) were purified by column chromatography.

9. $C_{14}H_{19}N_3S$ (261.00); Yield 43% (Ref. [41] 43%); m.p. 100–101 °C (for free base) and 285–287 °C (for dihydrobromide) (Ref. [41] 100–101 °C and for dihydrobromide 285–287 °C); ^1H NMR (δ in ppm; $CDCl_3$): 7.6–7.55 (d, 1H; J = 8 Hz); 7.40–7.35 (d, 1H; J = 7.9 Hz); 7.25–7.20 (dd, 1H; J = 7.9, 5.9 Hz); 7.05–7.00 (dd, 1H; J = 8.0, 5.9 Hz); 3.80–3.75 (m, $4H_{\text{"piperazine"}}$); 2.55–2.45 (t, $4H_{\text{"piperazine"}}$); 2.35–2.30 (t, 2H, J = 7.5 Hz); 1.60–1.55 (m, 2H); 1.00–0.90 (t, 3H; J = 7.3 Hz); $TLC_{(a)}$ R_f = 0.46.

10. $C_{14}H_{19}N_3O$ (245.00); Yield 50%; m.p. 92–94 °C (for free base) and 291–293 °C (for dihydrobromide); ^1H NMR (δ in ppm; $CDCl_3$): 7.4–7.36 (d, 1H; J = 8 Hz); 7.35–7.30 (d, 1H; J = 7.9 Hz); 7.25–7.20 (dd, 1H; J = 7.9, 5.9 Hz); 7.05–6.95 (dd, 1H; J = 8.0, 5.9 Hz); 3.75–3.70 (m, $4H_{\text{"piperazine"}}$); 2.55–2.40 (m, $4H_{\text{"piperazine"}}$); 2.35–2.30 (t, 2H, J = 7.5 Hz); 1.60–1.55 (m, 2H); 0.95–0.90 (t, 3H; J = 7.1 Hz); $TLC_{(a)}$ R_f = 0.41.

5.2. Pharmacology

All compounds were tested for H_3-antagonistic effects in vitro on the guinea-pig jejunum [49] 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). 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 g tension with Hugo Sachs Hebel-Messvorsatz (Tl-2)/HFmodem (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, cumulative concentration–response curves (half-log increments) of (*R*)-α-methylhistamine, H_3-agonist, were recorded until no further change in response was found. The tested compounds were added 20 min before generation of concentration–response curves with (*R*)-α-methylhistamine as H_3-agonist. 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 Arunlakshana and Schild [50] regression analysis where at least three concentrations were used.

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