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Histamine H_1 receptor ligands Part I. Novel thiazol-4-ylethanamine derivatives: synthesis and in vitro pharmacology

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Abstract

A series of 2-substituted thiazol-4-ylethanamines have been synthesized and tested for their histaminergic H_1-receptor activities. The compounds with 2-phenyl substitution, regardless of the different physicochemical properties of the *meta*-substituents at the phenyl ring, showed weak H_1-agonistic activity with pD_2 values ranging from 4.35 to 5.36. When the phenyl group was replaced by a benzyl group, the resulting compounds all exhibited weak H_1-antagonistic activity (pA_2: 4.14–4.82).

Keywords: Histamine H_1-receptor; H_1-receptor agonist; H_1-receptor antagonists; 2-(2-Phenylthiazol-4-yl)ethanamines; 2-(2-Benzylthiazol-4-yl)ethanamines

1. Introduction

Whereas a vast number of potent and selective histamine H_1-receptor antagonists have long been available either as effective therapeutic agents for allergic diseases or as chemical tools for pharmacological investigation [1], the search for histamine H_1-receptor agonists has been less successful. Recently it became apparent that histamine is not only a mediator of allergic reactions but also a neurotransmitter. Histamine acts, via the activation of H_1-receptors, as an endogenous anticonvulsant in the central nervous system and also plays an important role in seizure [2]. This means selective histamine H_1-receptor agonists are not only useful pharmacological tools but also potential therapeutic agents.

To date, most H_1-receptor agonists (full or partial) are histamine derivatives, i.e. they have an imidazol-4(5)-ylethanamine moiety in common [2–8]. The amino group in the ethylamine side chain is preferably primary and a substitution, especially phenyl, at the C2 position is beneficial [9–13]. At present, the best known H_1-receptor agonists are substituted 2-phenylhistamines **1** (Fig. 1) [12,13]. Most compounds of this series possess full intrinsic activity and their potency ranges from 0.5 to 128% relative to histamine. The substitution at the phenyl ring is preferably attached to the *meta* position and there is no clear structure–activity relationship trend (electronic, steric, etc.) as far as these substituents are concerned [12]. Replacement of the imidazole moiety by other aromatic heterocycles usually results in

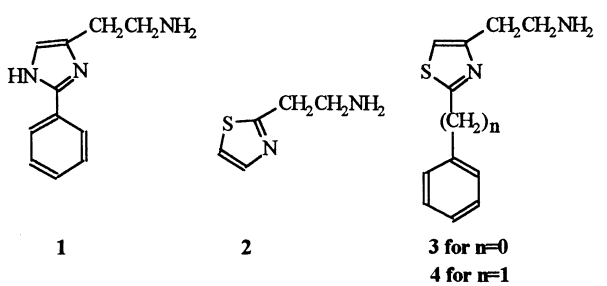

Fig. 1. Structures of some known histamine H_1-receptor agonists and the target molecules of this study.

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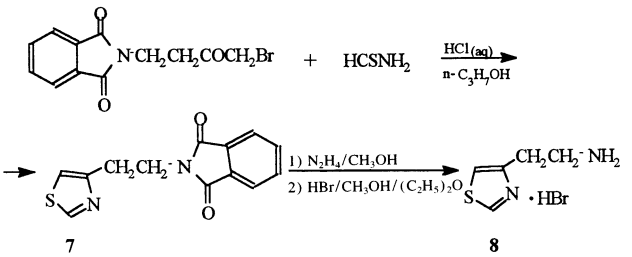
decreased activity [14–17] but some of these heterocyclic analogues, e.g. 2-(thiazol-2-yl)ethanamine (**2**), still possess full intrinsic activity. This implies that the N^{π}–N^{τ} tautomeric system of imidazole may not be necessary for the activation of H_1-receptors [1]. In the present study we have synthesized a series of novel thiazol-4-ylethanamines (**3** and **4**) in which a *meta*-substituted phenyl or benzyl is attached to position 2 of the thiazole nucleus. All these compounds were tested for their H_1-receptor activity by a functional assay in guinea-pig ileum. The synthesis and structure–activity relationships of these thiazole derivatives are the subjects of this report.

2. Chemistry

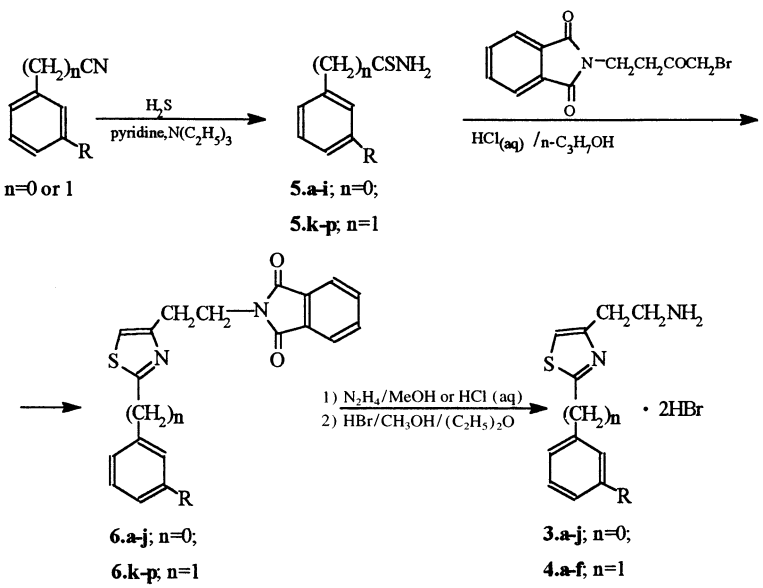
All 2-substituted thiazol-4-ylethanamine derivatives were prepared using the general method as shown in Scheme 1. The benzo- and phenylacetonitriles as starting materials were purchased from commercial sources. The appropriate *meta*-substituted thiobenzamides and thiophenylacetamides were directly obtained according to Fairful et al. [18] by the reaction of the nitrile with hydrogen sulfide in pyridine in the presence of triethylamine. 3-Nitrothiobenzamide (**5j**) was obtained according to Scheibye et al. [19] by the reaction of 3-nitrobenzamide and Lawesson's reagent in hexamethylphosphoamide (HMPA). All 4-[(2-phthalimido)-ethyl]thiazole derivatives were obtained by reaction of the appropriate thioamide and 1-bromo-4-phtalimidobutanone-2 [20] in *n*-propanol in the presence of concentrated hydrochloric acid. All phthalimide derivatives were purified by column chromatography. Subsequent hydrazinolysis, except for **5e** which was treated with 5 N HCl under reflux, basification with sodium hydroxide and extraction with chloroform led to the pure amines, after separation by column chromatography. All free bases were treated with methanolic HBr and hydrobromides were precipitated with dry diethyl ether. Likewise, 2-(thiazol-4-yl)ethanamine (**8**) was obtained from the hydrazinolysis of the corresponding phthalimide **7** which was prepared by the condensation of thioformamide and 1-bromo-4-phtalimidobutanone-2 [20] (Scheme 2).



Scheme 2. Synthesis of 2-(thiazol-4-yl)ethanamine (**8**).

3. Pharmacology

All compounds were tested for H_1 agonistic or antagonistic effects in vitro using standard methods, applying the guinea-pig ileum [24,25]. 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 (r.t.) (pH 7.4) containing (mM) NaCl (136.9); KCl (2.68); $NaHPO_4$ (7.19). After flush-



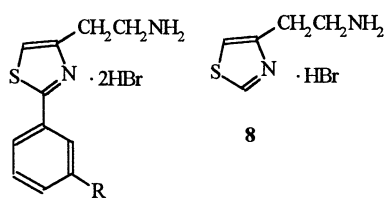
Scheme 1. Synthesis of 2-phenyl- and 2-benzyl-thiazol-4-ylethanamines (**3a**–**j** and **4a**–**f**).

ing the intraluminal contents, segments of about 2 cm long were cut and mounted for isotonic contractions in water-jacked 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); and glucose (5.5) at 37°C under a constant load of 0.5 g. After a 30 min equilibration period with washings every 10 min, a sub-maximal priming dose of histamine (1 μM) was given and washed out (standard washing procedure: 3 changes of buffer during 30 min). After washing out, a concentration response curve (CRC) of histamine was constructed followed by the CRCs of the compounds **8** and **3a**–**j**. Each curve was followed by a standard washing procedure. pD_2 values were calculated by standard methods. The antagonistic activity of given compounds was measured by recording a CRC for histamine in the presence of the testing compounds **4a**–**f** which were 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 [25]. In appropriate cases, the nature of the H_1-agonistic effect was checked by determining, using a standard method, the competitive antagonism by the H_1 antagonist temelastine (3 nM).

4. Results and discussion

2-(Thiazol-4-yl)ethanamine (**8**) and its 2-phenyl- and 2-benzyl-substituted derivatives (**3a**–**3j** and **4a**–**4f**) were tested for histamine H_1-receptor activity in vitro on isolated guinea-pig ileum as described in Section 6. 2-(Thiazol-4-yl)ethanamine (**8**) showed weak H_1-receptor agonistic activity with a pD_2 value of 4.70 (intrinsic activity = 1). Since this compound, like 2-(thiazol-2-yl)ethanamine (**2**), lacks the tautomerism that is present in histamine, the agonistic activity shown by this compound is consistent with the notion that the N^{τ}–H tautomer of histamine monocation is the active form of histamine at H_1-receptors [5,6]. As in the case of *meta*-substituted-2-(phenyl)histamine series [2], all derivatives of the present series with a phenyl group substituted at C2 position of the thiazole ring (**3a**–**j**) showed H_1-receptor agonistic activity. The potencies of these compounds (**3a**–**j**) are remarkably lower than those of their 2-phenylhistamine counterparts with pD_2 values ranging from

Table 1
Structures, formulas and results of the pharmacological screening on the isolated guinea-pig ileum for 2-[2-phenyl-4-thiazolyl]ethanamines (**3**) and for 2-(thiazol-4-yl)ethanamine (**8**)



3 **8**

Comp.	R	$pD_2 \pm$ SEM (n)*	Max. contraction [a] ± SEM (n)	Max. contraction [b] ± SEM (n) in the presence of 3 nM temelastine	Max. contraction [c] ± SEM (n) in the presence of atropine 10 nM
3a	H	4.80 ± 0.03 (10)	56.8 ± 4.45 (10)	59.5 ± 0.83 (2)	76.8 ± 4.78 (3)
3b	F	4.90 ± 0.08 (6)	71.7 ± 5.78 (6)	33.4 ± 1.46 (2)	n.d [d]
3c	Cl	5.15 ± 0.05 (6)	47.4 ± 4.73 (6)	22.5 ± 11.45 (2)	75.5 ± 4.74 (3)
3d	Br	5.19 ± 0.04 (6)	39.0 ± 3.19 (6)	0.0 ± 0.0 (2)	99.4 ± 14.98 (2)
3e	NO_2	5.03 ± 0.07 (10)	42.0 ± 7.30 (10)	18.8 ± 9.11 (4)	94.0 ± 5.77
3f	CF_3	5.36 ± 0.06 (6)	67.5 ± 6.58 (6)	0.0 ± 0.0 (2)	n.d [d]
3g	CH_3	4.87 ± 0.06 (6)	45.9 ± 7.99 (6)	0.0 ± 0.0 (2)	94.4 ± 7.81 (2)
3h	OH	4.80 ± 0.08 (10)	62.3 ± 5.36 (10)	89.0 ± 8.24 (4)	75.5 ± 6.27 (3)
3i	OCH_3	4.35 ± 0.04 (6)	59.4 ± 4.80 (6)	3.1 ± 3.1 (2)	89.5 ± 10.5 (2)
3j	NH_2	4.35 ± 0.04 (6)	68.1 ± 3.23 (6)	75.4 ± 6.69 (2)	88.9 ± 9.97 (3)
8		4.70 ± 0.09 (8)	97.2 ± 3.43 (8)	52.4 ± 0.63 (2)	n.d [d]
	histamine	6.73 ± 0.16 (11)	100 (11)	100 (4)	100

[a] Maximum height of contraction caused by the compound relative to histamine as 100%.
[b] Maximum height of contraction caused by the compound of the 2[e] CRC relative to its own reference (as 100%) in the presence of temelastine.
[c] Maximum height of contraction caused by the compound of the 2[e] CRC relative to its own reference (as 100%) in the presence of atropine.
[d] n.d., not determined.

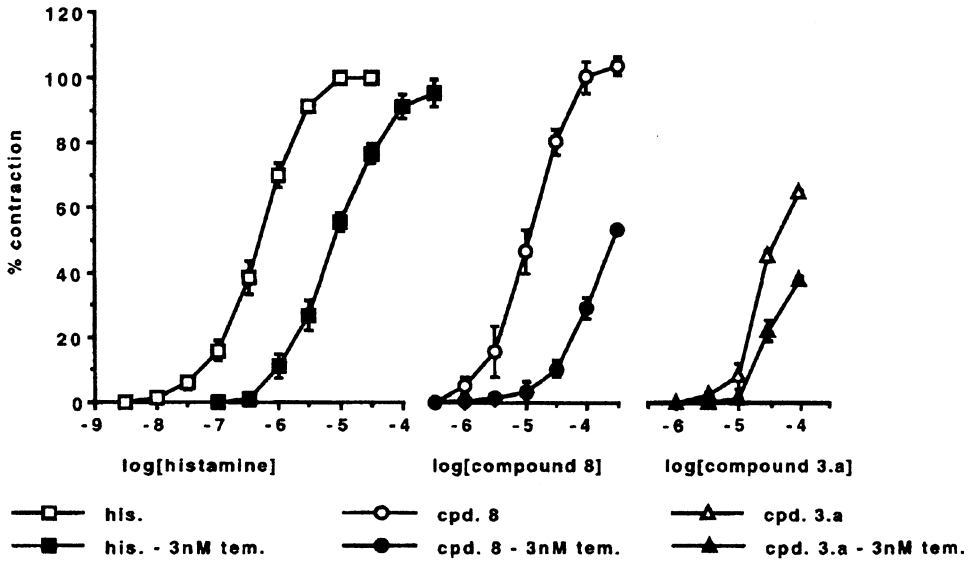


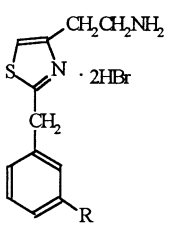
Fig. 2. Agonistic activity exerted by thiazole derivatives **3a** and **8** in comparison with histamine. Open symbols represent the dose–response curves of the agonists and closed symbols represent the dose–response curves after incubation with 3 nM temelastine, 0.5 h prior to the agonist challenge. Data are presented as means ± SEM.

4.35 to 5.36 (Table 1) and they all behave as partial agonists (intrinsic activity from 0.39 to 0.71). No definite structure–activity relationships can be drawn from the present series but it appears that higher potencies are found in compounds substituted by an electron-withdrawing group (Table 1).

The contractions caused by **3a**–**j** and **8** were antagonized by temelastine, a highly selective H_1-receptor antagonist [21]. For example, a rightward shift of the dose–response curves of **8** was observed after the treatment of the ileum with 3 nM temelastine (Fig. 2). It is not possible to calculate pA_2 values for temelastine, except for the full agonist **8**, for which temelastine pA_2 was found to be 9.33, not different from the value found using histamine as agonist ($pA_2 = 9.63$ in our hands). We observed with our other compounds (**3a**–**j**) a rapid depression of the maximum contractions of the organ upon applying high concentrations (> 0.1 μM). The cause of this decrease in contraction is unclear. For compounds **3a**, **3b**, **3h** and **3j** something other than the H_1 receptor seems to play a role in the contraction as well, because we observe only a partial antagonism by temelastine. Recently, several 2-substituted histamine derivatives have been found to stimulate G-proteins directly [22]. It remains to be determined whether such a mechanism also exists for the thiazole derivatives in the present study.

The results for compounds **8** and **3a**–**j** are summarized in Table 1. We have checked whether the compounds might activate muscarinic receptors, by applying atropine. Clearly, none of the compounds tested seems to activate a muscarinic receptor system. The benzyl derivatives (**4a**–**f**), which lost their intrinsic activity at H_1-receptors, acted as weak antagonists (Table 2). Although a significant decrease in H_1-agonistic activity has also been observed among *meta*-substituted-2-(benzyl)histamines compared with their 2-phenyl analogues, such a clear-cut transformation from agonist to antagonists by the simple replacement of a phenyl with a benzyl group is quite unique among H_1-receptor ligands. Since it has been suggested that the phenyl group of 2-phenylhistamines may bind to the same receptor site as the so-called '*cis* ring' of H_1-antagonists [23], it is not unreasonable to speculate that the agonistic 2-phenylthiazoles (**3a**–**j**) and the antago-

Table 2
Structures, formulas and results of the pharmacological screening on the isolated guinea-pig ileum for 2-[2-benzyl-4-thiazolyl]ethanamines (**4**)



4

Comp.	R	$pA_2 \pm$ SEM (n)
4a	H	4.16 ± 0.08 (15)
4b	F	4.53 ± 0.12 (5)
4c	Cl	4.82 ± 0.12 (3)
4d	Br	4.65 ± 0.11 (3)
4e	CH_3	4.63 ± 0.2 (4)
4f	OCH_3	4.14 ± 0.38 (4)
Temelastine		9.63 ± 0.07 (11)

nistic 2-benzylthiazoles (**4a**–**f**) bind to the receptor in a similar pattern, but the conjugation between the thiazole and phenyl rings is important for the activation of the receptor. At higher concentrations (> 100 μM), all 2-benzylthiazoles (**4a**–**f**) caused total suppression of the concentration–response curves for histamine.

5. Conclusions

Qualitative structure–activity relationships (H_1 agonism) as seen for 2-(*meta*-substituted)phenylhistamines are also found for the thiazolyl analogues, in which the N^{τ} has been exchanged for a sulfur atom. In the analogues benzyl derivatives however, the thiazole compounds behave as H_1 antagonists whereas the histamine derivatives are still (weak) agonists. Although the potency of the compounds synthesized is not very high, the agonistic activity exerted by 2-(thiazol-4-yl)ethanamine **8** and its 2-phenyl derivatives **3a-j** support the concept that the tautomerism of imidazole in histamine is not essential for the activation of H_1-receptors. The transformation of the agonistic 2-phenylthiazoles **3a**–**j** to the antagonistic 2-benzylthiazoles **4a**–**f** indicates that the conjugation between the two aromatic rings (benzene and thiazole) may be important for the activation of H_1-receptors. As the imidazole analogues show higher activities than the corresponding thiazoles, we suggest that the sulfur atom does not interact with a receptor site. Further studies are necessary to clarify this latter observation.

6. Experimental protocols

6.1. Chemistry

General methods. 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 ppm downfield from internal TMS as reference. ^{1}H NMR data are reported in order of multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; *, exchangeable by D_2O), number of protons, and approximate coupling constant in Hz. 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 (E. Merck). Column chromatography was carried out using Silica Gel 30–60 μm (J.T. Baker).

6.2. General method for compounds *5a–d*, and *5f–p* — preparation of thioamides

The appropriate nitrile (0.03 mol) is dissolved in at least an equal weight of pyridine (more if the nitrile is of low solubility), and triethylamine (0.03 mol) is added. Dry hydrogen sulfide is passed through the solution in a steady stream for 2–4 h for compounds **5a**–**d**, **5f**–**j** and 12–16 h for compounds **5k**–**p** at r.t. The mixture is then poured into water, and the thioamide collected by filtration. All thioamides were used in further reactions without extra purification; optimized spectral data were not obtained.

5a: C_7H_7NS (137); m.p.: 115–116°C, [m.p.: 115–116°C] [18]. Yield: 94.0%; ^{1}H NMR (DMSO): 8.15–8.25 (m, 5H, arom.); 9.75 (s*, 2H, NH_2C=S).

5b: C_7H_6FNS (155); m.p.: 110–111.5°C. Yield: 78.0%; ^{1}H NMR (DMSO): 8.0–8.2 (m, 1H, arom.); 8.4–8.75 (m, 2H, arom.); 9.1 (s, 1H, arom.); 10.2 (s*, 2H, NH_2C=S).

5c: C_7H_6ClNS (171.5); m.p.: 121–122°C. Yield: 77.0%; ^{1}H NMR (DMSO): 7.6–7.75 (m, 1H, arom.); 7.9–7.8 (m, 2H, arom.); 8.1 (s, 1H, arom.); 10.15 (s*, 2H, NH_2C=S).

5d: C_7H_6BrNS (215.9); m.p.: 126–127°C. Yield: 76.5%; ^{1}H NMR (DMSO): 7.1–7.3 (m, 1H, arom.); 7.5–7.7 (m, 2H, arom.); 7.9 (s, 1H, arom.); 10.0 (s*, 2H, NH_2C=S).

5f: $C_8H_6F_3NS$ (205); m.p.: 68–69°C. Yield: 97.5%; ^{1}H NMR (DMSO): 8.1–8.3 (m, 1H, arom.); 8.6–8.85 (m, 2H, arom.); 9.35 (s, 1H, arom.); 10.4 (s*, 2H, NH_2C=S).

5g: C_8H_9NS (151); m.p.: 88–90.5°C. Yield: 85.6%; ^{1}H NMR (DMSO): 2.35 (s, CH_3); 7.4–7.75 (m, 4H, arom.); 9.6 (s*, 2H, NH_2C=S).

5h: C_7H_7NOS (153); m.p.: 137–138.5°C. Yield: 40.0%; ^{1}H NMR (DMSO): 8.0–8.2 (m, 4H, arom.); 9.65 (s*, 2H, NH_2C=S); 9.9 (s*, HO).

5i: C_8H_9NOS (167); m.p.: 98–99.5°C. Yield: 90.0%; ^{1}H NMR (DMSO): 3.85 (s, OCH_3); 7.45–7.85 (m, 4H, arom.); 9.75 (s*, 2H, NH_2C=S).

5j: $C_7H_8N_2S$ (152); m.p.: 133.5–135°C. Yield: 72.0%; ^{1}H NMR (DMSO): 3.35 (s,* 2H, NH_2); 7.55–7.8 (m, 4H, arom.); 9.8 (s*, 2H, NH_2C=S).

5k: C_8H_9NS (151); m.p.: 98–99°C. Yield: 56.0%; ^{1}H NMR (DMSO): 3.4 (s, CH_2–benzyl); 7.6–7.9 (m, 5H, arom.); 9.8 (s*, 2H, NH_2C=S).

5l: C_8H_8FNS (169); m.p.: 75–76°C. Yield: 43.5%; ^{1}H NMR (DMSO): 4.35 (s, CH_2–benzyl); 7.8–8.1 (m, 4H, arom.); 10.3 (s*, 2H, NH_2C=S).

5m: C_8H_8ClNS (185.5); m.p.: 107.5–108.5°C. Yield: 47.0%; ^{1}H NMR (DMSO): 4.25 (s, CH_2–benzyl); 7.4–7.7 (m, 4H, arom.); 10.15 (s*, 2H, NH_2C=S).

5n: C_8H_8BrNS (229.9); m.p.: 126–127°C. Yield: ^{1}H NMR (DMSO): 51.4%; 4.15 (s, CH_2–benzyl); 7.25–7.6 (m, 4H, arom.); 10.05 (s*, 2H, NH_2C=S).

5o: $C_9H_{11}NS$ (165); m.p.: 78–79°C. Yield: 35.6%; ^{1}H NMR (DMSO): 2.4 (s, CH_3); 4.1 (s, CH_2–benzyl); 7.6–7.9 (m, 4H, arom.); 9.75 (s*, 2H, NH_2C=S).

5p: $C_9H_{11}NOS$ (181); m.p.: 83–84°C. Yield: 39.7%; ^{1}H NMR (DMSO): 4.3 (s, CH_2–benzyl); 4.65 (s, OCH_3) 7.4–7.7 (m, 4H, arom.); 9.95 (s*, 2H, NH_2C=S).

6.3. Preparation of 3-nitrothiobenzamide (*5e*)

3-Nitrobenzamide (0.01 mol) with Lawesson's reagent (0.005 mol) in 10.0 ml of HMPA was heated 4.0 h at 80°C.

The reaction mixture was allowed to cool to r.t. and was then poured into water. The suspension was extracted with ether. The combined ether phases were dried ($MgSO_4$) and the ether was distilled off. The residue was purified by column chromatography on Silica Gel, employing the same eluent as indicated by TLC.

5e: $C_7H_6N_2O_2S$ (182); m.p.: 126–127.5°C. Yield: 43.9%; ^{1}H NMR (DMSO): 8.15–8.25 (m, 1H, arom.); 8.6–8.9 (m, 2H, arom.); 9.25 (s, 1H, arom.); 10.35 (s*, 2H, NH_2C=S); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.34$).

*6.4. General method for compounds **6a–p** and **7** — preparation of 4-[(2-phthalimido)ethyl]thiazoles*

1-Bromo-4-phthalimido-2-butanone (0.01 mol) and an appropriate *meta*-substituted-thiobenzamide or *meta*-substituted-thiobenzylamide or thiourea (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 2.0 h. After cooling, the precipitate was filtered and washed with *n*-propanol and ether. The hydrochloride product was obtained as a brown solid. The free base, in each case, was obtained as follows: the hydrochloride of an appropriate phthalimide was mixed 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 solid. All phthalimide derivatives were purified by column chromatography on Silica Gel, employing the same eluent as was indicated by TLC.

7: $C_{13}H_{10}N_2O_2S$ (258); m.p.: 107.5–108.5°C, [m.p.: 101–102°C] [15]. Yield: 78.5%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.1–3.4 (t, $J = 7.0$ Hz, CH_2); 3.9–4.25 (t, $J = 7.0$ Hz, CH_2); 6.85 (s, $1H_{(5')}$-thiazole); 7.3–7.8 (m, 4H, arom.); 8.55 (s, $1H_{(2')}$-thiazole); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.30$).

6a: $C_{19}H_{14}N_2O_2S$ (334); m.p.: 122.5–123.5°C. Yield: 51.3%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3–3.25 (t, $J = 7.0$ Hz, CH_2); 3.95–4.1 (t, $J = 7.0$ Hz, CH_2); 6.9 (s, H-thiazole); 7.2–7.35 (m, 5H, arom.); 7.75–8.0 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.53$).

6b: $C_{19}H_{13}FN_2O_2S$ (352); m.p.: 117–118°C. Yield: 36.7%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.1–3.3 (t, $J =$ 7.0 Hz, CH_2); 4.0–4.2 (t, $J = 7.0$ Hz, CH_2); 6.1 (s, H-thiazole); 6.2–7.0 (m, 8H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.43$).

6c: $C_{19}H_{13}ClN_2O_2S$ (368.5); m.p.: 119–120°C. Yield: 30.5%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.1–3.25 (t, $J =$ 7.0 Hz, CH_2); 4.0–4.15 (t, $J = 7.0$ Hz, CH_2); 6.75 (s, H-thiazole); 6.95–7.2 (m, 2H, arom.); 7.3–7.7 (m, 6H, arom); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.68$).

6d: $C_{19}H_{13}BrN_2O_2S$ (412.9); m.p.: 126–127°C. Yield: 35.5%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.1–3.35 (t, $J =$ 7.0 Hz, CH_2); 4.0–4.25 (t, $J = 7.0$ Hz, CH_2); 7.05 (s, H-thiazole); 7.25–8.0 (m, 8H, arom.); TLC ((9:1 chloroform–ethyl acetate, $R_f = 0.70$).

6e: $C_{19}H_{13}N_3O_4S$ (379); m.p.: 199–200°C. Yield: 49.7%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.1–3.25 (t, $J =$ 7.0 Hz, CH_2); 3.95–4.1 (t, $J = 7.0$ Hz, CH_2); 7.05 (s, H-thiazole); 7.25–8.1 (m, 8H, arom.); TLC (19:1 chloroform–ethyl acetate, $R_f = 0.37$).

6f: $C_{20}H_{13}F_3N_2O_2S$ (402); m.p.: 144–145.5°C. Yield: 39.2%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.1–3.3 (t, $J =$ 7.0 Hz, CH_2); 4.0–4.2 (t, $J = 7.0$ Hz, CH_2); 7.05 (s, H-thiazole); 7.25–8.1 (m, 8H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.57$).

6g: $C_{20}H_{16}N_2O_2S$ (348); m.p.: 165–166.5°C. Yield: 62.0%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 2.25 (s, CH_3); 3.25–3.5 (t, $J = 7.0$ Hz, CH_2); 4.05–4.25 (t, $J = 7.0$ Hz, CH_2); 6.85 (s, H-thiazole); 7.0–7.15 (m, 2H, arom.); 7.35–7.7 (m, 6H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.39$).

6h: $C_{19}H_{14}N_2O_3S$ (350); m.p.: 113–114°C. Yield: 33.6%; ^{1}H NMR (DMSO) (δ): 3.1–3.25 (t, $J = 7.0$ Hz, CH_2); 4.0–4.2 (t, $J = 7.0$ Hz, CH_2); 6.95 (s, H-thiazole); 7.3–7.7 (m, 4H, arom.); 7.95–8.1 (m, 4H, arom.); 9.9 (s*, HO) TLC (9:1 chloroform–ethyl acetate, $R_f =$ 0.51).

6i: $C_{20}H_{16}N_2O_3S$ (364); m.p.: 106.5–108°C. Yield: 67.3%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.1–3.25 (t, $J =$ 7.0 Hz, CH_2); 3.8 (s, OCH_3); 4.0–4.15 (t, $J = 7.0$ Hz, CH_2); 7.0 (s, H-thiazole); 7.2–7.4 (m, 4H, arom.); 7.5–7.9 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.41$).

6j: $C_{19}H_{15}N_3O_2S$ (349); m.p.: 118–119°C. Yield: 42.8%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 2.9–3.05 (t, $J =$ 7.0 Hz, CH_2); 3.3 (s*, NH_2); 3.75–3.95 (t, $J = 7.0$ Hz, CH_2); 6.75 (s, H-thiazole); 6.9–7.1 (m, 4H, arom.); 7.45–7.75 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.47$).

6k: $C_{20}H_{16}N_2O_2S$ (348); m.p.: 151.5–152.5°C. Yield: 56.0%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.0–3.25 (t, $J =$ 7.0 Hz, CH_2); 3.95–4.15 (t, $J = 7.0$ Hz, CH_2); 3.25 (s, CH_2–benzyl); 6.9 (s, H-thiazole); 7.2–7.3 (m, 5H, arom.); 7.75–7.95 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.41$).

6l: $C_{20}H_{15}FN_2O_2S$ (366); m.p.: 142–143°C. Yield: 57.4%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.05–3.25 (t, $J = 7.0$ Hz, CH_2); 4.0–4.2 (t, $J = 7.0$ Hz, CH_2); 4.25 (s, CH_2–benzyl); 6.9 (s, H-thiazole); 7.05–7.35 (m, 4H, arom.); 7.75–7.95 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.37$).

6m: $C_{20}H_{15}ClN_2O_2S$ (382.5); m.p.: 86–87°C. Yield: 53.6%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.0–3.25 (t, $J =$ 7.0 Hz, CH_2); 3.9–4.1 (t, $J = 7.0$ Hz, CH_2); 4.2 (s, CH_2–benzyl); 6.75 (s, H-thiazole); 6.85–7.1 (m, 4H, arom.); 7.3–7.7 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.36$).

6n: $C_{20}H_{15}BrN_2O_2S$ (426.9); sticky oil. Yield: 54.2%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.0–3.2 (t, $J = 7.0$ Hz,

CH_2); 3.85–4.05 (t, $J = 7.0$ Hz, CH_2); 4.2 (s, CH_2–benzyl); 6.8 (s, H-thiazole); 6.9–7.1 (m, 4H, arom.); 7.2–7.6 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.46$).

6o: $C_{21}H_{18}N_2O_2S$ (362); m.p.: 91–92.5°C. Yield: 62.7%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 2.35 (s, CH_3); 3.0–3.25 (t, $J = 7.0$ Hz, CH_2); 4.0–4.2 (t, $J = 7.0$ Hz, CH_2); 4.25 (s, CH_2–benzyl); 6.9 (s, H-thiazole); 7.0–7.25 (m, 4H, arom.) 7.85–8.0 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.38$).

6p: $C_{21}H_{18}N_2O_3S$ (378); sticky oil. Yield: 59.5%; ^{1}H NMR ($CDCl_3$ + TMS) (δ): 3.05–3.25 (t, $J = 7.0$ Hz, CH_2); 4.75 (s, OCH_3); 4.0–4.15 (t, $J = 7.0$ Hz, CH_2); 4.25 (s, CH_2–benzyl); 6.9 (s, H-thiazole); 7.0–7.4 (m, 4H, arom.); 7.75–7.95 (m, 4H, arom.); TLC (9:1 chloroform–ethyl acetate, $R_f = 0.35$).

*6.5. General methods for compounds **3a–i**, **8**, and **4a–f** — preparation of 2-[2-phenyl and 2-benzyl)-4-thiazolyl]ethanamines*

An appropriate 4-[(2-phthalimido)ethyl]thiazole (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 vacuo provided a white sticky semi-solid, which was purified by column chromatography on Silica Gel, employing the same eluent as indicated by TLC. The title products were obtained as sticky oils. All free bases were treated with methanolic HBr and hydrobromides were precipitated with dry diethyl ether. 4-Phthalimido-2-butanone and 1-bromo-4-phthalimido-2-butanone were obtained according to the US patent [20].

8: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 2.0 (s*, NH_2); 2.85–3.0 (t, $J = 7.0$ Hz, CH_2); 3.05–3.2 (t, $J = 7.0$ Hz, CH_2); 7.05 (s, $1H_{('5')}$-thiazole); 8.8 (s, $1H_{('2')}$-thiazole); TLC (90:30:3 chloroform–methanol–concentrated ammonia, $R_f = 0.15$). $C_5H_8N_2S$·HBr (209); m.p.: 160–161°C, [$C_5H_8N_2S$·HCl m.p.: 181–183°C] [15]. Yield: 37%. *Anal.* Calc.: C, 28.71; H, 4.31; N, 13.40 Found: C, 28.48; H, 4.56; N, 13.09%.

3a: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.85 (s*, NH_2); 2.8–2.95 (t, $J = 7.0$ Hz, CH_2); 3.0–3.15 (t, $J = 7.0$ Hz, CH_2); 6.85 (s, H-thiazole); 7.3–7.45 (m, 5H, arom.); TLC (88:20:2 chloroform–methanol–concentrated ammonia, $R_f = 0.43$);$C_{11}H_{12}N_2S$·2HBr (366); m.p.: 153–154°C, [$C_{11}H_{12}N_2S$·2HCl; m.p.: 206–209°C] [26,27]. Yield: 31%. *Anal.* Calc.: C, 36.06; H, 3.82; N, 7.65. Found: C, 35.94; H, 3.93; N, 7.51%.

3b: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.95 (s*, NH_2); 2.9–3.0 (t, $J = 7.0$ Hz, CH_2); 3.05–3.2 (t, $J = 7.0$ Hz, CH_2); 7.0 (s, H-thiazole); 7.2–7.9 (m, 4H, arom.); TLC (50:10:1 chloroform–methanol–concentrated ammonia, $R_f = 0.32$); $C_{11}H_{11}FN_2S$·2HBr (384); m.p.: 239–240°C. Yield: 34%. *Anal.* Calc.: C, 34.37; H, 3.38; N, 7.29. Found: C, 34.13; H, 3.24; N, 7.08%.

3c: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 2.05 (s*, NH_2); 2.95–3.15 (t, $J = 7.0$ Hz, CH_2); 3.2–3.3 (t, $J = 7.0$ Hz, CH_2); 7.05 (s, H-thiazole); 7.25–8.05 (m, 4H, arom.); TLC (50:10:1 chloroform–methanol–concentrated ammonia, $R_f = 0.36$); $C_{11}H_{11}ClN_2S$·2HBr (400.5); m.p.: 224–225°C. Yield: 37%. *Anal.* Calc.: C, 32.95; H, 3.24; N, 6.99. Found: C, 32.82; H, 3.13; N, 6.64%.

3d: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 2.45 (s*, NH_2); 2.95–3.05 (t, $J = 7.0$ Hz, CH_2); 3.1–3.25 (t, $J = 7.0$ Hz, CH_2); 7.05 (s, H-thiazole); 7.3–8.2 (m, 4H, arom.); TLC (90:10:1 chloroform–methanol–concentrated ammonia, $R_f = 0.17$); $C_{11}H_{11}BrN_2S$·2HBr (445); m.p.: 230–232°C. Yield: 35%. *Anal.* Calc.: C, 29.66; H, 2.92; N, 6.29. Found: C, 29.51; H, 2.88; N, 6.13%.

3f: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.65 (s*, NH_2); 2.85–3.0 (t, $J = 7.0$ Hz, CH_2); 3.05–3.15 (t, $J = 7.0$ Hz, CH_2); 6.9 s, H-thiazole); 7.25–8.1 (m, 4H, arom.); TLC 100:10:1 chloroform–methanol–concentrated ammonia, $R_f = 0.33$) $C_{12}H_{11}F_3N_2S$·2HBr (434); m.p.: 224–226°C. Yield: 32% *Anal.* Calc.: C, 33.18; H, 2.99; N, 6.45. Found: C, 32.90; H, 2.82; N, 6.49%.

3g: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.95 (s*, NH_2); 2.1 (s, CH_3); 2.85–3.0 (t, $J = 7.0$ Hz, CH_2); 3.05–3.15 (t, $J = 7.0$ Hz, CH_2); 6.95 (s, H-thiazole); 7.2–7.5 (m, 4H, arom.); TLC (90:30:2 chloroform–methanol–concentrated ammonia, $R_f = 0.44$); $C_{12}H_{14}N_2S$·2HBr (380); m.p.: 234–236°C. Yield: 53%. *Anal.* Calc.: C, 37.89; H, 4.21; N, 7.30. Found: C, 37.81; H, 4.53; N, 7.50%. $C_{12}H_{14}N_2OS$·2HBr (396); m.p. 221–222°C. Yield: 47%. *Anal.* Calc.: C, 36.36; H, 4.04; N, 7.07. Found: C, 36.18; H, 3.96; N, 6.89%.

3h: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.85 (s*, NH_2); 2.75–2.90 (t, $J = 7.0$ Hz, CH_2); 3.0–3.2 (t, $J = 7.0$ Hz, CH_2); 6.95 (s, H-thiazole); 7.25–7.6 (m, 4H, arom.); 8.25 (s*, HO); TLC (90:10:1 chloroform–methanol–concentrated ammonia, $R_f = 0.21$) $C_{11}H_{12}N_2OS$·2HBr (382); m.p.: 264–266°C. Yield: 42%. *Anal.* Calc.: C, 34.55; H, 3.65; N, 7.33. Found: C, 34.38; H, 3.88; N, 7.05%.

3i: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.75 (s*, NH_2); 2.90–3.0 (t, $J = 7.0$ Hz, CH_2); 3.05–3.15 (t, $J = 7.0$ Hz, CH_2); 3.95 (s, OCH_3); 7.05 (s, H-thiazole); 7.4–7.8 (m, 4H, arom.); TLC (50:10:1 chloroform–methanol–concentrated ammonia, $R_f = 0.34$).

3j: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.80 (s*, NH_2); 2.70–2.85 (t, $J = 7.0$ Hz, CH_2); 2.9–3.05 (t, $J = 7.0$ Hz, CH_2); 3.30 (s*, NH_2, arom.); 6.85 (s, H-thiazole); 7.3–7.75 (m, 4H, arom.); TLC (100:50:5 chloroform–methanol–concentrated ammonia, $R_f = 0.21$) $C_{11}H_{13}N_3S$·3HBr (624); m.p.: 219–221°C. Yield: 33%. *Anal.* Calc.: C, 28.57; H, 3.46; N, 6.73. Found: C, 28.53; H, 3.55; N, 6.51%.

4a: ^{1}H NMR ($CDCl_3$ + TMS) (δ): 1.9 (s*, NH_2); 2.85–3.00 (t, $J = 7.0$ Hz, CH_2); 3.05–3.20 (t, $J = 7.0$

Hz, CH_2); 4.3 (s, CH_2, benzyl); 6.85 (s, H-thiazole); 7.4–7.6 (m, 5H, arom.); TLC (88:20:2 chloroform–methanol–concentrated ammonia, $R_f = 0.24$) $C_{12}H_{14}N_2S{\cdot}2HBr$ (380); m.p.: 146–147°C, [$C_{12}H_{14}N_2S{\cdot}$ dipicrate; m.p.: 143.5–144.5°C] [28]. Yield: 78%. *Anal.* Calc.: C, 37.89; H, 4.21; N, 7.37. Found: C, 37.64; H, 4.49; N, 7.12%.

4b: ^{1}H NMR ($CDCl_3 + TMS$) (δ): 1.65 (s*, NH_2); 2.80–2.95 (t, $J = 7.0$ Hz, CH_2); 3.00–3.15 (t, $J = 7.0$ Hz, CH_2); 4.3 (s, CH_2, benzyl); 6.90 (s, H-thiazole); 7.00–7.50 (m, 4H, arom.); TLC (90:30:2 chloroform–methanol–concentrated ammonia, $R_f = 0.40$) $C_{12}H_{13}FN_2S{\cdot}2HBr$ (398); m.p.: 220–221°C. Yield: 56%. *Anal.* Calc.: C, 36.18; H, 3.77; N, 7.03. Found: C, 36.02; H, 3.89; N, 7.13%.

4c: ^{1}H NMR ($CDCl_3 + TMS$) (δ): 1.75 (s*, NH_2); 2.80–2.95 (t, $J = 7.0$ Hz, CH_2); 3.00–3.15 (t, $J = 7.0$ Hz, CH_2); 4.25 (s, CH_2, benzyl); 6.85 (s, H-thiazole); 7.15–7.5 (m, 4H, arom.); TLC (90:30:2 chloroform–methanol–concentrated ammonia, $R_f = 0.46$) $C_{12}H_{13}ClN_2S{\cdot}2HBr$ (414.5); m.p.: 213–215°C. Yield: 51%. *Anal.* Calc.: C, 34.74; H, 3.62; N, 6.76. Found: C, 34.63; H 3.63; N, 6.72%.

4d: ^{1}H NMR ($CDCl_3 + TMS$) (δ): 1.85 (s*, NH_2); 2.8–2.95 (t, $J = 7.0$ Hz, CH_2); 3.00–3.15 (t, $J = 7.0$ Hz, CH_2); 4.25 (s, CH_2, benzyl); 6.85 (s, H-thiazole); 7.15–7.6 (m, 4H, arom.); TLC (90:30:2 chloroform–methanol–concentrated ammonia, $R_f = 0.36$) $C_{12}H_{13}BrN_2S{\cdot}2HBr$ (459); m.p.: 223–225°C. Yield: 48%. *Anal.* Calc.: C, 31.37; H, 3.27; N, 6.10. Found: C, 31.17; H, 3.19; N, 6.07%.

4e: ^{1}H NMR ($CDCl_3 + TMS$) (δ): 1.95 (s*, NH_2); 2.30 (s, CH_3); 2.80–2.95 (t, $J = 7.0$ Hz, CH_2); 3.00–3.15 (t, $J = 7.0$ Hz, CH_2); 4.25 (s, CH_2, benzyl); 6.80 (s, H-thiazole); 7.05–7.45 (m, 4H, arom.); TLC (90:30:2 chloroform–methanol–concentrated ammonia, $R_f = 0.30$) $C_{13}H_{16}N_2S{\cdot}2HBr$ (394); m.p.: 228–229°C. Yield: 63% *Anal.* Calc.: C, 39.59; H, 4.57; N, 7.11. Found: C, 39.38; H, 4.76; N, 7.09%.

4f: ^{1}H NMR ($CDCl_3 + TMS$) (δ): 1.80 (s*, NH_2); 2.85–3.00 (t, $J = 7.0$ Hz, CH_2); 3.05– 3.15 (t, $J = 7.0$ Hz, CH_2); 3.85 (s, OCH_3); 4.30 (s, CH_2, benzyl); 6.80 (s, H-thiazole); 6.9–7.4 (m, 4H, arom.); TLC (90:30:2 chloroform–methanol–concentrated ammonia, $R_f =$ 0.37). $C_{13}H_{16}N_2OS{\cdot}2HBr$ (410); m.p.: 174–175°C. Yield: 60%. *Anal.* Calc.: C, 38.05; H, 4.39; N, 6.83. Found: C, 37.89; H, 4.42; N, 6.87%.

*6.6. Preparation of 2-[2-(3-nitrophenyl)-4-thiazolyl]-ethanamine (**3e**)*

Hydrolysis of **6e** (0.02 mol) was carried out by heating with hydrochloric acid (25.0 ml 5 N) under reflux for 24 h, followed by washing with diethyl ether (3×20.0 ml), basification with sodium hydroxide to pH 12 and extraction with chloroform ($3 \times$ 15.0 ml) gave a crude product, which was purified by column chromatography on Silica Gel, employing the same eluent as indicated by TLC.

3e: ^{1}H NMR ($CDCl_3 + TMS$) (δ): 2.10 (s*, NH_2); 2.75–2.90 (t, $J = 7.0$ Hz, CH_2); 2.95–3.10 (t, $J = 7.0$ Hz, CH_2); 6.85 (s, H–thiazole); 7.3–8.5 (m, 4H, arom.); TLC (90:10:1 chloroform–methanol–concentrated ammonia, $R_f = 0.14$). $C_{11}H_{11}N_3O_2S{\cdot}2HBr$ (411); m.p.: 250–251°C. Yield: 37%. *Anal.* Calc.: C, 32.12; H, 3.16; N, 10.22. Found: C, 31.96; H, 3.21; N, 10.02%.

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