# Synthesis of 4-(ω-Aminoalkyl)- or 4-(ω-Lactamiminoalkyl)thiazoles by Ring Chain Transformation of Isothioureas with Lactam Derivatives

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*Dedicated to Prof. Roland Mayer on occasion of his 65th birthday*

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CH-Acidic isothioureas **1** react with lactam acetals **2** at the unsubstituted *N*-atom as well as at the acidic *S*-methylene group giving 4-(ω-aminoalkyl)thiazoles **6**. The latter are further transformed to 4-(ω-lactamiminoalkyl)thiazoles **8**, if lactim ethers **3** are used in reactions with isothioureas **1**.

Recently a new synthetic principle was elaborated for constructing a thiazole ring from a 1,4-binucleophilic C–S–C–N building block and an electrophilic *C*-synthon, using CH-acidic isothioamides or isothioureas and carboxylic acid derivatives, respectively.[1] We have tried now to apply this approach to the synthesis of 4-(ω-aminoalkyl)thiazoles **6**, which recently became available by an interesting ring chain transformation of semicyclic thioacylamidines **9** with acidic methyl halides **10**.[2]

In order to prepare compounds **6** starting from 1,4-binucleophilic isothioureas **1**, carboxylic acid derivatives have to be used, which not only contribute one carbon to the thiazole ring but also the aminoalkyl chain. This condition is fulfilled by lactam derivatives, which on nucleophilic attack may open the ring thus forming an aminoalkyl chain.

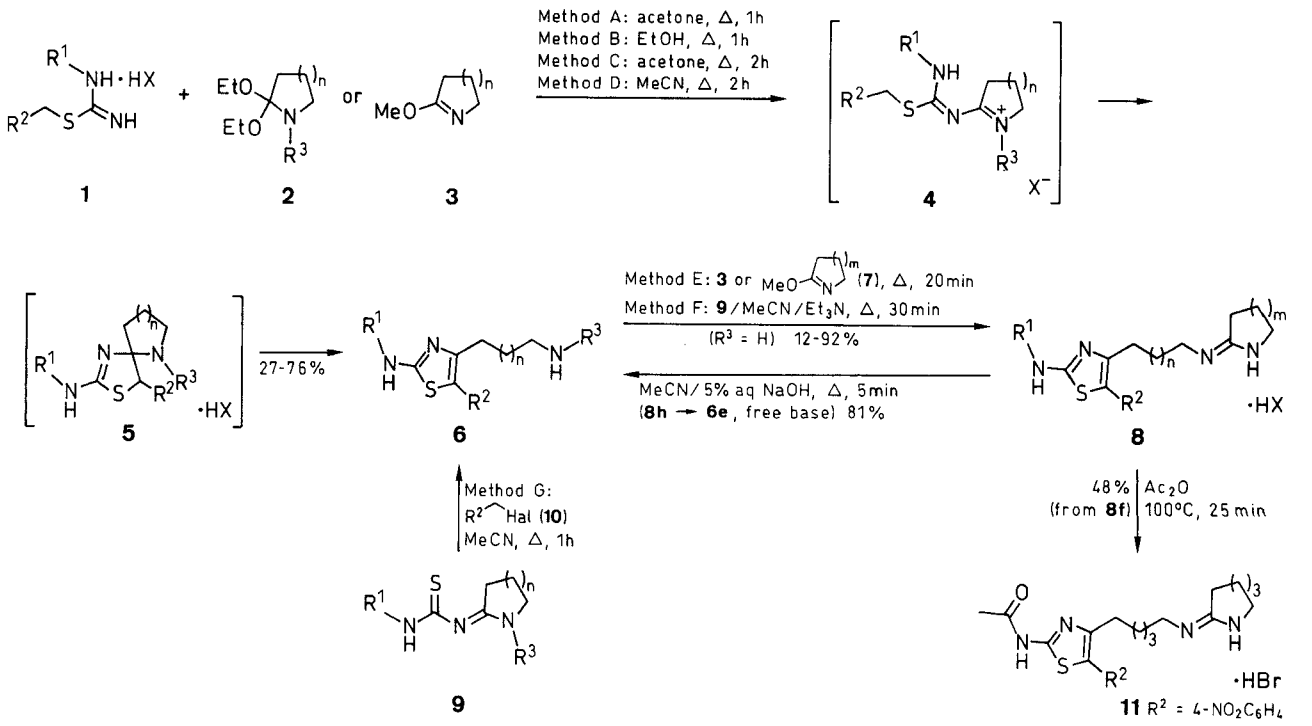
Treatment of isothioureas **1**, which are substituted by an electron-withdrawing aryl group $R^2$, with lactam acetals **2** gives 4-(ω-aminoalkyl)thiazoles **6** even in the absence of a base (Methods A and B).[3] In a comparable case **6a** the yield was lower than in the known synthesis[2] starting from a semicyclic thioacylamidine **9**. The structure of the new compounds **6** could be confirmed by typical fragments[2] in the mass spectra as well as by characteristic signals[2] in the $^1H$ NMR spectra (see Table). The *p*-cyanophenyl substituted compound **6c** was transformed to the corresponding free base (see experimental) by treatment with dilute sodium hydroxide. The mass spectrum of the obtained base is almost identical as compared to the corresponding salt **6c**. But interesting differences are found in the NMR spectra. While the absorptions of the two $CH_2$ groups adjacent to the thiazole ring and to the terminal amino group appear close to each other in case of the hydrobromide **6c**, no separation of these signals could be observed with the free base. This observation supports the assumption that protonation occurs at the terminal amino group NHR.[3] This fact is further supported by $^{13}C$ NMR spectroscopy, where the protonated aminoalkyl chain shows an upfield shift of the methylene carbon atoms in the salt **6c** which is typical for the protonation of aliphatic amines.[4] On the other hand the signals of the thiazole ring as well as of substituent $R^1$ are almost unaffected.

If lactim ethers **3** are employed in reactions with isothiuronium salts **1** (Method C and D), surprisingly no 4-(ω-aminoalkyl)thiazoles **6** are isolated, but compounds **8** having a terminal lactamimino substituent are formed.[3,5] Evidently, a subsequent reaction of the expected aminoalkylthiazoles **6** with lactim ether **3** has taken place. The same products **8** are obtained even if one equivalent lactim ether **3** is reacted with isothiuronium salts **1**. The yields are naturally below 50%. Apparently the aminoalkylthiazoles **6** primarily formed, are more nucleophilic than educts **1**, thus preferentially reacting with lactim ether **3** giving **8**. The presumed intermediacy of *N*-unsubstituted aminoalkylthiazoles **6** is supported by the formation of lactamiminoalkylthiazole **8h** in the reaction of lactim ether **3** (n = 3) with the *N*-unsubstituted aminoalkylthiazole **6e** · HBr[2] (Method E). By using lactim ethers **7**, which are different from **3**, 4-(ω-lactamiminoalkyl)thiazoles **8** can also be synthesized, where the number of methylene groups in the alkyl chain and in the lactam imine fragment are different (cf. **8g**). Curiously, a low yield of semicyclic 4-(ω-lactamiminoalkyl)thiazole (cf. **8i**) is also obtained if the semicyclic amidinothiourea **9** ($R^1$ = Et, n = 3) is treated with 4-cyanobenzylbromide (**10**; $R^2$ = 4-$NCC_6H_4$, Hal = Br) (Method G). Before, such products **8** have not been observed in this type of ring transformations.[2] In this case (**8i**, Method G) the semicyclic amidinothiourea **9** itself must act as an activated lactam derivative reacting with the corresponding primarily formed aminoalkylthiazole **6**. Ethylthiourea is eliminated as the leaving group, which can be detected in the reaction mixture. This ability of semicyclic amidinothioureas **9** to act as activated lactam derivative is demonstrated by the transformation of separately prepared 4-aminopentyl-5-(4-nitrophenyl)-2-ethylaminothiazole hydrobromide (**6e**), to the corresponding amidinopentylthiazole **8h** by treatment with **9** ($R^1$ = Et, $R^3$ = H, n = 3) (Method F).

The acetylation of the 4-(ω-amidinoalkyl)thiazole (**8f**) by means of acetic anhydride occurs at the 2-amino group with formation of product **11**.

Concerning the mechanism of the formation of aminoalkylthiazoles **6** and amidinoalkylthiazoles **8** it is interesting to note that an intermediate **4f** as free base could be isolated under mild conditions. On the other hand heating this reaction mixture affords the corresponding semicyclic amidinoalkylthiazole **8i**. The isothiourea intermediates **4** can be expected to undergo ring closure by attack of the deprotonated $SCH_2$ group at the semicyclic amidine C-atom giving spiro compounds **5** which finally open the previously formed lactamimine ring.

The structure of amidinoalkylthiazoles **8** is confirmed by spectroscopic data (see Table). In cases of compounds **8a** and **8f** having a free amino group in position 2 ($R^1$ = H), traces of products are detected in the mass spectra where this 2-amino group is transformed to the lactam imine moiety of the molecule. Similar transformations to non-




| 4, 6 | n | $R^1$ | $R^2$ | $R^3$ | X |
|---|---|---|---|---|---|
| a | 1 | H | 4-$NO_2C_6H_4$ | Me | Br |
| b | 1 | Et | 4-$NO_2C_6H_4$ | Me | Br |
| c | 1 | Et | 4-$NCC_6H_4$ | Me | Br |
| d | 3 | Et | 4-$NO_2C_6H_4$ | Me | Br |
| e | 3 | Et | 4-$NO_2C_6H_4$ | H | Br |
| f | 3 | Et | 4-$NCC_6H_4$ | H | |

| 8 | n | $R^1$ | $R^2$ | m | X |
|---|---|---|---|---|---|
| a | 1 | H | 4-$NO_2C_6H_4$ | 1 | Br |
| b | 1 | Et | 4-$NO_2C_6H_4$ | 1 | Br |
| c | 1 | Ph | 4-$NO_2C_6H_4$ | 1 | Br |
| d | 2 | Et | 4-$NO_2C_6H_4$ | 2 | Br |
| e | 2 | Et | 4-$NCC_6H_4$ | 2 | Br |
| f | 3 | H | 4-$NO_2C_6H_4$ | 3 | Br |
| g | 3 | Et | 4-$NO_2C_6H_4$ | 1 | Br |
| h | 3 | Et | 4-$NO_2C_6H_4$ | 3 | Br |
| i | 3 | Et | 4-$NCC_6H_4$ | 3 | Br |
| j | 3 | *i*-Pr | 4-$NO_2C_6H_4$ | 3 | Br |
| k | 3 | *i*-Pr | 2,4-$(NO_2)_2C_6H_3$ | 3 | Cl |
| l | 3 | Ph | 4-$NO_2C_6H_4$ | 3 | Br |
| m | 4 | Et | 4-$NO_2C_6H_4$ | 4 | Br |

bridged amidines were observed as the main reaction if isothioureas **1** were treated with formamide acetals.[1]

As shown in the case of compound **8h**, the terminal lactam imine moiety can be cleaved by hydrolysis with dilute sodium hydroxide affording the aminoalkylthiazole **6e** as free base.

Like the previously known synthesis[2] of aminoalkylthiazoles, i.e. from **9** and **10** the formation of 4-(ω-aminoalkyl)thiazoles **6** and 4-(ω-amidinoalkyl)thiazoles **8**, also represents a ring chain transformation, where one ring found in the reactant **2** or **3** is cleaved to an aminoalkyl chain in the product **6** or **8** while an original chain forms a heterocyclic ring. But, in contrast the starting partially saturated ring is not found in a heteroanalogous 1,3-dicarbonyl moiety but in the lactam derivative **2** or **3**. Similar ring transformations have already been used in the synthesis of other heterocycles than thiazoles, i.e. imidazolines,[6,7] oxazolines,[7-10] thiazolines,[7] triazoles[11-13] and oxazoles.[14]

***S*-(4-Cyanobenzyl)-*N*-ethyl-*N'N'*-(azepin-2-ylidene)isothiourea (4f):**
*O*-Caprolactim methyl ether[15] (**3**; n = 3, 6.35 g, 0.05 mol) was added to a solution of isothiourea **1** ($R^1$ = Et, $R^2$ = 4-$NCC_6H_4$ 6.00 g, 0.02 mol) in acetone (75 mL). After 24 h at ambient temperature the solvent was evaporated in vacuum and the residue recrystallized from benzene.

**2-Amino-4-(ω-aminoalkyl)thiazole Hydrohalides 6a–6d:**
Method A: *N*-Methylpyrrolidin-2-one diethylacetal[16] or *N*-methylazepin-2-one diethylacetal[16] (for **6d**) (0.01 mol) was added dropwise to a solution of isothiourea hydrobromide **1** (Hal = Br) (0.01 mol) in acetone (20 mL). The mixture was refluxed for 1–2 h. After cooling to r.t. the product was filtered by suction and recrystallized.

Method B: Analogous to Method A, but using EtOH as solvent instead of acetone.

**6c**:
UV (MeOH): $\lambda_{max}$ (log ε) = 235 (4.12), 260 sh (3.88), 348 nm (4.29).
$^{13}C$ NMR (DMSO-$d_6$/TMS, 62.5 MHz): δ = 14.2 ($CH_3$), 24.8 ($CH_2$), 26.8 ($CH_2$), 32.2 ($CH_3N$), 38.9 ($CH_3CH_2N$), 47.9 ($CH_2N$), 107.8 (C-4), 115.7 (NC–$C_{arom}$), 118.8 (CN), 128.8, 132.2 ($CH_{arom}$), 137.4 ($C_{arom}$), 148.8 (C-5), 167.0 (C-2).

**6d**:
$^{13}C$ NMR (DMSO-$d_6$/TMS, 75 MHz): δ = 14.5 ($CH_3$), 25.3 ($CH_2$), 25.8 ($CH_2$), 28.2 ($CH_2$), 29.9 ($CH_2$), 32.5 ($NCH_3$), 39.3 ($NCH_2$), 48.3 ($NCH_2$), 115.5 (C-4), 124.3, 128.2 ($CH_{arom}$), 140.3 ($C_{arom}$), 144.0 ($O_2N$-$C_{arom}$), 151.90 (C-5), 167.5 (C-2).

**4-(ω-Amidinoalkyl)-2-aminothiazoles 8:**
Method C: Lactim ether **3** (0.25 mol) was added dropwise to a solution of isothiuronium halide **1** (0.1 mol) in acetone (200 mL). The mixture was refluxed for 2 h and cooled to r.t. If the product did not precipitate, the mixture was concentrated or is diluted with a small amount of $Et_2O$. The product was filtered and recrystallized.

**Table 1.** Intermediate **4f**, 4-(ω-Aminoalkyl)-1,3-thiazoles **6** and 4-(ω-Lactamiminoalkyl)-1,3-thiazoles **8** and **11** Prepared

| Product | Yield (%)/ Method | mp (°C) | Molecular Formula[a] or Lit. mp (°C) | MS (70 eV) *m/z* (%) | $^1$H NMR (solvent/TMS)[b] δ, *J* (Hz) |
|---|---|---|---|---|---|
| **4f** | 66 | 109–111 (benzene) | $C_{17}H_{22}N_4S$ (314.5) | 166 (24), 149 (26), 116 (100), 96 (71), 89 (31), 69 (26), 55 (43), 45 (21), 41 (31), 39 (34) | $CDCl_3$: 1.12 (t, 3 H, $CH_3$), 1.60 (m, 6 H, $CH_2$), 2.38 (m, 2 H, $CH_2$), 3.08 (m, 4 H, $CH_2$), 4.30 (s, 2 H, $SCH_2$), 7.40 (s, 4 $H_{arom}$), 11.70 (br, 1 H, NH) |
| **6a** | 27/B | 280–282 (DMF) | 280–282[2] | – | – |
| **6b** | 62/A | 174–175 (EtOH) | $C_{15}H_{21}BrN_4O_2S$ (401.3) | 320 ($M^+$ – HBr, 10), 276 (30), 263 (100), 44 (57) | DMSO-$d_6$: 1.19 (t, 3 H, *J* = 7, $CH_3CH_2$), 2.07 (m, 2 H, $CH_2$), 2.57 (s, 3 H, $NCH_3$), 2.75 (m, 2 H, $CH_2C$=), 3.01 (2 H, m, $NCH_2$), 3.30 (m, 2 H, $NCH_2CH_3$), 7.51 (d, 2 $H_{arom}$, *J* = 9), 8.04 (m, 1 H, NH), 8.22 (d, 2 $H_{arom}$, *J* = 9) |
| **6c** | 76/B | 223–225 (DMF/ EtOH) | $C_{16}H_{21}BrN_4S$ (381.3) | 300 ($M^+$ – HBr, 2), 243 (25), 44 (100 | DMSO-$d_6$: 1.14 (t, 3 H, *J* = 8, $CH_3CH_2$), 1.98 (m, 2 H, $CH_2$), 2.50 (s, 3 H, $NCH_3$), 2.66 (m, 2 H, $CH_2C$=), 2.96 (m, 2 H, $NCH_2$), 3.66 (m, 2 H, $NCH_2CH_3$), 7.52 (d, 2 $H_{arom}$, *J* = 8), 7.75 (d, 2 $H_{arom}$, *J* = 8), 8.00 (t, 1 H, *J* = 4, NH), 8.62 (m, 2 H, NH) |
| **6d** | 47/A | 202–204 (*i*-PrOH) | $C_{17}H_{25}BrN_4O_2S$ (429.4) | 348 ($M^+$ – HBr, 10), 263 (30), 176 (31), 44 (100) | DMSO-$d_6$: 1.29 (t, 3 H, *J* = 7.5, $CH_3CH_2$), 1.79 (m, 6 H, $CH_2$), 2.61 (s, 3 H, $NCH_3$), 2.90 (m, 4 H, $CH_2$), 3.40 (q, 2 H, *J* = 7.5, $CH_2CH_3$), 7.46 (d, 2 $H_{arom}$, *J* = 9), 8.20 (d, 2 $H_{arom}$, *J* = 9) |
| **6e** | 81 | 130–133 (MeCN) | $C_{16}H_{22}N_4O_2S$ (334.4) | 334 ($M^+$, 5), 276 (12), 263 (16), 146 (11), 44 (68), 30 (100) | – |
| **8a** | 42/D | 263–265 (EtOH) | $C_{16}H_{20}BrN_5O_2S$ (426,3) | 412 (5), 345 ($M^+$ – HBr, 14), 98 (100), 97 (34) | $CF_3CO_2H$: 2.25 (m, 4 H, $CH_2$), 2.90 (m, 4 H, $CH_2$), 3.44 (m, 2 H, $CH_2$), 3.75 (m, 2 H, $CH_2$), 7.55 (d, 2 $H_{arom}$, *J* = 8), 7.68 (m, 2 H, NH), 8.28 (d, 2 $H_{arom}$, *J* = 8) |
| **8b** | 70/D | 180–182 (EtOH) | $C_{18}H_{24}BrN_5O_2S$ (454.4) | 373 ($M^+$ – HBr, 9), 98 (100), 97 (37) | $CF_3CO_2H$: 1.02 (t, 3 H, *J* = 7, $CH_3CH_2$), 1.88 (m, 4 H, $CH_2$), 2.50 (m, 4 H, $CH_2$), 3.09 (m, 4 H, $CH_2$), 3.35 (q, 2 H, *J* = 7, $NCH_2CH_3$), 7.20 (d, 2 H, *J* = 8), 7.58 (m, 2 H, NH), 7.94 (d, 2 $H_{arom}$, *J* = 8) |
| **8c** | 41/D | 258–261 ($MeNO_2$) | $C_{22}H_{24}BrN_5O_2S$ (502.4) | 421 ($M^+$ – HBr, 9), 98 (100), 97 (34) | $CF_3CO_2H$: 1.88 (m, 4 H, $CH_2$), 2.54 (t, 4 H, *J* = 7, $CH_2$), 3.05 (m, 2 H, $CH_2$), 3.38 (m, 2 H, $CH_2$), 7.02 (m, 5 H, $C_6H_5$), 7.50 (m, 2 H, NH), 7.94 (d, 2 $H_{arom}$, *J* = 8), 7.18 (d, 2 $H_{arom}$, *J* = 8) |
| **8d** | 72/C 66/H | 250–252 (EtOH) | $C_{20}H_{28}BrN_5O_2S$ (482.4) | 401 ($M^+$ – HBr, 20), 139 (36), 126 (100), 125 (60) | DMSO-$d_6$: 1.40 (t, 3 H, *J* = 7, $CH_2CH_3$), 1.92 (m, 8 H, $CH_2$), 2.62 (m, 4 H, $CH_2$), 3.40 (m, 6 H, $CH_2$), 7.78 (d, 2 $H_{arom}$, *J* = 8), 8.20 (m, 1 H, NH), 8.42 (d, 2 $H_{arom}$, *J* = 8), 9.31 (m, 1 H, NH) |
| **8e** | 61/D | 218–220 (MeCN) | $C_{21}H_{28}BrN_5S$ (462.5) | 381 ($M^+$ – HBr, 19), 139 (40), 126 (100), 96 (35), 82 (36), 55 (38) | $CF_3CO_2H$: 1.00 (t, 3 H, *J* = 7, $CH_2CH_3$), 1.48 (m, 8 H, $CH_2$), 2.25 (m, 4 H, $CH_2$), 3.08 (m, 6 H, $CH_2$), 6.81 (m, 1 H, NH), 7.15 (d, 2 $H_{arom}$, *J* = 8), 7.44 (d, 2 $H_{arom}$, *J* = 8) |
| **8f** | 31/D | 214–216 (EtOH) | $C_{20}H_{28}BrN_5O_2S$ (482.4) | 496 (5), 401 ($M^+$ – HBr, 27), 167 (35), 154 (52), 139 (52), 126 (47), 113 (39), 96 (100), 69 (30), 55 (41), 41 (31) | DMSO-$d_6$: 1.88 (m, 12 H, $CH_2$), 2.91 (m, 4 H, $CH_2$), 3.40 (m, 2 H, $CH_2$), 3.62 (m, 2 H, $CH_2$), 7.56 (m, 1 H, NH), 7.76 (m, 1 H, NH), 7.75 (d, 2 $_{arom}$, *J* = 8), 8.44 (d, 2 $H_{arom}$, *J* = 8), 9.42 (br, 1 H, NH) |
| **8g** | 67/E | 222–224 (MeCN) | $C_{20}H_{28}BrN_5O_2S$ (482.4) | 401 ($M^+$ – HBr, 21), 139 (35), 126 (86), 111 (51), 98 (100), 97 (46), 84 (40), 41 (33) | $CF_3CO_2H$: 1.32 (t, 3 H, *J* = 7, $CH_2CH_3$), 1.50 (m, 6 H, $CH_2$), 2.16 (m, 2 H, $CH_2$), 2.72 (m, 4 H, $CH_2$), 3.31 (m, 4 H, $CH_2$), 3.68 (m, 2 H, $CH_2CH_3$), 7.50 (d, 2 $H_{arom}$, *J* = 8), 7.84 (m, 2 H, NH), 8.22 (d, 2 $H_{arom}$, *J* = 8) |
| **8h** | 92/C 54/F 72/E | 217–219 (EtOH) | $C_{22}H_{32}BrN_5O_2S$ (510.5) | 429 ($M^+$ – HBr, 38), 167 (58), 154 (99), 153 (30), 139 (97), 126 (87), 125 (32), 111 (32), 96 (100), 55 (47), 41 (39), 30 (34) | DMSO-$d_6$: 1.40 (t, 3 H, *J* = 7, $CH_2CH_3$), 1.85 (m, 12 H, $CH_2$), 2.90 (m, 4 H, $CH_2$), 3.50 (m, 6 H, $CH_2$), 7.60 (d, 2 $H_{arom}$, *J* = 8), 8.19 (m, 1 H, NH), 8.45 (d, 2 $H_{arom}$, *J* = 8), 9.41 (m, 1 H, NH) |
| **8i** | 42/D 17/G | 211–213 (MeCN) | $C_{23}H_{32}BrN_5S$ (490.5) | 409 ($M^+$ – HBr, 44), 167 (50), 154 (35), 153 (33), 140 (32), 139 (90), 126 (85), 113 (46), 112 (34), 96 (100), 69 (32), 55 (54), 42 (31), 41 (46), 30 (40) | DMSO-$d_6$: 0.94 (t, 3 H, *J* = 8, $CH_2CH_3$), 1.41 (m, 12 H), $CH_2$), 2.50 (m, 2 H, $CH_2$), 2.98 (m, 4 H, $CH_2$), 3.22 (m, 4 H, $CH_2$), 7.25 (d, 2 $H_{arom}$, *J* = 8), 7.55 (d, 2 $H_{arom}$, *J* = 8), 7.65 (t, 1 H, NH), 8.90 (s, 1 H, NH), 9.20 (s, 1 H, NH) |
| **8j** | 74/C | 219–221 (MeCN) | $C_{23}H_{34}BrN_5O_2S$ (524.5) | 443 ($M^+$ – HBr, 34), 428 (37), 168 (38), 154 (69), 139 (67), 126 (63), 113 (29), 96 (100), 55 (44), 43 (33), 41 (43), 30 (33) | $CF_3CO_2H$: 1.31 (d, 6 H, *J* = 6, $CH_3$), 1.70 (m, 12 H, $CH_2$), 2.58 (m, 4 H, $CH_2$), 3.15 (m, 2 H, $CH_2$), 3.45 (m, 3 H, $CH_2$, CH), 7.08 (m, 1 H, NH), 7.48 (d, 2 $H_{arom}$, *J* = 8), 7.60 (m, 1 H, NH), 8.22 (d, 2 $H_{arom}$, *J* = 8) |

**Table 1.** (continued)

| Product | Yield (%)/ Method | mp (°C) | Molecular Formula[a] or Lit. mp (°C) | MS (70 eV) *m/z* (%) | $^1$H NMR (solvent/TMS)[b] $\delta$, *J* (Hz) |
|---|---|---|---|---|---|
| **8k** | 53/C | 176–178 (MeCN) | $C_{23}H_{33}ClN_6O_4S$ (524.1) | 488 ($M^+$ – HCl, 5), 139 (31), 96 (100), 55 (40), 43 (48), 42 (30), 41 (52), 30 (34) | $CF_3CO_2H$: 1.19 (d, 6H, *J* = 7, $CH_3$), 1.41 (m, 12H, $CH_2$), 2.12 (m, 2H, $CH_2$), 2.31 (m, 2H, $CH_2$), 2.85 (m, 2H, $CH_2$), 3.18 (m, 3H, $CH_2$, CH), 7.12 (m, 2H, NH), 7.45 (d, *J* = 8, $C_6H_3$), 7.69 (m, 1 $H_{arom}$), 8.22 (d, 1 $H_{arom}$, *J* = 8), 8.55 (m, 1H, NH) |
| **8l** | 63/E 32/D | 124–126 (acetone) | $C_{26}H_{32}BrN_5O_2S$ (558.6) | 477 ($M^+$ – HBr, 40), 167 (47), 154 (63), 139 (74), 126 (73), 113 (40), 112 (32), 96 (100), 69 (31), 55 (50), 42 (30), 41 (42), 30 (48) | $CF_3CO_2H$: 1.68 (m, 12H, $CH_2$), 2.60 (m, 4H, $CH_2$), 3.15 (m, 2H, $CH_2$), 3.42 (m, 2H, $CH_2$), 7.38 (m, 8H, $C_6H_5$ + 2 $H_{arom}$ + NH), 8.20 (d, 2 $H_{arom}$, *J* = 8), 9.60 (m, 1H, NH) |
| **8m** | 63/D | 166–168 (EtOAc/ MeOH) | $C_{24}H_{36}BrN_5O_2S$ (538.6) | 457 ($M^+$ – HBr, 28), 195 (39), 110 (100), 82 (75), 81 (39), 80 (70), 79 (35), 69 (38), 55 (35), 41 (45), 30 (31) | DMSO-$d_6$: 1.19 (t, 3H, *J* = 7, $CH_2CH_3$), 1.50 (m, 16H, $CH_2$), 2.54 (m, 4H, $CH_2$), 3.34 (m, 6H, $CH_2$), 7.53 (d, 2 $H_{arom}$, *J* = 9), 7.90 (m, 1H, NH), 8.21 (d, 2 $H_{arom}$, *J* = 9), 9.17 (br, 1H, NH) |
| **11a** | 48 | 205–207 (MeCN) | $C_{22}H_{30}BrN_5O_3S$ (524.5) | 443 ($M^+$ – HBr, 21), 167 (44), 154 (54), 139 (55), 126 (47), 113 (42), 96 (100), 55 (42), 43 (73), 41 (30) | $CF_3CO_2H$: 1.40 (m, 12H, $CH_2$), 2.15 (s, 3H, $CH_3$), 2.42 (m, 4H, $CH_2$), 2.88 (m, 2H, $CH_2$), 3.15 (m, 2H, $CH_2$), 7.00 (m, 2H, NH), 7.28 (d, 2 $H_{arom}$, *J* = 8), 7.95 (d, 2 $H_{arom}$, *J* = 8) |

[a] Satisfactory microanalyses obtained: C ± 0.33, H ± 0.24, N ± 0.27, Exceptions **8c**, C 0.54, H 0.34, **8k**, N 0.36, **8m**, C 0.43.
[b] $^1$H NMR spectra were recorded on a Tesla BS 587 FT-spectrometer, except for **6c** and **8c**, which were recorded at 250 MHz on a Bruker WP 250 spectrometer.

Method D: Analogous to Method C but using MeCN as solvent instead of acetone.

Method E: A mixture of **6**[2] (0.01 mol) and lactim ether **3** (0.01 mol) or **7** (0.01 mol) was refluxed for 20 min. After cooling to r.t., the product was filtered and recrystallized.

Method F: A mixture of **6e**[2] (0.6 g; 1.44 mmol), semicyclic amidinothiourea **9**[2] ($R^1$ = Et, $R^3$ = H, n = 3, 0.5 g, 2.51 mmol), MeCN (30 mL) and $Et_3N$ (1 mL) was heated to boiling for 30 min. After cooling to r.t. the product was suction filtered and recrystallized.

Method G: A solution of **9** ($R^1$ = Et, $R^3$ = H, n = 3; 3.98 g, 0.02 mol) and α-bromo-*p*-tolunitrile (**10**, $R^2$ = 4-$NCC_6H_4$, Hal = Br; 3.92 g, 0.02 mol) in MeCN (20 mL) was refluxed for 1 h. After cooling to r.t. the amidinoalkylthiazole **8** was filtered by suction and recrystallized.

Method H: Analogous to Method C, but using the corresponding lactim ethyl ether.

**8d:**

UV (MeOH): $\lambda_{max}$ (log ε) = 267 (4.10), 398 nm (4.10).

$^{13}$C NMR (DMSO-$d_6$/TMS, 75 MHz): $\delta$ = 13.7 ($CH_3$), 19.4 ($CH_2$), 22.3 ($CH_2$), 27.6 ($CH_2$), 28.0 ($CH_2$), 28.6 ($CH_2$), 28.8 ($CH_2$), 43.0 ($CH_2N$), 44.1 ($CH_2$), 45.2 ($CH_2N$), 118.2 (C-4), 126.3, 131.6 ($CH_{arom}$), 138.7 ($C_{arom}$), 149.6 ($O_2NC_{arom}$), 163.1 (C-5), 165.9 ($CH_2N$=C), 170.3 (C-2).

**8f:**

$^{13}$C NMR (DMSO-$d_6$/TMS, 20 MHz): $\delta$ = 23.1 ($CH_2$), 25.8 ($CH_2$), 26.8 ($CH_2$), 27.5 ($CH_2$), 28.0 ($CH_2$), 28.6 ($CH_2$), 29.4 ($CH_2$), 30.8 ($CH_2$), 36.2 ($CH_2N$), 42.9 ($CH_2N$), 115.4 (C-4), 123.5, 127.6 ($CH_{arom}$), 139.5 ($C_{arom}$), 144.0 (C-5), 150.8 ($O_2NC_{arom}$), 166.7 ($CH_2N$=C), 167.7 (C-2).

**8i:**

$^{13}$C NMR (DMSO-$d_6$, 62.6 MHz): $\delta$ = 14.2 ($CH_3$), 23.2 ($CH_2$), 25.9 ($CH_2$), 26.9 ($CH_2$), 27.6 ($CH_2$), 28.2 ($CH_2$), 28.7 ($CH_2$), 29.5 ($CH_2$), 30.8 ($CH_2$), 38.4 ($CH_2N$), 41.8 ($CH_2N$), 42.9 ($CH_2N$), 107.6 (C-4), 115.3 ($NCC_{arom}$), 118.8 (CN), 128.1, 132.5 ($CH_{arom}$), 137.8 ($C_{arom}$), 150.6 (C-5), 166.8 ($CH_2N$=C), 168.3 (C-2).

**Conversion of 6c · HBr to the Corresponding Free Base:**
A mixture of thiazole hydrobromide **6c** (0.19 g, 0.5 mmol) and 5% aq NaOH (25 mL) was briefly heated to boiling. After cooling to r.t., the product was filtered and recrystallized from MeOH/water; yield: 0.14 g (93%), mp 118–120°C.

$^1$H NMR (DMSO-$d_6$/TMS, 250 MHz): 1.15 (t, 3H, *J* = 7 Hz, $CH_3$), 1.82 (p, 2H, *J* = 7 Hz, $CH_2$), 2.32 (s, 3H, $NCH_3$), 2.60 (m, 4H, $CH_2C$=, $CH_2N$), 3.25 (q, 2H, *J* = 7 Hz, $CH_2N$), 7.48 (d, 2 $H_{arom}$, *J* = 8), 7.75 (m, 3H, 2 $H_{arom}$ + NH), 8.30 (s, 1H, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS, 62.5 MHz): $\delta$ = 14.3 ($CH_3$), 27.5 ($CH_2$), 28.1 ($CH_2$), 35.4 ($CH_3N$), 39.1 ($CH_3CH_2N$), 50.5 ($CH_2N$), 107.8 (C-4), 115.7 (CCN), 118.8 (CN), 128.1 (CH), 132.5 (CH), 137.9 ($C_{arom}$), 150.6 (5-C), 167.0 (C-2).

MS: (*m/z*) = 300 ($M^+$, 8), 256 (35), 243 (99), 44 (100).

**4-(5-Aminopentyl)-2-ethylamino-5-(4-nitrophenyl)-1,3-thiazole (6e, Free Base):**
A mixture of amidinoalkylthiazole **8h** (3 g, 6 mmol), MeCN (10 mL) and 5% aq NaOH (10 mL) was refluxed for 15 min. After standing overnight in a refrigerator the product was filtered off by suction and recrystallized from MeCN.

**2-Acetylamino-4-[5-(azepin-2-ylidenaminopentyl)]-5-(4-nitrophenyl)-1,3-thiazole Hydrobromide (11a):**
A mixture of 2-aminothiazole (**8f**; 0.96 g, 2 mmol) and acetic anhydride (20 mL) was heated for 25 min on a boiling water bath. Excess of acetic anhydride was evaporated and the residue recrystallized from MeCN (Table).

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