Synthesis of Spirocyclopropanated Analogues of Imidacloprid and Thiacloprid[‡]

Farina Brackmann,[a] Dmitrii S. Yufit,[b] Judith A. K. Howard,[b] Mazen Es-Sayed,[c] and Armin de Meijere*[a]

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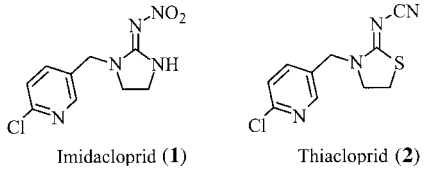
tert-Butyl *N*-[1-(hydroxymethyl)cyclopropyl]carbamate (**8**) was converted into spirocyclopropanated analogues **14**-CP and **14**-CT of the insecticide Thiacloprid (**2**) in six simple steps with overall yields of 24 % each, along with their regioisomers **13**-CP and **13**-CT in overall yields of 17 and 15 %, respectively. The spirocyclopropanated analogues **27**-CP and **27**-CT of the insecticide Imidacloprid (**1**) were prepared from **8** in five steps in an overall yield of 10 % each, along with their regioisomers **20**-CP and **20**-CT in an overall yield of 8 and 7 %, respectively. The key step in all preparations was a cocyclization of an appropiately protected (1-aminocyclopropyl)methyl derivative with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) or nitroguanidine (**22**). The structures of several final products and by-products were verified by X-ray crystal structure analyses.

Introduction

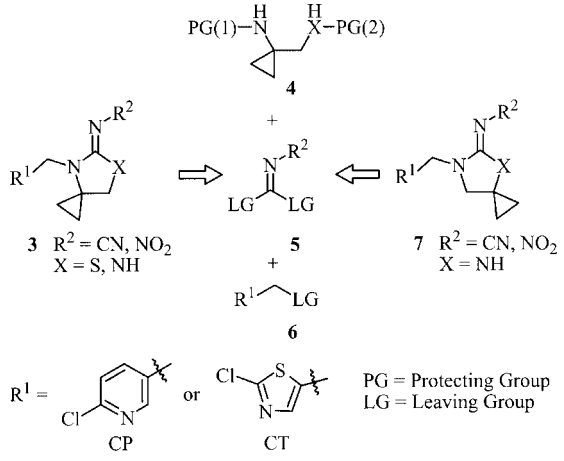
The relatively new non-natural insecticide Imidacloprid (**1**) is the first chloronicotinyl insecticide (CNI)™ which consists of the 2-(*N*-nitroimino)imidazolidine building block coupled with a (6-chloropyridin-3-yl)methyl (CPM) residue. Imidacloprid (**1**) was introduced to the market in 1991 and has become one of the most effective and widest used insecticides worldwide in crop protection and veterinary pest control in the last decade.[1] Encouraged by this success, numerous analogues have been synthesized.[2] The second example is the chloronicotinyl insecticide Thiacloprid (**2**) which contains a (*N*-cyanoimino)thiazolidine group. Thiacloprid (**2**) encompasses high insecticidal activity with a favorable ecobiological profile and safety to bees. It is particularly useful in horticulture as well as in modern crop protection systems.



In order to study the influence of spirocyclopropane-annelation on the saturated heterocycle upon the biological activities of these compounds, we have elaborated a synthetic approach to spirocyclopropanated analogues of **1** and **2**, and this paper summarizes our results.

Results and Discussion

The first goal was to develop a synthetic strategy which offers a regioselective access to spirocyclopropanated analogues **3** and **7** of Imidacloprid (**1**) and Thiacloprid (**2**) (Scheme 1).



Scheme 1. Retrosynthetic considerations concerning spirocyclopropanated analogues **3** and **7** of Imidacloprid (**1**) and Thiacloprid (**2**).

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[a] Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen,
Tammannstrasse 2, 37077 Göttingen, Germany
Fax: (internat.) +49-551-399475
E-mail: Armin.deMeijere@chemie.uni-goettingen.de
[b] Department of Chemistry, University of Durham,
Durham, South Rd., DH1 3LE, England
[c] Bayer CropScience AG,
Alfred-Nobel-Strasse 50, 40789 Monheim, Germany

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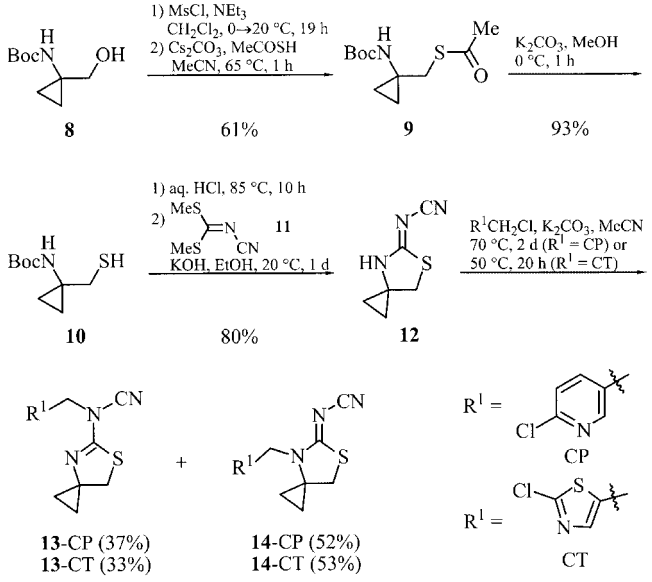
The crucial point of this strategy is the appropriate choice of the building block **4**, which should allow one to selectively functionalize each of the two nitrogen atoms (when X = N) or transform the functional group X into a sulfur-containing group, respectively, before cyclization with **5** followed by alkylation with **6**. *tert*-Butyl *N*-[1-(hydroxymethyl)cyclopropyl]carbamate (**8**), which can be synthesized in three steps (40 % overall yield) from *N*,*N*-dibenzyl-2-benzyloxyacetamide[3] starting with its reductive cyclopropanation (the de Meijere variant of the so-called Kulinkovich reaction[4]) was chosen as an appropriate starting material. Compound **8** can also be prepared in 56 % overall yield by monohydrolysis[5a] of commercially available diethyl cyclopropane-1,1-dicarboxylate followed by Curtius degradation[5b,5c] of the carboxylic acid residue and subsequent reduction[5d,5e] of the ester moiety.

Spirocyclopropanated Analogues of Thiacloprid (2)

Towards the conversion of the *N*-Boc-protected (1-aminocyclopropyl)methanol **8** into the spirocyclopropanated analogues **14**-CP and **14**-CT of Thiacloprid (**2**), the hydroxy function of **8** was transformed into the mesylate, and this was substituted by thioacetic acid according to an established procedure[6] to yield the thioester **9**. The latter was hydrolyzed using potassium carbonate[6] to furnish the thiol **10**. Deprotection of the amino group required heating of **10** in 6 N aqueous hydrochloric acid under reflux to cleave the intermediately formed *tert*-butyl thioether. Subsequent cyclization of the crude product with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) adopting a published protocol[7] afforded the heterocycle **12**. Whereas alkylation of the latter with 2-chloro-5-(chloromethyl)thiazole (CCMT) under basic conditions succeeded upon stirring the reaction mixture at 50 °C overnight, the reaction with 2-chloro-5-(chloromethyl)pyridine (CCMP) required a longer reaction time (2 d) and elevated temperature (70 °C). Surprisingly, two isomeric products **13** and **14** in a ratio of about 1:1.5 were formed in both cases (Scheme 2) They could, however, be separated by preparative thin layer chromatography.



Scheme 2. Synthesis of spirocyclopropanated analogues **14**-CP and **14**-CT of Thiacloprid (**2**).

By X-ray analyses of the chlorothiazole-substituted products **13**-CT and **14**-CT (Figure 1) they were proved to be the regioisomers resulting from alkylation either on the amino function of the heterocycle (major compounds, **14**-CP, **14**-CT) or on the nitrogen atom of the imino function (minor compounds, **13**-CP, **13**-CT).

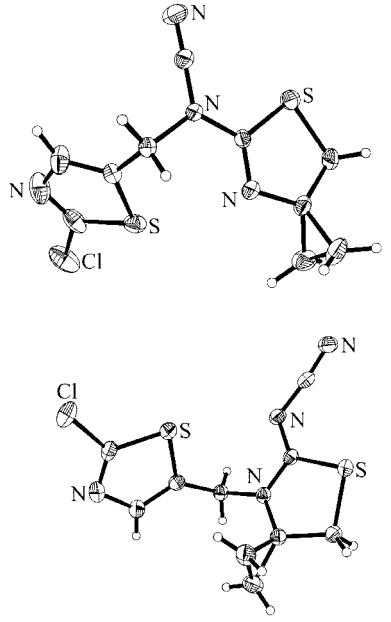


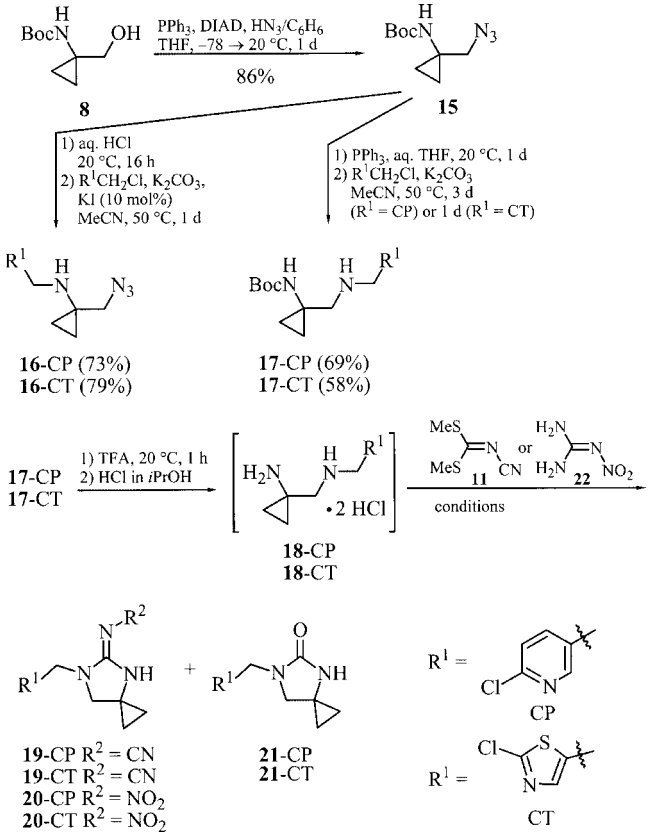
Figure 1. Structures of the chlorothiazole-substituted 6-thia-4-aza-spiro[2.4]heptanes **13**-CT and **14**-CT in the crystals.[8]

The overall yields of the spirocyclopropanated analogues of Thiacloprid **14**-CP and **14**-CT were 24 % over six steps in each case.

Spirocyclopropanated Analogues of Imidacloprid (1)

The transformation of the *N*-Boc-protected (1-aminocyclopropyl)methanol **8** into spirocyclopropanated analogues **19** and **20** of Imidacloprid (**1**) was performed following essentially the same logic as in the previous case (Scheme 3). The hydroxy function of **8** was first converted into an azido group by a Mitsunobu reaction[9] using hydrazoic acid as the nucleophile. The Boc group could be removed from the resulting azide **15**, and the deprotected amine was alkylated under iodide catalysis at 50 °C for 1 d with CCMP or CCMT, respectively, to yield the precursors **16**-CP and **16**-CT with an alkylated nitrogen on the three-membered ring in 69 and 72 % yield, respectively. However, after reduction of the azido to amino groups in **16**-CP and **16**-CT applying a Staudinger reaction,[10] the attempted cyclizations with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) adopting a published protocol[11] (EtOH, 90 °C, 2 d) only led to decomposition of the starting material. Another

portion of the *N*-Boc-protected primary amine obtained from the azide **15** by reduction with triphenylphosphane was alkylated with CCMP or CCMT on its amino group in the α-position of the cyclopropane moiety. To prevent the formation of undesired dialkylamino derivatives (cf.[12]), slightly substoichiometric amounts of CCMP or CCMT, respectively, were used in these reactions. While only decomposition of the starting material was observed at 70 °C, the alkylation proceeded smoothly at 50 °C, and gave only the monoalkylated products **17**-CP and **17**-CT in 69 and 72 % yield, respectively (Scheme 3). In this case, the alkylation with CCMP required a longer reaction time (3 d) than the alkylation with CCMT (1 d).



Scheme 3. Preparation of substituted 1-aminocyclopropylmethyl derivatives **16**-CP(CT) as well as **18**-CP(CT) and cyclizations of the latter with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) and nitroguanidine (**22**).

Deprotection of the cyclopropylamino moiety in **17** with trifluoroacetic acid (TFA) followed by treatment with hydrogen chloride in ethyl acetate led to the amines **18**-CP and **18**-CT with a free primary amino group at the cyclopropane ring. These compounds were used directly in the subsequent cocyclization reactions.

Surprisingly, the cocyclizations of **18**-CP(CT) with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) and nitroguanidine (**22**) differed significantly from known analogous reactions of similar substrates, but without a 1,1-disubstituted cyclopropane moiety (cf.[11]). Thus, an attempted cocyclization of **18**-CP with **11** failed completely (Table 1, Entry 1). Stirring of **18**-CT with two equivalents of potassium hydroxide and one equivalent of **11** in anhydrous EtOH at 70 °C for 1.5 d gave a mixture of two products, which could not be separated by column chromatography. Slow evaporation of some solvent from a solution of this mixture in hexane/Et_2O produced two types of crystals, which could be picked apart. X-ray crystal structure analyses of these crystals proved that the plate-like was the target product **19**-CT, the wedge-like was the spirocyclic urea derivative **21**-CT, respectively (Figure 2).

Table 1. Cocyclizations of 1-(aminomethyl)cyclopropylamines **18**-CP(CT) with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) and nitroguanidine (**22**). Compound **22** contained up to 20 % of water, if not otherwise specified.

Entry	Starting material	Reagent	Conditions	Product / Yield (%)	
1	**18**-CP	**11**	NEt_3, EtOH, 80 °C, 3 d	**19**-CP / 0	**21**-CP / 0
2	**18**-CT	**11**	KOH, EtOH, 125 °C, 2 d	**19**-CT / 25	**21**-CT / 36
3	**18**-CT	**11**	NEt_3, EtOH, 80 °C, 2.5 d[a]	**19**-CT / 55	**21**-CT / 14
4	**18**-CT	**11**	NEt_3, EtOH, mol. sieves 4 Å, 80 °C, 1 d	**19**-CT / 35	**21**-CT / 9
5	**18**-CT	**11**	NEt_3, DMF, mol. sieves 4 Å, 100 °C, 2 d	**19**-CT / <30	**21**-CT / <10
6	**18**-CT	**22**	KOH, H_2O, 100 °C, 2 d	**20**-CT / 0	**21**-CT / 0
7	**18**-CT	**22**	KOH, H_2O, 150 °C 5 d[a]	**20**-CT / 0	**21**-CT / 44
8	**18**-CT	**22**	NEt_3, MeCN/EtOH, 85 °C, 3 d[b]	**20**-CT / 0	**21**-CT / 0

[a] The reaction was performed in a tightly screwed Pyrex tube. [b] Anhydrous nitroguanidine (**22**) was used.

The crystal of **19**-CT contained two crystallographically independent molecules, with virtually identical geometrical parameters, but different orientations of the CT groups [the corresponding SCCN torsional angles are to –96.1(1) and 56.0(2)° in the two independent molecules]. Whereas the molecules of **13**-CT and **14**-CT in the crystals are connected by a number of weak C–H···N(nitroamide) interactions (the shortest H···N distances are in the range of 2.4–2.6 Å), the molecules of **19**-CT and **21**-CT are linked by hydrogen bonds. A pair of N–H···N(nitroamide) hydrogen bonds [N···N 2.858(2), 2.980(2)Å, N–H···N 167(2), 168(2)°] combines independent molecules of **19**-CT in dimers, and N–H···O hydrogen bonds [N···O 2.871(3)Å, N–H···O 170(3)°] link the molecules of **21**-CT in chains, orientated parallel to the *b*-axis.

^{1}H NMR spectra disclosed that **19**-CT and **21**-CT were formed as a 1:1.4 mixture, which corresponds to yields of 25 and 36 %, respectively (Entry 2). The urea derivative **21**-CT must arise from hydrolysis of the imino moiety in **19**-CT during the course of the reaction or upon work-up including column chromatography. Switching from potassium

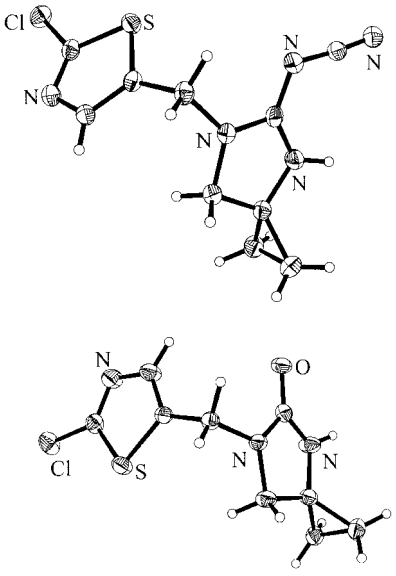


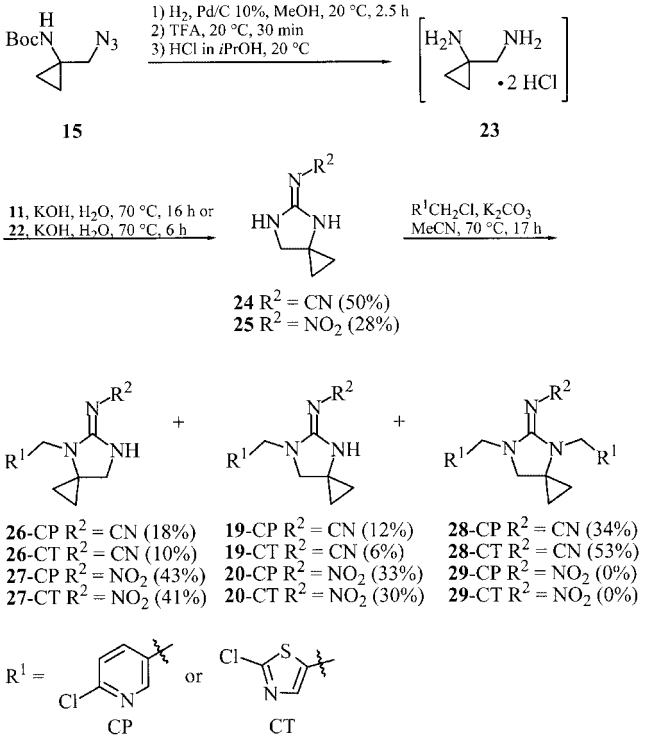
Figure 2. Structures of the spirocyclopropanated analogue **19**-CT of Imidacloprid (**1**) and the spirocyclic urea derivative **21**-CT in the crystals.[8]

hydroxide to anhydrous triethylamine increased the yield of **19**-CT to 55 %, yet, the undesired urea derivative **21**-CT was still formed in 14 % yield (Entry 3). Carrying out the reaction in the presence of molecular sieves 4 Å decreased the general yield, but the proportion of **19**-CT : **21**-CT was almost the same as in the previous case (ca. 3.9:1, Entry 4).

Even more discouraging were the attempted cocyclizations of **18**-CP(CT) with nitroguanidine (**22**). Not only did **18**-CP not react with **22** under different conditions, but the heating of **18**-CT with one equivalent of water-containing **22** and two equivalents of potassium hydroxide in water also did not cause any transformation within two days (Entry 6). Stirring of this reaction mixture at elevated temperature in a tightly screwed Pyrex tube for 5 d gave the urea **21**-CT in 44 % yield as the sole product (Entry 7), but no reaction was observed when the cocyclization was attempted under anhydrous conditions (anhydrous triethylamine and anhydrous nitroguanidine (**22**) in a mixture of MeCN/EtOH, Entry 8).

It is rather difficult to understand, why analogously substituted diamines, but without a 1,1-disubstituted cyclopropane moiety, enter the cocyclization reactions with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) and with nitroguanidine (**22**),[11] but amines derived from **16**-CP(CT) as well as **18**-CP(CT) react to a small extent only or not at all. While the former failure may be due to low thermal stability of diamines from **16**-CP(CT), the low reactivity of **18**-CP(CT) must be associated with the decrease of the nucleophilicity of its free amino group because of the significantly lower basicity of a cyclopropyl compared to a normal *sec*-alkylamine.[13] It is conceivable, that this decrease of basicity of a nitrogen atom adjacent to a cyclopropane moiety in the products **19**-CT, **20**-CT at the same time increases the electrophilicity of the imino moiety and makes it particularly susceptible to nucleophilic attack by water.

Since the (1-aminocyclopropyl)methanethiol generated by deprotection of **10** could successfully be cocyclized with **11**, an analogous reaction with the (aminocyclopropyl)-methylamine **23** prepared from the *N*-Boc-protected (1-aminocyclopropyl)methyl azide **15** in two simple steps, i.e. hydrogenolysis under palladium catalysis followed by Boc removal (Scheme 4) was attempted. Cocyclization with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) or aqueous nitroguanidine (**22**) furnished the spirocyclopropanated cyclic guanidines **24** and **25** as the sole products in 50 and 28 % yield, respectively, over three steps. Although the reaction was performed in water, no products resulting from hydrolysis of the imino group were detected.



Scheme 4. Preparation of spirocyclopropanated heterocycles **24**, **25** and their *N*-alkylation with CCMP or CCMT.

N-Alkylations of the spirocyclic nitroguanidine **25** with CCMP or CCMT, respectively, yielded mixtures of two isomeric products each in ratios of about 1:1.3, and in both cases they could not be separated by column chromatography. Applying two-dimensional NMR spectroscopy (HSQC, HMQC, NOE), these products were identified as the regioisomers **27**-CP(CT) and **20**-CP(CT) resulting from alkylation of the two secondary amino functions. In contrast to the alkylation of the thiazolidine derivative **12**, no alkylation of the imino function was observed in the cases of **24** and **25**. Analogous alkylations of the spirocyclic cyanoguanidine **24** gave mixtures of three chromatographically non-separable products, two-dimensional NMR spectroscopy of which revealed the two pairs of regioisomers **26**-CP(CT) and **19**-CP(CT) (resulting from alkylation of the different amino groups) as well as the twofold alkylation products **28**-CP(CT). As in the previous cases, no products

resulting from alkylation of the imino function were formed (Scheme 4).[14] The final separation and purification of these compounds for biological testing was carried out by preparative HPLC.[15]

Conclusions

The newly developed route to spirocyclopropanated analogues of the chloronicotinyl insecticides Imidacloprid (**1**) and Thiacloprid (**2**) led to numerous products of potentially high biological activity. Further evaluation of the biological potential of the described compounds is in progress.

Experimental Section

General Remarks: NMR spectra were recorded with a Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C NMR), a Varian UNITY-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR) Varian Inova 500 (500 MHz for ^{1}H and 128 MHz for ^{13}C NMR) or a Varian Inova 600 (600 MHz for ^{1}H and 151 MHz for ^{13}C NMR) instrument in $CDCl_3$, if not otherwise specified. Proton chemical shifts are reported in ppm relative to residual peaks of deuterated solvents. Multiplicities were determined by DEPT (Distortionless Enhancement by Polarisation Transfer) or APT (Attached Proton Test) measurements. For the mixtures of the compounds **26**, **19**, **28** and **27**, **20**, respectively, HMBC (Heteronuclear Multiple Bond Connectivity), HMQC (Heteronuclear Multiple Quantum Coherence) and NOE (Nuclear Overhauser Effect) spectra were also measured. Chemical shifts refer to $\delta_{TMS} = 0.00$ ppm according to the chemical shifts of residual solvent signals. IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets or oils between KBr plates. MS (EI at 70 eV or DCI with NH_3): Finnigan MAT 95 spectrometer. MS (HR-EI): pre-selected ion peak matching at $R >> 10000$ to be within ±2 ppm of the exact masses. HPLC: Kromasil 100 C18, 5 μm, 250 × 20 mm. Melting points: Büchi 510 capillary melting point apparatus, values are uncorrected. TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV$_{254}$. Preparative TLC: Macherey–Nagel, silica gel G/UV$_{254}$, layer thickness 0.25 mm (200 × 200 mm). Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie, Universität Göttingen. Starting materials: *tert*-Butyl [1-(hydroxymethyl)cyclopropyl]carbamate (**8**)[3a,5] and hydrazoic acid[16] were prepared according to previously published procedures. Anhydrous THF was obtained by distillation from sodium benzophenone ketyl, CH_2Cl_2 and MeCN from P_4O_{10}, EtOH and MeOH from magnesium, triethylamine from CaH_2. *S*,*S*-Dimethyl cyanodithioiminocarbonate (**11**) was dried in vacuo over P_4O_{10} and nitroguanidine (**22**) was dried in a drying oven at 110 °C for 1 h. 2-Chloro-5-(chloromethyl)thiazole (CCMT) and 2-chloro-5-(chloromethyl)pyridine (CCMP) were supplied by Bayer AG, nitroguanidine was supplied by NIGU GmbH. All other chemicals were used as commercially available. All operations in anhydrous solvents were performed under a nitrogen atmosphere in flame-dried glassware. Organic extracts were dried with $MgSO_4$.

***tert*-Butyl *N*-[1-(Acetylthiomethyl)cyclopropyl]carbamate (9):** Methanesulfonyl chloride (2.75 g, 24.0 mmol) was added dropwise at 0 °C to a stirred solution of *tert*-butyl *N*-[1-(hydroxymethyl)cyclopropyl]carbamate (**8**) (3.74 g, 20.0 mmol) and NEt_3 (2.43 g, 24.0 mmol) in anhydrous CH_2Cl_2 (100 mL). The reaction mixture was warmed to ambient temp. and stirred at this temp. for an additional 19 h. The solvent was evaporated under reduced pressure, water (60 mL) was added to the residue, and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried and concentrated under reduced pressure. The residue was taken up with MeCN (90 mL), the mixture stirred with cesium carbonate (6.78 g, 20.8 mmol) and thioacetic acid (1.58 g, 20.8 mmol) at 65 °C for 1 h, cooled to 25 °C, and the solvents evaporated under reduced pressure. Water (90 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried and concentrated under reduced pressure. Recrystallization of the residue from hexane/Et_2O yielded **9** (2.97 g, 61 %) as pale yellow needles, m.p. 89–90 °C. IR (KBr): $\tilde{\nu}$ = 3363 cm^{-1} (N–H), 3083 (C–H), 2992 (C–H), 2972 (C–H), 2934 (C–H), 1687 (C=O), 1508 (H–NCO), 1366 (*t*Bu), 1254 (*t*Bu), 1169 (O–*t*Bu). ^{1}H NMR (250 MHz): δ = 0.69–0.92 (m, 4 H, Cpr-H), 1.42 [s, 9 H, C(CH$_3$)$_3$], 2.33 (s, 3 H, CH$_3$), 3.17 (s, 2 H, CH$_2$S), 4.98 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, DEPT): δ = 14.7 (–, Cpr-C), 28.3 [+, C(*C*H$_3$)$_3$], 30.6 (+, CH$_3$), 33.5 (C$_{quat}$, Cpr-C), 36.6 (–, CH$_2$S), 79.6 [C$_{quat}$, *C*(CH$_3$)$_3$], 155.4 (C$_{quat}$, NCO), 195.2 (C$_{quat}$, SCO) ppm. MS (DCI): *m*/*z* (%) = 508 (< 1) [2M + NH$_4^+$], 452 (< 1) [2M + NH$_4^+$ – C$_4$H$_8$], 391 (< 1) [2M + NH$_4^+$ – H$_2$NCO$_2$ *t*Bu], 264 (12) [M + NH$_4^+$ + H], 263 (100) [M + NH$_4^+$], 246 (6) [M + H$^+$], 207 (34) [M + NH$_4^+$ – C$_4$H$_8$]. $C_{11}H_{19}NO_3S$ (245.34): calcd. C 53.85, H 7.81, N 5.71; found C 54.04, H 7.73, N 5.53.

***tert*-Butyl [1-(Mercaptomethyl)cyclopropyl]carbamate (10):** K_2CO_3 (3.34 g, 24.2 mmol) was added in one portion to a solution of the carbamate **9** (2.96 g, 12.1 mmol) in anhydrous, deoxygenated MeOH (100 mL) at 0 °C. After additional stirring at this temp. for 1 h, the solvent was evaporated under reduced pressure. Water (60 mL) was added to the residue, and the aqueous layer was extracted with EtOAc (4 × 55 mL). The combined organic layers were dried and concentrated under reduced pressure. Column chromatography of the residue (100 g of silica gel, 4 × 20 cm column, hexane/Et_2O, 3:1) yielded **10** (2.27 g, 93 %) as a colorless solid, m.p. 62–63 °C, R_f = 0.39. IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1} (N–H), 3078 (C–H), 3005 (C–H), 2979 (C–H), 2933 (C–H), 2564 (S–H), 1707, 1683 (C=O), 1524 (H–NCO), 1368 (*t*Bu), 1276 (*t*Bu), 1177 (O–*t*Bu). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.63–0.77 (m, 2 H, Cpr-H), 0.77–0.91 (m, 2 H, Cpr-H), 1.41 [s, 9 H, C(*C*H$_3$)$_3$], 2.70 (d, ^3J = 8.2 Hz, 2 H, CH$_2$S), 5.71 (br. s, 1 H, NH) ppm. The signal of the C(*C*H$_3$)$_3$-proton overlapped the signal of the SH-proton. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 14.8 (–, Cpr-C), 28.3 [+, C(CH$_3$)$_3$], 32.5 (C$_{quat}$ Cpr-C), 35.5 (–, CH$_2$S), 79.6 (C$_{quat}$, *C*(CH$_3$)$_3$], 155.4 (C$_{quat}$, NCO) ppm. MS (DCI): *m*/*z* (%) = 424 (2) [2M + NH$_4^+$], 368 (< 1) [2M + NH$_4^+$ – C$_4$H$_8$], 238 (12) [M + NH$_3$ + NH$_4^+$], 221 (100) [M + NH$_4^+$], 204 (15) [M + H$^+$], 182 (8) [M + NH$_3$ + NH$_4^+$ – C$_4$H$_8$], 165 (30) [M + NH$_4^+$ – C$_4$H$_8$]. $C_9H_{17}NO_2S$ (203.30): calcd. C 53.17, H 8.43, N 6.89; found C 53.42, H 8.18, N 6.80.

Cyclizations with *S*,*S*-Dimethyl Cyanodithioiminocarbonate (11) and Nitroguanidine (22). General Procedure 1 (GP1) for the Preparation of Spiroheterocycles 12, 19-CT, 21-CT, 24 and 25: To the solution of the respective starting material in EtOH or H_2O was added KOH or NEt_3 as well as **11** or **22**, respectively, and the resulting mixture was stirred at the indicated temp. for the indicated time. After cooling to ambient temp., the mixture was filtered through a pad of Celite, concentrated under reduced pressure, and the crude product was purified by column chromatography or preparative thin layer chromatography on silica gel, if not otherwise specified (see preparation of compound **25**).

***N*-Alkylation with 2-Chloro-5-(Chloromethyl)pyridine (CCMP) or 2-Chloro-5-(chloromethyl)thiazole (CCMT). General Procedure 2 (GP2) for the Preparation of Compounds 13, 14, 17, 19, 20, 26–29:**

A mixture containing the respective starting material, CCMP or CCMT and potassium carbonate in anhydrous MeCN was stirred at the indicated temp. for the indicated time. After cooling to ambient temp., the mixture was filtered through a pad of Celite, concentrated under reduced pressure, and the crude product was purified by column chromatography or preparative thin layer chromatography on silica gel.

(6-Thia-4-azaspiro[2.4]hept-5-ylidene)cyanamide (12): Carbamate **10** (470 mg, 2.31 mmol) was stirred with aq. 6 N HCl solution (20 mL) at 85 °C for 10 h. The volatile compounds were evaporated under reduced pressure, and the residue was treated with **11** (338 mg, 2.31 mmol) and KOH (130 mg, 2.31 mmol) in EtOH (20 mL) according to GP1 (20 °C, 1 d). Column chromatography of the residue (25 g of silica gel, 2 × 20 cm column, CH_2Cl_2/MeOH, 35:1) furnished **12** (283 mg, 1.85 mmol, 80 %) as a colorless solid, m.p. 140–141 °C, R_f = 0.35. IR (KBr): $\tilde{\nu}$ = 3134 cm^{-1} (N–H), 2192 (C≡N), 2161 (C≡N), 1586 (C=N), 1413, 1071, 958, 695, 670. ^1H NMR (250 MHz): δ = 0.88–1.07 (m, 2 H, Cpr-H), 1.08–1.24 (m, 2 H, Cpr-H), 3.51 (s, 2 H, CH_2S), 8.15 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, DEPT): δ = 12.3 (–, Cpr-C), 38.3 (–, CH_2S), 43.7 (C_{quat}, Cpr-C), 116.0 (C_{quat}, C≡N), 178.2 (C_{quat}, NNCS) ppm. MS (EI): *m*/*z* (%) = 153 (100) [M^+], 152 (70) [M^+ – H], 138 (26) [M^+ – NH], 125 (11), 120 (20), 111 (14) [M^+ – H_2NCN], 99 (4) [$HNCSNCN^+$], 85 (54) [$HSCNCN^+$], 71 (23), 68 (19) [M^+ – HSCNCN], 54 (12) [M^+ – HNCSNCN], 45 (22), 41 (51). HRMS (EI) calcd. for $C_6H_7N_3S$ [M^+] 153.0361, correct mass. $C_6H_7N_3S$ (153.20): calcd. C 47.04, H 4.61, N 27.43; found C 47.02, H 4.58, N 27.30.

***N*-(6-Chloropyridine-3-ylmethyl)-*N*-(6-thia-4-azaspiro[2.4]hept-4-en-5-yl)cyanamide (13-CP) and *N*-[4-(6-Chloropyridine-3-ylmethyl)-6-thia-4-azaspiro[2.4]-hept-5-ylidene]cyanamide (14-CP):** Preparative TLC (CH_2Cl_2/MeOH, 50:1) of the residue obtained from **12** (76.6 mg, 500 μmol), CCMP (81.0 mg, 500 μmol) and K_2CO_3 (276 mg, 2.00 mmol) in MeCN (10 mL) according to GP2 (70 °C, 2 d) furnished **13**-CP (52.0 mg, 37 %, R_f = 0.60) and **14**-CP (73.0 mg, 52 %, R_f = 0.23) as high viscous oils. **13-CP:** IR (KBr): $\tilde{\nu}$ = 2223 cm^{-1} (C≡N), 1617 (C=N), 1462, 1264, 1103. ^1H NMR (200 MHz): δ = 0.75–1.07 (m, 2 H, Cpr-H), 1.10–1.21 (m, 2 H, Cpr-H), 3.55 (s, 2 H, CH_2S), 4.76 (s, 2 H, CH_2Ar), 7.36 (d, ^3J = 8.3 Hz, 1 H, Ar-5-H), 7.75 (dd, ^3J = 8.3, ^4J = 2.6 Hz, 1 H, Ar-4-H), 8.40 (d, ^4J = 2.6 Hz, 1 H, Ar-2-H) ppm. ^{13}C NMR (50.3 MHz, APT): δ = 14.8 (–, Cpr-C), 43.1 (–, Cpr-C), 50.6 (–, CH_2S), 55.3 (–, CH_2Ar), 111.1 (–, C≡N), 124.5 (+, Ar-C-5), 128.7 (–, Ar-C-3), 139.2 (+, Ar-C-4), 150.2 (+, Ar-C-2), 152.1 (–, Ar-C-6), 154.9 (–, NNCS) ppm. MS (DCI): *m*/*z* (%) = 561/559/557 (6/25/30) [2M + H^+], 315/313 (5/12) [M + NH_3 + NH_4^+], 298/296 (26/67) [M + NH_4^+], 281/279 (41/100) [M + H^+]. HRMS (EI) calcd. for $C_{12}H_{11}ClN_4S$ [M^+] 278.0393, found 278.0393. $C_{12}H_{11}ClN_4S$ (278.76): calcd. C 51.70, H 3.98, N 20.10, Cl 12.72; found C 51.82, H 4.12, N 20.01, Cl 12.79. **14-CP:** IR (KBr): $\tilde{\nu}$ = 2162 cm^{-1} (C≡N), 1556 (CN), 1460, 1385. ^1H NMR (200 MHz): δ = 0.86–1.01 (m, 2 H, Cpr-H), 1.01–1.18 (m, 2 H, Cpr-H), 3.42 (s, 2 H, CH_2S), 4.34 (s, 2 H, CH_2Ar), 7.33 (d, ^3J = 8.4 Hz, 1 H, Ar-5-H), 7.61 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1 H, Ar-4-H), 8.19 (d, ^4J = 2.5 Hz, 1 H, Ar-2-H) ppm. ^{13}C NMR (50.3 MHz, APT): δ = 9.7 (–, Cpr-C), 37.0 (–, Cpr-C), 42.6 (–, CH_2S), 47.1 (–, CH_2Ar), 116.2 (–, C≡N), 124.6 (+, Ar-C-5), 130.4 (–, Ar-C-3), 137.9 (+, Ar-C-4), 148.1 (+, Ar-C-2), 151.3 (–, Ar-C-6), 175.4 (–, NNCS) ppm. MS (EI), *m*/*z* (%) = 280/278 (5/16) [M^+], 152 (12) [M^+ – $ClArCH_2^+$], 128/126 (32/100) [$ClArCH_2^+$]. HRMS (EI) calcd. for $C_{12}H_{11}ClN_4S$ [M^+] 278.0393, correct mass. $C_{12}H_{11}ClN_4S$ (278.76): calcd. C 51.70, H 3.98, N 20.10; found C 51.96, H 4.20, N 19.85.

***N*-(2-Chlorothiazol-5-ylmethyl)-*N*-(6-thia-4-azaspiro[2.4]hept-4-en-5-yl)cyanamide (13-CT) and *N*-[4-(2-Chlorothiazol-5-ylmethyl)-6-thia-4-azaspiro[2.4]hept-5-ylidene]cyanamide (14-CT):** Preparative TLC (CH_2Cl_2/MeOH, 50:1) of the residue obtained from **12** (76.6 mg, 500 μmol), CCMT (84.0 mg, 500 μmol) and K_2CO_3 (276 mg, 2.00 mmol) in MeCN (10 mL) according to GP2 (50 °C, 20 h) furnished **13**-CT (47.0 mg, 33 %, R_f = 0.60) and **14**-CT (76.0 mg, 53 %, R_f = 0.28) as colorless solids. **13-CT:** M.p. 105–107 °C. IR (KBr): $\tilde{\nu}$ = 2135 cm^{-1} (C≡N), 1622 (C=N), 1413, 1264, 1054. ^1H NMR (250 MHz): δ = 0.79–0.96 (m, 2 H, Cpr-H), 1.18–1.32 (m, 2 H, Cpr-H), 3.59 (s, 2 H, CH_2S), 4.87 (s, 2 H, CH_2Ar), 7.56 (s, 1 H, Ar-4-H). ^{13}C NMR (50.3 MHz, APT): δ = 14.8 (–, Cpr-C), 43.2 (–, Cpr-C), 46.4 (–, CH_2S), 55.2 (–, CH_2Ar), 110.6 (–, C≡N), 132.1 (–, Ar-C-5), 142.3 (+, Ar-C-4), 154.3 (–, Ar-C-2), 154.8 (–, NNCS) ppm. MS (EI): *m*/*z* (%) = 286/284 (1/4) [M^+], 249 (<1) [M^+ – Cl], 152 (16) [M^+ – CH_2ArCl], 134/132 (32/100) [CH_2ArCl^+], 71 (8), 45 (6), 41 (<1) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{10}H_9ClN_4S_2$ [M^+] 283.9957, found 283.9957. $C_{10}H_9ClN_4S_2$ (284.78): calcd. C 42.18, H 3.19, N 19.67, Cl 12.45; found C 42.22, H 3.43, N 19.48, Cl 12.28. **14-CT:** M.p. 103–105 °C, IR (KBr): $\tilde{\nu}$ = 3085 cm^{-1} (C–H), 2934 (C–H), 2194 (CN), 1558 (CN), 1521, 1055. ^1H NMR (250 MHz): δ = 0.91–1.05 (m, 2 H, Cpr-H), 1.13–1.27 (m, 2 H, Cpr-H), 3.39 (s, 2 H, CH_2S), 4.40 (s, 2 H, CH_2Ar), 7.38 (s, 1 H, Ar-4-H) ppm. ^{13}C NMR (50.3 MHz): δ = 9.9 (–, Cpr-C), 37.2 (–, Cpr-C), 38.8 (–, CH_2S), 47.0 (–, CH_2Ar), 115.9 (–, C≡N), 134.8 (–, Ar-C-5), 140.1 (+, Ar-C-4), 153.5 (–, Ar-C-2), 174.8 (–, NNCS) ppm. MS (EI): *m*/*z* (%) = 286/284 (9/24) [M^+], 249 (16) [M^+ – Cl], 152 (4) [M^+ – CH_2ArCl], 134/132 (36/100) [CH_2ArCl^+], 71 (13), 45 (10), 41 (2) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{10}H_9ClN_4S_2$ [M^+] 283.9957, correct mass. $C_{10}H_9ClN_4S_2$ (284.78): calcd. C 42.18, H 3.19, N 19.67, Cl 12.45; found C 42.31, H 3.34, N 19.55, Cl 12.34.

***tert*-Butyl [1-(Azidomethyl)cyclopropyl]carbamate (15):** Diisopropyl azodicarboxylate (5.76 g, 28.5 mmol), hydrazoic acid (28.5 mmol, 28.5 mL of a 1.0 M solution in benzene) and a solution of carbamate **8** (4.68 g, 25.0 mmol) in THF (50 mL) were added one after the other at –78 °C to a stirred solution of PPh_3 (7.87 g, 30.0 mmol) in anhydrous THF (200 mL). The reaction mixture was warmed to ambient temp., stirred at this temp. for an additional 18 h, and concentrated under reduced pressure. Column chromatography of the residue (200 g of silica gel, 4 × 30 cm column, hexane/CH_2Cl_2/Et_2O, 4:1:1, R_f = 0.46) gave **15** (4.57 g, 86 %) as a colorless oil which crystallized while kept at –26 °C overnight, m.p. 45–46 °C. IR (KBr): $\tilde{\nu}$ = 3350 cm^{-1} (N–H), 2985 (C–H), 2937 (C–H), 2874 (C–H), 2099 (N_3), 1690 (C=O), 1510 (H–NCO), 1369 (*t*Bu), 1296 (*t*Bu), 1174 (O–*t*Bu). ^1H NMR (250 MHz): δ = 0.71–0.79 (m, 2 H, Cpr-H), 0.81–0.88 (m, 2 H, Cpr-H), 1.43 [s, 9 H, $C(CH_3)_3$], 3.55 (s, 2 H, CH_2N_3), 5.08 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, DEPT): δ = 12.7 (–, Cpr-C), 28.3 [+, $C(CH_3)_3$], 33.3 (C_{quat}, Cpr-C), 56.9 (–, CH_2N_3), 79.9 [C_{quat}, $C(CH_3)_3$], 155.4 (C_{quat}, NCO) ppm. MS (DCI): *m*/*z* (%) = 247 (10) [M + NH_3 + NH_4^+], 230 (100) [M + NH_4^+], 213 (18) [M + H^+], 191 (6) [M + NH_4^+ + NH_3 – C_4H_8], 174 (28) [M + NH_4^+ – C_4H_8]. $C_9H_{16}N_4O_2$ (212.25): calcd. C 50.93, H 7.60, N 26.40; found C 51.19, H 7.69, N 26.11.

***N*-[1-(Azidomethyl)cyclopropyl]-*N*-[6-chloropy-ridin-3-yl)methyl]-amine (16-CP):** Azide **15** (425 mg, 2.00 mmol) was stirred with aq. 6 N HCl solution (20 mL) at ambient temp. for 16 h. The volatile compounds were evaporated under reduced pressure, and the residue was treated with CCMP (316 mg, 1.95 mmol), potassium iodide (33.2 mg, 200 μmol, 10 mol%) and K_2CO_3 (1.11 g, 8.00 mmol) in MeCN (25 mL) according to GP2 (50 °C, 1 d). Column chromatography of the residue (25 g of silica gel, 2 × 20 cm column, CH_2Cl_2/MeOH, 50:1, R_f = 0.25), yielded **16**-CP (339 mg, 73 %), as

a yellow oil. IR (KBr): $\tilde{\nu}$ = 3326 cm^{-1} (N–H), 3087 (C–H), 3008 (C–H), 2926 (C–H), 2854 (C–H), 2097 (N_3), 1587 1567, 1457, 1252, 1105, 1022, 824. ^1H NMR (250 MHz): δ = 0.49–0.62 (m, 2 H, Cpr-H), 0.62–0.75 (m, 2 H, Cpr-H), 1.86 (br. s, 1 H, NH), 3.30 (s, 2 H, CH_2N_3), 3.79 (s, 2 H, CH_2Ar), 7.23 (d, ^3J = 8.2 Hz, 1 H, Ar-5-H), 7.61 (dd, ^3J = 8.2, ^4J = 2.4 Hz, 1 H, Ar-4-H), 8.27 (d, ^4J = 2.4 Hz, 1 H, Ar-2-H) ppm. ^{13}C NMR (62.9 MHz, DEPT): δ = 12.7 (–, Cpr-C), 38.8 (C_{quat}, Cpr-C), 46.5 (–, CH_2N_3), 55.9 (–, CH_2Ar), 123.8 (+, Ar-C-5), 134.8 (C_{quat}, Ar-C-3), 138.7 (+, Ar-C-4), 149.1 (+, Ar-C-2), 149.9 (C_{quat}, Ar-C-6) ppm. MS (DCI): *m*/*z* (%) = 479/477/475 (22/83/100) [2M + H^+], 257/255 (3/8) [M + NH_4^+], 240/238 (18/48) [M + H^+]. $C_{10}H_{12}ClN_5$ (237.69): calcd. C 50.53, H 5.09, N 29.46, Cl 14.92; found C 50.29, H 5.08, N 29.29, Cl 14.92.

***N*-[1-(Azidomethyl)cyclopropyl]-*N*-[2-chlorothiazol-5-yl)methyl]-amine (16-CT):** Column chromatography (25 g of silica gel, 2 × 20 cm column, CH_2Cl_2/MeOH, 100:1, R_f = 0.20) of the residue obtained from the same quantities of starting material and reagents, and under the same conditions as in the preceding preparation, but with CCMT (328 mg, 1.95 mmol) as alkylating agent, furnished **16**-CT (376 mg, 79 %), as a yellow oil. IR (KBr): $\tilde{\nu}$ = 3316 cm^{-1} (N–H), 3087 (C–H), 3007 (C–H), 2920 (C–H), 2834 (C–H), 2098 (N_3), 1422, 1328, 1264, 1049. ^1H NMR (250 MHz): δ = 0.45–0.64 (m, 2 H, Cpr-H), 0.64–0.77 (m, 2 H, Cpr-H), 2.07 (br. s, 1 H, NH), 3.29 (s, 2 H, CH_2N_3), 3.97 (s, 2 H, CH_2Ar), 7.32 (s, 1 H, Ar-4-H) ppm. ^{13}C NMR (62.9 MHz, DEPT): δ = 12.6 (–, Cpr-C), 38.8 (C_{quat}, Cpr-C), 42.6 (–, CH_2N_3), 56.1 (–, CH_2Ar), 137.5 (+, Ar-C-4), 142.0 (C_{quat}, Ar-C-5), 151.1 (C_{quat}, Ar-C-2) ppm. MS (DCI): *m*/*z* (%) = 491/489/487 (40/100/98) [2M + H^+], 377/375 (14/18), 246/244 (21/37) [M + H^+], 208 (7) [M^+ – Cl]. $C_8H_{10}ClN_5S$ (243.71): calcd. C 39.43, H 4.14, N 28.74, Cl 14.55; found C 39.36, H 4.09, N 28.55, Cl 14.77.

***tert*-Butyl 1-{[(6-Chloropyridin-3-yl)methylamino]methyl}cyclopropylcarbamate (17-CP):** A solution of the azide **15** (425 mg, 2.00 mmol), PPh_3 (609 mg, 2.00 mmol) and water (36.0 mg, 2.32 mmol) in THF (20 mL) was stirred at ambient temp. for 1 d and then evaporated. The residue was treated with CCMP (316 mg, 1.95 mmol) and K_2CO_3 (415 mg, 3.00 mmol) in MeCN (25 mL) according to GP2 (50 °C, 3 d). Column chromatography of the residue (40 g of silica gel, 2 × 25 cm column, CH_2Cl_2/MeOH, 25:1, R_f = 0.16) yielded **17**-CP (419 mg, 69 %) as a pale yellow solid, m.p. 68–69 °C. IR (KBr): $\tilde{\nu}$ = 3367 cm^{-1} (N–H), 3077 (C–H), 3008 (C–H), 2986 (C–H), 2970 (C–H), 2934 (C–H), 1687 (C=O), 1504 (H–NCO), 1365 (*t*Bu), 1267 (*t*Bu), 1169 (O–*t*Bu), 754 (Ar). ^1H NMR (250 MHz): δ = 0.56–0.69 (m, 2 H, Cpr-H), 0.69–0.80 (m, 2 H, Cpr-H), 1.38 [s, 9 H, $C(CH_3)_3$], 1.66 (br. s, 1 H, NHAlk), 2.64 (s, 2 H, CH_2Alk), 3.79 (s, 2 H, CH_2Ar), 5.08 (br. s, NHBoc), 7.23 (d, ^3J = 8.1 Hz, 1 H, Ar-3-H), 7.63 (dd, ^3J = 8.1, ^4J = 2.1 Hz, 1 H, Ar-4-H), 8.28 (d, ^4J = 2.1 Hz, 1 H, Ar-6-H) ppm. ^{13}C NMR (62.9 MHz, DEPT): δ = 12.7 (–, Cpr-C), 28.3 [+, $C(CH_3)_3$], 33.0 (C_{quat}, Cpr-C), 49.9 (–, CH_2Alk), 55.1 (–, CH_2Ar), 79.4 [C_{quat}, $C(CH_3)_3$], 123.9 (+, Ar-C-5), 134.8 (C_{quat}, Ar-C-3), 138.6 (+, Ar-C-4), 149.2 (+, Ar-C-2), 149.8 (C_{quat}, Ar-C-6), 155.9 (C_{quat}, NCO) ppm. MS (EI): *m*/*z* (%) = 313/311 (2/6) [M^+], 256/254 (4/10) [M^+ – *t*Bu], 238/236 (2/8) [M^+ – H_2O – *t*Bu], 227/225 (2/8), 157/155 (6/20) [$CH_2NHCH_2ArCl^+$], 143/141 (14/30) [$HNCH_2ArCl^+$], 128/126 (15/38) [CH_2ArCl^+], 86/84 (31/48), 57 (100) [*t*Bu], 41 (16) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{15}H_{22}ClN_3O_2$ [M^+] 311.1401, correct mass. $C_{15}H_{22}ClN_3O_2$ (311.81): calcd. C 57.78, H 7.11, N 13.48, Cl 11.37; found C 57.62, H 7.19, N 13.22, Cl 11.24.

***tert*-Butyl 1-{[(2-Chlorothiazol-5-yl)methylamino]methyl}cyclopropylcarbamate (17-CT):** The residue obtained under the conditions of the previous preparation from **15** (1.06 g, 5.00 mmol), PPh_3 (1.52 mg, 5.80 mmol) and H_2O (90.0 mg, 5.00 mmol) was treated with CCMT (823 mg, 4.90 mmol) and K_2CO_3 (1.03 g, 7.50 mmol) in MeCN (25 mL) according to GP2 (50 °C, 1 d). Column chromatography of the residue (80 g of silica gel, 3 × 35 cm column, CH_2Cl_2/MeOH, 30:1, R_f = 0.15) yielded **17**-CT (908 mg, 58 %), as a pale yellow, highly viscous oil. IR (KBr): $\tilde{\nu}$ = 3326 cm^{-1} (N–H), 3089 (C–H), 3005 (C–H), 2977 (C–H), 2930 (C–H), 2821 (C–H), 1702 (C=O), 1502 (H–NCO), 1365 (*t*Bu), 1250 (*t*Bu), 1170 (O–*t*Bu), 1047. ^1H NMR (250 MHz): δ = 0.56–0.70 (m, 2 H, Cpr-H), 0.70–0.82 (m, 2 H, Cpr-H), 1.38 [s, 9 H, $C(CH_3)_3$], 1.79 (br. s, 1 H, NHAlk), 2.64 (s, 2 H, CH_2Alk), 3.93 (s, 2 H, CH_2Ar), 5.12 (br. s, 1 H, NHBoc), 7.28 (s, 1 H, Ar-4-H) ppm. ^{13}C NMR (62.9 MHz, DEPT): δ = 12.6 (–, Cpr-C), 28.2 [+, $C(CH_3)_3$], 32.8 (C_{quat}, Cpr-C), 45.6 (–, CH_2Alk), 54.6 (CH_2Ar), 79.4 [C_{quat}, $C(CH_3)_3$], 137.8 (+, Ar-C-4), 142.1 (C_{quat}, Ar-C-5), 150.9 (C_{quat}, Ar-C-2), 155.8 (C_{quat}, NCO) ppm. MS (EI): *m*/*z* (%) = 319/317 (<1/<1) [M^+], 262/260 (3/5) [M^+ – *t*Bu], 233/231 (<1/4), 202/200 (<1/1) [M^+ – H_2NCO_2 *t*Bu], 163/161 (2/8), 148/146 (6/14) [NCH_2ArCl^+], 134/132 (16/40) [CH_2ArCl^+], 57 (100) [*t*Bu$^+$], 41 (28) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{13}H_{20}ClN_3O_2S$ [M^+] 317.0365, correct mass. $C_{13}H_{20}ClN_3O_2S$ (317.83): calcd. C 49.13, H 6.34, N 13.22, Cl 11.15; found C 49.42, H 6.44, N 13.12, Cl 10.77.

***N*-[4-(2-Chlorothiazol-5-ylmethyl)]-4,6-diazaspiro[2.4]heptan-5-one (21-CT):** Carbamate **17**-CT (159 mg, 500 μmol) was stirred with TFA (0.5 mL) at ambient temp. for 1 h. All volatile components of the reaction mixture were removed in vacuo. To the residue was added a 5–6 M solution of HCl in *i*PrOH (2.5 mL), and the reaction mixture was evaporated. This operation was repeated three times. The crude residual dihydrochloride **18**-CT was treated with **22** (65.0 mg, 500 μmol, cont. 20 % of water) and KOH (56.1 mg, 1.00 mmol) in water (10 mL) according to GP1 (150 °C, 5 d). Column chromatography (15 g of silica gel, 1 × 15 cm column, $CHCl_3$/MeOH, 25:1) of the residue furnished **21**-CT (54 mg, 44 %, R_f = 0.30) as a light orange solid, m.p. 110–113 °C. IR (KBr): $\tilde{\nu}$ = 3228 cm^{-1} (N–H), 1700 (C=O), 1658, 1415, 1047. ^1H NMR (250 MHz): δ = 0.50–0.75 (m, 2 H, Cpr-H), 0.75–1.00 (m, 2 H, Cpr-H), 3.33 (s, 2 H, CH_2Cpr), 4.46 (s, 2 H, CH_2Ar), 5.90 (br. s, 1 H, NH), 7.37 (s, 1 H, 4-Ar-H) ppm. ^{13}C NMR (50.3 MHz, APT): δ = 11.4 (–, Cpr-C), 35.2 (–, Cpr-C), 39.8 (–, CH_2NH), 51.8 (–, CH_2Ar), 136.6 (–, Ar-C-5), 139.8 (+, Ar-C-4), 152.2 (–, Ar-C-2), 161.4 (–, NNCN) ppm. MS (DCI): *m*/*z* (%) = 508/506/504 (2/8/10) [2M + NH_4^+], 491/489/487 (6/24/33) [2M + H^+], 280/278 (3/7) [M + NH_3 + NH_4^+], 263/261 (37/100) [M + NH_4^+], 246/244 (48/18) [M + H^+]. $C_9H_{10}ClN_3OS$ (243.71): calcd. C 44.36, H 4.14, N 17.24; found. C 44.71, H 4.31, N 17.16.

{*N*-[4-(2-Chlorothiazol-5-ylmethyl)-4,6-diazaspiro[2.4]heptan-5-ylidene}cyanamide (19-CT) and *N*-[4-(2-Chlorothiazol-5-ylmethyl)]-4,6-diazaspiro[2.4]heptan-5-one (21-CT): a) The crude **18**-CT obtained as described in the previous preparation from **17**-CT (159 g, 500 μmol), was treated with **11** (73.1 mg, 500 μmol) and KOH (56.1 mg, 1.00 mmol) in EtOH (10 mL) according to GP1 (125 °C, 2 d, tightly screwed Pyrex tube). Column chromatography of the residue (15 g of silica gel, 1 × 15 cm column, CH_2Cl_2/MeOH, 25:1, R_f = 0.30) furnished an unseperable mixture of **19**-CT (33 mg, calculated yield 25 %) and **21**-CT (44 mg, calculated yield 36 %)[14] as a pale yellow solid. b) The crude **18**-CT obtained as described in the previous preparation from **17**-CT (159 g, 500 μmol), was treated with **11** (73.1 mg, 500 μmol) and NEt_3 (146 mL, 1.05 mmol) in EtOH (5 mL) according to GP1 (80 °C, 2.5 d). Column chromatography of the residue (15 g of silica gel, 1 × 15 cm column, CH_2Cl_2/MeOH, 25:1, R_f = 0.30) furnished an unseperable mixture of **19**-CT (73 mg, calculated yield 55 %) and **21**-CT (17 mg, calculated yield 14 %)[14] as a pale yellow solid. The spectroscopic data were

consistent with those of independently prepared **21**-CT (see above) and **19**-CT (see below).

(4,6-Diazaspiro[2.4]hept-5-ylidene)nitroamide (25): A solution of the azide **15** (2.12 g, 10.0 mmol) in MeOH (10 mL) was stirred with 10 % palladium on charcoal (212 mg, 2 mol%) under hydrogen at ambient temp. for 2.5 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was stirred with TFA (7 mL) at ambient temp. for 30 min. All volatile components of the reaction mixture were removed in vacuo. The residue was treated with a 1 M solution of HCl in *i*PrOH (5 mL) and the solvents evaporated. This operation was repeated four times. The crude residual 1-(aminomethyl)cyclopropylamine dihydrochloride (1.59 g, 100 %) was treated with nitroguanidine (**22**) (1.35 g, 13.0 mmol) and a solution of KOH [1.12 g, 20.0 mmol as a solution in water (2 mL)] in H_2O (20 mL) according to GP1 (70 °C, 6 h). The precipitate which was formed upon cooling of the reaction mixture was filtered off to give **25** (440 mg, 28 %) as a pale yellow solid, m.p. 225–227 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3397 cm^{-1} (N–H), 3222, 3149 (C–H), 1588 (NO_2) 1553, 1476, 1364, 1298 (NO_2), 1101. ^1H NMR (200 MHz, [D_6]DMSO): δ = 0.65–0.85 (m, 2 H, Cpr-H), 0.85–1.05 (m, 2 H, Cpr-H), 3.62 (s, 2 H, CH_2), 8.50 (br. s, 2 H, NH) ppm. ^{13}C NMR (500 MHz, [D_6]DMSO): δ = 11.1 (–, Cpr-C), 39.8 (C_{quat}, Cpr-C), 48.3 (–, CH_2), 162.0 (C_{quat}, NNCN) ppm. MS (EI): *m*/*z* (%) = 156 (20) [M^+], 110 (38) [M^+ – NO_2], 94 (22) [M^+ – NO_2 – NH_2], 55 (100) [$C_4H_7^+$, $C_3H_5N^+$]. HRMS (EI) calcd. for $C_5H_8N_4O_2$ [M^+] 156.0647, correct mass.

(4,6-Diazaspiro[2.4]hept-5-ylidene)cyanamide (24): 1-(Aminomethyl)cyclopropylamine dihydrochloride (811 mg, 5.10 mmol) prepared as described in the previous experiment was treated with *S*,*S*-dimethyl cyanodithioiminocarbonate (**11**) (819 mg, 5.60 mmol) and KOH (572 mg, 10.2 mmol) in H_2O (20 mL) according to GP1 (70 °C, 16 h). Column chromatography of the residue (25 g of silica gel, 2 × 20 cm column, $CHCl_3$/MeOH, 20:1, R_f = 0.30) furnished **24** (346 mg, 50 %) as a pale yellow solid, m.p. 170–171 °C. IR (KBr): $\tilde{\nu}$ = 3183 cm^{-1} (N–H), 2183 (C≡N), 1635 (C=N), 1528, 1416, 1255. ^1H NMR (250 MHz, CD_3OD): δ = 0.60–0.72 (m, 2 H, Cpr-H), 0.72–1.88 (m, 2 H, Cpr-H), 3.53 (s, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, DEPT): δ = 11.8 (–, Cpr-C), 41.2 (C_{quat}, Cpr-C), 50.9 (–, CH_2), 119.7 (C_{quat}, C≡N), 166.4 (C_{quat}, NNCN) ppm. MS (EI): *m*/*z* (%) = 136 (65) [M^+], 121 (100) [M^+ – NH], 108 (26) [M^+ – CNH_2], 68 (26) [$C_4H_6N^+$], 54 (18) [$C_3H_4N^+$], 41 (24) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_6H_8N_4$ [M^+] 136.0749, correct mass. $C_6H_8N_4$ (136.16): calcd. C 52.93, H 5.92, N 41.15; found. C 52.98, H 6.20, N 41.09.

[4-(6-Chloropyridin-3-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]nitroamide (27-CP) and [6-(6-chloropyridin-3-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]nitroamide (20-CP): [17] Column chromatography (15 g of silica gel, 2 × 15 cm column, $CHCl_3$/MeOH, 40:1, R_f = 0.23, 0.26) of the residue prepared from **25** (234 mg, 1.50 mmol), CCMP (243 mg, 1.50 mmol) and K_2CO_3 (829 mg, 6.00 mmol) in MeCN (15 mL) according to GP2 (70 °C, 17 h) furnished a mixture of the two regioisomers **27**-CP (181 mg, calculated yield 43 %) and **20**-CP (139 mg, calculated yield 33 %)[14] as a yellow foam. **27-CP:** M.p. 134–135 °C. IR (KBr): $\tilde{\nu}$ = 3355 cm^{-1} (N–H), 1562, 1537, 1464, 1436, 1298, 1242, 1032. ^1H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.65–0.74 (m, 2 H, Cpr-H), 0.97–1.05 (m, 2 H, Cpr-H), 3.84 (s, 2 H, CH_2Cpr), 4.24 (s, 2 H, CH_2Ar), 7.26 (d, ^3J = 8.2 Hz, 1 H, Ar-5-H), 7.60 (dd, ^3J = 8.2, ^4J = 2.5 Hz 1 H, Ar-4-H), 8.19 (d, ^4J = 2.5 Hz, 1 H, Ar-2-H), 8.31 (br.s, 1 H, NH) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 8.5 (Cpr-C), 39.8 (CH_2Cpr), 42.3 (Cpr-C_{quat}), 50.0 (CH_2Ar), 124.4 (Ar-C-5), 131.5 (C_{quat}, Ar-C-3), 137.9 (Ar-C-4), 147.9 (Ar-C-2), 150.8 (C_{quat}, Ar-C-6), 161.2 (C_{quat}, NNCN) ppm. MS (EI): *m*/*z* (%) = 283/281 (4/14) [M^+], 237/235 (16/51) [M^+ – NO_2], 199 (32) [M^+ – NO_2 – HCl], 128/126 (32/100) [$ClArCH_2^+$]. HRMS (EI) calcd. for $C_{11}H_{12}ClN_5O_2$ [M^+] 281.0680, correct mass. **20-CP:** M.p. 180–181 °C. IR (KBr): $\tilde{\nu}$ = 3343 cm^{-1} (N–H), 1547, 1463, 1446, 1287, 1269, 1190, 1131, 1108. ^1H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.77–0.83 (m, 2 H, Cpr-H), 1.08–1.14 (m, 2 H, Cpr-H), 3.49 (s, 2 H, CH_2Cpr), 4.54 (s, 2 H, CH_2Ar), 7.31 (d, ^3J = 8.2 Hz, 1 H, Ar-5-Ar), 7.67 (dd, ^3J = 8.2, ^4J = 2.5 Hz, 1 H, Ar-4-H), 8.04 (br.s, 1 H, NH), 8.27 (d, ^4J = 2.5 Hz, 1 H, Ar-2-H) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 12.3 (Cpr-C), 38.9 (Cpr-C_{quat}), 45.2 (CH_2Cpr), 52.0 (CH_2Ar), 124.7 (Ar-C-5), 129.8 (C_{quat}, Ar-C-3), 139.0 (Ar-C-4), 149.2 (Ar-C-2), 151.4 (C_{quat}, Ar-C-6), 160.3 (C_{quat}, NNCN) ppm. MS (EI): *m*/*z* (%) = 283/281 (22/67) [M^+], 237/235 (23/73) [M^+ – NO_2], 199 (39) [M^+ – NO_2 – HCl], 128/126 (31/100) [$ClArCH_2^+$]. HRMS (EI) calcd. for $C_{11}H_{12}ClN_5O_2$ [M^+] 281.0680, correct mass.

[4-(2-Chlorothiazol-5-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]nitroamide (27-CT) and [6-(2-Chlorothiazol-5-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]nitroamide (20-CT): [17] Column chromatography (15 g of silica gel, 2 × 15 cm column, $CHCl_3$/MeOH, 50:1, R_f = 0.22) of the residue prepared from **25** (315 mg, 2.02 mmol), CCMT (339 mg, 2.02 mmol) and K_2CO_3 (1.12 g, 8.10 mmol) in MeCN (20 mL) according to GP2 (70 °C, 17 h) furnished a mixture of the two regioisomers **27**-CT (238 mg, calculated yield 41 %) and **20**-CT (176 mg, calculated yield 30 %)[14] as a light brown foam. **27-CT:** M.p. 175–176 °C. IR (KBr): $\tilde{\nu}$ = 3304 cm^{-1} (N–H), 1565, 1547, 1445, 1288, 1209, 1048. ^1H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.81–0.91 (m, 2 H, Cpr-H), 1.07–1.14 (m, 2 H, Cpr-H), 3.56 (s, 2 H, CH_2Cpr), 4.64 (s, 2 H, CH_2Ar), 7.64 (s, 1 H, Ar-4-H), 8.00 (br.s, 1 H, NH) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, add. HMBC, HMQC, NOE): δ = 12.2 (Cpr-C), 40.7 (CH_2Cpr), 42.0 (Cpr-C_{quat}), 50.0 (CH_2Ar), 139.7 (C_{quat}, Ar-C-5), 140.9 (Ar-C-4), 153.1 (C_{quat}, Ar-C-2), 160.4 (C_{quat}, NNCN) ppm. MS (EI): *m*/*z* (%) = 289/287 (2/4) [M^+], 252 (23) [M^+ – Cl], 243/241 (10/27) [M^+ – NO_2], 134/132 (36/100) [$ClArCH_2^+$]. HRMS (EI) calcd. for $C_9H_{10}ClN_5O_2S$ [M^+] 287.0244, correct mass. **20-CT:** M.p. 190–192 °C. IR (KBr): $\tilde{\nu}$ = 3368 cm^{-1} (N–H), 1580, 1538, 1524, 1469, 1444, 1289, 1247, 1230, 1199, 1058, 1030. ^1H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.73–0.81 (m, 2 H, Cpr-H), 1.14–1.20 (m, 2 H, Cpr-H), 3.81 (s, 2 H, CH_2Cpr), 4.28 (s, 2 H, CH_2Ar), 7.34 (s, 1 H, Ar-4-H), 8.21 (br.s, 1 H, NH) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, add. HMBC, HMQC, NOE): δ = 8.7 (Cpr-C), 35.9 (CH_2Cpr), 39.0 (Cpr-C_{quat}), 51.7 (CH_2Ar), 139.6 (C_{quat}, Ar-C-5), 140.9 (Ar-C-4), 153.4 (C_{quat}, Ar-C-2), 159.8 (C_{quat}, NNCN) ppm. MS (EI): *m*/*z* (%) = 289/287 (<1/1) [M^+], 243/241 (31/82) [M^+ – NO_2], 205 (68) [M^+ – NO_2 – HCl], 134/132 (39/100) [$ClArCH_2^+$]. HRMS (EI) calcd. for $C_9H_{10}ClN_5O_2S$ [M^+] 287.0244, correct mass.

[4-(6-Chloropyridin-3-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]cyanamide (26-CP), [6-(6-Chloropyridin-3-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]cyanamide (19-CP) and [4,6-Bis(6-chloropyridin-3-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]cyanamide (28-CP): [17] Column chromatography (15 g of silica gel, 2 × 15 cm column, $CHCl_3$/MeOH, 50:1, R_f = 0.18, 0.25) of the residue prepared from **24** (190 mg, 1.40 mmol), CCMP (227 mg, 1.40 mmol) and K_2CO_3 (774 mg, 5.60 mmol) in MeCN (15 mL) according to GP2 (70 °C, 17 h) furnished a mixture of **26**-CP (66 mg, calculated yield 18 %), **19**-CP (44 mg, calculated yield 12 %) and **28**-CP (92 mg, calculated 34 %)[14] as a high viscous yellow oil. **26-CP:** M.p. 190–191 °C. IR (KBr): $\tilde{\nu}$ = 3177 cm^{-1} (N–H), 2170 (C≡N), 1603 (C=N), 1523, 1465, 1422, 1396, 1105, 811. ^1H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.55–0.65 (m, 2 H,

Table 2. Crystallographic data and parameters of the refinements of compounds **13**-CT, **14**-CT, **19**-CT and **21**-CT.

Identification code	**13**-CT	**14**-CT	**19**-CT	**21**-CT
Empirical formula	$C_{10}H_9ClN_4S_2$	$C_{10}H_9ClN_4S_2$	$C_{10}H_{10}ClN_5S$	$C_9H_{10}ClN_3OS$
Formula weight (g/mol)	284.78	284.78	267.74	243.71
Crystal system	monoclinic	orthorhombic	triclinic	monoclinic
Space group	$P2_1/c$	$Pna2_1$	$P\bar{1}$	$P2_1/n$
Unit cell dimensions				
a (Å)	5.2823(2)	13.4197(3)	5.7101(2)	5.9702(3)
b (Å)	12.0185(4)	13.1871(4)	14.0746(4)	8.1798(5)
c (Å)	19.9117(7)	6.9676(2)	14.9377(5)	21.713(1)
α (°)	90	90	101.29(1)	90
β (°)	97.44(2)	90	96.68(1)	95.64(2)
γ (°)	90	90	94.01(1)	90
Volume (Å^3)	1253.45(8)	1233.03(6)	1163.9(7)	1055.2(1)
Z	4	4	4	4
Density (calculated) (Mg/m^3)	1.509	1.534	1.528	1.534
Absorption coefficient (mm^{-1})	0.619	0.630	0.491	0.535
F_o	584	584	552	504
Crystal size (mm)	0.46 × 0.14 × 0.07	0.37 × 0.13 × 0.04	0.28 × 0.24 × 0.06	0.32 × 0.16 × 0.14
θ range for data collection (°)	1.98 to 30.00	2.17 to 29.99	1.82 to 30.00	1.88 to 27.49
Reflections collected	10370	14103	11571	8395
Independent reflections [R_{int}]	3655 [0.0222]	3577 [0.0249]	6623 [0.0190]	2427, [0.0336]
Data/restraints/parameters	3655/0/190	3577/1/190	6623/0/387	2427/0/176
Goof on F^2	1.046	1.036	1.032	1.037
R_1, wR_2 indices [$I > 2\sigma(I)$]	0.0346, 0.0913	0.0273, 0.0694	0.0366, 0.0936	0.0443, 0.1137
R_1, wR_2 indices (all data)	0.0458, 0.0989	0.0301, 0.0716	0.0509, 0.1025	0.0597, 0.1218
Largest diff. peak and hole, e·Å^{-3}	0.492 and –0.472	0.309 and –0.199	0.455 and –0.270	0.760 and –0.385

Cpr-H), 0.85–0.91 (m, 2 H, Cpr-H), 3.64 (s, 2 H, CH_2Cpr), 4.10 (s, 2 H, CH_2Ar), 7.24 (d, ^3J = 8.3 Hz, 1 H, Ar-5-H), 7.46 (br.s, 1 H, NH), 7.56 (dd, ^3J = 8.3, ^4J = 2.5 Hz, 1 H, Ar-4-H), 8.17 (d, ^4J = 2.5 Hz, 1 H, Ar-2-H) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 8.1 (Cpr-C), 37.9 (Cpr-C_{quat}), 39.5 (CH_2Cpr), 49.2 (CH_2Ar), 118.4 (C_{quat}, C≡N), 124.3 (Ar-C-5), 132.0 (C_{quat}, Ar-C-3), 137.9 (Ar-C-4), 148.0 (Ar-C-2), 150.6 (C_{quat}, Ar-C-6), 163.6 (C_{quat}, NNCN) ppm. MS (EI): *m/z* (%) = 263/261 (20/64) [M$^+$], 135 (50) [M$^+$ – ClArCH$_2$], 128/126 (32/100) [ClArCH$_2^+$]. HRMS (EI) calcd. for $C_{12}H_{12}ClN_5$ [M$^+$] 261.0781, correct mass. **19-CP:** M.p. 205–206 °C. IR (KBr): $\tilde{\nu}$ = 3217 cm^{-1} (N–H), 2178 (C≡N), 1609 (C=N), 1536, 1387, 1112. ^{1}H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.55–0.65 (m, 2 H, Cpr-H), 0.98–1.05 (m, 2 H, Cpr-H), 3.40 (s, 2 H, CH_2Cpr), 4.39 (s, 2 H, CH_2Ar), 7.28 (d, ^3J = 8.3 Hz, 1 H, Ar-5-H), 7.61 (dd, ^3J = 8.3, ^4J = 2.5 Hz 1 H, Ar-4-H), 7.66 (br.s, 1 H, NH), 8.24 (d, ^4J = 2.5 Hz, 1 H, Ar-2-H) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 11.4 (Cpr-C), 43.1 (Cpr-C_{quat}), 44.9 (CH_2Cpr), 53.3 (CH_2Ar), 118.9 (C_{quat}, C≡N), 124.5 (Ar-C-5), 130.3 (C_{quat}, Ar-C-3), 138.8 (Ar-C-4), 138.9 (Ar-C-2), 151.1 (C_{quat}, Ar-C-6), 163.0 (C_{quat}, NNCN) ppm. MS (EI): *m/z* (%) = 263/261 (24/74) [M$^+$], 135 (19) [M$^+$ – ClArCH$_2$], 128/126 (32/100) [ClArCH$_2^+$]. HRMS (EI) calcd. for $C_{12}H_{12}ClN_5$ [M$^+$] 261.0781, correct mass. **28-CP:** M.p. 142–144 °C. IR (KBr): $\tilde{\nu}$ = 2172 cm^{-1} (C≡N), 1589 (C=N), 1566, 1507, 1453, 1250, 1100, 819. ^{1}H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.55–0.65 (m, 2 H, Cpr-H), 0.91–0.65 (m, 2 H, Cpr-H), 3.47 (s, 2 H, CH_2Cpr), 4.34 (s, 2 H, CH_2Ar), 4.78 (s, 2 H, CH_2Ar), 7.26 (d, ^3J = 8.3 Hz, 1 H, Ar-5-H), 7.32 (d, ^3J = 8.3 Hz, 1 H, Ar-5-H), 7.57 (dd, ^3J = 8.3, ^4J = 2.5 Hz 1 H, Ar-4-H), 7.72 (dd, ^3J = 8.3, ^4J = 2.5 Hz 1 H, Ar-4-H), 8.20 (d, ^4J = 2.5 Hz, 1 H, Ar-2-H), 8.30 (d, ^4J = 2.5 Hz, 1 H, Ar-2-H) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 8.4 (Cpr-C), 40.5 (Cpr-C_{quat}), 41.1 (CH_2Cpr), 46.3 (CH_2Ar), 53.6 (CH_2Ar), 115.5 (C_{quat}, C≡N), 124.4 (Ar-C-5), 124.7 (Ar-C-5), 129.8 (C_{quat}, Ar-C-3), 131.7 (C_{quat}, Ar-C-3), 137.6 (Ar-C-4), 138.9 (Ar-C-4), 147.8 (Ar-C-2), 149.1 (Ar-C-2), 150.8 (C_{quat}, Ar-C-6), 151.4 (C_{quat}, Ar-C-6), 157.9 (C_{quat}, NNCN) ppm. MS (EI): *m/z* (%) = 390/388/386 (2/11/17) [M$^+$], 262/260 (15/49) [M$^+$ – ClArCH$_2$], 128/126 (30/100) [ClArCH$_2^+$]. HRMS (EI) calcd. for $C_{18}H_{16}Cl_2N_6$ [M$^+$] 386.0814, correct mass.

[4-(2-Chlorothiazol-5-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]cyanamide (26-CT), [6-(2-Chlorothiazol-5-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]cyanamide (19-CT) and [4,6-Bis(2-chlorothiazol-5-ylmethyl)-4,6-diazaspiro[2.4]hept-5-ylidene]cyanamide (28-CT): [17] Column chromatography (15 g of silica gel, 2 × 15 cm column, $CHCl_3$/MeOH, 35:1, R_f = 0.26, 0.29) of the residue prepared from **24** (136 mg, 1.00 mmol), CCMT (168 mg, 1.00 mmol) and K_2CO_3 (553 mg, 4.00 mmol) in MeCN (10 mL) according to GP2 (70 °C, 17 h) furnished a mixture of **26**-CT (27 mg, calculated yield 10 %), **19**-CT (17 mg, calculated yield 6 %) and **28**-CT (106 mg, calculated yield 53 %)[14] as a high viscous yellow oil. **26-CT:** M.p. 179–180 °C. IR (KBr): $\tilde{\nu}$ = 3170 cm^{-1} (N–H), 2183 (C≡N), 1616 (C=N), 1523, 1421, 1049. ^{1}H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.72–0.81 (m, 2 H, Cpr-H), 1.03–1.11 (m, 2 H, Cpr-H), 3.59 (s, 2 H, CH_2Cpr), 4.15 (s, 2 H, CH_2Ar), 7.28 (s, 1 H, Ar-4-H), 7.37 (br.s, 1 H, NH) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 8.1 (Cpr-C), 35.5 (CH_2Cpr), 42.7 (Cpr-C_{quat}), 49.1 (CH_2Ar), 117.8 (C_{quat}, C≡N), 137.0 (C_{quat}, Ar-C-5), 139.3 (Ar-C-4), 152.7 (C_{quat}, Ar-C-2), 162.7 (C_{quat}, NNCN) ppm. MS (EI): *m/z* (%) = 269/267 (16/46) [M$^+$], 232 (29) [M$^+$ – Cl], 134/132 (28/100) [ClArCH$_2^+$]. HRMS (EI) calcd. for $C_{10}H_{10}ClN_5S$ [M$^+$] 267.0345, correct mass. **19-CT:** M.p. 179–180 °C. IR (KBr): $\tilde{\nu}$ 3164 cm^{-1} (N–H), 2182 (C≡N), 1614 (C=N), 1522, 1421, 1049. ^{1}H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.62–0.70 (m, 2 H, Cpr-H), 0.96–1.03 (m, 2 H, Cpr-H), 3.46 (s, 2 H, CH_2Cpr), 4.46 (s, 2 H, CH_2Ar), 7.36 (s, 1 H, Ar-4-H), 7.66 (br.s, 1 H, NH) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 11.2 (Cpr-C), 37.9 (Cpr-C_{quat}), 40.3 (CH_2Cpr), 52.9 (CH_2Ar), 118.4 (C_{quat}, C≡N), 134.5 (C_{quat}, Ar-C-5), 140.4 (Ar-C-4), 152.4 (C_{quat}, Ar-C-2), 162.5 (C_{quat}, NNCN) ppm. MS (EI): *m/z* (%) = 269/267 (6/20) [M$^+$], 232 (36) [M$^+$ – Cl], 135 (11) [M$^+$ – ClArCH$_2$], 134/132 (37/100) [ClArCH$_2^+$]. HRMS (EI) calcd. for $C_{10}H_{10}ClN_5S$ [M$^+$]

267.0345, correct mass. **28-CT:** M.p. 145–146 °C. IR (KBr): $\tilde{\nu}$ = 3091 cm^{-1} (C–H), 2174 (C≡N), 1602 (C=N), 1515, 1420, 1037. ^1H NMR (600 MHz, add. HMBC, HMQC, NOE): δ = 0.62–0.81 (m, 2 H, Cpr-H), 0.96–1.11 (m, 2 H, Cpr-H), 3.50 (s, 2 H, CH_2Cpr), 4.35 (s, 2 H, CH_2Ar), 4.87 (s, 2 H, CH_2Ar), 7.34 (s, 1 H, Ar-4-H), 7.44 (s, 1 H, Ar-4-H) ppm. ^{13}C NMR (151 MHz, add. HMBC, HMQC, NOE): δ = 8.6 (Cpr-C), 36.6 (CH_2Cpr), 40.7 (Cpr-C_{quat}), 41.6 (CH_2Ar), 53.3 (CH_2Ar), 115.2 (C_{quat}, C≡N), 133.8 (C_{quat}, Ar-C-5), 136.4 (C_{quat}, Ar-C-5), 139.6 (Ar-C-4), 140.9 (Ar-C-4), 152.5 (C_{quat}, Ar-C-2), 153.0 (C_{quat}, Ar-C-2), 157.1 (C_{quat}, NNCN) ppm. MS (EI): *m/z* (%) = 402/400/398 (2/6/10) [M^+], 365/363 (12/31) [M^+ – Cl], 268/266 (9/28) [M^+ – $ClArCH_2$], 134/132 (37/100) [$ClArCH_2^+$]. HRMS (EI) calcd. for $C_{14}H_{12}Cl_2N_6S_2$ [M^+] 397.9942, correct mass.

Crystal Structure Determination: Suitable crystals of the compounds **13**-CT, **14**-CT, **19**-CT and **21**-CT for X-ray crystal structure determinations were obtained by slow evaporation of solvents from their solutions in hexane/Et_2O mixtures. The X-ray data were collected at 120.0 K with a Bruker SMART CCD 6000 diffractometer ($\lambda_{Mo\text{-}K\alpha}$, graphite monochromator, ω-scan, 0.3°/frame) equipped with Oxford Cryostream LT-device. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 for all data. Non-hydrogen atoms were refined with anisotropic displacement parameters, all H-atoms were located in the difference Fourier maps and refined isotropically. Crystallographic data and parameters of the refinements are listed in Table 2.[8]

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